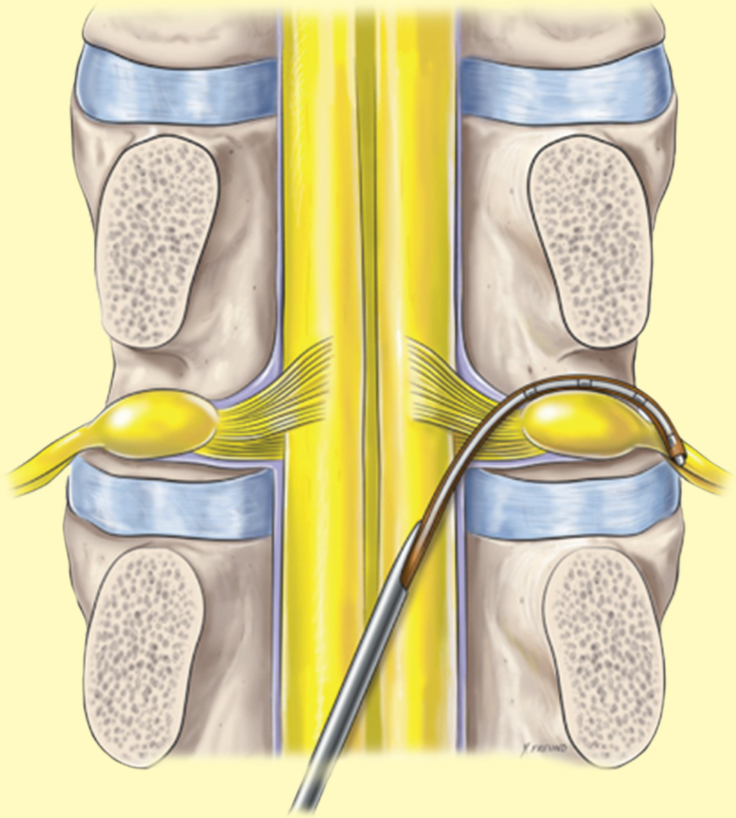
Stimulation of the Dorsal Root Ganglion (DRG) can provide long-term, focused pain relief, while avoiding unwanted side-effects such as positional dependencies. It is highly suited for the treatment of pain in focal and/or challenging locations, including the foot, knee, back, breast, and the groin.

Stimulation of the Dorsal Root Ganglion for the Treatment of Chronic Pain

Liong Liem

Stimulation of the Dorsal Root Ganglion for the Treatment of Chronic Pain



Liong Liem

Stimulation of the Dorsal Root Ganglion for the Treatment of Chronic Pain

Liong Liem

Printing of this thesis was sponsored by:

Bureau R&D Anesthesiologie
Sint Antonius Ziekenhuis
Nieuwegein

ISBN: 978-94-6182-639-8

Copyright © A. L. Liem, Nieuwegein, 2015. All rights reserved.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means mechanically, by photocopy, by recording, or otherwise, without the prior written permission of the holder of copyright.

Cover: a schematic representation of dorsal root ganglion stimulation.

Cover design by Yvan Freund, www.medical-art.fr

Layout and print by Off Page, Amsterdam, the Netherlands

Stimulation of the Dorsal Root Ganglion
for the Treatment of Chronic Pain

Stimulatie van het Dorsale Spinale Ganglion
voor de Behandeling van Chronische Pijn

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr. H.A.P. Pols

en volgens het besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

28 januari 2016 om 13:30 uur

door

An Liong Liem

geboren te Leiden

Erasmus University Rotterdam

Leescommissie

Promotor:	Prof.dr. F.J.P.M. Huygen
Co-promotor:	Dr. H.P.A. van Dongen
Overige leden:	Prof.dr. J.F. Lange
	Prof.dr. G.J. Kleinrensink
	Prof.dr. ir. M.J.A.M. van Putten

"By pushing the electrode a few millimeters ahead,
you pushed the technique 20 years forward."
Marshall Devor, Granada, Spain, 15th World Congress of Pain Clinicians, 2012,
referring to the difference in implant technique for DRG stimulation relative to that for conventional spinal cord stimulation.

CONTENTS

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Chronic pain

Chronic pain is a pain that lasts beyond the usual course of the acute disease or expected time of healing, which may need several types of treatments before pain relief may be accomplished. Chronic pain remains a worldwide issue with almost 40% prevalence in the worldwide population (1).

A study that gives a good impression about the epidemiology of chronic pain is the study by Breivik et al (2). The mean percentage of people with chronic pain in this study is 19%. A One in five European adult suffers from chronic pain. Chronic pain is often severe. 34% scores an 8 or higher on an 11-point numeric rating scale. Chronic pain has a negative influence on sleeping, functionality, and quality of life. 21% of the people with chronic pain in the Breivik study also have a confirmed diagnosis of depression. In 25% of the patients with chronic pain it influences their position in work. The natural course of chronic pain is unfavorable. 60 % of the patients with chronic pain have 2 till 15 years complaints, 21% even more then 20 years. 85% of the chronic pain patients have an known etiology of there pain. Osteoarthritis and rheumatoid arthritis are combined the most prevalent etiologies. Chronic pain patients tend to visit many physicians. 64% visited 2 to 5 different doctors (2).

Chronic pain has a large societal burden. In the U.S., the economic cost associated with chronic pain is estimated between $560-635 billion annually (3).

Treating chronic pain is a major therapeutic challenge, also for the pain physician (4). Chronic pain patients are treated with different therapy strategies. Besides therapies focusing on the etiology of the pain, patients are symptomatically treated with e.g. pharmacotherapy, physical therapy, and psychological therapy.

Non-surgical treatment for chronic pain currently includes pain medications, nerve blocks, and physical therapy; however, many patients are not responsive to these therapies or are not able to tolerate the side effects (3). More invasive treatments can include surgical interventions to release entrapment and/or ablate or repair nerves (3). All of these options are irreversible and may cause side effects like numbness while they may or may not provide pain relief (5). Another way of treatment that has the advantage of reversibility is the so-called electrical stimulation therapy. A popular way of electrical stimulation is spinal cord stimulation (SCS).

Spinal cord stimulation

The effects of electrical stimulation of the body or nervous system have been recognized for thousands of years in every culture. It is said that since circa 9000 BC, bracelets and necklaces of magnetite and amber were used to prevent headaches and arthritis (6,7).

The ancient Egyptians used electrical discharges of the Nile catfish to treat neuralgia, headaches and other painful disorders (8). The first documented attempt to use electricity for pain treatment appeared in circa 15 AD. A Roman physician, Scribonius Largus, observed torpedo fish shock relieved gout pain and he subsequently recommended torpedo fish therapy as a general treatment of pain (9). The first electrostatic generator

was presented by the German engineer Otto von Guericke in 1672, almost a century before the Leyden jar was developed. From then, man was able to generate, store and discharge electricity at any time, thus enabling physicians to provide on-demand electrotherapy in patients for the treatment of pain syndromes.

Since the 18th century, electro-analgesia therapy has been embedded in the armamentarium of physicians ((7). Its clinical application in English hospitals was called 'Franklinism', after the American statesman and scientist Benjamin Franklin. He acquired fame after observing that lightning and electrostatic charge on a Leyden jar were identical. Moreover, he was the first to discriminate positive and negative electricity and investigated the effects of muscle contraction after the administration of electrical shocks. The 19th century, also called 'the golden age of medical electricity', commenced with the discovery of the electrochemical battery in 1800. Several years later, Michael Faraday discovered the principle of electromagnetic induction, which was followed by the introduction of the electric generator in 1848 by Du Bois-Raymond. In those years electrical machines could be found in every doctor's consulting room. However, the number of skeptics who depicted electrotherapy as 'medical quackery' grew. Eventually, the Flexner report led to the legal exclusion of electrotherapy from clinical practice in 1910 (10). The association with 'quackery', the growing influence of the drug industry and the appearance of radiographic imaging all contributed to the loss of interest of science in the phenomenon of electro-analgesia. There was a reawakened interest in the application of electricity for pain treatment when Chaffee and Light presented a method for remote control of electrical stimulation of the nervous system in the early 1930s (11). The contemporary evolution of cardiac pacing techniques contributed to the development of the first neural stimulators. In the early years of the 20th century, the English neurologist Sir Henry Head postulated new conceptual basics for a theory of central inhibition of pain by non-painful stimuli. Melzack and Wall presented this concept as the Gate Control Theory in 1965 (12). The gate control theory, which is further described in chapter 1, page 24, states that stimulation of large primary afferent fibers 'close the gate' and inhibit nociceptive processes.

After first stimulating their own infra-orbital nerves, Wall and Sweet initiated the clinical therapeutic stimulation of peripheral nerves (7). Their initial results were promising, as the first patients experienced partial or complete pain alleviation during stimulation (13,14). Shealy et al. documented the first clinical application of spinal cord stimulation (SCS) or dorsal column stimulation (DCS) in 1967 (15). It was then presented as a novel analgesic method to relieve pain in a variety of chronic pain syndromes. SCS is actually a clinical outgrowth of the Gate Control Theory (12). The supposed mechanisms of action of SCS were predominantly described in these 'gating terms'. Initially, evidence for the efficacy of SCS in exerting a significant analgesic effect in a broad spectrum of neuropathic pain syndromes was lacking. In the 70's and 80's several studies appeared with the aim of unraveling the mechanisms of action of SCS (16). Numerous studies investigated the effects of SCS on noxious stimuli in healthy animals. SCS was administrated with current intensities that cannot be used in a clinical setting on conscious patients. Therefore, conclusions obtained from these studies cannot be translated 'from bench to bedside' without question. The development of a reliable

animal model of neuropathic pain made it possible to investigate the mechanisms of SCS more thoroughly (17). As further studies appeared there was more convincing evidence that supra-spinal interactions also play an eminent role in the analgesic effects of SCS. The mechanisms of SCS-induced pain relief appeared increasingly elusive and complex. A significant part of the current knowledge has been provided by a small number of prominent laboratories in this field (B. Linderoth M.D Ph.D. and B.A Meyerson M.D Ph.D., Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden, and Department of Neurosurgery, Karolinska University Hospital, Stockholm, Sweden. N.Saadé Ph.D., Professor, American University of Beirut, Beirut, Lebanon, and R. Foreman, Ph.D., Professor and Chair, Department of Physiology, Oklahoma Health Sciences Center, Oklahoma, City, Oklahoma). It was not until recently that a reawakened interest in exploring the mechanisms of action of SCS was expressed by Guan et al. (18). Over the years, many questions have been answered, although details of the mechanisms of SCS are still controversial and require additional evidence. In the last two decennia, SCS has been increasingly used as a neuromodulation technique in a narrow spectrum of pain diagnoses. It is estimated that, currently, more than 30,000 SCS systems are implanted every year worldwide (19).

Stimulation of the dorsal root ganglion (DRG)

SCS is not, however, without limitations and is not a panacea. Only about three in four patients have a successful trial period and about three in four patients who have a permanent implant report good pain relief (20). Although pain relief is sustainable, some reduction in effectiveness over time may occur (21,22). A requirement of this therapy is that, through a combination of appropriate placement of the leads against the target neural tissue and programming of the active electrodes to 'sculpt' the electrical fields, the perceptible paresthesias associated with treatment must overlap with the painful regions. It is recognized that establishing paresthesias with SCS can be difficult in axial locations (23) such as the low back (24,25) and the groin (26,27) and in distal extremities, such as the feet (28). Additionally, as a consequence of achieving acceptable pain-paresthesia concordance, patients may experience extraneous paresthesias in non-painful areas (29-31) that can range from merely annoying to frankly aversive. SCS is also susceptible to lead migration (20) and positional effects, in which gravitational or mechanical forces that result from movements of the body change the relative distance between the electrodes and the dorsal columns and result in changes in the perception of stimulation (32-34).

Because of the limitations associated with SCS, other neuromodulation targets have been explored. As such, the role of the dorsal root ganglion (DRG) in the development and maintenance of chronic pain has been a topic of investigation for some time and in the last decade has become a "hot topic". The DRG is composed of the cell bodies of the primary sensory neurons before they enter the spinal cord; it is located within the spinal foramen in the lateral epidural space. The DRG is known to be involved in the transduction of pain to the CNS, and neurons in the DRG show pathophysiologic changes during chronic pain states (35). A new neuromodulation system specifically designed to stimulate the DRG (Axium™ Neuromostimulator System, Spinal Modulation, Inc.), may

provide a promising new avenue for the treatment of chronic pain via stimulation of the DRG. Neuromodulation of the DRG has been shown to reduce neural excitation in vitro (36-38), and patients have been shown to have reduced pain with DRG stimulation in case studies (37,38) and in a small series of patients (39), and most recently, by our own group, in a multicenter, prospective study (40). In this latter study we showed that DRG stimulation can provide stimulation specificity, positional stability and, long-term relief, a combination that is difficult to obtain in other neurostimulation modalities (40). This makes stimulation of the DRG a very promising treatment for chronic pain (41).

REFERENCES

1. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. J Pain 2008 Oct;9(10):883-891.
2. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006 May;10(4):287-333.
3. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. 2011.
4. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain 2013 Jan;154(1):95-102.
5. Aasvang E, Kehlet H. Surgical management of chronic pain after inguinal hernia repair. Br J Surg 2005 Jul;92(7):795-801.
6. Schechter DC. Origins of electrotherapy. I. N Y State J Med 1971 May 1;71(9):997-1008.
7. Krabbenbos IP, Liem A, van Dongen E, Nijhuis H. Mechanisms of Spinal Cord Stimulation in Neuropathic Pain. : INTECH Open Access Publisher; 2012.
8. Kane K, Taub A. A history of local electrical analgesia. Pain 1975 Jun;1(2):125-138.
9. Stilling D. The first use of electricity for pain treatment. Medtronic Archive on Electro-Stimulation 1971.
10. Macklis RM. Magnetic healing, quackery, and the debate about the health effects of electromagnetic fields. Ann Intern Med 1993 Mar 1;118(5):376-383.
11. Chaffee EL, Light RU. A Method for the Remote Control of Electrical Stimulation of the Nervous System. Yale J Biol Med 1934 Dec;7(2):83-128.
12. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965 Nov 19;150(3699):971-979.
13. Wall PD, Sweet WH. Temporary abolition of pain in man. Science 1967 Jan 6;155(3758):108-109.
14. Wall P. The discovery of transcutaneous electrical nerve stimulation. Physiotherapy 1985;71:348-350.
15. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967 Jul-Aug;46(4):489-491.
16. Handwerker HO, Iggo A, Zimmermann M. Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. Pain 1975 Jun;1(2):147-165.
17. Meyerson BA, Herregodts P, Linderoth B, Ren B. An experimental animal model of spinal cord stimulation for pain. Stereotact Funct Neurosurg 1994;62(1-4):256-262.
18. Guan Y, Wacnik PW, Yang F, Carteret AF, Chung CY, Meyer RA, Raja SN. Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010 Dec;113(6):1392-1405.
19. Linderoth B, Meyerson BA. Spinal cord stimulation: exploration of the physiological basis of a widely used therapy. Anesthesiology 2010 Dec;113(6):1265-1267.
20. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. Neurosurgery 2006 Mar;58(3):481-96.
21. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008 Feb;108(2):292-298.
22. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008 Oct;63(4):762-70.
23. Alo KM, Yland MJ, Redko V, Feler C, Naumann C. Lumbar and Sacral Nerve Root Stimulation (NRS) in the Treatment of Chronic Pain: A Novel Anatomic Approach and Neuro Stimulation Technique. Neuromodulation 1999 Jan;2(1):23-31.
24. Oakley JC. Spinal cord stimulation in axial low back pain: solving the dilemma. Pain Medicine 2006;7:S58-S63.

25. Rigoard P, Desai MJ, North RB, Taylor RS, Annemans L, Greening C, Tan Y, Van den Abeele C, Shipley J, Kumar K. Spinal cord stimulation for predominant low back pain in failed back surgery syndrome; study protocol for an international multicenter randomized controlled trial (PROMISE study). Trials 2013;14:376.
26. Lepski G, Vahedi P, Tatagiba MS, Morgalla M. Combined spinal cord and peripheral nerve field stimulation for persistent post-herniorrhaphy pain. Neuromodulation 2013 Jan-Feb;16(1):84-8; discussion 88-9.
27. Schu S, Gulve A, Eldabe S, Baranidharan G, Wolf K, Demmel W, Rasche D, Sharma M, Klase D, Jahnichen G, Wahlstedt A, Nijhuis H, Liem L. Spinal Cord Stimulation of the Dorsal Root Ganglion for Groin Pain-A Retrospective Review. Pain Pract 2014.
28. Deer TR, Barolat G. Stimulation of the nervous system to treat neuropathic pain of the foot. Deer TR, ed. Atlas of Implantable Therapies for Pain Management. New York, Springer. 2011:81-86.
29. North RB, Lanning A, Hessels R, Cutchis PN. Spinal cord stimulation with percutaneous and plate electrodes: side effects and quantitative comparisons. Neurosurg Focus 1997 Jan 15;2(1):e3.
30. North R, Shipley J, Prager J, Barolat G, Barulich M, Bedder M, Calodney A, Daniels A, Deer T, DeLeon O, Drees S, Fautdch M, Fehrenbach W, Hernandez J, Kloth D, Krames ES, Lubenow T, North R, Osenbach R, Panchal SJ, Sitzman T, Staats P, Tremmel J, Wetzel T, American Academy of Pain M. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. Pain Med 2007 Dec;8 Suppl 4:S200-75.
31. North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN. Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine (Phila Pa 1976) 2005 Jun 15;30(12):1412-1418.
32. Barolat G, Schwartzman R, Woo R. Epidural spinal cord stimulation in the management of reflex sympathetic dystrophy. Stereotact Funct Neurosurg 1989;53(1):29-39.
33. Schade CM, Schultz DM, Tamayo N, Iyer S, Panken E. Automatic adaptation of neurostimulation therapy in response to changes in patient position: results of the Posture Responsive Spinal Cord Stimulation (PRS) Research Study. Pain Physician 2011 Sep-Oct;14(5):407-417.
34. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. Pain 2012 Mar;153(3):593-601.
35. McCallum JB, Kwok WM, Sapunar D, Fuchs A, Hogan QH. Painful peripheral nerve injury decreases calcium current in axotomized sensory neurons. Anesthesiology 2006 Jul;105(1):160-168.
36. Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. Neuromodulation 2013 Jul-Aug;16(4):304-11.
37. Neurostimulation of the L2 dorsal root ganglion for intractable disc pain: description of a novel technique. IFESS 3rd Annual Conference Proceedings; 1998.
38. Lynch PJ, McJunkin T, Eross E, Gooch S, Maloney J. Case report: successful epiradicular peripheral nerve stimulation of the C2 dorsal root ganglion for postherpetic neuralgia. Neuromodulation 2011 Jan;14(1):58-61.
39. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. Neuromodulation 2013 Jan-Feb;16(1):67-71.
40. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013 Sep-Oct;16(5):471-82; discussion 482.
41. A Safety and Effectiveness Trial of Spinal Cord Stimulation of the Dorsal Root Ganglion for Chronic Lower Limb Pain (ACCURATE). ClinicalTrials.gov, Identifier:NCT01923285(September 2014).

OUTLINE OF THE THESIS

OUTLINE OF THE THESIS

The research presented in this thesis was part of a collaboration between the Pain Department of the St Antonius Hospital in Nieuwegein and the Pain Department of the Erasmus Medical Center of the University of Rotterdam. Over the last years, we have been looking for better methods to stimulate the spinal cord and the DRG.

The aim of this thesis was to improve the clinical results in difficult patient populations using new and improved new technologies. In this context, we investigated what pain indications would benefit most from electrical stimulation of the DRG and defined appropriate patient selection criteria for this treatment. We studied (maintenance of) pain relief, paresthesia locations, and stability of the electrodes, as well as the therapeutic effect at different postures. Furthermore, the purpose of this work was to explore new technologies within the field of neuromodulation of the spinal cord. We look back to see what we have learned over the years and we look forward and discuss the potential future of spinal cord stimulation and especially stimulation of the DRG.

First, in **Chapter 1**, the mechanisms of spinal cord stimulation (SCS) from both a clinical and technological perspective are discussed. Then, in **Chapter 2**, a multicenter prospective trial is described which was conducted to evaluate the clinical performance of the neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the DRG described above, in patients with painful regions of the limbs and/or trunk. One year post-implantation, as described in **Chapter 3**, the subjects participated in further prospective follow-up addressing the maintenance of pain relief, improvement in mood, and quality of life for an additional six months, or one year in total after the implantation of the active DRG neurostimulator device. Since one prominent side-effect from neurostimulation techniques, and in particular SCS, is the change in intensity of stimulation when moving from an upright (vertical) to a recumbent or supine (horizontal) position, and vice versa, in **Chapter 4** the effects of posture changes on DRG stimulation intensity were investigated using a newly-developed scoring scale. Since different patients benefit from different therapies, **Chapter 5** reviews the SCS therapy and its mechanisms, and establishes a set of criteria for appropriate patient selection for neuromodulation of the DRG. **Chapter 6**, in turn, discusses neuropathic groin pain and its treatment options and recommendations and provides, based on a review of the knowledge base, a treatment algorithm for treatment of post-herniorrhaphy pain. Then in **Chapter 7**, the results from a retrospective review of data regarding the efficiency and safety of stimulation of the DRG in patients with groin pain of various etiologies are presented. Finally, **Chapter 8** discusses several novel approaches for neuropathic pain management, including pharmacological intervention, radiofrequency therapy, electrical stimulation, and gene therapy.

1

MECHANISMS OF SPINAL CORD STIMULATION FOR THE TREATMENT OF CHRONIC PAIN

Based on:

Mechanisms of spinal cord stimulation in neuropathic pain
Krabbenbos IP, Liem A, van Dongen E, Nijhuis H.
Topics in Neuromodulation Treatment, D.J. Carrillo-Ruiz, Editor. 2012, InTech. p. 89-110.

Dorsal root ganglion stimulation: a target for neuromodulation therapies
Liem AL, Krabbenbos IP, Kramer J.
Textbook of Neuromodulation: Springer; 2015. p. 53-59.

Stimulation of the dorsal root ganglion
Liong Liem.
Slavin V (ed): Stimulation of the Peripheral Nervous System. The Neuromodulation Frontier.
Prog Neurol Surg. Basel, Karger, 2016, vol 29, pp 213–224

ABSTRACT

Our understanding of the role of primary sensory neurons in the development and maintenance of chronic pain of varying diagnoses and etiologies has significantly increased over the past decade. The membrane properties of these cells are altered, which in turn results in an enhanced state of excitability involving multiple ion channels, second messenger systems and other physiological changes. These membrane alterations provide a fundamental opportunity to direct the delivery of therapy to a specific region of pathology as opposed to an upstream or downstream area as is so often the case in palliative neuromodulation techniques. Targeted stimulation of the dorsal root ganglion for the treatment of chronic pain is now technically feasible with recent implantable device innovations. Here, the evidence to support its effectiveness is reviewed. Previous techniques targeting the DRG have yielded excellent results demonstrating not only the safety of targeting the DRG, but also the potential opportunity for developing techniques that can provide longer-lasting pain relief. Preliminary results from completed and ongoing prospective studies suggest that DRG stimulation can provide good pain relief, while avoiding the unwanted side-effects of current neurostimulation techniques.

PHYSIOLOGICAL ANATOMY OF THE SPINAL CORD

A thorough understanding of the mechanisms of spinal cord stimulation needs a thorough knowledge of the anatomy and neurophysiology of the spinal cord and related structures. Furthermore, appreciation of the electrical characteristics of intraspinal structures is required. Primary afferent fibers have their cell bodies of the first order located in the dorsal root ganglia. Proximal to the dorsal root ganglion the afferent fibers form a single dorsal nerve root (14). Dorsal root fibers have a curved shape and an average diameter of 15 μm. As these axons proceed towards the dorsal column they bifurcate into ascending and descending pathways. A segregation of innocuous and nociceptive afferents occurs as the axons approach the spinal cord. The angle of the fibers varies as they enter the spinal cord, which has major consequences for their excitation thresholds. The dorsal horn of the spinal cord encompasses the grey matter of the spinal cord located dorsal to the central canal. In the 1950s Rexed distinguished six more-or-less different laminae of the spinal grey matter, using cytoarchitectonic criteria (15). Collaterals of large-diameter fibers, which mediate tactile sense and proprioception, enter the dorsal horn and extent mainly to lamina III and IV (14). The dorsal column refers to the area of white matter in the dorsomedial side of the spinal cord. Collaterals of large-diameters fibers occupy the largest part, about 85%, of the dorsal columns. Their averaged diameter diminishes from 12μm at the origin to 8μm a few segments rostrally (16). The fasciculus gracilis contains neurons of the dorsal column-medial lemniscus system, which carries primary afferents from the lower extremities, and synapses in the nucleus gracilis at the level of the foramen magnum. The fasciculus cuneatus is positioned more laterally in the dorsal column and carries primary afferent signals from the upper extremities (16). As the primary afferent fibers ascend, they gradually shift medially and dorsally. Therefore, the accessibility to dorsal medial-stimulating electrode changes as their location in the spinal cord varies. Posterior located ascending and descending pathways are most accessible at normal stimulation parameters (17). Hence, the anatomy and physiology of the spinal cord is complex, and understanding this is essential when discussing issues around the mechanisms of spinal cord stimulation.

ELECTRICAL STIMULATION OF THE SPINAL CORD

In spinal cord stimulation, a lead is positioned in the dorsal epidural space and connected to a subcutaneously implantable pulse generator (IPG). The rostrocaudal position of the lead, with multiple contacts, can be altered to enable electrical stimulation at several spinal levels. The cathode is positioned between the dorsal median sulcus and the dorsal root entry zone area. During a stimulation pulse, current flows from a negatively charged active electrode (cathode) to a positively charged electrode (anode). In principle, sufficiently high electrical stimulation can activate every neural structure in close proximity of the cathode (18). However, current flow chooses the path of lowest resistance

and is therefore directed through anatomic structures characterized by high electrical conductivity (see Table 1). Cerebrospinal fluid (CSF) obviously has the lowest electrical resistance and therefore conducts approximately 90% of injected current, followed by longitudinal white matter. Because of its anisotropic characteristics, transverse white matter has been proven to be less conductive than grey matter. Epidural fat and dura mater also demonstrate low conductivity. Vertebral bone is characterized by having the lowest electrical conductivity. Therefore it functions as an insulator and prevents surrounding tissues (e.g. the heart and pelvic structures) from being stimulated (17, 18).

Table 1. Conductivity of intraspinal structures

Compartment		Conductivity (S m^{-1})
Cerebrospinal fluid		1.7
White matter	(longitudinal)	0.60
	(transversal)	0.083
Grey matter		0.23
Epidural fat		0.04
Vertebral bone		0.04
Dura mater		0.03
Surrounding layer		0.004
Electrode insulation		0.001

Modified from [Holsheimer, 1995] (18)

Initially, it was thought that dorsomedial electrical stimulation first activated fibers in the dorsal column as implied by the name 'dorsal column stimulation' (19, 20). Coburn introduced the hypothesis that dorsal root fibers may also be involved, based on a theoretical study which indicated that dorsal root fibers have lower stimulation thresholds than dorsal column fibers (21). Moreover, the name 'dorsal column stimulation' has been proven to be physiologically simplistic. Despite the fact that the distance between electrodes and dorsal root fibers is higher compared to the dorsal column fibers, the activation threshold is predicted to be lower. Therefore, correct positioning of the lead in the radiological midline is essential to prevent excitation of dorsal roots. Several factors have been shown to contribute to lower dorsal root activation threshold, including the curved shape and larger fiber diameter of dorsal root fibers. Dorsal root fibers are activated in the dorsal root entry zone (DREZ), where fibers enter the dorsal horn, because of its lower activation threshold. Electrical activation of large fiber afferents in the dorsal root or dorsal column by configuration of cathodal and anodal contacts causes a tingling sensation, called paresthesia. Large fiber afferents are activated during stimulation within the usage range and can subsequently

'close the gate'. Excitation of dorsal root afferent fibers produces paresthesias in a few dermatomes, as only rootlets in close proximity to the cathode will be activated. Stimulation of one afferent Aβ fiber may elicit paresthesia in the whole corresponding dermatome. Lemniscal dorsal column fiber stimulation generates an extensive area of paresthesia coverage, because all dorsal column fibers below the level of the electrode may potentially be activated.

A prerequisite for effective pain management is to direct generated paresthesias to cover the whole painful area, which is often difficult to achieve because optimal lead positioning remains difficult. Several empirical and theoretical computer modeling studies have been performed in order to obtain a more thorough understanding of factors determining optimal lead positioning (21, 22). Holsheimer and colleagues investigated whether the geometry of a rostrocaudal array of electrode contacts and contact combination changes the stimulation threshold ratio of dorsal column and dorsal root fibers. Monopolar stimulation with a large cathode favors activation of dorsal root fibers. Preferential activation of dorsal column fibers is effectuated by tripolar stimulation with small contacts and small contact spacings. The problem of optimal lead positioning can be solved by increasing the number of electrode contacts, which increases contact points and anode-cathode combinations and therefore the probability for generating effective paresthesias. The leads are positioned a few segments rostral to the level of where target dorsal roots enter the spinal cord (23). Furthermore, several anatomical and technical factors have been reported to determine the topographical area of induced paresthesias, including pulse width and amplitude, nerve fiber diameter, electrode-spinal cord distance, and anode-cathode combination. Empirical studies have shown that incomplete paresthesia coverage of the painful area can be compensated for by increasing pulse width (PW) as the pulse amplitude extends caudally with increasing PW. (24).

The therapeutic range of spinal cord stimulation is between the perception threshold (PT) and discomfort threshold (DT) (See Figure 1). The perception threshold is defined as the lowest stimulus amplitude needed to elicit paresthesia. The discomfort threshold is defined as the stimulation amplitude above which paresthesia become unendurable. DT is generally reached at a mean stimulus amplitude of 40-60% above perception threshold. The PT for eliciting paresthesia is related to the activation of dorsal root fibers, indicated by the observation of progressively decreased PT as the electrode deviates from the midline (23).

At the cervical and low thoracic level some dorsal column fibers may be activated when the electrode-to-spinal distance is less than 2 mm. The electrode-to-spinal distance is largest in most patients at the mid-thoracic level (T4-T7). Therefore, it is unlikely that dorsal column fibers are stimulated within the therapeutic range, whereas paresthesiae get a segmentary distribution (25). It is well known that the range of stimulation amplitude between PT and DT is narrow and therefore stimulation regularly results in incomplete paresthesia coverage of the painful area. Only large fiber afferents in the dorsal column and dorsal roots are activated at voltages within the therapeutic range during SCS. In the dorsal column only superficially oriented fibers (0.20-0.25 mm depth) with a diameter > 9.4 μm are activated during SCS (18). The mean diameter of

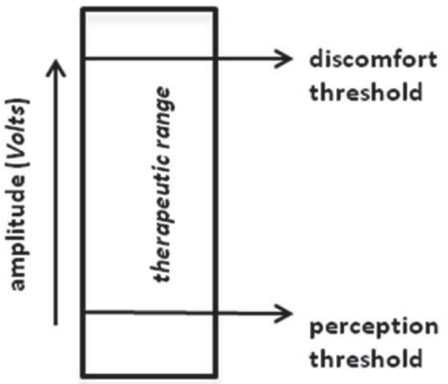


Figure 1. Therapeutic range in Spinal Cord Stimulation

large afferents in the dorsal root is 15μm. As voltage is increased to approximate DT, smaller fibers (±12 μm) are also excited. These proprioceptive fibers elicit segmental motor effects and uncomfortable sensations, which is a major drawback of dorsal root stimulation. This prevents stimulation amplitude from being increased in order to recruit more dorsal column fibers.

To increase SCS efficacy, recruitment of dorsal column fibers is maximized as it generally results in a broad paresthesia coverage of the painful area which is the main goal of SCS. Despite the fact that SCS techniques have developed enormously over the past decennia, there are some major drawbacks in the application of SCS that need to be solved (26). Computer modeling provides an important contribution to our knowledge about the physiological effects of spinal cord stimulation. Most clinical phenomena observed during spinal cord stimulation are predicted by computer modeling studies, which emphasizes their usefulness. However, because of large intersubject variation in anatomical characteristics, a computer model remains a simplification of reality. Conclusions drawn from these studies need to be questioned with regard to their clinical relevance (26). Close interdisciplinary collaboration is warranted in order to direct future research and provide a better understanding of the effects of electrical stimulation on spinal nerve fibers.

NEUROPHYSIOLOGICAL MECHANISMS OF SPINAL CORD STIMULATION

The well-known Gate Control Theory (GCT) was proposed by Melzack and Wall in 1965 (See Figure 2). The theory describes in an elegant and concise way, how activation of afferent Aβ fibers attenuates spinal pain transmission (6). The gate control theory hypothesizes that an excess of small fiber activity would 'open' the 'gate', while an excess of large fiber activity would 'close' the 'gate'. Moreover, large fibers have a lower activation threshold than small fibers for depolarization by an electrical field and they may be selectively stimulated. The GCT provided a framework for studying

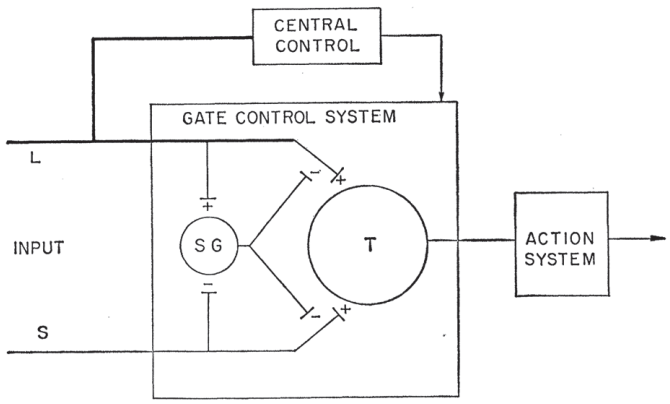


Figure 2. The Gate Control Theory.
Central transmission cells (T), located in the dorsal horn of the spinal cord, receive a balanced input of large (Aβ) and small (Aδ and C) fiber activity in peripheral nerves. Inhibitory interneurons, located in the substantia gelatinosa (SG), can be activated by large (L) afferents and can modulate pain transmission via projection to small (S) fibers and central transmission cells (Melzack and Wall; 6).

the interactions between local and distant excitatory and inhibitory systems in the dorsal horn (27). As previously mentioned, spinal cord stimulation is actually a clinical outgrowth of the gate control theory. The exact mechanism of SCS is still largely unknown, but the supposed mechanisms of actions of spinal cord stimulation (SCS) are still predominantly described in these 'gating' terms.

One would expect, at least theoretically, that spinal cord stimulation could alleviate nociceptive forms of pain. Despite a small number of reports, it is still very controversial whether spinal cord stimulation directly attenuates nociceptive pain. Moreover, spinal cord stimulation is clinically most often administrated in specific neuropathic pain conditions. Flexion reflex thresholds of the lower limbs (RIII responses) have been reported to be lowered in neuropathic pain patients, which is in agreement with former experimental findings in rats (28). They also showed a close relationship between the threshold of flexor responses (RIII) and the subjective sensation of pain. Spinal cord stimulation induced an increase of these abnormally lowered withdrawal thresholds, which are mediated through alpha and beta fibers. These observations suggest that SCS predominantly affects pain related to abnormal Aβ fiber function, as in allodynia (10, 17, 28-30).

Repetitive noxious stimulation of primary afferent fibers after peripheral nerve injury induces long-term changes in the excitability of spinal cord neurons (31). These plastic neural changes involve increased spontaneous and evoked firing rate of wide dynamic range (WDR) neurons in the dorsal horn and contribute to the development of chronic pain. SCS may effectuate a normalization of the hyperexcitability of these wide dynamic range cells in the dorsal horn in response to innocuous stimuli (32). Therefore, wide dynamic range neurons in the dorsal horn are thought to play a key role in spinal pain transmission and may play the integrative role of the 'transmission' (T) cells as described in the GCT (12, 33-35).

Since the 70's multiple studies have suggested that the mechanisms of action of SCS cannot solely be explained by interactions of neurons located in the dorsal horn and have postulated the existence of supraspinal loops (36, 37). In a series of studies Saadé and colleagues demonstrated the contribution of brainstem pain-modulating centers in inhibiting nociceptive processing (38-42). Roberts and Rees have shown that SCS in animals activates the anterior pretectal nucleus, which has descending pain inhibitory influences on lower segments (43). Furthermore, SCS produces increased activity in the somatosensory cortex (SI and SII areas) and cingulate gyri. These brain areas activated by spinal cord stimulation correspond to pain pathways involved in the processing of somatosensory (SI, SII) and affective components (cingulate gyri) of pain. Hence, during SCS both segmental and supraspinal (spinal-brainstem-spinal loops and thalamocortical systems) pathways are activated and contribute to the inhibition of neuropathic pain manifestation.

SPINAL CORD STIMULATORS

Introduction

Shortly after the gate control theory was proposed by Melzack and Wall, attention became focused upon the dorsal column as a target for pain management. The first reports described how an anesthetic needle was placed in the cerebrospinal fluid at the level of target nerve roots (44). An electrode was advanced through the needle and positioned along the dorsal column. Patients experienced significant pain relief during short periods of gentle electrical stimulation (7). After realizing that electrical stimulation in close proximity to sensory roots can alleviate chronic pain, more radical procedures were developed in order to allow chronic stimulation of the dorsal column (19). Shealy and colleagues first investigated the efficacy of dorsal column stimulation in cats, placing electrodes via cervical laminectomy. Shortly thereafter they reported that electrical stimulation of the dorsal columns of the thoracic spinal cord abolished intractable pain in a patient suffering inoperable bronchogenic carcinoma (9). They placed an intradural electrode dorsal to the spinal cord. The circuit design was based on a modified Medtronic device (Medtronic, Inc., Minneapolis, MN, USA) for the stimulation of the carotid sinus to control angina and hypertension (45). These procedures comprised major surgical interventions which were often complicated with equipment failure (lead breakage), cerebrospinal fluid leakage or infection. Furthermore, induced pain relief appeared to be transient.

These radicular methods of dorsal column stimulation were replaced in the mid 70's with percutaneously implantable flexible electrodes (46). A 17G thin-walled Tuohy spinal needle permitted leads to be inserted in the spinal cord and positioned close to the dorsal columns. The development of percutaneous inserted flexible leads allowed a trial of stimulation which mimicked that of the permanent implantable device. During trial stimulation, candidate suitability for permanent implantation was determined. However, the technique of inserting electrodes into the spinal cord seemed associated

with several complications including spinal fluid leaks, postdural puncture headache and infection (bacterial meningitis) (46). It was soon realized that permanent implantation of stimulators over the dorsum of the spinal cord under the dura would ultimately fail (47). The technique of epidural electrode placement evolved since complications like those seen after sub- or intradural electrode implantation, were less likely to occur.

Devices

Spinal cord stimulation (SCS) systems comprise trial or permanent (plate) electrodes, implantable pulse generators and radiofrequency (RF)-driven passive drivers. SCS systems have been produced by multiple manufacturers, including Medtronic, Cordis, Advanced Neuromodulation Systems, and Boston Scientific. Initially, SCS systems used unipolar electrodes to deliver stimulation. RF-driven passive drivers were nonprogrammable and could not be implanted. Because of the contribution of private industry to the development of neuromodulatory systems, equipment has improved enormously in the course of the last 40 years. Moreover, progressive advances in cardiac pacemaker technology were utilized in the design and technology of the implantable pulse generators (IPG).

Nowadays, systems are composed of complex electrode arrays, and an implantable pulse generator (IPG) or radiofrequency-driven radio receiver. The basic goal of these connected components is to provide an isolated electrical pathway to the neural structures being activated. Several electrodes, either percutaneous or plate, with octapolar or even up to 16 electrodes are available. Contact spacing and contact points vary according to the therapeutic goal (e.g., quadripolar electrodes for limb pain and octopolar electrodes for axial pain). Furthermore, multi-programmable and even rechargeable power units are available. Plate electrodes are permanently implanted and require an open procedure and direct visualization for implantation. Initially laminectomy was required to insert plate electrodes for spinal cord stimulation. More recently, thinner and more flexible plate electrodes have been developed, permitting insertion via a less invasive laminotomy.

SPINAL CORD STIMULATOR IMPLANTATION

Percutaneous techniques

First of all it is important to emphasize that the entire procedure of electrode placement is a sterile technique. Infection is potentially hazardous and requires re-operation and/or intravenous antibiotic therapy. Percutaneous placement is performed with the patient in the prone position on an X-ray-compatible table with pillows under the abdomen in order to create a kyphosis which facilitates electrode implantation. The prone position combined with sedation may potentially complicate airway management. Some clinicians prefer the lateral decubitus position as it facilitates subcutaneous implantation of the pulse generator in the buttock or lateral abdominal wall. Positioning is important as rotation of the spine increases the difficulty of electrode placement (16). The electrodes are placed under fluoroscopy

guidance to allow anteroposterior and lateral views in order to ensure midline lead placement and appropriate entry into the epidural space. The insertion point of a 17G Tuohy needle is usually in the midline, although a paramedian approach may also be employed.

Several methods have been used to identify the epidural space. Most clinicians use the loss-of-resistance technique. This technique comprises the use of a syringe filled with saline or air. When the needle is advanced through the ligamentum flavum, a sudden absence of resistance to injection is felt. There is no consensus as to whether air or a liquid should be used for identifying the epidural space when using the loss-of-resistance technique. It has been hypothesized that the use of liquid expands the epidural space and therefore predisposes to lead migration. Furthermore, liquid flush may attenuate the uniformity of paresthesias (48). Alternative approaches to needle placement have been described for specific circumstances where the loss-of-resistance technique seems inappropriate, for example, congenital underdeveloped ligamentum flavum or defects of the ligamentum flavum after spinal surgery. In these conditions identification of the epidural space using the loss-of-resistance technique is potentially difficult, because the level of resistance is unclear and the risk of false loss is present (49).

Zhu and colleagues described an approach for percutaneous lead placement which relies on lateral views of fluoroscopic landmarks to confirm when the needle tip enters the epidural space. When the epidural space is identified, electrodes are advanced rostrally under patient feedback in order to optimize their position. The lead is inserted at least a few centimeters into the epidural space to ascertain its position and to prevent migration of the lead. After lead placement it is important to confirm its position in the epidural space since accidental subarachnoidal placement has been described in the literature. Implantation of cervical electrodes below the cervical spine enlargement which extends from about C3 to Th2 is advisable. For the treatment of back and lower limb pain, identification of the epidural space at the level of Th12-L1, L1-2, or L2-3 is preferred. Electrode insertion for upper extremity pain is recommended at the level of Th1-2 or Th2-3 (16, 48).

For permanent stimulation, when optimal lead position is achieved, the leads are anchored and sutured internally. The leads may then be tunneled subcutaneously a few centimeters laterally to the flank, where they may be externalized for trial stimulation, or connected to an implanted pulse generator (50). The definitive placement of a spinal cord stimulator is preceded by a trial stimulation phase of approximately 7 days. The introduction of a test phase and thorough preoperative screening has increased the success rates of the procedure. After the trial period, the patient is asked whether the elicited paresthesias were effective in reducing the pain they were experiencing before the trial phase. If trial stimulation reduces the patient's pain by more than 50%, a permanent system is implanted.

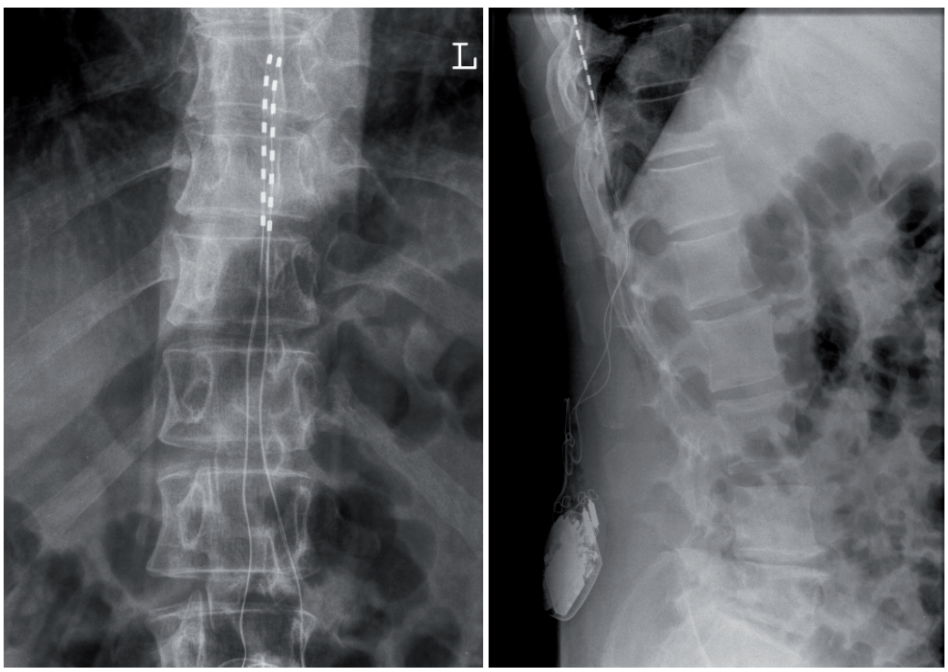


Figure 3. Percutaneously inserted epidural electrodes including pulse generator.

Surgical techniques

Most spinal cord leads are inserted percutaneously, as the technique is easier, less-invasive and less-expensive, compared to surgical methods. However, surgical lead placement may become a necessity if the patient's anatomy prevents percutaneous implantation of the leads, when lead breakage or dislodgement repeatedly requires lead revision, or when trial stimulation does not result in adequate paresthesia coverage (51). Surgical techniques involve electrode positioning under direct vision, following a minor laminotomy. Under fluoroscopic guidance the plate electrode is introduced into the epidural space. Laminotomy up to Th8-Th9 can be performed using spinal anesthesia (52). Moreover, during spinal anesthesia not all sensory transmission is blocked, which enables intraoperative testing for correct lead positioning.

However, laminotomy is generally performed using general anesthesia whereas accurate lead positioning relies on radiographic imaging, somatosensory evoked potentials or patient feedback. After paresthesia is elicited in the anatomic distribution of the patient's pain, a strain relief loop is placed in the epifascial plane and the lead is anchored (51). There are some advantages of surgical leads compared to percutaneous leads: higher success rates (up to 80-90%); less long-term migration rates, and better long term survival have been reported (53, 54). It has been suggested that increased effectiveness of stimulation and consequently higher success rates can be explained by the larger sized plate electrodes which cause compression of the cerebrospinal fluid space and bring electrodes into closer contact with the dorsal column of the spinal cord.

CLINICAL APPLICATION OF SPINAL CORD STIMULATION

Since SCS was first described as a last-resort modality for pain relief in a patient with terminal cancer (9), the clinical potential of active implantable dorsal column neuromodulation devices has been recognized and there have been massive advances in the application of such technology to the field of chronic pain management. Hardware has been miniaturized and made fully implantable with wireless programmers and remote controls. Sophisticated lead design combined with complex programming algorithms and refined implantation techniques have given implanting physicians unprecedented ability to provide pain relief for conditions that would otherwise be intractable (55-57). A wealth of published research spanning computer modeling, preclinical animal models, and clinical trials has supported these advances.

Although the initial costs associated with the SCS device can be steep, it is a cost-effective intervention (56, 58-60) and SCS has most likely enjoyed its surge in popularity due to the provision of three important benefits. Firstly, the effectiveness of the device can be tested prior to permanent implantation (61). Epidurally-placed leads are attached to a temporary external stimulator for several days and the permanent device is implanted only if the patient reports significant pain relief and is capable of operating the device. Hence, a patient who is unlikely to improve with the intervention may be identified before proceeding with an ultimately unnecessary procedure. Secondly, the SCS implantation procedure is minimally invasive (62). Leads are epidural and are placed via a percutaneous procedure. The implantable pulse generator device is housed subcutaneously. Although risks such as dural puncture do exist (63), the clinical risks associated with SCS are far lower than with open procedures such as spinal surgery. The third benefit of SCS is its reversibility (62) relative to ablative procedures. The leads and device can be removed in a minor procedure that leaves minimal scarring and no change in spinal function. These features have contributed to the movement of SCS up the 'pain ladder'. Once considered a somewhat capricious therapy of last resort, SCS is now recommended as a first-line intervention before more invasive or irreversible ablative options (64-66).

THE RISE OF A NEW INTERVENTION: STIMULATION OF THE DORSAL ROOT GANGLION

As outlined in the General Introduction, SCS is not, however, without limitations and is not a panacea. Therefore, other neuromodulation targets have been explored. Peripheral nerve stimulation (PNS) has moved neuromodulation closer to the site of pain transduction and/or transmission. Although undeniably satisfactory for a number of pain etiologies (82, 83), PNS is also prone to lead migration and can produce considerable local irritation (82). Other investigators have modified SCS techniques to identify feasible targets in the epidural space. Nerve root stimulation

has emerged as an effective therapy (84), particularly for pain in caudal dermatomal distributions (85). As a natural extension of nerve root stimulation, isolated case reports have discussed the extreme lateral placement of leads in an attempt to recruit the DRG (70, 86). This structure houses primary sensory neuron (PSN) somata inside the vertebral foramen and is an emerging target for a number of pain treatment options (87, 88).

The role of the dorsal root ganglion in the development and maintenance of chronic pain has been a topic of investigation for some time and in the last decade has become a "hot topic" (89-91). In general, both the early and later stages of injury or neuroinflammatory activation are characterized by several pathophysiologic alterations in PSN function.

Alterations in sodium channel expression and function, and increased production of neuroinflammatory intermediates all have an impact on the basic membrane excitability of the PSNs. As these cells become hyperexcitable the threshold for generating action potentials is lowered, which in turn produces a heightened "painful" input into the spinal cord. Neurons in the DRG have also been shown to produce ectopic, or spontaneous, action potentials that are generally not observed in healthy conditions. The secondary ramifications of this overactivity and increased action potential generation are manifested at the first synapse in the dorsal horn of the spinal cord. Increased excitatory amino

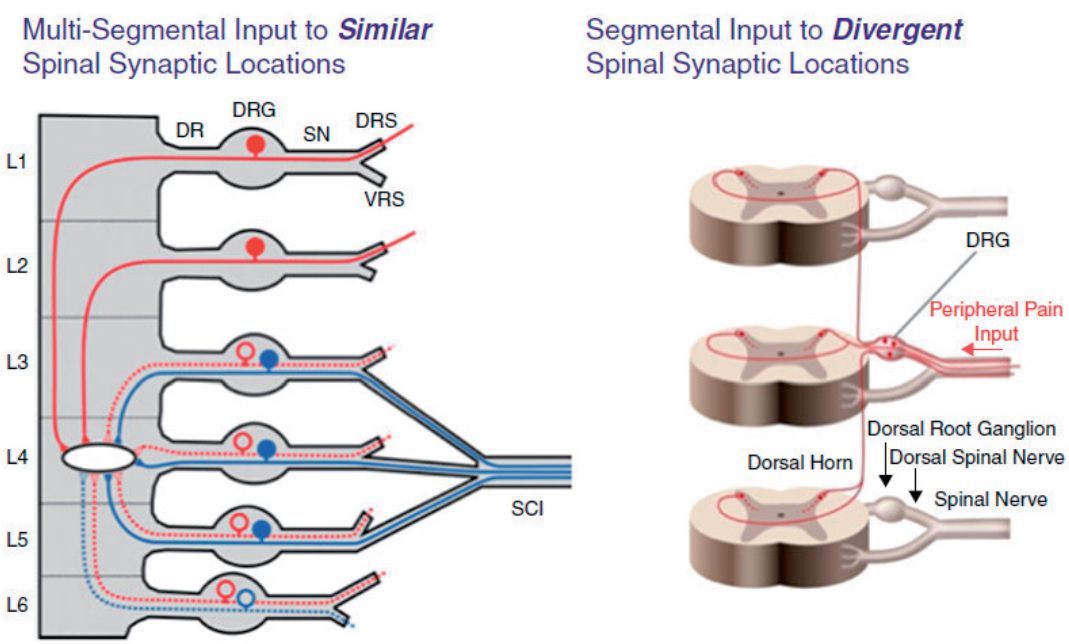


Figure 4. Convergence and divergence at the DRG.
Both divergent and convergence of sensory input have been documented. Left: figure demonstrating the convergence of sensory input into the CNS. Ganglionectomies performed in the 1970s and 1980s documented this associated with multilevel sensory input. Right: depicts the divergence of sensory input from a single level then synapsing at multiple spinal levels within the dorsal horn.

acid release, neuropeptide release and a host of other secondary neuroinflammatory cascades result from the effects on the DRG. Thus, the PSNs in the DRG contribute both to the development and maintenance of chronic pain conditions.

Electrical neurostimulation of the DRG has recently been called 'DRG stimulation of the spinal cord' due to its similarity to the SCS procedure. Leads are placed through percutaneous epidural antegrade access in the lateral recess of the spinal canal. The electrical field of DRG stimulation of the spinal cord electrodes thus placed is centrally biased by virtue of being medial to the bifurcation of the dorsal root and the ventral root, as well as orthodromic recruitment of spinal dorsal root fibers. Empirical evidence supporting the central structure and function of DRGs can be found in the paresthesias generated by stimulation of these structures. Although focal stimulation at regionally delimited areas is possible, DRG stimulation of the spinal cord can also produce diffuse paresthesias that approach dermatomal distributions (92), similar to traditional SCS. This is in contrast to PNS-generated paresthesias that are extremely focal and follow the nerve distribution (93). Thus, DRG stimulation of the spinal cord involves recruitment of a central nervous system structure while PNS involves electrode placement at or distal to the point where the rootlets exit the dura mater and the lateral vertebral foramen.

DEVICE AND IMPLANTATION

Few case reports have been published concerning DRG stimulation of the spinal cord for the treatment of chronic pain. There are conflicting reports on the effectiveness of the therapy, and this is likely due partly to differences in implantation techniques and also due to the fact that the equipment being used was not designed to target the DRG. On the whole, the stimulation leads used in the earlier reports were designed for an epidural midline approach and for targeting the dorsal columns. The contact size and spacing are inappropriate for the smaller target – this is important to remember when considering the potential limitations of earlier work in this area.

Recently, a new system was created which is specifically designed for stimulating the DRG; the Axium™ system (Spinal Modulation, Menlo Park, California, USA) is a constant-voltage primary-cell spinal neurostimulation device that accommodates up to four quadripolar cylindrical percutaneous leads that are placed via standard epidural loss-of-resistance methods using an antegrade approach. The leads have a slim 1-mm diameter profile and are very flexible under fluoroscopic guidance due to their external curved guidance sheath and hollow lumen. With these features, leads are especially amenable to placement near the DRGs in the lateral recesses of the intraspinal foramen, and conform to the exterior surface of the DRG without compressing the neural tissue. Initial testing has shown that 93% of leads could be deployed to the target foramen within two minutes of obtaining epidural access (92).

PROPOSED ANALGESIC MECHANISMS OF DRG STIMULATION OF THE SPINAL CORD

It has been established that a net increase in activity in the DRG neurons drives the neural changes in neuropathic pain conditions. Ablative interventions such as ganglionectomy and dorsal root entry zone lesions achieve their effect by preventing the hyperexcitable peripheral activity from being transmitted to the spinal cord and to supraspinal sites. DRG neurostimulation may serve a similar conceptual function by actively reducing the net nociceptive input to the spinal cord. Such reduction of PSN activity by field stimulation has been demonstrated in vitro (94). Thus, DRG stimulation of the spinal cord may restore the neural filtering function of the DRG that was lost in response to peripheral injuries. This could have consequences for all downstream neural structures, including the spinal cord, intraspinal nerves, rami communicantes, and the lumbar sympathetic trunk (95).

The gate control theory, in which activation of large-diameter sensory fibers blocks the transmission of nociceptive signals in small-diameter fibers, was proposed in 1965 (6); it is considered an underlying mechanism of action for SCS (19, 56, 62)and has been supported by recent empirical evidence (81). However, the gate control theory may be insufficient as an explanation for the mechanism of DRG stimulation of the spinal cord. This is because DRG stimulation of the spinal cord normalizes peripheral input before it arrives at the spinal cord, making the challenge of preferentially recruiting the dorsal fibers involved in the individual expression of the neuropathic condition unnecessary. It is possible that over time DRG stimulation of the spinal cord could reverse the central pathologic plasticity and reduce central sensitization. It is also possible that, if initiated early in the neuropathic pain development cascade, DRG stimulation of the spinal cord could prevent the maladaptive plastic changes. Further research is required for a more comprehensive understanding of the analgesic mechanisms of DRG stimulation of the spinal cord.

