Approach to Treatment Resistant Depression

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Objectives

- General approach to diagnosing and initial treatment of major depressive disorder (MDD)
- Considerations when diagnosing treatment resistant depression
- Strategies for addressing treatment resistant depression

Major Depressive Episode- DSM-V criteria

- 2-week period with at least five of the following
  - Depressed mood
  - Loss of interest in activities or pleasure
  - Decreased or increased appetite
  - Decreased energy
  - Psychomotor agitation or retardation
  - Insomnia or oversleeping
  - Feelings or worthlessness or unfounded guilt
  - Problems with thinking, concentration, or indecisiveness
  - Frequent thoughts of death or consideration of suicide
- Commonly comorbid with anxiety disorders, PTSD, and OCD

John	Alice
Depressed mood	Diminished pleasure
Insomnia	Hypersomnia
Weight loss	Weight gain
Psychomotor agitation	Psychomotor retardation
Inappropriate guilt	Loss of energy

1497 possible combinations with 5 more symptoms!

Ostergaard SD, et al. (2011) The heterogeniety of the depressive syndrome: when numbers get serious. Acta Psychiatr Scan; 124:495-496

Major Depressive Disorder- Epidemiology

- 21% lifetime prevalence
- Twice as common in women
- Mean age of onset is 30 years
- More common in those without close interpersonal relationships, divorced, or separated
- More common in rural areas
- No correlation with socioeconomic status

Major Depressive Disorder- Etiology

- Biological
  - Monoaminergic system
    - Serotonin
    - Norepinephrine
    - Dopamine
  - Acetylcholine
  - GLUT/GABA
  - Inflammation
  - Genetic
- Psychosocial

Initial Approach to Treatment

- Medication and/or psychotherapy
- Choice based on
  - Severity of symptoms
  - Patient choice and resources
  - Previous agents tried
  - Family history of response/non-response to Rx
  - Patient characteristics

Choosing an Antidepressant

- "All antidepressants on market are equally efficacious in the treatment of depression"
  - This is unlikely
- About 1/3 of patients will achieve remission and about 1/2 at least respond with an initial course
  - Response- 50% reduction in symptoms
  - Remission- Essentially no symptoms of depression (e.g. score of ≤7 on HDRS)

Choosing an Antidepressant

- Geriatric patients
  - Lexapro, Celexa, and Zoloft tend to be among the best tolerated and least likely to cause pharmacokinetic interactions
  - Effexor and Remeron have a low likelihood of interactions as well
  - Use TCA's cautiously
  - "Start low and go slow"

Choosing an Antidepressant

- Medical Conditions
  - Pain
    - May benefit from dual acting agents
  - Seizure, stroke, or head trauma
    - Avoid TCA's or Wellbutrin
  - Arrhythmia or CAD
    - Avoid TCA's

Choosing an Antidepressant

- Side effects
  - Weight gain
    - TCA's, Paxil, and Remeron are the worst
    - Prozac and Wellbutrin better
  - Sexual side effects
    - Most common long term side effect
    - SSRI’s and Clomipramine most problematic
    - Wellbutrin, Remeron, Viibryd, and Trintellix best

Choosing an Antidepressant

- Choosing target symptoms
  - Insomnia
    - Might benefit from Remeron or Trazodone
  - Hypersomnia and fatigue
    - Wellbutrin or Prozac
  - Cognitive deficits or executive functioning
    - Might benefit from a noradrenergic agent or Trintellix

Adequate Dosage

- Consider lower starting dose for
  - Elderly patients
  - Polypharmacy
  - Anxious patients
- Starting dose not always adequate
- SSRI plateau

Efficacy Plateau of Common AD's

- Celexa 30-40 mg
- Lexapro 10-15mg
- Prozac 20-30mg
- Paxil 20-30mg
- Zoloft 75-100mg
- Remeron 30mg
- Effexor 375mg

