

A decorative graphic consisting of blue circuit-like lines with small circles at the ends, extending horizontally from the left and right sides of the central black box.

TREATMENT RESISTANT DEPRESSION

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NCPA KEYNOTE LECTURE

SEPT 30, 2023



DICLOSURES

Off-label treatments will be discussed.

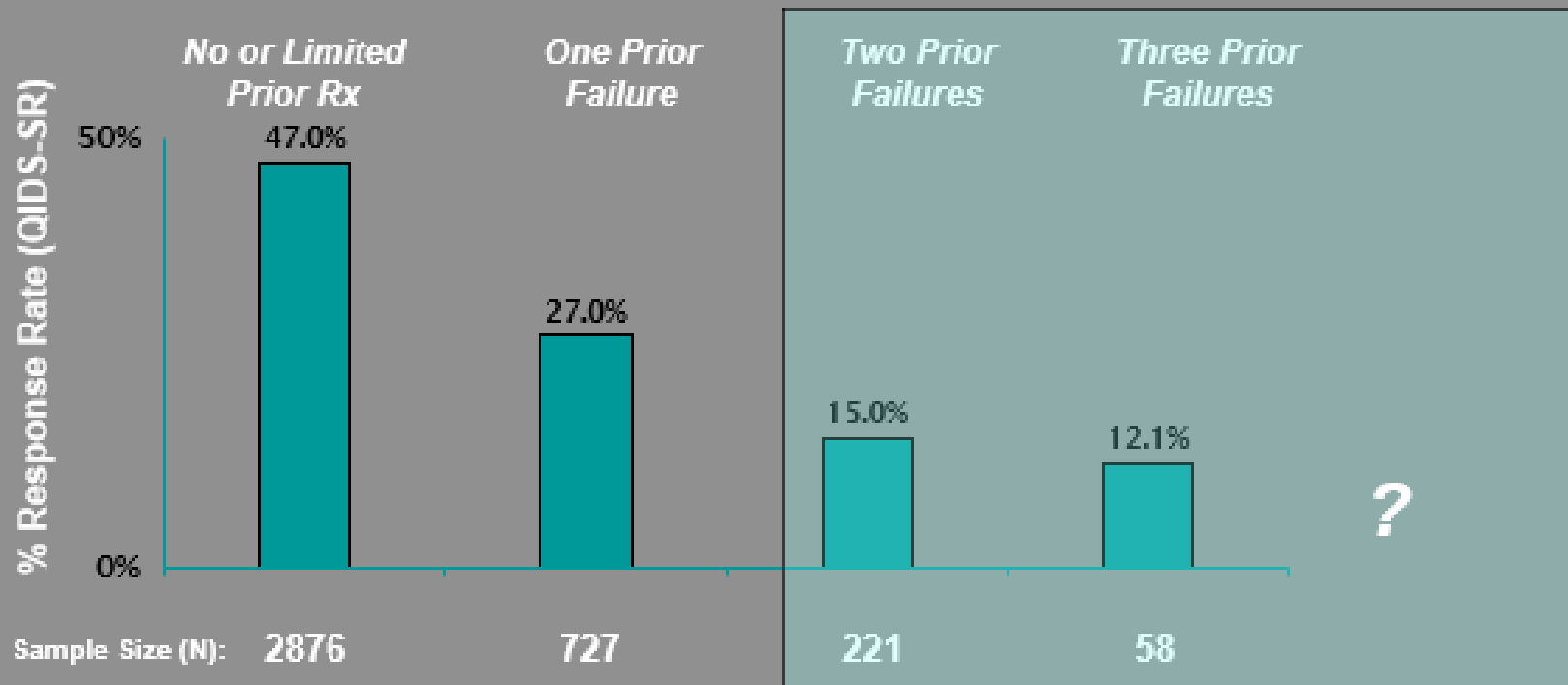
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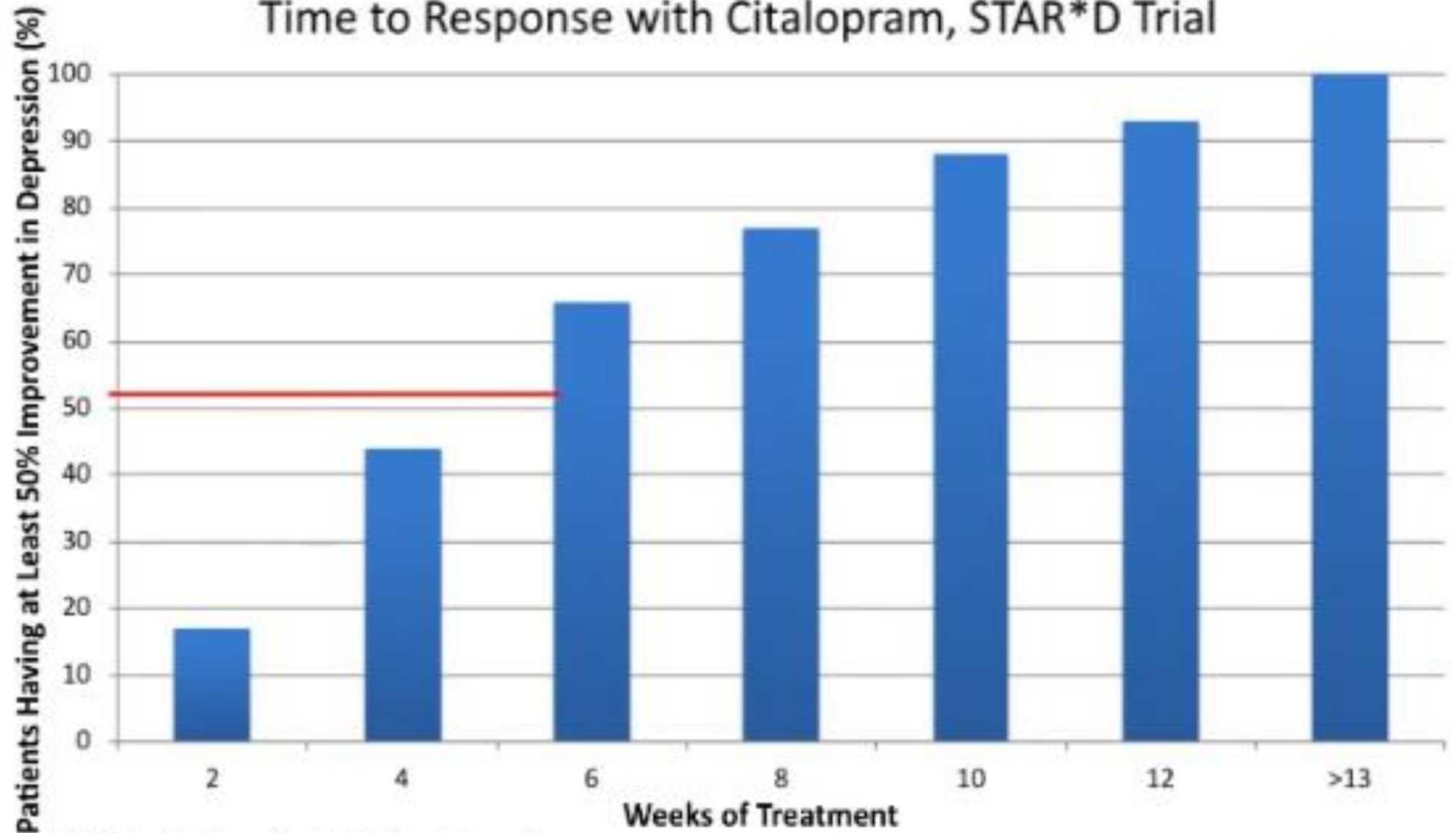
EDUCATIONAL OBJECTIVES

