AXSOME THERAPEUTICS

Novel Approaches to Address Treatment Resistant Depression: Targeting Multiple Mechanisms of Action

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Treatment-Resistant Depression (TRD)

TRD typically refers to the occurrence of an inadequate response following adequate antidepressant therapy among MDD patients

Table 2. Massachusetts General Hospital (MGH) Staging Method to Classify Treatment-Resistant Depression

(1) Nonresponse to each adequate (at least 6 weeks of an adequate dose of antidepressant) trial of a marketed antidepressant generates an overall score of resistance (1 point per trial)
(2) Optimization of dose, optimization of duration, and augmentation/combination of each trial (based on the MGH or Antidepressant Treatment Response Questionnaire) increase the overall score (.5 point per trial per optimization/strategy)
(3) ECT increases the overall score by 3 points

ECT, electroconvulsive therapy.

Fava, *Biol Psychiatry* 2003;53:649–659.

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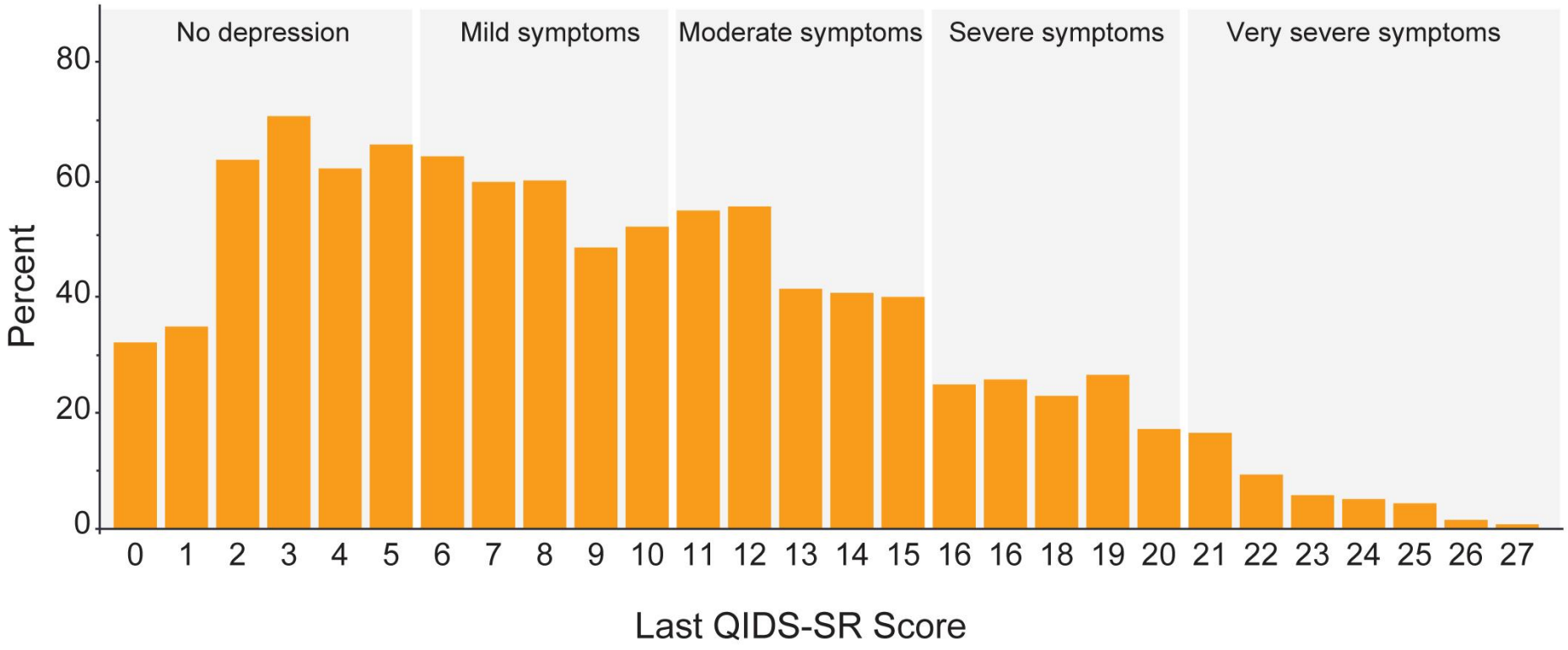
Overall Remission Rate in Level 1of STAR*D is 33% (N=943/2876)

Total exit scores on the 16-item quick inventory of depressive symptomatology, self-report (QIDS-SR), of 2,876 outpatients with nonpsychotic major depressive disorder.



Trivedi et al. *Am J Psychiatry*. 2006;163:28-40.

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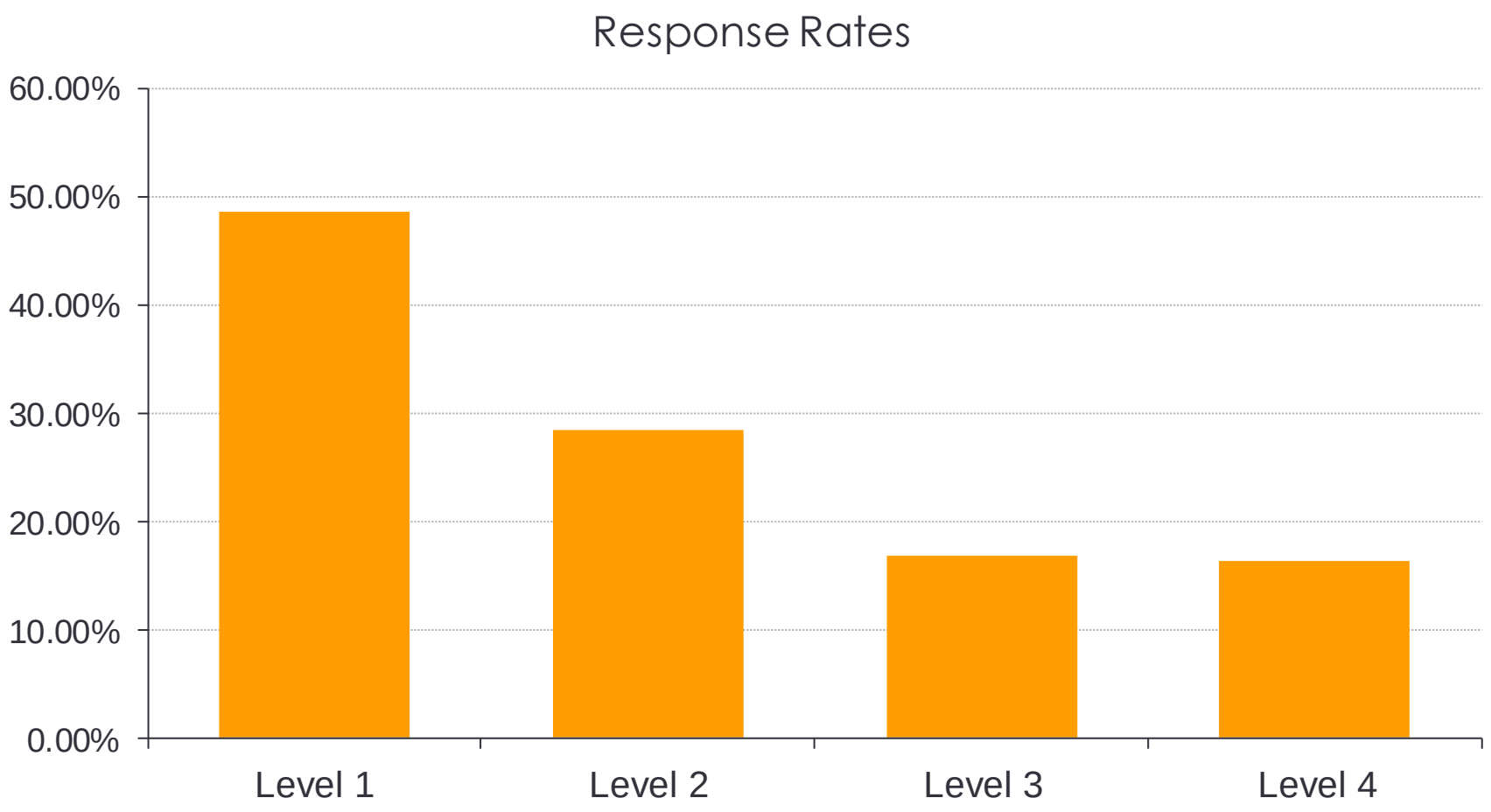
Response Rates to Antidepressant Therapies Across Levels 1-4 in the STAR*D Study



Rush et al, *Am J Psychiatry* 2006; 163:1905–1917.

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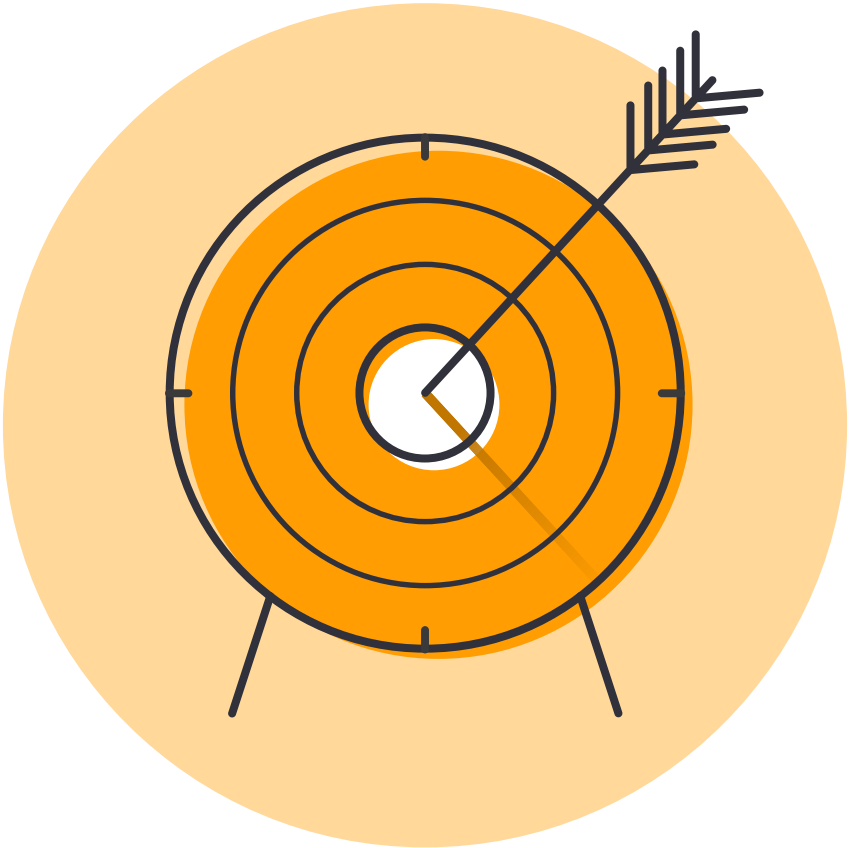
Novel Targets for the Treatment of TRD

- Glutamatergic System
- Inflammatory pathways
- Multiple, simultaneous targets (multimodal drug treatments)



Chang T, Fava M. The future of psychopharmacology of depression. *J Clin Psychiatry*. 2010 Aug;71(8):971-5

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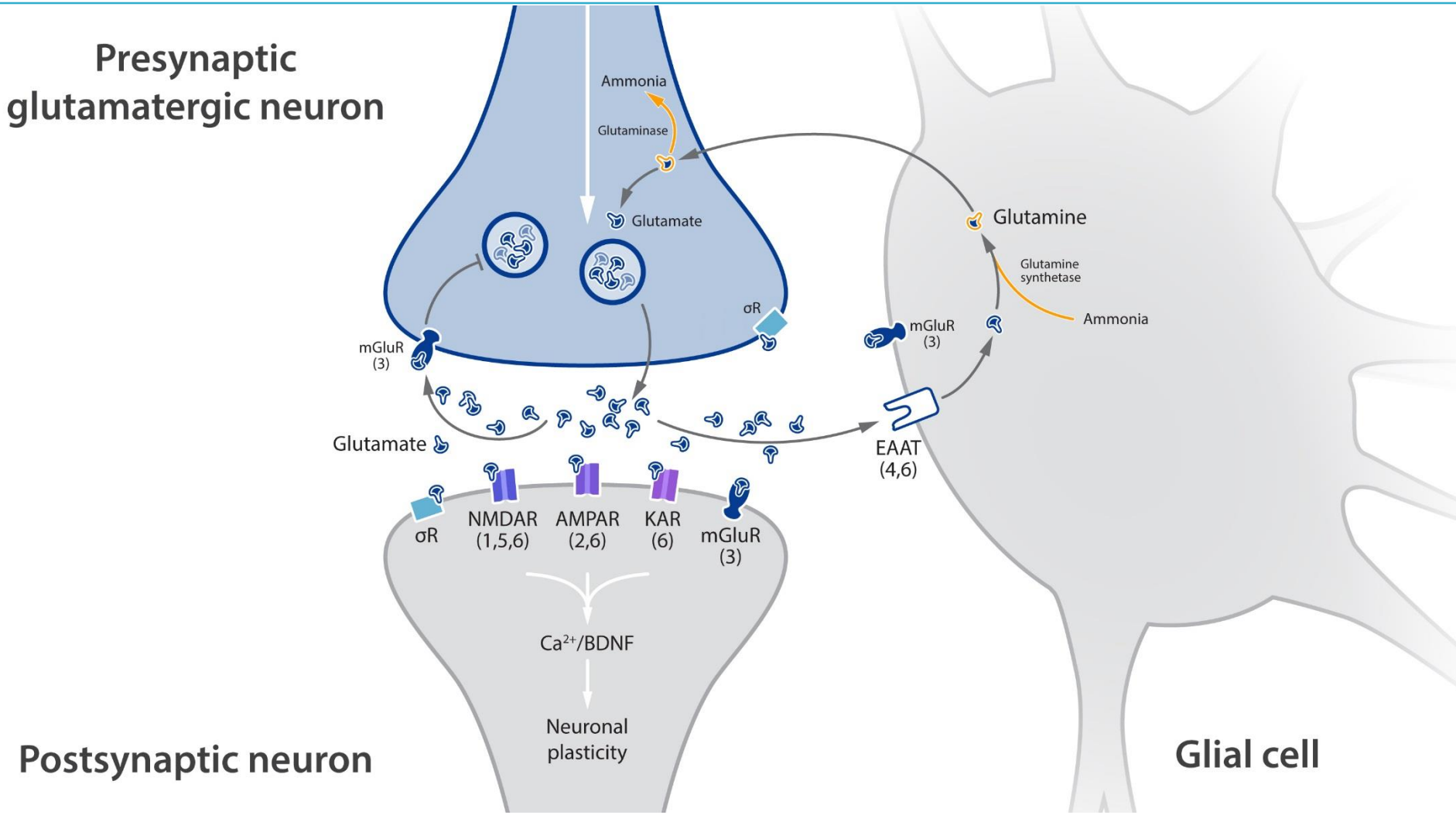
Novel Targets for the Treatment of TRD



Tokita et al, *Pharmacology, Biochemistry and Behavior* 100 (2012) 688–704

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Ketamine's Effects on Glutamatergic System and Inflammation

- Ketamine inhibits the NMDA receptor by two distinct mechanisms:
  - Ketamine blocks the open channel and thereby reduces channel mean open time, and
  - Ketamine decreases the frequency of channel opening by an allosteric mechanism[1]
- Acute administration of ketamine in rats increases hippocampal brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) levels during forced swimming test.[2]
- Ketamine has been showed anti-inflammatory actions in various immune cells, such as macrophages and peripheral leucocytes, stimulated with lipopolysaccharide (LPS) *in vitro* and *in vivo*.[3]

[1] Orser et al, *Anesthesiology*. 1997 Apr;86(4):903-17.
[2] Yang C et al, *Ups J Med Sci*. 2012 Sep 13. [Epub ahead of print])
[3] Takenaka et al, *Anesthesiology* 1994;80:402-408; Shimaoka et al, *Br J Anaesth* 1996;77:238-242; Kawasaki et al, *Anesth Analg* 1999;89:665-669.

