



# Refractory Depression

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WEXNER MEDICAL CENTER

## Objectives

- Define Depression and Treatment Resistant Depression (TRD)
- Extent of the problem
- Depression and comorbid medical illnesses
- Treatments in Refractory Depression
- Discuss novel treatments like Ketamine in Depression and Suicide

# Disclosures

**Grants/Research Support** – Otsuka, Novartis, Allergan, Janssen, Biogen & Relmada

**Consultant** – Janssen

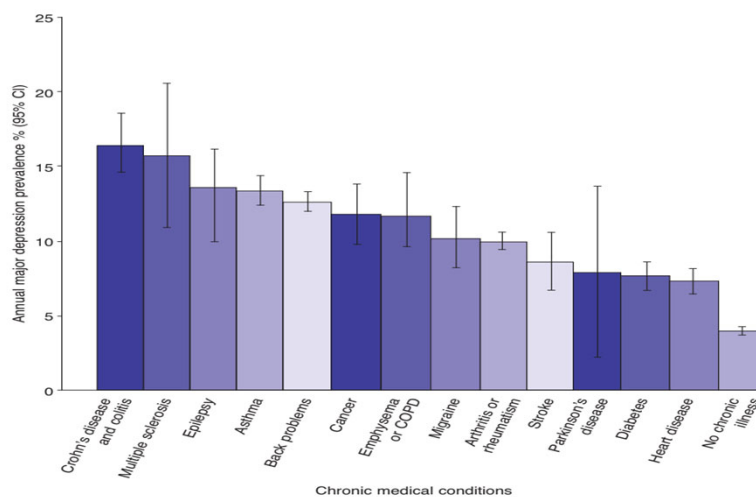
# Disclosures

Source	Research Funding	Honorarium or in-kind services	Consultant	Stock or Equity	Speakers Bureau
Janssen, Allergan, AssureRx, Forest, Otsuka, Shire	X				

# Extent of the problem

- According to WHO:  
Depression is the leading cause of disability worldwide, and is the major contributor to the overall global health burden of disease
- Centers for Disease Control and Prevention reported in 2018-Suicide rates rose in nearly every US State from 1999-2016. Rates spiked by >30% in half of the country
- Nearly 45,000 people committed suicide in 2016 making it one of the 3 leading causes of death on rise in US along with Alzheimer Disease and Drug OD and rates have not significantly decreased in recent years

## Depression in Physical Illness

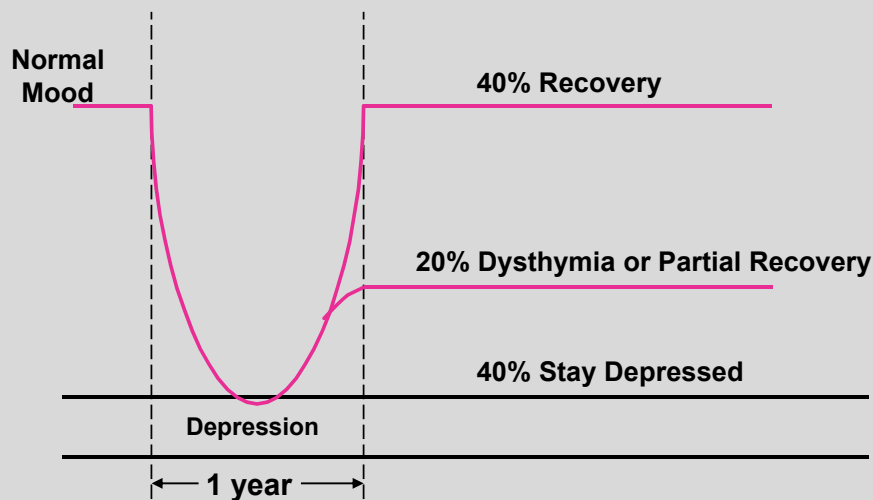


**Fig 1. Prevalence of major depression in self-reported long-term medical conditions.** Reproduced with kind permission of the *Canadian Journal of Psychiatry*.<sup>4</sup> CI = confidence interval; COPD = chronic obstructive pulmonary disease.

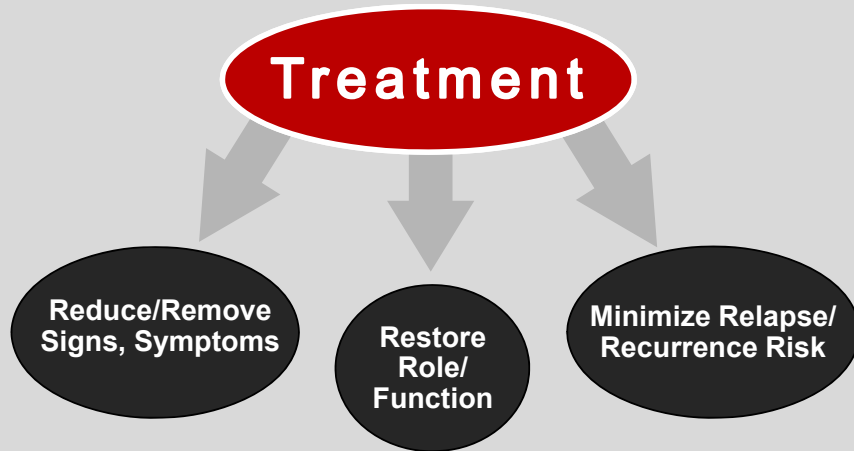
## MAJOR DEPRESSIVE EPISODE

- At least one of the following-Depressed mood or anhedonia -during the same 2 week period
- At least 5 (or more) of the following-
  - Depressed mood
  - Decreased interest or pleasure
  - Insomnia or hypersomnia
  - Significant weight loss or gain ( >5% change in body weight in a month) or changes in appetite
  - Psychomotor retardation
  - Fatigue or loss of energy
  - Decreased concentration or thinking, indecisiveness
  - Negative thinking - worthlessness, inappropriate or excessive guilt
  - Recurring thoughts of death or suicide
- Not organically caused
- Not uncomplicated bereavement or grief
- A change from previous functioning-clinically significant distress or impairment in social, occupational functioning

