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DISCLOSURES

-Consultant - St. Jude Medical

-Consultant - Horizon Pharma

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OUTLINE

Introduction

Clinical Evidence

Disease State: Complex Regional Pain Syndrome

DRG Patient Selection

Case Studies

DRG: REVIEW OF ANATOMY

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

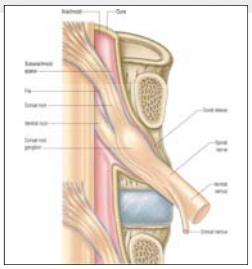


Image from: Gray's Anatomy (2005). Standing, S. (Ed.).

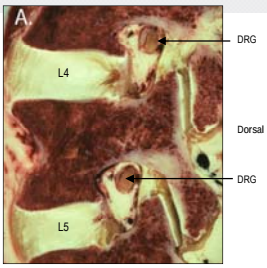
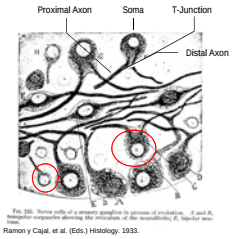


Image from: Hogan Q. Reg Anesth Pain Med. 2010.

THE PECULIAR PROPERTIES OF THE DORSAL ROOT GANGLION

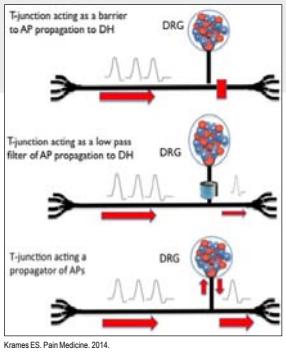
- Special structure: DRG neurons have a peculiar pseudounipolar morphology – unique in the nervous system
- Unique Function: T-junctions act as the filter function for cell transduction and potential neuromodulation target
- Highly Organized and Selective: Small and large soma consistent with axonal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

Devor, Pain Supplement 6. 1999.



Ramon y Cajal, et al. (Eds.) Histology. 1933.

THE IMPORTANCE OF THE T-JUNCTION



Krames ES. Pain Medicine. 2014.

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PATHOLOGICAL CASCADE LEADING TO NEUROPATHIC PAIN

Dorsal horn
- Increased neuronal discharge from primary sensory neurons
- Increase EAA release
- Increased ATP, NO release
- Increased neural peptide release

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

Nerve Injury at periphery

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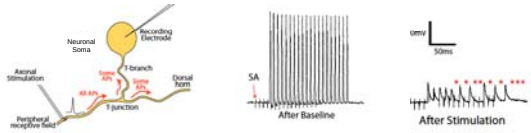
DRG STIMULATION MAY INCREASE FILTERING AT THE T-JUNCTION OF PRIMARY SENSORY NEURONS

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



Gemes G, et al. J Physiology. 2013.

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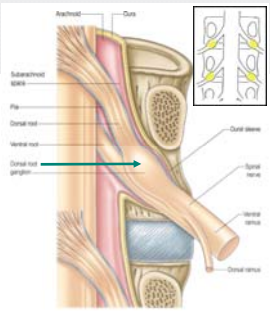
WHY TARGET THE DRG?



- 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

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

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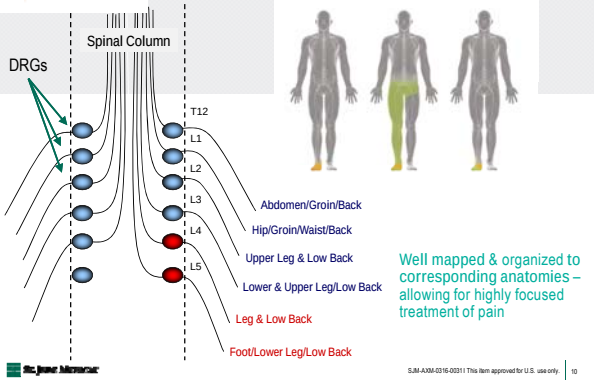
WHY TARGET THE DRG?



