New modalities in Spinal Cord Stimulation

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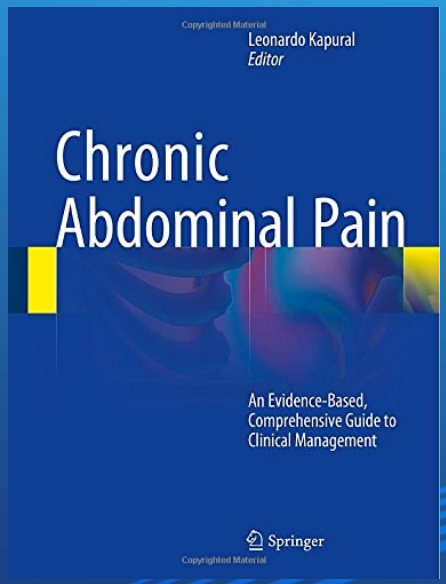
Conflict of Interest:

Scientific Advisory Board: Abbott, Nevro, Saluda, SPR Therapeutics, Neuros, Halyard

Consultant: Gimer Medical, Best Doctors

Research: Stimwave, Nevro, Neuros, Halyard, SPR Therapeutics, Boston Scientific, Medtronic, Saluda

I will be discussing one therapeutic approach (Compound Evoked Stimulation System) that is not FDA approved for use in USA



What is new in SCS - PNS

- High frequency stimulation
- (Nevro, Menlo Park, CA)
- DRG Stimulation
- (Abbott, Plano TX; Gimer, Taiwan)
- High Density Stimulation
- (Medtronic, Minneapolis)
- Burst Stimulation
- (Abbott, Plano, TX)
- Remote leads
- (Nalu, San Francisco; Stim Wave, Miami)
- ECAPS-Feedback
- (Saluda, Sidney, AU)

- High frequency stimulation
- (Neuros, Cleveland, OH)
- Elastic bipol lead
- (SPR Therapeutic, Cleveland,OH)
- External generator near-nerve lead system
- (Bioness, Valencia, CA)
- Micro-devices
- (several universities)
- Vagal stimulation
- (electroCore, NJ, etc)

Possible new indications for neuromodulation

- Pain
- Abdominal Pain
- Pelvic Pain
- Headaches
- Cervical radiculopathy

- Functional Restoration
- Spinal cord injury
- Parkinson
- Depression
- OCD
- Alzheimer's disease

New SCS technologies

Spine

SPINE Volume 42, Number 14S, pp S33–S34

SUMMARY STATEMENT

Summary Statement for the Spinal Cord Stimulation Focus Issue

F. Todd Wetzel, MD,* Kasra Amirdelfan, MD,† Gunnar B.J. Andersson, MD, PhD,‡ Leonardo Kapural, MD, PhD,§ David A. Provenzano, MD,¶ Jonathan Riley, MD,‖ B. Todd Sitzman, MD, MPH,** Peter Staats, MD,†† and Ricardo Vallejo, MD, PhD‡‡

In the last several years, spinal cord stimulation (SCS) has undergone a revolution with the development of truly different technologies in decades. Although the basic principle remains—the application of electric current to nervous tissue to treat intractable pain—the options for delivery are no longer limited to "traditional" tonic stimulation but also include high frequency (10 kHz), burst, and dorsal root ganglion techniques. This technical revolution has lead to significant and rapid improvement in outcomes and resulted in the advancement of the science.

are ripe for the development and application of new therapeutic strategies.

The goals of this special issue are to provide education about this technology by reviewing the available literature in a critical manner. High-quality evidence-based data from level I and II studies are clearly required for the evaluation of any new or evolving treatment. These data are provided in a comprehensive review by Amirdelfan. In an exhaustive review of treatments for chronic spinal pain syndromes, the author notes that strong evidence (level I and II, as noted

Source:

Spine

SPINE Volume 42, Number 14S, pp S61–S66

FOCUS ISSUE ARTICLE

Clinical Evidence for Spinal Cord Stimulation for Failed Back Surgery Syndrome (FBSS)

Systematic Review

Leonardo Kapural, MD, PhD,* Erika Peterson, MD,† David A. Provenzano, MD,‡ and Peter Staats, MD, MBA§

Study Design. A systematic review.

Failed back surgery syndrome (FBSS) is present in about 30% of the patients who have undergone

- **non-randomized studies can exaggerate the estimate of treatment effect by as much as 40%**
- **that may lead to erroneous conclusions regarding treatment effect**

Schultz KF, Chalmers I, Hayes RJ, et al. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA*. 1995;273:408–412.

RCTs

TABLE 3. Randomized Spinal Cord Stimulation Trials for the Treatment of Lumbar Spine Conditions

Author	Type of Study	Evidence Level	Number of Trial Patients	Number of Patients Progressing to Implant (%)	Type of Neuro-modulation	Type of Pain Pattern	Average % Pain Reduction	Functional Outcomes of Implanted System†	Compli-cation	Range of Follow-up	Patient Satisfaction
Kapural *et al.* 2016[30,31]	RCT	1	97 HF10 and 92 traditional SCS	90 HF10 and 81 traditional SCS	PE	Radicular and axial	Back: 67 for HF10, 41 for SCS Leg: 65.1 for HF10, 46 for SCS	ODI-HF10[16.5], SCS[13] GAF-HF10 (71), SCS (59)	LM-HF10 (3), SCS (5) WC-HF10 (4), SCS (3)	1–24 mo	HF10-S (86) SCS- S (86)
North *et al.* 2005[27]	RCT	1	38	29	PE	Radicular	SCS (52)	N/D	I (3), LM (9)	1.8–5.7 yrs average 2.9 yrs	SCS (47)
Kumar *et al.* 2008[28]	RCT	1	52 SCS+CMM and 48 CMM	41 CMM and 42* SCS+CMM	PE	Radicular and axial	SCS+CMM Leg [>50]; 1 mo (56), 6 mo (55), 12 mo (38), 24 mo (40)	N/D	I (10), LM (12)	1–24 mo	SCS: for pain reduction (66), for satisfied with treatment (93)

Parenthesis, (), contain percentage of patients and brackets, [], contain average percentage reduction/improvement.

The Evidence Level is based on the US Preventive Service Task Force definitions provided in Table 1.

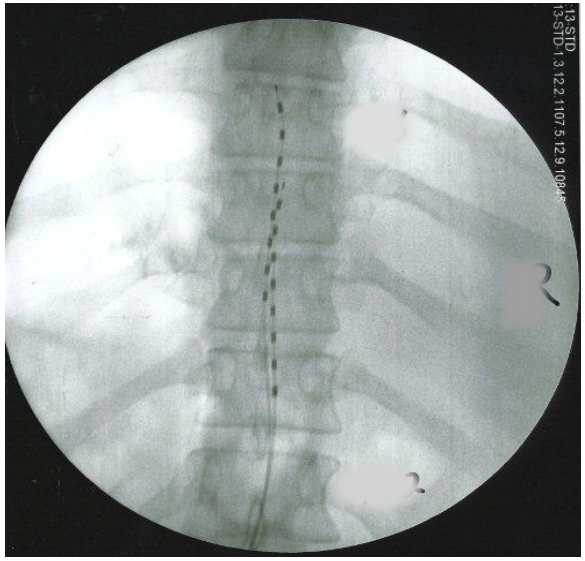
GAF, Global Assessment of Functionality; HF10, 10-kHz high-frequency; I, infection; LE, laminotomy electrodes; LM, lead migration; N/D, not documented; ODI, Oswestry Disability Index; PE, percutaneous electrodes; RCT, randomized control trial; S, success; WC, wound complication.

Forty-six patients of original 52 by 24 months, but 4 crossed to CMM, thus leaving 42.

Improvement in GAF, ODI. GAF and ODI data are 12-month values. At 24 months, 23.5% of HF10 patients had minimal disability compared with 9.9% of traditional SCS patients.

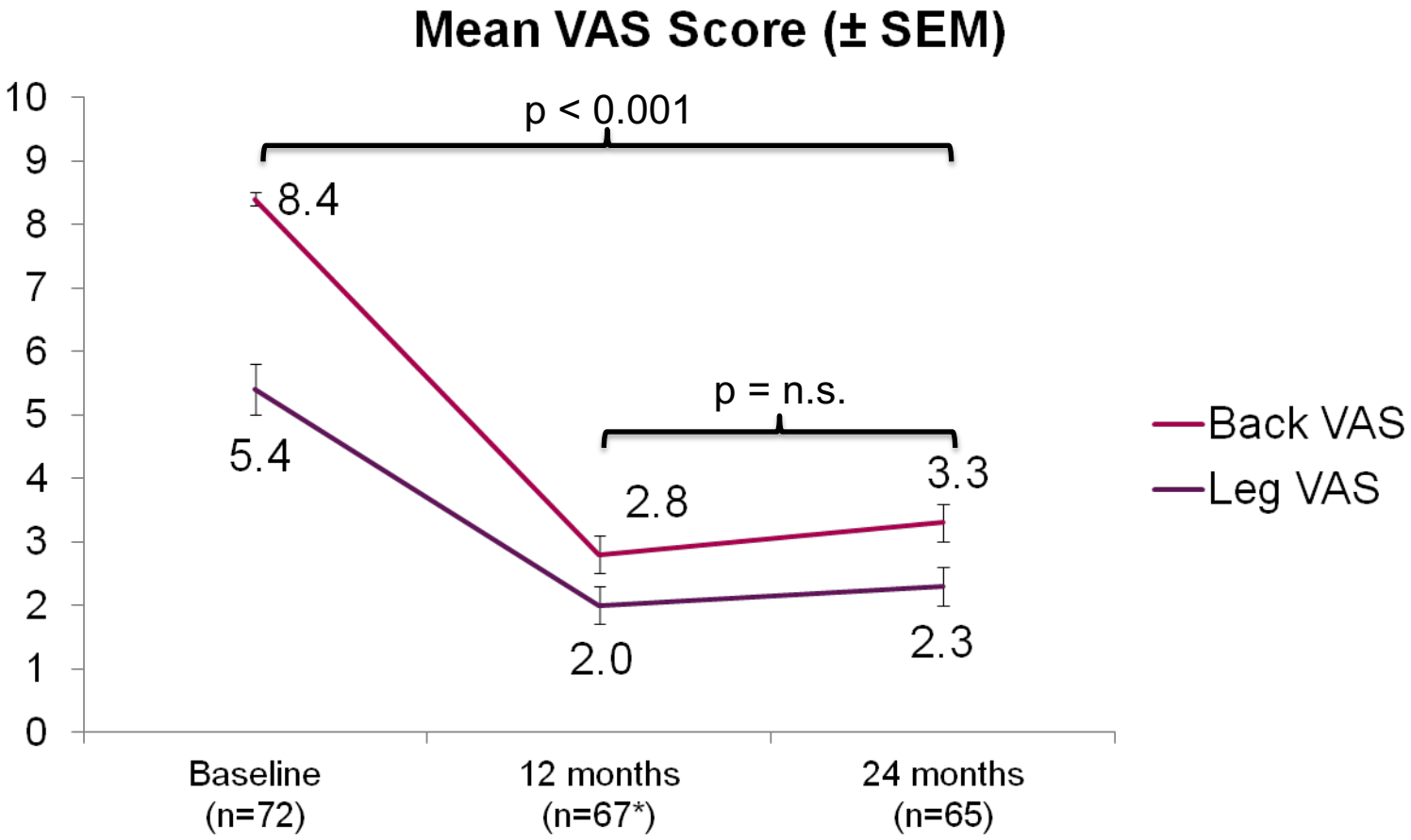
10 kHz SCS

- HF10 therapy leads are placed anatomically
  - Paresthesia mapping not required
  - **Anatomical lead placement (T8-T11) for back and leg pain**
  - No intra-operative programming
  - Consistent procedure time



EU Study: Significant and Durable Pain Relief

(Al-Kaisy, Van Buyten, Smet et al. Pain Medicine 2013)



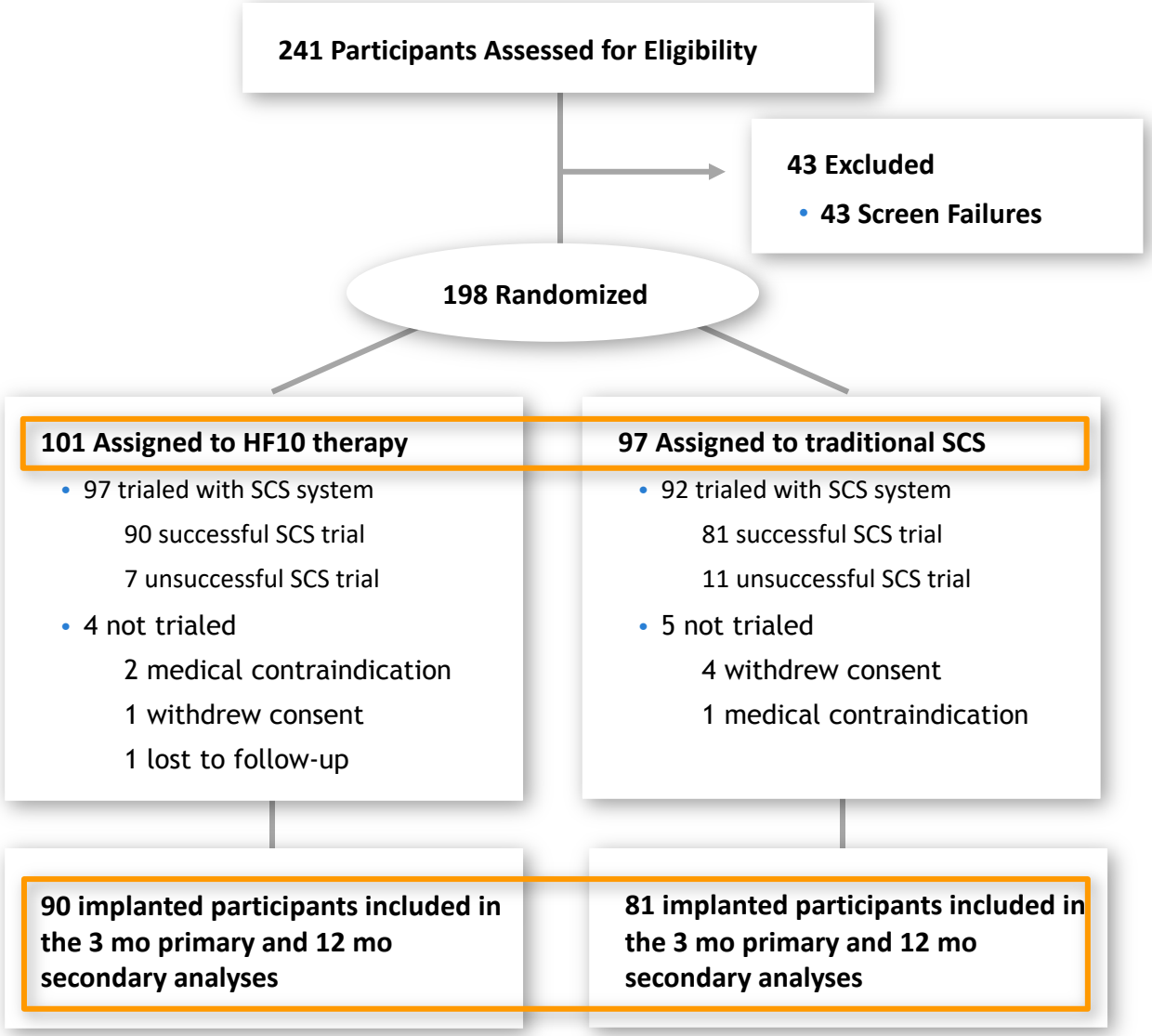
*: 1 patient missed 12-month visit

Level I Study Design

- SENZA-RCT Study
  - Comparative safety and effectiveness analyses
  - Parallel arm design generating clinical evidence for traditional SCS and 10 kHz therapy
  - Devices
    - Test: The investigational SCS system delivering 10 kHz therapy (10 kHz stimulation)
    - Control: Commercially available traditional SCS system delivering traditional SCS (2-1,200 Hz)