## NATURAL COURSE OF UNTREATED DEPRESSION

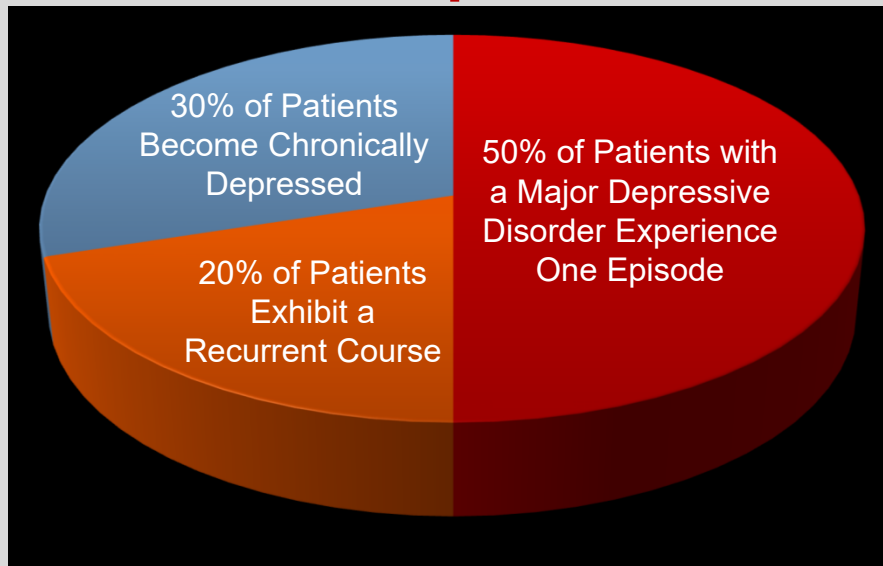


## Depressive Disorders: Treatment Goals



Adapted from WPA/PTD Educational Program on Depressive Disorders

## Recurrence of Depressive Disorders



Merikangas et al,  
WPA/PTD Educational Program on Depressive Disorders

## Treatment Resistant Depression( TRD)

- Typically refers to inadequate response to 2 or more treatment trials of adequate doses and duration
- TRD is relatively common in clinical practice ranging from 30-50%
- Accurate and systematic assessment of TRD is a challenge to researchers and clinicians
- Use of Clinician-rated like MGH ATRQ ( Antidepressant treatment response questionnaire) or self rated instruments can be helpful

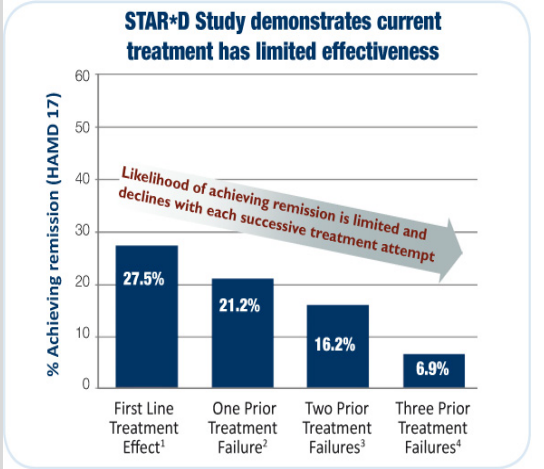
M Fava Society of Biological Psychiatry 2003

## And Problem is not getting better....

- Treatment resistant depression (TRD) is around 30-50% in patients who have received pharmacotherapy
- TRD costs employers in US up to \$48 billion/yr
- Health care resource use and costs were double(\$17,261) for employees with TRD compared with non-TRD depression (\$9,790) and quadruple without depression (\$4,782)
- Health care costs for employees with TRD increased with each treatment failure
- Employees with TRD were absent approx. 35.8 days per person per year, almost 6 times more than without depression

Greenberg Psych News 2018

# How Depression Is Treated



- Drug therapy has been the standard of care

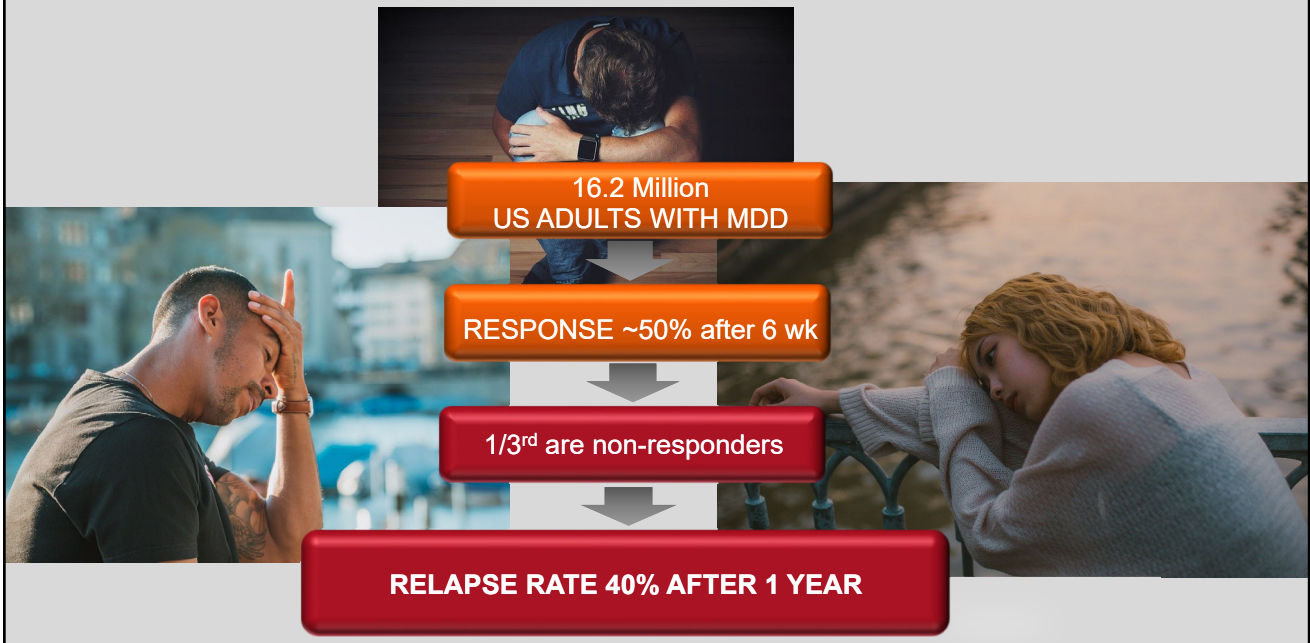
- But drug therapy...

...doesn't work for many people

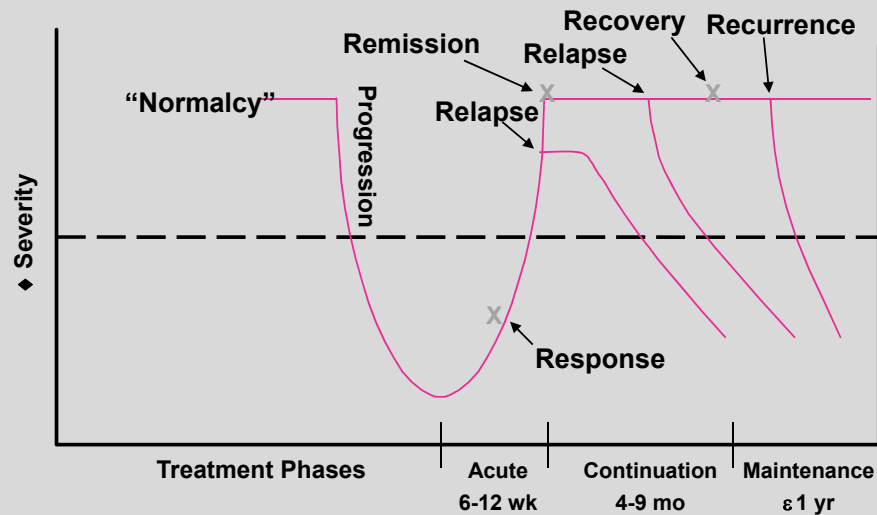
...may produce unwanted side effects in other parts of the body

