



CAROLINAS PAIN INSTITUTE, PA

*High-frequency spinal cord stimulation for chronic pain:
Clinical data and controversies*

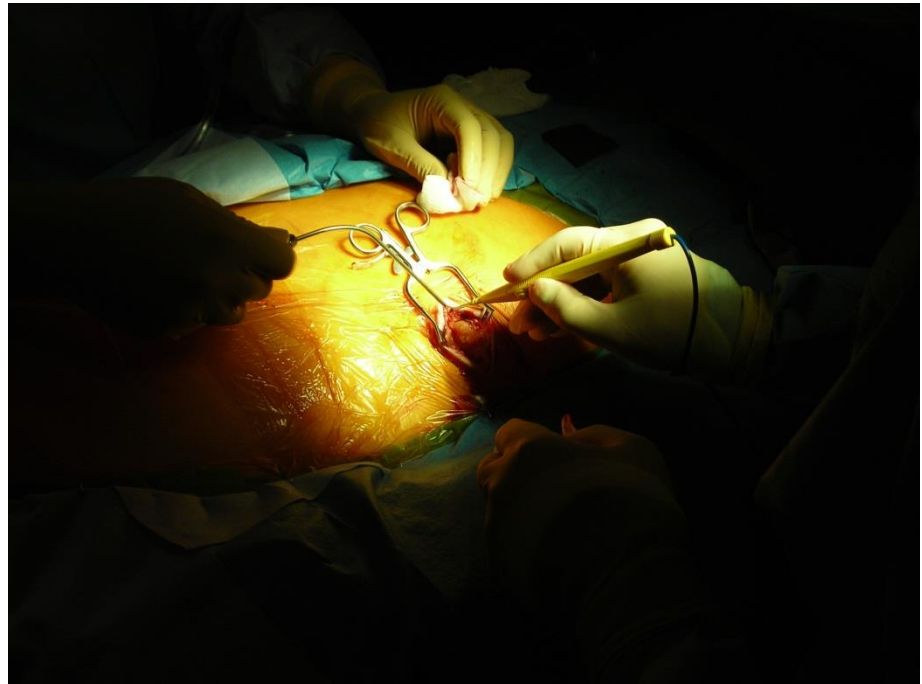
Leonardo Kapural, MD, PhD

Carolinus Pain Institute at Brookstown, Wake Forest Baptist Health

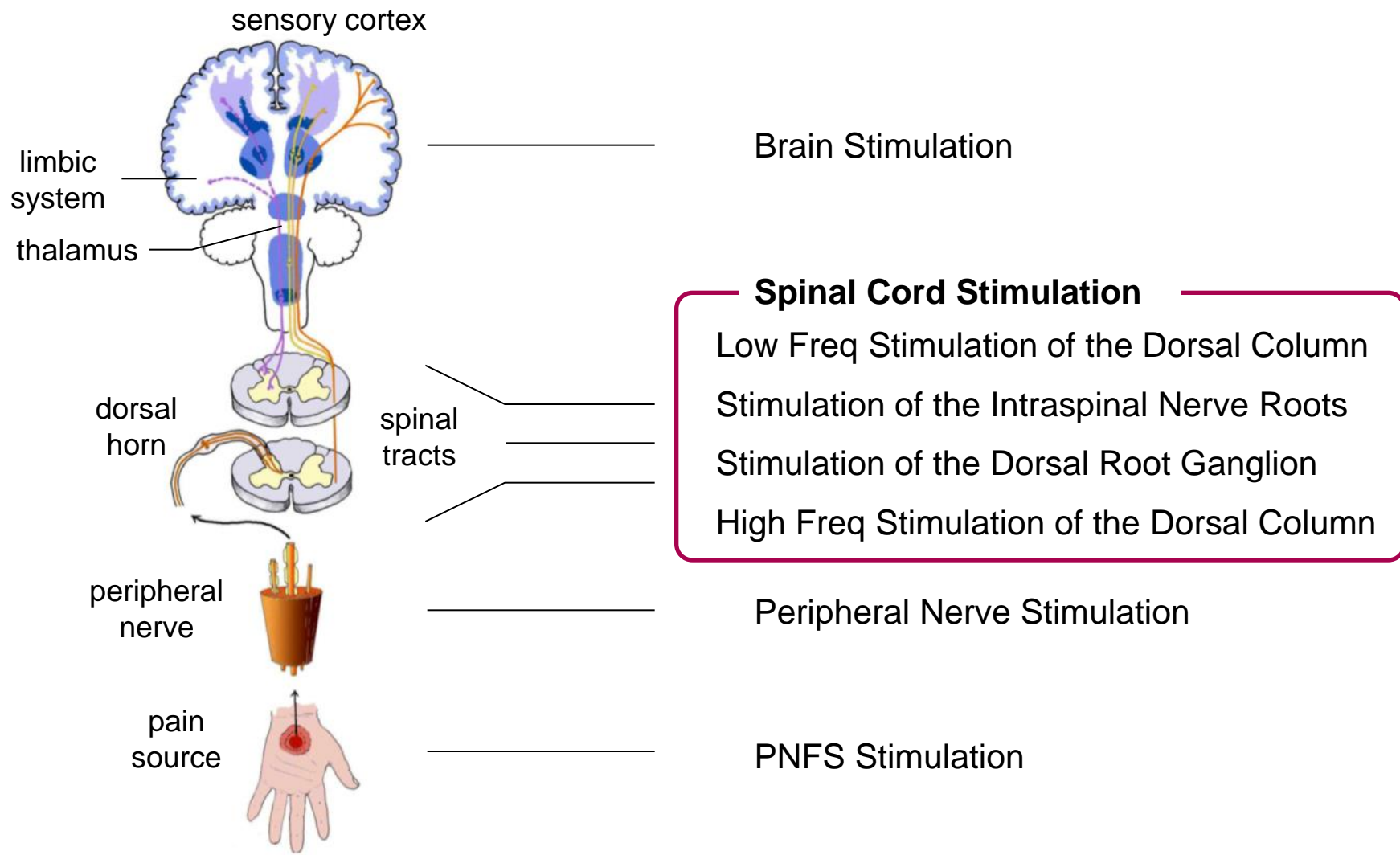
Professor, Department of Anesthesiology, Wake Forest University School of Medicine

Disclosure

- Consultant St Jude Medical and Medtronic
- Research Grants: Nevro, NDI, Bioness, Boston Scientific



