

Pharmacological Approaches to Treatment-Resistant Depression (TRD)

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First Steps in the Evaluation of TRD Patients

- Diagnostic reassessment
 - Is the patient unipolar or bipolar?
 - What are the psychiatric and medical comorbidities?
- Were the previous trials adequate in dose and duration?
- Are the blood levels of the antidepressant in a therapeutic range?
- What are the possible contributing factors?

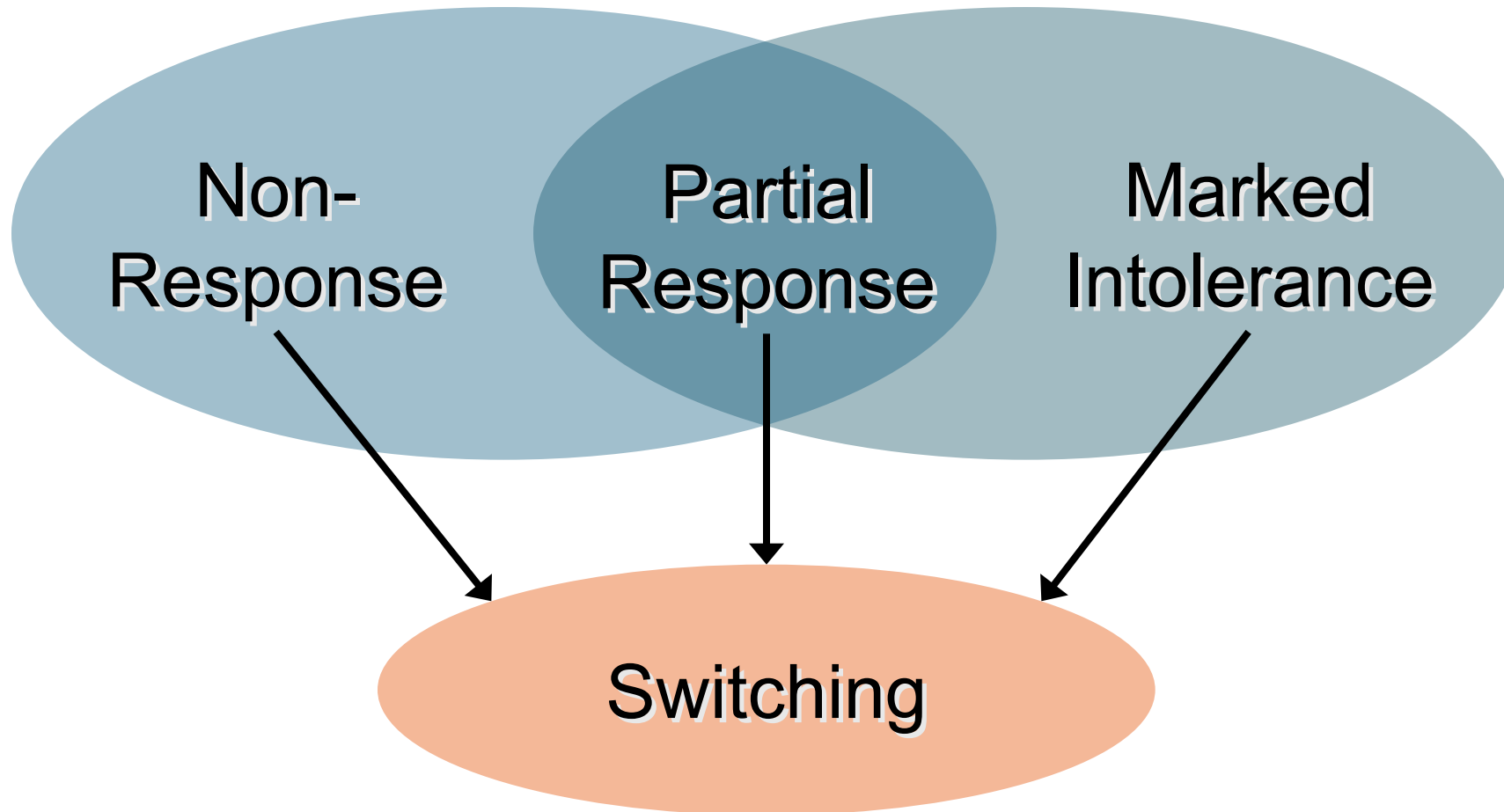
Contributing Factors to TRD

- Misdiagnosis (e.g., bipolar disorder)
- Psychiatric comorbidity (e.g., substance abuse, OCD, PTSD)
- Medical comorbidity (e.g., hypothyroidism)
- Psychotic features
- Pharmacokinetic factors
 - Concomitant use of metabolic inducers
 - Rapid/fast metabolizers