CLINICAL APPLICATION OF DRG STIMULATION OF THE SPINAL CORD

DRG stimulation of the spinal cord has demonstrated effectiveness for up to 12 months in a number of cohorts of mixed etiologies, including the radicular pain of failed back surgery syndrome (FBSS), complex regional pain syndrome (CPRS) in lower extremities, and chronic post-surgical pain (CPSP) (92, 96). Analgesia specific to chronic post-herniorrhaphy groin pain (74) and foot pain (97) has also been reported, suggesting that in addition to broad regional coverage, DRG-SCS is capable of achieving coverage of sub-dermatomal regions. Additionally, case reports involving patients with low back pain (98), post-herpetic neuralgia (99), amputation / deafferentation pain (100), phantom limb pain (101), visceral pain (102), body wall pain (103), and upper extremity pain (104) have been presented. Hitherto difficult to treat because of lack of targeted paresthesia, patients with CRPS of the knee, a small

sub-population of the larger CRPS cohort, have demonstrated good early clinical response. Similar results have been reported in post-surgical knee pain patients.

Pain-paresthesia overlap is typically established with a high degree of precision in DRG stimulation of the spinal cord, e.g., there is a high concordance of painful areas with paresthesia and very little extraneous stimulation (64). This is likely due to the recruitment of PSNs that project to the painful regions and allows sub-dermatomal paresthesia coverage to be established, a goal that in SCS may require complex lead design and programming (72). Importantly, DRG stimulation paresthesia distributions are maintained over time and appear largely indifferent to changes in body position (64). The stability of paresthesia may be due to the location of the DRG inside the bony enclosure of the vertebral foramen. This both helps to brace the lead in its desired position and ensures that the DRG and lead remain largely unperturbed by flexion or movement in the highly mobile spine. The CSF layer that surrounds the DRG is another relevant factor within the stimulation milieu. Since it is very narrow (105) limiting its potential role as a current sink to disperse electrical fields. Thus, DRG stimulation of the spinal cord can be achieved at low amplitudes, requiring on average about 15% of the power output of a dorsal column stimulation system (92). Given that a primary-cell SCS system may have an average battery lifetime of 3-5 years under normal use conditions (106, 107), this could represent a considerable reduction in battery-replacement procedures, along with reduced cost and morbidity risk.

CONCLUSIONS

DRG stimulation of the spinal cord is now technically feasible with recent implantable device innovations and the evidence to support its effectiveness is accumulating. Previous techniques targeting the DRG have yielded excellent results demonstrating not only the safety of targeting the DRG, but also the potential opportunity for developing techniques that can provide longer-lasting pain relief. Preliminary results from completed and ongoing prospective studies suggest that DRG stimulation can provide good pain relief, while avoiding the unwanted side-effects of current neurostimulation techniques.

REFERENCES

1. Schechter DC. Origins of electrotherapy. I. N Y State J Med 1971 May 1;71(9):997-1008.
2. Kane K, Taub A. A history of local electrical analgesia. Pain 1975 Jun;1(2):125-138.
3. Stilling D. The first use of electricity for pain treatment. Medtronic Archive on Electro-Stimulation 1971.
4. Macklis RM. Magnetic healing, quackery, and the debate about the health effects of electromagnetic fields. Ann Intern Med 1993 Mar 1;118(5):376-383.
5. Chaffee EL, Light RU. A Method for the Remote Control of Electrical Stimulation of the Nervous System. Yale J Biol Med 1934 Dec;7(2):83-128.
6. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965 Nov 19;150(3699):971-979.
7. Wall PD, Sweet WH. Temporary abolition of pain in man. Science 1967 Jan 6;155(3758):108-109.
8. Wall P. The discovery of transcutaneous electrical nerve stimulation. Physiotherapy 1985;71:348-350.
9. Shealy CN, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report. Anesth Analg 1967 Jul-Aug;46(4):489-491.
10. Handwerker HO, Iggo A, Zimmermann M. Segmental and supraspinal actions on dorsal horn neurons responding to noxious and non-noxious skin stimuli. Pain 1975 Jun;1(2):147-165.
11. Meyerson BA, Herregodts P, Linderoth B, Ren B. An experimental animal model of spinal cord stimulation for pain. Stereotact Funct Neurosurg 1994;62(1-4):256-262.
12. Guan Y, Wacnik PW, Yang F, Carteret AF, Chung CY, Meyer RA, Raja SN. Spinal cord stimulation-induced analgesia: electrical stimulation of dorsal column and dorsal roots attenuates dorsal horn neuronal excitability in neuropathic rats. Anesthesiology 2010 Dec;113(6):1392-1405.
13. Linderoth B, Meyerson BA. Spinal cord stimulation: exploration of the physiological basis of a widely used therapy. Anesthesiology 2010 Dec;113(6):1265-1267.
14. Light AR. Normal anatomy and physiology of the spinal cord dorsal horn. Appl Neurophysiol 1988;51(2-5):78-88.
15. Rexed B. The cytoarchitectonic organization of the spinal cord in the cat. J Comp Neurol 1952 Jun;96(3):414-495.
16. Barolat G, Sharan A. Spinal cord stimulation for chronic pain management. Seminars in Neurosurgery 2004;15:151-175.
17. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. Spine (Phila Pa 1976) 2002 Nov 15;27(22):2574-2583.
18. Holsheimer J. Which Neuronal Elements are Activated Directly by Spinal Cord Stimulation. Neuromodulation 2002 Jan;5(1):25-31.
19. Shealy CN, Taslitz N, Mortimer JT, Becker DP. Electrical inhibition of pain: experimental evaluation. Anesth Analg 1967 May-Jun;46(3):299-305.
20. Struijk JJ, Holsheimer J, Boom HB. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. IEEE Trans Biomed Eng 1993 Jul;40(7):632-639.
21. Coburn B. A theoretical study of epidural electrical stimulation of the spinal cord--Part II: Effects on long myelinated fibers. IEEE Trans Biomed Eng 1985 Nov;32(11):978-986.
22. Law JD, Miller LV. Importance and documentation of an epidural stimulating position. Appl Neurophysiol 1982;45(4-5):461-464.
23. Barolat G, Zeme S, Ketcik B. Multifactorial analysis of epidural spinal cord stimulation. Stereotact Funct Neurosurg 1991;56(2):77-103.
24. Holsheimer J, Buitenweg JR, Das J, de Sutter P, Manola L, Nuttin B. The effect of pulse width and contact configuration on paresthesia coverage in spinal cord stimulation. Neurosurgery 2011 May;68(5):1452-61; discussion 1461.
25. Holsheimer J, Wesselink WA. Effect of anode-cathode configuration on paresthesia coverage in spinal cord stimulation. Neurosurgery 1997 Sep;41(3):654-9; discussion 659-60.
26. Holsheimer J. Effectiveness of spinal cord stimulation in the management of chronic pain: analysis of technical drawbacks and solutions. Neurosurgery 1997 May;40(5):990-6; discussions 996-9.
27. Dickenson AH. Gate control theory of pain stands the test of time. Br J Anaesth 2002 Jun;88(6):755-757.
28. Garcia-Larrea L, Sindou M, Mauguiere F. Nociceptive flexion reflexes during analgesic neurostimulation in man. Pain 1989 Nov;39(2):145-156.
29. Carstens E, Campbell IG. Parametric and pharmacological studies of midbrain suppres-

sion of the hind limb flexion withdrawal reflex in the rat. Pain 1988 May;33(2):201-213.

30. Meyerson BA, Ren B, Herregodts P, Linderoth B. Spinal cord stimulation in animal models of mononeuropathy: effects on the withdrawal response and the flexor reflex. Pain 1995 May;61(2):229-243.
31. Rygh LJ, Svendsen F, Hole K, Tjolsen A. Natural noxious stimulation can induce long-term increase of spinal nociceptive responses. Pain 1999 Sep;82(3):305-310.
32. Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. Pain 1999 Feb;79(2-3):223-233.
33. Woolf CJ, Salter MW. Neuronal plasticity: increasing the gain in pain. Science 2000 Jun 9;288(5472):1765-1769.
34. Guan Y, Borzan J, Meyer RA, Raja SN. Windup in dorsal horn neurons is modulated by endogenous spinal mu-opioid mechanisms. J Neurosci 2006 Apr 19;26(16):4298-4307.
35. Cervero F. Spinal cord hyperexcitability and its role in pain and hyperalgesia. Exp Brain Res 2009 Jun;196(1):129-137.
36. Nyquist JK, Greenhoot JH. Responses evoked from the thalamic centrum medianum by painful input: suppression by dorsal funiculus conditioning. Exp Neurol 1973 Mar-Apr;39(2):215-222.
37. Bantli H, Bloedel JR, Thienprasit P. Supraspinal interactions resulting from experimental dorsal column stimulation. J Neurosurg 1975 Mar;42(3):296-300.
38. Saade N, Atweh AF, Tabet MS, Jabbur SJ. Inhibition of nociceptive withdrawal flexion reflexes through a dorsal column-brainstem-spinal loop. Brain Res 1985 Jun 3;335(2):306-308.
39. Saade NE, Tabet MS, Banna NR, Atweh SF, Jabbur SJ. Inhibition of nociceptive evoked activity in spinal neurons through a dorsal column-brainstem-spinal loop. Brain Res 1985 Jul 22;339(1):115-118.
40. Saade NE, Atweh SF, Jabbur SJ, Wall PD. Effects of lesions in the anterolateral columns and dorsolateral funiculi on self-mutilation behavior in rats. Pain 1990 Sep;42(3):313-321.
41. Saade NE, Atweh SF, Privat A, Jabbur SJ. Inhibitory effects from various types of dorsal column and raphe magnus stimulations on nociceptive withdrawal flexion reflexes. Brain Res 1999 Oct 30;846(1):72-86.
42. El-Khoury C, Hawwa N, Baliki M, Atweh SF, Jabbur SJ, Saade NE. Attenuation of neuropathic pain by segmental and supraspinal activation of the dorsal column system in awake rats. Neuroscience 2002;112(3):541-553.
43. Roberts M, Rees H. Physiological basis of spinal cord stimulation. Pain Rev 1994:1184-1198.
44. Melzack R, Wall PD. The challenge of pain. Penguin Books ltd. 2 nd ed. England; 1996. p. 234-235.
45. Golovac S. Spinal cord stimulation: uses and applications. Neuroimaging Clin N Am 2010 May;20(2):243-254.
46. Erickson DL. Percutaneous trial of stimulation for patient selection for implantable stimulating devices. J Neurosurg 1975 Oct;43(4):440-444.
47. Cook AW. Letter: Percutaneous trial for implantable stimulating devices. J Neurosurg 1976 May;44(5):650-651.
48. Brook AL, Georgy BA, Olan WJ. Spinal cord stimulation: a basic approach. Tech Vasc Interv Radiol 2009 Mar;12(1):64-70.
49. Zhu J, Falco F, Onyewu CO, Joesphson Y, Vesga R, Jari R. Alternative approach to needle placement in spinal cord stimulator trial/implantation. Pain Physician 2011 Jan-Feb;14(1):45-53.
50. North RB, Fischell TA, Long DM. Chronic dorsal column stimulation via percutaneously inserted epidural electrodes. Preliminary results in 31 patients. Appl Neurophysiol 1977 -1978;40(2-4):184-191.
51. Kumar K, Lind G. Spinal stimulation: Placement of surgical leads via laminectomy-techniques and benefits. Neuromodulation 2009;2:1005-1011.
52. Lind G, Meyerson BA, Winter J, Linderoth B. Implantation of laminotomy electrodes for spinal cord stimulation in spinal anesthesia with intraoperative dorsal column activation. Neurosurgery 2003 Nov;53(5):1150-3; discussion 1153-4.
53. Villavicencio AT, Leveque JC, Rubin L, Bulsara K, Gorecki JP. Laminectomy versus percutaneous electrode placement for spinal cord stimulation. Neurosurgery 2000 Feb;46(2):399-405; discussion 405-6.
54. North RB, Kidd DH, Olin JC, Sieracki JM. Spinal cord stimulation electrode design: prospective, randomized, controlled trial comparing percutaneous and laminectomy electrodes-part I: technical outcomes.

Neurosurgery 2002 Aug;51(2):381-9; discussion 389-90.

55. Bradley K. The Technology: The Anatomy of a Spinal Cord and Nerve Root Stimulator: The Lead and the Power Source. Pain Medicine 2006;7:S27-S34.
56. Kumar K, Abbas M, Rizvi S. The use of spinal cord stimulation in pain management. Pain Manag 2012 Mar;2(2):125-134.
57. Kumar K, Rizvi S. Historical and present state of neuromodulation in chronic pain. Curr Pain Headache Rep 2014 Jan;18(1):387-013-0387-y.
58. Hollingworth W, Turner JA, Welton NJ, Comstock BA, Deyo RA. Costs and cost-effectiveness of spinal cord stimulation (SCS) for failed back surgery syndrome: an observational study in a workers' compensation population. Spine (Phila Pa 1976) 2011 Nov 15;36(24):2076-2083.
59. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. Clin J Pain 2010 Jul-Aug;26(6):463-469.
60. Mekhail N, Wentzel DL, Freeman R, Quadri H. Counting the costs: case management implications of spinal cord stimulation treatment for failed back surgery syndrome. Prof Case Manag 2011 Jan-Feb;16(1):27-36.
61. Chincholkar M, Eldabe S, Strachan R, Brookes M, Garner F, Chadwick R, Gulve A, Ness J. Prospective analysis of the trial period for spinal cord stimulation treatment for chronic pain. Neuromodulation 2011 Nov-Dec;14(6):523-8; discussion 528-9.
62. Stojanovic MP, Abdi S. Spinal cord stimulation. Pain Physician 2002 Apr;5(2):156-166.
63. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. J Neurosurg 2004 Mar;100(3 Suppl Spine):254-267.
64. Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of Body Positional Effects on Paresthesias When Stimulating the Dorsal Root Ganglion (DRG) in the Treatment of Chronic Pain. Neuromodulation 2014 Aug 21.
65. National Institute for Health and ClinicalExcellence (NICE). Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin; NICE technology appraisal guidance 159. London, National Health Service 2011.
66. Poree L, Krames E, Pope J, Deer TR, Levy R, Schultz L. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. Neuromodulation 2013 Mar-Apr;16(2):125-141.
67. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. Neurosurgery 2006 Mar;58(3):481-96; discussion 481-96.
68. Kemler MA, de Vet HC, Barendse GA, van den Wildenberg FA, van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. J Neurosurg 2008 Feb;108(2):292-298.
69. Kumar K, Taylor RS, Jacques L, Eldabe S, Meglio M, Molet J, Thomson S, O'Callaghan J, Eisenberg E, Milbouw G, Buchser E, Fortini G, Richardson J, North RB. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery 2008 Oct;63(4):762-70; discussion 770.
70. Alo KM, Yland MJ, Redko V, Feler C, Naumann C. Lumbar and Sacral Nerve Root Stimulation (NRS) in the Treatment of Chronic Pain: A Novel Anatomic Approach and Neuro Stimulation Technique. Neuromodulation 1999 Jan;2(1):23-31.
71. Oakley JC. Spinal cord stimulation in axial low back pain: solving the dilemma. Pain Medicine 2006;7:S58-S63.
72. Rigoard P, Desai MJ, North RB, Taylor RS, Annemans L, Greening C, Tan Y, Van den Abeele C, Shipley J, Kumar K. Spinal cord stimulation for predominant low back pain in failed back surgery syndrome; study protocol for an international multicenter randomized controlled trial (PROMISE study). Trials 2013;14:376.
73. Lepski G, Vahedi P, Tatagiba MS, Morgalla M. Combined spinal cord and peripheral nerve field stimulation for persistent post-herniorrhaphy pain. Neuromodulation 2013 Jan-Feb;16(1):84-8; discussion 88-9.
74. Schu S, Gulve A, Eldabe S, Baranidharan G, Wolf K, Demmel W, Rasche D, Sharma M, Klase D, Jahnichen G, Wahlstedt A, Nijhuis H, Liem L. Spinal Cord Stimulation of the Dorsal Root Ganglion for Groin Pain-A Retrospective Review. Pain Pract 2014 Apr 1.
75. Deer TR, Barolat G. Stimulation of the nervous system to treat neuropathic pain of

the foot. Deer TR, ed. Atlas of Implantable Therapies for Pain Management. New York, Springer. 2011:81-86.

76. North RB, Lanning A, Hessels R, Cutchis PN. Spinal cord stimulation with percutaneous and plate electrodes: side effects and quantitative comparisons. Neurosurg Focus 1997 Jan 15;2(1):e3.
77. North R, Shipley J, Prager J, Barolat G, Barulich M, Bedder M, Calodney A, Daniels A, Deer T, DeLeon O, Drees S, Fautdch M, Fehrenbach W, Hernandez J, Kloth D, Krames ES, Lubenow T, North R, Osenbach R, Panchal SJ, Sitzman T, Staats P, Tremmel J, Wetzel T, American Academy of Pain M. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. Pain Med 2007 Dec;8 Suppl 4:S200-75.
78. North RB, Kidd DH, Olin J, Sieracki JM, Farrokhi F, Petrucci L, Cutchis PN. Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. Spine (Phila Pa 1976) 2005 Jun 15;30(12):1412-1418.
79. Barolat G, Schwartzman R, Woo R. Epidural spinal cord stimulation in the management of reflex sympathetic dystrophy. Stereotact Funct Neurosurg 1989;53(1):29-39.
80. Schade CM, Schultz DM, Tamayo N, Iyer S, Panken E. Automatic adaptation of neurostimulation therapy in response to changes in patient position: results of the Posture Responsive Spinal Cord Stimulation (PRS) Research Study. Pain Physician 2011 Sep-Oct;14(5):407-417.
81. Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. Pain 2012 Mar;153(3):593-601.
82. Slavin KV. Peripheral nerve stimulation for neuropathic pain. Neurotherapeutics 2008 Jan;5(1):100-106.
83. Deogaonkar M, Slavin KV. Peripheral nerve/field stimulation for neuropathic pain. Neurosurg Clin N Am 2014 Jan;25(1):1-10.
84. Haque R, Winfree CJ. Spinal nerve root stimulation. Neurosurg Focus 2006 Dec 15;21(6):E4.
85. Alo KM, McKay E. Selective Nerve Root Stimulation (SNRS) for the Treatment of Intractable Pelvic Pain and Motor Dysfunction: A Case Report. Neuromodulation 2001 Jan;4(1):19-23.
86. Weigel R, Capelle HH, Schmelz M, Krauss JK. Selective thoracic ganglionectomy for the treatment of segmental neuropathic pain. Eur J Pain 2012 Nov;16(10):1398-1402.
87. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. Pain Med 2013 Oct;14(10):1477-1496.
88. Deer TR, Levy RM, Kramer JM. Interventional perspectives on the dorsal root ganglion as a target for the treatment of chronic pain: a review. Minimally Invasive Surgery for Pain, MISP 2013;1:23-33.
89. Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does, and why it matters. Reg Anesth Pain Med 2010 May-Jun;35(3):306-311.
90. Waxman SG. The molecular pathophysiology of pain: abnormal expression of sodium channel genes and its contributions to hyperexcitability of primary sensory neurons. Pain 1999 Aug;Suppl 6:S133-40.
91. Sapunar D, Kostic S, Banozic A, Puljak L. Dorsal root ganglion - a potential new therapeutic target for neuropathic pain. J Pain Res 2012;5:31-38.
92. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. Neuromodulation 2013 Jan-Feb;16(1):67-71; discussion 71-2.
93. Alo KM, Abramova MV, Richter EO. Percutaneous peripheral nerve stimulation. Prog Neurol Surg 2011;24:41-57.
94. Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. Neuromodulation 2013 Jul-Aug;16(4):304-11; discussion 310-1.
95. Tsou HK, Chao SC, Wang CJ, Chen HT, Shen CC, Lee HT, Tsuei YS. Percutaneous pulsed radiofrequency applied to the L-2 dorsal root ganglion for treatment of chronic low-back pain: 3-year experience. J Neurosurg Spine 2010 Feb;12(2):190-196.
96. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013 Sep-Oct;16(5):471-82; discussion 482.
97. Wolf K. Long term outcomes using stimulation of the dorsal root ganglion (DRG) for foot

pain. NANS 2013: Today's Vision, Tomorrow Reality; Las Vegas, NANS, 2013 ;poster #357.

98. Nijhuis H, Liem L, Huygen F. A post-market cohort to assess the performance of a neurostimulator system for the management of intractable chronic back pain. Neuromodulation 2013;16:e140.
99. Klase D, Thoma R, Baranidharan G, Liem L, Patel NK, Love-Jones S, Espinet AJ, Verrills P, Schu S. Does convergence of multi-segmental afferent inputs at the spinal lamina enable treatment of post-herpetic neuralgia with dorsal root ganglion (DRG) stimulation possible? NANS 2013: Today's Vision, Tomorrow Reality; Las Vegas, NANS. 2013:poster #311.
100. Burger K, Moser H, Liem L, Klase D, Eldabe S. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of post amputation pain. NANS 2012: From Innovation to Reality, Las Vegas, NANS 2012:poster #145.
101. Bara GA, Maciaczyk J, Slotty P, Schu S, Vesper J. Dorsal root ganglion stimulation for treatment of phantom limb pain. NANS 2013: Today's Vision, Tomorrow Reality; Las Vegas, NANS. 2013:poster # 420.
102. Baranidharan G. Reduction in dermatomal hyperalgesia in patients with visceral pain treated with spinal cord stimulation (SCS) of the dorsal root ganglion (DRG). NANS 2013: Today's Vision, Tomorrow Reality; Las Vegas, NANS. 2013:poster # 360.
103. Gulve A, Eldabe S, Koneti K, Garner F, West S, King R, Chadwick R. Dorsal root ganglion stimulation for the treatment of body wall pain: Middlesbrough experience. NANS 2013: Today's Vision, Tomorrow Reality; Las Vegas, NANS. 2013:poster # 285.
104. Liem L, Demmel W, Thoma R, Neumann H, Rasche D, Schu S. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for chronic pain of the upper limbs- a multi center case series. Neuromodulation 2013;16:e141.
105. Brierley JB. The penetration of particulate matter from the cerebrospinal fluid into the spinal ganglia, peripheral nerves, and perivascular spaces of the central nervous system. J Neurol Neurosurg Psychiatry 1950 Aug;13(3):203-215.
106. Geurts JW, Smits H, Kemler MA, Brunner F, Kessels AG, van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: a prospective cohort study with long-term follow-up. Neuromodulation 2013 Nov-Dec;16(6):523-9; discussion 529.
107. McAuley J, Farah N, van Groningen R, Green C. A questionnaire-based study on patients' experiences with rechargeable implanted programmable generators for spinal cord stimulation to treat chronic lumbar spondylosis pain. Neuromodulation 2013 Mar-Apr;16(2):142-146.

2

THE SAFETY AND PERFORMANCE OF DORSAL ROOT GANGLION NEUROSTIMULATION IN THE TREATMENT OF CHRONIC PAIN

Modified from:
A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain
Liong Liem, Marc Russo, Frank J.P.M. Huygen, Jean-Pierre Van Buyten, Iris Smet, Paul Verrills, Michael Cousins, Charles Brooker, Robert Levy, Timothy Deer, Jeffery Kramer.
Neuromodulation 2013; 16: 471–82.

ABSTRACT

This multicenter prospective trial was conducted to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the dorsal root ganglia (DRG) neurophysiologically associated with painful regions of the limbs and/or trunk. To this end, thirty-two subjects were implanted with a novel neuromodulation device. Pain ratings during stimulation were followed up to 6 months and compared to baseline ratings. Subjects also completed two separate reversal periods in which stimulation was briefly stopped in order to establish the effects of the intervention. It was found that, at all assessments, more than half of subjects reported pain relief of 50% or better. At 6 months post-implant, average overall pain ratings were 58% lower than baseline ($p<0.001$), and the proportions of subjects experiencing 50% or more reduction in pain specific to back, leg and foot regions were 67%, 68%, and 89%, respectively. When stimulation was discontinued for a short time, pain returned to baseline levels. Discrete coverage of hard-to-treat areas was obtained across a variety of anatomical pain distributions. Paresthesia intensity remained stable over time and there was no significant difference in the paresthesia intensity perceived during different body postures/positions (standing up vs. lying down). In conclusion, the results of this clinical trial demonstrate that neurostimulation of the DRG is a viable neuromodulatory technique for the treatment of chronic pain. Additionally, the capture of discrete painful areas such as the feet combined with stable paresthesia intensities across body positions suggest that this stimulation modality may allow more selective targeting of painful areas and reduce unwanted side effects observed in traditional SCS.

INTRODUCTION

Electricity has been used for the neuromodulation of pain pathways for over a century (1). In the 1960s, development of the Gate Control theory and pioneering clinical work in spinal cord stimulation (SCS) ushered in the current era of neurostimulation as an accepted pain-treatment modality, particularly for chronic neuropathic pain in which more traditional options often prove ineffective (2, 3). Neurostimulation can offer relief for intractable pain conditions which may otherwise negatively impact on quality of life and participation in community and social roles, and take a heavy economic toll both in health care costs as well as lost productivity (4, 5).

Spinal cord stimulation (SCS) is a thoroughly tested and well-described neurostimulation technology; its usage has grown rapidly in the past 40 years and over 27,000 SCS devices are implanted per year in the US alone (6). Several recent systematic reviews have shown that it is a relatively safe and often effective treatment option for patients suffering from chronic, intractable pain (7, 8, 9). In the largest prospective trial published to date, SCS was found to significantly reduce lower limb pain associated with failed back surgery syndrome (FBSS) relative to a conventional medical management control group over an extended time period (10, 11). Similarly, SCS can be effective in the treatment of complex regional pain syndrome (CRPS) (12, 13, 14).

Despite its clinical utility for some patients, SCS therapy carries limitations. Twenty percent of subjects trialing an SCS system do not proceed beyond the trial stimulation (15). Overall, the treatment has been found to be a successful long-term solution in approximately 50% of patients that have a successful temporary trial stimulation (7, 11, 15, 16). Failures may be due to difficulty in programming the device to align the stimulation-associated paresthesias with the painful areas of the body, inability to derive the correct combination of pulse width, frequency, and amplitude of the electrical waveform needed to address the individual's pain, or due to device issues such as lead migration. SCS can also be vulnerable to positional or postural effects in which the intensity or location of paresthesias may change when the subject changes their body position such as moving from lying to sitting (17). This change is due to shifts in the relative distance between the stimulating electrodes and the dorsal columns through the effects of gravity or physical forces due to epidural lead placement in the highly mobile spine (7, 18, 19). Additionally, some patients may not tolerate the pins-and-needles sensation of the paresthesias associated with SCS, particularly if these are extraneous and located in non-painful areas of the body (20). These issues suggest that alternative neuromodulation techniques or targets should be investigated to allow the implanting physician to more properly address challenging pain presentations.

Housed within the bony structure of the bilateral vertebral foramen of each spinal level is the neural structure of the dorsal root ganglion (DRG), a cluster of primary sensory neuron somata enclosed in the dural sheath. These cells transmit sensory information, including nociceptive signals, from distal locations in the body to the dorsal columns of the spinal cord and thence to the rest of the central nervous system (21). Previous reports have implicated the DRG in the development and maintenance of chronic pain (22, 23). In animal models, several pathophysiologic changes in the DRG occur including

altered electrophysiological membrane properties (24), changes in the expression of integral membrane proteins (25), and altered gene expression (26). These changes may explain how the DRG can significantly contribute to chronic pain states (22).

In addition to the putative clinical value of DRG stimulation for long-term pain relief, it is possible that this modality may address the issues that make SCS untenable for some patients. Further, because the DRG is encased in bony vertebral structures, it may be possible to mitigate the over- or under-stimulation artifacts that some SCS patients report occur with certain movements or postures. The relative immobility of the bony vertebral structures surrounding the DRG may also provide some defense against lead migration. The cerebrospinal fluid (CSF) layer interposing the DRG and the lead is smaller than that between the spinal cord and the lead in dorsal column stimulation, and the stimulation targets are presumably located less deep than dorsal column fibers; together, this suggests that the energy requirements of a DRG stimulator will be lower than that of traditional SCS systems (27). The proximity of the leads to the DRG and the lack of CSF that could act as a current sink (28) may also reduce the power demands of the stimulator.

Given the success in treating various pain conditions with electrical neuromodulation techniques and the emerging role of the DRG in the development, maintenance, and treatment of chronic pain, we report on a novel stimulation system to treat chronic pain through electrical neuromodulation of the DRG. The aim of this study to evaluate the safety and effectiveness of neuromodulation of the DRG in a prospective, open-label, single-arm, internally controlled study across five clinical sites.

MATERIALS AND METHODS

Subjects

Subjects were recruited from investigators' practices at three European sites and four Australian sites from March 2011 through February 2012. All study elements were ethics committee-approved and each subject gave written informed consent prior to beginning any study activities.

To be eligible for the study, subjects were required to be 18 years or older; be diagnosed with chronic, intractable pain in the trunk, limbs, and/or sacral region for a minimum of six months; have a minimum baseline pain rating of 60 mm on the Visual Analog Scale (VAS; 0 mm indicates no pain and 100 mm indicates the worst possible pain); have failed other treatment modalities (e.g., pharmacological, surgical); have stable pain medication dosage for a minimum of 30 days prior to study enrollment; and have a stable pattern of neurological symptoms.

Exclusion criteria were presence of an escalating or changing pain condition within the month prior to enrollment in the study; pain primarily within a cervical dermatomal distribution; corticosteroid therapy at the intended site of stimulation within the past 30 days; coagulation disorder; diagnosis of a malignancy; radiofrequency treatment of an intended target DRG within the past 3 months; existing indwelling devices (e.g., urinary catheter, etc.); and existing spinal cord stimulators, ICDs or pacemakers.

Study design

After enrollment, subjects underwent a medical history review and brief physical/neurological examination and then completed baseline clinical assessments including VAS pain ratings for overall pain and specific anatomies (back, leg, foot), quality of life using the EQ-5D-3L (29), psychological disposition using the 30-item Brief Profile of Mood States (POMS), and the impact of pain on daily functions using the Brief Pain Inventory (BPI) through pain severity and pain interference composite scores. Pain severity is the average of worst pain in the last 24 hours, least pain in the last 24 hours, average and current pain scores. Pain interference is the average interference of seven daily functions during the past 24 hours: general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life.

After baseline assessments, subjects were implanted with quadripolar neurostimulation leads (described below) according to standard surgical procedures. The stimulating contacts were placed near relevant DRGs according to the individual's location and distribution of pain (see Figure 5). Stimulation leads were connected to an external neurostimulator, and the device was programmed with combinations of pulse width, amplitude, and frequency that generated the best pain/paresthesia overlap. On an average, the temporary trial phase lasted 9.4 (±1.0, standard error of the mean (SEM)) days, although the protocol allowed anywhere from 3-30 days. At the end of the

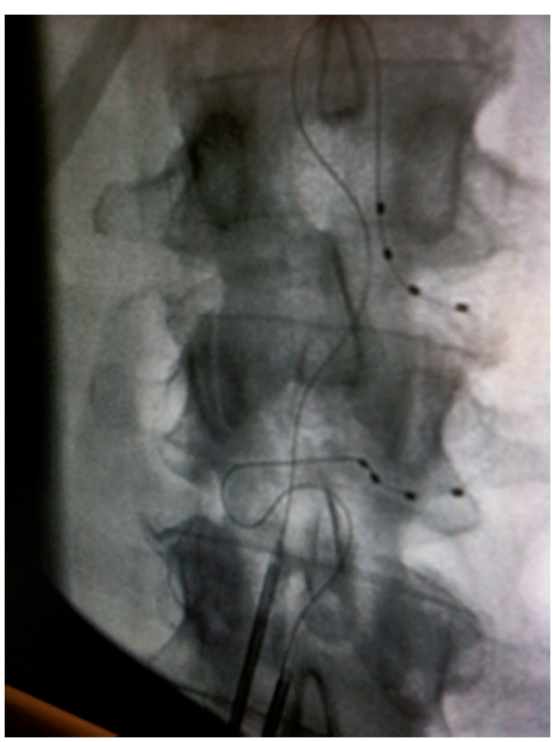


Figure 5. Fluoroscopic image of leads placed near the DRG.
Notice that second-most distal contact in each lead is underneath the pedicle.

trial period, stimulation was discontinued until (and if) the permanent neurostimulation system was implanted.

At the end of the trial period, subjects were asked to name the percentage of pain improvement experienced (in all areas of pain and overall) as a result of neurostimulation of the DRG. Subjects who achieved 50% or greater pain relief in their primary pain area during the trial period completed pre-implant pain ratings as a stimulation-off internal control and then received the fully-implantable neurostimulator under standard surgical procedure; data for only these subjects were included for analysis in this study. Stimulation was initiated within 24 hours of implantation. Subjects repeated the baseline assessments at 1 and 4 weeks post-implant. After the 4-week assessment, stimulation was temporarily suspended for approximately 1 week as another internal control; during this time, subjects had access to pain medication as well as rescue stimulation if needed. A stimulation-off pain assessment was completed at 5 weeks post-implant and stimulation was resumed. Clinical endpoints were again assessed at 2, 3 and 6 months post-implant, although it should be noted that three sites did not collect data for the 2-month point. Adverse events were monitored throughout the study. The study design is summarized below; see Figure 6.

The primary objective of the study was to evaluate the adverse event rate and paresthesia generation while the secondary objectives include pain relief as measured by VAS, quality of life as measured with the EQ-5D questionnaire, mood as measured by the POMS, and physical functioning as measured with the BPI.

Determining paresthesia intensity

Testing took place in the clinic at the post-implantation programming session, 0-1 days after the surgical procedure. A VAS for paresthesia (0= no feeling and 10= very intense) was used to determine the effect of body position on stimulation intensity. Subjects were asked to stand upright and, after adjusting the amplitude of stimulation in their preferred program to a comfortable level, to rate the perceived intensity of the paresthesia. Subjects then lay supine on an examination table without changing the stimulation parameters, and again rated their paresthesia intensity. The paresthesia intensity rating scale was validated during the clinical trial. The results of the validation are currently being drafted as a separate manuscript.

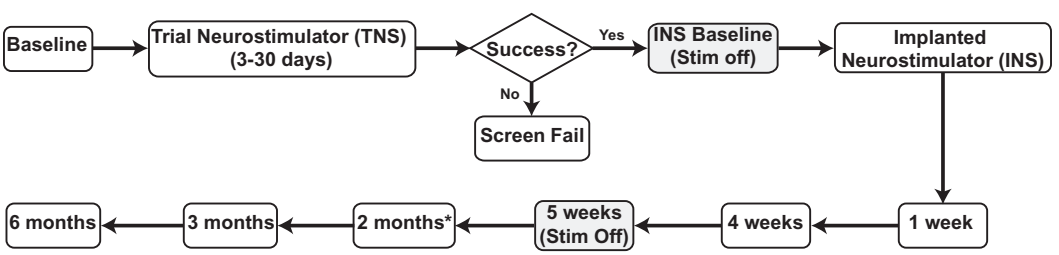


Figure 6. Schematic of the study design.
The * symbol indicates that 2 month data was not collected by three of the sites.

Device description and implantation technique

The Spinal Modulation Axium neurostimulator system is comprised of a stimulator device (an external trial neurostimulator [TNS] is used for the trial period, followed by an implanted neurostimulator [INS] if successful), up to four quadripolar percutaneous leads and wireless patient- and clinician programmer devices. Both TNS and INS are constant voltage devices.

Under monitored anesthesia care, leads are placed via an epidural approach, with access gained using the loss-of-resistance technique standard for this type of intervention. Leads are advanced in an anterograde fashion and then are steered into the intervertebral foramen near the DRG under fluoroscopic guidance. Appropriate lead position is determined through intraoperative device programming to confirm paresthesia overlap with the painful regions. If pain-paresthesia overlap is not achieved through programming, the leads are repositioned under fluoroscopy and programmed again. The DRG is in a consistent location anatomically, thus lead position can accurately reflect the ability to stimulate the ganglion. Also because cell bodies are present in the ganglion and not in the nerve root, coupled with the fact that many membrane alterations occur in the perikarya of primary sensory neurons and not nerve roots there are electrophysiological difference between these structures. In part the ability to steer an electric field around a ganglion provides an enhanced ability to provide acute and specific sub-dermatomal coverage compared to a nerve root. And although prior investigators had tried DRG stimulation, limitations were realized in both the methodology of lead placement and also ability to provide desired stimulation therapy. The technology utilized in the current study provides differences in both the lead delivery methods and also the ability to provide stimulation to the DRG compared to the older technology utilized in prior studies. For the trial period of up to 30 days, either trial or implant leads may be used. If trial leads are used, they are removed and replaced with implant leads at the end of a successful trial. If implant leads are used, disposable lead extensions are also employed to allow the leads to remain in place at the end of the trial period. Measures intended to limit lead migration, such as strain relief loops and use of lead anchors, are used. Stimulation programming is based on patient feedback; stimulation amplitude can be adjusted by the patient at any time.

Data management and analysis

ISO 14155 guidelines were adhered to during data collection. Data were gathered on pre-printed case report forms by site staff. Data quality and compliance with study procedures and regulatory requirements were confirmed at regular monitoring visits. Safety endpoints were expressed as the cumulative frequency of adverse events (AEs) related to the device and/or the procedure throughout the study. Clinical endpoints were analyzed using SPSS V20 (IBM, New York) through descriptive statistics and two-tailed paired t-tests (with the exception of the paresthesia ratings in different positions, which used unpaired t-tests) with significance levels set at p=0.05. All data are presented as average ± SEM. With the exception of the end of the trial period, the percentage of pain relief at every time point is expressed as the mean of the subjects' baseline-to-follow-up pain reduction percentage. Hypothesis testing for

pain ratings compares baseline VAS scores against scores at all follow-up time points for overall pain, and at 6 months post-implant for pain specific to back, legs, and feet.

This report represents a 6-month interim analysis of prospective results. As with any interim analysis of an ongoing study, the later follow-up time points in this report have fewer subjects than at baseline; this artifact is not an indication of study attrition.

2 RESULTS

Patient Demographics and Baseline Characteristics

Of the 51 individuals screened, 39 reported greater than 50% improvement in pain relief at the end of TNS while 12 subjects failed the trial (76.5% success rate). Thirty two subjects received the INS (females=17, males=15). The mean age of the males was 58.9 (± 8.9) years while the females had a mean age of 46.9 (± 12.5) years. All subjects had chronic pain of neuropathic origin of varying etiologies. The most common pain diagnoses were CRPS and FBSS. Subjects experienced pain located in the back, leg, and foot; many subjects experienced pain in more than one region. A number of subjects experienced pain in other diverse anatomical regions; owing to the small samples across heterogeneous locations, these 'other' locations were not analyzed. The distribution of subjects across diagnoses and pain locations is listed in Table 2.

Seven of the 39 subjects with >50% pain reduction at the end of TNS did not proceed to the INS stage. Two subjects had not indicated any reason for refusing the implant. One subject's pain had not recurred since TNS and hence refused any further intervention. Another subject, with 100% pain relief in one foot but none in the other, also did not receive the INS. One subject was withdrawn by the investigator while two more subjects withdrew from the study (atrial fibrillation and infection).

Lead Placement

Surgeons used implant leads during the TNS procedure for 22 of the 32 subjects who received an INS; in the other 10 subjects, the temporary trial leads were removed and replaced with implant leads during the INS procedure. Although the neurostimulation system could accommodate up to four leads, the majority of INS subjects (n=21) were implanted with two leads while 5 subjects were implanted with

Table 2. Breakdown of subject diagnoses and painful regions.

Diagnosis	Numbers of subjects with pain in specific regions				
	N	Back	Leg	Foot	Other regions
Complex regional pain syndrome	9	0	7	7	5
Failed back surgery syndrome	8	7	7	0	2
Postsurgery pain	5	3	2	2	4
Radicular pain	2	0	2	1	0
Lumbar stenosis	2	0	2	0	1
Disc-related pain	4	1	3	3	1
Others (peripheral nerve damage and pain after postvascular stenting)	2	0	3	1	1
Totals	32	11	26	14	14

only one lead. The average stimulation settings for all the implanted leads were: pulse width – 362 ms, amplitude – 907 mA and frequency – 46 Hz.

Safety

A total of 70 events (9 SAEs and 61 AEs) were reported in 24 subjects. No SAEs were definitely related to the study device. SAEs include: infection (3 events in 3 subjects), CSF hygroma, loss of paresthesia coverage, prolonged hospital stay, inflammation, temporary cessation of stimulation and ataxia (1 event each). All events were resolved and no clinical sequelae were reported. Further data collection is warranted to look for any delayed onset adverse events. Three SAEs were possibly related to the device (37.5%) and five were not related to the device (62.5%). Relationship of one SAE to the device has not been established. Majority of the SAEs were severe (55.6%). Thirty (49.2%) of the AEs were not related to the device. Most of the AEs (45 or 73.7%) were either mild or moderate while 16 (26.2%) of the AEs were deemed severe. The most common AEs (>3% occurrence) are listed in Table 3. Two lead revisions were performed in 2 different subjects for the following reasons: lead migration and loss of stimulation. Five devices were explanted (due to infection: 3; lack of efficacy: 1; subject non-compliance: 1) and one device was switched off (and the subject withdrawn from the study) before the 6 month follow-up period.

Effectiveness: overall pain

At baseline, the 32 subjects rated their overall pain as 77.6 mm (±2.1) out of a possible 100 mm. With the TNS, the 32 subjects' average pain rating dropped to 26.1 mm (±3.4), a 66.1% decrease and significantly lower than baseline ($p<0.001$). Stimulation was discontinued at the end of the trial phase until the permanent neurostimulation system was implanted. During this one-week (minimum) stimulation-off period, the average pain rating rebounded to 74.0 mm (±3.0), which was statistically indistinguishable from baseline levels ($p>0.05$).

One week after receiving the permanent INS, the 32 subjects reported that their average overall pain was reduced to 34.9 mm (±4.3). This represented an average 55.1% (±5.5%) decrease from baseline ($p<0.001$) and 50% or more pain relief for 53.1% of subjects. At four weeks post-implant, average pain was 36.6 mm (±4.6) across 32 subjects, a decrease of 52.7% relative to baseline ($p<0.001$). 62.5% of subjects achieved

Table 3. List of Adverse Events (AEs) and Serious Adverse Events (SAEs) with percentage of occurrence listed in parentheses.

Biologic AEs and SAEs		Device AEs and SAEs	
Description of the AE/SAE	Frequency	Description of the AE/SAE	Frequency
Infection	7 (10.0)	Uncomfortable stimulation	3 (4.1)
Cerebrospinal fluid leak or associated headache	6 (8.6)	Temporary cessation of stimulation	3 (4.1)
Inflammation	6 (8.6)		
Inadequate pain relief	4 (5.7)		
Flu-like symptoms/cough	4 (5.7)		
New injury/condition	5 (7.1)		
Temporary motor stimulation	8 (11.4)		
Other (unspecified)	8 (11.4)		

50% or better pain relief at this time point. Stimulation was temporarily suspended after the four-week assessment in order to verify intra-subject effectiveness; after a week without stimulation, subjects reported that their overall pain returned to near-baseline levels: 68.4 mm (±4.6; p=0.05). Stimulation was then restored. At 2 months post-implant (n=22), the average overall reported pain was 39.5 mm (±6.6; p<0.001), which was an average of 50.7% (±8.0%) decreased from baseline pain; 59.1% of subjects reported at least 50% pain relief. At 3 months post-implant (n=30), the average overall pain rating was 38.4 mm (±5.7; p<0.001), a 50.8% (±7.0%) decrease from baseline and pain relief of 50% or more for 60.0% of subjects. At 6 months post-implant, 25 subjects reported pain of 33.5 mm (±6.0; p<0.001), a 56.3% decrease from baseline. 52.0% of subjects had 50% or better pain relief at this time point. These data are depicted below; see Figure 7.

Pain relief was also assessed in specific regions: the back, legs, and feet. Not all subjects had pain in all of these regions. Back pain was reduced by 16.7% relative to the back-specific baseline at 1 week post-implant, by 45.9% at 4 weeks, by 49.7% at 3 months, and by 58.1% at 6 months. Relative to the leg-specific baseline, leg pain was reduced by 69.5% at 1 week post-implant, 68.6% at 4 weeks post-implant, by 72.4% at 3 months, and by 69.3% at 6 months. For the foot, pain was reduced relative to the foot-specific baseline by 78.5% at 1 week post-implant, by 58.6% at 4 weeks, by 67.8% at 3 months, and by 84.5% at 6 months (see Figure 8). The percentage of subjects with >50% improvement in their VAS is listed in Table 4.

Paresthesia: Steerability and positional stability

Stimulation was selective and highly steerable resulting in discrete paresthesia coverage in difficult to treat anatomies. Steerability of paresthesia was demonstrated through overlapping pain-paresthesia maps (see representative subject data in Figure 9). A total of 23 subjects were assessed at 6 months post-implant for stability of paresthesia intensity across body positions. Paresthesia intensity ratings were 4.0±0.5 and 3.8±0.5 for supine and upright positions, respectively. Paresthesia intensity ratings for the two positions were statistically indistinguishable (p>0.05).

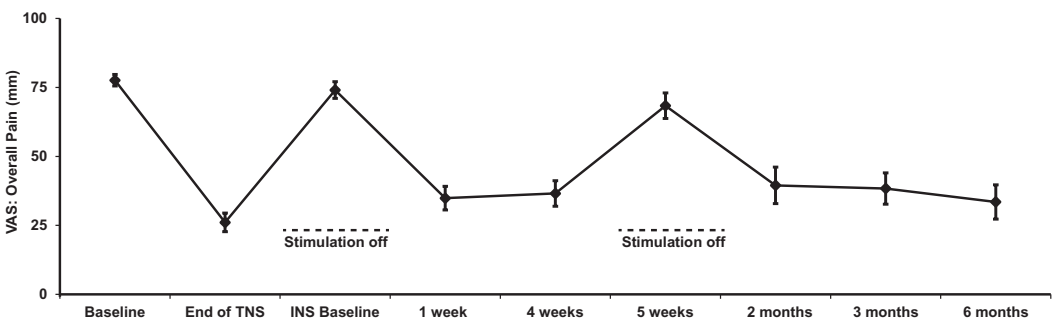


Figure 7. Pain ratings (VAS).
Overall pain ratings at baseline are reduced with DRG neurostimulation and rebound to pre-implant levels when stimulation was discontinued for one-week periods. Data points represent mean ± SEM.

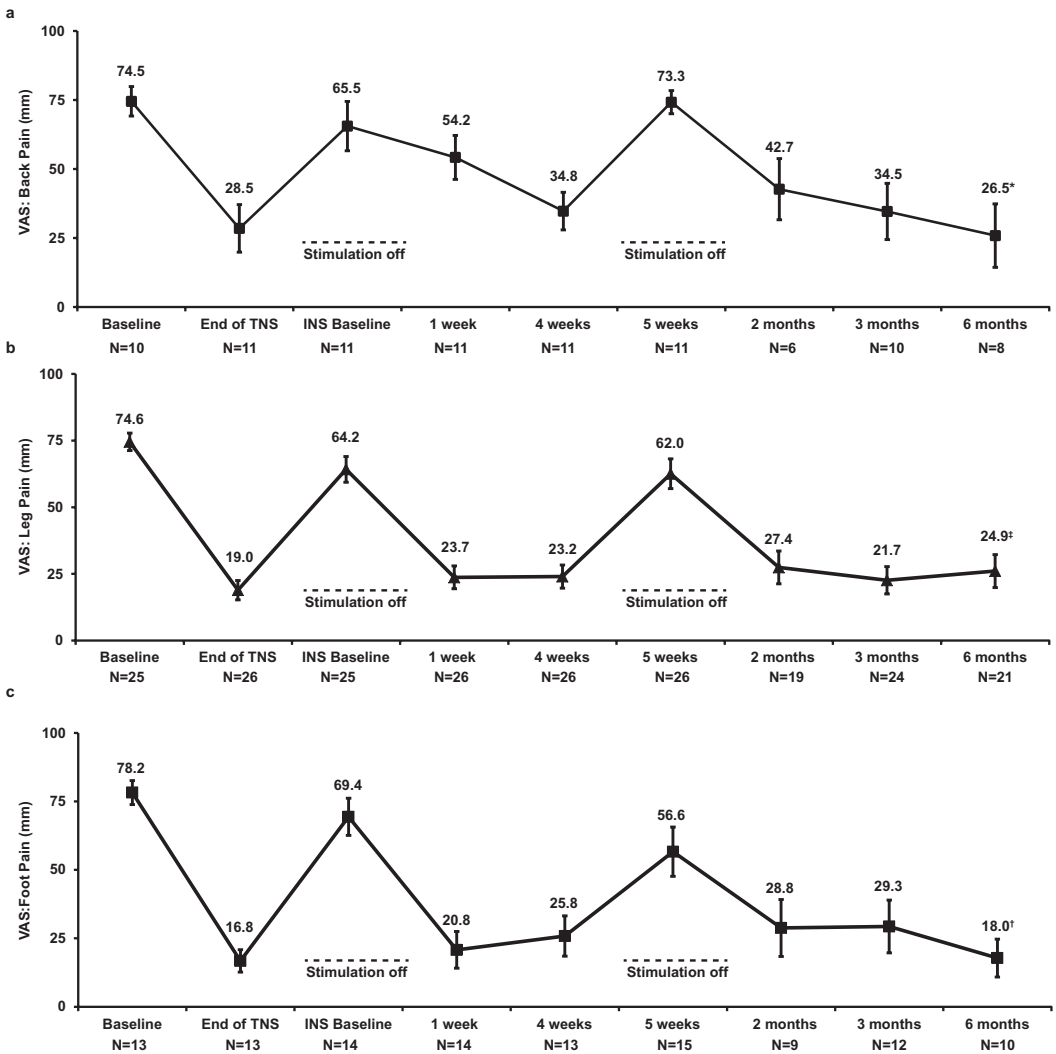


Figure 8. VAS in back, legs, and feet.
Pain ratings associated with FBSS and located in the (a) back, (b) legs, and (c) feet are reduced with DRG neurostimulation. Data points represent mean ± SEM. *p<0.05, ‡p<0.001, †p<0.005.

Table 4. Percentage of subjects with >50% VAS improvement.

	One week	Four weeks	Three months	Six months
Back pain	20.0	50.0	55.6	57.1
Leg pain*	76.0	76.0	78.3	70.0
Foot pain*	84.6	83.3	81.8	88.9

At baseline, number of subjects with back, leg, and foot pain were 11, 25, and 13, respectively.
*Leg pain and back pain VAS at baseline for one subject could not be obtained.
VAS, visual analog scale.

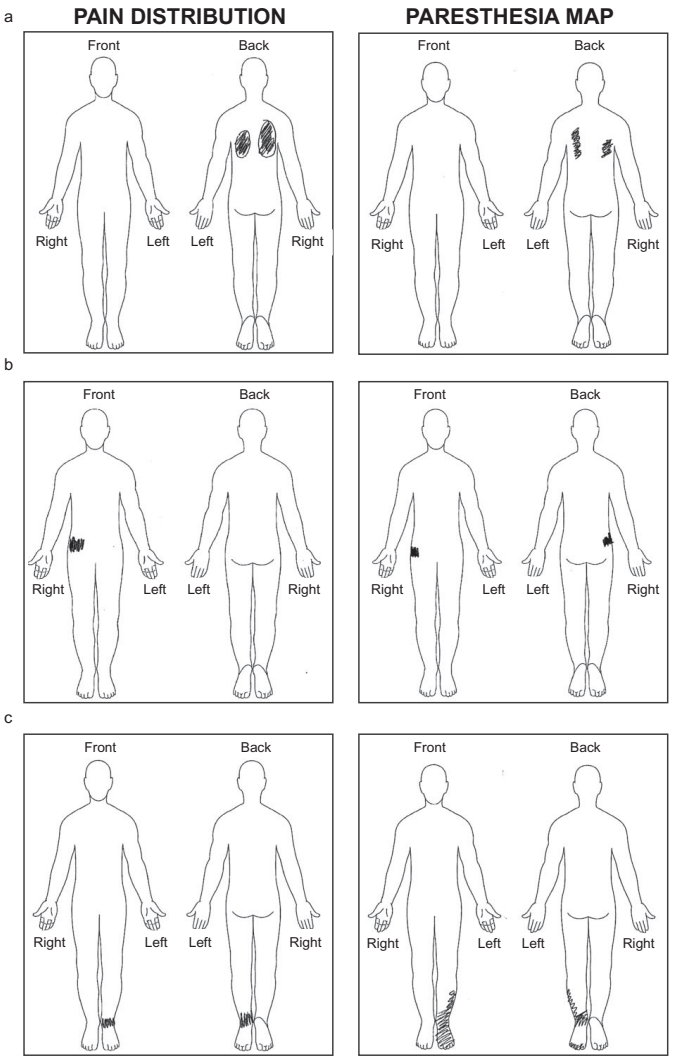


Figure 9. Pain and paresthesia.
Pain distribution (left column) and paresthesia map (right column) for 3 representative subjects (a, b, c) in the study. Note the overlap of pain-paresthesia and the discrete coverage possible with the electrical neuromodulation of the DRG.

Effectiveness: quality of life, mood, and function

Change in quality of life, as measured by EQ-5D-3L VAS, was assessed on a 100-mm scale with a rating of 100 corresponding to best imaginable health. At baseline, the self-rated score was 47.0 mm (±3.8). After one week of stimulation with the INS, the score increased to 64.1 mm (±3.6; $p<0.05$) (see Figure 10). The score remained significantly higher at all follow-up time points (*ps*<0.05). The number of subjects that reported problems at baseline in five different EQ-5D-3L subscales decreased significantly for mobility, usual activities and pain-discomfort domains (*ps*<0.05) (see Figure 11).

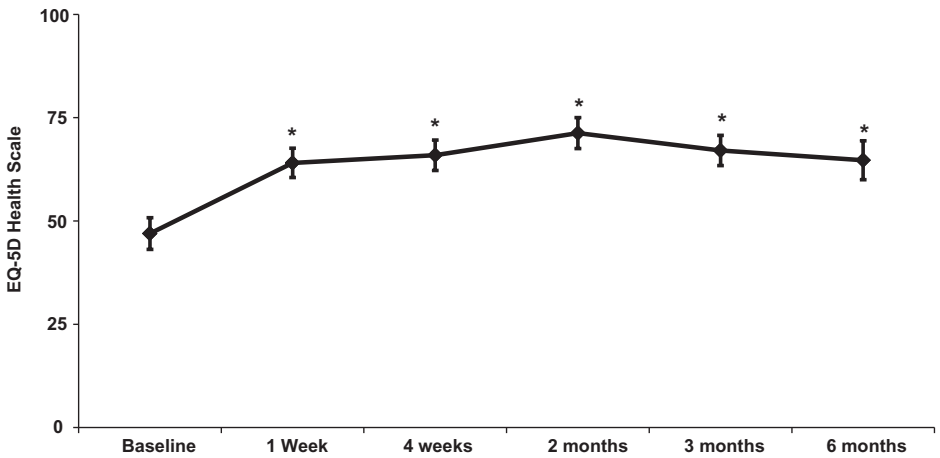


Figure 10. Health index.
Subjects' mean self-rated health index as reported on the EQ-5D-3L VAS scale of overall health increased over time, representing a subjective improvement in health. Data points represent mean ± SEM (*p<0.05).

The combination of individual dimension scores of the EQ-5D-3L can be converted into a single index value for health status that can be used in the clinical and economic evaluation of health care (30, 31). Index values were calculated based on general population valuation surveys that used time trade off (TTO) (Netherlands) (32) or VAS (Belgium) (33) methods in the countries where the trials were conducted. Index values for the general population in Australia were not available and hence not included in the calculations. The EQ-5D index values at baseline and at 6 months for the subjects included in the analysis were 0.289 ±0.054 (N=20) and 0.725 ±0.066 (N=15), respectively. The increase in the index value was statistically significant (p<0.001; see Figure 11).

Mood disturbance was self-reported with the POMS. Mean ratings on the tension, vigor, and fatigue subscales, as well as the total mood disturbance score, were statistically significantly improved at 6 months relative to baseline (p<0.05; see Table 5).

