Refractory Depression

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MedNet21
Center for Continuing Medical Education

The Ohio State University
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

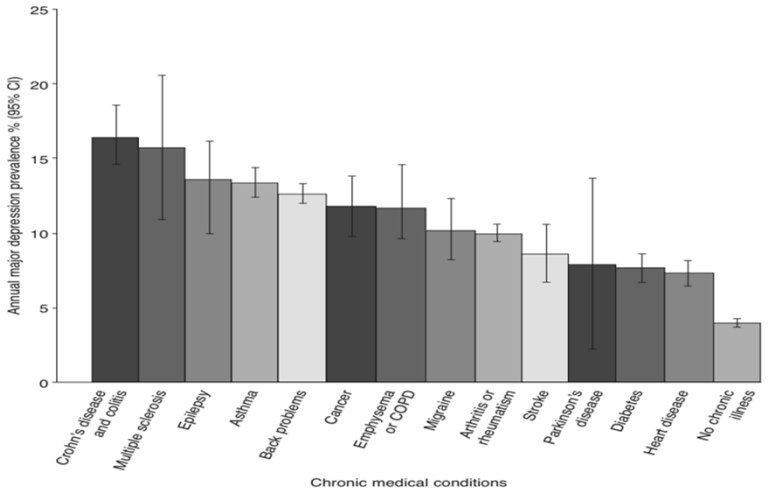

Fig 1. Prevalence of major depression in self-reported long-term medical conditions.
Reproduced with kind permission of the *Canadian Journal of Psychiatry*.[4]
CI = confidence interval; COPD = chronic obstructive pulmonary disease.

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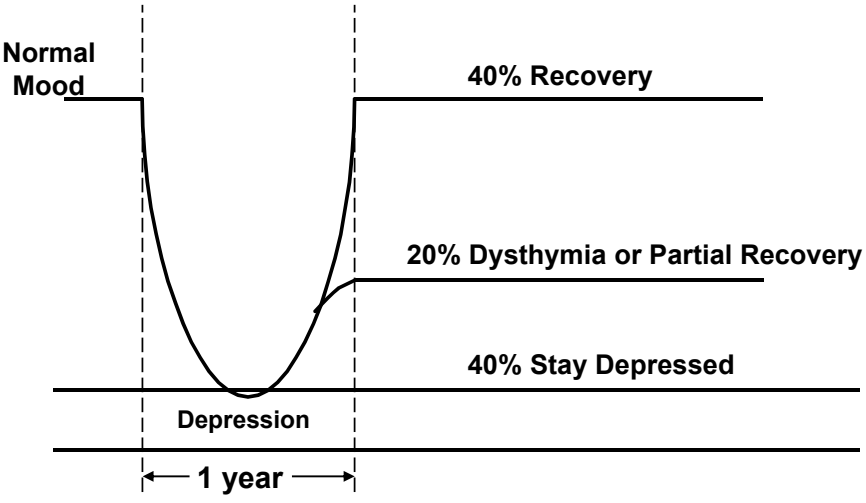
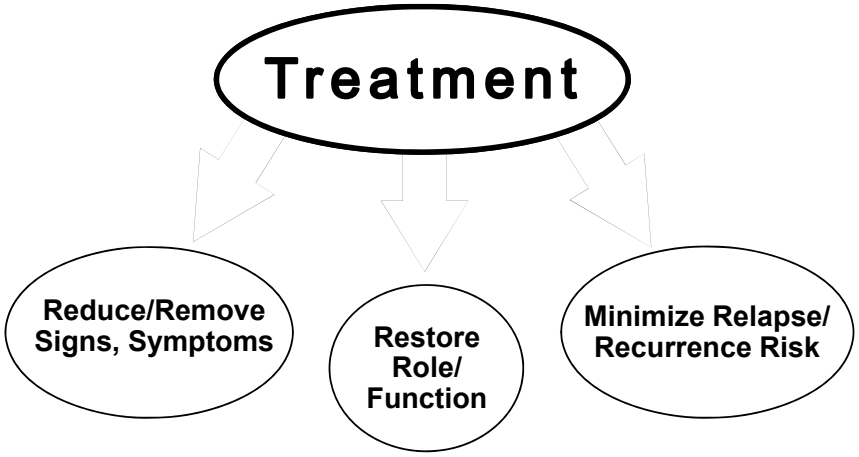
MAJOR DEPRESSIVE EPISODE

