Treatment Resistant Depression & Bipolar Disorder

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Disclosures: Dr. Roger McIntyre

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Dr. Roger McIntyre is a CEO of Braxia Scientific Corp.

Patterns and Correlates of Patient-reported Helpfulness of Treatment for Common Mental and Substance Use Disorders in the WHO World Mental Health Surveys

Significant predictors of patient-level treatment helpfulness decomposed through associations with the helpfulness of individual professionals and persistence in help-seeking pooled across diagnostic categories and number of professionals seen

	Patient-level treatment helpfulness				Helpfulness of individual professionals				Persistence in help-seeking after prior unhelpful treatment			
	%	SE	RR	95% CI	%	SE	RR	95% CI	%	SE	RR	95% CI
Focal diagnostic category												
Major depressive disorder	28.3	0.6	1.19*	1.12-1.26	26.6	0.8	1.11*	1.02-1.21	24.8	0.9	1.08*	1.04-1.11
Bipolar disorder												
Major depressive episode	3.1	0.2	0.94	0.75-1.17	3.9	0.5	0.85	0.62-1.16	4.2	0.6	1.06	0.97-1.16
Mania/hypomania	6.1	0.3	1.11	0.98-1.27	6.4	0.4	1.08	0.91-1.29	6.4	0.4	1.03	0.95-1.12

Kessler RC, et al. World Psychiatry. 2022 Jun;21(2):272-286.

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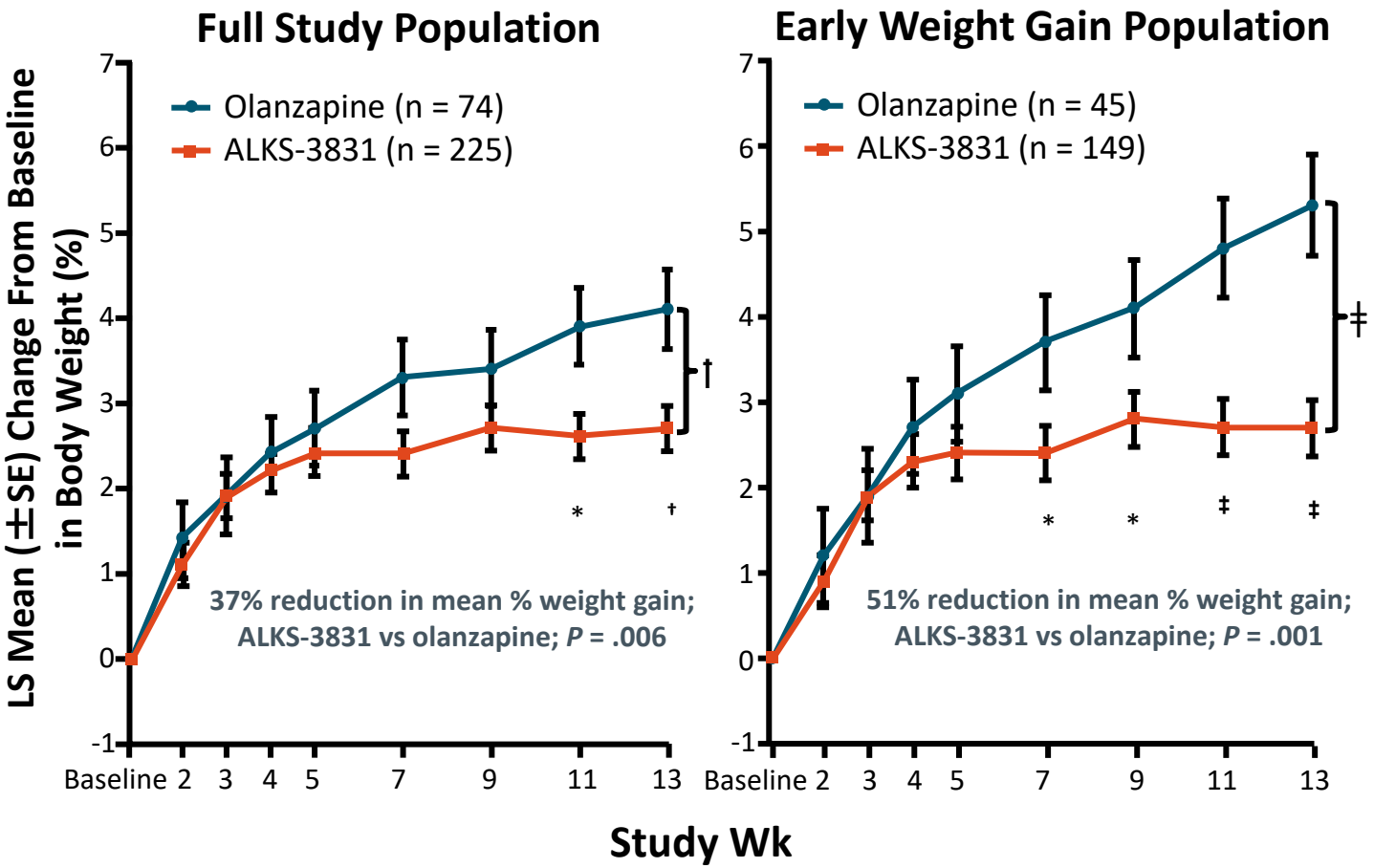
ALKS-3831: Olanzapine + Samidorphan (Opioid Antagonist)



*P <.05 vs olanzapine; †P 0.01 vs olanzapine; ‡P <.001 vs olanzapine

Dosage and Administration

Indication	Recommended Starting Dose (Olanzapine/ Samidorphan)	Recommended Dose (Olanzapine/ Samidorphan)
Schizophrenia (2.2)	5 mg/10 mg or 10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder (manic or mixed episodes) (2.3)	10 mg/10 mg or 15 mg/10 mg	5 mg/10 mg 10 mg/10 mg 15 mg/10 mg 20 mg/10 mg
Bipolar I disorder adjunct to lithium or valproate (2.3)	10 mg/10 mg	10 mg/10 mg 15 mg/10 mg 20 mg/10 mg

Silverman. Schizophr Res. 2018;195:245. Olanzapine/Samidorphan PI.

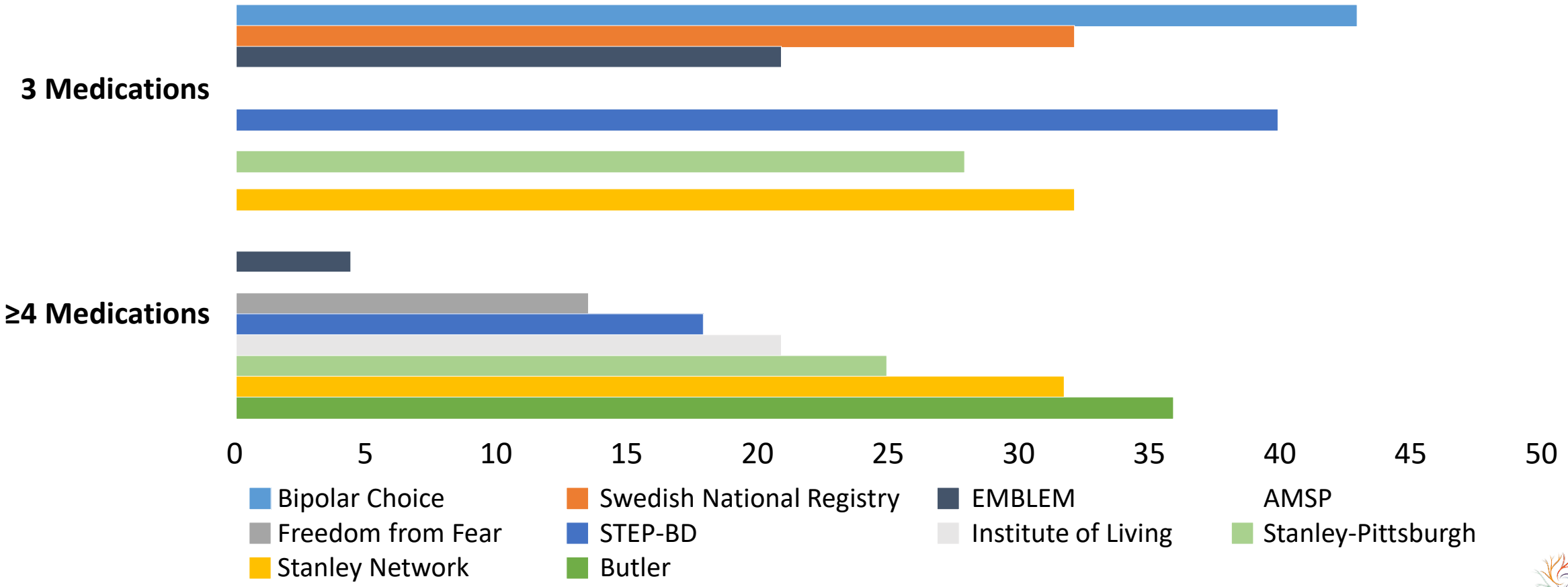
Slide credit: clinicaloptions.com

Second Generation Antipsychotic Drugs in Bipolar Depression

	Monotherapy		Adjunctive (to lithium or valproate)	
	Bipolar I	Bipolar II	Bipolar I	Bipolar II
Lumateperone*	✓	✓	✓	✓
Quetiapine[1]	✓	✓		
Olanzapine/Fluoxetine[2]	✓			
Lurasidone[3]	✓		✓	
Cariprazine[4]	✓			

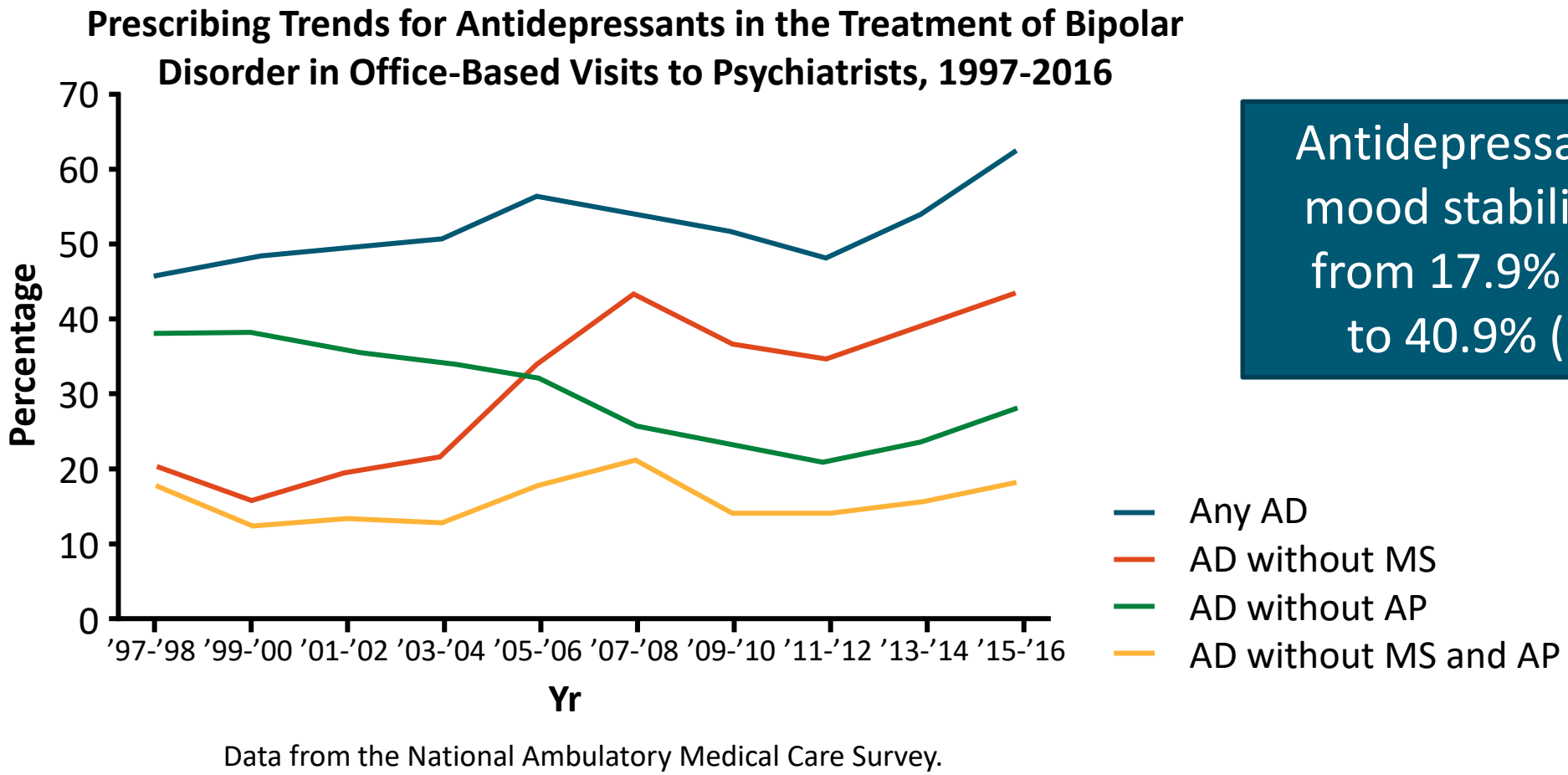
Complex Polypharmacy in Bipolar Disorder Is the Rule Rather Than the Exception

Representative Percentages of Patients With Bipolar Disorder Receiving 3 or >4 Psychotropic Medications During Postacute Maintenance Treatment Across Major Studies



Kim et al. J Clin Psychiatry. 2021;82:20r13263.

Rising Use of Antidepressants and Antidepressants Without Mood Stabilizers in Bipolar Disorder



Data from the National Ambulatory Medical Care Survey.

Antidepressants without a mood stabilizer increased from 17.9% (1997-2000) to 40.9% (2013-2016)

Rhee et al. Am J Psychiatry. 2020;177:706.

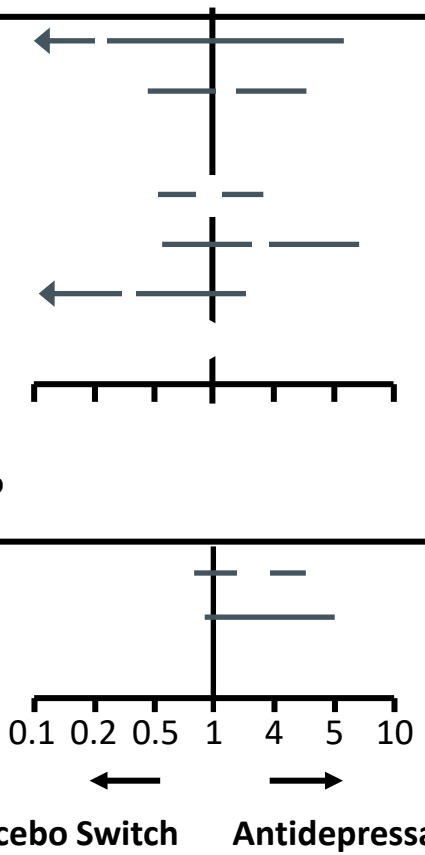
Modern Adjunctive Antidepressant Therapy: Switch Risk

Treatment-Emergent Affective Switches

(A) Acute treatment (B) 52-wk extensions

A	Antidepressant (n/N)	Placebo (n/N)	OR (95% CI)	*P* Value	Weight (%)
Nemeroff et al (2001)	0/35	2/43	0.234 (0.011-5.033)	.353	2.40
Tohen et al (2003)	5/86	19/370	1.140 (0.414-3.145)	.800	22.02
Shelton et al (2004)	0/10	0/10	..	..	..
STEP-BD (2007)	18/179	20/187	0.934 (0.476-1.829)	.841	50.08
Yatham et al (2016)	7/172	4/172	1.782 (0.512-6.201)	.364	14.57
CAPE-BD	3/39	7/35	0.333 (0.079-1.407)	.135	10.93
Overall			**0.926 (0.576-1.491)**	.753	100.00

B	Antidepressant (n/N)	Placebo (n/N)	OR (95% CI)	*P* Value	Weight (%)
Yatham et al (2016)	20/172	13/172	1.609 (0.773-3.349)	.203	57.45
CAPE-BD	19/60	11/59	2.022 (0.863-4.738)	.105	42.55
Overall			1.774 (1.018-3.091)	.043	100.00



McGirr. Lancet Psychiatry. 2016;3:1138.

Slide credit: clinicaloptions.com

International Guidance on the Evidence and Implementation of Ketamine and Esketamine

Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetal Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., Carlos Lopez Jaramillo, M.D., Ph.D., Siegfried Kasper, M.D., Kevin Kratiuk, B.Pharm., Jung Goo Lee, M.D., Ph.D., Yena Lee, H.B.Sc., Leanna M.W. Lui, Rodrigo B. Mansur, M.D., Ph.D., George I. Papakostas, M.D., Mehala Subramaniapillai, M.Sc., Michael Thase, M.D., Eduard Vieta, M.D., Ph.D., Allan H. Young, M.Phil., M.B.Ch.B., Carlos A. Zarate, Jr., M.D., Stephen Stahl, M.D., Ph.D.

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for its competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of ketamine and esketamine in adults with treatment-resistant depression. The authors also provide guidance for the implementation of these agents in clinical practice, with particular attention to practice parameters at point of care. Areas of consensus and future research vistas are discussed.

Am J Psychiatry 2021; 00:1–17; doi: 10.1176/appi.ajp.2020.20081251

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Ketamine in Bipolar Depression

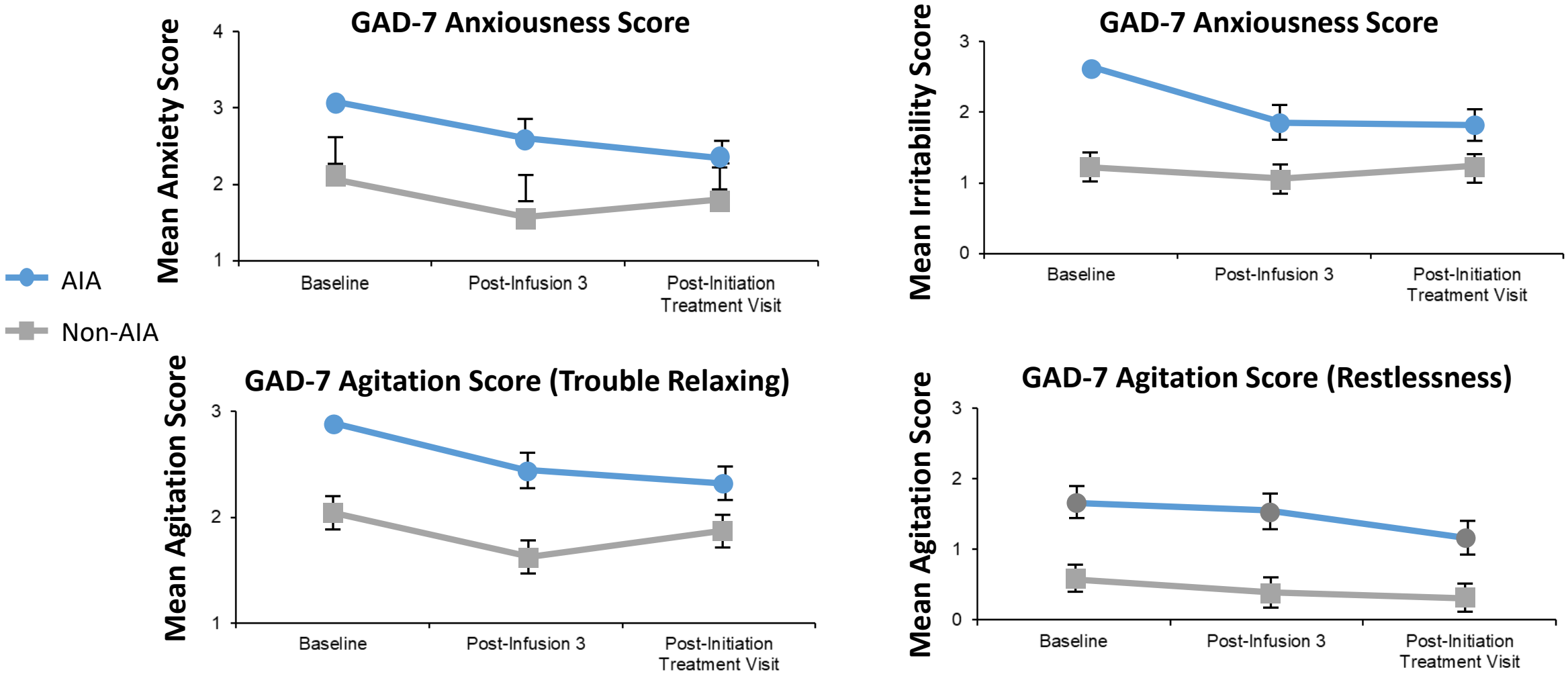
3 randomized trials in bipolar depression:

Authors	n	Day 3-4 Response, OR (95% CI)
Murrough et al[1]	24	4.67 (1.57-13.84)
Diazgranados et al[2]	18	15.55 (0.70-346.72)
Zarate et al[3]	15	3.92 (0.14-112.90)

2021 International Expert Opinion on Ketamine and Esketamine:
"The high rate of TRD in persons with bipolar disorder, as well as preliminary evidence supporting the safety and efficacy of ketamine, would justify consideration of ketamine as an investigational treatment in bipolar disorder."[4]

1. Murrough et al. Psychol Med. 2015;45:3571. 2. Diazgranados et al. Arch Gen Psychiatry. 2010;67:793.
3. Zarate et al. Biol Psychiatry. 2012;71:939. 4. McIntyre et al. Am J Psychiatry. 2021;178:383.

Ketamine Improves Anxiety, Agitation, and Irritability in Adults With Treatment-Resistant Bipolar Depression



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McIntyre et al. Bipolar Disord. 2020;22:831.

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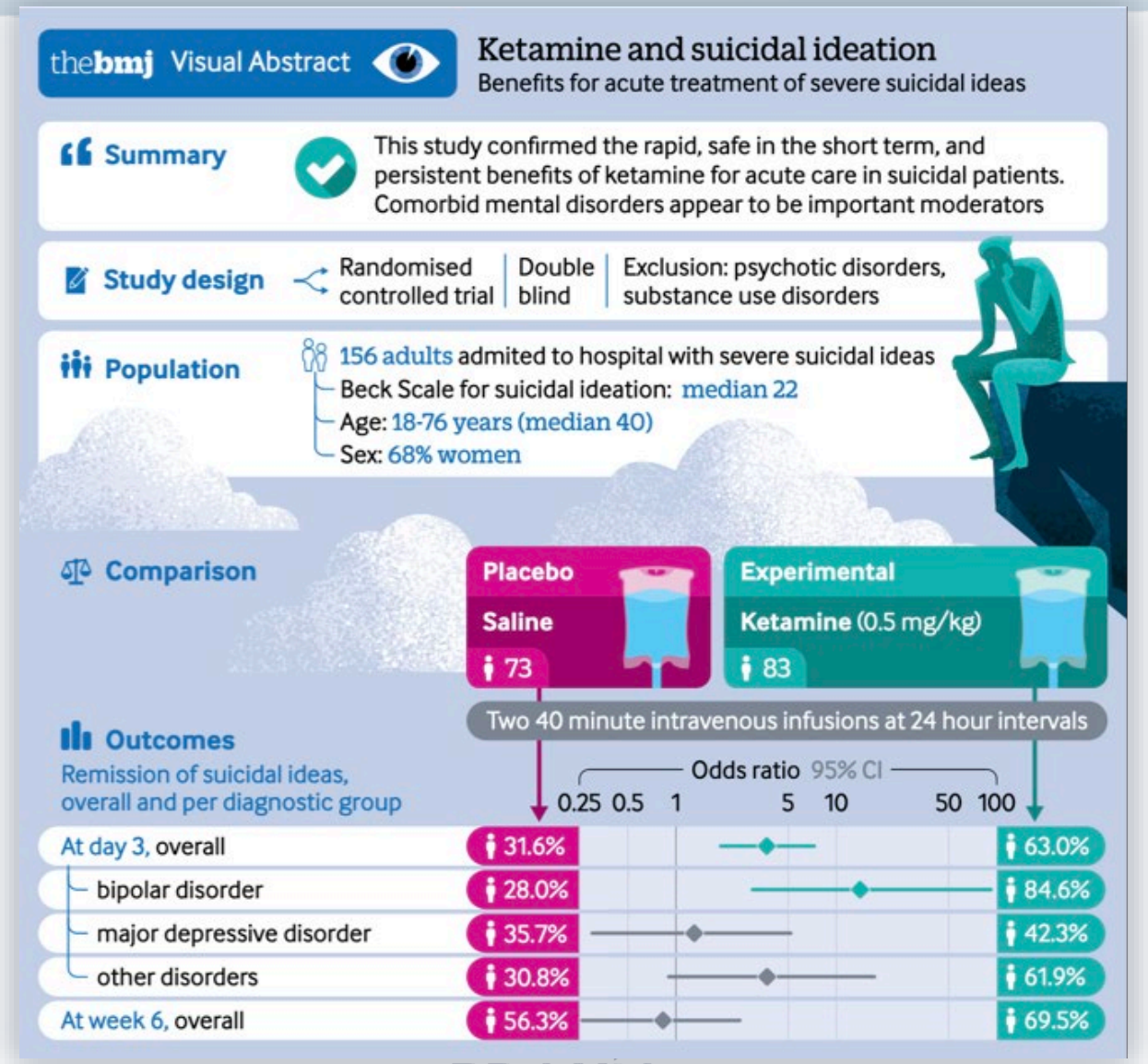
Ketamine for the Acute Treatment of Severe Suicidal Ideation: Double Blind, Randomised Placebo Controlled Trial



Abbar M, et al. BMJ. 2022;376:e067194.