Furukawa, T. et al. (2019). Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression. systematic review and dose-response meta-analysis. Lancet Psychiatry. Published online June 6.http://dx.doi.org/10.1016/S2215-0366(19)30217-2

Adequate Duration

- 4-week trial probably adequate
  - Meta-analysis 47 studies
    - 60% of improvement occurred in 1st 2 weeks
  - Only about 20% of those without improvement at 4 weeks will go on to respond by 8 weeks

1) Posternak MA, Zimmerman M. (2005). Is there a delay in the antidepressant effect? A meta-analysis. J Clin Psychiatry, 66(2):148-58. 2) Kudlow P, McIntyre, R, Lam, R. (2014) Early Switching Strategies in Antidepressant Non-Responders: Current Evidence and Future Research Directions. CNS Drugs, 28, 601-609.

Treatment Resistant Depression

- Definition for treatment resistance- failure of at least two different antidepressant trials of adequate dose and duration
- Is it “true” treatment resistance?
  - Diagnosis
  - Dose
  - Duration
  - Compliance

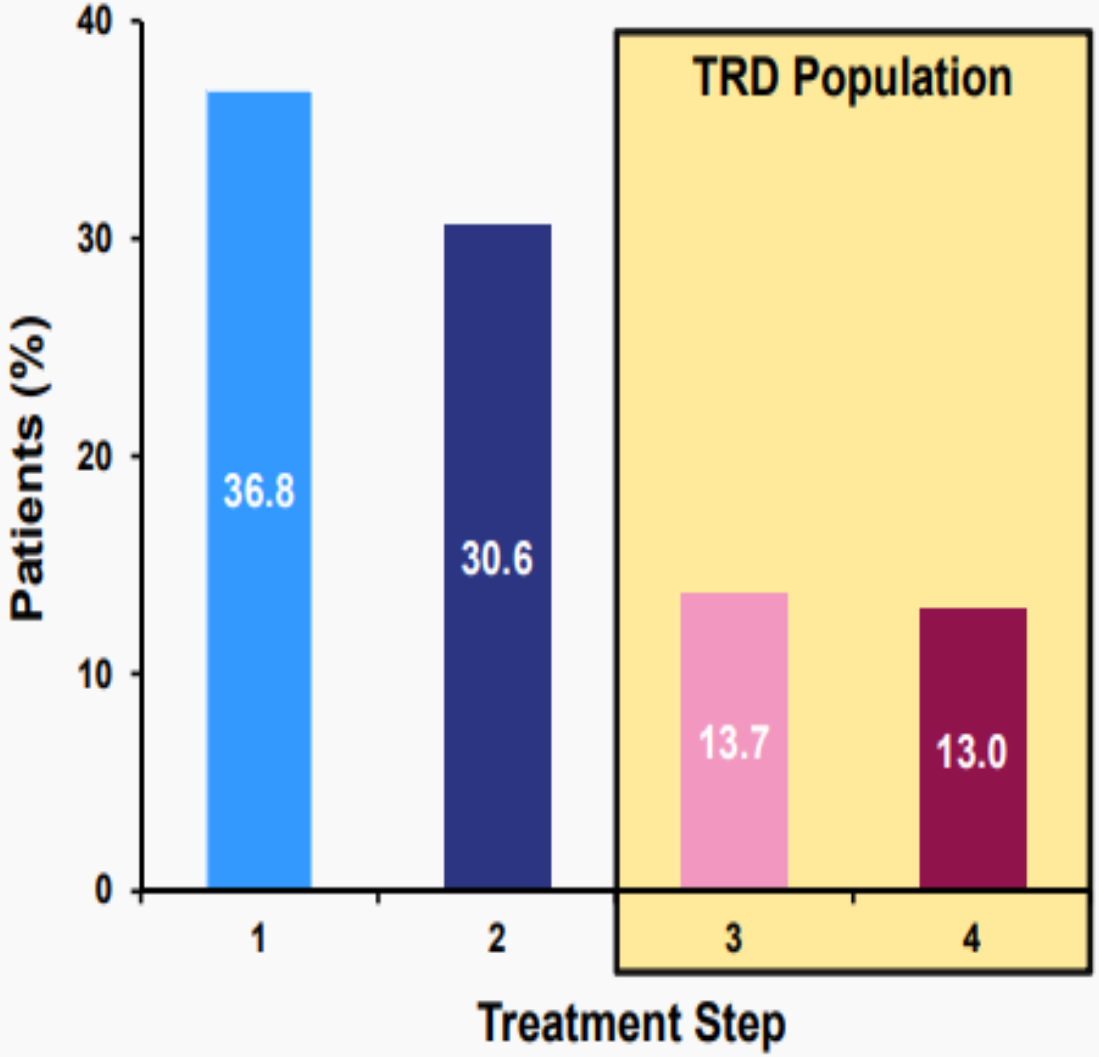
Treatment Resistant Depression

- STAR*D (Sequenced Treatment Alternatives to Relieve Depression)
  - Enrolled 4041 outpatients across the US in primary care and psychiatric settings
  - Designed to determine which treatments are most effective following non-remission or intolerance to an initial SSRI and other treatments

STAR*D Algorithm

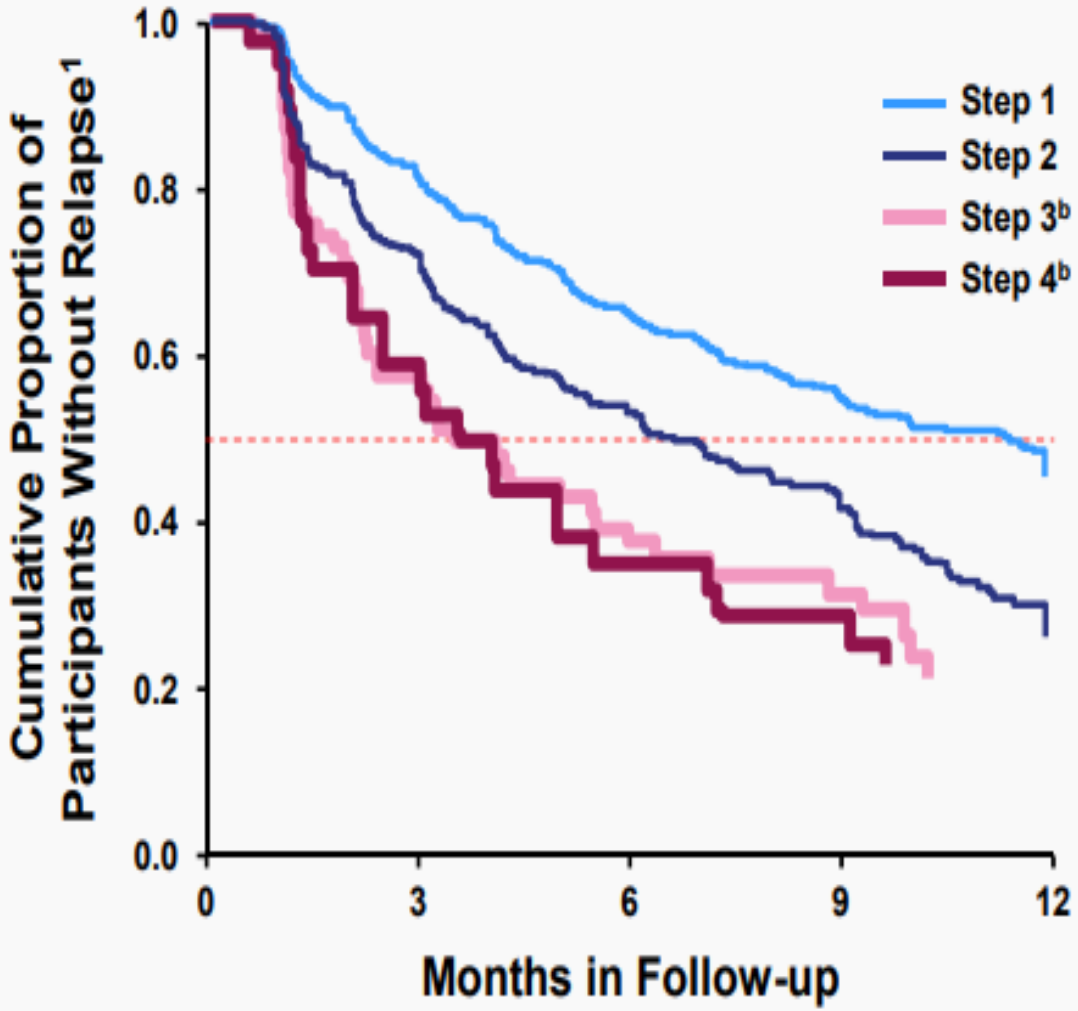
- **Level 1**
  - Celexa
- **Level 2**
  - Switch to Wellbutrin, CBT, Zoloft, or Effexor
  - Augment with Wellbutrin, Buspar, or CBT
- **Level 3**
  - Switch to Remeron or nortriptyline
  - Augment with Li or T_3
- **Level 4**
  - Switch to tranylcypromine or Remeron + Effexor

