Opioids and Neuromodulation: A Viable tool to Reduce Use and Best Practice Strategies

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University Hospitals Cleveland Medical Center
### Off-Label Product Use

*Will you be presenting or referencing off-label or investigational use of a therapeutic product?*

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Honoraria/Expenses</th>
<th>Consulting/Advisory Board</th>
<th>Funded Research</th>
<th>Royalties/Patent</th>
<th>Stock Options</th>
<th>Ownership/Equity Position</th>
<th>Employee</th>
<th>Other (please specify)</th>
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<td>Boston Scientific</td>
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<td>Fellowship Support</td>
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*X* No

**Yes, please specify:**
Opioids vs. Neuromodulation

❖ Scope
❖ Targets
❖ Evidence
❖ Challenges
❖ Is it a fair fight?
Scope of the Problem

❖ Chronic Noncancer Pain: 50 M in USA (2016)
❖ Despite lack of evidence for efficacy, # of opioid Rxs for chronic noncancer pain has dramatically ↑ → ↑ in misuse/deaths → epidemic proportions

❖ Neuromodulation: an alternative to opioids?

Targets

Pain stimulus

Pain message to brain via PTNs
Opioids

Opioid binding to the μ receptor ➔

- GDP ➔ GTP ➔
  - dissociates from the receptor
  - α subunit dissociates from the β/γ subunits
- GTP-α subunit inhibits adenylyl cyclase (AC) leading to a ↓ cAMP
- The β/γ subunits activate inwardly rectifying K⁺ (GIRK) channels, and inhibit voltage-sensitive Ca²⁺ channels (VSCC)
Analgesia + Euphoria

But also Pavlovian Learning

Learned association between receipt of the drug and the physiological and perceptual effects of the drug
SCS Mechanisms of Action

1. ↓ STT
2. ↓ preganglionic SNS
3. ↓ release of NE
4. Antidromic activation
5. CGRP and NO
6. Orthodromic activation

Spinal/segmental mechanisms:
- Aβ-fiber afferent
- Aδ/C-fiber afferent
- Inhibitory interneuron
- Excitatory interneuron
- Ascending projection neuron
- Descending projection neuron(s)

Supraspinal mechanisms:
- LC (Locus Coeruleus)
- RVM (Reticular Formation of the Medulla)
- NE (Norepinephrine)
- 5-HT (Serotonin)

Clinical Evidence:
- Decreased SSEPs
- Decreased RIII
- Reduced TS

Clinical Evidence:
- Decreased RIII
- Improved CPM

No Euphoria
The Evidence
96 RCT’s chronic noncancer pain

26,169 participants (61% F)

Compared to placebo

- Pain -0.69 cm on 10 cm VAS
- Physical functioning 2.04 pts on 100-pt SF-36
- Vomiting (5.9% opioids vs. 2.3% placebo)

Overall similar improvements with opioids to those seen with NSAID’s, TCA & anticonvulsants (low- to moderate-quality evidence)

SPINAL CORD STIMULATION VERSUS REPEATED LUMBOSACRAL SPINE SURGERY FOR CHRONIC PAIN: A RANDOMIZED, CONTROLLED TRIAL

OBJECTIVE: Persistent or recurrent radicular pain after lumbosacral spine surgery is often associated with nerve root compression and is treated by repeated operation or, as a last resort, by spinal cord stimulation (SCS). We conducted a prospective, randomized, controlled trial to test our hypothesis that SCS is more likely than reoperation to result in a successful outcome by standard measures of pain relief and treatment outcome, including subsequent use of health care resources.

METHODS: For an average of 3 years postoperatively, disinterested third-party interviewers followed 50 patients selected for reoperation by standard criteria and randomized to SCS or reoperation. If the results of the randomized treatment were unsatisfactory, patients could cross over to the alternative. Success was based on self-reported pain relief and patient satisfaction. Crossover to the alternative procedure was an outcome measure. Use of analgesics, activities of daily living, and work status were self-reported.

