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Neurostimulation and Treatment Refractory Illness

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Disclosures

- No Disclosures for Dr. Rettenmier

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Learning Objectives

Participant will :

- Identify psychiatric conditions currently FDA approved for the use of Electroconvulsive Therapy (ECT), Transmagnetic Stimulation (TMS), and Vagus Nerve Stimulation (VNS)
- Identify what preliminary requirements are recommended for each treatment
- Be able to identify side effects and contraindications to each of the mentioned treatments
- Gain a basic understanding of what to expect during a course of ECT/TMS as well as a general expectation of VNS response.
- Gain an understanding of how modalities have changed over time to improve the overall treatment experience.

Agenda

- What is Neurostimulation?
- ECT:
  - History, Indications, Advances and Practice Changes
  - What to expect with an ECT series?
  - What does an ECT treatment look like?
- TMS:
  - History, Indications, Advances and Practice Changes
  - What to expect with a TMS series?
  - What does TMS look like?
- VNS
  - History, Indications, Expectations

Neurostimulation

- The use of electrical or magnetic impulses to modulate the central or peripheral nervous system.
- Neurology and Neurosurgery often use to assist in controlling nerve signaling: pain management, control of Parkinsonism, hearing and visual prostheses, etc
- In Psychiatry, the first area of use was in electroconvulsive therapy beginning in the late 1930's
- Offers a targeted, non-systemic option that can alter neurochemicals by altering aberrant neuronal activity
- FDA cleared use of focal neurostimulation by Vagus nerve stimulation and transcranial magnetic stimulation for depression
- On going research looking at the use of magnetic seizure therapy, deep brain stimulation and direct current stimulation

Electroconvulsive Therapy

- Electroconvulsive therapy (ECT) is a therapeutic procedure which has demonstrated efficacy for patients who fall into certain diagnostic groups and for others who have not responded to conventional treatment.
  - It uses a small, carefully controlled electrical current between two electrodes that are applied to specific areas of the head in order to trigger the brain to experience a self-regulated seizure
  - To date, it is the most effective and reliable treatment offered for severe depression

1930's- 1970's

- **Dr. Ugo Cerletti: Rome, 1938**

  First use of electrical current to stimulate a seizure in a 40 y/o man diagnosed with schizophrenia

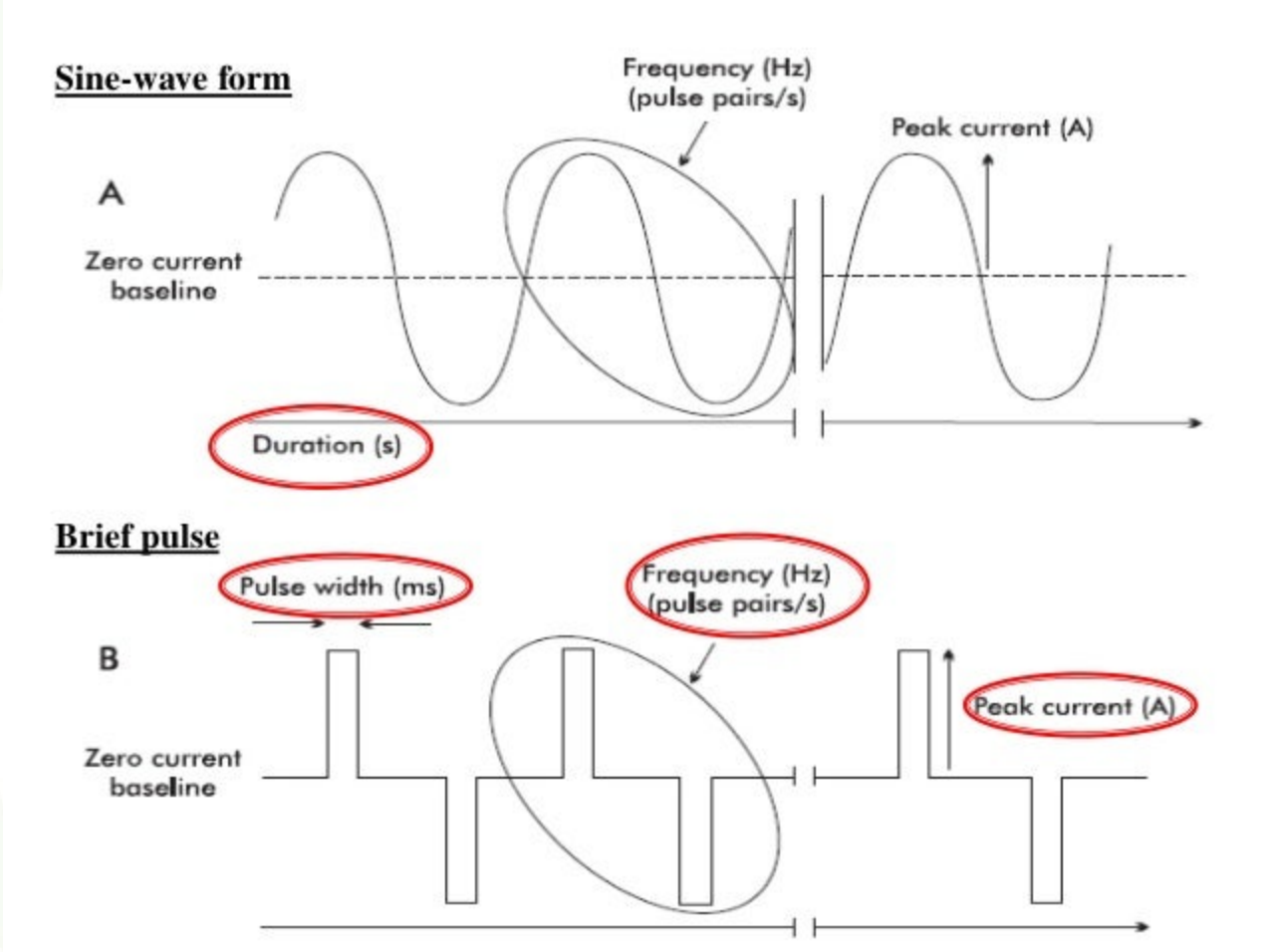
- 1950's: ECT on the decline
  - Anti-psychiatry movement
  - Advent of Neuroleptic medications
- Laws limiting ECT

United Artist

Wright, M.D.et.al.. Jefferson Journal of Psychiatry: 1990: Vol. 8 : Iss. 2 , Article 10

Then and Now: Practice Changes

- Sine wave vs pulsed electrical stimulation
  - Tolerability and recovery improvement
- Modification of Pulse Width
  - Ultrabrief vs Brief Pulse
- Improved evidence-based research
- Changes in Electrode positioning
- Changes in Monitoring
- Changes in anesthesia
  - Paralytics: 1951
  - Sedation: 1970s



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Mankad, M.V., et al. Clinical Manual of Electroconvulsive Therapy. APA Publishing, 2010, pp 3-7,15-17,48-49.