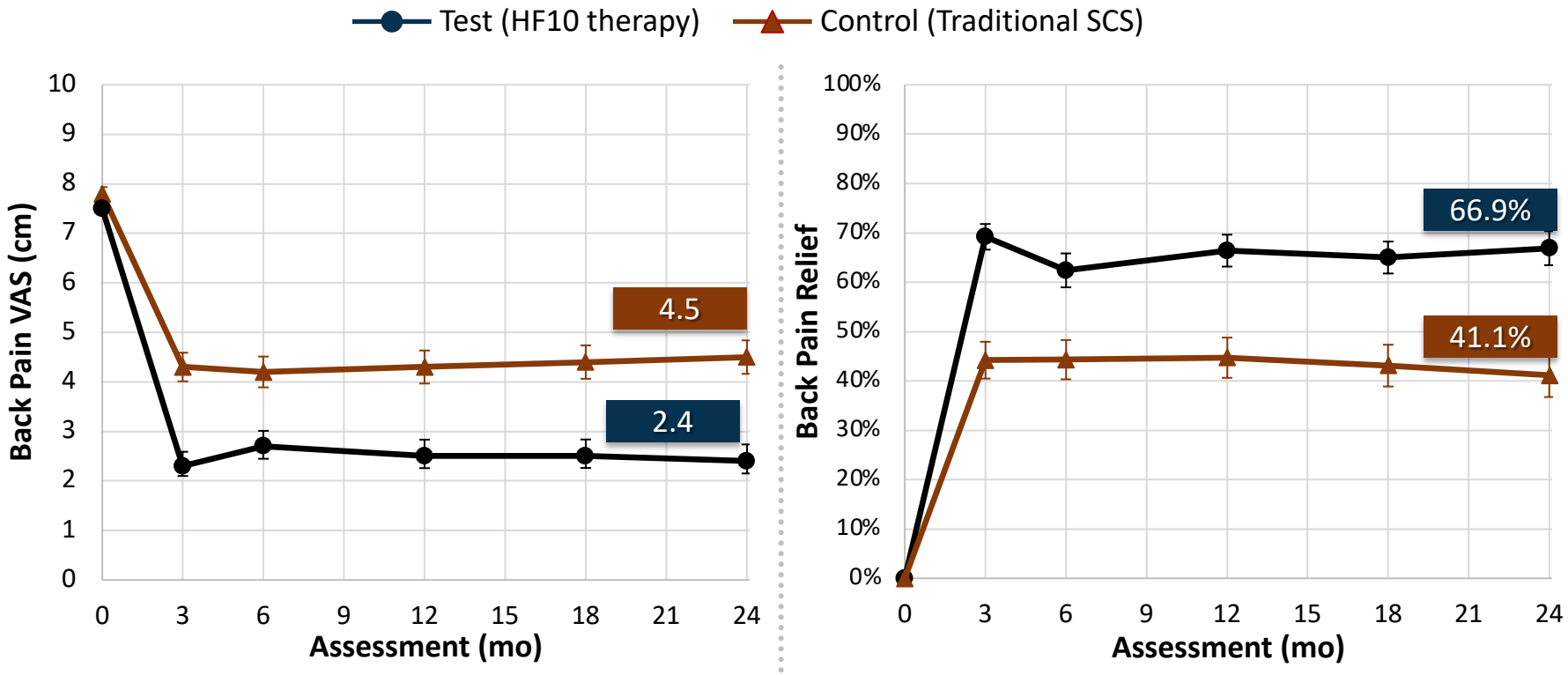
Kapural L, Yu C, Doust MW et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015

SENZA-RCT: Subject Flowchart



Back Pain at 24 Months

At 24 months, mean back pain VAS decreased **67%** with HF10 therapy compared to a decrease of **41%** for traditional SCS therapy



At 24mo: n=71 for control, n=85 for test

P<0.001

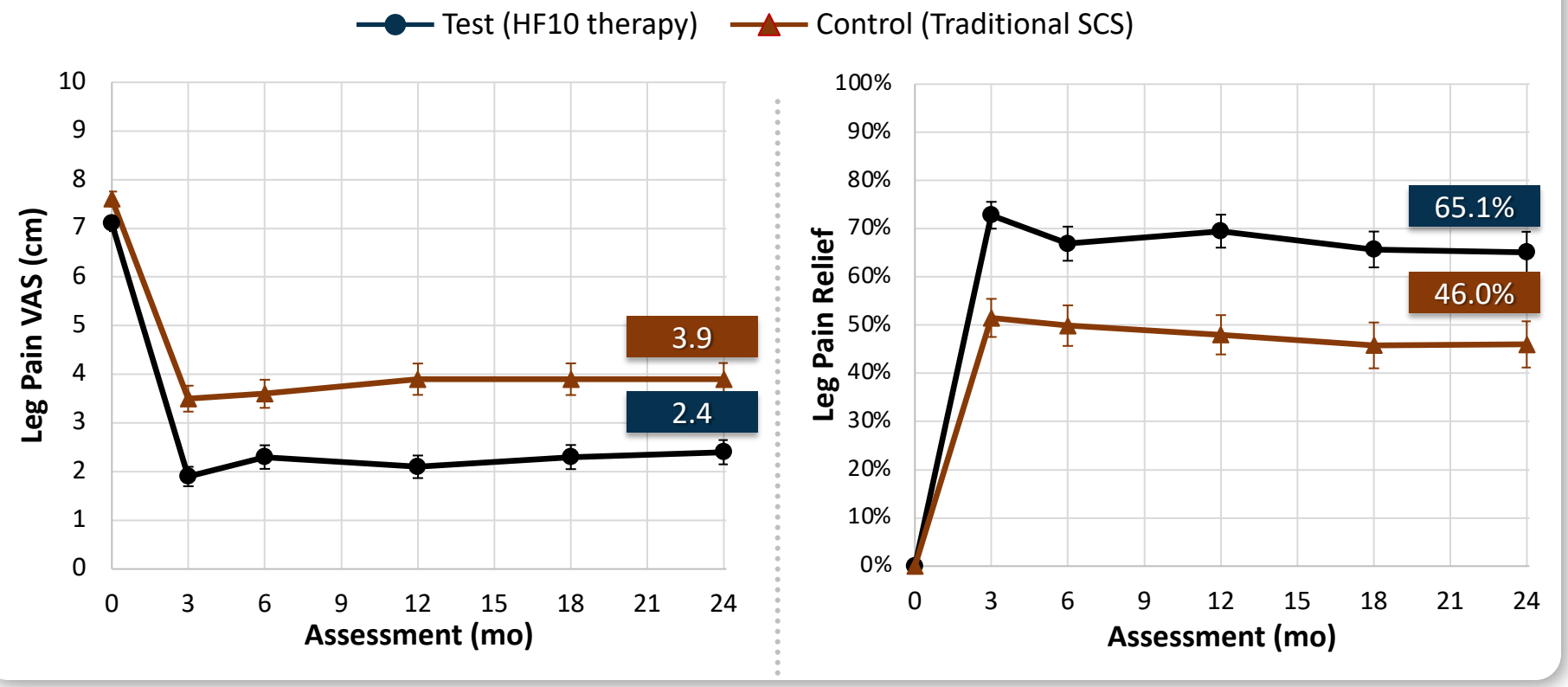
P<0.001

Kapural L, Yu C, Doust MW et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. **Anesthesiology 2015**

Kapural L, Yu C, et al. Comparison of 10 kHz High Frequency and Traditional Low Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-month Results from a Multicentre Randomized Controlled Pivotal Trial. **Neurosurgery 2016**

Leg Pain at 24 Months

At 24 months, mean leg pain VAS decreased **65%** with HF10 therapy compared to a decrease of **46%** for traditional SCS therapy

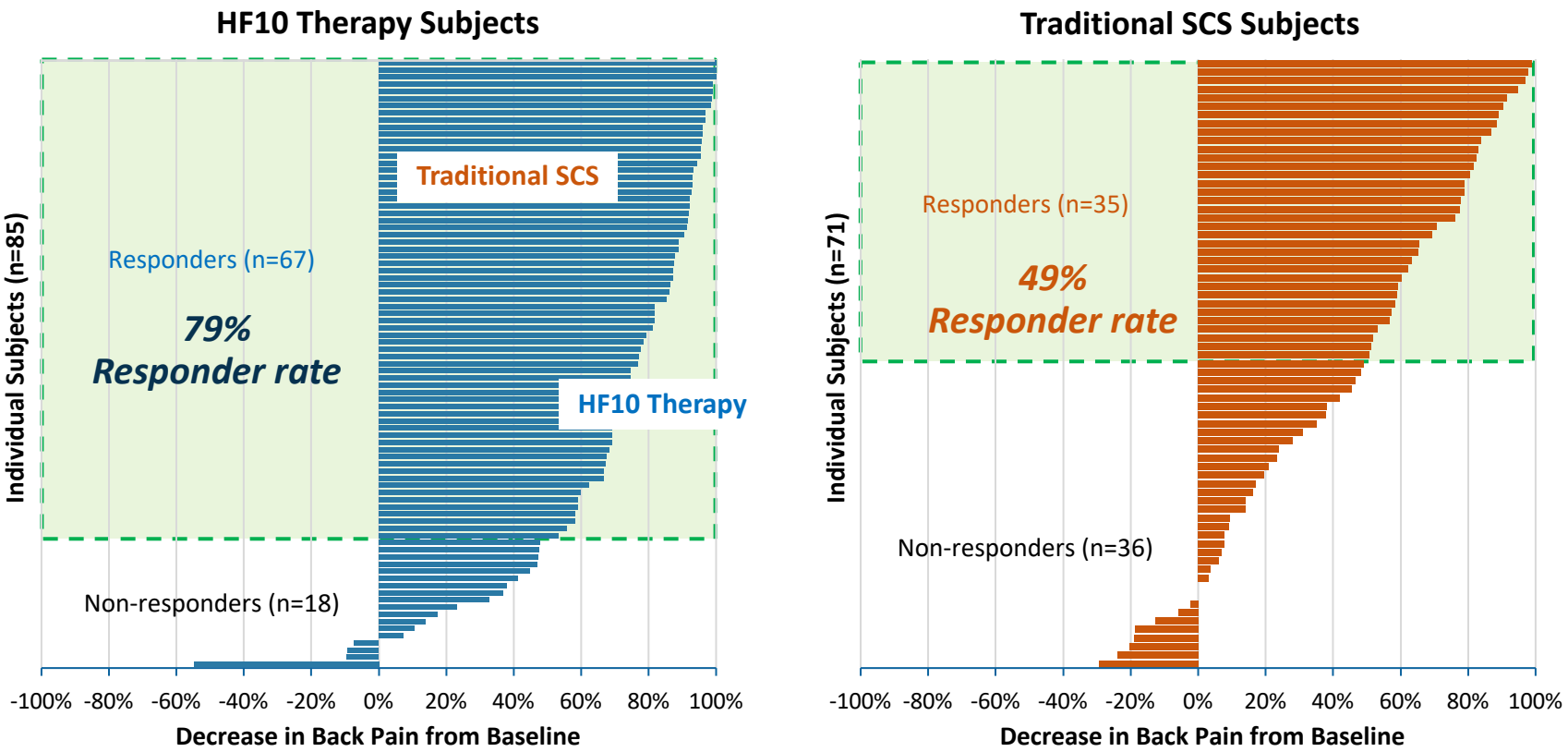


At 24 mo: n=71 for Control, n=85 for Test $P=0.027$

Kapural L, Yu C, et al. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. **Anesthesiology 2015**

Kapural L, Yu C, et al. Comparison of 10 kHz High Frequency and Traditional Low Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-month Results from a Multicentre Randomized Controlled Pivotal Trial. **Neurosurgery 2016**

Individual Back Pain Reduction at 24 Months

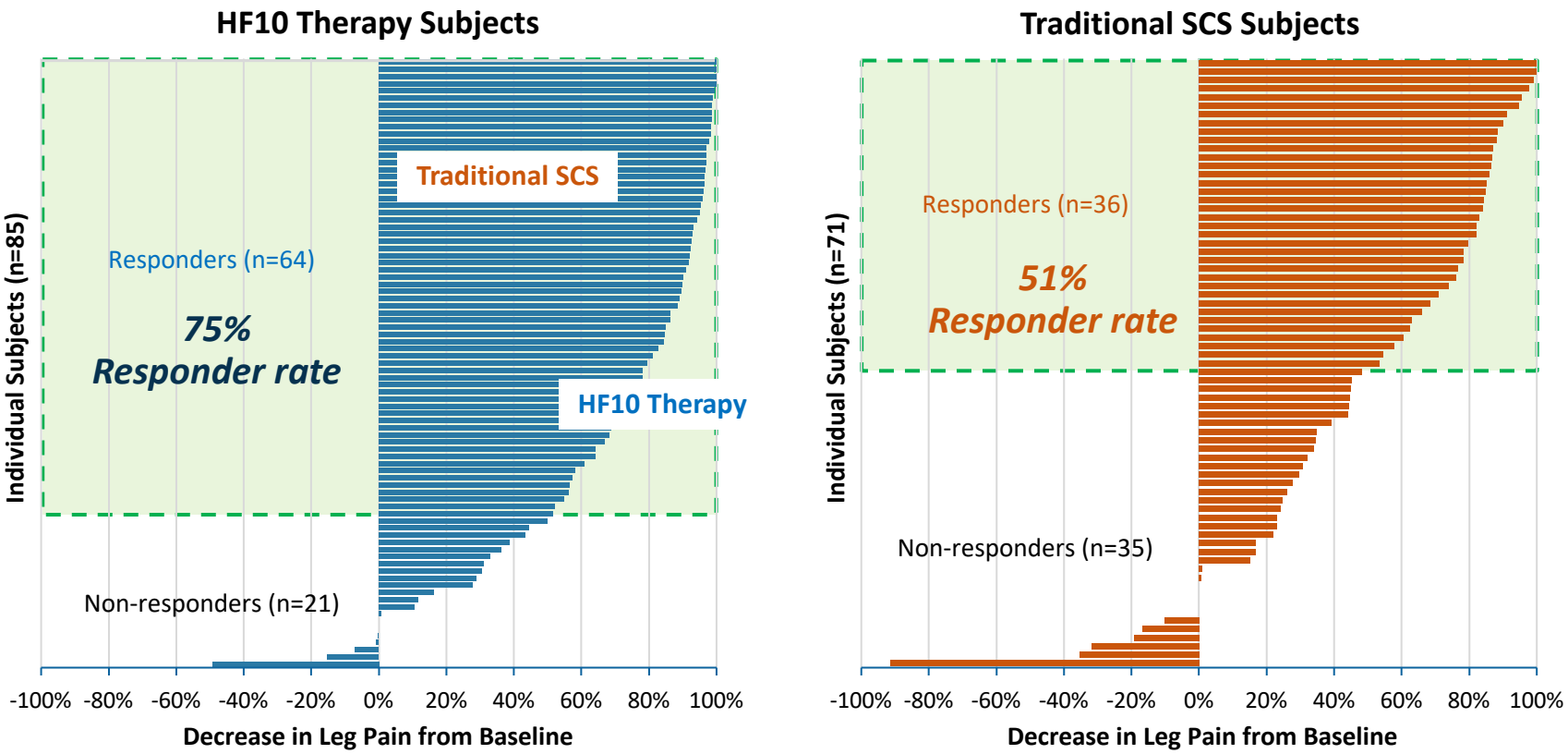


- Each horizontal line represents the response of a study subject.
- Responders (colored horizontal lines) are distinguished from non-responders (grey horizontal lines).