- Discuss the problem of treatment resistance in depressive illness according to STAR*D.
- Overview the concept of the electrochemical brain in terms of therapeutic targets for depression interventions.
- Describe the side effects, risks, indications, and comparative efficacy rates of Electroconvulsive Therapy (ECT), Transcranial Magnetic Stimulation (TMS), and Spravato/other forms of ketamine therapy

Depression and Treatment resistance: *STAR*D*



Time to Response with Citalopram, STAR*D Trial



STAR*D = Sequenced Treatment Alternatives to Relieve Depression.
Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

CLINICAL CASE

- Carlos is a 66 y/o married male who presents with his partner to consult with you about treatment options for his depression. He has been diagnosed with recurrent MDD, with one remote prior suicide attempt (hanging) in his 30's for which he was hospitalized. He works part time in IT at a community college. He says his current episode of depression has been about 3 years in duration but has worsened over the past few months.

CLINICAL CASE – CARLOS' TREATMENT HISTORY

- PMHx includes HTN (BP 150/90 in clinic) and GERD. He had 3-4 febrile seizures in childhood and surgery for Left TMJ dysfunction but no other surgeries or medical problems.
- Prior med trials during this depressive episode: Celexa, Wellbutrin, Abilify
- Current medications: fluoxetine, olanzapine, lisinopril, and omeprazole.
- He meets weekly with his psychotherapist of >10 years. PHQ-9 in clinic is 21 indicating severe depression. ROS +passive SI, -psychosis, -substance abuse

OPTIONS FOR CARLOS

Capitalizing on the electrochemical brain

- 
- Electroconvulsive Therapy
 - Transcranial Magnetic Stimulation

Targets in psychopharmacology

- Spravato/Ketamine
- Oral medications for TRD

ECT INDICATIONS

On-Label

- Class II
 - severe major depressive episodes (unipolar or bipolar) or catatonia in individuals aged 13 or over who are either treatment resistant or require a rapid response, such as in acute suicidality.
- Class III
 - Mania, Psychosis, refractory NMS, status epilepticus



ECT — COURSE OF TREATMENT

Index Treatment

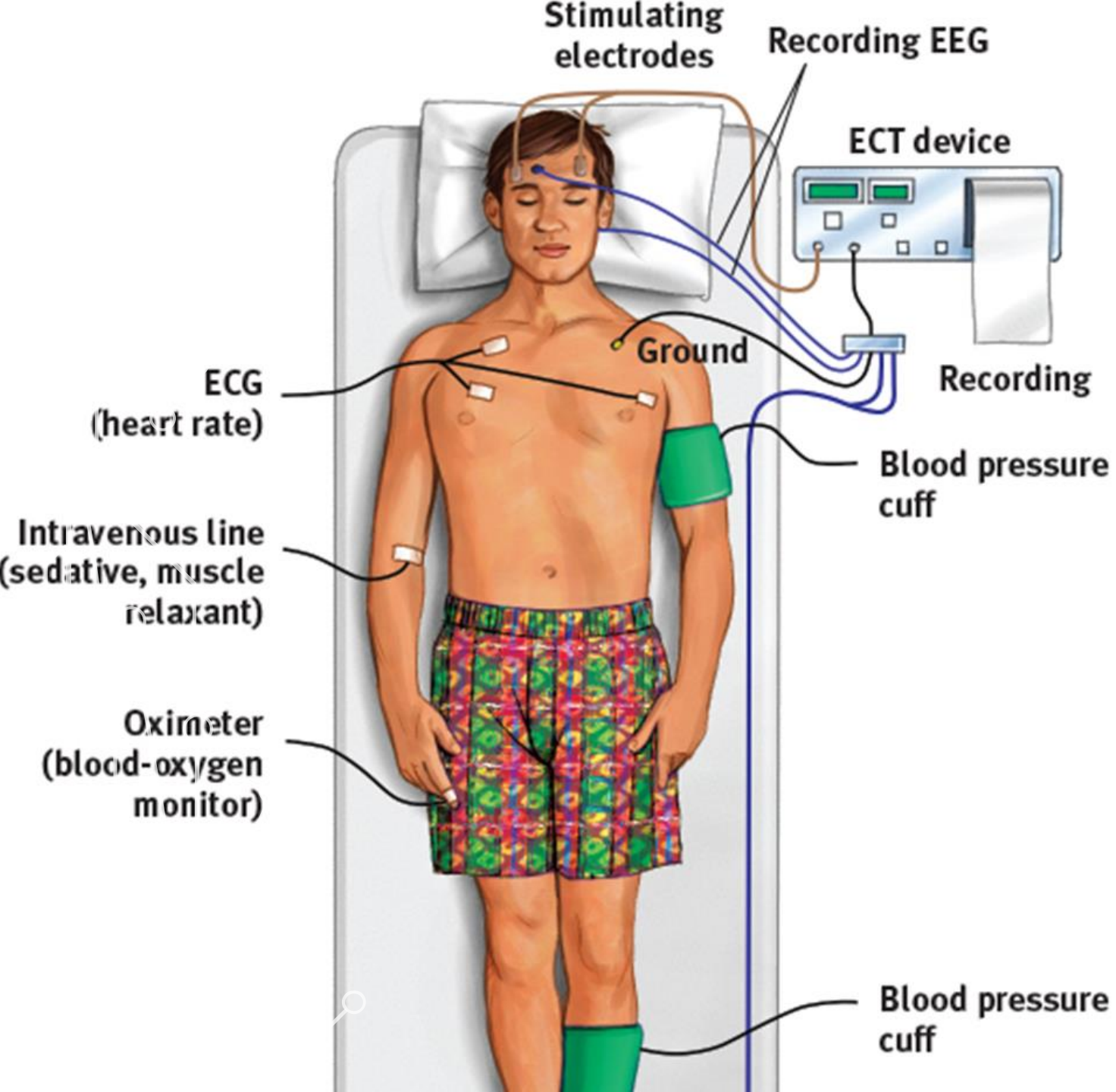
- 6 - 12 treatments, 2 - 3 treatments per week
- Treat until improvement plateaus