Who Qualifies?

American Psychiatric Association Practice Guidelines

Primary Use:

1. A need for rapid, definitive response because of the severity of a psychiatric or medical condition
2. When the risks of other treatments outweigh the risks of ECT
3. A history of poor medication response or good ECT response
4. The patient's strong preference

Secondary Use:

1. Poor response or intolerance to alternative treatments
2. Patient has a clinical condition that has deteriorated to a degree where urgent/emergent treatment is needed

Diagnoses/Where Does It Work Best?

- **FDA Approved Treatments:**
  - Major Depressive Disorder
  - Bipolar depression
  - Catatonia
- **Other Common Diagnoses:**
  - Mania
  - Psychosis
  - Self injury/aggression in ASD
  - Parkinson's Disease
  - Epilepsy

Depression

- Remission rates are generally reported to be 80-90%
- Severely Resistant Depression: 50-60%
- Older patients have most consistent benefit
  - Psychosis and catatonia
- Comorbid Personality Disorder: Borderline PD vs Other PD

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Prudic J, et al. *Am J Psychiatry* 1996; 153: 985– 992..

Lisanby, SH.. *NEJM.*. 2007;357(19): 1939-1945

Greenberg, RM et al.. Am J Geriatr Psychiatry. 2005;13(4): 268-281

Bipolar Disorder

- Often used for treatment refractory bipolar depression
  - Same effective response rate as unipolar depression
  - Potential to transition to mania
- Bipolar Mania
  - Clinical improvement in over 60% of patients
  - More rapidly effective than lithium in mania and in mixed states
- Delirium due to Acute Manic Episode

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Perugi et. al. *Curr Neuropharmacol*. 2017 Apr;15(3):359-371.

Small, J. G. et. al. *Archives of general psychiatry*, 1988: *45*(8) 727–732.

Schizophrenia and Schizoaffective Disorder

- Outside of the US, schizophrenia is one of the most common indications for ECT
- APA recommendations:
  - Previous response
  - Abrupt exacerbations
  - Catatonia
  - Schizoaffective disorder: mixed mood disorder with underlying primary schizophrenia
- Acute onset & first break psychosis- 40-60% response rate with synergistic antipsychotics
- Chronic schizophrenia: 5-10%
- Positive symptoms most likely to respond
- High rate of relapse with discontinuation

Kellner, C.H. *Convuls Ther,* 1995;*11*(3), 155-157.

ECT in the Elderly

- Highest response rate in ECT
- Special Considerations
  - Comorbid neurocognitive decline
  - Medical complications
  - Brain atrophy
- Prolonging Remission in Depressed Elderly (PRIDE) study
  - Phase 1 : efficacy of ECT + Venlafaxine
  - Phase 2 : evaluated efficacy of continuation ECT + medication VS medication only
  - Combination group with significantly lower HAM-D scores

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Lisanby SH, et. al.. Am J Geriatr Psychiatry. 2020 Mar;28(3):304-316.

Kellner CH. et. al. Am J Psychiatry. 2016 Nov 1;173(11):1110-1118.

Pediatric ECT

- Limited Use:
  - Reluctance to “use what are perceived to be drastic measures”
  - Child/adolescent psychiatrists’ lack of experience with ECT
  - Concern that ECT may cause “damage” to a developing brain
  - Legal regulations limiting/restricting use of ECT in minors of various ages
- AACAP Guidelines: Ethics Committee Report of 2012
- Common diagnoses
- Aggression in Autism

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Mankad, M.V., et al. Clinical Manual of Electroconvulsive Therapy. APA Publishing, 2010, pp 20
Park, S. E. et.al.. *The Psychiatric clinics of North America*, 2021: *44*(1), 23–33.

Contraindications to ECT

There are NO absolute contraindications regarding ECT; case by case evaluation

Medical Conditions with Increased Risk

- Space occupying lesions in the brain
- Other condition causing increased ICP
- Recent myocardial infarction
- Recent intracerebral hemorrhage
- Unstable vascular aneurysm or malformation
- Pheochromocytoma
- High anesthesia risk (ASA class 4-5)
- Patients in active withdrawal from alcohol or drugs
  - Caution when considering patients in early recovery
- Active pulmonary illness
- Pregnancy

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Mankad, M.V., et al. Clinical Manual of Electroconvulsive Therapy. APA Publishing. 2010, pp,28-30,39,140.

Course of ECT

- Typically between 8-14 treatments
- 2-3 treatments per week
- Once mood is stabilized/goal reached, will usually recommend a brief taper and then stopping treatments
- Maintenance:
  - Not usually recommended during first series, unless individual deemed to be treatment dependent

Maintenance ECT

- Up to 70% relapse if ECT discontinued without concurrent medication use
  - 30% at 6 months if mECT transition occurs
- Differs from Index course
  - Occurs over time with spacing of treatment – weeks to months
- Unique Side effects
  - More likely to struggle with memory deficits longer term
- Considered treatment dependent

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Prudic, J., et. al.. *The Journal of ECT, 2013; 29*(1), 3–12.

Common Side Effects

- Headaches
- Muscle aches
- Jaw soreness
- Nausea
- Dental implications
- Post-ictal disorientation
- Memory
  - Antegrade and Retrograde

Uncommon Adverse Events

- Prolonged seizure (one lasting > 3 minutes)
- Myocardial infarctions
- Arrhythmias
- Hypertension
- Ischemia
- Bronchospasm
- Status epilepticus (prolonged seizure or multiple seizures in succession w/o return to conscious state)
- Delirium
- Prolonged apnea due to pseudocholinesterase deficiency

What Does Treatment Look Like?

