New Neuromodulation Treatments for Mood Disorders

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Disclosures: Dr. Camprodon

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

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- **Scientific Advisory Board:** Feelmore Labs, Hyka Therapeutics
- **Consultant:** Neuronetics
Disclosures: Dr. Henry

My spouse/partner and I have the following relevant financial relationship with a commercial interest to disclose:

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- Forest: Research Grants
- Bristol Myers Squibb: Honoraria
- Sunovian (Sepracor): Honoraria, Research Grants
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- Bracco Diagnostics: Research Grants
- Biomedical Research Models: Stock ownership
- General Electric: Stock Ownership
- Abbott Labs: Former employee
- Roche Pharmaceuticals: wife is an employee
Neuropsychiatry: Disorders of Connectivity

- Cultural/religious
- Population dynamics
- Clinical syndromes
- Behavior/cognition/emotion
- Organ
- Circuits/systems
- Brain areas
- Synapses
- Cells
- Molecules
- Genes

Medications

Neuromodulation

Behavioral Rx
Brain Stimulation – Neuromodulation

**Invasive**
- Deep Brain Stimulation (DBS)
- Vagal Nerve Stimulation (VNS)
- Epidural Stimulation (ES)

**Convulsive**
- Electroconvulsive Therapy (ECT)
- Magnetic Seizure Therapy (MST)

**Noninvasive**
- Transcranial Magnetic Stimulation (TMS)
- Transcranial Direct Current Stimulation (tDCS)
- Transcranial Photobiomodulation (tPBM)
Transcranial Magnetic Stimulation

1831 Faraday’s Electromagnetic Induction

Anthony Barker 1984
Transcranial Magnetic Stimulation

1831 Faraday’s Electromagnetic Induction

Anthony Barker 1984

Primary Electric Current

Magnetic Field

Secondary Electric Current
Effectiveness Naturalistic Studies in MDD

Carpenter et al. 2012

- 339 patient with MDD naïve to TMS
- Concurrent medications/therapy
- Response Rate: 41.5-58%
- Remission Rate: 26.5-37.1%
- Age and severity predict outcome
- Treatment-resistant not a predictor
Why Consider TMS treatment for Depression?

STAR*D Study: Depression Treatment Outcomes

- Initial Trial: 28%
- Failed 1 Trial: 21%
- Failed 2 Med Trials: 16%
- Failed 3 Med Trials: 7%

Likelihood of achieving remission drops with each subsequent medication trial


Typical Insurance Coverage

FDA Approval for TMS
Anatomy of Therapeutic Targets

OCD Target: DMPFC/pre-SMA

MDD Target: DLPFC

Migraine Target: Occipital pole

Smoking Cessation: VLPFC/Insula
Localization: Neuronavigation
Individualized fcMRI-guided TMS
Clinical Response

(20 patients, open-label)

Failed medications in current episode: 7.06 (range 5-12)

* p < .05 from baseline
In perspective...

**STAR*D Study: Depression Treatment Outcomes**

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- Failed 1 Trial: 21%
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Typical Insurance Coverage

FDA Approval for TMS
Theta Burst Stimulation (TBS)

- Shorter duration
- Longer-lasting physiological and cognitive effects are established in mechanistic studies
FDA-cleared: TBS for MDD

Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial

Daniel M Blumberger, Fidel Vila-Rodriguez, Kevin E Thorpe, Kfir Feffer, Yoshihiro Noda, Peter Giacobbe, Yuliya Knyazhnytska, Sidney H Kennedy, Raymond W Lam, Zafiris J Daskalakis, Jonathan Downar

Response Rate: 39%-49%
Remission Rate: 20%-32%

FDA cleared in 2018
Accelerated TBS Protocol

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
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Accelerated TBS for MDD

Protocol
• iTBS (excitatory) to left DLPFC
• Pulse intensity: 90% vs 120% RMT
• 1800 pulses/session (3x 600 pulses)
• 10 sessions per day (50 min pause)
  • = 6 weeks of daily TBS
• 5 consecutive days (inpatient)
  • = 5 courses of TBS

22 patients (DBS candidates)
1 did not complete
19 remitters after 5 days (86.36% ITT)
TMS for Bipolar Depression

• FDA In 2020, the FDA granted **breakthrough device designation** to TMS for treating bipolar depression

• Traditional **10Hz protocols to the left DLPFC** seem effective, but unclear TBS is.
  – What is the right anatomical target for BD?
  – What is the right frequency of stimulation?
Transcranial Electrical Stimulation