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

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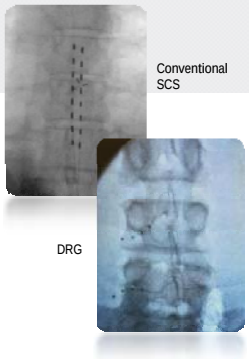
LIMITATIONS OF CONVENTIONAL SCS

Unstable Stimulation
- Susceptible to body position due to variations in distance between stimulation lead & target
- Lead migrations rates (percutaneous) reported between 9-27%[1,2,3]

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



Conventional SCS

DRG

1. Deer et al. Neuromodulation 2014.
2. Cameron T. J Neurosurg. 2004
3. Kim DD, et al. Pain Physician. 2011

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IS DESIGNED TO ADDRESS LIMITS OF CONVENTIONAL SCS

Unstable Stimulation

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]

Unspecific Stimulation

Separation of sensory & motor nerve fibers may prevent unintentional stimulation

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

High Energy Usage

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)

1. Van Buyten, J. P., et al. Pain Practice 2015..
2. Liem, L., et al. Neuromodulation 2015.

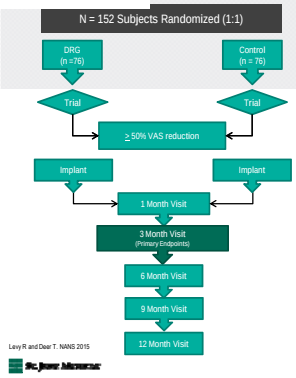
CLINICAL EVIDENCE

ACCURATE STUDY

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

URATE STUDY: OBJECTIVE AND STUDY DESIGN



- 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

Levy R and Deer T. NANS 2015

ACCURATE STUDY: ENDPOINTS

Primary endpoint: composite safety and efficacy* *Statistically powered for non-inferiority and superiority	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
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 (BPI) 5. Subject satisfaction

Levy R and Deer T. NANS 2015

BASELINE DEMOGRAPHICS

	DRG (n=76)	Control (n=76)	p-value
	Mean (SD)	Mean (SD)	
Age (years)	52.4 (12.7)	52.5 (11.5)	0.936
Gender (n/N (%))			
Male	37/76 (48.7)	37/76 (48.7)	
Female	39/76 (51.3)	39/76 (51.3)	1.000
Duration of Lower Limb Pain (years)	7.5 (7.5)	6.8 (7.6)	0.557
Primary Diagnosis (n/N (%))			
Complex Regional Pain Syndrome	44/76 (57.9)	43/76 (56.6)	
Peripheral Causalgia	32/76 (42.1)	33/76 (43.4)	0.870

Levy R and Deer T. NANS 2015

ACCURATE STUDY: OUTCOMES

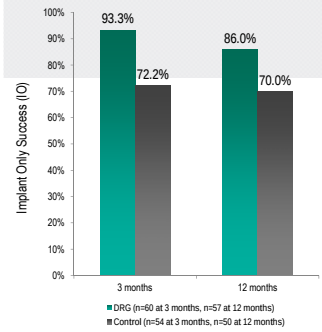
Levy R and Deer T. NANS 2015

PRIMARY ENDPOINT

- 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

Levy R and Deer T. NANS 2015

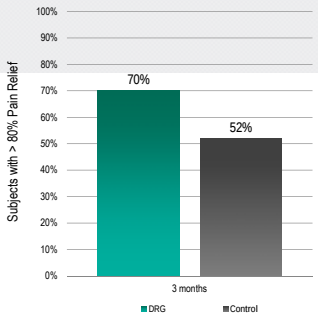
IMPLANT ONLY



Superiority Achieved	
P-value for non-inferiority at 3 months	<0.0001
P-value for superiority at 3 months	0.0011