Trivedi (2006) *Am J Psychiatry*; Rush (2006) *Am J Psychiatry*; Fava (2006) *Am J Psychiatry*; McGrath (2006) *Am J Psychiatry*

# TRD: A Large Patient Population- Treatment Challenges



## Clinical Status And Treatment Phases Of Depression



## ANTIDEPRESSANTS

SSRIs-selective serotonin reuptake inhibitors (eg fluoxetine)

SNRIs –selective serotonin and norepinephrine reuptake inhibitors (eg venlafaxine)

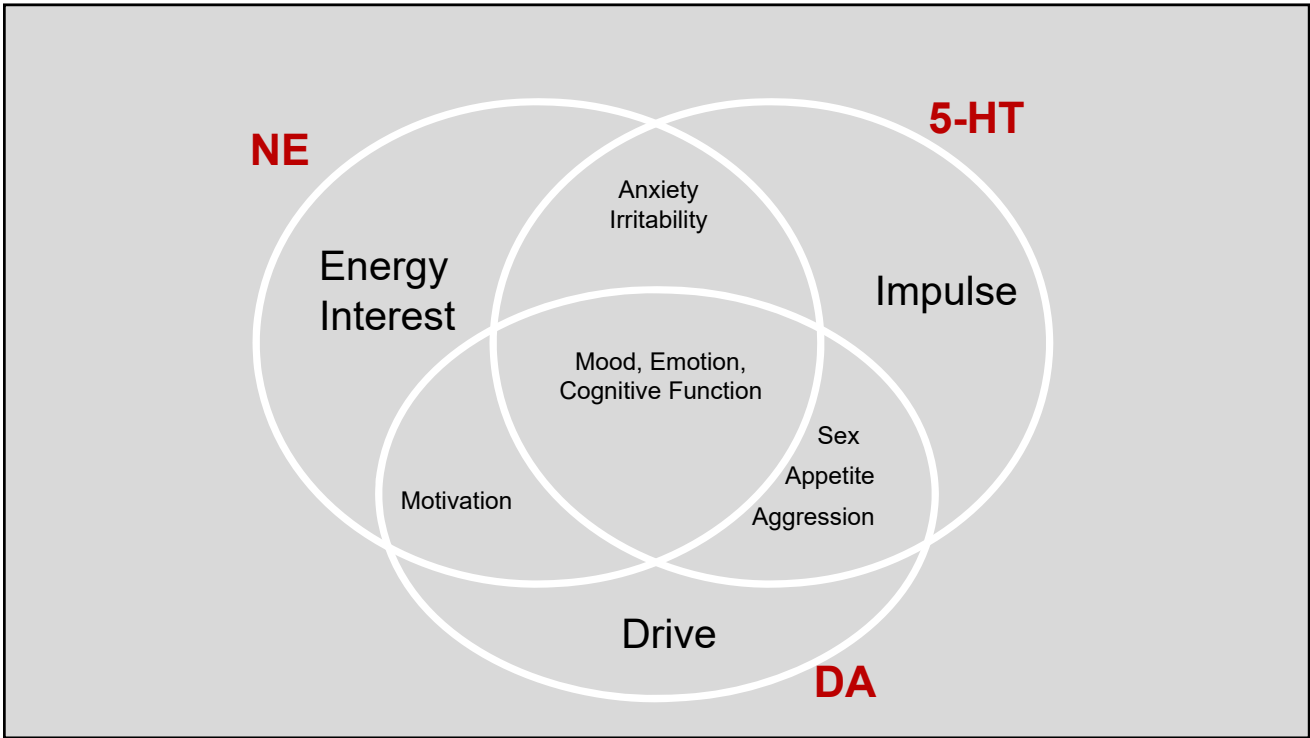
TCA tricyclic antidepressants (eg amitriptyline)

MAOIs- monoamine oxidase inhibitors (rarely used today)

Others or Atypical (eg Trazodone)

NOVEL Antidepressants- NMDA Receptor Modulators (eg Ketamine)





## PSYCHOTHERAPY FOR DEPRESSION

- High number of studies, meta-analysis, reviews exist
- Types of psychotherapy in treatment of depression
  - Cognitive behavioral therapy
  - Existential therapy
  - Psychodynamic therapy
  - Expressive-supportive therapy
  - Mindfulness and relaxation therapy
  - Educational therapy

## Clinical Approach to TRD

### Ensure Adequate Diagnosis

- Organic etiology of depressive symptoms
- Co-morbid psychiatric illness like substance abuse d/o, anxiety disorders, personality disorders

### Accurately assess treatment response

- Obtain collateral information from family, past records
- Use standard Assessment scale for depression and past treatment
- Differentiate between partial response vs non response
- R/o Tachyphylaxis

### Determine adequate trial of Treatment

- Compliance, Intolerance or other reasons
- Adequate trial dosage and duration

### Consider test of Pharmacogenomics

- NNDC TRD task force

## Highlights

- Treatment Resistant depression causes huge societal and personal burden worldwide
- Clinical depression is a serious psychiatric complication in medical illness
- Evidence that antidepressants are effective in reducing depression/depressive s/s is shown in clinical trials but there is no evidence for the superiority of one treatment modality over another
- Combined approaches to the treatment of depression may be more effective
- There are still inconsistencies across providers in terms of patient selection, duration, optimal dosing and frequency of the treatments in patients with co-morbid medical conditions
- There is growing interest in developing newer drugs with similar mechanisms with fewer side effects and rapid acting.



## Refractory Depression

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# Assessment of Therapeutic Adequacy

## • Antidepressant Treatment History Form (ATHF-SF)

**Pharmacotherapy**

*To be rated "Adequate" the pharmacotherapy trial must have been given at or above the minimum oral dose (or blood level) for a minimum of four weeks. The patient should not have shown marked clinical improvement or remission at the end of the treatment period, and there should not be evidence that the patient was substantially non-adherent with the treatment regimen.*

Medication	Brand Names	Minimum Oral Dose/day	Adequate Trial		Administered
			Yes	No	
<b>SSRIs</b>					
Citalopram	Celexa, Cipramil	20 mg			
Escitalopram	Lexapro, Cipralext, Sipralext	10 mg			
Fluvoxamine	Luvox (including CR), Floxyfral	200 mg			
Fluoxetine	Prozac, Sarafem	20 mg			
Paroxetine	Paxil, Pexeva, Brisdelle, Seroxat	20 mg			
Paroxetine CR	Paxil CR	25 mg			
Sertraline	Zoloft, Lustral, Serlain	100 mg			
<b>SNRIs</b>					
Desvenlafaxine	Pristiq, Khedezla, Desfax, Ellefore	50 mg			
Duloxetine	Cymbalta, Irenka	40 mg			
Levominlacipran	Fetzima	40 mg			
Venlafaxine	Effexor, Effexor XR	150 mg			

1. Sackeim HA, Aaronson ST, Bunker MT, et al. The assessment of resistance to antidepressant treatment: Rationale for the antidepressant treatment history form: Short form (ATHF-SF). *J Psychiatr Res.* 2019.