Treatment Strategies for TRD

- Switching
- Dose Increase
- Augmentation
- Combination

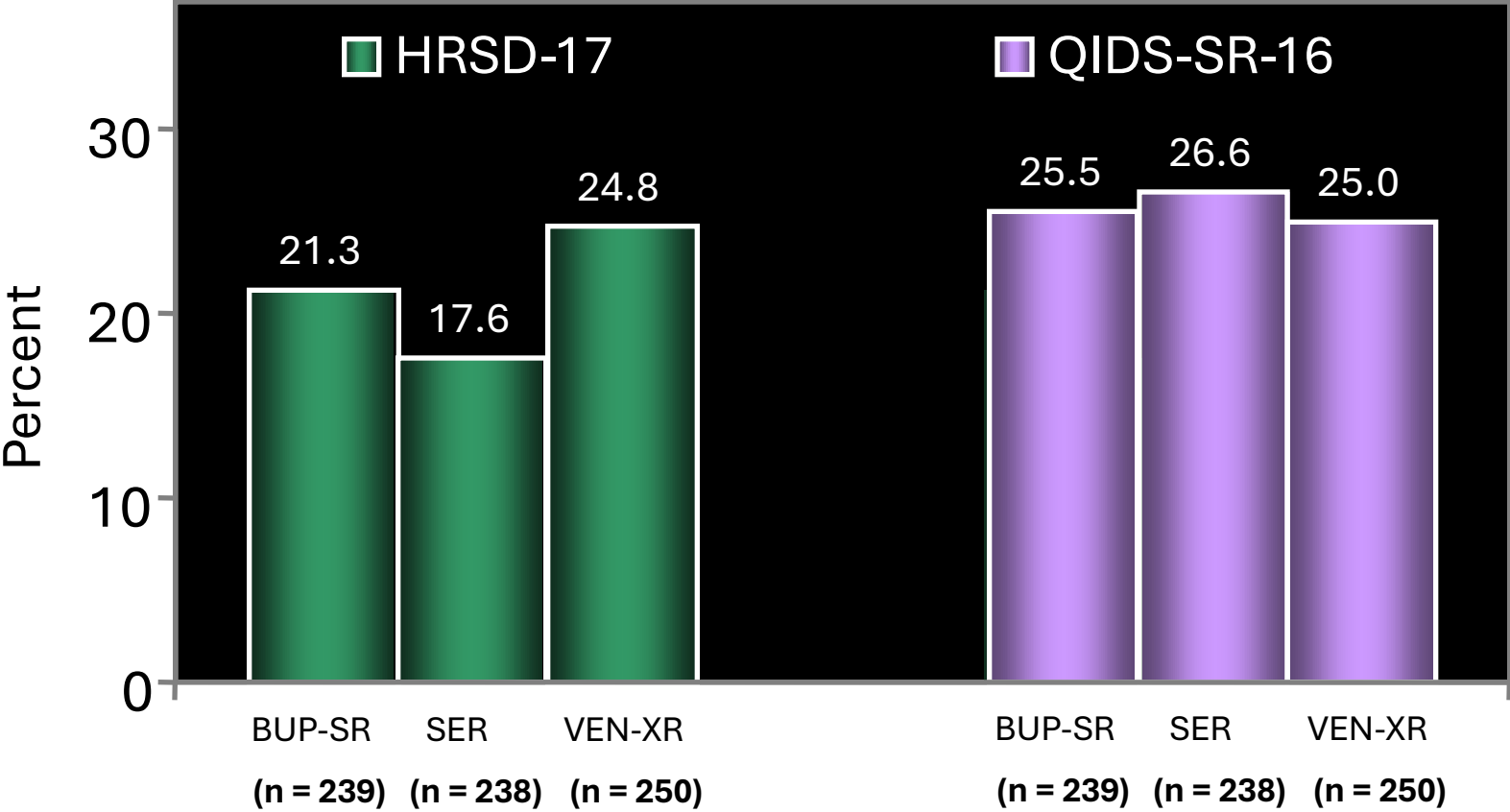
Switching Treatments: For Whom?