Table 5. Scores of Profile of Mood States (POMS).
Subscale and total scores at baseline and after 6 months demonstrated an improvement in mood that was statistically significant across multiple domains.

POMS Subscale	Baseline (N = 32)	Six months (N = 24)
Tension	6.3 ± 0.7	4.2 ± 1.0*
Depression	5.3 ± 0.8	3.3 ± 1.2
Anger	6.1 ± 0.9	3.6 ± 1.1
Vigor	5.9 ± 0.9	8.5 ± 1.0*
Fatigue	11.7 ± 0.9	6.9 ± 1.4*
Confusion	4.1 ± 0.5	4.3 ± 0.7
Total mood disturbance score	27.5 ± 3.5	13.8 ± 5.6*

Data represent mean ± SEM.
*p < 0.05.
POMS, Profile of Mood States; SEM, standard error of the mean; VAS, visual analog scale.

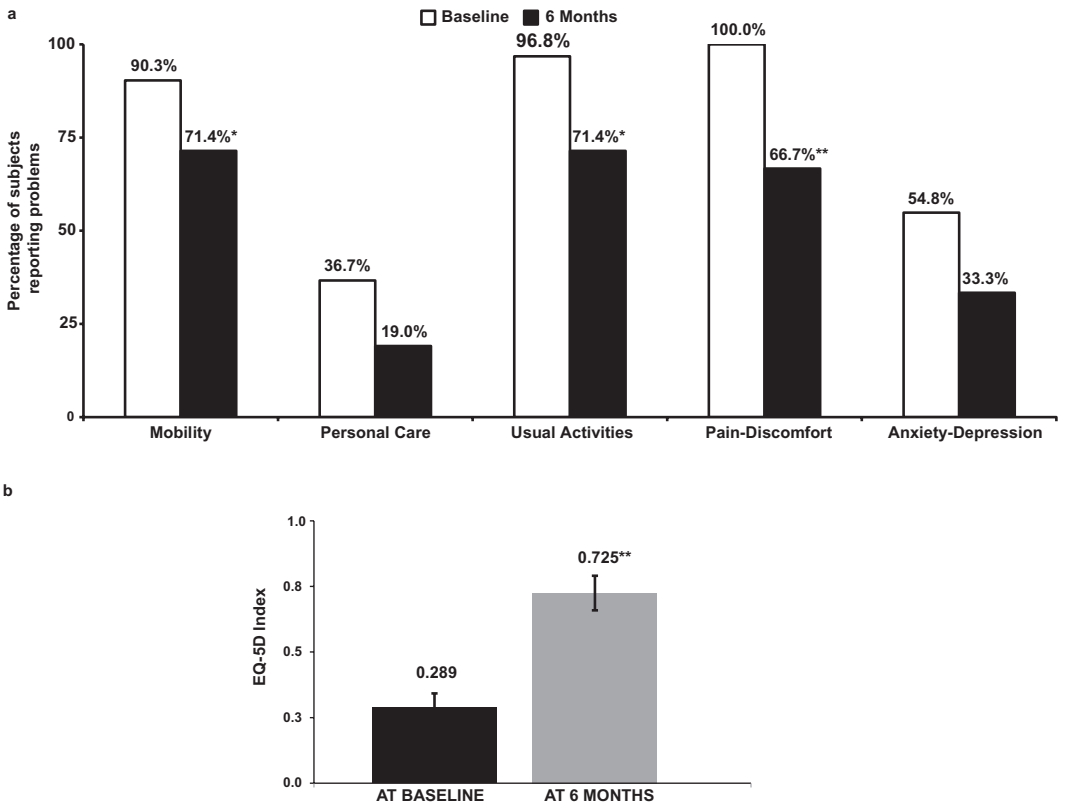


Figure 11. Subjects reporting problems (a quality of life measure).
(A) EQ-5D-3L domains are listed with the percentage of subjects who reported any problem at baseline and 6 months follow-up. (B) EQ-5D index value was significantly higher at the 6 month follow-up (*p<0.05, **p<0.001).

Pain interference (average of 7 domains) as described by the BPI improved from 6.6 (±0.4) at baseline to 4.1 (±0.5) (p<0.001), and maintained this level through 6 months post-implant, when the average rating was 3.8 (±0.6; p<0.001). Pain severity (composite score) was rated at 6.9 (±0.2) at baseline. At 1 week post-implant, pain severity decreased to 4.3 (±0.4; p<0.001). This reduction in pain was maintained through 6 months post-implant, when the average pain severity was 3.9 (±0.6) at (p<0.001, see Table 6).

Table 6. Brief Pain Inventory scores.
Pain interference and pain severity measured by BPI demonstrated sustained decrease from baseline.

	Baseline (*N* = 32)	One week (*N* = 32)	Four weeks (*N* = 29)	Two months (*N* = 22)	Three months (*N* = 29)	Six months (*N* = 24)
Pain interference	6.6 ± 0.4	4.1 ± 0.5*	3.5 ± 0.5*	3.1 ± 0.5*	3.6 ± 0.6*	4.0 ± 0.6*
Pain severity	6.9 ± 0.2	4.3 ± 0.4*	4.0 ± 0.4*	4.0 ± 0.5*	3.9 ± 0.5*	3.9 ± 0.6*

*$p < 0.001$.

DISCUSSION

A prospective, open-label clinical trial with an internally-controlled reversal design was conducted across five clinical sites to characterize the performance of a neurostimulation system designed for stimulation of the DRG for management of chronic pain. Conjectural differentiators of the DRG neurostimulation system relative to traditional SCS systems include selective stimulation or paresthesia coverage in the dermatomes, lack of postural effects, ability to drive paresthesia to areas that are typically difficult to treat using SCS (e.g., foot), and lower therapeutic power demands. The device demonstrated physical stability with lead migration of 3% (2 leads out of 67), which is well below the rate of migration for SCS with percutaneous leads placed over the dorsal columns, which have been reported at 13.2% in a literature review of 51 studies (7), and at 23% in a prospective study of implant techniques and reprogramming compared against radiographic evidence (34). Similar to previously-reported values (7,35), one subject reported uncomfortable stimulation, a usually transitory issue usually associated with developing an effective program for the individual. However, it should be noted that other neuromodulation systems using dorsal column stimulation elicited uncomfortable paresthesias, which could presume some dorsal root / dorsal root ganglia involvement (36).

At all active stimulation time points through 6 months post-implantation, the average pain relief across subjects was at least 50% as measured on the VAS. Differences between baseline pain and stimulation-on pain were statistically significant. The reduction in pain was also clinically significant; stimulation-induced absolute reductions in VAS were 40-50 mm, while the minimum clinically important difference in VAS for back and leg pain has been estimated at approximately 20-30 mm (37, 38). The reduction of pain as measured by the Brief Pain Inventory slightly differed in absolute values from the VAS results reported here, as may be expected when using multiple instruments with different psychometric properties (39), but showed the same patterns of pain relief.

DRG stimulation was effective for the pain associated with CRPS and FBSS, as well as for pain localized to the back, legs, and feet. The magnitude of pain relief in this study exceeded that reported in the largest controlled trial of SCS to date. Data from the PROCESS study describe that 50-60% of FBSS subjects achieved 50% or better leg pain relief through 6 months of SCS therapy (11); in this study, approximately 75% of clients reported this level of pain relief. PROCESS reported reduction in back pain from approximately 55 mm at baseline to approximately 40 mm at 4, 12, and 24-week follow-ups (11); despite higher baseline back pain, subjects in this study reported reductions to 25-30 mm at the same time points. However, significant methodological differences exist between the PROCESS randomized controlled trial and this open-label study which make direct comparisons of outcomes problematic. For instance, the PROCESS study's intent-to-treat analysis included all randomized subjects while this study excluded screen failures and explanted/switched-off subjects from analysis and may therefore emphasize the relative contribution of the positive outcomes. Recent observational and cohort studies of SCS for a variety of indications have reported overall pain relief (relative to

baseline) of 68% (40, 41), 52% (42), and 45% (43). A systematic review that included analysis of case studies reported that approximately 62% of SCS patients achieve 50% or better pain relief (8), although it was noted that due to heterogeneous design and methodologies, there is some difficulty in generalizing across this open-label knowledge base. Against these reports, the clinical results of DRG stimulation are promising.

The relief of foot pain is of special interest in this study. Reports of non-vascular neuropathic foot pain relief via SCS are few and small (12, 44, 45, 46), likely because foot coverage with traditional SCS systems are unable to cover discrete painful regions in the foot without generating extensive extraneous paresthesias or motor side effects. Additionally, the pain relief afforded to the feet by SCS is typically limited. In this study, approximately 80% of subjects with foot pain reported at least 50% foot pain relief, and the average pain relief was more than 70%. Importantly, the stimulation was able to cover the painful areas without generating large unwanted areas of paresthesia. Furthermore, significant positional effects of stimulation were not noted; paresthesia intensity subjects reported much the same paresthesia intensity when standing as compared to lying supine. This may be due in part to the location of the DRG inside the vertebral foramen (21, 47); they are presumably relatively physically stable throughout a subject's changes in position, unlike the highly mobile spine. Although it is possible that the DRGs may shift inside their enclosures with the effects of gravity, any such movements are likely to be slight, given their size and conformation. Thus, assuming stable lead placement via anchors and strain relief loops, it is anticipated that a patient's body movement would result in very little movement of the DRG or lead relative to each other.

Other secondary endpoints, including quality of life, functional status, and mood all improved during this study. Subjective ratings in these domains are often associated with clinically significant reduction in pain (48, 49, 50). Although the mediating effects of an individual's personal outlook (which may incorporate hope and resiliency (51)) and frequent contact with a pain specialist through study visits cannot be ruled out, these results suggest that improvement in pain through DRG stimulation establishes lifestyle improvements that would be appreciated holistically.

This study incorporated two reversal periods (also known as A-B-A) during which stimulation was temporarily stopped for a brief period of time. Pain ratings were captured during the stimulation-off periods, and again at resumption of the therapy. This internal-control methodology is more robust than a design implementing continuous therapy and may address the criticism inherent to pain research that an individual's historical (baseline) pain reporting may be influenced by faulty recall or psychological processes (52). This assumption is admittedly complicated by the fact that the subjects were unblinded. Pain ratings rebounded at both reversal time points which may lend credibility to the effectiveness of this therapeutic intervention and its durability over time. However, at the second reversal point, the rebound pain was statistically lower than baseline reports; this may represent a reluctance on the part of the subjects to report the full magnitude of effect, a possible increase in the use of rescue pain medications during the stimulation-off period, or a simple artifact of sample size.

Interpretation of this study should be informed by a number of points. First, pain relief in this study was calculated as percentage reductions in the visual analogue scale,

as opposed to the verbal rating scale ("on a scale of one to ten…"). Although the verbal scale is more convenient for many pain physicians to incorporate into clinical practice, the visual scale has been demonstrated to more closely represent the actual pain experience of the individual (53, 54). The verbal scale should more properly be considered interval data than ratio, establishing dichotomous statistical assumptions (54). Several recent landmark SCS trials, including the PROCESS study that was discussed previously in this section, have incorporated visual scales in their design (11, 14). However, much of the published literature makes use of the verbal scale, presumably for ease of use. Comparability of the results of this study with others using different pain rating methods should thus be interpreted judiciously, given that numeric ratings are used in the calculation of the percentage of pain relief relative to baseline. Additionally, external experiences may influence pain ratings; subjects may have learned, over the difficult course of dealing with a chronic pain condition, communication methods involving VAS ratings as part of their self-management (55, 56). Competing motivations in pain ratings contribute to the subjective nature of pain research. This issue is inherent, however, with all pain studies, and given that converging results were obtained across a number of different measures in this study, a high degree of confidence in the clinical outcomes of DRG neurostimulation can be assumed.

Effectiveness of the device, and the validity of stimulation-related pain reductions, is further supported by the rebound to baseline levels during reversal periods. It should be noted, though, that subjects were certainly aware of the stimulation on/off status of their device based on the presence or absence of paresthesias. Thus, the placebo effect cannot be ruled out. Placebo has been estimated to account for approximately one-quarter to one-third of the observed effect in pain studies (57, 58). Placebo-controlled studies are difficult or nearly impossible in neurostimulation, although some work has demonstrated that SCS out-performs placebo in experimental measures of pain (59). Further work, including stimulation at levels that are sub-threshold for inducing paresthesias but may be effective for pain mediation, will be needed to investigate the role of the intervention versus placebo. Continued surveillance is also necessary to confirm durable effectiveness, since these 6-month results are preliminary. With any novel device there may be scope for further optimization of the therapy over time and experience and there may be potential for improved programming and lead placement algorithms.

CONCLUSIONS

Neuromodulation of the DRG was effective for relieving chronic pain and was able to consistently provide discretely defined paresthesia coverage in challenging anatomical regions such as the back and foot. Consistent intensities of paresthesias were reported throughout tests involving different body positions, demonstrating a clinically important lack of positional effects. Device performance demonstrated good safety profile and subjects in this trial experienced improvements in health-related quality of life, mood, and pain symptoms. These results suggest that SCS of the DRG is a robust new tool for the pain physician's armamentarium.

REFERENCES

1. Gildenberg P. History of electrical neuromodulation for chronic pain. *Pain Medicine*. 2006;7:S7-S13.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150(699):971-979.
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):489-491.
4. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *JAMA*. 1998;280:147-151.
5. Blyth FM, March LM, Brnabic AJ, Cousins MJ. Chronic pain and frequent use of health care. *Pain*. 2004;111:51-58.
6. Praeger J. Estimates of annual spinal cord stimulator implant rises in the United States. *Neuromodulation*. 2010;13(1):68-69.
7. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg*. 2004;100(3):254-267.
8. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. *Spine*. 2005;30(1):152-160.
9. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *Eur J Pain*. 2006;10(2):91-101.
10. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*. 2007;132(1-2):179-188.
11. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in chronic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectivness of spinal cord stimulation. *Neurosurg*. 2008;63(4):762-770.
12. Kemler MA, Barendse GAM, Van Kleef M, et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *N Engl J Med*. 2000;343(9):618-624.
13. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. The effect of spinal cord stimulation in patients with chronic reflex sympathetic dystrophy: two years' follow-up of the randomized controlled trial. *Ann Neurol*. 2004;55(1):13-18.
14. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg*. 2008;108(2):292-298.
15. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58:481-496.
16. North RB, Kidd DH, Farrokhi F, Piantadosi SA. Spinal cord stimulation versus repeated lunbosacral spine surgery for chronic pain: a randomized, controlled trial. *Neurosurg*. 2005;56(1):98-106.
17. North RB. Neural interface devices: spinal cord stimulation technology. *Proceedings of the IEEE*. 2008;96(7):1108-1119.
18. He J, Barolat G, Holsheimer J, Struijk JJ. Perception threshold and electrode position for spinal cord stimulation. *Pain*. 1994;59:55-63.
19. Holsheimer J, Khan YN, Raza SS, Khan E. Effects of electrode positioning on perception threshold and paresthesia coverage in spinal cord stimulation. *Neuromodulation*. 2007;10(1):34-41.
20. Mathew L, Winfree C, Miller-Saultz D, Sonty N. Transcutaneous electrical nerve stimulator trial may be used as a screening tool prior to spinal cord stimulator implantation. *Pain*. 2010;150(2):327-331.
21. Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does and why it matters. *Reg Anesth Pain Med*. 2010;35(3):306-311.
22. Sapunar D, Kostic S, Banozic A, Puljak L. Dorsal root ganglion - a potential new therapeutic target for neuropathic pain. *J Pain Res*. 2012;5:31-38.
23. Van Zundert J, Patijn J, Kessels A, Lame I, van Suijlekom H, van Kleef M. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. *Pain*. 2007;127(1-2):173-182.
24. McCallum JB, Kwok WM, Sapunar D, Fuchs A, Hogan QH. Painful peripheral

nerve injury decreases calcium current in axotomized sensory neurons. *Anesthesiol*. 2006;105(1):160-168.

25. Rush AM, Dib-Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG. A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc Natl Acad Sci USA*. 2006;103(21):8245-8250.
26. Fields RD. New culprits in chronic pain. *Sci Am*. 2009;301(5):50-57.
27. Struijk JJ, Holsheimer J, Boom HBK. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. *IEEE Transactions on Biomedical Engineering*. 1993;40(7):632-639.
28. Struijk JJ, Holsheimer J, van Veen BK, Boom HBK. Epidural spinal cord stimulation: calculation of field potentials with special reference to dorsal column nerve fibers. *IEEE Transactions on Biomedical Engineering*. 1991;38(1):104-110.
29. The EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
30. Szende A, Oppe M, Devlin N. *EQ-5D value sets: inventory, comparative review and user guide (EuroQol Group Monographs)*. 2010.
31. EQ-5D index calculator. Available at: /www.economicsnetwork.ac.uk/health/Other_resources.
32. Essink-Bot ML, Stouthard M, Bonsel GJ. Generalizability of valuations on health states collected with the EuroQol questionnaire. *Health Economics*. 1993;2:237-246.
33. Cleemput I, Kind P, Kesteloot K. Re-scaling social preference data: implications for modelling. In: Kind P, Macran S, eds. *19th plenary meeting of the EuroQol group. Discussion papers*. University of York: Centre for Health Economics.
34. Kim D, 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;14:513-524.
35. Kinfe TM, Schu S, Quack FJ, Wille C, Vesper J. Percutaneous implanted padded lead for spinal cord stimulation: technical considerations and long-term follow-up. *Neuromodulation*. 2012;15:402-407.
36. Epstein LJ, Palmieri M. Managing chronic pain with spinal cord stimulation. *Mount Sinai Journal of Medicine*. 2012;79:123-132.
37. Hagg O, Fritzell P, Nordwall A, Group SLSS. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J*. 2003;12(1):12-20.
38. Parker SL, Adogwa O, Paul AR, et al. Utility of minimum clinically important difference in assessing pain, disability, and health state after transforaminal lumbar interbody fusion for degenerative lumbar spondylolisthesis. *J Neurosurg Spine*. 2011;14(5):598-604.
39. Atkinson TM, Mendoza TR, Sit L, et al. The Brief Pain Inventory and its 'pain at its worst in the last 24 hours' item: Clinical trial considerations. *Pain Medicine*. 2010;11(3):337-346.
40. Van Buyten JP, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. *Neuromodulation*. 2012 ;Early online.
41. Moriyama K, Murakawa K, Uno T, et al. A prospective, open-label, multicenter study to assess the efficacy of spinal cord stimulation and identify patients who would benefit. *Neuromodulation*. 2012;15(1):7-12.
42. Oakley JC, Krames ES, Prager JP, et al. A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study. *Neuromodulation*. 2007;10(3):262-278.
43. Pluijms WA, Slangen R, Bakkers M, et al. Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy: a pilot study. *British Journal of Anaesthesia*. 2012;109(4):623-9.
44. de Leon-Casasola OA. Spinal cord and peripheral nerve stimulation techniques for neuropathic pain. *Journal of Pain and Symptom Management*. 2009;38(2 Suppl):S28-S38.
45. Saranita J, Childs D, Saranita AD. Spinal cord stimulation in the treatment of complex regional pain syndrome (CRPS) of the lower extremity: a case report. *The Journal of Foot and Ankle Surgery*. 2009;48(1):52-55.
46. Olsson GL, Meyerson BA, Linderoth B. Spinal cord stimulation in adolescents with complex regional pain syndrome type I (CRPS-I). *European Journal of Pain*. 2008;12(1):53-59.
47. Haque R, Winfree CJ. Transforaminal nerve root stimulation: a technical report. *Neuromodulation*. 2009;12(3):254-257.
48. Skevington SM. Investigating the relationship between pain and discomfort and quality of life, using the WHOQOL. *Pain*. 1998;76(3):395-406.

49. Turk DC, Okifuji A. Assessment of patients' reporting of pain: an integrated perspective. *Lancet*. 1999;353(9166):1784-1788.
50. Deyo RA. Measuring the functional status of patients with low back pain. *Arch Phys Med Rehab*. 1988;69(12):1044-53.
51. Pincus T, Williams ACdC, Vogel S, Field A. The development and testing of the depression, anxiety, and positive outlook scale (DAPOS). *Pain*. 2004;109(1-2):181-188.
52. Haas M, Nyiendo J, Aickin M. One-year trend in pain and disability relief recall in acute and chronic ambulatory low back pain patients. *Pain*. 2002;95(1-2):83-91.
53. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9-19.
54. Ohnhaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain*. 1975;1(4):379-384.
55. Jensen MP, Nielson WR, Kerns RD. Toward the development of a motivational model of pain self-management. *J Pain*. 2003;4(9):477-492.
56. Turner JA, Calsyn DA, Fordyce WE, Ready LB. Drug utilization patterns in chronic pain patients. *Pain*. 1982;12(4):357-363.
57. Carrette S, Marcoux S, Truchon R, et al. A controlled trial of corticosteroid injections into facet joints for chronic low back pain. *NEJM*. 1991;325:1002-1007.
58. Mendelson G, Selwood TS, Kranz H, Loh TS, Kidson MA, Scott DS. Acupuncture treatment of chronic back pain: a double-blind placebo-controlled trial. *Pain*. 1983;74(1):49-55.
59. Marchand S, Bushnell MC, Molina-Negro P, Martinez SN, Duncan GH. The effects of dorsal column stimulation on measures of clinical and experimental pain in man. *Pain*. 1991;45:249-257.

3

ONE-YEAR OUTCOMES OF SPINAL CORD STIMULATION OF THE DORSAL ROOT GANGLION IN THE TREATMENT OF CHRONIC NEUROPATHIC PAIN

Modified from:
One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain
Liong Liem, Marc Russo, Frank J.P.M. Huygen, Jean-Pierre Van Buyten, Iris Smet, Paul Verrills, Michael Cousins, Charles Brooker, Robert Levy, Timothy Deer, Jeffery Kramer
Neuromodulation 2015; 18: 41-49

ABSTRACT

Spinal cord stimulation of the dorsal root ganglion (DRG-SCS) is a new therapy for treating chronic neuropathic pain. Previous work has demonstrated the effectiveness of DRG-SCS for pain associated with failed back surgery syndrome, complex regional pain syndrome, chronic post-surgical pain, and other etiologies through 6 months of treatment; this report describes the maintenance of pain relief, improvement in mood and quality of life through 12 months. Subjects with intractable pain in the back and/or lower limbs had been implanted with an active neurostimulator device. Up to four percutaneous leads were placed epidurally near DRGs. After prospectively tracking the subjects for 12 months, it was found that, overall, pain was reduced by 56% at 12 months post-implantation, and 60% of subjects reported greater than 50% improvement in their pain. Pain localized to the back, legs, and feet was reduced by 42%, 62%, and 80%, respectively. Measures of quality of life and mood were also improved over the course of the study and subjects reported high levels of satisfaction. Importantly, excellent pain-paresthesia overlap was reported, remaining stable through 12 months. These results suggests that, despite methodological differences in the literature, DRG-SCS appears to be comparable to traditional SCS in terms of pain relief and associated benefits in mood and quality of life. Yet its benefits include the ability to achieve precise pain-paresthesia concordance, including in regions that are typically difficult to target with SCS, and to consistently maintain that coverage over time.

INTRODUCTION

Relief of intractable neuropathic pain can be achieved via neuromodulation of the sensory tracts in the dorsal column of the spinal cord (1). Thousands of traditional spinal cord stimulation (SCS) devices are implanted every year (2) for failed back surgery syndrome (FBSS; 3), complex regional pain syndrome (CRPS; 4), and other indications. With reports of life-changing improvements in pain, quality of life, and associated variables (5), the value of traditional SCS as an intervention cannot be discounted.

However, traditional SCS is not a panacea. Up to 40% of implanted subjects do not appreciate satisfactory pain relief (6), although strict patient selection criteria may reduce the proportion of treatment failures (7). A particularly vexing limitation with this therapy is its tendency to lose effectiveness over time (8, 9), a trend that may affect as many as 50% of implanted patients (10). These problems may be linked to the importance of achieving concordance of paresthesia with the painful areas (11), a necessary condition for successful SCS therapy. Reprogramming or surgical repositioning of the leads (in the case of migration) may be attempted, but are not always satisfactory.

Converging evidence suggests that the DRG is a rich target for treating chronic pain (12, 13), including via neuromodulatory interventions (14). Stimulation of the somatotopically-organized DRG can result in sub-dermatomal patterns of paresthesia coverage (15), suggesting that recruitment of specific sensory neuron perikarya may allow more precise 'steering' of paresthesias in the body relative to traditional SCS. Given this, DRG-SCS may have some benefits especially in cases of pain distributions in regions that are typically difficult to treat with traditional SCS (focal distal distributions such as groin and foot). The main difference between DRG-SCS and traditional SCS may be in functional characteristics of the parenchyma activated by the leads. Traditional SCS recruits multiple fibers of passage in the dorsal columns and results in action potentials propagating ortho- and antidromically, potentially recruiting multiple dermatomes and structures outside of the dorsal columns, including primary sensory neurons (16). In contrast, DRG-SCS may directly activate the cell bodies of the very neurons that innervate the painful regions. This distinction may give rise to a different mechanism of action and therefore different interventional profiles for the two electrically active implantable technologies. On the other hand, it should be noted that because some dorsal column fibers arise from cell bodies in the DRG, it is possible that SCS and DRG-SCS share some cellular targets and have mechanistic similarities.

This report presents the durability of outcomes in a prospective study to assess the effect of DRG-SCS on pain, quality of life, and mood. It was hypothesized that outcomes, previously reported as positive at 6 months post-implant (17), would continue through 12 months.

MATERIALS AND METHODS

Methods have been described in detail in another recently-published report from this research group (17). Briefly, subjects were recruited with full informed consent at European and Australian sites under local Ethics Committee approval. All subjects were 18 years or older, diagnosed with chronic neuropathic pain (of 60 mm or more on a 100 mm visual analogue scale [VAS]) located in the trunk, sacrum, or lower limbs that was intractable to other conventional treatments, and with stable (30 days) pre-study neurological and medication profiles. Subjects with pain involving cervical segments, worsening pain, some corticosteroid or radiofrequency treatments, cancer, clotting disorders, and active implanted devices were excluded.

All subjects used the Spinal Modulation Axium™ DRG-SCS system, which is a constant voltage device with up to four quadripolar percutaneous leads. The delivery system consists of a flexible lead with a hollow inner lumen, a curved stylet that is inserted into the lumen to provide rigidity and directionality to the lead during implantation, and a sheath into which the lead, with the stylet in place, is loaded.

With the patient under local anesthesia and lightly sedated, the physician accessed the epidural space using a 14-gauge delivery needle, similar to the standard SCS implantation method. Once the delivery needle was in place, the leads were inserted anterogradely through the needle and steered into the neural foramen near the DRG using fluoroscopic guidance. Because the DRG is located between the medial and the lateral aspects of the lumbar pedicle (18), leads were placed such that a pair of contacts straddled the pedicle. Up to four leads could be deployed at up to four DRGs to capture the painful regions, depending on patient feedback regarding paresthesia coverage obtained in the intraoperative programming phase. Once adequate paresthesia was obtained, the stylet was partially removed and the lead advanced in the epidural space to create slack or a loop intended to prevent lead migration (see Figure 12). The sheath, needle and stylet were then completely removed. Permanent leads were anchored to the fascia using tissue anchors, tunneled to the subcutaneous stimulator pocket typically in the upper buttocks or abdomen, and connected. All incisions were sutured followed by appropriate wound care. Post-implantation programming of the permanent DRG-SCS system was based on individualized subject feedback. At home, subjects used a wireless controller to adjust the stimulation within pre-set limits.

Subjects completed baseline assessments and then trialed a temporary stimulator (implanted leads attached to an external stimulator) for up to 30 days. Subjects then received a permanent implanted neurostimulator (INS) if at least 50% pain relief was apparent during the trial period, and outcomes were tracked through 12 months. Subjects provided feedback regarding pain (standard 100-mm VAS [19] and Brief Pain Inventory [BPI]; 20, 21) in general and specific to the back, legs, and feet; quality of life (EQ-5D-3L; 22)[1]; mood (Profile of Mood States [POMS]; 23) and McGill Pain

[1] Australian data [n=10 at baseline and n=7 at 12 months] were not included in the EQ-5D index score calculation as country-specific value sets are not available.

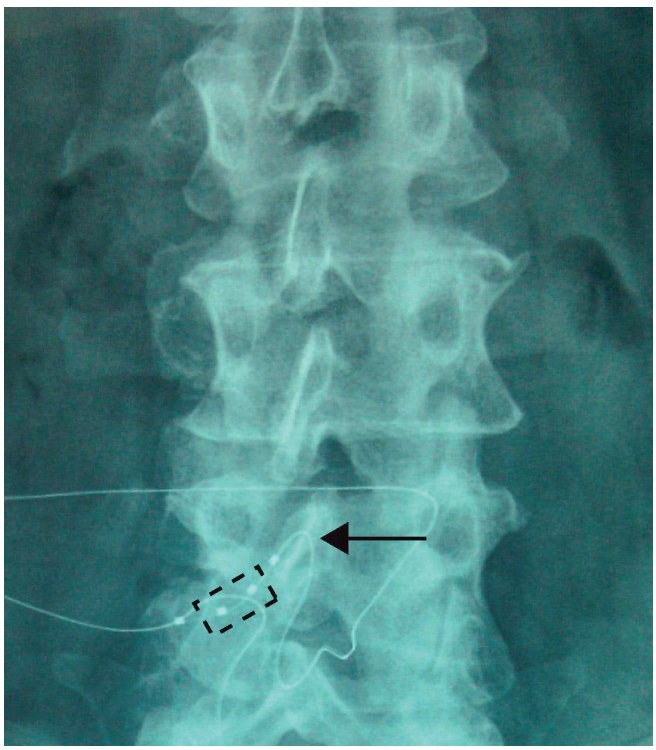


Figure 12. Fluoroscopic image of lead placement.
A representative fluoroscopic image obtained during implantation of the DRG-SCS device, illustrating placement of two pedicle-spanning contacts (boxed) and epidural lead slack (arrow).

Questionnaire (24). Pain and paresthesia distributions were captured on body maps. Subject satisfaction was rated on an 11-point Likert scale where 0 = not satisfied and 10 = very satisfied. Subjects' global impression of change (GIC, a 7-point Likert scale [25]) was also captured as a secondary outcome. Adverse events (AEs) were tracked throughout the study.

Standard data management procedures were employed, and data analysis was completed using SPSS V20 (IBM, Armonk, NY, USA). Data are presented as means ±SEM, with hypothesis testing employing two-tailed paired t-tests with $p<0.05$. Data in the baseline through six months' follow-up time point have been published previously (17), and are presented here to provide context regarding the durability of outcomes.

RESULTS

The DRG-SCS device was trialed in 51 subjects. Prior to this, some subjects had unsuccessfully used pulsed radiofrequency denervation (n=12), SCS (n=9), peripheral nerve stimulation (n=3), and transcutaneous electrical nerve stimulation (n=3). Subjects' demographics and pain etiologies were representative of chronic neuropathic pain populations (26; see Table 7).

Table 7. Subject demographics and etiology of pain.

	All subjects	Subjects with permanent DRG-SCS
Gender, *N*		
Female	27	17
Male	24	15
Age (years), mean ± SD	54.3 ± 13.3	52.5 ± 12.4
Etiology, *N*		
Failed back surgery syndrome	16	8
Complex regional pain syndrome	11	8
Chronic postsurgical pain	9	6
Disc-related pain	4	4
Radicular pain	3	2
Lumbar stenosis	2	2
Other	3	2
Postherpetic neuralgia	3	0

At the end of the trial period, 76.5% of subjects (N=39) had good outcomes, with average pain relief of 74.2% (±16.5), in contrast to the non-responders who reported an average pain relief of 5.0% (±8.7). Permanent INS devices were placed in 32 subjects; diagnoses were CRPS (n=8), FBSS including radicular pain (n=16), peripheral nerve damage (1), pain post-vascular stenting (1) and post-surgical neuropathic pain (n=6).[2] A total of 67 leads were implanted with most subjects receiving two each.

Between baseline and the 12-month follow-up, overall pain improved by 56.3% (±8.4), decreasing from 77.6 mm (±2.1; n=32) at baseline to 33.6 mm (±6.3; n=25; $p<0.005$) at 12 months. Back pain improved by 41.9% (±14.0), decreasing from 74.5 mm (±5.3; n=10) to 39.7 (±9.6; n=9; $p<0.05$). Leg pain improved by 62.4% (±10.8), decreasing from 74.6 mm (±3.3; n=25) to 28.7 (±7.2; n=20; $p<0.005$). Foot pain improved by 79.5% (±12.4), decreasing from 81.4 mm (±2.5; n=13) to 22.0 (±10.7; n=10; $p<0.05$). The proportion of subjects achieving at least 50% of their overall pain and pain located in the back, legs, and feet was 60.0%, 37.5%, 68.4%, 87.5%, respectively; see Figure 13. Pain as assessed by the BPI was also significantly and durably reduced through 12 months of the DRG-SCS intervention, in terms of pain severity and its interference with activities (6.9 ±0.2; n=32 vs. 3.2 ±0.6; n=25 and 6.5 ±0.4; n=32 vs. 3.3 ±0.5; n=25, respectively; ps<0.001; see Figure 14).

Quality of life ratings were better at the 12-month follow-up than at baseline. Subjects' EQ-5D VAS score increased from 47.0 (±3.8; n=32) at baseline to 68.4 (±4.7; n=25; $p<0.005$), a 64.0% (±18.8) improvement. Similarly, the EQ-5D index score increased from 0.298 (±0.238; n=22) at baseline to 0.698 (±0.267; n=18; $p<0.001$), a

[2] Note that the previous report (17) listed 9 subjects with CRPS and 5 with chronic post-surgical pain (CPSP). An error in acronym transposition led to one subject's etiology of pain being mis-labeled in the previous report; this has been corrected here.

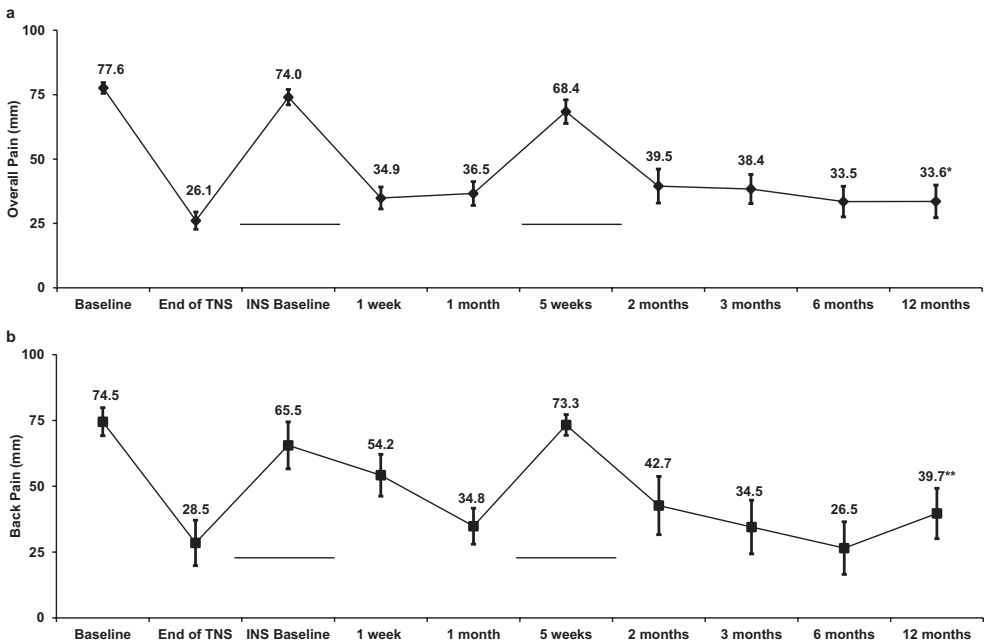


Figure 13 (upper part): Reduction in overall (upper graph) and back (lower graph) pain. DRG-SCS significantly reduced pain through 12 months post-implant. Solid lines represent follow-up time points with stimulation turned off (*p < 0.005, **p < 0.05, and ***p < 0.0005). TNS, trial neurostimulator; INS, implanted neurostimulator.

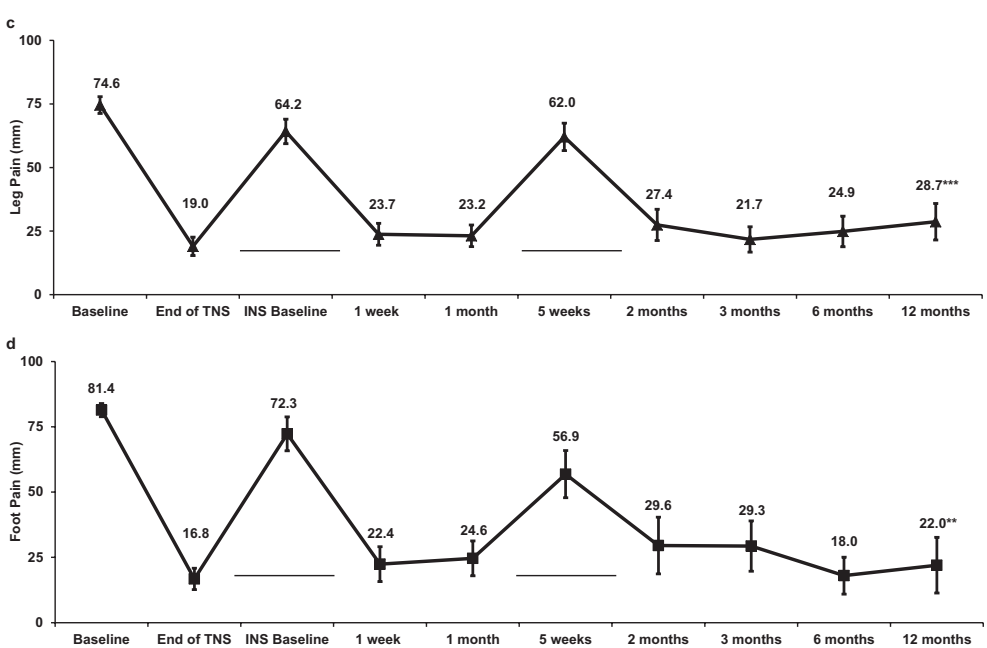


Figure 13 (lower part): Reduction in leg (upper graph) and foot (lower graph) pain. DRG-SCS significantly reduced pain through 12 months post-implant. Solid lines represent follow-up time points with stimulation turned off (*p < 0.005, **p < 0.05, and ***p < 0.0005). TNS, trial neurostimulator; INS, implanted neurostimulator.

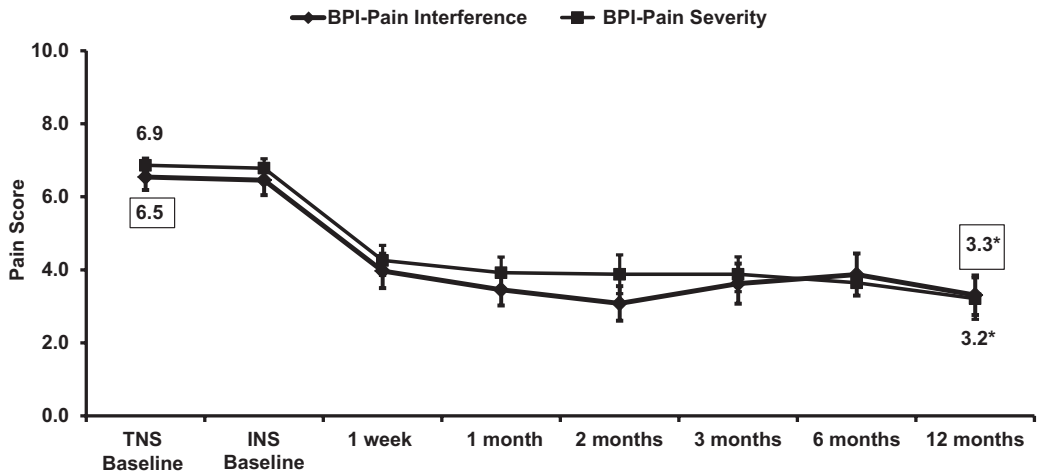


Figure 14. BPI scores.
Pain severity and interference with activity as measured by the Brief Pain Inventory (BPI) was significantly and durably reduced through 12 months of treatment with DRG-SCS. TNS, trial neurostimulator; INS, implanted neurostimulator.

134.2% (±12.2) improvement. In all five EQ-5D subscales, the proportion of clients reporting 'no problems' was larger at 12 months than at baseline. In most domains the change appeared to be because a substantial proportion of subjects with 'some problems' at baseline rated themselves as having 'no problems' at 12 months. For the pain-discomfort subscale, 72% of subjects reported 'a lot of problems' at baseline, but only 4% of subjects remained in this category at 12 months; see Figure 15.

Subjects rated their mood as improved between baseline and 12 months; there was a statistically significant improvement in four out of six domains of the POMS, and the total mood disturbance score decreased from 27.5 (±3.5; n=32) at baseline to 9.4 (±3.9; n=25; $p<0.05$; see Figure 16). Subjects were largely satisfied with DRG-SCS: for the item 'Pain relief provided by stimulation', the mean score was 7.52 (±0.57) with 10 of 25 subjects (40.0%) rated their satisfaction as 8 or higher. For the items 'Therapy in general', and 'Likelihood of undergoing the therapy again', the mean scores were 8.92 (±0.20) and 8.88 (±0.39), respectively. According to global impression of change (GIC) scores, 23 of 25 subjects (92.0%) rated their pain as "a little better", "better" or "much better" at 12 months as compared to before the device was implanted. Lastly, although it was not quantified for statistical comparison, considerable precision and durability of the pain-paresthesia overlap was noted; see Figure 17.

Subjects also completed the 78-item McGill Pain Questionnaire which is divided into 4 classes (sensory, affective, evaluative and miscellaneous) and 20 sub-classes. A weighted pain rating index (PRI) score was calculated based on the choice of descriptor words and their weighted rank value in each sub-class. Extent of pain relief can also be correlated based on the number of words chosen (NWC) to describe the pain. Significant decrease in both weighted PRI and NWC were observed at 12 months (N=21) compared to the baseline ($p<0.0001$, N=32, see Figure 18).

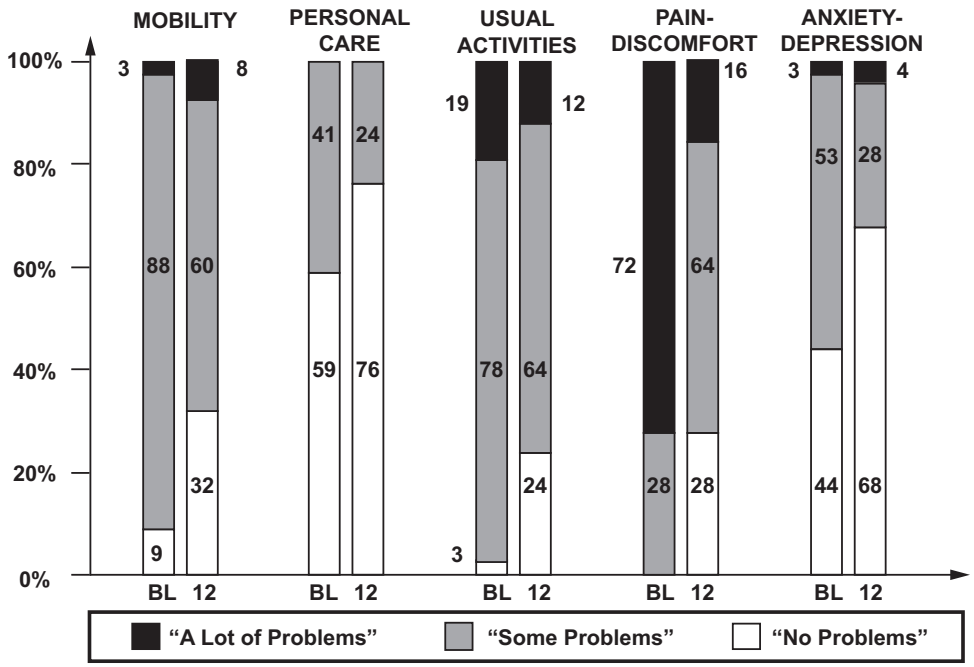


Figure 15. Proportion of subjects reporting problems (a quality of life measure).
The proportion of people reporting problems across EQ-5D subscales declined from baseline (BL) to 12 months, particularly for the pain–discomfort domain.

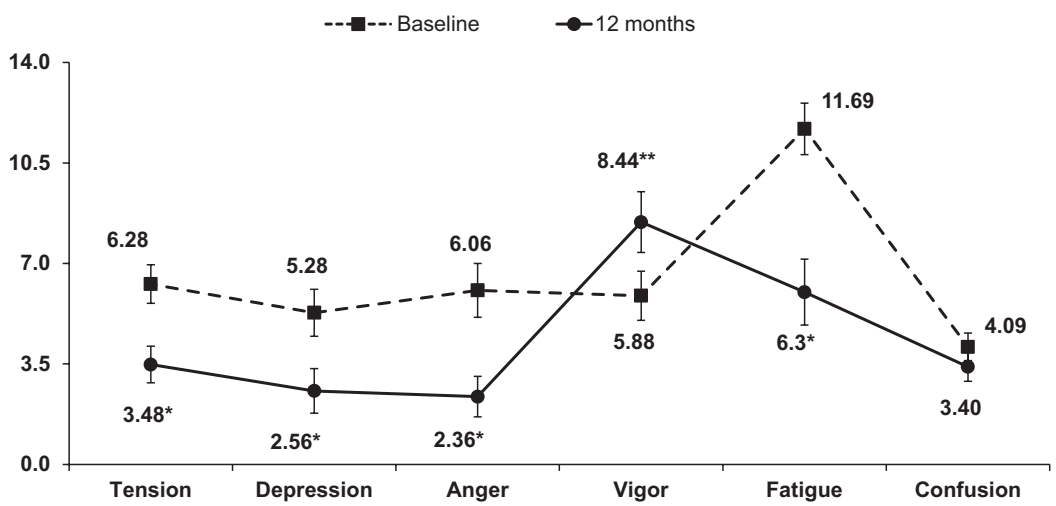


Figure 16. Mood ratings on the POMS.
Mood ratings improved significantly in four out of six domains on the POMS; the total mood disturbance score was also significantly lower after 12 months of DRG-SCS than at baseline. Notice the reversal in vigor and fatigue patterns at 12 months compared to baseline. *p<0.05, **p=0.06.

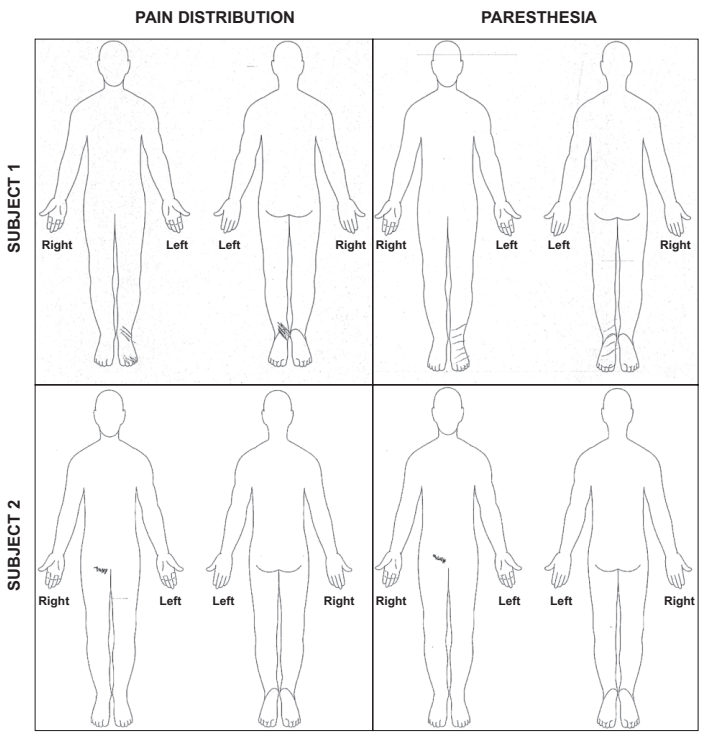


Figure 17. Pain and paresthesia distributions.
Paresthesia distributions precisely and discretely covered painful areas with very little extraneous coverage at 12 months post-implant, as illustrated in two representative subjects. Mapping was completed while subjects were standing.

There were 86 safety events reported across 29 subjects; approximately half were judged by the investigators to be related to the device (see Table 8). The most common AEs/SAEs were temporary motor stimulation (12 events; 14.6%), CSF leak with associated headache (7 events; 8.5%), and infection (7 events; 8.5%). Four lead revisions were completed, due to high impedance (two subjects, procedures at 2 months and 9 months post-implant), possible lead migration (2 months), and lead fracture (6 months). None of the SAEs were device related. One IPG revision was performed. Seven subjects had their devices explanted and were withdrawn from the study; 3 of these subjects had infections, 2 subjects did not comply with study procedures, and 2 subjects (one with post-appendectomy pain and another with neuropathic compartment syndrome) reported lack of efficacy. Two of the explants took place after 2 months, 4 explants took place after the 3-month follow-up, and one explant took place after 6 months.

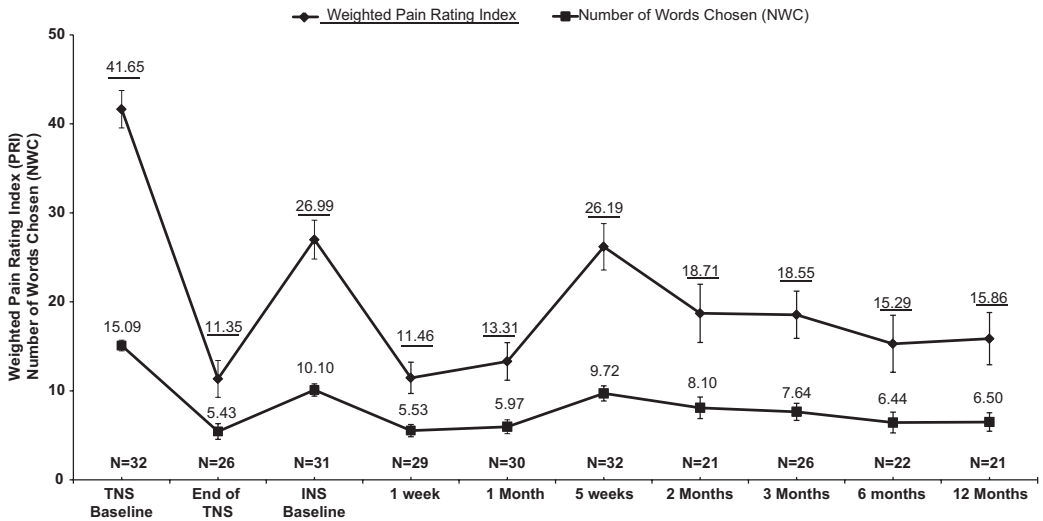


Figure 18. Ratings on the McGill Pain Questionnaire.
Compared with the baseline McGill Pain Questionnaire scores, weighted pain rating index (PRI) scores (underscored data values) and number of words chosen (NWC) decreased significantly at 12 months ($p < 0.0001$). Note the increase in weighted PRI and NWC when the stimulation was turned off at INS baseline and at 5 weeks. TNS, trial neurostimulator; INS, implanted neurostimulator.

Table 8. Numbers and device-relatedness of adverse events.

Treatment phase	Type of event		
	Serious adverse event	Adverse event	All
Trial DRG-SCS (*N* = 51), *N*	3	21	24
Permanent DRG-SCS (*N* = 32), *N*	6	56	62
Total, *N*	9	77	86
Events possibly, probably, or definitely related to device, *N* (%)	3 (37.5%)*	40 (51.9%)	43 (50.0%)

*Device-relatedness information was not available for one event.

DISCUSSION

Initial responder rates in SCS are approximately 80% (27). One-year pain relief outcomes for prospective SCS studies have been reported at 40-50% for radicular pain (28, 29, 30), although smaller samples have reported larger-magnitude pain relief, up to 70% in the leg (31) and 80% in the back (32). Studies have also reported improvements in secondary outcomes such as function, mood and quality of life (28, 29, 33). The results presented in this report are comparable to these benchmarks. Reduction in the SCS-related pain relief over time has been documented in systematic reviews (8, 34). In that context, the one-year maintenance of robust pain relief with DRG-SCS (56.3% relief of overall pain, with 60% of subjects attaining at least 50% pain relief) is promising indeed, though this must be tempered with the acknowledgment that the observational design of this relatively small study may inflate its effect (35). Recent findings with DRG-SCS for lower-limb CRPS, however,

agree that pain relief of more than 50% is durable through at least 12 months (14). A randomized controlled trial comparing outcomes with SCS against those DRG-SCS is needed to definitively evaluate these interventions.

It should be noted, however, that the statistics above were generated by studies across a number of methodologies; those studies employing conservative intent-to-treat designs may minimize the positive outcomes experienced by some individuals. In contrast, this study utilized a simple prospective cohort design in which subjects were treated in accordance with standard clinical practice. Although only two subjects (6.3% of the sample) were withdrawn from the study due to lack of effectiveness with the device, the exclusion of treatment failures from analysis could potentially accentuate positive outcomes. Regardless, high levels of subject satisfaction and favorable impressions of change support the effectiveness of DRG-SCS as a therapy for chronic pain. A relatively high overall incidence of adverse events was noted in this study as compared to that reported in SCS reviews (9, 36, 37). This is likely due to two factors. First, all AEs occurring during the study were reported, regardless of their relationship to the device, procedure, or study in order to provide transparency to clinical outcomes. Second, the two most frequently-occurring AEs in this study, temporary motor stimulation and CSF leak with associated headache, were consequences of the implant procedure and/or intraoperative programming. As clinical experience with this novel device and implant location have increased during the course of this and other clinical trials, implant techniques have been optimized. New refinements such as the implementation of acute needle incision angles for epidural access and avoidance of ventral lead placement are likely to minimize the occurrence of such events in future cases. Rates of biologic complications in this study, such as infection, were more comparable to published rates.

A beneficial feature of DRG-SCS is its precise coverage of discrete regions, and in areas that cannot easily be recruited in traditional SCS (14, 38). Importantly, paresthesia coverage can remain stable through 12 months (39). In follow-up post-market studies, stability of paresthesia and pain relief has been demonstrated over 15 months (38). Combined with the lack of positional effects (that is, differences in paresthesia intensity when standing vs. lying down; 39), DRG-SCS may provide some solutions for common complaints with SCS therapy. This may be due to the recruitment of the distally-extending sensory neurons, which may have different neurophysiological properties than the complex nociceptive and non-nociceptive sensory processing mechanisms of SCS (40).

CONCLUSIONS

Improvements in ratings of pain, mood, and quality of life with DRG–SCS have been demonstrated through 12 months of therapy. Additionally, good agreement in pain-paresthesia overlap and high levels of user satisfaction were noted. Although further study into long-term outcomes with DRG-SCS is needed, particularly to differentiate it from SCS and (potentially) peripheral nerve stimulation, the present study suggests that this intervention may hold some clear benefits.