Psychopharmacology
https://doi.org/10.1007/s00213-022-06105-9

REVIEW

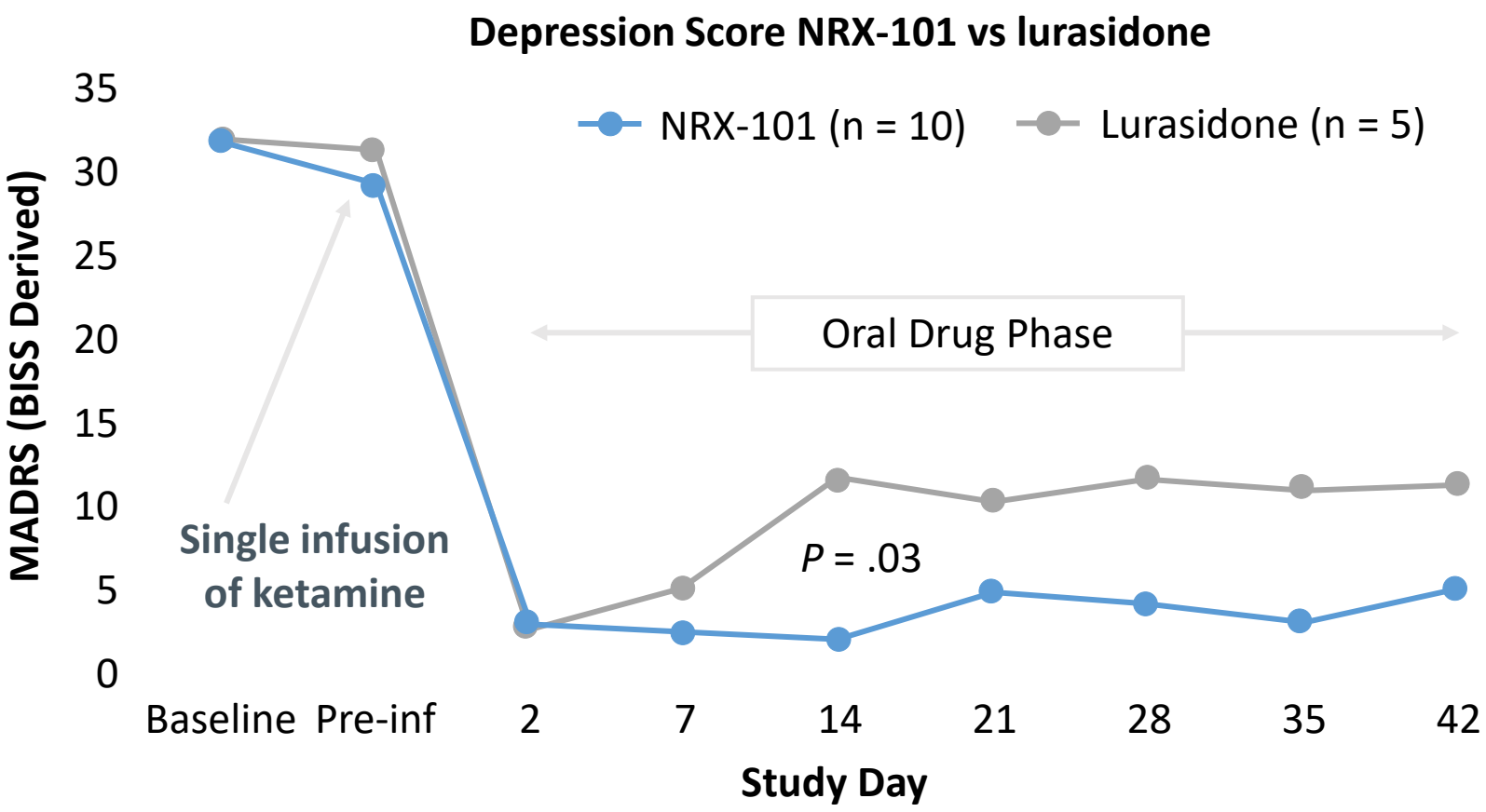
The effect of ketamine on anhedonia: improvements in dimensions of anticipatory, consummatory, and motivation-related reward deficits

Danica Nogo[1] · Ashitija K. Jasrai[1,2] · Haeun Kim[1,2] · Flora Nasri[1] · Felicia Ceban[1] · Leanna M. W. Lui[1] · Joshua D. Rosenblat[1] · Maj Vinberg[3,4] · Roger Ho[5,6] · Roger S. McIntyre[1,2]

Received: 22 August 2021 / Accepted: 23 February 2022

Treatments on the Horizon: NRX-101 (D-Cycloserine + Lurasidone)

Proof of Concept Clinical Trial



NRX-101:
Fixed-dose combination of lurasidone plus D-cycloserine (putative NMDA antagonist believed to increase glutamate/glutamine at the glycine site, with activity in the anterior cingulate cortex)

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ClinicalTrials.gov Identifier: NCT02974010

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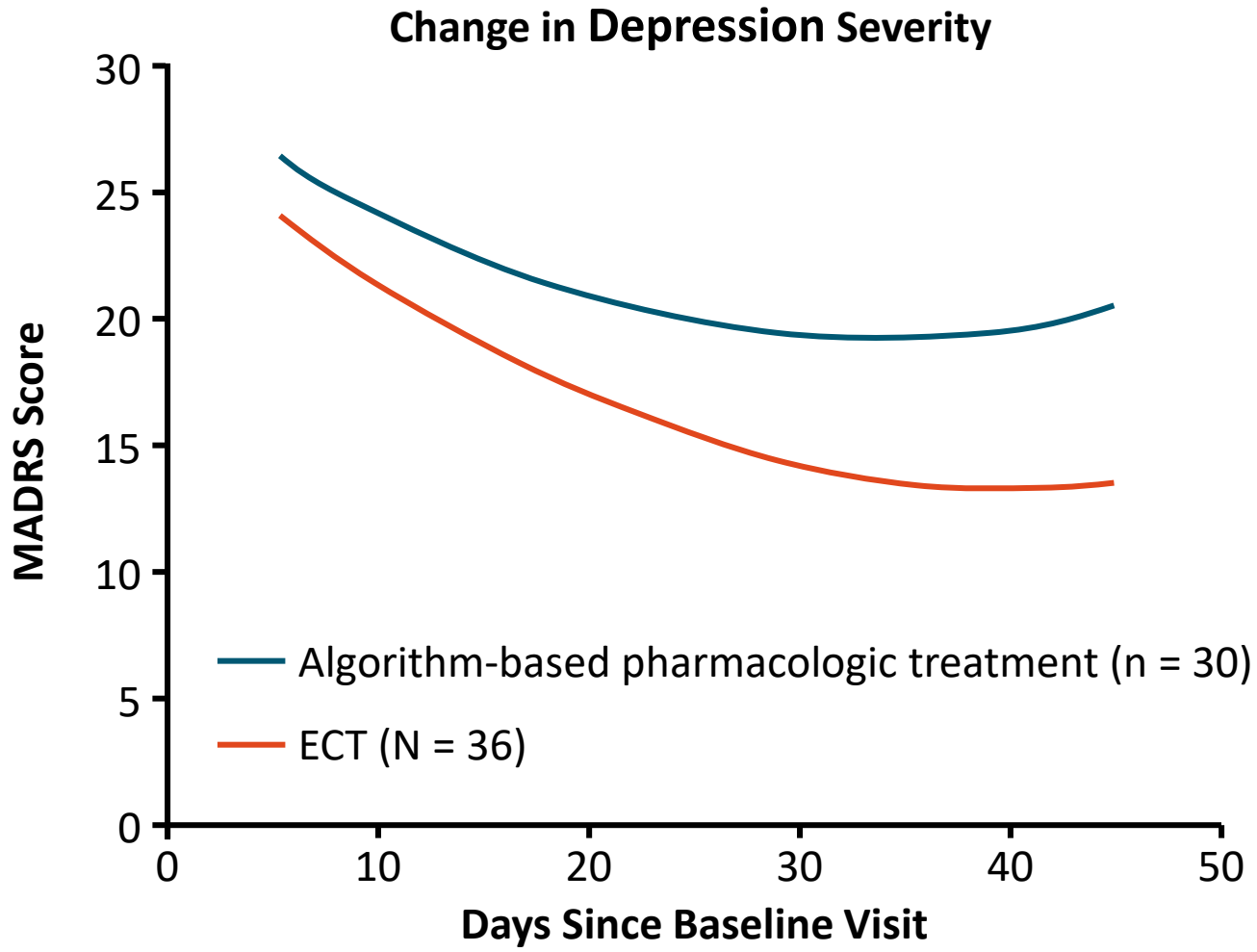
ECT for Treatment-Resistant Bipolar Depression



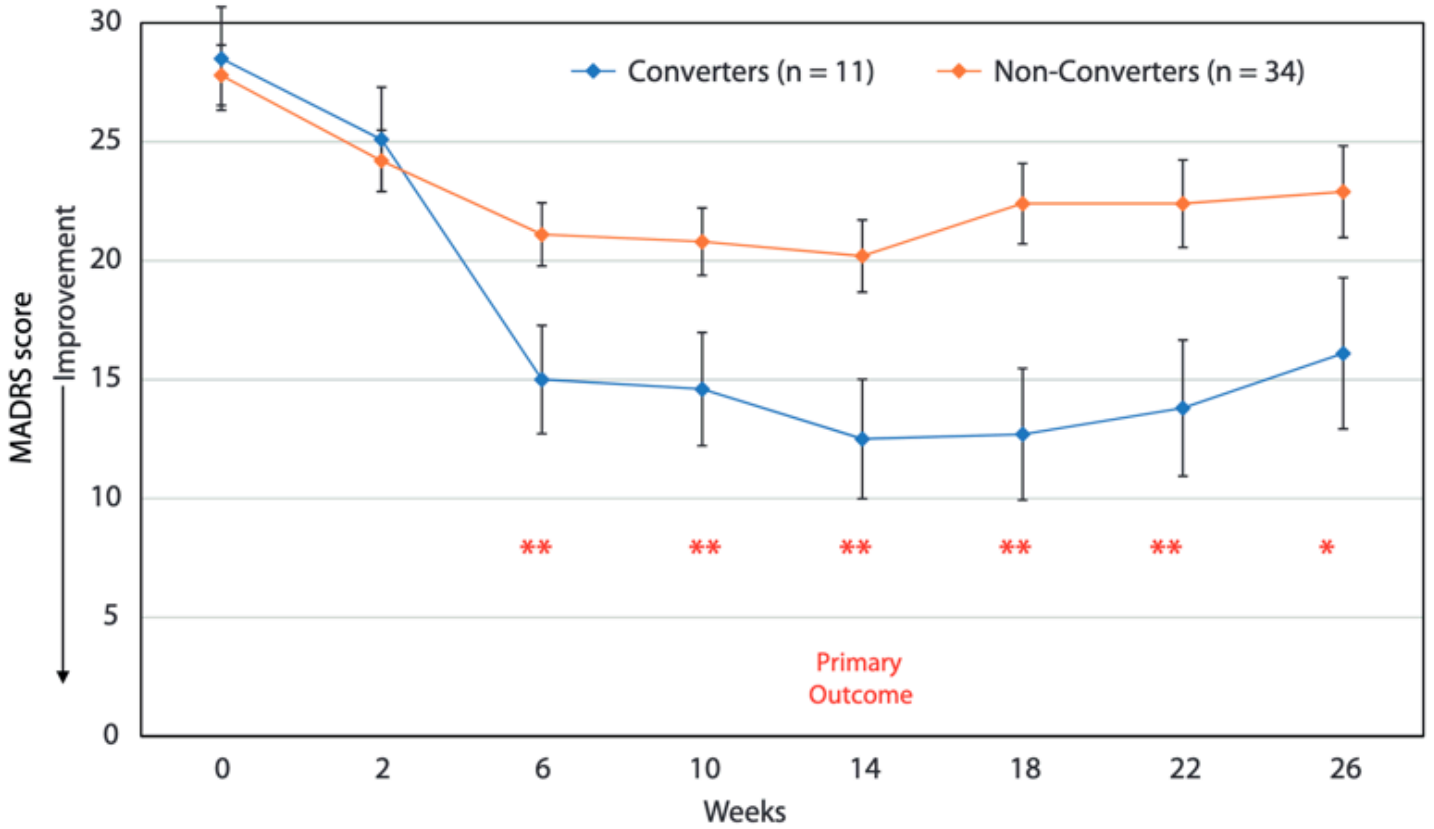
- Response rates at 6 wk:
  - Algorithm-based therapy: 35.0%
  - ECT: 73.9% (*P* = .01)
- Remission rates at 6 wk:
  - Algorithm-based therapy: 30.0%
  - ECT: 34.8% (*P* = .74)
- AEs possibly related to ECT:
  - Failing memory (n = 2)
  - Tension or inner unrest (n = 1)
  - Increased sweating (n = 3)
  - Diminished sexual desire (n = 2)
  - Headache (n = 1)
  - Tooth damage (n = 1)

Schoeyen. Am J Psychiatry. 2015;172:41.

Slide credit: clinicaloptions.com

Treating Insulin Resistance With Metformin as a Strategy to Improve Clinical Outcomes in Treatment-Resistant Bipolar Depression (the TRIO-BD Study): A Randomized, Quadruple-Masked, Placebo-Controlled Clinical Trial

Estimated Marginal Mean Changes From Baseline MADRS Scores Between Converters and Non-Converters



Mixed-model analyses adjusted for treatment, site, age, age at onset, marital status, baseline body mass index (BMI), baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores, conversion status at week 14, and conversion status × weeks of treatment. Bars at time points represent standard error at each time point.

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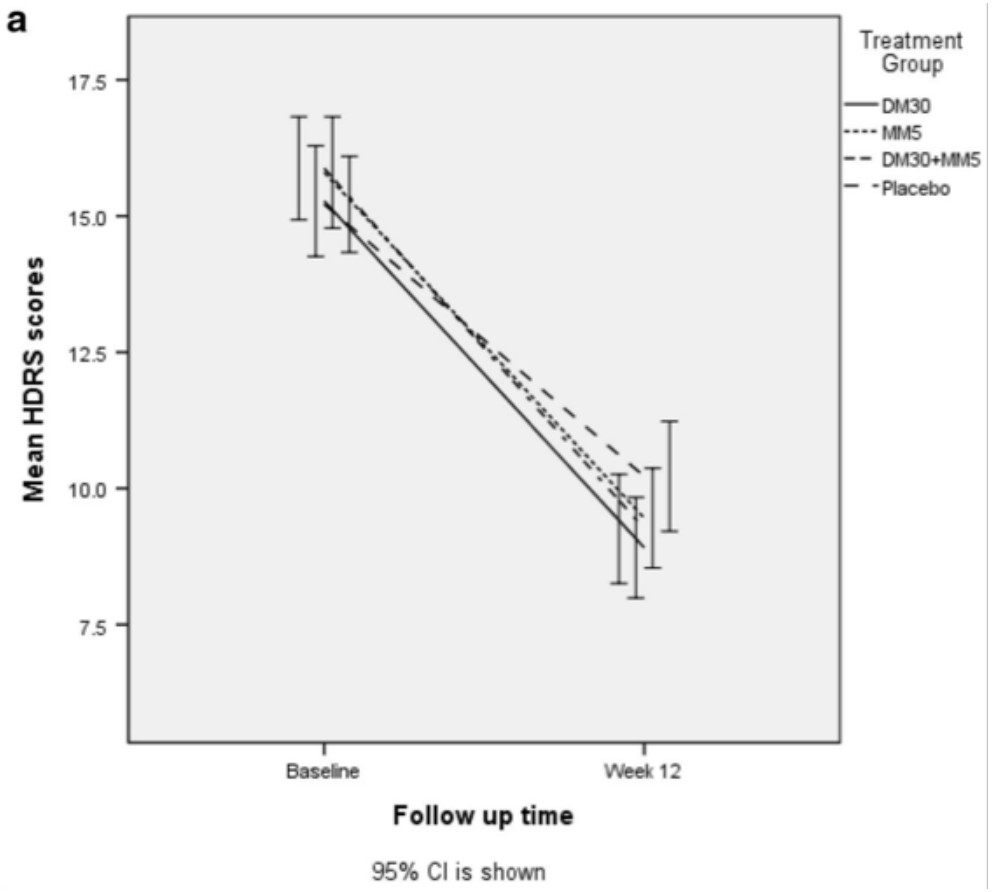
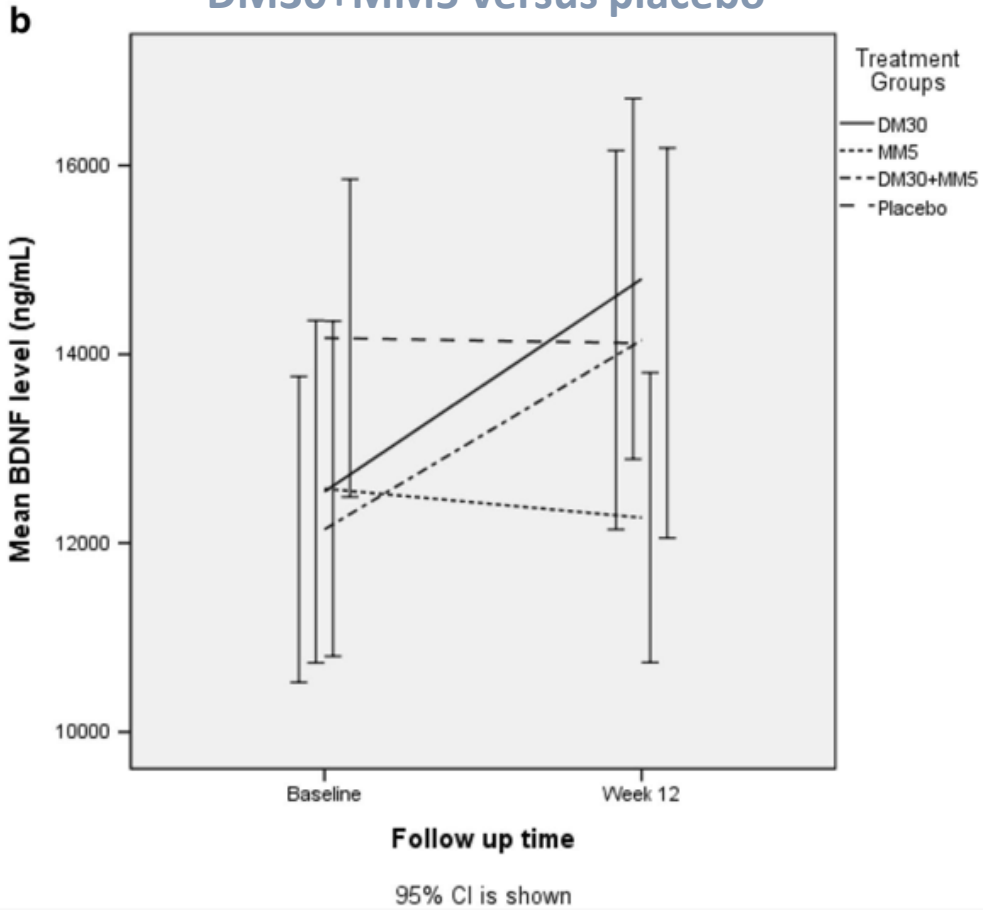
CV Calkin, et al. J Clin Psychiatry. 2022;83(2):21m14022.

Combination of Dextromethorphan and Memantine in Treating Bipolar Spectrum Disorder: A 12-week Double-Blind Randomized Clinical Trial

Difference in symptoms of depression in BD-II patients taking add-on DM30, MM5, and DM30+MM5 versus placebo



Difference in plasma BDNF levels in BD-II patients taking add-on DM30, MM5, and DM30+MM5 versus placebo



Lee SY, et al. Int J Bipolar Disord. 2020 Mar 2;8(1):11.

Molecular Psychiatry (2021) 26:3395–3406
https://doi.org/10.1038/s41380-021-01051-y

ARTICLE

Peripheral inflammatory biomarkers define biotypes of bipolar depression

Yena Lee[1,2] · Rodrigo B. Mansur[1,3] · Elisa Brietzke[4,5] · Dimitrios Kapogiannis[6] · Francheska Delgado-Peraza[6] · Justin J. Boutilier[7] · Timothy C. Y. Chan[8] · Nicole E. Carmona[9] · Joshua D. Rosenblat[1,3] · JungGoo Lee[10,11,12] · Vladimir Maletic[13] · Maj Vinberg[14,15] · Trisha Suppes[16,17] · Benjamin I. Goldstein[2,3,18,19] · Arun V. Ravindran[2,3] · Valerie H. Taylor[2,3,20] · Sahil Chawla[6] · Carlos Nogueras-Ortiz[6] · Victoria E. Cosgrove[16] · Nicole E. Kramer[16] · Roger Ho[21] · Charles A. Raison[22] · Roger S. McIntyre[1,2,3,19,23]

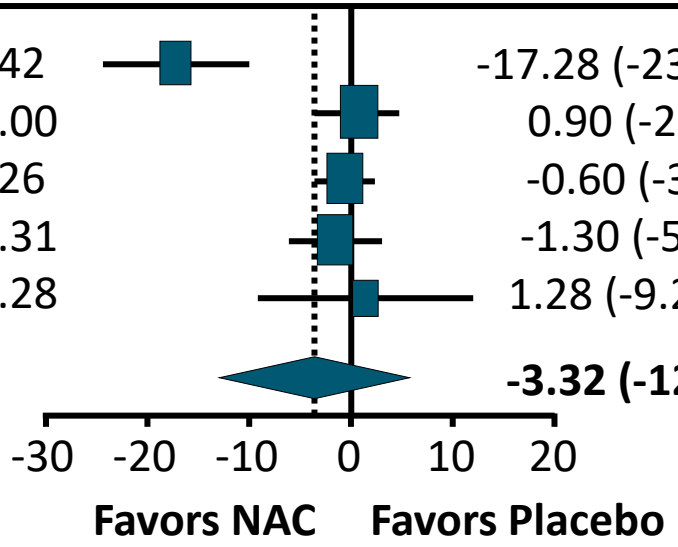
Received: 5 August 2020 / Revised: 25 January 2021 / Accepted: 12 February 2021 / Published online: 3 March 2021

NAC in Bipolar Depression: Systematic Review and Meta-Analysis of Randomized, Controlled Trials

MADRS change from baseline in depressive symptoms of bipolar depression in patients receiving NAC or placebo

Study	NAC Total	NAC Mean	NAC SD	Placebo Total	Placebo Mean	Placebo SD	MD (95% CI)	Weight, %
Magalhaes 2011	10	-18.20	8.68	7	-0.92	5.42	-17.28 (-23.99 to -10.57)	19.0
Berk 2012	59	-0.60	10.73	62	-1.50	11.00	0.90 (-2.97 to 4.77)	21.9
Ellegaard 2019	40	-13.80	7.04	40	-13.20	6.26	-0.60 (-352 to 2.32)	22.7
Berk 2019	52	-14.20	10.66	49	-12.90	10.31	-1.30 (-5.39 to 2.79)	21.7
Bauer 2019	8	-8.00	8.98	8	-9.28	12.28	1.28 (-9.26- to 11.82)	14.7
Random Effects Model	**169**			**166**			**-3.32 (-12.79 to 6.16)**	**100**

Heterogeneity: I^2 = 83%; t^2 = 47.2739; *P* <.01



NAC was not shown to be more effective than placebo

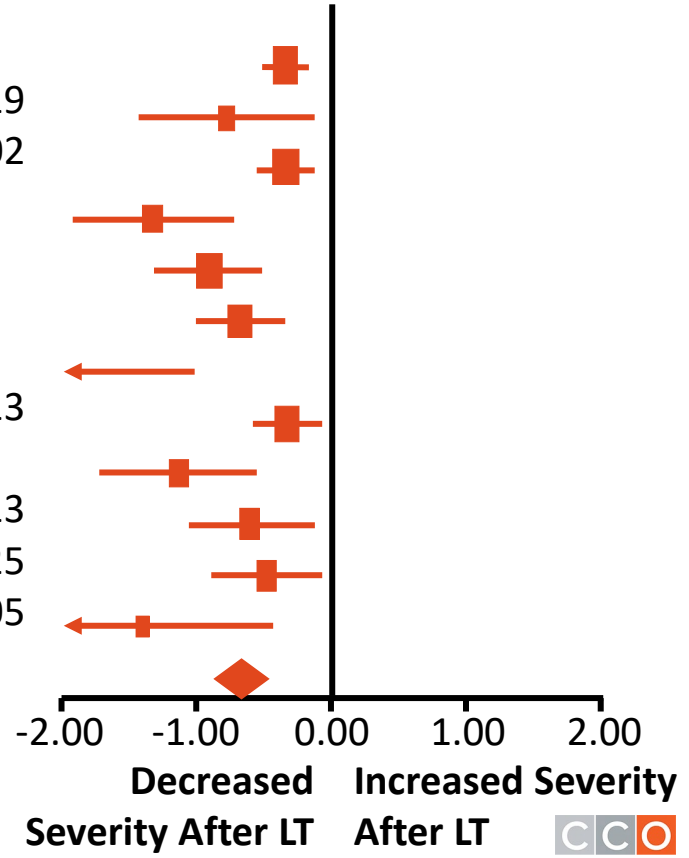
Pittas et al. Psychopharmacology. 2021;238:1729.