Switching: Rationales

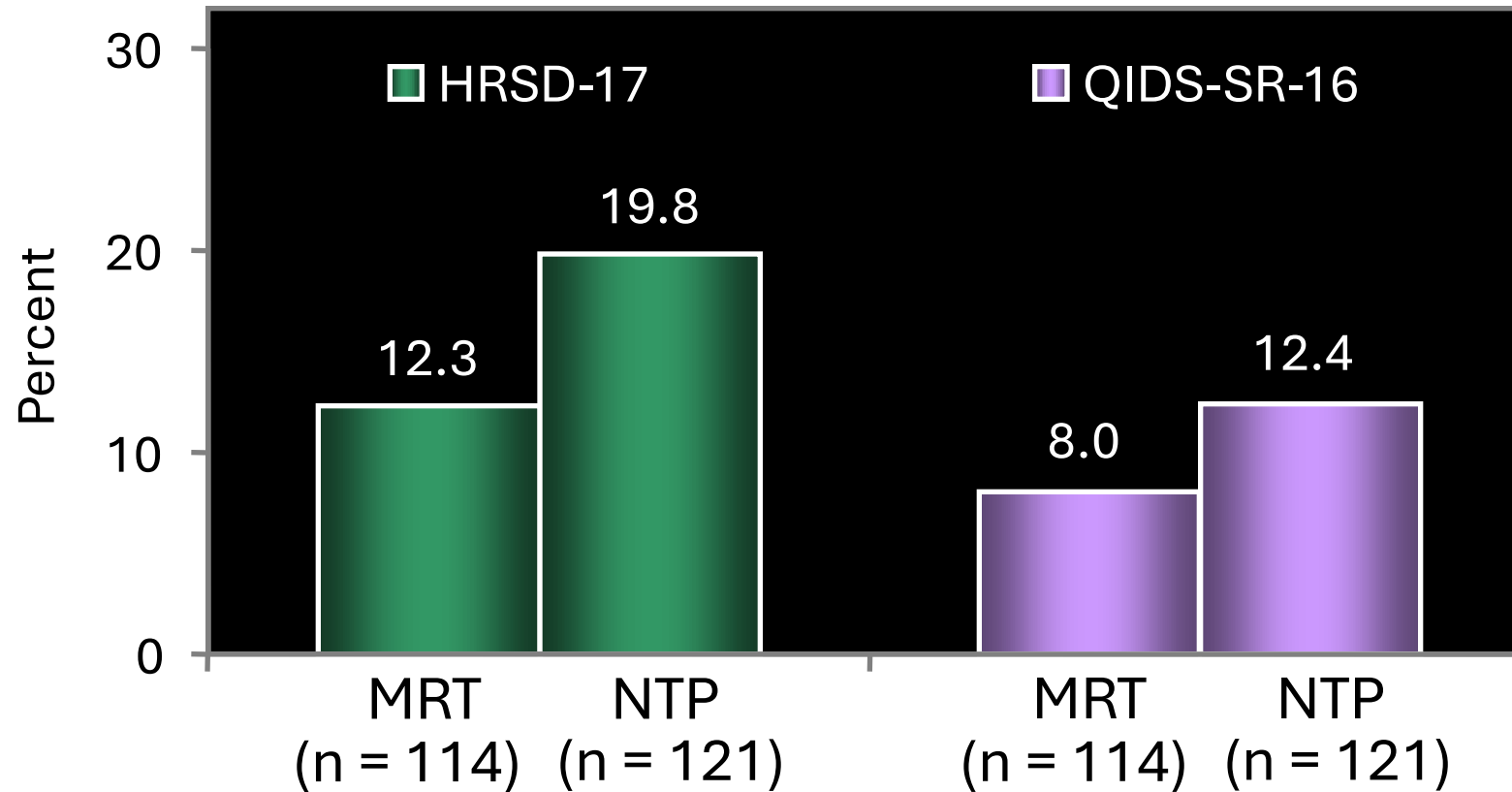
- Switch within Class:
 - There may be some differences across agents within the same class in pharmacological properties in vitro or in vivo (e.g., relatively greater uptake inhibition of other neurotransmitters such as norepinephrine or dopamine)
- Switch to a Different Class:
 - To obtain a different neurochemical effect (e.g., from a relatively serotonergic agent to a relatively noradrenergic agent)
 - A specific depressive subtype may be more responsive to one antidepressant class than another

Remission Rates in STAR*D Level 2 Switch (Bupropion vs Sertraline vs Venlafaxine)



Rush, et al. *N Engl J Med*. 2006;354(12):1231-42.