STAR*D Remission[a] Rates[1]



Time to remission: 5-7 weeks[1]

STAR*D Relapse Rates[1]



a. Remission definition: QIDS-SR16 ≤5; b. Treatment-Resistant Depression population

1. Rush AJ et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

Treatment Resistant Depression
Next Steps

- Switch or augment
  - Augmentation may be more effective than switching
  - Adding psychotherapy is reasonable
  - No clear guidance on how many augmentations to try before switching or vice versa

Treatment Resistant Depression
Next Steps

- Augmentation
  - Second generation antipsychotic
  - Lithium
  - Second antidepressant from different class
  - Thyroid hormone
  - Side effects
  - Cost and compliance

Augmentation with Atypical Antipsychotics

- Meta-analysis of 16 trials of different atypicals for augmentation
  - Response
    - OR= 1.69, 95% CI =1.46-1.95
  - Remission
    - OR= 2.00, 95% CI= 1.69-2.37
  - Mean odds ratios no different between atypicals
  - Onset of action early as one week
- Aripiprazole and quetiapine seem to have most data to support use

1)Nelson J, Papakostas G. (2009). Atypical Antipsychotic Augmentation in Major Depressive Disorder: A Meta-Analysis of Placebo-Controlled Randomized Trials. Am J Psychiatry, 166:980-991 2) Cantu' F et al. (2020) Augmentation with Atypical Antipsychotics for Treatment-resistant Depression. Journal of Affective Disorders, 280:45-53

Augmentation with Lithium

- Systematic review and meta-analysis of nine trials
- Augmentation of various antidepressants
- Response
  - OR = 2.89, 95% CI (1.65-5.05)
- Onset of action quite variable
- Aim for level of 0.6-0.9 mEq/L
- Reduces risk of suicide in those with MDD and BPAD

1)Nelson J, et al. (2014). A systematic review and meta-analysis of lithium augmentation of tricyclic and second-generation antidepressants in major depression. Journal of Affective Disorders, 168, 269-275. 2) Barowsky J, Schwartz T. (2006). An Evidence-Based Approach to Augmentation and Combination Strategies for Treatment-Resistant Depression. Psychiatry, 3(7):42-61. 3) Cipriania A, et al (2013) Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. BMJ, 346:36-46.