# Electroconvulsive Therapy

## ***Most frequent indications***

### Depressive Disorders

- Major Depressive Disorder
- Bipolar I/II Disorder, current episode depressed
- Schizoaffective Disorder, Depressed Type
- Schizoaffective Disorder, Bipolar Type, current episode depressed

### Manic Disorders

- Bipolar I Disorder
- Schizoaffective Disorder, Bipolar Type, current episode manic

### Catatonic Disorders

- Catatonia associated with another mental disorder
- Catatonia associated with another medical condition

### Schizophrenia

- Cases of incomplete response to clozapine

# Electroconvulsive Therapy

## Benefits and Risks

### Benefits:

- Effective in treatment resistant depression
- Average time to improvement with depressive disorders: ~7 treatments (6-12 treatments range)
- Provided Mondays, Wednesdays, Fridays

### Risks:

- Headache
- Nausea
- Myalgias
- Working memory disruption
- Emerging in treatment, persisting for 2-12 weeks post treatment (average)
- Serious morbidity and mortality (ischemia, cardiac or cerebral, arrhythmia, arrest)
- 2.2 per 100,000 incidence

# Electroconvulsive Therapy

## Efficacy and Speed of Response

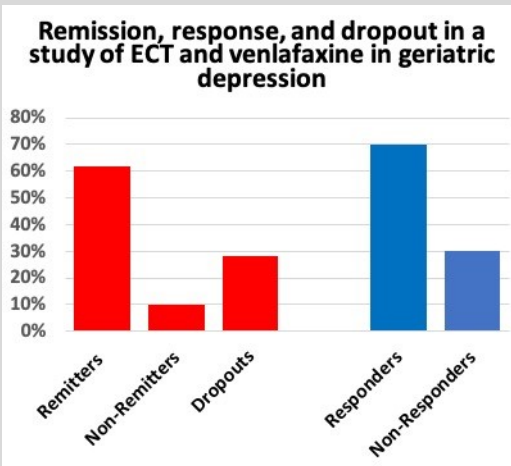
**Table 3. Proportion of Patients With Major Depressive Disorder (N = 253) Achieving Sustained Response and Remission by Electroconvulsive Therapy (ECT) Session Number**

ECT Session #	Onset of First Response <sup>a</sup>		Sustained First Response <sup>b</sup>		Attained Remission <sup>b</sup>	
	%	N	%	N	%	N
1	12.6	32	50.0	16	78.1	25
2	19.4	49	65.3	32	81.6	40
3	21.7	55	67.3	37	85.5	47
4	13.4	34	70.6	24	91.2	31
5	11.5	29	82.8	24	82.8	24
6	4.7	12	50.0	6	75.0	9
7	4.0	10	60.0	6	50.0	5
8	2.0	5	80.0	4	80.0	4
9	3.2	8	62.5	5	50.0	4
10	0.8	2		0		0
≥ 11 <sup>c</sup>	0.8	2		0		0

<sup>a</sup>Percentage of first responders who sustained the first response (based on Ns in first column); 60.9% of the total sample (154/253) sustained the first response.

<sup>b</sup>Percentage of first responders who eventually achieved remission (based on Ns in first column); 74.7% of the total sample (189/253) attained remission. Remission did not necessarily follow a sustained first response (remission may have followed a subsequent sustained response achieved later in the ECT course).

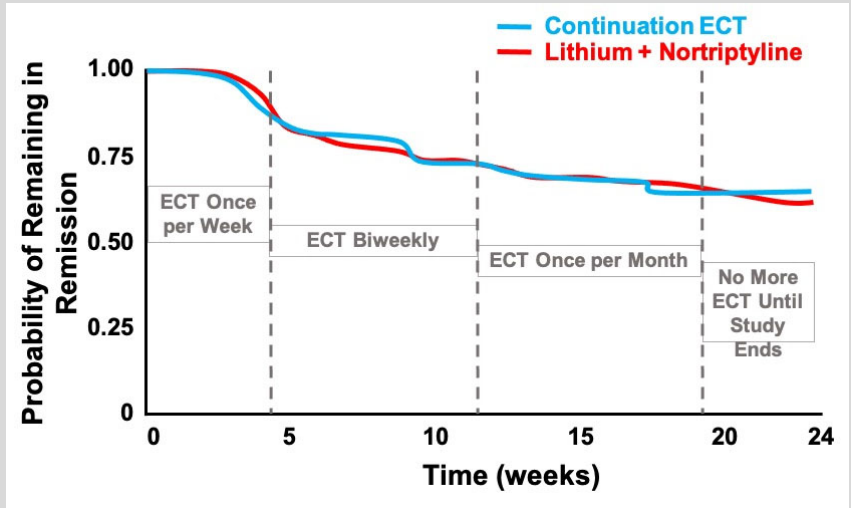
<sup>c</sup>5.9% (N = 15) of the total sample never achieved a first response.



1. HUSAIN MM, RUSH AJ, WENLE ZHAO, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): A consortium for research in ECT (CORE) report. *The Journal of clinical psychiatry*. 2016;77(11):1101-1109.  
 2. Kellner CH, Husain MM, Knapp RG, et al. Right unilateral ultrabrief pulse ECT in geriatric depression: Phase 1 of the PRIDE study. *Am J Psychiatry*. 2016;173(11):1101-1109.

# Electroconvulsive Therapy

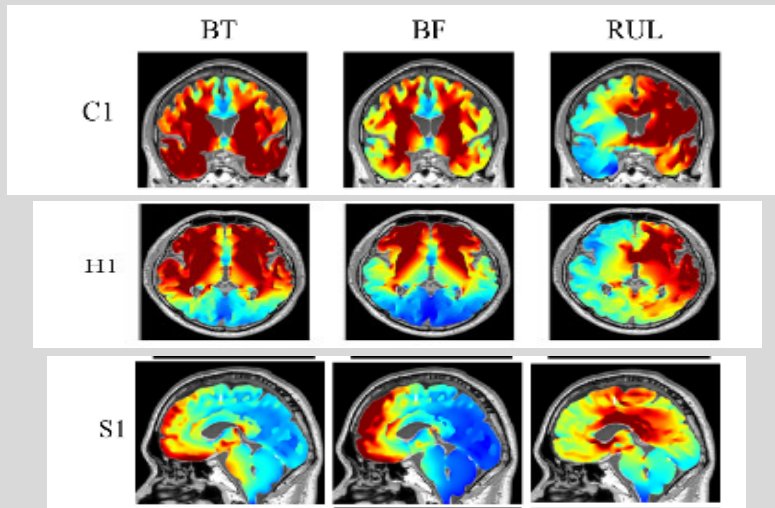
## Maintenance of Response



1. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: A multisite study from the consortium for research in electroconvulsive therapy (CORE). *Arch Gen Psychiatry.* 2006;63(12):1337-1344.