- 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

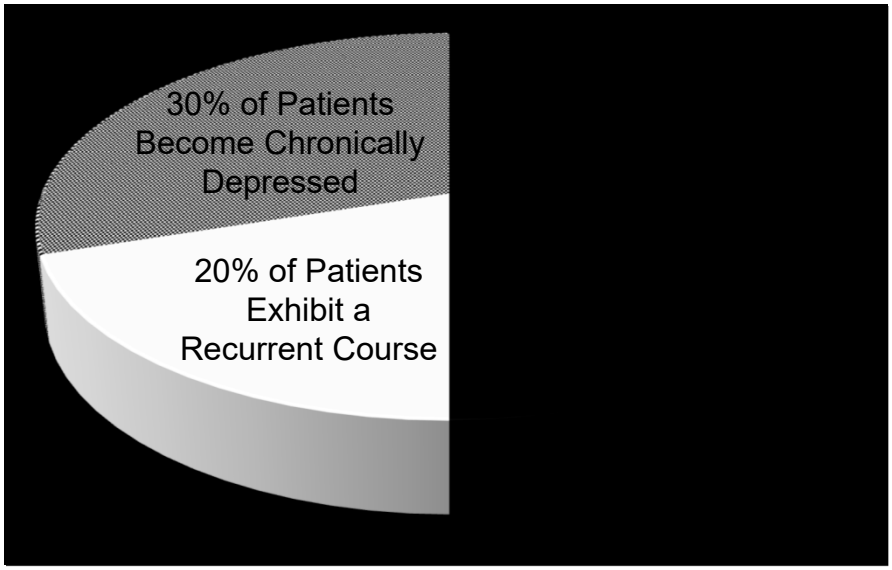


Depressive Disorders: Treatment Goals



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

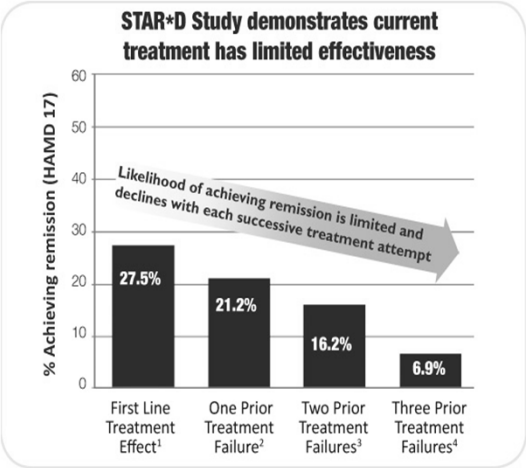
M Fava Society of Biological Psychiatry 2003

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
- Heath 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...

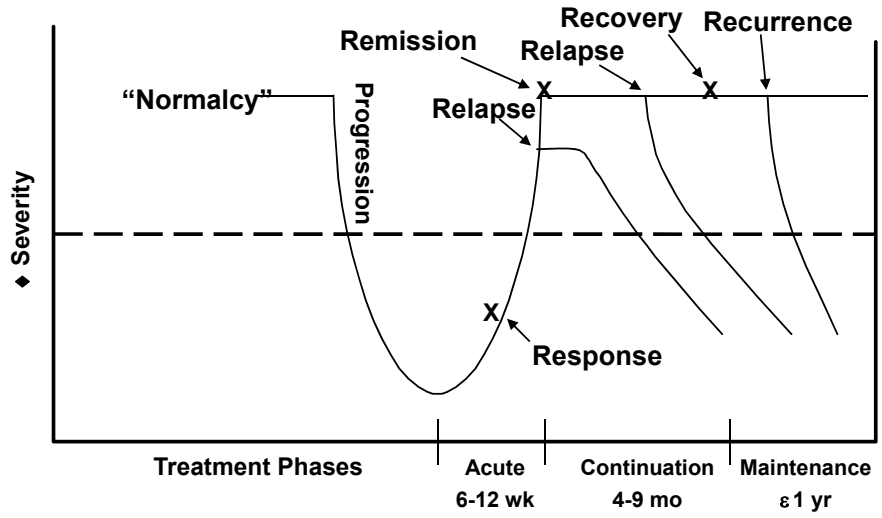
…doesn't work for many people

…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)

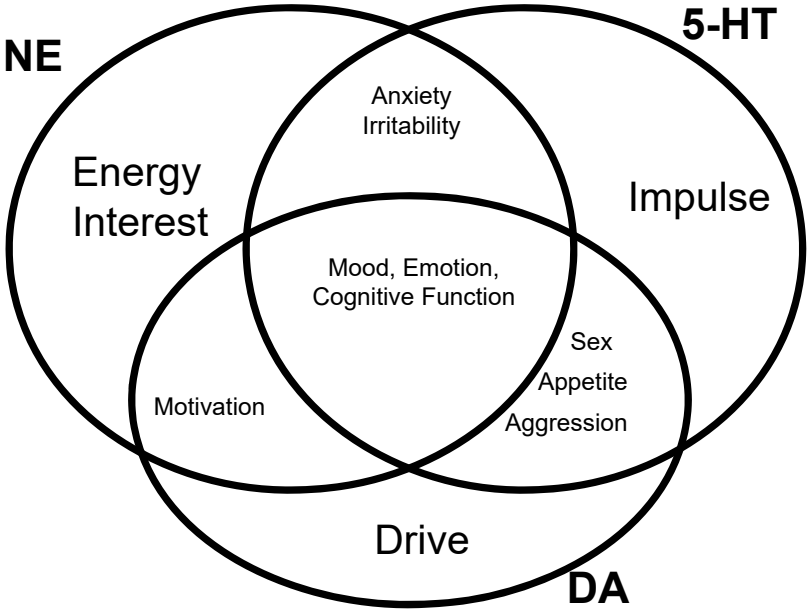
SNRIs –selective serotonin and norepinephrine reuptake inhibitors (eg venlafaxine)

TCAs tricyclic antidepressants (eg amitriptyline)

MAOIs- monoamine oxidase inhibitors (rarely used today)

Others or Atypical (eg Trazodone)

NOVEL Antidepressants- NMDA Receptor Modulators (eg Ketamine)


NE
5-HT
DA
Anxiety
Irritability
Energy
Interest
Impulse
Mood, Emotion,
Cognitive Function
Sex
Appetite
Aggression
Motivation
Drive


COULD CLUB DRUG
CURE
BREAKING NEWS
BREAKING NEWS
NEW TONIGHT
KETAMINE THERAPY FOR DEPRESSION

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 Yes*	*No*	*Administered*
SSRIs					
Citalopram	Celexa, Cipramil	20 mg			
Escitalopram	Lexapro, Cipralex, Sipralexa	10 mg			
Fluovoxamine	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			

