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Interventional Psychiatry and the Treatment of Refractory Depression

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- ***Stockholder (directly purchased):*** Sage Therapeutics, Inc.

Learning Objective 1

Analyze the latest clinical data on interventional methods to manage treatment-resistant depression.

Case History

- 68-year-old retired man with type 1 diabetes. He presents to the hospital with severe major depression for 12 months; admitted for worsening symptoms.
- In the current episode, he has failed 2 antidepressants (citalopram & venlafaxine) and 2 antipsychotic augmentation trials.
- What treatment should be next?

Treatment Refractory Depression: A Significant, but Poorly Defined Problem

- ~30% of MDD patients fail current treatments
  - High disability → high service utilization
- TRMD = major depression that fails to respond to "*x*" adequate antidepressant trials
- Problems with the TRMD definition
  - "Response" vs. "remission?"
  - What is "x?"
  - What is "adequate?"

MDD = major depressive disorder; TRMD = treatment-resistant major depression.
Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.

TRMD: Proposed Definition

- STAR*D remission rates
  - Remission rates at each stage
    - 37% → 31% → ***14% → 13%***
  - Remission + maintenance x 1 year
    - 26% → 14% → ***5% → 3%***

- Two-stage TRMD definition
  - Stage 1 TRMD: Failure of ≤ 2 adequate trials
  - Stage 2 TRMD: Failure of ≥ 3 adequate trials

Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917; Conway CR, et al. *JAMA Psychiatry*. 2017;74: 9-10.

TRMD Stages and Treatment

- **Stage 1 TRMD (1 or 2 failures)**
  - Less invasive, novel mechanism treatments
    - Switch antidepressant, try augmentation strategies
    - rTMS, ketamine, buprenorphine
    - Consider ECT
- **Stage 2 TRMD (3 or more failures)**
  - More invasive interventions likely required
    - ECT, VNS
    - More aggressive pharm (combos, MAOIs, TCAs)

ECT = electroconvulsive therapy; MAOIs = monoamine oxidase inhibitors; rTMS = repetitive transcranial magnetic stimulation; TCAs = tricyclic antidepressants; VNS = vagus nerve stimulation.

Conway CR, et al. *JAMA Psychiatry*. 2017;74: 9-10.

Interventional Psychiatry & TRMD

- *Electroconvulsive therapy*
  - Gold standard; good effect size even in TRMD; a lot known about its use; side effects are an issue; stigma
- Vagus nerve stimulation
  - Approved in 2005; parameters not well established; slow onset of effects; requires surgery
- Transcranial magnetic stimulation
  - 7 devices approved since 2008; less invasive; parameters not well established; efficacy in severe TRMD not certain
- Investigational Methods
  - DBS, MST, FEAST, tDCS…infusion & inhalation approaches

DBS = deep brain stimulation; FEAST = focal electrically administered seizure therapy; MST = magnetic seizure therapy; tDCS = transcranial direct current stimulation.

Effective Use of ECT

- Optimize acute course by adjusting electrode placement, stimulus parameters,, number of treatments and perhaps seizure length
  - Concurrent psychotropic medications improve outcomes but may add to memory problems (Sackeim et al., 2009)
- Sequence of treatment
  - RUL with ultrabrief pulses @ 6X threshold → Max Charge RUL → Bilateral with brief pulses @ 2X threshold → Max Bilateral
  - ECT “Failure” = Failure of Max Charge Bilateral ECT
- Identify effective maintenance treatment

What to expect from ECT?

- **Acute Clinical Response**
  - Good effect size: 0.9 vs. sham; 0.8 vs. meds (Lancet, 2003)
  - Overall remission rate: ~60+%
  - TRMD: ~50% initial response rate + high rates of early relapse without effective maintenance
- **Side-Effects**
  - Headaches, nausea, muscle soreness
  - Acute confusion
  - Memory impairment (Bilateral >> Unilateral)

Maintenance Treatment

- **Most ECT failures = failures of maintenance**
  - Without successful maintenance, most patients will relapse in 6 weeks – 6 months
    - 85% (placebo); 60% (nortrip); 40% (Li + nortrip)
- **Maintenance Strategies**
  - Medications (different classes, combinations)
  - Evidence-based psychotherapies
  - Maintenance ECT (Kellner et al., 2016 + meds)
  - rTMS / VNS?

Kellner CH, et al. *Am J Psychiatry*. 2016;173(11):1110-1118.