Maintenance treatment

- if failed medications after a successful ECT course at least once
- 50% Relapse within 6 months without medications or maintenance ECT

Pre-ECT Instructions/Precautions:

- *No driving* during ECT series and for 2 weeks thereafter, No work, School, contracts, major purchases, court cases, etc.
- NPO after MN prior to treatment



ECT - PROCEDURE

- General anesthesia
- Muscle relaxant
- Oxygen/ventilation (bag and mask)
- Continuous heart (EKG) and brain monitoring (EEG)
- Seizure lasts 30s - 2min



ECT EFFICACY IN DEPRESSION

Response

- **70% (NNT 3) in depressed adults**

Remission

- **83% in Depressed Elders (PRIDE) U01 NIMH sponsored study.**
- **52% in Depressed Adults (NNT 5)**

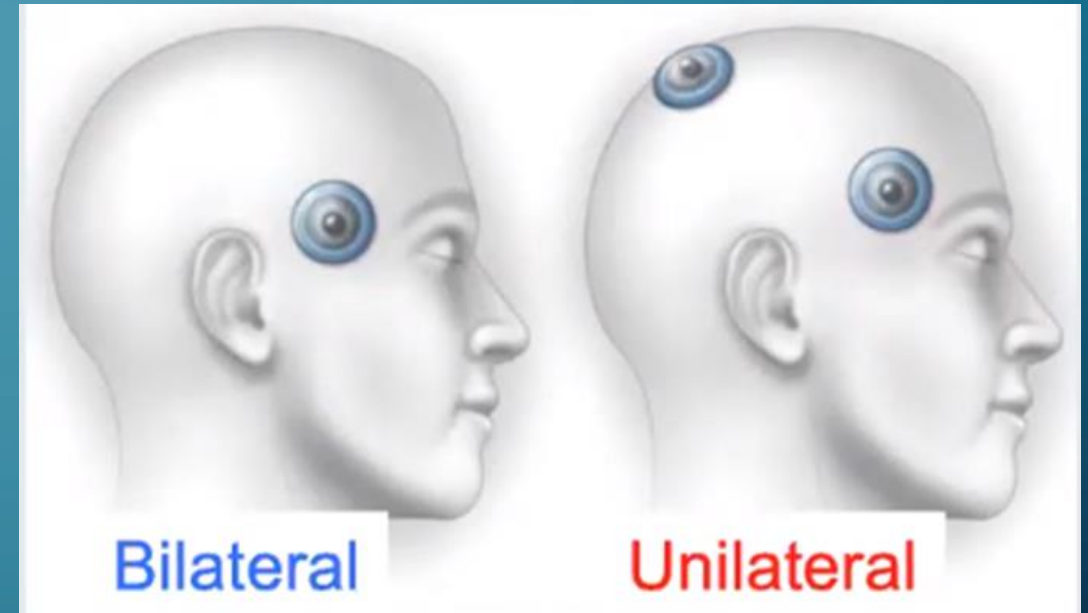
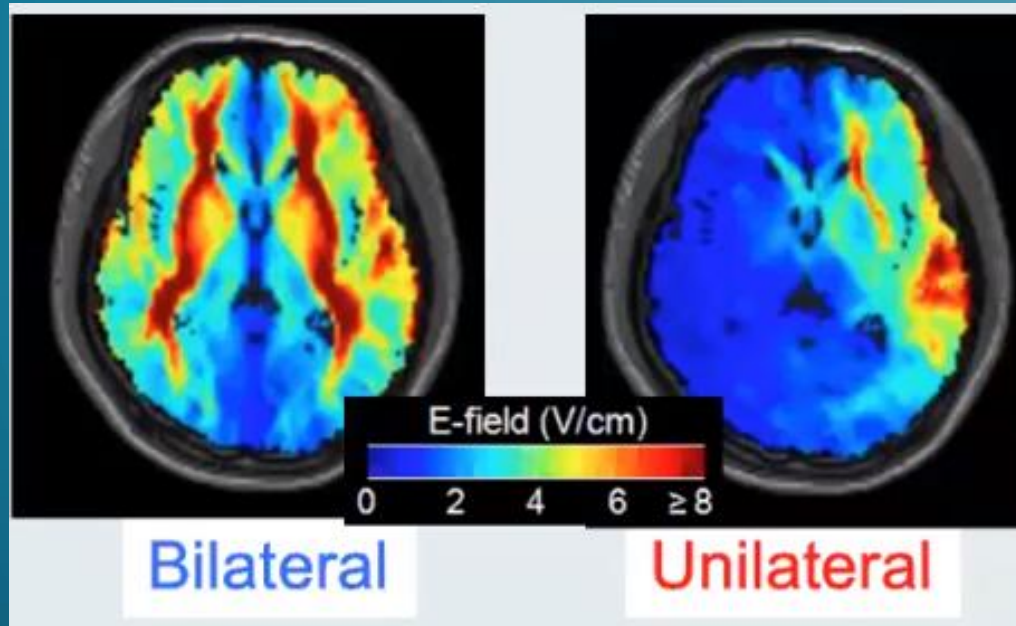
Response predictors:

- **Shorter duration of episode, less treatment resistance, greater age, psychotic features**

ECT RISKS/ SIDE EFFECTS

2 categories (Common/Rare)

Medical conditions increasing risk from
ECT