Image from mclean.org/ect

Right Unilateral

- Requires lower charge to reach seizure threshold
- Therapeutic range 4-6x seizure threshold
- Lower side effect profile
- Requires greater number of total treatments

What Does Treatment Look Like?

http://www.psych.med.umich.edu/ECT/how-does-ECT-work.asp

Bilateral

- Requires higher initial charge to reach seizure threshold
- Therapeutic range 1.5-2.5x seizure threshold
- Higher side effect profile
- Requires fewer number of total treatments

How It Works…

- We don't completely know
- Hypothesized mechanisms:
  - Neurochemical
  - Neuroendocrine
  - Anticonvulsant
  - Neuroplasticity
- Role of Imaging
  - MRI
  - MRS

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Piccinni, A., et. al. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology*, 2009:*19*(5), 349–355.
Freire, T. F., et. al. *Brain research bulletin*, 2016: *121*, 263–269.
Gbyl K. et. al. *Biol Psychiatry*. 2021 Jan 10;104:110048

ECT Clinical Considerations

Pros

- Rapid response for severe depression and other debilitating mental illness effects
- Safe, well tolerated
- Can be used in pregnancy
- No ongoing systemic side effects
- Insurance well versed with treatment outcomes
- Can be used for individuals with epilepsy

Cons

- Requires anesthesia and IV placement
- Individuals not recommended to work or drive during a series
- Short term memory side effects
- Treatment dependent potential
- Requires a certain medical stability
- Increased risk for potential COVID-19 exposure

ECT Moving Forward

- Computational Modeling to Optimize Delivered Stimulation in ECT
  - Allows for individualized treatment
  - Can target specific brain regions
  - Can follow with high density EEG
- Improving side effect profile (lessening cognitive burden)
  - Magnetic Seizure Therapy
  - Focal Electrically Administered Seizure Therapy

ECT During a Pandemic

- ECT is considered a life saving procedure
- Interventions to reduce risk:
    - Screening questionnaires
    - Testing as available
    - Personal protective equipment
    - HEPA filters
    - Viral filters on ambu bags
- Relationship with patients
- Supportive staff and administration

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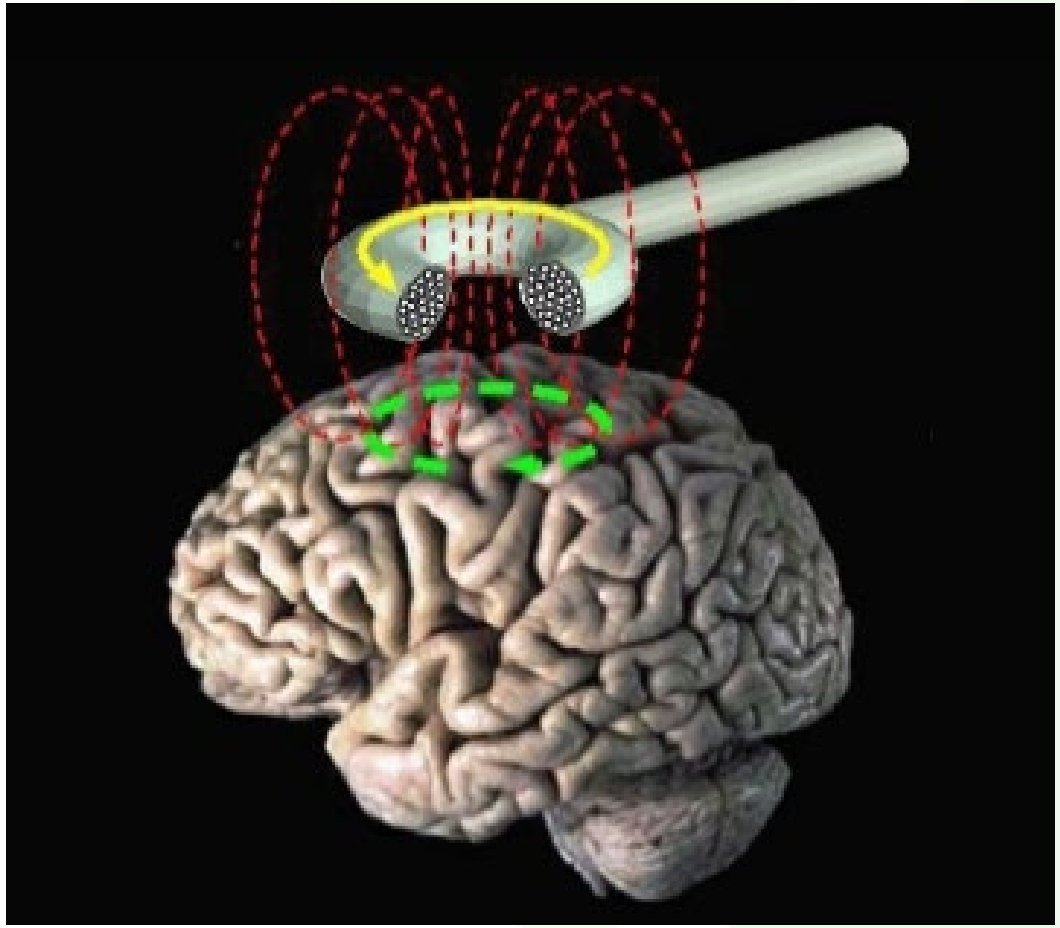
Transmagnetic Stimulation



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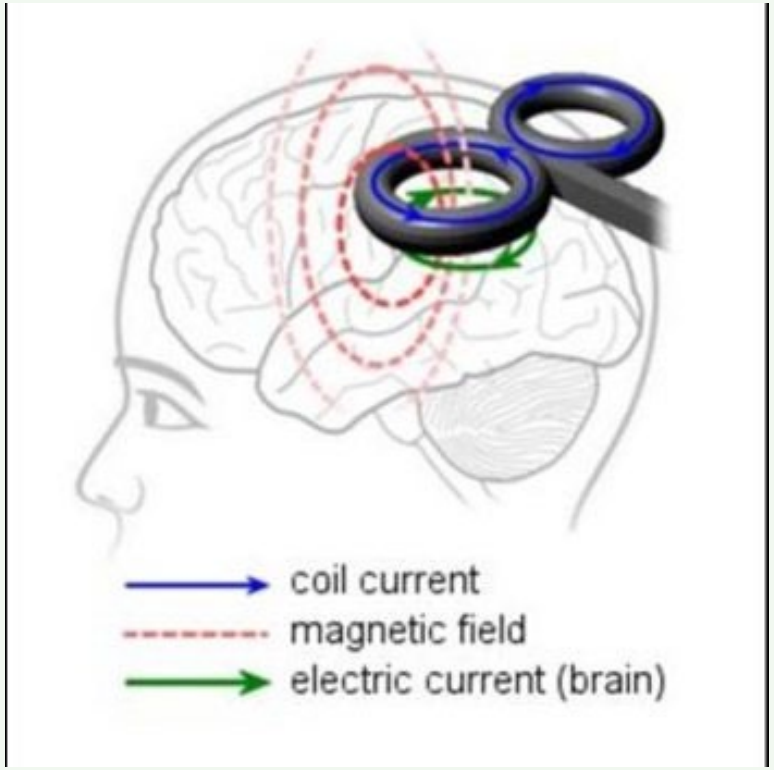
Transmagnetic Stimulation

What is It?