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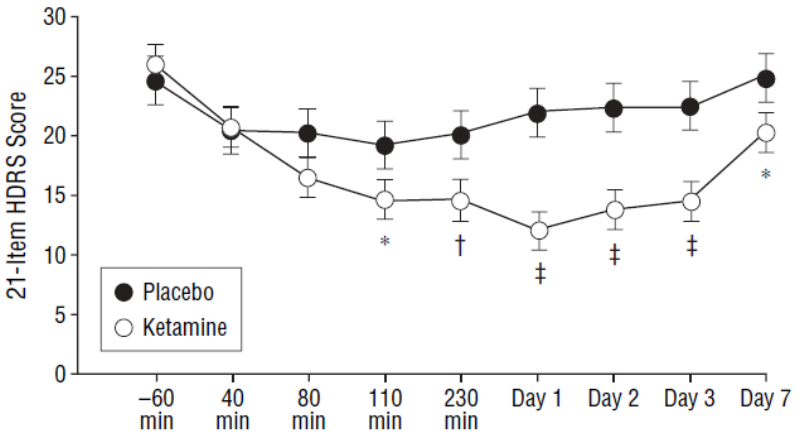
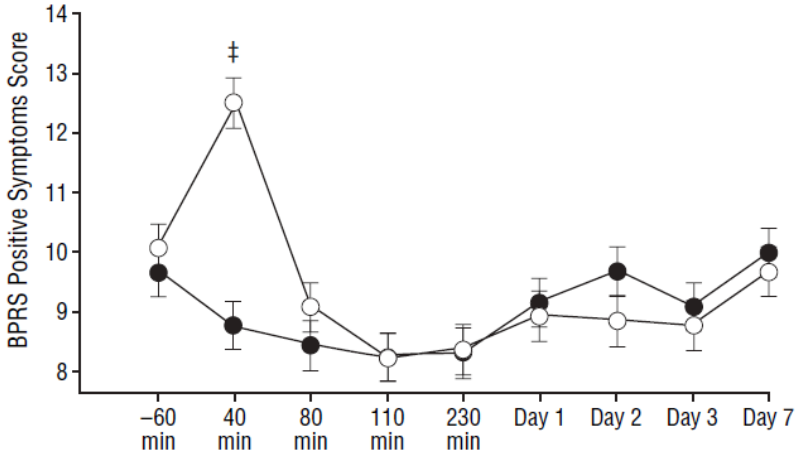
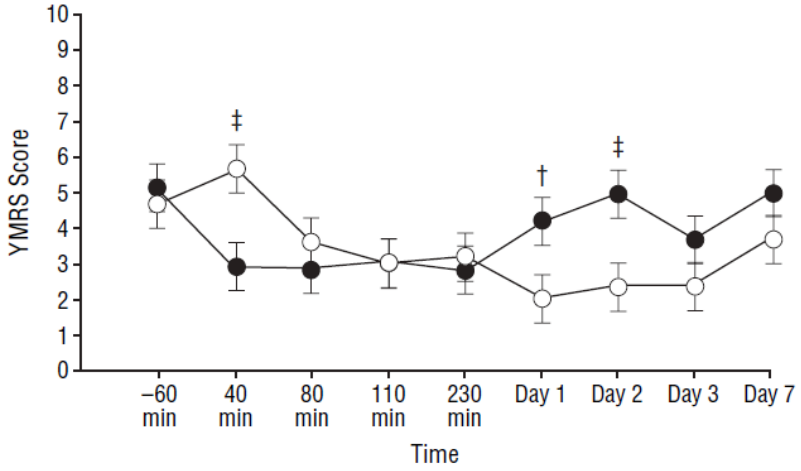
A Randomized, Placebo-Controlled, Double-Blind Crossover Study of Ketamine (0.5 mg/kg) in TRD (n=18)







Key takeaway: Demonstrated anti-depressant effect of ketamine.

Zarate et al, *Arch Gen Psychiatry*. 2006;63:856-864.

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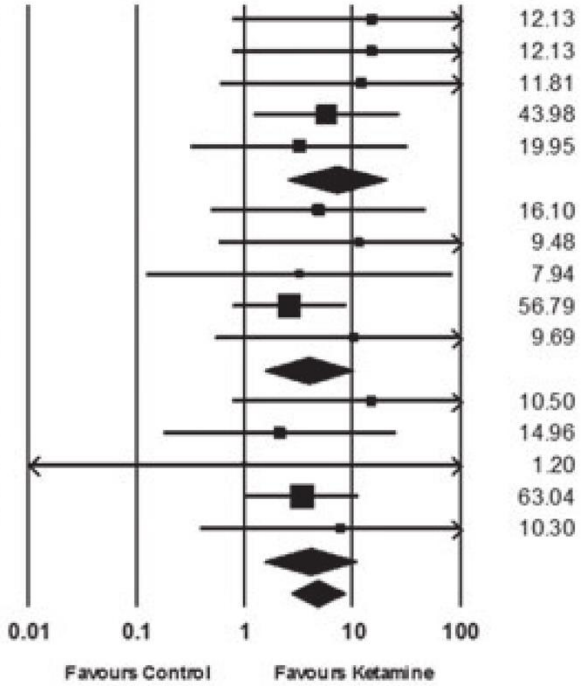
Meta-Analysis of Ketamine Studies in MDD:
Rates of clinical remission for ketamine vs. placebo

Group by Time point	Study name	Time point	Statistics for each study				Remission / Total		Relative weight
			Odds ratio	Lower limit	Upper limit	p-Value	Ketamine	Placebo	
1 day	Zarate et al, 2006	1 day	15.07	0.77	296.44	0.074	5 / 18	0 / 18	12.13
1 day	Diazgranados et al, 2010	1 day	15.07	0.77	296.44	0.074	5 / 18	0 / 18	12.13
1 day	Zarate et al, 2012	1 day	12.13	0.59	248.49	0.105	4 / 15	0 / 15	11.81
1 day	Murrough et al, 2013	1 day	5.75	1.20	27.49	0.028	16 / 48	2 / 25	43.98
1 day	Sos et al, 2013	1 day	3.22	0.32	32.89	0.324	3 / 30	1 / 30	19.95
1 day			7.07	2.50	19.95	0.000			
3 days	Zarate et al, 2006	3 days	4.86	0.49	48.57	0.179	4 / 18	1 / 18	16.10
3 days	Diazgranados et al, 2010	3 days	11.48	0.57	230.99	0.111	4 / 18	0 / 18	9.48
3 days	Zarate et al, 2012	3 days	3.21	0.12	85.20	0.486	1 / 15	0 / 15	7.94
3 days	Murrough et al, 2013	3 days	2.63	0.77	8.95	0.123	16 / 48	4 / 25	56.79
3 days	Sos et al, 2013	3 days	10.36	0.53	201.45	0.123	4 / 30	0 / 30	9.69
3 days			3.87	1.54	9.75	0.004			
7 days	Zarate et al, 2006	7 days	15.07	0.77	296.44	0.074	5 / 18	0 / 18	10.50
7 days	Diazgranados et al, 2010	7 days	2.13	0.18	25.78	0.554	2 / 18	1 / 18	14.96
7 days	Zarate et al, 2012	7 days	1.00	0.00	6598.45	1.000	0 / 15	0 / 15	1.20
7 days	Murrough et al, 2013	7 days	3.44	1.02	11.60	0.046	19 / 48	4 / 25	63.04
7 days	Sos et al, 2013	7 days	7.76	0.38	157.14	0.182	3 / 30	0 / 30	10.30
7 days			4.00	1.53	10.51	0.005			
Overall			4.67	2.66	8.19	0.000			



Key takeaway: Higher rates of clinical remission for ketamine vs. placebo.

McGirr et al, *Psychological Medicine* (2015), 45, 693–704.

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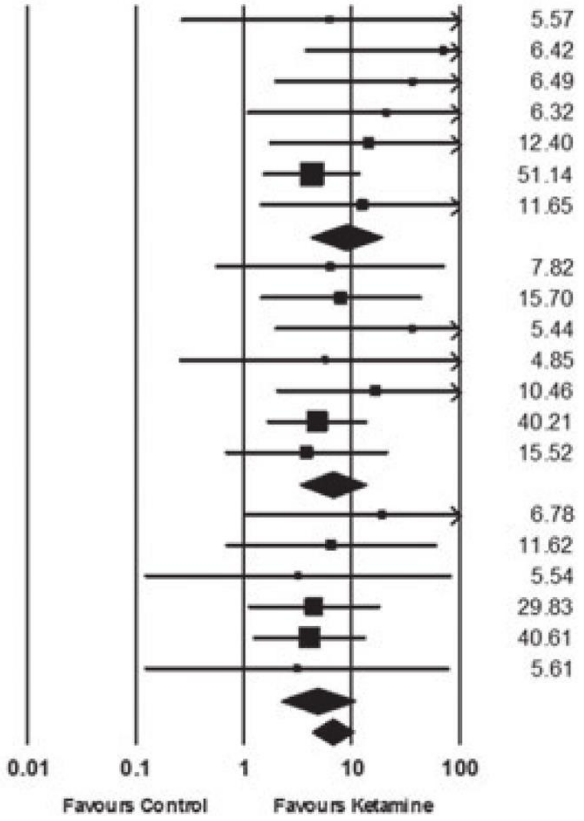
Meta-Analysis of Ketamine Studies in MDD:
Rates of clinical response for ketamine vs. placebo

Group by Time point	Study name	Time point	Statistics for each study				Response / Total		Relative weight
			Odds ratio	Lower limit	Upper limit	p-Value	Ketamine	Placebo	
1 day	Berman et al, 2000	1 day	6.33	0.26	152.86	0.256	2 / 9	0 / 9	5.57
1 day	Zarate et al, 2006	1 day	71.15	3.67	1379.46	0.005	12 / 18	0 / 18	6.42
1 day	Diazgranados et al, 2010	1 day	37.00	1.94	706.54	0.016	9 / 18	0 / 18	6.49
1 day	Zarate et al, 2012	1 day	21.21	1.07	420.80	0.045	6 / 15	0 / 15	6.32
1 day	Sos et al, 2013	1 day	14.50	1.72	122.40	0.014	10 / 30	1 / 30	12.40
1 day	Murrough et al, 2013	1 day	4.29	1.50	12.25	0.007	30 / 48	7 / 25	51.14
1 day	Lapidus et al. 2014	1 day	12.67	1.40	114.42	0.024	8 / 20	1 / 20	11.65
1 day			8.81	4.16	18.68	0.000			
3 days	Berman et al, 2000	3 days	6.40	0.55	74.89	0.139	4 / 9	1 / 9	7.82
3 days	Zarate et al, 2006	3 days	8.00	1.41	45.41	0.019	9 / 18	2 / 18	15.70
3 days	Diazgranados et al, 2010	3 days	37.00	1.94	706.54	0.016	9 / 18	0 / 18	5.44
3 days	Zarate et al, 2012	3 days	5.74	0.25	130.37	0.273	2 / 15	0 / 15	4.85
3 days	Sos et al, 2013	3 days	16.79	2.00	140.90	0.009	11 / 30	1 / 30	10.46
3 days	Murrough et al, 2013	3 days	4.83	1.63	14.30	0.004	29 / 48	6 / 25	40.21
3 days	Lapidus et al. 2014	3 days	3.86	0.67	22.11	0.130	6 / 20	2 / 20	15.52
3 days			6.63	3.33	13.18	0.000			
7 days	Zarate et al, 2006	7 days	19.24	0.99	373.01	0.051	6 / 18	0 / 18	6.78
7 days	Diazgranados et al, 2010	7 days	6.54	0.68	62.99	0.104	5 / 18	1 / 18	11.62
7 days	Zarate et al, 2012	7 days	3.21	0.12	85.20	0.486	1 / 15	0 / 15	5.54
7 days	Sos et al, 2013	7 days	4.50	1.09	18.50	0.037	10 / 30	3 / 30	29.83
7 days	Murrough et al, 2013	7 days	4.08	1.22	13.72	0.023	21 / 48	4 / 25	40.61
7 days	Lapidus et al. 2014	7 days	3.15	0.12	82.16	0.490	1 / 20	0 / 20	5.61
7 days			4.80	2.22	10.38	0.000			
Overall			6.58	4.31	10.06	0.000			



Key takeaway: Higher rates of clinical remission for ketamine vs. placebo.

McGirr et al, *Psychological Medicine* (2015), 45, 693–704.

