Deep Brain Stimulation for Treatment Resistant Mood Disorders

Peter Giacobbe BSc MD MSc FRCPC
Assistant Professor, University of Toronto
Department of Psychiatry - University Health Network
peter.giacobbe@uhn.on.ca

RABS 2012
Montreal, PQ
September 30th, 2012
<table>
<thead>
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<th>Disclosures</th>
<th>Details</th>
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<tr>
<td>Advisory board or similar committee</td>
<td>Eli Lilly Canada</td>
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<tr>
<td>Clinical trials or studies</td>
<td>Brain Cells Inc., Clera, GSK, St. Jude Medical</td>
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<tr>
<td>Honoraria or other fees</td>
<td>Astra-Zeneca, BMS, Eli Lilly Canada, Pfizer, St. Jude Medical</td>
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<tr>
<td>Research grants</td>
<td>Canadian Academy of Geriatric Psychiatry, CIHR, Department of Psychiatry – University Health Network, Eli Lilly Canada Inc., Michael J. Fox. Foundation for Parkinson’s Research, NARSAD, NIMH, Schizophrenia Society of Ontario</td>
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</tbody>
</table>
The Emergence of Brain Stimulation for Depression
A Renaissance for Brain Stimulation?

- Recognition that the brain is an electrochemical organ
- A substantial proportion of patients receive inadequate symptom relief from psychopharmacologic treatments
- The development of neurocircuitry models of the brain
- Advances in technology have provided multiple means of modulating activity in key structures in the brain

The Advent of the CANMAT Neurostimulation Guidelines

Research report
Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies

Sidney H. Kennedy, Roumen Miley, Peter Giacobbe, Rajamannar Ramasubbu, Raymond W. Lam, Sagar V. Parikh, Scott B. Patten, Arun V. Ravindran

a University of Toronto, Canada
b Queen’s University, Canada
c University of Calgary, Canada
d University of British Columbia, Canada
Deep Brain Stimulation for Psychiatric Illness
Deep Brain Stimulation (DBS)

- Stereotactic neurosurgical implantation of electrodes under MRI guidance.
- Target for stimulation is identified from three-dimensional MRI reconstruction of the brain.
- Two burr holes drilled under local anesthetic.
- Two quadripolar electrodes are advanced to the target location in the brain.
- The stimulation parameters can be dynamically adjusted over time based on the clinical picture.
The Surgical Technique of DBS

Modifiable parameters:
1. Active electrode location
2. Voltage
3. Frequency
4. Pulse Width
Deep Brain Stimulation for Neuropsychiatric Illness

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Patients Treated</th>
<th>Deep Brain Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>30,000-40,000</td>
<td>Globus pallidus internus, subththalamic nucleus</td>
</tr>
<tr>
<td>Chronic Pain</td>
<td>1500-2000</td>
<td>Ventral posterior medial and lateral thalamic nuclei, periventricular and periaqueductal gray matter</td>
</tr>
<tr>
<td>Tremor</td>
<td>500-1000</td>
<td>Ventralis intermedius thalamic nucleus, zona incerta</td>
</tr>
<tr>
<td>Dystonia</td>
<td>300-500</td>
<td>Globus pallidus internus</td>
</tr>
<tr>
<td>Cluster Headache</td>
<td>30-50</td>
<td>Posterior hypothalamus</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>20-50</td>
<td>Anterior thalamic nucleus</td>
</tr>
<tr>
<td>OCD</td>
<td>20-50</td>
<td>Anterior limb of internal capsule</td>
</tr>
<tr>
<td>Depression</td>
<td>20-50</td>
<td>Subgenual cingulate cortex, anterior limb of internal capsule, nucleus accumbens</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>10-50</td>
<td>Ventromedial thalamic nuclei, anterior limb of internal capsule, globus pallidus internus</td>
</tr>
</tbody>
</table>

Brain Targets for DBS for Treatment-Resistant Depression

Subgenual Cingulate Cortex as an Endophenotype of Antidepressant Response

Effect of Mood Challenges

Transient Mood Induction

Tryptophan Depletion

Effect of Antidepressant Treatments

Treatment with SSRI

Treatment with DBS

modified from Nemeroff, *FOCUS* (2008) 6: 3-14
SCC DBS for Treatment-Resistant Depression Trial in Toronto

- Male and female subjects between the ages of 18 and 75 years

- **Inclusion Criteria:**
  - Major Depressive Disorder – current episode > 12 months
  - Resistant to at least four adequate treatment trials including pharmacotherapies, ECT, and evidence based psychotherapy.
  - Hamilton Rating Scale for Depression (HRSD-17) score ≥ 20

- **Exclusion Criteria:**
  - Bipolar Disorder or Psychotic subtype of MDD
  - Alcohol or substance abuse/dependence within 12 months
  - Active suicidal ideation
  - Major medical illness, cardiac pacemaker/defibrillator, and other implanted stimulator.