Slide credit: clinicaloptions.com

Light Therapy in Treatment of Bipolar Depression

Study Name	TSD	Color	Statistics for Each Study				
			Hedges' g	Lower Limit	Upper Limit	Z Value	*P* Value
Benedetti F (2014)	Yes	White	-0.336	-0.504	-0.167	-3.896	0
Dauphinais, DR (2012)	No	White	-0.774	-1.422	-0.127	-2.345	0.019
Benedetti F (2010)	Yes	White	-0.334	-0.548	-0.120	-3.057	0.002
Benedetti F (2009)	Yes	Green	-1.331	-1.935	-0.727	-4.321	0
Wu JC (2009)	Yes	N/A	-0.908	-1.313	-0.504	-4.399	0
Benedetti F (2007)	Yes	Green	-0.682	-1.025	-0.339	-3.899	0
Sit D (2007)	No	N/A	-2.144	-3.296	-0.991	-3.645	0
Benedetti F (2005)	Yes	Green	-0.324	-0.580	-0.067	-2.473	0.013
Benedetti F (2003)	No	Green	-1.136	-1.712	-0.559	-3.861	0
Colombo C (2000) Red	Yes	Red	-0.598	-1.069	-0.127	-2.490	0.013
Colombo C (2000) White	Yes	White	-0.477	-0.895	-0.059	-2.237	0.025
Papatheodorou G (1995)	No	White	-1.419	-2.402	-0.435	-2.827	0.005
			-0.688	**-0.895**	**-0.481**	**-6.512**	**0**

Hedges' g and 95% CI



Light Therapy possibly useful in decreasing severity

Tseng et al. Eur Neuropsychopharmacol. 2016;26:1037.

Slide credit: clinicaloptions.com

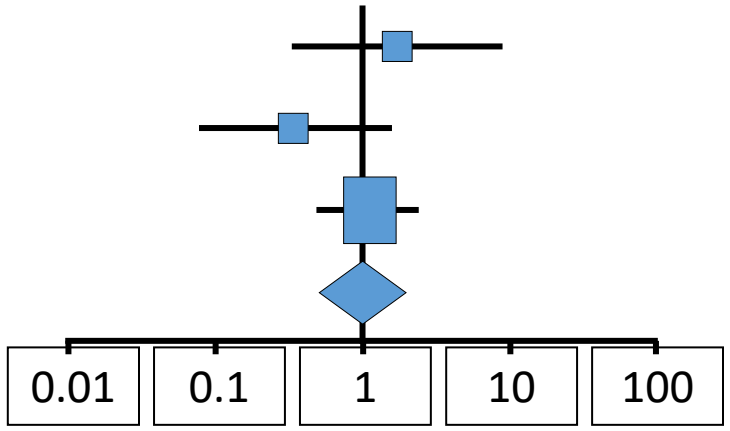
ECT Equally Effective in Treatment-Resistant Bipolar Disorder vs Major Depressive Disorder

Odd Ratios Measured From Response Rates
(≥50% Reduction in the Hamilton Depression Rating Scale Score)

Study Name	Odds Ratio	Lower Limit	Upper Limit	Z Value	*P* Value
Sienart P	1.692	0.328	8.721	0.629	.529
Medda P	0.338	0.073	1.560	-1.390	.164
Bailine S	1.075	0.490	2.355	0.180	.857
	0.940	0.494	1.786	-0.190	.849

Statistics for Each Study

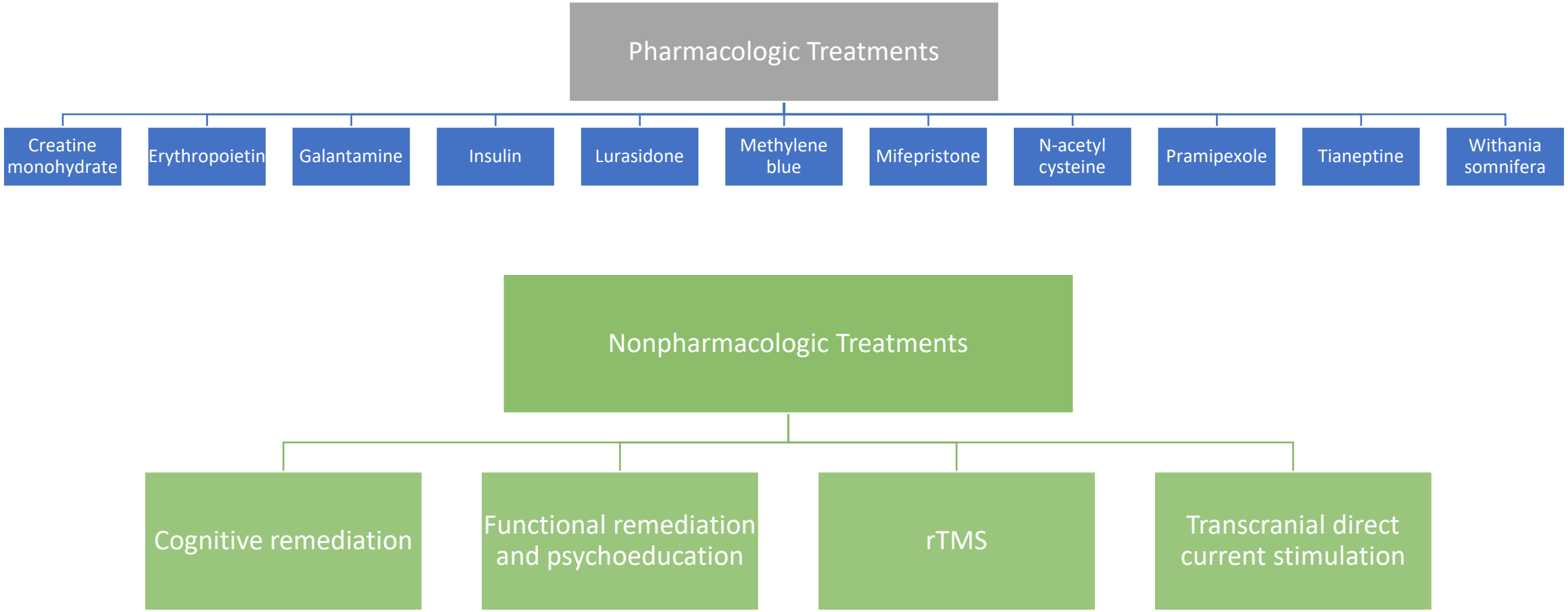
Odds Ratio and 95% CI



Bitemporal ECT was equally effective for acute TRBD-De vs unipolar TRD cases.

Fornaro et al. J Affect Disord. 2020;276:970.

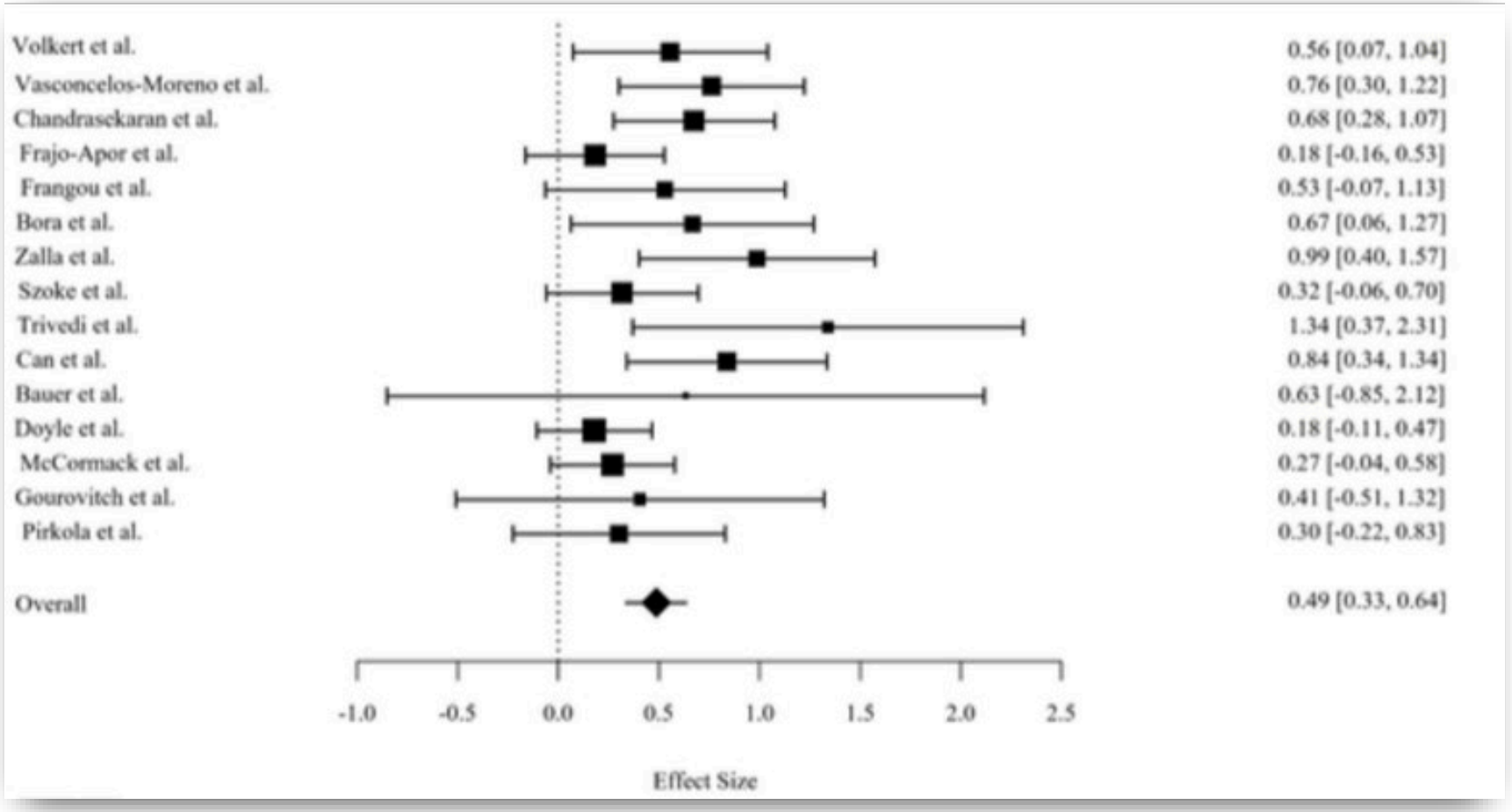
Treatments Explored for Possible Procognitive Effects in Bipolar Disorder



Tamura et al. CNS Spectr. 2021;1-22.

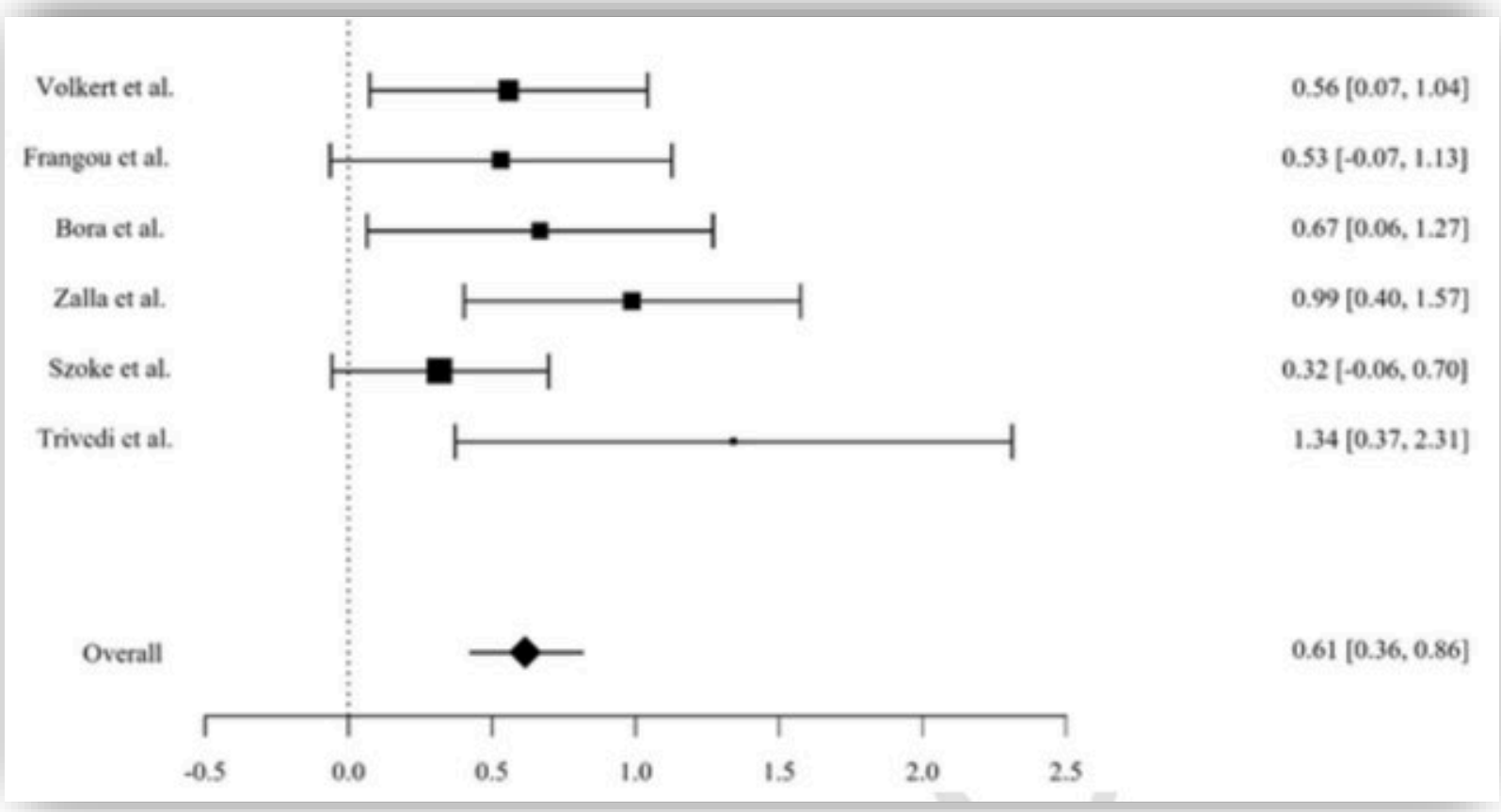
Evaluating Cognitive Function in Unaffected Relatives of Individuals with Bipolar Disorders: A Meta-Analysis

Forest plot displaying the effect size (ES) in Cohen's d of UR compared to HC across all domains of cognition



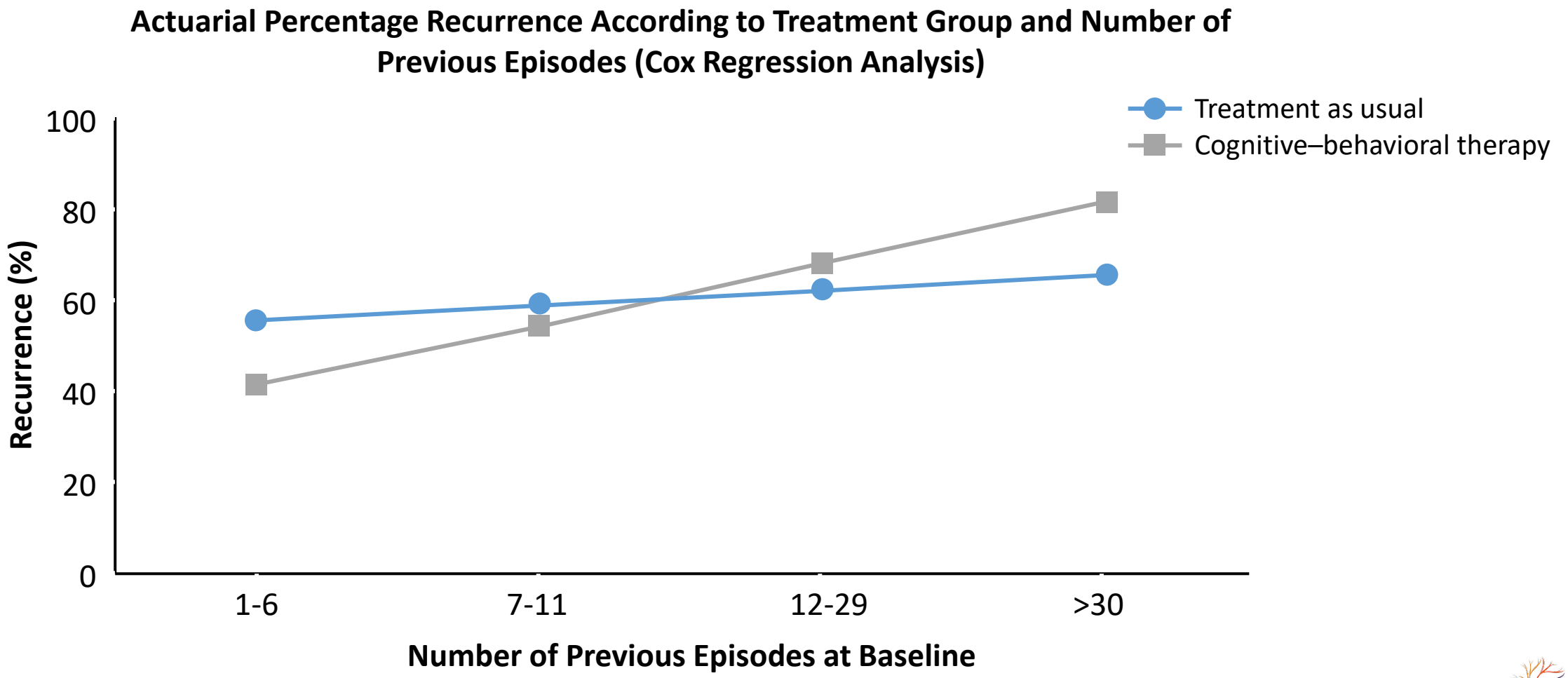
Evaluating Cognitive Function in Unaffected Relatives of Individuals with Bipolar Disorders: A Meta-Analysis

Forest plot displaying the ES in Cohen's d between UR and HC on the executive function domain



Gillissie ES, et al. J Psychiatr Res. 2022

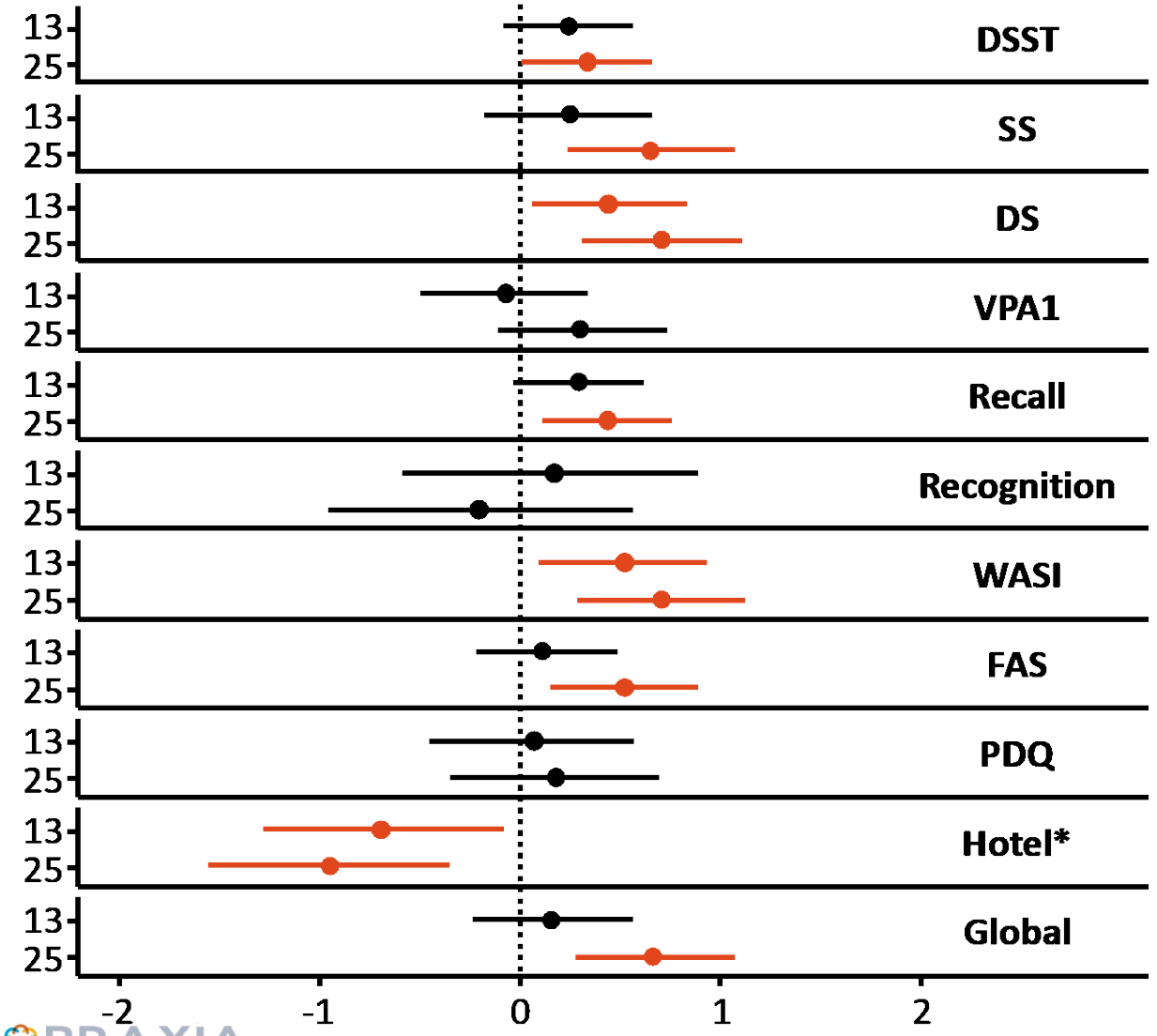
Cognitive–Behavioral Therapy Less Effective in Persons With Bipolar Disorder and Multiple Episode Illness



Scott et al. Br J Psychiatry. 2006;188:313.

Cognitive Remediation Improves Measures of Cognition, Patient Reported Outcomes, and Function in Adults With Bipolar Disorder

Cognitive outcomes after CRT and TAU. Effect size (time x group interactions) at Wk 13 and Wk 25 compared with pretreatment cognitive performance.



Strawbridge et al. Bipolar Disord. 2021;23:196.

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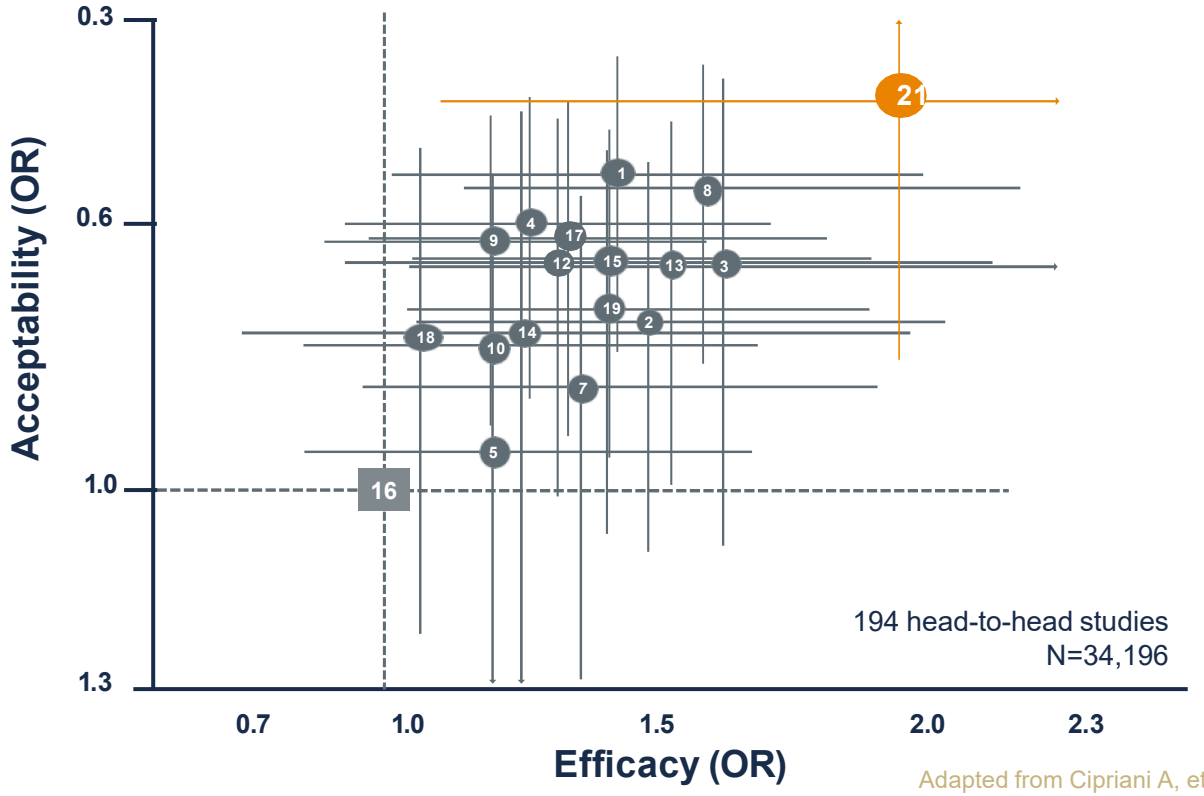
Efficacy and tolerability of antidepressants vs placebo[1]

- A large network meta-analysis including 522 trials and 116,477 patients compared 21 antidepressants in the acute treatment of MDD in adults
- All antidepressants were shown to be **more effective than placebo**

Comparative efficacy and tolerability analysis of head-to-head studies‡:



1 = agomelatine
2 = amitriptyline
3 = bupropion
4 = citalopram §
5 = clomipramine
7 = duloxetine
8 = escitalopram‖
9 = fluoxetine
10 = fluvoxamine
12 = milnacipran
13 = mirtazapine
14 = nefazodone
15 = paroxetine
16 = reboxetine
17 = sertraline
18 = trazodone
19 = venlafaxine
21 = vortioxetine

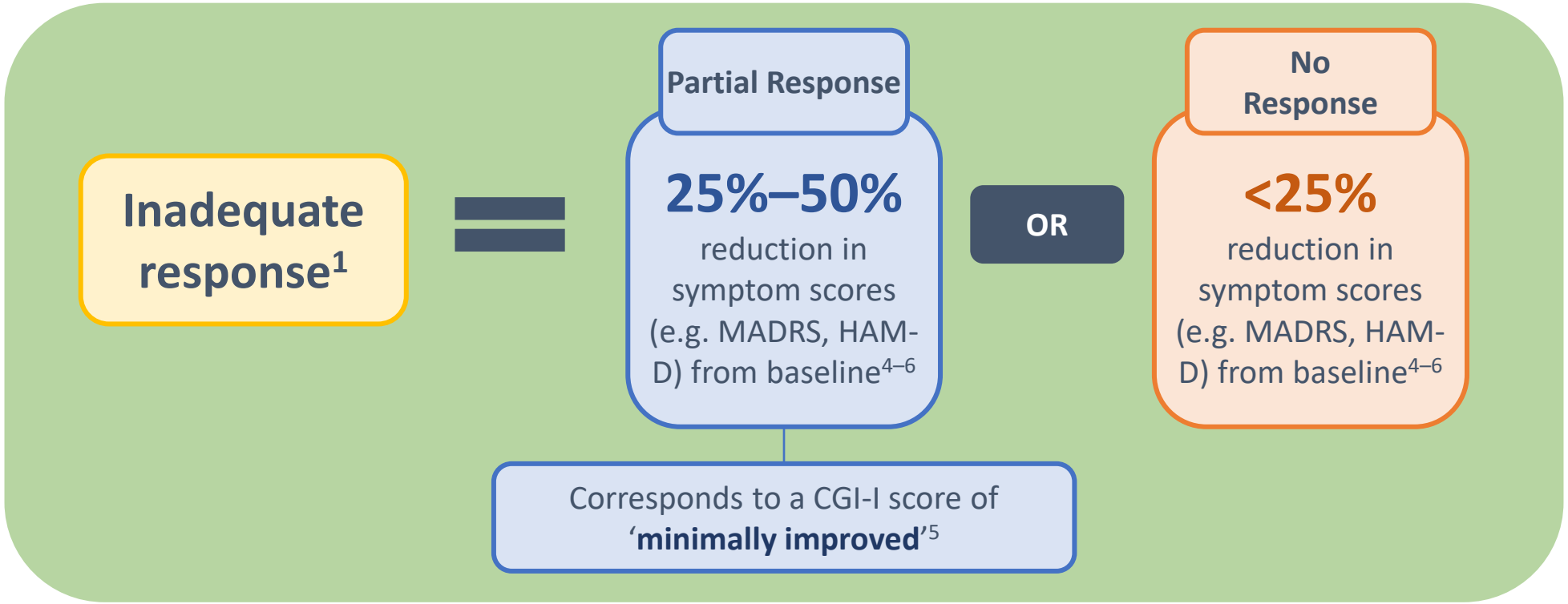
Adapted from Cipriani A, et al. 2018.