Innovative Targets For Neuromodulation



What is new in SCS - PNS

- High frequency stimulation
 - DRG Stimulation
 - Adoptive Spinal Cord Stimulation to Posture Change
 - Multi-lead delivery system
- High frequency stimulation
 - Elastic bipolar lead
 - External generator near-nerve lead system



High-frequency spinal cord stimulation

- Mechanisms?
- Animal studies, what have we learned (or not)
- Human studies, clinical practice (Europe, Australia)



High-frequency peripheral nerve stimulation

- HF Block of peripheral nerve occurs in 3 phases
 - Neurons fire before being blocked
 - If amplitude not high enough, asynchronous firing
 - Amplitude high enough motor blockade
 - Only indication-phantom and stump pain
-
- Bhadra et al, 2005



High-frequency (HF-10) SCS animal model

- Acute rat and goat neurostimulation model
- Microelectrode recordings of WDR neurons in dorsal horn
- Measured firing pattern in response to noxious stimulus
- Assessed ability of high frequency stimulation to alter firing pattern

Definitions:

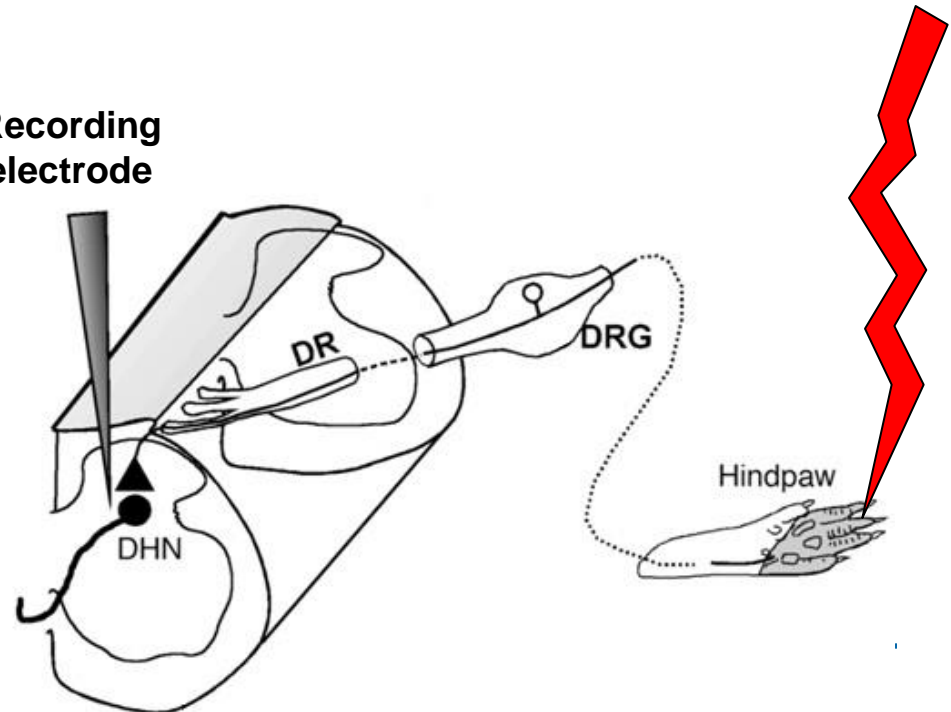
DRG = Dorsal Root Ganglion

DR = Dorsal Root

DHN = Dorsal Horn Neuron

(= 2nd order sensory neuron; WDR)

Recording
electrode



Microelectrode recordings of WDR neurons in dorsal horn

- High-frequency stimulation decreased WDR firing rate
- Attenuated response to both mechanical and electrical stimuli
- Effective in both rat and goat models
- HF-SCS attenuated nociceptive pain signal transmission



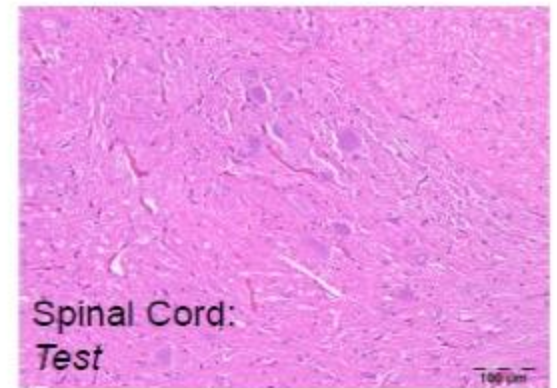
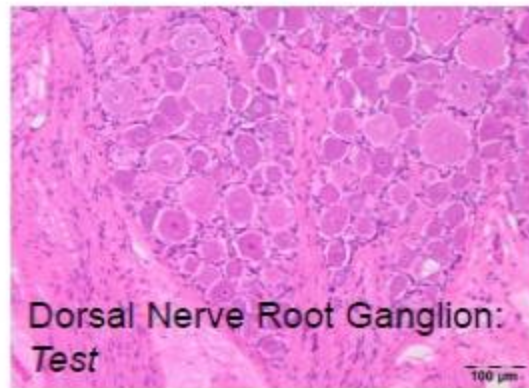
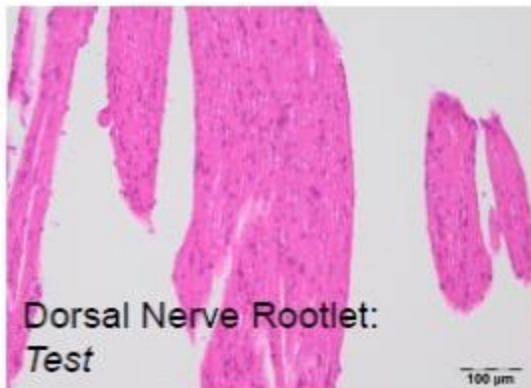
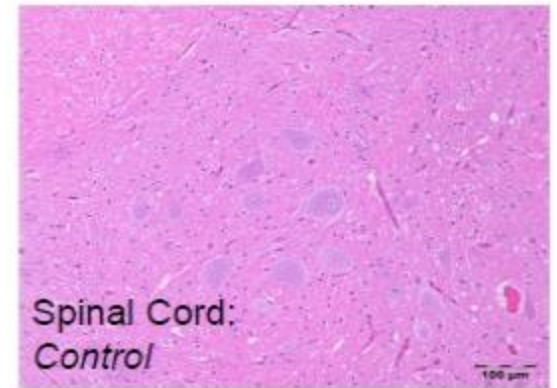
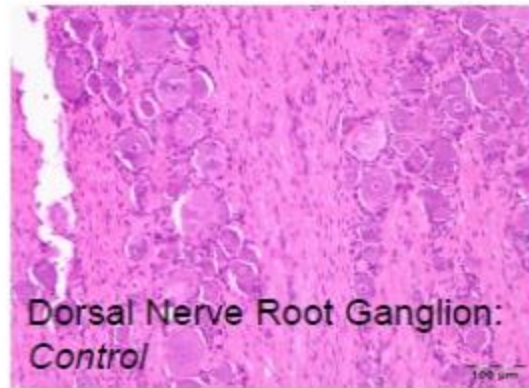
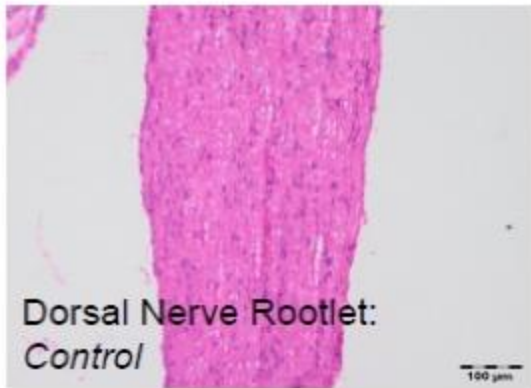
Pre-Clinical Testing: How HFS affects neural tissue