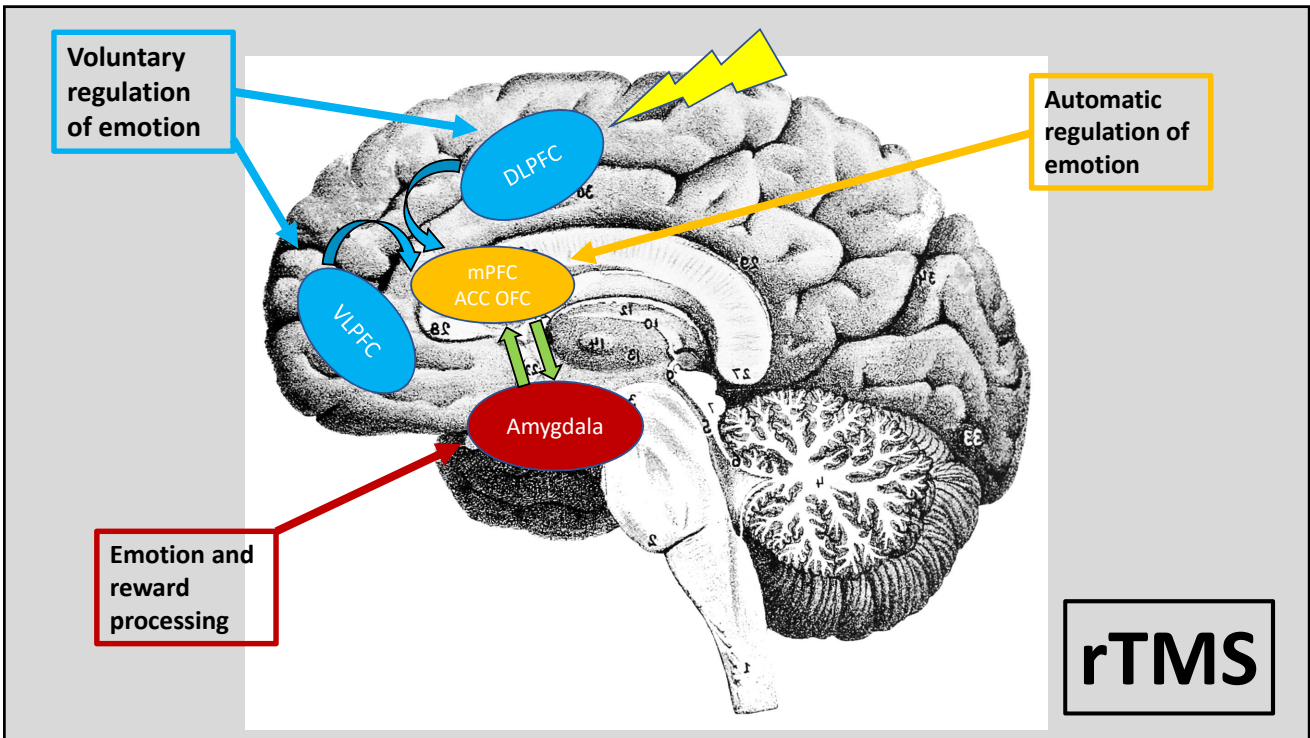
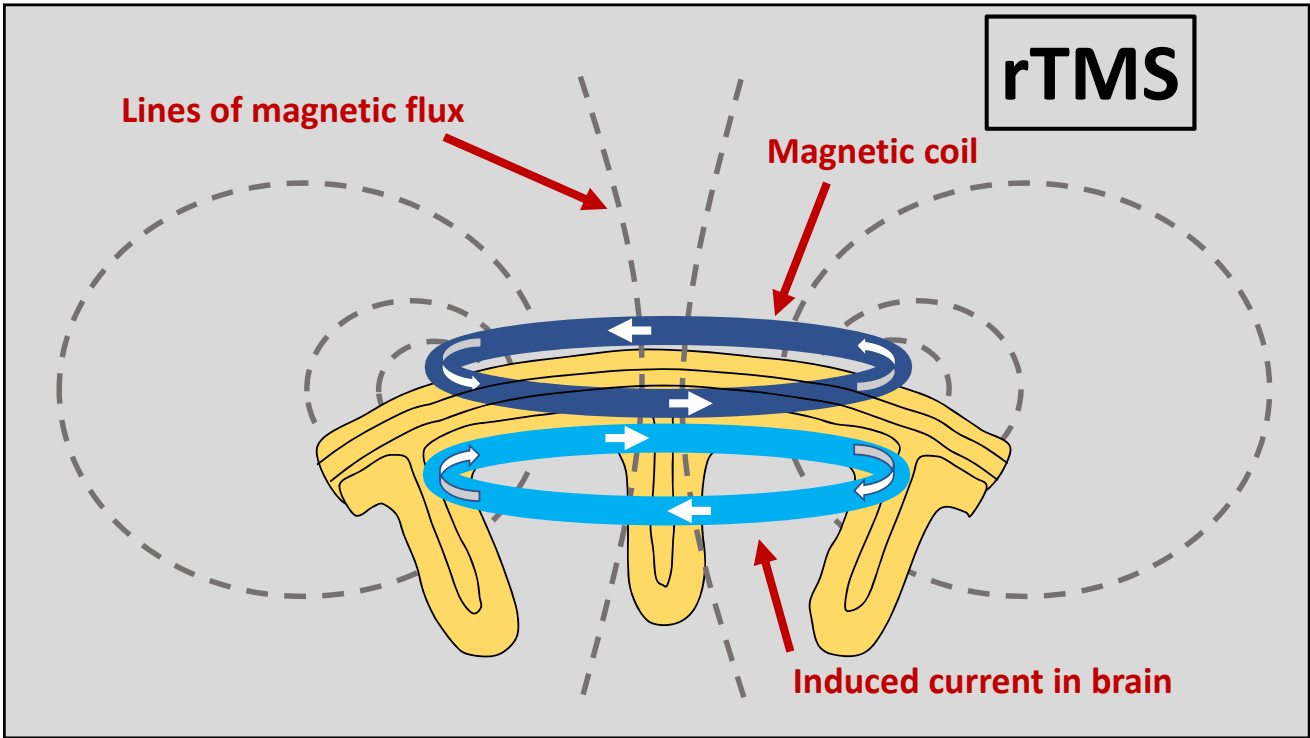
# Electroconvulsive Therapy

## Electrical field generation in the brain depending on placement



BT- bitemporal  
BF- bifrontal  
RUL- right unilateral

1. Bai S, Martin D, Guo T, Dokos S, Loo C. Computational comparison of conventional and novel electroconvulsive therapy electrode placements for the treatment of depression. *European Psychiatry.* 2019;60:71-78.



# TMS for Major Depressive Disorder: Outcomes

Comparison of response and remission rates based on PHQ-9 and CGI-S scores for the same patients or PHQ-9 scores only.

