PainWeek®

Dorsal Root Ganglion and Peripheral Nerve Stimulation: A More Targeted Approach for Nerve Pain

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Title & Affiliation

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Disclosures

- Consultant for Nevro, Camber Spine, Vertos

Learning Objectives

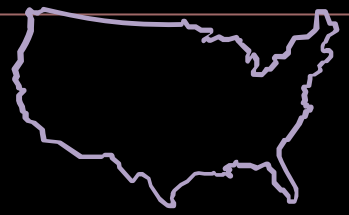
- Differentiate various neuromodulators
- Describe the role of dorsal root ganglion
- Discuss the clinical evidence of dorsal root ganglion therapy and peripheral nerve stimulation in the treatment of nerve pain

Agenda

- Chronic pain and its management
- Neurostimulation & DRG therapy
- DRG Neurostimulation System
- Steps to getting DRG Therapy
- Peripheral nerve stimulation

Prevalence of Pain

Chronic pain is one of the most common reasons Americans **seek medical care** and is associated with restrictions on mobility, anxiety, depression and **reduced quality of life**[1-3]



estimated that **50 million** people in the United States **suffer** from chronic pain[4]

billion is the estimated cost of chronic pain, stemming from medical costs, lost productivity and rehabilitation programs[5]

1 IN 10

ADULTS

The WHO estimates that globally, **one in 10 adults** are newly diagnosed with chronic pain each year[6]

pain affects **more Americans than diabetes, heart disease** and **cancer combined**[7]

People aged **45–64** are the most likely to report pain lasting **longer than 24 hours**[8]

1. Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. *Vital Health Stat 13*. February 2006(159):1-66.
2. Gureje O, Von Korff M, Simon GE, Gater R. Persistent pain and well-being: a World Health Organization study in primary care. *JAMA*. July 8, 1998;280:147-51.
3. Smith BH, Elliott AM, Chambers WA, et al. The impact of chronic pain in the community. *Fam Pract.* 2001;18:292-9.
4. Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *MMWR: Morbidity & Mortality Weekly Report.* 2018;67(36):1001-1006. doi:10.15585/mmwr.mm6736a2.
5. Institute of Medicine. *Relieving pain in America: a blueprint for transforming prevention, care, education, and research.* Washington, DC: National Academies Press; 2011.
6. International Association for the Study of Pain. Unrelieved pain is a major global healthcare problem. http://www.iasp-pain.org/AM/Template.cfm?Section=Home&Template=/CM/ContentDisplay .cfm&ContentID=2908.
7. National Institute of Health. Research Portfolio Online Reporting Tools (RePORT) Pain Management. Washington, DC. 2018.
8. National Center for Health Statistics. Health, United States, 2006: With Chartbook on Trends in the Health of Americans. Hyattsville, MD: 2006. https://www.cdc.gov/nchs/data/hus/hus06.pdf.

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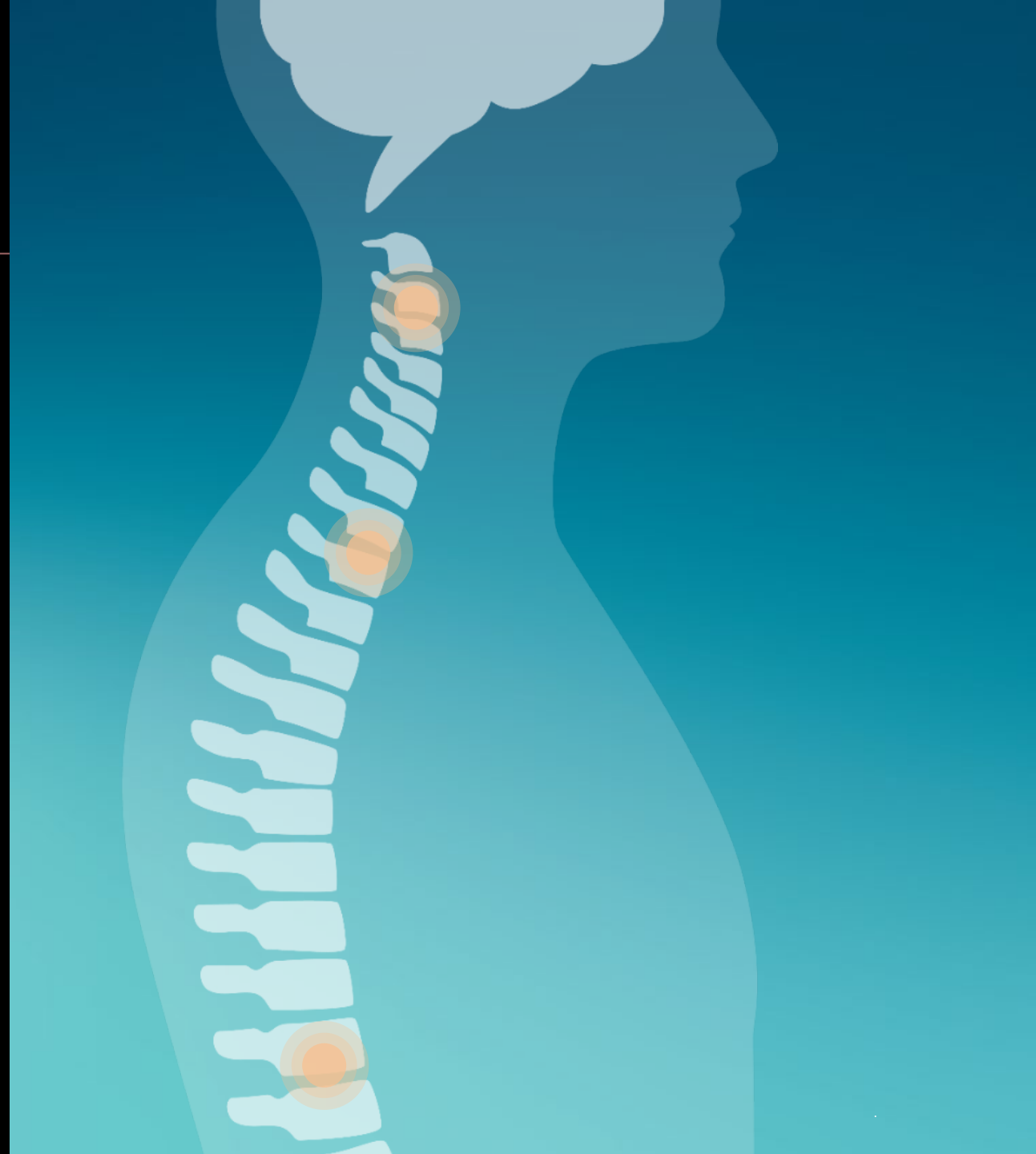
WHAT IS PAIN?

- The body's natural response to harm or possible damage
- Occurs when special nerve endings, called pain receptors, trigger a signal that travels through the spinal cord to the brain
- Signals can be released in response to illness, injury or chemical changes within the body



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HOW IS CHRONIC PAIN DIFFERENT?

- CHRONIC PAIN
  - Lasts longer than six months,[1] or longer than would generally be expected for recovery from a specific disease, injury or surgery
  - Sensation varies from person to person and the source of pain may be unknown
  - Limited or no pain relief provided by pain medications, surgeries or other therapies

- SYMPTOMS CAN INCLUDE:
  - Burning feeling
  - Stabbing or burning pain
  - Tingling or numbness
  - Sharp pricks or pinching sensations
  - Dull aches or discomfort
  - Tenderness

1. Cleveland Clinic. Acute vs. Chronic Pain. https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain. Reviewed January 26, 2017.

TREATMENTS FOR CHRONIC PAIN

FIRST TIER

- Cognitive and Behavioral Therapy
- NSAIDs
- TENS
- Biofeedback
- OTC Pain Medications
- Rehabilitation Therapy

SECOND TIER

- Opioids
- Nerve Blocks

THIRD TIER

- Radiofrequency Therapy
- Implantable Drug Pumps

Neurostimulation, including DRG Therapy may be recommended when other therapy options have failed