Beyond ECT

- Vagus nerve stimulation (VNS)
- Repetitive transcranial magnetic stimulation (rTMS)
- Investigational Methods

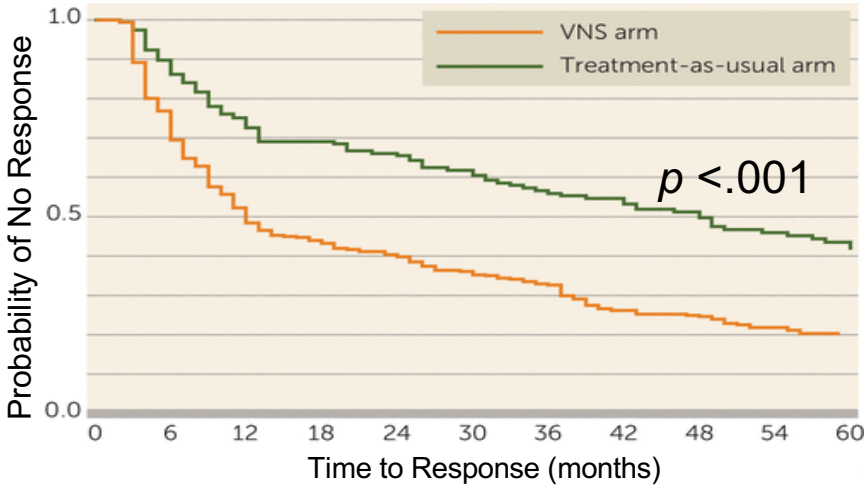
Vagus Nerve Stimulation (VNS)

- **Approved for epilepsy in 1997**
  - Stimulus parameters reasonably well defined
- **Use in psychiatry consistent with effects of other anticonvulsant treatments (including ECT)**
- **Requires surgery & pulse generator in chest**
- **Approved by FDA for refractory depression in 2005**
  - Stimulus parameters not as well defined
  - 0.5 ms, 0.25 mA pulses @ 20-30Hz x 30 s q 5 min

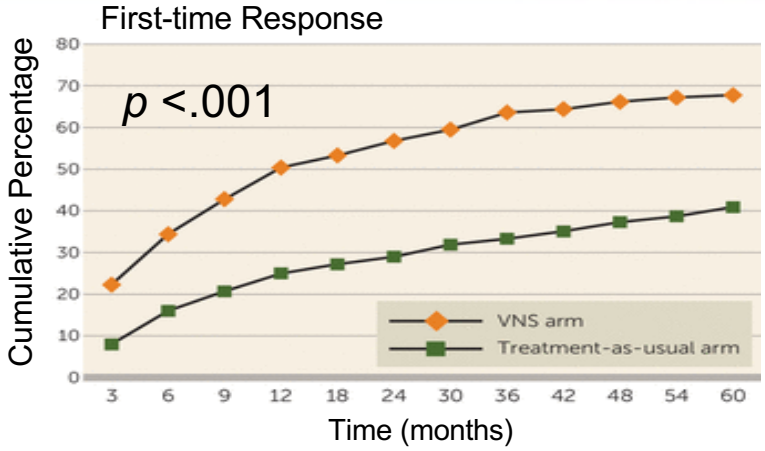
VNS & TRMD: 5-Year Observational Study

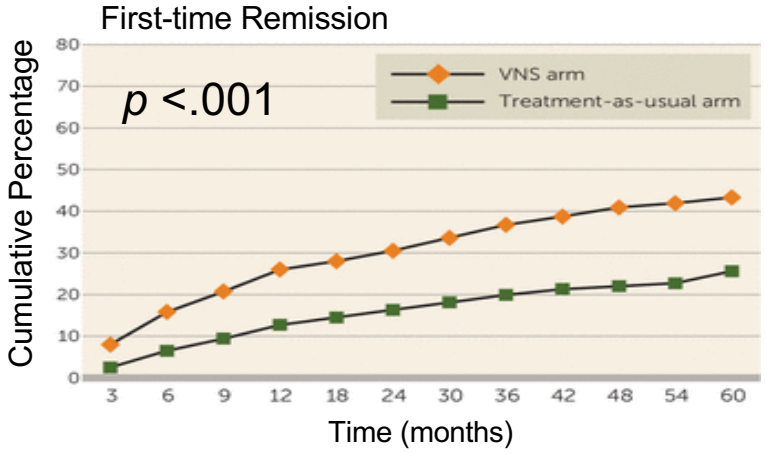
You Are in it for the Long Haul

- Non-psychotic TRMD patients (N=795)
- Unipolar or bipolar depression
- Episode of ≥ 2 years + ≥ 3 episodes
- Failed ≥ 4 treatments (including ECT)



