INTRODUCTION

Clinical Evidence

Disease State: Complex Regional Pain Syndrome

DRG Patient Selection

Case Studies

DISCLOSURES

- Consultant - St. Jude Medical
- Consultant - Horizon Pharma

OUTLINE

DORSAL ROOT GANGLION (DRG) STIMULATION
The DRG: A collection of pseudounipolar cell bodies of neurons surrounded by glial cells and the axons of the DRG sensory cells that form the primary afferent sensory nerve.

**THE PECULIAR PROPERTIES OF THE DORSAL ROOT GANGLION**

- **Special structure**: DRG neurons have a peculiar pseudounipolar morphology—unique in the nervous system.
- **Unique function**: T-junctions act as the filter function for cell transduction and potential neuromodulation target.
- **Highly organized and selective**: Small and large soma consistent with axonal specificity of sensory transduction therefore dictating electrophysiological selectivity.
- **Specialized membrane characteristics**: Somata of many DRG neurons have the specialized membrane characteristics necessary for spikes initiation, and some are even capable of repetitive firing.
- **Minimal CSF**: Subdural structure with minimal surrounding CSF unlike the spinal cord.

**THE IMPORTANCE OF THE T-JUNCTION**

T-junctions acting as a barrier to AP propagation to DRG.
PATHOLOGICAL CASCADE LEADING TO NEUROPATHIC PAIN

Dorsal horn
- Increased neural discharge from primary sensory neurons
- Increased EAA release
- Increased neural peptide release

DRGs
- Activate surrounding glia
- Release proinflammatory cytokines
- Ultimately stimulates neurons
- Increased membrane excitability

Nerve Injury at periphery
- Increased neural peptide release

The T-junction acts as a low-pass filter such that stimulation can inhibit the propagation of action potentials


WHY TARGET THE DRG?

- Known mechanisms & processes: DRGs are a 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

WHY TARGET THE DRG?

- Well mapped & organized to corresponding anatomies – allowing for highly focused treatment of pain

LIMITATIONS OF CONVENTIONAL SCS

- Unstable Stimulation
  - Susceptible to body position due to variations in distance between stimulation lead & target
  - Lead migrations rates (percutaneous) reported between 9-27% 1,2

- Unspecific Stimulation
  - Broad Stimulation Coverage: targeting spinal cord sensory nerves
  - Unspecific to anatomical location of pain/disease
  - Energy is delivered to multiple types of nerves, not just pain- or disease-specific nerves

- High Energy Usage
  - Significant energy loss to surrounding anatomy (i.e. cerebral spinal fluid, CSF) before stimulation reaches target in spinal cord

IS DESIGNED TO ADDRESS LIMITS OF CONVENTIONAL SCS

- Limited Cerebrospinal Fluid (CSF) around the DRG allows the leads to be closer to the anatomical target; potentially producing less postural effects (compared to conventional SCS) 1,2

- Separation of sensory & motor nerve fibers may prevent unintentional stimulation
  - Well mapped & organized to corresponding anatomies – allowing for highly focused treatment of pain

- Limited Cerebrospinal Fluid (CSF) around the DRG allows the leads to be closer to the anatomical target; potentially less energy needed to stimulate sensory fibers (compared to conventional SCS)
A Prospective, Randomized, Multi-Center, Controlled Clinical Trial to Assess the Safety and Efficacy of the Axium™ Neurostimulator System in the Treatment of Chronic Pain

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

Implant

6 Month Visit

9 Month Visit

12 Month Visit

1 Month Visit

15% VAS reduction
Paresthesia Intensity (post-hoc)

A subject was considered a primary endpoint success if the subject met 3 criteria:
- ≥50% pain relief in their primary area of pain at the end of the trial phase, and
- ≥50% pain relief in their primary area of pain at the 3 month visit post implant, and
- Freedom from stimulation-induced neurological deficit through 3 months

Statistically powered for non-inferiority and superiority

Secondary endpoints

1. Paresthesia Intensity (post-hoc)

Tertiary endpoints

1. Stimulation specificity
2. HR-QoL (SF-36)
3. Psychological disposition (Profile of Mood States: POMS)
4. Functional Status (BPQ)
5. Subject satisfaction