Responder rate: P<0.001

Each line represents a patient

Individual Leg Pain Reduction at 24 Months



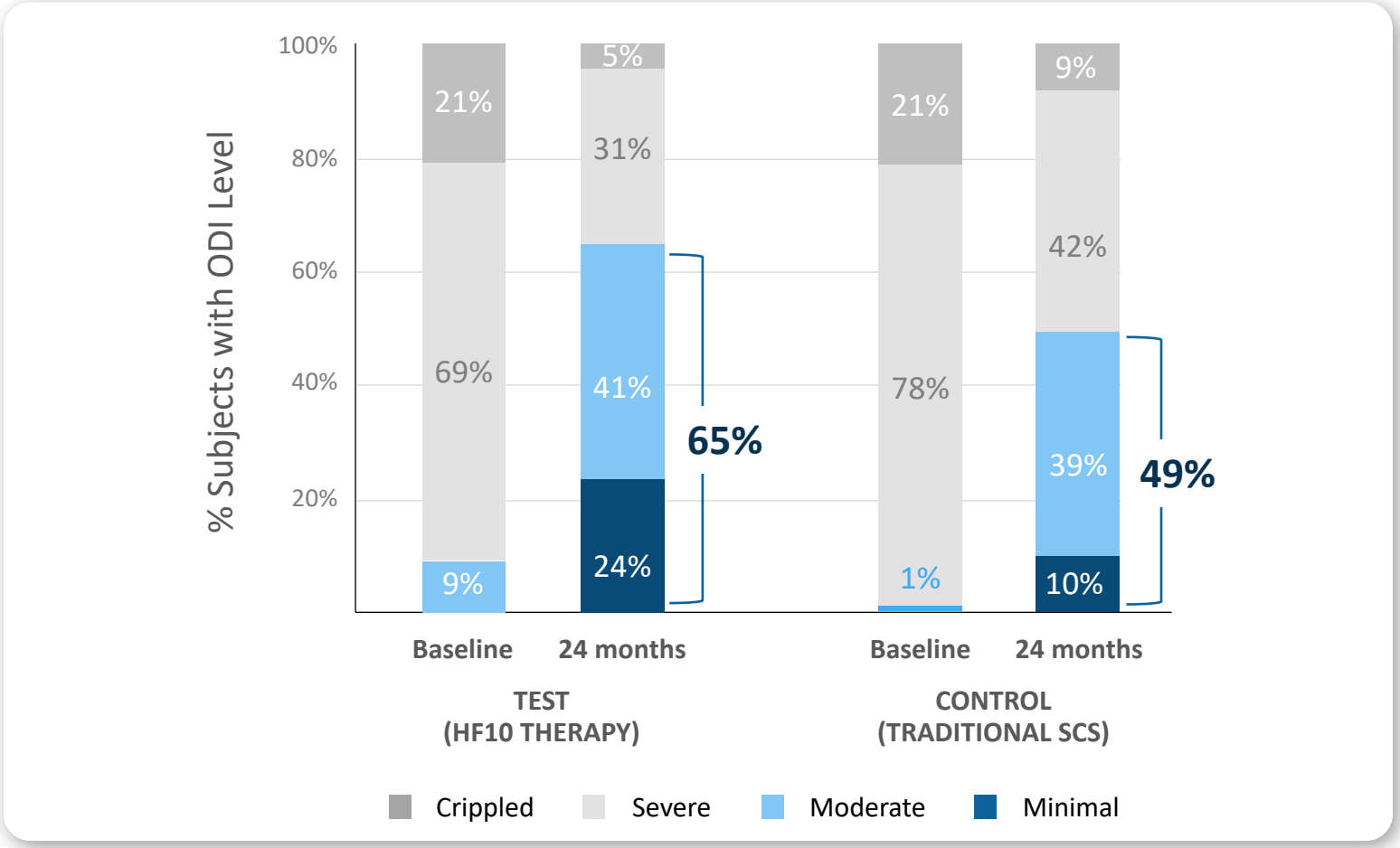
- Each horizontal line represents the response of a study subject.
- Responders (colored horizontal lines) are distinguished from non-responders (grey horizontal lines).

Responder rate: P=0.003

Each line represents a patient

Superior ODI Improvement at 24 Months

At 24 months, 65% of HF10 therapy subjects had minimal or moderate disability compared with 49% of traditional SCS subjects



ODI = Oswestry Disability Index

P=0.015

SENZA-RCT Published in Anesthesiology

ANESTHESIOLOGY
The Journal of the American Society of Anesthesiologists, Inc.

Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain

The SENZA-RCT Randomized Controlled Trial

Leonardo Kapural, M.D., Ph.D., Cong Yu, M.D., Matthew W. Doust, M.D., Bradford E. Gliner, M.S., Ricardo Vallejo, M.D., Ph.D., B. Todd Sitzman, M.D., M.P.H., Kasra Amirdelfan, M.D., Donna M. Morgan, M.D., Lora L. Brown, M.D., Thomas L. Yearwood, M.D., Ph.D., Richard Bundschu, M.D., Allen W. Burton, M.D., Thomas Yang, M.D., Ramsin Benyamin, M.D., Abram H. Burgher, M.D.

ABSTRACT

Background: Current treatments for chronic pain have limited effectiveness and commonly known side effects. Given the prevalence and burden of intractable pain, additional therapeutic approaches are desired. Spinal cord stimulation (SCS) delivered at 10 kHz (as in HF10 therapy) may provide pain relief without the paresthesias typical of traditional low-frequency SCS. The objective of this randomized, parallel-arm, noninferiority study was to compare long-term safety and efficacy of SCS therapies in patients with back and leg pain.

Methods: A total of 198 subjects with both back and leg pain were randomized in a 1:1 ratio to a treatment group across 10 comprehensive pain treatment centers. Of these, 171 passed a temporary trial and were implanted with an SCS system. Responders (the primary outcome) were defined as having 50% or greater back pain reduction with no stimulation-related neurological deficit.

Results: At 3 months, 84.5% of implanted HF10 therapy subjects were responders for back pain and 83.1% for leg pain, and 43.8% of traditional SCS subjects were responders for back pain and 55.5% for leg pain ($P < 0.001$ for both back and leg pain comparisons). The relative ratio for responders was 1.9 (95% CI, 1.4 to 2.5) for back pain and 1.5 (95% CI, 1.2 to 1.9) for leg pain. The superiority of HF10 therapy over traditional SCS for leg and back pain was sustained through 12 months ($P < 0.001$). HF10 therapy subjects did not experience paresthesias.

Conclusion: HF10 therapy promises to substantially impact the management of back and leg pain with broad applicability to patients, physicians, and payers. (ANESTHESIOLOGY 2015; 123:00-00)

WE present a multicenter, randomized, controlled trial evaluating the safety and efficacy of 10-kHz high-frequency (HF10) therapy, which is an innovative spinal cord stimulation (SCS) system for the management of chronic back and leg pain. This system delivers electrical stimulation pulses at high frequency (10,000 Hz) as compared with traditional low-frequency SCS systems (typically around 50 Hz). Previous work suggests that the higher-frequency system may treat back and leg pain to a greater degree. Moreover, it may be able to do so without producing paresthesias associated with low-frequency SCS, which some patients find uncomfortable.[1–3]

What We Already Know about This Topic

- Spinal cord stimulation (SCS) often relieves radicular pain but is relatively poorly effective for the treatment of back pain
- High-frequency SCS may improve the efficacy of SCS for the treatment of low back pain

What This Article Tells Us That Is New

- This randomized trial involving 198 participants demonstrated that high-frequency spinal cord stimulation (SCS) was superior to conventional SCS for the treatment of back pain and leg pain
- The effects of high-frequency stimulation relative to conventional stimulation persisted for 12 months

This article is featured in "This Month in Anesthesiology," page 1A. Full protocol available at: gliner@nevro.com. Raw data available at: gliner@nevro.com.

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Neurosurgery

RESEARCH—HUMAN—CLINICAL TRIALS

OPEN

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Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-Month Results From a Multicenter, Randomized, Controlled Pivotal Trial

BACKGROUND: Pain relief with spinal cord stimulation (SCS) has focused historically on paresthesias overlapping chronically painful areas. A higher level evidence supports the use of SCS in treating leg pain than supports back pain, as it is difficult to achieve adequate paresthesia coverage, and then pain relief, in the low back region. In comparison, 10-kHz high-frequency (HF10) SCS therapy does not rely on intraoperative paresthesia mapping and remains paresthesia-free during therapy.

OBJECTIVE: To compare long-term results of HF10 therapy and traditional low-frequency SCS.

METHODS: A pragmatic randomized, controlled, pivotal trial with 24-month follow-up was conducted across 11 comprehensive pain treatment centers. Subjects had Visual Analog Scale scores of ≥5.0/10.0 cm for both back and leg pain, and were assigned randomly (1:1) to receive HF10 therapy or low-frequency SCS. The primary end point was a responder rate, defined as ≥50% back pain reduction from baseline at 3 months with a secondary end point at 12 months (previously reported). In this article, 24-month secondary results are presented. Non-inferiority was first assessed, and if demonstrated the results were tested for superiority.

RESULTS: In the study, 198 subjects were randomized (101 HF10 therapy, 97 traditional SCS). One hundred seventy-one subjects (90 HF10 therapy, 81 traditional SCS) successfully completed a short-term trial and were implanted. Subjects averaged 54.9 ± 12.9 years old, 13.6 ± 11.3 years since diagnosis, 86.6% had back surgery, 88.3% were taking opioid

Neuromodulation: Technology at the Neural Interface

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(onlinelibrary.wiley.com) DOI: 10.1111/ner.12746

Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial

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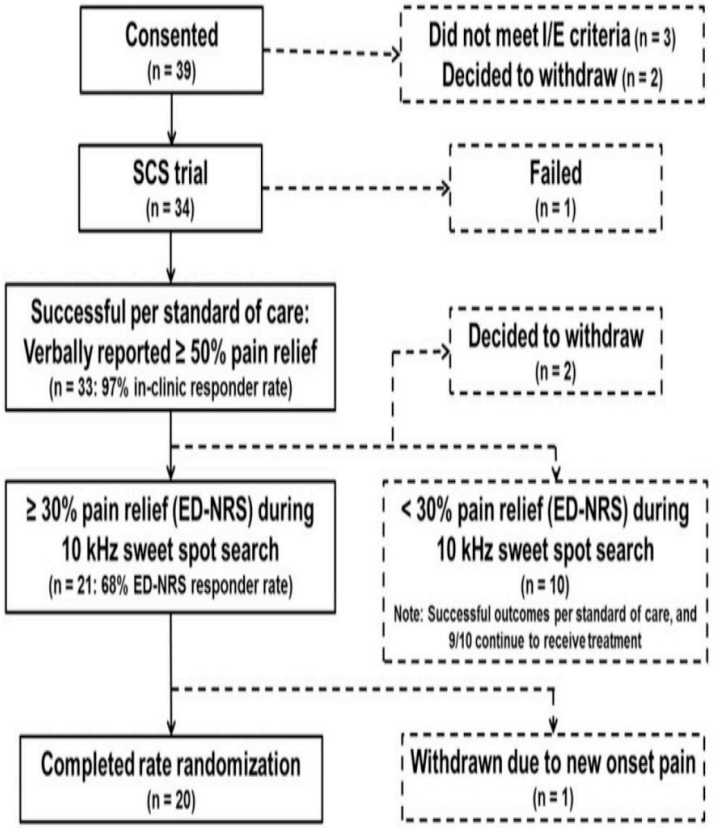
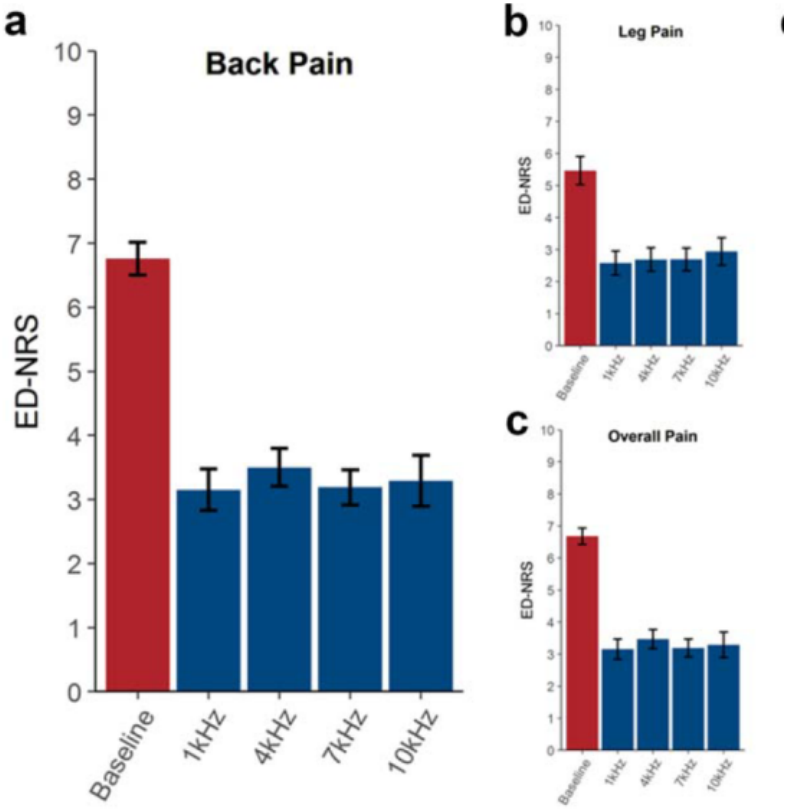
Objective: The PROCO RCT is a multicenter, double-blind, crossover, randomized controlled trial (RCT) that investigated the effects of rate on analgesia in kilohertz frequency (1–10 kHz) spinal cord stimulation (SCS).

Materials and Methods: Patients were implanted with SCS systems and underwent an eight-week search to identify the best location ("sweet spot") of stimulation at 10 kHz within the searched region (T8–T11). An electronic diary (e-diary) prompted patients for pain scores three times per day. Patients who responded to 10 kHz per e-diary numeric rating scale (ED-NRS) pain scores proceeded to double-blind rate randomization. Patients received 1, 4, 7, and 10 kHz SCS at the same sweet spot found for 10 kHz in randomized order (four weeks at each frequency). For each frequency, pulse width and amplitude were titrated to optimize therapy.


Consented
(n = 39)
Did not meet I/E criteria (n = 3)
Decided to withdraw (n = 2)
SCS trial
(n = 34)
Failed
(n = 1)
Successful per standard of care:
Verbally reported ≥ 50% pain relief
(n = 33: 97% in-clinic responder rate)
Decided to withdraw
(n = 2)
≥ 30% pain relief (ED-NRS) during
10 kHz sweet spot search
(n = 21: 68% ED-NRS responder rate)
< 30% pain relief (ED-NRS) during
10 kHz sweet spot search
(n = 10)
Note: Successful outcomes per standard of care, and
9/10 continue to receive treatment
Completed rate randomization
(n = 20)
Withdrawn due to new onset pain
(n = 1)


a
Back Pain
ED-NRS
Baseline
1kHz
4kHz
7kHz
10kHz
b
Leg Pain
ED-NRS
c
Overall Pain
ED-NRS

Critique

- **All frequencies using Precision SCS system and programmed by sponsor personnel , in a 5 day observation performed equally to traditional SCS for three month duration**
- **Not HF-10 therapy Leads placed based on paresthesias, PW varied (authors not familiar with HF-10),** specific bipole locations, pulse widths, amplitudes not reported
- **3 months follow up? Recharge burden- unless minimal amplitude, large duty cycling constraints**
- **If hypothesis that no difference exists between 1 and 10khz, non-inferiority study comparing to HF-10, free engineer access to reprogramming and 2 year follow up would be appropriate (remember SENZA, Accurate?)**
- **Patients, pain physicians, insurers interested in 5 day, 3 weeks, 3 m f/u data ? Demanding more nowadays !!**

Pain Medicine 2017; 0: 1–21
doi: 10.1093/pm/pnx241

OXFORD

Original Research Article

Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome

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efficacy of high-frequency SCS (HF) versus conventional frequency SCS (CF) on the patients with FBSS.

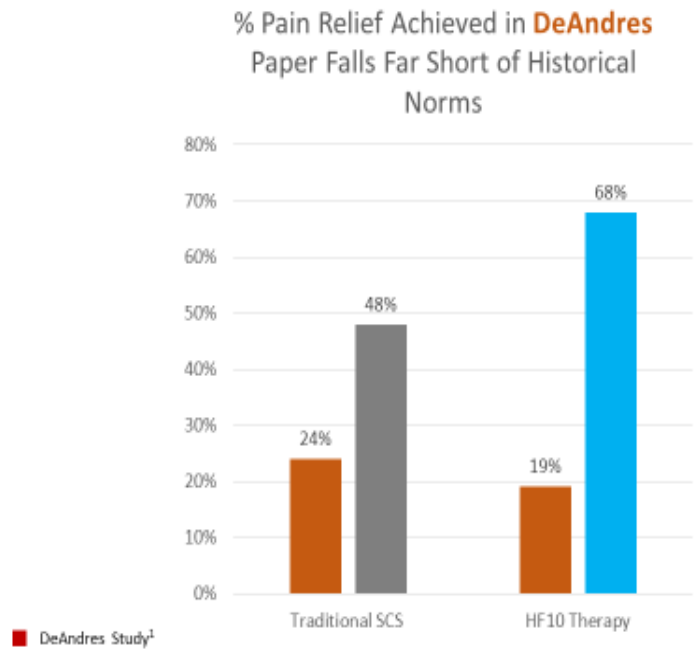
Design. Prospective, Randomized blind trial.

