PainWeek®

Electrical Tingles: Neuromodulation for the General Practitioner

Peter Pryzbylkowski, MD

Title & Affiliation

Peter Pryzbylkowski, MD
Interventional Pain Specialist
Relievus
Haddon Heights, NJ

Disclosure

- Consultant: Nevro, Vertos, Camber Spine

Learning Objectives

- Explain the use of electrical signals to block pain
- Review the theory of how neuromodulation works
- Explore the different products that are currently on the market
- Review the application of the devices in clinical practice
- Review data supporting the role of products in decreasing opioid use
- Discuss the process of trial and implantation of devices

History of Neuromodulation

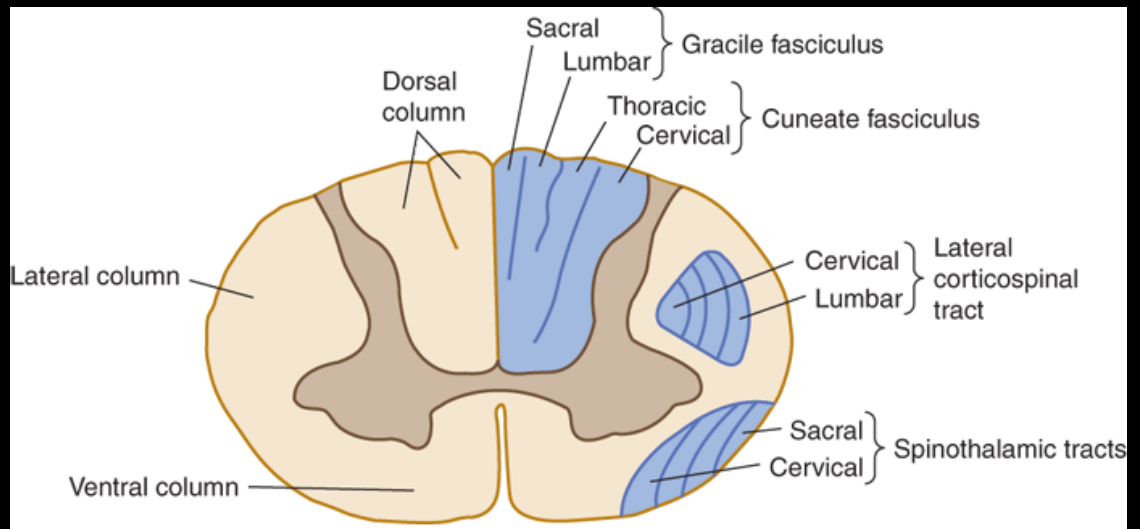
- First used to treat pain in 1967
- Gate theory was published in 1965
- Became more mainstream in 1980s
- 1989 FDA approved use of devices to treat chronic pain from nerve damage in trunk, arms or legs
- Year after year the devices continue to improve upon earlier iterations

Neuromodulation

- So what is it?
- Application of electrical signals to lessen pain complaints
- Drug/medication = electricity
- Types of neuromodulators
  - Spinal cord stimulators, dorsal column stimulators, dorsal root ganglion stimulators, peripheral nerve stimulators

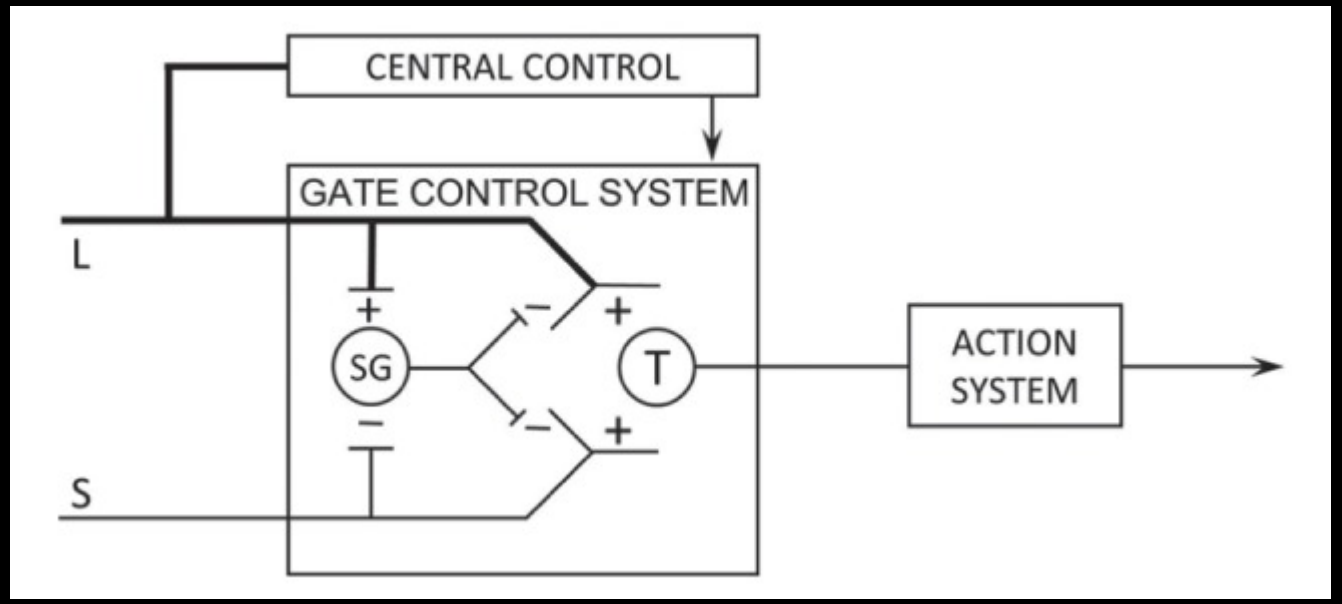
Mechanism of Action

- Continues to be elucidated
- Current thought is that it increases firing of inhibitory neurons in the dorsal spinal horn
  - Decreases transmission/signaling of painful stimulus from reaching brain
  - Gate control theory



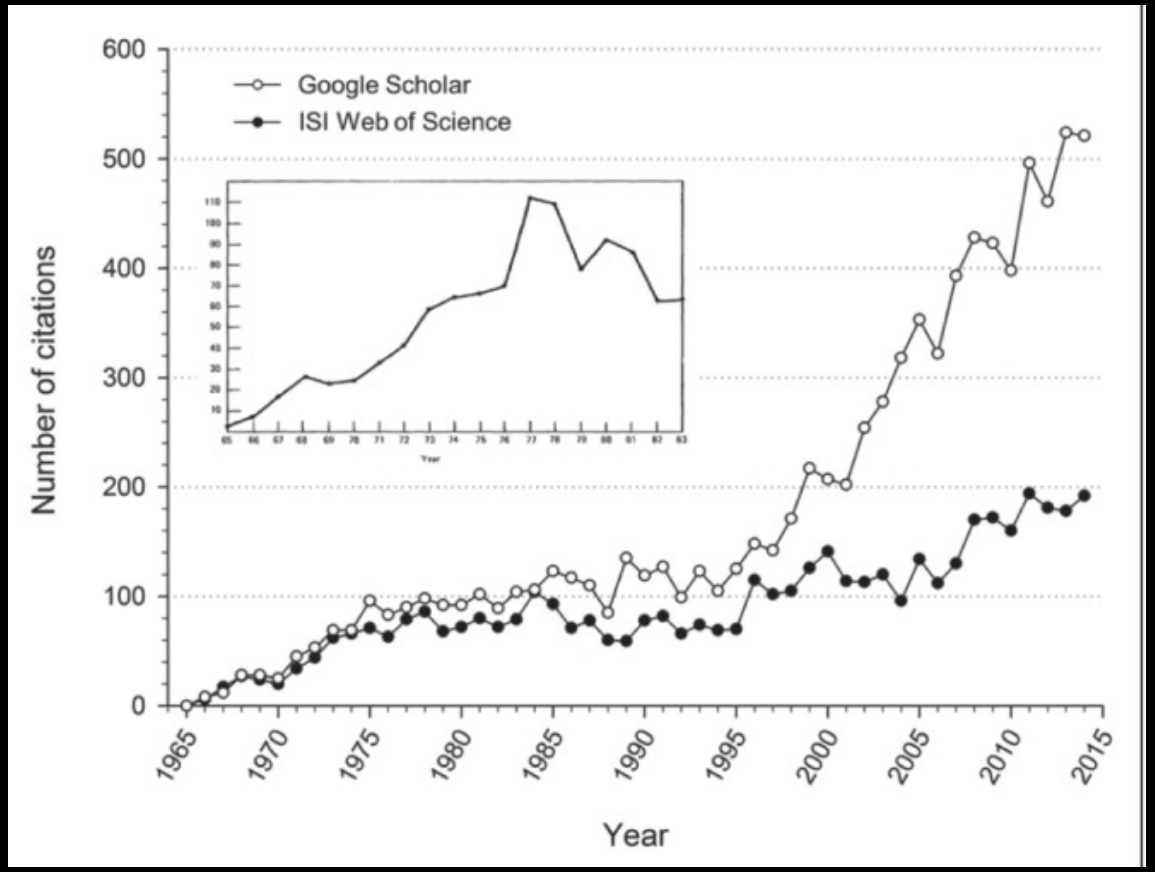
Gate Control Theory

- Published in 1965 in Science by Melzack and Wall
  - "Pain Mechanisms: A New Theory"
- Revolutionized theory of pain control