Levy R and Deer T. NANS 2015

HIGH RESPONDERS >80% VAS IMPROVEMENT POST-HOC ANALYSIS



- Percentage subjects obtaining at least 80% pain relief
- Implant Only responders at 3 months
- Trend towards significance at 3 months (p<0.055)

Levy R and Deer T. NANS 2015

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	
	Subjects with Paresthesia	Subjects without Paresthesia	Subjects with Paresthesia	Subjects without Paresthesia
N	35	19	43	6
% Mean VAS Decrease (SD)	81.4 (22.8)	86.0 (25.3)	70.2 (34.9)	48.1 (50.8)
% Median VAS Decrease	89.1	100.0	83.0	51.2
Difference between means 95% CI	-4.6 (-18.2, 8.9)		22.1 (-10.2, 54.5)	

* The instructions for use for the Control device requires the device be programmed for subjects to receive paresthesia. In addition, this endpoint was not adequately powered to detect significant differences in pain relief for subjects without and without paresthesia in this cohort.

Levy R and Deer T. NANS 2015

ACCURATE IDE CONCLUSIONS

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.

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.*

Levy R and Deer T. NANS 2015

* Groups were not statistically powered to show superiority over traditional tonic stimulation

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

*Please note that in 1994, a consensus group of pain medicine experts gathered by the International Association for the Study of Pain (IASP) reviewed diagnostic criteria and agreed to rename reflex sympathetic dystrophy (RSD) and causalgia, as complex regional pain syndrome (CRPS) types I and II, respectively.

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 disuse

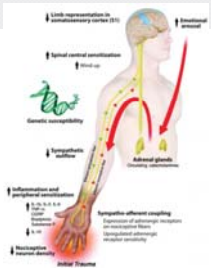


Image from: Bruehl S. Anesthesiology 2010.*

Bruehl S. BMJ 2015.

*DRG stimulation therapy with the Axium™ Neurostimulator system is not indicated for areas outside of the lower limbs.

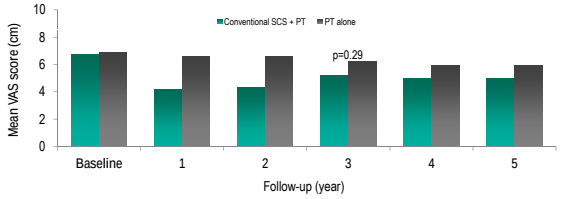
CLINICAL CHARACTERISTICS CHANGE OVER TIME

Acute phase – mixture of noxious sensations and sensory loss	Months – clinical features spread proximally	> 5 years
▪ Extremely painful limb ▪ Redness ▪ Warm (can quickly become cold) ▪ Swollen ▪ Allodynia ▪ Hyperalgesia ▪ Changes in sweating ▪ Changes in hair and nail growth ▪ Muscle weakness ▪ Mechanical and thermal hyperalgesia ▪ Reduction in voluntary motor control ▪ Hyperpathia ▪ Hypoesthesia, hypoalgesia, and hypothermesthesia	▪ 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

Marinus J, et al. Lancet Neurology 2011.

PAIN RELIEVING EFFECTS OF CONVENTIONAL SCS DIMINISH OVER TIME

- 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



Kemler MA, et al. NEJM 2000, 2006.