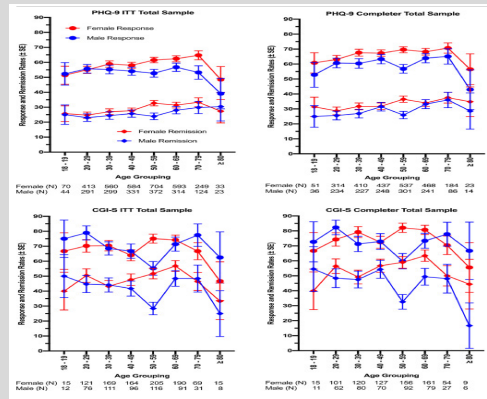
Response and remission rates for female and male patients as a function of age grouping for the intent-to-treat (ITT) and Completer Total samples, separately for self-report (PHQ-9) and clinician-rated (CGI-S) outcomes.

Outcome (Sample)	PHQ-9 No CGI-S	PHQ-9 both rated	CGI-S both rated
Response (ITT Total sample)	53.8% (1893/3521)	67.2% <sup>a</sup> (1000/1489)	69.4% <sup>b</sup> (1034/1489)
Response (Completer total sample)	62.7 % (1657/2644)	70.4% <sup>a</sup> (824/1170)	75.0% <sup>c</sup> (878/1170)
Remission (ITT total sample)	25.0% (879/3521)	34.8% <sup>a</sup> (518/1489)	46.5% <sup>c</sup> (692/1489)
Remission (Completer total sample)	29.7% (785/2644)	36.2% <sup>a</sup> (423/1170)	52.5% <sup>c</sup> (614/1170)

a  
p < 0.001 comparing PHQ-9 outcomes with and without concomitant CGI-S ratings based on z-test for independent proportions.

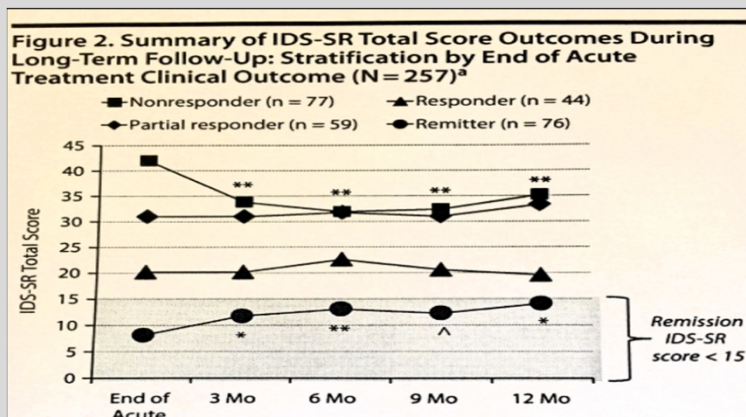
b  
p < 0.05 comparing outcomes on PHQ-9 and the CGI-S using McNemar's test for dependent proportions.

c  
p < 0.001 comparing outcomes on PHQ-9 and the CGI-S using McNemar's test for dependent proportions.



1. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with transcranial magnetic stimulation. *Journal of affective disorders*. 2020;277:65-74.

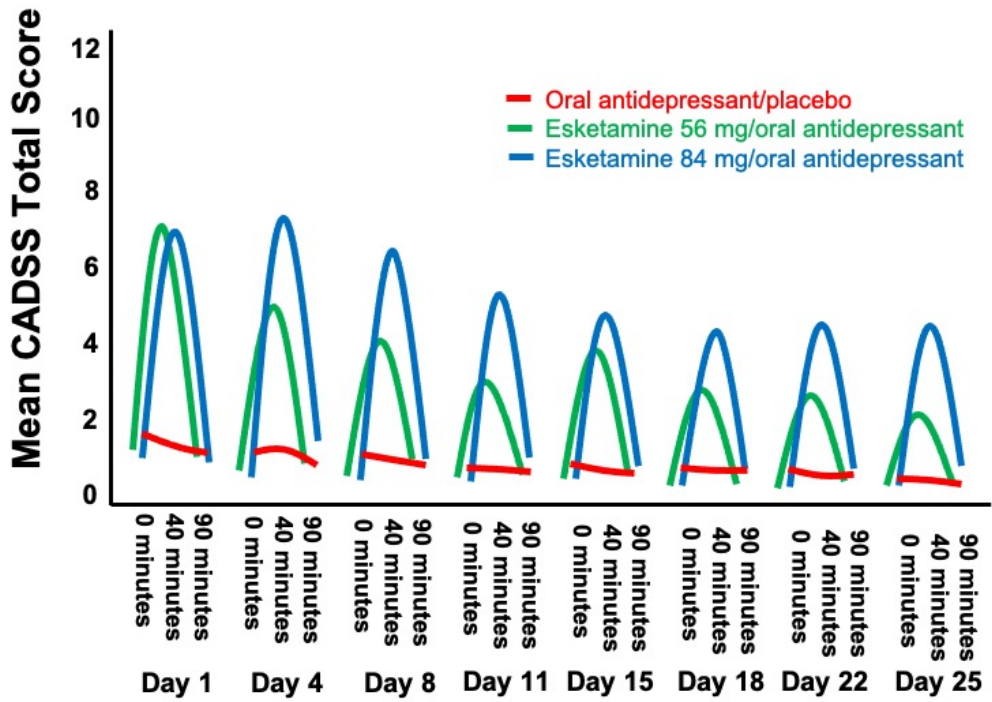
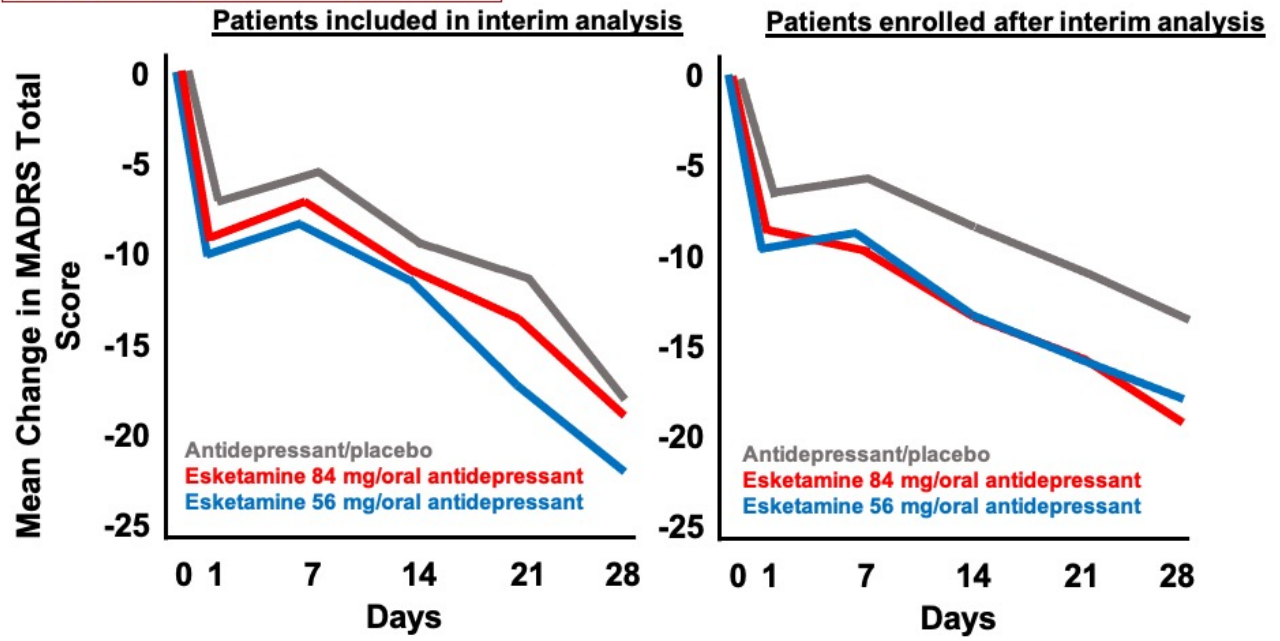
# TMS in Major Depressive Disorder