- TMS is a non-invasive, non-drug treatment used to treat psychiatric and neurological disorders.
- FDA Approved for
  - **Major Depressive Disorder without Psychosis (2008)**
  - **Obsessive Compulsive Disorder (2018)**
  - **Smoking Cessation (2021)**
  - **Migraines (2013)**



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Science of TMS

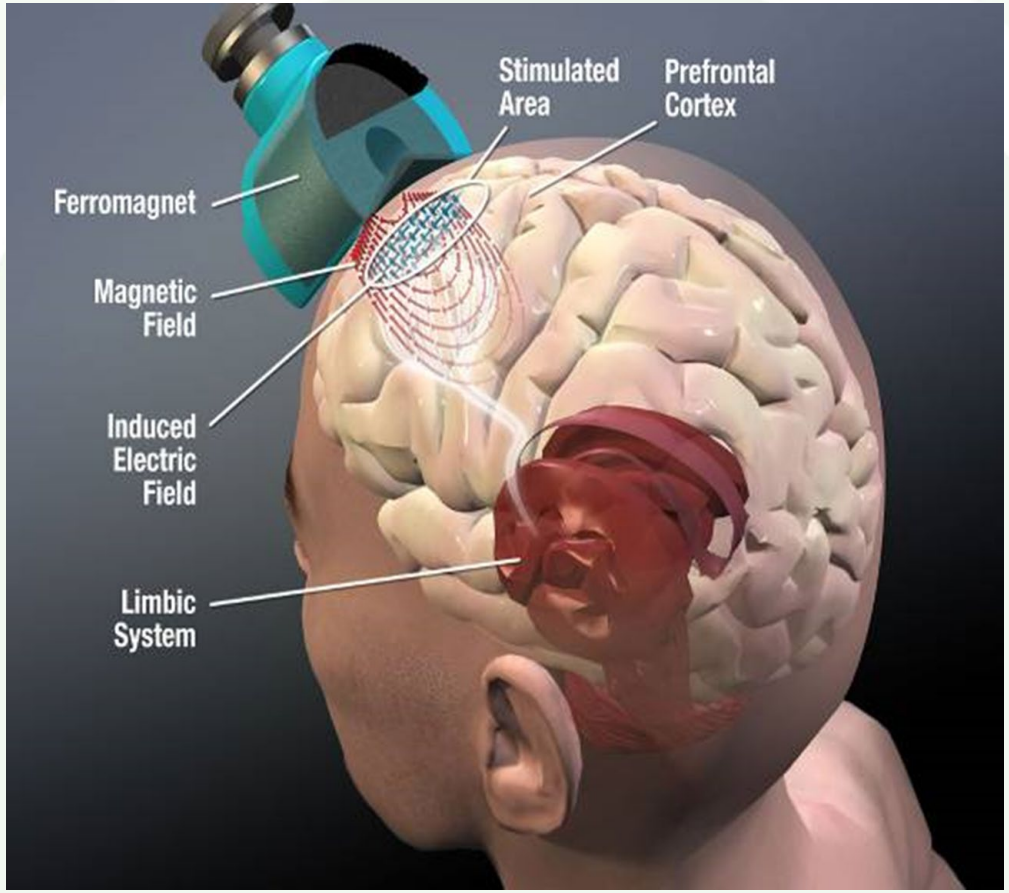
Pulse electricity around wire coils

Magnetic field crosses through skull

ELECTRIC field >**electric current** using ions in the body to carry charge

Triggers a depolarization/nerve cell action potential to make it fire

BRAIN STIMULATION!!



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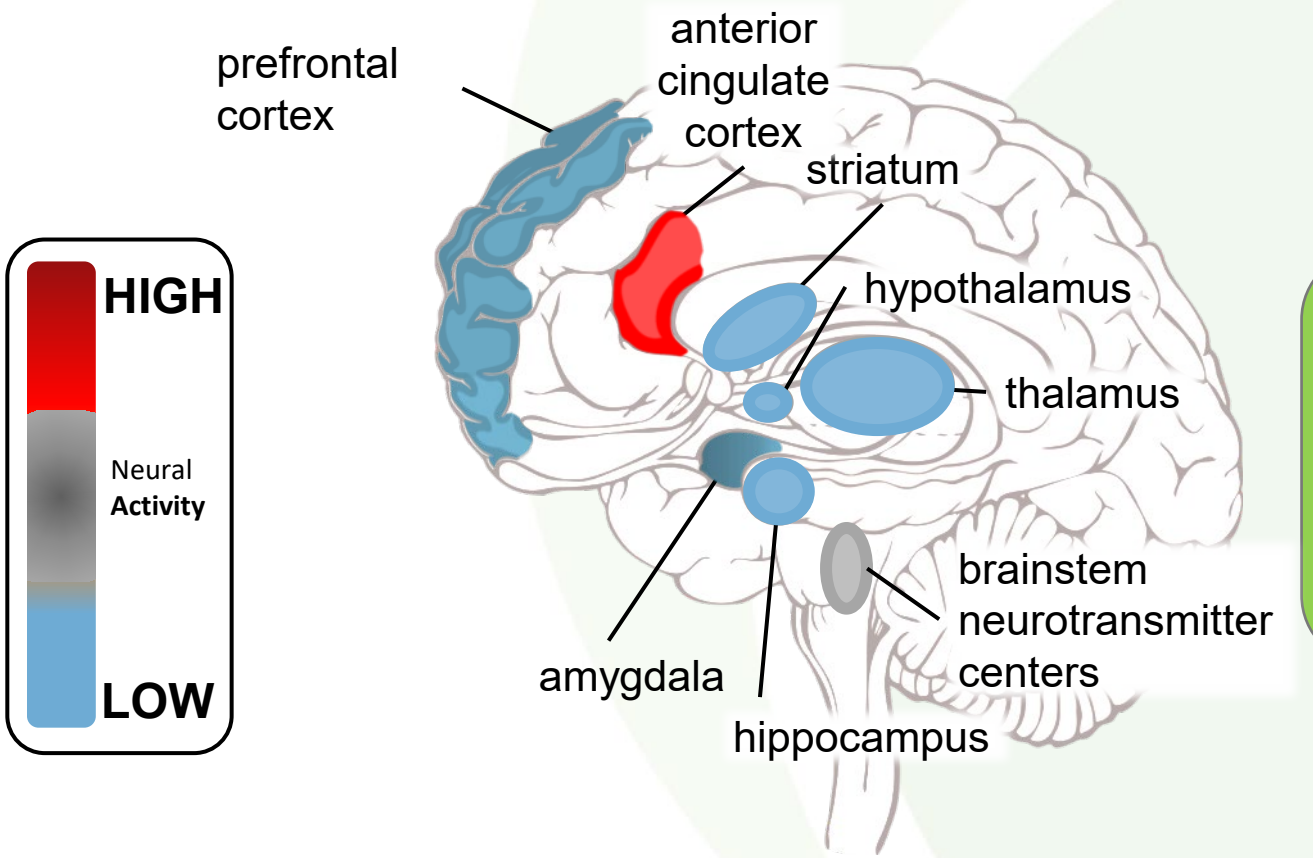
Clarification of Terms

rTMS = 'repetitive' TMS – this means that the stimulations come in trains (or packets) that can be of high or low frequency

iTBS - Intermittent theta burst stimulation (more on this later)

dTMS (deep TMS) = also delivers repetitive pulses, but the design of a dTMS coil will allow stimulation to reach slightly deeper/wider area of the brain

Major Depressive Disorder: Areas Impacted



In MDD, some areas of the brain are hypoactive and others are hyperactive.

