Objectives

- Recognize procedural interventions for spinal and visceral pain
- Describe advanced procedures for persistent pain
- Identify patients who may benefit from interventional procedures, spinal cord stimulators and/or intrathecal pumps
- Describe cost effectiveness and the advantages of spinal cord stimulators and intrathecal pumps
- Recognize the clinical evidence for using spinal cord stimulators and intrathecal pumps in practice

Disclosures

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- Media Work: Algiatry, LLC
- This presentation contains references to off-label or investigational use of drugs or products
Precise delivery of small doses of electricity directly to targeted nerve sites

**Definitions**

- Neuromodulation: “Technology impacting on the neural interface”
- Process: inhibition, stimulation, modification, regulation or therapeutic alteration of activity, electrically or chemically, in the central, peripheral, or autonomic nervous systems
- Neuromodulation: inherently nondestructive, reversible and adjustable

**Neurostimulation History**

- “For any type of gout, a live torpedo fish should be placed under the feet”
  - Scribonius Largus, Roman
- First documented medical application of electricity
- Headache as well
  - AD 46
- “Sea-torpedo should be applied alive to cure headache”
  - Claudius Galen, Roman
- “Cut the tail part from a live fish and place over face to treat drooping of eye lid”
  - 1596
- Electric Torpedo Fish: kill prey by discharging electrical current
**Neurostimulation History**

- **"Gate Control" theory (Melzack and Wall-1965)**
  - Stimulation of large diameter cutaneous afferents, or A beta fibers, inhibits transmission of pain signals from small, unmyelinated A-delta, C-fibers diameter fibers.

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**Neurostimulation History**

- **Gate Theory of Pain (1965):** enormous impact on electro-analgesia and lead to development of implantable neurostimulators.
- **Shealy (neurosurgeon):** implanted first dorsal column stimulator by laminectomy, 1967.
  - 70 y/o with bronchogenic CA.
  - Good relief until death (few days later).

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**Neuromostimulation History**

- **TENS units 1970’s**
  - Transcutaneous Electrical Nerve Stimulation
  - Initially, trial of tolerance to electrical stimulation before SCS implantation
  - Most widely used form of electrotherapy.
Neuromostimulation History

- **Calmare Therapy 2000’s**
  - FDA approved for chronic neuropathic and dystrophic pain in 2009
  - Used in Europe for chemotherapy-induced peripheral neuropathy (CIPN)
  - Marketed for CRPS, CIPN, PHN, phantom limb pain, so-called
  - Studies on FBSS, brachial plexopathy, CIPN
  - Many patients had dramatic relief without side effects
  - Mechanism - transmits 16 sequences of low frequency electrical stimulation, inhibits pain impulse transmission

Animal Studies

- Electrical stimulation may activate A alpha and Beta afferent fibers, trigger spinal inhibitory interneurons, and interrupt pain signals in dorsal horn
- SCS may release serotonin and NE into dorsal horn to decrease pain transmission pre- and post-synaptically
- Central Sensitization – changes in the spinal cord that lead to pain amplification following an injury or in chronic pain conditions
- SCS capable of blocking, and reversing central sensitization in the spinal cord
  - Early intervention may be quite important

Current Mechanism

- Animal Studies

Mechanism of Action

Spinal Cord Stimulation:
indications/applications
- Failed Back Surgery Syndrome
- Radicular Pain
- Postlaminectomy Pain
- Degen Disc Dz
- CRPS (RSD)
- Epidural Fibrosis
- Arachnoiditis
- Inoperable ischemic leg pain
- Refractory angina
- Interstitial cystitis

Device Components
- Pulse generators:
  - Conventional IPG (2-5 yrs), Rechargeable IPG (9-10 yrs)
- Transmitter/patient controller (programmer)
- Leads/Electrodes
- Clinician programmer
Candidates

- Failure of more conservative therapies
- 50% pain reduction with test lead
- Area of pain covered by paresthesias and well tolerated
- Mood/sleep/activity improvement
- Psychosocial comorbidities addressed

Trial

- Trial carried out first under fluoroscopy
- Electrode placed on top of epidural space
- At home trial lasts approx. 5-7 days
- If effective, implantation of electrode and battery occurs in the operating room

Implantation

(Operating Room)
Complications

- Lead migration -22.6%
- Lead connection failure -9.5%
- Lead breakage - 6%
- Pain at the IPG site – 12%
- Infection- 4.5% ( 2.5% with positive culture)
- Infection in diabetes 9% vs 4% non-diabetics

Failed Back Surgery Syndrome

Evidence

- Retrospective Studies
  - Review of 41 articles showed 50-60% of pts with FBSS reported >50% pain relief from SCS (Turner et al, 1995)
  - Long-term efficacy in 63% of FBSS pts after 3.5 yr follow up (Hieu et al, 1994)

