What Works in Treatment Resistant Depression?

Daniel Zigman, MD, FRCPC

Disclosures

- I have received honorarium from Aifred, an AI company for participating in a clinical trial
  - There is no relationship with this session
- I will be discussing off-label treatments

Objectives

- Define and recognize TRD
- Understand advantages and disadvantages of therapies that have proven beneficial in TRD
- Understand the role of ketamine/esketamine, second generation antipsychotics, lithium and other options

Overview

- Initial treatment of depression (CANMAT, Harv Psychopharm Algorithm)
- Next step strategies
- Treatment resistant depression

"Would the gentleman prefer an antidepressant?"

Poll

- A 35 year old business woman presents with a first depressive episode for the past 2 months in context of problems in family and stress at work
  - Depressed mood, crying daily, insomnia, decreased appetite, anxiety, impaired concentration, death wishes, -ve rumination
  - No substance use, psychiatric or medical comorbidity
  - Significant functional impairment, unable to work

- Which of the following treatment options would you chose?
  - A) SSRI
  - B) SNRI
  - C) Bupropion
  - D) Mirtazapine
  - E) CBT

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Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments

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CANMAT 2016 guidelines

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level 1 Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[a] (Tolvon)	α_2-Adrenergic agonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic agonist; 5-HT_2 antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} agonist; 5-HT_{1B} partial agonist; 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 antagonist	10-20 mg
Second line (Level 1 Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[e]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[a] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; 5-HT_2 antagonist	150-300 mg
Vilazodone (Viibryd)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} partial agonist	20-40 mg (titrate from 10 mg)
Third line (Level 1 Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

Kennedy, Can J Psychiatry, 2016

CANMAT 2016 guidelines

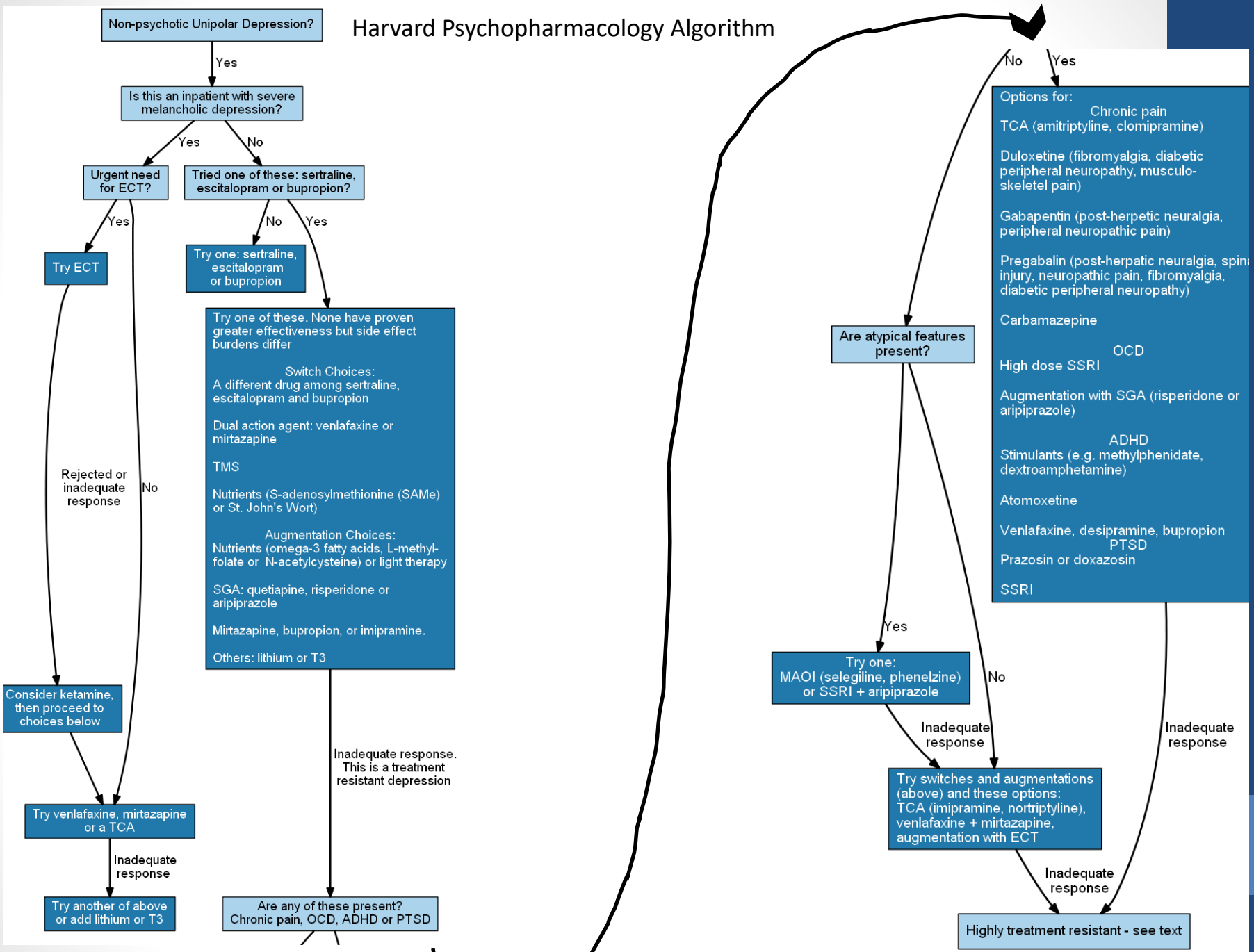
Table 5. Recommendations for Clinical Specifiers and Dimensions of Major Depressive Disorder.