REFERENCES

1. Jung JH, Ignatius MI, Schulz CF, Ornelas CO. Advances in spinal cord stimulation for treatment of chronic pain. *Curr Phys Med Rehabil Rep*. 2013;1:120-124.
2. Meyerson BA, Linderoth B. Mode of action of spinal cord stimulation in neuropathic pain. *J Pain Symptom Manage*. 2006;31:S6-S12.
3. Lee N, Vasudevan S. Spinal cord stimulation use in patients with failed back surgery syndrome. *Pain Management*. 2012;2(2):135-140.
4. Kumar K, Rizvi S, Bnurs SB. Spinal cord stimulation is effective in management of complex regional pain syndrome I: fact or fiction. *Neurosurgery*. 2011;69:566-580.
5. Epstein LJ, Palmieri M. Managing chronic pain with spinal cord stimulation. *Mount Sinai Journal of Medicine*. 2012;79:123-132.
6. Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician*. 2009;12:379-397.
7. Atkinson L, Sundaraj SR, Brooker C, et al. Recommendations for patient selection in spinal cord stimulation. *J Clin Neurosci*. 2011;18:1295-1302.
8. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain*. 2004;108:137-147.
9. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg*. 2004;100(3):254-267.
10. Sears NC, Machado AG, Nagel SJ, et al. Long-term outcomes of spinal cord stimulation with paddle leads in the treatment of complex regional pain syndrome and failed back surgery syndrome. *Neuromodulation*. 2011;14(4):213-8.
11. North RB, Ewend MG, Lawton MT, Piantadosi S. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. *Pain*. 1991;44:119-130.
12. Sapunar D, Kostic S, Banozic A, Puljak L. Dorsal root ganglion - a potential new therapeutic target for neuropathic pain. *J Pain Res*. 2012;5:31-38.
13. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Medicine*. 2013;14(10):1477-1496.
14. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Practice*. 2015;15(3);208-16.
15. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation*. 2013;16(1):67-72.
16. Smits H, van Kleef M, Holsheimer J, Joosten EAJ. Experimental spinal cord stimulation and neuropathic pain: Mechanism of action, technical aspects, and effectiveness. *Pain Practice*. 2013;13(2):154-68.
17. Liem L, Russo M, Huygen FJPM, et al. A multicenter, prospective trial to assess the safety and performance of the Spinal Modulation dorsal root ganglia neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16(5):471-482.
18. Hasegawa T, Yoshihiro M, Ryo W, An HS. Morphometric analysis of the lumbosacral nerve roots and dorsal root ganglia by magnetic resonance imaging. *Spine*. 1996;21(9):1005-1009.
19. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*. 1983;17(1):45-56.
20. Atkinson TM, Mendoza TR, Sit L, et al. The Brief Pain Inventory and its 'pain at its worst in the last 24 hours' item: Clinical trial considerations. *Pain Medicine*. 2010;11(3):337-346.
21. Tan G, Jensen MP, Thornby JI, Shanti BF. Validation of the Brief Pain Inventory for chronic nonmalignant pain. *J Pain*. 2004;5(2):133-137.
22. The EuroQol Group. EuroQol - A new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
23. Curran SL, Andrykowski MA, Studts JL. Short form of the Profile of Mood States (POMS-SF): psychometric information. *Psychol Assess*. 1995;7(1):80-83.
24. Melzack R, Katz J, Jeans ME. The role of compensation in chronic pain: analysis using a new method of scoring the McGill Pain Questionnaire. *Pain*. 1985;23(2):101-12.
25. Guy W. *Early Clinical Drug Evaluation Unit (ECDEU) assessment manual for psychopharmacology. Revised. NIMH publication*

DHEW publNO (Adm) 76-338. Bethesda MD: National Institute of Mental Health; 1976.

26. Bouhassira D, Lanteri-Minet M, Attal N, Laurent B. Prevalence of chronic pain with neuropathic characteristics in the general population. *Pain*. 2008;136(3):380-7.
27. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58:481-496.
28. Burchiel KJ, Anderson VC, Brown FD, et al. Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain. *Spine*. 1996;21(23):2786-2794.
29. Kemler MA, De Vet HC, Barendse GA, Van Den Wildenberg FA, Van Kleef M. Effect of spinal cord stimulation for chronic complex regional pain syndrome Type I: five-year final follow-up of patients in a randomized controlled trial. *J Neurosurg*. 2008;108(2):292-298.
30. Kumar K, Taylor RS, Jacques L, et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome. *Pain*. 2007;132(1-2):179-188.
31. Oakley JC, Krames ES, Prager JP, et al. A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study. *Neuromodulation*. 2007;10(3):262-278.
32. Rigoard P, Delmotte A, D'Houtaud S, et al. Back pain: a real target for spinal cord stimulation? *Neurosurgery*. 2012;70:574-585.
33. Eldabe S, Kumar K, Buchser E, Taylor RS. An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management.. *Neuromodulation*. 2010;13(3):201-9.
34. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess*. 2009;13(17):1-154.
35. Taylor RS, Taylor RJ, Van Buyten JP, Buchser E, North R, Bayliss S. The cost effectiveness of spinal cord stimulation in the treatment of pain: a systematic review of the literature. *Journal of Pain and Symptom Management*. 2004;27:370-378.
36. Kumar K, Wilson JR, Taylor RS, Gupta S. Complications of spinal cord stimulation, suggestions to improve outcome, and financial impact. *J Neurosurg Spine*. 2006;5:191-203.
37. Kumar K, Buchser E, Linderoth B, Meglio M, Van Buyten JP. Avoiding complications from spinal cord stimulation: practical recommendations from an international panel of experts. *Neuromodulation*. 2007;10(1):24-33.
38. Schu S, Gulve A, Eldabe S, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain-- a retrospective review. *Pain Practice*. 2015;15(4):293-9.
39. Kramer J, Liem L, Russo M, Huygen F, Smet I, Van Buyten JP. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. *Neuromodulation*. 2015;18(1):50-7.
40. de Andrade DC, Bendib B, Hattou M, Keravel Y, Nguyen JP, Lefaucheur JP. Neurophysiological assessment of spinal cord stimulation in failed back surgery syndrome. *Pain*. 2010;150(3):485-491.

4

LACK OF BODY POSITIONAL EFFECTS ON PARESTHESIAS WHEN STIMULATING THE DORSAL ROOT GANGLION IN THE TREATMENT OF CHRONIC PAIN

Modified from:
Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain
Jeffery Kramer, Liong Liem, Marc Russo, Iris Smet, Jean-Pierre Van Buyten, Frank Huygen
Neuromodulation 2015;18:50-57

ABSTRACT

One prominent side effect from neurostimulation techniques, and in particular spinal cord stimulation (SCS), is the change in intensity of stimulation when moving from an upright (vertical) to a recumbent or supine (horizontal) position, and vice versa. It is well understood that the effects of gravity combined with highly conductive cerebrospinal fluid provides the mechanism by which changes in body position can alter the intensity of stimulation-induced paresthesias. While these effects are well established for leads that are placed within the more medial aspects of the spinal canal, little is known about these potential effects in leads placed in the lateral epidural space and in particular within the neural foramina near the dorsal root ganglia (DRG). Therefore, we prospectively validated a newly-developed paresthesia intensity rating scale and compared perceived paresthesia intensities when subjects assumed upright versus supine bodily positions during neuromodulation of the DRG. We found that, on average, a strong relation between stimulation intensity (pulse amplitude) and perceived paresthesia intensity existed (R^2=0.83). No significant differences in paresthesia intensities were reported within subjects when moving from an upright (4.5 ±0.14) to supine position 4.5 (±0.12) ($p>0.05$). This effect persisted through 12 months following implant. In conclusion, these results demonstrate that neuromodulation of the DRG produces paresthesias that remain consistent across body positions, suggesting that this paradigm may be less susceptible to positional effects than dorsal column stimulation.

INTRODUCTION

Spinal cord stimulation (SCS) is a useful therapeutic tool and has provided pain relief availability to thousands of patients with challenging chronic conditions (1, 2). Although methodologically diverse, the clinical literature spans three decades and is largely positive regarding the effectiveness of SCS for failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS), and a number of other neuropathic pain conditions (3, 4, 5).

A well-documented clinical issue with SCS, however, is position-related changes in the perception of neurostimulation (6). When patients change their posture from upright to supine or prone (and vice-versa), they can feel an uncomfortable increase in stimulation or a loss of paresthesia. This is because a patient's individualized stimulation program that provides optimal paresthesia coverage and pain relief when, for instance, standing may be uncomfortably intense or not intense enough when sitting or lying down (7, 8). Impedance does not change with posture, but the energy requirements to achieve therapeutic paresthesias do (9). Position-related changes in stimulation are primarily due to changes in the thickness of the cerebrospinal fluid (CSF) layer interposing the spinal cord and the epidurally-placed leads (7). CSF layer thickness changes because the spinal cord moves inside the spinal canal, and relative to the SCS leads, due to the biomechanical forces associated with bending of the spine or with the gravitational effects inherent with particular postures (10, 11).

The patient or clinician can partially mitigate these issues in a number of ways. Some patients create multiple stimulation programs within their device to address variations in posture-related paresthesia thresholds—one for standing, others for sitting or sleeping (7, 12). Patients can then switch to the appropriate program in anticipation of, or just after, changing their position. Patients may also address positional changes by maintaining the same program throughout the day but adjusting its pulse amplitude higher or lower (8). These responses to positional stimulation are technology-based and necessitate the patient having their SCS patient programmer with them at all times. These responses also assume that patients are willing and able to control the device with their patient programmer, which not all patients may be (8, 13). It has been noted that better outcomes are achieved by those patients who have a thorough understanding of their device's function and can capably control it through the patient programmer interface (8); it would then follow that patients who are less comfortable interacting with the technology may be at a clinical disadvantage.

Patients who choose not to use their patient programmer frequently, who do not take a nuanced approach to using their patient programmer, or who find themselves without it, may implement behavioral compensatory strategies such as limiting the number of times they change position during the day or by maintaining a consistently low amplitude that will not result in unpleasant perturbations with changes in posture (but also provide sub-optimal pain relief) (8). For some patients, the frequent interaction necessary for maintenance of optimal comfort and therapy may be inconvenient and impact negatively on their satisfaction with SCS therapy (13, 14, 15, 16). At worst, patients may conclude that SCS is ineffective and discontinue its use. In some patients,

the unpleasantness of positional changes in stimulation can be significant enough to necessitate explant of the device (17). Given the costs associated with SCS devices, implantation, and maintenance (2, 18), the pain, stress, and risks associated with surgical implantation, and its potential for excellent pain relief with optimal stimulation (19), it is unfortunate that the need for constant adjustments based on patients' activities could limit using the device to its full potential.

An analogous issue can be found in diabetes, another chronic condition that requires frequent, daily maintenance from the patient. Although many patients adhere to a schedule of testing their blood sugar and self-administering insulin, some do not, presumably due to the disruption of daily life that these activities represent. These patients may develop later complications of poorly-controlled blood sugar levels. Continuous glucose monitoring and implantable, automatic insulin pumps that assure compliance with virtually no daily maintenance have been developed in response. In addition to improved clinical outcomes, these options are associated with higher patient satisfaction (20, 21) and health-related quality of life including physical and psychosocial domains (22, 23). Based on these findings, it may also be that a technological solution could be an appropriate solution to address the problem of positional stimulation in SCS.

To address patient preference for SCS programs that can be adjusted based on their activities to optimize paresthesia coverage and pain relief (24), automatic position-responsive adjustments to stimulation amplitude have been tested in one SCS device (14, 15). Although results were largely positive regarding pain relief, patient preference, and a general questionnaire regarding outcomes, subjects reported just as many uncomfortable stimulation events with the automatic adjustment algorithm turned on as turned off (15, 25, 26). Additionally, although the automatic adjustment algorithm did reduce the number of programming button-presses per day, patients still made an average of 21 amplitude adjustments per day, which is not inconsiderable (15). This suggests that fairly frequent level of interaction with the device is required even with position sensors (26), and that the goal of truly automatic adjustment for position remains elusive.

In addition to the solutions described above, another approach may be to develop a device or implantation strategy that is resistant to positional changes altogether. Neuromodulation of the dorsal root ganglion (DRG) for pain relief is one such option. DRG neuromodulation has been demonstrated to be safe and effective (27, 28, 29, 30), even for patients who had previously failed SCS treatment. Therapeutic thresholds for DRG neuromodulation are far below motor thresholds and can achieve good paresthesia coverage and pain relief without lead migration or sensory changes (31).

DRG neuromodulation involves epidural neural structures that are inside immobile bony intravertebral structures, and thus much less susceptible to biomechanical perturbations than the dorsal columns of the spinal cord. It is possible that this method of stimulation may show minimal changes in paresthesia intensities or location due to changes in position, obviating the need for volitional patient interaction with the device or complicated technological solutions altogether. The aims of this study were to 1) validate a new tool for quantifying the intensity of paresthesia and 2) compare the paresthesia intensities and distributions generated by electrical neuromodulation of the DRG between two body positions over time.

MATERIALS AND METHODS

This study was conducted as a sub-study as part of a larger investigation; subjects were also enrolled in an international clinical trial involving DRG neuromodulation for the treatment of chronic pain. The methods of enrollment, inclusion and exclusion criteria, method of implantation, primary and secondary effectiveness outcomes and results of that study are extensively described and discussed in an earlier report (27). All the positioning testing described here took place in the participating clinics under medical supervision, after approval of the local medical ethical review committees, and with the written informed consent of the enrolled patients.

System Testing and Implantation

Under monitored anesthesia care, subjects were placed prone on the procedure table. Epidural access was obtained utilizing the loss of resistance technique, and leads were percutaneously placed under direct fluoroscopic guidance. Leads were steered to the appropriate spinal levels and placed in the lateral recess within the neural foramen. Following lead placement intraoperative programming was completed to steer therapy to the appropriate anatomical regions. Subjects trialed the DRG neuromodulation system for 3-30 days, after which if subjects achieved 50% pain relief and they wanted the implanted system they received the fully implantable device.

Validation Testing of the Paresthesia Intensity Scale

A small group of subjects participated in validation testing for a new paresthesia intensity scale developed for this study: an 11-point numerical rating scale where 0= no feeling and 10= very intense paresthesia. Validation testing of the scale was carried out with the subject in a sitting position. Within 4 weeks of implantation of the permanent stimulator system, each subject's preferred settings of active contacts and polarities were recorded and their effective range of pulse amplitudes (between perception and discomfort thresholds) were identified according to standard practice. After this, stimulation was turned off and then re-applied at randomly selected stimulation intensities within each subject's effective range. At all stimulation intensities, pulse width and stimulation frequency were held constant. Subjects, who were blinded to the intensity level, were asked to rate the perceived paresthesia intensity using the scale described above. Between 5-10 data points were gathered per subject.

Paresthesia Testing Between Two Body Positions

Upright and supine postures were selected for testing in all subjects because these were considered to be the most broadly salient to daily living and were expected to produce maximum positional effects in paresthesia intensities, if any such effects existed. Prior to each testing session, subjects stood upright and self-adjusted their stimulation to their preferred program and a comfortable intensity. These settings (pulse width, stimulation frequency, and stimulation intensity) were held

constant throughout the testing. While standing, subjects drew the location of their perceived paresthesias on a body map and rated their paresthesia intensity on the scale described above. The stimulation was then turned off briefly while the subject assumed a supine position on an examining table. Stimulation was then resumed at the same settings, and subjects repeated the paresthesia mapping and intensity ratings while supine. Testing was completed at nine time points: at trial stimulation programming, end of trial stimulation, post-implant programming, 1 week, 1 month, 2 months, 3 months, 6 months and 12 months post-implant. In order to minimize the duration of the repeated testing sessions, perception and maximum tolerable thresholds were not captured.

Data Analysis

Using SPSS V20 (IBM, New York), descriptive statistics including means and standard errors of the mean (SEM) were generated for all variables. For the paresthesia intensity scale validation testing, the associations between pulse amplitudes and paresthesia intensity ratings were determined on an intra-subject basis due to the heterogeneity of preferred stimulation amplitudes across individuals. Across subjects, a grand mean of the linear regression coefficients of variance was calculated. For paresthesia intensity ratings across body positions and over time, comparisons (post-implant vs. 12 months) used two-tailed paired t-tests. Significance levels were set at $p<0.05$ with Bonferroni correction for multiple tests. The locations of perceived paresthesias were assessed through qualitative examination of subjects' pain map drawings.

RESULTS

Validation Testing of the Paresthesia Intensity Scale

Subjects were 6 men and 4 women, with an average age of 55.0 (±12.9) years. Subjects were implanted with DRG neurostimulators for FBSS (n=4), CRPS (n=1), peripheral neuropathy (n=1) and lumbosacral radicular pain (n=4). A representative fluoroscopic image of leads placed at L4 and L5 DRGs is shown (see Figure 19). During testing, pulse widths and stimulation frequencies were held constant at the subjects' preferred settings (pulse width: 450 μs ± 118, range 300-720; stimulation frequency: 37 Hz ± 11, range 22-60).

The average threshold for perception of paresthesia was 1159 μA (± 907, range 350-2900). The average threshold for the maximum tolerable paresthesia sensation was 1521 μA (± 939, range 475-3200). There was a strong relationship between perception and maximum tolerable thresholds across subjects (R^2=0.92). The difference between the maximum tolerable and perception thresholds for each subject formed the effective range of stimulation amplitudes for testing. Subjects' perceived intensity of paresthesias were strongly positively associated with stimulation intensities; intra-subject coefficients of variance ranged from 0.51 to 0.98 (n=10; see Figure 20). Across 10 subjects, there was a strong positive association between stimulation amplitude and perceived paresthesia intensity (grand mean R^2=0.83).

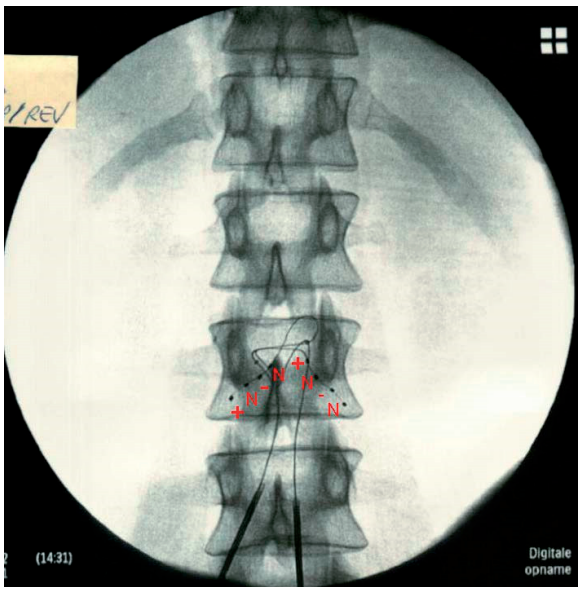


Figure 19. Representative fluoroscopy image.
This image is from one of the subjects in the study with polarities of the contacts identified. C- Cathode, A- Anode and N-No connection (high impedance).

Paresthesia Testing Between Two Body Positions

The 32 subjects described previously (27) participated in paresthesia testing. At each of the testing sessions, the subjects selected their preferred pulse width, stimulation frequency, and stimulation amplitude, and these were held constant throughout the sessions.

When standing, the average paresthesia intensity rating across all subjects and time points was 4.5 (±0.14). When supine, the value was 4.5 (±0.12); there was no statistically significant difference ($p>0.05$). At each of the nine time points, paresthesia intensity ratings varied between 4.0 and 5.0 for both body positions. Overall, ratings did not differ significantly between body positions or across time (*p*s>0.05; see Figure 21); the grand means also did not differ (see Figure 22).

On body maps, subjects consistently reported paresthesia coverage in the legs, back, feet, and groin. Qualitatively, subjects produced consistent drawings for each body position and over time (see Figure 23 and Figure 24). In exceptional cases, small changes in paresthesia location were noted but corrected either through lead revision or reprogramming.

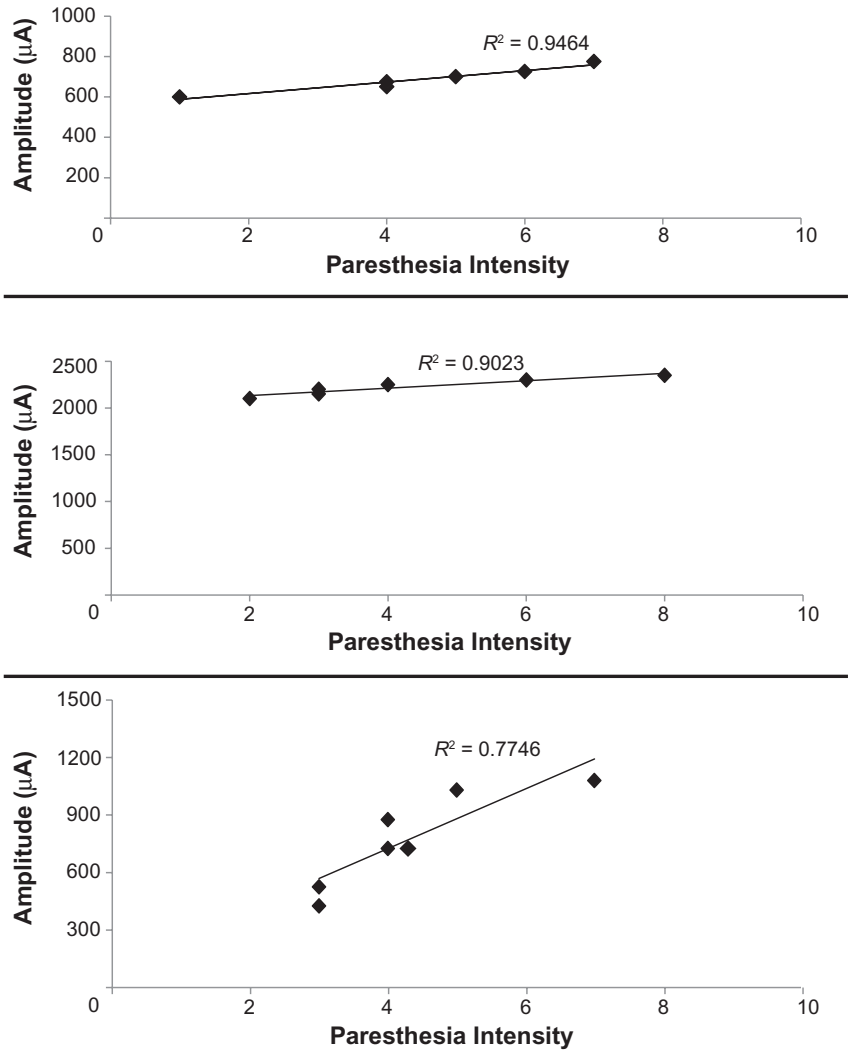


Figure 20. Stimulation amplitude and perception of paresthesia intensity. Stimulation amplitude is plotted against subject reported paresthesia intensity for three of the ten subjects. Paresthesia intensity perceived by subjects varied linearly with the stimulation amplitude with an average coefficient of variance of 0.83.

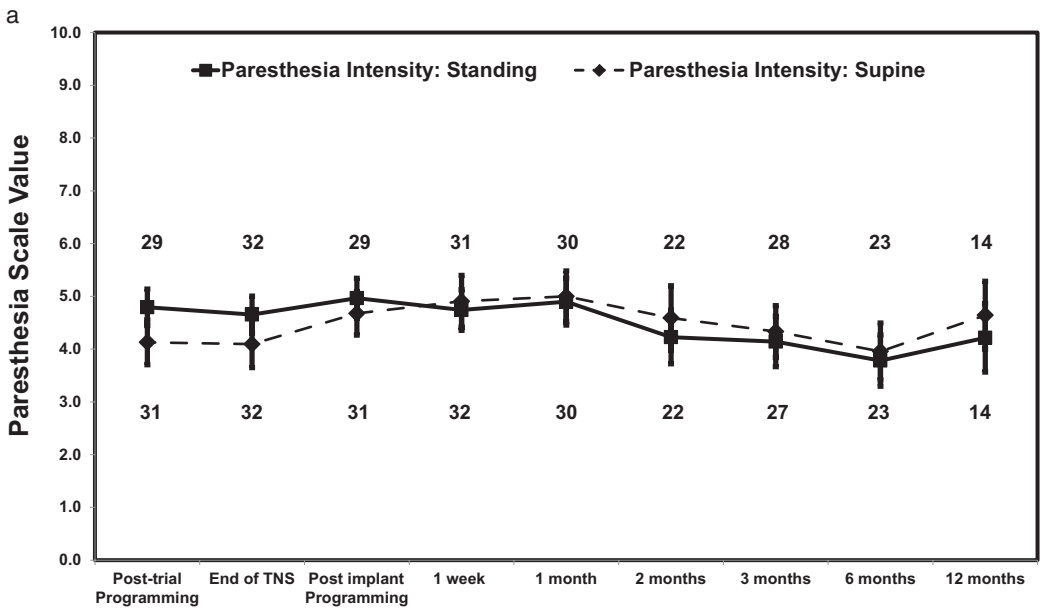


Figure 21. Paresthesia intensities across body postures and time.
Paresthesia intensity at different follow-up time points did not vary significantly either with body position or across time (ps>0.05; two time points tested per manuscript text). Sample sizes for each time point for upright and supine positions are presented above and below the line graph, respectively.

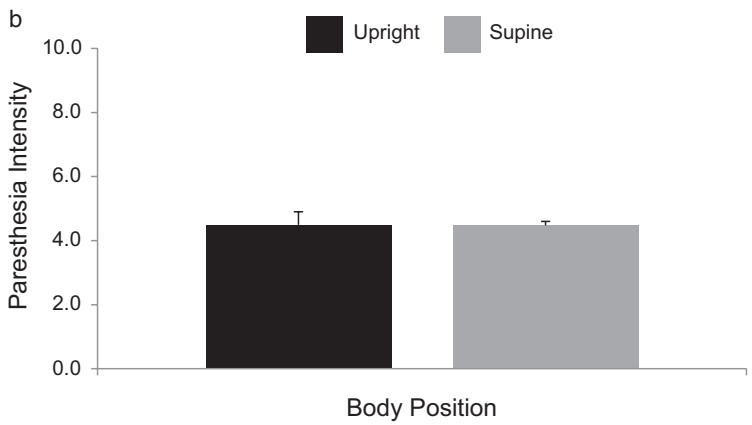


Figure 22. Grand means of paresthesia intensities across body postures.
The grand mean of the paresthesia intensity at the 9 different follow-up time points was not significantly different for the two body positions (p>0.05).

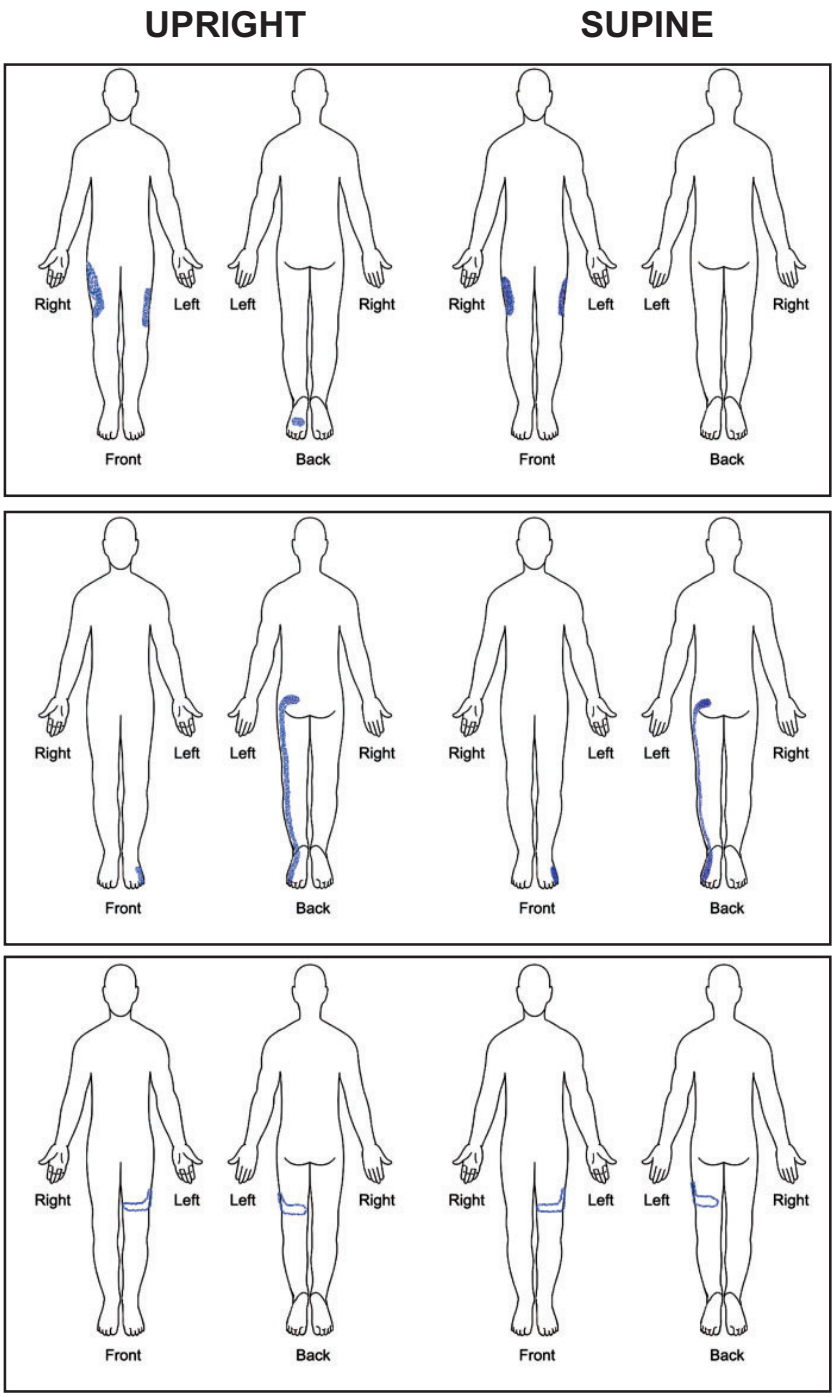


Figure 23. Paresthesia locations across different body postures.
Anatomical representations of paresthesia locations for three representative subjects when in the upright and supine positions. Note the similar paresthesia distributions in the examples shown. Subjects verbally reported similar paresthesia distributions.

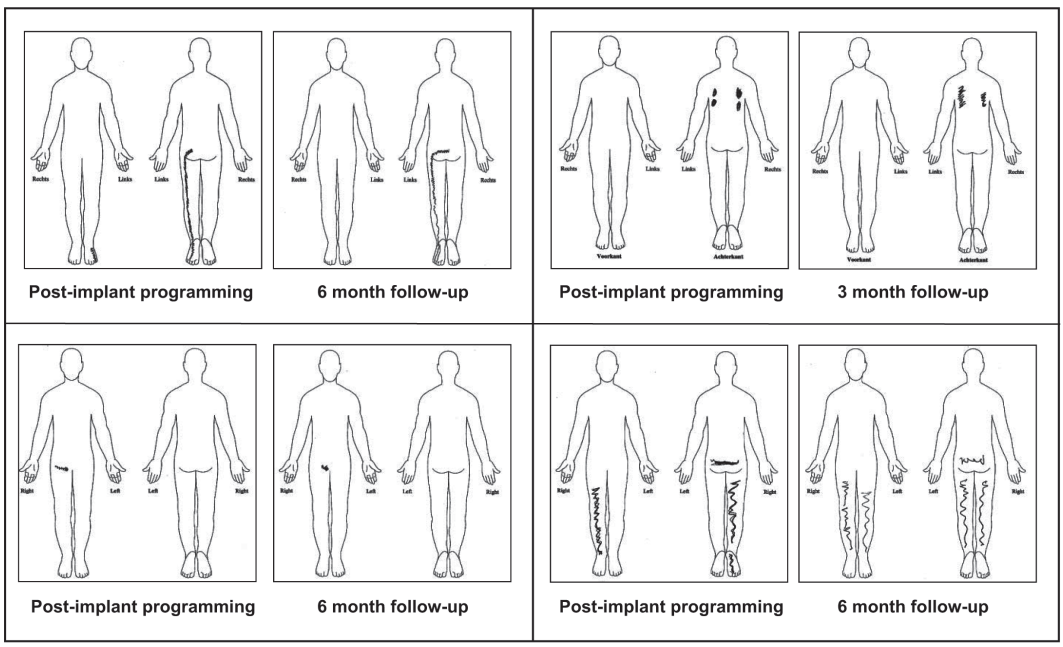


Figure 24. Paresthesia locations over time.
Anatomical distributions of paresthesias for four representative subjects over time. Apart from paresthesia intensities remaining constant between body positions over time, the relative distributions of paresthesias also remained consistent. *Note that the last subject (lower right quadrant) had additional leads turned on to capture the left leg within 6 months of implantation – thus the additional paresthesia markings in the left leg at 6 months).

DISCUSSION

Subjects were a representative sample of both the larger study from which this sub-study was recruited and of DRG neuromodulation patients in general. Subjects first tested an 11-point paresthesia intensity rating scale; face validity of this new tool had been established through professional consensus and its functional similarity with other numeric rating scales in common use in pain management (32). A strong and consistent relationship was found between blinded presentations of randomized stimulation amplitudes and perceived paresthesia intensity ratings, establishing the internal validity of this instrument. It is likely that this relationship would hold true across other programming parameters. Thus, this paresthesia intensity rating scale appears to be a useful instrument that can be adopted for clinical use across neuromodulatory interventions.

During validation testing, a great deal of heterogeneity between subjects was noted in the programming settings, the perception- and maximum tolerable paresthesia thresholds, and the effective range of stimulation amplitudes. The wide range of stimulation parameters available in modern SCS devices suggests that heterogeneity in the functional responses to neurostimulation is accepted as a matter of course. DRG neuromodulation is also very much an individualized intervention, and the individual

differences of the subjects in this study underscore the need for nuanced and knowledgeable programming of the device. As a point of clarification, the thresholds are reported here on a per-lead basis; per-contact thresholds cannot be captured due to the bipolar nature of the programming.

Subjects reported paresthesia intensity ratings under constant programming settings in two common body positions, upright and supine. Scores were similar for both positions, and varied minimally over the 12-month follow-up period. Paresthesia locations were likewise stable across body positions and time. In normal clinical use, this lack of perceived differences in position-dependent paresthesias may mean that patients would not need to manually adjust their stimulation program when moving from one position to another.

Explanations for the positional and temporal stability of paresthesia with DRG neuromodulation, in contrast to the commonly-experienced positional effects in SCS, may involve the anatomy of the target structures. With SCS, positional effects are likely due to a combination of the distance between the electrodes and the dorsal columns as well as the overall thickness of the CSF layer at the implanted spinal level. The distance between the lead(s) and the dorsal columns can change when the patient moves, due to small movements of either the spinal cord or the lead (or both) as a result of mechanical forces and bending, or the effects of gravity (10, 33). Thus, the thickness of the CSF layer between the leads and the targets varies with body position (34). This determines the effective stimulation intensity received by the spinal cord (35), and impacts paresthesia thresholds (36). Because the energy delivered to neural tissues is proportionate to the square of the distance between the lead and target, even relatively small changes in distance can equate to proportionately large increases in energy delivery and, thus, paresthesia intensity.

When the leads are relatively far from the dorsal columns (for instance, when upright), patients perceive that the stimulation decreases or goes away, although it should be noted that perceptible paresthesia may not be necessary for pain relief (37). This can occur more frequently with lead placement in the mid-thoracic region, where the CSF is naturally thicker than it is at the cervical and thoracic enlargements (10, 36, 38). With the increased distance between the lead and the target, the stimulation no longer penetrates as deeply into the dorsal columns, and some of the relevant fibers can no longer be recruited (39). The patient is likely to respond to this change in paresthesia by increasing the intensity of stimulation so as to re-activate the necessary dorsal column fibers (10, 40). This can lead to field potentials increasing in area and spreading across the entire dorsal extra-neural space and preferentially recruiting dorsal roots while not achieving adequate penetration into the dorsal columns of the spinal cord (41). Power consumption is predictably high with thick CSF layers (11), which may necessitate frequent recharging or replacement of batteries.

When the leads are relatively close to the spinal cord (for instance, when lying supine), patients often perceive that the paresthesias are more intense. This is because shallow CSF thicknesses result in lower thresholds and activation of more, and deeper, dorsal column fibers (39). It may be possible to recruit medial fibers that serve axial regions such as the low back with a shallow CSF thickness, but a possible side effect

is that dorsal root activation above discomfort thresholds may also occur. This is due to the lateral spread of the electric field and the lower activation thresholds of dorsal roots relative to dorsal column fibers based on their conformation and diameter (38, 41). Dorsal root activation during SCS can induce paresthesias at low levels of stimulation, or unpleasant motor recruitment at high levels (42). Unwanted dorsal root activation with SCS can be prevented through careful lead placement (43, 44) and/or programming (45), although patients typically respond to uncomfortable stimulation by turning their stimulation amplitude down.

In addition to the changes in stimulation that accompany changes in body position, SCS patients may also experience lead migration (46, 17) and changes in impedance due to fibrosis around the leads (47, 48) or to being surrounded by epidural fat, thus dissipating energy before penetration of the dura mater (49). This may result in the lack of paresthesias in the desired location and/or intensity for their activity level or body position. The patient may perceive less effectiveness and satisfaction (14).

DRG stimulation may be less susceptible to all of these mechanisms of positional effects because of DRG anatomy. Because a very thin layer of CSF surrounds the DRG (50), the distance between the leads and the neural target is quite small. Clinically this may result in the achievement of highly specific paresthesia locations, such as the feet. DRGs are small structures and relatively physically fixed within bony intravertebral structures (51, 52) so they are presumably more immobile during a patient's changes in position than the spinal cord. Leads may move slightly relative to the DRG during patient movements, but with the use of lead anchors and strain relief loops (53, 54, 55) this movement is likely minimal and the patterns of stimulation are likely to remain constant across different positions and over time.

The data and conclusions in this report should be considered against some limitations that may contribute to hypothesis generation for future work that expands upon these findings. One limitation is that the paresthesia intensity scale validation results were based on a ten-subject sample and may have low statistical power. Future research with larger samples will produce more robust results; in fact, a large study employing the paresthesia intensity scale as a key endpoint is currently in preparation. The paresthesia intensity testing across body positions used a larger sample than the validation testing; however, the negative findings have some risk of being a statistical type-II error, in which low statistical power limits the ability to detect a difference between conditions.

Only two static body positions were tested in this study. Because it is possible that DRG neuromodulation may be susceptible to positional effects under the mechanical forces induced by other postures, future work may benefit from including a greater variety of positions, such as sitting, lateral bending, and twisting the trunk. Testing during dynamic motions may reveal additional information about positional effects with DRG neuromodulation, since SCS patients report that positional effects tend to be noticed with certain movements, such as moving from a standing to sitting position, or reaching and stretching (8).

This study focused on the perception of paresthesia intensity, not pain. The effectiveness of DRG neuromodulation for pain has been reported elsewhere (27), and therefore a broad inference can be drawn that there is a relationship between stable

paresthesias and stable pain relief over time. However, it would be of considerable clinical interest to explicitly pair pain and paresthesia assessments in a future study.

Validation testing for the paresthesia intensity scale involved capturing the perception and maximum tolerable paresthesia thresholds. Threshold assessments were not completed during the positional testing, however, in order to not over-burden the subjects. Comparisons of threshold levels during different body positions, and over time, could reveal important information about the function and perception of DRG neuromodulation. For example, evidence using SCS suggests that thresholds vary between different body positions are linearly related (34). The impact of impedance changes due to fibrotic encapsulation on paresthesia perceptions and pain relief is not yet known. Confirmatory studies would require this information.

CONCLUSIONS

This report describes a neurostimulation system that may be largely impervious to the perceived effects of changes in position/posture because most of the causes of this phenomenon in SCS either do not exist or are largely mitigated with DRG neuromodulation. Neuromodulation of the DRG has been shown to produce paresthesias that are minimally susceptible to the biomechanical perturbations associated with different body positions in SCS. Paresthesia intensities and coverage locations remain consistent when standing vs. supine, as well as over time (up to 12 months). This is likely due to the different anatomical structures and neurophysiological pathways associated with DRG neuromodulation as compared with stimulation of the dorsal columns of the spinal cord. DRG neuromodulation is a promising step toward achieving consistently effective pain relief independent of body position. This report provides some evidence for these hypotheses; initial findings are positive although further research is necessary.

REFERENCES

1. Deer TR. The role of neuromodulation by spinal cord stimulation in chronic pain syndromes: current concepts. *Techniques in Regional Anesthesia and Pain Management*. 1998;2(3):161-167.
2. Stojanovic MP, Abdi S. Spinal cord stimulation. *Pain Physician*. 2002;5(2):156-166.
3. Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. *Pain Physician*. 2009;12:379-397.
4. Guerts JW, Smits H, Kemler MA, Brunner F, Kessels AG, van Kleef M. Spinal cord stimulation for complex regional pain syndrome type I: a prospective cohort study with long-term follow-up. *Neuromodulation*. 2013;16(6):523-9.
5. Mekhail NA, Mathews M, Nageeb F, Guiguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. *Pain Practice*. 2010;11(2):148-153.
6. North RB. Neural interface devices: spinal cord stimulation technology. *Proceedings of the IEEE*. 2008;96(7):1108-1119.
7. Cameron T, Alo KM. Effects of posture on stimulation parameters in spinal cord stimulation. *Neuromodulation*. 1998;1(4):177-183.
8. Ross E, Abejon D. Improving patient experience with spinal cord stimulation: implications of position-related changes in neurostimulation. *Neuromodulation*. 2011;e-pub ahead of print:DOI: 10.1111/j.1525-1403.2011.00407.x.
9. Abejon D, Feler CA. Is impedance a parameter to be taken into account in spinal cord stimulation? *Pain Physician*. 2007;10:533-540.
10. He J, Barolat G, Holsheimer J, Struijk JJ. Perception threshold and electrode position for spinal cord stimulation. *Pain*. 1994;59:55-63.
11. Holsheimer J, Khan YN, Raza SS, Khan E. Effects of electrode positioning on perception threshold and paresthesia coverage in spinal cord stimulation. *Neuromodulation*. 2007;10(1):34-41.
12. Henderson JM, Levy RM, Bedder MD, et al. NANS training requirements for spinal cord stimulation devices: selection, implantation, and follow-up. *Neuromodulation*. 2009;12(3):171-174.
13. North R, Shipley J. Practice parameters for the use of spinal cord stimulation in the treatment of chronic neuropathic pain. *Pain Medicine*. 2007;8(S4):S200-S275.
14. Schade CM, Schultz D, Tamayo N, Iyer S, Panken E. Automatic adaptation of neurostimulation therapy in response to changes in patient position: results of the posture responsive spinal cord stimulation (PRS) research study. *Pain Physician*. 2011;14:407-417.
15. Schultz DM, Webster L, Kosek P, Dar U, Tan Y. Sensor-driven position-adaptive spinal cord stimulation for chronic pain. *Pain Physician*. 2012;15:1-12.
16. Webster LR, Schultz DM, Roberts JR, et al. Results of the RestoreSensor study: assessment of device programming for position-adaptive spinal cord stimulation. Paper presented at: 28th Annual Meeting of the American Academy of Pain Medicine (AAPM), 2012; Palm Springs, CA.
17. Cameron T. Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review. *J Neurosurg*. 2004;100(3):254-267.
18. Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. *European Journal of Pain*. 2006;10:91-101.
19. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in chronic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectivness of spinal cord stimulation. *Neurosurgery*. 2008;63(4):762-770.
20. Tansey M, Laffel, L, et al. Satisfaction with continuous glucose monitoring in adults and youths with Type 1 diabetes. *Diabetic Medicine*. 2011;28(9):1118-1122.
21. Gentry CK, Cross LB, Gross BN, McFarland MS, Bestermann WH. Retrospective analysis and patient satisfaction assessment of insulin pump therapy in patients with type 2 diabetes. *Southern Medical Journal*. 2011;104(1):24-28.
22. Jenkins AJ, Krishnamurthy B, Best JD, et al. An algorithm guiding patient responses to real-time continuous glucose monitoring improves quality of life. *Diabetes Technology & Therapeutics*. 2011;13(2):105-109.
23. Rubin RR, Peyrot M. Health-related quality of life and treatment satisfaction in the Sensor-

Augmented Pump Therapy for A1C Reduction 3 (STAR 3) Trial. *Diabetes Technology & Therapeutics*. 2012;14(2):143-151.

24. Alo KM, Yland MJ, Kramer DL, Charnov JH, Redko V. Computer assisted and patient interactive programming of dual octrode spinal cord stimulation in the treatment of chronic pain. *Neuromodulation*. 1998;1(1):30-45.
25. Medtronic. *Advanced pain therapy using neurostimulation for chronic pain* 2011. Clinical summary 2011-11.
26. Richter EO. Position sensing for spinal cord stimulation: examining the treatment paradigm. *Minimally Invasive Surgery for Pain*. 20113;1(1):64-69.
27. Liem L, Russo M, Huygen FJPM, et al. A multicenter, prospective trial to assess the safety and performance of the Spinal Modulation dorsal root ganglia neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16:471-482.
28. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Practice*. Accepted for publication.
29. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation*. 2013;16(1):67-72.
30. Schu S, Gulve A, ElDabe S, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain – a retrospective review. *Pain Practice*. Accepted for publication.
31. Alo KM, Yland MJ, Redko V, Feler C, Naumann C. Lumbar and sacral nerve root stimulation (NRS) in the treatment of chronic pain: a novel anatomic approach and neuro stimulation technique. *Neuromodulation*. 1999;2(1):23-31.
32. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9-19.
33. Holsheimer J, den Boer JA, Struijk JJ, Rozeboom AR. MR assessment of the normal position of the spinal cord in the spinal canal. *American Journal of Neuroradiology*. 1994;15:951-959.
34. Olin JC, Kidd DH, North RB. Postural changes in spinal cord stimulation perceptual thresholds. *Neuromodulation*. 1998;1(4):171-175.
35. Struijk JJ, Holsheimer J, Boom HBK. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. *IEEE Transactions on Biomedical Engineering*. 1993;40(7):632-639.
36. Struijk JJ, Holsheimer J, Barolat G, He J, Boom HBK. Paresthesia thresholds in spinal cord stimulation: a comparison of theoretical results with clinical data. *IEEE Transactions on Rehabilitation Engineering*. 1993;1(2):101-108.
37. de Ridder D, Vanneste S, Plazier M, Van Der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery*. 2010;66:986-990.
38. Holsheimer J, Barolat G. Spinal geometry and paresthesia coverage in spinal cord stimulation. *Neuromodulation*. 1998;1(3):129-136.
39. Holsheimer J. Which neuronal elements are activated directly by spinal cord stimulation. *Neuromodulation*. 2002;5(1):25-31.
40. Holsheimer J, Wesselink WA. Effect of anode-cathode configuration on paresthesia coverage in spinal cord stimulation. *Neurosurgery*. 1997;41(3):654-660.
41. Barolat G. Epidural spinal cord stimulation: anatomical and electrical properties of the intraspinal structures relevant to spinal cord stimulation and clinical correlations. *Neuromodulation*. 1998;1(2):63-71.
42. North RB, Lanning A, Hessels R, Cutchis PN. Spinal cord stimulation with percutaneous and plate electrodes: side effects and quantitative comparisons. *Neurosurgical Focus*. 1997;2(1):E5.
43. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. *Spine*. 2002;27(22):2574-2583.
44. Struijk JJ, Holsheimer J. Transverse tripolar spinal cord stimulation: theoretical performance of a dual channel system. *Med & Biol Eng & Comput*. 1996;34:273-279.
45. Yearwood TL, Hershey B, Bradley K, Lee D. Pulse width programming in spinal cord stimulation: a clinical study. *Pain Physician*. 2010;13:321-335.
46. Moffitt MA, Lee DC, Bradley K. Spinal Cord Stimulation: Engineering Approaches to Clinical and Physiological Challenges. In: Greenbaum E, Zhou D, eds. *Biological and Medical Physics, Biomedical Engineering. Implantable Neural Prostheses 1: Devices and Applications*. Dordrecht Heidelberg London New York: Springer Science + Business Media; 2009.
47. Grill WM, Mortimer JT. Electrical properties of implant encapsulation tissue. *Annals of Biomedical Engineering*. 1994;22:23-33.

48. Pinzon EG. Spinal cord stimulation. *Practical Pain Management*. May/June 2005:69-75.
49. Alo K, Varga C, Krames E, et al. Factors affecting impedance of percutaneous leads in spinal cord stimulation. *Neuromodulation*. 2006;9(2):128-135.
50. Brierly JB. The penetration of particulate matter from the cerebrospinal fluid into the spinal ganglia, peripheral nerves, and perivascular spaces of the central nervous system. *J Neurol Neurosurg Psychiat*. 1950;13:203-215.
51. Hogan QH. Labat lecture: the primary sensory neuron: where it is, what it does and why it matters. *Reg Anesth Pain Med*. 2010;35(3):306-311.
52. Haque R, Winfree CJ. Transforaminal nerve root stimulation: a technical report. *Neuromodulation*. 2009;12(3):254-257.
53. Renard VM, North RB. Prevention of percutaneous electrode migration in spinal cord stimulation by a modification of the standard implantation technique. *Journal of Neurosurgery: Spine*. 2006;4(4):300-303.
54. Kumar K, Buchser E, Linderoth B, Meglio M, Van Buyten JP. Avoiding complications from spinal cord stimulation: practical recommendations from an international panel of experts. *Neuromodulation*. 2007;10(1):24-33.
55. Henderson JM, Schade CM, Sasaki J, Caraway DL, Oakley JC. Prevention of mechanical failures in implanted spinal cord stimulation systems. *Neuromodulation*. 2006;9(3):183-191.

5

PROPER PATIENT SELECTION FOR NEUROSTIMULATION OF THE DORSAL ROOT GANGLION IN THE TREATMENT OF CHRONIC PAIN

Modified from:
Neurostimulation of the dorsal root ganglion (DRG) by spinal cord stimulation (SCS): a review of proper patient selection
Deer TR ; Liem AL ; Pope J ; Amirdelfan K ; Burton AW ; Staats P ; Russo M ; Kramer J.
Minimally Invasive Surgery for Pain, MISP, 2015, vol 3.

ABSTRACT

Spinal cord stimulation (SCS) is an effective treatment for neuropathic pain, but may not be appropriate for a sub-set of patients including those with complex or axial pain distributions that can be difficult to treat with traditional SCS, those bothered by undesirable paresthesias, and those who experience complications such as lead migration or positional stimulation. Neuromodulation of the dorsal root ganglion by spinal cord stimulation (DRG-SCS) may provide a number of advantages. This report reviews the therapy and its mechanisms, and establishes a set of criteria for appropriate patient selection for DRG-SCS. These include moderate to severe neuropathic pain that is refractory to conventional treatment; radicular and axial pain arising from conditions such as failed back surgery (FBSS), complex regional pain syndrome (CRPS) and peripheral causalgia, chronic post-surgical pain (CPSP), and deafferentation pain such as amputation/phantom limb pain; and pain in focal, discrete regions that are typically difficult to treat with conventional SCS, such as the breast, groin, knee, or foot. Avenues for future research are discussed.

INTRODUCTION

Spinal cord stimulation (SCS) is a well-established and effective treatment for neuropathic pain. Systematic reviews and guidelines documents recommend its use when more conservative interventions have failed (1, 2, 3, 4), although its precise place in the pain management algorithm for specific indications is debated due to the absence of a critical mass of Level I evidence. Regardless, up to 30,000 patients receive SCS devices each year in the US alone according to reimbursement figures (5), suggesting that this clinical option is well-accepted in the field on the basis of clinical outcomes and cost effectiveness. Additionally, patients report that SCS therapy can result in improvements in pain control with corresponding benefits noted in quality of life, mood, activity, and other personally-relevant domains of functioning (6, 7).

In SCS therapy, electrodes are placed in the epidural space and overlying the dorsal column of the spinal cord. Electrical pulses from an implanted generator at conventional frequencies and above-threshold amplitudes produce perceptible paresthesias in the regions of the body that are somatotopically represented in the stimulated regions of the spinal cord (8, 9). Although perceptible paresthesias may not be necessary for pain relief when using conventional waveforms and frequencies (10, 11), paresthesias that completely overlap with the painful regions are a necessary indicator that electrical stimulation is being delivered to the correct neural target (12, 13). Side effects, such as undesirable paresthesias that are uncomfortably intense and extraneous paresthesias outside of the target pain area created by the recruitment of non-neuropathic fibers are not desired and can be perceived as unpleasant (14). Likewise, motor recruitment (15) or paresthesias that change in intensity or location with movement or changes in body position (16) are to be avoided as part of the goals of SCS programming. Achieving ideal paresthesia coverage (e.g., paresthesias over 100% of the painful area and over 0% of the non-painful regions) is rare (17, 18), but acceptable distributions are possible with iterative approximations based on patient feedback. First, fluoroscopic visualization and verbal feedback from the conscious patient during intraoperative programming can instruct the implanter's precise steering of the leads to the correct neural positioning. Second, the patient's feedback during post-implantation programming – the clinician-led process of selecting active anodes/cathodes and combinations of pulse frequency, pulse width, and amplitude for a variety of activities and/or body positions – is critical to achieving optimal outcomes. Patients may report that subtle differences in programming can produce very different paresthesias, both in location and in subjective quality. Paresthesias can change over time due to fibrotic encapsulation, lead migration, or neural plasticity (19); if paresthesia is lost, re-programming can restore optimal paresthesia distributions in some patients. In other patients the change in the perception of paresthesia over time may be due to psychological processes that can be addressed with counseling. Another option with such patients may be to change the programming to burst pattern stimulation, which has been shown to be paresthesia-free (10) and may potentially improve outcomes by removing paresthesias as a salient psychological cue. Additionally, positional effects may become more pronounced over time; one SCS system has implemented complex position adaptation features to mitigate the effect of body position changing (16).

There are many hypotheses for the pain-relieving mechanisms of SCS. It is though that preferentially recruiting large-diameter fibers in the dorsal column with SCS (20) may silence pain signals carried by small-diameter fibers. The neurochemical and physiological interaction of these neurons with second-order interneurons, other neurons in the spinal network, the glial syncytium, ascending/descending fibers, and peripheral afferents/efferents has not been precisely elucidated. Ultimately, SCS appears to produce its analgesic effects via a net decrease in the neuropathic pain-induced hyperexcitability of the dorsal column (21, 22).

SCS systems are implanted most often for radicular pain in the extremities (often associated with failed back surgery syndrome [FBSS]), back pain, complex regional pain syndrome (CRPS), chronic postsurgical pain, and ischemic pain in the extremities (4, 8, 9, 13). A positive response during the temporary trial period is generally considered predictive of good long-term pain relief outcome with SCS (9). Short delays from the diagnosis of chronic pain to implantation (23), and lack of adverse psychological factors (24, 25) are also positive predictors of optimal outcomes with SCS. Approximately 3 in 4 patients proceed to implant after having had a positive trial (26, 27). Moreover, 75-80% of SCS patients have pain relief of 50% or more in the years following implantation (6, 26). On the other hand, these statistics indicate that there is a substantial sub-set of patients for whom the original selection criteria for SCS were not sufficiently accurate. When SCS therapy is inadequate, or it becomes less effective over time, reprogramming and/or lead repositioning are typically attempted. Thus, the treatment failures reported across multiple studies exist despite presumably good pain-paresthesia overlap, suggesting that other mechanisms may be at play (19).

A number of technological adaptations have been developed to optimize SCS therapy. Innovative lead designs are now available, in both percutaneous and laminotomy paddle forms, providing a significant number of options for programming combinations across numbers of leads, numbers of electrodes, electrode spacing, and electrode alignment (9, 28, 29). Midline vs. lateral placement of single or multiple leads within the epidural space has also been investigated (30). Such approaches have been extended to include stimulation of the dorsal root, with varying success (31, 32). Outcomes in those early studies were hampered by small sample sizes and the physical limitations of SCS leads in the relatively cramped lateral recesses of the epidural space (33, 34).

Despite these early challenges, the dorsal root ganglion (DRG) remains an attractive target for spinal cord stimulation. Primary sensory neurons (PSNs) in this structure are implicated in the initiation and maintenance of neuropathic pain conditions (33) and are a target for effective pain management interventions such as radiofrequency (RF) denervation (35, 36.) Despite being irreversible and therefore an option of last resort, the effectiveness of ganglionectomies (37) and dorsal root entry zone lesions (38) also indicate that these primary sensory structures are key elements of the neuropathic pain pathway. Additionally, SCS at the site of the PSN, instead of the dorsal column of the spinal cord, carries some logical parsimony. By modulating pain signals at the first somatic site on the pathologic pain sensory pathway, one can create an opportunity to normalize the initial input before entry into the spinal cord pain pathways. Thus, the need to modulate multiple complex interactions in the spinal cord through SCS is obviated.

A novel SCS device has been developed to specifically target the DRG. It has been commercially available since 2011 outside of the United States and is currently under regulatory consideration in the USA (IDE G110186). Evidence has been collected from over 500 cases worldwide. From this information, trends are emerging regarding the etiologies that are amenable to treatment with DRG-SCS. This information is presented below to describe this intervention's selection criteria.

DEVICE AND IMPLANTATION

The Axium™ DRG-SCS system (Spinal Modulation, Inc.; Menlo Park, CA, USA) is fully-implantable and patient-managed via an RF remote control, and can accommodate up to four percutaneous leads which have a narrow diameter of 1 mm with a quadripolar linear array spanning 20 mm at the distal end. The leads have a hollow lumen that that allows for more flexibility than conventional SCS leads. The leads are loaded into a curved sheath, temporarily stiffened with a stylet for deployment and can be easily steered around the epidural space (see Figure 25).