Katz, Rosenbloom. The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management. Pain Research and Management. 2015 Nov-Dec; 20(6): 285-286
Melzack, Wall. Pain mechanisms: A new theory. Science. 1965:150:971-9

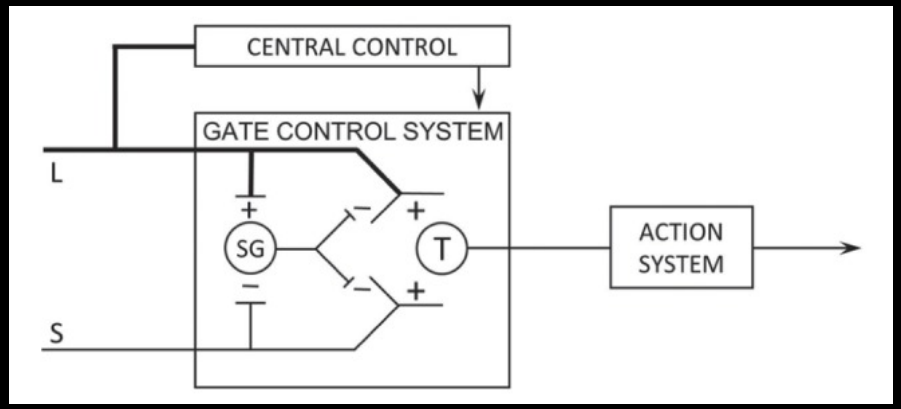
Gate Control Theory



Katz, Rosenbloom. The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management. Pain Research and Management. 2015 Nov-Dec; 20(6): 285-286

Gate Control Theory

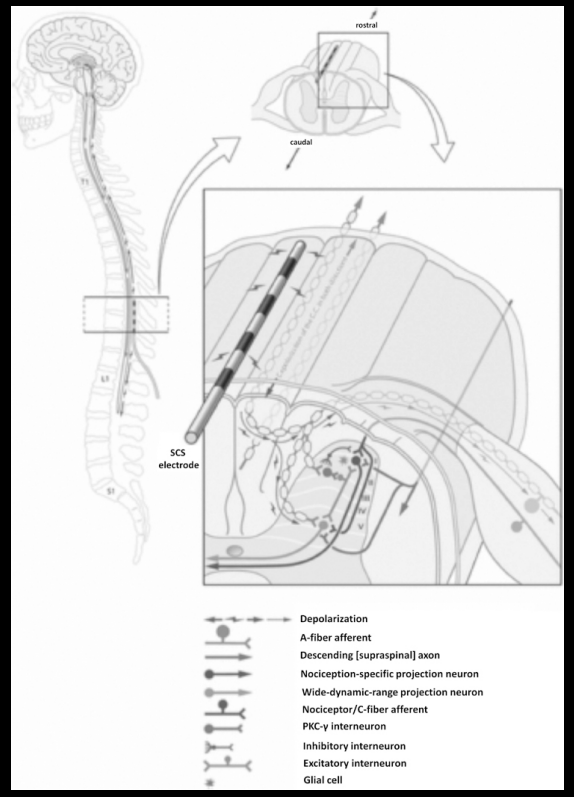
- Gating mechanism in spinal dorsal horn modulates transmission of nerve impulses from afferent fibers to spinal cord transmission cells
  - The gating mechanism is affected by the relative activity in large and small diameter fibers with the former inhibiting transmission (closing the gate) and the latter facilitating transmission (opening the gate)
  - Gating mechanism is also modulated by descending nerve impulses from the brain
  - Burn example



Katz, Rosenbloom. The golden anniversary of Melzack and Wall's gate control theory of pain: Celebrating 50 years of pain research and management. Pain Research and Management. 2015 Nov-Dec; 20(6): 285-286

Neuromodulation and the Gate Control Theory

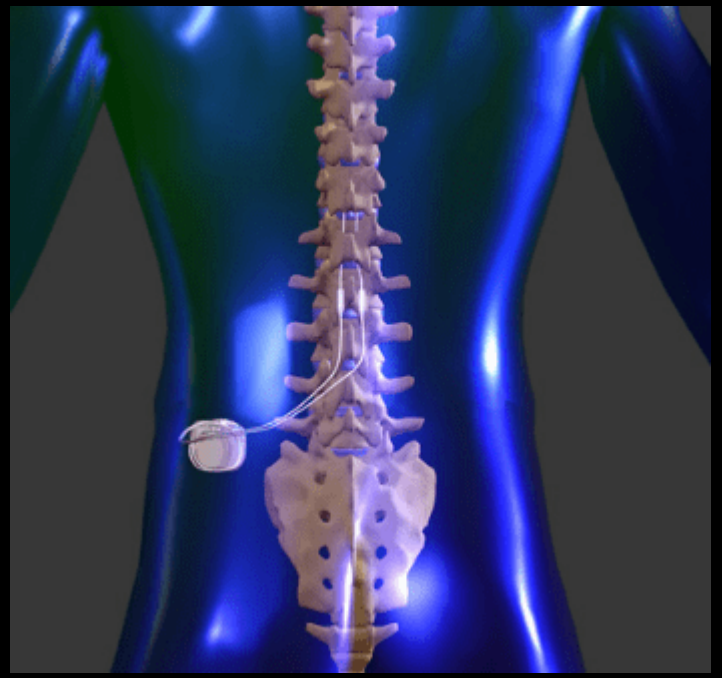
- Conventional SCS devices believed to relieve pain by:
  - Activation of Aβ fibers resulting in variable effects on sensory and pain thresholds
  - Potentiation of inhibition



Sdrulla, Guan, Raja. Spinal cord stimulation: clinal efficacy and potential mechanisms. Pain Practice. 2018;18 (8):1048-1067

Neuromodulation

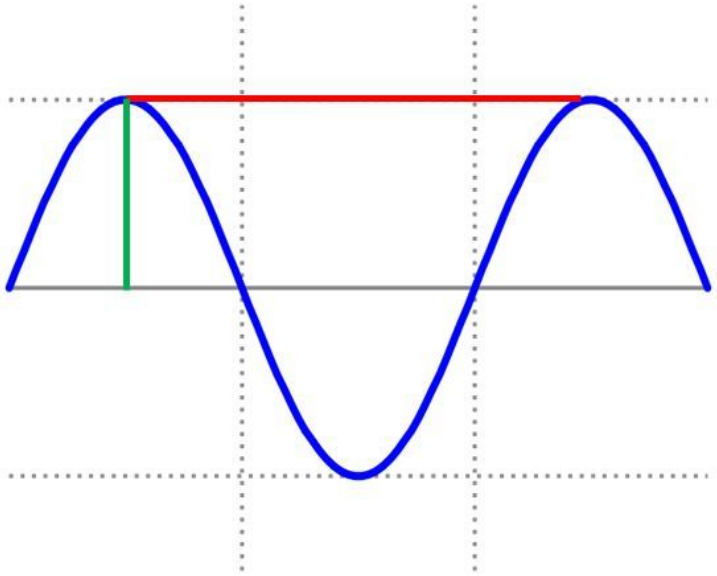
- FDA approved
  - Alleviation of pain in trunk, arms or legs
  - Chronic regional pain syndrome
    - AKA RSD or causalgia
- Most common indication/usage
  - Failed back surgery syndrome
    - Post laminectomy pain syndrome
    - Chronic pain syndrome
- Pacemaker companies
  - Developed a lot of the initial technology



Amplitude, Frequency, Pulse Width

- Parameters we can change with SCS devices
  - Frequency is how often device delivers charge and depolarization
  - Amplitude is relative strength of charge delivered
  - Pulse width is duration of charge delivery
- Tonic or low frequency
  - 20-120Hz range
  - patients perceive individual pulses
- High frequency
  - pulses start to blend so no perception occurs