Adding Second Antidepressant from Different Class- Remeron

- STAR*D
  - Those who had failed three prior trials given tranylcypromine or venlafaxine + mirtazapine
  - Outperformed tranylcypromine
    - Not statistically significant
  - 13.7% remitted with Remeron + Venlafaxine

Adding Second Antidepressant from Different Class- Remeron

- 480 primary care pts treated with SSRI or SNRI for at least six weeks-still depressed
- Randomized to mirtazapine 30mg or placebo over 52 weeks
- No statistically significant difference compared to placebo
- Limitation
  - Only went to 30mg of mirtazapine

Kessler D, et al (2018). Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial (MIR). BMJ. 363:k4218

Adding Second Antidepressant from a Different Class-Wellbutrin

- 1522 treatment resistant VA pts
  - Switch to Wellbutrin
    - Remission 22.3%
  - Augment with Wellbutrin
    - Remission 26.9%
  - Augment with Abilify
    - Remission 28.9%

Mohamed S, et al. (2017). Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. JAMA, 318(2):132.

Augmentation with Thyroid Hormone

- Open label use in STAR*D after failing two trials of antidepressant monotherapy
  - 25% remitted
- RCT's with TCA show mixed results
- Open label uncontrolled studies with SSRI's are positive

Touma, K et al. (2017) Liothyronine for depression: A Review and Guidance for Safety Monitoring. Innov Clin Neuorsci, 14(3-4):24-29

Augmentation with Thyroid Hormone (T3)

- Check baseline TSH and start 25 mcg/d and increase to 50 mcg/d if no improvement after 1-2 weeks
- Adequate trial should be six weeks
- Check TSH a month later and then yearly
- Use cautiously in those with cardiovascular disease

2022 Systematic Review and Meta-analysis. Nunez, et al.

- Adult patients with treatment resistant depression (refractory to ≥1 agents)
- Augmentation agents examined
  - Stimulants
    - Lisdexamfetamine, dextroamphetamine/amphetamine, methylphenidate, pramipexole, modafinil/armodafinil
  - Thyroid hormones

Nunez et al. (2022) Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. J Affect Disord. 302:385-400.

2022 Systematic Review and Meta-analysis. Nunez, et al.

- Mood stabilizers
  - Lithium and lamotrigine
- Atypical antipsychotics
  - Olanzapine/Olanzapine+fluoxetine, quetiapine, aripiprazole, brexpiprazole, risperidone, cariprazine, ziprasidone
- Antidepressants
  - Mirtazapine, bupropion, venlafaxine, nortriptyline, amitriptyline
- Buspirone

Nunez et al. (2022) Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. J Affect Disord. 302:385-400.

2022 Systematic Review and Meta-analysis. Nunez, et al.

- Separation from placebo
  - T3 (RR=1.90, CI=1.16-3.11)
  - Nortriptyline (RR=2.05, CI=1.02-4.11)
  - Aripiprazole (RR=1.57, CI 1.36-1.82)
  - Brexpiprazole (RR=1.56, CI=1.15-2.11)
  - Quetiapine (RR=1.34, CI=1.14-1.56)
  - Lithium (RR=1.25, CI=1.00-1.56)
  - Modafanil (RR=1.26, CI=1.07-1.48)
  - Olanzapine+fluoxetine (RR=1.23, CI=1.00-1.50)
  - Cariprazine (RR=1.20, CI=1.01-1.42)
  - Lisdexamfetamine (RR=1.18, CI=1.03-1.37)

Nunez et al. (2022) Augmentation strategies for treatment resistant major depression: a systematic review and network meta-analysis. J Affect Disord. 302:385-400.