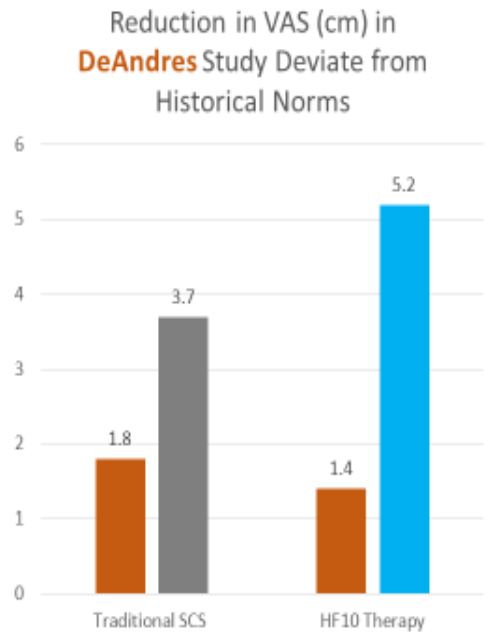
Setting. Academic University Pain Medicine Center.

Subject. Seventy eight patients with FBSS diagnosis based on internationally recognized criteria, and refractory to conservative therapy for at least 6 months, have been initially recruited, and

Methods. Sixty subjects met the eligibility criteria and were randomized and scheduled for the trial phase.The patients were randomly assigned in either, one of the two groups: CF SCS or HF SCS. Within the study methods, special attention was paid to standardizing patient programming, so that these parameters would not impact the results. The

	Baseline	12 Mo	% Relief	Reduction in VAS
DeAndres CF	7.69	5.86	24%	1.8
Traditional SCS Studies (Weighted Avgs)	7.74	4.05	48%	3.68
DeAndres HF10	7.5	6.06	19%	1.4
HF10 therapy studies (weighted avgs)	7.67	2.47	68%	5.2



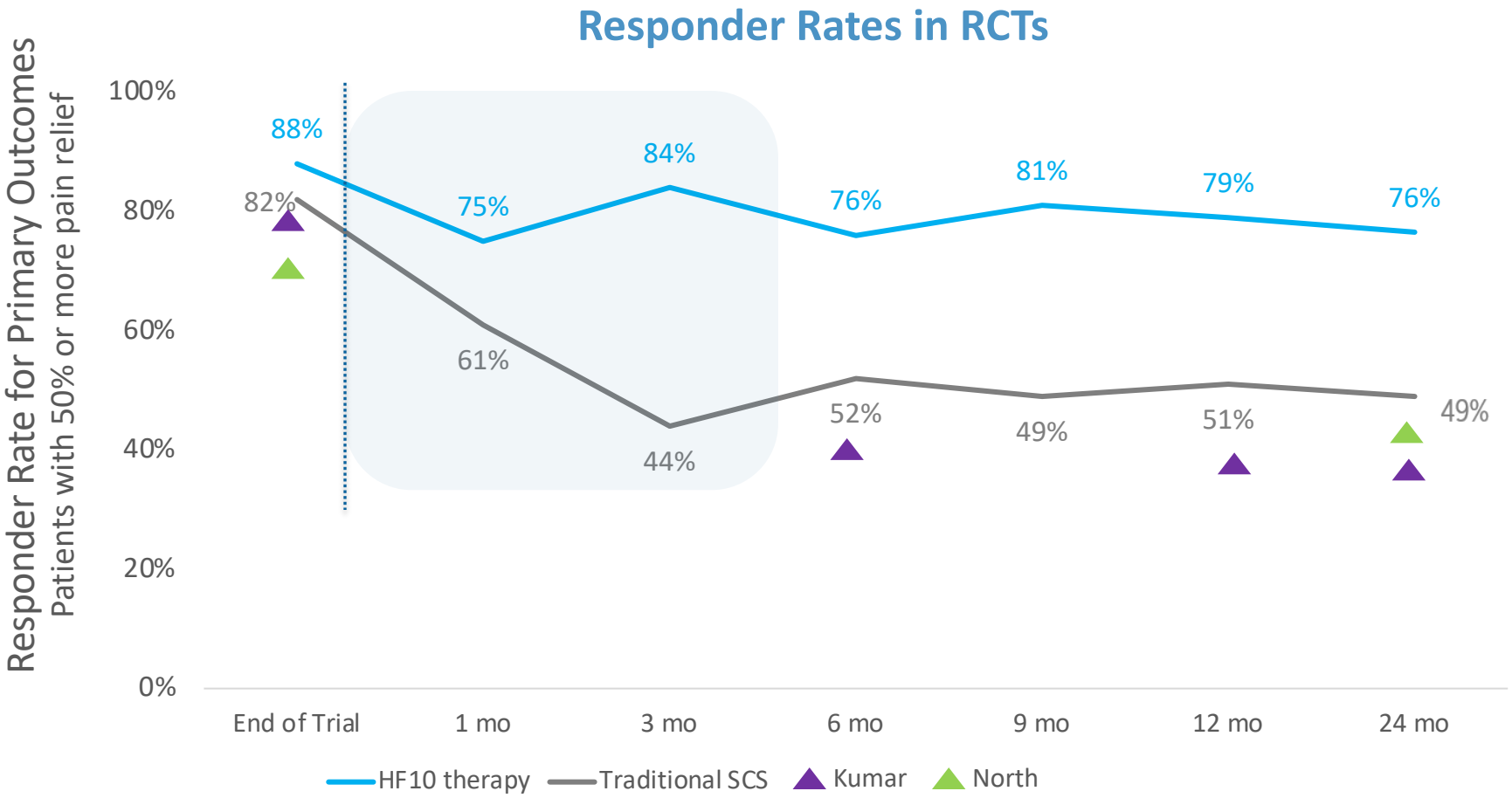


1. DeAndres, Jose. Prospective, Randomized Blind Effect-on-Outcome Study of Conventional vs High-Frequency Spinal Cord Stimulation in Patients with Pain and Disability Due to Failed Back Surgery Syndrome. Pain Medicine 2017; 0: 1–21
2. Traditional SCS studies include Kumar, Oakley, SENZA-RCT
3. HF10 therapy studies include SENZA-RCT, SENZA-EU, Van Buyten 12 month results from his practice (poster)

DeAndres et al, Pain Medicine 2017

- Outcomes far worse than any study in SCS (40 years)
- *No* adverse events of any kind: no implant/generator site pain, no infections, no uncomfortable paresthesia's
- Blinded? Patients told will receive two different treatments, one with other without paresthesia, trial and implant both open label, follow-up different companies, open label
- Traditional stimulation, reprogramming based on loss of coverage, HF-10 reprogramming based on ??, not reported
- ODI average 27 !

Comparison of Response Rates Across Prospective RCTs



n = 171 to 12 months (n = 90 test, n = 81 control); n = 156 at 18 and 24 months (n = 85 test, n =71 control)
p-value < 0.001 at all time points 3 months and beyond

1..Kapural L, et al. Comparison of 10-kHz High-Frequency and Traditional Low-Frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: 24-month Results from a Multicenter, Randomized, Controlled Pivotal Trial. Neurosurgery. Published 09 2016 [Epub ahead of Print]. 2. Kumar K, et al. 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;63:762–70. 3. North RB, et al. Spinal Cord Stimulation Versus Repeated Lumbosacral Spine Surgery for Chronic Pain: A Randomized, Controlled Trial. Neurosurgery 2005;56:98–106.

Complications:

TABLE 1. Common Adverse Events Across the Randomized Prospective Studies for FBSS and Over Last 11 Yrs

Common Adverse Events	North *et al* 2005 (Traditional SCS)	Kumar *et al* 2008 (Traditional SCS)	Al-Kaisy *et al* 2014 (10 kHz SCS)	Kapural *et al* 2016 (Traditional SCS Arm)	Kapural *et al* 2016 (10 kHz SCS Arm)
Generator/implant site pain	n/a	12%	8.4%	13.4%	12.9%
Uncomfortable paresthesias	n/a	12%	0.0%	11.3%	0.0%
Lead migration	n/a	14%	4.8%	5.2%	3.0%

Note an improvement in lead migration frequency over time, while the numbers on generator/implant site pain remain similar. Obviously, those who received subthreshold 10 kHz SCS had no paresthesias during stimulation (Kapural et al, 10 kHz therapy arm; Al-Kaisy et al, 2014), and consequently no uncomfortable stimulation as opposed to traditional SCS (Kumar et al 2008, Kapural et al, traditional low-frequency SCS arm 2016).

FBSS indicates failed back surgery syndrome; SCS, spinal cord stimulation.

ECAP

Electrically Evoked Compound Action Potential

PAIN® 153 (2012) 593–601

PAIN®

www.elsevier.com/locate/pain

Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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ABSTRACT

Electrical stimulation of the spinal cord provides effective pain relief to hundreds of thousands of chronic neuropathic pain sufferers. The therapy involves implantation of an electrode array into the epidural space of the subject and then stimulation of the dorsal column with electrical pulses. The stimulation depolarises axons and generates propagating action potentials that interfere with the perception of pain. Despite the long-term clinical experience with spinal cord stimulation, the mechanism of action is not understood, and no direct evidence of the properties of neurons being stimulated has been presented. Here we report novel measurements of evoked compound action potentials from the spinal cords of patients undergoing stimulation for pain relief. The results reveal that Aβ sensory nerve fibres are recruited at therapeutic stimulation levels and the Aβ potential amplitude correlates with the degree of coverage of the painful area. Aβ-evoked responses are not measurable below a threshold stimulation level, and their amplitude increases with increasing stimulation current. At high currents, additional late responses are observed. Our results contribute towards efforts to define the mechanism of spinal cord stimulation. The minimally invasive recording technique we have developed provides data previously obtained only through microelectrode techniques in spinal cords of animals. Our observations also allow the development of systems that use neuronal recording in a feedback loop to control neurostimulation on a continuous basis and deliver more effective pain relief. This is one of numerous benefits that in vivo electrophysiological recording can bring to a broad range of neuromodulation therapies.

1. Introduction

Spinal cord stimulation (SCS) induces tactile paraesthesia, a pleasant tingling sensation, as a result of the stimulation of nerve fibres in the dorsal column (DC). The qualitative description of the induced paraesthesia has been used to hypothesise that Aβ fibres are recruited during SCS [17]. The paraesthesia supplants the feeling of pain in the body areas innervated by the stimulated fibres. The goal of SCS is to completely cover—in a perceptual sense—the area of pain with paraesthesia because high levels of coverage are essential for effective pain relief [1].

SCS was first attempted [23] in the 1960s after research into the gate control theory of pain, where it was observed that nonnoxious (eg, touch and vibration) activation of superficial fibres in the DC of the spinal cord inhibits pain transmission by a gate at the spinal segmental level [16]. Meyerson and colleagues have postulated that SCS ameliorates pain through gamma-aminobutyric acid (GABA)-ergic and adenosine related inhibitory mechanisms [12,17]. They propose that electrical stimulation produces orthodromic and antidromic action potentials [12] and that the antidromic activity regulates transmission of pain via an interneuron pool and second-order wide-dynamic-range neurons (Fig. 1). There is also evidence that supraspinal mechanisms may play a role in pain relief [4]; however, the role of ascending activation vs local activation at the segmental level is currently not understood.

Evidence for the recruitment of particular fibre types during SCS has previously been restricted to simulated computer models. Holsheimer [8] concluded that SCS recruits a small number of Aβ fibres (approximately 60), with a diameter between 9.4 and 10.7 μm, in the DC (at the T11 segment). Because the DC is innervated by 12 dermatomes at this level, Holsheimer concluded that there are only 4–5 fibres per dermatome recruited during SCS [8]. The relatively small number of fibres (4–5 per dermatome) with sufficient diameter in the superficial DC has been confirmed in microscopic analysis of human spinal cord sections [5]. Feirabend et al. studied the diameter and distribution of fibres in the

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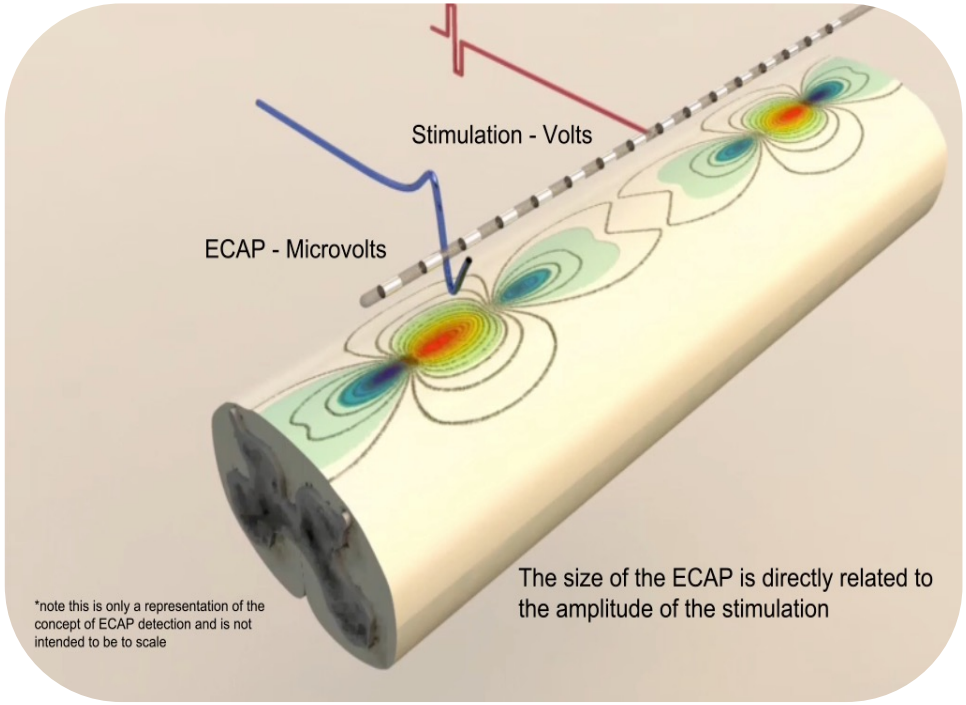
0304-3959/$36.00
doi:10.1016/j.pain.2011.11.023

ECAPS: electrically-evoked compound action potentials are a direct view of the human spinal cord response to SCS

ECAPS are a measure of dorsal column activation **in humans**[1]

ECAP amplitude is a direct measurement of neural recruitment and reflection of the extent of pain relief[1,2]



Electrophysiological response of dorsal column structures activated by SCS (ECAP) confirms at low and high amplitudes conduction velocities are observed in the Aβ fiber conduction range[1]

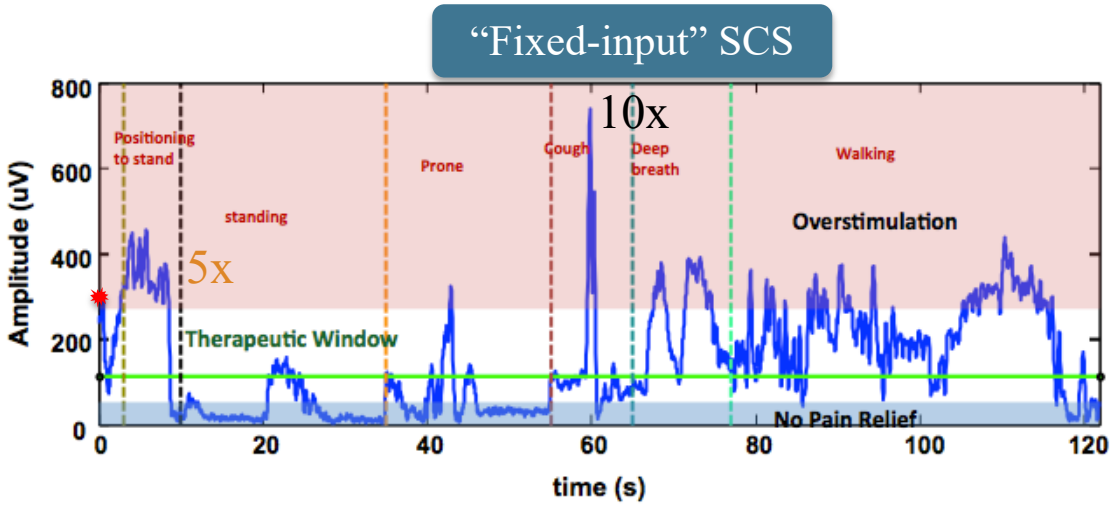
1. Parker et al., Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *PAIN,* 153 (2012) , 593–601.
2. Yang et al., *Neuroscience* 199 (2011), 470–480.