Levy R and Deer T. NANS 2015

BASELINE DEMOGRAPHICS

<table>
<thead>
<tr>
<th>DRG (n=76)</th>
<th>Control (n=76)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td></td>
<td>52.4 (12.7)</td>
<td>52.5 (11.5)</td>
</tr>
<tr>
<td>Gender (n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37/76 (48.7)</td>
<td>37/76 (48.7)</td>
</tr>
<tr>
<td>Female</td>
<td>39/76 (51.3)</td>
<td>39/76 (51.3)</td>
</tr>
<tr>
<td>Duration of Lower Limb Pain (years)</td>
<td>7.5 (7.5)</td>
<td>6.8 (7.6)</td>
</tr>
<tr>
<td>Primary Diagnosis (n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex Regional Pain Syndrome</td>
<td>44/76 (57.9)</td>
<td>43/76 (56.6)</td>
</tr>
<tr>
<td>Peripheral Causalgia</td>
<td>32/76 (42.1)</td>
<td>33/76 (43.4)</td>
</tr>
</tbody>
</table>

Levy R and Deer T. NANS 2015

ACCURATE STUDY: OUTCOMES
A subject was considered a primary endpoint success if they met 3 criteria:
- ≥50% pain relief in their primary area of pain at the end of the trial phase, and
- ≥50% pain relief in their primary area of pain at the 3 month visit post implant, and
- Freedom from stimulation-induced neurological deficit through 3 months

IMPLANT ONLY

Superiority Achieved

P-value for non-inferiority at 3 months <0.0001
P-value for superiority at 3 months 0.0011
Percentage subjects obtaining at least 80% pain relief

Implant Only responders at 3 months

Trend towards significance at 3 months (p<0.055)

HIGH RESPONDERS >80% VAS IMPROVEMENT POST-HOC ANALYSIS

PARESTHESIA-FREE ANALGESIA

At 12 months, more than a third of DRG stimulation patients experienced no paresthesia, while having, on average an 86% reduction in pain, suggesting that DRG stimulation may provide paresthesia-free analgesia.*

DRG Control

<table>
<thead>
<tr>
<th>Subjects with Paresthesia</th>
<th>Subjects without Paresthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Mean VAS Decrease (SD)</td>
<td>81.4 (22.8) 86.0 (25.3) 79.2 (24.9) 48.1 (50.8)</td>
</tr>
<tr>
<td>% Median VAS Decrease</td>
<td>89.1 100.0 83.0 51.2</td>
</tr>
</tbody>
</table>

Difference between means 95% CI

-4.6 (-18.2, 8.9)

-22.1 (-10.2, 54.5)

DRG Stimulation offered patients:

- Sustained and superior pain relief: After 12 months, significantly more DRG stimulation patients achieved pain relief and treatment success versus control SCS (74.2% vs. 53.0%)
- Improved therapeutic targeting: DRG stimulation patients reported better stimulation targeting in their area of pain without extraneous paresthesia (94.5% vs. 61.2%)
- Enhanced quality of life and functionality: DRG stimulation patients experienced improved quality of life measures, psychological disposition and physical/activity levels*
- Reduced paresthesia: At 12 months, more than a third of DRG stimulation patients experienced no paresthesia and had on average an 86% reduction in pain, suggesting that DRG stimulation may provide paresthesia-free analgesia.*

The 12-month outcome data have confirmed DRG stimulation provides long-term, sustained and superior pain relief over traditional SCS for patients with chronic lower limb pain due to Complex Regional Pain Syndrome (CRPS) and peripheral causalgia.

ACCURATE IDE CONCLUSIONS

At 12 months, more than a third of DRG stimulation patients experienced no paresthesia, while having, on average an 86% reduction in pain, suggesting that DRG stimulation may provide paresthesia-free analgesia.*
DISEASE STATE:
Complex Regional Pain Syndrome

WHAT IS COMPLEX REGIONAL PAIN SYNDROME (CRPS)?
Historically also known as causalgia, reflex sympathetic dystrophy (RSD)®.

“CRPS is a chronic pain condition characterized by continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of pain after trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor edema, and/or trophic findings.”

International Association for the Study of Pain

PATHOPHYSIOLOGY OF CRPS IS NOT FULLY UNDERSTOOD

Multifactorial process involving both peripheral and central mechanisms

- Possible mechanisms involved in CRPS
- Nerve injury
- Ischemic-reperfusion injury or oxidative stress
- Central sensitization
- Peripheral sensitization
- Altered sympathetic nervous system function or sympatho-afferent coupling
- Inflammatory and immune related factors
- Brain changes
- Genetic factors
- Psychological factors and disease
CLINICAL CHARACTERISTICS CHANGE OVER TIME

**Acute phase – mixture of noxious sensations and sensory loss**

- Extremely painful limb
- Redness
- Swelling
- Allodynia
- Hyperalgesia
- Changes in sweating
- Changes in hair and nail growth
- Muscle weakness
- Mechanical and thermal hyperalgesia
- Reduction in voluntary motor control
- Hypoesthesia, hypalgesia, and hypothermesthesia

**Months – clinical features spread proximally**

- Warm limb often becomes cold
- Dystonia, tremor, and myoclonus may develop
- Activity of the limb exacerbates signs and symptoms
- Clinical features may spread proximally (but not distally) and emerge on the opposite or ipsilateral limb
- Urological symptoms
- Syncope
- Mild cognitive defects

**> 5 years**

- Allodynia
- Hyperalgesia
- Changes in sweating
- Changes in hair and nail growth
- Muscle weakness
- Mechanical and thermal hyperalgesia
- Reduction in voluntary motor control
- Hyperpathia
- Hypoesthesia, hypalgesia, and hypothermesthesia

Objective: Prospective RCT to determine whether treatment of CRPS with conventional SCS and PT is more effective than PT alone.