*Antidepressive response was defined by a reduction of ≥50% of the total score on a standardised observer-rating scale for depression (HAM-D or MADRS). †Acceptability was defined based on all-cause discontinuation of the treatments. LOCF data are reported as OR in comparison with reboxetine, which is the reference drug. Error bars represent 95% credibility intervals. ‡A network meta-analysis of only head-to-head studies included a single direct study comparison of vortioxetine at a dose of 10 mg/day and venlafaxine at a dose of 150 mg/day. The error bars, indicating 95% credibility intervals, reflect limited data for vortioxetine in this network meta-analysis. §Citalopram is indicated for depression and prevention of relapse/recurrence, panic disorder with or without agoraphobia, and obsessive-compulsive disorder. §Escitalopram is indicated for the treatment of major depressive episodes, panic disorder with or without agoraphobia, social anxiety disorder (social phobia), generalised anxiety disorder and obsessive-compulsive disorder. Prescribing information for citalopram, escitalopram and vortioxetine can be found at the end of this slide deck. Registration status may differ from country to country. HAM-D = Hamilton Depression Rating Scale; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; OR = odds ratio.

1. Cipriani A, et al. Lancet. 2018;391:1357-1366.

How are inadequate response and partial response defined?

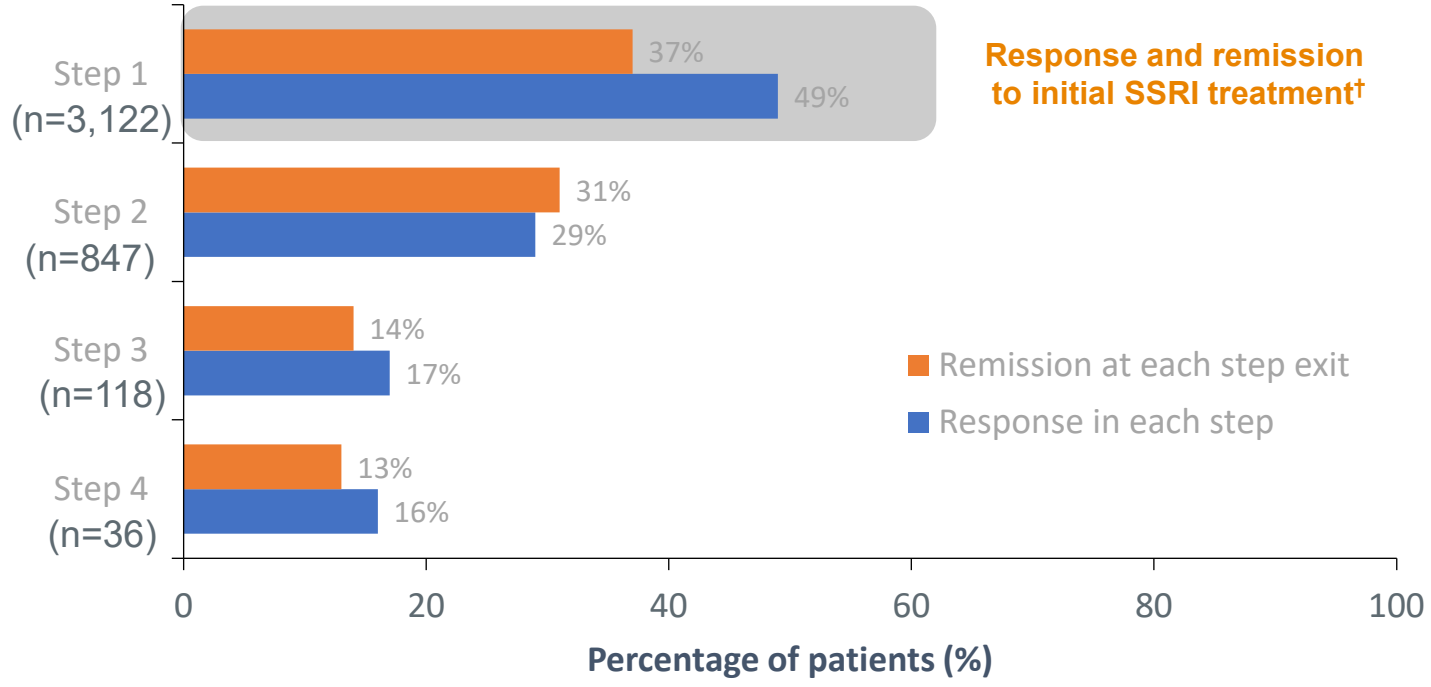
Guidelines recommend assessing improvement no more than **2 weeks after starting** a medication[1–3]



CANMAT = Canadian Network for Mood and Anxiety Treatments ; CGI-I = Clinical Global Impression – Improvement; HAM-D = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; WFSBP = World Federation of Societies of Biological Psychiatry. 1. CANMAT guidelines: Kennedy SH, et al. Can J Psychiatry. 2016;61:540-560; 2. WFSBP guidelines: Bauer M, et al. World J Biol Psychiatry. 2017;21:166-176; 3. NICE guidelines: National Institute for Health and Care Excellence (NICE). 2009. Depression in adults: treatment and management. Available at: https://www.nice.org.uk/guidance/ng222/resources/depression-in-adults-treatment-and-management-pdf-66143832307909. Accessed August 2022; 4. Lam RW, et al. Can J Psychiatry. 2016;61:510-523; 5. Nierenberg A, et al. J Clin Psychiatry. 2001;62 Suppl 16:5-9; 6. Hirschfeld RMA, et al. J Clin Psychiatry. 2002;63(9):826-37.

Approximately 60% of patients with MDD do not respond adequately to initial antidepressant treatment[1]

Patients achieving response at each treatment step in the STAR*D study†[1]



Adapted from Rush AJ, et al. 2006.[1]

Continuous treatment optimisation and monitoring of treatment responses is often required for patients with MDD to achieve remission[2]

†At Step 1, patients received citalopram as their first treatment step. Response defined as 50% or more reduction in QIDS-SR16 score from entry score at each step. Remission defined as QIDS-SR16 score ≤5 at exit from the indicated treatment step. Study population: outpatients with MDD aged 18–75 years, female (Step 1, 62.2%; Step 2, 59.1%; Step 3, 50.5%; Step 4, 48.8%). Citalopram is indicated for depression and prevention of relapse/recurrence, panic disorder with or without agoraphobia and obsessive-compulsive disorder. Prescribing information for citalopram can be found at the end of this slide deck. MDD = major depressive disorder; QIDS-SR16 = Self-reported 16-item Quick Inventory of Depressive Symptomatology; SSRI = selective serotonin reuptake inhibitor; STAR*D = Sequenced Treatment Alternatives to Relieve Depression. 1. Rush AJ, et al. Am J Psychiatry. 2006;163:1905-1917; 2. Habert J, et al. Prim Care Companion CNS Disord. 2016;18:e1-e11.

Patients with MDD and partial response present various challenges for treatment in clinical practice

Low work productivity[1]

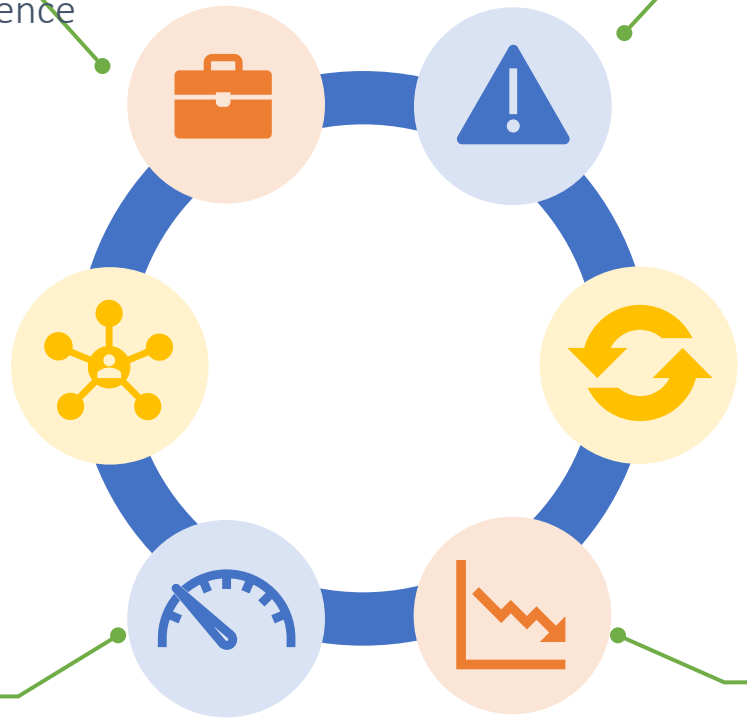
Partial responders are 1.4x more likely to experience significant **work productivity loss**

Comorbid conditions[2]

80% of partial responders have **at least 1 comorbid condition**

Unsatisfied with treatment[3]

~25% of partial responders are **not satisfied** with their treatment



Residual symptoms[4–6]

Common residual symptoms include **anhedonia, emotional blunting** and **cognitive impairment**

Failure with multiple treatment options[3]

83% of partial responders fail to respond to **at least 2 antidepressants**

Poor prognosis[7]

Partial responders are 2.35x more likely to **relapse**

MDD = major depressive disorder.

1. Knoth RL, et al. Am J Manag Care. 2010;16(8):e188-e196; 2. Gao K, et al. J Affect Disord. 2013;148:256-264; 3. Mago R, et al. BMC Psychiatry. 2018;18:33; 4. Conradi HJ, et al. Psychol Med. 2011;41:1165-1174; 5. Culpepper L, et al. Am J Med. 2015;128:S1-S15; 6. Goodwin GM, et al. J Affect Disord. 2017;221:31-35; 7. Judd LL, et al. Am J Psychiatry. 2000;157:1501–4.

Patterns and Correlates of Patient-reported Helpfulness of Treatment for Common Mental and Substance Use Disorders in the WHO World Mental Health Surveys

Significant predictors of patient-level treatment helpfulness decomposed through associations with the helpfulness of individual professionals and persistence in help-seeking pooled across diagnostic categories and number of professionals seen

	Patient-level treatment helpfulness				Helpfulness of individual professionals				Persistence in help-seeking after prior unhelpful treatment			
	%	SE	RR	95% CI	%	SE	RR	95% CI	%	SE	RR	95% CI
Focal diagnostic category												
Major depressive disorder	28.3	0.6	1.19*	1.12-1.26	26.6	0.8	1.11*	1.02-1.21	24.8	0.9	1.08*	1.04-1.11
Bipolar disorder												
Major depressive episode	3.1	0.2	0.94	0.75-1.17	3.9	0.5	0.85	0.62-1.16	4.2	0.6	1.06	0.97-1.16
Mania/hypomania	6.1	0.3	1.11	0.98-1.27	6.4	0.4	1.08	0.91-1.29	6.4	0.4	1.03	0.95-1.12

Kessler RC, et al. World Psychiatry. 2022 Jun;21(2):272-286.

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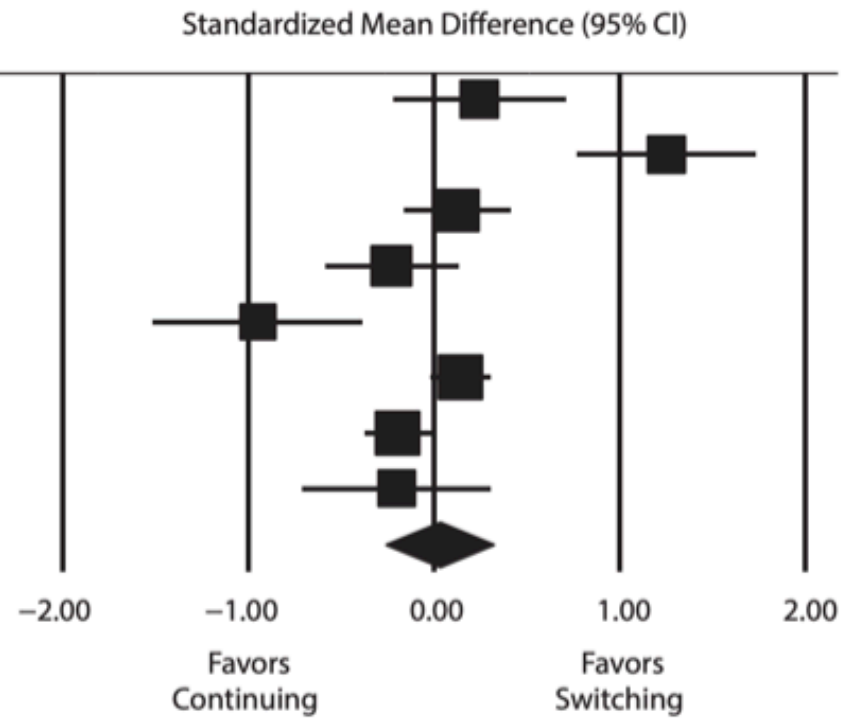
Broad Analysis (dose escalation allowed in the continuation arms): Switching to a New Antidepressant Versus Continuation of the Initial Antidepressant in Patients With Major Depressive Disorder After Nonresponse to Antidepressant Monotherapy

Standard Mean Difference

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



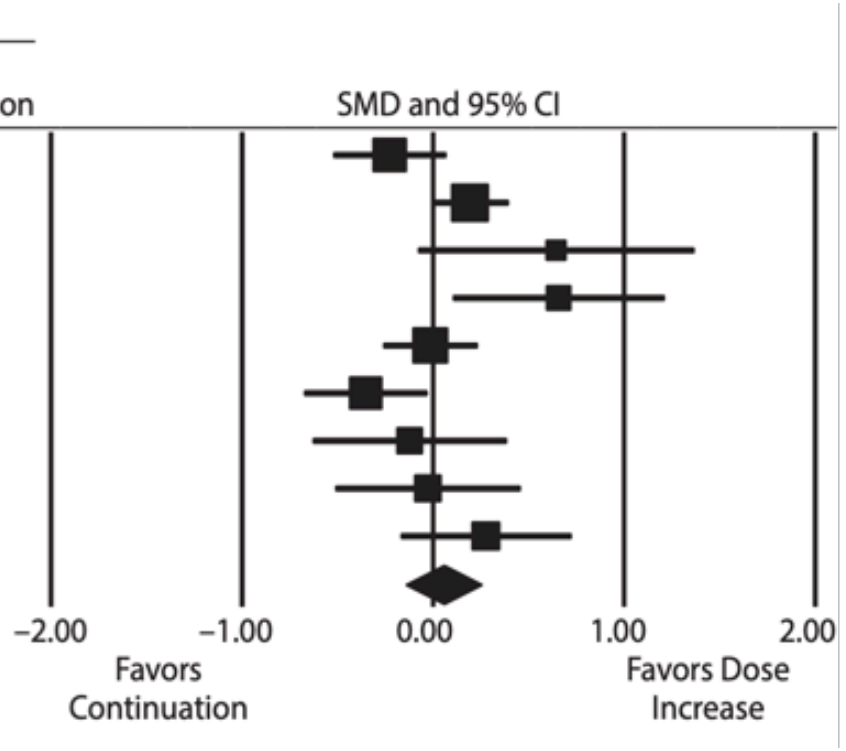
Bschor T, et al. J Clin Psychiatry. 2018 Jan/Feb;79(1):16r10749.

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

Dose Increase Versus Unchanged Continuation of Antidepressants After Initial Antidepressant Treatment Failure

All studies

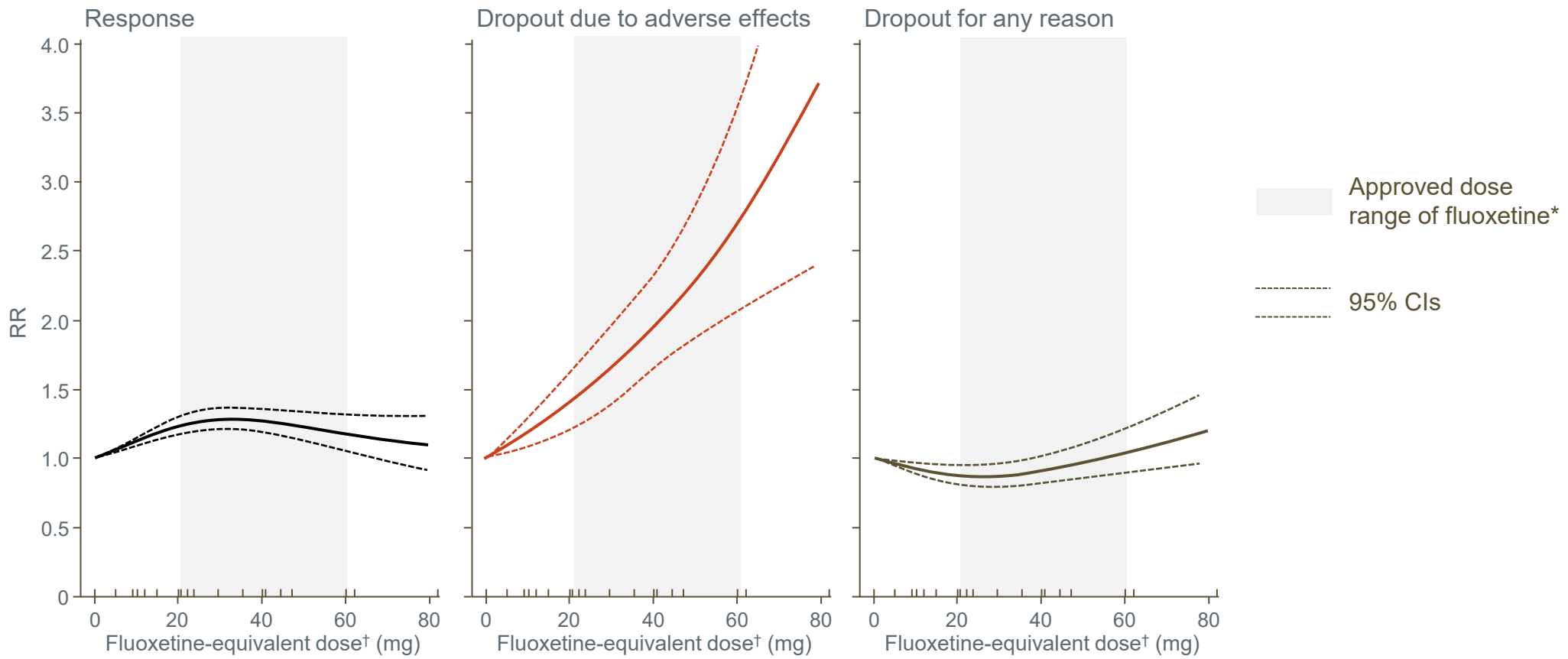
		Statistics for Each Study				Sample Size	
Study	SMD	Standard Error	Lower Limit	Upper Limit	*P* Value	Dose Increase	Continuation
Benkert et al 1997[26]	−0.227	0.151	−0.523	0.069	0.133	90	84
Dornseif et al 1989[29]	0.193	0.104	−0.011	0.397	0.063	180	189
Heiligenstein et al 2006[20]	0.645	0.370	−0.079	1.369	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**



Rink L, et al. J Clin Psychiatry. 2018 May/Jun;79(3):17r11693.

Increasing doses of SSRIs were associated with linear increase in AEs, whereas response rates were not

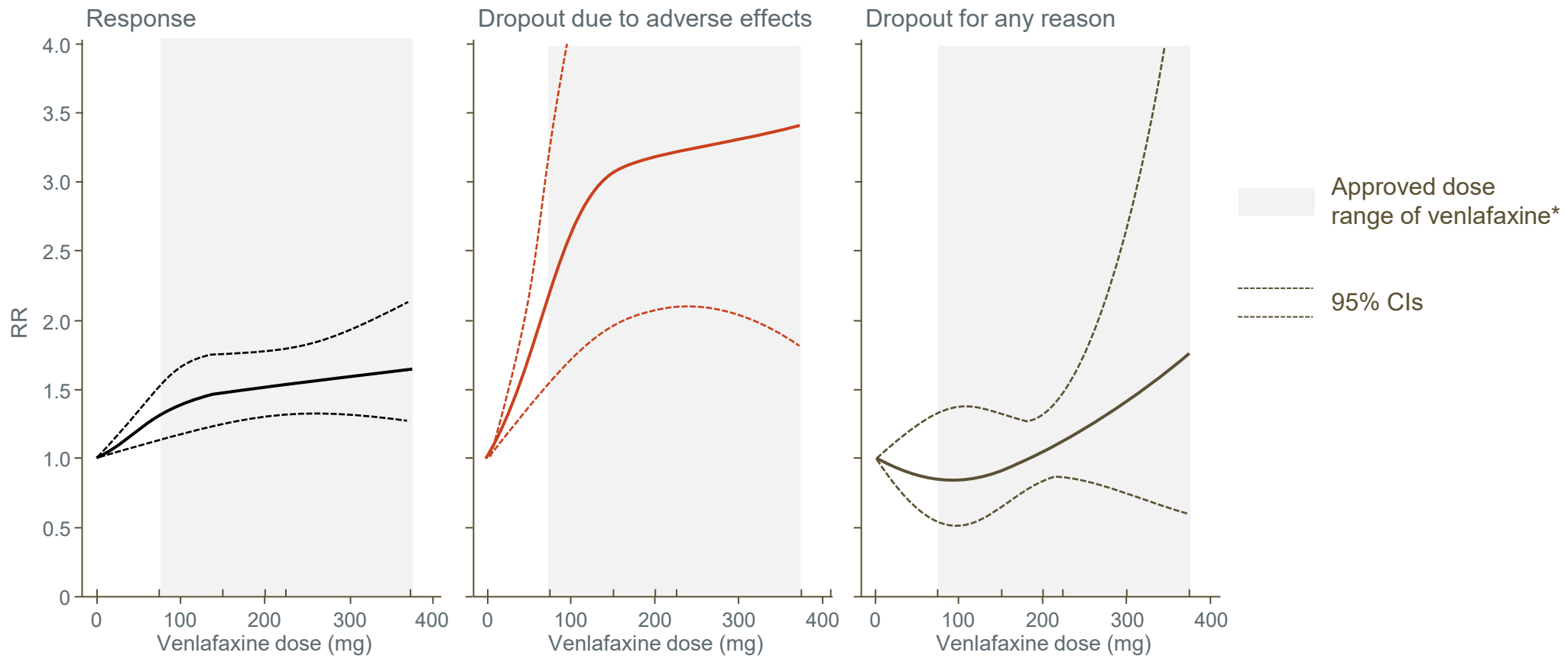
Meta-analysis: Dose-outcome relationships for SSRIs (99 treatment groups)



Each tick on the x-axis represents the dose examined in a treatment group. *Obtained from the Summary of Product Characteristics for fluoxetine. † Doses of citalopram, escitalopram, paroxetine and sertraline were converted to fluoxetine equivalents. An abbreviated Prescribing Information for citalopram and escitalopram can be found at the end of this slide deck. For further information please consult your local Summary of Product Characteristics. AE=adverse event; CI=confidence interval; RR=risk ratio; SSRI=selective serotonin reuptake inhibitor. Furukawa TA et al. Lancet Psychiatry 2019;6:601-9.