SNRIs		*Minimum Oral Dose/day*	*Adequate Trial Yes*	*No*	*Administered*
Desvenlafaxine	Pristiq, Khedezla, Desfax, Ellefore	50 mg			
Duloxetine	Cymbalta, Irenka	40 mg			
Levomilnacipran	Fetzima	40 mg			
Venlafaxine	Effexor, Effexor XR	150 mg			

1. *Sacke*im 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

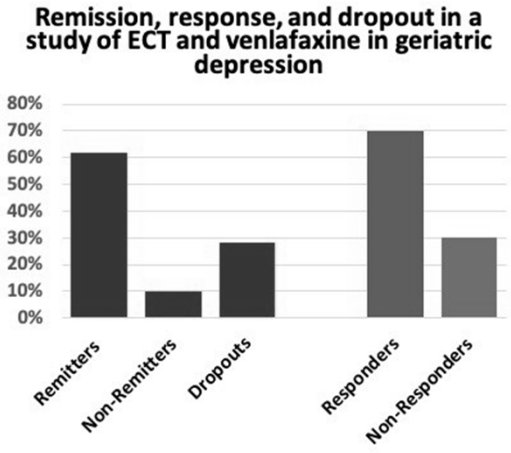
Electroconvulsive Therapy

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

	Onset of First Response		Sustained First Response[a]		Attained Remission[b]	
ECT Session #	%	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[c]	0.8	2		0		0

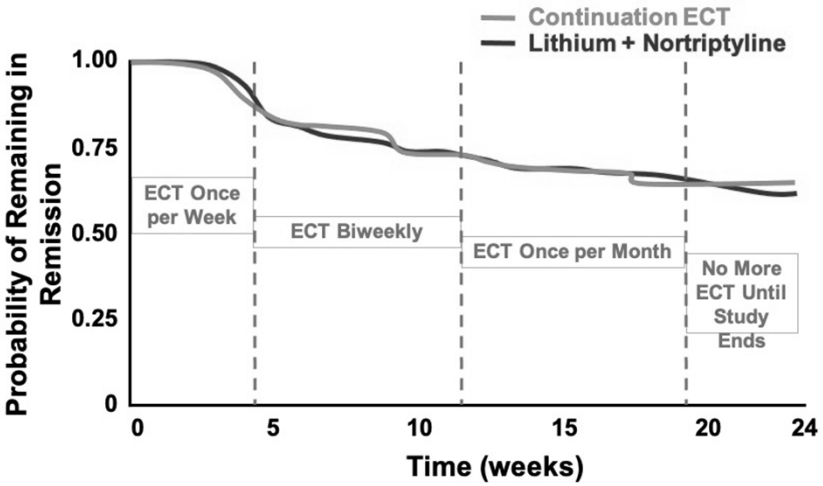
[a]Percentage of first responders who sustained the first response (based on Ns in first column); 60.9% of the total sample (154/253) sustained the first response.
[b]Percentage of first responders who eventually achieved remission (based on Ns in first column); 74.7% of the total sample (189/253) attained remission. Remission did not necessarily follow a sustained first response (remission may have followed a subsequent sustained response achieved later in the ECT course).
[c]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 cli*
2. 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

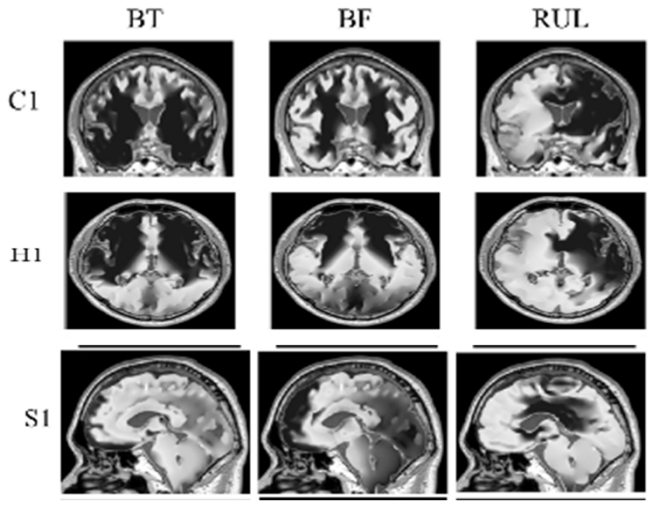
Maintenance of Response



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.