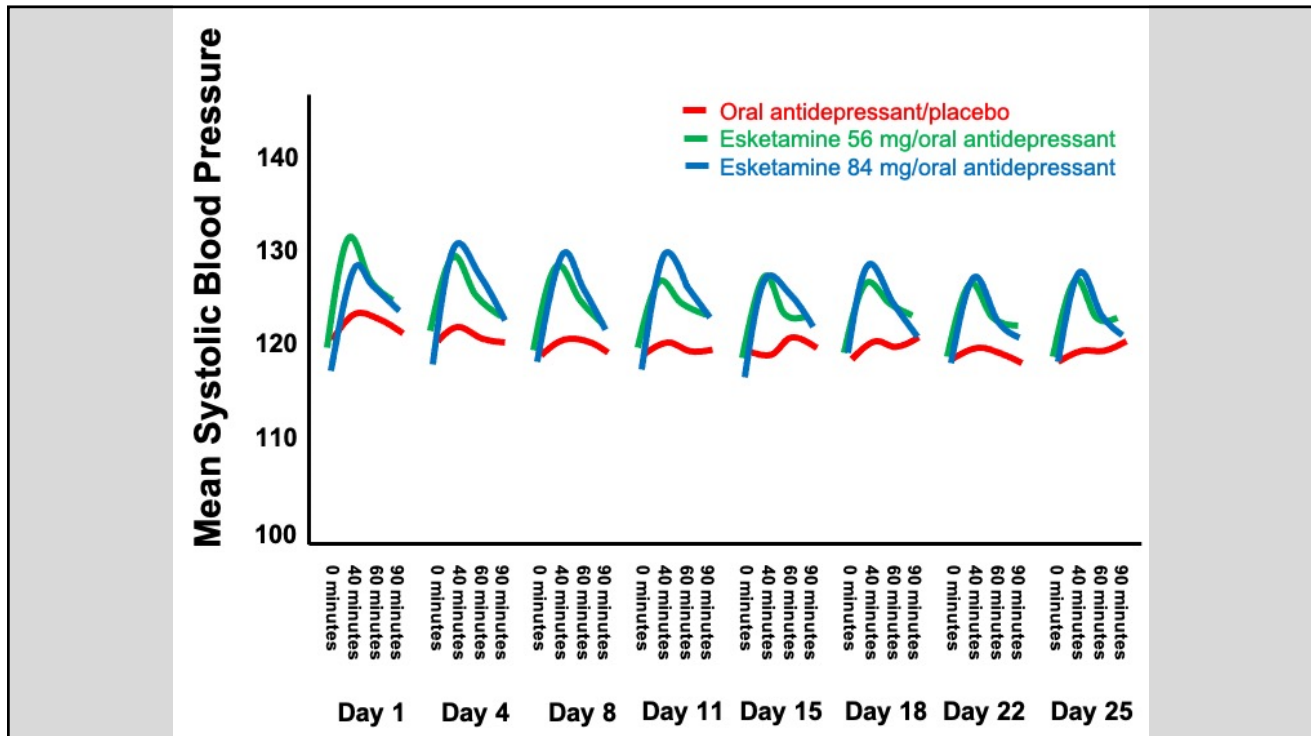


1. Dunner DL, Aaronson ST, Sackeim HA, et al. A multisite, naturalistic, observational study of transcranial magnetic stimulation for patients with pharmacoresistant major depressive disorder: Durability of benefit over a 1-year follow-up period. *J Clin Psychiatry*. 2014;75(12):1394-1401.