Venlafaxine Had an Increasing Dose-Efficacy Relationship Only in the Lower Approved Dose Range (75–150 mg), But Dropouts Due to AEs Increased Steeply with Increasing Doses at This Range

Meta-analysis: Dose-outcome relationships for venlafaxine (16 treatment groups)

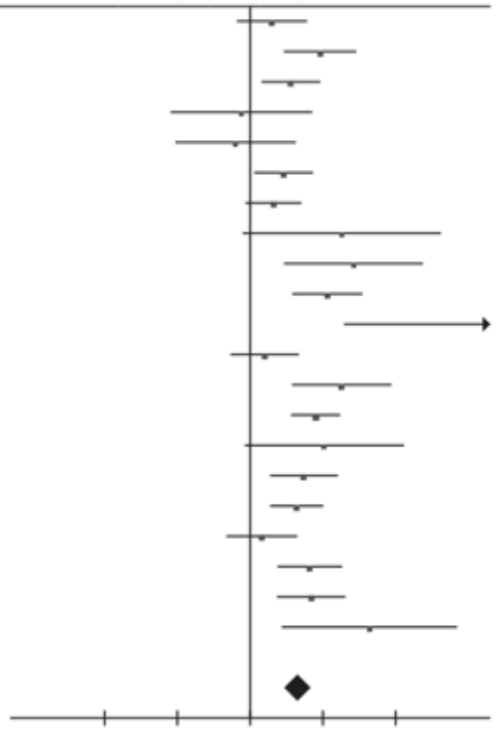


Each tick on the x-axis represents the dose examined in a treatment group. *Obtained from the Summary of Product Characteristics for venlafaxine. AE=adverse event; CI=confidence interval; RR=risk ratio. Furukawa TA et al. Lancet Psychiatry 2019;6:601-9.

Long-Term Acute-Phase Treatment With Antidepressants, 8 Weeks and Beyond: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials

Primary Outcome Second-Line Analysis: Treatment Effect (standardized mean difference [SMD]) After 12 Weeks of Antidepressant Monotherapy Versus Placebo in Randomized Double-Blind Trials

Study or Subgroup	SMD	SE	Antidepressant, Total	Placebo, Total	Weight, %	SMD, IV, Random (95% CL)
Bose et al, 2008[18]	0.15	0.1235	129	134	5.8	0.15 (–0.09, 0.39)
Cunningham et al, 1997[19]	0.48	0.1269	179	99	5.7	0.48 (0.23, 0.73)
Dunlop et al, 2011[20]	0.28	0.1032	285	142	6.6	0.28 (0.08, 0.48)
Fava et al, 1998[21]	–0.06	0.2486	109	19	2.5	–0.06 (–0.55, 0.43)
Fava et al, 2005[22]	–0.1	0.2112	47	43	3.2	–0.10 (–0.51, 0.31)
GlaxoSmithKline, 1991[23]	0.23	0.1035	550	113	6.6	0.23 (0.03, 0.43)
GlaxoSmithKline, 2005[24]	0.16	0.0985	210	204	6.8	0.16 (–0.03, 0.35)
Heller et al, 1971[25]	0.63	0.3477	23	14	1.5	0.63 (–0.05, 1.31)
Jarrett et al, 1999[26]	0.71	0.2434	36	36	2.6	0.71 (0.23, 1.19)
Khan et al, 1998[27]	0.53	0.1229	253	93	5.8	0.53 (0.29, 0.77)
Lopez-Rodriguez et al, 2004[28]	1.7	0.5385	10	10	0.7	1.70 (0.64, 2.76)
Malt et al, 1999[16]	0.1	0.1203	243	129	5.9	0.10 (–0.14, 0.34)
McGrath et al, 2000[29]	0.63	0.1742	102	52	4.1	0.63 (0.29, 0.97)
Montgomery et al, 2013[30]	0.45	0.0861	276	277	7.4	0.45 (0.28, 0.62)
Mynors-Wallis et al, 1995[31]	0.51	0.2796	27	26	2.1	0.51 (–0.04, 1.06)
Rapaport et al, 2003[32]	0.37	0.119	210	109	6.0	0.37 (0.14, 0.60)
Rapaport et al, 2009[33]	0.32	0.0931	336	179	7.1	0.32 (0.14, 0.50)
Robinson et al, 2014[34]	0.08	0.1243	204	95	5.8	0.08 (–0.16, 0.32)
Silverstone and Ravindran, 1999[35]	0.41	0.1134	241	118	6.2	0.41 (0.19, 0.63)
Stahl, 2000[17]	0.42	0.1201	209	107	5.9	0.42 (0.18, 0.66)
Thomson et al, 1982[36]	0.82	0.3076	31	28	1.8	0.82 (0.22, 1.42)
Total (95% CL)			3,710	2,027	100.0	0.34 (0.25, 0.43)



Heterogeneity: $\tau^2 = 0.02$, $\chi^2_{20} = 43.28$ ($P = .002$), $I^2 = 54\%$
Test for overall effect: $Z = 7.37$ ($P < .00001$)

[a]Weighted according to random-effects analysis.
Abbreviations: CL = confidence limit, SE = standard error.

Henssler j, et al. J Clin Psychiatry. 2018 Jan/Feb;79(1):15r10545.

Most Frequently Prescribed First-Line Antidepressants and Adjunctive Treatments

First-line Antidepressants	Percent
Selective serotonin reuptake inhibitors (SSRIs)	53.4
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	23.6
Norepinephrine and specific serotonergic antidepressants (NaSSAs)	8.2
Tricyclic antidepressants (TCAs)	5.1
Melatonergic antidepressants	5.0
Other antidepressants	4.7

Adjuncts to First-Line Antidepressants	Percent
Benzodiazepines and related drugs	33.2
Antidepressants	29.0
Antipsychotics	24.2
Mood stabilizers	10.1
Pregabalin	7.3
Low-potency antipsychotics/low-dose quetiapine (<100 mg/day)	6.6

Data from 1181 adult in- and outpatients with major depressive disorder in retrospective assessment of current prescription trends in European university/academic psychiatric centers

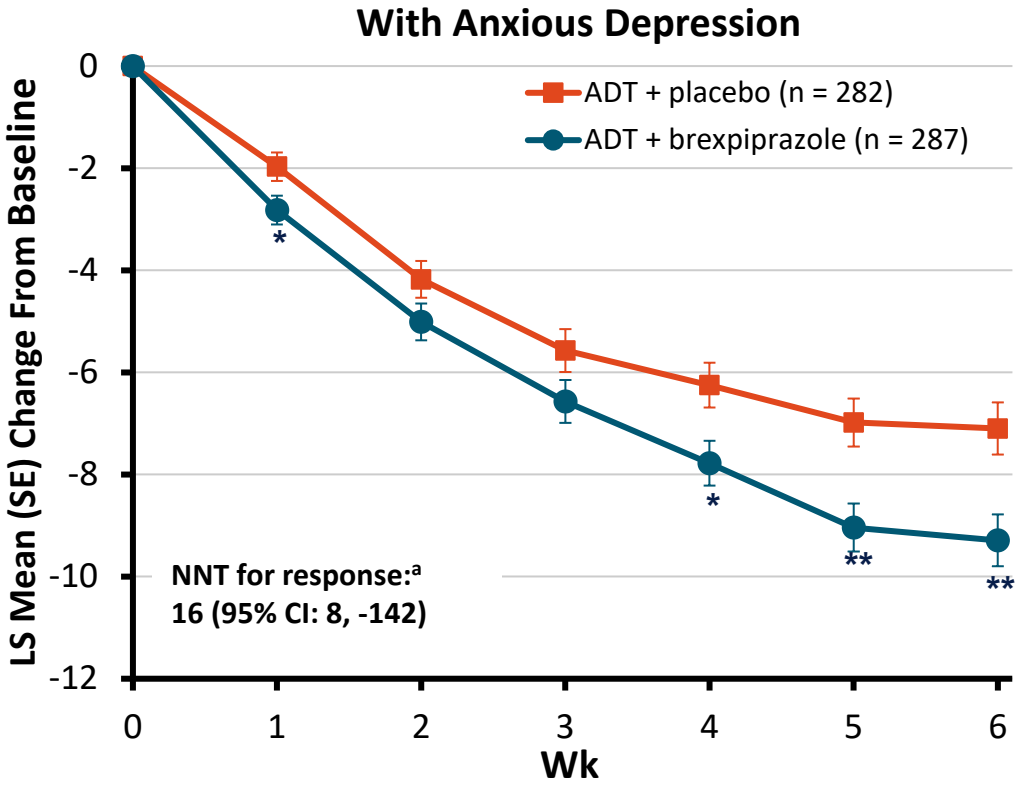
Dold M et al. Eur Neuropsychopharmacol 2016;26(12):1960-71.

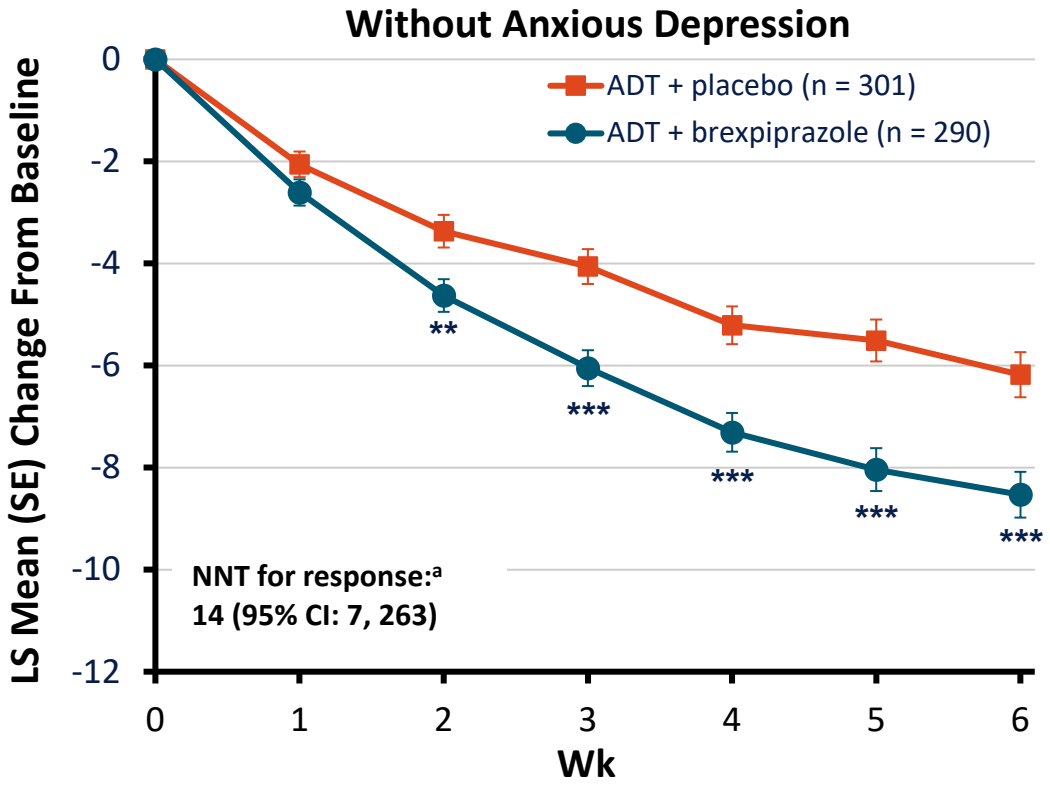
Second Generation Antipsychotics for Adjunctive Treatment of Major Depressive Disorder

FDA Approved	At Least 1 Positive Trial	Ongoing Trials
▪ Olanzapine/fluoxetine combination ▪ Aripiprazole ▪ Quetiapine XR ▪ Brexpiprazole	▪ Ziprasidone ▪ Risperidone ▪ Cariprazine ▪ Lurasidone (mixed features/anxiety)	▪ Lumateperone

Aripiprazole PI. Brexpiprazole PI. Quetiapine XR PI. Olanzapine/fluoxetine PI. Wang. Chonnam Med J. 2016;52:159a. Earley. Psychopharmacol Bull. 2018;48:62. NCT04985942.

Adjunctive Therapy With Brexpiprazole: Patients With and Without Anxious Depression





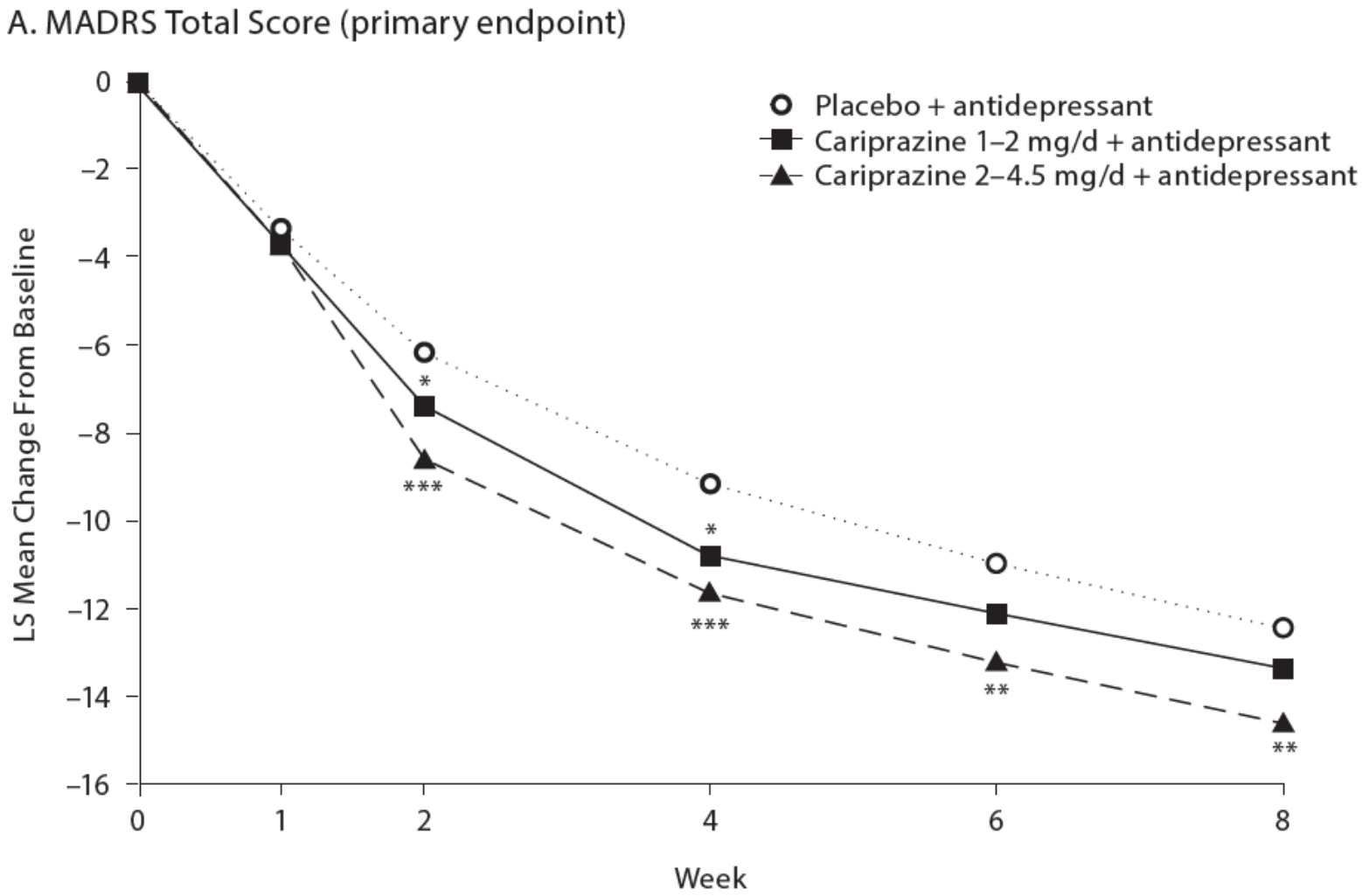
*P <.05. **P <.01. ***P <.001 vs placebo. MMRM.

[a]Response defined as ≥50% reduction from baseline in MADRS total score.

MADRS total baseline for patients with anxious depression: ADT + placebo, 28.6; ADT + brexpiprazole, 28.9.

MADRS total baseline for patients without anxious depression: ADT + placebo, 24.8; ADT + brexpiprazole, 24.6.

Adjunctive Cariprazine (2–4.5 mg/day) is Effective for MDD With Inadequate Antidepressant Response



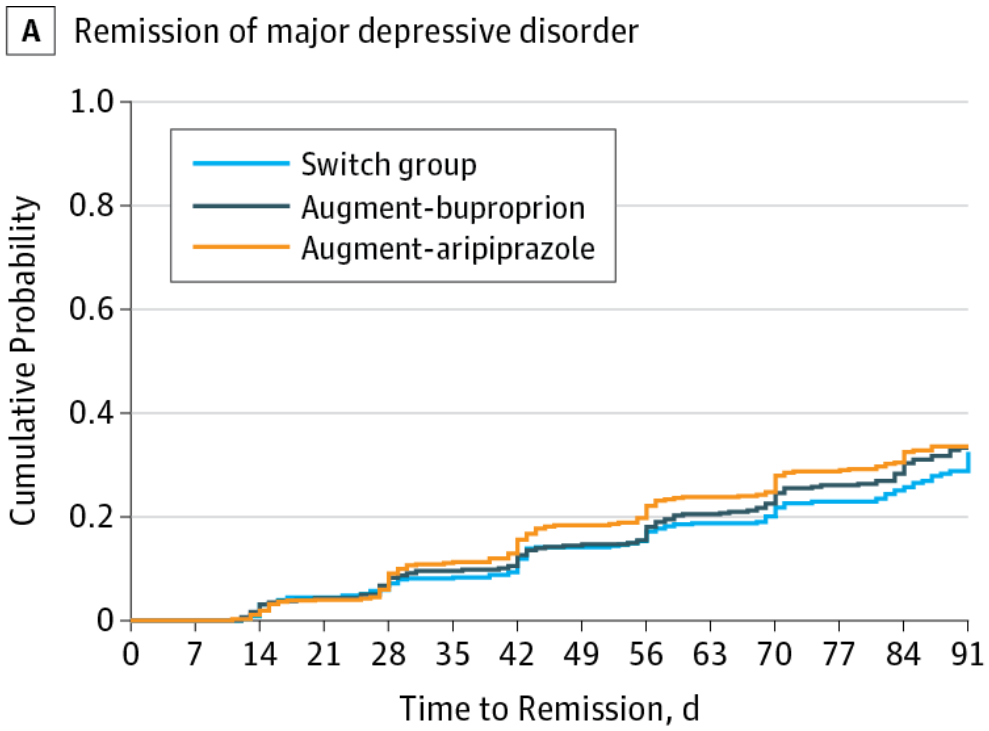
Treatment-emergent adverse events (TEAEs) that occurred in ≥ 10% of patients in either cariprazine group and at incidence greater than placebo were akathisia, insomnia, and nausea

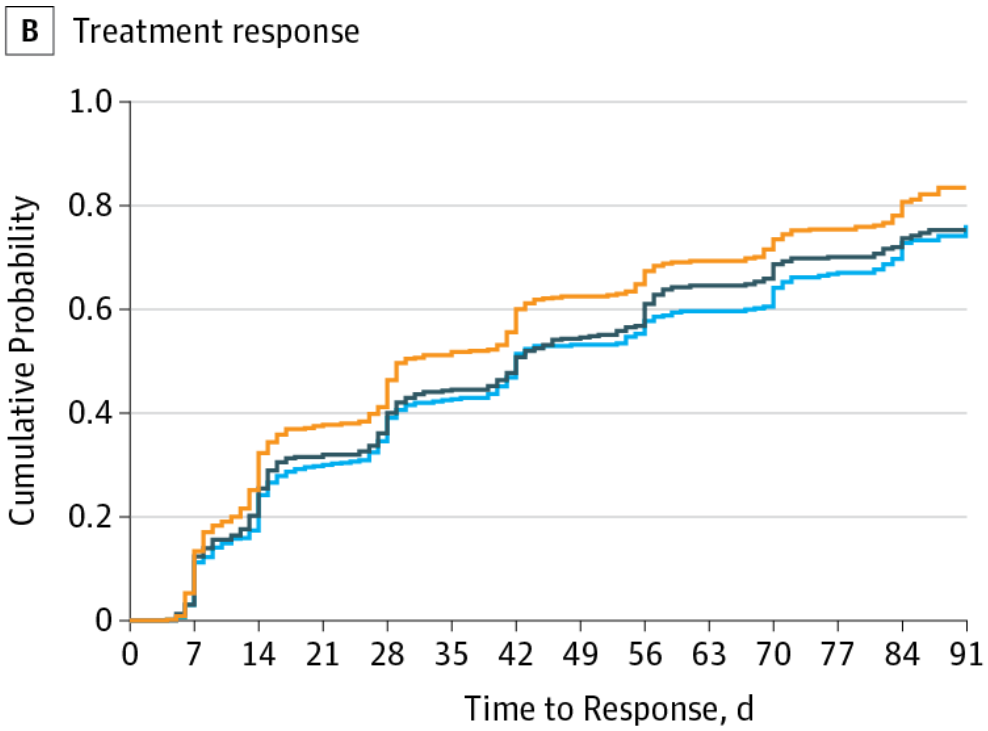
*P<.05. **P<.01. ***P<.001 versus placebo for pairwise comparisons; not adjusted for multiple comparisons

LS=least squares
MADRS = Montgomery-Åsberg Depression Rating Scale

Durgam S et al. J Clin Psychiatry 2016;77(3):371-8.

Switching Antidepressants vs. Atypical Antipsychotic Augmentation vs. Antidepressant Combination





No. at risk

Switch group	511	477	428	379	331	292	221
Augment-buproprion	506	475	431	387	352	305	247
Augment-aripiprazole	505	467	427	383	341	307	245

511	395	294	218	173	141	77
506	386	292	223	174	124	79
505	357	272	198	149	116	72

Mohamed S et al. JAMA 2017;318(2):132-45.

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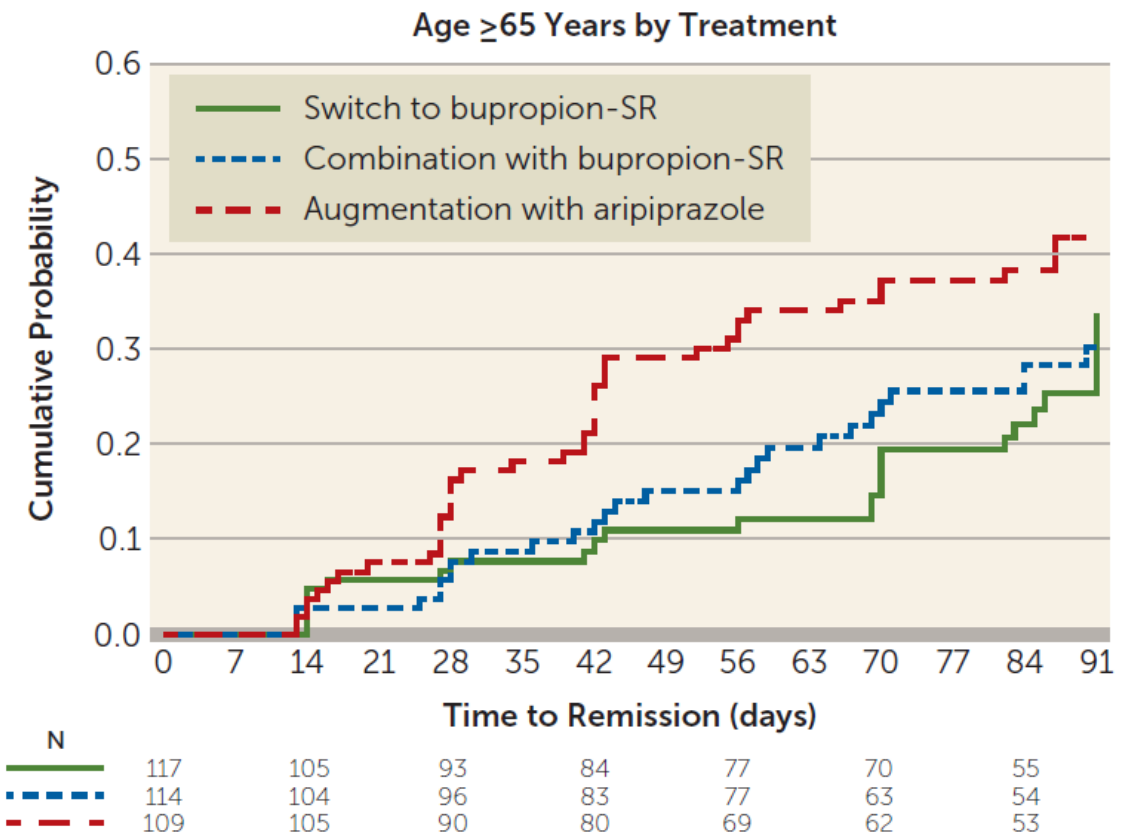
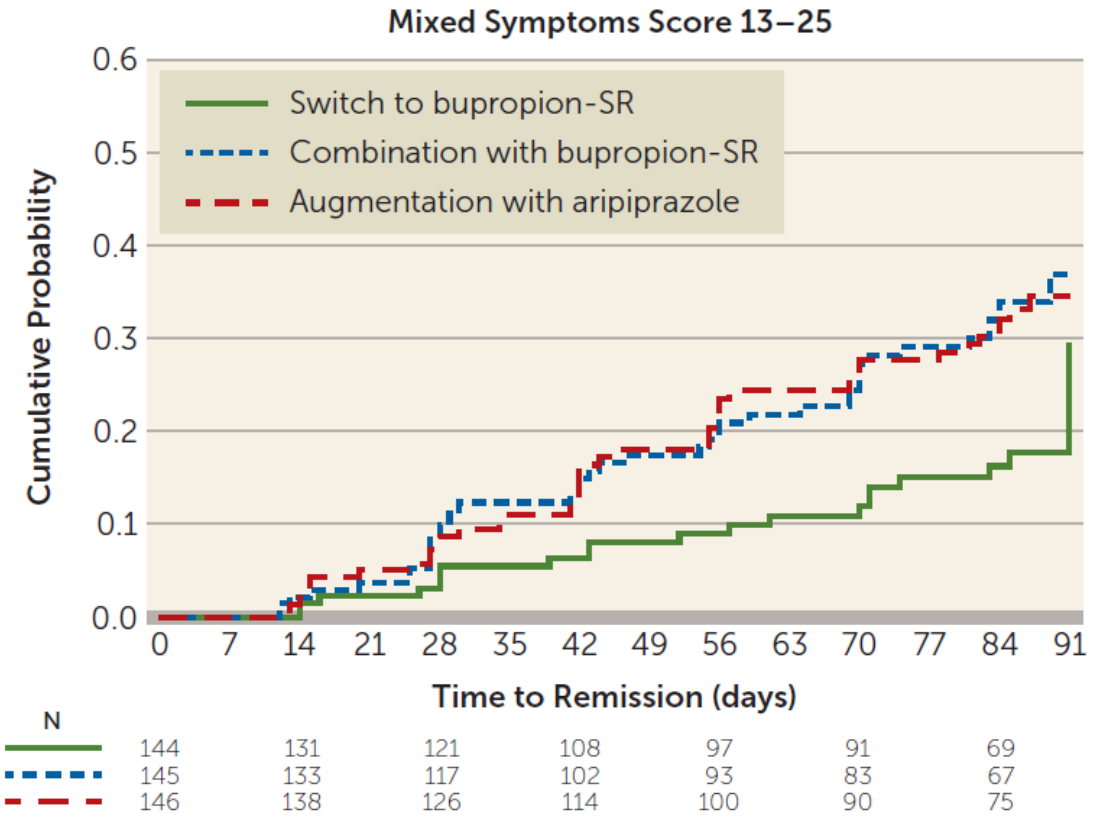
Moderators of Depression Remission in Patients Without Adequate Response to At Least One Antidepressant

Higher Remission Rates With Aripiprazole Augmentation Among Those Age 65 Years or Older



Lower Remission Rates With Switch to Bupropion-SR Among Those Endorsing the Greatest Levels of Mixed Symptoms



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Zisook S et al. Am J Psychiatry 2019;176(5):348-57.