RESULTS: Among 45 patients (90%) available for follow-up, SCS was more successful than reoperation (9 of 19 patients versus 3 of 26 patients, \( P < 0.01 \)). Patients initially randomized to SCS were significantly less likely to cross over than were those randomized to reoperation (5 of 24 patients versus 14 of 26 patients, \( P = 0.02 \)). Patients randomized to reoperation required increased opiate analgesics significantly more often than those randomized to SCS (\( P < 0.025 \)). Other measures of activities of daily living and work status did not differ significantly.

CONCLUSION: SCS is more effective than reoperation as a treatment for persistent radicular pain after lumbosacral spine surgery, and in the great majority of patients, it obviates the need for reoperation.

KEY WORDS: Chronic pain, Electrical stimulation, Failed back surgery syndrome, Low back pain, Lumbar radiculopathy, Randomized controlled trial, Spinal cord stimulation
- 50 patients
- Mean number of prior LS spine surgeries = 2.5 ± 1.1
- Randomized: SCS or reoperation
- Allowed to cross-over if unsatisfactory
  - immediately if they failed a 3-day SCS trial
  - after 6-month from failing surgery

## Results

<table>
<thead>
<tr>
<th></th>
<th>Assigned</th>
<th>Crossed over</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized to reoperation</td>
<td>26</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>Randomized to spinal cord stimulation</td>
<td>24</td>
<td>5 (21%)</td>
</tr>
<tr>
<td>Nonrandomized reoperation</td>
<td>38</td>
<td>14 (37%)</td>
</tr>
</tbody>
</table>

\(^a\) Values are numbers of patients and percentages.

5/24 (21\%) SCS patients vs. 14/26 (54\%) re-operation patients elected to cross over (P = 0.02)
Spinal cord stimulation vs. Repeated lumbosacral spine surgery for chronic pain

9 (47%) of 19 patients randomized to SCS and 3 (12%) of 26 patients randomized to reoperation achieved at least 50% pain relief ($P < 0.01$)

North RB et al., *Neurosurgery* 2005; 56:98-107

<table>
<thead>
<tr>
<th></th>
<th>Opioid use stable or decreased</th>
<th>Opioid use increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation</td>
<td>15/26 (58%)</td>
<td>11/26 (42%)</td>
</tr>
<tr>
<td>Spinal cord stimulation</td>
<td>20/23 (87%)</td>
<td>3/23 (13%)</td>
</tr>
</tbody>
</table>
PROCESS RCT: SCS vs. CMM

- 100 Patients; **mostly leg pain after previous spine surgery**
  - 52 SCS
  - 48 CMM

- Criteria for implant
  - ≥ 80% overlap of pain with stimulation-induced paresthesiae
  - and ≥ 50% relief of leg pain on the VAS

Kumar K et al., Pain. 2007 Nov;132(1-2):179-88
Primary outcome: $\geq 50\%$ leg pain relief

Significantly more SCS patients (48% vs 9%) achieved the primary outcome ($p=0.0001$)

@ 6-Month

<table>
<thead>
<tr>
<th></th>
<th>CMM</th>
<th>SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>2%</td>
<td>47%</td>
</tr>
<tr>
<td>3 months</td>
<td>9%</td>
<td>56%</td>
</tr>
<tr>
<td>6 months</td>
<td>9%</td>
<td>48%</td>
</tr>
</tbody>
</table>

$N = \begin{array}{ll}
47 & 51 \\
44 & 50 \\
44 & 50 \\
\end{array}$

$a$ Significant difference ($P=0.00012$) between groups at 6 months
Leg Pain

Intent to Treat 50% PR
37% SCS
2% CMM

As Treated 50% PR
47% SCS
7% CMM

Kumar K et al., Neurosurgery. 2008 Oct;63(4):762-70; discussion 770
Opioid Use: SCS vs. CMM

❖ AT 6 MONTHS
➢ trend towards ↓ consumption of opioids

❖ AT 24 MONTHS
➢ No ↓ in number of pts receiving systemic opioids
➢ No ↓ in morphine daily equivalents consumed