- Model: SCS lead implant and HF-SCS in goat model
- Sample: n=12 ; half continuous stimulation; half no stimulation
- Duration: 10 day follow-up
- Rationale: - Axonal degeneration is common marker in neurodegenerative diseases
 - - Histologically detectible 5-7 days post nerve injury
 - - Supports 10 day evaluation to detect injury effect
- *Butt et.al, European Journal of Pain Supplements 5 (2011) 15–295*



No difference histologically ; Butt et al, 2011

H&E stains:



Conventional and kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of neuropathic mechanical hypersensitivity

Yang et al., IASP, Milan 2012

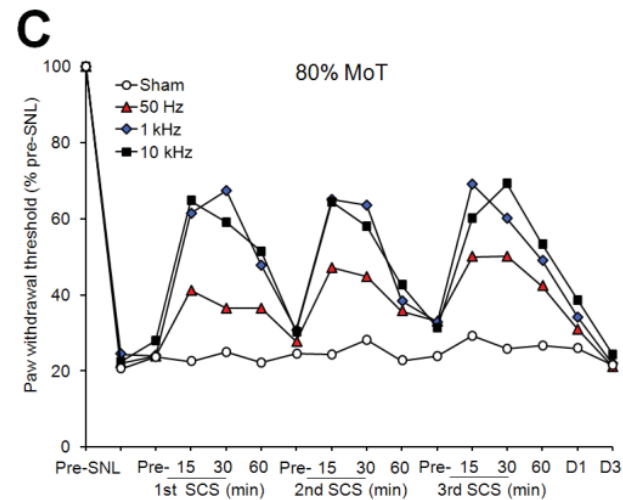
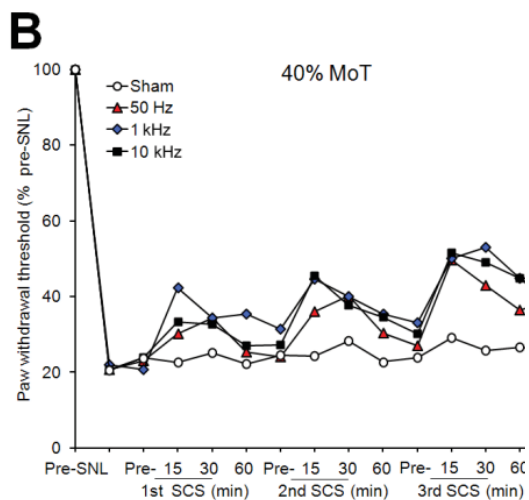
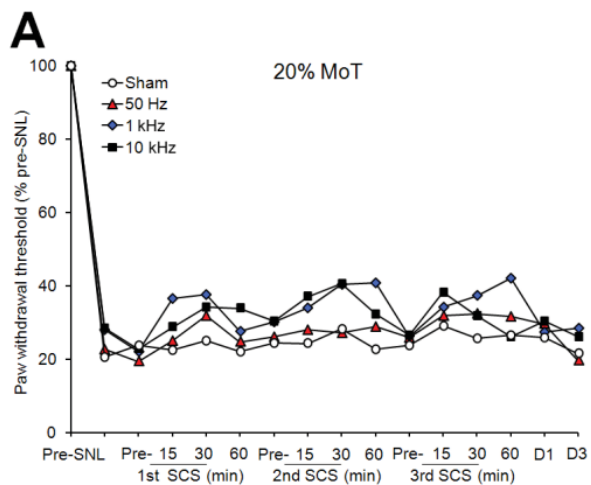
- HF SCS at 1, 3, 10 KHz compared to conventional 50 Hz in a preclinical rat model of neuropathic pain
- Nerve injured animals 2 weeks after injury, SCS or sham, is delivered for 30 minutes for 3 days
- **single intensity** (80, 40, or 20 % motor threshold with pulse with 0.024 ms.
- Animals were tested for SCS effects pre-SCS, during SCS (15 minutes) and 30 and 60 minutes after SCS was started.



Sub-threshold (20% MoT)

Threshold (40% MoT)

Supra-threshold (80% MoT)



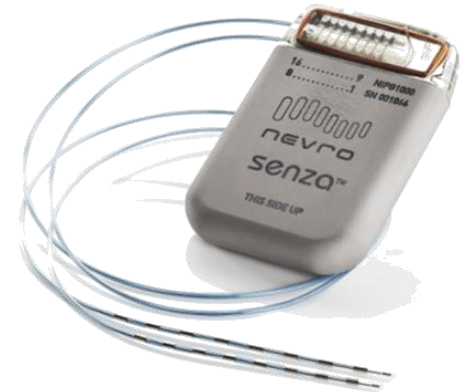
Conventional and kilohertz-frequency spinal cord stimulation produces intensity- and frequency-dependent inhibition of neuropathic mechanical hypersensitivity; **Yang et al., IASP, Milan 2012**

- SCS at high amplitude, high-frequency (1kHz) results in greater reduction of neuropathic mechanical hypersensitivity vs. (50Hz)
- At low amplitude (20% MoT), no frequencies effective
- SCS-induced pain inhibition depends on both intensity and frequency of stimulation.