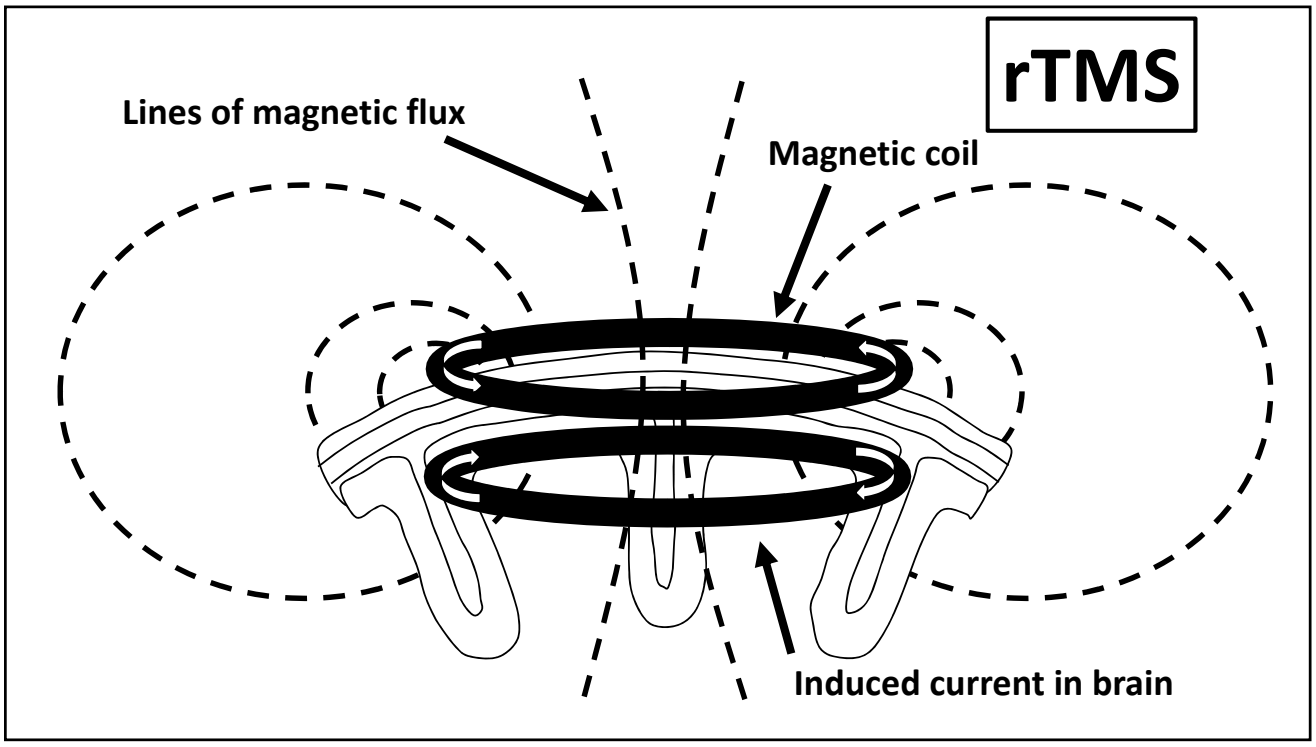
Electroconvulsive Therapy

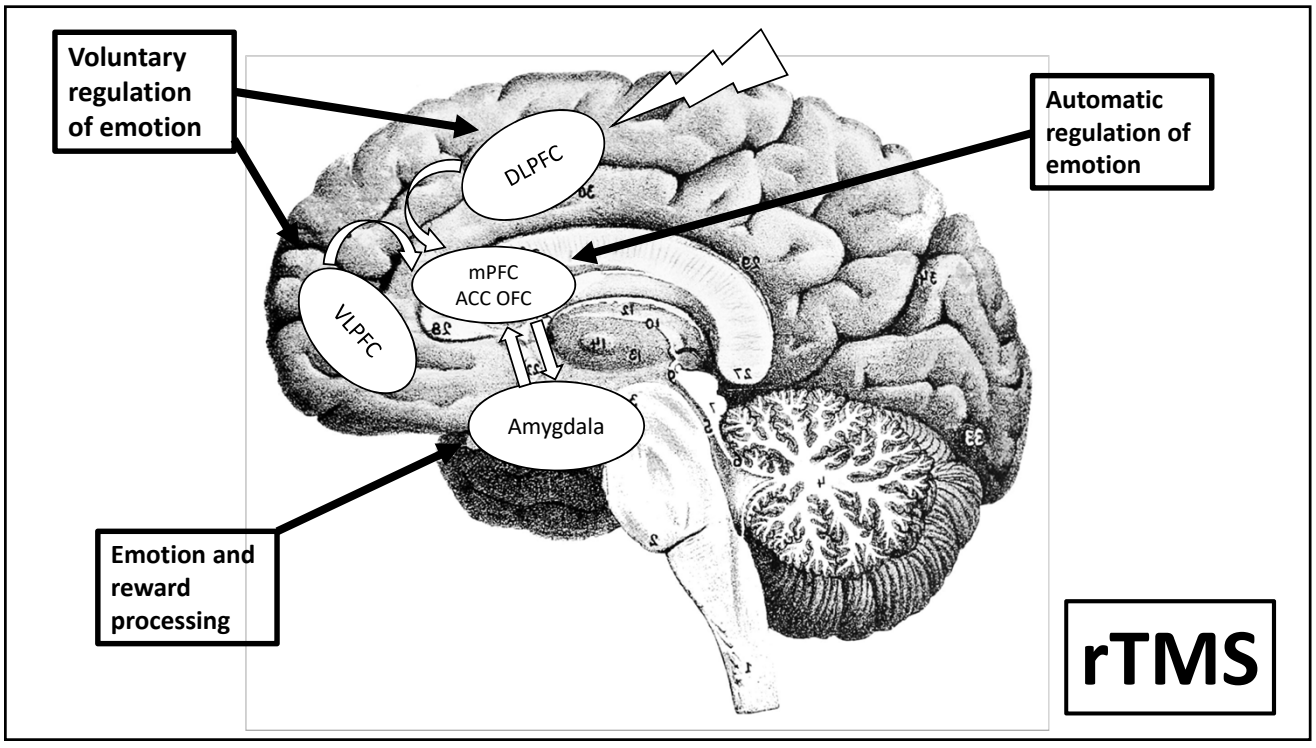
Electrical field generation in the brain depending on placement



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.


rTMS
Lines of magnetic flux
Magnetic coil
Induced current in brain


Voluntary regulation of emotion
Automatic regulation of emotion
DLPFC
mPFC
ACC OFC
VLPFC
Amygdala
Emotion and reward processing
rTMS

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.