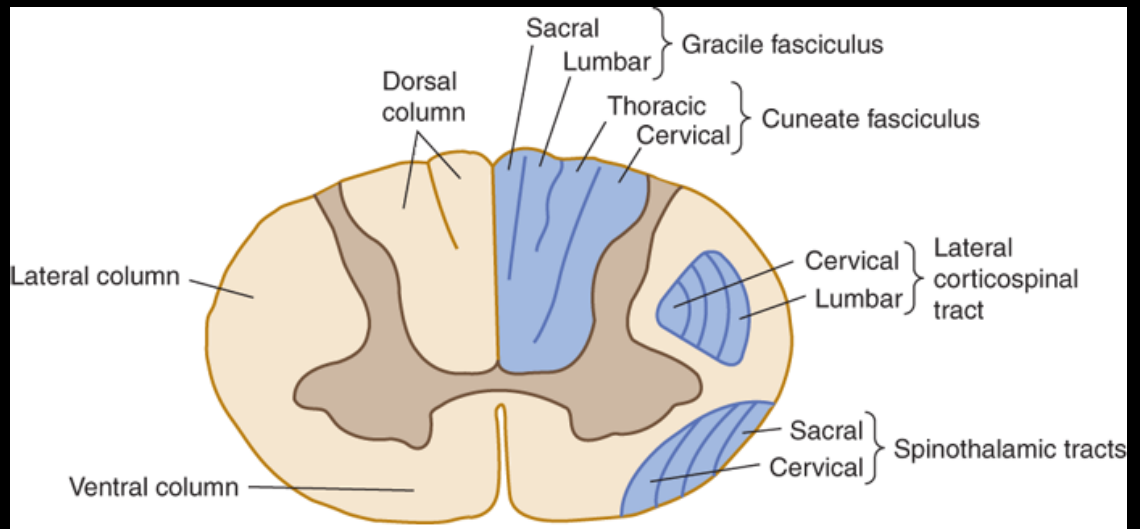
Dorsal Root Ganglion (DRG) Stimulation

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**

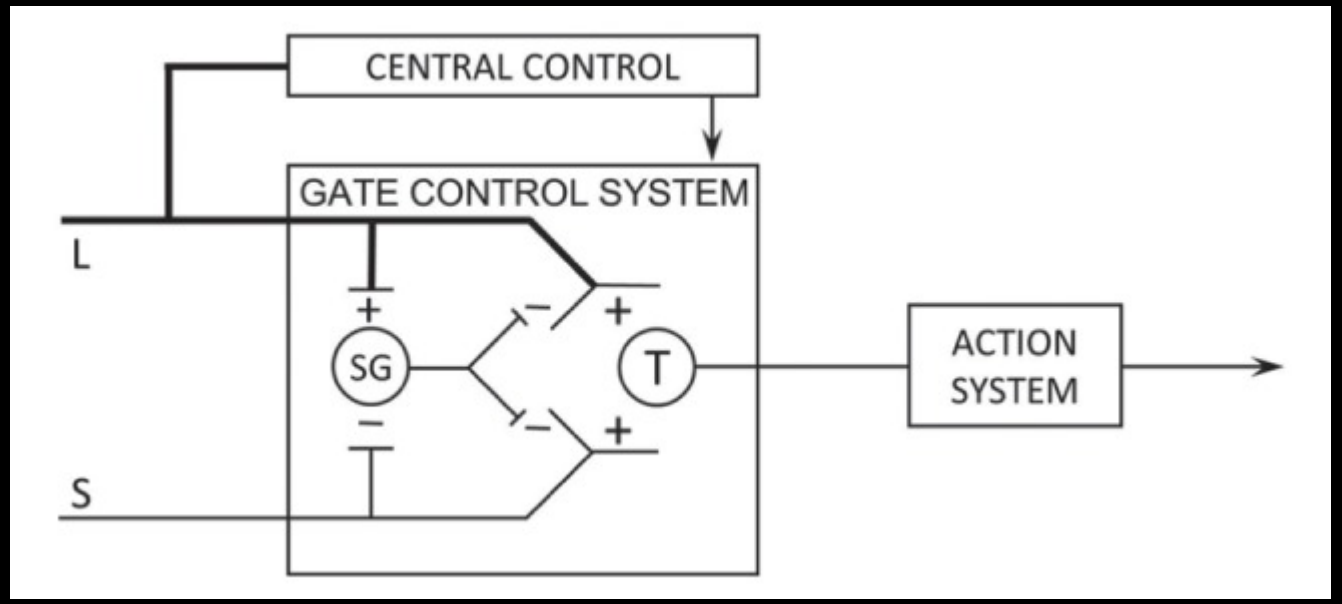
Mechanism of Action

- 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

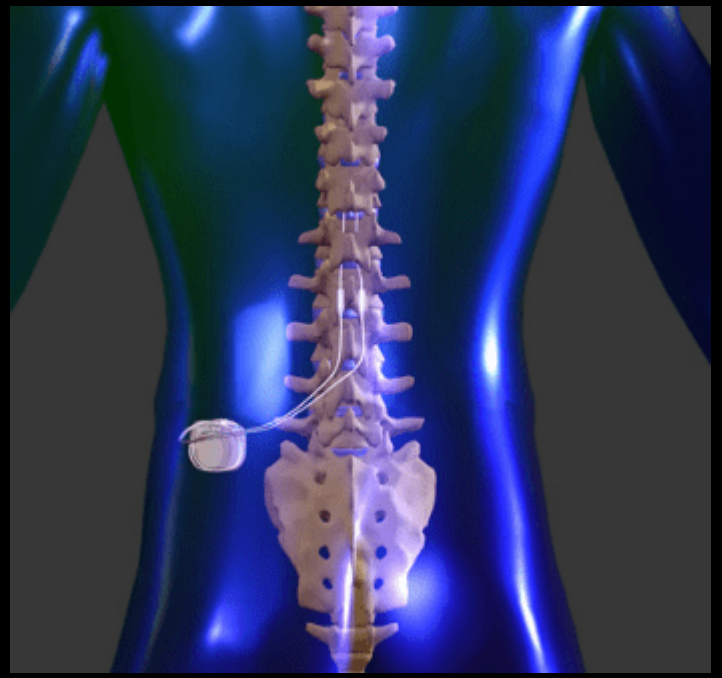
Gate Control Theory

- 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

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

- 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

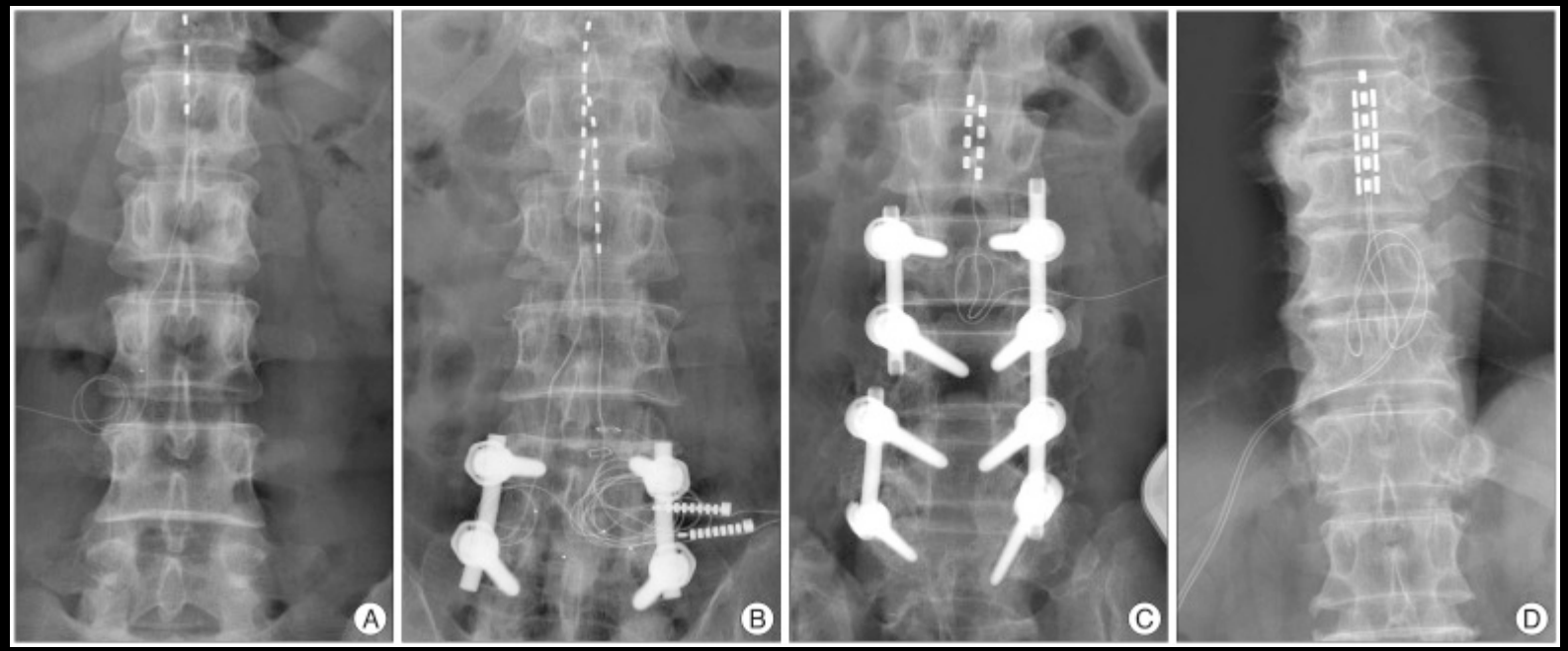


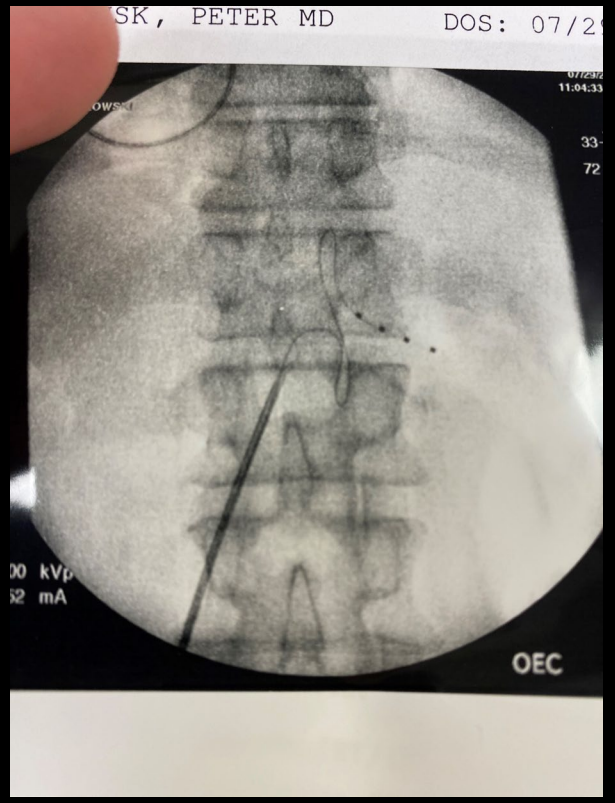
Amplitude, Frequency, Pulse Width

- 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

Differences Between SCS and DRG Therapy

- They are not the same
- Main difference lies in placement of electrodes





NEUROSTIMULATION THERAPY

- Spinal cord stimulation (SCS) is a well-established therapy, recommended by doctors for **more than 50 years**[1]
- Worldwide, approximately **34,000** patients undergo SCS each year[2]
- Uses **mild electrical pulses to change pain signals** as they travel from the spinal cord to the brain
- May help to reduce pain to a manageable level and to return to a more normal lifestyle

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1. Kennedy J, et al. Prevalence of persistent pain in the US adult population: new data from the 2010 national health interview survey. The Journal of Pain. 2014;15(10):979-984.
2. http://askaboutpain.com/#concern

NEUROSTIMULATION FOR CRPS AND CAUSALGIA

Initial research showed that traditional SCS showed minor improvements for patients with CRPS[1].