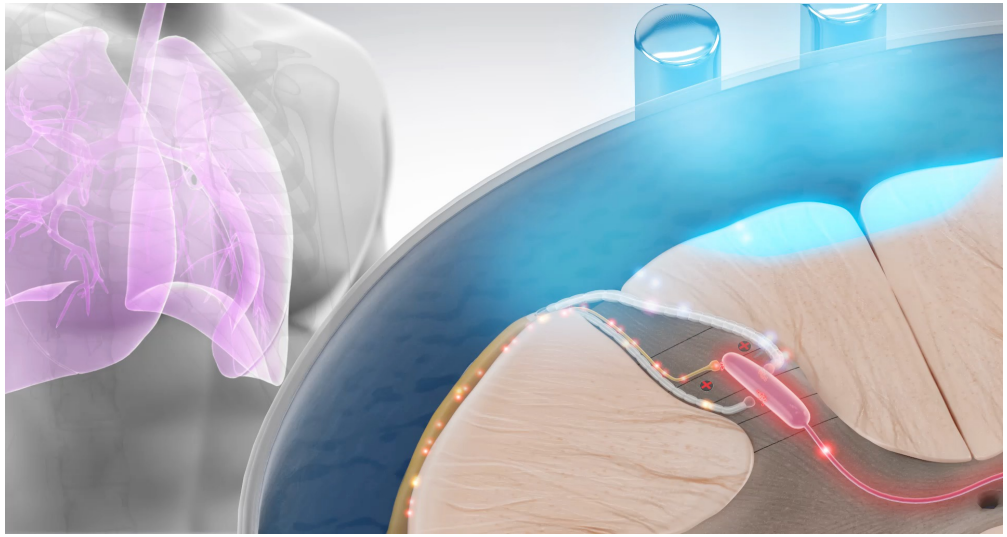
“Fixed-input” SCS systems deliver large variation in electrical dosage to dorsal column[1]

Fixed input SCS defines all spinal cord stimulation that delivers a fixed amplitude pulse train without regulating dorsal column fiber recruitment

When the energy input is fixed, variation in recruitment is as much as 10x the activation threshold

With “fixed-input” SCS, the therapy is mostly outside the therapeutic window due to movement and unique patient physiology

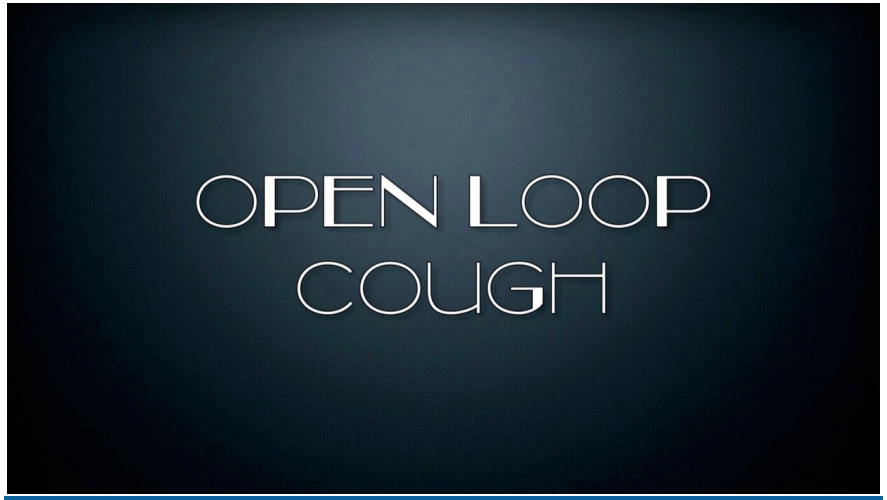




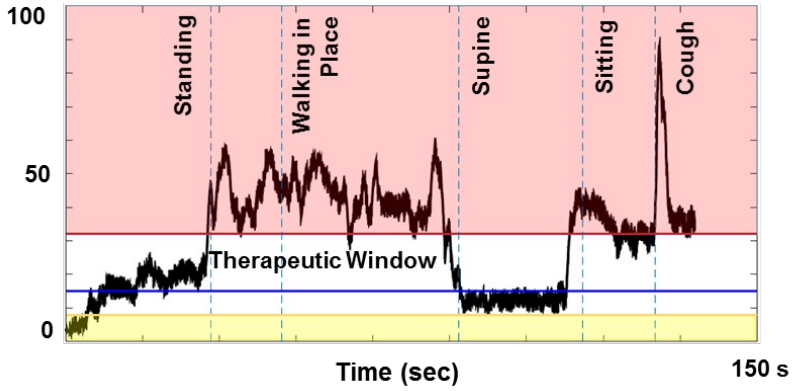
1. Data on File. Saluda Medical

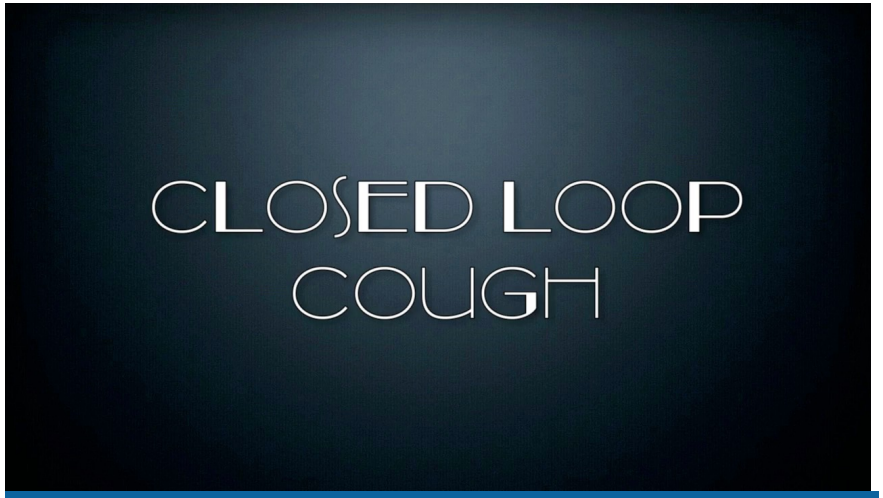
Sensory adaptation results in a different sensory experience

Closed loop stimulation capitalizes on each patient's unique neurophysiology (ECAP) to optimize and maintain constant neural recruitment by modulating amplitude in real-time

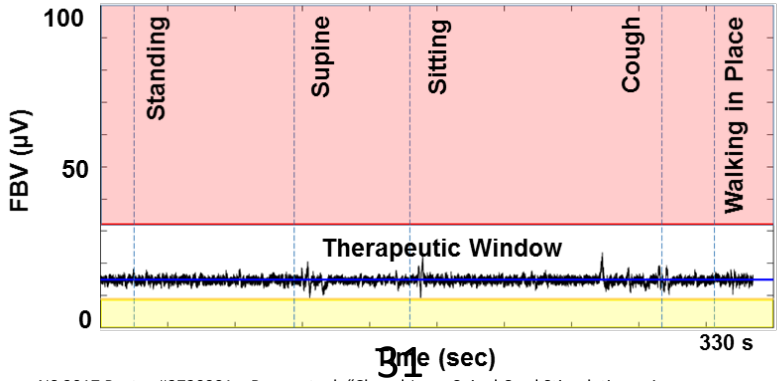


SENSORY EXPERIENCE ASSOCIATED WITH THE "SPARK" IN THE LEGS IS ACTIVATION OF NOCICEPTORS





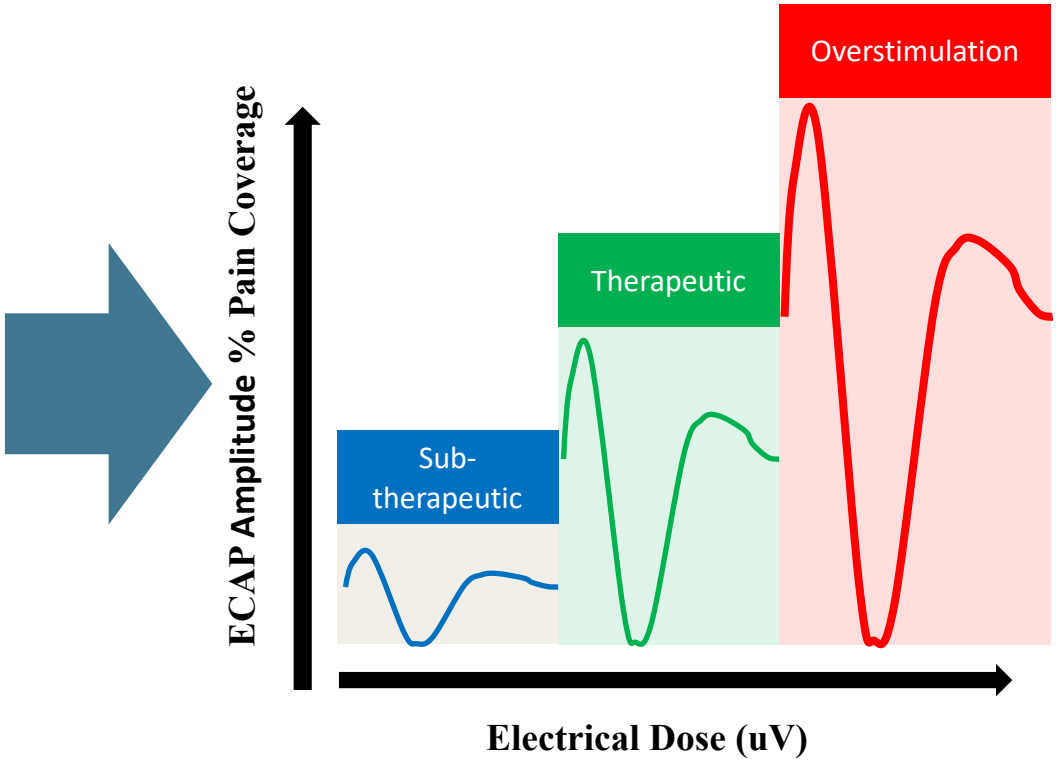
CONSISTENT OUTPUT = DIFFERENT SENSORY EXPERIENCE



Source: NS 2017 Poster #2720901 – Russo et. al. "Closed-Loop Spinal Cord Stimulation – A Novel Stimulation Paradigm to Mitigate Tolerance?"

The Dose Response Curve[1]

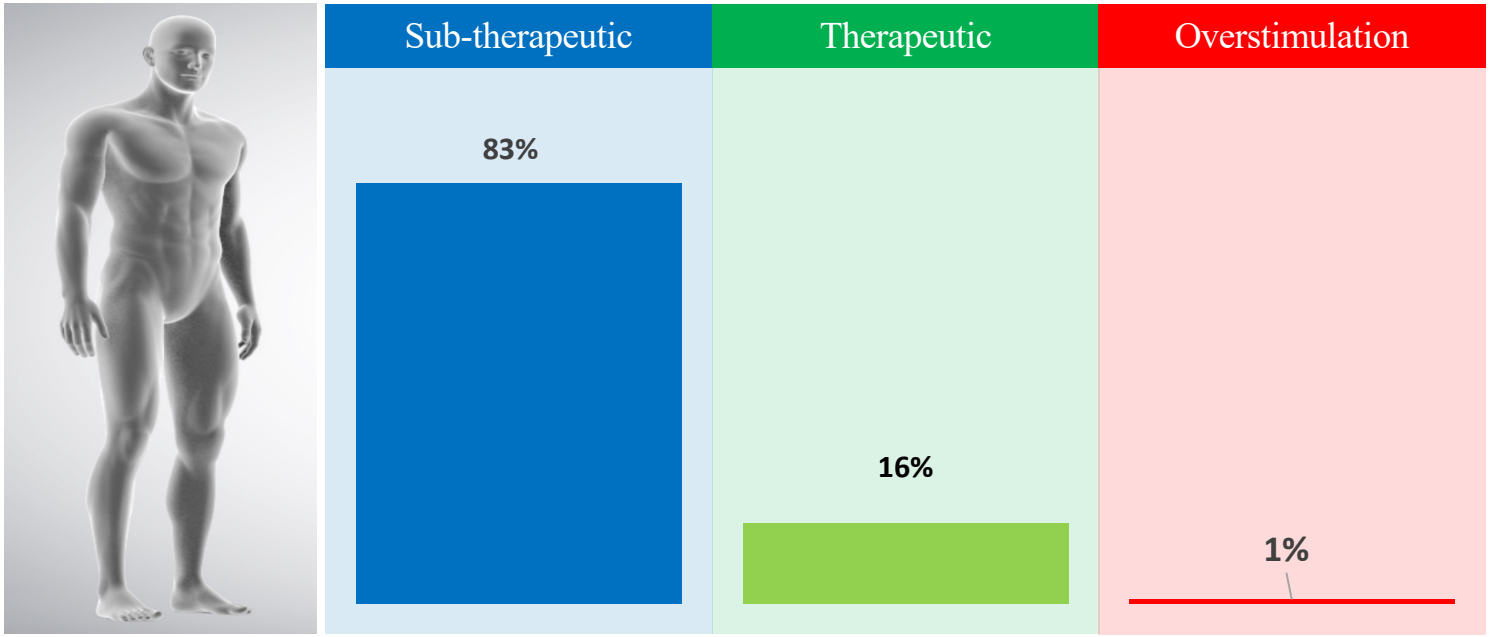
As electrical dose is increased, dorsal column activation increases (ECAP amplitude), and patients report increasing percentages of pain coverage until it reaches a noxious point where the stimulation becomes painful.



1. Parker et al., Compound action potentials recorded in the human spinal cord duringneurostimulation for pain relief. *PAIN,* 153 (2012) , 593–601.