Amplitude, Frequency



Wavelength (λ)

Distance between identical points on consecutive waves

Amplitude

Distance between origin and crest (or trough)

Frequency (ν)

Number of waves that pass a point per unit time

Speed

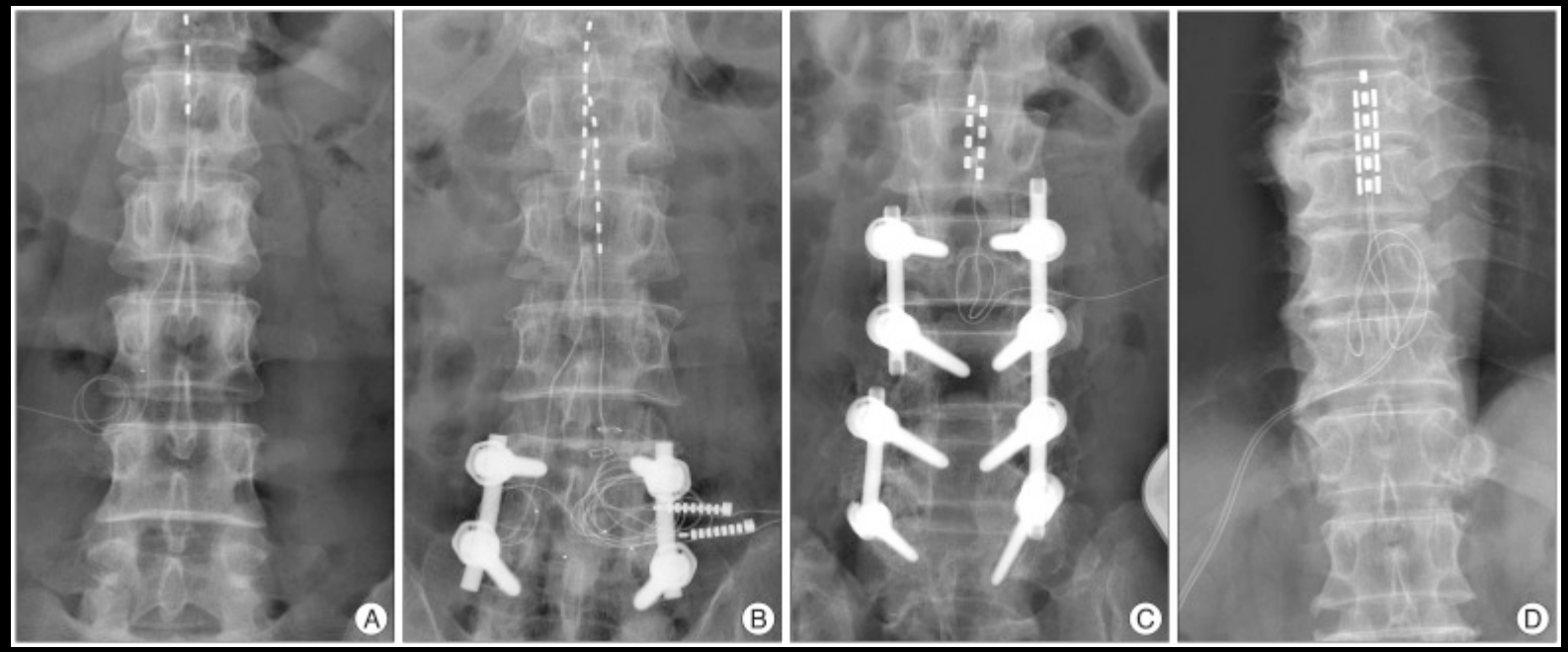
= wavelength x frequency

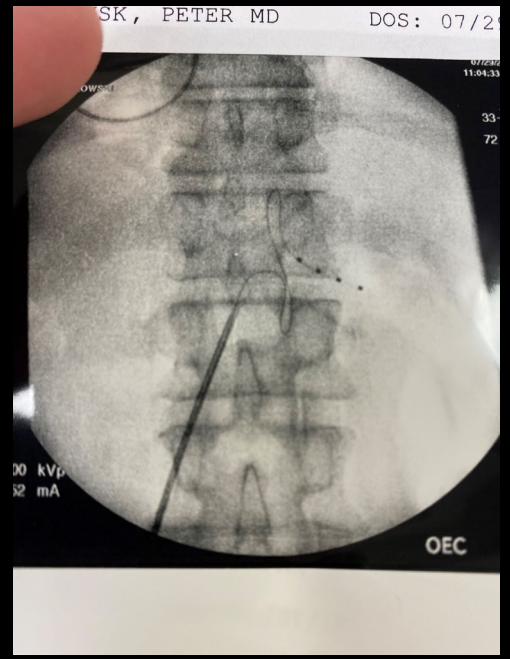
Traditional vs High Frequency vs DRG

- Traditional AKA “low frequency,” “tonic”
  - Tens unit sensation, paresthesia present, can go up to 1200Hz
- High frequency, paresthesia not present, 10,000Hz
- DRG (dorsal root ganglion) stimulators
  - Low frequency, used for focal pain locations

Electrodes

- Typically 8 electrodes per lead with two leads typically used
- Surgeons can place paddle leads with different configurations
- DRG 4 electrodes





Evidence for Neuromodulation

- Kumar study
- RCT conventional medical management (CMM) vs SCS for neuropathic pain
  - Primary outcome was patients reporting 50% or more relief of leg pain
  - Secondary outcomes were improvement in back pain, QOL, functional capacity, use of medication, patient satisfaction
- Compared with CMM group the SCS group saw
  - Improved back and leg pain, better QOL, greater treatment satisfaction

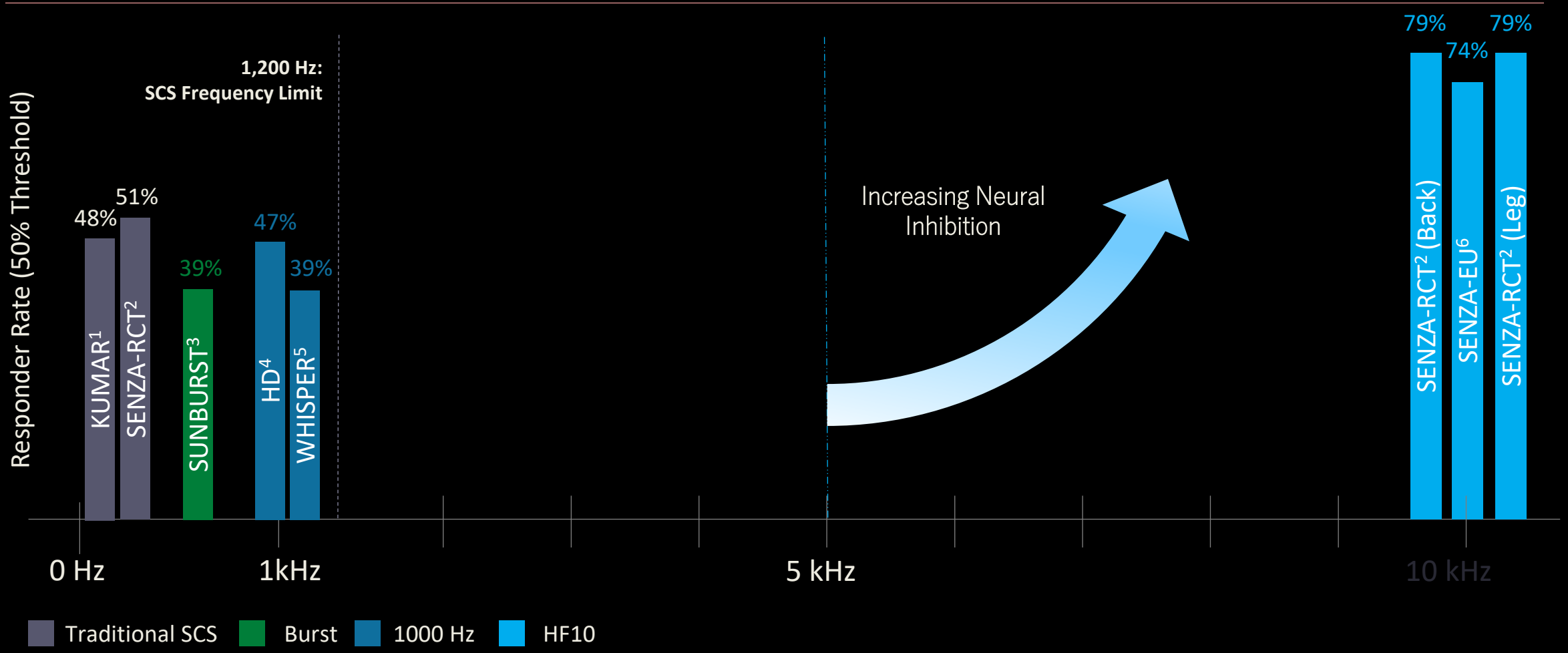
Kumar, Taylor, Jacques et al. Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomized controlled trial in patients with failed back surgery syndrome. Pain. 2007 Nov;132(1-2): 179-88