- **transcranial Direct Current Stimulation (tDCS)**
- **transcranial Alternating Current Stimulation (tACS)**
- **transcranial Random Noise Stimulation (tRNS)**
tDCS for MDD

Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial
Colleen K. Loo, Angelo Alonzo, Donel Martin, Philip B. Mitchell, Veronica Galvez and Perminder Sachdev

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study
Results From a Factorial, Randomized, Controlled Trial
Andre R. Brunoni, MD; Leonardo Valente, MD; Alessandra Baccaro, BA; Tamires A. Zanto, BS; Janaina F. de Oliveira, BS; Alessandra Goulart, MD, PhD; Paulo S. Boggio, PhD; Paulo A. Lotufo, MD, PhD; Isabela M. Bensenhor, MD, PhD; Felipe Fregni, MD, PhD

Trial of Electrical Direct-Current Therapy versus Escitalopram for Depression
# tDCS for MDD

The Sertraline vs Electrical Current Therapy for Treating Depression Clinical Study

Results From a Factorial, Randomized, Controlled Trial

Andre R. Brunoni, MD, PhD; Leandro Valiergo, MD; Alessandra Baccaro, BA; Tamires A. Zanato, BS; Janaina F. de Oliveira, BS; Alessandra Goulart, MD, PhD; Paulo S. Boggio, PhD; Paulo A. Lotufo, MD, PhD; Isabela M. Benerer, MD, PhD; Felipe Fregni, MD, PhD

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## Table 2. Response and Remission Rates According to Montgomery-Asberg Depression Rating Scale Scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
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<tbody>
<tr>
<td></td>
<td>Response</td>
<td>Remission</td>
<td>Response</td>
</tr>
<tr>
<td>Sham tDCS and placebo</td>
<td>11 (36.7%)</td>
<td>6 (20.0%)</td>
<td>9 (30.0%)</td>
</tr>
<tr>
<td>Sham tDCS and sertraline</td>
<td>10 (33.3%)</td>
<td>5 (16.7%)</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>Active tDCS and placebo</td>
<td>9 (30.0%)</td>
<td>4 (13.3%)</td>
<td>12 (40.0%)</td>
</tr>
<tr>
<td>Active tDCS and sertraline</td>
<td>16 (53.3%)</td>
<td>6 (20.0%)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td><em>P value</em></td>
<td>.25</td>
<td>.89</td>
<td>.14</td>
</tr>
</tbody>
</table>
Home-based tDCS for MDD

- CE approved
- FDA approved IDE and pivotal trial
Standard vs Optimized Montage

Traditional Bipolar Montage: L+ - R-

Individualized multielectrode High Definition tDCS
Established pro-cognitive effects of tDCS

Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder

Also for patients with MDD

Archival Report

Transcranial Direct Current Stimulation to the Left Dorsolateral Prefrontal Cortex Improves Cognitive Control in Patients With Attention-Deficit/Hyperactivity Disorder: A Randomized Behavioral and Neurophysiological Study

Archival Report

Beyond Mood in MDD: Cognition

Established pro-cognitive effects of tDCS
<table>
<thead>
<tr>
<th>ECT</th>
<th>Psychotherapy</th>
<th>Pharmacology</th>
<th>DSM</th>
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<tr>
<td>Classical -1900</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Von Auenbrugger - 1764</td>
<td>1940’s – 1960’s</td>
<td></td>
<td></td>
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<tr>
<td>Von Meduna -1934</td>
<td>Object Relations – 1920’s – 1950’s</td>
<td></td>
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<tr>
<td>Cerletti and Bini - 1938</td>
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<td>NYC/Cincinnati - 1940</td>
<td></td>
<td></td>
<td>III – R 1987</td>
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<td>Succinylcholine – 1951</td>
<td></td>
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<td>1958 -Lancaster</td>
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<td></td>
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<tr>
<td>Cuckoo’s Nest – 1975</td>
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<td></td>
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<tr>
<td>Blatchley - 1976</td>
<td></td>
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<tr>
<td>Seizure threshold</td>
<td>Limbic – Cortical Dysreg</td>
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<tr>
<td>2003 UK ECT Review Group</td>
<td></td>
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<td>DSM-5 2013</td>
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<td></td>
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<td>RDoC 2008</td>
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</table>
ECT Utilization in U.S. 2014