"Fixed-input" SCS systems may drive patients to utilize sub-therapeutic electrical doses due to overstimulation events[2]

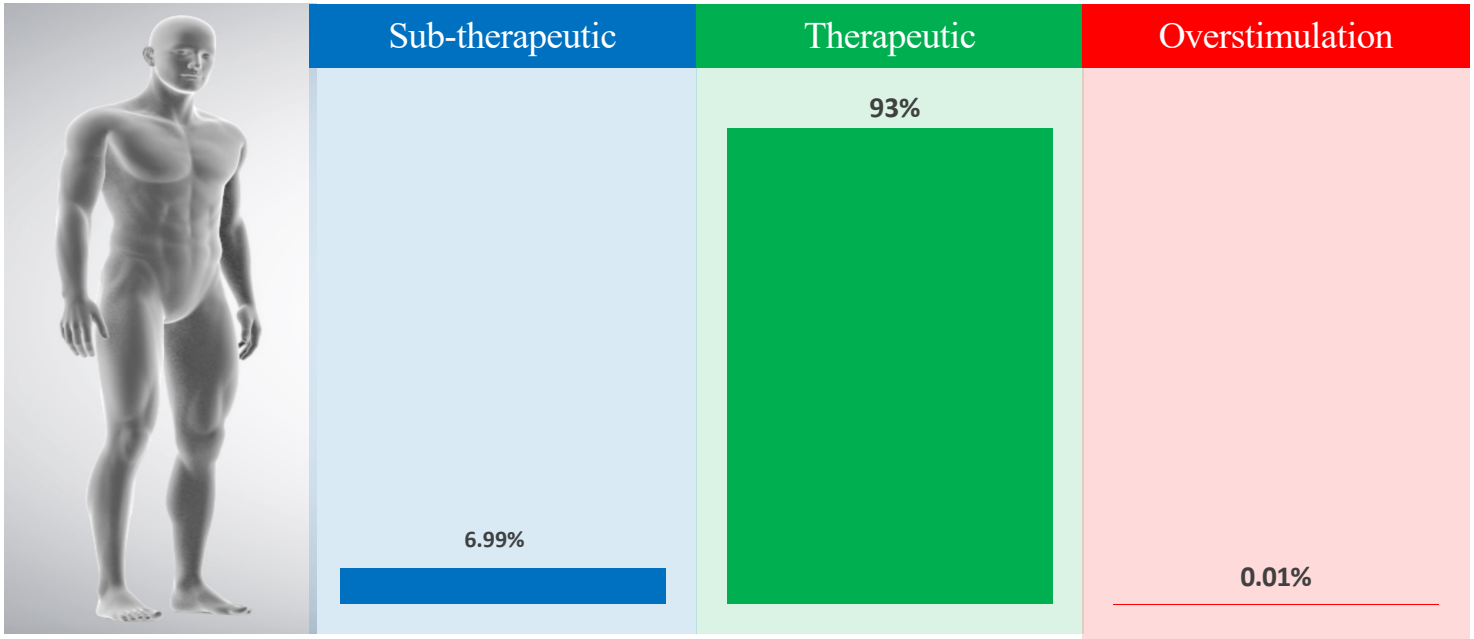
Patient 0301 experienced **6,800 overstimulation events** in 9 days which drove the subject to utilize a sub-therapeutic dosage as a result[1,2]



1. Study Subject 0301 participated in IRB approved Panorama US IDE Feasibility Study. 2. Data on file.

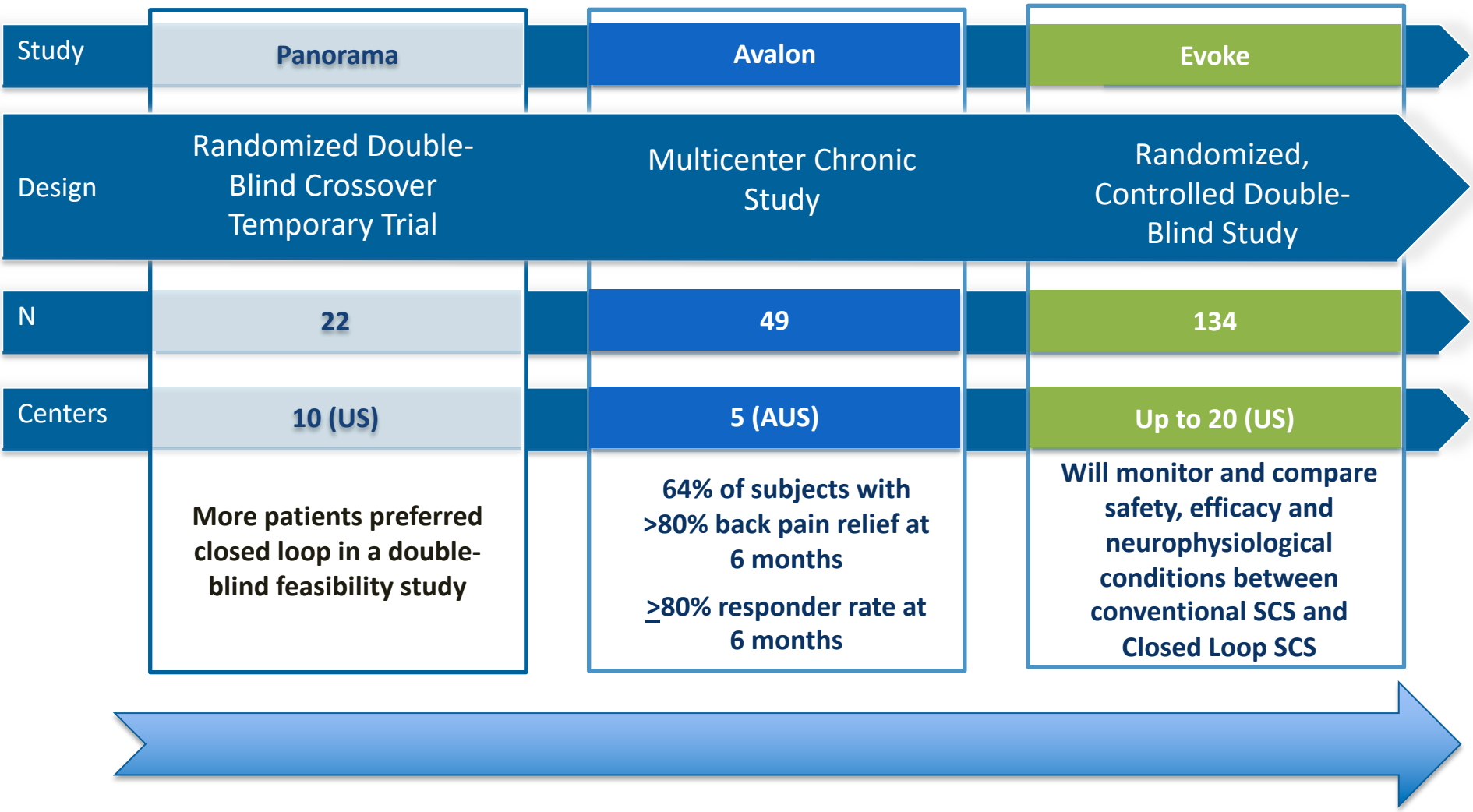
Closed-loop control delivers and maintains a therapeutic electrical dose while preventing overstimulation of the dorsal column

When patient 0301 crossed over to closed loop control the patient utilized a higher stimulation dose that was maintained at a **therapeutic level 93%** of the time[1,2]



1. Study Subject 0301 participated in IRB approved Panorama US IDE Feasibility Study. 2. Data on file.

Path to Building Higher Scientific Evidence in Chronic Studies



*22 patients provided analyzable data

**RCT comparing EVOKE with & without feedback

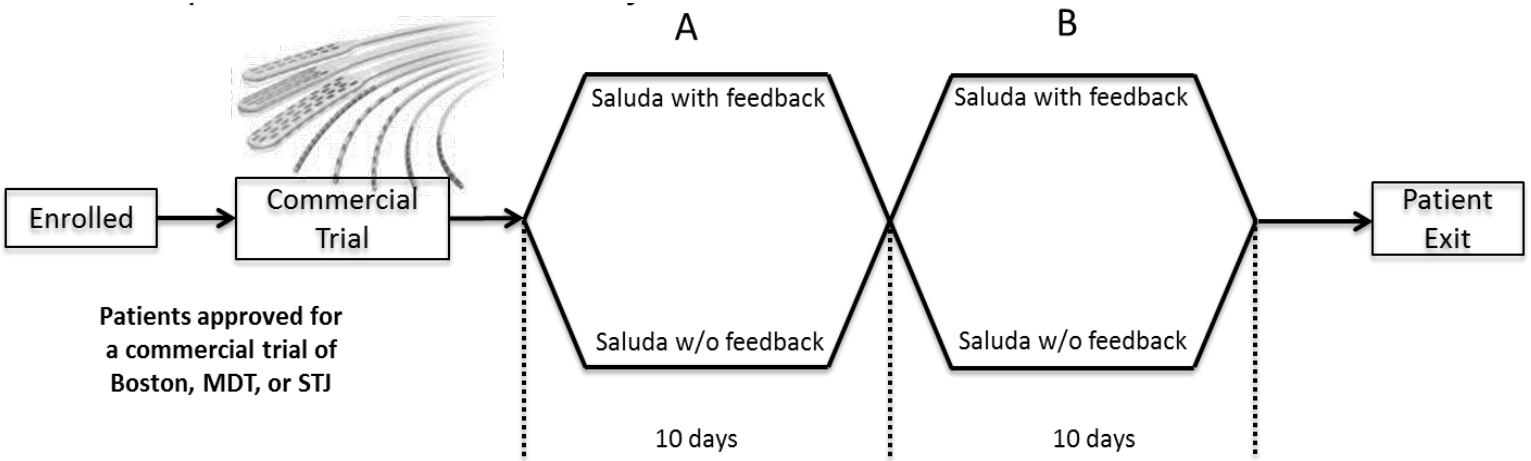
Short term feasibility study to better understand neurophysiological activity as a result of SCS and human behaviour in response

North American Neuromodulation Society 19th Annual Meeting
Las Vegas, Nevada December 10 – 13, 2015

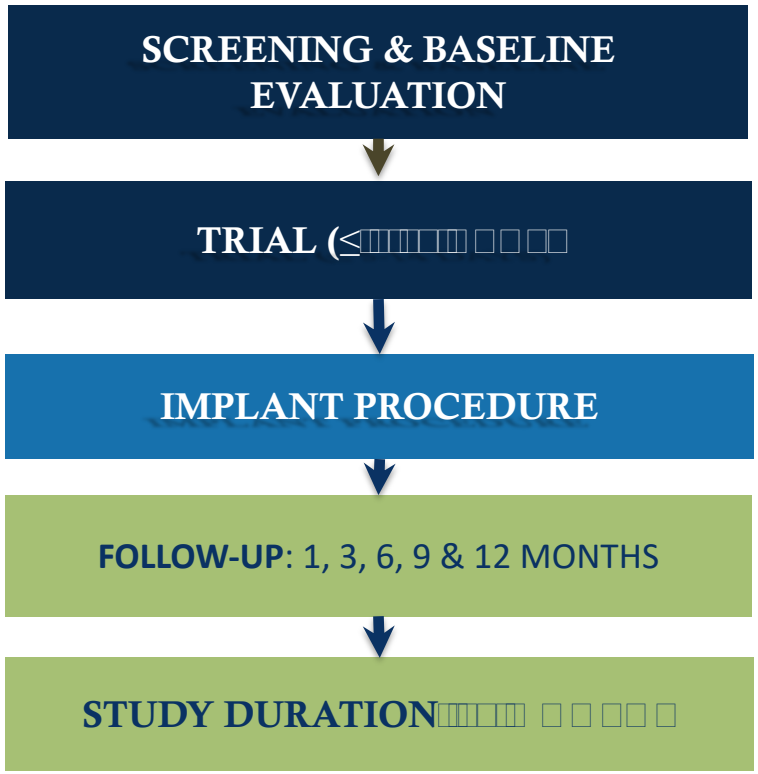
Dr. Steven M. Rosen:
Randomized Double-Blind Crossover Study Examining The Safety And Effectiveness Of Closed-Loop Control In Spinal Cord Stimulation

Feasibility Study (Panorama): randomized double blinded crossover

- Comparing closed-loop to traditional SCS
- 10 centers in the USA
- 22 patients included in analysis
- 25 days acute study, using commercially available leads



Avalon study design:
Prospective, multi-center, open label study



Primary outcome

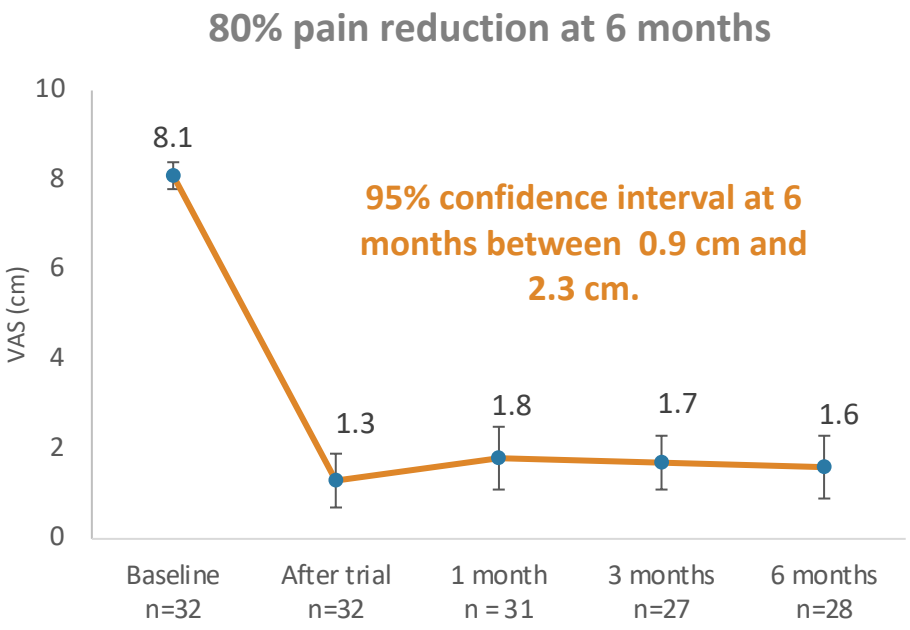
- To evaluate the long-term safety and performance of a feedback controlled, closed-loop SCS system using ECAPs to treat chronic pain of the trunk and/or limbs

Secondary outcomes

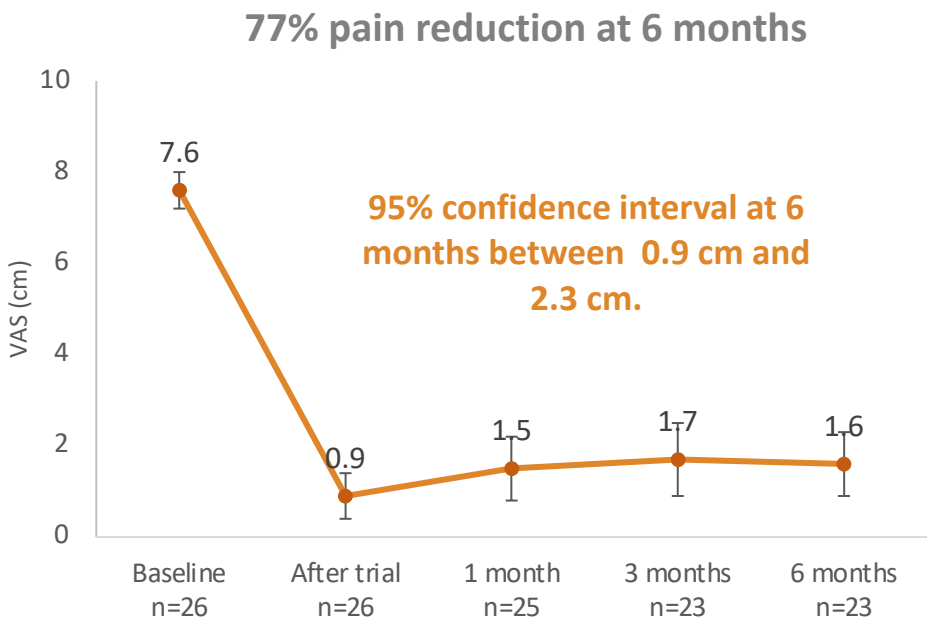
- Pain and patient satisfaction
- Quality of life, function, disability and sleep
- Neurophysiology of neural stimulation including dose and therapeutic window measures
- To evaluate different stimulation paradigms and procedures