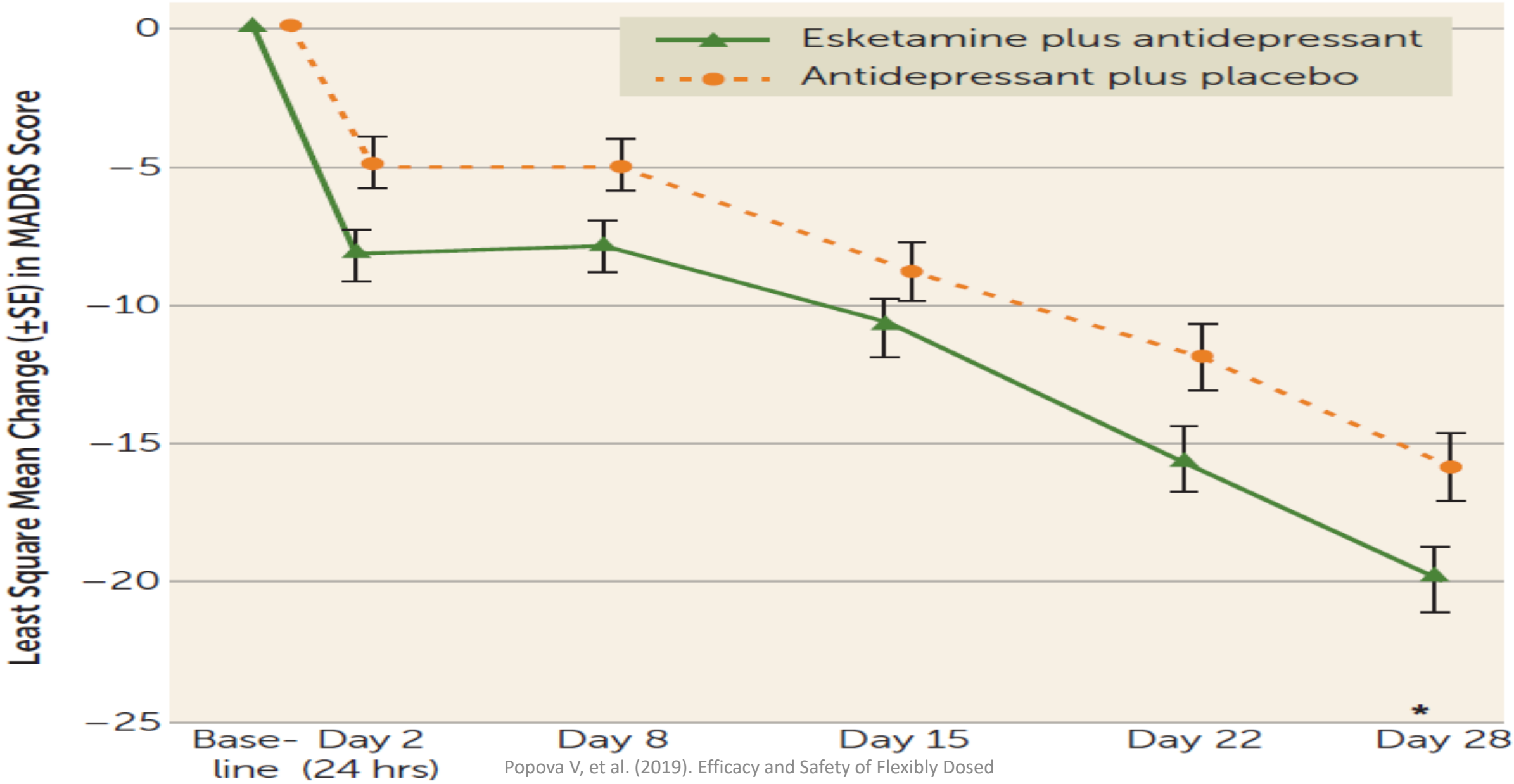
Exercise

- May benefit mood in several ways
  - Decrease in pro-inflammatory cytokines
  - Increase in BDNF
  - Increase in 5-HT, NE, and DA
  - Increase in self-esteem
- Meta-analysis (Nebiker, 2018)
  - Moderate to large effect size for endurance exercise
  - Large effect size for neuromuscular exercise
  - Duration of endurance exercise and intensity of neuromuscular exercise may strengthen effect

1)Xie Y, et al. (2021) The Effects and Mechanisms of Exercise on the Treatment of Depression. Front Psychiatry, 12:705559 2)Nebiker L, et al. (2018) Moderating Effects of Exercise Duration and Intensity in Neuiromuscular vs Endurance Exercise Interventions for the Treatment of Depression: A Meta-Analytical Review. Front Psychiatry. 19:9:305

Ketamine

- History
- Mechanism
  - NMDA antagonist
  - Ultimately increases neuronal growth allowing for neuronal plasticity
- IV ketamine
- Esketamine (Spravato)
  - Nasal delivery
  - FDA approval March 2019
  - For use with antidepressant



Popova V, et al. (2019). Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active Control Study. Am J Psychiatry, 176:428-438.