*Mayberg, Lozano, Voon et al., Neuron (2005) 45:651-60*
SCC DBS for TRD: Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>20</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Age at Enrollment (yrs)</td>
<td>47.4 ± 10.4</td>
<td>49.6 ± 14.2</td>
<td>45.3 ± 5.6</td>
</tr>
<tr>
<td>Age of Onset of MDD (years)</td>
<td>27.1 ± 8.3</td>
<td>24.4 ± 9.2</td>
<td>29.2 ± 7.3</td>
</tr>
<tr>
<td>Length of Current Episode (years)</td>
<td>6.9 ± 5.6</td>
<td>6.8 ± 6.0</td>
<td>7.0 ± 5.5</td>
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<tr>
<td>Number of Lifetime MDE (n)</td>
<td>3.9 ± 3.1</td>
<td>3.6 ± 2.6</td>
<td>4.1 ± 3.5</td>
</tr>
<tr>
<td>Positive Family History MDD (n)</td>
<td>14/20</td>
<td>6/9</td>
<td>8/11</td>
</tr>
<tr>
<td>Received ECT (n)</td>
<td>17/20</td>
<td>8/9</td>
<td>9/11</td>
</tr>
<tr>
<td>Received Psychotherapy</td>
<td>20/20</td>
<td>9/9</td>
<td>11/11</td>
</tr>
<tr>
<td>Baseline HRSD-17</td>
<td>24.4 ± 3.5</td>
<td>24.4 ± 3.9</td>
<td>24.3 ± 3.3</td>
</tr>
</tbody>
</table>

Antidepressant Effects of SCC DBS for TRD

Percent of Subjects Meeting Criteria for Response or Remission by Time

What are the Long-Term Antidepressant Effects of SCC DBS?
Positive Long-Term Antidepressant Outcomes with SCC DBS

A. Patients Who Responded

B. Patients Who Remitted

Progressive Improvements in Quality of Life Associated with Long-Term SCC DBS

C. SF-36 Subscale Scores: Intent-to-Treat

D. SF-36 Dimension Scores: Intent-to-Treat

Serious Adverse Events in the Long-Term Follow-Up

- 70.1 patient-years of follow-up
- 8 patients were hospitalized for medical reasons on a total of 12 occasions.
- Half of these admissions were for psychiatric reasons and the other half were for non-psychiatric reasons.
- Two patients died by possible suicide, one by colon cancer.
- There was no evidence that any of the adverse events, including the deaths, were due to DBS device failure or changes in the stimulation parameters.
SCC DBS: Results from Other Centres
## Multi-Center Trial of SCC DBS: Patient Demographics

<table>
<thead>
<tr>
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<th>UBC</th>
<th>McGill</th>
<th>U of T</th>
<th>Total</th>
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<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>5</td>
<td>6</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>2 F/ 3 M</td>
<td>5 F/ 1 M</td>
<td>6 F / 4 M</td>
<td>13 F/ 8 M</td>
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<tr>
<td><strong>Age at Surgery</strong></td>
<td>43.6 ± 10.0 (35-59)</td>
<td>49.5 ± 3.5 (44-53)</td>
<td>47.9 ± 4.6 (39-55)</td>
<td>47.3 ± 6.1 (35-59)</td>
</tr>
<tr>
<td><strong>Age MDD Onset</strong></td>
<td>24 ± 6.2 (19-34)</td>
<td>29.7 ± 10.6 (16-42)</td>
<td>27.5 ± 6.7 (19-39)</td>
<td>27.3 ± 7.7 (16-42)</td>
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<tr>
<td><strong>Duration of Current MDE</strong></td>
<td>5.2 ± 3.5 (2-9)</td>
<td>2.3 ± 0.5 (2-3)</td>
<td>6.4 ± 4.1 (2-12)</td>
<td>5.0 ± 3.7 (2-12)</td>
</tr>
<tr>
<td><strong>Baseline HDRS-17</strong></td>
<td>27.4 ± 6.2 (20-34)</td>
<td>28.6 ± 5.1 (24-37)</td>
<td>26.6 ± 3.5 (18-31)</td>
<td>27.6 ± 4.5 (18-37)</td>
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<tr>
<td><strong>Melancholic features</strong></td>
<td>4 (80%)</td>
<td>5 (83%)</td>
<td>9 (90%)</td>
<td>18 (90%)</td>
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</table>
Multi-Center Trial of SCC DBS: Clinical Results

• At 6 months, the average decline in the HRSD-17 was 43.3% at 6 months and 41.4% at 12 months with SCG DBS.