**TRANSFORM-1- Spravato**

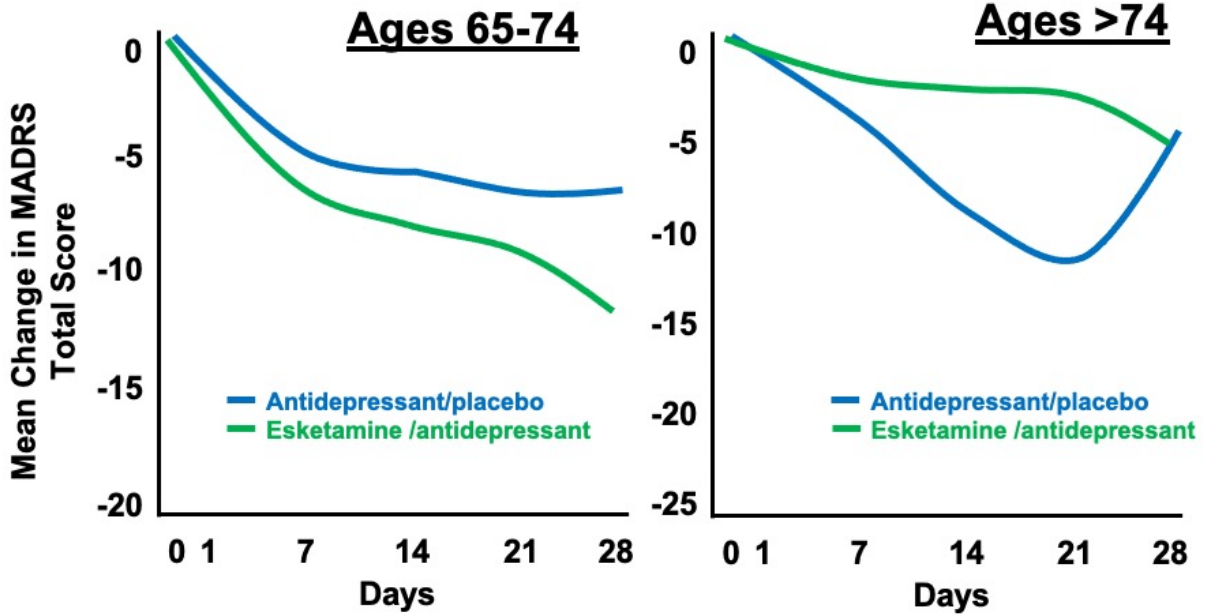




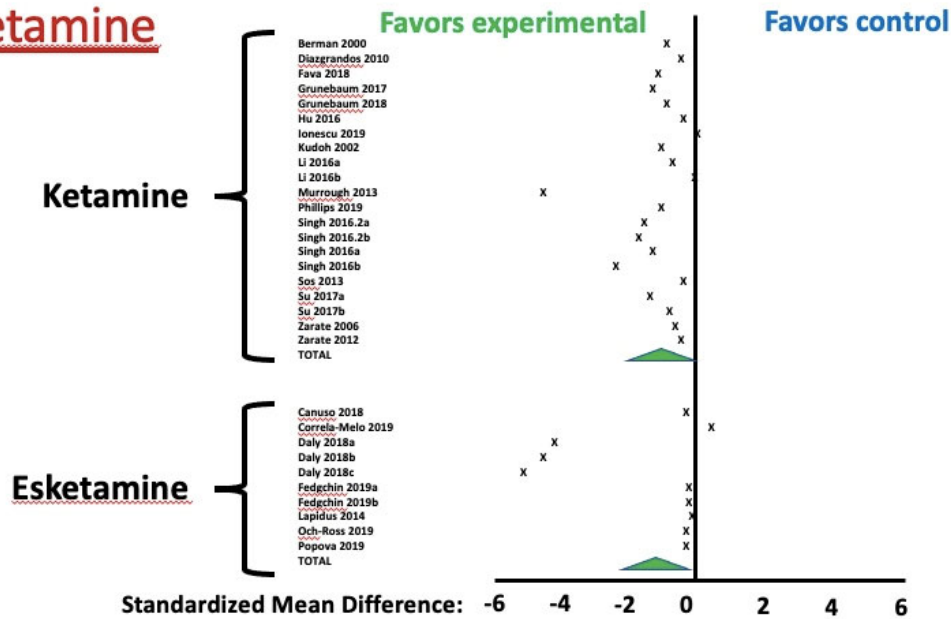
### **Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study**

- Compared different doses of esketamine (28, 56, 84 mg) in patients with TRD started on a new oral antidepressant (one of several)
  - Least square mean change in MADRS primary outcome
    - Allows for comparisons between unequal groups
- MADRS change at 24 hrs statistically significant (-5 placebo to ~-8 Spravato)
- At day 28, continued statistically significant difference favoring Spravato (~-16 placebo to ~-20 Spravato)

**TRANSFORM-1- Spravato**

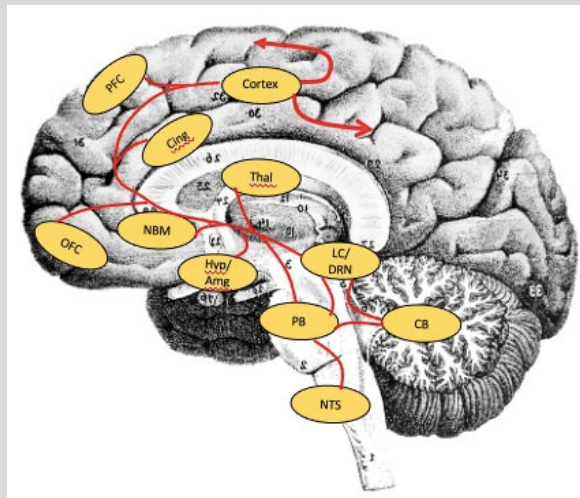


**Comparison of controlled trials utilizing ketamine and esketamine**

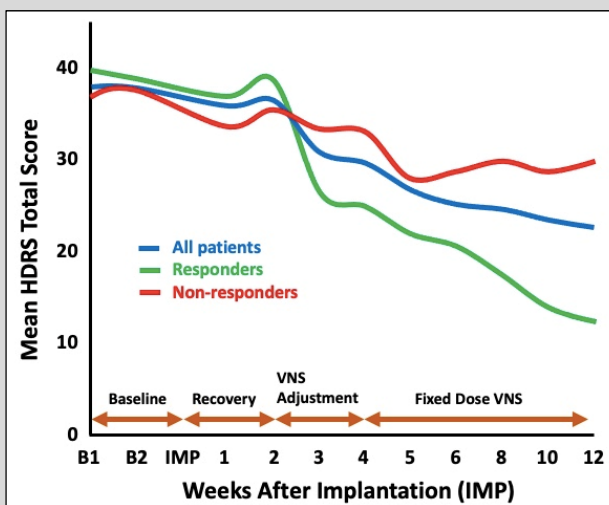
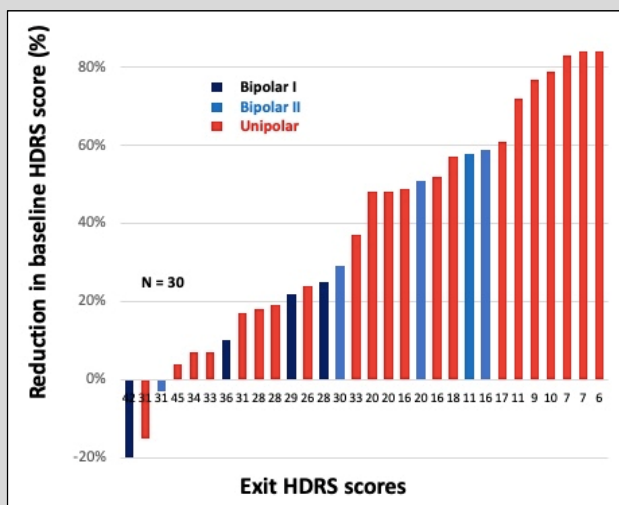


## Vagus Nerve Stimulation

- FDA-approved in 2005
- Indications:
  1. Major depressive disorder
  2. Adjunctive treatment
  3. Age > 18
  4. Two or more adequate trials



## Vagus Nerve Stimulation



1. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: A multicenter study. *Biol Psychiatry*. 2000;47(4):276-286. [http://eutils.ncbi.nlm.nih.gov/doi/50006-3223\(99\)00304-2](http://eutils.ncbi.nlm.nih.gov/doi/50006-3223(99)00304-2) [pii].

## 5 year outcomes with VNS

- Compared to Treatment as Usual (TAU), VNS showed cumulative response rates of almost 70% at 60 months (40% TAU)
  - Remission rates >40% (VNS) v 25% (TAU)
- Patient with response had approximately 50% probability of sustaining response at 60 months, versus 30% with TAU
- Patients with ECT non-response history were ~10% less likely to achieve response with VNS
- Comorbid anxiety disorders and presence of Bipolar Disorder did not appear to meaningfully impair response with VNS

**TABLE 2. Analysis of Suicidality and Mortality Among Patients With Treatment-Resistant Depression Receiving Treatment as Usual With or Without Adjunctive Vagus Nerve Stimulation (VNS) (Safety Population)**

Measure	VNS Group (N=494)	Treatment-as-Usual Group (N=301)
Number of deaths during study participation	7	8
Exposure (patient-years)	1,985.08	926.49
All-cause mortality per 1,000 person-years	3.53	8.63
Number of suicides during study participation	2	2
Suicides per 1,000 person-years	1.01	2.20