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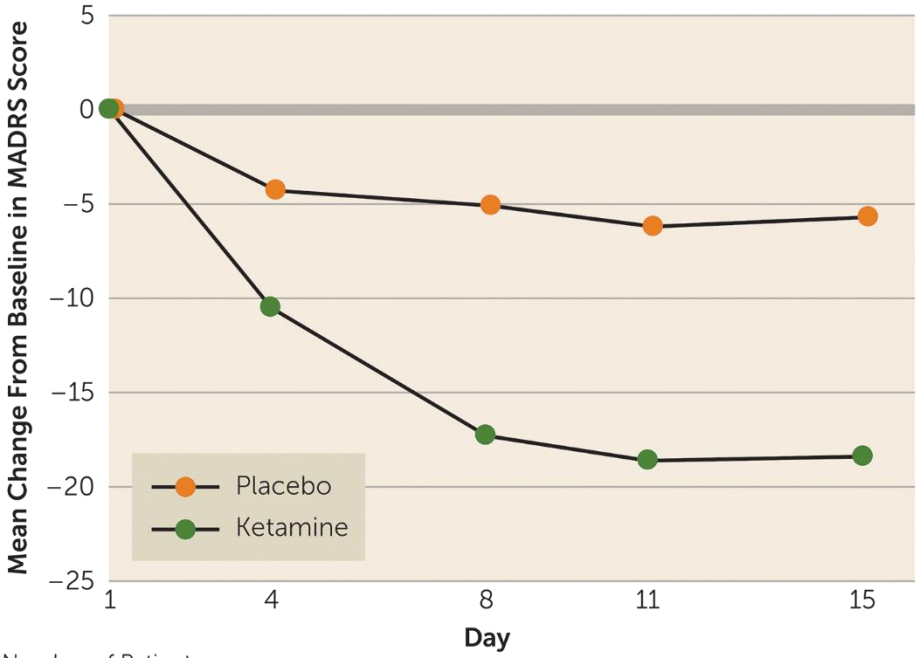
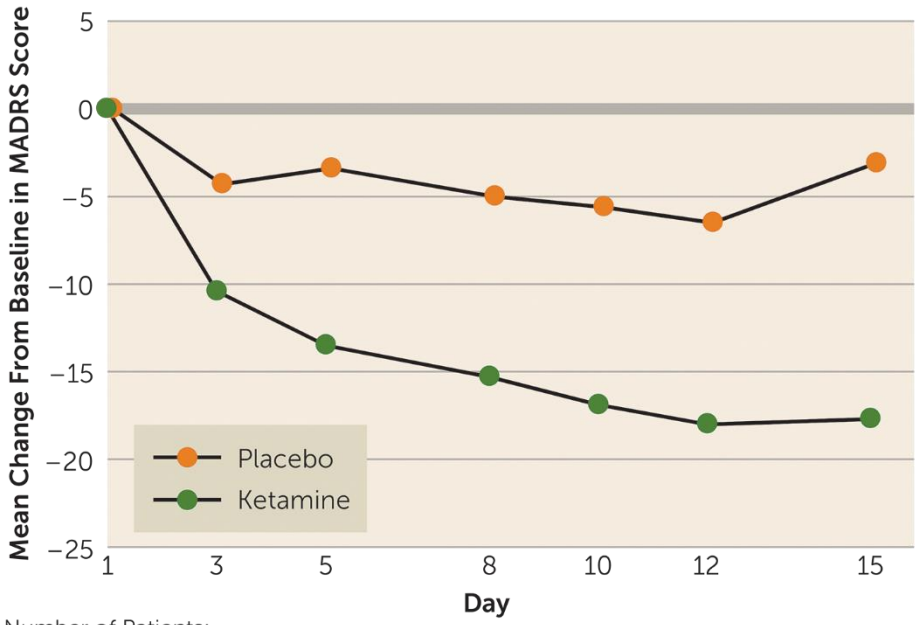
Intravenous Ketamine in Adult Patients with Treatment-Resistant Depression: A Dose-Frequency Study*



Number of Patients:

Placebo	16	15	13	13	13
Ketamine	18	17	15	16	16



Number of Patients:

Placebo	16	16	15	16	16	14	16
Ketamine	17	17	13	16	16	11	13

Key takeaway: IV ketamine shows antidepressant effect in TRD supporting a glutamatergic role.

*TRD assessed with ATRQ by SAFER rater.
Singh et al, *Am J Psychiatry*. 2016 Aug 1;173(8):816-26.

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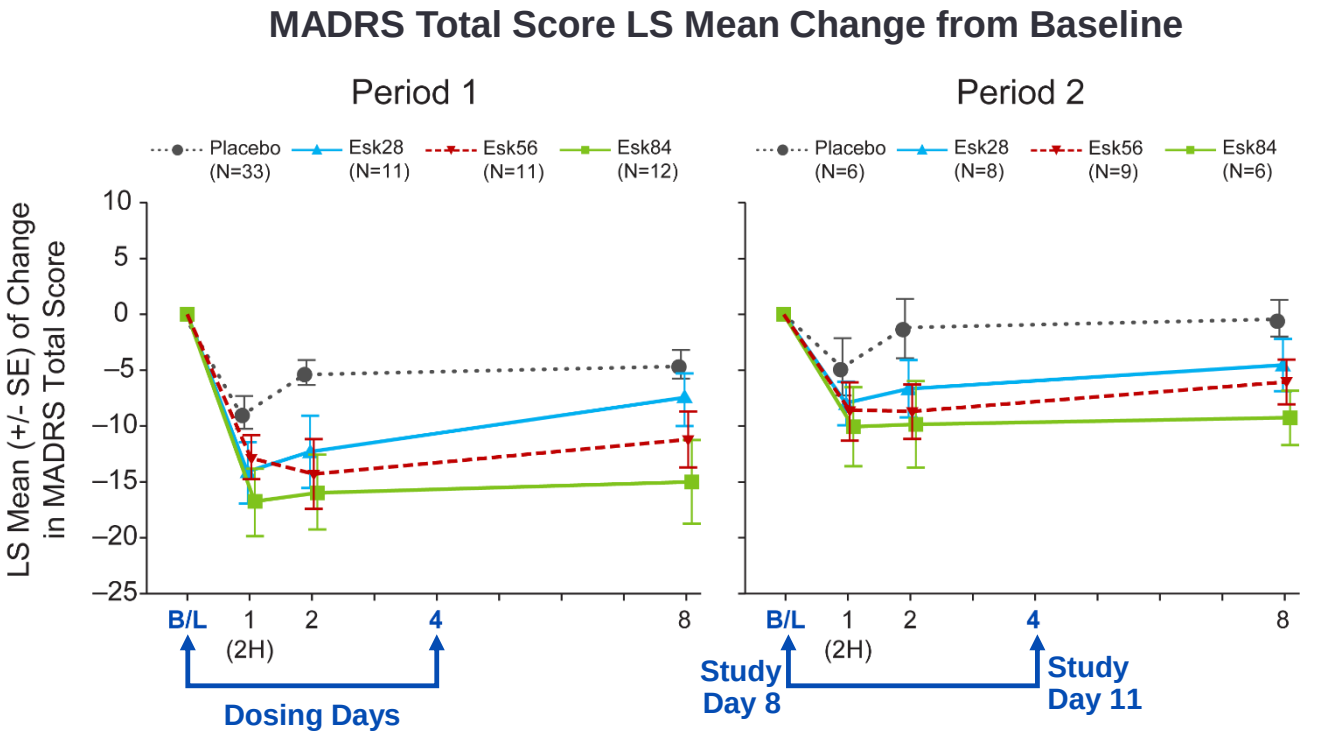
A Double-Blind, Doubly-Randomized, Placebo-Controlled Study of Intranasal Esketamine in TRD*

Key takeaway: further support of glutamatergic role in TRD



	Esk 28	Esk 56	Esk 84
Period 1 and Period 2 combined			
Mean (SE) differences from placebo	-4.2 (2.09)	-6.3 (2.07)	-9.0 (2.13)
90% CI	-7.67, -0.79	-9.71, -2.88	-12.53, -5.52
One sided p-value	0.021	0.001	<0.001

*TRD assessed with ATRQ by SAFER rater. Daly et al, *JAMA Psychiatry*. 2018 Feb 1;75(2):139-148.
Abbreviations: CI = confidence interval; DB = double-blind; Esk = esketamine; MADRS = Montgomery-Åsberg Depression Rating Scale; SE = standard error.

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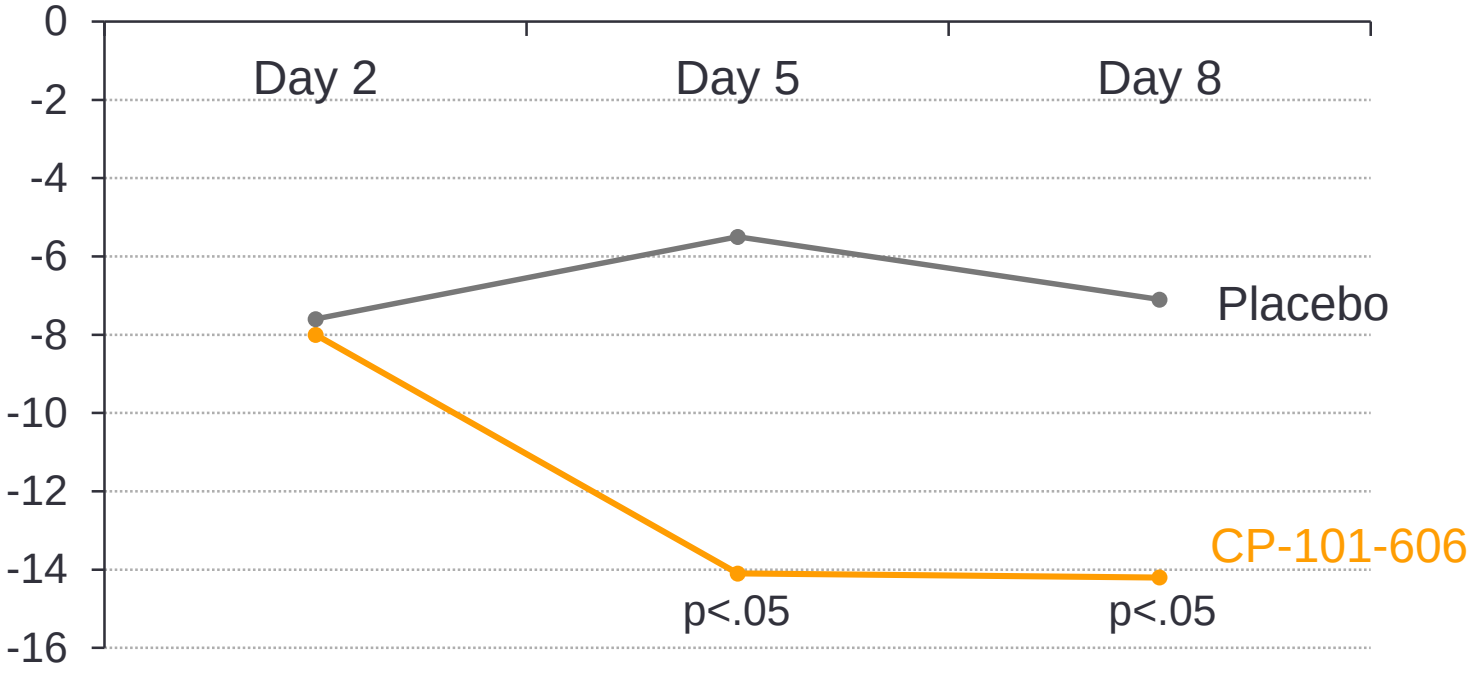
POC Study in TRD Patients of NR2B Subunit Selective N-Methyl-D-Aspartate Antagonist, CP-101,606 (n=30)



Preskorn et al, *J Clin Psychopharmacol* 2008;28:631–637.

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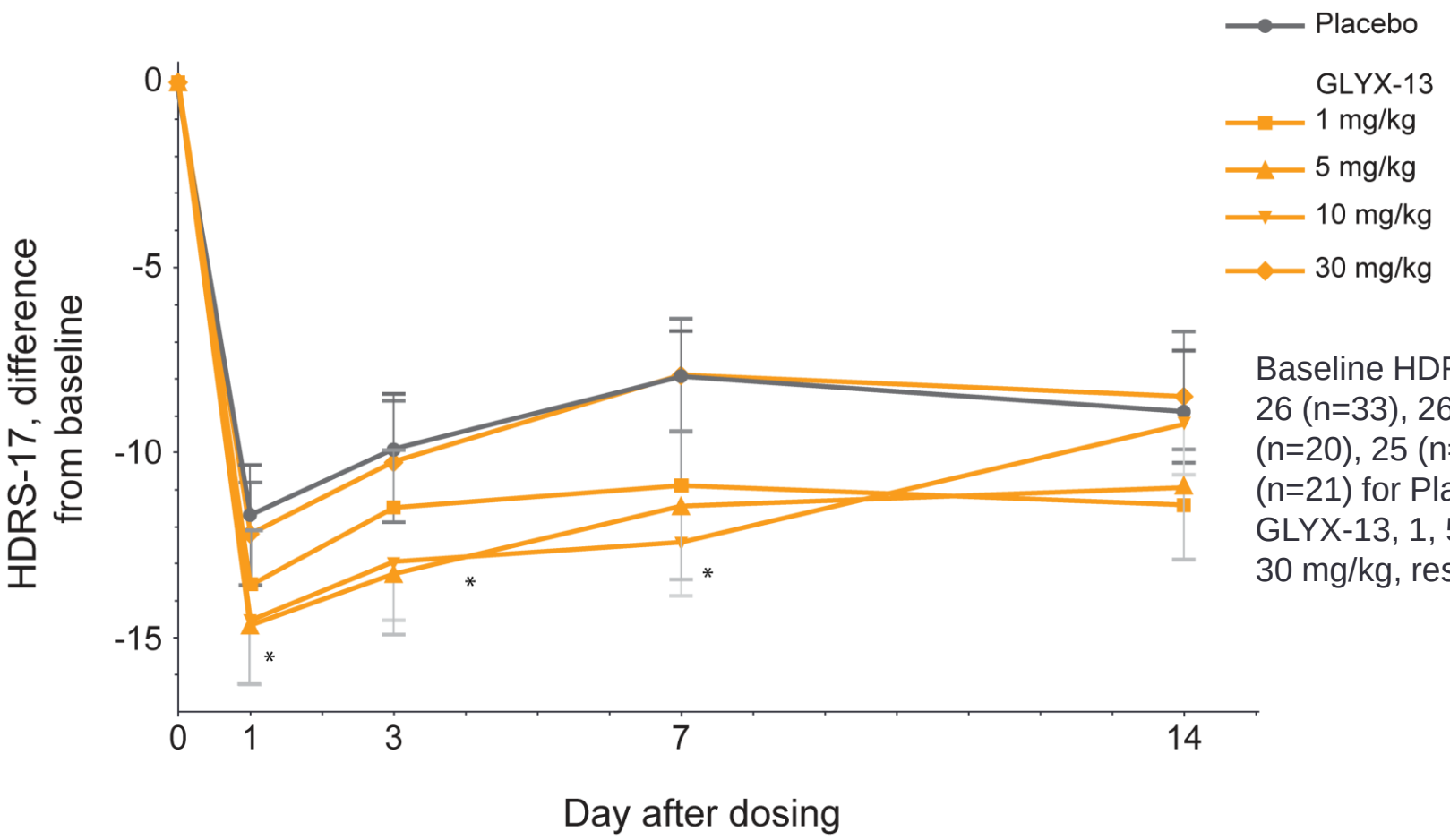
Double-Blind Study of GLYX-13 in TRD*



Baseline HDRS-17 was 26 (n=33), 26 (n=25), 25 (n=20), 25 (n=17), 25 (n=21) for Placebo and GLYX-13, 1, 5, 10, and 30 mg/kg, respectively.