• Responses seen at 3 months tend to be maintained at one year.

• Comparable findings to the results of single center proof-of-principle study.

SCC DBS: International Results

- 10 patients with TRD and 7 patients with Bipolar II Depression
- Increasing rates of response and remission over time
- The effects of SCC DBS on improving depressive symptoms were reported to be similar for both patients with TRD and BD
- Eight patients with TRD received chronic, open-label bipolar stimulation in the SCC
- A third of patients (3/8) met criteria for remission after 1 month of active stimulation, which increased to 50% at the one year mark.

Puigdemont, Pérez-Egea, Portella et al. *International Journal of Neuropsychopharmacology* (2011)
What are the Mediators of Response to SCC DBS?
SCC DBS for TRD: Clinical Subtypes

• No baseline demographic or illness characteristics have been identified to predict antidepressant response to SCC DBS.
• Greatest experience with melancholic depressive symptoms
• Bipolarity?
• Anxiety?
Exploring the Mechanism of Action of DBS with QEEG

<table>
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<th>Per Session</th>
<th>Resting Eyes Closed</th>
<th>N – Back Task</th>
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<tbody>
<tr>
<td>DBS – On (n=11)</td>
<td></td>
<td>0-Back: Attention</td>
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<tr>
<td></td>
<td></td>
<td>3-Back: Working Memory</td>
</tr>
<tr>
<td>DBS – Off (n=9)</td>
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<td></td>
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</table>

Focus of Analysis: Session 1 (ON) vs. Session 2 (OFF) within subject comparisons for 0-Back and 3-Back conditions
2-Way Within Subject ANOVA

P-values (-log10 P)

Range = [0 5]

Stimulator Effect

P < 0.05 (FDR)

Task Effect

P < 0.05 (FDR)

Significant Bits

Significant

Task Effect

50 Hz

4 ms

Range = [0 5]
HAM-D and Gamma Correlation

FC2 - Electrode 20

ON vs OFF (3-Back Condition)

Spearman Correlation (Non-Parametric) P < 0.05
Conclusions
SCC DBS for Mood Disorders: Findings to Date

- To date there have been published results from 69 patients worldwide who have received SCC DBS for a refractory mood disorder.
- By far the most evidence exists for the antidepressant effects of SCC DBS for patients with TRD.
- One year outcomes with SCC DBS for TRD appear to be comparable across centers and investigators.
- Progressively superior results being seen with long-term follow-up beyond one year.
- The reason for the elevated rates of response observed over time is unclear.
- Elucidating the short and long-term neurophysiological and psychological adaptations that occur with chronic SCC DBS may help to elucidate the mechanisms of this putative treatment and improve patient outcomes.
### Summary of CANMAT Neurostimulation Guidelines

<table>
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<th>Overall Recommendation</th>
<th>Acute Efficacy</th>
<th>Relapse Prevention</th>
<th>Safety and Tolerability</th>
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<tbody>
<tr>
<td>ECT</td>
<td>First-line</td>
<td>Level 1</td>
<td>Level 1</td>
<td>Level 1</td>
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<tr>
<td></td>
<td>Second-line for treatment resistant or intolerant populations</td>
<td></td>
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<td></td>
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<td>rTMS</td>
<td>Second-line</td>
<td>Level 1</td>
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<td>VNS</td>
<td>Third-line</td>
<td>Level 3</td>
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<td>Investigational</td>
<td>Level 3</td>
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Acknowledgements

• Dr. S. Kennedy
• Dr. A. Lozano
• Dr. J. Daskalakis
• Dr. N. Lipsman
• Dr. J. Downar
• Dr. C. Hamani
• Dr. H. Mayberg

• **Referrals for DBS for TRD:**
  – Phone (416) 340-4672
  – Fax (416) 340-4198
  – Email: peter.giacobbe@uhn.ca