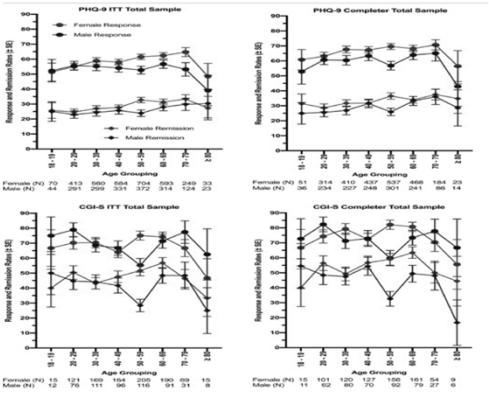
Outcome (Sample)	PHQ-9 No CGI-S	PHQ-9 both rated	CGI-S both rated
Response (ITT Total sample)	53.8% (1893/3521)	67.2%[a] (1000/1489)	69.4%[b] (1034/1489)
Response (Completer total sample)	62.7 % (1657/2644)	70.4%[a] (824/1170)	75.0%[c] (878/1170)
Remission (ITT total sample)	25.0% (879/3521)	34.8%[a]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

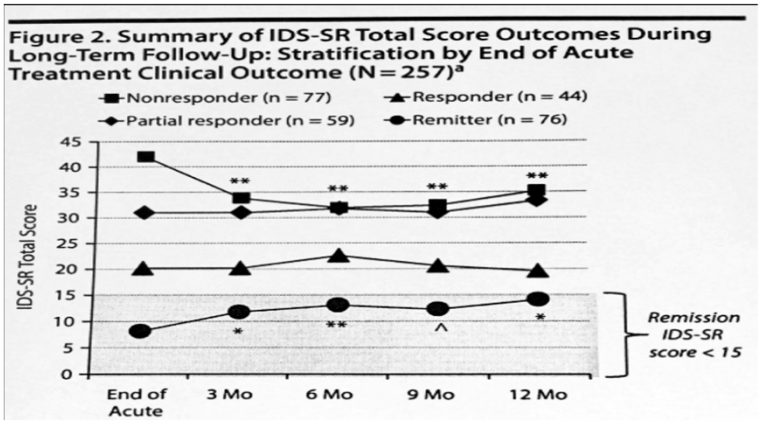
c $p < 0.001$ comparing outcomes on PHQ-9 and the CGI-S using McNemar's test for dependent proportions.