*TRD assessed with ATRQ by SAFER rater.
Preskorn et al, *Journal of Psychiatric Practice* 2015 Vol. 21, No. 2: 140-149.

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Depression and Inflammation

- Meta-analysis of dozens of studies supports relationship between depression and inflammation:[1]
  - Medically-healthy MDD patients exhibit elevated serum interleukin (IL)-6, IL-1 (esp. IL-1-beta), and acute phase C reactive protein (CRP)
- Increased serum tumor necrosis factor alpha (TNF-α) in MDD
- Immune-based treatment for hepatitis C and certain cancers, e.g., interferon (IFN), can induce clinical depression essentially indistinguishable from typical MDD

[1]Howren et al, *Psychosom Med*. 2009 Feb;71(2):171-86.
[2]Shelton and Miller, *Prog Neurobiol*. 2010 Aug;91(4):275-99.
[3]Capuron et al, *Neuropsychopharmacology*. 2002 May;26(5):643-52; Raison et al, *Trends Immunol*. 2006 Jan;27(1):24-31.

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Cytokine Abnormalities observed in MDD

Table 1 Cytokines and chemokine profiles in Major Depressive Disorder ($n=49$) compared with age and gender matched healthy controls ($n=49$)

	MDD mean ± SD	Control mean ± SD	Rank sum *Z*	Rank sum *p*
MIP-1α	463.8 ± 706.88	60.33 ± 95.91	− 5.929	0.0000*
MCP-1	191.00 ± 381.69	56.66 ± 106.19	− 3.420	0.0006*
IL-1α	223.75 ± 258.50	2.06 ± 8.45	− 8.585	0.0000*
IL-1β	42.53 ± 105.19	1.29 ± 4.07	− 6.060	0.0000*
IL-2	65.19 ± 316.57	10.58 ± 43.43	− 4.316	0.0000*
IL-3	40.53 ± 261.34	1.14 ± 4.53	− 0.903	0.3667
IL-4	13.72 ± 50.31	2.90 ± 11.45	− 3.269	0.0011*
IL-5	24.03 ± 100.63	3.78 ± 12.69	− 1.046	0.2954
IL-6	5.98 ± 14.22	1.23 ± 6.16	− 3.291	0.0010*
IL-7	1.70 ± 3.10	0.17 ± 1.16	− 3.280	0.0010*
IL-8	231.19 ± 754.78	1.09 ± 3.50	− 7.556	0.0000*
IL-10	8.68 ± 36.76	0.70 ± 3.39	− 4.192	0.0000*
IL-12p70	17.40 ± 84.09	0.39 ± 1.91	− 3.425	0.0006*
IL-13	21.45 ± 98.85	4.13 ± 14.51	− 2.825	0.0047
IL-15	0.96 ± 5.06	0.24 ± 1.62	− 4.005	0.0001*
Eotaxin	167.08 ± 365.27	23.57 ± 62.61	− 4.861	0.0000*
GM-CSF	141.30 ± 606.87	8.52 ± 24.81	− 4.330	0.0000*
IFNγ	24.46 ± 25.43	6.67 ± 11.90	− 5.057	0.0000*
IP-10	163.01 ± 171.24	130.71 ± 120.09	− 1.456	0.1453
TNF-α	7.84 ± 45.34	3.13 ± 11.73	0.415	0.6784

p values (with asterisks) significant after Bonferroni correction for 20 tests ($p<0.0025$).
MDD = Major Depressive Disorder, SD = standard deviation.

Simon et al, *Eur Neuropsychopharmacol*. 2008 Mar;18(3):230-3.

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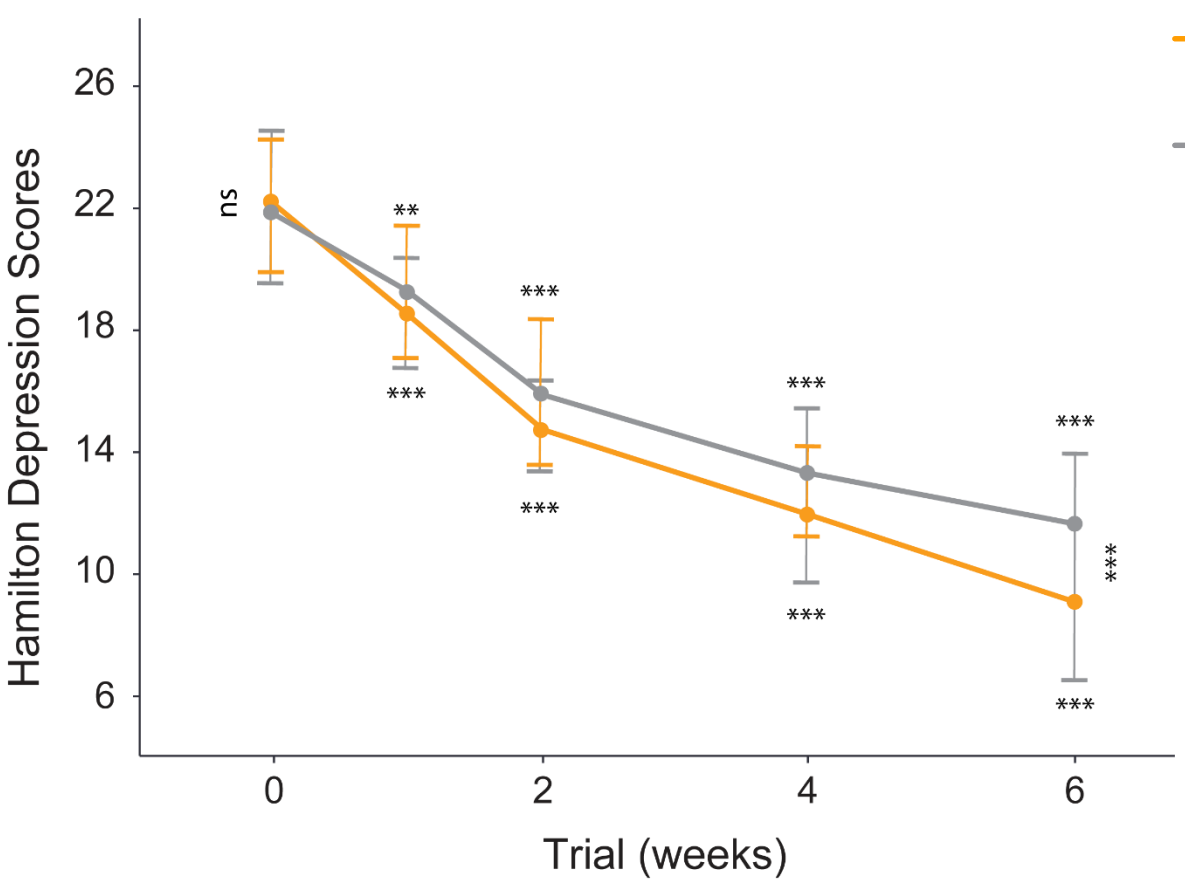
Clinical Trial of Adjunctive Cyclooxygenase-2 Inhibitor Celecoxib Treatment in MDD Patients: a Double-Blind & Placebo-Controlled Trial



Cap. Fluoxetine 40 mg/day + Cap. Celecoxib 400 mg/day

Cap. Fluoxetine 40 mg/day + Cap. placebo

Mean ± SD of the two protocols on the Hamilton Rating Scale scores.

ns, nonsignificant.
** ≤0.01
*** ≤0.001

Akhondzadeh et al, *Depression and Anxiety*. 26:607–611 (2009).

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SAMe, Methylfolate and Omega-3 Fatty Acids and Inflammation

- The anti-inflammatory effects of SAMe have been attributed to its ability to reduce the expression of the pro-inflammatory cytokine TNF-α and to increase the expression of the anti-inflammatory cytokine IL-10.[1]
- Folic acid protects motor neurons against inflammation and apoptosis in SOD1 G93A transgenic mice.[2]
- A significant reduction with Omega-3 fatty acids (fish oil) in plasma concentrations of inflammatory biomarkers, including TNF-α and IL-6, has been observed in numerous studies.[3-7]

[1]McClain et al, *Alcohol* 2002;27(3):185-92.
[2]Zhang et al, *Neuropharmacology*. 2008 Jun;54(7):1112-9.
[3]Wang et al, *Nutrition*. 2012 Jun;28(6):623-9.
[4]Moertl et al, *Am Heart J* 2011;161(5):915-9.
[5]Zhao et al, *J Int Med Res* 2009;37(6):1831-41.
[6]Papageorgiou et al, *Eur J Clin Nutr* 2011;65(4):514-9.
[7]Tartibian et al, *Clin J Sport Med* 2011;21(2):131-7.

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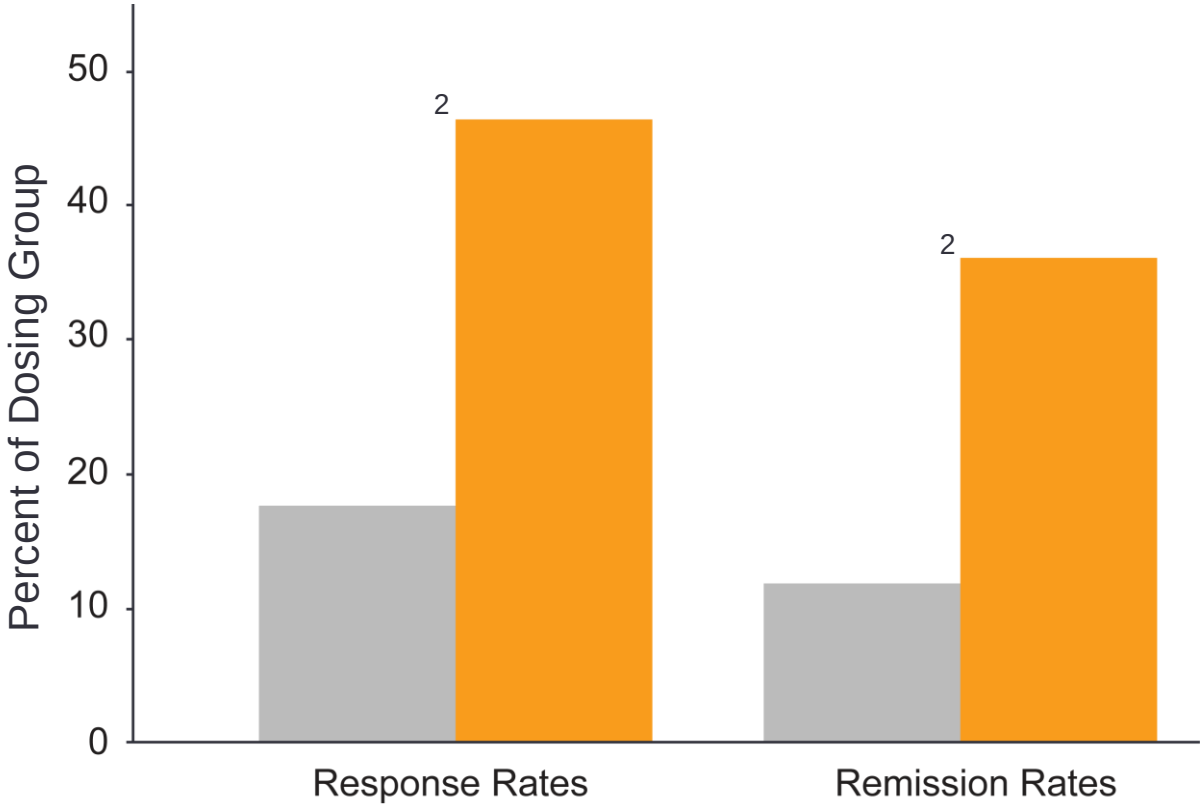
Double-Blind Study of SAMe (1600 mg/d) Augmentation in SSRI-Resistant Depressed Patients



HAM-D response and remission rates among antidepressant nonresponders randomly assigned to S-adenosyl Methionine (SAMe) or placebo.[1]

[1]Data depict last observation carried forward (LOCF) for all patients randomly assigned.

[2]Significant difference between groups ($p<0.05$, Fisher's exact test).

Papakostas G et al; *Am J Psychiatry* 2010; 167:942–948.