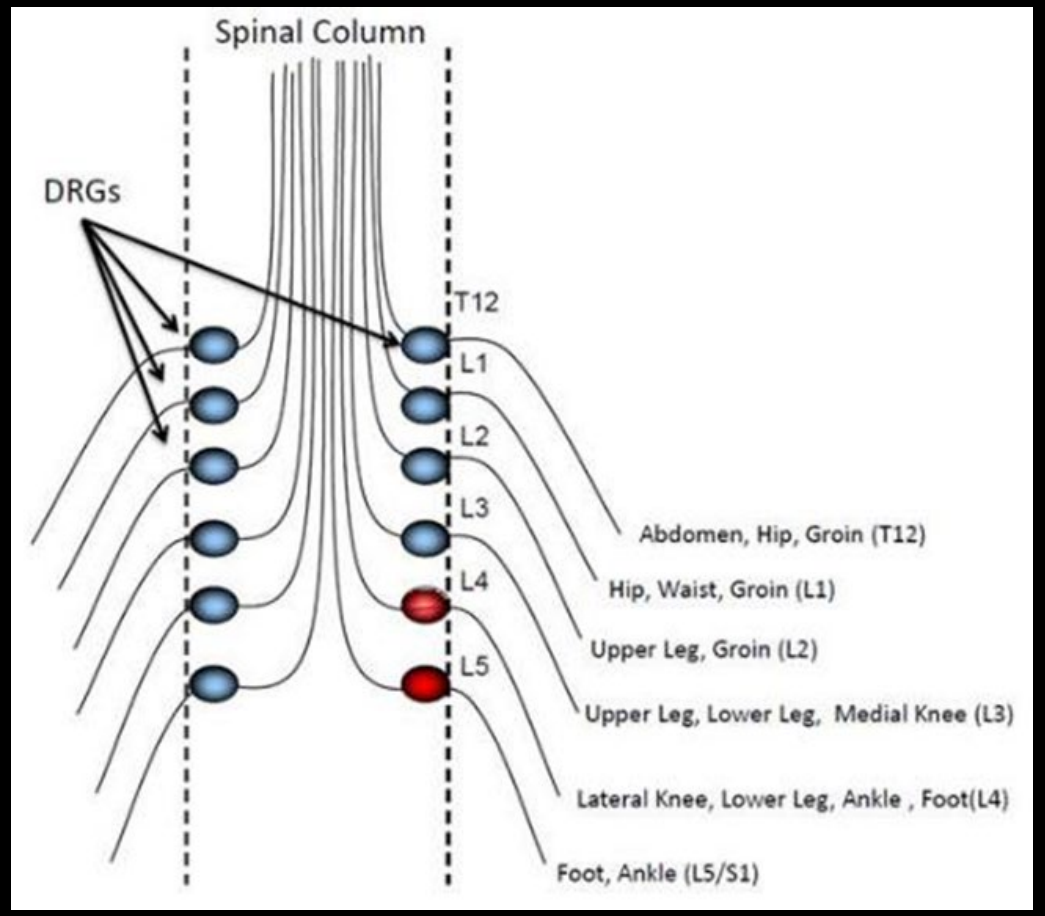
Alternatively, by stimulating the DRG, one is able to achieve therapeutic coverage and pain relief in difficult-to-treat focal chronic intractable pain conditions[1].

1. Deer T, Levy R, et al. 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. Pain. 2017;158(4):669-681.

A DIFFERENT APPROACH: STIMULATING THE DRG

1. Everyone has clusters of nerve cells along their spine called **Dorsal Root Ganglion (DRG)**

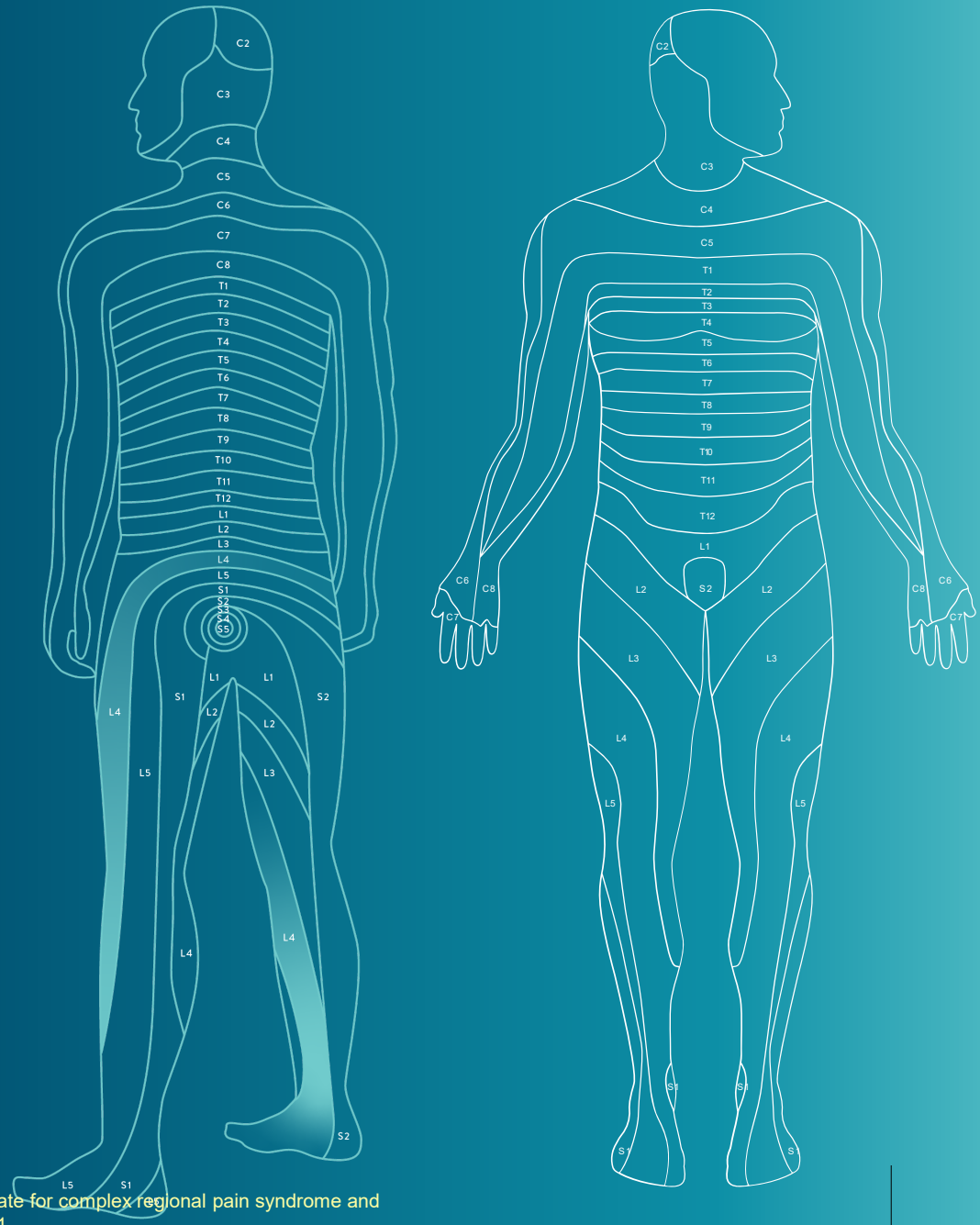
2. **DRG** nerves control pain signals from specific areas of the body where someone experiences pain



A DIFFERENT APPROACH: STIMULATING THE DRG

3 **DRG therapy** is a form of neurostimulation where the mild electrical signals target specific DRGs that are involved in a person's localized pain[1].