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

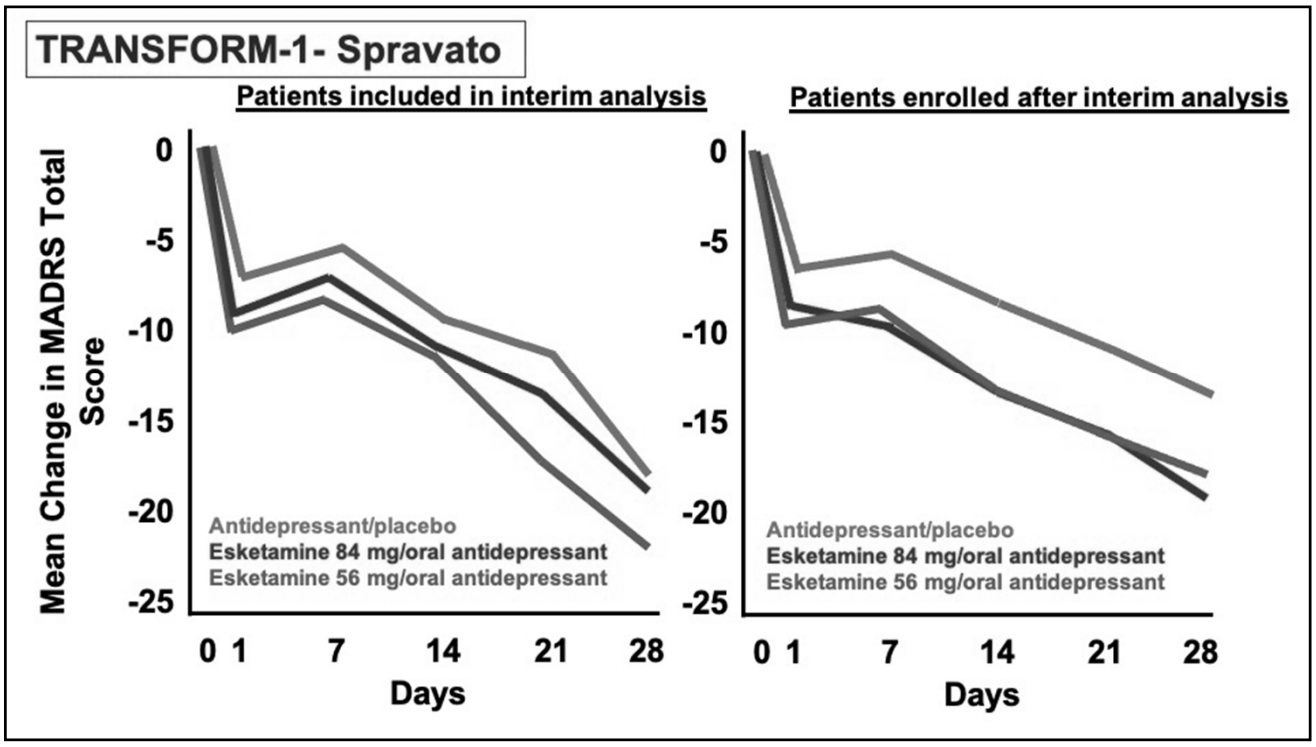


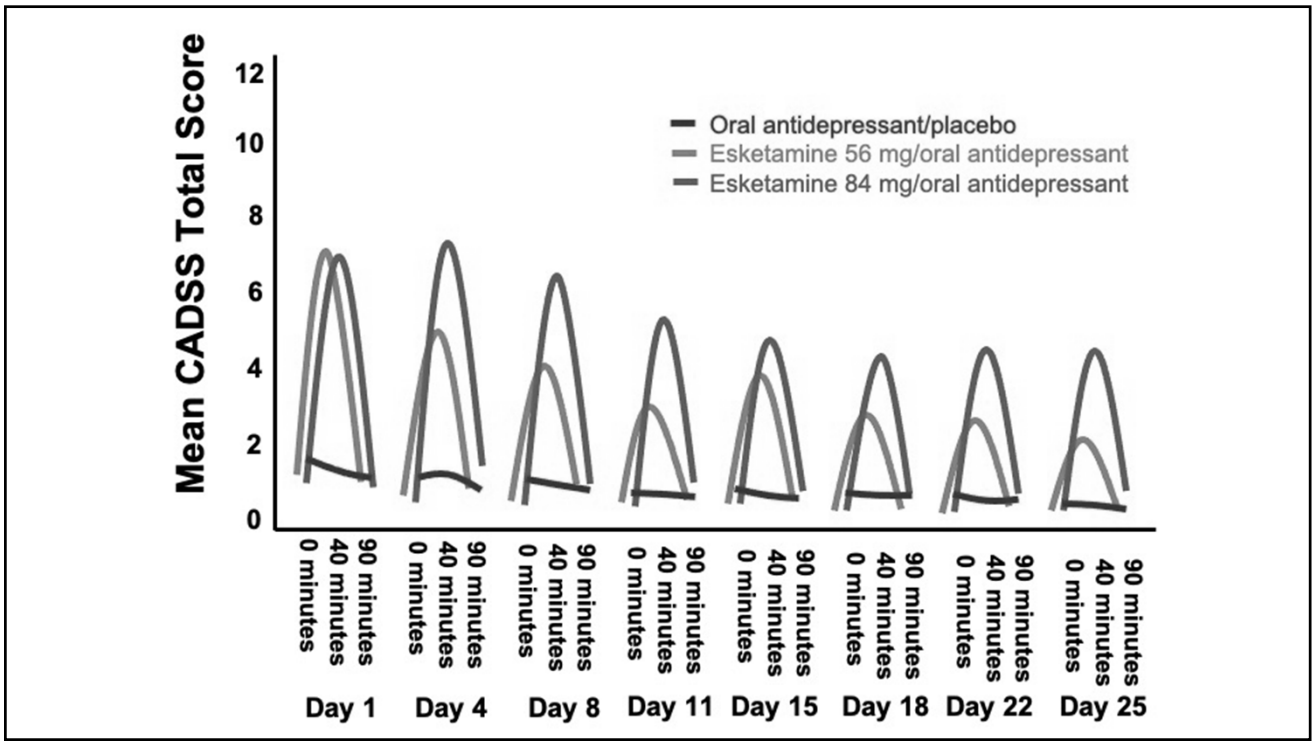
1. Sackeim HA, Aaronson ST, Carpenter LL, et al. Clinical outcomes in a large registry of patients with major depressive disorder treated with transcranial magnetic stimulation. *Journal of affective disorders*. 2020;277:65-74. .

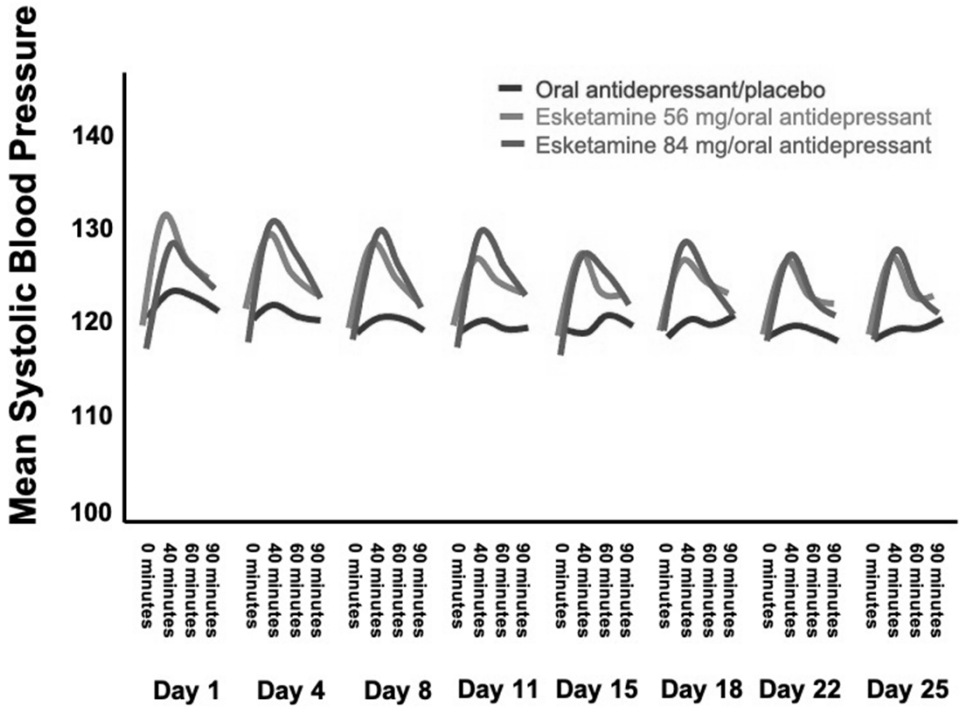
TMS in Major Depressive Disorder



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.