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Major Depression: Who Qualifies?

Typical Insurance Requirements:

- MDD, without psychotic features (recurrent or single episode)
- Medication trials (1-4) of adequate dose and duration
- Some require Failed Trial of Psychotherapy
- Candidate for ECT or had past ECT and wants TMS as less invasive option
- Regular standardized symptom assessment scales (PHQ9, MADRS, CGI)
- Must use FDA-cleared device, TMS trained psychiatrist
- Other exclusions - substance abuse, dementia, medical exclusions
- Can treat 'off-label' but may not be covered by insurance

Biologic Effects of TMS

Immediate Effects

- Induces electric current
- Depolarizes neurons in superficial cortex- serves as a gateway to trigger other circuits in the brain.
- Leads to local and trans-synaptic changes in brain activity

Proposed Longer Term Effects

- Change in cerebral blood flow/metabolism
- Alteration of monoamine concentrations
  - 5HT, DA, NE…
- GABA, glutamate effects
- HPA system changes (hypothalamus-pitu-adrenal): cortisol, TSH
- Serotonin-receptor modulation
- Increased BDNF signaling (growth and connections in neurons)
- Plasticity effects (rewiring)

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Lisanby SH, Belmaker RH. *Depress Anxiety*. 2000;12(3):178-187; Kim EJ et al. *Neurosci Lett*. 2006;405(1-2):79-83; Shajahan PM et al *Prog Neuropsychopharmacol Biol Psychiatry*. 2002;26(5):945-954; Teneback CC et al. *Neuropsychiatry Clin Neurosci*. 1999;11(4):426-435; Epstein CM et al. *Neurology*. 1990;40(4):666-670; George MS et al. *NeuroReport*. 1995;6(14):1853-1856.; Post A, Keck, ME *J. of Psych Rsch.* 2001; Baekin et al 2011 .

TMS Clinical Considerations

Pros:

- Non-invasive
- Safe, well tolerated
- No drug-drug interactions
- No Systemic side effects
- No anesthesia needed
- No ‘down time’
- No negative effect on cognition
- Any side effects are usually mild/transient

Cons:

- Currently rather time consuming, requires commitment to treatment.
- Does not work immediately (yet), not suitable for emergent cases.
- Insurance hoops
- Patients that might benefit are not covered by insurance

Side Effects of TMS

Most side effects are mild to moderate and transient.

- Scalp sensitivity and headache, usually dissipates after 1st week of treatment, treat with OTC meds.
- Facial Muscle Twitching (during treatment) – muscle fatigue later
- Eye, jaw or tooth pain
- Less common: anxiety/insomnia
- Uncommon: Vasovagal response/syncope
- Rare ~ 1/1000 patients: Seizure, tends to occur early in treatment; does not cause epilepsy.

Medical Considerations

Contraindications

- Ferrous Metal & Implants in the head or Neck area (Similar to MRI)
- Shrapnel, surgical clips, welding fragments
- Pacemakers, VNS
- Intracardiac lines
- Ocular or cochlear implants
- Implanted medication pumps
- Tattoos with metal ink
- Braces, amalgam fillings and most dental implants are OK

Other considerations

- Medications that lower seizure thresholds
  - Stimulants, bupropion, clozapine, imipramine
- Seizure disorders
- Multiple TBIs, concussions
- Substance Use/Alcohol/Drugs
- Brain Tumors
- Recent strokes or bleeding in the brain
- Severe cardiovascular disease
- Pregnancy

Response and Remission Rates in a Large TMS Database

- **For 2,053 patients with PHQ9 (patient rated) data getting L sided TMS and completing treatment:**
  - Response rate 68.9%
  - Remission rate 35.8%
- **For 615 patients with CGI-S (physician rated) data:**
  - Response rate 83.1%
  - Remission rate 62.3%

- **'Real life' naturalistic study (N=307): 50-60% response rate, 33% remission rate**

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Sackeim HA. et. al. *J Affect Disord*. 2020 Dec 1;277:65-74.
Carpenter, L.L. et. al. *Depress Anxiety,* 29: 587-596.

What does treatment look like?

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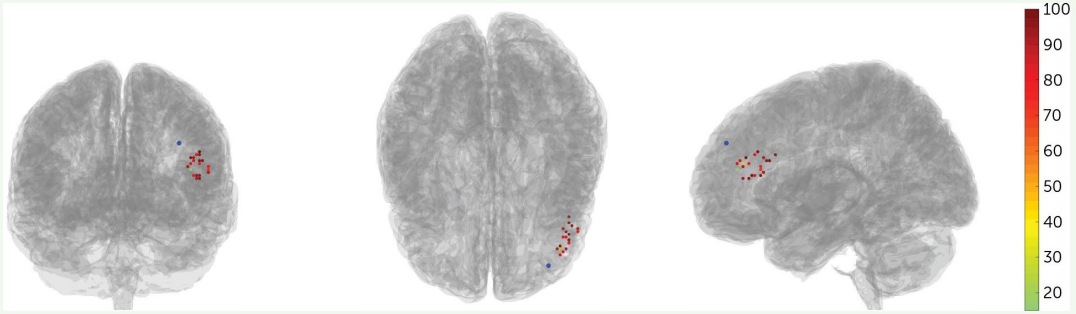
In the News….SAINT/SNT protocol

Intensive Treatment over 5 days

- 10 mins per hour (1800 pulses)x 10 hours = 18,000 pulses per day x 5 days.
- Intensity: 90% MT
- fMRI guided to find best placement L-DLPFC-subgenual cingulate relationship



