Neuromodulatie voor rugpijn: nieuwe inzichten.

Dr. K. De Smedt
RESTORATIVE NEUROSTIMULATION FOR REFRACTORY CHRONIC LOW BACK PAIN: RESULTS FROM THE REACTIV8-A CLINICAL TRIAL

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on behalf of the
ReActiv8-A investigators

ReActiv8 is CE marked for the treatment of chronic low back pain and available for sale in Europe. CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use.

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Chronic Low Back Pain
High prevalence, huge burden and few effective therapies

- CLBP formally defined as LBP >90 days but typically much longer (years)\(^1\)
- Linked to disability, reduced quality of life, depression, anxiety and sleep disorders\(^1\)
- Prevalence \(\approx 6\%\), life time prevalence 23%\(^2\)
- Economic impact of days lost from work, disability benefits and health resource utilization as high as 1.7% of GDP\(^3\)
- Available treatment options have limited effectiveness\(^4\)

Chronic Low Back Pain
Often of nociceptive nature

- 15% are suitable candidates for spine surgery\(^1\) with clear association between identifiable pathology on imaging and symptoms\(^3\)

- Remaining 85% have “non-specific chronic low back pain” (NSCLBP)

- Predominant nociceptive pain in at least 70% of NSCLBP patients\(^3\)
  - Caused by mechanical stress or damage to non-neural structures
  - Frequently referred to as **Chronic Mechanical Low Back Pain** (CMLBP)

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CMLBP patients are usually not well served with available treatment options:

- Physical therapy? → Effects not clinically relevant\(^1,\)\(^2\) (multiple RCTs).
- Surgery? → Fusion historically tried but no longer supported by guidelines and payors.
- SCS? → only indicated for neuropathic pain\(^3,\)\(^4\)
- Denervation (e.g. RF)? → short to medium term relief at best; no functional improvements\(^5\)
- Cognitive Behavioral Therapy? → only addresses psychosomatic aspects\(^6\) (coping)
- Opioids? → severe side effects, addiction and mortality\(^7\)

If symptom treatment is ineffective, should we treat the possible cause?

\(^3\) Veizi E, & Hayek SM; Neuromodulation 2014
\(^5\) Maas ET et al; Cochrane Database 2015
\(^7\) Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain, BMJ 2015;350:g6380
Functional Instability and Joint Overload can lead to CMLBP

- Multifidus is strongest functional stabilizer of the spine.¹
- Following acute injury, arthrogenic inhibition of the lumbar multifidus can occur and lead to ongoing functional instability and joint overload leading to Chronic Mechanical Low Back Pain.²,³

2. O’Sullivan PB; Man Ther 2005
3. Seminowicz DA et al; J of Neuroscience 2011
**Multifidus Activation Facilitates Recovery**

- Targeted motor control exercises to **activate the lumbar multifidus** and **restore functional stability** have shown to facilitate recovery,\(^{1-3}\) however many patients can’t learn or do them.

- **Restorative Neurostimulation** to activate the lumbar multifidus is a promising new option.\(^4\)

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1. Hebert JJ et al; Archives of PM&R 2010
2. Costa LOP et al; Phys Ther 2009
3. Kasai, R; J of Phys Ther Science; 2006
4. Deckers, K et al; Neuromodulation; 2015
Medial Branch Motor Stimulation Activates the Multifidus

- Implantable system, implanted through a short and easy procedure.
- Generates episodic contractions of Lumbar Multifidus by stimulating the L2 medial branch.
- Patient controlled 30 minute sessions, twice daily, started by remote control while prone.
- Muscle contractions are well tolerated.
Movie hypothesis and surgical technique.

https://youtu.be/w2GlfxMGizI
ReActiv8-A Trial

International, multicenter, prospective, single arm trial to collect performance and safety data.

### Key Inclusion Criteria

- Disabling CLBP despite PT and drugs
- Low Back Pain NRS of ≥6.0 and ≤9.0

### Key Exclusion Criteria

- Prior back surgery or indicated for surgery
- Leg pain > back pain
- Recent medial branch rhizotomy

### Baseline Characteristics (N=53)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>44 ± 10</td>
</tr>
<tr>
<td>Gender (Male – Female)</td>
<td>43% - 57%</td>
</tr>
<tr>
<td>Duration of Back Pain (years)</td>
<td>14 ± 11</td>
</tr>
<tr>
<td>Low Back Pain NRS</td>
<td>6.8 ± 1.2</td>
</tr>
<tr>
<td>Disability on Oswestry Disability Index (ODI)</td>
<td>44.9 ± 10.1</td>
</tr>
<tr>
<td>Quality of Life on EQ-5D</td>
<td>0.434 ± 0.185</td>
</tr>
<tr>
<td>Opioids</td>
<td>72%</td>
</tr>
</tbody>
</table>
ReActiv8-A Trial Results: Improvement in Pain