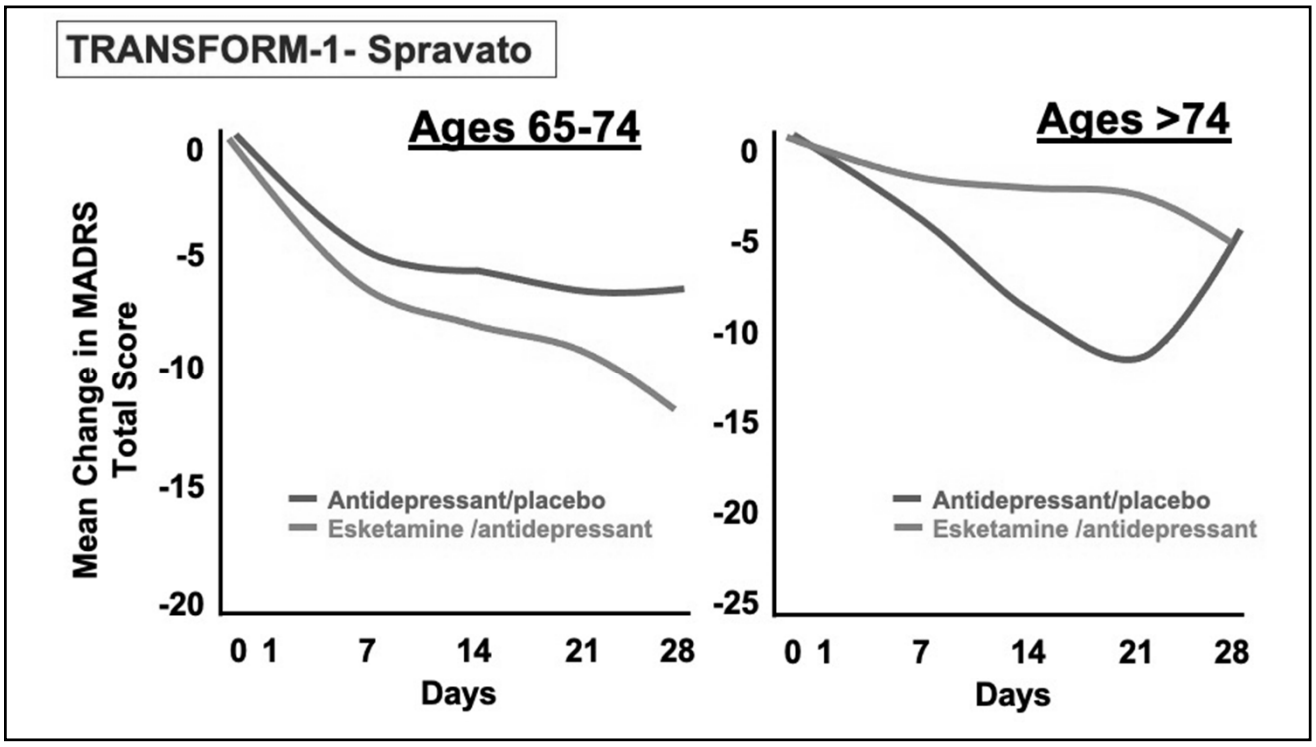

TRANSFORM-1- Spravato
Patients included in interim analysis
Patients enrolled after interim analysis
Mean Change in MADRS Total Score
0
-5
-10
-15
-20
-25
Antidepressant/placebo
Esketamine 84 mg/oral antidepressant
Esketamine 56 mg/oral antidepressant
0 1 7 14 21 28
Days