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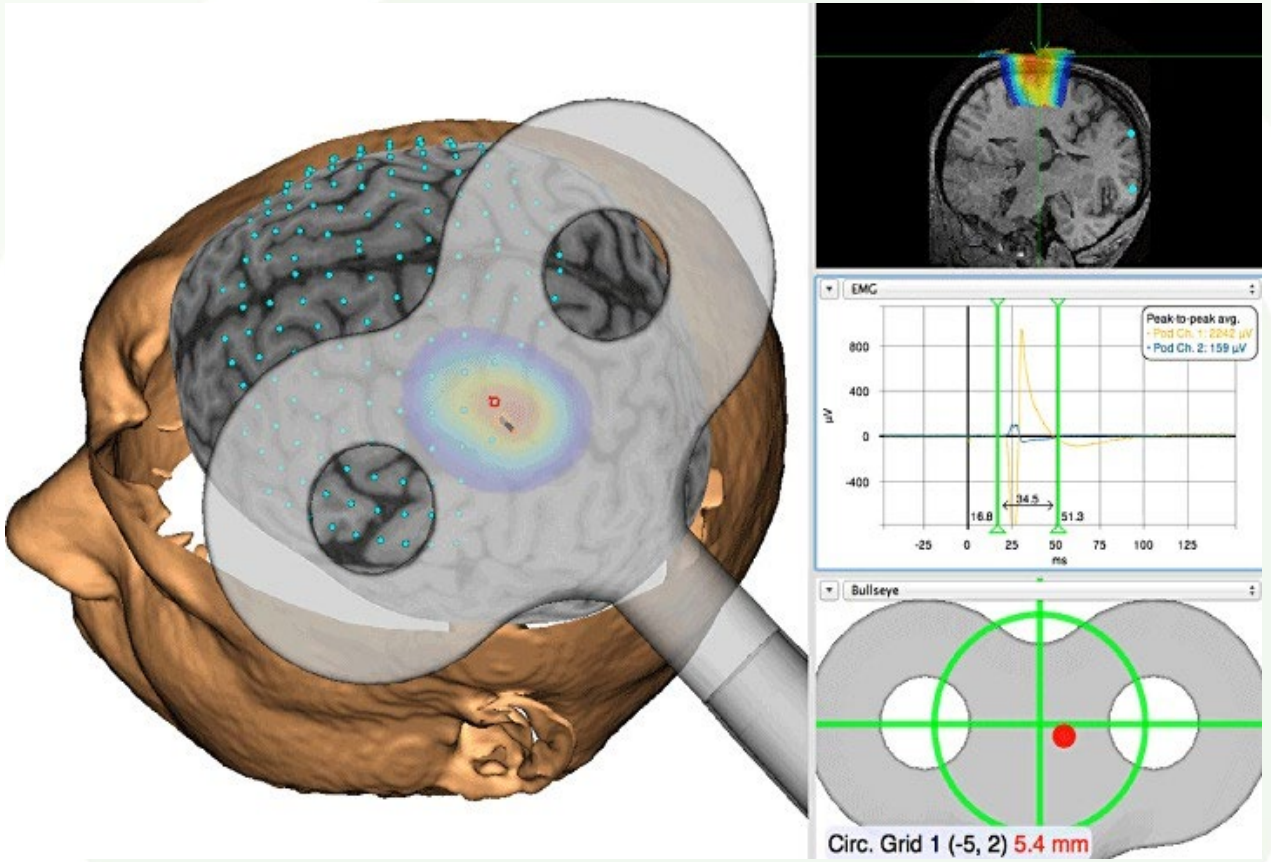
More Individualized Treatment
Neuro-navigation



- Requires Brain MRI w/ 1-2cm slices
- More precise location
- need more studies to show benefit justifies cost

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Fitzgerald, P., et. al. N*europsychopharmacol* **34,** 1255–1262 (2009).

Individualized Treatment?
Alpha waves and Oscillator Relationships

Oscillator: repeated variations over a neutral point; continuous repeated variation over time. (ex: pendulum of clock)

Neural oscillations: **brainwaves**, rhythmic or repetitive patterns of neural activity.

Alpha brainwaves : when awake, but relaxed/idle; for most 8-12Hz

Entrainment= synchronization of 2 oscillators, one often driving the other.

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Vosskuhl J. et. al. Front. Hum. Neurosci. 2018: 12:211.

Roelofs, C.L. et. al. *Clinical Neurophysiology. 2021: 643-649.*

“Seeing” Results: EEG clues

- EXACT mechanism not really known, but we know it changes networks and connections in the brain.
- Heterogenous etiology causing depression and other illnesses (some respond to TMS, some don’t)
- EEG can look at brain microstates before and after TMS.
- Certain changes in microstates **are associated with clinical response with TMS** (increase in the M2 microstate, decrease in the M3)
- Non-responders showed no significant change in any of the 6 microstates.

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Jan 2022: Brain Stim, Gold et al

Vagus Nerve Stimulator

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Vagus Nerve Stimulator

- Implanted device in the upper chest with leads tunneled under the skin and wrapped around the left vagus nerve in the neck
- Sends small electrical current for 30 second every 5 minutes
- 24/7 targeted treatment
  - Only interrupted by magnet placed over the device

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American Psychiatric Association (APA) Treatment Guidelines 2010

FDA Approval

- **Treatment resistant depression 2005**
    - Treatment of chronic or recurring depression (unipolar and bipolar type) for patients 18 years or older who have experienced at least one depressive episode that did not respond to **four** different pharmaceutical antidepressant treatments
- Not indicated for MDD with psychotic features or schizoaffective disorder
- Other considerations including comorbid unstable personality disorders

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O'Reardon, J. et. al. Psychiatry. 2006: May; 3(5): 54-63.
American Psychiatric Association (APA) Treatment Guidelines 2010

Side Effects

- Voice alteration
- Hoarseness
- Coughing
- Dyspnea
- Dyspepsia
- Headaches
- Paresthesia

- Heart Palpitations
- Rarely vocal cord paralysis
- Asystole during insertion (1 per 1,000)
- Infection
- Pain at incision site
- Hypomanic symptoms
- Mania

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Sackeim HA, et. al. *Neuropsychopharmacology. 2001: 713-28.*
Ben-Menachem E. *J Clin Neuropysiol. 2001; 10:415-8.*

Contraindications

- Presence of bilateral or left cervical vagotomy
- Use of short-wave diathermy, microwave diathermy, or ultrasound diathermy
- MRI- need to use specialized send-receive coil