4 **DRG therapy** is designed to target difficult-to-treat chronic pain in specific areas of the lower body – such as the pelvis, groin, hip, knee, ankle, and foot – in adult patients with CRPS and causalgia[2]



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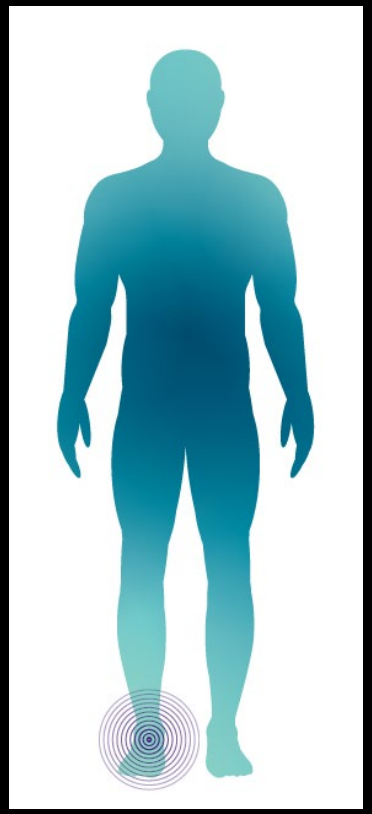
1. Deer T, Levy R, et al. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: a randomized comparative trial. Pain. 2017;158(4):669-681.
2. Proclaim™ DRG Neurostimulation System Clinician's Manual. Plano, TX. 2017

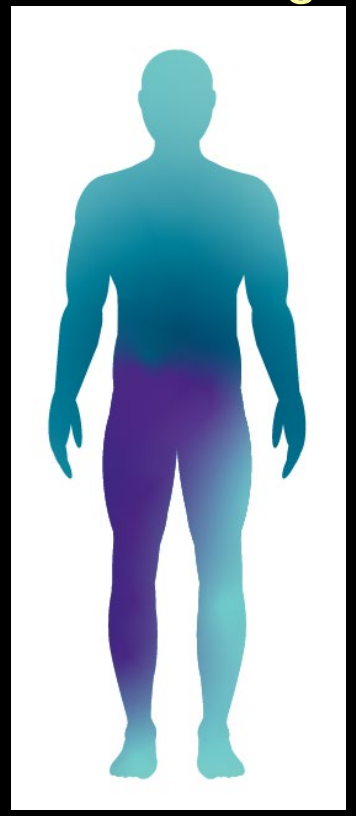
A DIFFERENT APPROACH: STIMULATING THE DRG

5

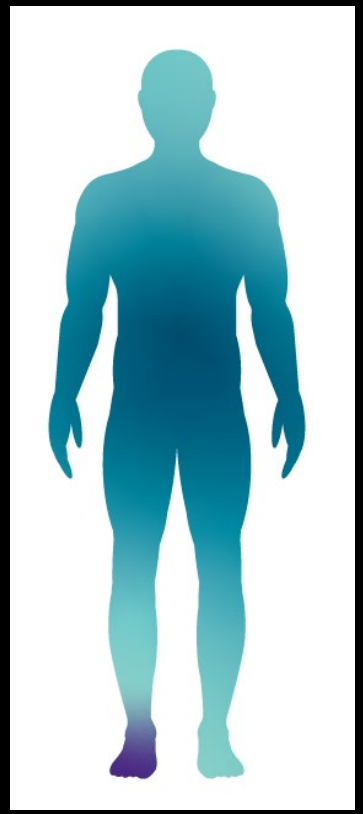
- DRG Therapy has the unique ability to help manage chronic pain in targeted parts of the lower extremities due to CRPS and causalgia[1].



AREA OF PAIN



STIMULATION WITH **CONVENTIONAL TONIC SCS**



STIMULATION WITH **DRG THERAPY**

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1. Proclaim™ DRG Neurostimulation System Clinician's Manual. Plano, TX. 2017

Clinical Evidence

DRG DELIVERS TARGETED RELIEF AT THE SOURCE WITH CONSISTENT, SAFE, AND SUPERIOR OUTCOMES

DRG therapy is backed by the ACCURATE clinical trial

The largest randomized, head-to-head, controlled neuromodulation trial for the treatment of CRPS and causalgia.

Deer et al. **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. Pain. 2017 Apr; 158 (4):669-681**

Proven to Provide Superior and Long-term Pain Relief

REDUCE PAIN
an average of

81.4%

At 12 months

PROVIDES PERSISTENT
pain relief to

86% OF PATIENTS

At 12 months

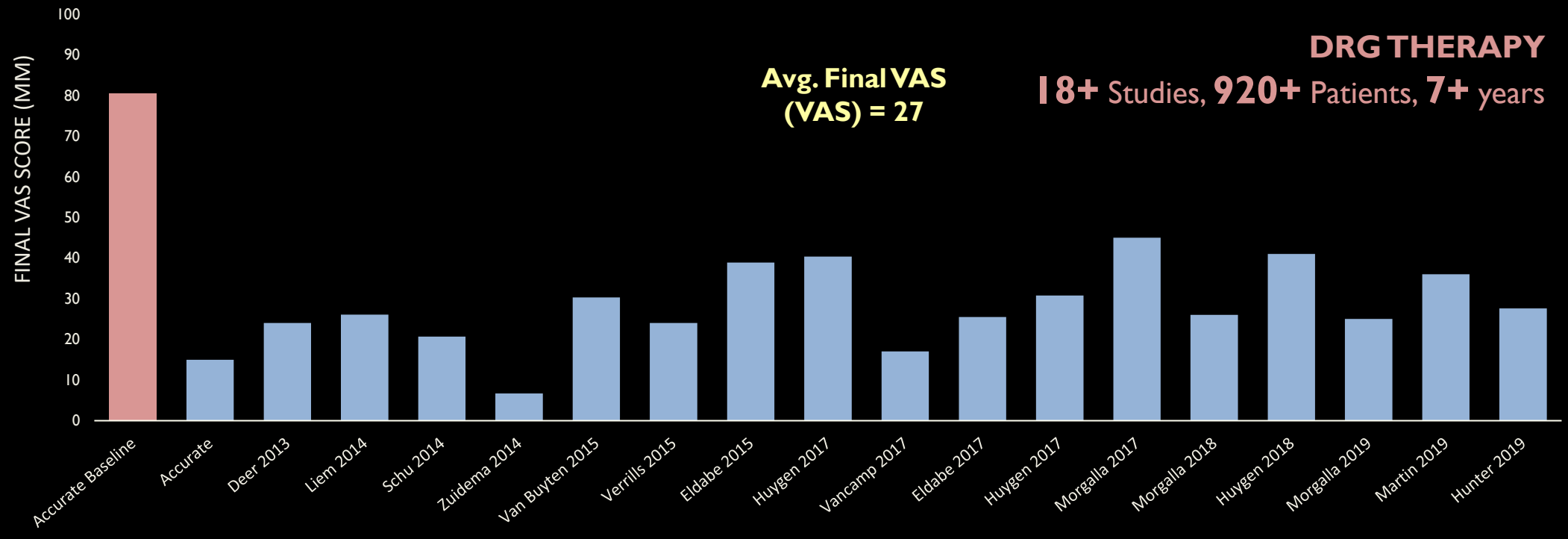
MORE THAN 8 OUT OF 10
PEOPLE

EXPERIENCED SIGNIFICANT PAIN RELIEF
AT 12 MONTHS

PAINWEEK®

Deer et al. 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. Pain. 2017 Apr; 158 (4):669-681