High-Frequency (HF10) SCS

- Commercial Availability: Europe & Australia (not available in US)
- Manufacturer: Nevro Corporation, Menlo Park, CA
- Device: Senza™ High Frequency SCS system
- Frequency: up to 10 kHz
- Pulse width: up to 1000 ms
- Amplitude: up to 15 mA
- Charge balanced, biphasic waveforms
- Rechargeable IPG
- 10 year battery life under typical HF10 SCS therapy settings
- Nevro Corp. 10186-ENG-Physician Manual Rev G. 2012. Menlo Park, CA, U.S.A.



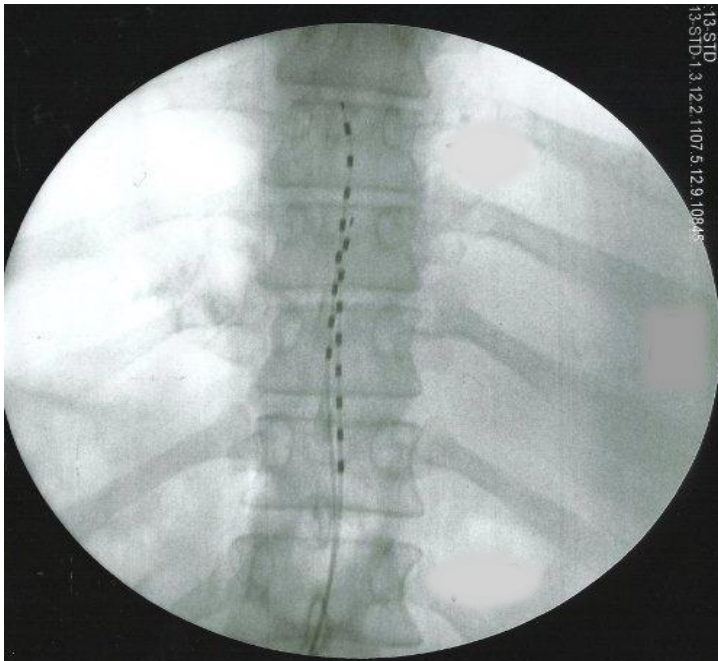
HF 10 initial premises

- Treating effectively back pain, including predominant back pain with concomitant leg pain
- patients who failed conventional SCS, pain relief in many of these patients
- patients who perceive conventional SCS as uncomfortable. The lack of paresthesia-improving quality of sleep and for addressing posture related changes in sensation



Lack of Paresthesia Simplifies Procedure

- Conventional SCS requires intraoperative paresthesia mapping
 - Potentially uncomfortable for patient, frequent adjustments
 - Can lead to wide range in procedure times



HF-10 SCS Lead Positioning:

- No paresthesia mapping
 - Anatomically positioned
 - Overlapping leads along midline
- Shorter, predictable procedure times



All SCS Manufacturers Warn of Unpleasant Stimulation as a Result of Posture Changes

St. Jude:

- Changes in posture “or abrupt movements may result in a decrease or increase in the perceived level of stimulation. Perception of higher levels of stimulation has been described by some patients as uncomfortable, painful, or jolting.”STJ Eon mini Clinician Manual, page 5, 2007

Boston Scientific:

- Changes in posture “Patients should be advised that or abrupt movements may cause decreases, or uncomfortable or painful increases, in the perceived stimulation level.”Boston Scientific Precision® Physician Implant Manual, page 10, 2008

Medtronic:

- “Postural **changes**, and other activities, may cause shocking or jolting.”Medtronic Neurostimulation Systems for Pain Therapy Brief Disclosure, 2007



US Pilot Study (HF 10):

5 sites, 24 patients

- Pts. scheduled for conventional SCS trial
- Baseline VAS back pain score > 5
- Baseline VAS back pain > leg pain

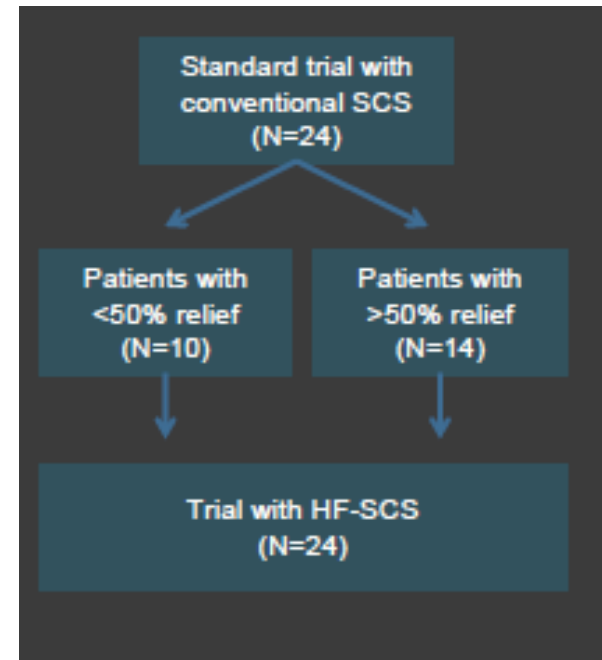
Trial all with conventional SCS

Follow with temporary trial of HF- SCS

-Measured outcomes:

Pain relief using Visual Analog Scale (VAS)