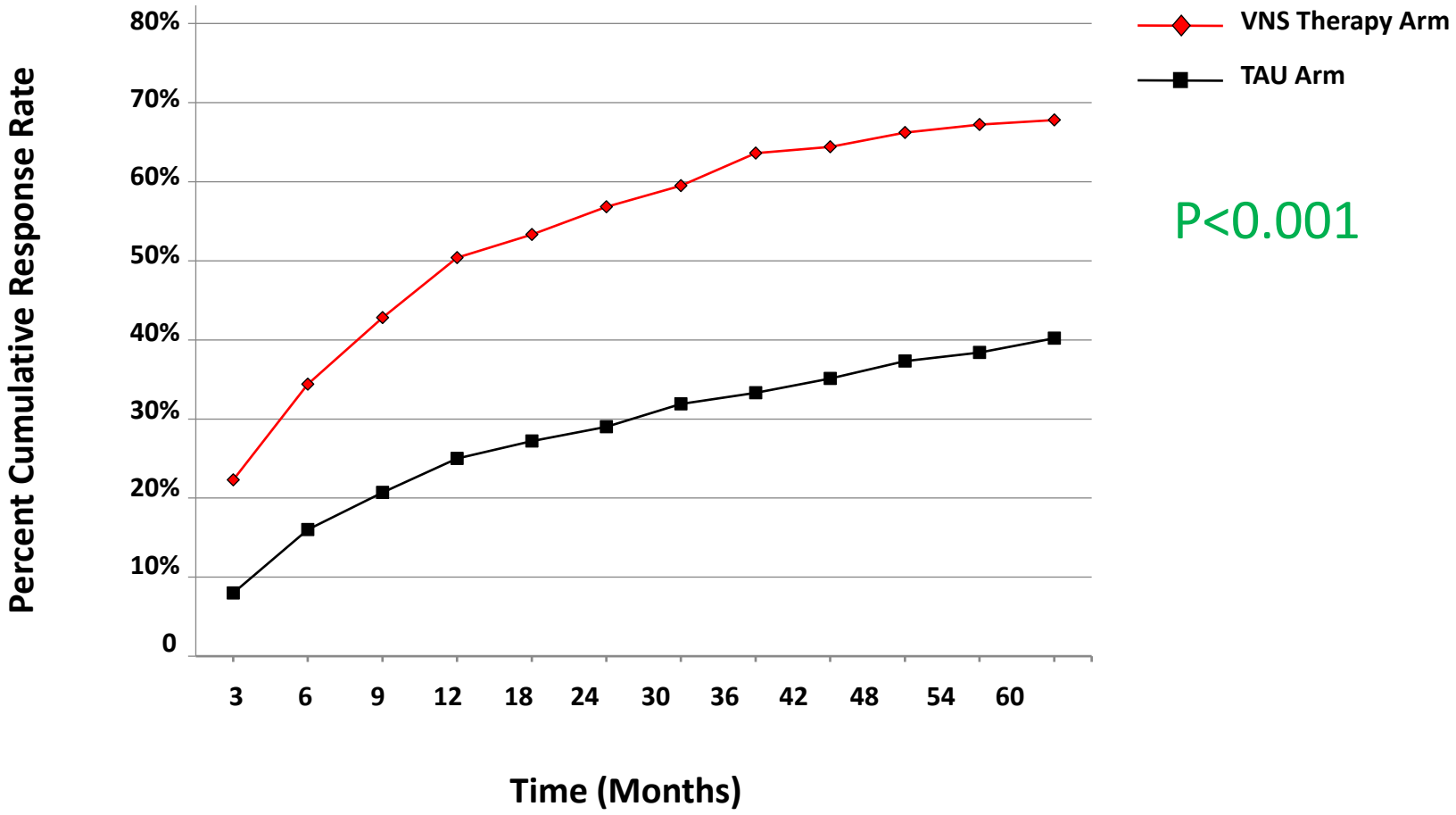
American Psychiatric Association (APA) Treatment Guidelines 2010

D-23 VNS Registry

- 5-year, prospective, open-label, non-randomized, observational registry study at 61 centers
    - Patients with unipolar or bipolar depression comparing 494 patients in the VNS arm (including D-21 rollover patients) and 301 in the treatment as usual (TAU) at the same medical centers
- Patients that completed the D-21 Dose Finding Study were also eligible to enroll (rollover) in the TRD Registry and be included within the VNS Therapy group
    - The study design permitted subjects to choose which treatment arm they were in at screening, either VNS or TAU
    - Subjects were followed for five years
- Study data was collected for the registry between January 2006 and June 2014 (ClinicalTrials.gov Identifier: NCT00320372).

Aaronson et al, AJP 2017

Primary Efficacy Endpoint: Percentage of First-Time Responders Over Time



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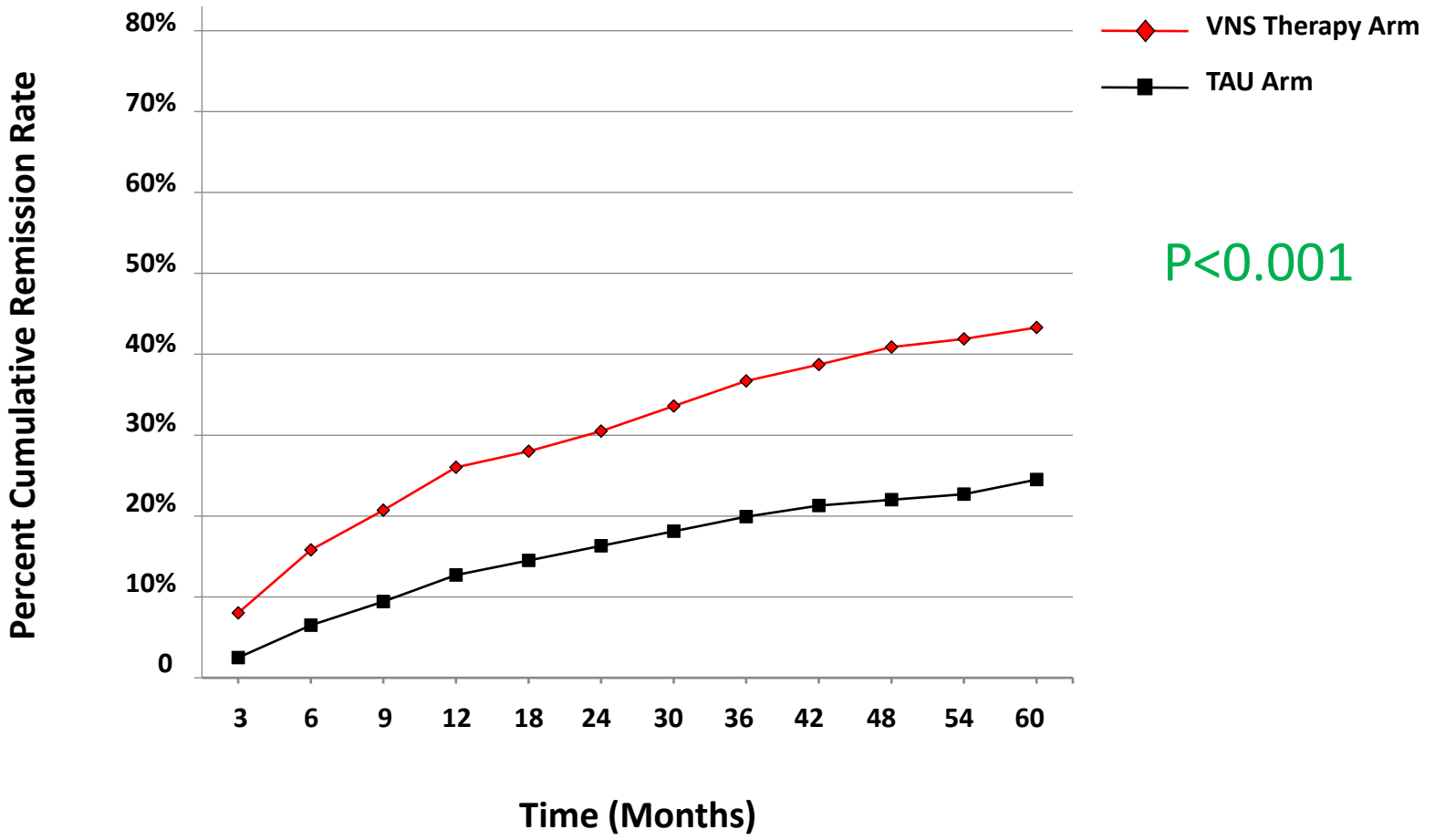
Percentage of First-Time Remitters over Time