Specifiers/ Dimensions	Recommendations (Level of Evidence)	Comments
With anxious distress[a]	• Use an antidepressant with efficacy in generalized anxiety disorder (Level 4)	• No differences in efficacy between SSRIs, SNRIs, and bupropion (Level 2)
With catatonic features[a]	• Benzodiazepines (Level 3)	• No antidepressants have been studied
With melancholic features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• TCAs and SNRIs have been studied
With atypical features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• Older studies found MAO inhibitors superior to TCAs
With psychotic features[a]	• Use antipsychotic and antidepressant cotreatment (Level 1)	• Few studies involved atypical antipsychotics
With mixed features[a]	• Lurasidone[b] (Level 2) • Ziprasidone[b] (Level 3)	• No comparative studies
With seasonal pattern[a]	• No specific antidepressants have demonstrated superiority (Level 2 and 3)	• SSRIs, agomelatine, bupropion, and moclobemide have been studied
With cognitive dysfunction	• Vortioxetine (Level 1) • Bupropion (Level 2) • Duloxetine (Level 2) • SSRIs (Level 2)[b] • Moclobemide (Level 3)	• Limited data available on cognitive effects of other antidepressants and on comparative differences in efficacy
With sleep disturbances	• Agomelatine (Level 1) • Mirtazapine (Level 2) • Quetiapine (Level 2) • Trazodone (Level 2)	• Beneficial effects on sleep must be balanced against potential for side effects (e.g., daytime sedation)
With somatic symptoms	• Duloxetine (pain) (Level 1) • Other SNRIs (pain) (Level 2) • Bupropion (fatigue) (Level 1) • SSRIs[b] (fatigue) (Level 2) • Duloxetine[b] (energy) (Level 2)	• Few antidepressants have been studied for somatic symptoms other than pain • Few comparative antidepressant studies for pain and other somatic symptoms

MAO, monoamine oxidase; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]*DSM-5* specifiers.
[b]Comparisons only with placebo.

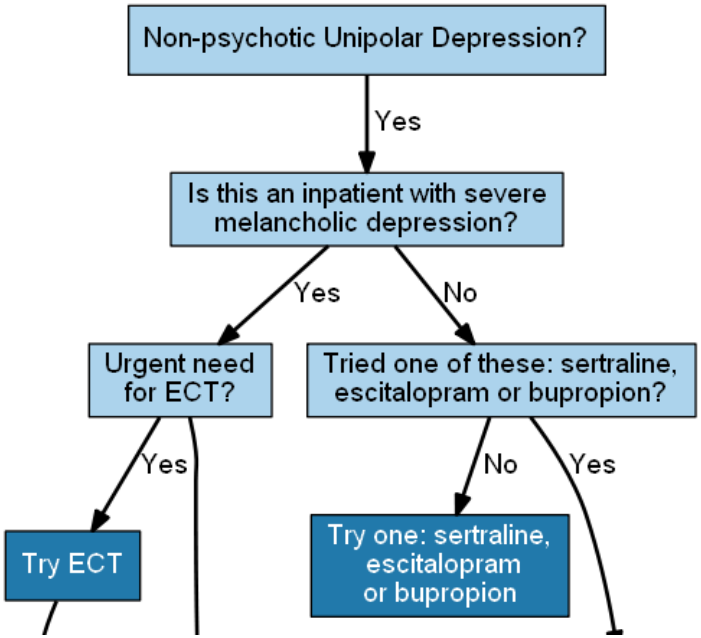
Kennedy, Can J Psychiatry, 2016

Harvard Psychopharmacology Algorithm



Giakoumatos CI, Osser D.. Harv Rev Psychiatry. 2019 Jan/Feb;27(1):33-52.

Harvard Psychopharmacology Algorithm



Giakoumatos CI, Osser D.. Harv Rev Psychiatry. 2019 Jan/Feb;27(1):33-52.

Poll

- A 35 year old business woman presents with a first depressive episode for the past 4 months
  - Depressed mood, crying daily, insomnia, decreased appetite, anxiety, impaired concentration, death wishes, -ve rumination
  - Tried sertraline 50 mg x 4 wk then increased to 100 mg x4 wk
  - No improvement

- Which of the following treatment options would you chose?
  - A) Switch to 2nd SSRI
  - B) increase dose to 150 mg
  - C) Add mirtazapine
  - D) Add aripiprazole
  - E) Switch to CBT

"Of course you feel great. These things are loaded with antidepressants."

Is there a benefit to increasing doses of SSRIs?

META-ANALYSES

Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure in Patients With Major Depressive Disorder: A Systematic Review and Meta-Analysis of Randomized, Double-Blind Trials

Lena Rink; Cora Braun; Tom Bschor, MD; Jonathan Henssler, MD; Jeremy Franklin, PhD; and Christopher Baethge, MD

"*Currently, dose increase [of SSRIs] cannot be recommended after antidepressant treatment failure. Other strategies such as antidepressant combination or augmentation with Li or SGA are preferable.*

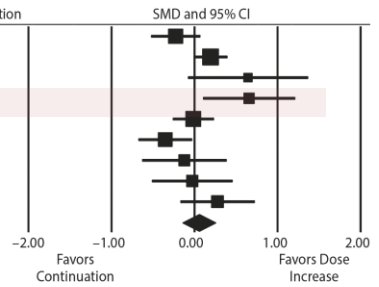
More research is needed, particularly on antidepressants other than SSRIs and on longer prerandomization treatment periods"

Possible exception of escitalopram / citalopram

Figure 2. Dose Increase Versus Unchanged Continuation of Antidepressant Pharmacotherapy After Initial Treatment Failure

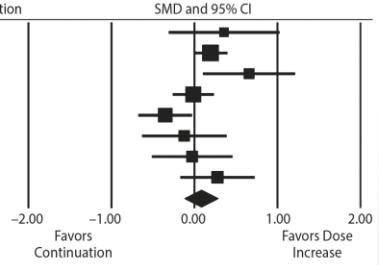
A. All studies

Study	SMD	Statistics for Each Study: Standard Error	Lower Limit	Upper Limit	*P* Value	Sample Size: Dose Increase	Continuation
Benkert et al 1997[26]	−0.227	0.151	−0.523	0.069	0.133	90	84
Dornseif et al 1989[29]	0.193	0.104	−0.011	0.397	0.063	180	189
Heiligenstein et al 2006[20]	0.645	0.370	−0.079	1.369	0.081	14	14
Kim et al 2016[22]	0.658	0.283	0.104	1.213	0.020	25	25
Kornstein et al 2008[28]	−0.014	0.127	−0.261	0.234	0.915	118	130
Licht and Qvitzau 2002[18]	−0.352	0.165	−0.676	−0.029	0.033	97	98
Ruhé et al 2009[21]	−0.122	0.260	−0.631	0.387	0.638	30	27
Schweizer et al 1990[27]	−0.027	0.248	−0.513	0.459	0.914	36	41
Schweizer et al 2001[19]	0.278	0.228	−0.169	0.725	0.223	38	37
	0.053	**0.100**	**−0.143**	**0.248**	**0.598**	**628**	**645**



