Stimulation and/or Surgical Approaches to Psychiatric Illness

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Current Depression Model
Current OCD Model
Fronto-striato-thalamo-frontal Circuit

TH = Thalamus
OFC = Orbitofrontal Cortex
CN = Caudate Nucleus
Psychiatric Neurotherapeutics

- Definition = surgical & device-based treatments
- Electroconvulsive therapy (ECT)
- Vagus Nerve Stimulation (VNS)
- Transcranial Magnetic Stimulation (TMS)
- Psychiatric Neurosurgery
  - Lesion (ablative) procedures
  - Deep Brain Stimulation (DBS)
• Used since 1930s; “gold standard” for TRD
• Numerous meta-analyses* have found ECT more effective than sham or medication and bilateral ECT more effective than unilateral
• Often require maintenance ECT, may be associated with cognitive side effects

VNS Therapy for Treatment-Resistant Depression
Vagus Sensory Afferents Go to Midbrain, Limbic, and Prefrontal Structures
VNS for TRD

• Approved by FDA for TRD in 2005 despite primary outcome measure (active versus sham) difference at 8 weeks being $p=0.06$. Ultimately approved based on secondary outcome measures (next slide)

• Insurers have used this to classify VNS for TRD as investigational despite FDA approval and reimbursement is currently virtually nonexistent
Pivotal Study vs Comparative Study: Secondary Analysis

HAMD$_{24}$ and IDS-SR$_{30}$ Categorical Outcomes at 12 Months (Observed Cases)

- **HAMD$_{24}$**
  - Response: Pivotal study (n=181) vs Comparative study (n=104) p=0.003
  - Remission: Pivotal study vs Comparative study p=0.031

- **IDS-SR$_{30}$**
  - Response: Pivotal study (n=180) vs Comparative study (n=112) p=0.029
  - Remission: Pivotal study vs Comparative study p=0.006

FDA Approved 2005

Newer VNS for TRD Data

- VNS Registry study included 795 pts with TRD treated with TAU alone or TAU + VNS and followed for 5 years

CMS Reconsideration of coverage decision expected Nov 2018
Decreases with VNS (all scans across time)

Z > 2.45
General Principles

• Uses magnetic field introduced on scalp surface to generate electrical stimulation of focal areas of brain cortex

• Unlike ECT, does not involve general anesthesia of seizures

• Approved by US FDA for use in treatment of depression
Figure 8: The induced electric field profile of single and double coils differ widely because of their geometry. The induced electric field of a circular coil is zero directly under its centre and reaches maximum approximately under the mean diameter. In the case of double coils it is at a maximum directly under the coil centre and has two smaller characteristic peaks on either side. See Table 1 for winding details.
Figure A. Common high frequency rTMS protocols currently applied in the treatment of mood disorders. Brief trains are applied once per minute for twenty minutes. Patient receives ten treatments over a two week period.
Clinical Efficacy for MDD

• Initially, many small sample size sham-controlled studies with variability in stimulation parameters, stimulation site, trial duration, etc.

• Nonetheless, meta-analyses and recent large multisite trials (Neuronetics\(^1\) n=301 & NIH\(^2\) n=190) support positive outcomes for rTMS (FDA approved 2008).

• Deep TMS (Brainsway) approved 2013 (pivotal trial with 230 TRD patients).
Clinical Efficacy of Figure 8 Coil rTMS for OCD

• Multiple rTMS targets for OCD have been explored
• The DLPFC (depression target, approved by FDA for depression) has, generally, not been found to be efficacious for OCD
• Only two controlled trials of rTMS for OCD have been positive, each at a different (but similar) target: the dmPFC and pre-SMA
BrainsWay deep TMS
Deep TMS for OCD

• Approved by FDA for OCD in August 2018
• After six weeks of treatment, active > sham (p=0.0157)
• 38.1% in active and 11.1% in sham group were responders (p=0.0033)
• 54.8% in active and 26.7% in sham were partial responders (p=0.0459)
Epidural Cortical Stimulation for Treating Major Depression

PROSPECT Feasibility Study

Study Design

- Multi-center US trial
- 12 subjects
- Single-blinded, sham-controlled
- Assess device and procedure safety
- Assess efficacy via depression scales (HDRS, MADRS) and quality of life measures (GAF, Q-LES-Q)
Surgical Target

- Left Hemisphere
- Posterior array 2 cm anterior to precentral sulcus
- Inferior array above inferior frontal sulcus
- Target area is middle third of middle frontal gyrus
- Brodmann area 9/46
- Target used in rTMS trials
Surgical Target
Inclusion/Exclusion Criteria

### Inclusion

- Non-psychotic, unipolar major depressive disorder (MDD)
  - Current major depressive episode (MDE) lasting for at least 2 years
  - Or at least 4 lifetime MDEs with the current episode lasting for at least 1 year
- Minimum score of 20 on the 28 item Hamilton Depression Rating Scale (HDRS28)
- Score of 60 or lower out of 100 points in the Global Assessment of Function (GAF) scale
- Failed response to at least four different antidepressant treatments