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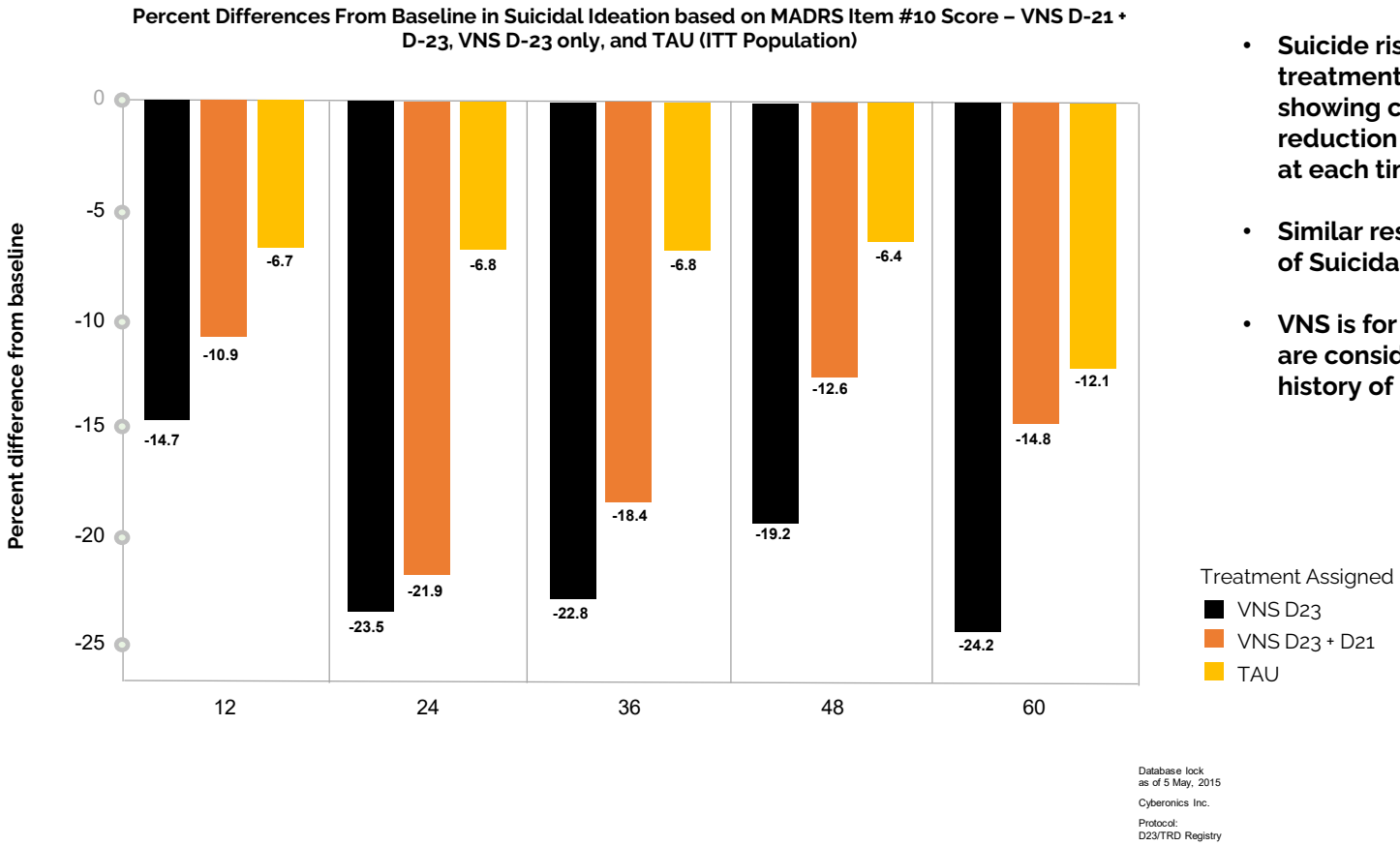
D-23 VNS Registry – US Suicidality

Safety Outcomes – **Suicidality** – MADRS Item 10 (≥4)



MADRS Item 10 - Suicidality

- **Suicide risks decreased over time in all treatment groups, with VNS D-23 patients showing consistently better profile in reduction post-baseline than the TAU patients at each time point**
- **Similar results with QIDS-SR and Assessment of Suicidality**
- **VNS is for both patients who have had ECT or are considering it. 57% of D23 patients had a history of ECT exposure.**

Final Clinical Study Report: Treatment-Resistant Depression Registry (D-23)
Submitted to the FDA on August 1, 2015

RECOVER Study

- Centers for Medicare and Medicaid rescinded their non-coverage determination for VNS in 2019 and agreed to fund a coverage with evidence development randomized controlled trial for up to 1000 patients with chronic severe depression who had failed at least four antidepressants and are Medicare recipients
- Currently enrolling in many sites across the US
- Can be patients with unipolar or bipolar depression
- All patients implanted with VNS, blind randomization to activate the device immediately after implant or delay by one year

Learning Objectives

Participant will :

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Questions....

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