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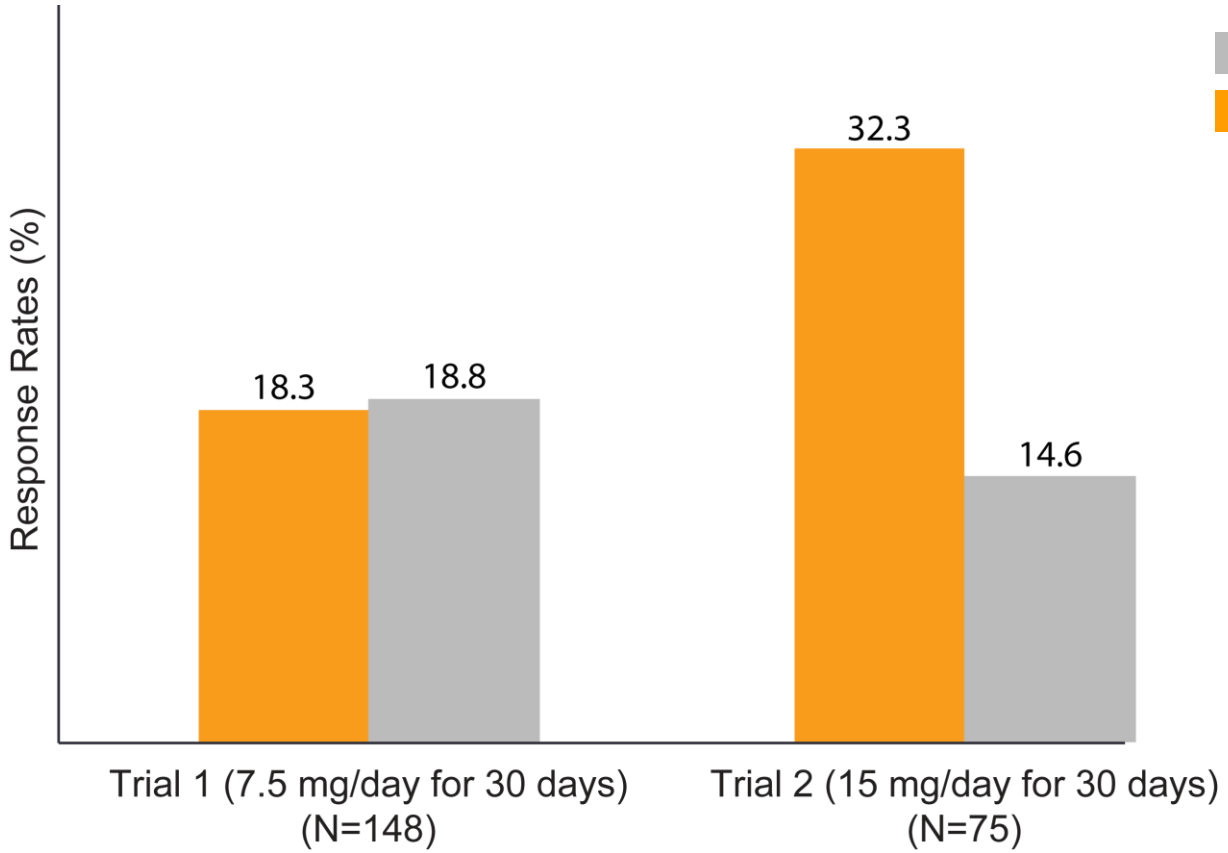
Double-Blind Study of L-Methylfolate (L-MTHF) Augmentation of SSRIs - SPCD



Pooled response rate in two trials of the L-Methylfolate (MTHF) compared with placebo as an adjunct to SSRIs in patients with SSRI-resistant depression.[1]

[1]Response was defined as a reduction of ≥50% in Hamilton Depression Rating Scale score during treatment or a final score of ≤7. Significant difference between groups in trial 2 (p=0.04). The pooled analysis was conducted as described in Fava et al.[2]

Papakostas G et al; *Am J Psychiatry* 2010; 167:942–948.
[2]Fava M et al; *Psychother Pschosom* 2003; 72:115-127.

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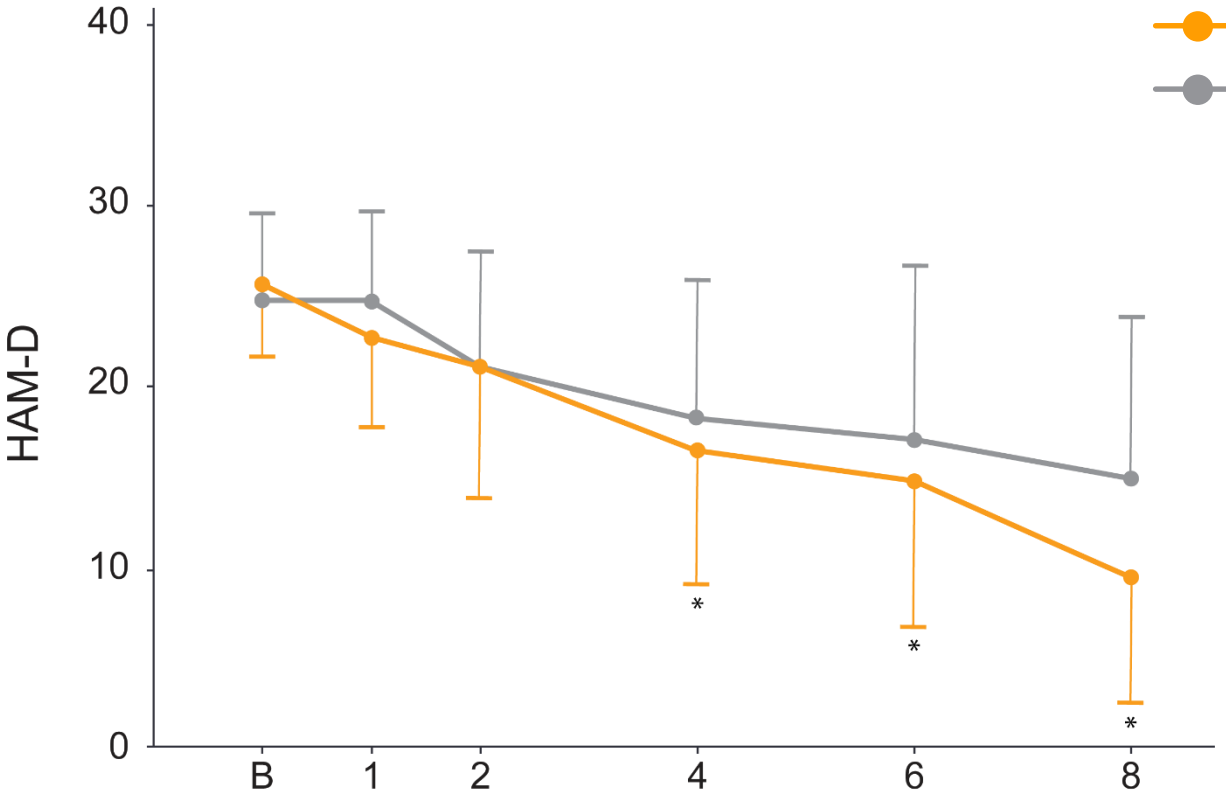
Omega-3 Fatty Acid (1.2 gr/day) Augmentation of Citalopram Treatment for Patients With Major Depressive Disorder (n=42)



Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean ± SD

*$p < 0.05$, computed via regression modeling

Gertsik et al, *J Clin Psychopharmacol* 2012;32: 61-64.

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Inflammatory Markers as Moderators of Response to EPA

Table 3. Change in HAM-D-17 total score from baseline to treatment week 8 for subjects treated with EPA vs PLA with high inflammation on individual biomarkers and pairs of biomarkers at baseline[a]

High inflammatory status on	*Change from baseline to treatment week 8*						*Standardized treatment effect size at treatment week 8*		*EPA vs PLA at treatment week 8*			*Significance of treatment-by-time interaction*		
	EPA			*PLA*										
Individual biomarkers	LS-mean	s.e.m.	*N*	LS-mean	s.e.m.	*N*	ES[b]	95% CI	*t*	df[c]	*P*-value	F	df	*P*-value
hs-CRP	−12.44	1.54	15	−7.99	1.86	8	−0.78	−1.67 to +0.11	−1.84	42.8	0.073	1.70	1, 90.6	0.195
IL-6	−9.78	1.44	15	−7.84	1.40	12	−0.37	−1.13 to +0.40	−0.96	54.0	0.341	0.42	1, 104	0.518
IL-1ra	−12.14	1.16	23	−9.63	1.61	11	−0.46	−1.18 to +0.27	−1.26	72.1	0.213	0.31	1, 127	0.580
Leptin	−8.99	1.29	19	−5.61	1.46	13	−0.62	−1.34 to +0.11	−1.72	63.3	0.090	1.01	1, 101	0.318
Adiponectin	−11.69	1.10	21	−8.81	1.06	21	−0.58	−1.20 to +0.04	−1.88	94.9	0.063	1.69	1, 159	0.195
10 Pairs of biomarkers														
hs-CRP+IL-6	−12.00	1.68	10	−4.44	2.30	4	−1.47	−2.77 to −0.17	−2.65	22.2	*0.015*	4.13	1, 51.9	*0.047*
hs-CRP+IL-1ra	−12.74	1.60	13	−7.05	3.66	2	−0.99	−2.53 to +0.54	−1.42	25.1	0.167	1.18	1, 54.2	0.281
hs-CRP+leptin	−10.56	1.91	12	−6.30	2.52	5	−0.67	−1.74 to +0.40	−1.34	28.3	0.192	0.87	1, 64.6	0.354
hs-CRP+adiponectin	−12.12	1.70	9	−3.56	2.33	4	−1.72	−3.10 to −0.34	−2.92	18.9	*0.009*	3.66	1, 47.5	0.062
IL-6+IL-1ra	−11.53	1.98	9	−7.41	2.21	6	−0.72	−1.79 to +0.35	−1.35	23.7	0.189	0.68	1, 56.1	0.415
IL-6+leptin	−10.15	1.63	12	−3.15	1.96	6	−1.30	−2.38 to −0.22	−2.74	32.1	*0.010*	3.94	1, 65.3	0.051
IL-6+adiponectin	−10.27	1.68	11	−7.46	2.03	6	−0.52	−1.53 to +0.49	−1.06	27.7	0.300	0.28	1, 65.7	0.597
IL-1ra+leptin	−10.22	1.66	14	−5.80	2.54	5	−0.73	−1.78 to +0.32	−1.43	32.1	0.162	0.60	1, 71.4	0.441
IL-1ra+adiponectin	−12.99	1.44	12	−10.44	2.33	4	−0.52	−1.67 to +0.63	−0.92	28.1	0.367	0.00	1, 52.9	0.954
Leptin+adiponectin	−9.88	1.27	15	−5.42	1.86	6	−0.92	−1.92 to +0.07	−1.99	38.2	0.054	1.22	1, 72.1	0.274

Abbreviations: CI, confidence interval; EPA, eicosapentaenoic acid; ES, effect size; HAM-D-17, 17-item Hamilton Depression Rating Scale; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; LS, least squares; MMRM, mixed model repeated measures analysis; PLA, placebo. [a]HAM-D-17 was administered at baseline and at 2-week intervals during the 8-week study. MMRM analyses were performed on change from baseline to week 8 for subsets of ($N=155$) evaluable subjects with all five biomarkers present at baseline, testing the significance of effects of treatment, time and treatment-by-time interaction, covarying for the baseline HAM-D-17 score. [b]By Cohen's *d* effect size: difference between LS-mean change/pooled s.d. for each pair of treatments (s.d. per group computed from s.e.m. of LS-mean from MMRM). A negative effect size indicates that the EPA group improved more than the PLA group (had a larger negative LS-mean change). [c]Degrees of freedom were determined using the Satterthwaite approximation method. *P* values in italics are <0.05.

Rapaport MH et al, *Molecular Psychiatry* (2016) 21, 71–79.

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Why the Combination of Dextromethorphan and Bupropion?

Dextromethorphan effects on:

- Glutamatergic system
- Monoamine systems
- Inflammatory responses

Bupropion effects on:

- Monoamine systems
- Inflammatory responses

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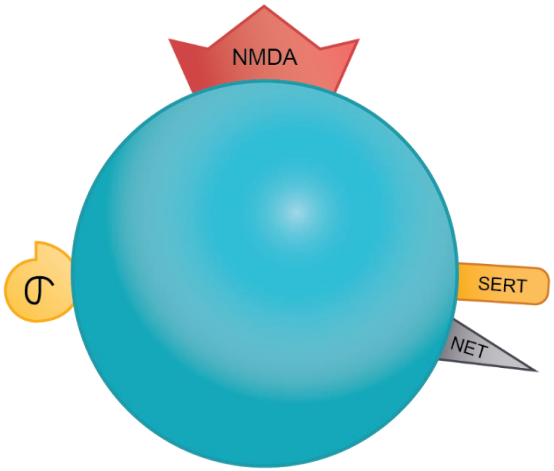
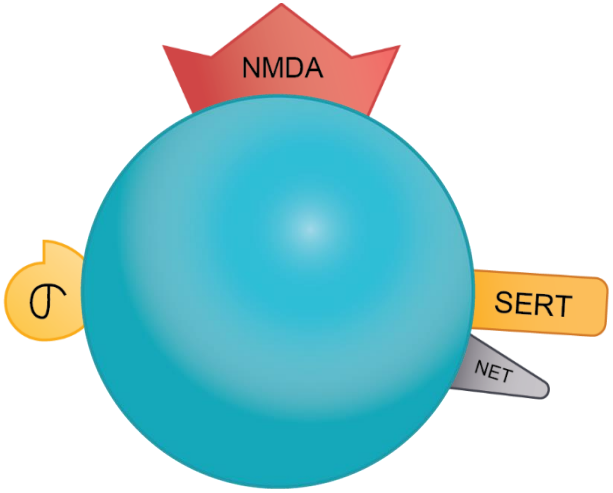
Dextromethorphan has Ketamine-like Activity on Multiple Receptors

Comparison of Pharmacologic Properties

Ketamine



Dextromethorphan



SERT: DM >> ketamine[2]

NET: DM >> ketamine[2]

NMDA antagonism: DM > ketamine

σ1 agonism: DM > ketamine

Abbreviations: DM = Dextromethorphan; SERT= Serotonin Reuptake Transporter; NET = Norepinephrine Reuptake Transporter; NMDA = N-methyl-D-aspartate.
Courtesy of Stephen M. Stahl, MD.

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Dextromethorphan and Monoamines:
Radioligand Binding Data with Dextromethorphan

Table 1
Radioligand binding data with dextromethorphan (DM) and dextrorphan (DX).