Evidence for Neuromodulation

- Deer study
- Multicenter, prospective RCT
  - Following successful trial 100 patients were randomized after implant to receive 12 weeks of tonic stim followed by 12 weeks of burst
  - Primary endpoint assessed the noninferiorty of the within-subject difference between tonic and burst for mean daily VAS score
    - Burst stimulation is non inferior to tonic stim
    - Significantly more subjects 70.8% preferred burst over tonic; preference was sustained over 1 year

Deer, Slavin, Amirdelfan et al. Success using neuromodulation with burst (sunburst) study: results from a prospective randomized controlled trial using a novel burst waveform. Neuromodulation. 2018 Jan:21(1):56-66

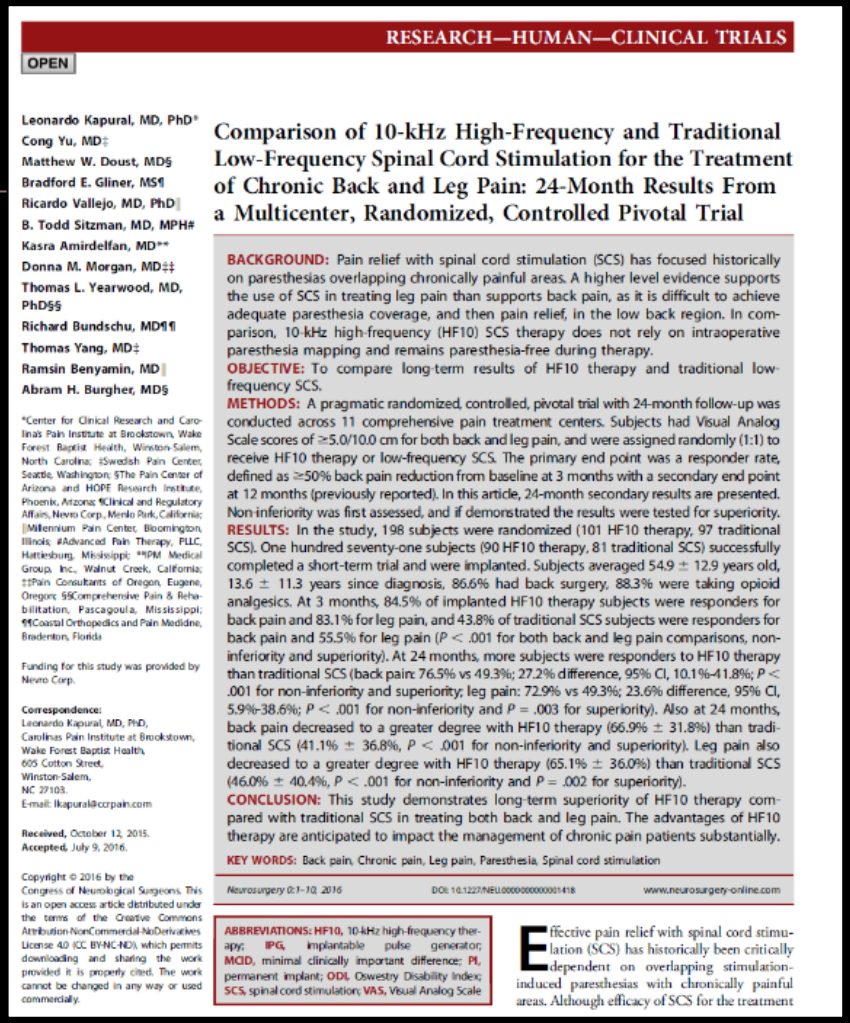
Frequency Matters



PAINWEEK

Evidence for Neuromodulation

- SENZA Study
- Head to head study of low vs high frequency
- 24 month outcomes
  - **Sustained, clinically superior outcomes**
  - **Long term, durable pain relief: 24 MONTHS**
    - **<u>76% responder rate</u>**
    - **<u>2.4 cm VAS</u> for both back and leg pain**
  - **Only device labeled as paresthesia-free**
  - **"Top Pain Paper of the Year"**



RESEARCH—HUMAN—CLINICAL TRIALS

OPEN

Leonardo Kapural, MD, PhD*
Cong Yu, MD‡
Matthew W. Doust, MD§
Bradford E. Gliner, MS¶
Ricardo Vallejo, MD, PhD‖
B. Todd Sitzman, MD, MPH#
Kasra Amirdelfan, MD**
Donna M. Morgan, MD‡‡
Thomas L. Yearwood, MD, PhD§§
Richard Bundschu, MD¶¶
Thomas Yang, MD‡
Ramsin Benyamin, MD‖
Abram H. Burgher, MD§

*Center for Clinical Research and Carolinas Pain Institute at Brookstown, Wake Forest Baptist Health, Winston-Salem, North Carolina; ‡Swedish Pain Center, Seattle, Washington; §The Pain Center of Arizona and HOPE Research Institute, Phoenix, Arizona; ¶Clinical and Regulatory Affairs, Nevro Corp., Menlo Park, California; ‖Millennium Pain Center, Bloomington, Illinois; #Advanced Pain Therapy, PLLC, Hattiesburg, Mississippi; **PM Medical Group, Inc., Walnut Creek, California; ‡‡Pain Consultants of Oregon, Eugene, Oregon; §§Comprehensive Pain & Rehabilitation, Pascagoula, Mississippi; ¶¶Coastal Orthopedics and Pain Medicine, Bradenton, Florida

Funding for this study was provided by Nevro Corp.

Correspondence:
Leonardo Kapural, MD, PhD,
Carolinas Pain Institute at Brookstown,
Wake Forest Baptist Health,
605 Cotton Street,
Winston-Salem,
NC 27103.
E-mail: lkapural@ccrpain.com

Received, October 12, 2015.
Accepted, July 9, 2016.

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 analgesics. 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 ($P < .001$ for both back and leg pain comparisons, non-inferiority and superiority). At 24 months, more subjects were responders to HF10 therapy than traditional SCS (back pain: 76.5% vs 49.3%; 27.2% difference, 95% CI, 10.1%-41.8%; $P < .001$ for non-inferiority and superiority; leg pain: 72.9% vs 49.3%; 23.6% difference, 95% CI, 5.9%-38.6%; $P < .001$ for non-inferiority and $P = .003$ for superiority). Also at 24 months, back pain decreased to a greater degree with HF10 therapy (66.9% ± 31.8%) than traditional SCS (41.1% ± 36.8%, $P < .001$ for non-inferiority and superiority). Leg pain also decreased to a greater degree with HF10 therapy (65.1% ± 36.0%) than traditional SCS (46.0% ± 40.4%, $P < .001$ for non-inferiority and $P = .002$ for superiority).

CONCLUSION: This study demonstrates long-term superiority of HF10 therapy compared with traditional SCS in treating both back and leg pain. The advantages of HF10 therapy are anticipated to impact the management of chronic pain patients substantially.

