1 **Alternative Treatments:**

Neuromodulation Approaches to

Treatment Resistant Depression

Audrey R. Tyrka, MD, PhD
Assistant Professor
Brown University Department of Psychiatry
Associate Chief, Mood Disorders Program
Butler Hospital
Providence, Rhode Island

2 ## Disclosures

3 ## Overview

- Electroconvulsive therapy (ECT)
- Magnetic seizure therapy (MST)
- Repetitive transcranial magnetic stimulation (TMS)
- Vagus nerve stimulation (VNS)
- Deep brain stimulation (DBS)
- Considerations for new/experimental treatments

4 ## Electroconvulsive Therapy (ECT)

- Developed in 1930s, FDA-approved in 1979
- Patient under anesthesia
- 6 to 12 treatments (2-3/wk),
- Brief electrical pulse passed through scalp produces seizure on EEG
- Muscle paralysis prevents convulsive movement

5 ## Electroconvulsive Therapy (ECT)

- Considered the “gold standard” for severe depression
- Used for other severe disorders including mania, schizophrenia, and catatonia
- Often administered in the inpatient setting (hospitalized for 2-4 weeks)
- Can also be administered as an outpatient in some settings

6 ## Electroconvulsive Therapy (ECT)

- Treatment parameters influence the efficacy and tolerability of ECT
- Bilateral appears more effective than unilateral treatment
- Relatively higher doses of stimulation more effective
- However, higher doses and bilateral treatments associated with more cognitive side effects, particularly in elderly individuals.

7 Electroconvulsive Therapy vs. SHAM

Trial	# of Participants	Standard Effect Size (95% CI)
Wilson, 1963	12	-1.078 (-2.289 to 0.133)
West, 1981 25-1.255 (-2.170 to -0.341)		
Lambourn, 1978	40	-0.170 (-0.940 to 0.600)
Freeman, 1978	40	-0.629 (-1.264 to 0.006)
Gregory, 1985	69	-1.418 (-2.012 to -0.824)
Johnstone, 1980	70	-0.739 (-1.253 to -0.224)
Pooled fixed effects		-0.911 (-1.180 to -0.645)
Pooled random effects		-0.908 (-1.270 to -0.537)

8 Effects of ECT vs. Pharmacotherapy

9 ECT Limitations

- Headache, jaw ache, soar throat muscle aches
- Cognitive side effects: memory
- Access: hospital, often inpatient
- Anesthesia risks
- Cost (generally covered by insurance)
- Maintenance (30%-84% of those who remit experience relapse in 6 months)

10 Magnetic Seizure Therapy (MST)

- Investigational
- Magnet-induced stimulus (like TMS)
- High intensity
- Target “antidepressant regions”
- Fewer side effects than ECT
- 3 sessions/week
- Same as ECT
  - Anesthesia
  - Tonic-clonic seizure
  - Monitor EEG, vital signs

11 MST: Shorter Period of Post-Ictal Disorientation and Inattention

12 Transcranial Magnetic Stimulation (TMS)

- Recent FDA approval
- Patient sits in chair and has treatment coil positioned on head (target site left dorsolateral prefrontal cortex)
- 40 min daily for 4-6 wks
- Strong, pulsed magnetic fields pass through skull and produce small electrical currents in the brain that can activate brain cells

13 Potential Advantages of TMS

- No anesthesia
- Most common side effects are scalp pain or discomfort, particularly in the first week
- No systemic side effects such as cognitive effects, weight gain, sexual dysfunction, gastrointestinal

- Greater control over site and intensity of stimulation

14 ## TMS Limitations

- Device approved by FDA for those with only one treatment
- Optimal stimulation parameters?
- Maintenance Treatment ?
- 5 days/week for 4 to 6 weeks
- High Cost; will this be covered by insurance companies?

15 ## Neuronetics TMS Trials: Patient Criteria

- Male or female outpatients with major depressive episode, of moderate to severe symptom severity
- Baseline HAM-D 17 total score > 20, Item 1 > 2
- Treatment resistance defined by lack of response to at least one and no more than four antidepressant treatments in current episode
- Duration of current episode $\leq$ 3 years
- Clinically appropriate to discontinue existing antidepressant medications. Off antidepressants for the TMS trial.

16 ## TMS
Acute Study Outcomes

A. MADRS

(p=.058)

B. HAMD17

(p=.005)

O'Reardon et al, 2007

Biological Psychiatry

17

TMS Response and Remission Rates in Neuronetics Acute Study

18 **Highly Significant Outcomes in Subset (n=164) who did not respond to ONE Adequate Antidepressant Trial**

19 **Meta-Analysis of the Antidepressant Efficacy of High-Frequency rTMS**

20 **Sequential Right- and Left-Sided Adjunct TMS**

- TMS added to medication treatment
- Patients who had not responded to 2 adequate trials of medication
- Dorsolateral Prefrontal Cortex

21 **Vagus Nerve Stimulation (VNS)**

- FDA approved for epilepsy in 1997
- FDA approved for Treatment Resistant Depression in July 2005
- Implanted in over 30,000 patients worldwide
- Pulse generator implanted in left chest wall, wire attached to left vagus nerve in the neck
- Mild electrical pulses to the vagus nerve for transmission to the brain

22 **Vagus Nerve Stimulation (VNS)**

- Intermittent stimulation
  - 30 s on/5 min off
  - 24/7 continuous cycles
- Simple in-office programming (dosing) by treating physician
- Patient provided with Magnet that can turn VNS off
- No known interactions with medications

23 **VNS: Pathway to the Brain**

24 **Studies Into Potential Mechanism of Action of VNS Therapy**

25 **VNS Pivotal Study Design**

26 **VNS Pivotal Study: Baseline Patient Characteristics**

27 **Acute VNS Pivotal Study Results: LOCF 12-Week Response Rates**

28 **VNS Pivotal Study Design**

29 **Long-Term Response VNS Pivotal Study**

30 **Adjunctive VNS vs Treatment as Usual: Comparison of Patient Populations**

31 **VNS Pivotal Study vs. Comparative Study (TAU): Primary Analysis**

32 **VNS vs TAU: 12-Month $HAMD_{24}$**

33 **VNS Longer-Term Adverse Events**

34 **VNS: Limitations**

- Long term data not randomized
- Delayed antidepressant response
- Surgical procedure
- Cosmetic issues
- MRI contraindication
- Battery life (6-10 yr)
- Cost/insurance issues

35 **Deep Brain Stimulation (DBS)**

- FDA approved for Parkinson's and tremor, and now OCD. Under study for Treatment-Resistant Depression
- MRI to locate the target, then surgical holes in skull for electrode placement
- Two chest-wall internal pulse generators
- Stimulation parameters programmed by computer, through "wand"

36 **DBS: Subcallosal Cingulate Region (n=20)**

37 **DBS of Ventral Anterior Limb Internal Capsule/Ventral Striatum (n=15)**

38 **DBS Nucleus Accumbens (n=3)**

39 **Deep Brain Stimulation Limitations**

- Considerable surgical risk
- Cosmetic issues
- Battery life
- Limited, short-term, open-label data in psychiatry
- 2 Large Multi-center studies just recently started
- Optimal Targets and stimulation parameters?
- Future MRIs problematic
- Risk of hypomania

40 **The New Frontier: Neuromodulation of Treatment Resistant Depression**