- Systematic Review
  - 72 case studies in FBSS: 62% of FBSS pts treated with SCS achieved at least 50% pain relief & 53% D/C’d their analgesics (Taylor et al, 2006)

Failed Back Surgery Syndrome

- Prospective, Multicenter Case Series
  - 70 pts at one year F/U showed statistically sig improvement in QOL measures with SCS for back and leg pain (Burchiel et al, 1996)

- Randomized, Controlled trial
  - 50 pts with FBBS randomized to repeat surgery or SCS. At 3 yrs, 47% of SCS group reported 50% pain relief and required significantly fewer opioids v 12% relief in the reoperation group (Kero et al, 2005)
Failed Back Surgery Syndrome

- Systematic Review
  - **SCS & Analgesia**: 5 case series (level 3 evidence and 2 include FBSS and CRPS) report mild to moderate pain improvement. Greater relief in leg pain v. back pain.
  - **Functional Improvement**: No conclusion. All studies uncontrolled and insufficient detail re: work rates.
  - **Pain & Function over Time**: Literature suggests diminution of pain relief over time.
    - Among 40 FBSS pts, 85% benefit at 12 mos. and 70% benefit at 24 mos.
  - **Complications**: Among 18 articles, average of 34% of pts had undesirable outcome with permanent SCS (av. F/U < 4 yrs)
    - Most common adverse event: SCS revision due to electrode repositioning (23%), not due to equipment failure.

(Shaw et al. Pain 2004)

Complex Regional Pain Syndrome

- **Evidence**
  - 1 prospective RCT, 3 prospective studies without matched controls, 8 retrospective studies.
    - Total pts = 260
  - **Mechanism**: presumed suppression of SNS vasoconstrictor activity.
  - **RCT in CRPS I (class I evidence)**:
    - Randomized pts to SCS plus PT group (24 pts) or to PT alone (18 pts).
    - Both groups continued med management.

**Complex Regional Pain Syndrome (CRPS)**

RCT in CRPS I

- **6 month F/U**
  - Pain significantly improved (50% or >) in SCS + PT group, but not increased in PT-only group (NNT 3)
  - No difference in functional status beyond PT

- **1 year F/U**
  - Pain significantly improved at 1 year for SCS + PT, and increased for PT-only group
  - No difference in functional status but SCS + PT did report better mood which resulted in less anxiety/depression

- **3 year F/U**
  - Pain alleviating effect of SCS in CRPS group no longer stat. sig.

- **5 year F/U**
  - 10 pts excluded from study. Total 22 in SCS + PT group and 13 controls
  - Pain alleviating effect of SCS in CRPS group no longer stat. sig.


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**Postherpetic Neuralgia (PHN)**

- Mixed results in treating PHN
  - **Kumar et al.** (1996): 16/20 (80%) PHN pts reported pain relief after implantation, 10/16 (62%) had pain relief at av. F/U of 7.3 yrs
  - **Meglio et al.** (1989): 6/10 pts with chronic PHN reported 53% pain relief with SCS over 46 month F/U period
  - **Harke et al.** (2002): 23/28 pts (82%) with PHN >2 yrs evaluated prospectively reported pain relief of 50% or >. 18/23 (78%) had pain relief at av. 1.8 yrs. 7 pts (25%) reported improved ADLs. >50% no longer needed pain meds during SCS treatment.

- Level of evidence low, but SCS may offer alternative approach in refractory patients

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**Peripheral Vascular Disease**

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Peripheral Vascular Disease

Limb salvage
- Controlled studies comparing addition of SCS to conservative treatment
- Six studies of 450 pts were included
- Limb salvage after 12 months significantly higher in SCS group

Ubbink et al. The Cochrane Database of Systematic Reviews 2005;3

Peripheral Vascular Disease

Conclusion
- SCS appears effective in reducing ischemic pain in pts with critical limb ischemia (rest pain or necrosis) and has a modest effect on limb salvage

INTRACTABLE ANGINA
**Intractable Angina**

**Cost Effectiveness**

- Two-year follow-up of 104 patients randomized in ESBY study revealed SCS group showed significant cost savings overall.
- SCS group showed decrease in hospital days secondary to cardiac morbidity.

Andrell, Cardiology, 2003

**Conclusion**

- Good evidence that SCS decreases myocardial oxygen demand, improves myocardial microcirculatory blood flow, and does not conceal ongoing myocardial ischemia (Mannheimer et al. 1988 and 1993, Eliasson et al. 1996).
- No known survival benefit.