Receptor	K_i or % inhibition DM	K_i or % inhibition DX	Radioligand	K_i of radioligand	Reference
5-HT transport	40 nM	484 nM	[^{3}H]paroxetine, 0.2 nM	0.2 nM	Werling et al., 2007b
Sig1-R	150 nM	118 nM	[^{3}H]pentazocine, 2 nM	5 nM	Werling et al., 2007b
NA transport	6000 nM	6200 nM	[^{3}H]nisoxetine, 2 nM	0.7 nM	Pubill et al., 1998
NMDAR	962 nM	148 nM	[^{3}H]MK-801, 0.5 nM	1.6 nM	Jaffe et al., 1989
NMDAR	2120 nM	892 nM	[^{3}H]MK-801, 3 nM	1.6 nM	Werling et al., 2007b
Adrenergic α1D	*830 nM*	NT	[^{3}H]prazosin, 0.1 nM	0.1 nM (K_d)	Avanir data on file
Adrenergic α1A	*3000 nM*	NT	[^{3}H]prazosin, 0.2 nM	0.15 nM (K_d)	Avanir data on file
Sigma-2	*11,060 nM*	11,325 nM	[^{3}H]DTG, 2.5 nM	21 nM	Chou et al., 1999
5-HT$_{1B/D}$	*61% at 1000 nM*	54% at 1000 nM	[^{3}H]GR 125,743, 0.3 nM	0.24 nM	Werling et al., 2007b
Adrenergic α-2	*60% at 1000 nM*	NC	[^{3}H]yohimbine, 2 nM	1.4 nM	Werling et al., 2007b
Histamine-1	*NC at 1000 nM*	95% at 1000 nM	[^{3}H]mepyramine, 2 nM	1.5 nM	Werling et al., 2007b

Abbreviations: 5-HT — serotonin; NA — noradrenaline; NMDAR — *N*-methyl-D-aspartate glutamate receptor, NT — not tested, NC — no significant competition of radioligand binding (less than 30% inhibition at 1000 nM). Data on adrenergic radioligand binding is from Avanir data on file, obtained from Cerep, Celle l'Evescault, France, July 25, 2012.
Note: Dextromethorphan did not significantly inhibit radioligand binding at 10,000 nM at several other sites (Avanir data on file from Ricerca Biosciences, Taipei, Taiwan, November 2010). These inactive binding sites for dextromethorphan include: adenosine A1, A2A, A3, adrenergic α1B, α2A, β1, β2, bradykinin B1, B2, calcium channel dihydropyridine, calcium channel N-type, cannabinoid CB1, dopamine D1, D2S, D3, D4.2, endothelin ET_A, ET_B, epidermal growth factor, $GABA_A$ flunitrazepam, $GABA_A$ muscimol, $GABA_{B1A}$, glucocorticoid, glutamate kainate, glutamate NMDAR agonist site, glutamate NMDAR glycine site, strychnine-sensitive glycine, histamine H1, H2, H3, imidazole I2, interleukin IL-1, leukotriene, melatonin MT1, muscarinic M1, M2, M3, neuropeptide Y Y1, Y2, nicotinic α1, opiate μ, δ, κ, phorbol ester, platelet activating factor, potassium channel K_{ATP}, potassium channel hERG, prostanoid EP4, purinergic P2X, P2Y, rolipram, serotonin 5-HT_{2A}, 5-HT_{2B}, 5-HT_3, tachykinin NK1, testosterone, thyroid hormone, dopamine transporter.
Note — Any functional significance of radioligand binding activity at ~1000 nM and greater concentrations and without functional pharmacologic testing is not known and needs confirmation with functional tests (these data are shown in italics in the table). For example, clinically useful serotonin 5-HT_{1B} agonists (sumatriptan, dihydroergotamine) have K_i values for radioligand binding of 3 nM to 440 nM (Buzzi & Moskowitz, 1991), and the selective adrenergic α1D antagonist BMY 7378 has a K_i value for radioligand binding of 0.4 nM (Goetz et al., 1995).

Taylor et al, *Pharmacol Ther*. 2016; 164;170-182.

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Dextromethorphan and Inflammation

- Dextromethorphan and its metabolites protect rats against MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)- and lipopolysaccharide (LPS)-induced dopaminergic neuron damage *in vitro* and *in vivo*.[1]
- Chronic heroin-use-induced TNF-α and IL-8 levels were significantly reduced in patients treated for 12 weeks with add-on dextromethorphan.[2]

[1]Zhang et al, 2004 *FASEB J* 18:589–591; 2005 *FASEB J* 19:395–397; 2006 *FASEB J* 20:2496–2511.
[2]Chen et al, *J Neuroimmune Pharmacol*. 2012 Dec;7(4):1025-33.

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Bupropion and Monoamines

- Bupropion and two of its metabolites, hydroxybupropion, and threohydrobupropion, were shown to decrease the uptake of NE and DA into rat and mouse synaptosomes.
- Bupropion's activity as a DA transporter inhibitor is further supported by a recent study showing approximately a 3-fold increase in expression of the immediate early gene c-fos in human DA transporter cells.
- Microdialysis studies following acute administration of bupropion demonstrate that extracellular NE and DA concentrations are increased in the nucleus accumbens.
- Studies assessing DA transporter occupancy following administration of bupropion in humans have demonstrated measurable occupancy.
- All of the above studies provide strong evidence for a dual NE/DA mechanism of action of bupropion.

Fava et al, Prim Care Companion *J Clin Psychiatry*. 2005;7(3):106-13.

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Bupropion and Inflammation

- Bupropion lowers levels of TNF, interferon-gamma, and interleukin-1 beta *in vivo*.[1]
- Mice challenged with an otherwise lethal dose of LPS were protected by bupropion and levels of the anti-inflammatory cytokine interleukin-10 were increased.[1]
- Bupropion may suppress TNF synthesis by mediating increased signaling at beta-adrenoreceptors and D1 receptors, resulting in increased cAMP that inhibits TNF synthesis.[1]
- Bupropion pretreatment reduced intestinal ischemia/reperfusion injury and blunted serum elevations of TNF-alpha and interleukin-1.[2]

[1]Brustolim et al, *Int Immunopharmacol*. 2006 Jun;6(6):903-7.
[2]Camara-Lemarroy et al, *Transplant Proc*. 2013 Jul-Aug;45(6):2502-5.

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AXS-05: A Combination of Glutamate, Monoamine and Anti-inflammatory Mechanisms

Mechanism of Action	DM	BUP	**AXS-05** DM+BUP
NMDA Receptor Antagonist	✓		✓
Sigma-1R Agonist	✓		✓
Norepinephrine Reuptake Inhibitor	✓	✓	✓
Serotonin Reuptake Inhibitor	✓		✓
Dopamine Reuptake Inhibitor		✓	✓
▼TNF-α	✓	✓	✓
▼Interferon-γ		✓	✓
▼IL-1β		✓	✓
▼IL-8	✓		✓

Glutamate signaling

Monoamine signaling

Anti-inflammatory

DM = Dextromethorphan; BUP = Bupropion. ✓ = Present

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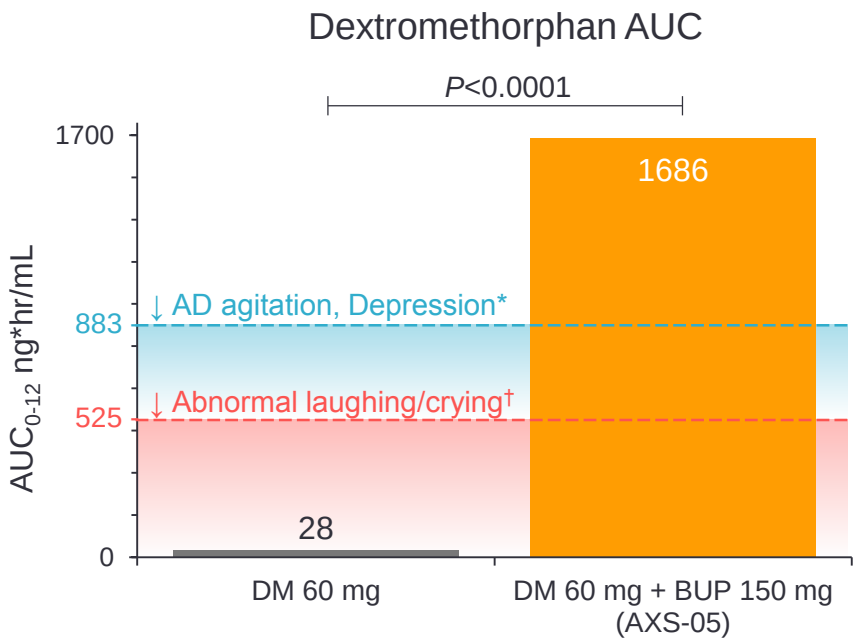
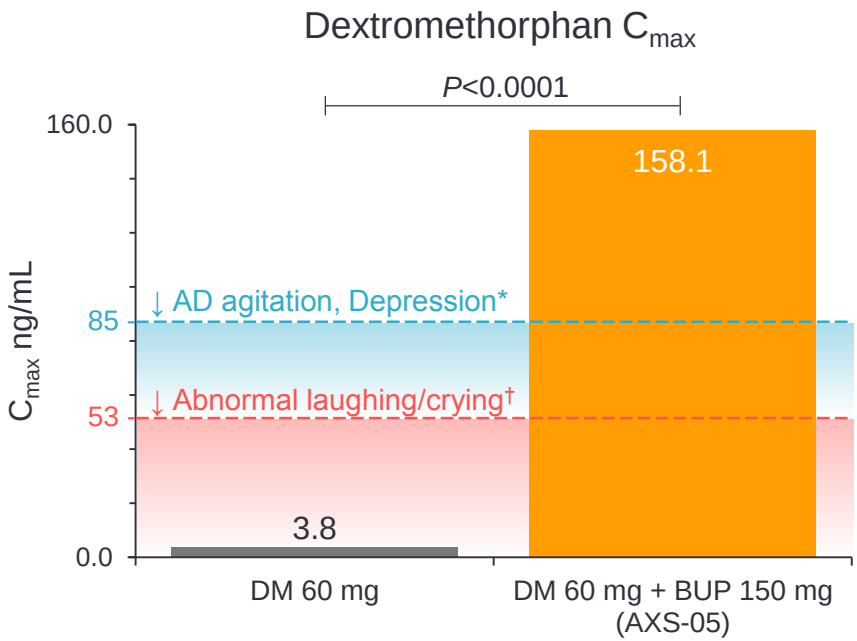
Bupropion Increases Dextromethorphan Levels
Phase 1 Results





- Dextromethorphan (DM) 60 mg dosed alone, or in combination with Bupropion (BUP) 150 mg, twice daily in healthy volunteers. Plasma concentrations measured on Day 8.

DM concentrations associated with reported therapeutic responses shown (dotted lines).

* DM plasma concentrations reported with dose (DM 30 mg + Q 10 mg) resulting in reduction of agitation symptoms in AD patients, and of depressive symptoms in AD and PBA patients.

† DM plasma concentrations reported with dose (DM 20 mg + Q 10 mg) resulting in reduction in emotional symptoms in PBA patients.

Axsome data on file.
Therapeutic DM concentrations from NDA 021879, FDA Clinical Pharmacology Review.
DM, Dextromethorphan; Q, Quinidine; BUP, Bupropion; AD, Alzheimer's disease; PBA, pseudobulbar affect

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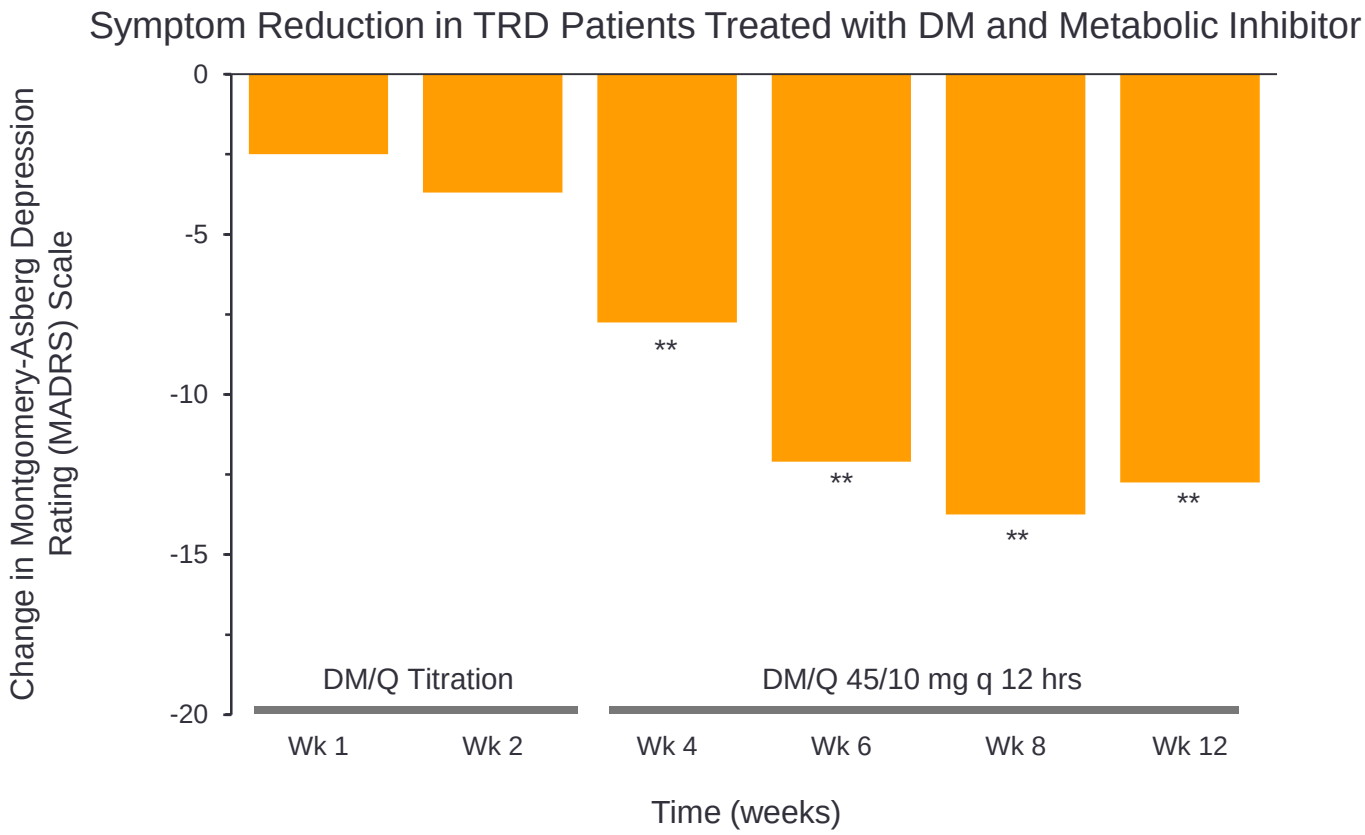
Dextromethorphan/Quinidine (45/10 mg/day) Pharmacotherapy in TRD Patients: A POC, Open Clinical Trial



- Failed 2 to 10 prior treatments
- 45% of patients had ≥ 50% reduction in MADRS

** Indicated pairwise comparison between time point and baseline is significant at $p < 0.01$, with Bonferroni adjustment for multiple comparisons.
Murrough et al, *J Affective Disorders* 218 (2017) 277–283.