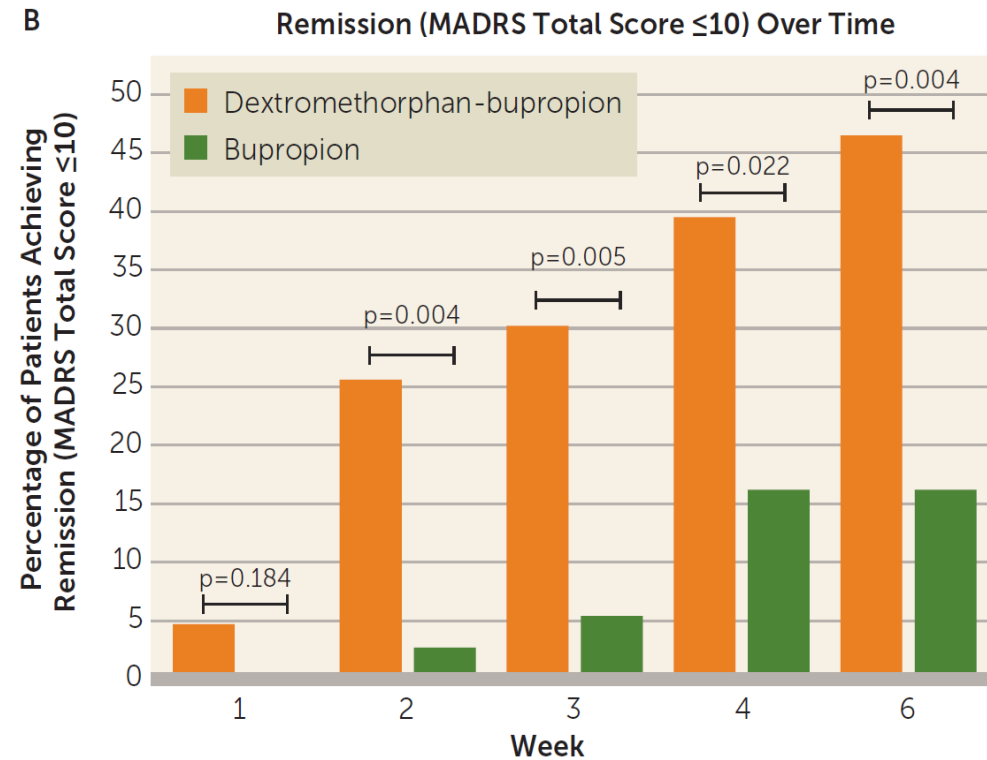
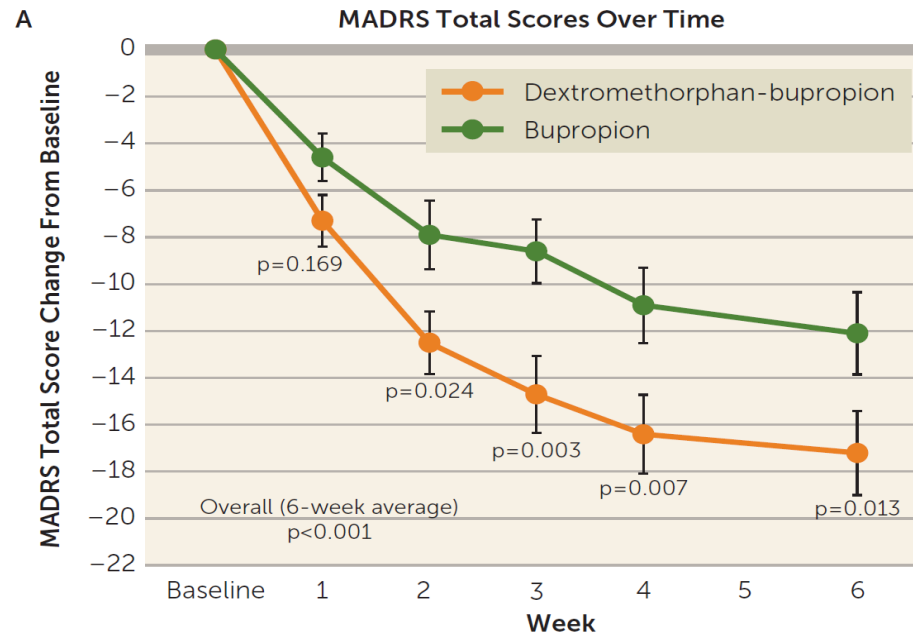
Remission Rates in STAR*D Level 3 Switch (Mirtazapine/MRT vs Nortriptyline/NTP)



Fava, et al. *Am J Psychiatry*. 2006 Jul;163(7):1161-72.