VAS reduction over time

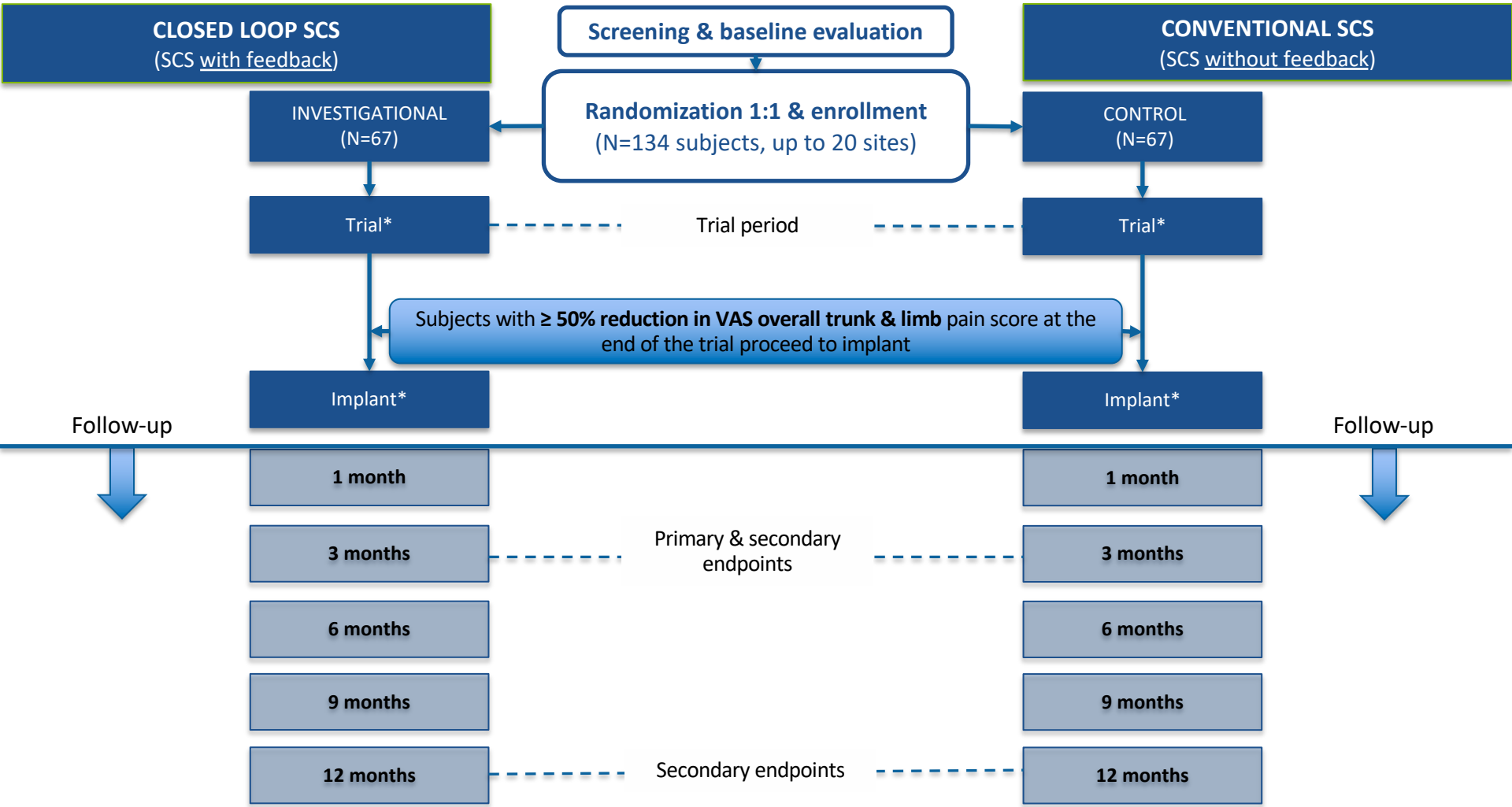
Low Back Pain



Leg Pain



EVOKE Study Design: Double-Blinded Randomized Controlled

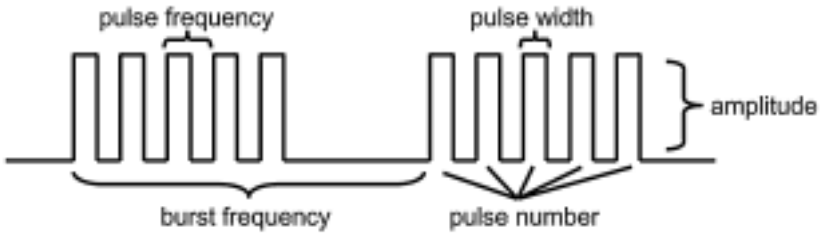


* All patients programmed using ECAPS

Study Duration: up to 3 years

Burst stimulation

- Burst paresthesia-based subthreshold stimulation, many patients still feel stimulation
  - Burst pulse frequency 500 Hz, burst frequency is 40 Hz
  - Paresthesia-based mapping required for trial and implant



1. Deer et al, Pain Medicine News, December 2015 | Volume: 13(12)
2. DeRidder et al, Neuromodulation online DOI:10.1111/ner.12368
3. Illustration: Crosby et al, Neuromodulation 2015; 18: 1-8

1

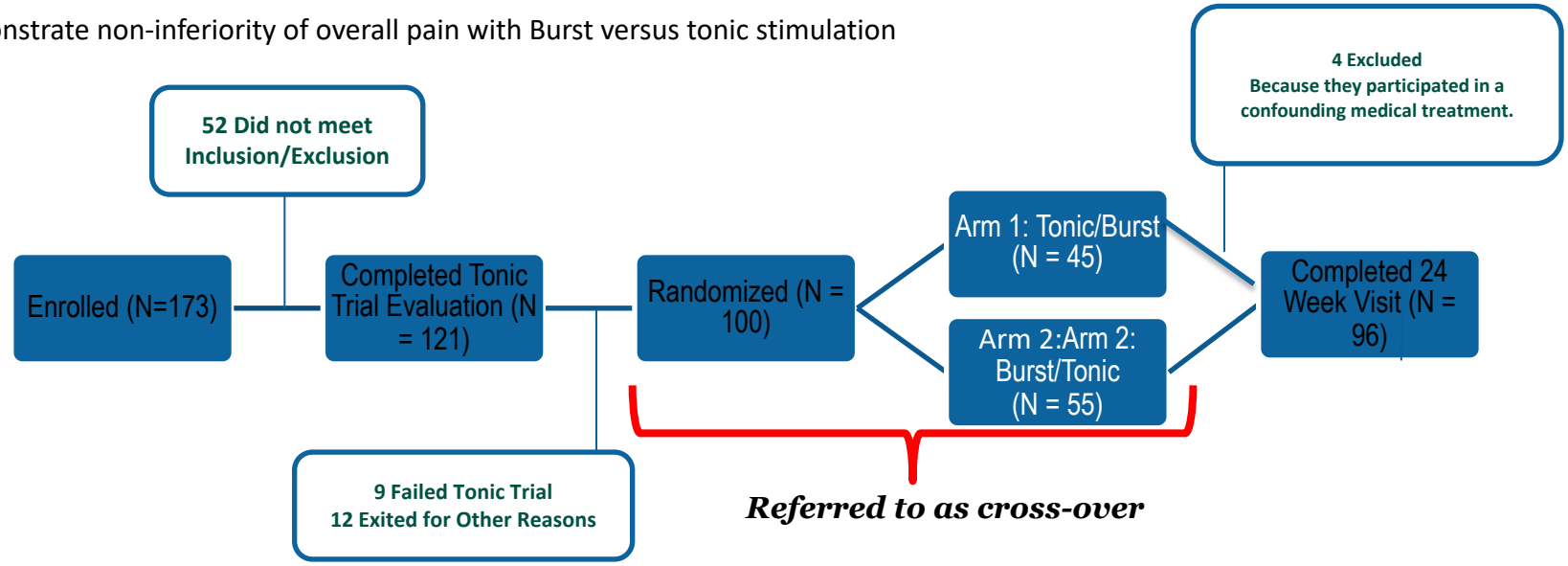
The SUNBURST study was designed* to drive FDA approval and demonstrated BurstDR to be superior to Tonic stimulation

**A single pivotal study can't answer all questions, a portfolio of evidence is needed*

SUNBURST Study Design

A Prospective, Randomized, Controlled Trial Assessing Burst Stimulation for chronic pain

- Demonstrate the safety and effectiveness of a neurostimulation system that delivers both Burst and tonic stimulation
- Demonstrate non-inferiority of overall pain with Burst versus tonic stimulation



Key Takeaway-

- The trial design (using cross over) is an extremely robust design but creates a higher bar for BurstDR than in many other studies.
- The end point as opposed to just comparing BurstDR to tonic is really assessing the incremental value of BurstDR vs. tonic . All patients are Tonic Responders in the trial implant phase.

1

The SUNBURST study was designed* to drive FDA approval and demonstrated BurstDR to be superior to Tonic stimulation

**A single pivotal study can't answer all questions, a portfolio of evidence is needed*

SUNBURST IDE: Inclusion/exclusion criteria[1,2]

Key Inclusion Criteria:

- Successful SCS tonic trial system evaluation
- Chronic, intractable pain of trunk and/or limb
- Average 7-day VAS of 60 mm or higher prior to SCS tonic trial
- Stable pain medications

Key Exclusion Criteria:

- More than mild depression symptoms (BDI>24)
- History of substance abuse

Key Takeaway-

- At the time of the SUNBURST study we did not have a BurstDR enabled trial system
- All patients were shown to be Tonic Responders.
- This creates bias as a patient would compare the outcome of paresthesia-free BurstDR to their experience with tonic
- This design is unique to Sunburst among current level one studies. Still Burst DR was superior.

1. St. Jude Medical™ Proclaim™ Neurostimulation System Clinician's Manual. Plano, TX. 2016.
2. St. Jude Medical™ Prodigy™ Neurostimulation System Programming and Reference Manual. Plano, TX. 2016.

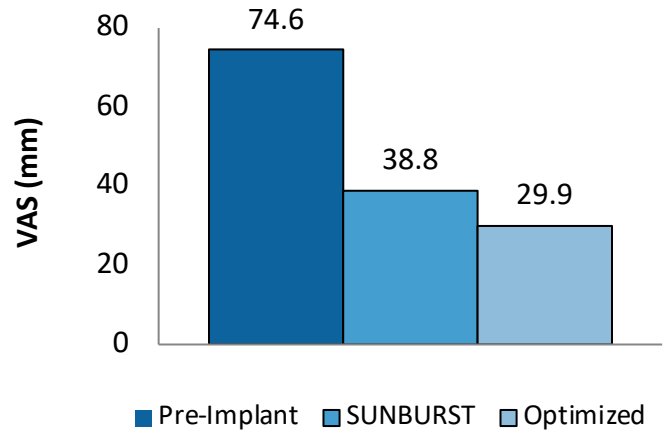
2

The SUNBURST study and early international clinical experience helped us learn how to best use BurstDR therapy

Key Learnings

- SUNBURST was early in the BurstDR clinical experience in the US

Clinical Results



Key Take aways.

- The Optimization Study demonstrates that decreased amplitudes , provides better pain relief and less energy utilization than the early programming methods used in SUNBURST

DRG Stimulation

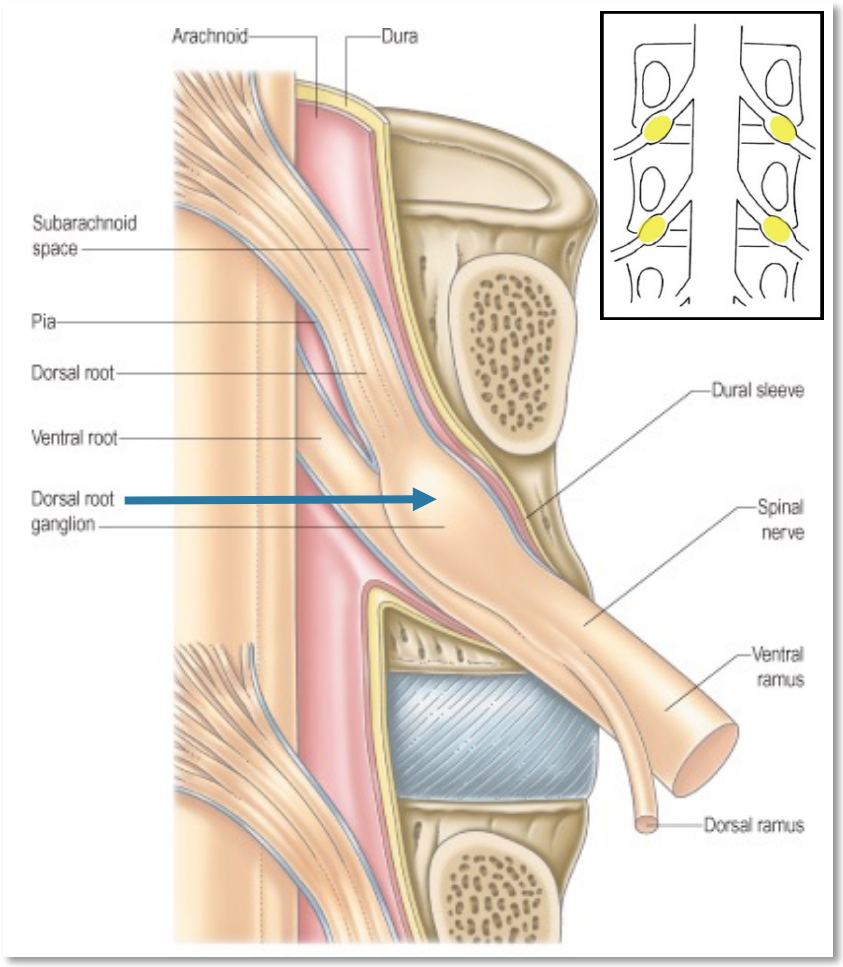
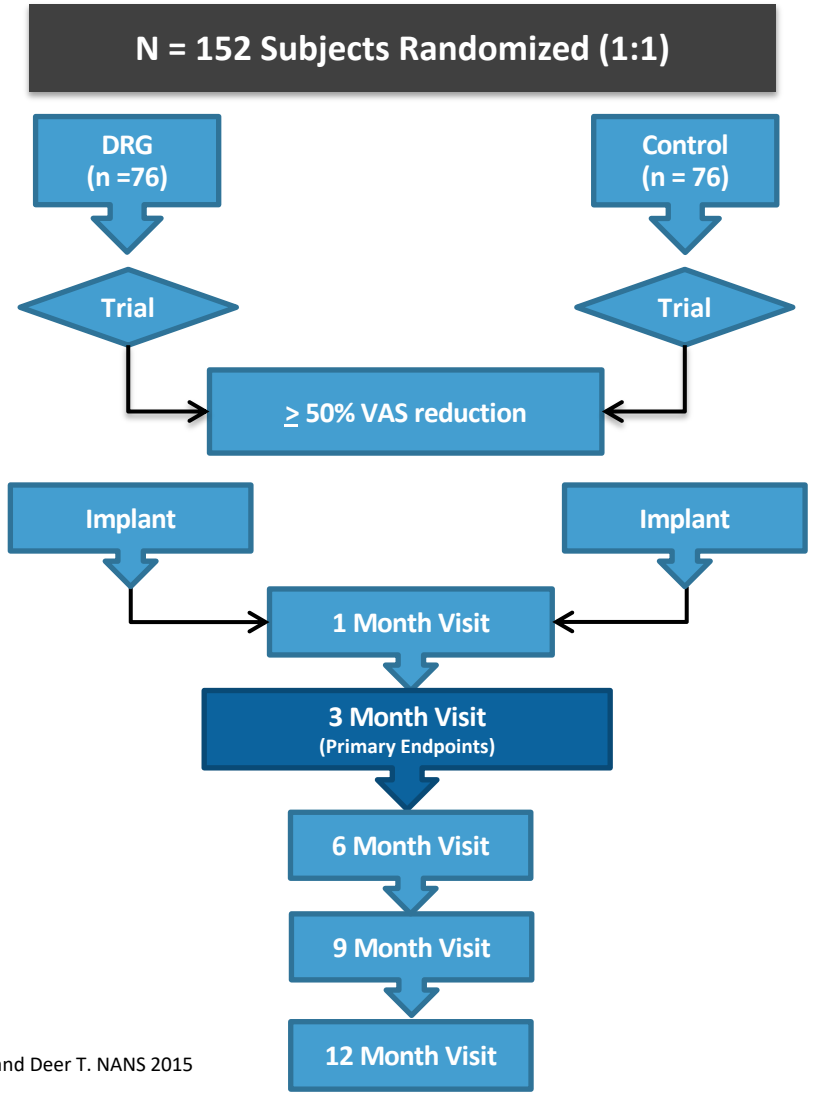


Image from: Gray's Anatomy (2005). Standring, S. (Ed.).