### Exclusion

- Other Axis I or Axis II diagnosis
- Previous brain surgery, other serious medical condition or other implanted device
- Active suicidal ideations
- Recent history of substance abuse
# Included Subjects

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
<td>6 female, 6 male</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>48±6 (39-56)</td>
</tr>
<tr>
<td><strong>Years since onset of MDD</strong></td>
<td>27±10 (11-42)</td>
</tr>
<tr>
<td><strong>Failed treatments</strong></td>
<td>9.8±1.7 (7-13)</td>
</tr>
<tr>
<td><strong>ECT treatments</strong></td>
<td>10 of 12 subjects</td>
</tr>
<tr>
<td></td>
<td>16.5±23.2 (0-84)</td>
</tr>
<tr>
<td><strong>Duration of current MDE (yrs)</strong></td>
<td>6.9±8.1 (1.3-30)</td>
</tr>
<tr>
<td><strong>Baseline HDRS</strong></td>
<td>34.3±5.3 (27.8-46.4)</td>
</tr>
<tr>
<td><strong>Baseline MADRS</strong></td>
<td>32.2±4.0 (26.4-40.6)</td>
</tr>
<tr>
<td><strong>Baseline GAF</strong></td>
<td>42.0±5.3 (35-50)</td>
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Effect of Therapy on Depression Scores

Trend: Cortical stimulation improves depression scores at 8 weeks relative to sham

<table>
<thead>
<tr>
<th></th>
<th>HDRS</th>
<th>MADRS</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 8</td>
</tr>
<tr>
<td>HDRS</td>
<td>Active</td>
<td>34.4±6 .5</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>34.0±3 .0</td>
</tr>
<tr>
<td>MADRS</td>
<td>Active</td>
<td>32.0±5 .1</td>
</tr>
<tr>
<td></td>
<td>Sham</td>
<td>32.2±2 .1</td>
</tr>
</tbody>
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P-values: HDRS, p=0.14; MADRS p=0.23
Active Stimulation at 8 and 16 Weeks

Trend: Subjects continue to improve with active cortical stimulation from 8 to 16 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>8 Weeks</th>
<th>16 Weeks</th>
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</thead>
<tbody>
<tr>
<td>HDRS</td>
<td>34.3±5.0</td>
<td>27.0±8.9</td>
<td>25.7±11.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-21±23%)</td>
<td>(-26±29%)</td>
</tr>
<tr>
<td>MADRS</td>
<td>32.1±3.8</td>
<td>25.0±9.0</td>
<td>21.8±10.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(-22±27%)</td>
<td>(-32±35%)</td>
</tr>
<tr>
<td>GAF</td>
<td>42.3±5.8</td>
<td>52.3±13.3</td>
<td>60.1±13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(25±32%)</td>
<td>(46±34%)</td>
</tr>
</tbody>
</table>

* 16-wk time point for sham stimulation patients, 8-wk time point for active stimulation patients
** 24-wk time point for sham stimulation patients, 16-wk time point for active stimulation patients

All p-values > 0.5
Electrode Location Influences Outcome

**Graph 1:**
- Improvement in HDRS at 8 Weeks (%)
- Distance from Precentral Sulcus (mm)
- $r' = 0.41$
- $p = 0.03$ by ANOVA of the linear fit

**Graph 2:**
- Improvement in HDRS (%)
- 8 Weeks of CS
- 16 Weeks of CS
- Distance from Precentral Sulcus
  - $\geq 20$mm
  - $< 20$mm
- $p = 0.024$
- $p = 0.065$

Plus/minus and error bars represent standard deviation.
Baseline Metabolic Activity Predicts Patient Response

- Baseline FDG-PET acquired prior to implantation
- Magnitude of decreased metabolism at left DLPFC correlates with magnitude of improvement with active stimulation ($p<.001$)
- Potential exists for improving the subject selection process

Ablative Limbic System Surgery
Prior Treatment Criteria

• Ensure:
  – Multiple serial adequate trials of antidepressants
  – Adequate trial of multiple serial augmentation strategies
  – Adequate trials of alternative monotherapies
  – Adequate trial of psychotherapy (especially CBT)
  – Adequate trial of ECT
Anterior Cingulotomy
Anterior Cingulotomy
Effectiveness of Cingulotomy for MDD

- 33 patients undergoing anterior cingulotomy
- At mean f/u of 30 months, 12 (36%) were responders and 12 (39%) were partial responders
- Therefore, approximately 75% received some benefit
- Minimal adverse events

Baseline subgenual PFC metabolism predicts subsequent response to anterior cingulotomy for major depression

Effectiveness of Cingulotomy for OCD

- Total n = 64; mean f/u = 63.8 months
- Full response (35%+ YBOCS improvement) = 47%
- Partial response (25-34% YBOCS improvement) = 22%
- Minimal adverse events

Deep Brain Stimulation
Coronal T1 or T2 (when T1 not available) MRI scans of the four patients (S1-S4), demonstrating electrode placement.