LIMITED CLINICAL EVIDENCE TO SUPPORT TRADITIONAL CRPS TREATMENT REGIMENS

Treatment	Category	Supporting Clinical Studies Status
Multidisciplinary treatment	Standard	None
PT and OT	Standard	Positive
Oral corticosteroids (for acute CRPS)	Standard	Positive
Anticonvulsants	Standard	Equivocal
Analgesic antidepressants	Standard	None
Transdermal lidocaine	Standard	None
Opioids	Standard	None
Sympathetic nervous system blocks	Standard	Negative
Conventional spinal cord stimulation	Standard	Positive, but < 5 year efficacy
Pain focused on psychological therapy	Standard	None
Graded motor imagery or mirror therapy	Uncommon	Positive
Calcitonin	Uncommon	Positive
Topical dimethylsulfoxide (DMSO)	Uncommon	Positive (warm CRPS)
Oral N-acetylcysteine	Uncommon	Positive (cold CRPS)
Bisphosphonates	Emerging	Positive
Subanesthetic intravenous ketamine	Emerging	Positive
Intravenous immunoglobulin	Emerging	Positive
Oral tadalafil	Emerging	Positive
Intrathecal baclofen (CRPS + dystonia)	Emerging	Positive
Low dose oral naltrexone	Emerging	None

DRG THERAPY PATIENT SELECTION

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[1,2]. This neuropathic condition results in chronic pain, generally restricted to the innervation pattern of the damaged nerve(s).

Common example: Ilioinguinal neuralgia following hernia repair.

But, Who Are These Patients?

1. van Eijs F, Stanton-Hicks M, Van Zundert J, Faber CG, Lubenow TR, Mekhail N, van Kleef M, Huygen F. Pain Pract. 2011 Jan-Feb;11(1):70-87. Epub 2010 Aug 27.
2. Bonica's Management of Pain. Scott M. Fishman , Jane C. Ballantyne , James P. Rathmell (Eds.). Lippincott Williams & Wilkins, 2010.

PATIENT IDENTIFICATION

Diagnosis	
CRPS I (RSD)	CRPS II (Peripheral Causalgia)
Cause	
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/work accidents, complex fractures, tibial plateau, trimaleolar ankle	
Anatomical Pain Area	
Hip	Groin
Knee	Ankle
Foot	

DRG STIMULATION THERAPY: SUMMARY

- 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:

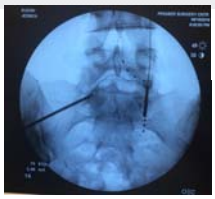
- Trial Neurostimulator (not shown)
- Implantable Neurostimulator Kit
- 50cm and 90cm SlimTip™ Trial Lead Kits
- 50 cm and 90cm SlimTip Implant Lead Kits
- 50cm Lead Extension Kit
- Patient Programmer Kit (not shown)
- Clinical Programmer Kit
- 22cm Small and Big Curve Delivery Sheath Kits

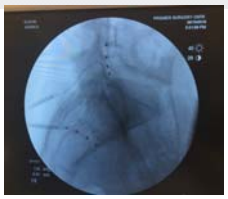
CASE STUDIES

CASE 1

- 34 year old female that presents today with complaints of right foot/ankle pain which began approximately 8 year(s) 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,achy, 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, robaxin, neurontin, percocet, ultram/ tramadol, lidoderm patch in the past.
- She has undergone 3 foot/ankle surgeries in the past with incomplete pain relief.

CASE 1





CASE 2

- Patient is a 52 year old male that presents with complaints of right leg pain which began approximately 15year(s) 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 reports that the pain does radiate from knee to foot
- The pain began gradually and is continuous in nature.
- 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 worsened by 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.

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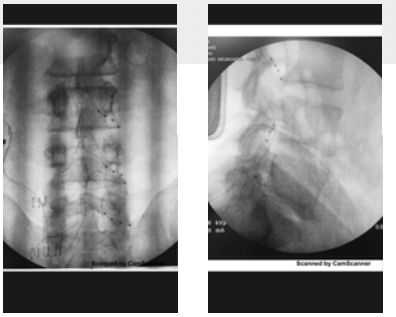
CASE 2



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CASE 3

- Patient is a 60 year old female that presents with complaints of billateral leg , ankle, foot pain which began approximately 18 year(s) 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.

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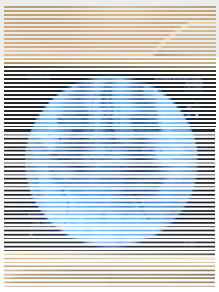
CASE 3



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