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Addressing Clinical Trial Risk in MDD

TYPES OF HETEROGENEITY	STRATEGIES TO ADDRESS HETEROGENEITY & PLACEBO RESPONSE
• Pathophysiological • Treatment history • Diagnostic • Background treatment	• Prospective active treatment lead-in • Independent assessments—SAFER • Standardized treatment

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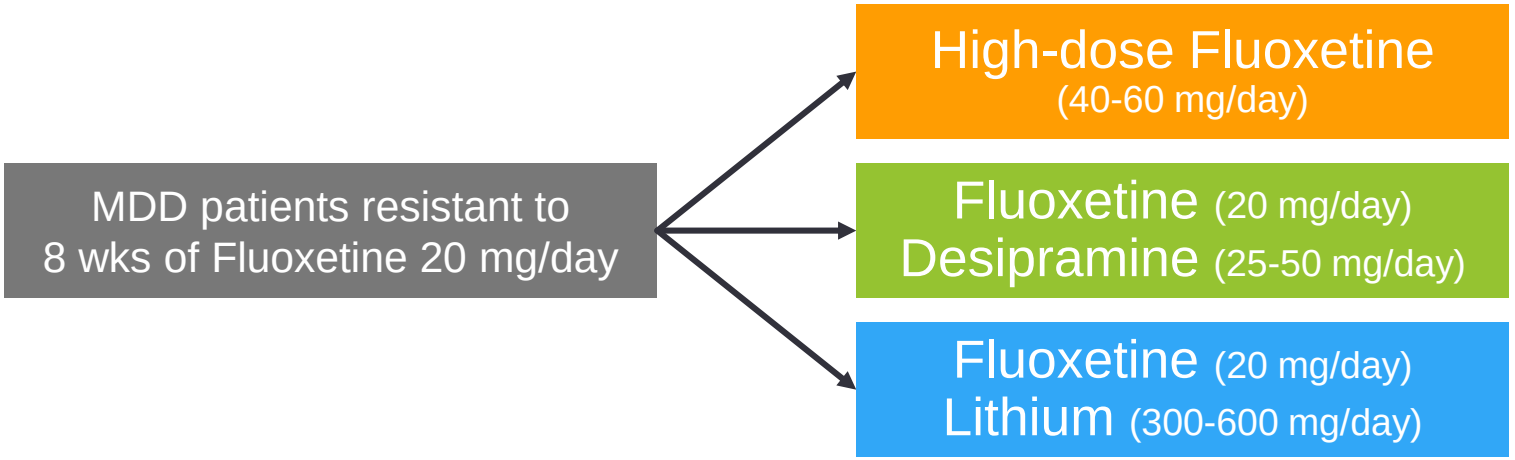
Prospective Active Treatment Lead-in Design

Double-Blind Study of High-Dose Fluoxetine vs. Lithium or Desipramine Augmentation of Fluoxetine in Partial Responders and Non-responders to Fluoxetine



Fava M et al. *Am J Psychiatry* 1994; 15(9): 1372-1374.
Fava M. *J Clin Psychopharmacol*. 2002 Aug;22(4):379-387.

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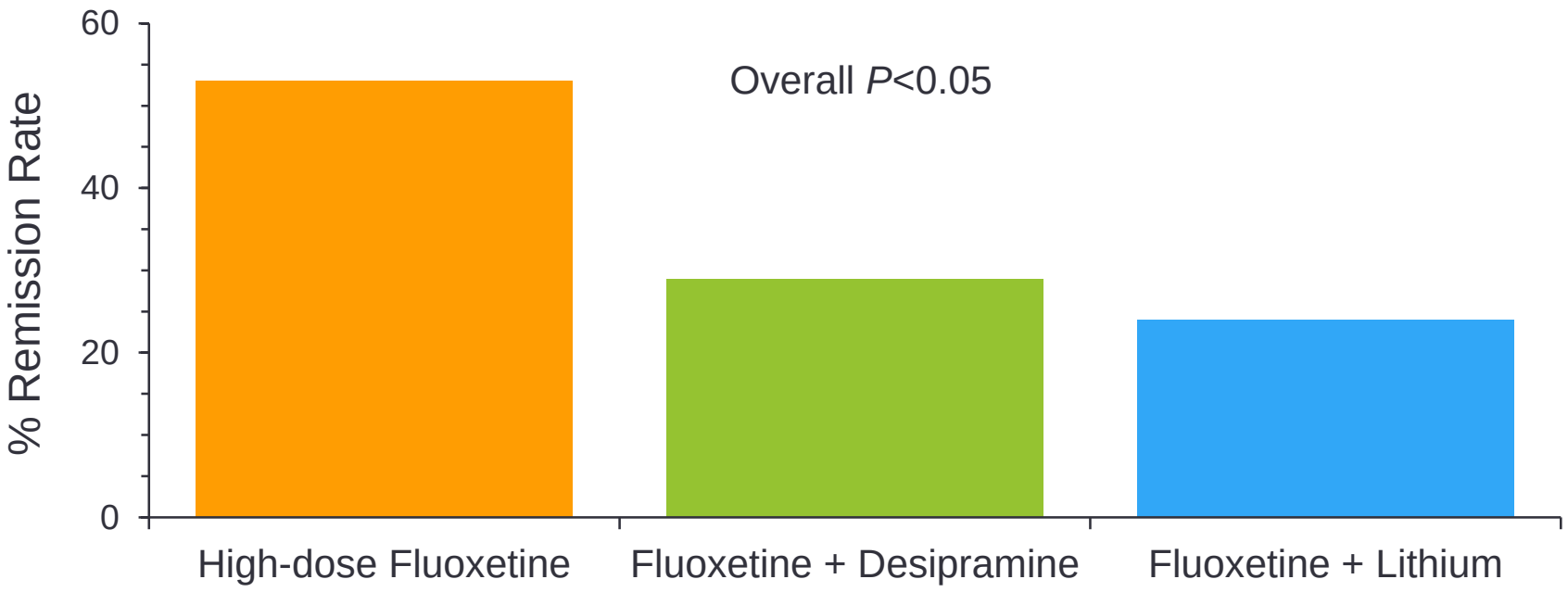
Prospective Active Treatment Lead-in Design: Results

Double-Blind Study of High-Dose Fluoxetine vs. Lithium or Desipramine Augmentation of Fluoxetine in Partial Responders and Non-responders to Fluoxetine



Fava M et al. *Am J Psychiatry* 1994; 15(9): 1372-1374.

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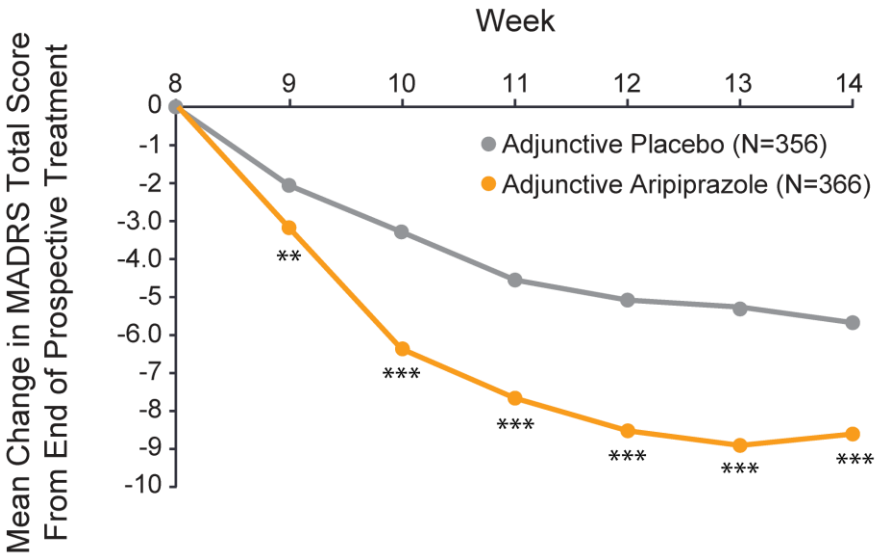
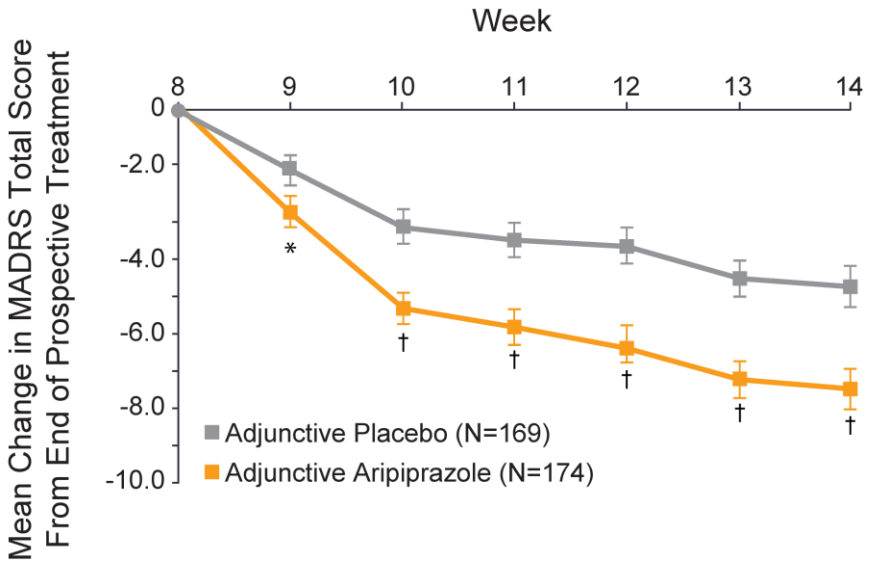
Three Double-Blind Studies of Adjunctive Aripiprazole to ADT in MDD—Two Pooled Studies[1] & a Single Study[2]

TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period



**$p < 0.01$ vs. placebo
***$p < 0.001$ vs placebo

Change in mean (±SE) MADRS Total score during the randomized, double-blind treatment phase (LOCF)



*$p < 0.05$ vs. placebo
†$p < 0.001$ vs. placebo

SE, standard error; MADRS, Montgomery-Åsberg Depression Rating Scale; LOCF, last observation carried forward.

[1]Thase et al, Prim Care Comp *J Clin Psych*. 2008;10(6):440-7.
[2]Berman, RM, Fava M, Thase ME, et al. *CNS Specr.* Vol 14, No. 2009.

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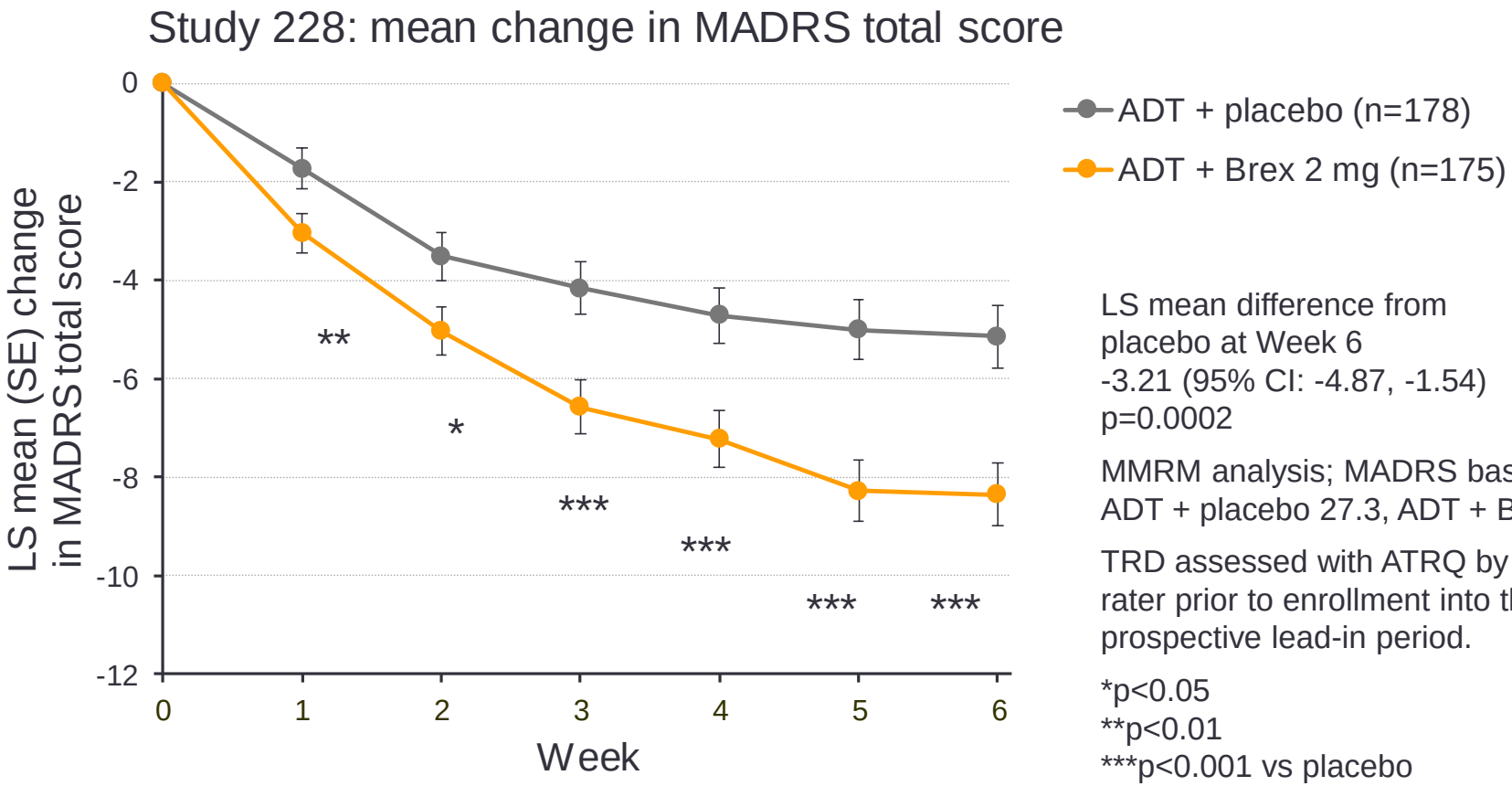
Double-Blind Study of Adjunctive Brexpiprazole to ADT in MDD – Study 228[1]



LS mean difference from placebo at Week 6
-3.21 (95% CI: -4.87, -1.54)
p=0.0002

MMRM analysis; MADRS baseline: ADT + placebo 27.3, ADT + Brex 26.9

TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period.