5 year analysis compared 31 patients with SCS device and 13 patients in control group.

After 3 years, pain-alleviating effect of conventional SCS in CRPS patients is no longer statistically significant.

LIMITED CLINICAL EVIDENCE TO SUPPORT TRADITIONAL CRPS TREATMENT REGIMENS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Category</th>
<th>Supporting Clinical Studies Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multidisciplinary treatment</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>PT and OT</td>
<td>Standard</td>
<td>Positive</td>
</tr>
<tr>
<td>Oral corticosteroids for acute CRPS</td>
<td>Standard</td>
<td>Positive</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Standard</td>
<td>Equivocal</td>
</tr>
<tr>
<td>Analgesic antidepressants</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>Transdermal lidocaine</td>
<td>Standard</td>
<td>None</td>
</tr>
<tr>
<td>Sympathetic nervous system blocks</td>
<td>Standard</td>
<td>Negative</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Uncommon</td>
<td>Positive</td>
</tr>
<tr>
<td>Topical dimethylsulfoxide (DMSO)</td>
<td>Uncommon</td>
<td>Positive (warm CRPS)</td>
</tr>
<tr>
<td>Oral N-acetylcysteine</td>
<td>Uncommon</td>
<td>Positive (cold CRPS)</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Emerging</td>
<td>Positive</td>
</tr>
<tr>
<td>Subanesthetic intravenous ketamine</td>
<td>Emerging</td>
<td>Positive</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>Emerging</td>
<td>Positive</td>
</tr>
<tr>
<td>Oral tadalafil</td>
<td>Emerging</td>
<td>Positive</td>
</tr>
<tr>
<td>Intrathecal baclofen (CRPS + dystonia)</td>
<td>Emerging</td>
<td>Positive</td>
</tr>
<tr>
<td>Low dose oral naltrexone</td>
<td>Emerging</td>
<td>None</td>
</tr>
</tbody>
</table>
APPROVED INDICATIONS FOR DRG STIMULATION THERAPY

CRPS I (RSD)
Characterized by extreme pain out of proportion to the original injury with evidence of allodynia and hyperalgesia.

CRPS II (Peripheral Causalgia)
Painful condition arising from damage to a nerve\(^2\). This neuropathic condition results in chronic pain, generally restricted to the innervation pattern of the damaged nerve(s).

Common example: Ilioguinal neuralgia following hernia repair.

But, Who Are These Patients?


PATIENT IDENTIFICATION

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>CRPS I (RSD)</th>
<th>CRPS II (Peripheral Causalgia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Surgical Nerve Injury e.g. arthroscopy, joint replacement, complex fractures, amputation, hernia repair, nerve ablation</td>
<td>Radiation/Chemical Nerve Injury e.g. chemotherapy, radiation therapy, Crush Injury e.g. car crash accidents, complex fractures, fibular plateau, triple talar ankle</td>
</tr>
<tr>
<td>Anatomical Pain Area</td>
<td>Hip</td>
<td>Groin</td>
</tr>
</tbody>
</table>

Surgical Nerve Injury
- e.g. arthroscopy, joint replacement, complex fractures, amputation, hernia repair, nerve ablation

Radiation/Chemical Nerve Injury
- e.g. chemotherapy, radiation therapy

Crush Injury
- e.g. car crash accidents, complex fractures, fibular plateau, triple talar ankle

Anatomical Pain Area
- Hip
- Groin
- Knee
- Ankle
- Foot
Unique pain processes and anatomical considerations make the Dorsal Root Ganglion (DRG) an ideal interventional target to treat various focal chronic pain conditions:

- Well mapped & organized to corresponding anatomies – allowing for highly focused treatment of pain
- Ability to adapt current SCS needle techniques due to predictable and accessible location of the DRG
- More precise targeting and less energy requirements due to limited CSF around the DRG
- Prevention of unintentional stimulation due to the separation of sensory and motor fibers

The ACCURATE study, the largest clinical trial ever performed in CRPS patients, showed that DRG stimulation provided:

- Sustained and superior pain relief
- Improved therapeutic targeting

Further clinical trials should be conducted to fully understand the efficacy of DRG stimulation for the treatment of chronic intractable pain in other anatomical locations.