• General Population
  - 2014 Marketscan database (N=47,258,528)
  - 5.56 ECT patients per 100,000.
  - 0.25% of patients with a mood disorder.
  - Co-morbid psychiatric disorder (RR = 5.70)
  - Multiple Psychototropic Medications (d = 0.77)
  - Substance use disorder (RR = 1.97)

Wilkinson ST et al., Psychiatr Serv 2018 69:542-8
QUESTIONS

1. What is current clinical use of ECT?
   A. MDD
   B. Catatonia
   C. Psychosis
   D. Adolescents
   E. COVID

2. What is the “Best Way” to do ECT?
   A. Brief vs Ultra-Brief Pulse
   B. FEAST

3. What do you do after ECT?
   A. Medication Management
   B. Maintenance ECT
Clinical Indications for ECT

<table>
<thead>
<tr>
<th>Disease Responsive to ECT</th>
<th>Clinical Circumstances</th>
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<tbody>
<tr>
<td>Major Depression</td>
<td>Need for rapid, definitive clinical response (severity, safety)</td>
</tr>
<tr>
<td>Mania</td>
<td>Treatment Resistance, Intolerance to medications/therapy</td>
</tr>
<tr>
<td>Catatonia/Trisomy 21 Disintegrative Disorder</td>
<td>History of positive response to ECT</td>
</tr>
<tr>
<td>Psychosis: Schizophrenia/schizoaffective disorder</td>
<td>Patient’s Preference</td>
</tr>
<tr>
<td>Parkinson’s Disease (on-off) NMS Intractable Seizures</td>
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Weiner, R, 2001 
Rudorfer et al.1997
## Clinical Predictors of Response to ECT

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Mania</th>
<th>Psychosis</th>
<th>Catatonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Positive</strong></td>
<td>- Psychomotor retardation</td>
<td>- Severe mania (+/- psychosis)</td>
<td>- Good prognosis signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Psychotic symptoms</td>
<td>- Mixed states</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>- Age</td>
<td></td>
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<tr>
<td><strong>Negative</strong></td>
<td>- Antidepressant Medication failure</td>
<td>- Irritability</td>
<td></td>
<td></td>
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<td></td>
<td>- Chronicity of episode</td>
<td></td>
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Rudorfer MV et al., 1997
Pinna M et al., 2016
Molecular Predictors of ECT Response

- Increased Plasma HVA levels
- Increased NAA, Glx levels
- Increased TNF-α Polymorphisms
- Val/Val genotype of COMT
- APOE E4 carriers

Pinna M et al., 2016
COVID

• Limited Availability
  -- Resources diverted to COVID pts and other procedures.
  -- Dosing paradigm more definitive.

• Bag mask ventilation increases droplets
  -- Ventilation changes
  -- PPE for providers
What Does ECT Do to the Brain

• Electrode placement
• Metabolic effects
Post-Stroke Depression

- Robinson and colleagues (1984,1987): Left frontal or left basal ganglia regions had a significantly higher incidence of depression.
- Restricted to the first 2 months following stroke.

Robinson RG et al., Brain 1984; 107:81-93.
Robinson RG, Jorge RE. https://doi.org/10.1176/appi.ajp.2015.15030363
Mayberg Depression Model

Adapted from Mayberg, 2003
Effects of ECT on Brain Glucose

- 6 (4F) subjects with MDD
- Medication Free for at least 2 weeks
- Quantitative Fluoro-deoxy glucose PET.

- ROI analysis: 61 regions across 5 slices
- CMRglu decreased 61/61 regions
- Δ CMRglu correlated with decrease in L post frontal lobe (r = 0.84); R ant frontal lobe (r = 0.82); and right parietal (r = 0.83).

(Henry, Schmidt, Matochik, Stoddard, & Potter, 2001)
Absolute CMRglu Pre-Post ECT

(Henry, Schmidt, Matochik, Stoddard, & Potter, 2001)
BEST WAY TO DO ECT?

• Efficacy without side effects
• Electrode Placement
• Stimulus
• Dose
• Anesthesia
Electrode Placement

Figure 1. Changes in regional cerebral blood flow (rCBF) in depressed patients acutely after a single ECT treatment, as a function of electrode placement. CBF values at 32 brain regions were expressed as ratios of values 50 min after a treatment relative to 30 min before the treatment (post/pre × 100). Values of 100 indicate no change. The ratio scores were color coded so that purple and blue colors correspond to postictal CBF reductions, whereas orange and red colors correspond to postictal CBF increases. The brain shapes are displayed in a 185 × 112 matrix. Pixels were interpolated from all 16 detectors in each hemisphere, with each detector value multiplied by an inverse-square factor equal to \( \frac{2^{16}}{r^2} \), and \( r \) being the distance in pixels to the center of each detector. All pixels within a radius of 5 from the center of each detector were set to the value of that detector. Changes in the left and right hemispheres are presented separately for patients treated with right unilateral ECT (n = 28) or bilateral ECT (n = 26). Relative positions of the rCBF detectors are labeled on the representation of the left hemisphere of patients treated with right unilateral ECT [Nobler et al., 1994].
Evolution of ECT Technique