KEY WORDS: Back pain, Chronic pain, Leg pain, Paresthesia, Spinal cord stimulation

Neurosurgery 0:1–10, 2016 DOI: 10.1227/NEU.0000000000001418 www.neurosurgery-online.com

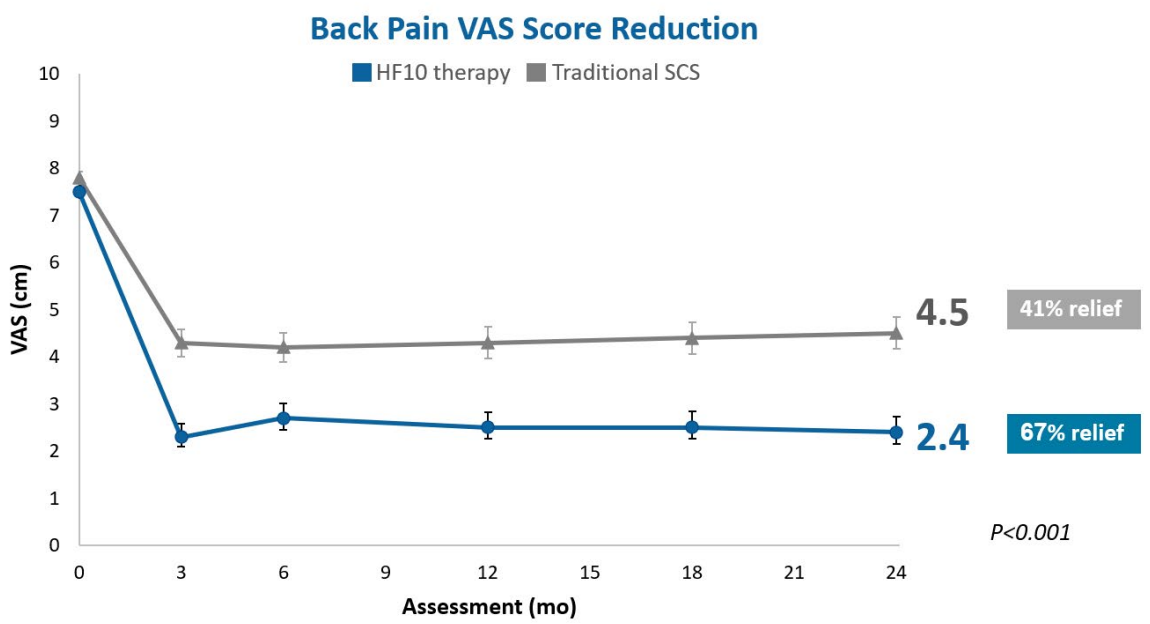
ABBREVIATIONS: HF10, 10-kHz high-frequency therapy; **IPG,** implantable pulse generator; **MCID,** minimal clinically important difference; **PI,** permanent implant; **ODI,** Oswestry Disability Index; **SCS,** spinal cord stimulation; **VAS,** Visual Analog Scale

Effective pain relief with spinal cord stimulation (SCS) has historically been critically dependent on overlapping stimulation-induced paresthesias with chronically painful areas. Although efficacy of SCS for the treatment

Kapural, Leonardo 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 Vol. 123 No 4. October 2015.

Evidence for Neuromodulation….High Frequency

Durable Back Pain Relief to 24 Months

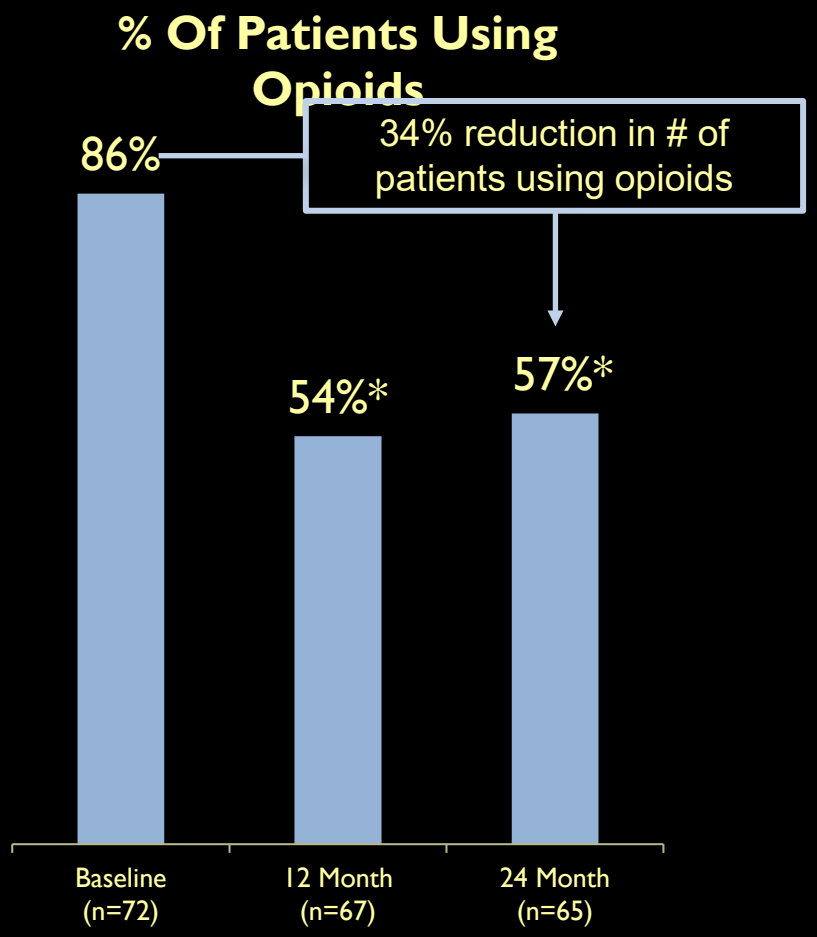


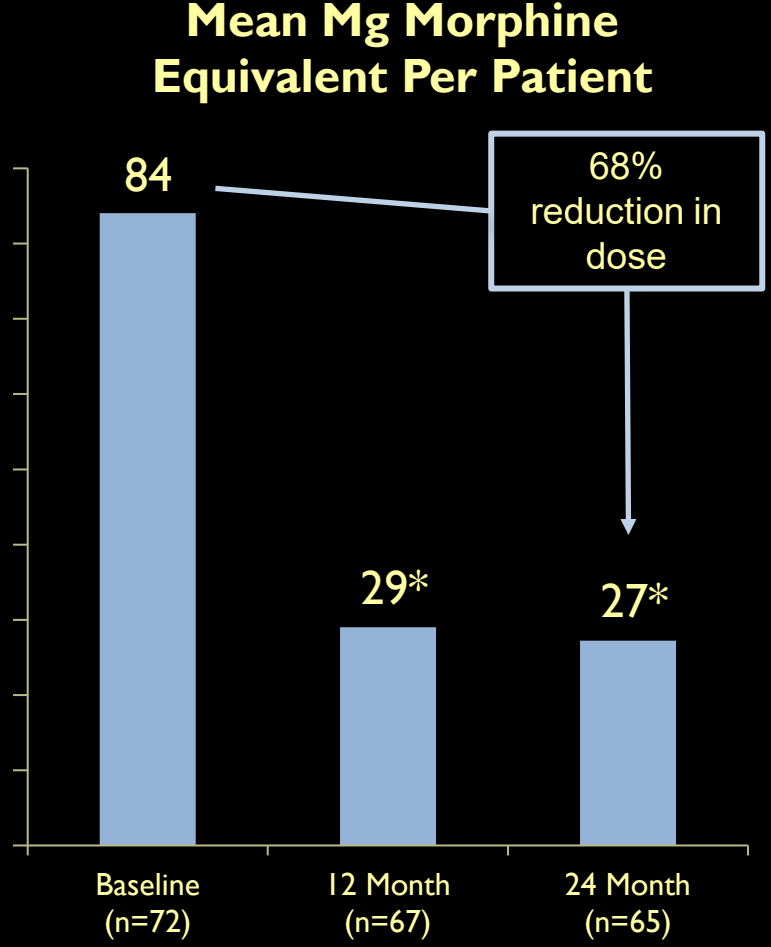
HF10 Therapy: Superior Back Pain All Time Points Measured

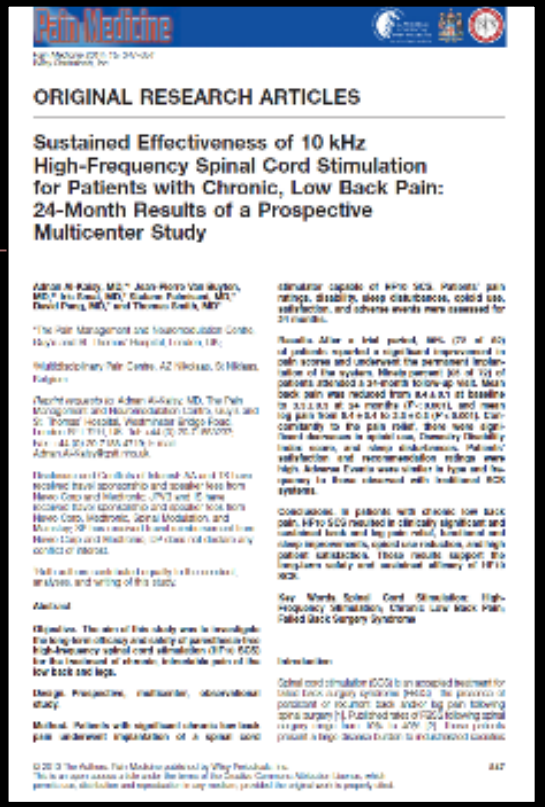
PainWeek®

Kapural, Leonardo 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 Vol. 123 No 4. October 2015.

