Off-label treatments will be discussed.

Opinions and recommendations expressed in this lecture do not represent the position of the Department of Veterans Affairs.
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**

<table>
<thead>
<tr>
<th>% Response Rate (QIDS-SR)</th>
<th>No or Limited Prior Rx</th>
<th>One Prior Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>47.0%</td>
</tr>
<tr>
<td></td>
<td>0%</td>
<td>27.0%</td>
</tr>
</tbody>
</table>

Sample Size (N): 2876 727

| Two Prior Failures | 15.0% | 221 |
| Three Prior Failures | 12.1% | 58  |
Time to Response with Citalopram, STAR*D Trial

Patients Having at Least 50% Improvement in Depression (%)

Weeks of Treatment

2 4 6 8 10 12 >13

Patients having at least 50% improvement in depression.

STAR*D = Sequenced Treatment Alternatives to Relieve Depression.
• 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

- **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
• 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.
OPTIONS FOR CARLOS

Capitalizing on the electrochemical brain

- Electroconvulsive Therapy
- Transcranial Magnetic Stimulation

Targets in psychopharmacology

- Spravato/Ketamine
- Oral medications for TRD
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

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)

Naturalistic TMS response rates:
TMS - SIDE EFFECTS

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

Capitalizing on the electrochemical brain

- Electroconvulsive Therapy
- Transcranial Magnetic Stimulation

Targets in psychopharmacology

- Spravato/Ketamine
- Oral medications for TRD
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

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Restrictions/cautions</th>
</tr>
</thead>
</table>
| • Diagnosis of MDD, current depressive episode of at least moderate severity  
  • 4 prior adequate trials OR  
  • Suicidal Ideation | • unmanaged HTN  
  • significant CV disease  
  • hx hemorrhagic stroke,  
  • acute/ACTIVE SI  
  • history of mania/psychosis  
  • SUD  
  • Age > 65 | • 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”
OPTIONS FOR CARLOS

- Capitalizing on the electrochemical brain
  - Electroconvulsive Therapy
  - Transcranial Magnetic Stimulation

- Targets in psychopharmacology
  - Spravato/Ketamine
  - Oral medications for TRD
### ORAL PHARMACOLOGY FOR TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER

<table>
<thead>
<tr>
<th>FDA Approved oral medications for TRD:</th>
<th>Adjunct: Vraylar, Seroquel XR, Abilify, Rexulti</th>
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<tbody>
<tr>
<td>Monotherapy:</td>
<td>Symbyax</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Off-Label</th>
<th>Cytomel (T3 or liothyronine)</th>
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<tbody>
<tr>
<td>Lithium</td>
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<table>
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<tr>
<th>Other considerations</th>
<th>AXS-05/Auvelity (not studied in treatment resistant population)</th>
</tr>
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<tr>
<td>MAO-I</td>
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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.