Patient #1: 33F
Patient #2: 24F
Patient #3: 52F
Patient #4: 55M
# DBS Patient Demographics*


<table>
<thead>
<tr>
<th></th>
<th>Mean (years)</th>
<th>Minimum (years)</th>
<th>Maximum (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Implantation</td>
<td>37.1</td>
<td>22.0</td>
<td>59.0</td>
</tr>
<tr>
<td>Age at OCD Onset</td>
<td>15.1</td>
<td>7.0</td>
<td>34.0</td>
</tr>
<tr>
<td>Symptom Duration</td>
<td>22.0</td>
<td>8.0</td>
<td>41.0</td>
</tr>
<tr>
<td>Gender</td>
<td>M = 53.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>F = 46.2%</td>
<td></td>
<td></td>
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<tr>
<td>History of Depression</td>
<td>Yes = 88.5%</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>No = 11.5%</td>
<td></td>
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</tbody>
</table>
Y-BOCS Scale

Percent of Improvement with DBS Follow-up Study Results

* Within-subject change statistically significant (p ≤ .001, two-sided test).
Improvement in Score with DBS Follow-up Study Results

* Within-subject change statistically significant (p ≤ .001, two-sided test).
VC/VS DBS for OCD

• Approved by FDA under the HDE mechanism in 2009
• Reimbursed by third party payers
Methods

• 15 subjects from MGH, Brown University, and Cleveland Clinic with treatment resistant depression
• Similar inclusion/exclusion as cortical stimulation and anterior cingulotomy
• Mean baseline MADRS was 34.8 (7.3)
• Device implantation followed by stimulation two weeks later
• Primary outcome measure was MADRS
Results

- 8/15 subjects experienced at least a 50% reduction of MADRS scores at 3 months follow-up
- 5/15 subjects experienced remission (MADRS score of 10 or less) at 3 months follow-up
- Adverse events included two instances of worsening depression (device inadvertently turned off) and one instance of hypomania (resolved with reduction of stimulation parameters)
However...

• Large, multisite randomized controlled trial for potential FDA approval... NEGATIVE!!

• Results being prepared for publication
DBS: Subgenual Cingulate (Cg25) Region
Table 2. Hamilton Depression Rating Scale, HAMD$_{17}$, Scores over Time for Each Subject

<table>
<thead>
<tr>
<th>Time</th>
<th>Hamilton Score$^a$</th>
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<tbody>
<tr>
<td></td>
<td>Pt 1$^b$</td>
</tr>
<tr>
<td>Pre-op baseline</td>
<td>29</td>
</tr>
<tr>
<td>1 week post-op (acute stimulation)</td>
<td>5</td>
</tr>
<tr>
<td>2 week post-op (DBS off)</td>
<td>9</td>
</tr>
<tr>
<td>1 month</td>
<td>10</td>
</tr>
<tr>
<td>2 months</td>
<td>13</td>
</tr>
<tr>
<td>3 months</td>
<td>2</td>
</tr>
<tr>
<td>4 months</td>
<td>4</td>
</tr>
<tr>
<td>5 months</td>
<td>5</td>
</tr>
<tr>
<td>6 months</td>
<td>5</td>
</tr>
</tbody>
</table>

$^a$Clinical response: decrease HDRS score >50%.

Clinical remission: absolute HDRS score <8.

$^b$Clinical responders.

$^c$Clinical nonresponders

- **Response in 4 of 6 patients**


*This information concerns a use that has not been approved by the US Food and Drug Administration.*
DBS of Subcallosal Cingulate

18% Remission and 41% Response @ 24 weeks
36% Remission and 36% Response after 1 year
58% Remission and 92% Response after 2 years

Holtzheimer et al, Arch Gen Psychiatry.\Published online January 2, 2012.

This information concerns a use that has not been approved by the US Food and Drug Administration.
However...

• Large, multisite randomized controlled trial for potential FDA approval...

Halted following interim futility analysis!!
Nucleus Accumbens Target

• At 12 month f/u, 5 of 10 TRD pts achieved at least 50% reduction of HDRS

• No controlled trials to date

Six of seven TRD patients met criteria for response after only 7 days of stimulation

Initial proof of concept

No controlled trials to date
Future Directions

• Surgical interventions to potentiate neurotransmitter release

Future Directions

• Surgical introduction of neurotrophic factors
Future Directions

- Optogenetics
Future Directions: Closed Loop DBS
Collaborators

Massachusetts General Hospital
Psychiatric Neurosurgery Committee Emad Eskandar, Darin Dougherty, Cris Cusin, Karleyton Evans, Alice Flaherty, Bruce Price, Scott Rauch (emeritus)
Center for Morphometric Analysis Nikos Makris, David Kennedy, Verne Caviness
PET Laboratory
Tom Brady, Alan Fischman, Nat Alpert

Butler Hospital Site
Ben Greenberg, Steve Rasmussen, et al

Cleveland Clinic Site
Don Malone, Ali Rezai et al

University of Florida Site
Wayne Goodman et al

Medical College Wisconsin
Brian Koppell et al