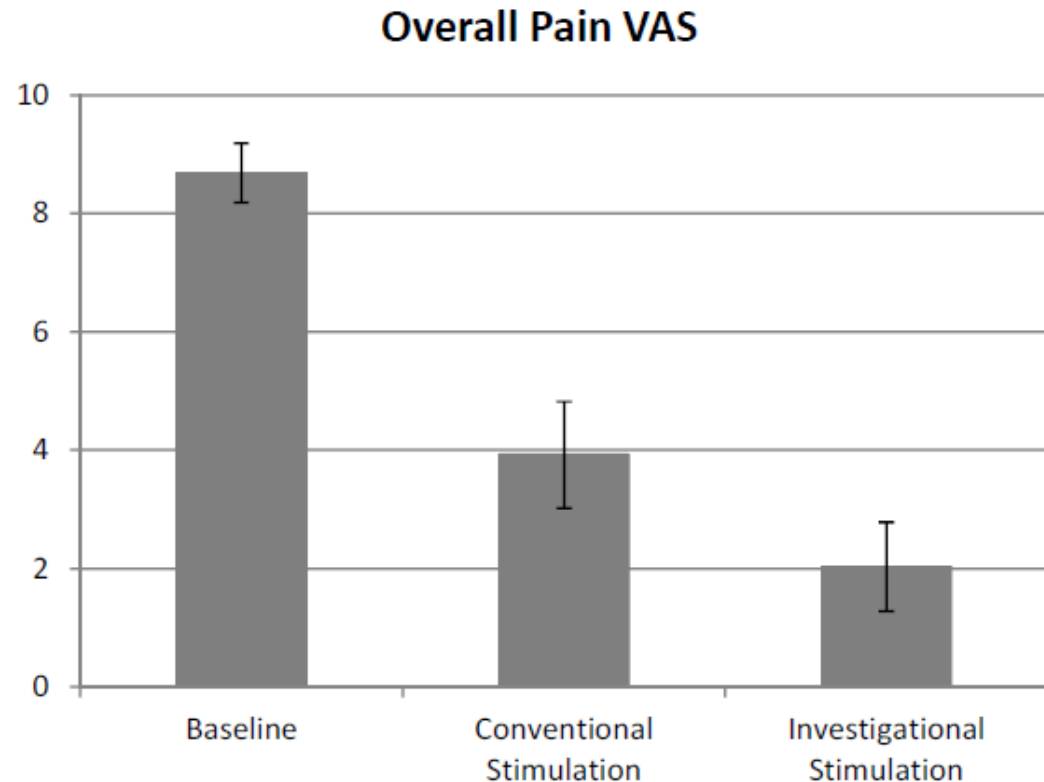
Patient's preferred therapy



Tiede et al. Novel SCS parameters in patients with predominant back pain.
Neuromodulation 2013 Feb; Ahead of Print

US Pilot Study

- Standard and HF-SCS tested on each patient
- HF-SCS effective in reducing pain
- Patients reported significantly reduced back and leg pain vs. baseline

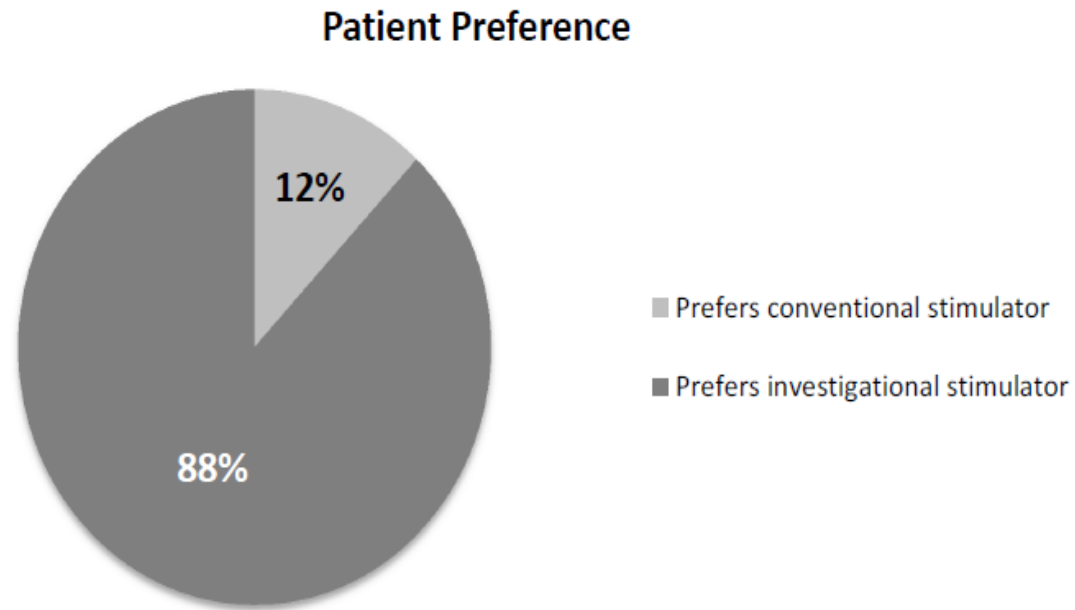


Tiede et al. Novel SCS parameters in patients with predominant back pain. *Neuromodulation* 2013 Feb; Ahead of Print



US Pilot Study

- No safety issues or complications noted
- Pain relief was paresthesia-free
- Strong patient preference for HF-SCS
- Results supported expanding to permanent implant study

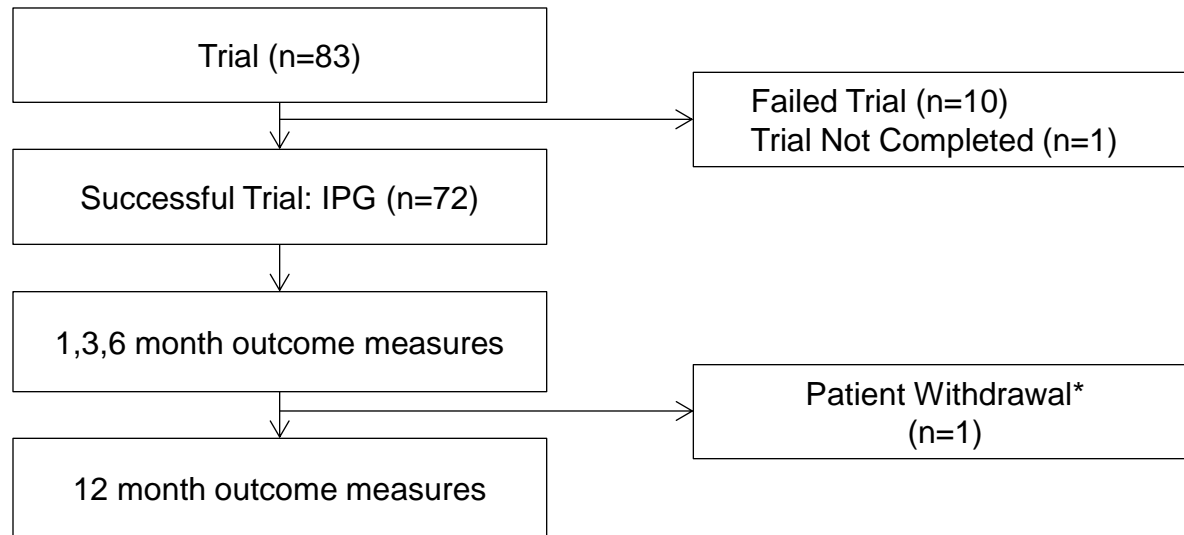


Tiede et al. Novel SCS parameters in patients with predominant back pain.
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EU Study Van Buyten et al, Neuromodulation 2013;16:59-65.