COGNITIVE SIDE EFFECTS OF ECT

CLINICAL CASE

- Carlos is open to ECT but worried about taking a month off work to undergo such a “drastic” treatment. He heard about a newer “magnet therapy” from his therapist and wants to know if he’s a candidate for TMS.

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REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (RTMS)

- Initial FDA Approval 2008 (MDD)
- Additional on-label indications:
 - Obsessive Compulsive Disorder
 - Smoking Cessation
 - Anxious Depression
 - Pre-surgical Mapping



TMS EFFICACY (DEPRESSION)

Pivotal Trials:

- Clinically Significant Response rates of ~24% and remission rates of 17.4%
 - med washout, short duration, higher levels of treatment resistance

Naturalistic TMS response rates:

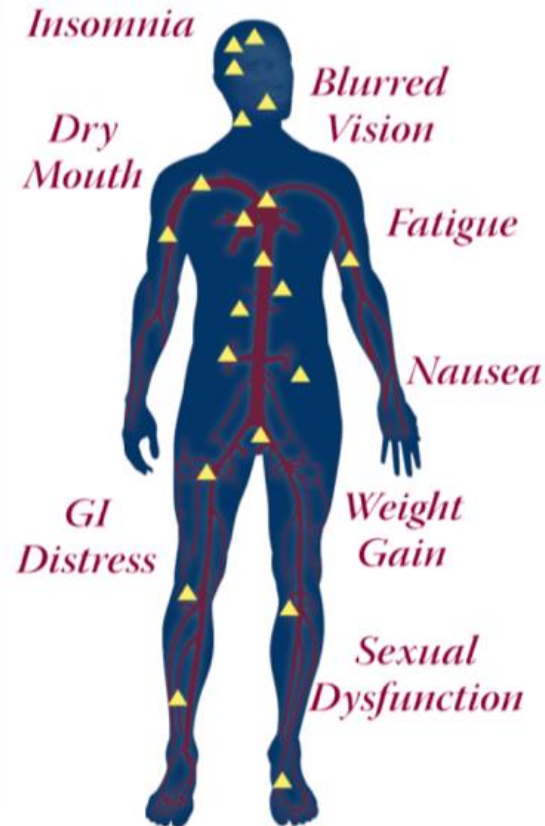
- Cohort Study Carpenter et al 2012 (N=307)
 - Response rates 58% Remission rates 37.1%
 - Effect sizes ~0.6 (cohen's D)
- Meta-analysis Brunoni et al 2017 in JAMA (N=1,371)
 - NNT=6 (response) NNT=8 (remission)