B. Adults, major depression, SSRI

Study	SMD	Statistics for Each Study: Standard Error	Lower Limit	Upper Limit	*P* Value	Sample Size: Dose Increase	Continuation
Benkert et al 1997[26]	0.357	0.340	−0.310	1.023	0.295	32	18
Dornseif et al 1989[29]	0.193	0.104	−0.011	0.397	0.063	180	189
Kim et al 2016[22]	0.658	0.283	0.104	1.213	0.020	25	25
Kornstein et al 2008[28]	−0.014	0.127	−0.261	0.234	0.915	118	130
Licht and Qvitzau 2002[18]	−0.352	0.165	−0.676	−0.029	0.033	97	98
Ruhé et al 2009[21]	−0.122	0.260	−0.631	0.387	0.638	30	27
Schweizer et al 1990[27]	−0.027	0.248	−0.513	0.459	0.914	36	41
Schweizer et al 2001[19]	0.278	0.228	−0.169	0.725	0.223	38	37
	0.079	**0.100**	**−0.118**	**0.276**	**0.432**	**556**	**565**



Abbreviations: SMD = standardized mean difference, SSRI = selective serotonin reuptake inhibitor.

Switching vs. Augmenting

Table 12. Factors to Consider in Choosing between Switching to Another Antidepressant Monotherapy or Adding an Adjunctive Medication (Level 3 Evidence).

Consider switching to another antidepressant when:

- It is the first antidepressant trial.
- There are poorly tolerated side effects to the initial antidepressant.
- There is no response (<25% improvement) to the initial antidepressant.[a]
- There is more time to wait for a response (less severe, less functional impairment).
- Patient prefers to switch to another antidepressant.

Consider an adjunctive medication when:

- There have been 2 or more antidepressant trials.
- The initial antidepressant is well tolerated.
- There is partial response (>25% improvement) to the initial antidepressant.
- There are specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a response (more severe, more functional impairment).
- Patient prefers to add on another medication.

[a]For the initial antidepressant trial. In subsequent trials, lack of response (<25% improvement) may not be a factor for choosing between switch and adjunctive strategies.

Kennedy, Can J Psychiatry, 2016

Limited evidence to support switching

Table 1. Characteristics of Studies Included In a Systematic Meta-Analysis Comparing Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy

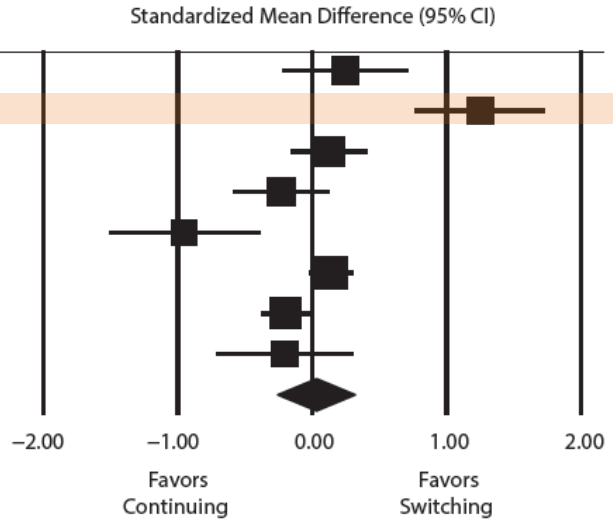
Study/First Author	Year of Publication	Initial and Continuation Antidepressant	Switch Antidepressant	Follow-Up Time (wk)	N After Randomization[a]	Dose Escalation Allowed in the Continuation Arm?	Low Risk of Bias According to Cochrane Collaboration Tool for Assessing Risk of Bias?
Ferreri[28]	2001	Fluoxetine	Mianserin	6	71	No	Yes
Corya[29]	2006	Venlafaxine	Fluoxetine	12	119	No	No
Souery[27]	2011	Desipramine or citalopram	Desipramine or citalopram	4	59	No	Yes
Shelton[30]	2005	Nortriptyline	Fluoxetine	8	210	No	No
Romera[32]	2012	Escitalopram	Duloxetine	4	566	Yes	Yes
Bose[33]	2012	Escitalopram	Duloxetine	8	472	Yes	Yes
Petrescu[34]	2014[b]	Any SSRI	Duloxetine	8	52	Yes	No
Zhu[31]	2003	Various SSRIs	Mirtazapine	6	78	Yes	No

[a]A total of 1,627 patients were included in the meta-analysis.
[b]Published as abstract only.
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

?? MRT, BUP, VORT could be exceptions

A. Standardized Mean Differences

Study/First Author	Standardized Mean Difference	Standard Error	Variance	Lower Limit	Upper Limit	*Z* Value	*P* Value
Ferreri 2001[28]	0.245	0.239	0.057	−0.223	0.713	1.025	.305
Zhu 2003[31]	1.251	0.248	0.061	0.766	1.737	5.052	.000
Shelton 2005[30]	0.127	0.148	0.022	−0.162	0.416	0.862	.389
Corya 2006[29]	−0.229	0.184	0.034	−0.589	0.132	−1.244	.213
Souery 2011[27]	−0.948	0.289	0.083	−1.513	−0.382	−3.285	.001
Romera 2012[32]	0.143	0.084	0.007	−0.022	0.308	1.694	.090
Bose 2012[33]	−0.196	0.092	0.009	−0.377	−0.015	−2.121	.034
Petrescu 2014[34]	−0.200	0.260	0.067	−0.709	0.308	−0.772	.440
Combined estimate	0.031	0.147	0.022	−0.258	0.319	0.207	.836