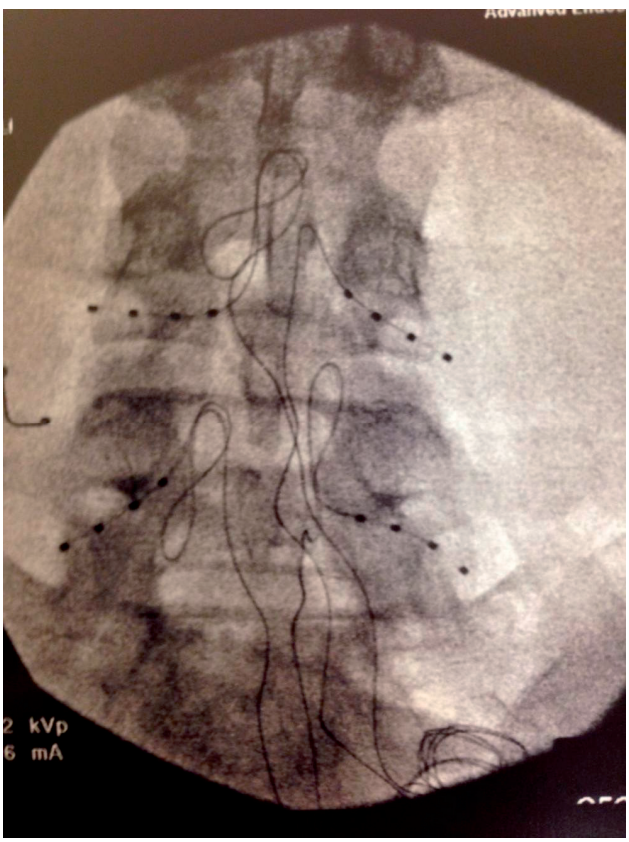


Figure 25. DRG lead placement.
Leads are placed bilaterally over L4 and L5 DRGs for treating foot pain. Image courtesy: Dr. Peter Staats.

To implant the device, epidural access is gained through a standard minimally-invasive loss-of-resistance technique, after standard prophylactic antibiotics and the leads are advanced in an anterograde manner to the targeted DRG of interest. A retrograde technique may also be utilized at the experienced physician's discretion. Leads are steered to their DRG-apposing sites under fluoroscopic guidance, and appropriate placement is confirmed via electrode activation and patient feedback regarding the locations of perceived paresthesias. Distal ends of the leads are tunneled to the subcutaneous pocket created for the neurostimulator in the flank or buttock and connected. All incisions are closed with standard post-operative care followed by antibiotics and analgesics. As it is standard of care with SCS due to its reliable prediction of future outcomes, implantation is typically preceded by a temporary trial period, in which the distal ends of the epidural leads are connected to an external neurostimulator for a period of several days or weeks. During this time, the patient is able to evaluate the effectiveness of the therapy. If more than 50% pain relief is achieved and both the clinician and the patient feel that a permanent implant is the right choice, the patient proceeds to permanent implantation.

SELECTION CRITERIA FOR SCS OF THE DRG

Patient characteristics

To be considered for DRG-SCS, the patient must have first engaged in a treatment protocol including diagnosis of the neural pain generator and initiation of a stepwise pain management algorithm, and have subsequently failed conservative multi-modal treatment options. Patients must also have had a good screening response to a temporary trial of DRG-SCS and have demonstrated an ability to operate the DRG-SCS system. Contraindications include psychological instability or significant untreated psychiatric comorbidity based on a comprehensive psychological evaluation; uncontrolled or irreversible coagulopathy; immunosuppression or active infection; or spinal conditions that may limit epidural access such as spinal stenosis, grade III spondylolisthesis, previous lumbar fusion surgery at the desired DRG level, and/or cauda equina compression. Other potential issues include uncontrolled substance addiction and progressive neurological diseases. These characteristics are similar to those recommended for SCS (39) and have been employed in prospective studies (40, 41).

Pain characteristics

Also similar to the SCS literature (39), the pain intended for treatment with DRG-SCS should have the following characteristics:

1. Primarily neuropathic in nature;
2. Duration of pain lasting at least 3 months;
3. Moderate to severe pain intensity (e.g., 60 mm or more on a 100-mm visual analogue scale [VAS]); and
4. Stable location and nature of pain.

Pain etiology

In addition to reports on cohorts with mixed pain etiologies (41, 40), the effectiveness of DRG-SCS has been established for pain associated with FBSS (42, 43, 44), CRPS and peripheral causalgia (45, 46), post-surgical neuropathy (47), focal mono-neuropathies such as Meralgia Paresthetica (48), and amputation / phantom limb syndrome (49, 50).

Pain locations

DRG-SCS has shown good relief outcomes for pain located in the upper extremities (51), back (52), body wall (53), viscera (54), groin (55), lower extremities (56), knee (57), and foot (58, 59). Notably, excellent pain-paresthesia concordance with little extraneous stimulation has been reported, even for extremely discrete pain distributions (60; see Table 9).

DISCUSSION

The patient selection criteria for DRG-SCS have some similarities to those for SCS of the dorsal column, but DRG-SCS expands the potential patient population. DRG-SCS is labelled for chronic neuropathic pain (in Europe under CE Mark) of the trunk and/or limbs (in Australia), and is in testing for applicability to CRPS and peripheral causalgia of the lower limbs in the USA. DRG-SCS has, however, demonstrated effectiveness across a variety of etiologies and body locations. DRG-SCS indications may be expanded relative to conventional SCS as this modality appears to readily treat pain in distributions that are typically difficult to treat with SCS. The challenge with complex sites such as the axial low back and the groin is achieving full paresthesia concordance with painful regions. For discrete extremity pain locations like the knee and foot, large regions of extraneous paresthesias may be problematic. DRG-SCS appears to provide more acceptable treatment profiles. This is hypothesized to occur because recruitment of PSNs allows for direct communication with the painful areas. In contrast, the combination of spinal geometry and electrical fields generated by dorsal column stimulation may mean that the fibers of interest in the spinal cord cannot be recruited in a straightforward manner. This has been suggested by modeling studies that have concluded that dorsal column stimulation's depth of penetration into the spinal cord and the specificity of fiber recruitment is highly dependent on lead location and stimulation parameters (61).

DRG-SCS is effective for upper extremity pain, which necessitates cervical lead placement. This has previously not been feasible because the angle of the lateral foramen with the spinal canal was too acute to negotiate with conventional SCS leads (34). The form factors of the novel DRG-SCS leads address this issue. During the implantation procedure, a flexible curved external sheath is used to guide electrodes to the neural target. The lead is then ejected from the sheath; its extremely flexible structure can be maneuvered to conform to the exterior of the entire DRG just below medial and lateral aspects of the pedicle in the epidural space.

Table 9. Patient selection criteria for DRG-SCS.

Patient characteristics	Pain characteristics
Must have: Failed conservative pain management algorithms; Had a good response to screening DRG-SCS; Demonstrated an ability to operate the system. **Must/should not have:** Psychological / psychiatric issues; Medical comorbidities such as coagulopathy, immunosuppression or active infection; Spinal conditions that may limit access to the target site such as spinal stenosis, spondylolisthesis, and/or cauda equina compression; Substance addiction; Progressive neurological disease.	Primarily neuropathic in nature; Duration of at least 3 months; Moderate to severe (e.g., 60 mm on a 100-mm VAS); Stable in location and nature. **Pain etiology** FBSS; CRPS / peripheral causalgia; Chronic post-surgical /post-traumatic pain; Meralgia Paresthetica; Amputation / phantom limb syndrome. **Pain locations** Upper extremities; Back; Body wall; Viscera; Groin; Lower extremities; Knee; Foot.

In addition to these innovations in treatment delivery, it has been reported that the paresthesias produced with DRG-SCS are stable in intensity and location over time and across different body positions (62). This suggests that leads placed at the DRG are less susceptible to migration and/or positional effects than leads in the epidural space over the dorsal columns, although this preliminary observation will require long-term confirmation. Stability may be due to the bony structures that enclose the DRG and provide some incidental immobile scaffolding for the lead, in addition to the standard anchoring and strain-relief loop implant procedures common to this and other SCS implantation techniques. The lack of large amounts of cerebrospinal fluid (CSF) between the electrode and the DRG may also account for a more stable energy delivery to the neural target tissue versus the traditional SCS placement where CSF thickness will need to be taken into consideration during programming. Thus, DRG-SCS may provide a more viable option than dorsal column placement at sites that are particularly prone to migration, such as the cervical spine (63), or positional effects, such as upper-mid thoracic regions (62, 64).

Recommendations in this report are limited by as-yet incomplete characterization of the breadth of DRG-SCS treatment capability. For example, long-term pain relief outcomes with DRG-SCS are not yet fully understood. Although a prospective sample has reported good outcomes through 12 months (40), expanding on these outcomes through an intent-to-treat design with survival analysis will provide more robust evidence. Additionally, conventional SCS has demonstrated effectiveness for angina pectoris (65) and may be applicable for congestive heart failure (66), but DRG-SCS has not been applied in cardiovascular indications. However, the reported ability to achieve chest

wall paresthesias with thoracic DRG-SCS (53) and positive vascular changes observed with DRG-SCS for CRPS (45) suggests that this may be feasible. Reports of DRG-SCS applications in other pain conditions, such as brachial plexus avulsion (67) and post-herpetic neuralgia (68), are accumulating.

Because DRG-SCS is a relatively new intervention, the current knowledge base is largely informed by multi-center European and Australian prospective studies and case reports. Information that may emerge from large multi-center prospective controlled studies currently active in the United States (for example, NCT01923285) may refine the patient selection criteria outlined here. Additionally, as with conventional SCS, there would be value in developing prospective testing paradigms that could be applied either before or during the trial period to enhance prognostication. Some preliminary work has been completed regarding identification of optimal lead placement sites via transforaminal epidural injections of local anesthetics (69) and intraoperative paresthesia locations (70).

CONCLUSIONS

Indications for DRG-SCS are similar to those for conventional dorsal column stimulation and include neuropathic pain located in the trunk or limbs due to FBSS, CRPS and peripheral causalgia, post-surgical neuropathy, and other etiologies. Patient selection criteria may be broader for DRG-SCS, however, because clinical evidence suggests that this intervention is highly suited to treatment of focal or challenging locations including foot, knee, back, breast and groin. Treatment of pain modalities that are prone to migration or positional effects are also is also especially amenable to treatment with SCS of the DRG. DRG-SCS may prove to be a substantial advancement in the field of neuromodulation. Further refinement of patient selection will only enhance this option for patients who suffer from chronic pain and potentially other disease states.

REFERENCES

1. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. *Pain*. 2004;108:137-147.
2. Simpson EL, Duenas A, Holmes MW, Papaioannou D, Chilcott J. Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin: systematic review and economic evaluation. *Health Technol Assess*. 2009;13(17):1-154.
3. Boswell MV, Trescot AM, Datta S, et al. Interventional techniques: evidence-based practice guidelines in the management of chronic spinal pain. *Pain Physician*. 2007;10:7-111.
4. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol*. 2007;14(9):952-970.
5. Prager J. Estimates of annual spinal cord stimulator implant rises in the United States. *Neuromodulation*. 2010;13(1):68-69.
6. Eldabe S, Kumar K, Buchser E, Taylor RS. An analysis of the components of pain, function, and health-related quality of life in patients with failed back surgery syndrome treated with spinal cord stimulation or conventional medical management. *Neuromodulation*. 2010;13(3):201-9.
7. Kelly GA, Blake C, Power CK, O'Keeffe D, Fullen BM. The impact of spinal cord stimulation on physical function and sleep quality in individuals with failed back surgery syndrome: a systematic review. *Eur J Pain*. 2012;16(6):793-802.
8. Krabbenbos IP, van Dongen EPA, Nijhuis HJA, Liem AL. Mechanisms of spinal cord stimulation in neuropathic pain. In: Carrillo-Ruiz J, ed. *Topics in Neuromodulation Treatment*.
9. Epstein LJ, Palmieri M. Managing chronic pain with spinal cord stimulation. *Mount Sinai Journal of Medicine*. 2012;79:123-132.
10. de Ridder D, Vanneste S, Plazier M, Van Der Loo E, Menovsky T. Burst spinal cord stimulation: toward paresthesia-free pain suppression. *Neurosurgery*. 2010;66:986-990.
11. Wolter T, Kiemen A, Porzelius C, Kaube H. Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study. *European Journal of Pain*. 2012;16(5):648-655.
12. North RB, Ewend MG, Lawton MT, Piantadosi S. Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. *Pain*. 1991;44:119-130.
13. Simpson BA. Spinal cord stimulation. *British Journal of Neurosurgery*. 1997;11(1):5-11.
14. North RB, Lanning A, Hessels R, Cutchis PN. Spinal cord stimulation with percutaneous and plate electrodes: side effects and quantitative comparisons. *Neurosurgical Focus*. 1997;2(1):E5.
15. Struijk JJ, Holsheimer J, Boom HBK. Excitation of dorsal root fibers in spinal cord stimulation: a theoretical study. *IEEE Transactions on Biomedical Engineering*. 1993;40(7):632-639.
16. Schade CM, Schultz D, Tamayo N, Iyer S, Panken E. Automatic adaptation of neurostimulation therapy in response to changes in patient position: results of the posture responsive spinal cord stimulation (PRS) research study. *Pain Physician*. 2011;14:407-417.
17. Yearwood TL, Hershey B, Bradley K, Lee D. Pulse width programming in spinal cord stimulation: a clinical study. *Pain Physician*. 2010;13:321-335.
18. Kim CH, Issa M, Vaglienti R. Use of observational mechanical gateway connector in spinal cord stimulation trials. *Pain Physician*. 2011;14:525-530.
19. 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;14:513-524.
20. Holsheimer J. Which neuronal elements are activated directly by spinal cord stimulation. *Neuromodulation*. 2002;5(1):25-31.
21. Oakley JC, Prager JP. Spinal cord stimulation: mechanisms of action. *Spine*. 2002;27(22):2574-2583.
22. Yakhnitsa V, Linderoth B, Meyerson BA. Spinal cord stimulation attenuates dorsal horn neuronal hyperexcitability in a rat model of mononeuropathy. *Pain*. 19999;79(2-3):223-233.
23. Kumar K, Toth C, Nath RK, Laing P. Epidural spinal cord stimulation for treatment of chronic pain-- some predictors of success. A 15-year experience. *Surg Neurol*. 1998;50:110-121.
24. Burchiel KJ, Anderson VC, Wilson BJ, Denison DB, Olson KA, Shatin D. Prog-

nostic factors of spinal cord stimulation for chronic back and leg pain. *Neurosurgery*. 1995;36(6):1101-1110.

25. Nelson DV, Kennington M, Novy DM, Squitieri P. Psychological selection criteria for implantable spinal cord stimulators. *Pain Forum*. 1996;5(2):93-103.
26. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery*. 2006;58:481-496.
27. Mekhail NA, Mathews M, Nageeb F, Guiguis M, Mekhail MN, Cheng J. Retrospective review of 707 cases of spinal cord stimulation: indications and complications. *Pain Practice*. 2010;11(2):148-153.
28. Bradley K. The technology: the anatomy of a spinal cord and nerve root stimulator: the lead and the power source. *Pain Medicine*. 2006;7(S1):S27-S34.
29. Sankarasubramanian V, Buitenweg JR, Holsheimer J, Veltink P. Electrode alignment of transverse tripoles using a percutaneous triple lead approach in SCS. *J Neural Eng*. 2011;8(1):016010.
30. North RB, Kidd DH, Olin J, et al. Spinal cord stimulation for axial low back pain: a prospective, controlled trial comparing dual with single percutaneous electrodes. *Spine*. 2005;30(12):1412-1418.
31. Alo KM, Yland MJ, Redko V, Feler C, Naumann C. Lumbar and sacral nerve root stimulation (NRS) in the treatment of chronic pain: a novel anatomic approach and neuro stimulation technique. *Neuromodulation*. 1999;2(1):23-31.
32. Weigel R, Capelle HH, Krauss JK. Failure of long-term nerve root stimulation to improve neuropathic pain. *J Neurosurg*. 2008;108:921-925.
33. Deer TR, Levy RM, Kramer JM. Interventional perspectives on the dorsal root ganglion as a target for the treatment of chronic pain: a review. *Minimally Invasive Surgery for Pain*. 2013;1(1):23-33.
34. Kellner CP, Kellner MA, Winfree CJ. Spinal nerve root stimulation. *Prog Neurol Surg*. 2011;24:180-188.
35. Tsou HK, Chao SC, Wang CJ, et al. Percutaneous pulsed radiofrequency applied to the L-2 dorsal root ganglion for treatment of chronic low-back pain: 3-year experience. *Journal of Neurosurgery: Spine*. 2010;12(2):190-196.
36. Shanthanna H, Chan P, McChesney J, Thabane L, Paul J. Pulsed radiofrequency treatment of the lumbar dorsal root ganglion in patients with chronic lumbar radicular pain: a randomized, placebo-controlled pilot study. *Journal of Pain Research*. 2014;7:47-55.
37. Weigel R, Capelle HH, Schmelz M, Krauss JK. Selective thoracic ganglionectomy for the treatment of segmental neuropathic pain. *European Journal of Pain*. 2012;16:1398-1402.
38. Aichaoui F, Mertens P, Sindou M. Dorsal root entry zone lesioning for pain after brachial plexus avulsion: results with special emphasis on differential effects on the paroxysmal versus the continuous components. A prospective study in a 29-patient consecutive series. *Pain*. 2011;152(8):1923-1930.
39. National Institute for Health and Clinical Excellence (NICE). *Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin; NICE technology appraisal guidance 159*. London, UK: National Health Service (NHS); 2011.
40. Liem L, Russo M, Huygen FJPM, et al. A multicenter, prospective trial to assess the safety and performance of the Spinal Modulation dorsal root ganglia neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16:471-482.
41. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation*. 2013;16(1):67-72.
42. Liem L, Russo M, Van Buyten JP, Huygen F. Dorsal root ganglion stimulation for the treatment of failed back surgery syndrome. Paper presented at: The 6th World Congress of the World Institute of Pain, 2012; Miami Beach, Florida.
43. Liem L, Russo M, Van Buyten JP, Smet I, Huygen F. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of failed back surgery syndrome (FBSS). Paper presented at: 16th Annual Meeting of the North American Neuromodulation Society, 2012; Las Vegas.
44. Nijhuis H, Liem L, Huygen F. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of chronic low back pain in FBSS: Prospective results and potential mechanisms. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
45. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional

pain syndrome: a prospective case series. *Pain Practice*. 2014;2015;15(3);208-16.

46. Verrills P, Mitchell B. Single center experience in Australia using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for peripheral causalgia and other neuropathic pain conditions. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
47. Espinet AJ. An Australian case series in chronic post-surgical pain (CPSP) treated with spinal cord stimulation (SCS) of dorsal root ganglion (DRG). Paper presented at: 17th Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
48. Zuidema X, Breel J, Green AL, et al. Dorsal root ganglion (DRG) stimulation for the treatment of Meralgia Paresthetica. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
49. Burger K, Moser H, Liem L, Klase D, ElDabe S. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of post amputation pain. Paper presented at: 16th Annual Meeting of the North American Neuromodulation Society, 2012; Las Vegas.
50. Bara GA, Slotty P, Maciaczyk J, Schu S, Vesper J. Dorsal root ganglion stimulation for treatment of phantom limb pain. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
51. Liem L, Demmel W, Thoma R. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for chronic pain of the upper limbs – A multi-center case series. Paper presented at: 11th World Congress of the International Neuromodulation Society, 2013; Berlin.
52. Nijhuis H, Liem L, Huygen F. A post-market cohort to assess the performance of the Spinal Modulation neurostimulator system for the management of intractable chronic back pain. Paper presented at: 11th World Congress of the International Neuromodulation Society, 2013; Berlin.
53. Koneti K, Gulve A, Eldabe S, Hughes J, West S, Garner F. Dorsal root ganglion stimulation for the treatment of body wall pain: Middlesbrough experience. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
54. Baranidharan G. Reduction in dermatomal hyperalgesia in patients with visceral pain treated with spinal cord stimulation (SCS) of the dorsal root ganglion (DRG). Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
55. Schu S, Gulve A, Eldabe S, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain-- a retrospective review. *Pain Practice*. 2015;15(4):293-9.
56. Gulve A, ElDabe S. Dorsal root ganglion stimulation for treatment of neuropathic pain in the lower extremity: Middlesbrough experience. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
57. van Bussel CM, Green AL, Fitzgerald JJ, et al. Treating a challenging patient population of complex regional pain syndrome (CRPS) of the knee with spinal cord stimulation (SCS) of the dorsal root ganglion (DRG). Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
58. Wolf K. Long term outcomes using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for foot pain. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
59. Wolf K, Strowitzki M. Dorsal root ganglion (DRG) stimulation for post-surgical foot pain: four case reports. *Neuromodulation*. Submitted: In review.
60. Moir L, Bojanic S, Green A, Fitzgerald J, Aziz T. Treating focal neuropathic pain with dorsal root ganglion stimulation. Paper presented at: Neuromodulation Society of the United Kingdom and Ireland (NSUKI) Annual Scientific Meeting, 2013; Oxford, UK.
61. Holsheimer J. Effectiveness of spinal cord stimluation in the management of chronic pain: analysis of technical drawbacks and solutions. *Neurosurgery*. 1997;40(5):990-999.
62. Kramer J, Liem L, Russo M, Huygen F, Smet I, Van Buyten JP. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. *Neuromodulation*. 2013; 2015;18(1):50-7.
63. Rosenow JM, Stanton-Hicks M, Rezai AR, Henderson JM. Failure modes of spinal cord stimulation hardware. *J Neurosurg Spine*. 2006;5:183-190.
64. Struijk JJ, Holsheimer J, Barolat G, He J, Boom HBK. Paresthesia thresholds in spinal cord stimulation: a comparison of theoretical results with clinical data. *IEEE Transactions on Rehabilitation Engineering*. 1993;1(2):101-108.

65. Lanza GA, Grimaldi R, Greco S, et al. Spinal cord stimulation for the treatment of refractory angina pectoris: a multicenter randomized single-blind study (the SCS-ITA trial). *Pain*. 2011;152(1):45-52.
66. Torre-Amione G, Khalil N, Siller J, Alo KM. Focused review: the rationale behind the use of spinal cord stimulation for the treatment of congestive heart failure. *Journal of Neurosurgical Review*. 2011;1(1).
67. Thoma R, Neumann H, Smet I, Van Buyten JP. Pathophysiology of brachial plexus lesion and the role of dorsal root ganglion (DRG) in modulation of pain. Paper presented at: 17th Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
68. Klase D, Thoma R, Baranidharan G, et al. Does convergence of multi-segmental afferent inputs at the spinal lamina enable treatment of post-herpetic neuralgia with dorsal root ganglion (DRG) stimulation possible? Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
69. Bara GA, Slotty J, Maciaczyk J, Schu S, Vesper J. Predictability of dorsal root ganglion stimulation via prior transforaminal epidural injections for the treatment of peripheral neuropathies. Paper presented at: 17th Annual Meeting of the North American Neuromodulation Society, 2013; Las Vegas.
70. Zuidema X, Breel J, Wille F. Paresthesia mapping: a practical workup for successful implantation of the dorsal root ganglion stimulator in refractory groin pain. *Neuromodulation*;17(7):665-9.

6

MANAGEMENT OF POST-HERNIORRHAPHY CHRONIC NEUROPATHIC GROIN PAIN

Modified from:
Management of post-herniorrhaphy chronic neuropathic groin pain:
a review of the literature and practice recommendations
Liong Liem, Nagy Mekhail
(accepted for publication in Pain Practice)

ABSTRACT

Chronic neuropathic groin pain is a sequela of hernia surgery that occurs at unacceptably high rates, causing widespread impacts on quality of life. Although the medical community is beginning to recognize the role of surgical technique in the initiation and maintenance of post-herniorrhaphy neuropathic pain, little information exists regarding pain management strategies for this condition. This review presents a summary of the pain condition state, its treatment options, and treatment recommendations and, based on a review of the knowledge base, a treatment algorithm for treatment of post-herniorrhaphy pain was developed. In addition to conventional pharmacologic approaches, recent technological developments including neuromodulation are indicated for this type of pain. The risks of certain surgical techniques, including mesh implantation and neurectomy, are discussed from a pain management perspective. It is expected that cross-disciplinary awareness of surgeons for non-surgical pain management options in the treatment of chronic neuropathic post-herniorrhaphy pain will contribute to better clinical outcomes.

INTRODUCTION

The development of chronic neuropathic pain is a serious risk for any surgical procedure. Criteria have been articulated; clinically relevant post-surgical chronic pain 1) develops or increases following a surgical procedure and may or may not have been preceded by a pain-free period; 2) lasts for 3-6 months and has an impact on daily life; 3) excludes continuation of a pre-existing problem or other cause (e.g., persistent infection); and 4) is localized to the surgical field and/or projects to the nerve innervation /dermatome related the surgical field (1, 2). Chronic neuropathic post-surgical pain following hernia repair is localized to the groin and can extend to the inner thigh, abdomen, and genitals (3, 4). It is usually described as sharp, shooting, burning, or cramping and can be worsened by physical or sexual activity. Changes in sensation can also accompany the pain, including numbness, paresthesias, and allodynia/hyperalgesia. Similar to other neuropathic pain conditions, chronic groin pain presents with a wide range of severity and personal consequences, and most sufferers report negative effects in quality of life, social and recreational activity, and relationships (5). In severe and intractable cases, mobility is affected and disability can result (6). Pain may be progressive over time, and some patients report suicidality (7). The societal cost of chronic neuropathic groin pain has not been quantified but can certainly be presumed to offset a portion of the reported cost-effectiveness of hernia repairs (8).

Worldwide, 27% of men and 3% of women will undergo surgical hernia repair during their lifetimes (9, 10), and this rate may be higher among certain groups such as athletes (11). In the UK, more than 70,000 inguinal herniorrhaphies are performed each year (12). Owing to improved surgical procedures and products over the decades, the risk of hernia recurrence has been eclipsed by chronic pain as the most likely negative sequela of hernia surgery (13, 14). Rates of chronic pain after herniorrhaphy have been reported after 5-25%-- and as many as 54%, according to one review-- of herniorrhaphy procedures (12, 15, 16). Approximately 2-10% of procedures may result in severe pain and/or disability (16, 17, 18).

The development of chronic groin pain following surgical hernia repair is associated with patient characteristics such as younger age (patients under 40 are more likely to report chronic pain than those over 60; 19), higher body mass index, pre-operative pain conditions, working status (20), and psychological factors such as low pre-surgery optimism and sense of control over pain (21). Chronic post-herniorraphy pain may also be iatrogenic, involving trauma to the inguinal nerves during surgery or their post-surgical mechanical irritation (7, 22, 23, 24). Anatomically, the inguinal nerves do not have the protection of a layer of fascia; these 'naked nerves' are especially prone to irritation and are at risk of irritation from surgical dissection and the placing/fixation of surgical mesh for structural support (13).

Herniologists have developed strategies aimed at preventing the development of chronic pain. Many center on surgical techniques. A randomized controlled trial comparing the open Lichtenstein technique with anterior-approach transinguinal preperitoneal repairs showed much lower rates of pain with the latter: 3.5% of patients

had resting pain and 12% with pain during activity, compared with 20%/ 60% with the open technique (14). The method of securing the supporting mesh also plays a role: using absorbable suture instead of nonabsorbable monofilament sutures to hold the mesh against the fascia reduces the 1-year risk of pain development by 2.2% (23). Based on these and similar findings, recommendations for surgical techniques that carefully limit trauma to the nerves have been developed (25).

Perioperative treatment with a single dose of gabapentin has demonstrated some value in preventing pain (26), unlike intraoperative local infiltration of anesthetic (27). Prophylactic neurectomies with wide resection of the inguinal nerves during hernioplasty may reduce the incidence of chronic pain development (28, 29). A randomized controlled trial of tension-free hernioplasties with nerve identification showed that 1.1% of patients with nerves excised during the procedure experienced moderate/severe pain 3 months after the surgery, while approximately 10% of the patients with preserved nerves did (30). A systematic review of planned neurectomy also concluded that the approach is effective at preventing the development of pain (31). However, it has also been reported in a cohort of 736 patients that neurolysis, when combined with the Lichtenstein repair technique, was predictive of chronic pain after 6 months (22), and the procedure is known to alter sensation (31).

After the point that post-herniorrhaphy pain becomes entrenched, a number of approaches have been applied for its amelioration. There is a lack of evidence-based information regarding the best pharmacological options; a single randomized trial showed a non-significant trend for topical capsaicin to out-perform placebo (32). As such, many patients trial a frustrating series of medications. For patients who cannot tolerate or prefer to limit their use of systemic pharmaceuticals, local infiltrations may be employed (33), although the ideal agents (anesthetic and/or steroid) and techniques are debated. Cryotherapy of the inguinal nerves is another effective intervention at the peripheral level (34, 35). Segmental pain control has also been achieved via regional blocks at L1-L2 (4) and with radiofrequency (RF) nerve ablation and pulsed RF of the affected dorsal root ganglia (DRG) (36, 37, 38, 39).

Additionally, surgical revisions may be attempted to address chronic neuropathic postherniorrhaphy pain. Reoperation may involve removal of the mesh or sutures/ staples or surgical resection of inguinal nerves (40, 41, 42). Rates of pain relief following reoperation range from 62%-100% (41, 43, 44, 45, 46), although there is considerable variability in pain assessment and reporting. Some recommend that neurectomy procedures be delayed until after at least one year has elapsed post-herniorrhaphy and after non-surgical pain management options have been exhausted (40) because the procedure is irreversible, can lead to numbness in the affected regions, can contribute to neuroma formation, and may complicate some neuromodulatory pain management interventions (35, 46). A sample of 46 patients requiring surgery to treat pain that developed after a hernia repair, 44 triple neurectomies and 2 single neurectomies were performed. Mesh was repaired in 42 of these cases, in addition to removal of some mesh and/or plug in 40 (47). In a recent review of 25 studies of reoperation for persistent pain after hernia surgery, 93% of the procedures took an open approach for mesh replacement, removal, and/or neurectomy (48).

Algorithms have recently been developed for the stepwise management of chronic neuropathic groin pain. In one, developed in a pain management clinic during the treatment of 29 post-herniorrhaphy pain patients, it was proposed that chronic neuropathic pain of greater than 3 mm on the VAS should be managed through a comprehensive pain clinic for complete examination and ultrasound-guided nerve blocks and placement of a peripheral nerve stimulator if indicated (49). Another algorithm, based on the consensus of 15 international hernia experts, suggested that after a delay of 3-6 months with basic analgesics, a surgeon should differentiate between the nociceptive and neuropathic components of the pain based on physical exam, ultrasonography, and experience. Pain due to anatomical pathologies (e.g., recurrence of hernia, meshoma), should be addressed surgically by an expert, with neurectomies recommended as a last resort. The pain team should lead treatment options such as local infiltrations for diagnosis and treatment for pain without anatomical abnormalities (50).

Even with such algorithms, there remains a considerable unmet need for managing chronic post-herniorrhaphy neuropathic pain. It has been reported that re-operation for post-surgical pain has a success rate of approximately 90% (2, 47). Nerve blocks, while often effective, may require more than three injections in some cases and considerable neuropathic pain can remain. In a report of 43 patients treated with either nerve stimulator-guided or ultrasound-guided nerve blocks for post-herniorrhaphy pain, 21% of patients required more aggressive treatments (51), such as the neuromodulatory options described below.

Transcutaneous electronic nerve stimulation (TENS) has been demonstrated to provide some relief during the initial postoperative period (52) and is thought to relieve chronic post-herniorrhaphy pain through mechanisms similar to other neuropathic conditions (53). It has been anecdotally noted, however that patients tend to find TENS electrodes inconvenient and/or uncomfortable due to the location of the pain. Peripheral nerve stimulation (PNS) and peripheral nerve field stimulation (PNfS), in which electrodes are implanted near nerves or in the region of pain, has similar effectiveness for groin pain as for other types of neuropathic pain (54, 55, 56, 57), but is also as subject to limitations such as challenges in placing the pulse generator, migration, and irritation from the lead (58).

A number of reports applying spinal cord stimulation (SCS) at the T7-T9 levels have indicated some applicability to chronic neuropathic groin pain, in some cases relieving 75% or more (59, 60, 61). However, a limitation of SCS with groin pain as with all axial pain distributions is that it is extremely difficult to achieve selective coverage of the painful regions (62, 63); patients may find it necessary to tolerate 'a pair of pants' of extraneous paresthesia in order to also capture the relatively discrete painful region. It has been proposed that dorsal root ganglia (DRG) stimulation may be a pain management option (64) that is a viable alternative to SCS for this pain distribution, because the recruitment of distally-projecting sensory neurons can may be more precisely selected to achieve a limited region of paresthesia. Nerve root stimulation for groin pain had disappointing long-term results in a preliminary case report (65), but larger sample and more precise electrode placement may show better effectiveness. Indeed, a recently-developed implantable neurostimulator with small, flexible leads for placement of

electrodes against DRGs has showed promising results across a number of studies (66, 67, 68), including pain specific to the groin (64) when leads are placed against the T11-L2 DRGs (see Figure 1) or as empirically established with pre-implant testing (69; see Table 1). The value of DRG stimulation for groin pain was highlighted in one of the recently-published algorithms; of the 25 patients described in the series, all but one were managed successfully. The remaining patient failed PNS treatment due to previous neurectomy. Instead, DRG stimulation was successfully applied (49). Results of a landmark study in DRG stimulation show that this modality is effective for pain of the lower limb (which can include pain that extends into the groin; 70) and a number of prospective studies on DRG stimulation for inguinal/groin pain are currently underway at European centers (e.g., NCT02349659, NCT02346656, and NCT02337699; www.clinicaltrials.gov). It should be noted, however, that lead placement at the DRG is not typically achievable with conventional SCS devices because lead diameter and rigidity prevents maneuvering into the lateral vertebral foramen. Specially-designed leads, a curved introducer sheath, and steering under fluoroscopic guidance are required (67).

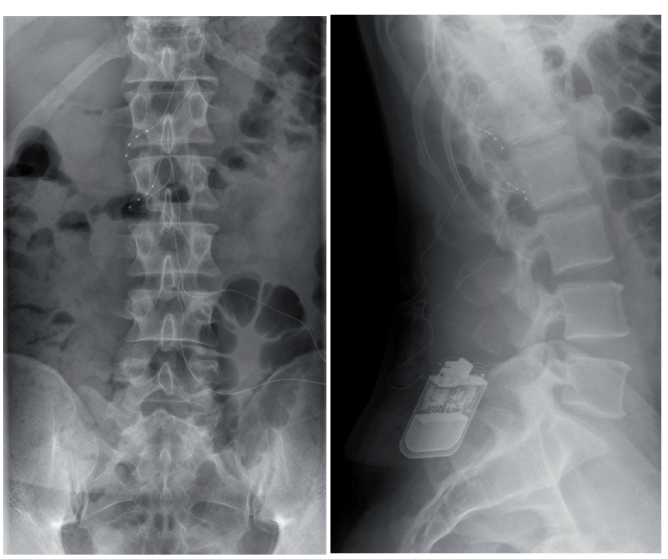


Figure 1. For effective neuromodulation of groin pain, leads can be placed against DRGs. In this image, the male patient had right-sided groin pain. Leads were placed at the right L1 and L2 DRGs (anterior-posterior view in image on left; lateral view showing the IPG location in image on right).

Table 1. Literature summary of DRG stimulation for groin pain.

Reference	Number of patients with groin pain	Outcomes with DRG stimulation
Schu et al., 2015 (68).	29 of 29	Successful trial in 25 (86%). At last follow-up (mean = 28 weeks), the mean pain reduction was 71%, and 82% of patients had 50% or better pain relief.
Zuidema, Breel, Wille, 2014 (69).	3 of 3 case studies	Case 1: 100% pain relief Case 2: 90% pain relief Case 3: 90% pain relief
Liem, Krabbenbos, Kramer, 2014 (64).	1 of 4 case studies	88% reduction in VAS.
Weigel, Capelle, Krauss 2008 (65).	2 of 3 case studies	Case 1: Despite a successful trial, side effects appeared and effectiveness ceased by 12 months. Case 2: Despite a successful trial, pain returned after 2 months. Reprogramming recaptured paresthesias but not pain relief.
Voorbrood et al., 2015 (49).	1 of 29 patients treated with PNS	One patient had an unsuccessful outcome with PNS and was offered DRG stimulation as the next-line treatment (results of DRG stimulation not presented).
Liem et al., 2013 and 2015 (66, 67).	Not specified. Groin pain could be included if all other inclusion criteria were met. A total of 9 subjects with postsurgical pain and 3 subjects with 'other' pain were included.	51 trial implantations were converted to 32 permanent implants (63%), and overall pain was reduced by 56% from 77.6 mm at baseline to 33.5 at 6 months and 33.6 at 12 months.

PAIN MANAGEMENT CLINICAL PATHWAY RECOMMENDATIONS

Based on this knowledge base and our clinical experience across with approximately 20 patients per year with post-herniorrhaphy chronic neuropathic pain, we have articulated a set of pain management recommendations that form a consistent framework for our treatment decisions (see Figure 2). Broadly, these recommendations align with the philosophy of the World Health Organisation's 'pain ladder', in which milder interventions are trialed first and, if unsuccessful, replaced or augmented with stronger options (17). The recommendations below are from a non-surgical pain management perspective.

Patients with chronic groin pain are typically referred to our pain clinic by their hernia repair surgeons, after it is established (via ultrasound and/or MRI) that surgical options do not exist. We first conduct a physical examination and pain management medical workup in accordance with recommendations for uniform assessment procedures (72, 73). If, during the course of assessments, a hernia recurrence is detected, we refer the

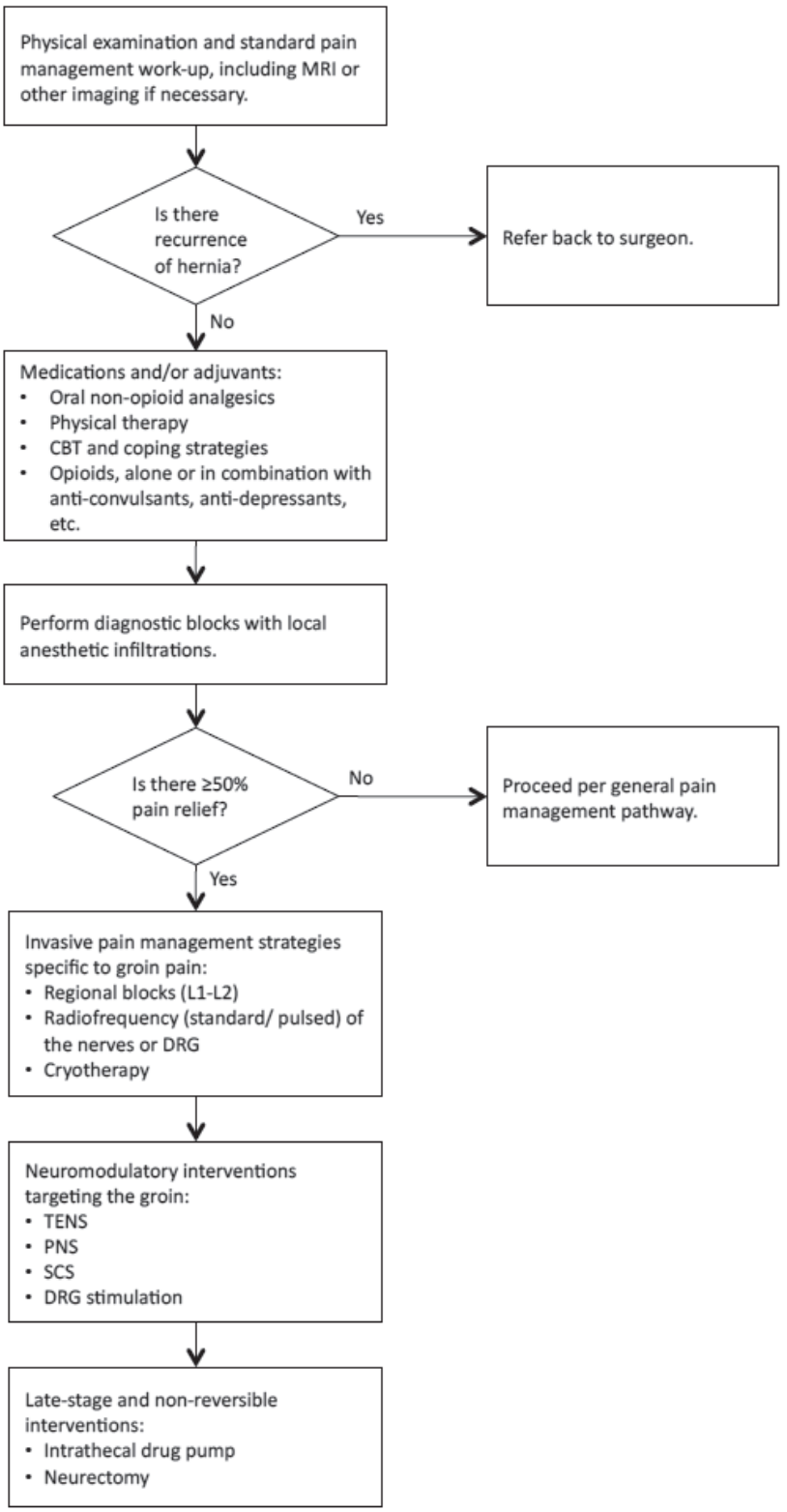


Figure 2. A pain management algorithm.
This algorithm outlines treatment for chronic post-herniorrhaphy neuropathic groin pain.

patient back to the surgeon because there is therefore likely a nociceptive component to the pain that might be amenable to surgical approaches.

Patients with chronic groin pain are typically referred to our pain clinic by their hernia repair surgeons, after it is established (via ultrasound and/or MRI) that surgical options do not exist. We first conduct a physical examination and pain management medical workup in accordance with recommendations for uniform assessment procedures (71, 72). If, during the course of assessments, a hernia recurrence is detected, we refer the patient back to the surgeon because there is therefore likely a nociceptive component to the pain that might be amenable to surgical approaches.

A diagnostic infiltration of local anesthetics at the iliohypogastric or ilioinguinal or genital branch of the genitofemoral nerve (external spermatic nerve) under ultrasound guidance is typically employed. If positive (i.e., 50% groin pain relief), groin-specific pain management interventions are initiated. Unless otherwise indicated, we initially prescribe oral analgesics alongside recommendations for physical therapy and psychological support. If pain relief is inadequate, one or more of the following standard pain management options, all of which are supported by the published knowledge base for a variety of pain etiologies (see Table 2), are trialed according to suitability for the individual presentation: regional lumbar blocks of local anesthetics at L1/L2 (73, 74), pharmacological options such as epidurallocal injections of combinations of other drugs like corticosteroids and clonidine (75, 76), conventional or pulsed RF nerve ablation, pulsed RF at the involved nerves/ DRGs (77, 78, 79, 80), and cryotherapy of peripheral nerves (34). Neurostimulation is trialed if these options are unsatisfactory (81, 82). TENS (83, 84), PNS (57, 85), and SCS (86, 87) may be effective, but In particular, DRG neurostimulation is the preferred modality for groin pain in our clinic because of the ability to achieve specific and discrete coverage of the affected area. If pain remains intractable, implanted intrathecal drug pumps may be considered (88). Neurectomy (89) is considered an option of last resort in serious cases due to its non-reversible nature. Thus, for groin pain we recommend moving neuromodulatory options 'up the pain ladder'. Future research, including the comparison of DRG neurostimulation with neurectomy procedures, will be needed to confirm the validity of this algorithm.

Table 2. Literature evidence for pain management options.

Type of pain management treatment	Reference	Type of report	Evidence summary
Regional blocks	Datta et al., 2007 (73)	Systematic review	"There is strong evidence that nerve root pain may be relieved with a selective nerve root block… and moderate evidence for selective nerve root blocks in the preoperative evaluation of patients with negative or inconclusive imaging studies, but with clinical findings of nerve root irritation."
	Abrahams et al., 2009 (74)	Systematic review and meta-analysis	Risk ratio of nerve block failure of 0.41.

Table 2. Literature evidence for pain management options. (*Continued*)

Type of pain management treatment	Reference	Type of report	Evidence summary
Epidural steroids	Buenaventura et al., 2009 (75)	Systematic review	Level II-1 evidence exists for short-term pain relief and Level II-2 evidence exists for long-term pain relief.
	Abdi et al., 2007 (76)	Systematic review	Strong evidence for short-term pain relief and limited evidence for long-term pain relief.
Radiofrequency (standard/ pulsed) of the nerves or DRG)	Geurts et al., 2001 (77)	Systematic review	Moderate-to-limited evidence for RF procedures being more effective than placebo.
	Chua, Vissers, Sluijter, 2010 (78)	Systematic review	Inadequate evidence of PRF for lumbosacral pain.
	Werner et al., 2012 (79)	Systematic review	Limited evidence for PRF for post-surgical pain following inguinal hernia.
	Pope, Deer, Kramer, 2013 (80)	Systematic review	Evidence is of mixed quality regarding the applicability of RF treatments targeting the DRG.
Cryotherapy	Fanelli et al., 2001 (34)	Observational study	Pain relief up to 100%; 80% of subjects decreased analgesia use.
Neurostimulation (general)	Cruccu et al., 2007 (81)	Society guidelines	Evidence is mixed, but neurostimulation treatments are warranted in intractable cases.
	Johnson and Martinson, 2007 (82)	Meta-analysis	Neurostimulation is an effective treatment modality.
TENS	Khadilkar et al., 2005 (83)	Systematic review	Inadequate evidence of TENS as a sole treatment for back pain.
	Brosseau et al., 2002 (84)	Meta-analysis	Inadequate evidence of TENS as a sole treatment for back pain.
PNS	Verrills et al., 2011 (57)	Observational study	Average pain relief of 57%.
	Deogaonkar and Slain, 2014 (85)	Review	Good outcomes, but few high-quality studies.
SCS	Taylor, 2006 (86)	Systematic review and meta-analysis	Good evidence for use of SCS in FBSS and CRPS.
	Turner et al., 2004 (87)	Systematic review	Studies of mixed quality recommend SCS for pain.
DRG stimulation	See Table 1.		
Intrathecal drug pump	Prager et al., 2014 (88)	Professional consensus	Valuable system carrying both risks and benefits.
Neurectomy	Amid, 2004 (89)	Observational study	80% of patients recovered completely.

CONCLUSIONS

Chronic neuropathic groin pain following herniorrhaphy is a significant problem within pain management and there is a need for well-defined diagnostic criteria and treatment pathways. This paper represents one of the first attempts to develop these clinical tools from a pain management perspective. There is a need for further prospective research on this pain condition.

REFERENCES

1. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101:77-86.
2. Werner MU, Kongsgaard UE. Defining persistent post-surgical pain: is an update required? Brit J Anaesth. 2014;113(1):1-14.
3. Brandon CJ, Jacobson JA, Fessell D, et al. Groin pain beyond the hip: how anatomy predisposes to injury as visualized by musculoskeletal ultrasound and MRI. American Journal of Roentgenology. 2011;197:1190-1197.
4. Hakeem A, Shanmugam V. Current trends in the diagnosis and management of post-herniorraphy chronic groin pain. World J Gastrointest Surg. 2011;3(6):73-81.
5. Heniford BT, Walters AL, Lincourt AE, Novitsky YW, Hope WW, Kercher KW. Comparison of generic versus specific quality-of-life scales for mesh hernia repairs. J Am Coll Surg. 2008;206:638-644.
6. Courtney CA, Duffy K, Serpell MG, O'Dwyer PJ. Outcome of patients with severe chronic pain following repair of groin hernia. Br J Surg. 2002;89(10):1310-1314.
7. Fischer JE. Hernia repair: why do we continue to perform mesh repairs in the face of the human toll of inguinodynia? Am J Surg. 2013;206(4):619-623.
8. Palmqvist E, Larsson K, Anell A, Hjalmarsson C. Prospective study of pain, quality of life and the economic impact of open inguinal hernia repair. Br J Surg. 2013;100(11):1483-1488.
9. Primatesta P, Goldacre MJ. Inguinal hernia repair: incidence of elective and emergency surgery, readmission and mortality. Int J Epidemiol. 1996;25(4):835-9.
10. Burcharth J, Pedersen M, Bisgaard T, Pedersen C, Rosenberg J. Nationwide prevalence of groin hernia repair. PLOS One. 2013;8(1):e54367.
11. Paajanen H, Ristolainen L, Turunen H, Kujala UM. Prevalence and etiological factors of sport-related groin injuries in top-level soccer compared to non-contact sports. Arch Orthop Trauma Surg. 2011;131:261-266.
12. Poobalan AS, Bruce J, Cairns W, et al. A review of chronic pain after inguinal herniorrhaphy. Clin J Pain. 2003;19:48054.
13. Chen DC, Amid PK. Prevention of inguinodynia: the need for continuous refinement and quality improvement in inguinal hernia repair. World J Surg. 2014;38:2571-2573.
14. Koning GG, Keus F, Koeslag L, et al. Randomized clinical trial of chronic pain after the transinguinal preperitoneal technique compared with Lichtenstein's method for inguinal hernia repair. Br J Surg. 2012;99:1365-1373.
15. Kehlet H. Chronic pain after groin hernia repair. Br J Surg. 2008;95:135-136.
16. Eklund A, Montgomery A, Bergkvist L, Rudberg C. Chronic pain 5 years after randomized comparison of laparoscopic and Lichtenstein inguinal hernia repair. Br J Surg. 2010;97:600-608.
17. World Health Organization. Cancer pain relief: with a guide to opioid availability - 2nd ed. Geneva: WHO. ISBN 92-4-154482-1.
18. Cunningham J, Temple WJ, Mitchell P, Nixon JA, Preshaw RM, Hagen NA. Cooperative hernia study: pain in the postoperative patient. Annals of Surgery. 1996;224(5):598-602.
19. Poobalan AS, Bruce J, King PM, Chambers WA, Krukowski ZH, Smith WCS. Chronic pain and quality of life following open inguinal hernia repair. Br J Surg. 2001;88(8):1122-1126.
20. Tsirline VB, Colavita PD, Belyansky I, Zemlyak AY, Lincourt AE, Heniford BT. Preoperative pain is the strongest predictor of postoperative pain and diminished quality of life after ventral hernia repair. Am Surg. 2013;79(8):829-836.
21. Powell R, Johnston M, Smith WC, et al. Psychological risk factors for chronic postsurgical pain after inguinal hernia repair surgery: a prospective cohort study. Eur J Pain. 2012;16:600-610.
22. Reinpold WM, Nehls J, Eggert A. Nerve management and chronic pain after open inguinal hernia repair: a prospective two phase study. Ann Surg. 2011;254(1):163-8.
23. Jeroukhimov I, Wiser I, Karasic E, et al. Reduced postoperative chronic pain after tension-free inguinal hernia repair using absorbable suture: a single-blind randomized clinical trial. J Am Coll Surg. 2014;218:102-107.
24. Taylor C, Layani L, Liew V, Ghusn M, Crampton N, White S. Laparoscopic inguinal hernia repair without mesh fixation, early results of a large randomised clinical trial. Surg Endosc. 2008;22(3):757-62.

25. Voropai DA, Akkersdijk WL. Nerve management and chronic pain after inguinal hernia repair. Annals of Surgery. 2015;261(1):e11-e12.
26. Sen H, Sizlan A, Yanarates O, et al. The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol. 2009;26(9):772-776.
27. Kurmann A, Fischer H, Dell-Kuster S, et al. Effect of intraoperative infiltration with local anesthesia on the development of chronic pain after inguinal hernia repair: a randomized, triple-blinded, placebo-controlled trial. Surgery. 2015;157:144-154.
28. Mui WLM, Ng CSH, Fung TMK, et al. Prophylactic ilioinguinal neurectomy in open inguinal hernia repair: a double-blind randomized controlled trial. Ann Surg. 2006;244(1):27-33.
29. Zannoni M, Luzietti E, Viani L, Nisi P, Caramatti C, Sianesi M. Wide resection of inguinal nerves versus simple section to prevent postoperative pain after prosthetic inguinal hernioplasty: our experience. World J Surg. 2014;38(5):1037-43.
30. Nasir IUI, Iftikhar M, Aslam R, Alam J. Chronic postoperative pain following groin hernia repair: a comparison between nerve preservation and nerve excision. Khyber Journal of Medical Sciences. 2015;7(2):226-230.
31. Johner A, Faulds J, Wiseman SM. Planned ilioinguinal nerve excision for prevention of chronic pain after inguinal hernia repair: a meta-analysis. Surgery. 2011;150:534-41.
32. Bischoff JM, Ringsted TK, Petersen M, Sommer C, Uceyler N, Werner MU. A capsaicin (8%) patch in the treatment of severe persistent inguinal postherniorrhaphy pain: a randomized, double-blind, placebo-controlled trial. PLOS One. 2014;DOI: 10.1371/journal.pone.0109144.
33. Bischoff JM, Koscielnak-Nielsen ZJ, Kehlet H, Werner MU. Ultrasound-guided ilioinguinal/iliohypogastric nerve blocks for persistent inguinal postherniorrhaphy pain: a randomized, double-blind, placebo-controlled, crossover trial. Anesth Analg. 2012;114(6):1323-9.
34. Fanelli RD, DeSiena MR, Lui FY, Gersin KS. Cryoanalgesic ablation for the treatment of chronic postherniorrhaphy neuropathic pain. Surgical Endoscopy and Other Interventional Techniques. 2003;17(2):196-200.
35. Walega DR, Chung B. Chronic postherniorrhaphy pain following inguinal hernia surgery: Etiology, risk factors, anatomy, and treatment options. Techniques in Regional Anesthesia and Pain Management. 2011;15(3):104-109.
36. Cohen SP, Stojanovic MP, Crooks M, et al. Lumbar zygapophysial (facet) joint radiofrequency denervation success as a function of pain relief during diagnostic medial branch blocks: a multicenter analysis. The Spine Journal. 2008;8:498-504.
37. Cohen SP, Foster A. Pulsed radiofrequency as a treatment for groin pain and orchialgia. Urology. 2003;61(3):645.
38. Rozen D, Parvez U. Pulsed radiofrequency of lumbar nerve roots for treatment of chronic inguinal herniorraphy pain. Pain Physician. 2006;9:153-156.
39. Rozen D, Ahn J. Pulsed radiofrequency for the treatment of ilioinguinal neuralgia after inguinal herniorrhaphy. Mt Sinai J Med. 2006;73(4):716-8.
40. Alfieri S, Amid PK, Campanelli G, et al. International guidelines for prevention and management of post-operative chronic pain following inguinal hernia surgery. Hernia. 2011;15:239-249.
41. Aasvang E, Kehlet H. Surgical management of chronic pain after inguinal hernia repair. Br J Surg. 2005;92(7):795-801.
42. Vuilleumier H, Hubner M, Demartines N. Neuropathy after herniorrhaphy: indication for surgical treatment and outcome. World J Surg. 2009;33:841-845.
43. Vuilleumier H, Hubner M, Demartines N. Neuropathy after herniorrhaphy: indication for surgical treatment and outcome. World J Surg. 2009;33:841-845.
44. Magnusson N, Gunnarsson U, Nordin P, Smedberg S, Hedberg M, Sandblom G. Reoperation for persistent pain after groin hernia surgery: a population-based study. Hernia. 2015;19(1):45-51.
45. Amid PK. A 1-stage surgical treatment for postherniorrhaphy neuropathic pain. Arch Surg. 2002;137:100-104.
46. Chen DC, Hiatt JR, Amid PK. Operative management of refractory neuropathic inguinodynia by a laparoscopic retroperitoneal approach. JAMA Surg. 2013;148(10):962-7.
47. Campanelli G, Bertocchi V, Cavalli M, et al. Surgical treatment of chronic pain after inguinal hernia repair. Hernia. 2013;17:347-353.
48. Werner MU. Management of persisten post-surgical inguinal pain. Langenbecks Arch Surg. 2014;399:559-569.