Decreased Opioid Use in SENZA-EU Trial with HF10 therapy After 2 Years






Pain Medicine

ORIGINAL RESEARCH ARTICLES

Sustained Effectiveness of 10 kHz High-Frequency Spinal Cord Stimulation for Patients with Chronic, Low Back Pain: 24-Month Results of a Prospective Multicenter Study

* p-value < 0.001 compared to Baseline

PainWeek

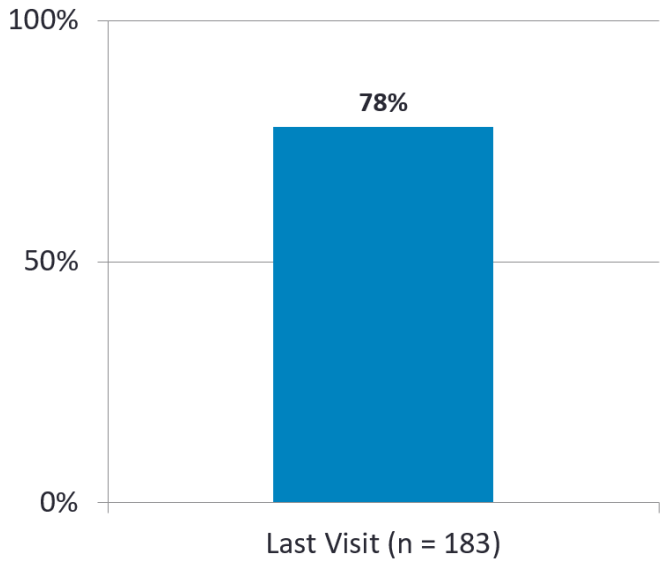
Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med. 2014 Mar; 15(3):347-54

Opioid Reduction in Real World Practice

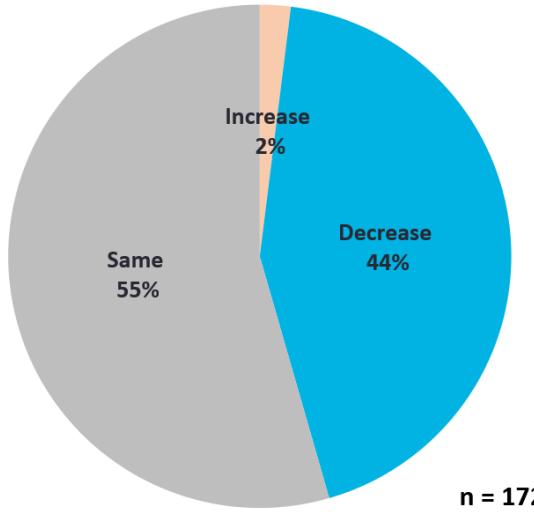
Results in My Permanent Implant Patients

PROACTIVE PATIENT SUPPORT

Responder Rate (>= 50% pain relief)



Last Visit Medication Change of IPG Patients



n = 172

Average number of months between IPG procedure and last visit is 17.3 (min=1.0, max=48.8)

Rev 2020195A

Evidence for Neuromodulation

- New indication in 2021
- PDN
- Published in JAMA Neurology April 2021
- Compared traditional medical management vs high frequency spinal cord stimulation

Peterson et al. Effect of High-frequency spinal cord stimulation in patients with painful diabetic neuropathy. JAMA Neurology 2021. 78 (6) 687-698

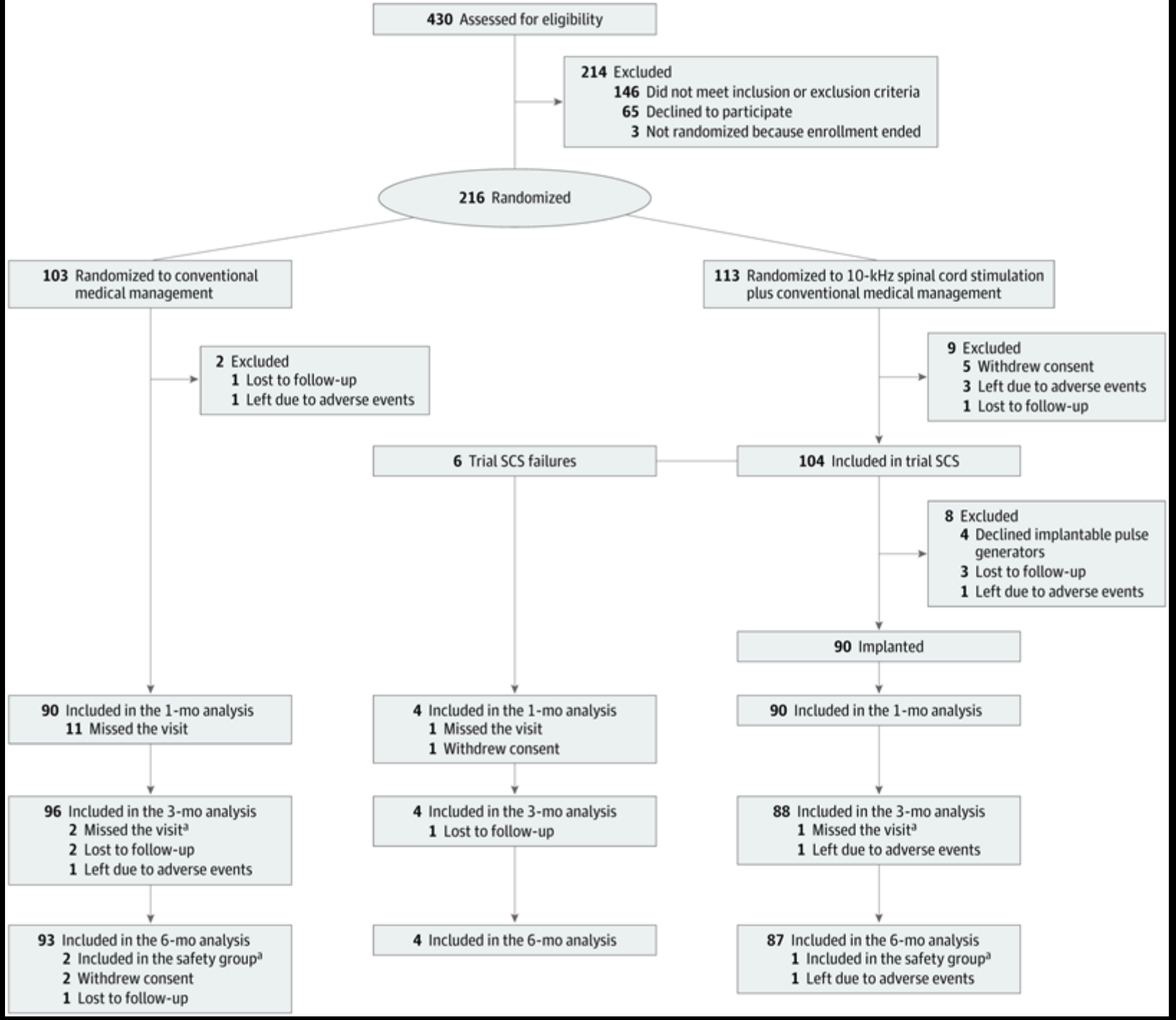
Table. Baseline Characteristics for All Randomized Patients