TMS - SIDE EFFECTS

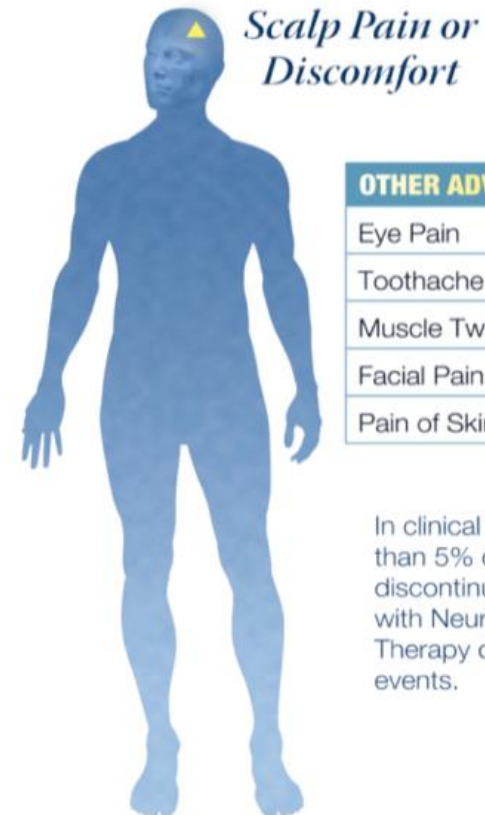
DRUG THERAPY

OTHER ADVERSE EVENTS

Nervousness
Weakness
Abnormal Ejaculation
Constipation
Anxiety
Impotence
Diarrhea
Increased Appetite
Dizziness
Sweating
Decreased Appetite
Tremor
Drowsiness
Decreased Sexual Interest
Headache/Migraine
Treatment Discontinuation
Side Effects



TMS THERAPY



OTHER ADVERSE EVENTS

Eye Pain
Toothache
Muscle Twitching
Facial Pain
Pain of Skin

In clinical trials, fewer than 5% of patients discontinued treatment with NeuroStar TMS Therapy due to adverse events.

From product labeling for currently marketed antidepressant medications; adverse events occurring at an incidence >5% incidence and 2x the rate of placebo treatment (Neuronetics, Inc, data on file)



TMS - CONTRAINDICATIONS

Non-removable *Metallic Objects*
in or Near the Head (“30 cm”)

Seizure disorder

Sleep deprivation

Pregnancy

TMS- PROCEDURE



- 30 treatments (5 days/week x 6 weeks) + 6 treatment taper
- No restrictions - Can drive, work, continue school
- Medication considerations
- Theta Burst and Accelerated protocols
- Time to symptom improvement
- Durability

CLINICAL CASE

- Carlos feels better about the side effect profile of rTMS, especially since he will be able to drive himself to sessions and continue to work while getting the treatment. “But doc,” he says, “I don’t know if I can make it a whole month before I start feeling better.” He tells you he read an add on social media about rapidly-acting “at-home-ketamine therapy,” and wonders if this is an option.