Bschor, J Clin Psychiatry 2016

Journal of Affective Disorders 274 (2020) 315–325

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Short and long-term treatment outcomes of stepwise psychopharmacotherapy based on early clinical decision in patients with depressive disorders

Jae-Min Kim[a,*], Robert Stewart[b,c], Hee-Ju Kang[a], Ju-Wan Kim[a], Hee-Joon Lee[a], Min Jhon[a], Ju-Yeon Lee[a], Sung-Wan Kim[a], Il-Seon Shin[a]

[a] Department of Psychiatry, Chonnam National University Medical School, Gwangju, Korea
[b] Psychology and Neuroscience, King's College London, Institute of Psychiatry, London, UK
[c] South London and Maudsley NHS Foundation Trust, London, UK

N=1262, Naturalistic study

Received antidepressant monotherapy

If no >30% improvement after 3 weeks, could

- Maintain on same treatment and adjust dose
- Switch to another ADM
- Augment w/ buspiron, Li, T3, SGAs (aripip, risp, olan, quet, and zipras).
- Combine with ADM of different MoA

-> Augmentation and combinations outperformed maintenance and switch

Table 11. Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

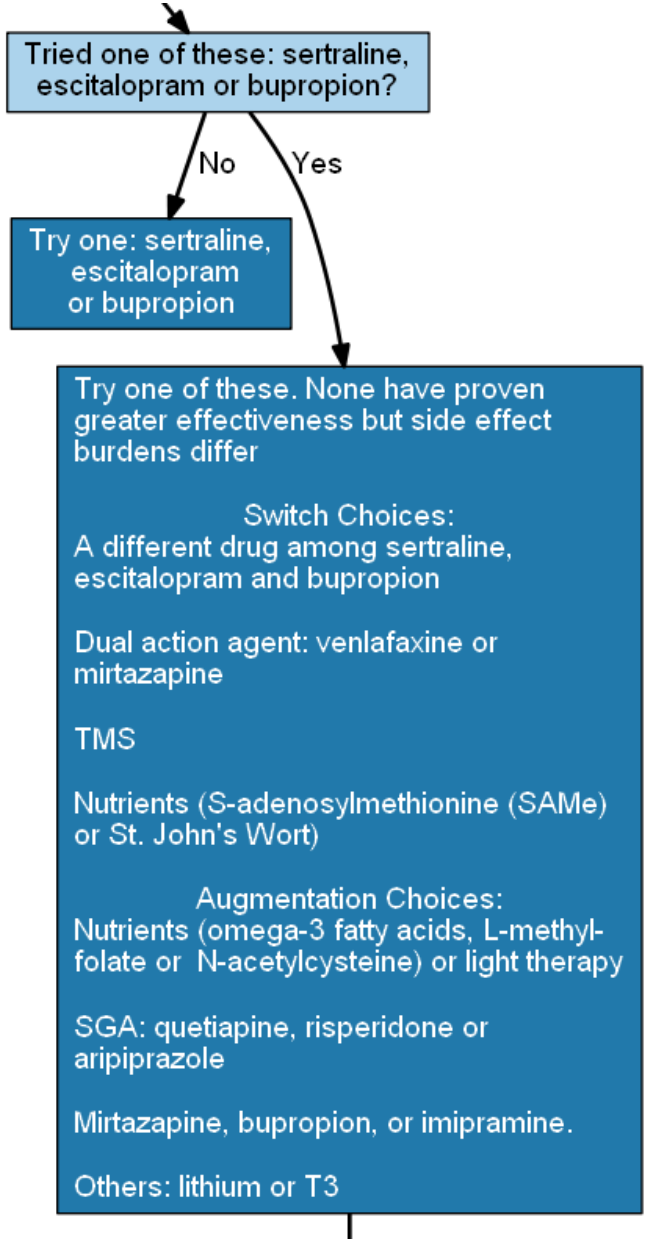
CANMAT 2016

Psychotherapies

- Psychotherapies also effective at this stage
  - CBT most effective and psychodynamic least
  - Supported by Cochrane meta-analysis
  - Most psychotherapy studies use 1 ADM failure
  - Many patients with depression refuse therapy (>70% in STAR*D)

Ijaz., Cochrane Database Syst Rev 2018; 5:CD010558.