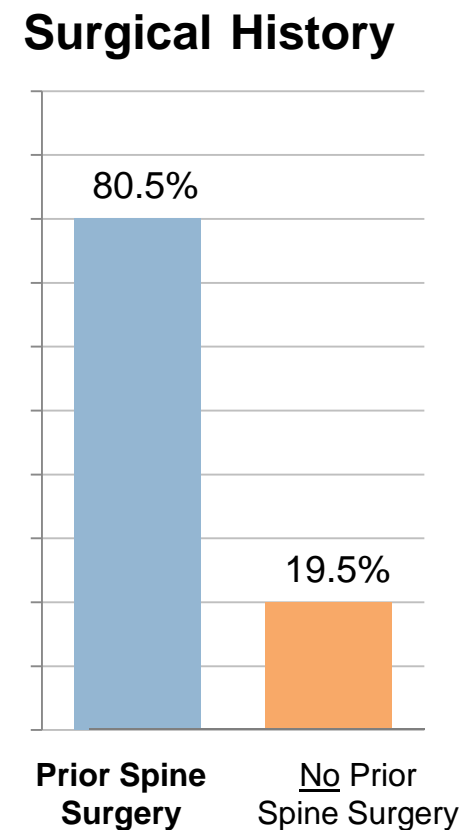
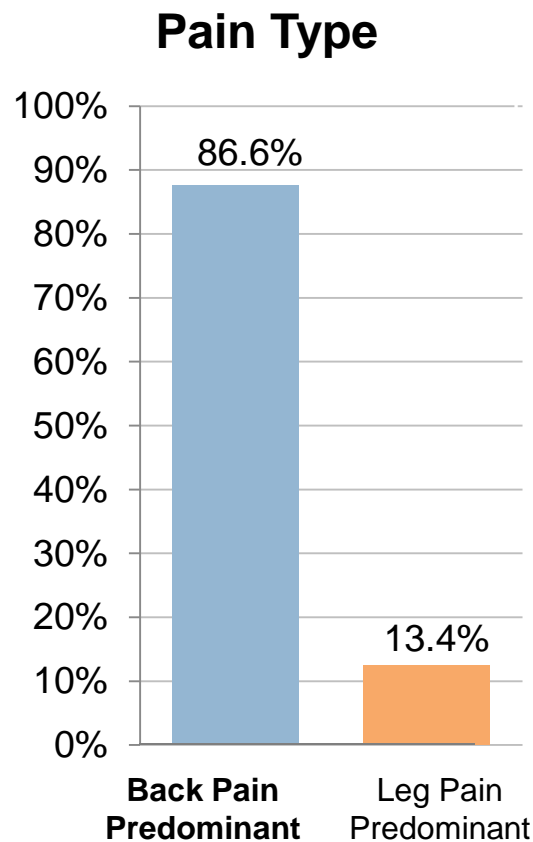
- Prospective, open-label study: Belgium and UK
- Key Inclusion Criteria: VAS back pain score ≥ 5 out of 10
- Key Exclusion Criteria: Standard contraindications used for SCS
- Key Safety Measure: Neurological assessment conducted at follow-up visits



EU Study Van Buyten et al, Neuromodulation 2013;16:59-65.

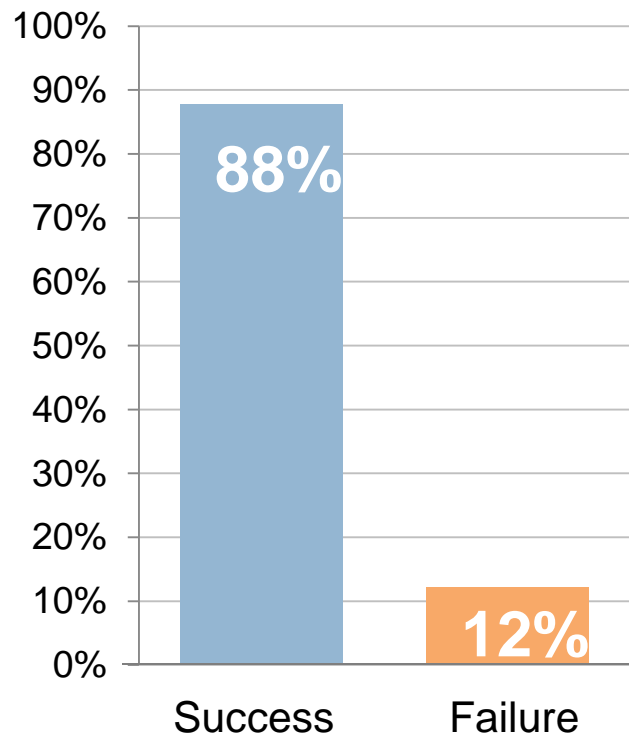
Baseline Demographics

Baseline Demographics	
Mean age:	50 ± 10
Gender:	58% female
VAS Back:	8.4 (± 1.2)
VAS Leg:	5.4 (± 3.2)
Predominant back pain:	86.6% (71/82)
Prior spine surgery:	80.5% (66/82)