OPTIONS FOR CARLOS

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EXPANDING TARGETS FOR REFRACTORY DEPRESSION PHARMACOTHERAPY: BEYOND MONOAMINES

- Types of Neurotransmitters
 - **Amino acids:** γ -aminobutyric acid (GABA), aspartate, glutamate, glycine, D-serine
 - Gases: carbon monoxide (CO), hydrogen sulfide (H₂S), nitric oxide (NO)
 - **Monoamines:** dopamine, epinephrine, histamine, norepinephrine, serotonin
 - Peptides: β -endorphin, amphetamines, somatostatin, enkephalin
 - Purines: adenosine, adenosine triphosphate (ATP)
 - Trace amines: octopamine, phenethylamine, tryptamine
 - Other molecules: acetylcholine, anandamide
 - Single ions: zinc

EXPANDING TARGETS FOR REFRACTORY DEPRESSION

PHARMACOTHERAPY: GLUTAMATE MODULATION

Racemic ketamine
(primarily
intravenous
administration)

Intranasal
Esketamine
(Spravato)

Auvelity (bupropion
+
dextromethorphan)




KETAMINE: OFF-LABEL USE IN TRD

Approved by FDA in the 1970s as a Schedule III non-narcotic substance for use IV or IM to induce and maintain short-term sedation and general anesthesia

First demonstrated to have antidepressant effects in humans around 2000, with numerous studies demonstrating rapid benefit for depression, suicidality, PTSD.

Serial infusions dosed at 0.5mg/kg shown to be non-inferior to ECT for depression (Anand 2023 NEJM)



KETAMINE INFUSIONS – SIDE EFFECTS AND RISKS

- Side Effects: dissociation, confusion, and hallucinations, tachycardia, hypertension
- Potential for abuse and addiction (central sensitization of opioid receptors)
- Known unknowns regarding optimal dosing, durability of effect with repeated dosing, the impact on co-occurring conditions, and long-term outcomes
- Unregulated off-label use



ESKETAMINE (SPRAVATO®)

TYPE

- S-isomer of racemic ketamine, NMDA receptor blockade

INDICATIONS

- March 5, 2019, FDA approval for use in conjunction with oral antidepressant for TRD in adults
- July 31, 2020, FDA approval for depressive symptoms in adults with MDD with acute suicidal ideation or behavior.



EFFICACY/RISKS/SIDE EFFECTS

ACUTE PHASE:

- NNT of 8 (response) and 6 (remission) at 4 weeks
- NNH values <10, dissociation (26.1% vs. 3.7%), vertigo (26.1% vs. 2.8%), nausea (26.1% vs. 6.4%), dizziness (20.9% vs. 4.6%), and dysgeusia (24.3% vs. 11.9%).

MAINTENANCE PHASE

- Relapse reduced from 58% to 26%
- NNT values <10 for relapse and/or maintenance of remission
- NNH = non-significant

SPRAVATO INCLUSION/EXCLUSION

Inclusion

- Diagnosis of MDD, current depressive episode of at least moderate severity
- 4 prior adequate trials OR
- Suicidal Ideation

Exclusion

- unmanaged HTN
- significant CV disease
- hx hemorrhagic stroke,
- acute/ACTIVE SI
- history of mania/psychosis
- SUD
- Age > 65

Restrictions/cautions

- NO driving (day of treatment)
- Sedatives/ETOH

SPRAVATO TREATMENT SCHEDULE

(week 1-4) 56-84 mg twice weekly ->



(weeks 5-8) 56-84 mg once weekly ->



(weeks 9 ->) 56-84 mg q2wks ->



“Taper as tolerated”

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ORAL PHARMACOLOGY FOR TREATMENT- RESISTANT MAJOR DEPRESSIVE DISORDER

FDA Approved oral medications for TRD:	Adjunct: Vraylar, Seroquel XR, Abilify, Rexulti
	Monotherapy: Symbyax
Off-Label	Cytomel (T3 or liothyronine)
	Lithium
Other considerations	AXS-05/Auvelity (not studied in treatment resistant population)
	MAO-I

CLINICAL CASE

- Formulation: Carlos is a 66 y/o M with recurrent severe episode of non-psychotic MDD +SI that is refractory to >5 medication trials including two trials of medications on-label for TRD. His age >65 may exclude him from Spravato. He has no medical contraindications to rTMS, and while his depression is severe enough to warrant trials of IV ketamine or ECT, he favors an initial trial of rTMS because he can drive himself to appointments and continue working. He would like to talk with you more next visit about accelerated (off-label) rTMS treatment protocols that might expedite results.

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