**AXIUM™ NEUROSTIMULATION SYSTEM**

Axium™ Neurostimulation System is the first and only FDA approved implantable neuromodulation system that targets the Dorsal Root Ganglion (DRG).

Major components:
- Trial Neurostimulator (not shown)
- Implantable Neurostimulator Kit
- 50cm and 90cm SlimTip™ Trial Lead Kits
- 50cm and 90cm SlimTip Implant Lead Kits
- 50cm Lead Extension Kit
- Patient Programmer Kit (not shown)
- Clinical Programmer Kit
- 22cm Small and Big Curve Delivery Sheath Kits

**CASE STUDIES**
CASE 1

- 34 year old female that presents today with complaints of right foot/ankle pain which began approximately 8 years ago following a MVA in which her right foot/ankle were pinned after a front end collision.
- She reports that the pain does not radiate.
- The pain began suddenly and is continuous in nature.
- She describes the pain as constant, dull, ache, numbness, tingling, pressure like, tender.
- She reports a current level of pain as 7/10 which at worst is rated as a 9/10 and at best is rated as a 5/10.
- She reports that pain is worsened by increased activity, walking, prolonged standing, driving, lifting, going down stairs
- She reports that pain is slightly better with lying down, resting, medication.
- She has been seen by primary care doctor, physical therapy, orthopedic, podiatrist, psychiatrist for previous treatment.
- She has tried anti-inflammatory, mobic, naproxen, ibuprofen, voltaren, neurontin, percocet, ultram/tramadol, lidoderm patch in the past.
- She has undergone 3 foot/ankle surgeries in the past with incomplete pain relief.

CASE 2

- 52 year old male that presents with complaints of right leg pain which began approximately 15 years ago.
- He reports the pain began as a result of work injury in which he had a fall onto his right leg while transferring a patient.
- He describes the pain as sharp, stabbing, shooting, throbbing, burning, aching, numbness, tingling.
- He reports a current level of pain as 5/10 which at worst is rated as a 8/10 and at best is rated as a 4/10.
- He reports that pain is worse with increased activity, walking, driving.
- He reports that pain is better with resting and medication.
- He has been seen by orthopedist for previous treatment.
- He has tried Morphine. He has tried Physical Therapy in the past.
- He has had imaging studies done within the past year including triple phase bone scan of LLE with findings consistent with Complex Regional Pain Syndrome.
Case 2

Patient is a 60 year old female that presents with complaints of bilateral leg, ankle, foot pain which began approximately 18 years ago and left hand/wrist pain which began 9 years ago.

She reports the pain began as a result of no inciting event.

She has been confirmed to have complex regional pain syndrome of her left wrist/hand and the right lower leg.

She reports that the pain does not radiate.

The pain began suddenly and is continuous in nature.

She describes the pain as sharp, stabbing, shooting, throbbing, burning, aching, numbness, tingling.

She reports a current level of pain as 7/10 which at worst is rated as a 9/10 and at best is rated as a 5/10.

She reports that pain is worsened by increased activity, walking, standing, lifting.

She reports that pain is better with resting.

She has been seen by primary care doctor, neurosurgeon, psychiatrist, pain physician for previous treatment.

She has tried neurontin, oxycontin, morphine, percocet, vicodin, lidoderm.

She has tried spinal injections, spine surgery, and dorsal column stimulators for CRPS in her left hand and bilateral foot/ankle which is no longer providing adequate pain relief.

Case 3

Patient is a 60 year old female that presents with complaints of bilateral leg, ankle, foot pain which began approximately 18 years ago and left hand/wrist pain which began 9 years ago.

She reports the pain began as a result of no inciting event.

She has been confirmed to have complex regional pain syndrome of her left wrist/hand and the right lower leg.

She reports that the pain does not radiate.

The pain began suddenly and is continuous in nature.

She describes the pain as sharp, stabbing, shooting, throbbing, burning, aching, numbness, tingling.

She reports a current level of pain as 7/10 which at worst is rated as a 9/10 and at best is rated as a 5/10.

She reports that pain is worsened by increased activity, walking, standing, lifting.

She reports that pain is better with resting.

She has been seen by primary care doctor, neurosurgeon, psychiatrist, pain physician for previous treatment.

She has tried neurontin, oxycontin, morphine, percocet, vicodin, lidoderm.

She has tried spinal injections, spine surgery, and dorsal column stimulators for CRPS in her left hand and bilateral foot/ankle which is no longer providing adequate pain relief.