Temporary Trial Results; Van Buyten et al, Neuromodulation 2013;16:59-65

Trial Success Rate

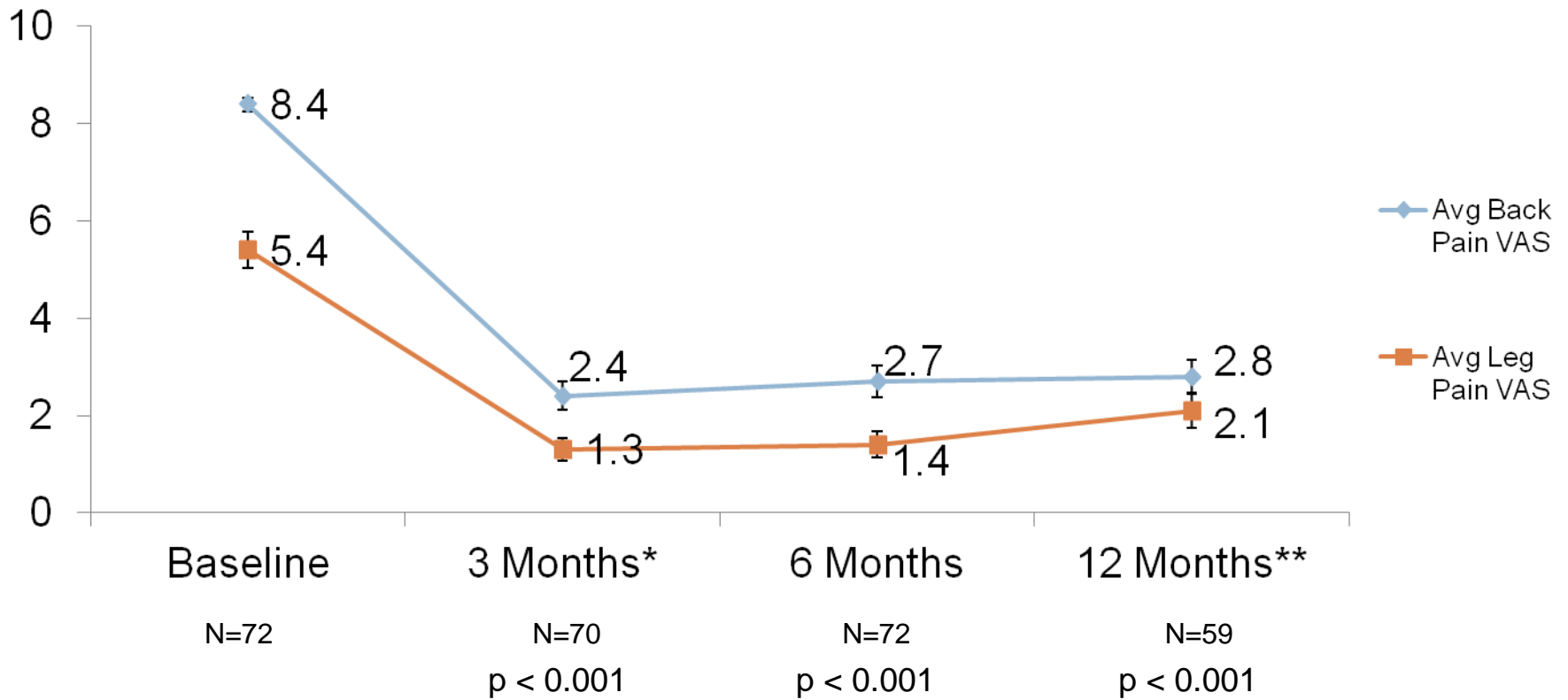


- High temp trial success rate
- 72/82 patients (88%) successful and went to permanent implant
- Mainly back pain and FBSS patients
- Difficult to treat population



Pain Relief at 12 Months;

Smet et al, 2011; Van Buyten et al, Neuromodulation 2013;16:59-65

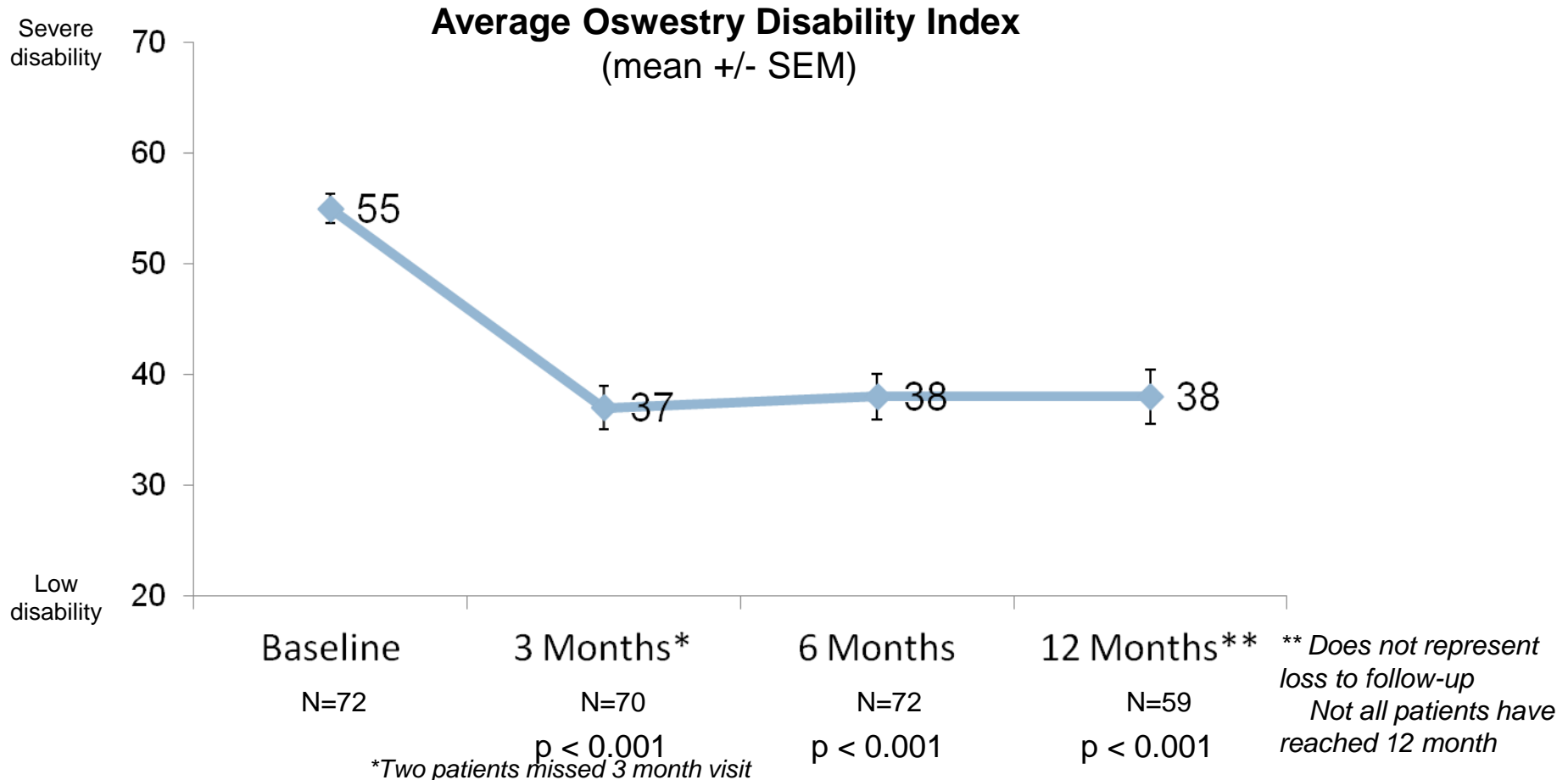


*Two patients missed 3 month visit



Improved Function at 12 Months

Smet, et al, NANS 2011



Van Buyten et al, Neuromodulation 2013;16:59-65

- 72 out of 82 patients (88%) trialed with HF-10 SCS had positive results -permanent implantation.
- At six-month follow-up, 74% >50% pain reduction
- ODI decreased significantly
- sleep disturbance improved
- patient satisfaction high
- safety profile similar to conventional