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Use of Low-Dose Quetiapine Increases the Risk of Major Adverse Cardiovascular Events: Results From a Nationwide Active Comparator-Controlled Cohort Study

Risk of major adverse cardiovascular events and secondary outcomes with use of low-dose quetiapine (QUE) compared to use of Z-drugs (ZDR)

	N. patients QUE/ZDR	N. events QUE/ZDR	Follow-up QUE/ZDR	Hazard ratio (95% CI)	p
Major adverse cardiovascular events					
Intention-to-treat analysis (adjusted)	22,827/131,582	877/11,464	73/817	1.13 (1.02-1.24)	0.014
As-treated analysis (adjusted)	60,564/454,552	850/5,513	59/272	1.11 (1.00-1.24)	0.046
As-treated analysis (fully adjusted)	60,564/454,552	850/5,513	59/272	1.52 (1.35-1.70)	<0.001
Non-fatal myocardial infarction					
Intention-to-treat analysis (adjusted)	22,828/131,588	138/2,895	74/829	0.91 (0.73-1.14)	0.42
As-treated analysis (adjusted)	60,564/454,552	109/1,307	59/273	0.69 (0.52-0.90)	0.007
As-treated analysis (fully adjusted)	60,564/454,552	109/1,307	59/273	0.91 (0.69-1.21)	0.53
Non-fatal ischemic stroke					
Intention-to-treat analysis (adjusted)	22,827/131,586	267/4,378	74/825	0.98 (0.83-1.15)	0.81
As-treated analysis (adjusted)	60,564/454,552	256/1,920	59/273	1.01 (0.83-1.21)	0.95
As-treated analysis (fully adjusted)	60,564/454,552	256/1,920	59/273	1.37 (1.13-1.68)	0.002
Death from cardiovascular causes					
Intention-to-treat analysis (adjusted)	22,828/131,593	565/6,262	74/837	1.26 (1.11-1.43)	<0.001
As-treated analysis (adjusted)	60,564/454,552	558/2,903	59/274	1.37 (1.20-1.56)	<0.001
As-treated analysis (fully adjusted)	60,564/454,552	558/2,903	59/274	1.90 (1.64-2.19)	<0.001

Follow-up in 1,000 person-years. The intention-to-treat analysis is adjusted for baseline confounding by fine stratification weights. The as-treated analysis is adjusted for baseline confounding by inverse probability of treatment weights, or fully adjusted by inverse probability of treatment weights and informative censoring by inverse probability of censoring weights.

Højlund M, et al. World Psychiatry. 2022 Oct;21(3):444-451.

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International Guidance on the Evidence and Implementation of Esketamine

Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation

Roger S. McIntyre, M.D., Joshua D. Rosenblat, M.D., M.Sc., Charles B. Nemeroff, M.D., Ph.D., Gerard Sanacora, M.D., Ph.D., James W. Murrough, M.D., Ph.D., Michael Berk, Ph.D., M.B.B.Ch., Elisa Brietzke, M.D., Ph.D., Seetal Dodd, Ph.D., Philip Gorwood, M.D., Ph.D., Roger Ho, M.D., M.B.B.S., Dan V. Iosifescu, M.D., Carlos Lopez Jaramillo, M.D., Ph.D., Siegfried Kasper, M.D., Kevin Kratiuk, B.Pharm., Jung Goo Lee, M.D., Ph.D., Yena Lee, H.B.Sc., Leanna M.W. Lui, Rodrigo B. Mansur, M.D., Ph.D., George I. Papakostas, M.D., Mehala Subramaniapillai, M.Sc., Michael Thase, M.D., Eduard Vieta, M.D., Ph.D., Allan H. Young, M.Phil., M.B.Ch.B., Carlos A. Zarate, Jr., M.D., Stephen Stahl, M.D., Ph.D.

Replicated international studies have underscored the human and societal costs associated with major depressive disorder. Despite the proven efficacy of monoamine-based antidepressants in major depression, the majority of treated individuals fail to achieve full syndromal and functional recovery with the index and subsequent pharmacological treatments. Ketamine and esketamine represent pharmacologically novel treatment avenues for adults with treatment-resistant depression. In addition to providing hope to affected persons, these agents represent the first non-monoaminergic agents with proven rapid-onset efficacy in major depressive disorder. Nevertheless, concerns remain about the safety and tolerability of ketamine and esketamine in mood disorders. Moreover, there is uncertainty about the appropriate position of these agents in treatment algorithms, their comparative effectiveness, and the appropriate setting, infrastructure, and personnel required for its competent and safe implementation. In this article, an international group of mood disorder experts provides a synthesis of the literature with respect to the efficacy, safety, and tolerability of ketamine and esketamine in adults with treatment-resistant depression. The authors also provide guidance for the implementation of these agents in clinical practice, with particular attention to practice parameters at point of care. Areas of consensus and future research vistas are discussed.

Am J Psychiatry 2021; 00:1–17; doi: 10.1176/appi.ajp.2020.20081251

Novel Glutamatergic Modulators for the Treatment of Mood Disorders: Current Status

Broad glutamatergic modulators

- **(R,S)-ketamine**
- **Esketamine**
- (R)-ketamine
- (2R,6R)-hydroxynorketamine
- Dextromethorphan (DXM)
- Nuedexta (DXM/quinidine)
  Deudextromethorphan (AVP-786)
- **Axsome (AXS-05)**
- **Dextromethadone (REL-1017)**
- Nitrous oxide
- AZD6765
- CLE100
- AGN-241751

Subunit (NR2B)-specific N-methyl-d-aspartate (NMDA) receptor antagonists

- Eliprodil (EVT-101)
- Traxoprodil (CP-101,606)
- Rislenemdaz (MK-0657/CERC-301)

Glycine site modulators

- D-cycloserine (DCS)
- NRX-101, rapastinel (GLYX-13)
- Apimostinel (NRX-1074)
- Sarcosine
- 4-Chlorokynurenine (4-Cl-KYN/AV-101)

Metabotropic glutamate receptor (mGluR) modulators

- Basimglurant
- AZD2066
- RG1578
- TS-161

Mammalian target of rapamycin complex (mTORC1) activators

- NV-5138

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Henter ID et al. CNS Drugs 2021;35(5):527-43.

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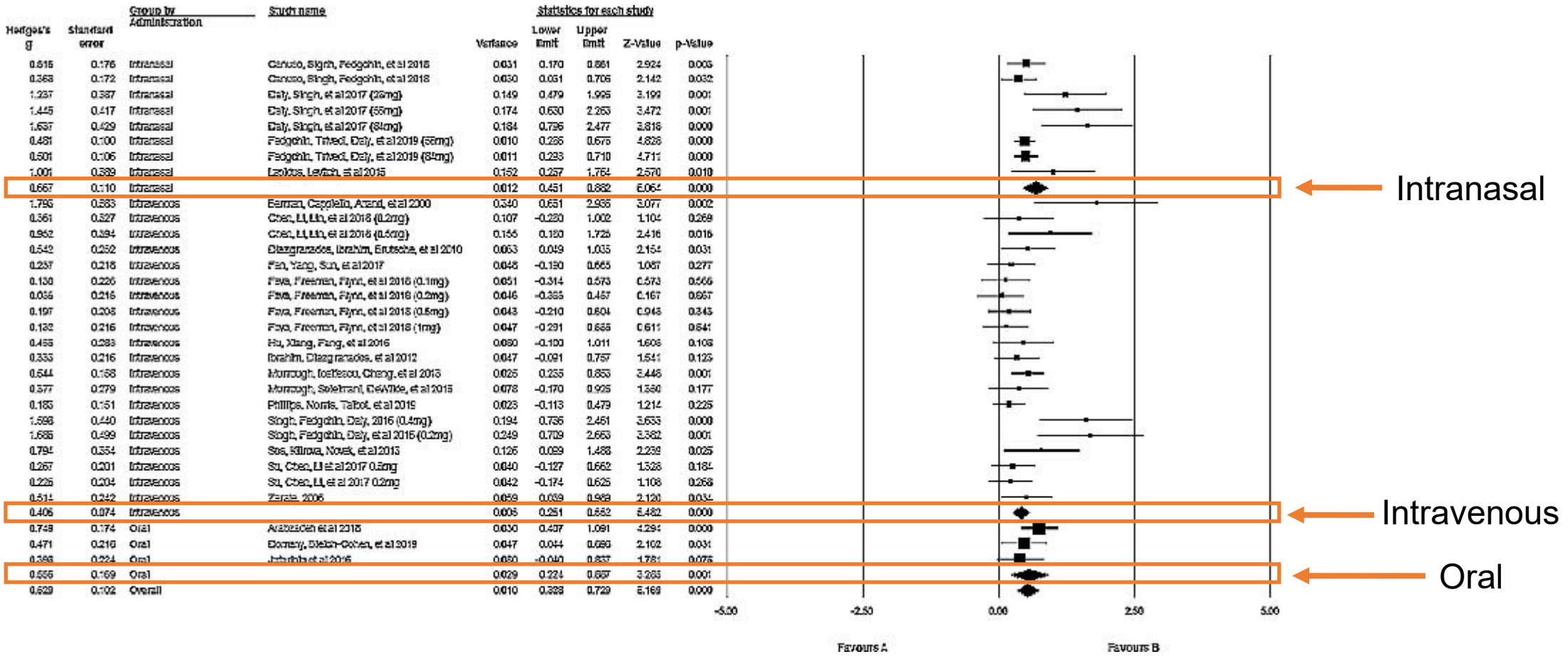
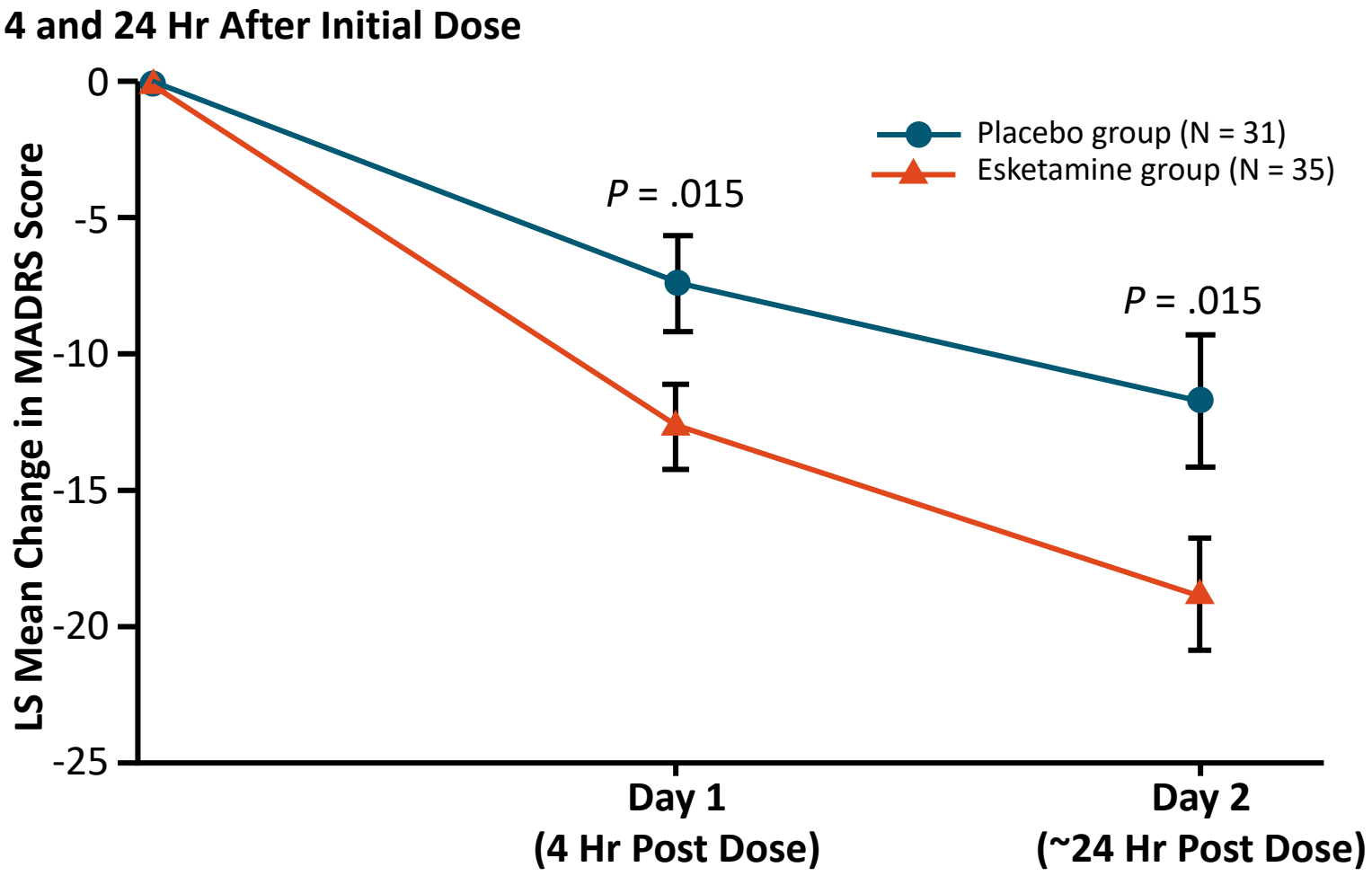
Efficacy of Intravenous, Intranasal and Oral Ketamine in Adults With TRD



McIntyre RS et al. J Affect Disord 2020;276:576-85.

Esketamine for MDD With Active Suicidal Ideation and Intent: MDD Improvement at 4- and 24-Hr Post Dose



Esketamine significantly improved symptoms as little as 4 hr post dose; effects continued at 24 hr

Canuso et al. Am J Psychiatry. 2018;175:620.

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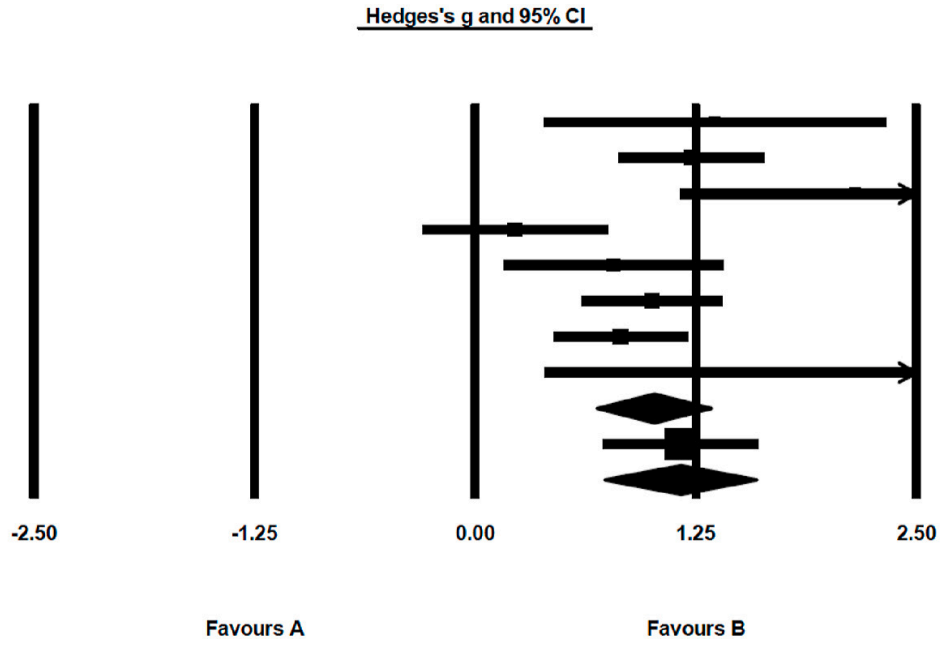
The Acute Antisuicidal Effects of Single-Dose Intravenous Ketamine and Intranasal Esketamine in Individuals With Major Depression and Bipolar Disorders: A Systematic Review and Meta-analysis

Group by Subgroup within study	Study name	Control	Time point	Statistics for each study						
				Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
0.5mg/kg IV racemic ketamine	Grunebaum, M.F., 2017	Midazolam	Combined	1.361	0.491	0.241	0.399	2.323	2.773	0.006
0.5mg/kg IV racemic ketamine	Grunebaum, M.F., 2018	Midazolam	Combined	1.228	0.207	0.043	0.822	1.634	5.924	0.000
0.5mg/kg IV racemic ketamine	Hu, Y.D., 2016	Saline	Combined	2.155	0.502	0.252	1.172	3.139	4.294	0.000
0.5mg/kg IV racemic ketamine	Ionescu, D.F., 2019	Saline	230min/4h	0.227	0.263	0.069	-0.289	0.744	0.862	0.388
0.5mg/kg IV racemic ketamine	Murrough, J.W., 2015	Midazolam	24h	0.786	0.313	0.098	0.173	1.399	2.512	0.012
0.5mg/kg IV racemic ketamine	Phillips, J.L., 2020	Midazolam	Combined	1.004	0.199	0.040	0.613	1.394	5.033	0.000
0.5mg/kg IV racemic ketamine	Price, R.B., 2014	Midazolam	24h	0.826	0.190	0.036	0.454	1.198	4.349	0.000
0.5mg/kg IV racemic ketamine	Sinyor, M., 2018	Midazolam	2h	1.634	0.628	0.395	0.402	2.866	2.600	0.009
0.5mg/kg IV racemic ketamine				1.015	0.166	0.027	0.691	1.340	6.126	0.000
84mg esketamine	Canuso, C.M., 2018	Saline	Combined	1.166	0.220	0.048	0.735	1.597	5.302	0.000
84mg esketamine				1.166	0.220	0.048	0.735	1.597	5.302	0.000



The forest plot for all studies included, grouped by administration. Squares plot effect size of individual studies, diamonds plots summary measures of each formulations and overall findings. **Favours A (Placebo); Favours B (Es/ketamine).**

Xiong J et al. J Psychiatr Res 2021;134:57-68.

Psychopharmacology
https://doi.org/10.1007/s00213-022-06105-9

REVIEW

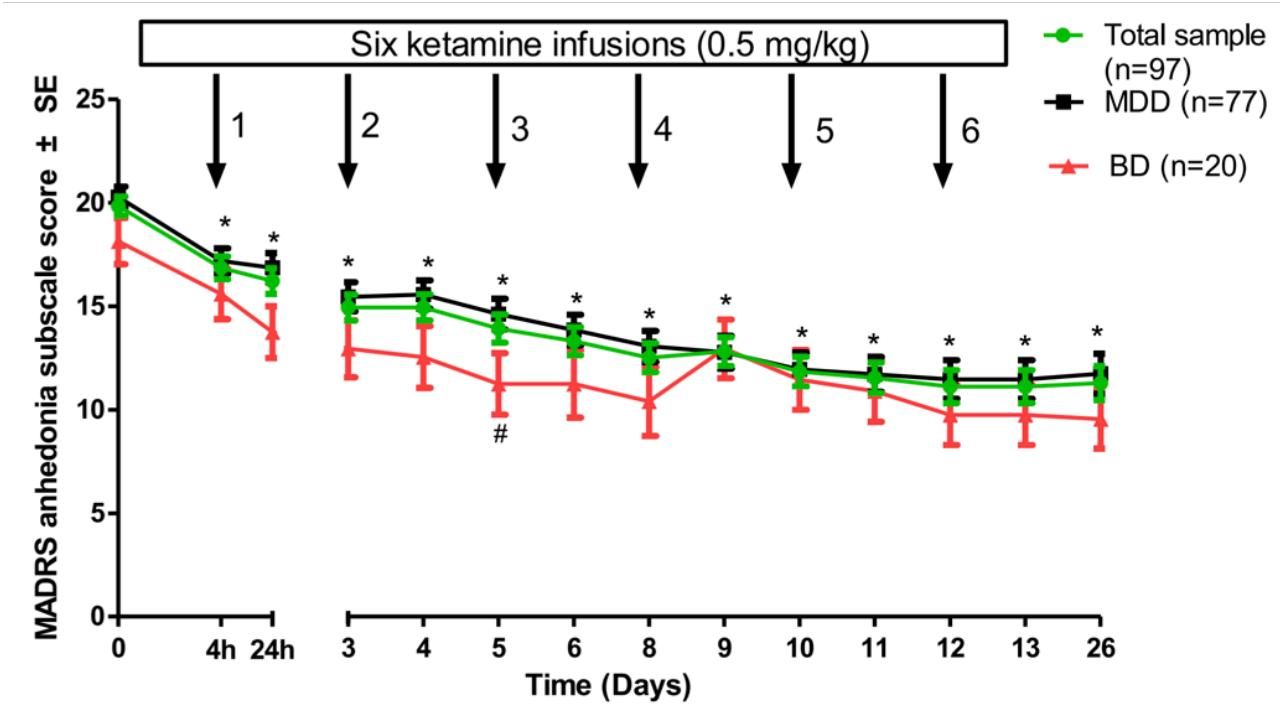
The effect of ketamine on anhedonia: improvements in dimensions of anticipatory, consummatory, and motivation-related reward deficits

Danica Nogo[1] · Ashitija K. Jasrai[1,2] · Haeun Kim[1,2] · Flora Nasri[1] · Felicia Ceban[1] · Leanna M. W. Lui[1] · Joshua D. Rosenblat[1] · Maj Vinberg[3,4] · Roger Ho[5,6] · Roger S. McIntyre[1,2]

Received: 22 August 2021 / Accepted: 23 February 2022

Comparative Effectiveness of Repeated Ketamine Infusions in Treating Anhedonia in Bipolar and Unipolar Depression

Change in MADRS anhedonia subscale score of patients with MDD and BD following six ketamine infusions



Abbreviations: BD=bipolar depression; MDD=major depressive disorder; MADRS= Montgomery–Åsberg Depression Rating Scale; SE=standard error.

Zheng W, et al. J Affect Disord. 2022 Mar;300:109-113.