❖ No protocol was described for pain medication management during the study

Kumar K et al., Neurosurgery. 2008 Oct;63(4):762-70; discussion 770
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Enrolled (N = 83)</th>
<th>Discontinued from study before permanent implant* (N = 11)</th>
<th>Permanent implant (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender—N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>48 (57.8%)</td>
<td>6 (54.5%)</td>
<td>42 (58.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>35 (42.2%)</td>
<td>5 (45.5%)</td>
<td>30 (41.7%)</td>
</tr>
<tr>
<td>Diagnosis—N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failed back surgery syndrome</td>
<td>67 (80.7%)</td>
<td>10 (90.9%)</td>
<td>57 (79.2%)</td>
</tr>
<tr>
<td>Chronic pain without prior surgery</td>
<td>16 (19.3%)</td>
<td>1 (9.1%)</td>
<td>15 (20.8%)</td>
</tr>
<tr>
<td>Pain type—N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary back pain</td>
<td>72 (86.7%)</td>
<td>10 (90.9%)</td>
<td>62 (86.1%)</td>
</tr>
<tr>
<td>Primary leg pain</td>
<td>11 (13.3%)</td>
<td>1 (9.1%)</td>
<td>10 (13.9%)</td>
</tr>
<tr>
<td>Age—(mean [years] ± SD)</td>
<td>50.4 ± 9.5</td>
<td>47.8 ± 11.1</td>
<td>50.8 ± 9.2</td>
</tr>
<tr>
<td>Years since diagnosis—(mean [years] ± SD)</td>
<td>9.7 ± 8.1</td>
<td>14.7 ± 9.6</td>
<td>8.9 ± 7.6</td>
</tr>
<tr>
<td>Baseline VAS scores (mean ± SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>8.4 ± 1.2</td>
<td>8.1 ± 1.1</td>
<td>8.4 ± 1.2</td>
</tr>
<tr>
<td>Leg pain</td>
<td>5.4 ± 3.2</td>
<td>5.2 ± 3.3</td>
<td>5.4 ± 3.2</td>
</tr>
</tbody>
</table>

*Ten patients discontinued due to trial phase failure. One patient did not complete trial phase.
SD, standard deviation; VAS, visual analog scale.

Persistent ↓ VAS Scores

Mean VAS Score (± SEM)

- **Back Pain VAS**
  - Baseline: 8.4
  - 6 months: 2.7*
  - 12 months: 2.8*
  - 24 months: 3.3*

- **Leg Pain VAS**
  - Baseline: 5.4
  - 6 months: 1.4*
  - 12 months: 2.0*
  - 24 months: 2.3*

*: P value < 0.001 compared with baseline
At 24-months

❖ Only 57% of patients were consuming systemic opioids compared to 86% at baseline
❖ Mean morphine daily equivalents (MMDE) consumed decreased from 84 mg at baseline to 27 mg at 24 months

Open Label RCT Comparing 10 KHz SCS to Conventional SCS

241 Participants assessed for eligibility

43 Excluded
43 Screen failures

198 Randomized

101 Assigned to HF10 therapy
  97 Trialed with SCS system
  90 Successful SCS trial
  7 Unsuccessful SCS trial
  4 Not trialed
  2 Medical contraindication
  1 Withdrew consent
  1 Lost to follow-up

97 Assigned to traditional SCS
  92 Trialed with SCS system
  81 Successful SCS trial
  11 Unsuccessful SCS trial
  5 Not trialed
  4 Withdrew consent
  1 Medical contraindication

90 Implanted participants included in the 3 mo primary and 12 mo secondary analyses

81 Implanted participants included in the 3 mo primary and 12 mo secondary analyses

Kapural L, Yu C, Gliner B et al. for the SENZA Investigators. 10 kHz high frequency therapy is superior to traditional low frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. Anesthesiology 2015;123:851–860.
10 kHz SCS Therapy RCT

Kapural L, Yu C, Gliner B et al. for the SENZA Investigators. 10 kHz high frequency therapy is superior to traditional low frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. Anesthesiology 2015;123:851–860.
At 12-Month

<table>
<thead>
<tr>
<th></th>
<th>HF10</th>
<th>Traditional SCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Opioid use</td>
<td>35.5%</td>
<td>26.4%</td>
</tr>
<tr>
<td>↓ MMDE</td>
<td>18.8%</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>(112.7 → 87.9 mg)</td>
<td></td>
</tr>
</tbody>
</table>