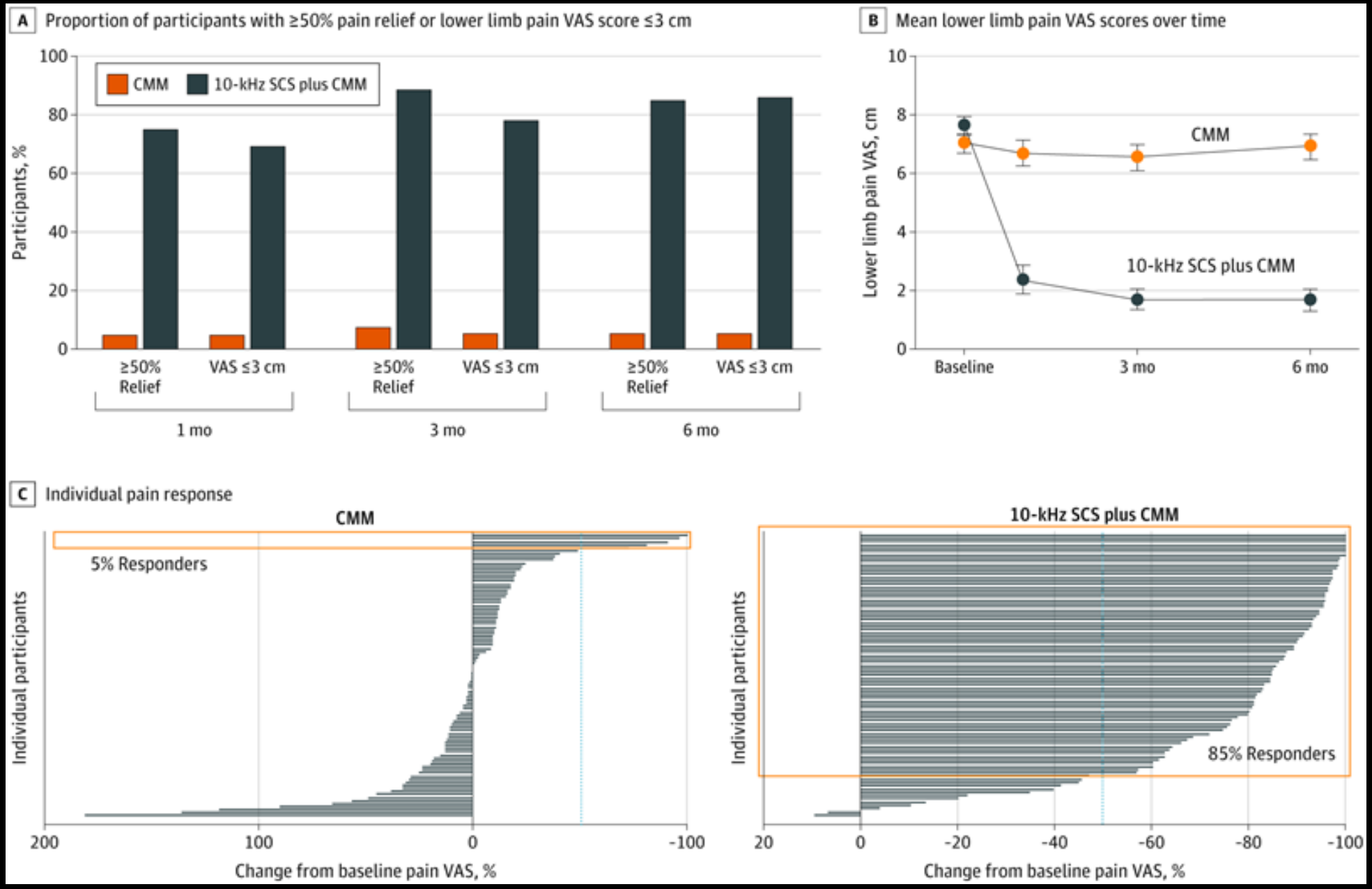
Characteristic	No. (%)		Standardized difference[a]
	CMM (n = 103)	10-kHz SCS plus CMM (n = 113)	
Age, y			
Mean (SD)	60.8 (9.9)	60.7 (11.4)	0.01
Median (IQR)	62.0 (55.0-67.5)	61.0 (55.0-70.0)	
Sex			
Male	66 (64.1)	70 (61.9)	0.04
Female	37 (35.9)	43 (38.1)	
Race			
White	85 (82.5)	87 (77.0)	0.14
Black or African American	13 (12.6)	18 (15.9)	
Native Hawaiian or other Pacific Islander	1 (1.0)	3 (2.7)	
American Indian or Alaska Native	0	2 (1.8)	
Asian	1 (1.0)	1 (0.9)	
Other	3 (2.9)	2 (1.8)	
Diabetes			
Type 1	3 (2.9)	8 (7.1)	0.19
Type 2	100 (97.1)	105 (92.9)	
Duration, y			
Diabetes			
Mean (SD)	12.2 (8.5)	12.9 (8.5)	0.09
Median (IQR)	10.4 (6.3-15.2)	12.0 (6.4-18.6)	
Peripheral neuropathy			
Mean (SD)	7.1 (5.1)	7.4 (5.7)	0.06
Median (IQR)	5.4 (2.9-10.0)	5.7 (3.1-10.1)	
Lower limb pain VAS			
Mean (SD), cm	7.1 (1.6)	7.5 (1.6)	0.22
Median (IQR), cm	7.2 (6.2-8.2)	7.5 (6.6-8.6)	
<7.5 cm	57 (55.3)	54 (47.8)	0.15
≥7.5 cm	46 (44.7)	59 (52.2)	
HbA_{1c}			
Mean (SD), %	7.4 (1.2)	7.3 (1.1)	0.11
Median (IQR), %	7.3 (6.6-8.2)	7.3 (6.3-8.2)	
<7.0%	40 (38.8)	46 (40.7)	0.04
≥7.0%	63 (61.2)	67 (59.3)	
BMI[b]			
Mean (SD)	33.9 (5.2)	33.6 (5.4)	0.06
Median (IQR)	34.3 (30.9-37.1)	33.6 (29.8-36.3)	
Severity of neuropathic pain			
DN4			
Mean (SD)	6.5 (1.9)	6.6 (1.7)	0.12
Median (IQR)	6 (5-8)	7 (5-8)	
<3	3 (2.9)	1 (0.9)	0.15
≥3	99 (97.1)	112 (99.1)	
mNSS			
Mean (SD)	6.9 (1.1)	6.8 (1.3)	0.05
Median (IQR)	7 (6-8)	7 (6-8)	
Mild (3-4)	2 (2.0)	2 (1.8)	NA
Moderate (5-6)	33 (32.4)	46 (40.7)	
Severe (7-9)	67 (65.7)	65 (57.5)	
Pain medications			
Anticonvulsants			
Gabapentin	50 (48.5)	63 (55.8)	0.14
Pregabalin	29 (28.2)	25 (22.1)	0.14
Antidepressants			
SNRIs	29 (28.2)	25 (22.1)	0.14
TCAs	14 (13.6)	10 (8.8)	0.15
Opioids	44 (42.7)	50 (44.2)	0.03
Topicals	9 (8.7)	11 (9.7)	0.03
Diabetes medications			
Insulin	47 (45.6)	51 (45.1)	0.01
Oral and noninsulin injectable medications	84 (81.6)	88 (77.9)	0.09

Abbreviations: BMI, body mass index; CMM, conventional medical management; DN4, Douleur Neuropathique; HbA_{1c}, hemoglobin A_{1c}; IQR, interquartile range; mNSS, modified Neuropathy Symptom Score; NA, not applicable; SCS, spinal cord stimulation; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; VAS, visual analogue scale.

[a] Possible imbalances in baseline characteristics were evaluated with a standardized difference effect size index (Cohen *d*). Index scores less than 0.20 suggest the groups are well matched, whereas scores of 0.20 or greater indicate small differences, of 0.50 or greater indicate medium differences, and of 0.80 or greater indicate large differences between the groups.

[b] Calculated as weight in kilograms divided by height in meters squared.

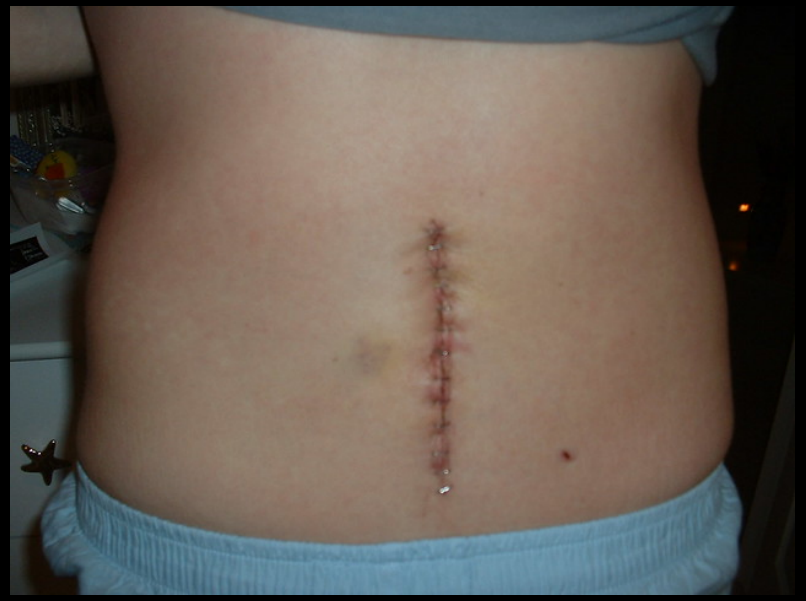

430 Assessed for eligibility
214 Excluded
146 Did not meet inclusion or exclusion criteria
65 Declined to participate
3 Not randomized because enrollment ended
216 Randomized
103 Randomized to conventional medical management
113 Randomized to 10-kHz spinal cord stimulation plus conventional medical management
2 Excluded
1 Lost to follow-up
1 Left due to adverse events
9 Excluded
5 Withdrew consent
3 Left due to adverse events
1 Lost to follow-up
6 Trial SCS failures
104 Included in trial SCS
8 Excluded
4 Declined implantable pulse generators
3 Lost to follow-up
1 Left due to adverse events
90 Implanted
90 Included in the 1-mo analysis
11 Missed the visit
4 Included in the 1-mo analysis
1 Missed the visit
1 Withdrew consent
90 Included in the 1-mo analysis
96 Included in the 3-mo analysis
2 Missed the visit[a]
2 Lost to follow-up
1 Left due to adverse events
4 Included in the 3-mo analysis
1 Lost to follow-up
88 Included in the 3-mo analysis
1 Missed the visit[a]
1 Left due to adverse events
93 Included in the 6-mo analysis
2 Included in the safety group[a]
2 Withdrew consent
1 Lost to follow-up
4 Included in the 6-mo analysis
87 Included in the 6-mo analysis
1 Included in the safety group[a]
1 Left due to adverse events