Esketamine long term trial

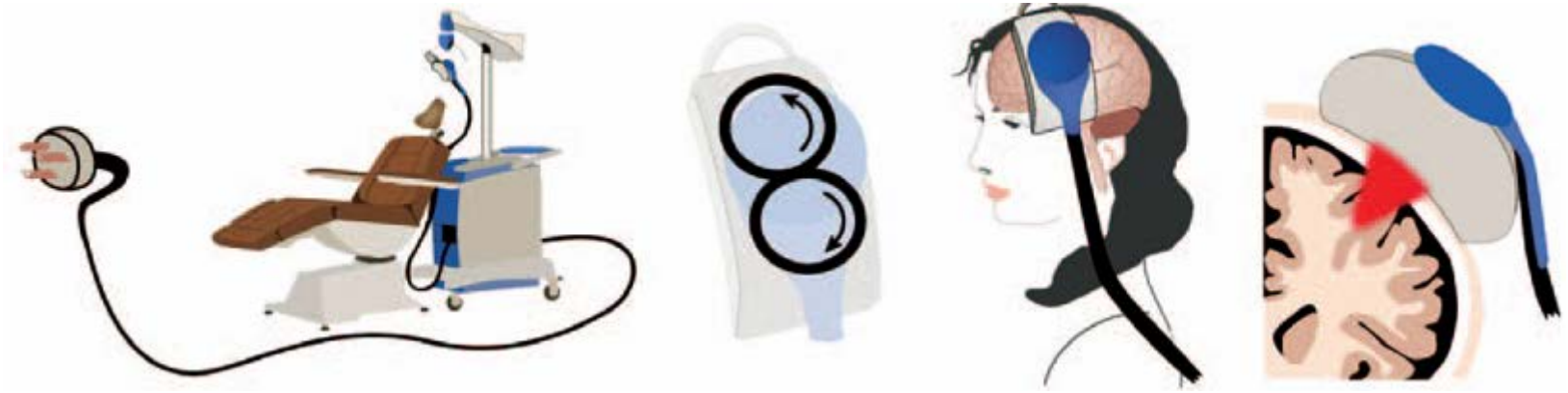
- 297 pts who remitted or responded to esketamine
- Maintenance for 80 weeks
  - Adjunctive esketamine or placebo given q week or every other week

	Esketamine + AD	Placebo + AD
Relapse in Remitters	27%	45%
Relapse in Responders	26%	58%

Daly EJ, et al. (2019) Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry doi: 10.1001/jamapsychiatry.2019.1189

Transcranial Magnetic Stimulation (TMS)

- Creates a powerful current near the scalp creating a brief but powerful magnetic field
- This magnetic pulse encounters neurons and induces current within the neuron



TMS

- Exact mechanism unknown
- Patient reclines in chair and device is held against L prefrontal area
- Typical treatment is a 20-40 minute session, 5 days a week for 4-8 weeks
- Safety and side effects
  - No reports of any lasting neurological, cognitive, or CV sequelae
  - Seizures possible but very rare
  - Headaches are probably MC complaint
  - Scalp pain

TMS

- Meta-Analysis of 18 studies of rTMS versus sham in pts with treatment resistant depression
- Response
  - rTMS 26%
  - Sham 9%
  - NNT=8
- Remission
  - rTMS 21%
  - Sham 6%
  - NNT=10

Gaynes B, et al. (2014) Repetitive Transcranial Magnetic Stimulation for Treatment Resistant Depression: A Systematic Review and Meta-Analysis. J Clin Psychiatry. 75(5):477-489.