Double-Blind Study in Moderate/Severe MDD of Auvelity [45 mg Dextromethorphan (NMDA Receptor Antagonist and Sigma-1 Agonist)/105 mg Bupropion] vs. Bupropion (105 mg)(n=80) bid

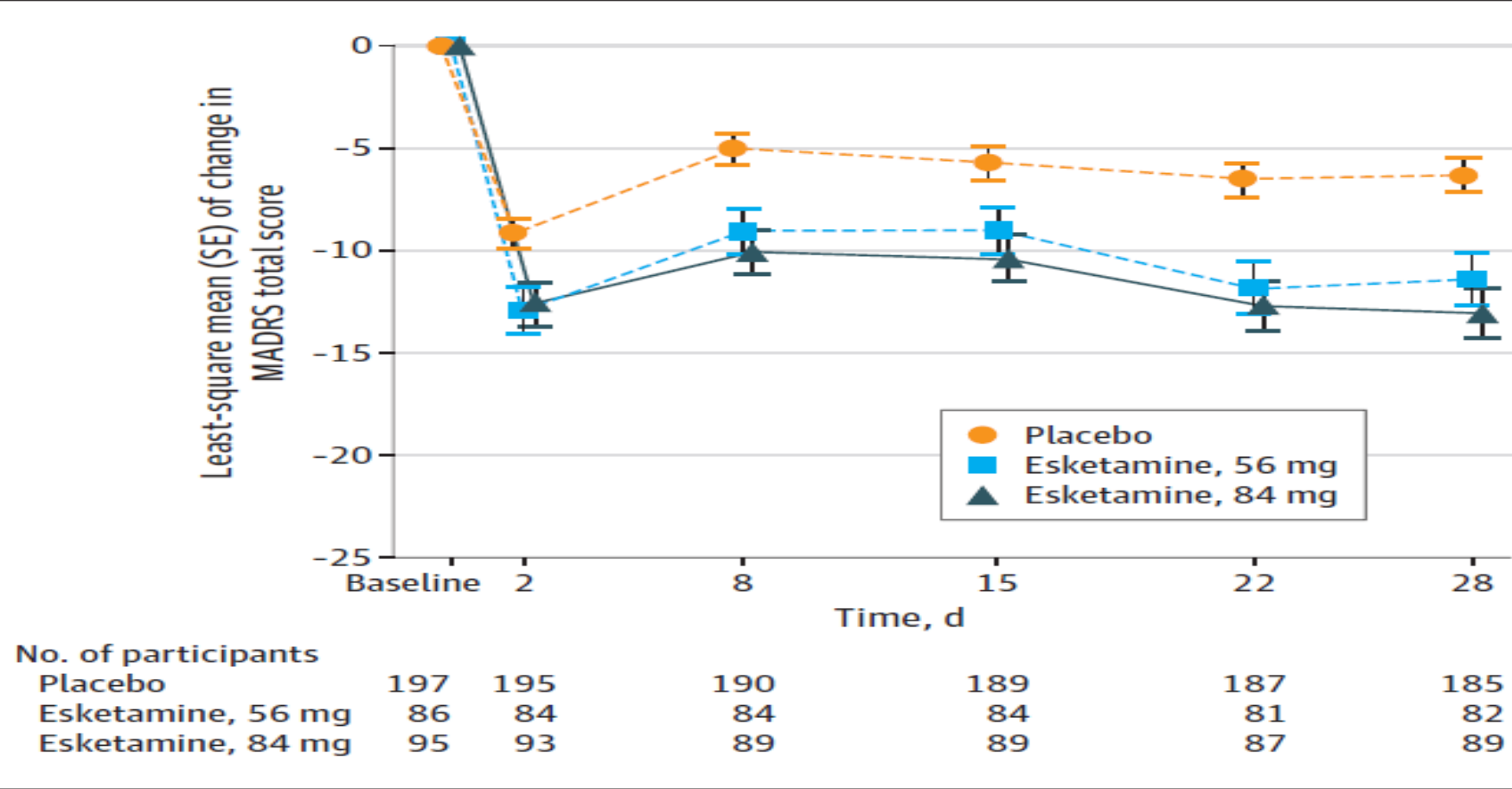
FIGURE 2. MADRS total scores and remission over time in a phase 2 trial of AXS-05 (dextromethorphan-bupropion) for major depressive disorder^a



Tabuteau, et al. *Am J Psychiatry*. 2022;179:490–499. doi: 10.1176/appi.ajp.21080800.