A
Proportion of participants with ≥50% pain relief or lower limb pain VAS score ≤3 cm
Participants, %
CMM
10-kHz SCS plus CMM
≥50% Relief
VAS ≤3 cm
1 mo
3 mo
6 mo
B
Mean lower limb pain VAS scores over time
Lower limb pain VAS, cm
CMM
10-kHz SCS plus CMM
Baseline
3 mo
6 mo
C
Individual pain response
CMM
5% Responders
Individual participants
Change from baseline pain VAS, %
10-kHz SCS plus CMM
85% Responders
Individual participants
Change from baseline pain VAS, %

PainWeek

Procedure Overview (Trial)

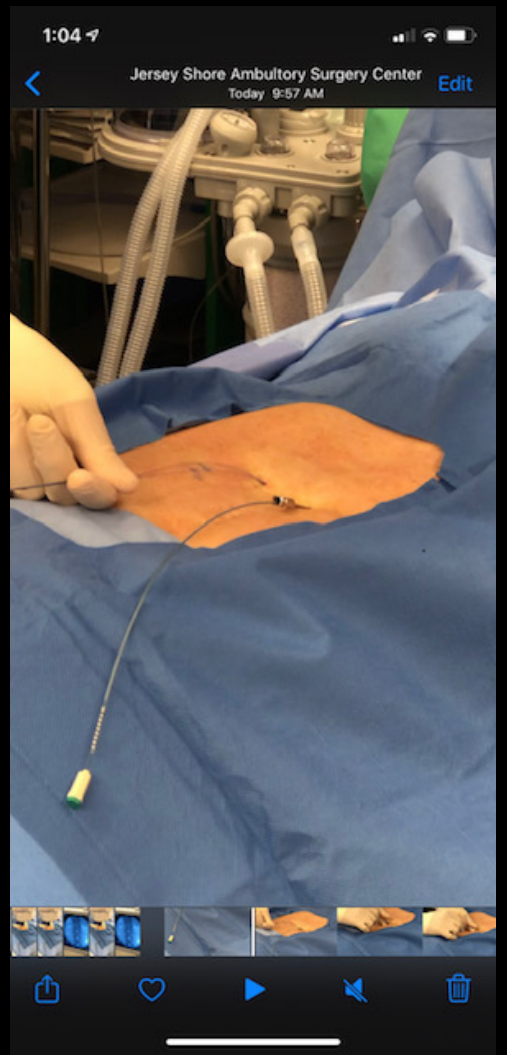
- Only pain procedure that requires psychiatric/psychological clearance by insurance company
  - Patient is malingering or faking symptoms
  - Patient will call if there is infection or issues with device
  - Most of these patients have undergone previous spine surgery
  - Large scar present on back



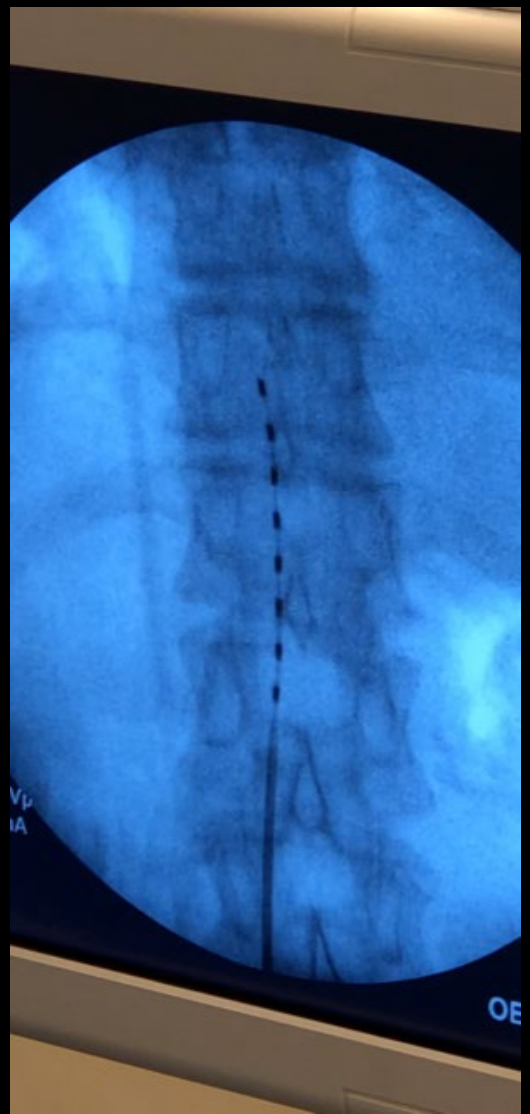
Procedure Overview (Trial)

- Placement of percutaneous electrodes into epidural space
- Just like performing an epidural. Done under xray
  - Rather than injecting medication electrodes are placed
  - Trial leads stay in place for 5-7days and are connected to a battery
    - If >50% pain reduction
    - Implant can be performed

Procedure Overview (Trial)

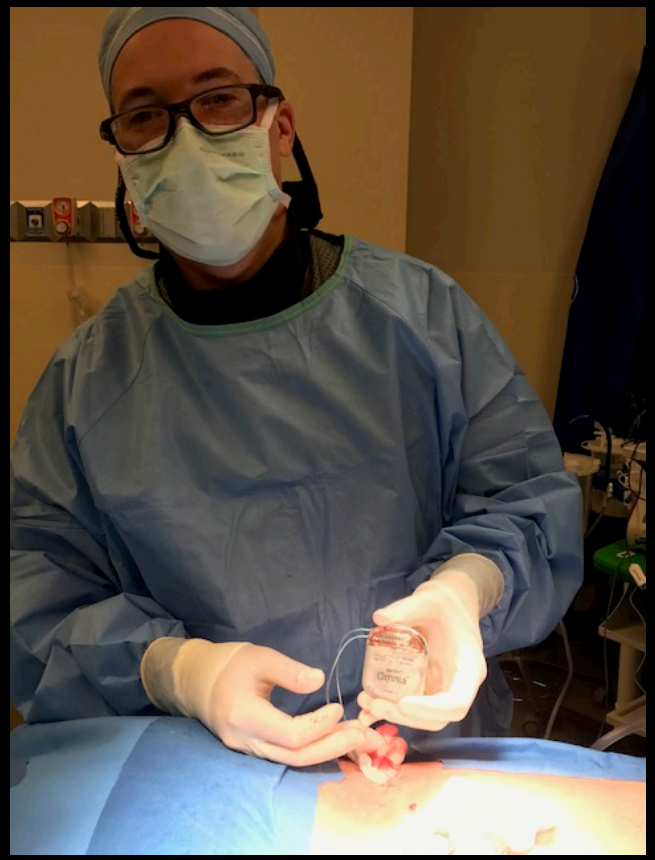


Procedure Overview (Trial)



Procedure Overview (Permanent Implant)

- Leads are again placed into epidural space and then tunneled under skin to a battery
  - Battery, which powers the device, is placed in the flank
- Battery
  - Rechargeable vs Non-Rechargeable



Complications/Risks of Procedure

- Infection
  - Epidural abscess
    - Paralysis
- Bleeding
  - Epidural hematoma
    - Paralysis
- Lead migration/lead fracture
  - Loss of efficacy

Contraindications

- Severe uncontrolled psychological disorders
  - Schizophrenia, depression, bipolar disorder
- Bleeding disorder
- Use of blood thinners or NSAIDs
- Active infection
- Relative contraindication
  - Need for continued MRI studies
    - Most newer devices have MRI approval

Questions