Harvard Psychopharmacology Algorithm



DZ commentary

I favor switch for milder depression and poor tolerability

+ vortioxetine

SAMe is expensive
SJW has many RxIx

L-methyl-folate not in CAN

+ brexpiprazole

Giakoumatos CI, Osser D.. Harv Rev Psychiatry. 2019 Jan/Feb;27(1):33-52.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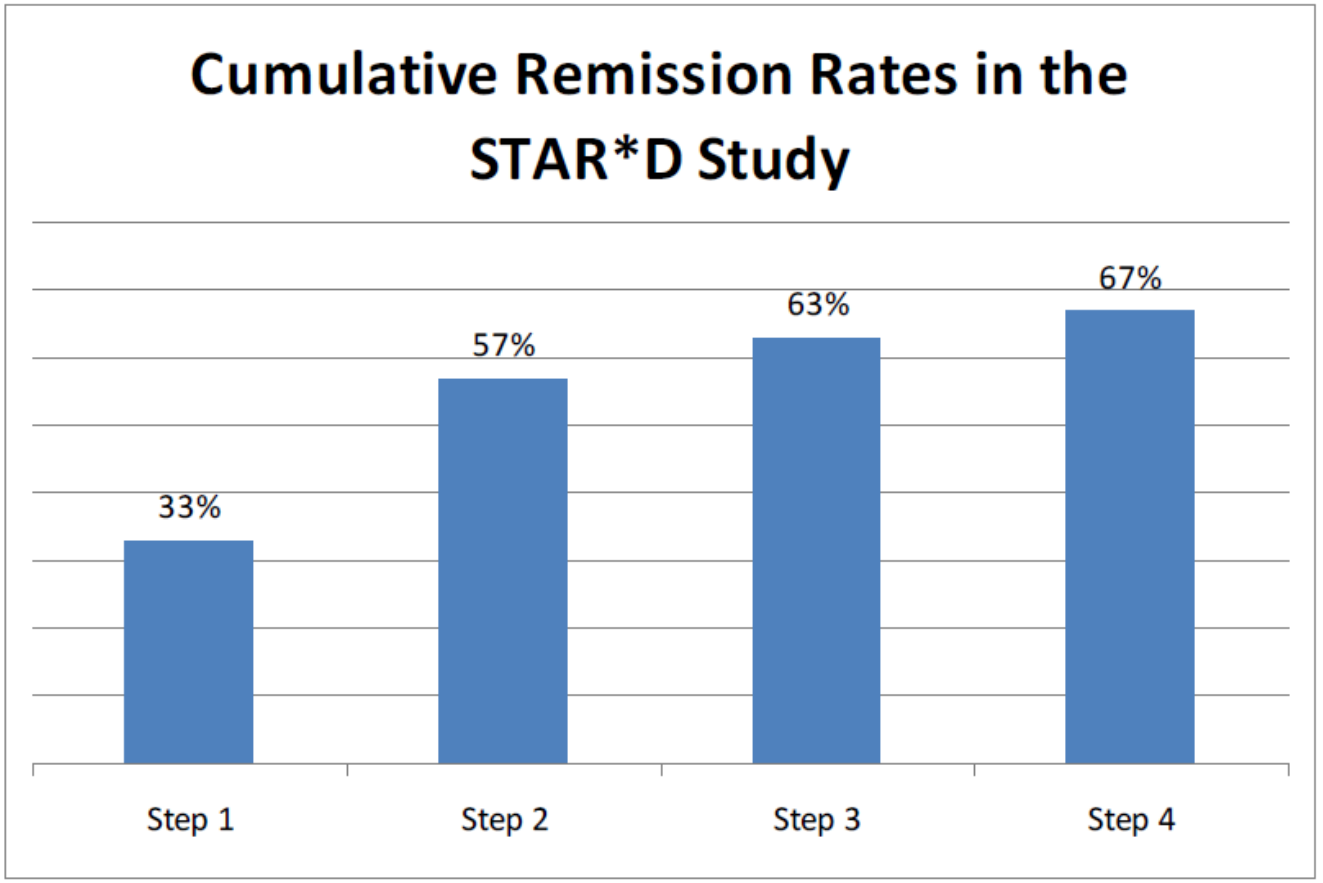
Treatment resistant depression (TRD)

- 67% do not remit after 1st ADM
- 43% do not remit after 2 ADM
- Diminishing returns after 2 treatments



Israel, J. Pharmaceuticals 2010, 3, 2426-2440

Treatment Resistant Depression

- No uniform definition exists
- One proposed definition is the failure to remit after an adequate trial of 2 treatments with different mechanisms
  - Includes a depression focused therapy (CBT or IPT >8 weeks)
- Suggests and inflection point at which further treatments may have lower chance of benefit

Conway, et al. *JAMA Psychiatry.* 2017;74(1):9-10.

Poll

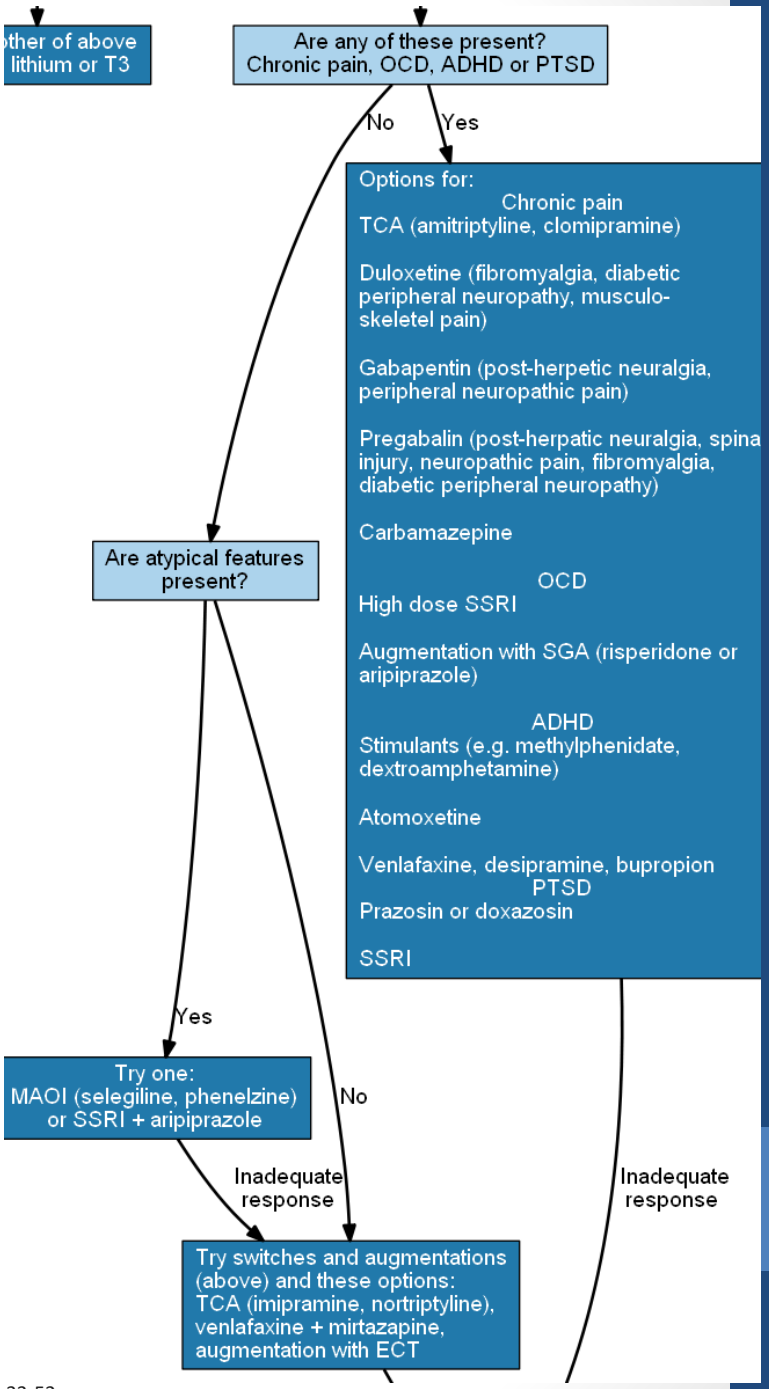
- When I see a patient with treatment resistant depression, I will:

  - A) Usually refer them for follow-up in a psychiatric clinic
  - B) Usually refer them for a psychiatric consultation then resume follow-up with recommendations
  - C) Refer only complex patients with comorbidities for a psychiatric consultation / follow-up
  - D) Usually feel comfortable treating most of them on my own without a psychiatric consultation
  - E) Only refer the most complex or treatment refractory patients for psychiatric assessment

Approach to Care

- Reassess diagnosis
  - BAD, MDD w/ psychotic features
- Assess for comorbidity
  - SUD, BPD, ADHD, OCD, PTSD, chronic pain
- Assess medication adherence, adequacy of trials
- Consider referral

- If a comorbidly is present, try treating that
- If atypical features are present, consider an MAOI or SSRI + aripiprazole
- Otherwise try dual action agents, augmentations, ECT



Giakoumatos CI, Osser D.. Harv Rev Psychiatry. 2019 Jan/Feb;27(1):33-52.

What works in TRD?

- 2015 network meta-analysis 48 trials, N=6654
  - Quetiapine XR, Aripiprazole, Lithium, Thyroid hormone all effective for TRD
  - SGAs had more robust effect than lithium or thyroid hormone

- 2015 meta-analysis 11 trials N=3341
  - SGAs may be more effective in patients who have failed to benefit from more standard antidepressant trials

Wang, Int J Neuropsychopharm. 2015;18(8) 1-10
Zhou, *J Clin Psychiatry*. 2015; 76(4)e487-498

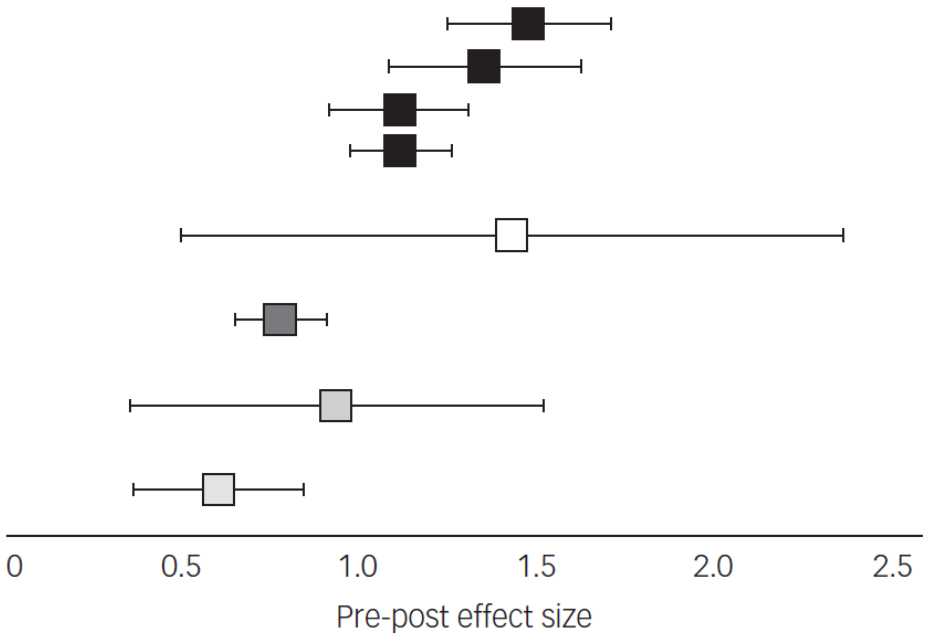
BJPsych | The British Journal of Psychiatry (2019)
214, 42–51. doi: 10.1192/bjp.2018.233

Review

Augmentation therapies for treatment-resistant depression: systematic review and meta-analysis†

Rebecca Strawbridge, Ben Carter, Lindsey Marwood, Borwin Bandelow, Dimosthenis Tsapekos, Viktoriya L. Nikolova, Rachael Taylor, Tim Mantingh, Valeria de Angel, Fiona Patrick, Anthony J. Cleare and Allan H. Young

	Treatment class	k	ES
	NMDA-targeting agents	3	1.48
	Pharmacological (other*)	4	1.36
	Mood stabilisers	8	1.12
	Antipsychotics	10	1.12
**	Psychological therapies	3	1.43
	Pill placebo	16	0.78
	Psychological placebo	3	0.94
	Short-term treatments	2	0.61



** used different definition of TRD

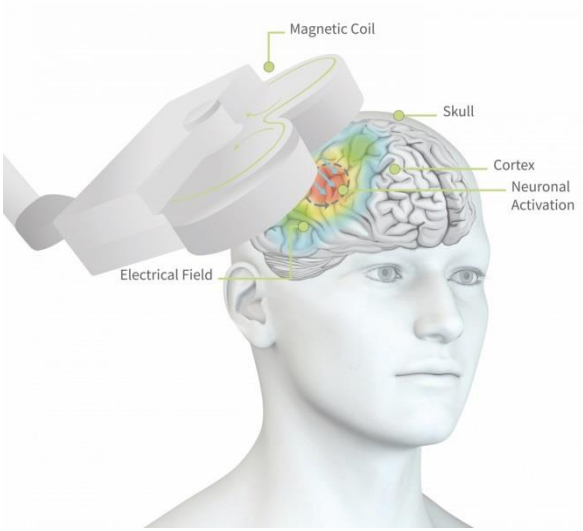
- *“Our findings also confirms previous work indicating that aripiprazole and – to a lesser extent – lithium are effective treatments, supporting their current recommendation as first-line therapies. Although the measured ESs with these two pharmacotherapies are similar to other options, the fact that they have been more thoroughly investigated in a larger number of studies underlines their status as first-choice options”*