- 1938 – Sine Wave
- 1976 – Brief Pulse
- 1963, 2008 - Ultra-Brief Pulse
- 2003 - MST
- 2009 – FEAST
Ultra-Brief v Brief Pulse ECT

- Brief Pulse showed decreases in autobiographical, verbal and non-verbal memory, and processing speed.
- Ultra-brief less decline in autobiographical and anterograde memory. (Verwijk et al., 2012)
- Systematic Review of Efficacy. (Tor et al., 2015)
  - BP better than UBP (8.7 v 9.6)
  - BP more remissions than UBP (OR 0.71)
Dosing Strategies

- Age/Sex Determined
- Fixed High Dose
- Titrate Seizure Threshold
Seizure Threshold Dose

**Unilateral**
- 50%: 35% response rate
- 150%: 30% response rate
- 500%: 65% response rate

**Bilateral**
- 150%: 65% response rate

Responder = ≥ 60% reduction HRSD

(Sackeim et al., 2000)
Antidepressant Response

- 2003 – UK ECT Review Group
- **Real vs Sham ECT on Depression:**
  - 6 trials, 256 patients, 2 sine wave
  - Mean difference HDRS 9.7 (95% CI 5.7–13.5)
- **Bilateral vs Unilateral ECT:**
  - 22 trials, 1408 patients, Duration, Placement, Number varied
  - Mean difference HDRS 3.6 (95% CI 2.2–5.2) - Bilateral
- **ECT vs Pharmacotherapy:**
  - 18 trials, 1144 patients, Duration, Placement, Number varied
  - Mean difference HDRS 5.2 (95% CI 1.4 – 8.9)
  - TCA’s, MAOI’s, Tryptophan, SSRI’s, Li
  - Variable definitions of treatment refractoriness (4 trials).

(UK ECT Review Group, 2003)
ECT and MANIA

• Milstein et al., (1987)
• 17 patients with Mania
• First 6 treated with nondominant UL treatment without improvement until switched to BL
• Next 11 patients treated with BL first.
• Both groups showed improvement but not until BL treatment.

Milstein et al., Convuls Ther 1987; 3:1-9
ASVERSE EFFECTS: Memory
Medication Management

• Drugs that raise seizure threshold.
  1. Benzodiazepines
  2. Antiepileptic Agents

• Drugs that lower seizure threshold.
  1. Aminophylline/caffeine
  2. Buproprion

• Lithium.
Anesthesia Options

- Pentathol
- Methohexital
- Etomidate
- Propofol
- Divided Dosing Strategy
KETAMINE AUGMENTATION

• 1995-2016: 24 published articles using ketamine anesthesia/augmentation of ECT in the literature.
• Improvement early but not sustained.
• Overall clinical efficacy not different.
• Significant Limitations in study design.

AFTER THE ACUTE COURSE OF ECT

- No Treatment
- Maintenance ECT
- Maintenance Medications/Psychotherapy
Maintenance ECT

• Rationale: Acute ECT has high relapse rate. Treatment resistance.

• Efficacy: 61% PT vs 32% ECT +PT relapsed 1 yr.

Nordenskjold et al J ECT 2013; 29:86-92

• Schedule: 1x/week – 4 weeks

1x/2 weeks

1x/3 weeks

1x/4 weeks – 6-12 months.
POST-ECT MEDICATIONS

- RCT
- ECT + **Nortriptyline** vs Venlafaxine
- n = 319
- Post ECT + Li, no PBO x 6 months
- n = 122
- No difference between arms
- 50% relapsed; 33.6% remission; 16.4% dropped out.

Prudic J et al., J ECT. 2013; 29:3-12
LITHIUM PLUS NT vs VEN POST ECT

Prudic J et al., J ECT. 2013; 29:3-12
CONCLUSIONS

• ECT continues to be the “gold-standard” for treatment resistant depression.
• MOA likely reflects both global and localized effects
• Major Effect is a reduction in metabolic activity: ? GABA.
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• Tara Lauriat, Ph.D.