*p<0.05
**p<0.01
***p<0.001 vs placebo

Thase et al, Prim Care Comp *J Clin Psych*. 2008;10(6):440-7.
NCT01360645, Otsuka (PYXIS *Protocol 331-10-228*) CSR.

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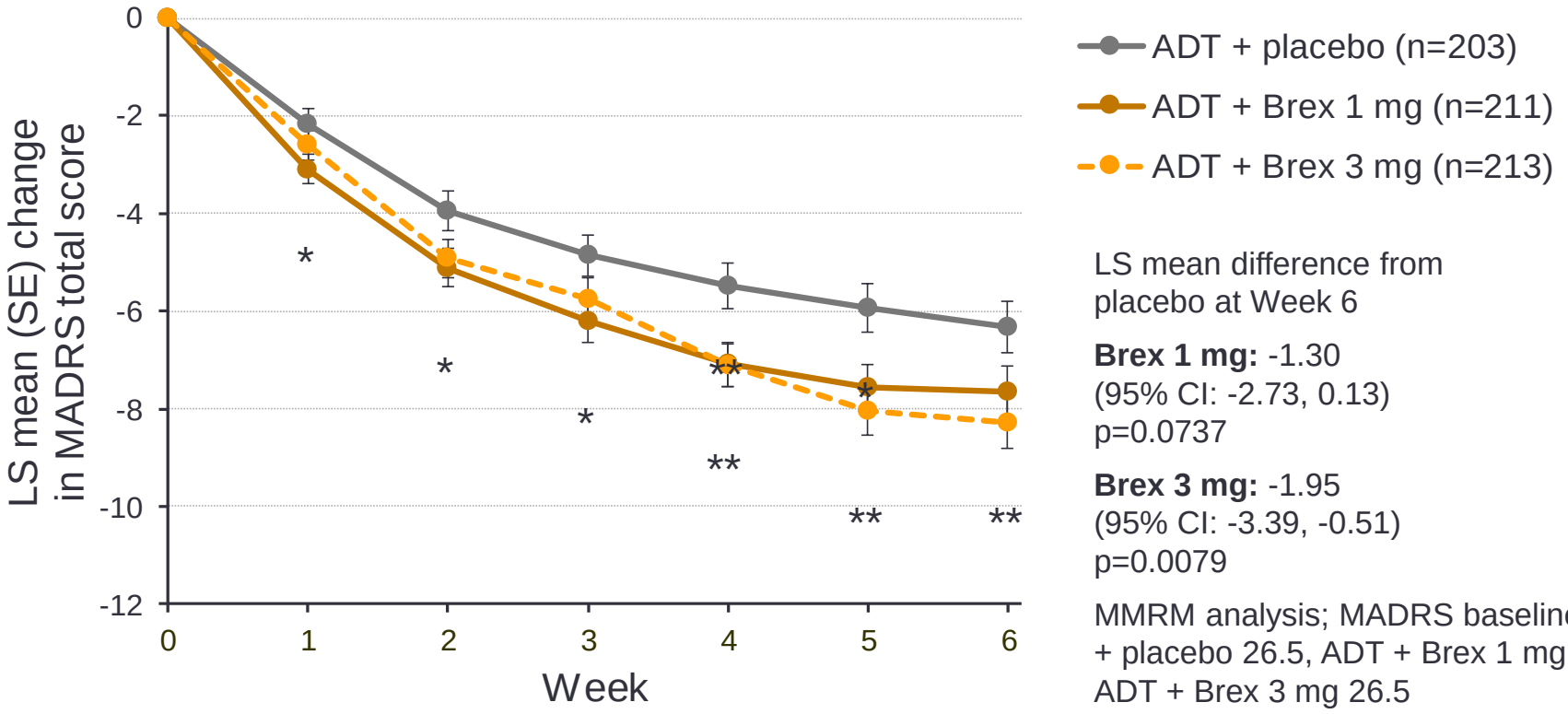
Double-Blind Study of Adjunctive Brexpiprazole to ADT in MDD – Study 227[1]

Study 227: LS mean (SE) change in MADRS total score



LS mean difference from placebo at Week 6

Brex 1 mg: -1.30
(95% CI: -2.73, 0.13)
p=0.0737

Brex 3 mg: -1.95
(95% CI: -3.39, -0.51)
p=0.0079

MMRM analysis; MADRS baseline: ADT + placebo 26.5, ADT + Brex 1 mg 26.9, ADT + Brex 3 mg 26.5

TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period.

*p<0.05
**p<0.001 vs placebo

[1]NCT01668797, Otsuka (Polaris *Protocol* 331-10-227) CSR.

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Independent Assessment: SAFER Interview

- Appropriate selection of patients in clinical trials critical
- SAFER tool improves the selection of patients for trials by confirming:
  - The identified patient is a valid patient for clinical trials
  - The patient's symptoms reflect the current state of illness, and
  - The patient's symptoms can be reliably measured with appropriate measurement tools

Targum SD, Pollack MH, Fava M. *CNS Neurosci Ther*. 2008 Spring;14(1):2-9.

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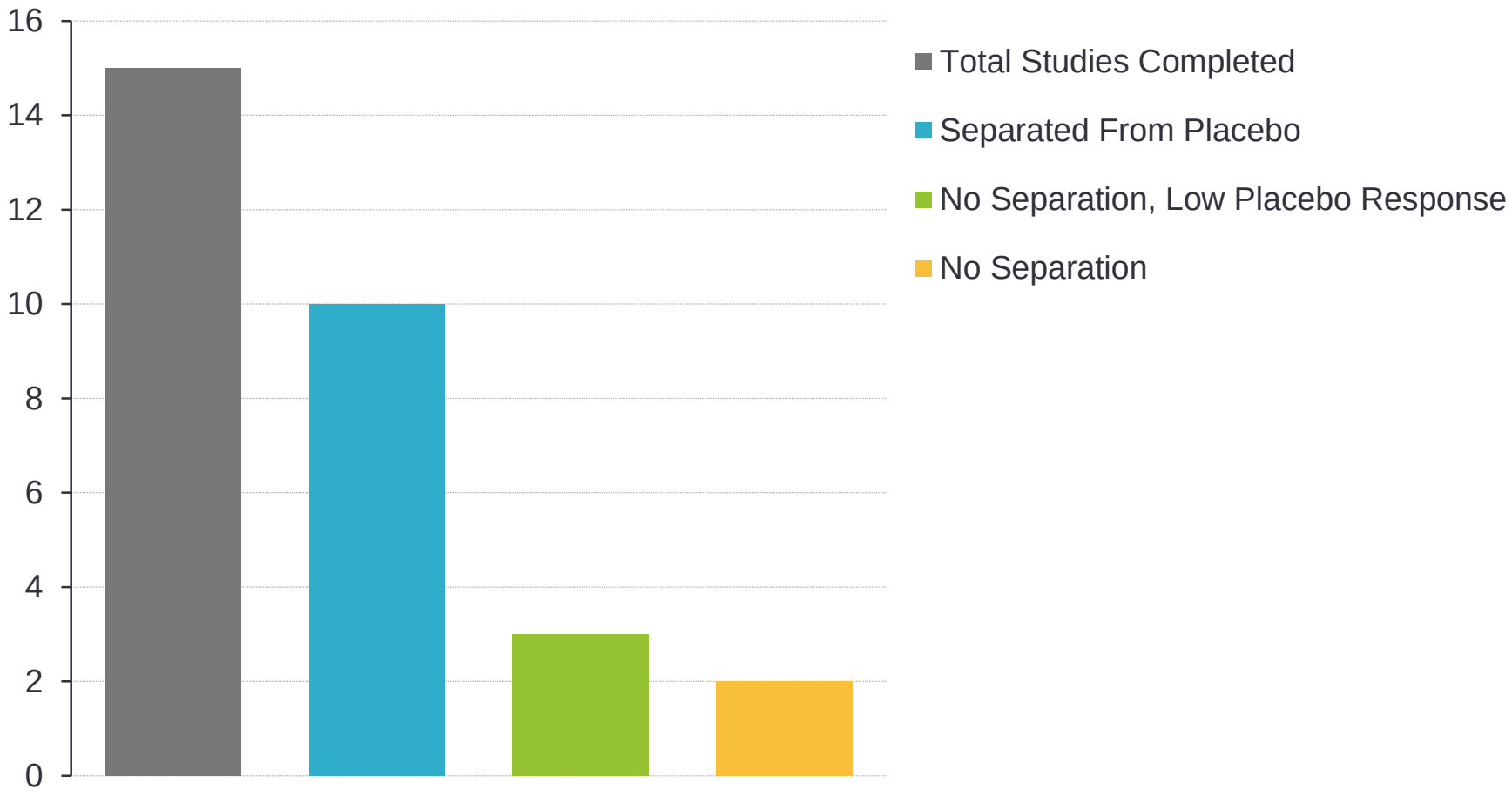
SAFER Results in Completed Studies



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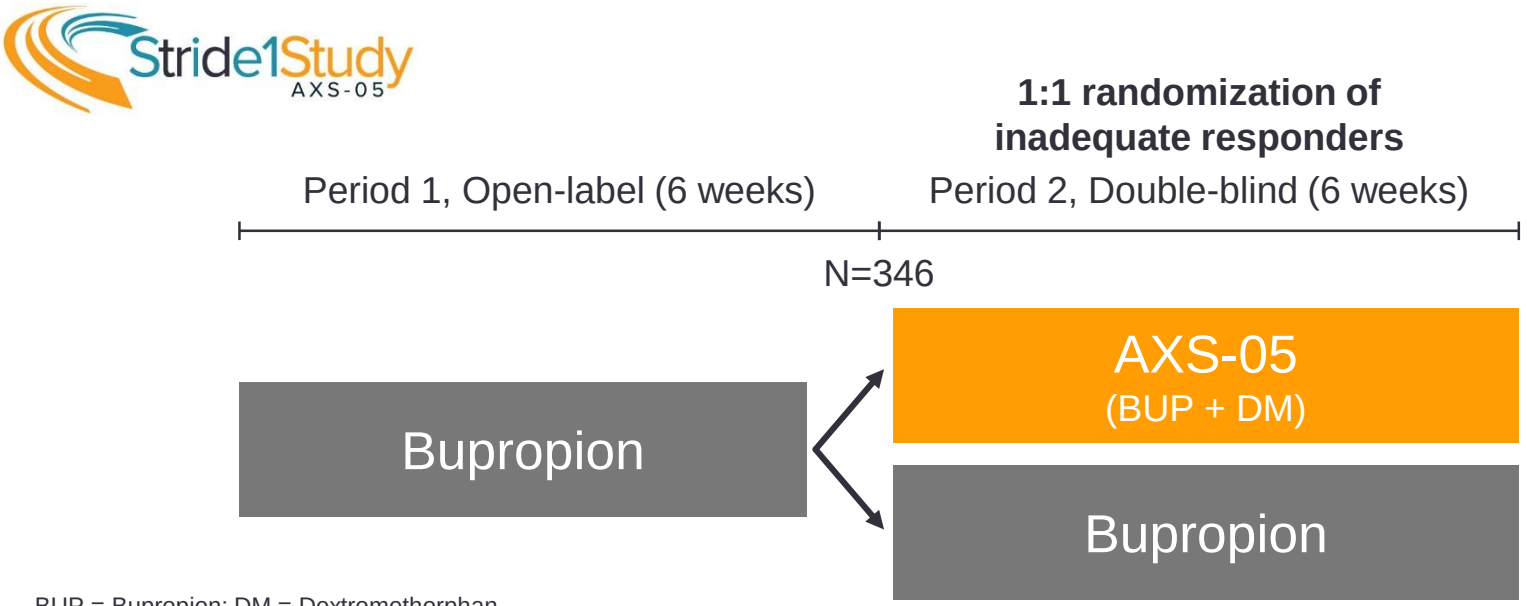
Design of STRIDE-1 Study



BUP = Bupropion; DM = Dextromethorphan.

- Randomized, double-blind, active controlled trial—subjects must have failed 1 or 2 prior adequate ADTs.
- 6-week open-label bupropion lead-in.
- Inadequate responders to bupropion randomized to AXS-05 or placebo.
- Primary endpoint: Change in MADRS from randomization to end of double-blind period.
- Incorporates independent assessments.

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Benefits of STRIDE-1 Design

Prospective Lead-in Enrichment Design:

- Prospective assessment assures that patients are truly resistant—only patients who fail open-label bupropion are randomized.
- Complements historical assessment of previous ADT failure.
- Mitigates effects of treatment history and course of illness heterogeneity.
- Eliminates variability of different background treatments seen with augmentation approaches.

Independent Assessments:

- Minimizes pathophysiological heterogeneity
- Minimizes diagnostic misclassification

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Conclusions

- Glutamate abnormalities are present in MDD patients.
- Drugs that modulate glutamatergic neurotransmission have shown antidepressant effects, in some cases quite rapid.
- Several studies support a relationship between depression and inflammation.
- Medications with anti-inflammatory properties have shown promise in the treatment of MDD.
- AXS-05 combines glutamatergic, monoamine, and anti-inflammatory mechanisms.
- Design of STRIDE-1 should produce an enriched population, minimize heterogeneity, and reduce placebo response.

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Q&A

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Thank you.

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