- Your patient who has tried 3 antidepressants, 2 augmentation agents and 6 months of therapy asks if there are other treatment options than traditional antidepressant therapies

- Specifically, he has heard of ketamine psilocybin and wants more information about these options as well as non-medication strategies

rTMS

- Typically involves 5x per week, 45 min sessions
- 2014 meta-analysis for TRD
  - 3x greater response and 5x greater remission than sham control in TRD patients with NNT of 9
  - S/E – well tolerated, occ headaches



https://brainclinics.com/rtms/

Gaynes, J Clin Psychiatry 2014;75(5):477–489

ECT

- May be treatment of choice
  - Psychotic depression
  - Severe suicidality
  - Malnutrition secondary to food refusal
  - Catatonia
  - Recurrent depression with previous good response to ECT

- Older age is associated with a good response. BPD to be associated with decreased ECT efficacy.

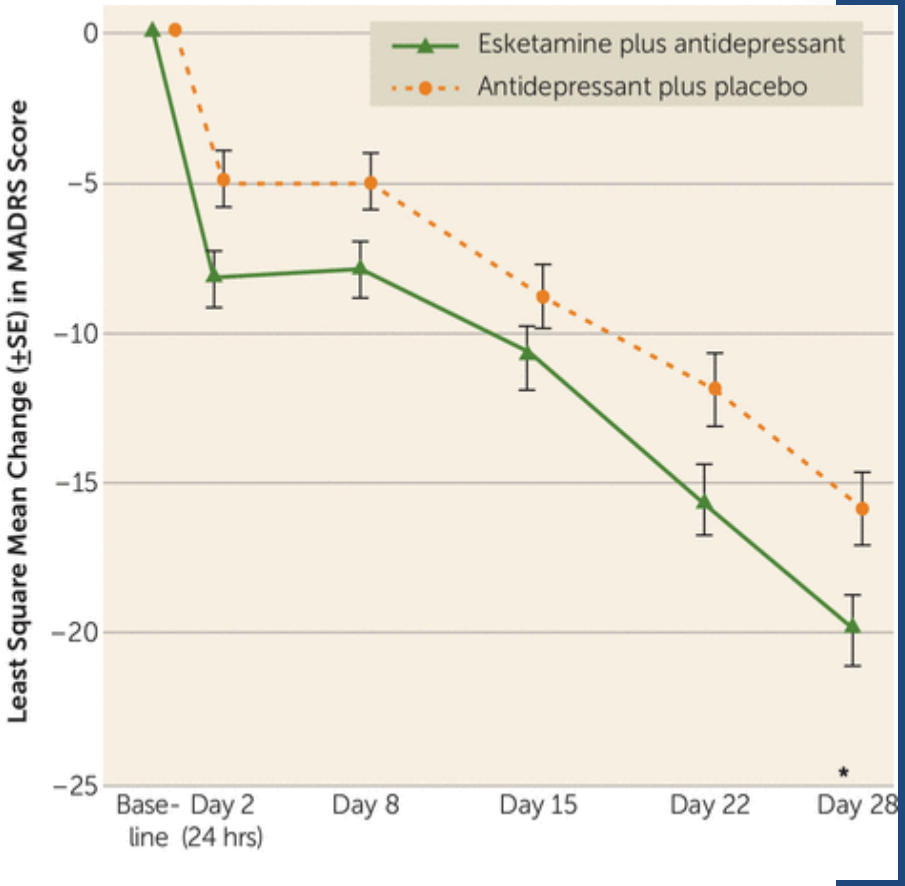
Esketamine / Ketamine

- Ketamine - used as anesthetic since 1960s
  - Rapid antidepressant effects demonstrated in early 2000s
  - Poorly orally available, traditionally given IV or intranasal
- Intranasal esketamine (S-ketamine) – approved in Canada in 2020 for mod to severe depression resistant to 2 med trials
  - Approved as add-on to oral antidepressant
  - Must be administered in clinic setting, risk of misuse
- Benefits may be seen within 1 hour, usually last 3-7 days
- IV ketamine may be more effective than IN esketamine
- S/E - sedation, nausea, vertigo, dissociation

Bahji, J Affect Disord, 2021. Jan; 278:542-555

Esketamine

- 2-5 prev ADM trials
- Randomized to:
  - new AD + ESK
  - new AD + placebo
- response
  - 50-60% vs 36-50%
  - NNT 8
- Remission
  - 30-40% vs. 20-24%
  - NNT 6



Popova, Am J Psychiatry. Volume 176. (6) June 2019. 428-43
Citrome. *J Affect Dis.*271, 15 June 2020, 228-23

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

At-home, sublingual ketamine telehealth is a safe and effective treatment for moderate to severe anxiety and depression: Findings from a large, prospective, open-label effectiveness trial

Thomas D. Hull [a,*,1], Matteo Malgaroli [b,1], Adam Gazzaley [c], Teddy J. Akiki [d], Alok Madan [e], Leonardo Vando [f], Kristin Arden [f], Jack Swain [f], Madeline Klotz [f], Casey Paleos [f]

- 1247 patients
- SL ketamine 5mg / kg (ie. 300-450 mg)
- Supervised by telehealth