PRODUCES CONSISTENT, SAFE RESULTS IN DIVERSE CLINICAL SETTINGS AROUND THE WORLD



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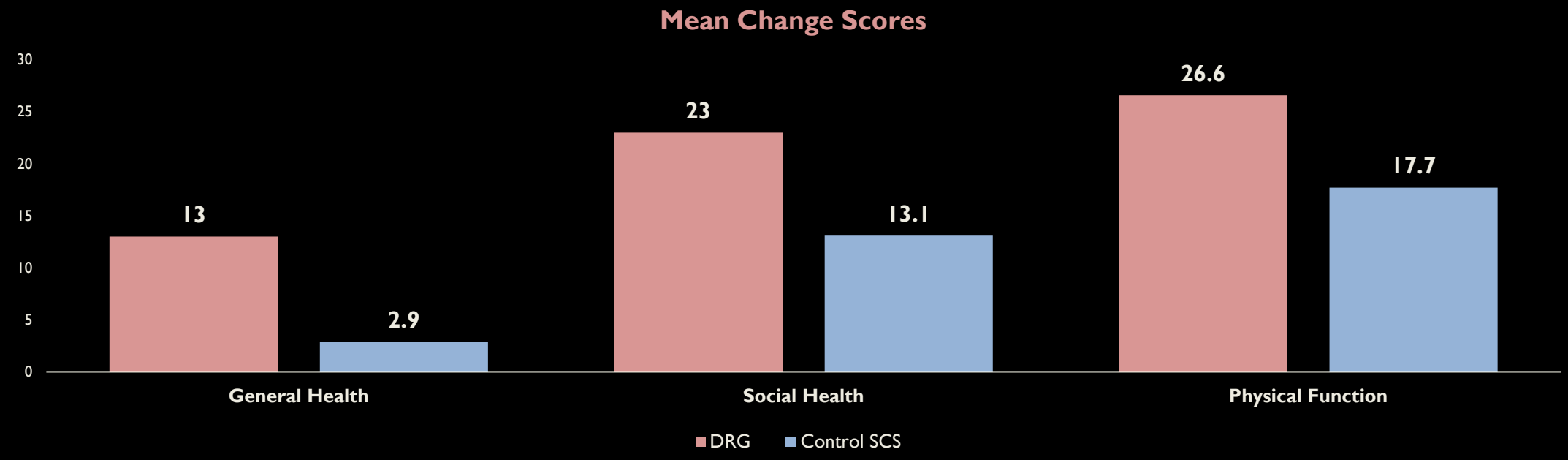
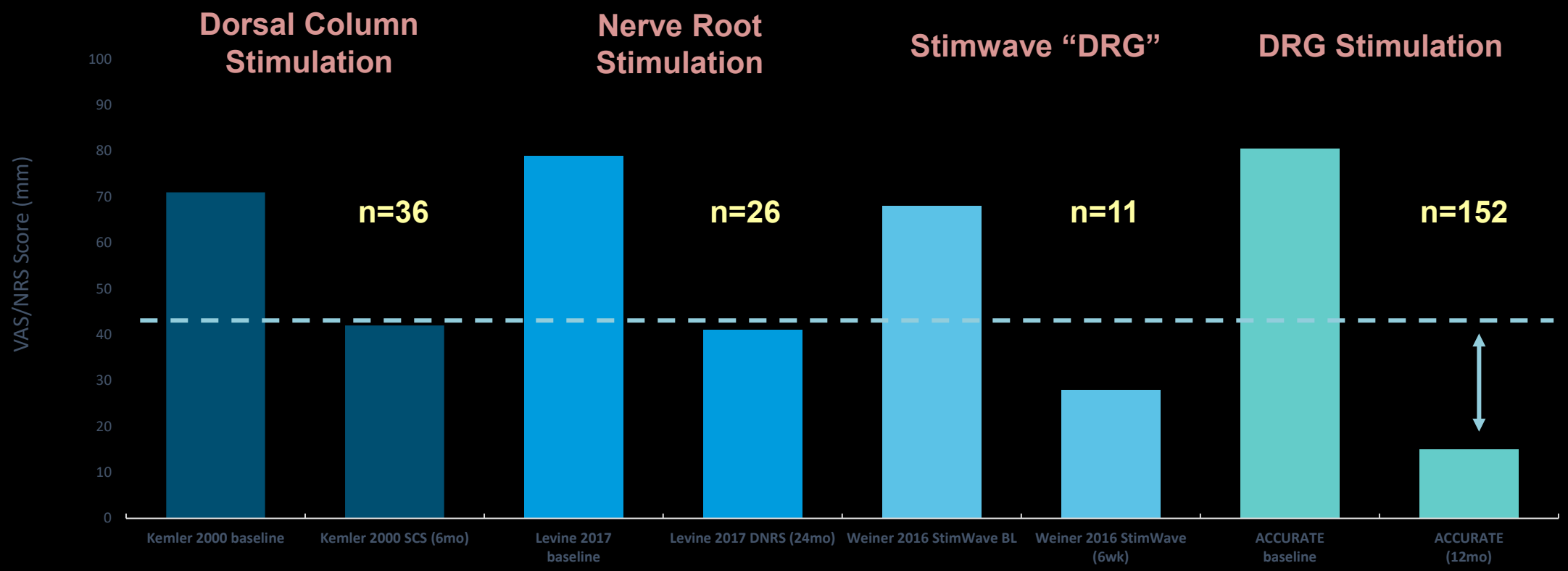
Proclaim DRG Has Also Shown Statistically Greater Improvements in Overall Change in Physical Function, General Health, and Social Function at 12 Months



Deer et al. 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. Pain. 2017 Apr; 158 (4):669-681

DRG Study Compared to Other Therapies

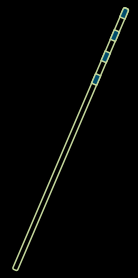


Kemler et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. NEJM. 2000 Aug 31;343(9):618-24

Levine et al. Successful Long-term Nerve Root Stimulation for Chronic Neuropathic Pain: A Real World, Single Center Canadian Experience. Pain Physician. 2017 Feb;20(2):95-106

Weiner et al. Treatment of FBSS Low Back Pain with a Novel Percutaneous DRG Wireless Stimulator: Pilot and Feasibility Study. Pain Med. 2016 Oct;17(10):1911-1916

The Invisible Trial System

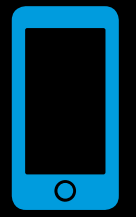


TEMPORARY LEADS

Thin wires that deliver low-energy electrical pulses from the battery to interrupt your pain signals

EXTERNAL BATTERY

Leads are connected to a small external battery, worn outside of the body, typically on your lower back



PATIENT CONTROLLER

An Apple iPod‡ that enables you to adjust the therapy

Peripheral Nerve Stimulators

Peripheral Nerve Stimulation

- Also known as PNS
- Application of electrical signals to peripheral nerves
- Can be used in setting of focal pain complaint
- Similar to DRG
- Both differ from traditional Spinal Cord Stimulation
- Currently in its infancy in terms of therapeutic option

PNS

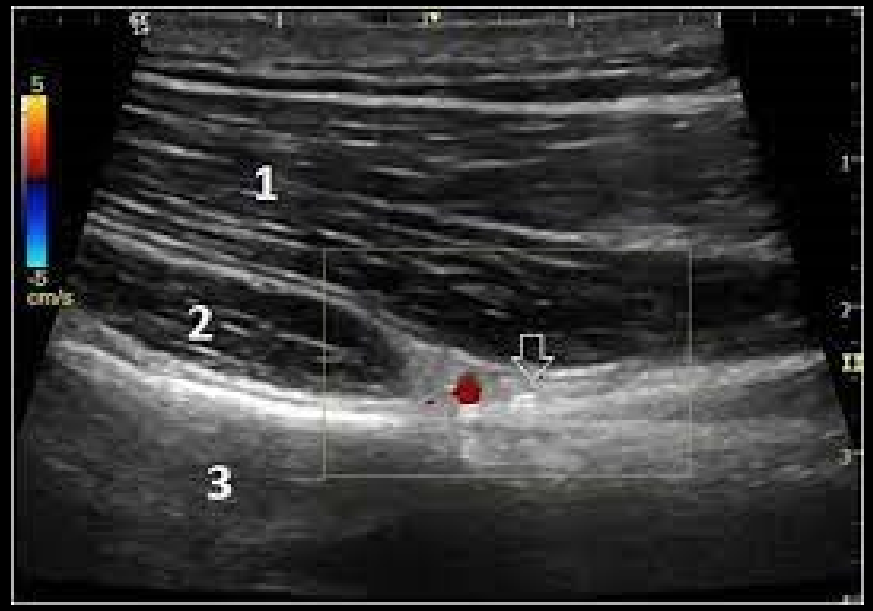
- Performed under Ultrasound or Xray Guidance
- Typically being used for focal pain complaints
- Chronic pain of knee, shoulder, foot/ankle

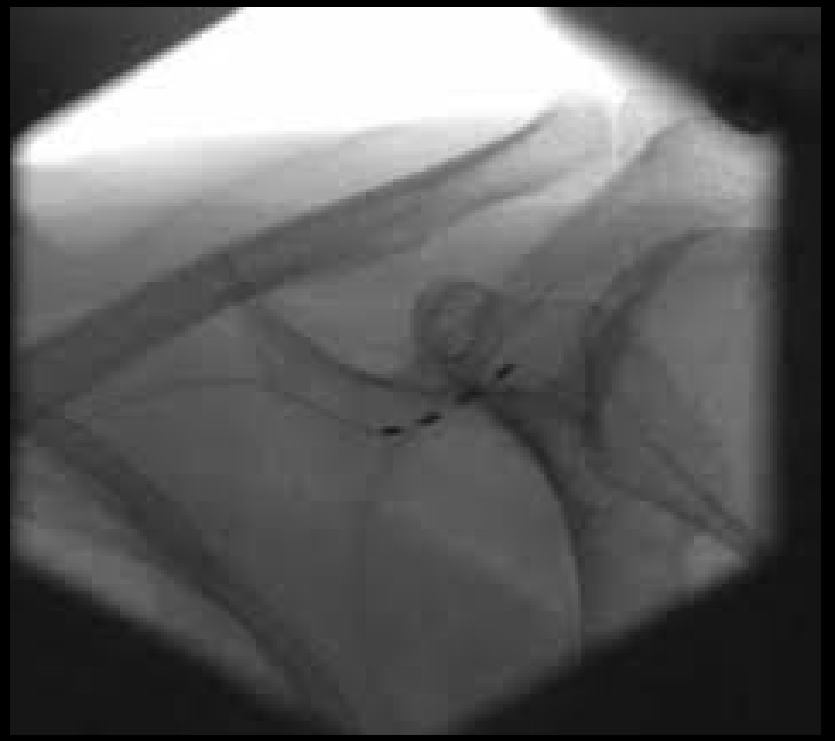
Targets for PNS

- Headache and facial pain
  - Greater and lesser occipital nerve
    - Branches of C2 and C3 nerve roots
  - Supraorbital and infraorbital nerves
- Upper Extremities
  - Ulnar, median, radial
    - Shoulder
      - Suprascapular, axillary nerve
- Lower Extremities
  - Femoral, sciatic, tibial, saphenous nerve