Eric Buchser, MD, *Lausanne, Switzerland*
Comment to published article in Neuromodulation

- “remarkable trial, which has already had stimulating effects in the field of spinal cord stimulation”
- Credible analgesic efficacy of sub-threshold dorsal column stimulation is suggested, which confirms similar previous anecdotal observations.
- Yet, the superiority of the therapy remains to be demonstrated and the reader should remember that uncontrolled studies unavoidably embellish the results”



Perruchoud C, et al. 2013. Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study. *Neuromodulation* 2013; e-pub ahead of print

- 33 patients followed, 5 excluded (technical problems)
- Primary outcome GPI
- Since the last visit to the pain clinic my overall pain control is the following: 1) very much improved; 2) much improved; 3) minimally improved; 4) unchanged; 5) minimally worse; 6) much worse; and 7) very much worse

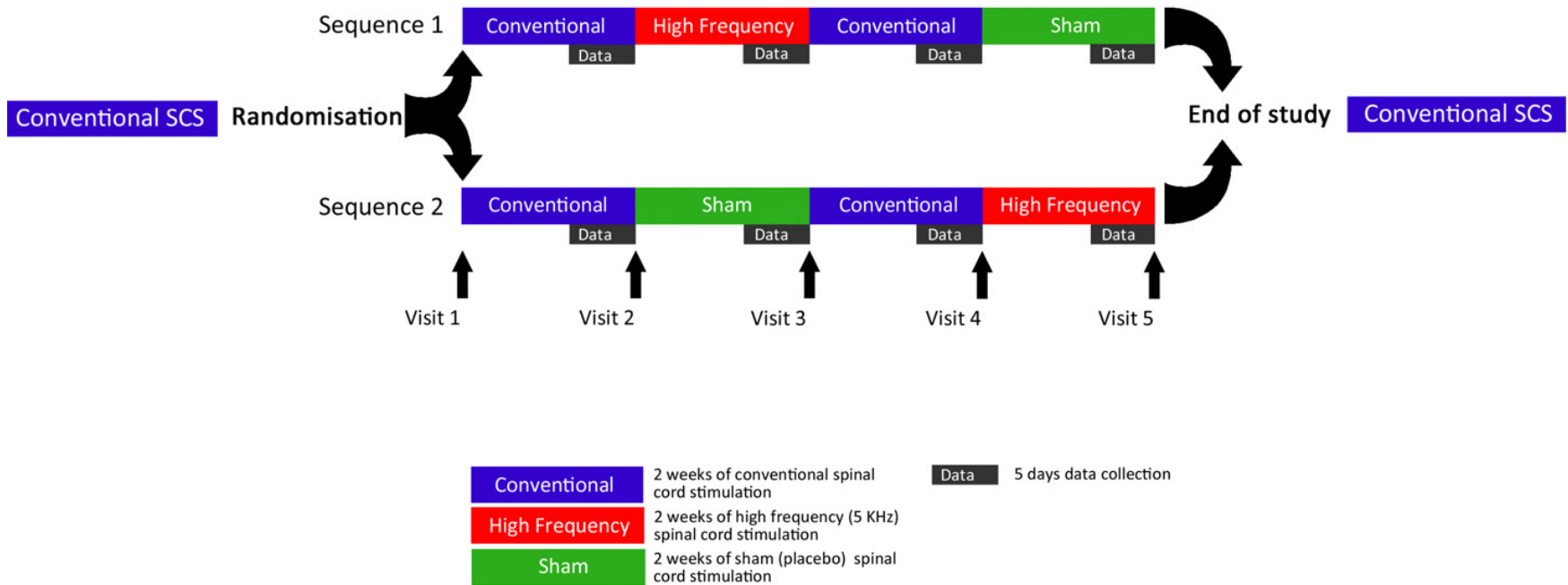


Perruchoud C, et al. 2013. Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study. *Neuromodulation* 2013; e-pub ahead of print

- HFSCS were programmed:
- no more than three active contacts
- leads were not in precise anatomical position, but whatever placement of the leads was achieved with past implant
- Current amplitude kept below sensory threshold, frequency increased to 5000 Hz, then current amplitude progressively increased to sensory threshold
- Amplitude decreased again below threshold amplitude until unable to feel paresthesias
- Pulse width adjusted to 60 msec



Perruchoud C, et al. 2013. Analgesic Efficacy of High-Frequency Spinal Cord Stimulation: A Randomized Double-Blind Placebo-Controlled Study. *Neuromodulation* 2013; e-pub ahead of print



GPE

- The primary end point is proportion of responders
- responding to HF SCS 42.4% (14/33) vs. 30.3% (10/33) sham
- “period effect,” 51.5% (17/33) improved at visit 3 and 21.2% (7/33) at visit 5
- Sequence 1 (HFSCS first), 9/17 responded to HFSCS vs. 2/17 sham
- Sequence 2 (sham first), 5/16 responded to HFSCS vs. 8/16 to sham
- At visit 3, a similar proportion responded to both: 9/17 patients (52.9%) with HFSCS vs. 8/16 (50%) with sham
- At visit 5, however, 5/16 patients (31.3%) responded to HFSCS vs. only 2/17 patients (11.8%) sham



Pain

- mean pain VAS on sham is 4.26 vs. 4.35 on HF; the difference (HF minus sham) = -0.09 (95% CI, -0.68 to 0.86; $p = 0.82$).
- “period effect” irrespective of treatment:
- at visit 3 is 3.99 vs. 4.63
- at visit 5; the difference (HF - sham) = -0.64 (-1.41 to -0.14; $p = 0.11$)



US FDA Study HF-10

- Non-inferiority study comparing HF SCS with conventional stimulation system



Clinical cases-not a sham

- 41 y/o female postlaminectomy syndrome back and leg pain; stimulator off at 5 months after implant
- 31 y/o male DDD, postlaminectomy syndrome; program change
- 48 y/o female post-laminectomy syndrome; requesting removal of the lead during the trial



Summary:

- High-frequency stimulation represents an important advance in SCS therapy
- Offers possibility of enhanced efficacy in back pain patients *and* pain relief without paresthesia
- Sustained HF-stimulation well tolerated in animal and clinical studies
- US pivotal trial enrollment completed



What needs to be done!!!

- Great substrate for the blind randomized controlled trials
- Can do within subject control trials with subthreshold stimulation
- True efficacy needs to be determined



Thank You

IkapuralMD@gmail.com



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