Neurostimulation in Treatment Resistant Depression

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With each successive treatment failure, the landscape changes:

Major Depression
Current Treatment Landscape

Unmet Medical Needs

STAR*D Study demonstrates that current treatment has limited effectiveness


Likelihood of discontinuing treatment increases with each new medication attempt

Vagal Nerve Stimulation
The VNS Therapy System Components

Rationale for VNS Therapy in depression

- Anatomical projections of vagus nerve into areas of the brain known to be implicated in depression
- Evidence of mood improvement in epilepsy studies, irrespective of seizure control
- Use of anticonvulsants as mood stabilizers/augmentation has established history in psychiatry
- Neuroimaging data have demonstrated that VNS Therapy affects many areas of the brain implicated in neuropsychiatric disorders
- Effects on neurotransmitters implicated in depression
- Activity in animal antidepressant model (FST)

Pivotal Study Long-Term Analyses Demonstrate Response Rates Increase Over Time During Adjunctive VNS Therapy

![Bar chart showing % Response over time for IDS-SR, HRSD, and MADRS scales.]

Response defined as ≥50% reduction in IDS-SR, HRSD, MADRS compared with baseline.

24-month Data on File, Cyberonics, Inc.

fMRI Shows Increased Limbic Activity in Brains of Patients With TRD During VNS Therapy

fMRI= functional magnetic resonance imaging.
Data from the Medical University of South Carolina Center for Advanced Imaging Research.
Transcranial Magnetic Stimulation

TMS: Sylvanus P. Thompson (1910) London
Best Practices Treatment Guideline for Depression
Based on 2010 APA guidelines and

Adapted from: Practice Guideline for the Treatment of Patients with Major Depressive Disorder, 3rd Edition, APA (2010)

Treating the Brain as an Electrochemical Target

Brain activity can be altered:

- Chemically (eg, via drugs)
- Electrically (eg, via TMS)

- **Drug action is anatomically diffuse and systemic**
- **TMS is focused, non-invasive and non-systemic**

Major brain regions known to be involved in mood regulation

Pizzigalli (2011) Neuropsychopharmacology
Transcranial Magnetic Stimulation (TMS)

- The treatment coil produces MRI-strength magnetic field pulses.
- Magnetic field pulses pass unimpeded through the cranium for 2-3 cm. and induce a small electric current.
- Induced electric currents stimulate the firing of nearby neurons, causing the release of neurotransmitters and clinical effects.

Targeted Effects on Mood Circuits in Brain

Activation of fronto-cingulate brain circuit following a course of TMS applied to the left dorsolateral prefrontal cortex in patients with Major Depression

Deep Brain Stimulation

Neuroanatomy of Depression
Rationale for Targeting the Ventral Capsule/Ventral Striatum

1. VS is a central node in the limbic-cortical-subcortical network thought to be involved in emotional processing
2. VS is central in processing reward and pleasure information
3. VS is ideally suited to modulate reward-motivated behavior
4. VC contains white matter tracts connecting VS to areas mentioned above
Operative Results and Post-op Management

- Immediate feeling of a “smile” or “giggle” when stimulator turned on
- Increase in subjective mood immediately, decrease in anxiety
  - Described pattern of both short term and long term changes leading to improvement
- Continued on home medications, recovery period, discharged on POD 3

Intravenous Ketamine
Ketamine Response Rates to Ketamine in a Double-Blind Placebo Crossover Trial in Patients with Treatment-Resistant Major Depression (N=18)

Response: 50% decrease in HAMD from baseline

Historical Control

62-65%

Venlafaxine
SSRI
Bupropion

Zarate et al. Arch Gen Psychiatry 2006;63:856-64.
Relative abundance of neurotransmitters

- Glutamate ~60% of synapses
- GABA ~30% of synapses
- Monoamines, peptides, other AAs (e.g. glycine) <5%

Glutamate Pharmacology

- Glutamate is one of the most common transmitters in the CNS
  - Fast, excitatory transmitter; receptors on almost all neurons. Transmitter in ~60% of neurons, esp cortex, limbic structures.
- Glutamate binds to 4 classes of receptor
  - three "ionotropic" receptor classes - ligand-gated ion channels which are characterized by the different ligands that bind to them:
    - AMPA
    - kainic acid
    - N-methyl-D-aspartate or NMDA
  - one G-protein coupled or "metabotropic" receptor class.
Glutamate Function

- Under physiological conditions, activation of ionotropic receptors in neurons initiates transient depolarization and excitation.
- AMPA-Rs mediate the fast component of excitatory postsynaptic currents.
- NMDA-Rs underlie a slower component.
- AMPA-Rs modulate Ca++ influx through NMDA-Rs.
  - Depolarization of the postsynaptic neuronal membrane via AMPA-Rs relieves the Mg++ block of the NMDA-R ion channel (this occurs in NMDA-R under resting conditions). This allows controlled Ca++ influx through the NMDA-R. This voltage-dependent modulation of the NMDA-R results in activity-driven synaptic modulation.
- Glutamate overactivity can lead to neuronal death due to Ca++ toxicity, other associated mechanisms.

NMDA- Receptors

Structure - tetramers of two NR1 subunits and two NR2 subunits (some brain areas have NR3 subunits).