PNS Targets

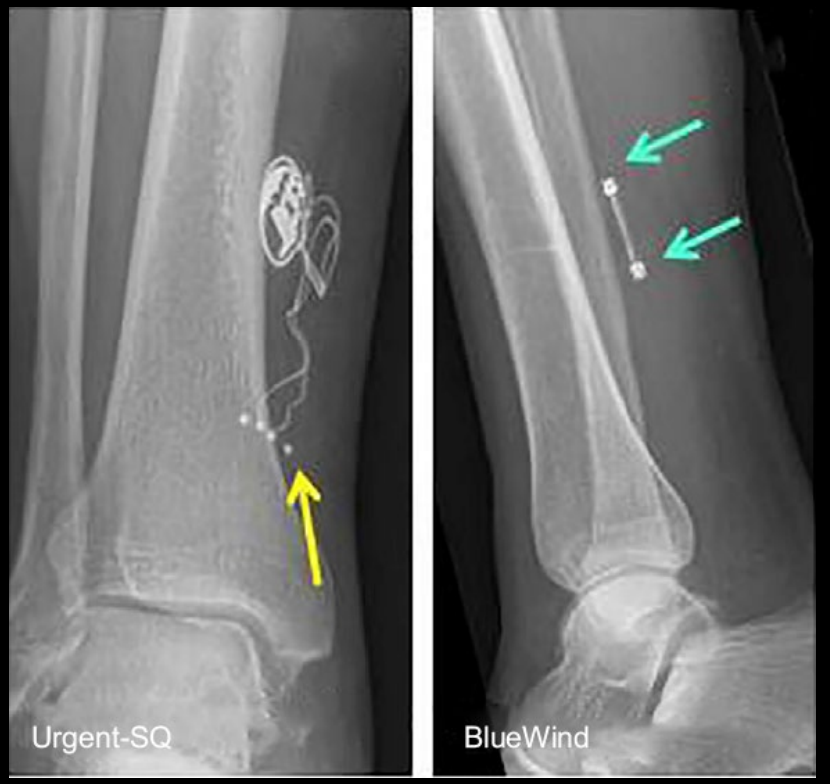
- Suprascapular Nerve





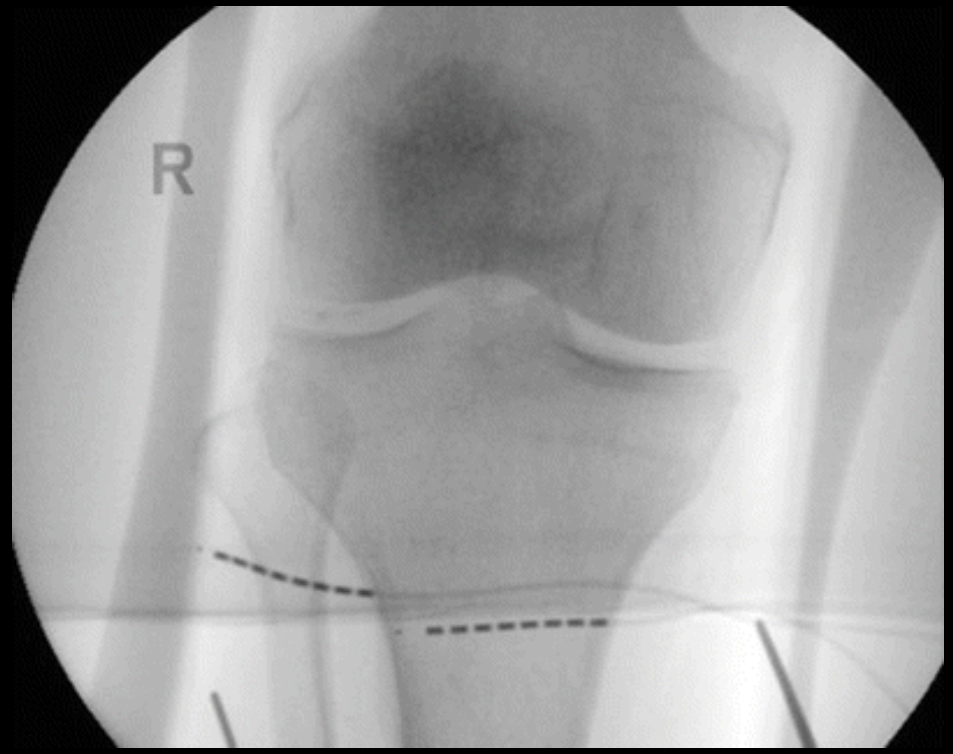
PNS Targets

- Tibial Nerve



PNS Targets

- Genicular nerves

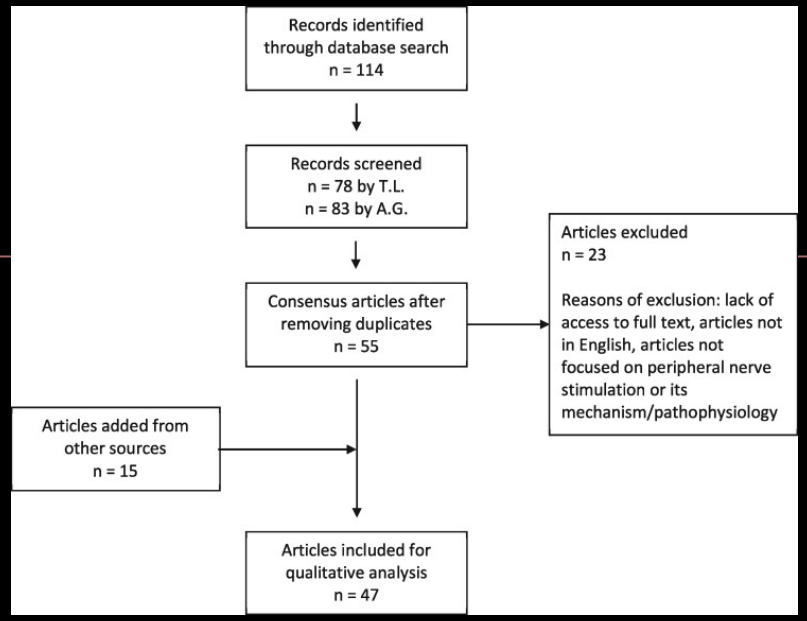


PNS

- Many companies are on the market
- SPRINT PNS, Moventis, Saluda, Stimwave etc
- Data continues to be generated and very limited
  - No prospective RCT's
  - Most are case series reviewing use of products

PNS Mechanism of Action

- Origin based on gate control theory
- Exact mechanism is unknown
- Animal, human and imaging studies demonstrate
  - Peripheral and central analgesic mechanism of PNS by modulating inflammatory pathways, the autonomic nervous system, endogenous pain inhibition pathways, involvement of cortical and sub cortical areas



Lin et al. Mechanism of Peripheral Nerve Stimulation in Chronic Pain. Pain Med. 2020 Aug 1;21 (Suppl 1): S6-S12

PNS Mechanism of Action

- Peripheral nerve fibers are modulated when an electrical current is applied
- Activation of A Beta fibers which in turn activate inhibitory interneurons and inhibit C fibers from carrying nociceptive input
- Afferent inhibition is theory behind PNS
- Chronic pain arising from the peripheral nerve increases the local concentration of mediators such as endorphins and prostaglandins, which leads to increases in blood flow
  - PNS may have a direct effect on reducing this increased concentration of bio-inflammatory mediators, blood flow and pain transmission

Deer et al. A review of the bioelectronic implications of stimulation of the peripheral nervous system for chronic pain conditions. Bioelectronic Medicine. 2020; 6:9

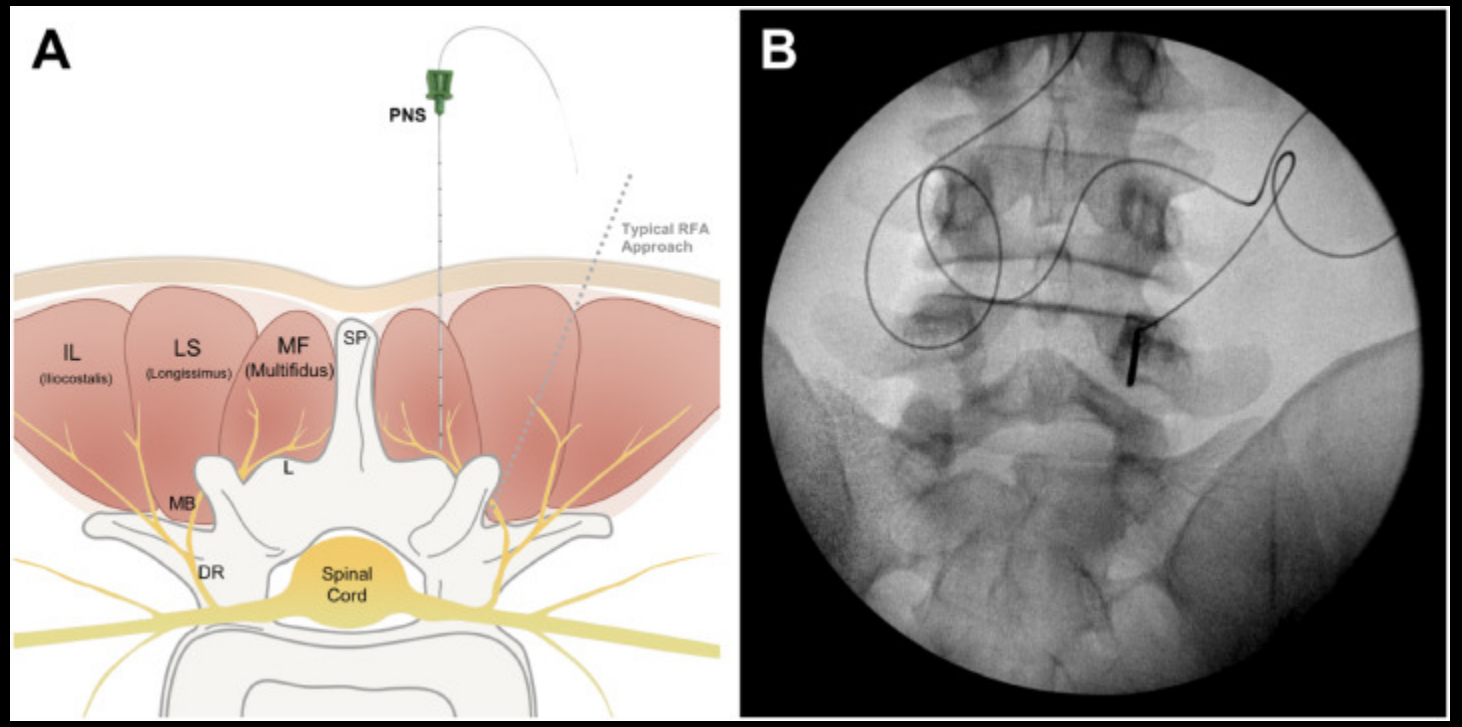
PNS Evidence

- Mostly case reports
- RCT’s are in the process of enrolling with these companies