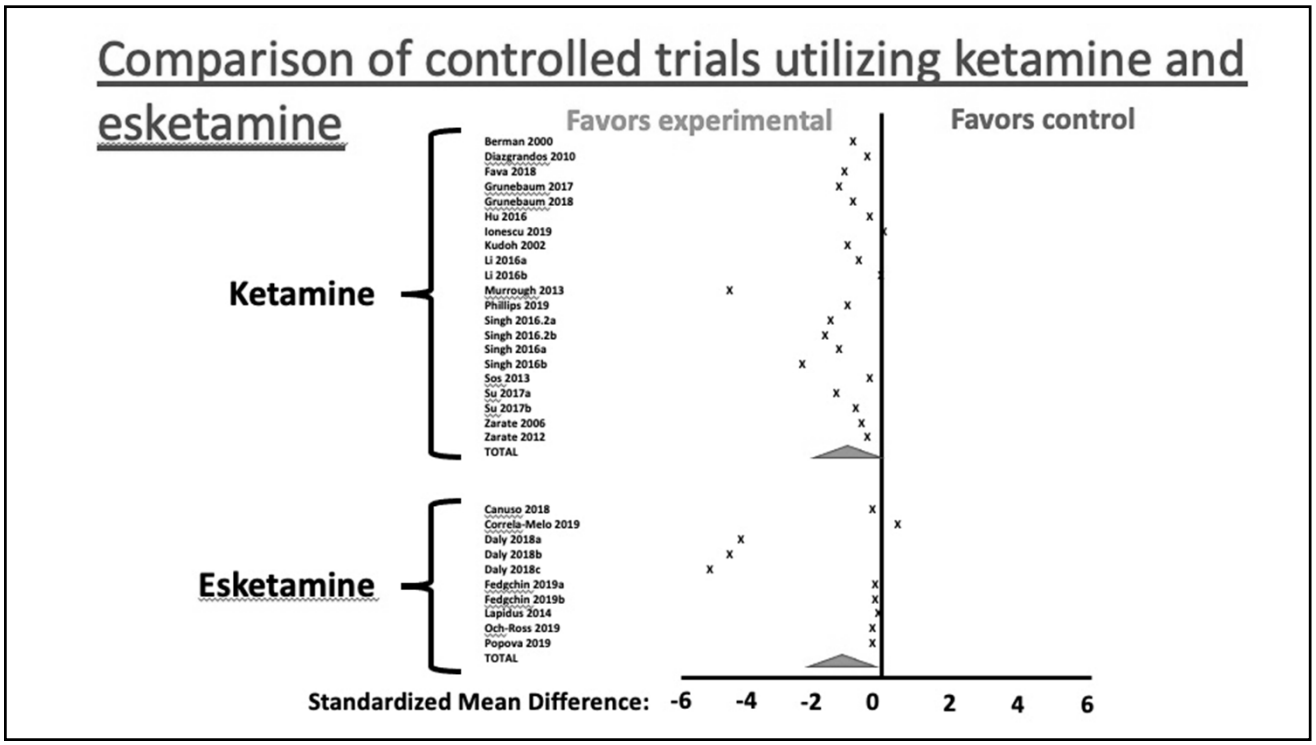

Mean CADSS Total Score
12
10
8
6
4
2
0
Oral antidepressant/placebo
Esketamine 56 mg/oral antidepressant
Esketamine 84 mg/oral antidepressant
0 minutes
40 minutes
90 minutes
Day 1
Day 4
Day 8
Day 11
Day 15
Day 18
Day 22
Day 25



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

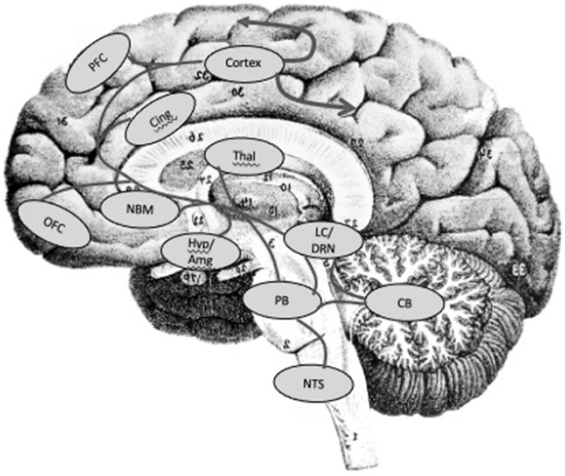
- Compared different doses of esketamine (28, 56, 84 mg) in patients with TRD started on a new oral antidepressant (one of several)
  - Least square mean change in MADRS primary outcome
    - Allows for comparisons between unequal groups
- MADRS change at 24 hrs statistically significant (-5 placebo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


TRANSFORM-1- Spravato
Ages 65-74
Ages >74
Mean Change in MADRS Total Score
0
-5
-10
-15
-20
-25
0 1 7 14 21 28
Days
Antidepressant/placebo
Esketamine /antidepressant

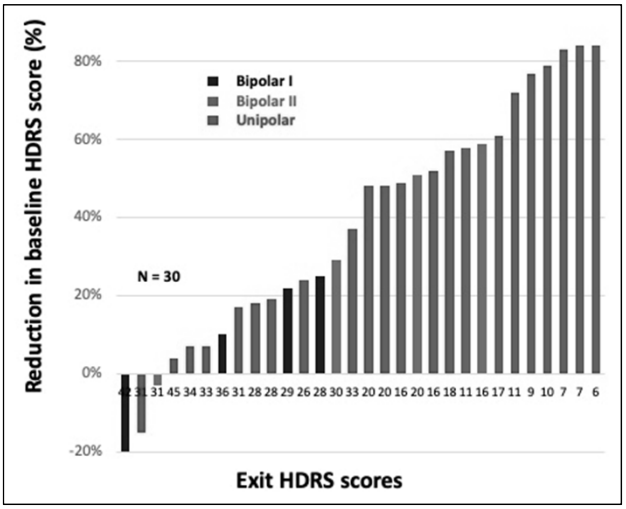

Comparison of controlled trials utilizing ketamine and esketamine
Favors experimental
Favors control
Ketamine
Berman 2000
Diazgrandos 2010
Fava 2018
Grunebaum 2017
Grunebaum 2018
Hu 2016
Ionescu 2019
Kudoh 2002
Li 2016a
Li 2016b
Murrough 2013
Phillips 2019
Singh 2016.2a
Singh 2016.2b
Singh 2016a
Singh 2016b
Sos 2013
Su 2017a
Su 2017b
Zarate 2006
Zarate 2012
TOTAL
Esketamine
Canuso 2018
Correla-Melo 2019
Daly 2018a
Daly 2018b
Daly 2018c
Fedgchin 2019a
Fedgchin 2019b
Lapidus 2014
Och-Ross 2019
Popova 2019
TOTAL
Standardized Mean Difference:
-6 -4 -2 0 2 4 6

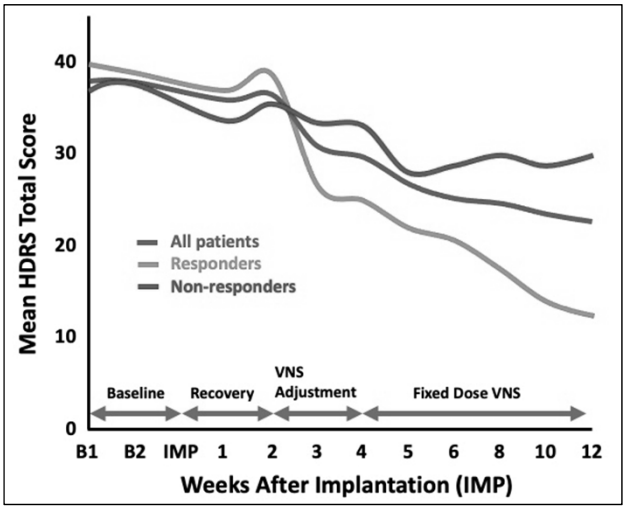
Vagus Nerve Stimulation

- 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: S0006-3223(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