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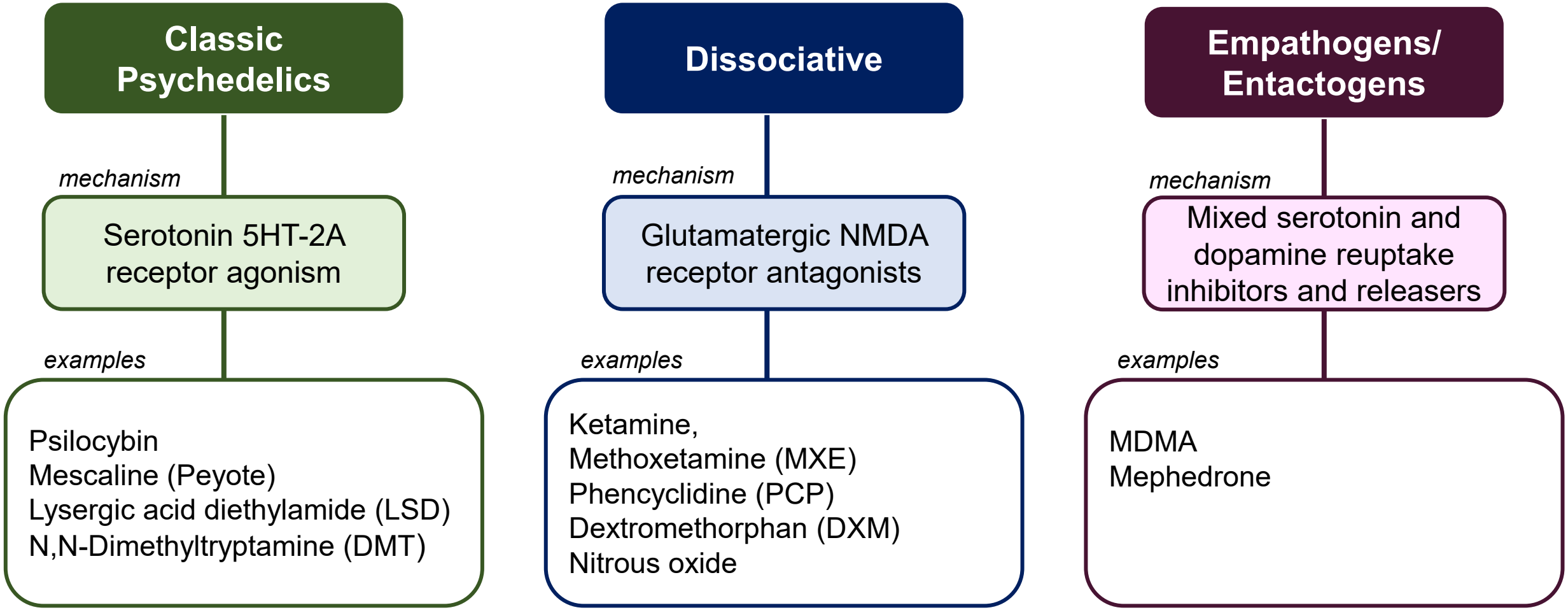
Hallucinogens



Reiff CM et al. Am J Psychiatry 2020;177(5):391-410.

Psychedelics: Definition and Classification

Do not cause physical addiction, craving, delirium...
Produce thought, mood, and perceptual changes
Experiences similar to dreams, religious experiences, or acute psychosis

Adapted from Grinspoon and Bakalar 1979.

Tryptamine Derivatives

- LSD
- Psilocybin
- DMT - active in ayahuasca

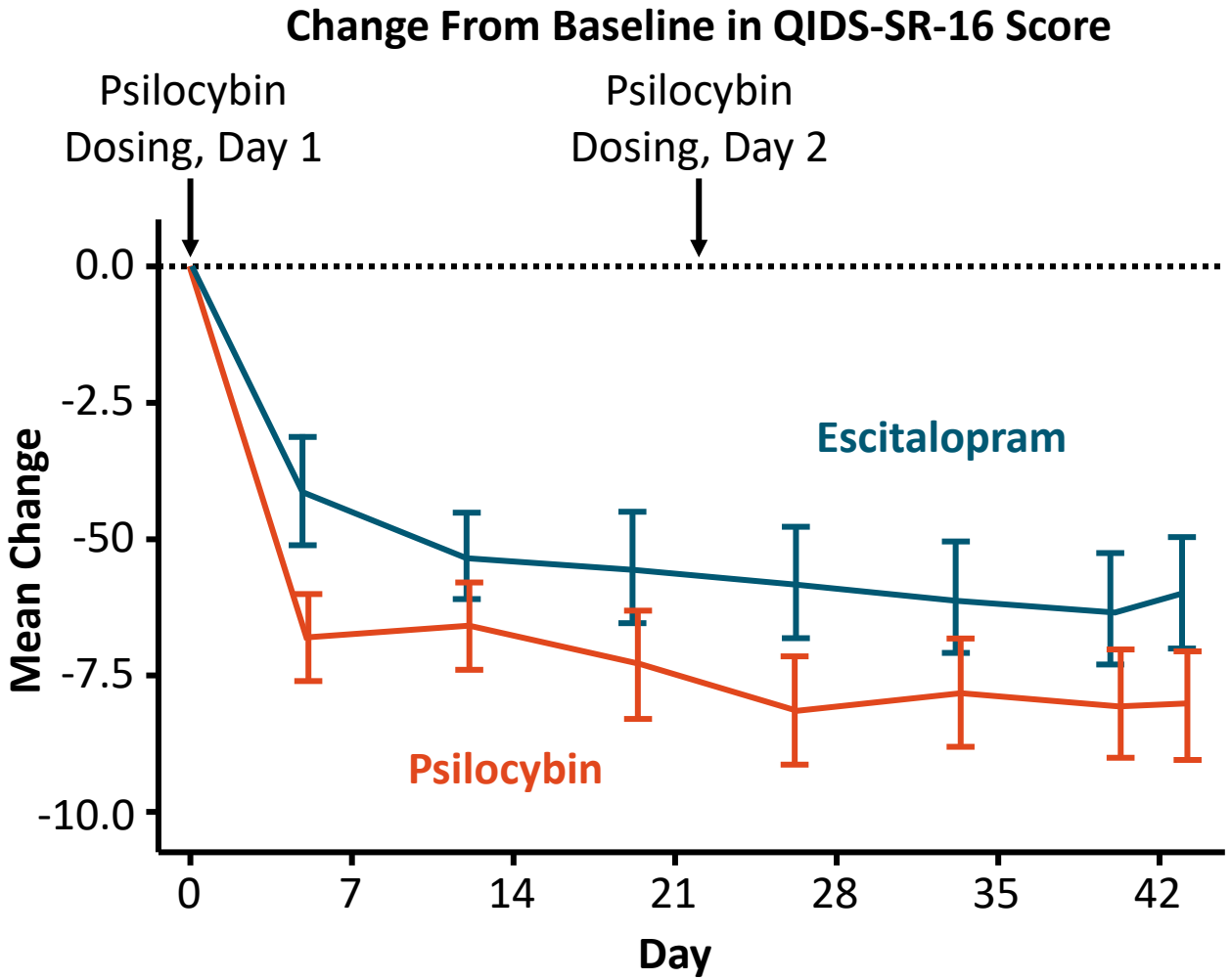
Phenylethylamines

- Mescaline - main psychoactive agent in peyote
- MDMA

Grinspoon et al. Psychedelic Drugs Reconsidered. 1979. Johnson et al. Pharmacol Ther. 2019;197:83.

Slide credit: clinicaloptions.com

Psilocybin vs Escitalopram for Depression

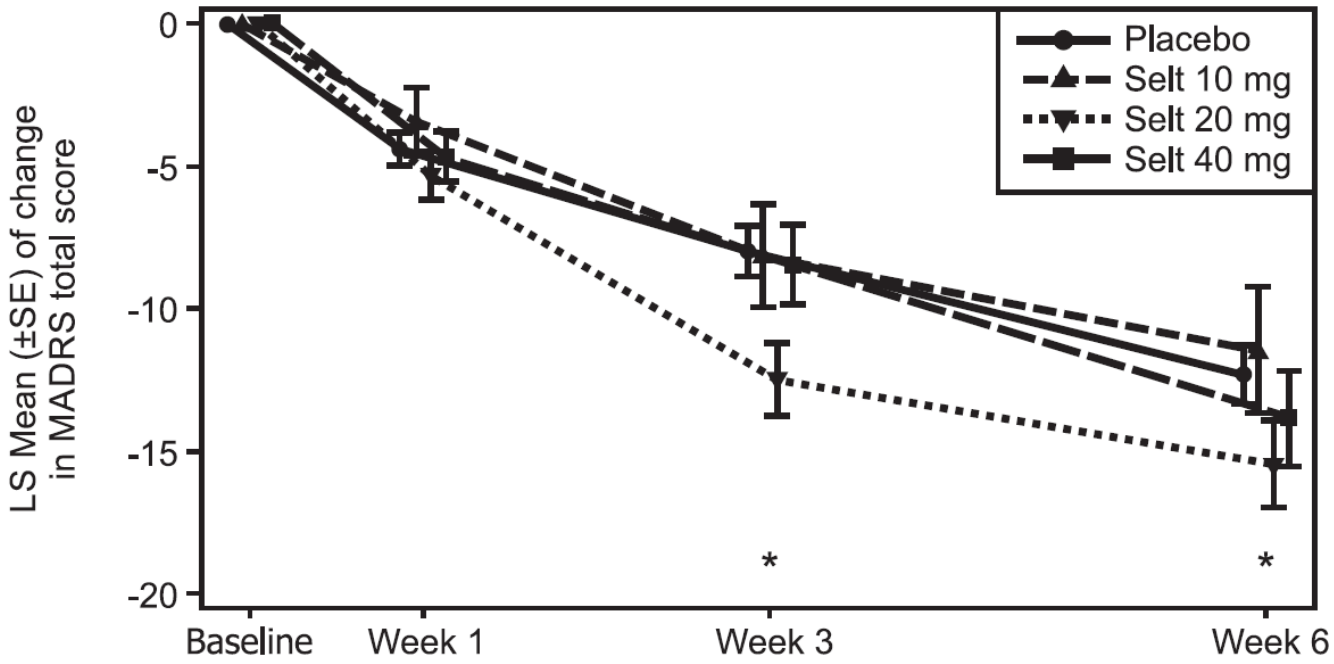


Psilocybin vs Escitalopram for Depression		
N=59 adults with moderate to severe MDD	Psilocybin (two 25 mg doses 3 wk apart) + placebo (microcrystalline cellulose) n = 30	Escitalopram (10 mg daily [3 wk], then 20 mg [3 wk]) + placebo (psilocybin, 1 mg dose 3 wk apart) n = 29
Change in QIDS-SR-16 depressive symptom score at 6 wk (range, 0-27; higher score = greater depression)	-8.0±1.0	-6.0±1.0
	Difference, -2.0 points (95% CI: -5.0 to 0.9)	
Overall incidence of adverse events was similar in the 2 groups.		
No significant difference between psilocybin and escitalopram in QIDS-SR-16 score change from baseline.		

Carhart-Harris et al. NEJM. 2021;384:1402.

Slide credit: clinicaloptions.com

Seltorexant (MIN-202), a Selective Orexin-2 Receptor Antagonist, Shows Antidepressant Effect



No. of Patients (LS mean [SE]):				
Placebo	137	136 (-4.4 [0.59])	133 (-8.0 [0.86])	124 (-12.3 [1.03])
Selt 10 mg	33	30 (-3.4 [1.21])	29 (-8.1 [1.80])	26 (-11.5 [2.20])
Selt 20 mg	61	60 (-5.3 [0.84])	58 (-12.5 [1.26])	55 (-15.5 [1.53])
Selt 40 mg	52	51 (-4.7 [0.92])	49 (-8.5 [1.38])	47 (-13.8 [1.66])

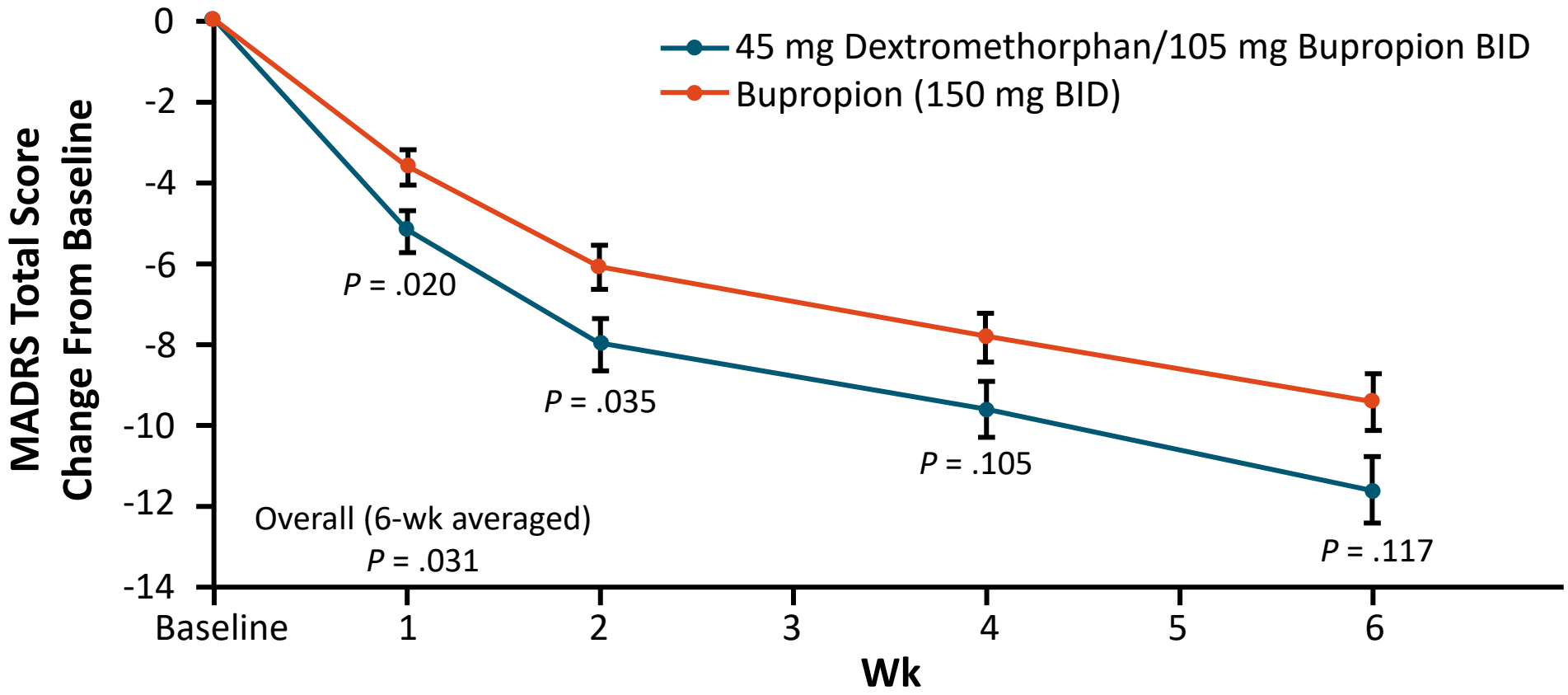
*seltorexant 20 mg vs placebo p<.10
N=283

LS: least squares
MADRS: Montgomery-Åsberg Depression Rating Scale
SE: standard error

Improvement in MADRS score at Week 6 for seltorexant 20 mg was greater in patients with baseline insomnia

Savitz A et al. Int J Neuropsychopharmacol 2021;24(12):965-76.

Dextromethorphan 45 mg/Bupropion 210 mg vs Bupropion 300 mg vs Placebo



- Wk 1 CGI-I: separated; *P* = .045
- Wk 6 MADRS remission: 47% vs 16%; *P* = .0004

ASCP 2019. Poster.

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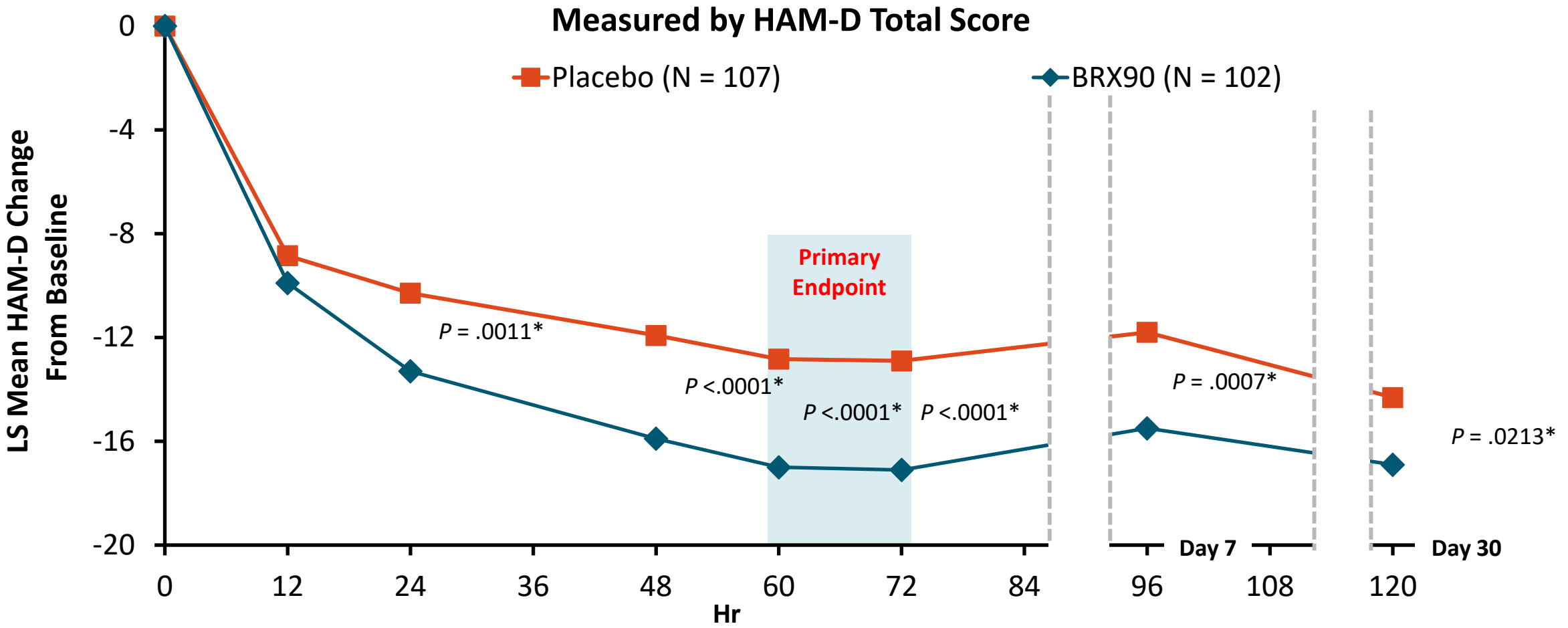
Brexanolone Injection Antidepressant Effects vs Placebo



*LS mean difference in change from baseline of HAM-D total score with brexanolone injection vs placebo. Mixed effect model for repeat measures included study, pooled center, treatment, baseline antidepressant use, visit time point, and treatment-by-visit time point interaction terms as fixed effects and baseline total score as a covariate.

Meltzer-Brody et al. Lancet. 2018;392:1058.

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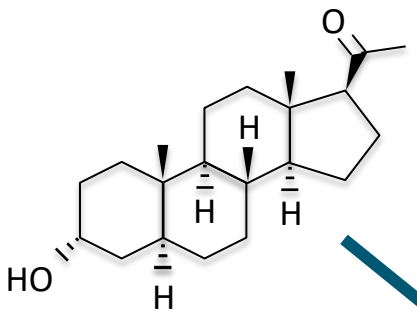
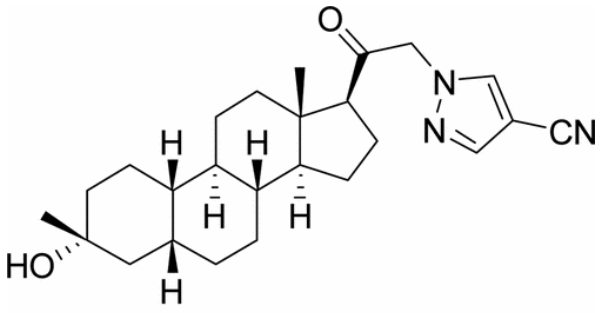
Zuranolone

Brexanolone

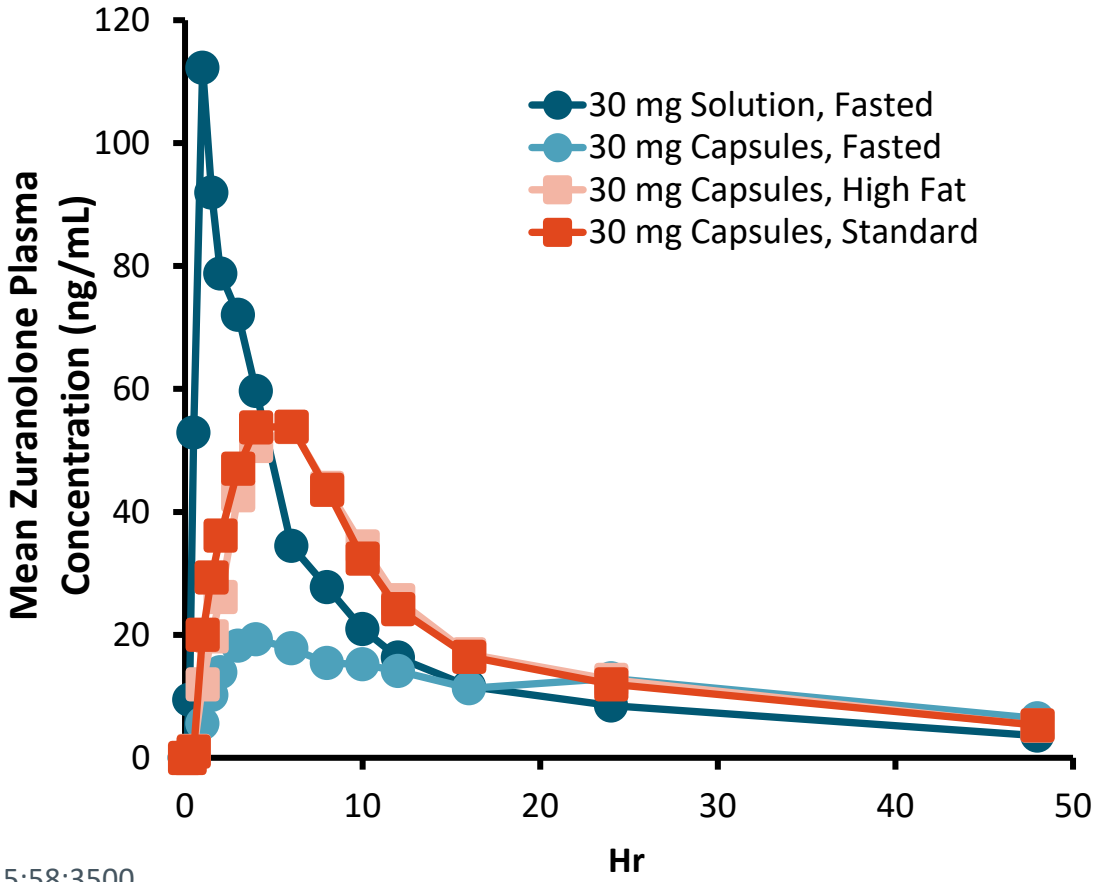


Improvement in practical applications: addition of cyanopyrazole ring[1-3]

Zuranolone



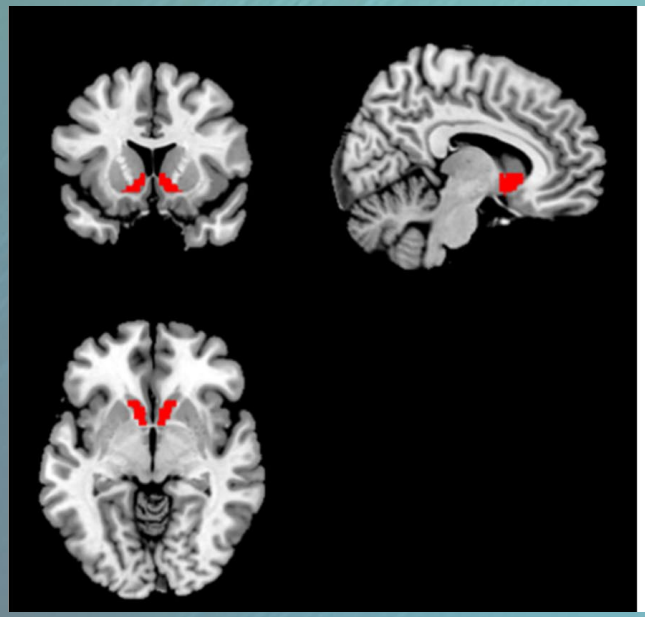
Zuranolone Plasma Concentration Over Time[4]

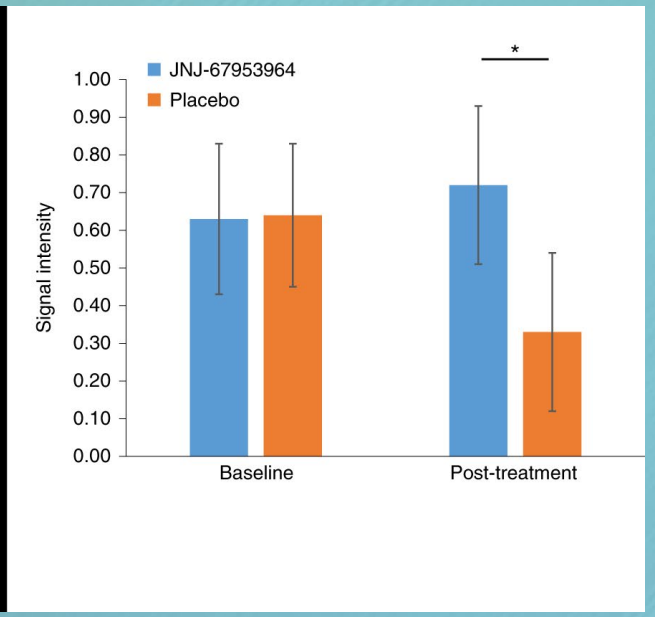


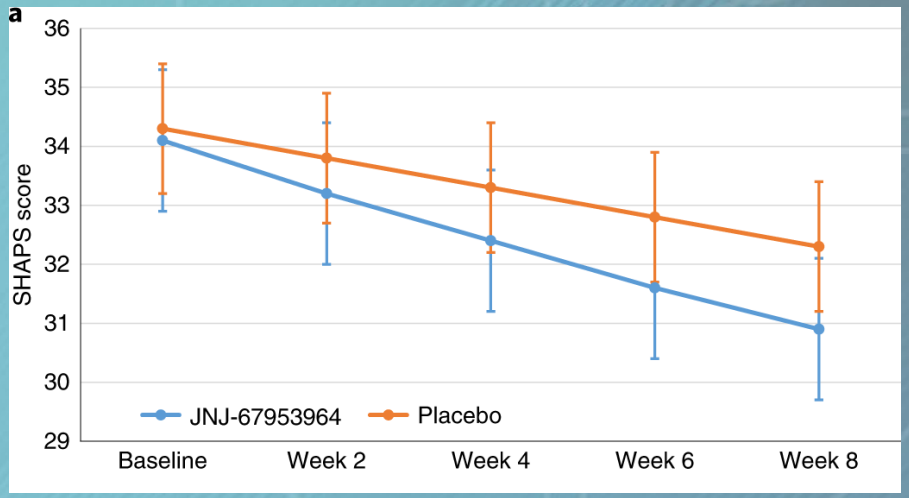
1. Hoffmann et al. Clin Pharmacokinet. 2020;59:111. 2. Martinez Botella et al. J Med Chem. 2015;58:3500.
3. Martinez Botella et al. J Med Chem. 2017;60:7810. 4. Hoffmann et al. ASCPT. 2018.

