Treatment Resistant Depression: Neurostimulation and Future Treatment Strategies

Updates in Science, Practice and Policy
University of Utah School of Medicine Alumni Association - September 15th, 2012
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Disclosures

• I am listed as co-inventor on a University of Utah owned patent for depression biomarkers

Goals

• Understand the scope of treatment resistant depression
• Gain an understanding of current and future treatment options for depression
• Be able to identify treatment options for your patients

A Significant Percentage of Patients With Major Depressive Disorder Remain Poorly Served

14 Million US Adults
7.2 Million Treated
6.8 Million Untreated
3.2 Million Adequately Treated
4 Million Poorly Served

• Inadequate response
• Intolerant to side effects


Treatment Options

• Augmentation Strategies
• Neurostimulation Treatments
• Investigational Treatments

Augmentation

• Second Generation Atypical Antipsychotics
  Risperidone, Aripiprazole, Quetiapine, Ziprasidone
• Mood Stabilizers
  lithium, depakote, lamotrigine, tegretol
Neurostimulation Techniques

- Electroconvulsive Therapy (ECT)
- Transcranial Magnetic Stimulation (TMS)
- Vagal Nerve Stimulation (VNS)

Electroconvulsive Therapy

- Remains the “gold standard”
- Effective in 60-90% of patients
- Requires general anesthesia
- Memory impairment
- Associated with stigma

Lead Placements

Vignette

- 16 yo girl admitted after psychotic break while on trip in Europe. 6 weeks of unrelenting psychosis and began to show signs of Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome

- Similar to Malignant Catatonia but induced by anti-psychotic medications
- High muscle rigidity, fever and stupor all arrive more concurrently
- 50% mortality even with aggressive treatment
- ICU
Transcranial Magnetic Stimulation

TMS Therapy® in Clinical Practice
• Non-invasive
• No anesthesia or sedation
• Outpatient procedure easily performed in psychiatrists’ offices
• Approximately 40-minute procedure
• Acute treatment administered daily for 4-6 weeks
• Observed therapy

What is TMS? (Transcranial Magnetic Stimulation)¹
• Electric energy within insulated coil induces MRI-strength magnetic fields
• Magnetic fields pass unimpeded through the cranium for 2-3 cm
• In turn inducing an electric current in the brain
• This stimulates the firing of nerve cells and the release of neurotransmitters

Typical Course of Treatment
* 20-30 treatments (avg of 25 with “tapering” phase of 5)
* 120% of motor threshold over the Dorsal Lateral Prefrontal Cortex (DLPFC)
* 10 pulses per second (10 hz), 4 seconds “on” 26 seconds “off” x 37 minutes = 3,000 pulses per session
* (in Canada 2 sessions per day x 10 days)

Is TMS Effective?
* Manufacturer sponsored studies are the largest.
* NIMH sponsored study - positive “Daily left prefrontal transcranial magnetic therapy for major depressive disorder” George MS et al, Archives General Psychiatry, May 2010
* FDA approval granted for patients that have failed 1 trail of antidepressants
* Similar efficacy to STAR*D data = more treatment failures = less robust outcome
* American Psychiatric Association November 2010 – Practice Parameters for Depression lists TMS as standard of care along with therapy, psychopharmacology & ECT.
Investigational Techniques

- Magnetic Convulsive Therapy
- Deep Brain Stimulation (DBS)
- Ketamine
- Isoflurane
- Biomarkers

Magnetic Convulsive Therapy

- Garcia-Toro, et al – 2001 - 20 pts double blind sham – 4 treatments x 60 mins

Deep Brain Stimulation

Burst Suppression with Isoflurane

- Garcia-Toro, et al – 2001 - 20 pts double blind sham – 4 treatments x 60 mins
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Patient Selection
18-65 years old referred through clinical practice for ECT
Primary dx of Major Depression or Bipolar Depression
Exclusions:
Primary psychotic disorder, dysthymia or personality disorder.
Significant premorbid cognitive impairment
Unstable symptomatic coronary artery disease
Poorly compensated congestive heart failure
History of TIA or neurologic signs in the past year
Susceptibility to malignant hyperthermia
Pregnancy
Any other contraindication to isoflurane treatment
Deemed incompetent to consent

Study Design and Methods
Open label, nonrandomized feasibility trial to assess treatment and cognitive effects of Isoflurane relative to ECT

8-10 Treatments (2.5-3 weeks)

Follow-up @ 4 weeks post last treatment

Methods
At each time point (baseline, immediate post treatment series & 1 month) we collected:
• Serum for the biomarker study
• HAM-D 24
• Neurocognitive testing

Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane</th>
<th>ECT</th>
<th>ISO vs ECT (p)</th>
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<tbody>
<tr>
<td># patients</td>
<td>8</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>% Female</td>
<td>75%</td>
<td>40%</td>
<td></td>
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<tr>
<td>Age yrs (SD)</td>
<td>35.4(9.90)</td>
<td>41.6(12.56)</td>
<td>0.128</td>
</tr>
<tr>
<td>% Outpatient</td>
<td>100%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>Pre – WTAR (SD)</td>
<td>117 (9.78)</td>
<td>108(14.18)</td>
<td>0.184</td>
</tr>
<tr>
<td>Pre – HAMD (SD)</td>
<td>26.3 (14.53)</td>
<td>38.65 (9.34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MDD 296.33</td>
<td>82.6%</td>
<td>80%</td>
<td></td>
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<tr>
<td>Bipolar 296.53</td>
<td>37.5%</td>
<td>20%</td>
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Results:
Clinical Response (HAM-D 24)

<table>
<thead>
<tr>
<th></th>
<th>Isoflurane</th>
<th>ECT</th>
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<tr>
<td>Acute Response</td>
<td>75% (6/8)</td>
<td>90% (18/20)</td>
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<tr>
<td>1 month follow up</td>
<td>43% (3/7)</td>
<td>68% (13/19)</td>
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*Response = 50% or > reduction in HAM-D 24 score from baseline

Biomarkers for Depression:
Background
Major depressive disorder is a multisystem disease
Diagnostic criteria are clinical
NIMH, DSM-V seek measurable biological correlate of disease
Advantages include
- corroboration of clinical diagnosis
- monitoring of therapeutic efficacy
- improved understanding of disease and treatment mechanisms

We assessed whether WBC gene expression could be used as a marker of disease

Where do we start?
MDD is a complex, multisystem disorder
Its etiologies and presentations are heterogeneous

Why do we need biomarkers?
Current classification is effective and therapy successful for a majority of patients
Significant proportion of patients refractory to available treatment
- MDD etiologies and heterogeneous and mechanisms are incompletely understood
- Pharmacotherapy onset may take weeks
Areas of work to date

Genetics, genomics and protein synthesis

Genetics – mutations and polymorphisms
Gene expression – we will evaluate mRNA levels to understand baseline and treatment effects
Protein – gene expression regulation, environment

What does WBC gene expression have to do this MDD?

qPCR of peripheral markers as surrogate for changes in the brain
- Brain tissue is unavailable
- CNS and PNS have close interaction
- Peripheral Leukocytes
  - Mediate immune response
  - Factors affecting them pass BBB
  - Express many of the same receptors and proteins as tissue
- Measure gene expression with real time quantitative PCR (qPCR)
- Linked to disease states
- Rapid, non-invasive, repeated measures

Iga et al 2008

Gene Expression Correlates with Disease Severity

R² = 0.368

Gene expression sums were compared to disease severity, using the Hamilton Depression Rating Scale clinical interview (HAM-D-24)

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