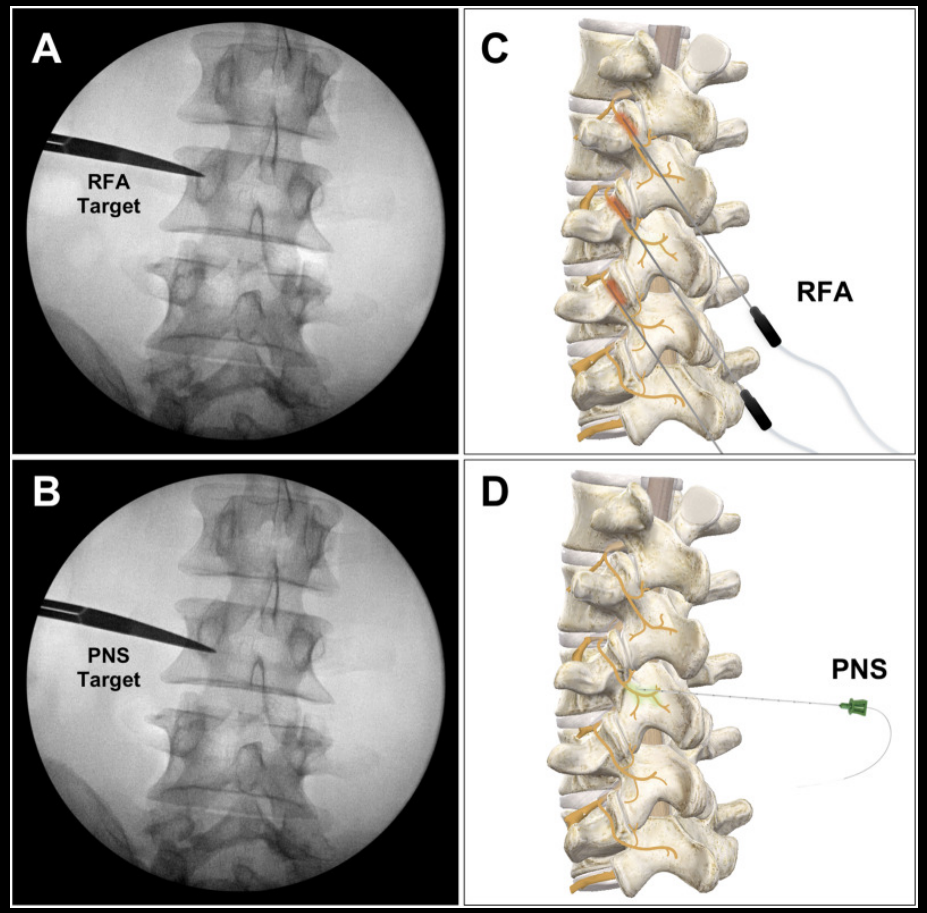
PNS As a Treatment for Low Back Pain

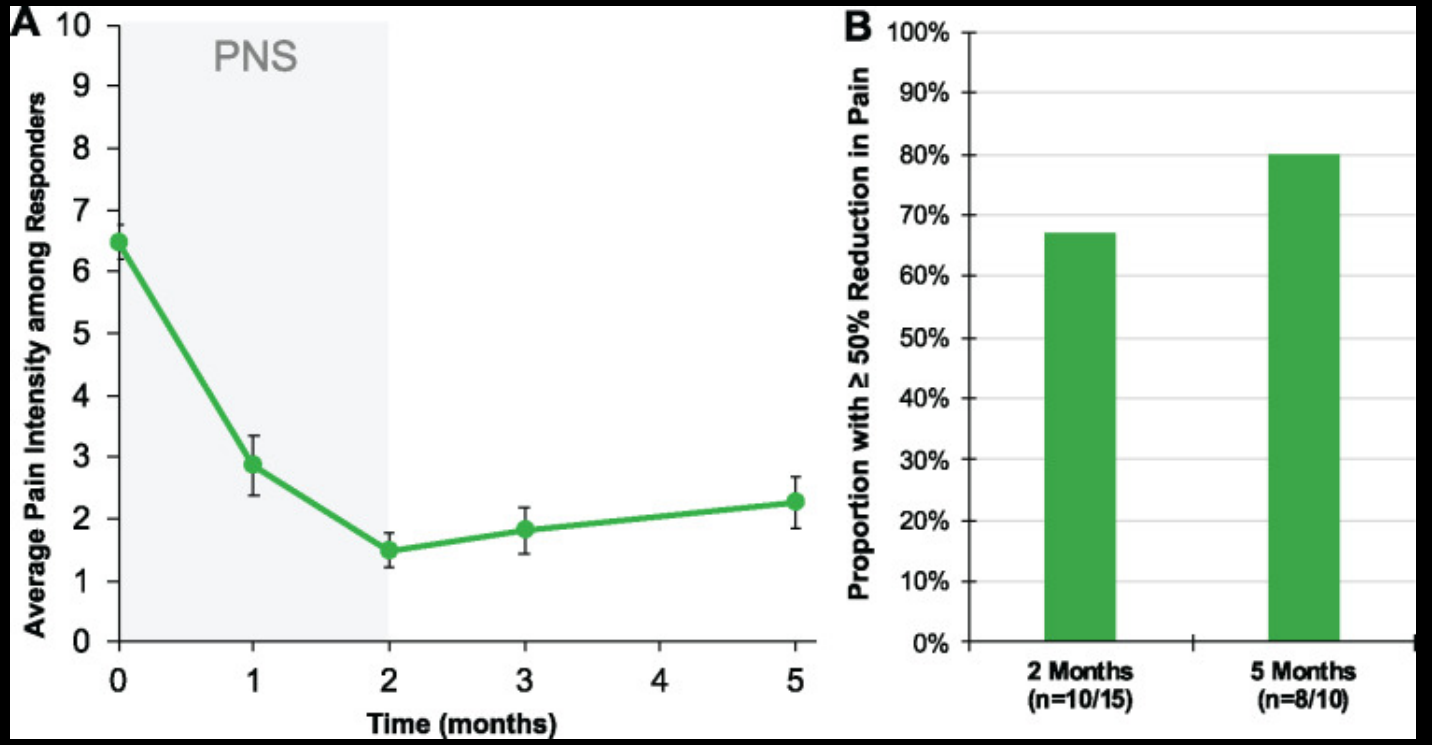
- Percutaneous Peripheral Nerve Stimulation of the Medial Branch Nerves for the Treatment of Chronic Axial Back Pain in Patients After Radiofrequency Ablation. Deer et al. Pain Medicine 2021 Mar 18;22(3):548-560.
  - Methods: Individuals with a return of chronic axial pain after radiofrequency ablation underwent implantation of percutaneous PNS leads targeting the medial branch nerves. Stimulation was delivered for up to 60 days, after which the leads were removed. Participants were followed up to 5 months after the start of PNS. Outcomes included pain intensity, disability, and pain interference.

PNS for Low Back Pain



PNS for Low Back Pain





PNS for Low Back Pain

- Results: Highly clinically significant (≥50%) reductions in average pain intensity were reported by a majority of participants (67%, n = 10/15) after 2 months with PNS, and a majority experienced clinically significant improvements in functional outcomes, as measured by disability (87%, n = 13/15) and pain interference (80%, n = 12/15). Five months after PNS, 93% (n = 14/15) reported clinically meaningful improvement in one or more outcome measures, and a majority experienced clinically meaningful improvements in all three outcomes (i.e., pain intensity, disability, and pain interference).

Real World Evidence of Sustained Improvements Following Percutaneous PNS: A Retrospective Cross-Sectional Follow-Up Survey of 354 Patients

Pingree, MJ, MD[1]; Hurdle, MFB, MD[2]; Spinner, DA, DO[3]; Valimahomed, A, MD[4]; Crosby ND, PhD[5], Boggs JW, PhD[5]

[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Jacksonville, FL; [3]Mount Sinai Health System, NY, NY; [4]Gramercy Pain Center, Holmdel, NJ; [5]SPR Therapeutics, Cleveland, OH

ASPN
THE AMERICAN SOCIETY of PAIN & NEUROSCIENCE

BACKGROUND

- A percutaneous PNS system was designed to provide PNS treatment for up to 60 days without the need for permanent implantation of hardware.
- In prospective studies across multiple common pain indications, a majority of patients experienced sustained pain relief following up to 60-days of PNS treatment.[1-8]
- This retrospective, cross-sectional, follow-up survey of patients that previously underwent implantation of 60-day PNS presents the largest set of real-world data to date regarding the effectiveness and long-term impact of the 60-day PNS treatment.