Clinically important, statistically significant and lasting improvement in pain\(^1\) (NRS)

### Proportion of Patients with Clinically Important Improvement in Pain (NRS)

- 90 days: 63% (N=52)
- 6 months: 61% (N=52)
- 1 year: 57% (N=47)
- 2 years: 62% (N=34)

### Mean NRS Scores

- Baseline: 6.8 (N=53)
- 90 days: 4.3 (N=52)
- 6 months: 4.6 (N=51)
- 1 year: 4.4 (N=47)
- 2 years: 4.3 (N=34)

* P<0.001

1. Ostelo RWJG et al; Spine 2008
**ReActiv8-A Trial Results: Improvement in Disability**

Clinically important, statistically significant and lasting improvement in disability\(^1\) (ODI)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Proportion of Patients</th>
<th>Mean ODI Scores (0-100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days (N=52)</td>
<td>52%</td>
<td>44.9 ± 3.9</td>
</tr>
<tr>
<td>6 months (N=47)</td>
<td>57%</td>
<td>31.3 ± 3.9</td>
</tr>
<tr>
<td>1 year (N=47)</td>
<td>60%</td>
<td>32.8 ± 3.9</td>
</tr>
<tr>
<td>2 years (N=34)</td>
<td>68%</td>
<td>30.7 ± 3.9</td>
</tr>
</tbody>
</table>

\(\text{Mean ODI Score ± SD/SE}\)

* \(P<0.001\)

1. Ostelo RWJG et al; Spine 2008
ReActiv8-A Trial Results: Improvement in Quality of Life

Clinically important, statistically significant and lasting improvement in quality of life\(^1\) (EQ-5D)

**Proportion of Patients with Clinically Important Improvement in Quality of Life (EQ-5D)**

- 90 days \((N=52)\)
- 6 months \((N=51)\)
- 1 year \((N=51)\)
- 2 years \((N=51)\)

\[88\% \quad 82\% \quad 81\% \quad 82\%\]

**Mean EQ-5D Scores**

- Baseline \((N=53)\)
- 90 days \((N=52)\)
- 6 months \((N=47)\)
- 1 year \((N=47)\)
- 2 years \((N=34)\)

\[0.434, 0.647, 0.622, 0.654, 0.636\]

\(* P<0.001\)

\(^1\) Soer R et al; *Spine J* 2012
**Results Summary**

Patients can do more, have less pain and a better quality of life.

- Proportion of subjects with clinically important improvements in one, two or three key endpoints (NRS, ODI, EQ-5D)

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>40%</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>6 months</td>
<td>45%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>1 year</td>
<td>47%</td>
<td>17%</td>
<td>23%</td>
</tr>
<tr>
<td>2 years</td>
<td>47%</td>
<td>27%</td>
<td>18%</td>
</tr>
</tbody>
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- Treatment Satisfaction (Subject assessment)

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Satisfied</th>
<th>Very Satisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 days</td>
<td>73%</td>
<td>15%</td>
</tr>
<tr>
<td>6 months</td>
<td>73%</td>
<td>12%</td>
</tr>
<tr>
<td>1 year</td>
<td>60%</td>
<td>21%</td>
</tr>
<tr>
<td>2 years</td>
<td>79%</td>
<td>6%</td>
</tr>
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Safety Profile

- Early experience led to a revised surgical approach to reduce risk of lead stress and subsequent conductor fracture.
  - Initial (lateral) approach resulted in repetitive sharp bending of lead as it crosses two layers of fascia
  - Current (midline) approach and lead routing with 50 leads has shown to mitigate risk

- Only one lead migration out of 156 (0.6%)
- No infections
- 7 patients with SAE – none related to study or device
- No Unanticipated Adverse Device Effects
ReActiv8-A Trial
Conclusions

- New treatment approach for CMLBP targeting functional instability (cause)
- Clinically important, statistically significant, and lasting improvement in pain, disability, and quality of life
- Restorative Neurostimulation offers a safe and effective treatment option for subjects with CMLBP who are not candidates for surgery
- Other trials ongoing to gather further evidence
ReActiv8-B Clinical Trial Description*

- International, multi-center, prospective, randomized, sham controlled, triple blinded trial, with one way crossover
  - 128 Pivotal Subjects for FDA submission
  - Estimate enrollment complete around end 2017, results in 2018
- Primary outcome: responder analysis
  - “Responder” is a subject with ≥30% improvement in low back pain VAS without increase in drugs prescribed and taken for pain in the 14 days prior to endpoint
  - Trial is successful if difference in responder rate between treatment and control arms
- Control arm subjects crossed over to full stimulation at 120 days
- Multiple secondary outcomes

* See https://clinicaltrials.gov/show/NCT02577354