**Chronic Pancreatitis**

**Two Main Etiologies**

- Chronic Pancreatitis
  - Incidence: 5-12/100,000
  - Prevalence: 50/100,000

- Pancreatic Cancer
  - Incidence: 12/100,000
  - Very high mortality rate

80-90% have pain.

Yamasaki and Lowenfels, The Epidemiology of Pancreatitis and Pancreatic Cancer, Gastroenterology 2013, 144:1252-1261
Chronic Pancreatitis

Painful Diabetic Neuropathy

* Systematic review on SCS treatment efficacy January 1980-March 2010
* 3 prospective case series, 1 retrospective cohort study (25 patients)
* At 1 yr SCS > 50% pain relief in 63% patients
* After 1 yr analgesic use decreased in SCS patients
* 60% discontinued medications
* No major adverse effects reported

Painful Diabetic Neuropathy

- Pluijms et al - first pilot study
- Reduction in pain score
- Enhanced Sleep
- Short term improvement in QoL

Success Rate

Time elapsed prior to intervention affects pain relief

Cost-Effectiveness: SCS vs Alternative

SCS Innovations

- Full Body MRI Compatibility & Position Sensing – Medtronic
- Sixteen Contact Lead & Programming – Boston Scientific
- Paddle Electrode – St. Jude
- High Frequency Stimulation (Analgesia without Paresthesia) – Nevro
- Miniaturization – Stimwave

High Frequency SCS Therapy (10 kHz)

**Device**
- Capable of HF10 therapy (no paresthesias)
- Senza® SCS System (Nevro, Menlo Park, CA)
- Pulse rate of 2 to 10,000 Hz
- MR conditional for head and extremities for 1.5T and 3T scanners
- CE marked and FDA approved with 10+ year, rechargeable battery life

**High Frequency SCS Therapy**

**Procedure**
- Traditional lead placement requires intraoperative paresthesia mapping
  - Goal is to cover areas of pain with paresthesias
  - Paresthesia based lead placement (T6-T10) for back and leg pain
- Requires patient feedback
- HF10 therapy leads are placed anatomically
  - Paresthesia mapping not required
  - Anatomical lead placement (T8-T11) for back and leg pain
  - No intra-operative programming
  - Two, staggered leads with maximum electrodes over T9-T10 area


Observational, Multicenter Center
- 65 implanted patients at 24 month follow up with chronic LBP with or without leg pain
- 79% FBSS, 22% LBP without prior surgery (Degen. Disc Dz)
- 86% with primary LBP, 14% with primary leg pain
- Back and leg pain significantly reduced; function, opioid use, sleep much improved; no specific adverse events related to HF SCS

RCT comparative study using HF SCS versus traditional SCS for LBP (Anesthesiology 2015)
Percutaneous IPGs and Anchors

Circuitry enclosed within lead

Wireless Power Transfer and Recharging

Wireless Programming

No Implantable Batteries

Four contacts

Wireless, Miniaturized System
Stimwave

Wireless System Overview

Wireless Power Transmitter
Acts as an “External Pulse Generator”
Charges Wirelessly, Programmed Wirelessly,
Transmits Power Wirelessly

Implanted Lead with
Rechargeable Battery

Pilot Study

Twelve patients with FBSS implanted serially with Medtronic SCS and Stimwave SCS

4 week trial

Same effective relief: paresthesia coverage

Implantable Drug Delivery System
Innovations

Flowonix: Thin, 10 yr usage, precise delivery

Personal Therapy Manager: Breakthrough Pain

Implantable Drug Delivery System (IDDS)

- Indications:
  - Chronic, severe low back pain unresponsive to other therapies (FBSS), cancer-related pain, spasticity-associated conditions

- Sources:
  - Spine surgery, degenerative spine disease, cancer, multiple sclerosis, spinal cord injury

- Approaches
  - Single shot versus continuous infusion
  - Nociceptive – single shot IT; Neuropathic or Mixed – continuous
  - Trial catheter placed into cerebrospinal fluid/epidural space with aid of fluoroscopy; medication delivered through catheter; pain and side effects assessed; 50% relief; side effects low
  - CA pain prognosis ok to implant if less than 3 months
  - If effective, catheter and pump implanted in the operating room
  - Overnight stay recommended with monitoring of vent., LOC, oxygenation


Intraspinal Infusion Medications

FDA APPROVED:

- Opioids: Morphine

- α2 agonists: Clonidine
  - Epidural only: CA pain

- N-type calcium channel blocker: Ziconotide

- GABA B agonist: Baclofen
  - Spasticity

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**Polyanalgesic Consensus Guidelines for Management of Nociceptive Pain by Intraspinal Drug Delivery**

Line 1
Morphine or Hydromorphone or Ziconotide or Fentanyl
(Morphine + bupivacaine) or (Ziconotide + opioid) or (Hydromorphone + bupivacaine)