49. Voorbrood CEH, Burgmans JPJ, Van Dalen T, et al. An algorithm for assessment and treatment of postherniorrhaphy pain. Hernia. 2015;19(4):571-577.
50. Lange JFM, Kaufmann R, Wijsmuller AR, et al. An international consensus algorithm for managment of chronic postoperative inguinal pain. Hernia. 2015;19:33-43.
51. Thomassen I, van Suijlekom JA, van de Gaag A, Ponten JEH, Nienhuijs SW. Ultrasound-guided ilioinguinal/iliohypogastric nerve blocks for chronic pain after inguinal hernia repair. Hernia. 2013;17:329-322.
52. Ahmed MT. Effect of transcutaneous electrical nerve stimulation on postoperative pain after inguinal hernia repair: a randomized placebo-controlled trial. Turk J Phys Med. 2010;56:170-6.
53. Johnson MI, Bjordal JM. Transcutaneous electrical nerve stimulation for the management of painful conditions: focus on neuropathic pain. Expert Rev Neurother. 2011;11(5):735-753.
54. Possover M. Use of the LION procedure on the sensitive branches of the lumbar plexus for the treatment of intractable postherniorrhaphy neuropathic inguinodynia. Hernia. 2013;17:333-337.
55. Carayannopoulos A, Beasley R, Sites B. Facilitation of percutaneous trial lead placement with ultrasound guidance for peripheral nerve stimulation trial of ilioinguinal neuralgia: a technical note. Neuromod. 2009;12(4):296-301.
56. Rosendal F, Moir L, de Pennington N, Green AL, Aziz TZ. Successful treatment of testicular pain with peripheral nerve stimulation of the cutaneous branch of the ilioinguinal and genital branch of the genitofemoral nerves. Neuromod. 2013;16(2):121-4.
57. Verrills P, Vivian D, Mitchell B, Barnard A. Peripheral nerve field stimulation for chronic pain: 100 cases and review of the literature. Pain Med. 2011;12(9):1395-405.
58. Chen YF, Bramley G, Unwin G, et al. Stimulation of peripheral nerves for the treatment of refractory pain (including peripheral nerve field). Birmingham: Systematic reviews referred by the NICE Interventional Procedures Programme on behalf of the NICE Interventional Procedures Advisory Committee (IPAC).
59. Elias M. Spinal cord stimulation for post-herniorrhaphy pain. Neuromod. 2000;3(3):155-157.
60. Yakolev AE, Ellias Y. Spinal cord stimulation as a treatment option for intractable neuropathic cancer pain. Clin Med Res. 2008;6(3/4):103-106.
61. Yakovlev AE, Al Tamimi M, Barolat G, et al. Spinal cord stimulation as alternative treatment for chronic post-herniorrhaphy pain. Neuromod. 2010;10(13):288-291.
62. Oakley JC. Spinal cord stimulation in axial low back pain: solving the dilemma. Pain Med. 2006;7(S1):S58-S63.
63. Yearwood TL, Hershey B, Bradley K, Lee D. Pulse width programming in spinal cord stimulation: a clinical study. Pain Physician. 2010;13:321-335.
64. Liem AL, Krabbenbos IP, Kramer J. Dorsal root ganglion stimulation: a target for neuromodulation therapies. In: Knotkova H, Rasche D, eds. Textbook of Neuromodulation. Berlin: Springer Science + Business Media; 2014.
65. Weigel R, Capelle HH, Krauss JK. Failure of long-term nerve root stimulation to improve neuropathic pain. J Neurosurg. 2008;108:921-925.
66. Liem L, Russo M, Huygen FJPM, et al. A multicenter, prospective trial to assess the safety and performance of the Spinal Modulation dorsal root ganglia neurostimulator system in the treatment of chronic pain. Neuromodulation. 2013;16(5):471-482.
67. Liem L, Russo M, Huygen FJPM, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. Neuromodulation. 2015;18:41-49.
68. Schu S, Gulve A, Eldabe S, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain-- a retrospective review. Pain Practice. 2015;15(4):293-299.
69. Zuidema X, Breel J, Wille F. Paresthesia mapping: a practical workup for successful implantation of the dorsal root ganglion stimulator in refractory groin pain. Neuromodulation. 2014;17(7):665-669.
70. Levy R, Deer T. Results of the U.S. Pivotal Study; International Perspectives And Comparisons Of Prospective Research: Dorsal Root Ganglion Spinal Stimulation Plenary Session. Paper presented at: International Neuromodulation Society (INS) 12th World Congress, 2015; Montreal.
71. Kehlet H, Bay-Nielsen M, Kingsnorth A. Chronic postherniorrhaphy pain -- a call for uniform assessment. Hernia. 2002;6(4):178-181.

72. Haanpaa M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. Pain. 2011;152(1):14-27.
73. Datta S, Everett CR, Trescot AM, et al. An updated systematic review of the diagnostic utility of selective nerve root blocks. Pain Physician. 2007;10:113-128.
74. Abrahams MS, Aziz MF, Fu RF, Horn JL. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth. 2009;3:408-17.
75. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. Pain Physician. 2009;12(1):233-251.
76. Abdi S, Datta S, Trescot AM, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. Pain Physician. 2007;10:185-212.
77. Guerts JW, van Wijk R, Stolker RJ, Groen GJ. Efficacy of radiofrequency procedures for the treatment of spinal pain: a systematic review of randomized clinical trials. Regional Anesthesia and Pain Medicine. 2001;26(5):394-400.
78. Chua NHL, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications - a review. Acta Neurochir. 2011;153:763-771.
79. Werner MU, Bischoff JM, Rathmell JP, Kehlet H. Pulsed radiofrequency in the treatment of persistent pain after inguinal herniotomy: a systematic review. Regional Anesthesia & pain Medicine. 2012;37(3):340-343.
80. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. Pain Medicine. 2013;14(10):1477-1496.
81. Cruccu G, Aziz TZ, Garcia-Larrea L, et al. EFNS guidelines on neurostimulation therapy for neuropathic pain. Eur J Neurol. 2007;14(9):952-970.
82. Johnson M, Martinson M. Efficacy of electrical nerve stimulation for chronic musculoskeletal pain: a meta-analysis of randomized controlled trials. Pain. 2007;130(1-2):157-165.
83. Khadilkar A, Milne S, Brosseau L, et al. Transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a systematic review. Spine. 2005;30(23):2657-2666.
84. Brosseau L, Milne S, Robinson V, et al. Efficacy of the transcutaneous electrical nerve stimulation for the treatment of chronic low back pain: a meta-analysis. Spine. 2002;27(6):596-603.
85. Deogaonkar M, Slavin KV. Peripheral nerve/field stimulation for neuropathic pain. Neurosurg Clin N Am. 2014;25(1):1-10.
86. Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/ failed back surgery syndrome: results of a systematic review and meta-analysis. J Pain Symptom Manage. 2006;31(4@):S13-S19.
87. Turner JA, Loeser JD, Deyo RA, Sanders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain. 2004;108:137-147.
88. Prager J, Deer T, Levy R, et al. Best practices for intrathecal drug delivery for pain. Neuromodulation. 2014;17(4):354-372.
89. Amid PK. Causes, prevention, and surgical treatment of postherniorrhaphy neuropathic inguinodynia: triple neurectomy with proximal end implantation. Hernia. 2004;8(4):343-9.

7

SPINAL CORD STIMULATION OF THE DORSAL ROOT GANGLION FOR THE TREATMENT OF CHRONIC GROIN PAIN

Modified from:
Spinal cord stimulation of the dorsal root ganglion for groin pain:
a retrospective review
Stefan Schu, Ashish Gulve, Sam ElDabe, Ganesan Baranidharan, Katharina Wolf,
Walter Demmel, Dirk Rasche, Manohar Sharma, Daniel Klase, Gunnar Jahnichen,
Anders Wahlstedt, Harold Nijhuis, Liong Liem.
Pain Pract. 2015;15(4):293-9

ABSTRACT

Spinal cord stimulation (SCS) is a standard treatment option for chronic neuropathic pain. However, some anatomical pain distributions are known to be difficult to cover with traditional SCS-induced paresthesias and/or may also induce additional, unwanted stimulation. We present the results from a retrospective review of data from patients with groin pain of various etiologies treated using neuromodulation of the dorsal root ganglion (DRG). To this end, data from twenty-nine (29) patients with neuropathic groin pain were reviewed. Patients underwent trial therapy where specifically designed leads were implanted at the target DRGs between T12 and L4. Patients who had a successful trial (>50% improvement) received the fully implantable neuromodulation system. Pain scores were captured on a visual analog scale (VAS) at baseline and at regular follow-up visits. In total, twenty-five (25) patients (86.2%) received fully implantable neurostimulators, and the average follow-up period was 27.8 ± 4.3 (standard error of the mean, SEM) weeks. The average pain reduction was 71.4 ± 5.6%, and 82.6% (19/23) of patients experienced a >50% reduction of their pain at the latest follow-up. Individual cases showed improvement with a variety of etiologies and pain distributions; a sub-analysis of post-herniorrhaphy cohort also showed significant improvement. In conclusion, early findings suggest that neuromodulation of the DRG may be an effective treatment for chronic neuropathic pain conditions in the groin region. This technique offers a useful alternative for pain conditions that do not always respond optimally to traditional SCS therapy. Neuromodulation of the DRG provided excellent cross-dermatomal paresthesia coverage, even in cases with patients with discrete pain areas. The therapy can be specific, sustained, and independent of body position.

INTRODUCTION

Chronic pain remains a world-wide issue with almost 40% prevalence in the worldwide population (1). In the U.S., the economic cost associated with chronic pain is estimated between $560-635 billion annually (2). Of the chronic pain conditions, pain of the groin is a common condition, especially after surgical interventions (3). Treatment of post-operative pain of the groin remains a serious public health concern. For example, abdominal wall hernias were the third leading cause of ambulatory care visits for gastrointestinal complaints in the U.S. in 2004 (4). Of those patients with inguinal hernia repairs, an estimated 7-20% of patients have pain after corrective surgery, about 12% of patients reported that the pain impairs function, and approximately 30% is neuropathic in nature (5,3). Chronic, neuropathic pain in these post-surgical cases may be caused by neuronal transection, neuronal entrapment, neuromas, nerve ischemia from post-surgical fibrosis, or nerve compression of the ilioinguinal, iliohypogastric, or genitofemoral nerves.

Non-surgical treatment for chronic pain currently includes pain medications, nerve blocks, and physical therapy; however, many patients are not responsive to these therapies or are not able to tolerate the side effects (2). More invasive treatments can include surgical interventions to release entrapment and/or ablate or repair nerves (2). All of these options are irreversible and may cause side effects like numbness while they may or may not provide relief (5).

Spinal cord stimulation (SCS) can be an effective and reversible treatment option for chronic neuropathic pain (6), and some positive results have been seen using neurostimulation with groin pain (7-10). An early case series from Simspon reported that for six (6) SCS patients with "idiopathic chronic focal pain (loin, groin, etc.)," three patients received substantial benefit and the remaining three received modest benefit (7). Yakovlev et al. published a report of fifteen (15) patients treated with SCS for post-herniorrhaphy pain with good success, including reduced pain and medication use in all patients at twelve (12) months follow-up (8). Lepski et al. presented results of four (4) patients with post-herniorraphy pain who had both SCS and peripheral nerve stimulation (PNS) and showed that while both methodologies showed improved pain relief, the two stimulation modalities were more effective when combined (9). Additionally, Elias reported on two successful SCS cases of post-herniorraphy pain (10).

Effective pain relief with SCS relies on the stimulation-induced paresthesia overlapping the pain area (11). Some anatomical pain distributions, including the groin, are known to be difficult to cover with SCS-induced paresthesias (12) and/or may also induce additional, unwanted stimulation in non-pain areas (12,9). Selective paresthesia coverage of the groin is likely difficult due to the anatomical trajectory of the peripheral nerves into the spinal cord, and the relatively small number of these fibers compared to those relaying information from other body structures. These issues may limit the ability of SCS to successfully treat chronic neuropathic groin pain.

Peripheral nerve field stimulation (PNFS) has also been shown to be successful in the treatment of groin pain in several case series or reports (13-16). However, due to the potential for erosion and migration of the stimulation leads (17), along with the potential

need for high stimulation amplitudes, alternative neurostimulation approaches are still being sought and likely explains the relative paucity of published outcomes.

A new neuromodulation system specifically designed to stimulate the dorsal root ganglion (DRG) (Axium™ Neurostimulator System, Spinal Modulation, Inc.), may provide a promising new avenue for the treatment of chronic pain. The DRG is composed of the cell bodies of the primary sensory neurons before they enter the spinal cord; it is located within the spinal foramen in the lateral epidural space. The DRG is known to be involved in the transduction of pain to the CNS, and neurons in the DRG show pathophysiologic changes during chronic pain states (18). Neuromodulation of the DRG has been shown to reduce neural excitation in vitro (20,21), and patients have been shown to have reduced pain with DRG stimulation in both case studies (20,21) and in a small series of patients (22), and most recently in a multicenter, prospective study (23). Liem et al. showed that DRG stimulation can provide stimulation specificity, positional stability, and long-term relief, a combination that is difficult to obtain in other neurostimulation modalities (23). Consequently, we hypothesized that neuromodulation of the DRG may be especially useful for targeting the groin, a pain area that is difficult to treat with other neurostimulation modalities. We present the results from twenty-nine (29) patients (retrospective chart review data) suffering from groin pain of various etiologies.

METHODS

Data was obtained through a retrospective chart review at 11 sites in Europe. Data release authorization was obtained for each patient before including them in this analysis.

Data analyzed to ensure that the patients had been diagnosed with chronic, intractable neuropathic pain of the groin and had failed other treatment modalities with inadequate pain relief using oral medications and/or interventional procedures or surgical intervention. All patients were 18 years of age or older. Patients with previous posterior fusion, severe foraminal stenosis at the expected target level, presence of current indwelling implantable devices such as cardiac devices, spinal cord or peripheral nerve stimulators, or vascular access catheters, and pregnancy were not considered candidates for implantation. The primary pain area was in the groin, but patients were not excluded if they had pain in other areas as well.

As described in detail in a previous publication (22), patients underwent a procedure to implant quadripolar DRG stimulation leads (Spinal Modulation, Inc., Menlo Park, CA, USA). The dorsal horn receives sensory input from the groin through T11 and L3 DRGs. Leads were placed at these levels until the maximum cumulative pain coverage with stimulation-induced paresthesia was achieved through intra-operative programming (see Figure 27).

Patients were then trailed for three to thirty days with the ultimate duration of follow-up at the discretion of the treating physician based on usual clinical practice for SCS. If the trial stimulation results in >50% pain reduction, patients received a permanent

implant and if necessary, followed by programming. During the follow-up visits, patients had their stimulation parameters reprogrammed if paresthesia did not cover the entire area of discomfort. Overall pain and segmental pain (i.e., groin) were measured using a 0–100 mm visual analog scale (VAS).

RESULTS

Patient Diagnoses

A total of twenty-nine (29) groin pain patients were included in this analysis (see Table 10). The most frequent diagnosis was herniorraphy (N = 13), and the remaining patients had a variety of pain etiologies, many related to post-surgical pain.

Table 10. Diagnosis summary.

Diagnosis Summary	Count
Herniorrhaphy	13
Femoral vascular access†	2
Failed back surgery syndrome (FBSS)	2
Other surgery*	7
Peripheral nerve lesion following kidney surgery	1
Unknown	4
Total	29

*Nerve entrapment (1), Pfannenstiel (1), appendectomy (1), testicular torsion (1), scrotal pain (1), hysterectomy (1), aneurysm (1).
†Damage to genitofemoral nerve in one patient and unknown in the other.

Results of Trial Stimulation

From February 2012 through January 2013, a total of 49 permanent leads were implanted in 29 patients (Mean = 1.69 leads/patient) at 11 centers (Private hospitals: 4, Academic institutions or teaching hospitals: 7). Patients received either one (N=12), two (N=12) or three leads (N=5) to cover their pain area. All leads were placed unilaterally. Each author implanted anywhere between one to eight patients.

Of the twenty-nine (29) patients trialed, the vast majority had a positive trial (N = 25; 86.2%). Diagnoses for the four patients who failed the trial (14.3%) include pain post-herniorrhaphy (3), and pain post-femoral vascular access (1). These patients either had one (N=3) or three (N=1) leads implanted during trial stimulation.

Figure 27 shows fluoroscopies of 2 patients that were implanted with multiple leads during the trial stimulation. Leads were implanted over T10, T11 and T12 DRGs in one patient (left) and over L1 and L2 DRGs in the other (right). During trial stimulation period, it was established that a single lead was enough to provide paresthesia and pain relief in these patients (T12 and L1, respectively). Hence, the other lead(s) were removed during the implantation of the pulse generator.

Aggregate Permanent Implant Outcomes

Data was available for 23 patients with an average follow-up of 27.8 weeks ± 4.3 weeks (standard error of the mean, SEM, median: 26.0 weeks, range: 0-68 weeks). The mean VAS at baseline (N = 25) for this patient cohort was 74.5 ± 1.8 mm, and the mean VAS at follow-up (N = 23) was 20.7 ± 3.9 mm, a mean improvement of 71.4% (± 5.6%). One patient had no follow-up data while one patient had the device removed. A large majority of patients (82.6% or 19 of 23) had an improvement of >50%, and nearly half (47.8%; 11 of 23) had over 80% improvement in their pain score at the last follow-up.

Thirteen patients had follow-up data for 6 months or longer. Their mean VAS at baseline and follow-up were 75.0 ± 2.5 mm, and 24.1 ± 6.1 mm, a mean improvement of 67.5 (± 8.6)%. 76.9% (or 10/13) of these patients had greater than 50% pain relief while 53.8% (or 7/13) had >80% pain relief. Mean follow-up time was 42.5 ± 3.7 weeks for this cohort.

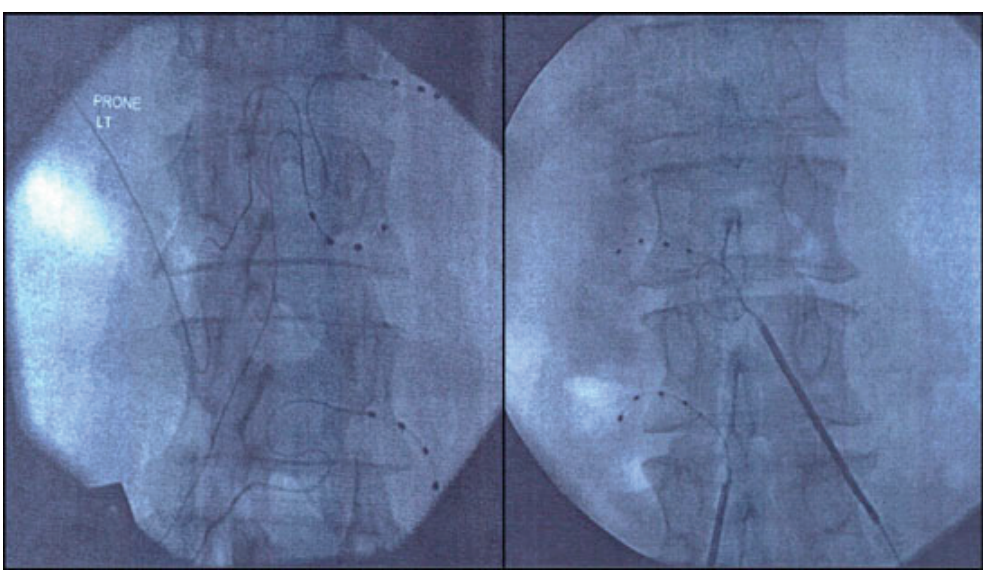


Figure 27. Fluoroscopies of lead placement over target DRGs in 2 patients.

Pain-Paresthesia Maps

Figure 28 shows a patient with a very localized painful area (left) with overlapping paresthesias (right). This example demonstrates that for a focal region of pain, DRG stimulation can be very effective at covering the painful areas without extending paresthesia to non-painful ones.

Figure 29 (a) depicts the pain distribution for another patient with localized pain of the upper thigh at baseline. At the four-week follow-up visit, the area of pain was significantly reduced (Figure 29 (b)). The paresthesia spread was minimal, limited to only

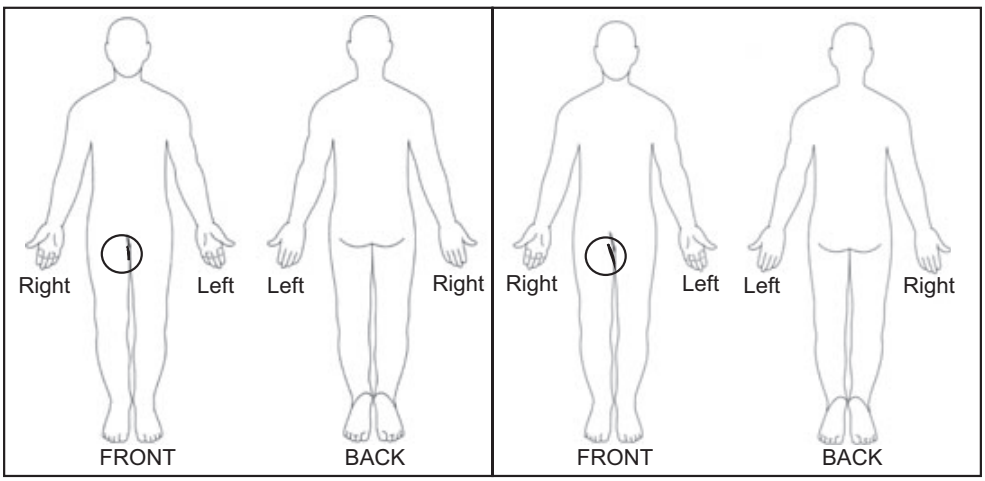


Figure 28. Pain and paresthesia specificity over time.
Pain (left) and paresthesia (right) areas (circled) for one of the patients at 4 weeks demonstrating specificity of paresthesia that can be elicited with DRG neuromodulation.

a very small region. Additionally, the paresthesia was largely unaffected by positional changes (upright vs. supine) (Figure 29 (c) and (d)).

Pain (left panel) and paresthesia (right panel) maps for a third patient are shown in Figure 30. Despite numerous discrete areas of pain, at six months, the stimulation was able to cover 100% of the painful areas while avoiding stimulation in non-painful ones using two leads over L1 and L2 DRGs demonstrating the specificity and temporal stability of this neuromodulatory technique.

Taken together, these examples demonstrate the following aspects of paresthesia elicited by DRG neuromodulation: specificity, avoidance of extraneous coverage, minimal change with position and temporal stability.

Post-herniorrhaphy pain

As discussed above, post-herniorrhaphy pain is an especially common form of groin pain and comprises the vast majority of the patients in our cohort. Twelve patients were trialed for post-herniorrhaphy pain, and of those ten (10; 83.3%) had a successful trial. Ten patients had follow-up data, and the mean follow-up time for these patients was 17.4 ± 5.7 weeks.

Table 11 shows the results from these patients. The mean VAS reduction was 76.8 ± 8.2%. The vast majority of the patients (8 out of 10; 80.0%) had more than 50% improvement in their VAS scores at their last follow-up; 5 of 10 (50.0%) had more than 80% improvement.

Five post-herniorrhaphy pain patients had follow-up data for 6 months or longer. Their mean VAS at baseline and follow-up were 67.6 ± 2.3 mm, and 17.4 ± 7.0 mm, a mean improvement of 74.3 (± 11.0)%. Four out of the five (80%) patients had greater than 50% pain relief while two patients had >80% pain relief. The mean follow-up time was 30.6 ± 7.6 weeks.

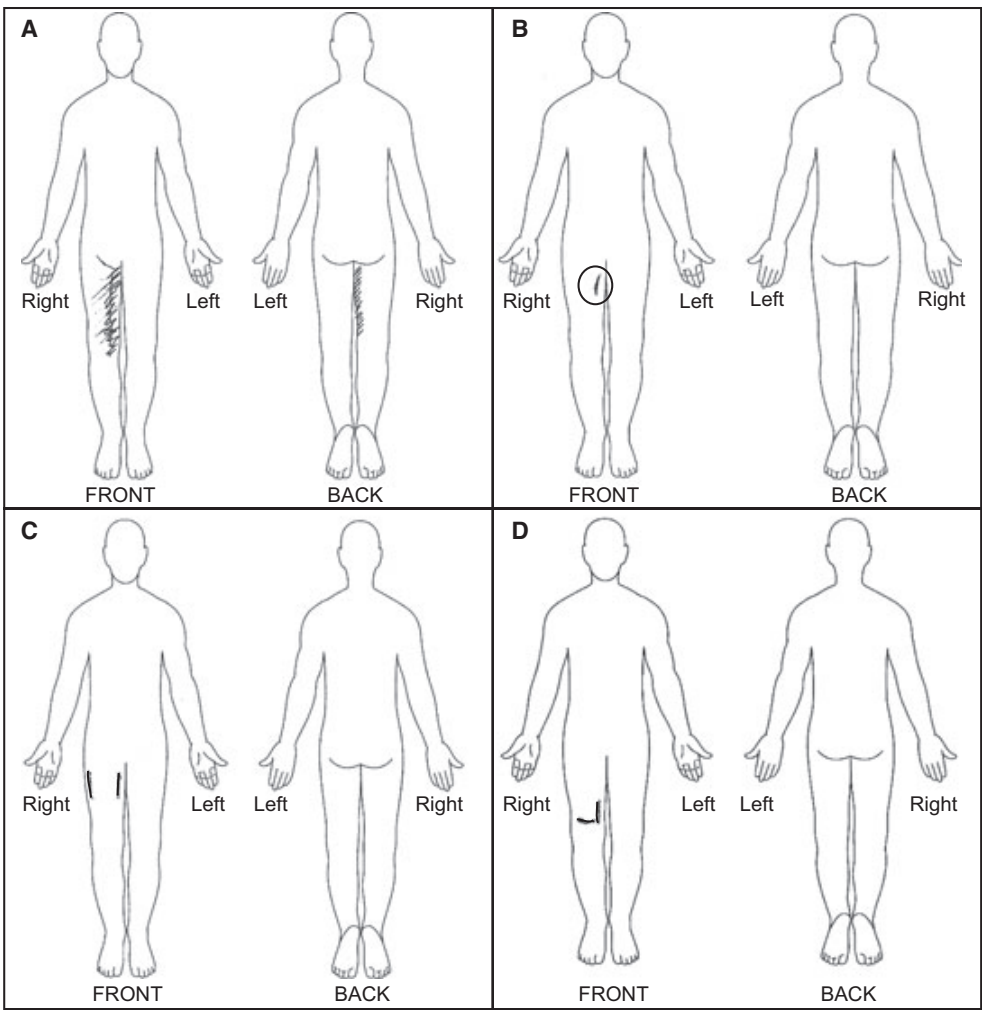


Figure 29. Stability of paresthesia over time and with changes in posture. Pain distribution at (a) baseline and at (b) four weeks post-implant (circled). Paresthesia distribution with the patient (c) upright and (d) supine at four-weeks.

Table 11. Outcomes of postherniorrhaphy pain patients.

	Baseline	Follow-Up
VAS (mean ± SEM) (mm)	73.7 ± 2.8	16.3 ± 5.4
Count	11	10
Patients with > 50% improvement (%)	–	8 (80.0)
Patients with > 80% improvement (%)	–	5 (50.0)

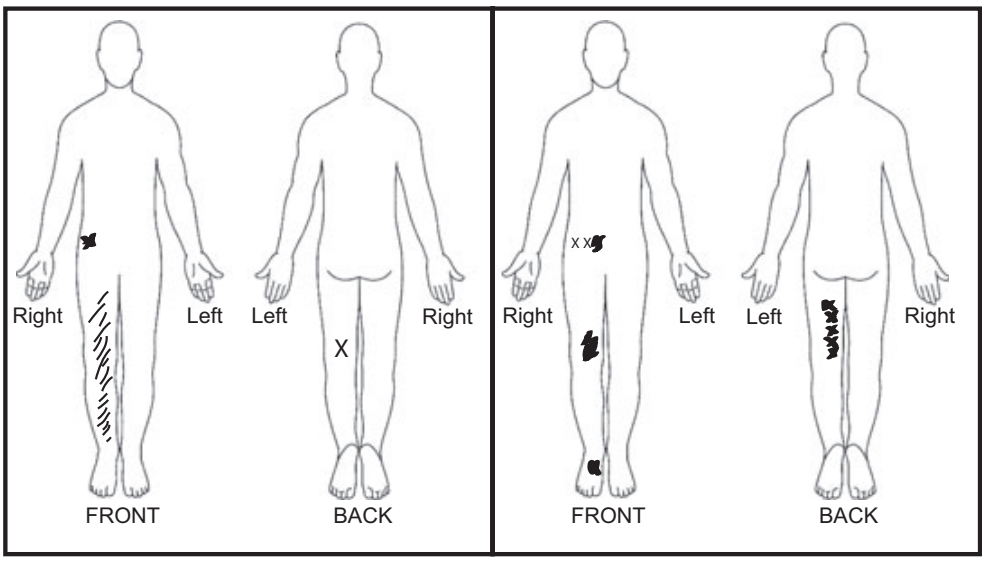


Figure 30. Complete paresthesia coverage and pain relief is obtainable.
At 6 months, one of the patients reported 100% paresthesia coverage (right) over the areas of pain (left) with a VAS of 0 mm.

DISCUSSION

This retrospective review of patients with groin pain receiving DRG stimulation indicates that this modality may offer long-term, sustained, and targeted groin pain relief, a pain area that is difficult to treat with other types of neurostimulation (12). In particular, compared with traditional SCS, the ability to precisely target paresthesia coverage and maintain that specificity with time and changes in body position may be a significant benefit of DRG stimulation. Additionally, we have shown that a subset of patients with post-herniorrhaphy pain show significant improvement with DRG stimulation. While data was not collected at pre-determined intervals as in a prospective study, analysis of data from patients with greater than 6 months follow-up showed stable outcomes with a mean pain relief similar to the entire cohort (68.3% ± 9.3% vs. 71.0% ± 5.6%, respectively).

The advantages of DRG stimulation described here can likely be ascribed to the unique anatomy and physiology of the DRG. The neurons in the DRG provide very specific dermatomal sensory information, and the DRG is housed inside the spinal foramen. When the small Axium™ electrodes are placed along the DRG body in the foramen, the limited cerebral spinal fluid in the space prevents current from spreading and from stimulating the spinal cord or the ventral root. Because the stimulation does not spread, the paresthesias are confined to a specific location represented in the targeted DRG. Especially when compared to SCS or PNFS, the DRG electrodes are also more likely to be stable with body position. Additionally, DRG neurons have been shown to be hyperexcitable in some neuropathic pain disorders (24), and may become more excitable after peripheral nerve damage (25). Koopmeiners et al. have shown

that DRG stimulation suppresses the neuronal firing of the DRG cells, which may be the mechanism through which DRG stimulation relieves neuropathic pain (19).

For groin pain, these advantages appear to be especially pronounced, likely due to the innervation of the groin and the anatomy of these nerves as they enter the spinal cord. The groin is primarily innervated by the ilioinguinal, iliohypogastric, or genitofemoral nerves, which enter the spinal foramen at the level of L1 (ilioinguinal and iliohypogastric) and L2 (genitofemoral). From there, these spinal nerves enter the spinal cord at about the level of the T11-T12 vertebrae. (See the review by Gruener and Biller (26) for further information.) Stimulation at these spinal levels is known to also provide paresthesias in the leg and buttocks (27). As noted in Barolat et al., stimulation of the perineum[1] is difficult and paresthesia is often simultaneously perceived in the anterior thigh area (12).

Through the use of DRG neuromodulation at the level of L1 and L2, we gain direct access to the nerves that innervate the groin, providing focused paresthesias and pain relief. In contrast, stimulation of the dorsal columns at the level of T11-L1 likely stimulates leg and buttocks fibers, which are larger and more plentiful. At this level, there is also a significant amount of CSF that spreads out stimulation, often to unwanted areas (27).

CONCLUSIONS

This paper shows the first results of DRG stimulation for the treatment of chronic neuropathic groin pain and is, to our knowledge, the largest reported cohort of groin pain patients treated with neurostimulation. Results indicate that DRG stimulation may be a useful therapy for the treatment of this common and difficult-to-treat condition. Additional prospective studies are necessary to further show the benefit of DRG stimulation for the treatment of groin pain.

[1] In this paper, the larger groin area is all labeled as the "perineum."

REFERENCES

1. Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, Borges GL, Bromet EJ, Demytteneare K, de Girolamo G, de Graaf R, Gureje O, Lepine JP, Haro JM, Levinson D, Oakley Browne MA, Posada-Villa J, Seedat S, Watanabe M: Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *J Pain* 2008, 9(10):883-91.
2. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. Washington (DC), National Academies Press (US) 2011.
3. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS: The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain* 2013, 154(1):95-102.
4. Everhart JE, Ruhl CE: Burden of digestive diseases in the United States part I: overall and upper gastrointestinal diseases. *Gastroenterology* 2009, 136(2):376-86.
5. Aasvang E, Kehlet H: Surgical management of chronic pain after inguinal hernia repair. *Br J Surg* 2005, 92(7):795-801.
6. Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS: EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol* 2007, 14(9):952-70.
7. Simpson BA: Spinal cord stimulation in 60 cases of intractable pain. *J Neurol Neurosurg Psychiatry* 1991, 54(3):196-9.
8. Yakovlev AE, Al Tamimi M, Barolat G, Karasev SA, Merkulov YA, Resch BE, Yakovleva VE: Spinal cord stimulation as alternative treatment for chronic post-herniorrhaphy pain. *Neuromodulation* 2010, 13(4):288-90.
9. Lepski G, Vahedi P, Tatagiba MS, Morgalla M: Combined spinal cord and peripheral nerve field stimulation for persistent postherniorrhaphy pain. *Neuromodulation* 2013, 16(1):84-8.
10. Elias M: Spinal cord stimulation for postherniorrhaphy pain. *Neuromodulation* 2000, 3(3):155-7.
11. North RB, Ewend MG, Lawton MT, Piantadosi S: Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. *Pain* 1991, 44(2):119-30.
12. Barolat G, Massaro F, He J, Zeme S, Ketcik B: Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man. *J Neurosurg* 1993, 78(2):233-9.
13. Stinson LW Jr, Roderer GT, Cross NE, Davis BE: Peripheral Subcutaneous Electrostimulation for Control of Intractable Post-operative Inguinal Pain: A Case Report Series. *Neuromodulation* 2001, 4(3):99-104.
14. Rauchwerger JJ, Giordano J, Rozen D, Kent JL, Greenspan J, Closson CW: On the therapeutic viability of peripheral nerve stimulation for ilioinguinal neuralgia: putative mechanisms and possible utility. Pain Pract *2008* 8(2):138-43.
15. Verrills P, Vivian D, Mitchell B, Barnard A: Peripheral nerve field stimulation for chronic pain: 100 cases and review of the literature. *Pain Med* 2011, 12(9):1395-405.
16. Rosendal F, Moir L, de Pennington N, Green AL, Aziz TZ: Successful treatment of testicular pain with peripheral nerve stimulation of the cutaneous branch of the ilioinguinal and genital branch of the genitofemoral nerves. *Neuromodulation* 2013, 16(2):121-4.
17. Stuart RM, Winfree CJ: Neurostimulation techniques for painful peripheral nerve disorders. *Neurosurg Clin N Am* 2009, 20(1):111-20.
18. McCallum JB, Kwok WM, Sapunar D, Fuchs A, Hogan QH: Painful peripheral nerve injury decreases calcium current in axotomized sensory neurons. *Anesthesiology* 2006, 105(1):160-8.
19. Koopmeiners AS, Mueller S, Kramer J, Hogan QH: Effect of Electrical Field Stimulation on Dorsal Root Ganglion Neuronal Function. *Neuromodulation* 2013 Feb 19, 16(4):304-11.
20. Wright RE, Colliton JW: Neurostimulation of the L2 dorsal root ganglion for intractable disc pain: description of a novel technique. *IFESS 3rd Annual Conference Proceedings* 1998, Lucerne, Switzerland.
21. Lynch PJ, McJunkin T, Eross E, Gooch S, Maloney J: Case report: successful epiradicular peripheral nerve stimulation of the C2 dorsal root ganglion for postherpetic neuralgia. *Neuromodulation* 2011, 14(1):58-61.
22. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM: A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation* 2013 Jan-Feb;16(1):67-71.

23. Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J: A Multicenter, Prospective Trial to Assess the Safety and Performance of the Spinal Modulation Dorsal Root Ganglion Neurostimulator System in the Treatment of Chronic Pain. *Neuromodulation* 2013;16:471-82.
24. Rush AM, Dib-Hajj SD, Liu S, Cummins TR, Black JA, Waxman SG: A single sodium channel mutation produces hyper- or hypoexcitability in different types of neurons. *Proc Natl Acad Sci* 2006, May;103(21):8245-50.
25. Sapunar D, Ljubkovic M, Lirk P, McCallum JB, Hogan QH: Distinct membrane effects of spinal nerve ligation on injured and adjacent dorsal root ganglion neurons in rats. *Anesthesiology* 2005, Aug:103(2):360-76.
26. Gruener G, Biller J: Spinal Cord Anatomy, Localization, and Overview of Spinal Cord Syndromes. *Continuum: Lifelong Learning Neurol* 2008, 14(3):11-35.
27. Holsheimer J, Barolat G: Spinal geometry and paresthesia coverage in spinal cord stimulation. *Neuromodulation* 1998, Jul;1(3):129-36.

8

THERAPEUTIC STRATEGIES FOR TARGETING THE DORSAL ROOT GANGLION FOR THE TREATMENT OF CHRONIC PAIN

Modified from:
A Review of Spinal Cord Stimulation (SCS) as a Treatment Modality
For Interventional Pain Management
Liem A.L.; van Dongen E.P.A;Huygen F.J.; Staats P.; Kramer J.
(*accepted for publication in Regional Anesthesia and Pain Medicine*)

ABSTRACT

Chronic neuropathic pain is a widespread problem with negative personal and societal consequences. Despite considerable clinical neuroscience research, the goal of development of effective, reliable, and durable treatments has remained elusive. The critical role played by the dorsal root ganglion (DRG) in the induction and maintenance of chronic pain has been largely overlooked in these efforts, however. It may be that, by targeting this site, robust new options for pain management will be revealed. This review summarizes recent advances in the knowledge base for DRG-targeted treatments for neuropathic pain: (1) pharmacological options including the chemical targeting of voltage-dependent calcium channels, transient receptor potential channels, neurotrophin production, potentiation of opioid transduction pathways, and excitatory glutamate receptors; (2) ablation or modulation of the DRG via continuous thermal radiofrequency and pulsed radiofrequency treatments; (3) implanted electrical neurostimulator technologies; and (4) interventions involving the modification of DRG cellular function at the genetic level by employing viral vectors and gene silencing methods.

INTRODUCTION

Patients commonly perceive pain in a defined anatomical region, and although neuropathic pain may have been initiated by peripheral nerve injury, the entire somatosensory system is involved. Pain management strategies have been developed that target the nervous system at various sites. For peripheral nerve involvement, oral and topical medications, local anesthetic and corticosteroid injections (1, 2), neurolysis (3), and peripheral nerve stimulation (PNS) have been utilized (4). Similarly, the spinal cord has been targeted with intrathecal drug delivery devices (5) and spinal cord stimulation (SCS; 6). Brain sites in the pain projection system have seen a number of systemic medications deployed, including several antidepressant and anticonvulsants as first and second line agents, as well as third line agents such as opioids (1 ,7). These therapies, although in use for decades, are suboptimal for many patients. Neuropathic pain is problematic for as many as 11.2% of general-practice patients (8), and many continue to experience intractable pain and/or unacceptable side effects. The link between chronic pain and suicidality (9) suggests that current gold-standard treatments are inadequate. In recent years, there has been renewed interest in the preclinical and early-clinical search for novel and effective strategies that target specific sites in the nervous system.

The dorsal root ganglion (DRG) is one such target, with multimodal opportunities for pain management. Previously, the DRG had been largely overlooked in pain management algorithms, either because structural access was too difficult, it was considered redundant to other (treated) neural targets, or it was considered mechanistically unimportant. However, because the DRG is the structure at the communication point moving from the peripheral to the central nervous system, it requires critical re-examination regarding its functional role in the initiation and maintenance of chronic pain (10 , 11, 12). This review is intended to summarize current pain medicine literature pertaining to the DRG and its role in emerging treatment strategies.

PHYSIOLOGY AND PATHOPHYSIOLOGY OF THE PRIMARY SENSORY NEURON

A complex interplay between the peripheral and central nervous systems underlies the perception of somatosensory events. The DRG is located, both anatomically and functionally, at the junction of the two. A DRG appears bilaterally on each sensory dorsal root, proximal to the peripheral mixed nerve's point of convergence with motor efferent fibers (13, 14), although it is noted that additional unmyelinated afferents enter the spinal cord via ventral roots (15).

Although descended from common progenitor cell lines with the spinal cord (16, 17) and encapsulated in the dural sac with the rest of the central nervous system, peripheral arborizations are a major proportion of many DRG cells (18). The DRG contains the somata of primary sensory neurons (PSNs), a population comprised of large cells that are lightly-staining (Aα and Aβ neurons) and of small darkly-staining cells (Aδ and C neurons,

involved in nociception; 10). A large proportion of the cellular makeup of the DRG, however, are satellite glial cells (SGCs), which invaginate the microvilli-covered surfaces of PSNs and completely envelop them. Despite the physical insulation from other PSNs that this creates, electrophysiological recordings have shown that PSN membrane depolarizations induce subthreshold excitations in neighboring PSNs (18). This is likely via deployment of the complex neurochemical system expressed in PSNs, although it has been demonstrated that SGCs may also take an active role in bidirectional cellular communication within the DRG (19). PSNs are pseudo-unipolar; a single process extends from each cell body to bifurcate in the white matter of the dorsal root. One process extends into the periphery, for meters in some cases, and terminates in somatosensory transduction receptors (encapsulated mechanoreceptors or bare nerve endings). The proximal process terminates in the superficial layers of the dorsal column of the spinal cord (14). An action potential generated by sensory impulses from the periphery may result in depolarizations in the DRG, or may simply continue through to the proximal process and the spinal cord, thus bypassing the DRG altogether (20). This is a unique property of the DRG resulting from its embryological origin as a bipolar neuron prior to differentiation into its adult pseudo-unipolar phenotype (21). The receptive fields of DRGs can be discrete and sub-dermatomal (22), likely due to the inter-segmental convergence of DRG projections or branching of PSN dendrites (23, 24, 25).

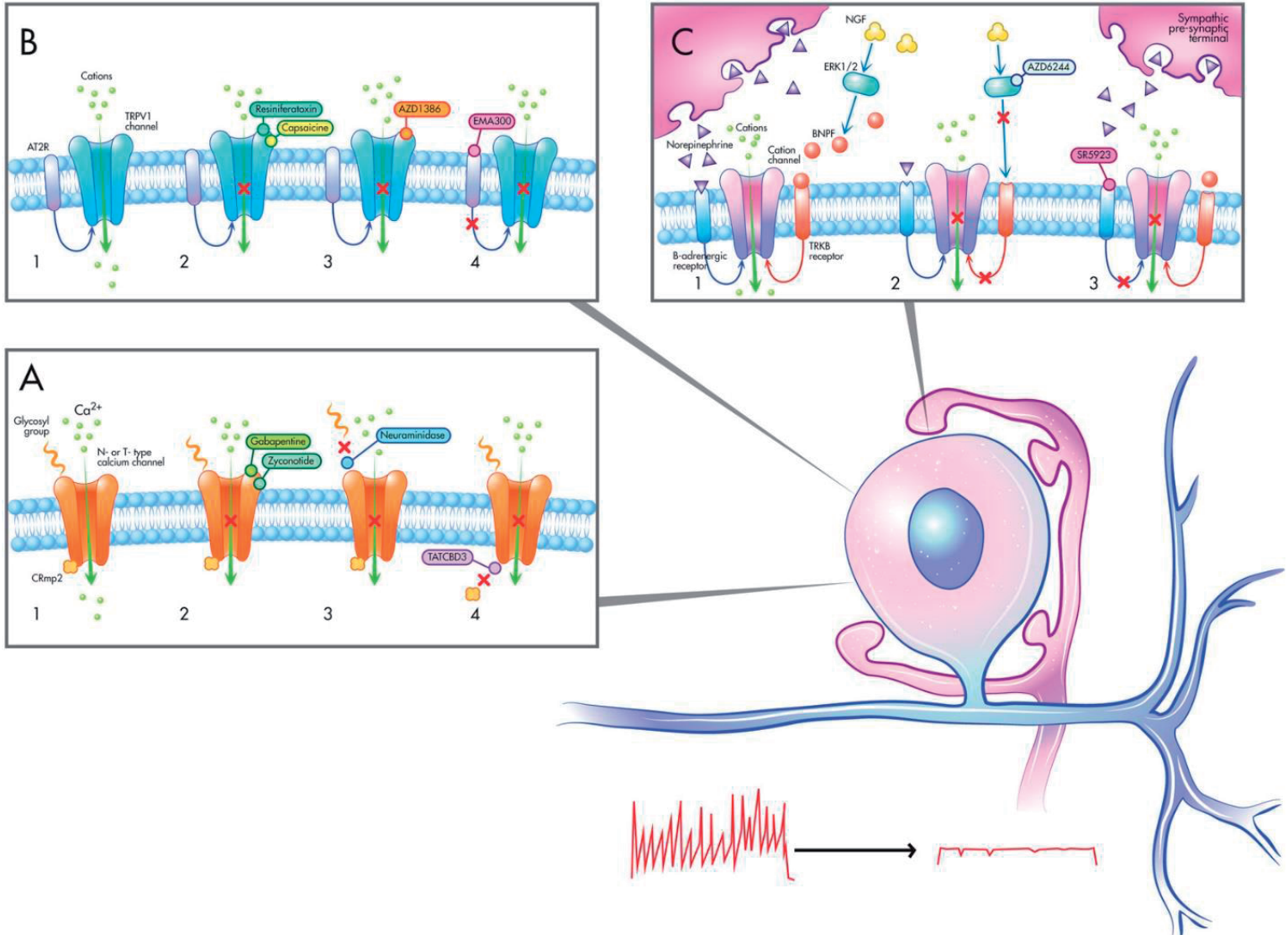
CHEMICAL TARGETING OF THE DRG

Nociceptors in the DRG are sensitive to a rich array of chemoligands and signaling molecules, all of which are ripe for investigation (see Figure 1). The sensitization of primary sensory neurons is due to increased cell surface trafficking of a number of pain-facilitating structures (26). For example, DRG neuron cell membranes richly express voltage-dependent calcium channels. At depolarized membrane potentials (i.e., resulting from activity at ligand-gated ion channels), the channels are activated and their permeability greatly increases, allowing rapid influx of calcium ions into the neuron. Intracellular calcium can then initiate biochemical cascades such as neurotransmitter release at presynaptic terminals in the dorsal horn of the spinal cord. A number of pharmacologically-distinct voltage-dependent calcium channels exist; N- and T-type channels in the Cav2 and Cav3 gene families are involved in pain perception (27, 28). Chronic pain is characterized by sensitization and hyperexcitation of DRGs; this is thought to be due to the upregulation of N- and T-type channels following nerve injury and subsequent inflammatory response (27). Newer-generation pain medications such as gabapentin and ziconotide target subunits of these calcium channels (27 , 29). Moderate evidence supports the use of oral gabapentin for postherpetic neuralgia and painful diabetic neuropathy (30). The anti-allodynic effects of gabapentin was mediated by blocking surface trafficking of a2d1 and a2d2 heteromeric protein subunits of voltage-gated calcium channels in primary sensory and dorsal horn neurons (26), which suggests a strong theoretical rationale for intrathecal administration of gabapentin, despite the recent failure

of a Phase 2 clinical trial (31). When administered within appropriate therapeutic windows and in a slow titration, intrathecal ziconotide is recommended as a first-line option after conservative medical treatments have failed (32). The side effects associated with off-target blockade of N- and T-type calcium channels may limit the effectiveness of these compounds; for example, ziconotide must be delivered intrathecally to limit the neurocognitive, psychiatric, and ataxic side effects that can be encountered with systematic routes of administration. Thus, one might postulate that more precise administration (e.g., directly at the DRG) of such compounds may be preferable.

In addition, new analgesic pathways are being investigated regarding the regulation of voltage-gated calcium channels in DRG neurons. For example, collapsin response mediator protein 2 (CRMP2) is a regulator peptide of the Cav2.2 channel. A CRMP2 antagonist, TAT-CBD3, interfered with CRMP2- Cav2.2 interactions and acutely inhibited Cav2.2 currents and reduced nocifensive behaviors in a rodent model of hypersensitivity. This was achieved with systemic injections (in contrast to intrathecal delivery) and lower safety concerns than with direct Cav2.2 blockade (27). Similarly, in rodent models with painful neuropathies associated with streptozocin (STZ)-induced diabetes, inhibition of the glycosylation of Cav3.2 via neuraminidase reduced calcium currents in small DRG cells and reduced hyperalgesia via peripheral injections (33).

Transient receptor potential (TRP) channels are chemoreceptors that detect noxious signals; the most thoroughly-studied of this family is the mammalian TRPV1 or vanniloid channel. TRPV1 receptors are activated by capsaicin, low-pH conditions with free hydrogen ions (a by-product of inflammation), and heat, allowing inward nonselective cationic transmembrane traffic. Cell membranes of DRG neurons contain large amounts of TRPV1 and TRPA1 channels. Because their translation is upregulated by the inflammatory responses that accompany nerve injury (34), and TRPV1 knockout mice display attenuated thermal hyperalgesia (35), it has been established that these channels are involved in nociception. Topical application of capsaicin is an established analgesic due to the paradoxical desensitization of TRPV1 with prolonged agonist exposure (36). Similarly, injections of resiniferatoxin (a capsaicin analogue) at the site of the sensory ganglia results can temporarily desensitize or permanently anesthetize the region of pain via selective neurotoxicity--a so-called molecular scalpel (37). TRPV1 antagonists have been demonstrated to be effective in animal models of neuropathic pain, postoperative pain, cancer, and osteoarthritis (35). A number of TRP antagonist compounds are in clinical development (34); for example, recent early-phase trials of oral AZD1386 have shown it to provide rapid analgesia for esophageal pain and tooth-extraction pain (38, 39). In humans, TRPV1 antagonists are generally well-tolerated aside from transient hyperthermia symptoms (35). TRPV1 channels can also be targeted by 'upstream' pharmacomodulation, such as via antagonism of the angiotensin II Type 2 receptor (AT2R) to produce analgesia by blocking phosphorylation of TRPV1 channels in the DRG (40). Such strategies, and the local and/or intrathecal application of TRPV1 antagonists may be valuable in avoiding involvement of the TRPV1 populations expressed in the hippocampus because they may be involved in learning/memory and depression (35).


B
Cations
TRPV1 channel
AT2R
Resiniferatoxin
Capsaicine
AZD1386
EMA300
1
2
3
4
C
NGF
ERK1/2
AZD6244
Sympathic pre-synaptic terminal
Norepinephrine
Cations
Cation channel
BNPF
SR5923
B-adrenergic receptor
TRKB receptor
1
2
3
A
Glycosyl group
Ca2+
N- or T- type calcium channel
Gabapentine
Zyconotide
Neuraminidase
TATCBD3
CRmp2
1
2
3
4

The role of glia in the genesis of chronic pain has been studied in the dorsal horn of the spinal cord (41, 42) and in the DRG (43, 44). Certainly, primary sensory neurons play a role in the activation of glia via downstream neurotransmitter release in the dorsal horn (41). As an intermediary in the pathophysiologic process within the DRG itself, however, the role of glial cells is less well-known. Histologic and functional studies have demonstrated that glia can form functional units with neuronal somata within the DRG (45). Although the exact ramifications of these cell-cell connections are unknown, it is interesting to speculate on the effects gap junctions might play when a therapeutic electrical field in placed across the ganglia. Because it is reasonable that glia may modulate the functioning of DRG neurons in pathological pain conditions, these cellular populations deserve more attention.

Neurotrophins play a role in pain signaling in the DRG and, as such, are another target for chemical modulation at this structure. Nerve growth factor (NGF) is released by injured DRG neurons in neuropathic pain conditions, thus contributing to sensitization (46). The role of neurotrophins has been established via the relatively pain-insensitive phenotype of a novel knock-in mouse model that expresses mutant NGF (TrkA) receptors (47). More directly, subcutaneous injections of NGF creates persistent mechanical hyperalgesia in humans. Anti-NGF therapy, by blocking its release or antagonizing the TrkA receptor has dramatically attenuated pain in clinical trials. However, an unacceptably high rate of osteonecrosis makes this approach untenable (46). It may be the case, however, that the relevant neurotrophin signaling in neuropathic pain perception may not lie directly with the NGF-TrkA communication, but rather with

◀ **Figure 1.** Schematic representation of several possible molecular options for chemomodulation of chronic pain at the DRG.

In chronic pain conditions, a number of ion channel structures and chemoligands are upregulated. The resultant increase in activity and membrane trafficking may initiate or maintain pain. Conversely, the targeted reduction in activity at the cellular level can prevent or reverse hypersensitivity and therefore ameliorate pain. (A) N-and T-type Ca channels proliferate in the DRG neuron cellular membrane under neuropathic conditions and are mediated by glycosylation and interaction with the regulator peptide CRMP2. Their inward currents increase nociceptive communication (1). Calcium currents can be reduced via medications that directly target specific subunits of the channel protein structure; gabapentin and ziconotide are two examples of antagonists that are effective pain medications (2). Calcium channel currents can also be inhibited via indirect means; application of neuraminidase inhibits the glycosylation that is necessary for normal channel function (3) and TAT-CBD3 blocks the function of CRMP2 (4). (B) Vanilloid receptors including TRPV1 are upregulated in pain conditions, influenced by the function of its regulator peptide AT2R, and their cationic currents are algogenic (1). Prolonged application of agonists such as capsaicin and resiniferatoxin paradoxically desensitize TRPV1 channels and reduce cationic currents (2), similar to the action of antagonists such as AZD1386 (3). Additionally, antagonism of AT2R with EMA300 reduces TRPV1 currents (4). (C) Neurotrophins play a role in chronic pain. NGF is transported to DRG cell bodies under painful conditions and induces BDNF production via the ERK1/2 pathway. BDNF then binds at TrkB receptors and increases cation channel currents. Neurotrophin activity can also induce sprouting of sympathetic efferents into the DRG. Norepinephrine released from the sympathetic neurons is a ligand for β3 adrenoreceptors, which also induce cationic currents (1). Inhibition of BDNF production via application of AZD6244, an ERK1/2 antagonist, reduces cationic currents (2). Similarly, antagonism of the β3 adrenoreceptor with SR59230 reduces cationic currents (3).

the induction of brain-derived neurotrophic factor (BDNF) in DRG neurons. It has been shown that NGF release activates extracellular signal-regulated kinases 1 and 2 (ERK1/2), which then induce BDNF mRNA. AZD6244, a selective inhibitor of ERK1/2 activation, prevented production of BDNF in vitro, and in a rat model of chronic pain, prevented the establishment of new pain and also reversed existing pain (48).

The release of neurotrophic factors may support the phenomenon of sympathetic nerve sprouting into the DRG under conditions of nerve injury and neuropathic pain induction. Because of this, noradrenaline is released, taken up at the G protein-linked β3 adrenoreceptors, and stimulates the co-release of adenosine triphosphate (ATP) along with other neurotransmitters. This is involved in neuron-glia nociceptive transmission within the DRG and establishes pain. As demonstrated in a rodent model of chronic pain, selective inhibition of β3 adrenoreceptors with SR59230A reduces allodynia (49).

Careful testing of the biochemical cascade that underlies the neural transmission of pain has shown that major reorganizations in the cellular machinery driving protein expression occurs in the presence of chronic nerve injury. Such changes share the activation of adenosine monophosphate kinase (AMPK) as a common factor; this enzyme may therefore be a new target for the treatment of pain. Indeed, treatment of nerve-injured rats with the AMPK activators metformin (a common diabetes medication) and A769662 alleviated neuropathic allodynia whilst also normalizing the cellular biochemistry (50). This may have some applicability to one of the recognized problems with prolonged opioid pain treatment, that being attenuated efficacy over time. In addition to tolerance, opioids ironically counteract their own efficacy by inducing inflammatory responses in DRGs that mimic the responses following nerve injury. These inflammatory response are mediated by matrix metalloproteinases (MMPs), zinc-dependent pro-inflammatory enzymes that break down cellular signaling molecules and are implicated in maintaining chronic pain conditions by influencing neuron-neuron and neuron-glia communication. Because MMPs are the key mechanism for opioid-limitation, molecules that inhibit MMP activity are being developed as enhancers of opioid analgesia (51).