Electroconvulsive Therapy (ECT)

- Use of small electrical current to induce generalized seizure
- Main indication is treatment of severe treatment resistant depression
- Mechanism of action not entirely clear
  - Monoamine release
  - Neuroendocrine hypothesis
  - Anticonvulsant properties
  - Neurogenesis

History of ECT

- 1934 Meduna
    - Observed that patients with dementia praecox improved when they had seizures
    - Induced seizures with IM camphor and later Metrazol
- 1938 Cerletti and Bini
    - First to use electricity to induce therapeutic seizure
    - Much more reliable than chemical agents
    - Within a few years started to be used regularly for mood disorders
- 1950s
    - Use began to decline
        - Intro of AP and AD Rx
        - Media
- Modern ECT bears little resemblance to early ECT

Indications for ECT

- Used as a primary treatment
  - Rapid psychological or physical deterioration
    - No time to wait for Rx response
  - History of good response to ECT

Indications for ECT

- Secondary treatment
  - History of poor response or intolerance to medications
  - Factors to consider when considering ECT
    - Accurate diagnosis, compliance, substance abuse, medical comorbidities
    - Number of medications tried
    - Adequacy of the trial
    - Severity of symptoms
    - Patient preference

Efficacy

- Systematic review and meta-analysis of treatment resistant patients
  - Unipolar depression
    - Response 74.2%
    - Remission 52.3%
  - Bipolar depression
    - Response 77.1%
    - Remission 52.3%

Bahji A, et al (2019) ECT beyond unipolar and major depression: systematic review and meta-analyisi of electroconvulsive therapy in bipolar depression. Acta Psychiatr Scand 139:214-226.

Efficacy

- Comparison with AD
  - 13 RCT's with 892 patients
  - TCA, MAOI, SSRI, TCA + Li
  - Odds of response with ECT about 4X greater than medications (OR=3.72; CI 95% 2.60, 5.32)

)Pagnin D, et al. (2004) Efficacy of ECT in depression: a meta-analytic review. J ECT, 20:13

Speed of Response

- Objective symptoms improve first
- Progressive symptomatic improvement in 1st week
- Complete remission in 3-4 weeks
- Consortium for Research in ECT (CORE)
  - 34% achieved remission ≤6 treatments
  - 65% achieved remission ≤10 treatments
  - More than half had initial response by 3rd treatment

Husain MM, Rush AJ, Fink M, et al. (2004) Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. J Clin Psychiatry. 65:485-491.

Factors Predicting Response

- Positive
  - Psychomotor retardation
  - Psychosis
  - Catatonia
  - Advanced age
- Negative
  - Longer duration of episode
  - Borderline personality disorder

1) Rasmussen KG. (2002) When is ECT indicated in psychiatric disorders? Current Psychiatry; 1(2) 2) Hickie I, Mason C, et al. (1996) Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. Br J Psychiatry; 169(1):68-74 3) Haq AU, et al. (2015) Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. J Clin Psychiatry : 76:1374 4) Feske U, et al. (2004) Clinical outcome of ECT in patients with major depression and comorbid borderline personality disorder. Am J Psychiatry : 161:2073

Adverse Effects

- Relatively safe procedure
  - Mortality is around 2-10/100,000
- Headache, muscle soreness, and nausea
- Cognitive side effects
  - Cognitive side effects from depression per se
  - Anesthesia and post-ictal effects
  - Are NOT associated with brain damage
    - Neuronal sprouting and synaptogenesis with animal models

Summary

- Depression is a common illness
- Only around one half of patients will respond and one third will remit to initial antidepressant
- Around a third of patients have treatment resistant depression and accurate diagnosis is essential
- Switching or augmenting medications are usual first steps
- ECT should be given strong consideration for some patients with TRD