- **Known mechanisms & processes:** DRGs are known target for pain relief
- **Predictable & accessible location** in the epidural space within the neural foramen: easy target for neuromodulation by adapting current SCS needle techniques
- **Limited Cerebrospinal Fluid (CSF)** around the DRG allows the leads to be closer to the anatomical target & requires less energy to stimulate (compared to conventional SCS)
- **Separation of sensory & motor nerve fibers** prevents unintentional stimulation

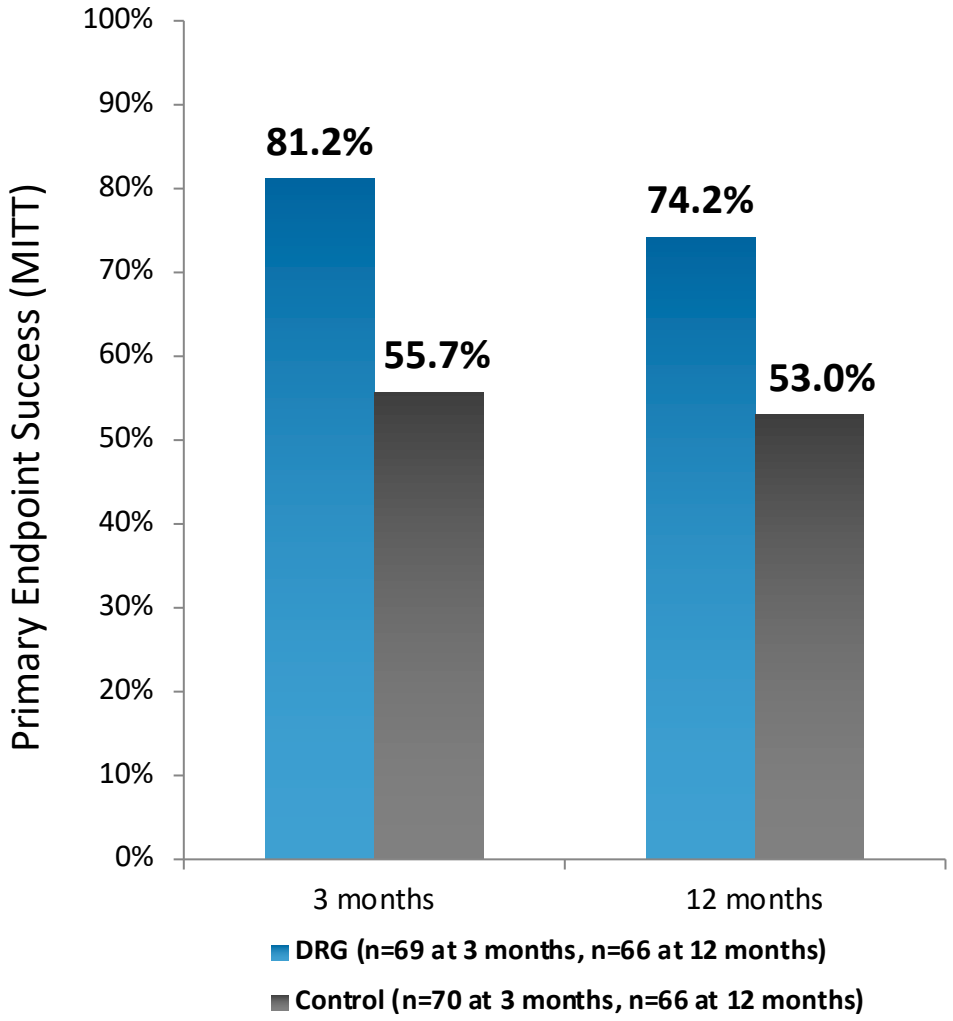
Accurate study: study design



Levy R and Deer T. NANS 2015

- Objective: To assess the safety and efficacy
  of DRG stimulation compared to a commercially available SCS device
- 152 subjects enrolled
- Randomized 1:1 ratio
  - DRG vs.
  - Control (commercially available SCS device)
- 22 Investigational sites
- 3 month Primary Endpoint
- Subject population
  - Chronic, intractable pain of the **lower limbs**
  - **Complex Regional Pain Syndrome (CRPS) or Peripheral Causalgia**

Accurate study results: MITT POPULATION



Superiority Achieved	
P-value for non-inferiority at 3 months	<0.0001
P-value for superiority at 3 months	**0.0004**

Levy R and Deer T. NANS 2015

Accurate Study

Research Paper

PAIN®

OPEN

Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial

Timothy R. Deer[a,*], Robert M. Levy[b], Jeffery Kramer[c], Lawrence Poree[d], Kasra Amirdelfan[e], Eric Grigsby[f], Peter Staats[g], Allen W. Burton[h], Abram H. Burgher[i], Jon Obray[j], James Scowcroft[k], Stan Golovac[l], Leonardo Kapural[m], Richard Paicius[n], Christopher Kim[a], Jason Pope[a], Thomas Yearwood[o], Sam Samuel[p], W. Porter McRoberts[q], Hazmer Cassim[r], Mark Netherton[s], Nathan Miller[t], Michael Schaufele[u], Edward Tavel[v], Timothy Davis[w], Kristina Davis[c], Linda Johnson[c], Nagy Mekhail[p]

Abstract

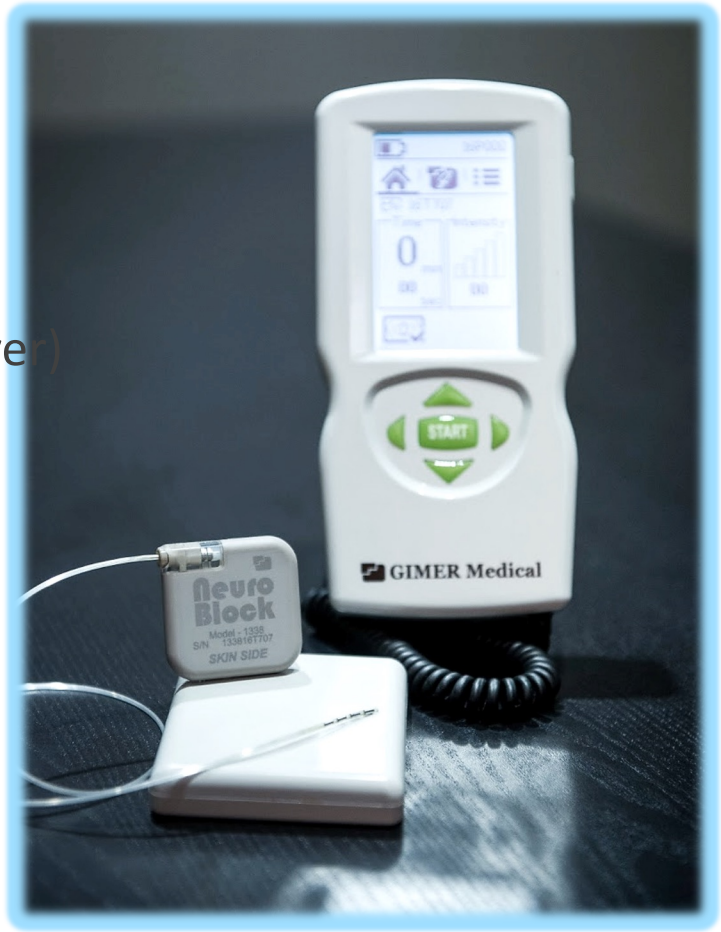
Animal and human studies indicate that electrical stimulation of dorsal root ganglion (DRG) neurons may modulate neuropathic pain signals. ACCURATE, a pivotal, prospective, multicenter, randomized comparative effectiveness trial, was conducted in 152 subjects diagnosed with complex regional pain syndrome or causalgia in the lower extremities. Subjects received neurostimulation of the DRG or dorsal column (spinal cord stimulation, SCS). The primary end point was a composite of safety and efficacy at 3 months, and subjects were assessed through 12 months for long-term outcomes and adverse events. The predefined primary composite end point of treatment success was met for subjects with a permanent implant who reported 50% or greater decrease in visual analog scale score from preimplant baseline and who did not report any stimulation-related neurological deficits. No subjects reported stimulation-related neurological deficits. The percentage of subjects receiving ≥50%

Ultra-high frequency DRG Stimulation

- Battery-less system
  - External

  Programmer: Communication

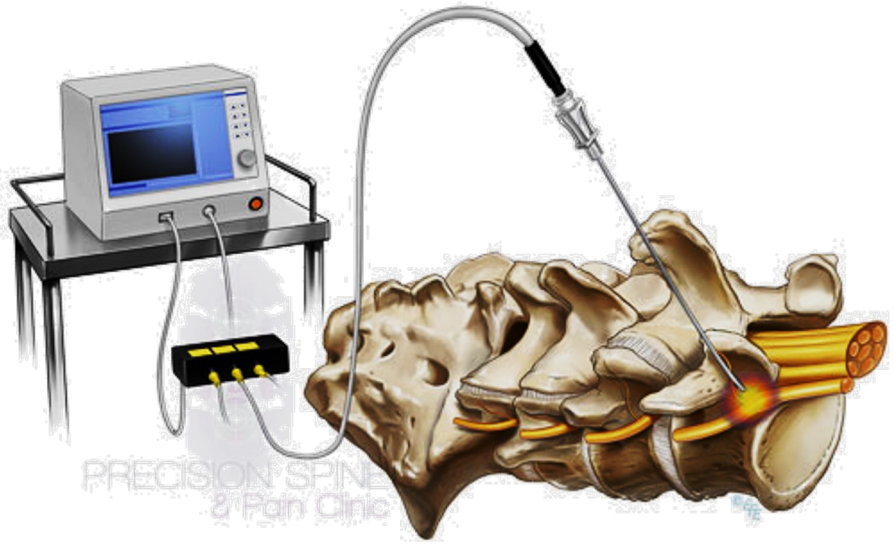
  Cube: Wireless powering
  - Implantable Pulse Generator (Receiver)
  - Implantable Lead
  - 250-500 K DRG stim
- Lead- four electrodes



Ultra-high frequency DRG Stimulation

Pulsed Radiofrequency (PRF) uses radiofrequency current in short (20 ms), high-voltage bursts(±20V); the “silent” phase (480 ms) of PRF allows time for heat elimination, generally keeping the target tissue(Dorsal Root Ganglion, DRG or Nerve root) below 42° C

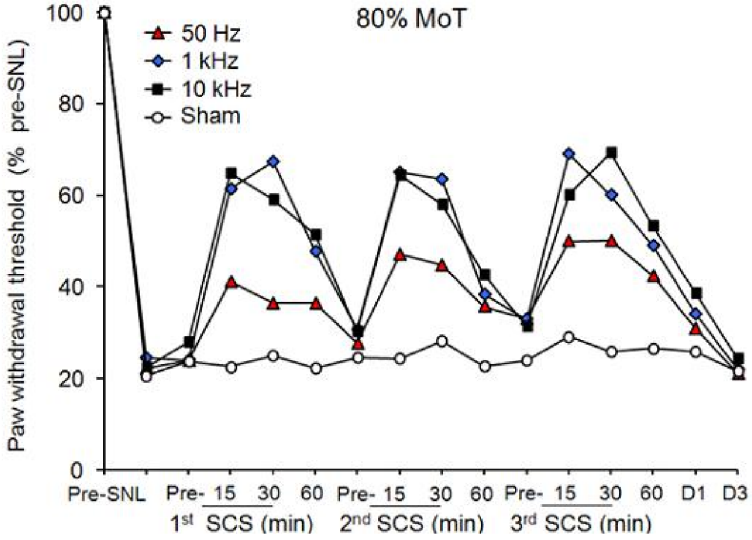
Treatment theory was high electrical field inhibit c-fiber response



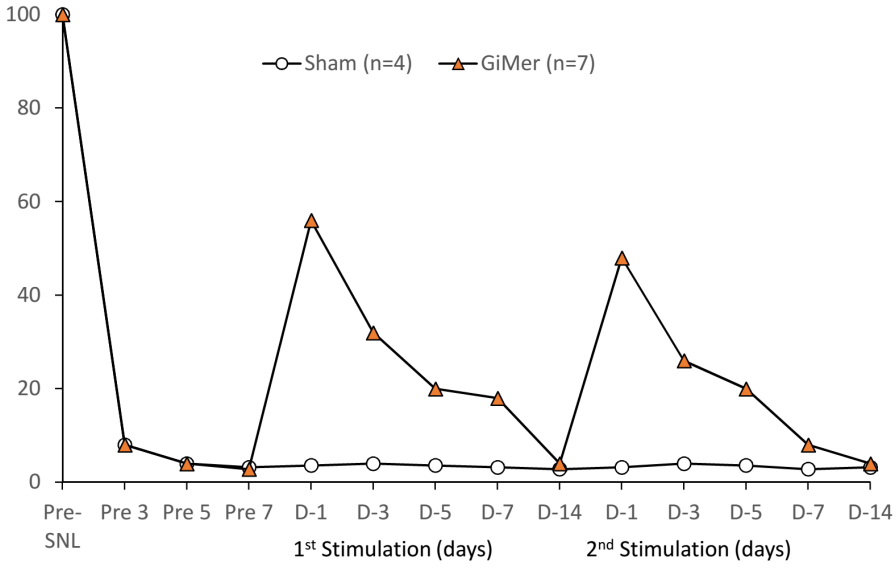
Ultra-high frequency DRG Stimulation

John Hopkins University & Medtronic (US)

Sham = Spinal Nerve Ligation(SNL)



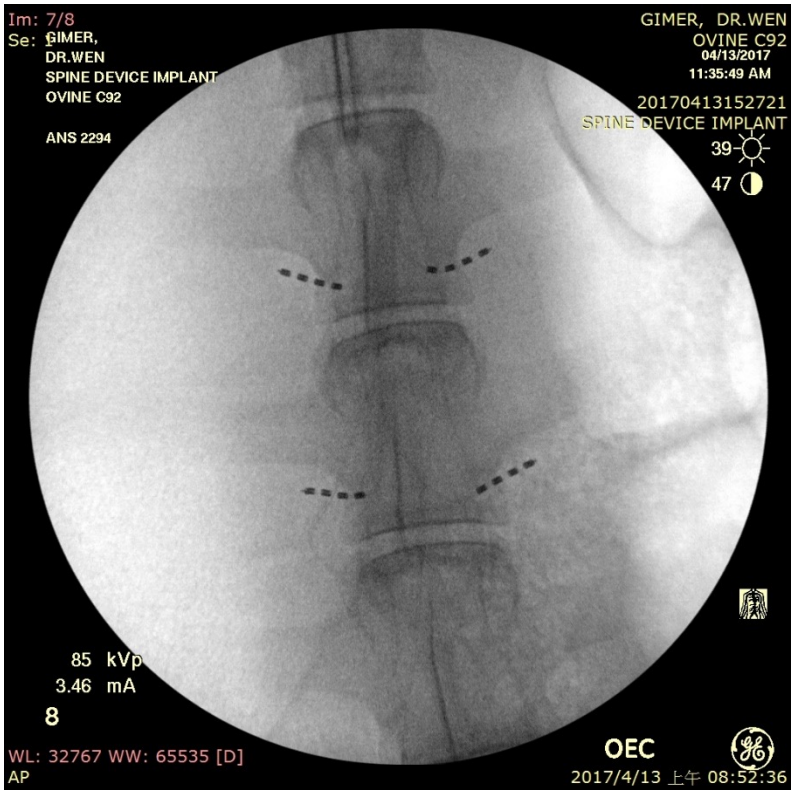
China Medical Center & GiMer Medical (TW)

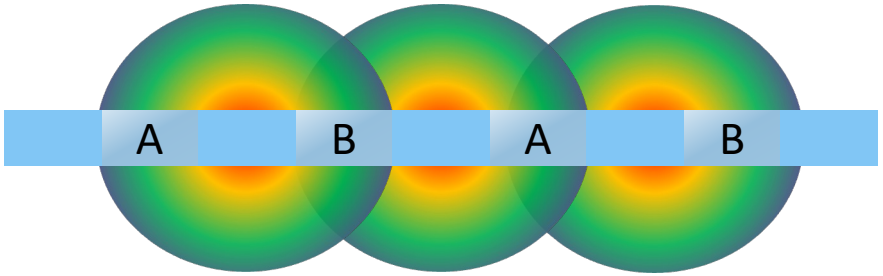


Ref: Anesthesiology. 2013 Aug;119(2):422-32. doi: 10.1097/ALN.0b013e31829bd9e2.

Preclinical studies showed superior pain-relief lasting days per 5 min. treatment session

Ultra-high frequency DRG Stimulation





Conclusions

- Back and Leg Pain Relief
  - 10 kHz- 75-80% of the patients > 50% of pain relief
  - 40-90 Hz ~50% of the patients > 50% of pain relief
  - Burst stim > 50% of the patients > 50% of pain relief
  - Closed-loop stimulation- ongoing trial
  - Complications rate-all time low
  - Cost-still very high, but considering cost of medications, durable and very cost-effective
  - Careful patients selection still most important predictor of SCS success

An evidence-based decision process…

- Makes use of an unbiased, systematic review of the evidence
- Emphasizes the best evidence
- Employs rules for linking evidence to recommendations
- Produces explicit, defensible recommendations

Thank You lkapuralMD@gmail.com