Aticaprant, Kappa Opioid Receptor Antagonist, Studied as Adjunct for TRD

- Ongoing phase 3 clinical trial (VENTURA-1) investigating aticaprant as augmentation to antidepressant therapy for TRD in patients with moderate-to-severe anhedonia
- Phase 2a study found increased ventral striatum neural activation during reward anticipation and reduced anhedonia (SHAPS) with aticaprant treatment (JNJ-67953964)

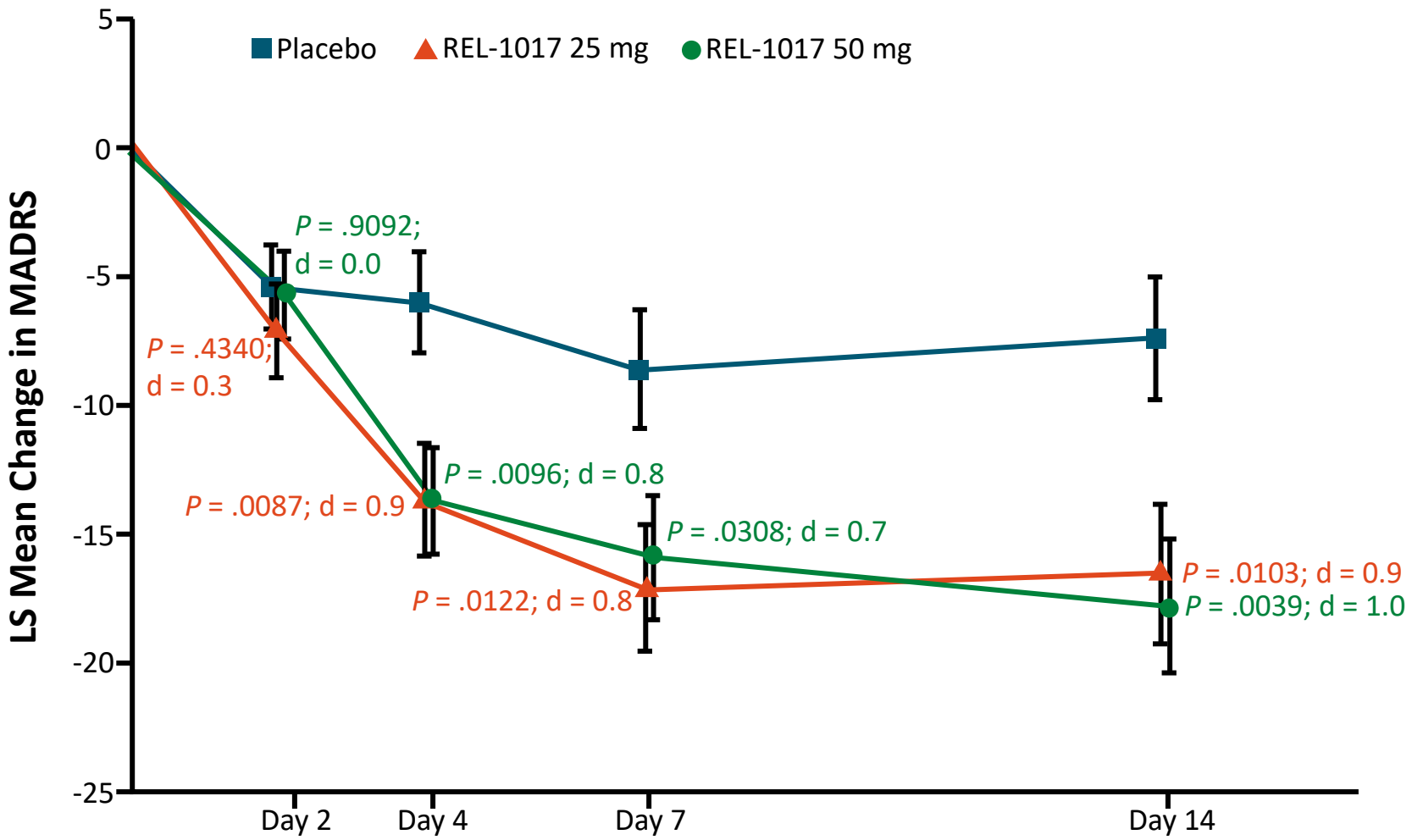






https://www.clinicaltrials.gov/ct2/show/NCT05455684; Krystal AD et al. Nat Med 2020;26(5):760-8.

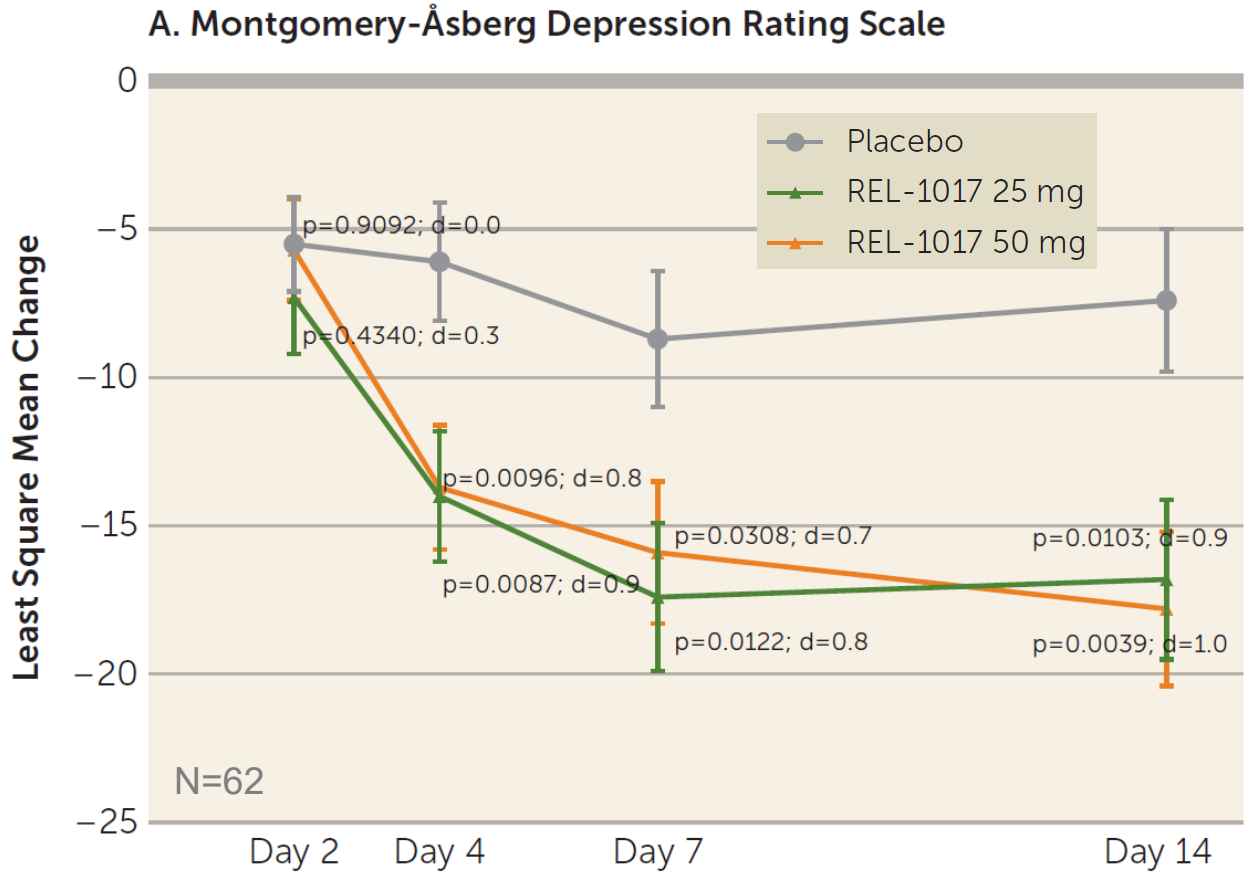
Rel-1017: Adjunctive Treatment for MDD



- REL-1017: "esmethadone"
- NMDAR antagonist
- Significantly increased plasma levels of BDNF with effects on neural plasticity

De Martin, et al. 2021 *Front. Pharmacol.* 12:671859. Pappagallo M. American Society of Clinical Psychopharmacology, June 1, 2021

Efficacy and Safety of REL-1017 (Esmethadone) as Adjunctive Treatment in MDD: A Phase 2a Randomized Double-Blind Trial



- The most common treatment-emergent adverse events that occurred in at least 5% of all patients were headache, constipation, nausea, and somnolence
- No evidence of dissociative or psychotomimetic effects, opioid effects, or withdrawal signs and symptoms

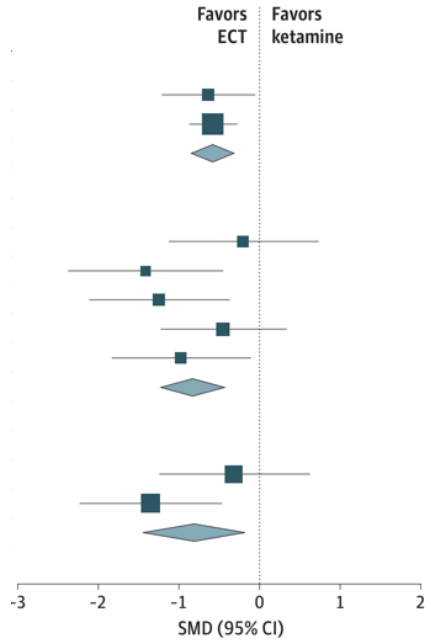
Fava M et al. Am J Psychiatry 2022;179(2):122-31.

Goodwin et al NEJM 2022

Efficacy and Safety of Ketamine vs Electroconvulsive Therapy Among Patients With Major Depressive Episode A Systematic Review and Meta-analysis

Severity of Depressive Symptoms Between Electroconvulsive Therapy (ECT) and Ketamine in Patients With Major Depressive Episode

Study	ECT		Ketamine		SMD (95% CI)
	Total	Mean (SD)	Total	Mean (SD)	
MADRS					
Basso et al,[36] 2020	24	-17.420 (7.4900)	25	-13.000 (6.1500)	-0.636 (-1.211 to -0.061)
Ekstrand et al,[37] 2021	91	-22.300 (9.6100)	95	-16.200 (11.3500)	-0.577 (-0.870 to -0.283)
Total (95% CI)	115		120		-0.589 (-0.850 to -0.327)
Heterogeneity: $\tau^2=0$; $\chi^2=0.03$; $df=1$; $P=.86$; $I^2=0\%$					
HDRS					
Ghasemi et al,[38] 2014	9	-21.880 (5.8500)	9	-20.670 (5.4200)	-0.204 (-1.131 to 0.723)
Kheirabadi et al,[39] 2019	12	-12.500 (3.5000)	10	-7.700 (2.9500)	-1.415 (-2.371 to -0.458)
Sharma et al,[41] 2020	13	-21.190 (5.8400)	12	-14.500 (4.3800)	-1.246 (-2.115 to -0.376)
Kheirabadi et al,[40] 2020 (IM)	12	-12.330 (5.0300)	15	-10.140 (4.4400)	-0.451 (-1.221 to 0.319)
Kheirabadi et al,[40] 2020 (oral)	12	-12.330 (5.0300)	12	-8.170 (2.9800)	-0.972 (-1.826 to -0.117)
Total (95% CI)	58		58		-0.832 (-1.221 to -0.444)
Heterogeneity: $\tau^2=0.0475$; $\chi^2=5.1$; $df=4$; $P=.28$; $I^2=22\%$					
BDI					
Ghasemi et al,[38] 2014	9	-26.780 (8.7000)	9	-23.780 (9.5100)	-0.313 (-1.245 to 0.618)
Sharma et al,[41] 2020	13	-30.650 (5.7700)	12	-20.450 (8.6800)	-1.350 (-2.233 to -0.466)
Total (95% CI)	22		21		-0.859 (-1.500 to -0.218)
Heterogeneity: $\tau^2=0.3225$; $\chi^2=2.5$; $df=1$; $P=.11$; $I^2=60\%$					



Rhee TG, et al. JAMA Psychiatry. 2022 Oct 19. Online ahead of Print.

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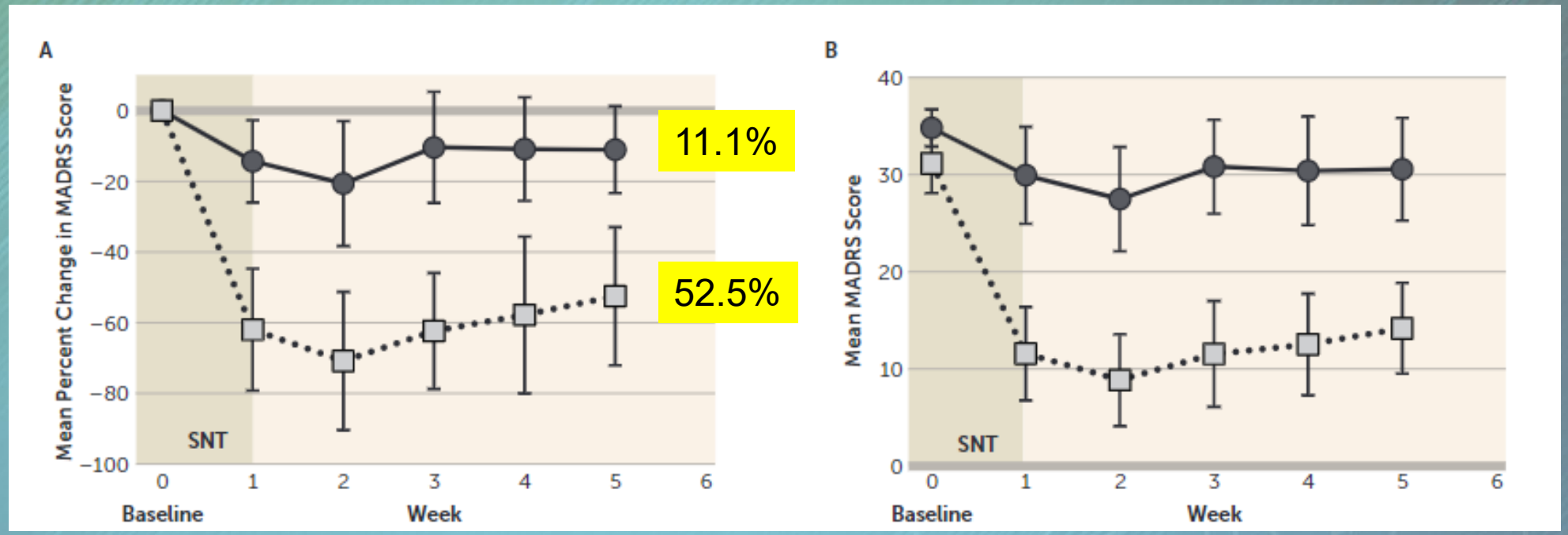
Theta Burst rTMS: Stanford Neuromodulation Therapy Protocol

Effect sizes: 1.7 1.4 1.8 1.5 1.4

10 sessions over 5 days

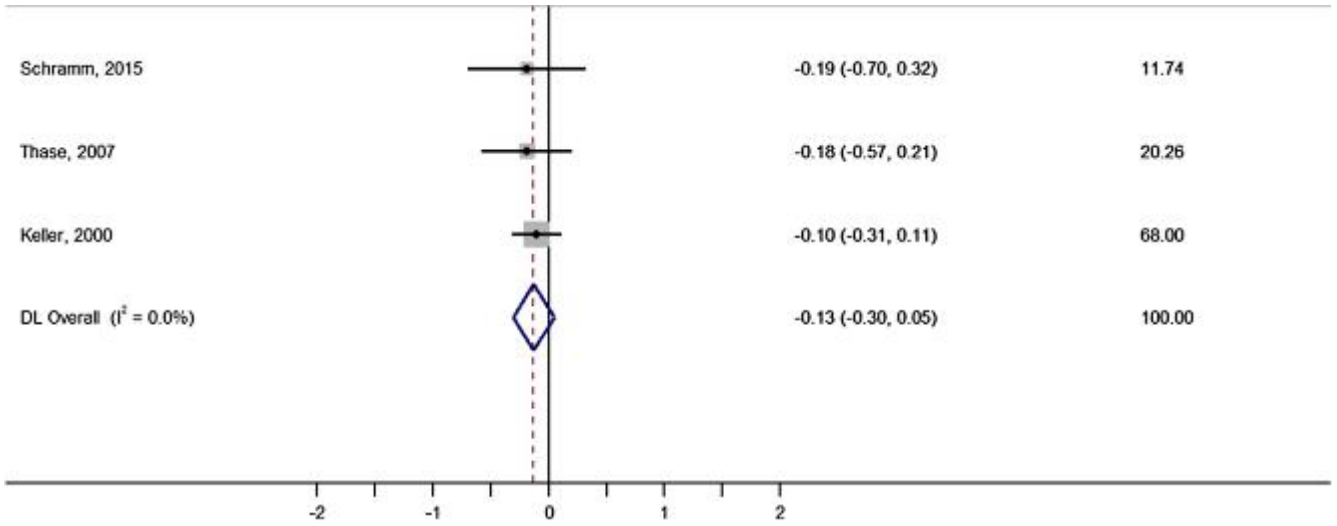
18,000 pulses



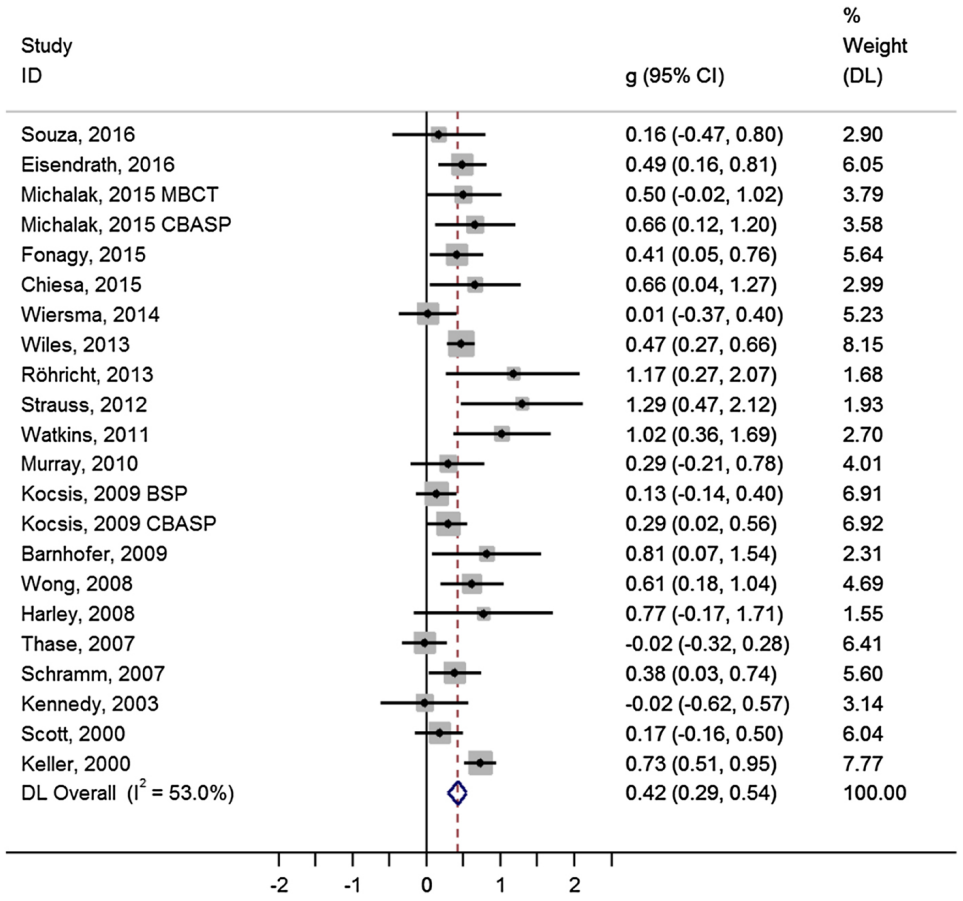
At 4-week follow-up: response = 86%
remission = 79%

Cole EL et al. Am J Psychiatry 2022;179(2):132-41.

Psychotherapy Not Useful on Its Own But Is Useful in Combination for Treating TRD



Psychotherapy alone not superior to TAU,
but effective as adjunct to TAU



TAU; routine treatments such as clinical management and/or the continuation, optimization or next step pharmacotherapy.

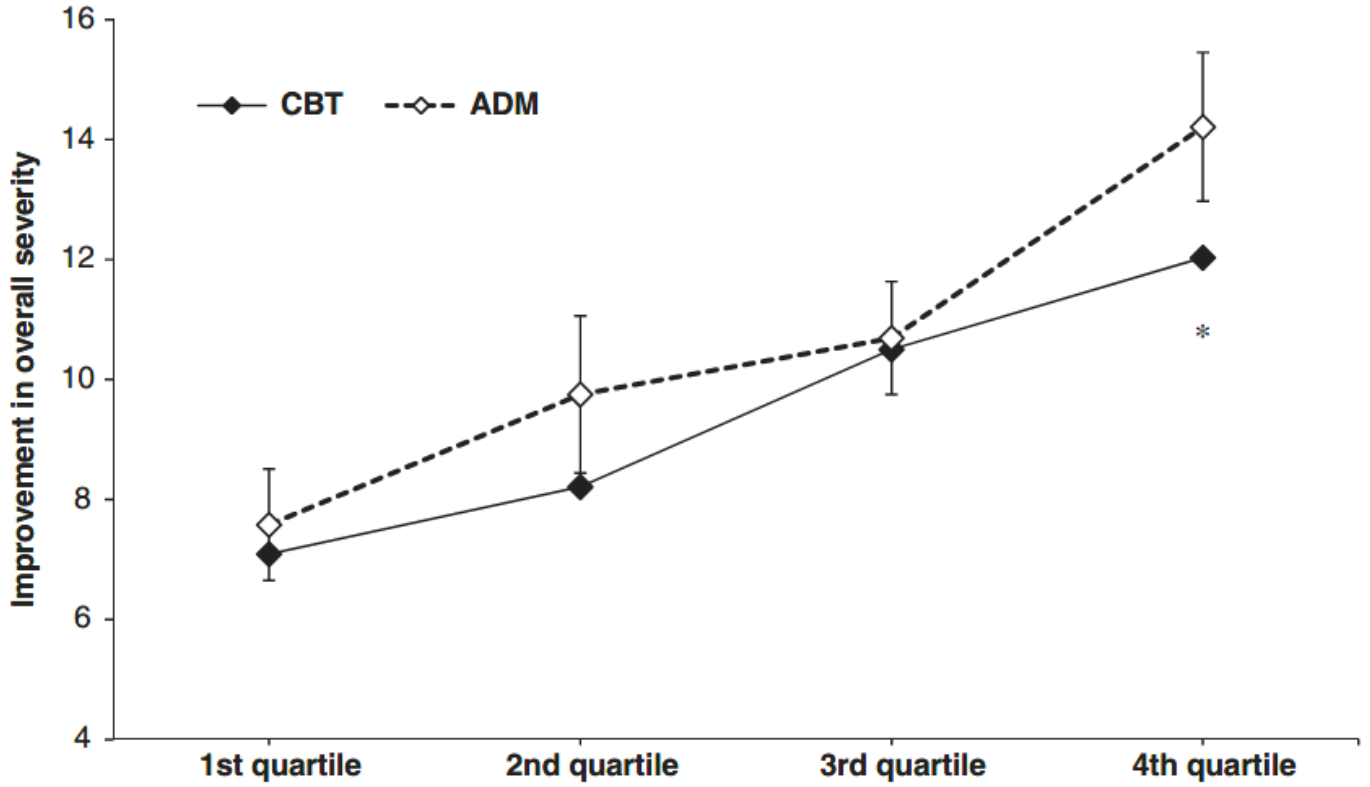
CRTCE

van Bronswijk S et al. Psychol Med 2019;49(3):366-79.

BRAXIA ACADEMY

Brain and Cognition DISCOVERY FOUNDATION

Antidepressants Are More Effective Than Psychotherapy in Targeting Fatigue, Cognitive Impairment, and Motivational Deficits



ADM: antidepressant medication
CBT: cognitive behavioral therapy

Five symptoms (i.e., “depressed mood,” “feelings of guilt,” “suicidal thoughts,” “psychic anxiety,” and “general somatic symptoms”) showed larger improvements in the medication compared to the CBT condition (effect sizes ranging from .13 to .16), whereas no differences were found for the twelve other symptoms.

Boschloo L et al. World Psychiatry 2019;18(2):183-91 .

Treatment Resistant Depression & Bipolar Disorder

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Clinical Professor State University of New York (SUNY) Upstate Medical University, Syracuse, New York, USA
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