Binding sites on the extracellular domain: NR1: co-agonist glycine; NR2: glutamate. For efficient ion channel opening, the NMDA receptor requires both glutamate and the co-agonist glycine.

Binding sites in the ion channel: Mg2+; PCP/ketamine site

NMDA antagonists: Synthetic antagonists include:
- MK-801 (dizocilpine)
- Phencyclidine
- Ketamine
- Dextromethorphan
- Memantine, Amantadine
- Procyclidine

NMDA modulators: Mg2+ blocks the NMDA channel in a voltage-dependent manner.
- Na+, K+, and Ca2+ not only pass through the NMDA receptor channel but also modulate the activity of NMDA receptors.
- Zn2+ blocks the NMDA current in a non-competitive and voltage-independent manner.
- The activity of NMDA receptors is also sensitive to the changes in H+ concentration, and is partially inhibited by the ambient concentration of H+ under physiological conditions.
Single Dose Ketamine Infusion Studies (1)

- Diazgranados; Arch Gen Psych 2010
- Treatment refractory bipolar depression, unmedicated
- Randomized, double blind, 2 period crossover
- Ketamine (0.5mg/kg) or placebo via 40 minute IV infusions
- Assessments to 14 days

Ketamine Responders (%)

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MADRS Time after infusion

Ketamine
Placebo

Percent of responders (>50% ↓ HAMD)

Main side effects of ketamine: Perceptual disturbances and dizziness; confusion; elevated blood pressure; euphoria; increased libido
- Generally occurred in 1st 20min of infusion.

Single Dose Ketamine Infusion Studies (2)

- Zarate, Arch Gen Psych 2006
- Treatment resistant MDD, unmedicated
- Single 0.5mg/kg IV infusion; placebo controlled, crossover design

Percent responders (≥50% ↓HAMD)

Percent in remission (HAMD <7)

Main side effects of ketamine: Perceptual disturbances and dizziness; confusion; elevated blood pressure; euphoria; increased libido
- Generally occurred in 1st 20min of infusion.
Electro Convulsive Therapy

• Early (Pre-ECT) History

• In the 1933 Dr. Manfred Sakel developed Insulin Coma Therapy (Insulin-shock behandlung) – treated opioid dependent pt’s first, later schizophrenia.
• Txs were occasionally, but not always, accompanied by seizures.
• Sakel later claimed to have invented convulsive therapy, but this is disputed.
History of Convulsive Therapies

- 1938 – Ugo Cerletti and Lucio Bini induce seizures in Rome using electrical stimuli

- 1940 – Renato Almansi and David Impasto administer ECT at Columbus Hospital in NYC. Lothar Kalinowsky starts giving ECT at Psychiatric Institute

- 1940 – A.E. Bennett uses curare for muscle relaxation with Metrazol convulsive therapy

- 1952 – Holmberg uses succinylcholine as a muscle relaxant with ECT
Electrical Stimulus

- Brief-pulse square-wave AC
- Voltage approx. 200V (based upon 220 Ω impedance)
- Current 0.9A
- Frequency 30 - 70Hz
- Pulsewidth 0.5 - 2 msec
- Duration 0.1 - 8 sec
- Charge 25 - 504mC (5 - 99J)
How does it work?
• Seizure - 15 to 180 sec (by EEG)
• Low-dose RUL ECT - Less effective clinically despite adequate seizure duration
• Down-regulation of beta receptors
• Up-regulation of 5HT2 receptors
• GABA (anti-convulsant theory of ECT)
• BDNF (reversal of hippocampal atrophy)

Anticonvulsant theory of ECT
• Increasing seizure threshold during a course of ECT is associated with clinical response
• Hypothesis: linked anticonvulsant and antidepressant response to ECT
ECT induced seizure

• Discharge of neuronal population which is:
  – Paroxysmal
  – Synchronous
  – Repetitive

• Post-ictal suppression follows seizure
  – Inhibitory interneurons
  – GABA (as detected by MRS)

ECS (ECT) induced depolarization

NE, 5HT → cAMP → PKA → CREB → BDNF

Modern (Modified) ECT

- General anesthesia (propofol 1mg/kg, etomidate 0.15mg/kg, methohexital 1mg/kg))
- Muscle relaxant (succinylcholine 1mg/kg, mivacurium 0.15mg/kg))
- Anticholinergic (glycopyrrolate 0.2mg, atropine 0.4mg)
- Oxygen/ventilation by mask
- Continuous cardiac and EEG monitoring
- (Other pre- and post-medications as indicated – NTG, Beta-blockers, promethazine, ketorolac, midazolam, sumatriptan, sodium amytal)

Diagnostic Indications

- MDD
- BPAD
- Psychosis (Schizophrenia, SAFD)
- Catatonia
- NMS
- PD
- Delirium
Reasons to consider ECT first

• Severe suicidality
• Catatonia/NMS
• Patient preference (usually previous ECT)
• Pregnancy and severe psychiatric illness

All Modalities Are Needed

• Dent: the only site in North America with all Tx’s
• There will always be none responders
• Avoids using only one treatment for all
• Our patients deserve the best treatments
Thank You

Questions?