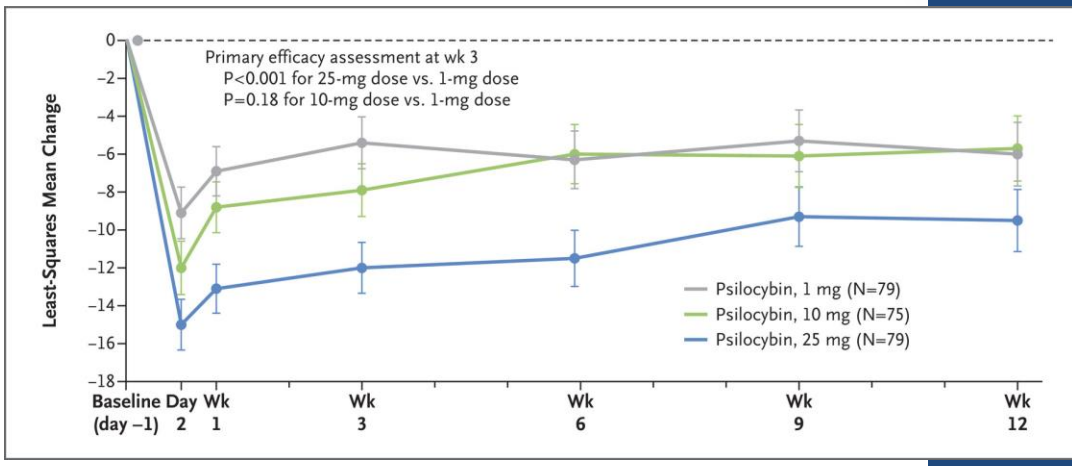
- Response rates 62.8%, remission 32.6%
- 4 patients dropped out due to adverse events
- 2 removed due to nonadherence

- Others groups have used 1.5-3 mg/kg (e.g. Swainson et al, 2020)

Psilocybin

- 5-HT releasing hallucinogen.
- Activates 5-HT2A receptors
- Phase 2 studies

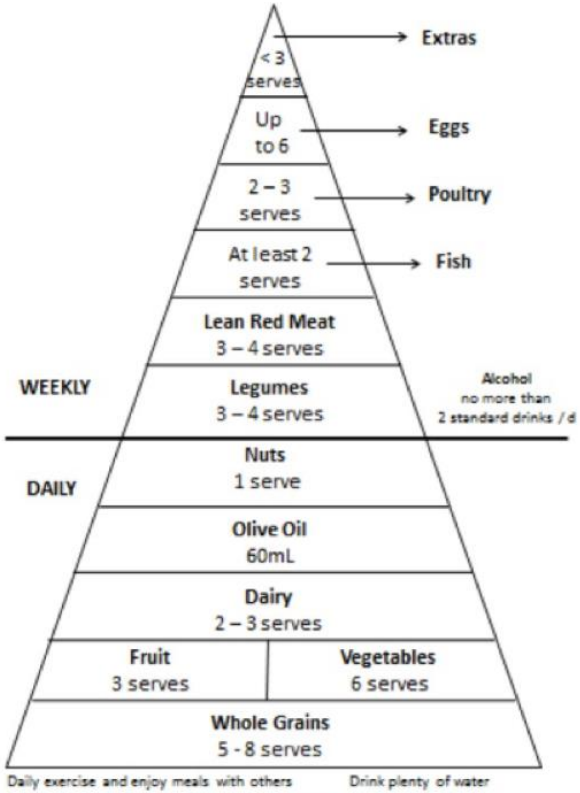
- Goodwin et al 2022
  - TRD 2-4 ADM trials
  - Psilocybin 25 mg, 10 mg or 1 mg
  - 6-8 hr psychedelic assisted therapy + 2 sessions
  - -> Remission 29% in 25 mg vs. 8% in 1 mg at 3 wk (NNT = 5)
  - -> Remission 20% in 25 mg vs. 10% in 1 mg at 12 wk (NNT = 10)
  - -> SAE in 9% of 25 mg vs. 1% of 1 mg



Goodwin GM. Et al. 2022, N Engl J Med 2022; 387:1637-1648

ModiMed Diet

- The SMILES trial
  - N = 67
  - 12 wk RCT of diet intervention vs. Social support
  - Remission 32% vs. 8 % control (NNT =4)
- Replicated in 2 other studies



The ModiMedDiet Food Pyramid

For handout:
https://www.moodtreatmentcenter.com/wp-content/uploads/2020/12/minddiet.pdf

Jacka FN *et al.* BMC Med 2017; 15(1):1

Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Aripiprazole (2-5 mg) or quetiapine XR (150-300 mg)

- A) I am very comfortable using them / use them frequently
- B) I have used them occasionally
- C) I have treated several patients who have taken them, but don't start them myself
- D) I have rarely/never used them or seen patients who have taken them
- E) I did not realize they were used for TRD

Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Lithium (for unipolar depression augmentation)

- A) I am very comfortable using it / use it frequently
- B) I have used it occasionally
- C) I have treated several patients who have taken it, but don't start it myself
- D) I have rarely/never used it or seen patients who have taken it
- E) I did not realize it was used for TRD

Poll

- Regarding each of the following treatments, rate your experience/comfort with…

rTMS

  - A) I refer patients for it frequently
  - B) I have referred patients for it occasionally
  - C) I have treated several patients who have used it
  - D) I have rarely/never seen patients who have used it
  - E) I did not realize it was used for TRD

Poll

- Regarding each of the following treatments, rate your experience/comfort with…

Esketamine / ketamine

- A) I refer patients for it frequently
- B) I have referred patients for it occasionally
- C) I have treated several patients who have used it
- D) I have rarely/never seen patients who have used it
- E) I did not realize it was used for TRD

Summary - Choosing treatments

- Aripiprazole
  - (+) best studied, ease of dosing, motivation
  - (-) nausea, akathisia, weight gain
- Brexpiprazole
  - (+) possibly less akathisia than aripiprazole
  - (-) more expensive, not covered
- Quetiapine XR
  - (+) anxiety, sleep, mood
  - (-) sedation, ++weight gain
- Lithium
  - (+) anti-suicide, anxiety
  - (-) tremor, sedation, toxicity, need for monitoring

- Thyroid hormone (T3 or L-thyroxine)
  - (+) energy
  - (-) anxiety, tachycardia
- rTMS
  - (+) well tolerated
  - (-) availability, cost, 5x per week
- Ketamine/esketamine
  - (+) rapid response, anti-suicide
  - (-) cost, office administration, transient HTN