The NMDA receptor is an ionotropic glutamate receptor and it is important in synaptic plasticity, including the unwanted neuroplasticity after neuronal injury that establishes chronic pain. The NR2B subunit of the NMDA receptors is particularly key in chronic pain mediated by the DRG. In the dorsal horn of the spinal cord (the synaptic target of DRG neurons), NR2B subunits are upregulated in a neuropathic pain model of nerve transection. NR2B subunit-containing NMDA receptors are localized primarily in pain-relevant structures and so are a likely target. Local peripheral injections of NMDA receptor antagonists such as MK801 block pain. Similarly, NR2B antagonists, such as ifenprodil and related compounds, are effective in neuropathic pain in animals and in patients, and have a better safety profile than noncompetitive NMDA receptor blockers (52) such as ketamine or memantine (53).

RADIOFREQUENCY TREATMENTS

Conventional continuous thermal radiofrequency (RF) neural ablation and pulsed RF (PRF) are interventions that aim to either ablate or modulate a nerve to provide pain relief (54). RF probes create an electrical circuit with the target tissue at their exposed tip, generating a continuous radiofrequency wave at approximately 1 MHz; the resultant electromagnetic field causes the ions and electrolytes in the surrounding tissue to vibrate and generate heat (54, 55, 56). Probe temperature of 42o-45oC can produce reversible lesions which heal over time (54), but conventional RF delivered at therapeutic levels routinely reach temperatures of up to 80oC 90oC for durations of up to 90 seconds3 minutes, which is well over the neuro-destructive threshold (54, 57, 58). The size of the lesion created is proportional to the probe temperature (depending on the impedance of the target tissue) and duration of application (59). RF ablation targeting the DRG has been well characterized (11), including its use for been described for cervical radicular pain with a positive Spurling (cervical compression) test and diagnostic nerve block (60, 61, 62). In this one study, thermal RF adjacent to the DRG relieved pain at 2 months post-treatment, although some inflammation and loss of muscle strength were reported (54, 63, 56, 57). Another study of RF at cervical DRGs reported no significant differences in outcomes with probe temperatures of 40oC and 67oC (56, 60, 64). In the thoracic region, partial DRG denervation via RF resulted in excellent or good results for over 80% of patients at a median follow-up of 24 months (65).

PRF techniques use similar technology, but energy is delivered in an intermittent fashion; for example, current may be applied in 20 msec pulses at 2 Hz for 120 seconds. Because of the significant proportion of time that the current is switched off, the heat generated during the active circuit phase is "washed out" as it dissipates throughout the surrounding tissue. Thus, higher voltages can be used in PRF than in conventional RF without raising the average temperature into permanently damaging ranges (54, 56, 60, 66). PRF generates minimal tissue damage, most of it at the ultrastructural level (66). For its application in the DRG (11), its mechanism of action appears to might involve expression of activating transcription factor 3, an indicator of cellular stress, specifically in the DRG neurons with small-diameter Aδ and C fibers (67). This may induce neuroplastic changes, such as long term depression, which underpin its pain-relieving properties (66). Because of its favorable safety profile relative to conventional RF especially in regard to the risk of differentiation pain at RF probe temperatures above 42 °C, PRF has rapidly become the preferred modality (56, 60).

PRF at cervical DRG relieved significantly more pain than sham treatment at both 3 and 6 months post-treatment (56, 60, 68, 69). Lumbosacral radicular pain has also been treated via PRF of lumbar DRGs (57, 60); ideal candidates for lumbar RF treatment can be selected using both a thorough neurological exam as well as a positive passive straight leg raise test to identify the involved spinal levels (60, 70). PRF has also been successfully employed for chronic post-herniorrhaphy pain (71). It provides effective pain relief, at least in the short-term (72), and some evidence supports the notion that its efficacy is potentiated by targeting the DRG being a better target (73). However, results have been mixed, and a report of PRF application near the DRG for a number of pain etiologies

showed good outcomes for disc herniation and spinal stenosis, but not for failed back surgery syndrome. This was unexpected, given previous beneficial experiences of PRF for radicular leg pain, but the inclusion of complex mixed neuropathic/nociceptive pain patterns in this patient cohort may have complicated the treatment algorithm (74).

STIMULATION BASED THERAPIES

Neuropathic pain conditions are characterized by aberrant activity in DRG neurons. The inflammatory biochemical cascades initiated by trauma to primary sensory neurons dendrites results in hyperexcitability and a pattern of ectopic discharge (75, 76, 77). Such damage could be initiated by peripheral injuries or by deformities of the vertebral column resulting in mechanical nerve compression (78, 79). It is thought that this pathologically-heightened neural communication to the spinal cord produces the perception of chronic nerve pain, including allodynia (80, 81).

Because it has been established that electrical field stimulation of dissociated DRG cell bodies reduces the frequency and amplitude of their ectopic discharges (82), it would logically follow that neuromodulation interventions applied to the DRG would be effective treatments for pain. The DRG has, indeed, been identified as a critical target for pain neuromodulation by a number of experts (12, 83, 84), and preclinical work has provided converging evidence suggesting that harnessing modulating activity in the DRG could be a primary driver in pain treatments (85, 86, 87).

In humans, epidural spinal cord stimulation (SCS) implantation techniques were modified to bring electrodes in close apposition to dorsal nerve roots (the proximal dendrites of neurons), with some success in achieving adequate paresthesia coverage of painful areas and resultant pain relief (88, 89). Attempts to target the DRG directly for neuromodulation were laborious (90), as gaining access to the foramen with conventional tools was cumbersome. Recently, a specially-designed SCS system incorporating highly flexible small-diameter leads has been introduced, allowing electrodes to be apposed with the DRG cell bodies in the vertebral foramen via standard retrograde percutaneous placement under fluoroscopic guidance. Pain outcomes with this novel approach to neuromodulation have been encouraging; in its first prospective cohort (N=10), pain was reduced by an average of 70% over four weeks (91). Later, a prospective series of 32 subjects with neuropathic pain of mixed etiologies reported 58% overall relief of pain at 6 months post-implant (n=25; 92) and 56% at 12 months (n=25; 93). Effectiveness in pain relief for focal, non-dermatomal distributions of neuropathic pain of the lower extremity (94), knee (95), and groin (96) have also been reported in small samples. Putative benefits of DRG neuromodulation relative to traditional SCS may include the insensitivity of perceptible stimulation intensity to the body's position (97) and the ability to identify the relevant DRGs prior to implant via transforaminal paresthesia mapping, a brief and low-risk procedure (98). The utility of recently-emerged SCS technologies, such as burst (99) and high-frequency stimulation (100) when applied to the DRG is not yet known, but the combination of these approaches would be surmised to open additional neuromodulatory options.

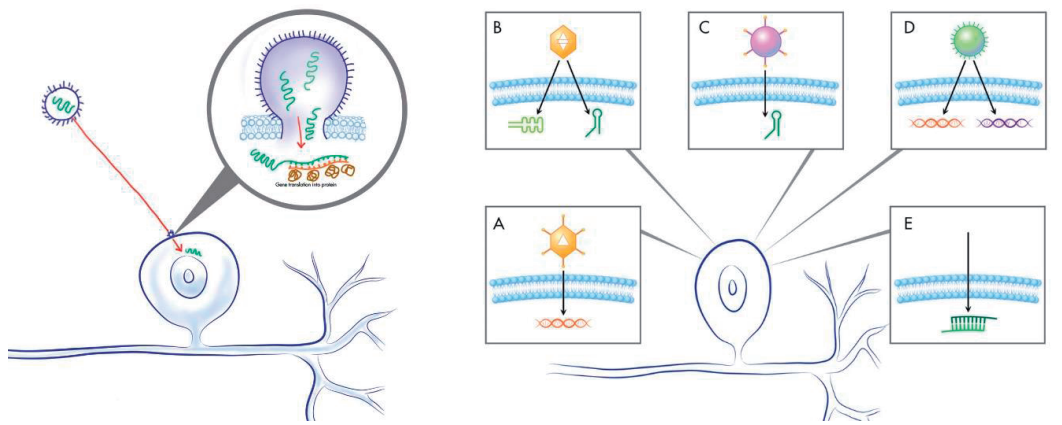


Figure 2. Representational summary of gene therapies for chronic pain targeting the DRG. (Left) The genetic material of interest is engineered and incorporated into a viral vector. The virus penetrates the cell membrane and delivers its genetic payload which up- or downregulates translation into the peptide of interest. (Right) For treating chronic pain, genetic therapies targeting the DRG are in an emerging state and some have been tested only in vitro or in cell cultures. Others, however, have been tested via intrathecal and local subcutaneous (in the region of pain) injections. Reports have included: (A) Helper-dependent adenovirus vector delivery of the Hexb gene; (B) Adeno-associated virus vector delivery of microRNA inducing miR-7a (left) and small hairpin RNA for knockdown of $Na_{1.3}$ (right); (C) Lentivirus vector delivery of small hairpin RNA against TNF-α; (D) HSV-1 vector delivery of the genes for opioid receptor agonists and their precursors (left) and the gene for GAD (right); and (E) Vectorless delivery of small interfering RNA against Rab7 and HDAC6.

GENE THERAPIES

DRG-mediated pain has become a target for the translational application of genetic therapies. The most commonly-applied approach is genetic transfer via viral vectors (Figure 2). For this method, the viral genome is modified to replace the replicating portion of the virus DNA with the therapeutic DNA. When delivered to target cells, the membrane-permeabilizing machinery of the virus is exploited to delivers the therapeutic payload into the cell. Once inside the host cell, the engineered DNA is translated into the protein of interest. Vectors include nonviral plasmid-based gene transfer vectors, adenovirus, adeno-associated virus, and retroviral-based gene transfer systems (101).

In rodent models, helper-dependent adenoviral vectors have proven effective at transducing DRG neurons in vivo, and can be targeted directly to DRG peptides. This vector has demonstrated utility in delivering genetic therapy in knockout mice models of a sensory deficit syndrome, ameliorating genetically-impaired DRG sensory function without affecting CNS or motor system function (102). Similar technology has also been successfully applied to resolve the putative algogenic hyperexcitability of DRG neurons in rodent models of chronic pain. MicroRNA of miR-7a, which inhibits translation of specific genes into proteins and has a role in normal nociception, was transfected into DRG neurons via an adeno-associated virus (AAV) vector. Behavioral testing showed that

chronic neuropathic pain (but not acute pain) was abolished. Cellular hyperexcitability was reduced in vitro, and the over-expression of the β-2 subunit of the voltage-gated sodium channel (103). Downregulation of the voltage-gated sodium channel Na1.3 can also be achieved via AAV vector delivery of small hairpin RNA against Na1.3. There was high transduction efficiency, little behavioral effects due to the surgical procedure, and mechanical allodynia was reduced (104).

Upregulating translation of the analgesic gene prepro-β-endorphin (ppβEP), delivered via AAV vector to DRGs via intrathecal injection, reversed mechanical allodynia in a rat model of neuropathic pain in a naloxone-reversible manner (105). Using complementary methods to down-regulate protein expression, a lentiviral vector used to silence tumor necrosis factor α (TNF-α, a peptide involved in the genesis of neuropathic pain) in a spinal nerve transection mouse model of neuropathic pain reduced molecular markers of neuronal injury and inflammation, and also reduced mechanical allodynia and neuronal cell death in the DRG (106).

Because DRG-mediated pain typically presents in a discrete dermatomal or sub-dermatomal distribution, vectors employing the herpes simplex virus 1 (HSV1) may be particularly well-suited to this application. Therapeutic genes conjugated to replication-defective HSV1 vectors can be injected intradermally in the regions of pain. The vectors are then taken up by the sensory nerve endings and retrogradely transported to DRGs where the proteins of interest are produced. Then they are released into the dorsal horn of the spinal cord to modulate nociceptive neurotransmission. In rodent models of STZ diabetic peripheral neuropathy, four different antinociceptive genes have been thus tested, with varying levels of success: enkephalin, endomorphin, and two forms of the γ-aminobutyric acid (GABA) producing the enzyme glutamic acid decarboxylase (GAD65 or GAD67). The GAD therapies were more effective at reducing mechanical allodynia, proving more effective better as analgesia than gabapentin injections (107).

Early-phase human clinical trials of intradermal injection of the gene for preproenkephalin with a replication-defective HSV1-based vector had a dose-dependent analgesic effect. Such intradermal inoculation has been termed the nerve-targeting drug delivery system (NTDDS) and may also have utility for delivering neuroprotective proteins or other antinociceptive proteins to DRG neurons that lack native supplies (101).

Small interfering RNA (siRNA) methods have also been employed to target DRG-mediated pain. siRNA interferes with the expression of complementary genetic sequences and prevents protein translation. Rab7-mediated lysosomes, which limit the effectiveness of opioids in chronic pain conditions, were silenced via an intrathecal injection of Rab7-siRNA. In these cells, opioid receptors regained their responsiveness to opioids, making this a potentially attractive adjunctive treatment (108). Similarly, the knockdown of histone deacetylase (HDAC) production via siRNA delivery prevented much of the tissue disruption, neuronal degeneration, and aberrant functioning after trauma (109).

CONCLUSIONS

Neuropathic pain is characterized by aberrant hyperactivity in DRGs and as such therefore, the DRG is an attractive target for novel pain relief interventions. All of the approaches outlined in this review – pharmacological, radiofrequency ablation/ modulation, electrical stimulation, and gene therapy —share the same ultimate mechanism of action, which is to achieve an overall reduction of net activity in the DRG and to prevent modulate the pain message from being communicated that the level of the spinal cord. With recent increased interest in interdisciplinary collaboration, medical science is poised to make innovative advances toward personally relevant and cost-effective solutions in pain management. This holds tremendous promise for individuals with intractable conditions and for society as a whole. It is anticipated that future research, especially that involving interdisciplinary collaboration, will uncover additional interventional options at this neural site.

REFERENCES

1. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:162-73.
2. Richards N, McMahon SB. Targeting novel peripheral mediators for the treatment of chronic pain. *Br J Anaesth*. 2013;111(1):46-51.
3. Kyriacou S, Pastides PS, Singh VK, Jeyaseelan L, Sinisi M, Fox M. Exploration and neurolysis for the treatment of neuropathic pain in patients with a sciatic nerve palsy after total hip replacement. *Bone Joint J*. 2013;95-B:20-2.
4. Goroszeniuk T, Pang D. Peripheral neuromodulation: a review. *Curr Pain Headache Rep*. 2014;18:412-422.
5. Wilkes D. Programmable intrathecal pumps for the management of chronic pain: recommendations for improved efficiency. *J Pain Res*. 2014;7:571-577.
6. Wolter T. Spinal cord stimulation for neuropathic pain: current perspectives. *J Pain Res*. 2014;7:651-663.
7. Argoff CE, Viscusi ER. The use of opioid analgesics for chronic pain: minimizing the risk for harm. *Am J Gastroenterol Suppl*. 2014;2:3-8.
8. Shadd JD, Ryan BL, Maddocks H, McKay SD, Moulin DE. Neuropathic pain in a primary care electronic health record database. *Eur J Pain*. 2015;19(5):715-21.
9. Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: an epidemiologic perspective. *Clin J Pain*. 2008;24(3):204-210.
10. Deer TR, Levy RM, Kramer JM. Interventional perspectives on the dorsal root ganglion as a target for the treatment of chronic pain: a review. *Minimally Invasive Surgery for Pain*. 2013;1(1):23-33.
11. Pope JE, Deer TR, Kramer J. A systematic review: current and future directions of dorsal root ganglion therapeutics to treat chronic pain. *Pain Med*. 2013;14(10):1477-1496.
12. Sapunar D, Kostic S, Banozic A, Puljak L. Dorsal root ganglion - a potential new therapeutic target for neuropathic pain. *J Pain Res*. 2012;5:31-38.
13. Blumenfeld H. Neuroanatomy through clinical cases. Sunderland, MA.: Sinauer; 2002.
14. Gray H. *Anatomy: Descriptive and Surgical*. 15 ed. New York, NY: Barnes & Noble, Inc; 2010.
15. Coggeshall RE, Applebaum ML, Fazen M, Stubbs III TB, Sykes MT. Unmyelinated axons in human ventral roots, a possible explanation for the failure of dorsal rhizotomy to relieve pain. *Brain*. 1975;98(1):157-166.
16. Hjerling-Leffler J, Marmigere F, Heglind M, et al. The boundary cap: a source of neural crest stem cells that generate multiple sensory neuron subtypes. *Development*. 2005;132(11):2523-2632.
17. Kalcheim C, Le Douarin NM. Requirement of a neural tube signal for the differentiation of neural crest cells into dorsal root ganglia. *Dev Biol*. 1986;116:451-466.
18. Devor M. Unexplained peculiarities of the dorsal root ganglion. *Pain Suppl*. 1999;6:S27-S35.
19. Zhang X, Chen Y, Wang C, Huang LYM. Neuronal somatic ATP release triggers neuron-satellite glial cell communication in dorsal root ganglion. *PNAS*. 2007;104(23):9864-9869.
20. Kandel ER, Schwartz JH, Jessell TM. *Principles of Neural Science*. Vol 4. New York, NY: McGraw-Hill, Health Professions Division; 2000.
21. Moore KL, Persaud TVN, Torchia MG. *The Developing Human: Clinically Oriented Embryology*. Philadelphia, PA: Saunders/Elsevier; 2008.
22. Kumar K, Rizvi S. Historical and present state of neuromodulation in chronic pain. *Curr Pain Headache Rep*. 2014;18:387.
23. Lee MW, McPhee RW, Stringer MD. An evidence-based approach to human dermatomes. *Clin Anat*. 2008;21:363-373.
24. Malykhina AP, Qin C, Greenwood-Van Meerveld B, Foreman RC, Lupu F, Akbarali HI. Hyperexcitability of convergent colon and bladder dorsal root ganglion neurons after colonic inflammation: mechanism for pelvic organ cross-talk. *Neurogastroenterol Motil*. 2006;18:936-948.
25. Ohtori S, Takahashi K, Yamagata M, et al. Neurones in the dorsal root ganglia of T13, L1 and L2 innervate the dorsal portion of lower lumbar discs in rats. *J Bone Joint Surg*. 2001;83B:1191-4.
26. Ma W, Quirion R. Targeting cell surface trafficking of pain-facilitating receptors to treat chronic pain conditions. *Expert Opin Ther Targets*. 2014;18(4):459-472.

27. Feldman P, Khanna R. Challenging the catechism of therapeutics for chronic neuropathic pain: Targeting CaV2.2 interactions with CRMP2 peptides. *Neurosci Lett*. 2013;557:27-36.
28. Francois A, Pizzoccaro A, Laffray S, Bourinet E. T-type calcium channels in pain neuronal circuits. In: Weiss N, Koschak A, eds. *Pathologies of Calcium Channels*. Berlin: Springer-Verlag; 2014.
29. McGivern JG. Targeting N-type and T-type calcium channels for the treatment of pain. *Drug Discov Today*. 2006;11(5/6):245-253.
30. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. April 2014;4:1-86.
31. Rauck R, Coffey RJ, Schultz D, et al. Intrathecal gabapentin to treat chronic intractable noncancer pain. *Anesthesiology*. 2013;119:675-86.
32. Pope JE, Deer TR. Ziconotide: a clinical update and pharmacologic review. *Expert Opin Pharmacother*. 2013;14(7):957-966.
33. Todorovic SM, Jevtovic-Todorovic V. Targeting of Cav3.2 T-type calcium channels in peripheral sensory neurons for the treatment of painful diabetic neuropathy. *Eur J Physiol*. 2014;466:701-706.
34. Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. *Nat Rev Drug Discov*. 2009;8(1):55-68.
35. Gunthorpe MJ, Chizh BA. Clinical development of TRPV1 antagonists: targeting a pivotal point in the pain pathway. *Drug Discovery Today*. 2009;14(1/2):56-67.
36. Vyklicky L, Novakova-Tousova K, Benedict J, et al. Calcium-dependent desensitization of vanilloid receptor TRPV1: a mechanisms possibly involved in analgesia induced by topical application of capsaicin. *Physiol Res*. 2008;57(Suppl 3):S59-S68.
37. Brederson JD, Kym PR, Szallasi A. Targeting TRP channels for pain relief. *Eur J Pharmacol*. 2013;716:61-76.
38. Krarup AL, Ny L, Astrand M, et al. Randomised clinical trial: the efficacy of a transient receptor potential vanilloid 1 antagonist AZD1386 in human oesophageal pain. *Aliment Pharmacol Ther*. 2011;33(10):1113-22.
39. Quiding H, Jonzon B, Svensson O, et al. TRPV1 antagonistic analgesic effect: a randomized study of AZD1386 in pain after third molar extraction. *Pain*. 2013;154(6):808-12.
40. Smith MT, Woodruff TM, Wyse BD, Muralidharan A, Walther T. A small molecule angiotensin II type 2 receptor (AT2R) antagonist produces analgeisa in a rat model of neuropathic pain by inhibition of p38 mitogen-activated protein kinase (MAPK) and p44/p42 MAPK activation of the dorsal root ganglia. *Pain Med*. 2013;14(10):1557-1568.
41. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nature Rev Neurosci*. 2009;10:23-36.
42. Watkins LR, Maier SF. Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. *Physiological Rev*. 2002;82(4):981-1011.
43. Wu A, Green CR, Rupenthal ID, Moalem-Taylor G. Role of gap junctions in chronic pain. *J Neurosci Res*. 2012;90(2):337-345.
44. Ji RR, Berta T, Nedergaard M. Glia and pain: is chronic pain a gliopathy? *Pain*. 2013;154(Suppl 1):S10-28.
45. Rozanski GM, Nath AR, Adams ME, Stanley EF. Low voltage-activated calcium channels gate transmitter release at the dorsal root ganglion sandwich synapse. *J Physiol*. 2013;591(22):5575-5583.
46. Dai RP, Zhou XF. Neurotrophins and pain. In: Kostrzewa RM, ed. *Handbook of Neurotoxicity*. New York: Springer Science + Business; 2014.
47. Gorokhova S, Gaillard S, Urien L, et al. Uncoupling of molecular maturation from peripheral target innervation in nociceptors expressing a chimeric TrkA/TrkC receptor. *PLOS Genet*. 2014;10(2):e1004081.
48. Matsuoka Y, Yang J. Selective inhibition of extracellular signal-regulated kinases 1/2 blocks nerve growth factor to brain-derived neurotrophic factor signaling and suppresses the development of and reverses already established pain behavior in rats. *Neuroscience*. 2012;206:224-236.
49. Kanno T, Yaguchi T, Nishizaki T. Noradrenaline stimulates ATP release from DRG neurons by targeting Beta3 adrenoceptors as a factor of neuropathic pain. *J Cell Physiol*. 2010;224:345-351.
50. Melemedijian OK, Asiedu MN, Tillu DV, et al. Targeting adenosine monophosphate-activated protein kinase (AMPK) in preclinical models reveals a potential mechanism for the treatment of neuropathic pain. *Mol Pain*. 2011;7:70-84.
51. Berta T. Enhancement of opioid-induced acute analgesia by targeting the peripheral

MMP-9-dependent neuro-glial signalling. *Schwiez Med Forum*. 2013;13(12):258-260.

52. Wu LJ, Zhuo M. Targeting the NMDA receptor subunit NR2B for the treatment of neuropathic pain. *Neurotherapeutics*. 2009;6:693-702.
53. Muir KW, Lees KR. Clinical experience with excitatory amino acid antagonist drugs. *Stroke*. 1995;26:503-513.
54. Panchal SJ, Perni A. Radiofrequency Ablation. In: Wallace MS, Staats P, eds. *Pain Medicine and Management*. New York: McGraw-Hill, Medical Pub. Division; 2005.
55. Saberski L, Fitzgerald J, Ahmed M. Cryoneurolysis and Radiofrequency Lesioning. In: Raj PP, ed. *Practical Management of Pain*. St. Louis, MO: Mosby; 2000.
56. Van Boxem K, Huntoon M, Van Zundert J, Patijn J, van Kleef M, Joosten EA. Pulsed radiofrequency: a review of the basic science as applied to the pathophysiology of radicular pain: a call for clinical translation. *Reg Anaesth Pain Med*. 2014;39(2):149-59.
57. Nagda JV, Davis CW, Bajwa ZH, Simopoulos TT. Retrospective review of the efficacy and safety of repeated pulsed and continuous radiofrequency lesioning of the dorsal root ganglion/segmental nerve for lumbar radicular pain. *Pain Phys*. 2011;14(4):371-6.
58. Cosman ER, Dolensky JR, Hoffman RA. Factors that affect radiofrequency heat lesion size. *Pain Med*. 2014;15(12):2020-2036.
59. Goldberg SN, Gazelle GS, Dawson SL, Rittman WJ, Mueller PR, Rosenthal DI. Tissue ablation with radiofrequency: Effect of probe size, gauge, duration, and temperature on lesion volume. *Acad Radiol*. 1995;2(5):399-404.
60. van Boxem K, van Eerd M, Brinkhuizen T, Patijn J, van Kleef M, van Zundert J. Radiofrequency and pulsed radiofrequency treatment of chronic pain syndromes: the available evidence. *Pain Pract*. 2008;8(5):385-93.
61. van Kleef M, Spaans F, Dingemans W, Barendse GA, Floor E, Sluiijter ME. Effects and side effects of a percutaneous thermal lesion of the dorsal root ganglion in patients with cervical pain syndrome. *Pain*. 1993;52(1):49-53.
62. Viikari-Juntura E, Porras M, Laasonen EM. Validity of clinical tests in the diagnosis of root compression in cervical disc disease. *Spine*. 1989;14(3):253-7.
63. van Kleef M, Liem L, Lousberg R, Barendse G, Kessels F, Sluijter M. Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: a prospective double blind randomized study. *Neurosurg*. 1996;38(6):1127-31.
64. Slappendel R, Crul BJ, Braak GJ, et al. The efficacy of radiofrequency lesioning of the cervical spinal dorsal root ganglion in a double blinded randomized study: no difference between 40 degrees C and 67 degrees C treatments. *Pain*. 1997;73(2):159-63.
65. Stolker RJ, Vervest ACM, Groen GJ. The treatment of chronic thoracic segmental pain by radiofrequency percutaneous partial rhizotomy. *J Neurosurg*. 1994;80(6):986-992.
66. Chua NHL, Vissers KC, Sluijter ME. Pulsed radiofrequency treatment in interventional pain management: mechanisms and potential indications—a review. *Acta Neurochir*. 2011;153(4):73-771.
67. Hamann W, Abou-Sherif S, Thompson S, Hall S. Pulsed radiofrequency applied to dorsal root ganglia causes a selective increase in ATF3 in small neurons. *Eur J Pain*. 2006;10(2):171-176.
68. Van Zundert J, Lame IE, de Louw A, et al. Percutaneous pulsed radiofrequency treatment of the cervical dorsal root ganglion in the treatment of chronic cervical pain syndromes: a clinical audit. *Neuromodulation*. 2003;6(1):6-14.
69. Van Zundert J, Patijn J, Kessels A, Lame I, van Suijlekom H, van Kleef M. Pulsed radiofrequency adjacent to the cervical dorsal root ganglion in chronic cervical radicular pain: a double blind sham controlled randomized clinical trial. *Pain*. 2007;127(1-2):173-182.
70. Vroomen PC, de Krom MC, Knottnerus JA. Diagnostic value of history and physical examination in patients suspected of sciatica due to disc herniation: a systematic review. *J Neurol*. 1999;246(10):899-906.
71. Rozen D, Parvez U. Pulsed radiofrequency of lumbar nerve roots for treatment of chronic inguinal herniorraphy pain. *Pain Physician*. 2006;9:153-156.
72. Simopoulos TT, Kraemer J, Nagda JV, Aner M, Bajwa ZH. Response to pulsed and continuous radiofrequency lesioning of the dorsal root ganglion and segmental nerves in patients with chronic lumbar radicular pain. *Pain Physician*. 2008;11:137-144.
73. Cohen SP, Sireci A, Wu CL, Larkin TM, Williams KA, Hurley RW. Pulsed radiofrequency of the dorsal root ganglia is superior to pharmacotherapy or pulsed radiofrequency of the intercostal nerves in the treat-

ment of chronic postsurgical thoracic pain. *Pain Phys*. 2006;9:227-236.

74. Abejon D, Garcia-del-Valle S, Fuentes ML, Gomez-Arnau JI, Reig E, van Zundert J. Pulsed radiofrequency in lumbar radicular pain: clinical effects in various etiological groups. *Pain Pract*. 2007;7(1):21-26.
75. Wall PD, Devor M. Sensory afferent impulses originate from dorsal root ganglia as well as from the periphery in normal and nerve injured rats. *Pain*. 1983;17:321-339.
76. Kajander KC, Wakisaka S, Bennett GJ. Spontaneous discharge originates in the dorsal root ganglion at the onset of a painful peripheral neuropathy in the rat. *Neurosci Lett*. 1992;138(2):225-228.
77. Zheng Q, Fang D, Cai J, Wan Y, Han JS, Xing GG. Enhanced excitability of small dorsal root ganglion neurons in rats with bone cancer pain. *Mol Pain*. 2012;8:24.
78. Omarker K, Myers RR. Pathogenesis of sciatic pain: role of herniated nucleus pulposus and deformation of spinal nerve root and dorsal root ganglion. *Pain*. 1998;78(2):99-105.
79. Howe JF, Loeser JD, Calvin WH. Mechanosensitivity of dorsal root ganglia and chronically injured axons: A physiological basis for the radicular pain of nerve root compression. *Pain*. 1977;3(1):25-41.
80. Song Y, Li HM, Xie RG, et al. Evoked bursting in injured Aβ dorsal root ganglion neurons: A mechanism underlying tactile allodynia. *Pain*. 2012;153(3):657-665.
81. Kim YI, Na HS, Kim SH, et al. Cell type-specific changes of the membrane properties of peripherally-axotomized dorsal root ganglion neurons in a rat model of neuropathic pain. *Neuroscience*. 1998;86(1):301-309.
82. Koopmeiners AS, Mueller S, Kramer J, Hogan QH. Effect of electrical field stimulation on dorsal root ganglion neuronal function. *Neuromodulation*. 2013;16(4):304-11.
83. Krames ES. The role of the dorsal root ganglion in the development of neuropathic pain. *Pain Med*. 2014;15(10):1669-1685.
84. Liem AL, Krabbenbos IP, Kramer J. Dorsal root ganglion stimulation: a target for neuromodulation therapies. In: Knotkova H, Rasche D, eds. *Textbook of Neuromodulation*. New York: Springer Verlag; 2015.
85. Amir R, Michaelis M, Devor M. Membrane potential oscillations in dorsal root ganglion neurons: role in normal electrogenesis and neuropathic pain. *J Neurosci*. 1999;19(19):8589-8596.
86. Devor M, Janig W, Michaelis M. Modulation of activity in dorsal root ganglion neurons by sympathetic activation in nerve-injured rats. *J Neurophys*. 1994;71(1):38-47.
87. Tu WZ, Cheng RD, Cheng B, et al. Analgesic effect of electroacupuncture on chronic neuropathic pain mediated by P2X3 receptors in rat dorsal root ganglion neurons. *Neurochem Int*. 2012;60(4):379-386.
88. Alo KM, Yland MJ, Redko V, Feler C, Naumann C. Lumbar and sacral nerve root stimulation (NRS) in the treatment of chronic pain: a novel anatomic approach and neuro stimulation technique. *Neuromodulation*. 1999;2(1):23-31.
89. Haque R, Winfree CJ. Transforaminal nerve root stimulation: a technical report. *Neuromodulation*. 2009;12(3):254-257.
90. Lynch PJ, McJunkin T, Eross E, Gooch S, Maloney J. Case report: successul epiradicular peripheral nerve stimulation of the C2 dorsal root ganglion for postherpetic neuralgia. *Neuromodulation*. 2011;14(1):58-61.
91. Deer TR, Grigsby E, Weiner RL, Wilcosky B, Kramer JM. A prospective study of dorsal root ganglion stimulation for the relief of chronic pain. *Neuromodulation*. 2013;16(1):67-72.
92. Liem L, Russo M, Huygen FJPM, et al. A multicenter, prospective trial to assess the safety and performance of the Spinal Modulation dorsal root ganglia neurostimulator system in the treatment of chronic pain. *Neuromodulation*. 2013;16:471-482.
93. Liem L, Russo M, Huygen FJPM, et al. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. *Neuromodulation*. 2015;18(1):41-8.
94. van Bussel CM, Stronks DL, Huygen FJPM. Successful treatment of intractable complex regional pain syndrome type I of the knee with dorsal root ganglion stimulation: a case report. *Neuromodulation*. 2015;18(1):58-60.
95. Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of dorsal root ganglia for the management of complex regional pain syndrome: a prospective case series. *Pain Pract*. 2015;15(3):208-16.
96. Schu S, Gulve A, Eldabe S, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain-- a retrospective review. *Pain Practice*. 2015;15(4):293-9.
97. Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of body positional effects on paresthesias when stimulating

the dorsal root ganglion (DRG) in the treatment of chronic pain. *Neuromodulation*. 2015;18(1):50-7.

98. Zuidema X, Breel J, Wille F. Paresthesia mapping: a practical workup for successful implantation of the dorsal root ganglion stimulator in refractory groin pain. *Neuromodulation*. 2014;17(7):665-669.
99. De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb back pain. *World Neurosurg*. 2013;5:642-649.
100. Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. *Pain Medicine*. 2014;15:347-354.
101. Fink DJ, Wolfe D. Gene therapy for pain: a perspective. *Pain Manage*. 2011;1(5):379-81.
102. Terashima T, Oka K, Kritz AB, Kojima H, Baker AH, Chan L. DRG-targeted helper-dependent adenoviruses mediate selective gene delivery for therapeutic rescue of sensory neuronopathies in mice. *J Clin Invest*. 2009;119(7):2100-2112.
103. Sakai A, Saitow F, Miyake N, Shimada T, Suzuki H. miR-7a alleviates the maintenance of neuropathic pain through regulation of neuronal excitability. *Brain*. 2013;136(9):2738-2750.
104. Samad OA, Tan AM, Cheng X, Foster E, Dib-Hajj SD, Waxman SG. Virus-mediated shRNA knockdown of Na1.3 in rat dorsal root ganglion attenuates nerve injury-induced neuropathic pain. *Mol Ther*. 2013;21(1):49-56.
105. Storek B, Reinhardt M, Wang C, et al. Sensory neuron targeting by self-complementary AAV8 via lumbar puncture for chronic pain. *PNAS*. 2008;105(3):1055-1060.
106. Ogawa N, Kawai H, Terashima T, et al. Gene therapy for neuropathic pain by silencing of TNF-a expression with lentiviral vectors targeting the dorsal root ganglion in mice. *PLoS ONE*;9(3):e92073.
107. Wang Y, Nowicki MO, Wang X, et al. Comparative effectiveness of antinociceptive gene therapies in animal models of diabetic neuropathic pain. *Gene Ther*. 2013;20:742-750.
108. Mousa SA, Shaqura M, Khalefa BI, et al. Rab7 silencing prevents mu-opioid receptor lysosomal targeting and rescues opioid responsiveness to strengthen diabetic neuropathic pain therapy. *Diabetes*. 2013;62:1308-1319.
109. Riveccio MA, Brochier C, Willis DE, et al. HDAC6 is a target for protection and regeneration following injury in the nervous system. *PNAS*. 2009;106(46):19599-19604.

GENERAL DISCUSSION

Modified from:
How can spinal cord stimulation advance chronic pain treatment in 2015?
Liem A.L.; Verrills P.; Bezemer R.; Almirdelfan K.; Levy R.; Kramer J.
(*accepted for publication in Pain Management*)

GENERAL DISCUSSION

History of Neurostimulation: The Evolution of Modern Spinal Cord Stimulation

One of the first instances of the use of electrical stimulation for the treatment of pain dates back thousands of years to the ancient Egyptians, who utilized electrical discharges produced by the Nile catfish to treat pain disorders such as neuralgia and headaches (1,2). The first documented historical account of the use of electrical stimulation for the treatment of pain goes back to circa 15 AD (1, 3). This account describes how an ancient Roman physician, named Scribonius Largus, had used the electrical shock delivered by the torpedo fish as a treatment for gout pain (1, 3).

Electrical stimulation became a commonly used therapy in Western medicine during the 18th century (1). In hospitals in the UK, this medical application of electro-analgesic therapy was commonly referred to as 'Franklinization' or 'Franklinism', thereby crediting the American inventor and statesman, Benjamin Franklin (1). Benjamin Franklin had already gained public notoriety for his work with electricity and was also recognized for investigating the effects of electrical shock to induce muscle contraction (1). The use of electrical stimulation in medicine took a tremendous leap forward in the 19th century with the invention of the electrochemical battery in 1800, followed by the discovery of Faraday's principals of electromagnetic induction and, finally, with the development of the electromagnetic generator by Du Bois-Raymond in 1848 (1). It is these early technological advances that provide the general physical principals, which make modern neurostimulation possible. Even so, electrotherapy came under fire in the late 19th century as "medical quackery" and it was not until the 1930s that electrical stimulation was again reconsidered seriously as an appropriate medical therapy targeting the nervous system (1, 4).

The origin of contemporary neurostimulation is directly linked to the development of cardiac pacemaker technology in the early 20th century (1). It was also at this time that Sir Henry Head, an English neurologist, postulated a theory of *"central inhibition of pain by non-painful stimuli"* (1). It was his work that became the basis for the *Gate Control Theory*, as presented by Melzack & Wall in 1965 (1, 5).

Gate Control is the theory on which modern neurostimulation is based, and it was only two short years later, in 1967, when the first neurostimulation device was implanted by Shealy *et al.* (6, 7). It has been over 40 years since that first implant and the field of neuromodulation has evolved significantly. The aim of this chapter is to: 1) provide a brief introduction of the gate control theory and the general mechanism of action of neuromodulation; 2) review the primary clinical indications for spinal cord stimulation (SCS) modalities and their outcomes; and 3) describe the different iterations in the evolution of SCS technology and discuss the latest innovations in neuromodulation: mainly focusing on DRG stimulation, high-frequency stimulation, and burst-pattern stimulation.

Initial Concepts in Spinal Cord Stimulation: Gate Control Theory and Mechanism of Action

The *Gate Control Theory* is a model that describes the central modulation of pain in the human nervous system (8). This theory provides the basis for understanding the mechanism of action of SCS. To understand the gate control theory, one must first understand that there are many different types of sensory nerve fibers (8). These sensory fibers can be differentiated mainly by their diameter, but also by whether or not they are myelinated and what type of sensory information they carry (8). Generally, large-diameter, densely myelinated fibers (i.e. A-α, A-β fibers) are capable of fast transmission of highly evolved sensory modalities, such as proprioception, vibration, pressure, and fine touch (8). Smaller diameter fibers (i.e. A-δ, C fibers) may be lightly myelinated, or not at all, and are only capable of slower transmission of very rudimentary sensory modalities, such as crude touch, temperature, and pain (8).

The original theory, as described in 1965, suggests that there is a 'gate' which regulates pain signals being transmitted from the dorsal horn of the spinal cord to the brain (1, 5, 8, 9). The activation of afferent small-diameter fibers (which transmit pain signals) cause the gate to remain 'open'; however, the gate can be 'closed' with the activation of large-diameter fibers (1, 5, 8, 9). These large-diameter, heavily myelinated fibers occupy approximately 85% of the white matter tract in the spinal cord, known as the dorsal (posterior) column (1, 8). The fibers of the dorsal column ascend ipsilaterally toward the *dorsal (posterior) column nuclei,* found in the medulla (1, 8). The pathway is collectively referred to as the *dorsal column-medial lemniscal tract* and is responsible for transmitting highly evolved sensory modalities (i.e. vibratory, fine touch, and proprioceptive signals) to the brain (1, 8). The somatotopic organization of the dorsal column is important to note, as it becomes relevant to lead placement in SCS therapy. The fibers of the dorsal column are found mainly on the posterior medial aspect of the spinal cord (1, 8). They are further divided into two 'bundles' as they ascend toward the medulla (1, 8). As the tract ascends toward the brain, fibers are added on laterally with each ascending spinal level (8). Thus, the more lateral of these bundles, known as the *fasciculus cuneatus*, carries information from the upper thorax (above T6), the upper extremities and the neck (8). The medial bundle of fibers, called the *fasciculus gracilis,* is responsible for carrying sensory fibers from the lower extremities and the lower trunk (below T6).

Spinal cord stimulation, in general, operates on the principal that by electrically stimulating the non-nociceptive large-diameter A-β fibers, contained in the dorsal column, the 'gate' is closed and smaller afferent fibers (i.e. C fibers) are unable to transmit pain signals. Although modern SCS is based on the principals of the gate control theory, the exact mechanism is not yet entirely elucidated. Although several theories have been proposed, further research is still required.

Indications for Spinal Cord Stimulation

SCS therapy is typically used in patients with refractory pain despite medical/surgical management (10, 11). SCS involves the placement of electrical leads into the epidural space along the posterior aspect of the spinal cord. The leads are advanced to the

desired spinal levels to be treated and lay upon the dorsal column within the epidural space. The leads are connected to a power supply; typically either an implantable pulsed generator (IPG), which has its own on-board battery, or a radiofrequency receiver, which can be charged by an external device (1). Many modern stimulators are highly programmable; thereby, giving the operator control over several variables in order to "personalize" the stimulator to their needs.

According to Mekhail, *et al., "As many as 50,000 neurostimulators are implanted worldwide each year for a variety of indications"* (6). Clinically, the main indications for SCS include failed back surgery syndrome (FBSS), neuropathic pain, and complex regional pain syndrome (CRPS). The most common indication for SCS is FBSS, which is described as *"…intractable chronic pain that may affect the legs, buttocks, or lower back"* (6, 9). Of the nearly 1.1 million patients annually that have spinal surgery in the USA, approximately *"…40% of these patients will not get (the desired) relief from the surgery and will go on to develop chronic pain"* as a result (6, 12). It is this patient population that is then diagnosed with FBSS.

Initially, FBSS is generally treated conservatively (6). Conservative management generally includes pharmacotherapy, physical therapy, selective nerve blocks, and epidural steroid injections (6). Neurostimulation is reserved mainly for patients with FBSS that is refractory to conservative management. There is a wealth of literature that demonstrates the effectiveness of SCS in patients with FBSS (6, 13-17). According to the literature, success of SCS therapy in patients with FBSS is defined as at least a 50% reduction in pain in addition to an increase in the patient's functionality and activities of daily living (ADL) (6, 14, 18, 19). Despite all the available data on SCS, only two published randomized controlled trials, have evaluated SCS for patients with FBSS (6, 20, 21). The first of these, described by North *et al.,* demonstrated that patients who underwent SCS therapy had more significant pain relief as well as increased functionality as compared to those patients who underwent a surgical revision (6, 21). In that study it was also reported that *"…when given the choice, many patients who received (surgical) reoperation would choose SCS over reoperation"* (6, 21). The second randomized controlled trial, by Kumar *et al.*, evaluated 100 patients with FBSS, predominantly presenting with lower extremity radicular pain (6, 20). Their study demonstrated that in patients with FBSS, presenting as neuropathic pain, SCS therapy with conservative medical management (CMM) was superior to CMM alone (6, 20). At 6 months, 24 of the SCS patients (48% of the group) had achieved a greater than 50% reduction in pain, whereas only 4 of the conservative medical management patients (9% of the group) had similar reductions in pain.

SCS therapy is a very appropriate option for patients with intractable pain. However, it does have some unwanted effects. Due to the nature of stimulation of the dorsal column fibers, patients may experience paresthesia in the area targeted for treatment. This is a result of the types of nerve fibers found in the dorsal column (i.e. A-β fibers) as well as the type of sensory information that these fibers carry. Unfortunately, some patients cannot tolerate the paresthesia. This, in part, has been a driving force to better understand the mechanism of action of SCS therapys as well as the development of newer spinal modulation technologies. The exact mechanism of action is still not well described and further research is necessary.

SCS has been used effectively for the treatment of chronic pain syndromes, such as complex regional pain syndrome and failed back syndrome (22, 23). However, it is not a perfect treatment modality. According to the literature, as many as 20% of patients beginning SCS therapy will not progress past the trial phase (24, 25). In addition, only 50% of patients that undergo a successful trial will continue to have long-term success with a conventional SCS device (10, 21, 24-26). The many factors contributing to the failure of conventional techniques in SCS include: incorrect lead placement, lead migration, difficulty programming the device, and incorrect pulse width, frequency, or amplitude of the waveform, etc. (23-25).

New Targets Within the Spine: Dorsal Root Ganglia

In this thesis we focused on a new anatomical target for neurostimulation: the dorsal root ganglion (DRG). Our aim was to improve the clinical results in difficult patient populations using new and improved technologies. To this end, a multicenter prospective trial was conducted to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the DRG in patients with painful regions of the limbs and/or trunk. We showed the efficacy and safety at 6 months post implantation. The majority of individuals in this 6- month study participated in a further prospective follow-up addressing the maintenance of pain relief, improvement in mood, and quality of life for an additional 6 months after implantation of the active DRG neurostimulator device. In this context, we also investigated what pain indications would benefit most from electrical stimulation of the DRG and we defined appropriate patient selection criteria for this treatment. In addition, we studied pain relief and the maintenance thereof, paresthesia locations, and the stability of the electrodes as well as the effect of posture changes. Furthermore, the aim was also to explore new technologies within the field of neuromodulation of the spinal cord. We look back to see what we have learned over the years and we look forward and discuss the potential future of spinal cord stimulation and, especially, stimulation of the DRG.

SCS at the dorsal root ganglia (DRG-SCS) seems to be a promising new target for the treatment of intractable neuropathic pain (23, 25). In one multicenter prospective trial, designed to assess the safety and efficacy of DRG-SCS, more than half of the patients reported a greater than 50% reduction in pain (25). This study also reported that, at 6 months, overall pain ratings were 58% lower than at baseline ($P<0.001$) (25). In addition, *"…the proportions of subjects experiencing 50% or more reduction in pain specific to back, leg, and foot regions were 57%, 70%, and 89%, respectively"* (25). By changing the target of stimulation from the dorsal column to the DRG, we believe that this new technique may help reduce the failure rate of traditional SCS therapies (23, 25). For example, the bony vertebral structures that surround the DRG may help to provide some defense against lead migration (25). Finally, with certain patient populations (i.e. complex regional pain syndrome) DRG-SCS may actually provide a better outcome than traditional SCS (22, 23, 25). DRG-SCS has the potential to become a very useful modality in that, by changing the anatomical target of stimulation, this modality can be more focused on selective painful regions of the body while also reducing unwanted side-effects of traditional SCS (25).

Since one prominent side-effect from neurostimulation techniques, and in particular from SCS, is the change in intensity of stimulation when moving from an upright (vertical) to a recumbent or supine (horizontal) position, and vice versa, the effects of posture changes on DRG stimulation intensity were investigated using a newly-developed scoring scale. We found that the influence of posture change in DRG neurostimulation is much less than in conventional dorsal column stimulation. This can be explained by the much narrower relation of the stimulator with respect to the stimulated nervous tissue. During posture change, the electrical file in the dorsal column hardly changes. In conventional dorsal column stimulation, the electrical fields reaching the dorsal columns are highly dependent on the width of the spinal liquor area, which is under constant influence of the patient's posture.

Since different patients need different treatments, the next step was to review the literature on SCS therapy and its mechanisms, in order to establish a set of criteria for appropriate patient selection for neuromodulation of the DRG. This is important not only in terms of efficacy, but also in relation to healthcare costs. With the availability of increasing numbers of different therapies, treatment algorithms have to be developed in order to apply the right therapy to the right patients; this is a development towards a more personalized application of medicine. Therefore, we further investigated neuropathic groin pain and its treatment options and recommendations. Based on a review of the literature, we aimed to develop a treatment algorithm for treatment of post-herniorrhaphy pain. Furthermore, we present retrospectively analyzed data from patients with groin pain of various etiologies who were treated with neurostimulation of the DRG; these data show that DRG stimulation is an effective treatment for this form of chronic pain.

A limitation of our studies is the lack of control groups. There is a strong need for randomized controlled trials in which conventional dorsal column stimulation is compared to DRG stimulation. Meanwhile, such a trial has started in the USA: an FDA-controlled trial (NCT01923285). The first preliminary data, as presented at the World Congress of the International Neuromodulation Congress by Levy et al., look very promising. On the primary combined endpoint of efficacy and safety, DRG stimulation shows superiority compared to conventional dorsal column stimulation. However, further research is necessary to assess the appropriate indications for each technique.

Wave Form Patterning – Burst vs. Tonic SCS and High Frequency Stimulation

Another approach to improve the efficacy of neurostimualation could be a change in stimulation wave form pattern. Underlying the basis of all neuromodulation therapies is the manipulation of neural events through chemical or electrical methodologies. The modification of neural events through the use of electrical fields can take many forms including stimulation of excitable cells through membrane depolarization, inhibition of activity through hyperpolarization or activity dependent depolarization block or a hybrid of underlying mechanisms. Of course the application of electrical fields across neural tissues produces a very non-physiologic perturbation – which is ultimately the goal in order to provide an effect or to override a pathologic

disease condition. The predominant stimulation platforms provide tonic frequency stimulation patterns of a fixed frequency.

Recently described by De Ridder *et al.*, burst stimulation is an example of the next step in the evolution of spinal cord stimulator technology (11, 27). According to the literature, this type of stimulation uses *"intermittent packets of closely spaced high-frequency stimuli… The design consists of 40 Hz burst mode with 5 spikes at 500 Hz per burst, with a pulse width of 1 ms…"* (27). A mechanism that may explain the significance of burst stimulation has been proposed in the literature: *"It is known that in the absence of some large A-β fibers, the small unmyelinated C fibers start firing spontaneously..."* (11, 28-30). The literature goes further to describe this spontaneous firing as a "burst pattern" in that the C fibers generate several high frequency bursts of spontaneous action potentials for a short period (11, 28-30). This is attributed to the high input resistance in very small nerve fibers (i.e. C fibers; < 0.3μm) (11, 31, 32). This can allow for *"spontaneous opening of single Na^+ channels at the resting potential (which) can produce 'Na^+ sparks' that can trigger action potentials in the absence of any other input"* (11, 31, 32). Thus, without the inhibitory effect of the A-β fibers on the pain 'gate', C fibers can spontaneously induce hyperalgesia (11, 28-32). It is hypothesized that because burst stimulation 'mimics' the spontaneous burst frequency, produced by the small-diameter fibers (C fibers), of the pain gate, that it results in a more effective therapy than tonic stimulation (11, 33).

The significance of burst frequency SCS is demonstrated, as described by De Ridder *et al.*, via a retrospective two center comparative study, consisting of 102 patients (27). The patients were split into two groups: the first group responded to traditional tonic stimulator treatment while the second group failed tonic stimulator treatment (27). Both groups were eventually switched to the burst spinal cord stimulators. The study measured the response to burst stimulation using the numeric rating scale (NRS) (27). Patients reported an average NRS score of 7.8 at baseline (27). The NRS scores decreased to 4.9 with the conventional tonic stimulation and to 3.2 with burst frequency stimulation (27). The study reports that, collectively, 62% of patients who initially did not respond well to the tonic stimulation did in fact respond to burst stimulation, with an average of 43% pain reduction (27). Of the patients who initially responded well to the tonic stimulation, once switched to burst stimulation, the average reduction in pain rose from 50.6% to 73.6% (27).

Burst stimulation is a very significant development in the field of neuromodulation. One of the reasons why patients may fail conventional stimulation modalities is their inability to tolerate the paresthesia produced by tonic stimulation of the dorsal column (34). The initial data on burst frequency SCS suggests that it may be a superior modality as compared to tonic stimulation (11, 27, 33). Also, burst frequency stimulation has the potential to be a next-line therapy for those patients who fail traditional tonic stimulation therapy. However, it is important that further comparative studies are performed to evaluate the superior efficacy of burst frequency stimulation, as well as its safety.

As noted in the literature, many patients find the paresthesia induced by traditional stimulation to be uncomfortable (34, 35). A new development in SCS technology, using

high-frequency stimulation, has shown promise in providing pain relief for patients without generating paresthesia (34). This high-frequency stimulation, also known as HF10 SCS, generates pulsed frequencies in the range of 10 kHz with a 30 μs pulse width, as compared to traditional tonic stimulators currently on the market which operate in a significantly lower range of about 50 Hz (34, 36). The HF10 SCS waveform is also reported to be biphasic and charge-balanced (34, 36).

Developed under the trade name Senza by Nevro Corp., this high-frequency 10 kHz stimulator is not yet available in the United States. However, preliminary multicenter prospective studies in both the US and the EU have shown very promising results in terms of both safety and efficacy (34, 36, 37). The very first study of this device in the United States was a proof of concept study in which 24 patients, across 5 participating medical centers, were selected to have the HF10 SCS device implanted (34, 36). These 24 patients were selected as they had already met the selection criteria for traditional SCS stimulation (34, 36). However, instead, these patients received only a 4-day trial with the traditional SCS device, which was then followed by another 4-day trial with the HF10 SCS device (34, 36). Outcomes were measured using the visual analog scale (VAS) for pain (34, 36). The results show that, when compared to baseline, there was a significant reduction in both general VAS pain scores: 8.68 - 2.03 (P<0.001) and back pain scores: 8.12 - 1.88 (P<0.001) when treated with the high-frequency stimulation (34, 36). The study also reported that 87.5% of the 24 patients preferred the HF10 SCS device to the traditional stimulator (34, 36).

So far, the data on HF10 stimulation is very promising. This technology has the potential to treat patients with intractable pain without one of the most troublesome adverse reactions of traditional stimulation: i.e. paresthesia. However, the device is not FDA approved for sale in the United States, although it is available for use in the EU. More research is required to evaluate safety and efficacy of the device. Also, randomized controlled trials should be performed to assess andd confirm the superiority of the HF10 SCS system over conventional SCS.

CONCLUSIONS

Since 1967, the field of neuromodulation has evolved and changed significantly. The gate control theory is still generally accepted as the underlying principal behind the function of SCS. However, the mechanism of action is not yet fully elucidated, although several theories have been proposed. Additional research on the exact mechanisms involved in SCS will enhance the development of this technology. Recent neuromodulation evolution has focused on identifying newer, more specific therapeutic targets within the spinal canal, such as DRG-SCS, as well as identifying newer waveforms and frequencies to provide more therapeutically effective stimulation with less or minimal unwanted paresthesia. As it now stands, SCS is still a very important treatment modality for patients with intractable back pain. New developments in SCS will make it a safe and more effective modality, especially for those patients who have exhausted all other available therapies.