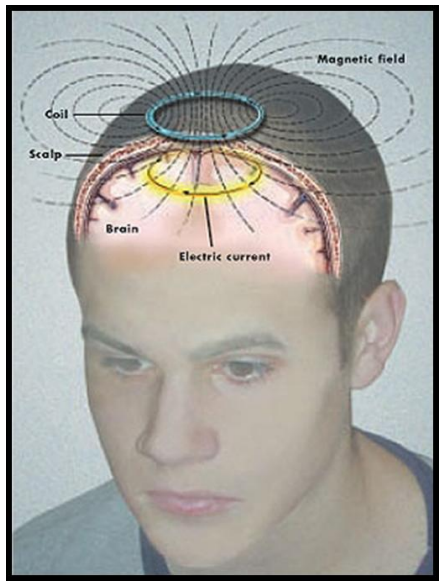
Aaronson ST, et al. *Am J Psychiatry*. 2017;174:640-648.





Repetitive Transcranial Magnetic Stimulation (rTMS)

- **Electromagnetic coil generates a fluctuating field to induce currents in neocortex**
  - Penetrates ~ 2-3 cm into cortex
  - 7 devices FDA approved since 2008
- **Stimulation parameters**
  - 1.5-3k, 0.1 ms pulses/day
    @ 90-120% motor threshold
    x 15-20 days (5x/wk)
  - Left DLPFC = 10 Hz
  - Right DLPFC = 1 Hz



rTMS: Current Status

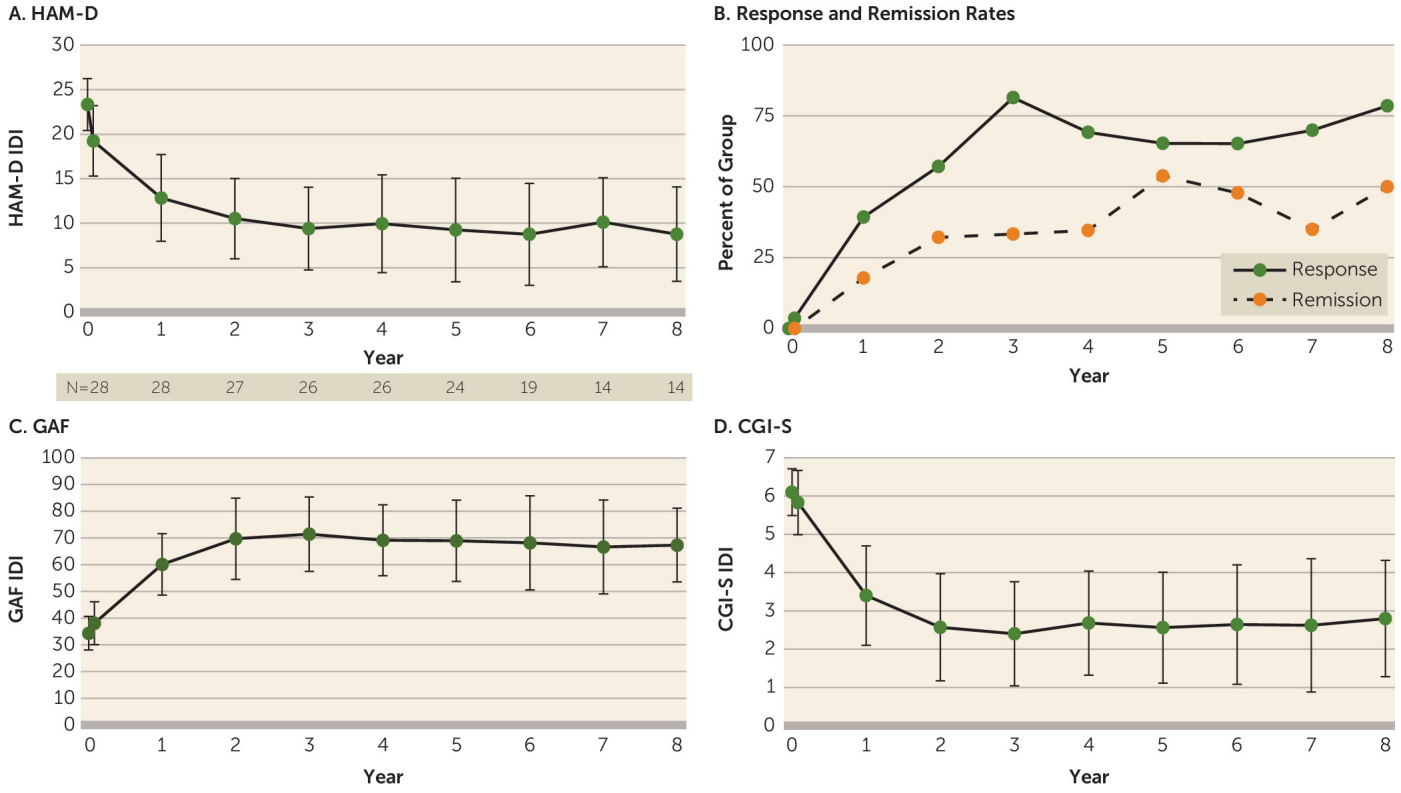
- **Optimal parameters not defined**
  - Multiple stimulation paradigms appear to have benefit
    - Bilateral, priming low freq, high freq, low freq, iTBS >> SHAM = accelerated, synchronized and deep rTMS (Brunoni et al., 2017)
  - WUSM: 10Hz x 40, 0.25 ms pulses to Left-DLPFC q 30s (3000/day) @ 120% MT x 15-20 days; 5 days/week
- **Effectiveness in "refractory" depression is uncertain**
  - Modest effects but may be comparable to meds
    - ~15% acute remission on HAM-D for 2-3 prior failures
    - Effect size 0.42 (2-4 failures); 0.83 (1 failure) (Lisanby et al., 2009)
- **May have unique uses**
  - Patient preference, postpartum depression, pregnancy