Line 3
Opioid (morphine, hydromorphone, or fentanyl) + clonidine or Sufentanil

Line 4
Opioid + clonidine + bupivacaine or Sufentanil + bupivacaine OR clonidine

Line 5
Sufentanil + bupivacaine + clonidine


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**Polyanalgesic Consensus Guidelines for Management of Neuropathic Pain by Intraspinal Drug Delivery**

Line 1
Morphine or Ziconotide or (Morphine + bupivacaine)

Line 2
Hydromorphone or (Hydromorphone + bupivacaine) or (Hydromorphone + Clonidine) or (Morphine + clonidine)

Line 3
Clonidine or (Ziconotide + opioid) or fentanyl or (Fentanyl + bupivacaine) or (Fentanyl + clonidine)

Line 4
(Opioid + clonidine + bupivacaine) or (Bupivacaine + clonidine)

Line 5
Baclofen


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**Hormonal Considerations**

<table>
<thead>
<tr>
<th>Change in Hormone Level</th>
<th>Physical Effects</th>
<th>Hormone Function Tests</th>
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</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Fatigue</td>
<td>Serum levels</td>
</tr>
<tr>
<td>Follicle stimulating hormone</td>
<td>Decreased libido</td>
<td>Serum levels</td>
</tr>
<tr>
<td>Luteinizing hormone</td>
<td>May impact breast tissue</td>
<td>Serum Levels</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Fatigue, Impotence, fat storage</td>
<td>Serum Levels, should be accompanied with a Prostate Specific Antigen in Men</td>
</tr>
</tbody>
</table>

Non-Malignant Pain

- Systematic Review
  - 77% of patients trialed were implanted
  - Pain relief
    - All studies reported pain improvement
      - Pre-IDDS: pain at 82 (0-100 scales)
      - 45 at 6 months
      - 54 at 1 year
    - Success rates ranged from 38% - 56% at 6 mos to 30%-44% at 1 year
- Impact on functioning
  - All reported improvement in physical functioning, but serious methodological flaws (i.e., validated measures of physical functioning)
  - One study: 88% at same work status, 11% worse status, 21% better status at 1 yr.
  - Unable to reach conclusions about changes in work status

Turner et al. Clin J Pain, 2007 (programmable pumps only; effectiveness and complications with IDDS pumps in association with FBSS patients exclusively; 4 FBSS and other pain diagnoses; No ziconotide studies met criteria for effectiveness)

Cancer Pain

- Randomized, controlled trial
  - Compared intrathecal pump plus medical management to medical management alone
    - Refractory cancer pain patients
  - N=200 pts
  - Follow up: 6 months
  - IT morphine or other analgesics
  - Medical management: opioids +/- adjuncts
- Outcome
  - IT patients
    - Reported greater reduction in pain and toxicity
    - Significant decrease in fatigue and elevated level of consciousness
    - Improved survival- 54% alive at 6 mos v. 37% in the med. management group (secondary outcome measure)

Smith TJ et al. Journal of Clinical Oncology, 2002

Complications

- Average 27 Month Follow UP
  - Biologic complications
    - Pump malposition - 17%
    - Wound infection - 12%
    - Meningitis - 2%
  - Drug complications
    - N/V - 33%
    - Pruritus - 26%
    - Urinary Retention - 24%
    - Similar to former systematic reviews in cancer treatment and
  - Hardware complications
    - 27% pts with 1 or more equipment revisions

Complications

Intrathecal Catheter Tip Granuloma

- Incidence: 1.16% after 6 years of therapy
- See decrease in therapeutic effect most often
- Dx: MRI with gadolinium or CT myelogram
- Rx: MRI with gadolinium or CT myelogram
- If decrease in drug concentration, reduce dose of drug or move catheter 2-3 cm. Repeat imaging in 6 months. If increased, replace catheter, use saline, give oral.

Bottros MM, Christo PJ. *Journal of Pain Research* 2014:7;615-626

Cost Effectiveness

Non-Malignant Pain

Annual cost comparison: IDT compared with CPT during a 5-year period

<table>
<thead>
<tr>
<th>Year</th>
<th>IDT ($)</th>
<th>CPT ($)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>16,785</td>
<td>8,848</td>
</tr>
<tr>
<td>2</td>
<td>10,595</td>
<td>6,533</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>5</td>
<td>9,460</td>
<td>8,043</td>
</tr>
<tr>
<td>Total</td>
<td>29,410</td>
<td>36,000</td>
</tr>
</tbody>
</table>

Mean annual cost: 5,882 (IDT), 7,600 (CPT)


IDT – Intrathecal Drug Therapy
CPT – Conventional Pain Therapies

Thank you