REFERENCES

1. Imre P. Krabbenbos, et al., *Mechanisms of Spinal Cord Stimulation in Neuropathic Pain - Chapter 5*, in *Topics in Neuromodulation Treatment*, D.J. Carrillo-Ruiz, Editor. 2012, InTech. p. 89-110.
2. Kane, K. and A. Taub, *A history of local electrical analgesia*. Pain, 1975. **1**(2): p. 125-38.
3. Stillings, D., *The first use of electricity for pain treatment*. Medtronic Archive on Electro-Stimulation, 1971.
4. Chaffee, E.L. and R.U. Light, *A Method for the Remote Control of Electrical Stimulation of the Nervous System*. Yale J Biol Med, 1934. **7**(2): p. 83-128.
5. Melzack, R. and P.D. Wall, *Pain mechanisms: a new theory.* Science, 1965. **150**(3699): p. 971-9.
6. Mekhail, N.A., et al., *Clinical applications of neurostimulation: forty years later.* Pain Pract, 2010. **10**(2): p. 103-12.
7. Shealy, C.N., J.T. Mortimer, and J.B. Reswick, *Electrical inhibition of pain by stimulation of the dorsal columns: preliminary clinical report*. Anesth Analg, 1967. **46**(4): p. 489-91.
8. Blumenfeld, H., *Neuroanatomy through clinical cases*. 2002, Sunderland, Mass.: Sinauer. 263-285.
9. North, R.B., *Chapter 52: Spinal Cord Stimulation*, in *Pain Medicine and Management*, M.S. Wallace and P. Staats, Editors. 2005, McGraw-Hill, Medical Pub. Division: New York. p. 285-289.
10. Cameron, T., *Safety and efficacy of spinal cord stimulation for the treatment of chronic pain: a 20-year literature review.* J Neurosurg, 2004. **100**(3 Suppl Spine): p. 254-67.
11. De Ridder, D., et al., *Is Preoperative Pain Duration Important in Spinal Cord Stimulation? A Comparison Between Tonic and Burst Stimulation*. Neuromodulation, 2014.
12. Wilkinson, H., *The Failed Back Surgery Syndrome: Etiology and Therapy*. 2nd ed. 1991, Philadelphia, PA: Harper and Row.
13. Van Buyten, J.P., *Neurostimulation for chronic neuropathic back pain in failed back surgery syndrome.* J Pain Symptom Manage, 2006. **31**(4 Suppl): p. S25-9.
14. North, R.B. and A.H. Guarino, *Spinal cord stimulation for failed back surgery syndrome: technical advances, patient selection and outcome.* Neuromodulation, 1999. **2**(3): p. 171-8.
15. Devulder, J., et al., *Spinal cord stimulation: a valuable treatment for chronic failed back surgery patients.* J Pain Symptom Manage, 1997. **13**(5): p. 296-301.
16. Burchiel, K.J., et al., *Prospective, multicenter study of spinal cord stimulation for relief of chronic back and extremity pain*. Spine (Phila Pa 1976), 1996. **21**(23): p. 2786-94.
17. Barolat, G., *A Prospective Multicenter Study to Assess the Efficacy of Spinal Cord Stimulation Utilizing a Multi-channel Radiofrequency System for the Treatment of Intractable Low Back and Lower Extremity Pain. Initial Considerations and Methodology.* Neuromodulation, 1999. **2**(3): p. 179-83.
18. Van Buyten, J.P., et al., *Efficacy of spinal cord stimulation: 10 years of experience in a pain centre in Belgium.* Eur J Pain, 2001. **5**(3): p. 299-307.
19. Taylor, R.S., *Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis.* J Pain Symptom Manage, 2006. **31**(4 Suppl): p. S13-9.
20. Kumar, K., et al., *Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome.* Pain, 2007. **132**(1-2): p. 179-88.
21. North, R.B., et al., *Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial.* Neurosurgery, 2005. **56**(1): p. 98-106; discussion 106-7.
22. Van Buyten, J.P., et al., *Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series.* Pain Pract, 2014.
23. Liem, L., et al., *One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion in the Treatment of Chronic Neuropathic Pain*. Neuromodulation, 2014.
24. Kumar, K., G. Hunter, and D. Demeria, *Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience.* Neurosurgery, 2006. **58**(3): p. 481-96; discussion 481-96.
25. Liem, L., et al., *A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain.* Neuromodulation, 2013. **16**(5): p. 471-82; discussion 482.

26. Kumar, K., et al., *The effects of spinal cord stimulation in chronic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation.* Neurosurgery, 2008. **63**: p. 762-770.
27. De Ridder, D., et al., *A Two Center Comparative Study on Tonic Versus Burst Spinal Cord Stimulation: Amount of Responders and Amount of Pain Suppression.* Clin J Pain, 2014.
28. Ali, Z., et al., *Uninjured C-fiber nociceptors develop spontaneous activity and alpha-adrenergic sensitivity following L6 spinal nerve ligation in monkey.* J Neurophysiol, 1999. **81**(2): p. 455-66.
29. Wu, G., et al., *Early onset of spontaneous activity in uninjured C-fiber nociceptors after injury to neighboring nerve fibers.* J Neurosci, 2001. **21**(8): p. RC140.
30. Wu, G., et al., *Degeneration of myelinated efferent fibers induces spontaneous activity in uninjured C-fiber afferents.* J Neurosci, 2002. **22**(17): p. 7746-53.
31. Faisal, A.A., L.P. Selen, and D.M. Wolpert, *Noise in the nervous system.* Nat Rev Neurosci, 2008. **9**(4): p. 292-303.
32. Rall, W., *Time constants and electrotonic length of membrane cylinders and neurons.* Biophys J, 1969. **9**(12): p. 1483-508.
33. De Ridder, D., et al., *Burst spinal cord stimulation for limb and back pain.* World Neurosurg, 2013. **80**(5): p. 642-649 e1.
34. Russo, M. and J.P. Van Buyten, *10-kHz High-Frequency SCS Therapy: A Clinical Summary.* Pain Med, 2014.
35. Barolat, G., et al., *Mapping of sensory responses to epidural stimulation of the intraspinal neural structures in man.* J Neurosurg, 1993. **78**(2): p. 233-9.
36. Tiede, J., et al., *Novel spinal cord stimulation parameters in patients with predominant back pain.* Neuromodulation, 2013. **16**(4): p. 370-5.
37. Van Buyten, J.P., et al., *High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study.* Neuromodulation, 2013. **16**(1): p. 59-65; discussion 65-6.

SUMMARY AND CONCLUSIONS

SUMMARY AND CONCLUSIONS

Our understanding of the role of primary sensory neurons in the development and maintenance of chronic pain of varying diagnoses and etiologies has significantly increased over the past decade. The membrane properties of these cells are altered, which in turn results in an enhanced state of excitability involving multiple ion channels, second messenger systems and other physiological changes. These membrane alterations provide a fundamental opportunity to direct the delivery of therapy to a specific region of pathology as opposed to an upstream or downstream area as is so often the case in palliative neuromodulation techniques.

In Chapter 1, the mechanisms behind spinal cord stimulation are described and it is discussed how DRG stimulation is now technically feasible with recent implantable device innovations and the evidence to support its effectiveness is reviewed. Previous techniques targeting the DRG have yielded excellent results demonstrating not only the safety of targeting the DRG, but also the potential opportunity for developing techniques that can provide longer-lasting pain relief. Preliminary results from completed and ongoing prospective studies suggest that DRG stimulation can provide good pain relief, while avoiding the unwanted side-effects of current neurostimulation techniques.

In Chapter 2, a multicenter prospective trial was described which was conducted to evaluate the clinical performance of a new neurostimulation system designed to treat chronic pain through the electrical neuromodulation of the dorsal root ganglia (DRG), in patients with painful regions of the limbs and/or trunk. It was found that neuromodulation of the DRG was effective for relieving chronic pain and was able to provide discretely defined paresthesia coverage in challenging anatomical regions such as the back and foot. Consistent intensities of paresthesias were reported throughout tests involving different body positions, demonstrating a clinically important lack of positional effects. The device performance demonstrated a good safety profile and subjects experienced improvement in health-related quality of life, mood, and pain symptoms. These results suggest that SCS of the DRG is a robust new tool for the pain physician's armamentarium.

One year post-implantation, as described in Chapter 3, outcomes in the same subjects were revisited prospectively to address the maintenance of pain relief, improvement in mood, and quality of life one year after the implantation of the active DRG neurostimulator device. Improvements in ratings of pain, mood, and quality of life with DRG stimulation were demonstrated for 12 months of therapy. Additionally, there was good agreement between pain-paresthesia overlap and high levels of user satisfaction. Although further study into long-term outcomes with DRG stimulation is needed, particularly in order to differentiate it from SCS and (potentially) peripheral nerve stimulation, the study suggests that this intervention may provide clear benefits.

Subsequently, Chapter 4, described the prospective validation of a newly-developed paresthesia intensity rating scale and compared perceived paresthesia intensities when subjects assumed upright versus supine bodily positions during neuromodulation of the DRG. The DRG neurostimulation system appeared to be largely impervious to the effects of change in position/posture since most causes of this phenomenon in SCS

were either absent, or were largely mitigated with DRG neuromodulation. In this report, neuromodulation of the DRG was shown to produce paresthesias that are minimally susceptible to the biomechanical perturbations seen with different body positions in SCS. Furthermore, paresthesia intensities and coverage locations remained consistent when standing vs. supine, as well as over time (up to 12 months). This is most likely due to the different anatomical structures and neurophysiological pathways associated with DRG neuromodulation, compared with stimulation of the dorsal columns of the spinal cord. DRG neuromodulation is a promising step toward achieving consistently effective pain relief, independent of body position. This study provided supportive evidence for these hypotheses.

Chapter 5, then, reviewed the SCS therapy and its mechanisms, and established a set of criteria for appropriate patient selection for neuromodulation of the DRG stimulation since in a subset of patients, traditional SCS may not provide sufficient pain relief and DRG stimulation may provide a number of advantages. Chronic neuropathic pain is a significant problem within pain management and there is a need for well-defined diagnostic criteria and treatment pathways. This paper represents one of the first attempts to develop appropriate clinical tools from a pain management perspective.

Chapter 6 discussed neuropathic groin pain and its treatment options and recommendations and provided, based on a review of the knowledge base, a treatment algorithm for treatment of post-herniorrhaphy pain. Indications for DRG stimulation are similar to those for conventional dorsal column stimulation and include neuropathic pain located in the trunk or limbs due to FBSS, CRPS, post-surgical neuropathy, and other etiologies. Patient selection criteria may be broader for DRG stimulation than traditional SCS, since clinical evidence suggests that this intervention is highly suited to treatment of focal or challenging locations including foot, knee, back, and groin. Pain conditions that are prone to SCS lead migration or positional effects are especially amenable to treatment with DRG stimulation. As the field of neuromodulation progresses, targeting the DRG may prove to be one of the most substantial technological advances. Further refinement of patient selection will enhance this treatment option for patients suffering chronic pain and potentially other disease states.

In Chapter 7, the results from a retrospective review of data from patients with groin pain of various etiologies treated using neuromodulation of the DRG were presented. This study presented the first results of DRG stimulation for the treatment of chronic neuropathic groin pain and is, based on the literature, the largest reported cohort of groin pain patients treated with neurostimulation. By using DRG neuromodulation at the level of L1-L2, direct access to the nerves that innervate the groin was gained, providing focused paresthesias and pain relief. In contrast, stimulation of the dorsal columns at the level of T11-L1 most likely stimulates leg and buttock fibers, which are larger and more plentiful. At this level, there is also a significant amount of cerebrospinal fluid that disperses stimulation, often to unwanted areas. Results indicate that DRG stimulation may be a useful therapy for the treatment of this common and difficult-to-treat condition. Additional prospective studies are necessary to further explore the potential benefit of DRG stimulation for the treatment of refractory groin pain.

Chapter 8, finally, discussed several novel approaches for neuropathic pain management, including pharmacological intervention, radiofrequency therapy, electrical stimulation, and gene therapy. It described how each of these approaches share the same ultimate mechanism of action; i.e., reducing of the overall net activity in the DRG and preventing the pain message from being communicated to the spinal cord.

SAMENVATTING EN CONCLUSIES

SAMENVATTING EN CONCLUSIES

Gedurende het afgelopen decennium is de kennis omtrent de rol van de primaire sensorische neuronen in het ontstaan en het onderhouden van chronische pijn door verschillende ziekteoorzaken enorm toegenomen. Het is onder andere duidelijk geworden dat de membraaneigenschappen van deze neuronen veranderen tijdens de ontwikkeling van chronische pijn. De primaire sensorische neuronen geraken in een verhoogde exciteerbare status, waarbij meerdere ion-kanalen, second-messenger systemen en andere complexe fysiologische veranderingen betrokken zijn. Het zijn juist deze veranderende membraaneigenschappen die fundamenteel een therapeutische target vormen voor een specifiek klein pathofysiologische gebied. Dit in tegenstelling tot een groter "stroomopwaarts of stroomafwaarts" gebied zoals zo vaak het geval is bij de toepassing van palliatieve neuromodulatie-technieken.

In **Hoofdstuk 1** worden de onderliggende mechanismen voor het gebruik van ruggenmergstimulatie beschreven en wordt DRG stimulatie (de behandeling van chronische pijn door elektrische neuromodulatie van de dorsale root ganglia) bediscussieerd. Door recente innovaties is het mogelijk DRG stimulatie effectief en veilig toe te passen. Een literatuurreview wordt gegeven. Het is niet alleen mogelijk door middel van DRG stimulatie veilig te stimuleren, maar er bestaat ook een potentie om de bestaande technieken verder door te ontwikkelen, zodat langdurige pijnverlichting wordt bereikt. Voorlopige resultaten van voltooide en lopende prospectieve studies suggereren dat DRG stimulatie kan leiden tot een adequate pijnverlichting zonder de ongewenste bijwerkingen van de huidige neurostimulatie-technieken.

In **Hoofdstuk 2** wordt een multicenter prospectieve studie beschreven waarin het klinisch gebruik van een nieuw DRG neurostimulatie-systeem werd geëvalueerd bij patiënten met pijn in de extremiteiten en/of romp. Het bleek dat neuromodulatie van het DRG effectief was in het verlichten van chronische pijn en het mogelijk met behulp van de beschreven techniek discrete stimulatie-paresthesieën te verkrijgen in moeilijk te stimuleren anatomische gebieden zoals rug en voet. De verkregen paresthesieën waren consistent, zelfs tijdens tests met verschillende lichaamshoudingen. Lichaamsposities zijn blijkbaar klinisch irrelevant. De studie beschrijft een apparaat met een goed veiligheidsprofiel en de beschreven studie-patiënten rapporteerden een verbetering in hun gezondheid gerelateerde kwaliteit van leven, een verbetering van hun stemming en minder pijnklachten.

In **Hoofdstuk 3** worden de resultaten 1 jaar na implantatie van een DRG neurostimulatie systeem beschreven. Het betreft dezelfde studie-populatie als in hoofdstuk 2. Pijnverlichting, stemmingsverbetering, en kwaliteit van leven werden weer bestudeerd in deze prospectieve analyse. Op alle onderzochte aspecten werd verbetering gezien 1 jaar na starten van de DRG stimulatie. Tevens was er een goede correlatie tussen de mate van overlappen pijn/paresthesie gebied en de mate van tevredenheid van patiënt-gebruiker. Hoewel verder onderzoek naar de lange-termijn resultaten met DRG stimulatie nodig is, met name ook om de positie van DRG stimulatie ten opzichte van SCS en perifere zenuwstimulatie vast te stellen, suggereren deze eerste resultaten duidelijk al voordelen.

Vervolgens wordt in **Hoofdstuk 4** de prospectieve validatie van een nieuw ontwikkeld "paresthesia intensity rating scale" beschreven. Gedurende neuromodulatie van de DRG werden paresthesie intensiteiten gescoord door proefpersonen in rechtop positie en in liggende positie. Het DRG neurostimulatie-systeem leek grotendeels ongevoelig voor de effecten van positieverandering. Dit verschijnsel wordt vaker gezien bij SCS, door biomechanische oorzaken. Bij DRG stimulatie blijft tevens de dekking c.q. overlap paresthesie/pijngebied constant tijdens staan en liggen, dit was ook na 12 maanden reproduceerbaar. Een verklaring voor de gevonden verschillen met SCS is dat bij SCS het dorsale gedeelte van het ruggenmerg wordt gestimuleerd en bij DRG stimulatie specifieke anatomische structuren dan wel neurofysiologische paden worden gestimuleerd. DRG stimulatie lijkt een veelbelovende stap richting een consistente effectieve lichaamshouding-onafhankelijke chronische pijnbestrijding.

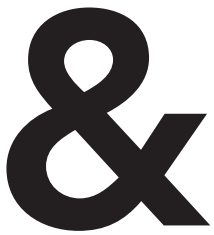
In **Hoofdstuk 5** wordt een overzicht gegeven over het toepassen van SCS therapie en worden de werkingsmechanismen beschreven. Adequate definiëring van selectie criteria voor het toepassen van DRG stimulatie is belangrijk daar een subgroep traditioneel in aanmerking komend voor SCS onvoldoende pijnreductie heeft door SCS en DRG mogelijke voordelen biedt in deze subgroep. Het is van belang zich te blijven realiseren dat chronisch neuropathische pijn een groot pijn behandel probleem vormt en een goed gedefinieerd klinisch diagnostisch en zorgpad vereist. Dit hoofdstuk beschrijft een eerste aanzet om te komen tot zo'n klinisch pad.

In **Hoofdstuk 6** worden de behandelopties en de behandelaanbevelingen rondom neuropathische liespijn besproken. Een behandel-algoritme voor de behandeling van post-liesbreukchirurgiepijn wordt beschreven. De indicaties voor het toepassen van DRG stimulatie en SCS stimulatie zijn gelijk en omvatten neuropathische pijn gelokaliseerd in romp of ledematen veroorzaakt door FBSS,CRPS, en bv postoperatieve neuropathie. Klinisch bewijs suggereert dat DRG stimulatie zeer geschikt is voor de pijnbehandeling van focale of uitdagende locaties, waaronder voet, knie, rug en lies. Een grotere patiëntengroep komt daardoor in aanmerking voor DRG stimulatie dan voor de traditionele SCS stimulatie. Lead migratie en lichaamshoudingeffecten bij SCS maakt deze behandeling vaak minder geschikt bij bepaalde pijnsyndromen, zoals pijn na liesbreukchirurgie. Nieuwe technologische ontwikkelingen binnen het DRG neuromodulatie onderzoeksterrein kunnen leiden tot een verbetering van de neuropathische pijnbehandelstrategie. Dit zal dan weer leiden tot verdere verfijning van de behandelbare ziektebeelden en een betere selectie van patiënten voor de verschillende behandelopties

Hoofdstuk 7 beschrijft de resultaten van DRG stimulatie in een groep patiënten met liespijn. De oorzaak van de liespijn was divers. Het is , gebaseerd op de literatuur, een studie met het grootste gerapporteerde cohort patiënten die de behandeling van chronische pijn in de lies door DRG stimulatie ondergaat. De DRG neuromodulatie werd toegepast op niveau L1-L2, door directe stimulatie van de zenuwen die de lies innerveren, leidend tot zeer lokale paresthesieën en pijnverlichting. Dit in tegensteling tot SCS waar stimulatie van de het dorsale gedeelte van ruggenmerg plaatsvindt op niveau T12-L1, met als resultaat meer stimulatie van been en bil zenuwen daar deze zenuwvezels hier zowel groter als talrijker aanwezig zijn. Bovendien is er op dit niveau

ook een aanzienlijke hoeveelheid cerebrospinale vloeistof. Deze vloeistof divergeert de stimulatie naar ongewenste gebieden. De resultaten tonen aan dat DRG een nuttige (aanvullende) therapie kan zijn voor deze vaak voorkomende en moeilijk te behandelen pijnaandoening. Aanvullende prospectieve studies zijn nodig om de voordelen van DRG stimulatie voor de behandeling van de refractaire liespijn verder te exploreren.

Afsluitend worden in **Hoofdstuk 8** de verschillende nieuwe behandelopties voor neuropathische pijn besproken, zoals farmacologische therapie, radiofrequente therapie, elektrische stimulatie, en gentherapie. Al deze behandelbenaderingen hebben een overeenkomstig werkingsmechanisme: het onderdrukken van de DRG activiteit en het voorkomen van pijntransmissie naar het ruggenmerg. Het DRG als behandelbaar schakelstation.



ADDENDUM

MANUSCRIPTS

Journal papers

- Liong Liem, Nagy Mekhail. Management of post-herniorrhaphy chronic neuropathic groin pain: a review of the literature and practice recommendations. (accepted for publication in Pain Practice)
- Liem A.L.; van Dongen E.P.A;Huygen F.J.; Staats P.; Kramer J. A Review of Spinal Cord Stimulation (SCS) as a Treatment Modality For Interventional Pain Management. (accepted for publication in Regional Anesthesia and Pain Medicine)
- Liem A.L.; Verrills P.; Bezemer R.; Almirdelfan K.; Levy R.; Kramer J. How can spinal cord stimulation advance chronic pain treatment in 2015? (accepted for publication in Pain Management)
- Liong Liem, Marc Russo, Frank J.P.M. Huygen, Jean-Pierre Van Buyten, Iris Smet, Paul Verrills, Michael Cousins, Charles Brooker, Robert Levy, Timothy Deer, Jeffery Kramer. One-year outcomes of spinal cord stimulation of the dorsal root ganglion in the treatment of chronic neuropathic pain. Neuromodulation 2015; 18: 41-49.
- Jeffery Kramer, Liong Liem, Marc Russo, Iris Smet, Jean-Pierre Van Buyten, Frank Huygen. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. Neuromodulation 2015;18:50-57
- Deer TR ; Liem AL ; Pope J ; Amirdelfan K ; Burton AW ; Staats P ; Russo M ; Kramer J. Neurostimulation of the dorsal root ganglion (DRG) by spinal cord stimulation (SCS): a review of proper patient selection. Minimally Invasive Surgery for Pain, MISP, 2015, vol 3.
- Stefan Schu, Ashish Gulve, Sam ElDabe, Ganesan Baranidharan, Katharina Wolf, Walter Demmel, Dirk Rasche, Manohar Sharma, Daniel Klase, Gunnar Jahnichen, Anders Wahlstedt, Harold Nijhuis, Liong Liem. Spinal cord stimulation of the dorsal root ganglion for groin pain: a retrospective review. Pain Pract. 2014.
- Liong Liem, Marc Russo, Frank J.P.M. Huygen, Jean-Pierre Van Buyten, Iris Smet, Paul Verrills, Michael Cousins, Charles Brooker, Robert Levy, Timothy Deer, Jeffery Kramer. A multicenter, prospective trial to assess the safety and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013; 16: 471–82.

Book chapters

- Liem AL, Krabbenbos IP, Kramer J. Dorsal root ganglion stimulation: a target for neuromodulation therapies. Textbook of Neuromodulation: Springer; 2015. p. 53-59.
- Liong Liem. Stimulation of the dorsal root ganglion. Slavin V (ed): Stimulation of the Peripheral Nervous System. The Neuromodulation Frontier. Prog Neurol Surg. Basel, Karger, 2016, vol 29, pp 213–224.
- Krabbenbos IP, Liem A, van Dongen E, Nijhuis H. Mechanisms of spinal cord stimulation in neuropathic pain. Topics in Neuromodulation Treatment, D.J. Carrillo-Ruiz, Editor. 2012, InTech. p. 89-110.

CO-AUTHORS

Allen Burton
Anders Wahlstedt
Ashish Gulve
Charles Brooker
Daniel Klase
Dirk Rasche
Eric van Dongen
Frank Huygen
Ganesan Baranidharan
Gunnar Jahnichen
Harold Nijhuis
Imre Krabbenbos
Iris Smet
Jason Pope
Jean-Pierre van Buyten
Jeffery Kramer
Kas Amirdelfan
Katharina Wolf
Manohar Sharma
Marc Russo
Michael Cousins
Nagy Mekhail
Peter Staats
Paul Verrills
Rick Bezemer
Robert Levy
Sam ElDabe
Stefan Schu
Timothy Deer
Walter Demmel

ABOUT THE AUTHOR

Dr. Liem was born in Leiden, The Netherlands. He graduate at the Free University College of Medicine in Amsterdam. He completed his residency in anesthesiology, intensive care, and pain management at the St Antonius Hospital in Utrecht. He is board certified in anesthesiology as well as pain medicine by the Dutch Society of Anesthesiology. Dr. Liem has, since 1981, extensive experience in the use of interventional pain procedures and implanting neurostimulators to treat chronic pain. Currently he leads the multidisciplinary Pain Unit at the St. Antonius Hospital in Nieuwegein. Furthermore, he is Fellow of International Pain Practice according to the World Institute of Pain and was founder and president of the Benelux Neuromodulation Society. He has been Treasurer of the International Neuromodulation Society and member of the Editorial Board of the journal Neuromodulation. He has been principal investigator on several clinical trials and is participating in international consensus and appropriateness boards on pain and spasticity. He has published several articles and book chapters on pain and neuromodulation and often speaks at national and international conferences in the Netherlands and abroad on pain topics and he is frequently invited to train physicians in the use of pain management techniques. In 2010 Dr. Liem received the Sam Hassenbusch prize in Budapest. Over the last years, he has focused on completing his scientific work on stimulation of the dorsal root ganglion for the treatment of chronic pain to obtain his Doctorate of Philosophy at the Erasmus University of Rotterdam in 2015.

PHD PORTFOLIO

(last 5 years)

Licenses:

Registratiecommissie Geneeskundig Specialisten Anesthesiologie	until 02/08/2019
Nederlandse Vereniging voor Anesthesiologie, Herregistratie aandachtsgebied Pijngeneeskunde	until 01/01/2020

Clinical Experience:

St. Antonius Hospital Nieuwegein:	1985-present	Consultant Anesthesia & Pain
Onze Lieve Vrouwe Gasthuis Amsterdam:	2008-2012	Consultant Pain
Fellow Interventional Pain Practice:	2009-present	World Institute of Pain

Memberships:

- International Association for the study of Pain (IASP)
- Dutch Society of Anesthesiology (NVA), Pain Medicine
- International Neuromodulation Society (INS)
- American Society of Anesthesiology (ASA)
- Benelux Neuromodulation Society (BNS)
- North American Neuromodulation Society (NANS)
- Dutch Pain Society (DPS)
- Nederlandse Vereniging voor Neuromodulatie (NVvN)
- BIG registration/ Medical License: 39 022 492 901

Courses:

Winner of the Samuel J. Hassenbusch 111, MD, PhD, FIPP Prize, 100% score on the WIP FIPP examination, Budapest 2009

Journals:

Pain, Pain Practice, Neuromodulation, Lancet, NtvG, Spine, Medisch Contact, BMJ, J Neurol Neurosurg Psychiatry, Neurology, JAMA, American Journal of Physical Medicine & Rehabilitation, Anesthesia, Neurosurgery

Posters:

- L. Liem, M Russo, F J P M Huygen, J-P Van Buyten, I Smet, P Verrills, M Cousins, C Brooker, R Levy, T Deer, J Kramer. One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion (DRG-SCS) in the Treatment of Chronic Neuropathic Pain. Pain, 2014. San Juan, Puerto Rico. Jun 19-22, 2014. (Winner of the best poster award)

- H Nijhuis, L Liem, F Huygen. A post-market study to assess the performance of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) system for the management of chronic intractable pain, 20th Annual Napa Pain Conference, Napa, CA, Aug 23-25, 2013. (Winner of second best poster award)

Boards:

2002-2006	Founder and first president BNS (Benelux Neuromodulation Society)
2006-2009	Editorial Board Neuromodulation
2006-2012	Treasurer INS (International Neuromodulation Society)
2008- current	NACC (Neuromodulation Appropriateness Consensus Committee). To advance the safety and efficacy of electrical neurostimulation in treating patients with diseases that involve pain.
2008- current	PACC(PolyAnalgesic Consensus Committee). To evaluate current research, update the treatment algorithm and provide evidence-based recommendations for intrathecal therapy for the management of pain.
2007-current	Board Neuromodulation Academy
2009-2011	Chair Quality Control Commission NVvN
2012-current	Data Safety Monitoring Board (DSMB) for ICON study (medically Intractable chronic Cluster headache Occipital Nerve stimulation study)
2014-current	HerniaSurge guidelines- European Hernia Society guidelines on the treatment of inguinal hernia in adult patients
2009-current	reviewer for Neuromodulation, Pain, Neurology
2014	Member Expert Physician Panel St Jude Medical
2012-current	Member USER Advisory Group (UAG) Spinal Modulation

Teaching:

- Workshops, masterclasses, mentoring, coordinator and supervisor pain education St Antonius Hospital Nieuwegein
- Presentations for EFIC, IASP, WIP, ASA, ASRA, ESRA, INS, BNS, APS, WVSIPP, NVA (Anesthesiologen dagen), NVNA, ECMT, NSUKI, SASP, WSPC, EANS, BPS, ESA, Ned ver Plastische Chirurgie, Ned Ver v Cardiologie, LUMC, Erasmus MC, Bergen University, NVDG, NANS, Reval Centrum Hoogstraat, Voorop Eikenboom, IFESS/ INS, PEPS, Dystrofie Pat Vereniging, Univ of Birmingham, Frankfurt, Turku, Milan, Maastricht(Trigeminal Neuralgia)Refresher Course WIP, Koln, Dallas, Antwerpen, Ontario, Tutzinger Schmerzkurs, Munich, Gent, Philips R&D India, Murnau DGNM, Montreux Swiss Pain Society, NYNJSIPP New Jersey, Australian Neuromodulation Society Canberra, European Hernia Society Gdansk, Berlin, Granada, Miami, Middelburg, London, Budapest, Nappa, Madrid, Aachen, Athens, Seoul, Cardiff, New York, Florence, Montreal, Mallorca
- Industry sponsored cadaver courses St Jude, Medtronic, Boston Scientific, Spinal Modulation

- Mentoring implant techniques
- IFMS participant
- Teach the teacher, Train the trainer
- Toronto Ultrasound Pain Course Basic and Advanced

Studies:

- Principal investigator of many clinical trials and clinical research, (Ziconotide, SCS, DRG stimulation) within St Antonius Hospital, Nieuwegein, The Netherlands
- Suicide Mortality, Suicidal Ideation and Psychological Problems in Dutch Anesthesiologists :Marieke Liem, A.Liong Liem, Eric P.A. van Dongen, Ina C. Carels, Marjan van Egmond, and Ad J.F.M Kerkhof.(Suicidology Online)
- A prospective Trial to Assess the Safety and Performance of the Stimulation of the Dorsal Root Ganglion (completed)
- GASPA: "dorsal root GAnglion Stimulation as treatment for Postsurgical pAin"
- Determining the efficacy of chordotomy using laser evoked potentials: a pilot study (Chordo study), Liem, Krabbenbos, van Dongen

Completed Studies:

- Principal investigator of many clinical trials and clinical research, (Ziconotide, SCS, Subcutaneous Stimulation/Periferal Nerve Field Stimulation, DRG stimulation) within St Antonius Hospital, Nieuwegein, The Netherlands
- PRIME: Patient Registry of Intrathecal Pain Management in Europe
- Promise

Invited Lectures:

- Liem L, Huygen F. The Dorsal Root Ganglion as a Neurostimulation Target for the Treatment of Chronic Neuropathic Pain – Early Experience in The Netherlands. 7th Annual Meeting of the German Society of Neuromodulation (DGNM), Aachen, Nov 25-26, 2011.
- Liem L, Russo M, Draper C, Kramer J, Brooker C, Smet I, Van Buyten J-P, Huygen F. Effects of Posture on Paresthesia Intensity in DRG Stimulation. North American Neuromodulation Society, 15th Annual Meeting, Las Vegas, Dec 8-11, 2011.
- Liem L, Russo M, Van Buyten J-P, Huygen F. Dorsal Root Ganglion Stimulation for the Treatment of Failed Back Surgery Syndrome. The 6th World Congress: World Institute of Pain. Miami Beach, Florida, Feb 4-6, 2012.
- Russo M, Brooker C, Verrills P, Cousins M, Van Buyten J-P, Liem L. Dorsal Root Ganglion Stimulation for the Treatment of Chronic Neuropathic Foot Pain. The 6th World Congress: World Institute of Pain. Miami Beach, Florida, Feb 4-6, 2012.
- Huygen F, Liem L. Anatomy and pathophysiology of the dorsal root ganglion in chronic pain. 15th World Congress of Pain Clinicians, Granada, Spain, Jun 27-30, 2012.
- Liem L, Huygen F. Initial clinical results of DRG stimulation for the treatment of chronic pain. 15th World Congress of Pain Clinicians, Granada, Spain, Jun 27-30, 2012.

- Liem L, Van Buyten J-P, Russo M, Smet I, Huygen F. Dorsal root ganglion stimulation for the treatment of complex regional pain syndrome. 14th World Congress on Pain, International Association for the Study of Pain (IASP). Milan, Italy, Aug 27-31, 2012.
- Liem L, Huygen F, Russo M, Van Buyten J-P, Smet I. Effects of dorsal root ganglion stimulation in the treatment of chronic, intractable pain: Long-term results from two prospective clinical trials. 8th Annual Meeting of the German Society of Neuromodulation (DGNM), Berlin, Nov 23-24, 2012.
- Burger K, Moser H, Liem L, Klase D, ElDabe S. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of post amputation pain. North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Schu S, Liem L, Russo M, Gulve A, ElDabe S, Baranidharan G, Wolf K, Demmel W, Rasche D, Sharma M. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain – A multi-center case series. North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Liem L, Demmel W, Schu S. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for chronic pain of the upper limbs – A multi-center case series. North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Kramer J, Liem L, Russo M, Huygen F, Smet I, Van Buyten J-P. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Liem L, Huygen F, Russo M, Van Buyten J-P, Smet I. Effects of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of chronic, intractable pain: Long-term results from two prospective clinical trials. North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Liem L, Russo M, Van Buyten J-P, Smet I, Huygen F. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of failed back surgery syndrome (FBSS). North American Neuromodulation Society, 16th Annual Meeting, Las Vegas, Dec 6-9, 2012.
- Liem L, Schu S, Russo M, et al. Treatment of neuropathic groin pain with dorsal root ganglion stimulation. 35th International Congress of the European Hernia Society, Gdansk, Poland, May 12-15, 2013.
- Liem L, Huygen F, Russo M, et al. Effects of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of chronic, intractable pain: Long-term results from prospective clinical trials. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.
- Kramer J, Liem L, Russo M, et al. Lack of body positional effects on paresthesias when stimulating the dorsal root ganglion (DRG) in the treatment of chronic pain. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.

- Schu S, Liem L, Russo M. et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain – A multi-center case series. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.
- Liem L, Nijhuis H, Huygen F. A post-market cohort to assess the performance of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) neuromodulation system for the management of chronic intractable pain. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.
- Nijhuis H, Liem L, Huygen F. A post-market cohort to assess the performance of the Spinal Modulation neurostimulator system for the management of intractable chronic back pain. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.
- Liem L, Demmel W, Thoma R, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for chronic pain of the upper limbs – A multi-center case series. International Neuromodulation Society 11th World Congress, Berlin, Germany, Jun 8-13, 2013.
- Liem L, Schu S, Russo M, et al. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for groin pain – A multi-center case series. Pain, 2013, Palm Beach, FL, Jul 11-14, 2013.
- H Nijhuis, L Liem, F Huygen. A post-market study to assess the performance of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) system for the management of chronic intractable pain, 20th Annual Napa Pain Conference, Napa, CA, Aug 23-25, 2013. (Winner of second best poster award)
- H Nijhuis, L Liem, F Huygen. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of chronic low back pain in FBSS: Prospective results and potential mechanisms. North American Neuromodulation Society, 17th Annual Meeting, Las Vegas, Dec 5-8, 2013.
- S Schu, A Gulve, S ElDabe, G Baranidharan, K Wolf, W Demmel, D Rasche, M Sharma, D Klase, G Jahnichen, A Wahlstedt, H Nijhuis, L Liem. Long-term follow-up of a retrospective, multi-center case series of spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of intractable groin pain. North American Neuromodulation Society, 17th Annual Meeting, Las Vegas, Dec 5-8, 2013.
- D Klase, R Thoma, G Baranidharan, L Liem, N K Patel, S Love-Jones, A J Espinet, P Verrills, S Schu. Does convergence of multi-segmental afferent inputs at the spinal lamina enable treatment of post-herpetic neuralgia with dorsal root ganglion (DRG) stimulation possible? North American Neuromodulation Society, 17th Annual Meeting, Las Vegas, Dec 5-8, 2013.
- L Liem, A Gulve, S ElDabe, M Sharma, A L Green, F Huygen. Preliminary results from two prospective multi-centre studies on the treatment of intractable groin pain with spinal cord stimulation (SCS) of the dorsal root ganglion (DRG). North American Neuromodulation Society, 17th Annual Meeting, Las Vegas, Dec 5-8, 2013.
- S ElDabe, A Wahlstedt, E Leljevahl, K Burger, H Moser, D Klase, S Schu, E Francois, B Vanderick, H Nijhuis, L Liem. Neurophysiology of the dorsal root ganglion

(DRG): A translational premise for neuromodulation in the treatment of chronic pain. Mechanisms of Action (MoA). Orlando. Mar 28-30, 2014.

- D Klase, R Thoma, G Baranidharan, L Liem, N K Patel, S Love-Jones, A J Espinet, P Verrills, S Schu. Does convergence of multi-segmental afferent inputs at the spinal lamina enable treatment of post-herpetic neuralgia with dorsal root ganglion (DRG) stimulation possible? Mechanisms of Action (MoA). Orlando. Mar 28-30, 2014.
- Liem, Nijhuis, Huygen, Gulve, Sharma, Patel, Love-Jones, Green, Baranidharan, Bush, ElDabe. Treatment of chronic post-surgical pain (CPSP) using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) neurostimulation: results from two prospective studies. World Institute of Pain (WIP), 7th annual congress. Maastrict. May 7-10, 2014.
- L Liem, M Russo, FJPM Huygen, I Smet, P Verrills, M Cousins, C Brooker, R Levy, T Deer, J Kramer, J-P Van Buyten. Health-Related Patient-Reported Outcomes Demonstrate that Dorsal Root Ganglion (DRG) Neurostimulation for Chronic Neuropathic Pain Provides Long-Term Benefits Across Multiple Dimensions. World Institute of Pain (WIP), 7th annual congress. Maastrict. May 7-10, 2014.
- J-P Van Buyten, I Smet, L Liem, M Russo, C M van Bussel, A L Green, J J Fitzgerald, S Bojanic, L Moir, T Aziz, M L Sharma, F J P M Huygen. Long term outcomes using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of complex region pain syndrome (CRPS). World Institute of Pain (WIP), 7th annual congress. Maastrict. May 7-10, 2014.
- H Nijhuis, L Liem, F Huygen. Spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) for the treatment of chronic low back pain in FBSS: Prospective results and potential mechanisms. World Institute of Pain (WIP), 7th annual congress. Maastrict. May 7-10, 2014.
- J-P Van Buyten, I Smet, L Liem, M Russo, C M van Bussel, A L Green, J J Fitzgerald, S Bojanic, L Moir, T Aziz, M L Sharma, F J P M Huygen. Long term outcomes using spinal cord stimulation (SCS) of the dorsal root ganglion (DRG) in the treatment of complex region pain syndrome (CRPS). Pain, 2014. San Juan, Puerto Rico. Jun 19-22, 2014.
- L Liem, M Russo, F J P M Huygen, J-P Van Buyten, I Smet, P Verrills, M Cousins, C Brooker, R Levy, T Deer, J Kramer. One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion (DRG-SCS) in the Treatment of Chronic Neuropathic Pain. Pain, 2014. San Juan, Puerto Rico. Jun 19-22, 2014. (Winner of the best poster award)
- L. Liem. Neuromodulation modalities in the treatment of pain. XXI Congress of the European Society of Stereotactic and Functional Neurosurgery (ESFFN), Maastricht, 17-20 September 2014. Expert Panel
- L Liem, H Nijhuis, FJPM Huygen, A Gulve, M Sharma, N K Patel, S Love-Jones, A L Green, G Baranidharan, D Bush, S ElDabe. Treatment of chronic post-surgical pain using spinal cord stimulation of the dorsal root ganglion: results from two prospective studies 4th Biannual International Multidisciplinary Pain Congress, Eindhoven, The Netherlands, Oct. 1-4, 2014.

- L. Liem, Dorsal Root Ganglion Stimulation, State of The Art of The Procedure. Satelite Symposium The 15th World Congress on Pain. Buenos Aires 5 th Oktober 2014 Advances in Neuromodulation from Molecules to Functional Outcomes. IASP Special Interest Group on Neuromodulation (SIGN)
- Van Buyten JP, Liem L, Russo M, Green AL, Sharma ML, Kramer J, Subbaroyan J, Staats P, Huygen FJPM. "Long-term symptom relief in complex regional pain syndrome (CRPS) with stimulation of dorsal root ganglion (DRG): Potential mechanisms underlying effects on allodynia and sympatholysis." NY & NJSIPP Pain Medicine Symposium 2014, Jersey City. Nov. 6-9, 2014.
- L. Liem, F.J.P.M. Huygen, J.P. Van Buyten, M. Russo, P. Verrills, T. Deer, R. Levy, J. Subbaroyan, J. Kramer. Probabilistic paresthesia maps of epidurally placed leads over an intraspinal nerve structure: The dorsal root ganglion (DRG). 13th ASRA Annual Pain Medicine Meeting. San Francisco. Nov. 13-16, 2014.
- Kramer J, Liem L, Grigsby E, Huygen FJPM, Deer T, Russo M, Verrills P, Van Buyten JP, Subbaroyan J, Levy R. "Stimulation of the Dorsal Root Ganglion (DRG): Insights into Somatic Sensory Mapping." North American Neuromodulation Society, 18th Annual Meeting, Las Vegas, Dec 11-14, 2014.
- Nijhuis H, Liem L, Huygen FJPM. "Prospective Results of L2 Dorsal Root Ganglion (DRG) Stimulation for the Treatment of Chronic Low Back Pain in Failed Back Surgery Syndrome (FBSS)." North American Neuromodulation Society, 18th Annual Meeting, Las Vegas, Dec 11-14, 2014.
- Van Buyten JP, Liem L, Russo M, Green AL, Sharma ML, Kramer J, Subbaroyan J, Staats P, Huygen FJPM. "Long-term symptom relief in complex regional pain syndrome (CRPS) with stimulation of dorsal root ganglion (DRG): Potential mechanisms underlying effects on allodynia and sympatholysis." NY & NJSIPP Pain Medicine Symposium 2014, Jersey City. Nov. 6-9, 2014.
- L. Liem. An update on Neuromodulation, Hamad Medical Corporation, Department of Anesthesia, Qatar, Head Prof. Dr .M. Marcus, December 30, 2014
- L. Liem, Resultaten 12 maanden observationele studie met DRG stimulatie, Pijndagen 2015, Passende Zorg als norm, 16 & 17 januari 2015, Tovoli Vredenburg, Utrecht (WIP, VVAP, Dutch Pain Society, NVA)
- L. Liem, Targeted spinal cord stimulation (SCS) for treatment of groin pain. A multicentre case series in dorsal root ganglion (DRG) stimulation. 1st World Conference on Abdominal Wall Hernia Surgery, Milan, April 25-29, 2015
- L. Liem, Mini Interventional Technique Future and Beyond ,Worldmedicinepark, Mallorca, 7-10 May 2015
- L. Liem, Neuromodulation for lumbosacral radiculair pain state of the art and what is new? May 31, 2015, ESA Berlin
- L. Liem, Int perspectives and comparisons of prospective research:dorsal root ganglion spinalcord stimulation, June 8, 2015, INS World Congress, Montreal

Abstracts:

Author of over 50 abstracts presented at various (inter)national congresses.

- Bell RF, Liem L. Percutaneous cervical cordotomy in intractable cancer pain. Tidsskr Nor Laegeforen 2005 Oct 6;125(19):2650-2651.
- Deer T, Krames ES, Hassenbusch S, et al. Future directions for intrathecal pain management: a review and update from the interdisciplinary polyanalgesic consensus conference 2007. Neuromodulation 2008 Apr;11(2):92-97.
- Deer T, Krames ES, Hassenbusch S, et al. Management of intrathecal catheter-tip inflammatory masses: an updated 2007 consensus statement from an expert panel. Neuromodulation 2008 Apr;11(2):77-91.
- Deer T, Krames ES, Hassenbusch SJ, et al. Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2007 Oct;10(4):300-328.
- Deer TR, Krames E, Mekhail N, et al. The appropriate use of neurostimulation: new and evolving neurostimulation therapies and applicable treatment for chronic pain and selected disease states. Neuromodulation 2014 Aug;17(6):599-615; discussion 615.
- Deer TR, Levy R, Prager J, et al. Polyanalgesic Consensus Conference--2012: recommendations to reduce morbidity and mortality in intrathecal drug delivery in the treatment of chronic pain. Neuromodulation 2012 Sep-Oct;15(5):467-82; discussion 482.
- 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 Aug;17(6):515-50; discussion 550.
- Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation 2014 Aug;17(6):571-97; discussion 597-8.
- Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference--2012: recommendations on trialing for intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2012 Sep-Oct;15(5):420-35; discussion 435.
- Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. Neuromodulation 2012 Sep-Oct;15(5):436-64; discussion 464-6.
- Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference--2012: consensus on diagnosis, detection, and treatment of catheter-tip granulomas (inflammatory masses). Neuromodulation 2012 Sep-Oct;15(5):483-95; discussion 496.
- Liem LA, van Dongen VC. Magnetic resonance imaging and spinal cord stimulation systems. Pain 1997 Mar;70(1):95-97.

- Linderoth B, Rasche D, Tronnier VM, Duarte RV, Raphael JH, Ashford RL, Kretzschmar M, Groß W, Seidel J, Peters FT. German Society of Neuromodulation (DGNM) Joint Meeting with the Neuromodulation Society of the United Kingdom and Ireland (NSUKI) 23–24 November 2012, Berlin, Germany.
- Slavin KV, Liem L. Treatment of Chronic Chest Wall Pain in a Patient With Loeys-Dietz Syndrome Using Spinal Cord Stimulation COMMENTS 2011.
- Snijders TJ, Veldhuijzen DS, Liem KS, Baakman AC, van Gijn J, van Wijck AJ. Sensory profiles in chronic, unexplained pain. Chronic, unexplained pain 2012:99.
- Stoof JC, Liem AL, Mulder AH. Release and receptor stimulating properties of p-tyramine in rat brain. Arch Int Pharmacodyn Ther 1976 Mar;220(1):62-71.
- van der Ploeg JM, Vervest HA, Liem AL, Schagen van Leeuwen JH. Transcutaneous nerve stimulation (TENS) during the first stage of labour: a randomized clinical trial. Pain 1996 Nov;68(1):75-78.
- Van Dongen V, Liem A. Phantom limb and stump pain and its treatment with spinal cord stimulation. Journal of Rehabilitation Sciences 1995;8:110-114.
- van Gijn J, Giesbergen PC, Hoogenraad TU. Attacks of pain in the leg from classic syringomyelia. J Neurol Neurosurg Psychiatry 1997 Sep;63(3):410.
- van Kleef M, Liem L, Lousberg R, Barendse G, Kessels F, Sluijter M. Radiofrequency lesion adjacent to the dorsal root ganglion for cervicobrachial pain: a prospective double blind randomized study. Neurosurgery 1996 Jun;38(6):1127-31; discussion 1131-2.
- Wijbenga J, Nijhuis H, Liem A. First experience with ziconotide treatment in the Netherlands: 164. Reg Anesth Pain Med 2007;32(5):52.
- Wolf K, Liem A. Spinal cord stimulation with percutaneous paddle leads in patients with low back pain: Results of 51 patients in two implantation centers. Neuromodulation 2011;14(5):446.
- Van Buyten JP, Smet I, Liem L, Russo M, Huygen F. Stimulation of Dorsal Root Ganglia for the Management of Complex Regional Pain Syndrome: A Prospective Case Series. Pain Pract.2015;15(3):208-16

Book chapters:

- Liem AL, Krabbenbos IP, Kramer J. Dorsal Root Ganglion Stimulation: A Target for Neuromodulation Therapies. Textbook of Neuromodulation: Springer; 2015. p. 53-59.
- Krabbenbos IP, Liem A, van Dongen E, Nijhuis H. Mechanisms of Spinal Cord Stimulation in Neuropathic Pain - Chapter 5, in Topics in Neuromodulation Treatment, D.J. Carrillo-Ruiz, Editor. 2012, InTech. p. 89-110.
- Liong Liem. Stimulation of the dorsal root ganglion. Progress in Neurological Surgery, Peripheral Nerve Stimulation, Editor K.V. Slavin

Peer-reviewed articles (this thesis):

- Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. A multicenter, prospective trial to assess the safety

and performance of the spinal modulation dorsal root ganglion neurostimulator system in the treatment of chronic pain. Neuromodulation 2013; 16: 471–82.

- Schu S, Gulve A, Eldabe S, Baranidharan G, Wolf K, Demmel W, Rasche D, Sharma M, Klase D, Jahnichen G, Wahlstedt A, Nijhuis H, Liem L. Spinal Cord Stimulation of the Dorsal Root Ganglion for Groin Pain-A Retrospective Review. Pain Pract. 2014, DOI:10.1111/papr.12194
- Kramer J, Liem L, Russo M, Smet I, Van Buyten JP, Huygen F. Lack of Body Positional Effects on Paresthesias When Stimulating the Dorsal Root Ganglion (DRG) in the Treatment of Chronic Pain. Neuromodulation 2015; 18: 50-57 (Editor's choice)
- Liem L, Russo M, Huygen FJ, Van Buyten JP, Smet I, Verrills P, Cousins M, Brooker C, Levy R, Deer T, Kramer J. One-Year Outcomes of Spinal Cord Stimulation of the Dorsal Root Ganglion in the Treatment of Chronic Neuropathic Pain. Neuromodulation 2015; 18: 41-49 (Editor's choice)
- Deer T.R.; Liem A.L.; Pope J.; Amirdelfan K.; Burton A.W.; Staats P.; Russo M.; Kramer J. Neurostimulation of the Dorsal Root Ganglion (DRG) by Spinal Cord Stimulation (SCS): A Review of Proper Patient Selection. Minimally Invasive Surgery for Pain, MISP,2015, vol 3.
- Liem A.L.; van Dongen E.P.A; Amirdelfan K.; Staats P.; Burton A.; Kramer J. The Dorsal Root Ganglion (DRG) as a therapeutic target for chronic pain. Reg Anest Pain Med (accepted)
- Liem A.L.; Verrills P.; Bezemer R.; Levy R.; Huygen F.; Kramer J. How can spinal cord stimulation advance chronic pain treatment in 2015 ? Pain Manag. 2015, Future Medicine (accepted)

ACKNOWLEDGEMENTS

In de eerste plaats wil ik de patiënten, die mee hebben gedaan aan dit onderzoek en hun naasten, bedanken voor hun vertrouwen en hun toestemming tot deelname aan deze nieuwe vorm van pijnbehandeling. Ik realiseer mij dat het soms een hele opgave was om telkens, soms van ver, naar het ziekenhuis te komen voor de nacontroles. Zonder uw medewerking was dit proefschrift niet tot stand gekomen.

Daarnaast gaat mijn dank uit naar een ieder die heeft meegeholpen bij het succesvol afronden van dit proefschrift. Beste mentoren, collega's, vrienden en familie: dank voor de begeleiding, de plezierige samenwerking, vriendschap en liefde.

Bij de voorbereiding van dit proefschrift hebben veel mensen een bijdrage geleverd, mij al die tijd gesteund en geinspireerd. Hiervoor ben ik hen veel dank verschuldigd. Hieronder een lijst van hen die mij met name een enorme dienst hebben bewezen en plezier hebben gegeven in het doen van klinisch onderzoek:

You have my sincere gratitude and deep respect.

Alize Karlas
Allen Burton
Allison Foster
Annemarie van der Meer
Carin Wensing
Charles Brooker
Cindy van der Mark
Dan Brounstein
Dave Mugan
Eric van Dongen
Frank Huygen
Gerrie Aikema
Harold Nijhuis
Henk Koers
Huub Hacking
Imre Krabbenbos
Iris Smet
Isabelle Smink
Jacqueline van Engelen
Jason Pope
Jean Pierre van Buyten
Jeffery Kramer
Jey Subbaroyan
Kas Almirdelfan
Leon Timmerman
Liesbeth Ament
Marc Russo
Margo Lambooy
Marijke Muntendam
Mariska Hazendonk
Marja de Regt
Michael Cousins
Miranda van Maurik
Nagy Mekhail
Nathalie de Korte
Paul Verrils
Peter Siegers
Peter Staats
Rae Bell
Ralph Aarsman
Ralph Zastrow
Rick Bezemer
Robert Levy
Samira Balouah
Sander van Geel
Sjoerd van Egeraat
Sophie Liem
Stefan Schu
Tim Palmer
Timothy Deer
Willem Bart Slooff
Willem-Jan Hofste
Yvan Freund

Verder zijn er een paar mensen die ik in het bijzonder wil bedanken:

Mijn promotor, Prof. dr. F.J.P.M. Huygen. Beste Frank, de eerste afspraak over het doen van een gezamenlijk onderzoek naar DRG stimulatie in 2010 was het eerste begin van dit proefschrift. Ik wil je bedanken voor de steun, vertrouwen en de mogelijkheid die je mij hebt geboden om dit proefschrift te schrijven. De eerste patienten waren aanvankelijk best lastig en de resultaten niet goed. Met jouw kennis en ervaring hebben we dit later sterk kunnen verbeteren. We hebben uren met elkaar gesproken tijdens lange vluchten en in hotel lobby's; ondanks je drukke werkzaamheden vond je later altijd een oplossing om wat tijd vrij te maken om aan de hoofdstukken en dit proefschrift te werken.

Mijn co-promotor, Dr. E.P.A van Dongen. Beste Eric, zonder jouw hulp was dit proefschrift nooit af geweest. Ik wil je bedanken voor al je wetenschappelijke adviezen en hulp bij het schrijven van dit proefschrift. Zoals het altijd in een goede maatschap gaat, vonden we vaak tijd om er samen aan te werken. Dank voor je geduld en hulp.

Het zal vanaf nu niet meer nodig zijn om voor het OK-programma uit en tussendoor, aan deze thesis te werken. Ik hoop nog wel samen onderzoek met je te doen in de toekomst.

Daarnaast zou ik ook graag de leden van de leescommissie (Prof. dr. J.F. Lange, Prof. dr. G.J. Kleinrensink en Prof. dr. ir. M.J.A.M. van Putten) hartelijk willen bedanken voor het beoordelen van dit proefschrift.

I 'd like to express thanks to Allison Foster and Rick Bezemer for their priceless guidance and editorial genius in helping this book to emerge out of the digital realm, into the form of a manuscript and finally a thesis. Rick you were an inspirer of this wonderful journey. I will remember to stay in touch in the future, it is a privilege working with you.

H.P. Siegers. Beste Piet, het stond voor mij vast dat jij mijn paranymf zou worden. Bijna dertig jaar doen we de meest complexe pijnpatienten. Je hebt me altijd scherp gehouden; zonder diagnose, geen behandeling. Je hebt me veel bijgebracht over de neurologie en bleef altijd hameren over het doen van een goede anamnese en lichamelijk onderzoek. Jij hebt eigenlijk het EPD van ons ziekenhuis gebouwd en wij hebben daar als afdeling Pijnbestrijding al vroeg de vruchten van geplukt. Daarnaast bleef je, samen met Hub Hacking en Henk Koers, altijd trouw naar ons multidisciplinair spreekuur komen, en bespraken we altijd alle patienten voor de neuromodulatie.

Lieve Sophie, je ging me voor met promoveren. "Pap, nog even volhouden, je bent er bijna." Meestal zijn dergelijke opbeurende teksten van vader naar kind en niet andersom. Maar daarom juist ben jij mijn paranymf. Ik kon je niet verleiden om anesthesiologie te gaan doen maar verloskunde/gynaecologie is ook goed. Het is goed dat je je eigen wil gaat volgen. Zullen we samen nog een keer de marathon lopen?

Lieve Caroline, Rob en Suzanne, veel dank voor jullie geduld. Ik ben trots op jullie.

Lieve Liesbeth, je haalt het beste in mij naar boven, zonder jou had ik dit nooit kunnen doen. De laatste twee jaar heb je mij altijd uit de wind gehouden en mij alle gelegenheid en tijd gegeven om dit proefschrift af te maken. Dank voor alle sportieve, vrolijke, bemoedigende en liefdevolle momenten. Ik hoop dat er nog veel zullen volgen.

EPILOG

Collaboration is one of the hallmarks of how great things can be accomplished and through the sharing of expertise and experiences we can become more complete. My first introduction to Dr. Liong Liem, an accomplished anesthesiologist and interventional pain management physician, was in Madrid through introductions by Dr. Tim Deer. I was working at Spinal Modulation as the chief scientist responsible for taking a new neurostimulation technology, dorsal root ganglion stimulation, from the initial pre-clinical research phase into the next phase of clinical work. The jump, or chasm, that exists from concept development and initial experimental work to actual clinical application can be a daunting one, and quite often new therapies fail as a result of a lack of foresight and careful clinical introduction. Liong provided much needed knowledge and experience to help the introduction of DRG stimulation into clinical practice. Liong provided not only a highly functional knowledge of neurostimulation, but also a very technical knowledge base and he had decades of experience with implantation of these types of devices. Our collaboration focused on refining the design of the device for DRG stimulation, selecting the right patients for the treatment, and setting up the first clinical trial. Expanding the patient populations for further clinical application of the therapy has been one of the greatest scientific experiences in my life. Liong can also, I think, take great pride in helping to provide key clinical input into the use of the therapy and to help bringing it forward and thereby allow its use in so many patients to provide relief from the unending and unyielding torture of chronic pain.

Jeffery Kramer, PhD
Associate Professor
University of Illinois College of Medicine, Peoria, IL, USA
Chief Scientific Officer Spinal Modulation