Lisanby SH, et al. *Neuropsychopharmacology*. 2009;34(2):522-534.

Investigational Methods

- **Magnetic Seizure Therapy (MST)**
- **Focal Electrically Administered Seizure Therapy (FEAST)**
- **Transcranial Direct Current Stimulation (tDCS)**
- **Others: CES, EpCS, low field MR stimulation**
- **Deep Brain Stimulation (DBS)**
- **Infusion/inhalation Methods**
  - NMDA antagonists; GABAergic neurosteroids?

Outcomes of Subcallosal Cingulate DBS: The Long Haul Redux

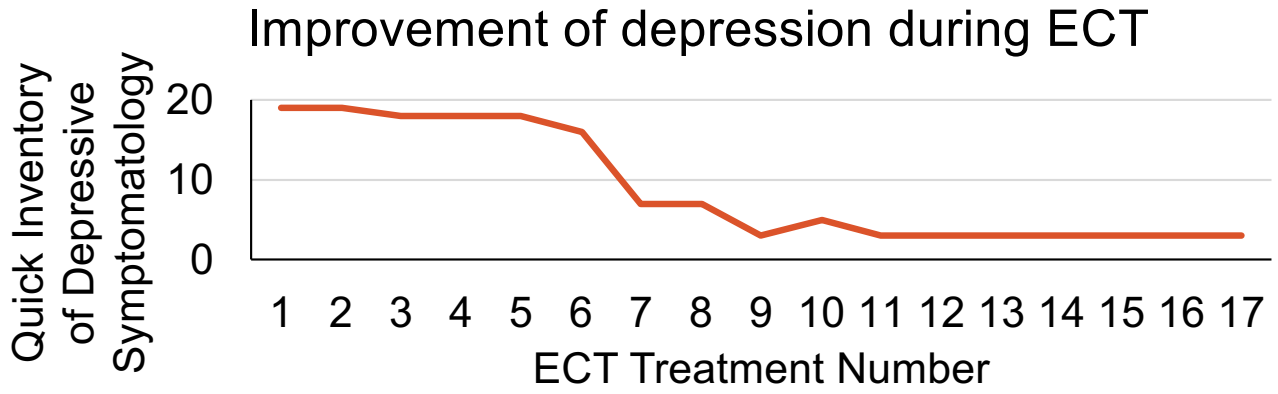


N = 28

Crowell AL, et al. *Am J Psychiatry*. 2019;176(11):949-956.

Case History (cont.)

- 68-year-old retired man with type 1 diabetes. He presents to the hospital with severe major depression for 12 months; admitted for worsening symptoms.
- In the current episode, he has failed 2 antidepressants (citalopram & venlafaxine) and 2 antipsychotic augmentation trials.
- RUL ECT!



RUL = Right unilateral (ECT).

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Describe how to stage treatment-resistant depression and its treatment, including the role of interventional (neuromodulation) methods.

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.

ECT: Key Factors

- **Generalized Brain Seizure**

- **Electrical Factors**
  - Electrode placement (RUL vs. BL vs. Bifrontal)
  - Electrical dosing & seizure threshold
  - Stimulus parameters (charge)
    - Frequency (Hz)
    - Pulse width (ultrabrief vs. brief)