METHODS

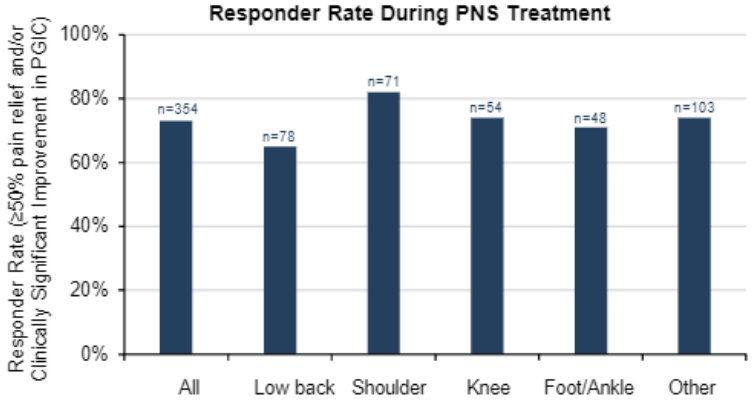
- Retrospective, cross-sectional, follow-up survey distributed via email by device manufacturer to 2,028 patients who underwent treatment from 03/2018 to 12/2020 and opted-in to provide data. Patients were compensated $15 for their time to complete the survey.
- Survey data were combined with baseline and treatment data from the existing database.
- Survey items included:
  - Worst pain (BPI-3)
  - Average pain (BPI-5)
  - Percent pain relief (BPI-8)
  - Changes in medication usage
  - Patient Global Impression of Change (PGIC)

- Responders defined by ≥50% reduction in patient-reported percent pain relief and/or clinically significant improvement in PGIC
- Studies suggest composite endpoints that account for multiple domains can provide a more comprehensive and sensitive assessment of patient responses.[9,10]

RESULTS

60-Day PNS Treatment Outcomes

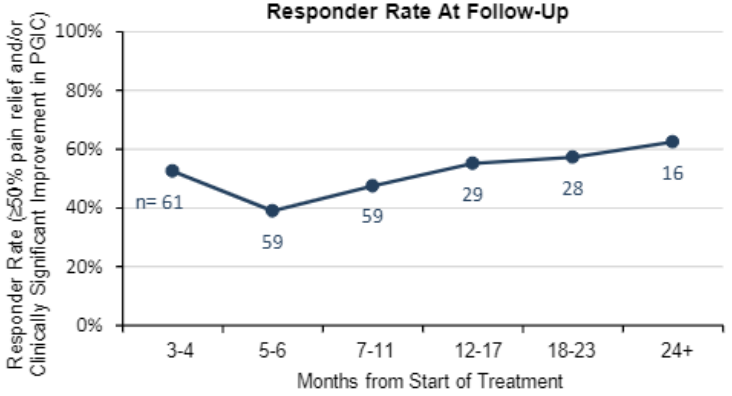
- 354 survey respondents with average duration of follow up of 7.6 months (ranging up to 30 months) from the start of PNS treatment.
- Most common treatment areas were low back, shoulder, knee, and foot/ankle.



- Average and worst pain scores were categorized by severity as mild/none (≤4), moderate (>4 and ≤6), or severe (>6).[11]
- Mean average pain (BPI-5) rating dropped from severe at baseline (6.2 ± 1.9) to a mild severity (3.5 ± 2.4).
- Mean worst pain (BPI-3) decreased from severe (8.8 ± 1.5) at baseline to moderate severity (5.5 ± 2.8).

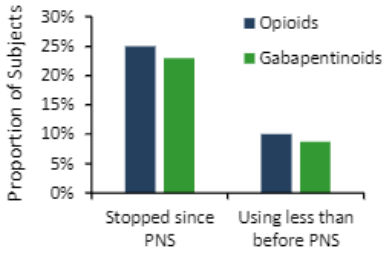
Long-term Follow-up Outcomes

- A majority of patients had sustained long-term improvements at the time of survey completion, including those 24+ months post-PNS.



Among those using opioids or gabapentin at baseline:

- 35% had stopped or reduced opioid usage at the time of the survey (n=56/160)
- 32% had stopped or reduced gabapentin usage at the time of the survey (n=58/183)



CONCLUSIONS

- This study presents the largest body of real-world evidence to-date supporting the prolonged effectiveness of 60-day PNS treatment for pain previously published across multiple clinical trials.
- These real-world data coupled with published clinical trial outcomes support the use of a 60-day PNS treatment across a wide range of pain conditions in broader clinical practice.

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PainWeek

Percutaneous Peripheral Nerve Stimulation for Chronic Pain in Amputees: 12-Month Follow-Up of a Multicenter, Randomized, Placebo-Controlled Trial

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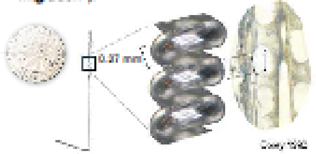
INTRODUCTION

- Peripheral nerve stimulation (PNS) has historically been used to treat a wide range of chronic pain states but has generally required a short trial (4-7 days) followed by implantation of a permanent system for sustained relief.[1]
- A recent study found that a 60-day PNS treatment provided significant relief of post-amputation pain.[2,3] This work presents long-term secondary outcomes from the study up to 12 months from the start of the 60-day treatment.

MINIMALLY INVASIVE, PERCUTANEOUS PNS:

- Wearable stimulator and percutaneous fine-wire (<0.3 mm), coiled lead (designed to anchor in tissue) could mitigate infection risk[4] and other limitations of conventional neuromodulation (e.g., invasiveness, lead migration[5]).

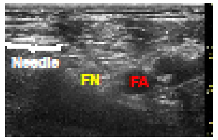


MATERIALS & METHODS

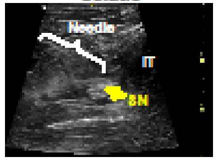
Participants: 28 traumatic lower extremity amputees with baseline residual (RLP) and/or phantom limb pain (PLP) ≥ 4 provided written consent and enrolled. Participants were randomized 1:1.

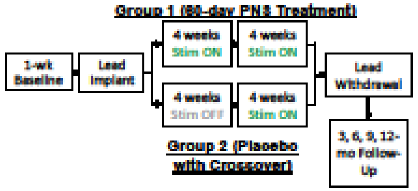
Lead Implantation: Percutaneous PNS leads remotely targeted the sciatic and/or femoral nerves proximal to the regions of RLP and PLP under ultrasound guidance.

Femoral



Sciatic





Long-Term Follow-up (secondary endpoints):

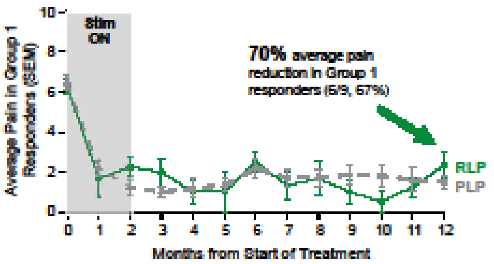
- Average residual and phantom limb pain (BPI-5)
- Average interference of RLP and PLP (BPI-9)
- Beck Depression Inventory II (BDI-II)

All statistical analyses conducted by an independent biostatistician.

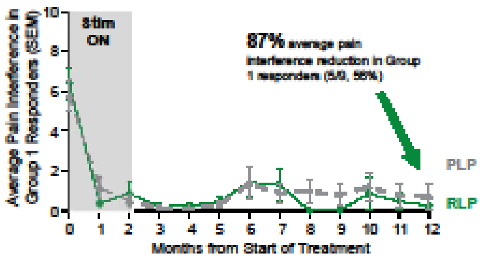
FN = femoral nerve; FA = femoral artery; SN = sciatic nerve; IT = ischial tuberosity

RESULTS

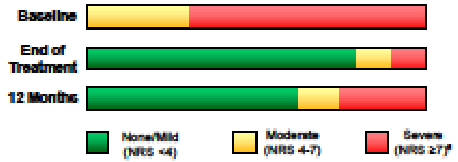
Average Pain

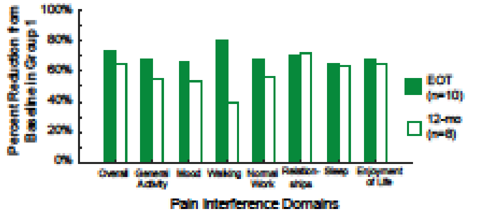


Average Pain Interference



Severity of Worst Region of Pain (RLP or PLP):





10/12 (83%) participants in Group 1 were reduced one or more severity categories including 9 (75%) to Mild or No Pain.
5/14 (36%) in Group 2 were reduced by one category but none (0%) were reduced below Moderate Pain at the end of the placebo period.

__Depression:__ Average reductions in BDI-II score in Group 1 (32% at EOT, 16% at 12 months) were clinically significant and statistically greater than Group 2 at the end of the placebo period (8% increase, $p<0.035$).

__Safety:__ No serious or unanticipated adverse device effects were reported

DISCUSSION

- Percutaneous PNS delivered for up to 60 days may provide significant and enduring pain relief through one year, enabling subsequent improvements in function and quality of life.
- Potential mechanism includes activation of large diameter sensory fibers that generates non-painful input focally from the region of pain to reverse maladaptive expansion of cortical nociceptive representations.
- A 60-day PNS treatment may preclude the need for a permanent implant in some patients.

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Questions