- Methodology for ↓ opioid not described
- Improvements in opioid usage not reported in the 24-month follow up study

DRG & Burst Stimulation RCT’s

- No reported data on Opioid consumption in the SUNBURST and ACCURATE trials

40 Hz: 5 bursts @ 500 Hz

Deer T et al., Success Using Neuromodulation With BURST (SUNBURST) Study: Results From a Prospective, Randomized Controlled Trial Using a Novel Burst Waveform. *Neuromodulation* 2018; 21: 56–66.

Deer T 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
Claims Data Retrospective Study

- Market database 1/2010 → 12/2014
- 5,476 patients; 59.7% F
- 390 explants (7.1%) by 1-yr
  - Younger and tobacco users
- MED ≥ 90 → more likely explant

Neuromodulation ≠ Neurostimulation
Predictive Value of Trialing

Dominguez E et al., Pain Practice, Volume 2, Number 4, 2002 315–325
Prospective “Microdosing” Study

### Table 3

Mean opioid dose (mg/day) from baseline to 3 months postimplant

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Estimate</th>
<th>SE</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>58</td>
<td>126.71</td>
<td>12.92</td>
<td>(100.83, 152.58)</td>
</tr>
<tr>
<td>3 months</td>
<td>58</td>
<td>3.80</td>
<td>0.90</td>
<td>(2.01, 5.60)</td>
</tr>
<tr>
<td>Decrease</td>
<td></td>
<td>122.91</td>
<td>12.61</td>
<td>(97.65, 148.16)</td>
</tr>
</tbody>
</table>

SE = standard error; CI = confidence interval.

Real World Study

Combination TIDD

<table>
<thead>
<tr>
<th>Subjects:</th>
<th>Male</th>
<th>26</th>
<th>46%</th>
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</thead>
<tbody>
<tr>
<td>Female</td>
<td>31</td>
<td></td>
<td>54%</td>
</tr>
<tr>
<td>Mean age at implant</td>
<td>64.4 [median 66]</td>
<td>Range: 38-84</td>
<td></td>
</tr>
<tr>
<td>Mean symptom duration</td>
<td>7.5 years</td>
<td>Range: 0.9-24</td>
<td></td>
</tr>
<tr>
<td>Etiology of Pain:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-laminectomy syndrome</td>
<td>57</td>
<td>100.00%</td>
<td></td>
</tr>
<tr>
<td>Oral opioids</td>
<td>MEDD [mg /day]</td>
<td>56 ± 10</td>
<td>95% CI ± 18.3</td>
</tr>
<tr>
<td>Average VAS Score:</td>
<td>8.42 ± 1.76</td>
<td>95% CI ± 0.42</td>
<td></td>
</tr>
</tbody>
</table>

❖ All: hydromorphone + bupivacaine
❖ All: PTM device

24 Months Follow up

- Baseline MEDD: 56±10 mg/24 h →
  - 12.5±4 mg/day @ 12 mo post-implant
  - 15±5.7 mg/day @ 24 mo post-implant
- =>79% decrease following implant
- 20/51 of the pts on opioids or 39% ceased using oral opioids completely
Feasibility of a Study?
Study Criteria

❖ Compare Opioid Naïve patients to SCS vs. opioids? Unlikely to find patients

❖ Likely Scenario

➢ FBSS patients on opioids **willing to wean off**
  ✓ Best practice pain management vs. Neuromodulation
  ✓ Allowed to cross over in 6 months
  ✓ Clear guidelines on weaning α to improvement in pain relief
  ✓ Other...

➢ Funding?

➢ Device types
Conclusions: Opioids vs. Neuromodulation

❖ Opioids = major crisis
   ➢ Euphoria = confounder

❖ Neuromodulation is a helpful intervention in many chronic noncancer pain states and may be an alternative to opioids
   ➢ Evidence is needed
      ✓ Complex but doable (though not a fair fight)
Thank You!!

If you find yourself in a fair fight, your tactics suck.

— John Steinbeck —