Double-Blind, Placebo-Controlled Trial of Intranasal Esketamine Monotherapy in TRD (n=378)

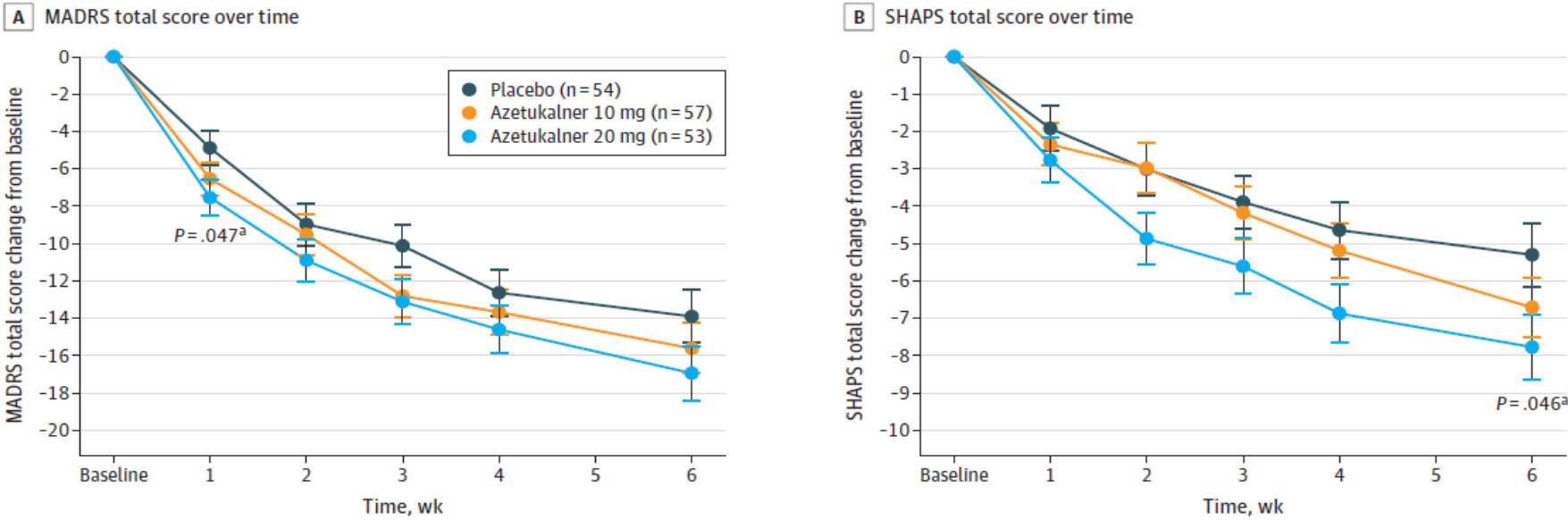
Figure 2. Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score: Change Over Time in the Double-Blind Phase



Janik et al, JAMA Psychiatry
2025 Jul 2:e251317.

A Double-Blind, Placebo-Controlled Trial of Azetukalner, a KV7 potassium channel opener, in participants with MDD (n=168)

Figure 2. Least-Squares Mean Changes in Montgomery-Åsberg Depression Rating Scale (MADRS) and Snaith-Hamilton Pleasure Scale (SHAPS) Total Scores From Baseline Over Time in the Modified Intent-to-Treat Population



Butterfield et al, JAMA Netw Open.
2025 May 1;8(5):e2514278.

The modified intent-to-treat population included all randomized participants who received at least 1 dose of study treatment and at least 1 postrandomization MADRS score. A mixed-effect model for repeated measures was used to perform the analysis, with change from baseline as the outcome variable; the baseline MADRS score as a covariate; and treatment group, visit (up to week 6 visit), and treatment-by-visit

interaction as fixed effects. All doses were taken once daily with food with no titration. The modified intent-to-treat population per week 1 treatment represents 2 participants in the 20-mg group who changed to the 10-mg group during week 1.

^a Azetukalner 20 mg vs placebo, nominal $P < .05$.

The probiotic *Bifidobacterium breve* CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: A randomized, placebo-controlled clinical trial

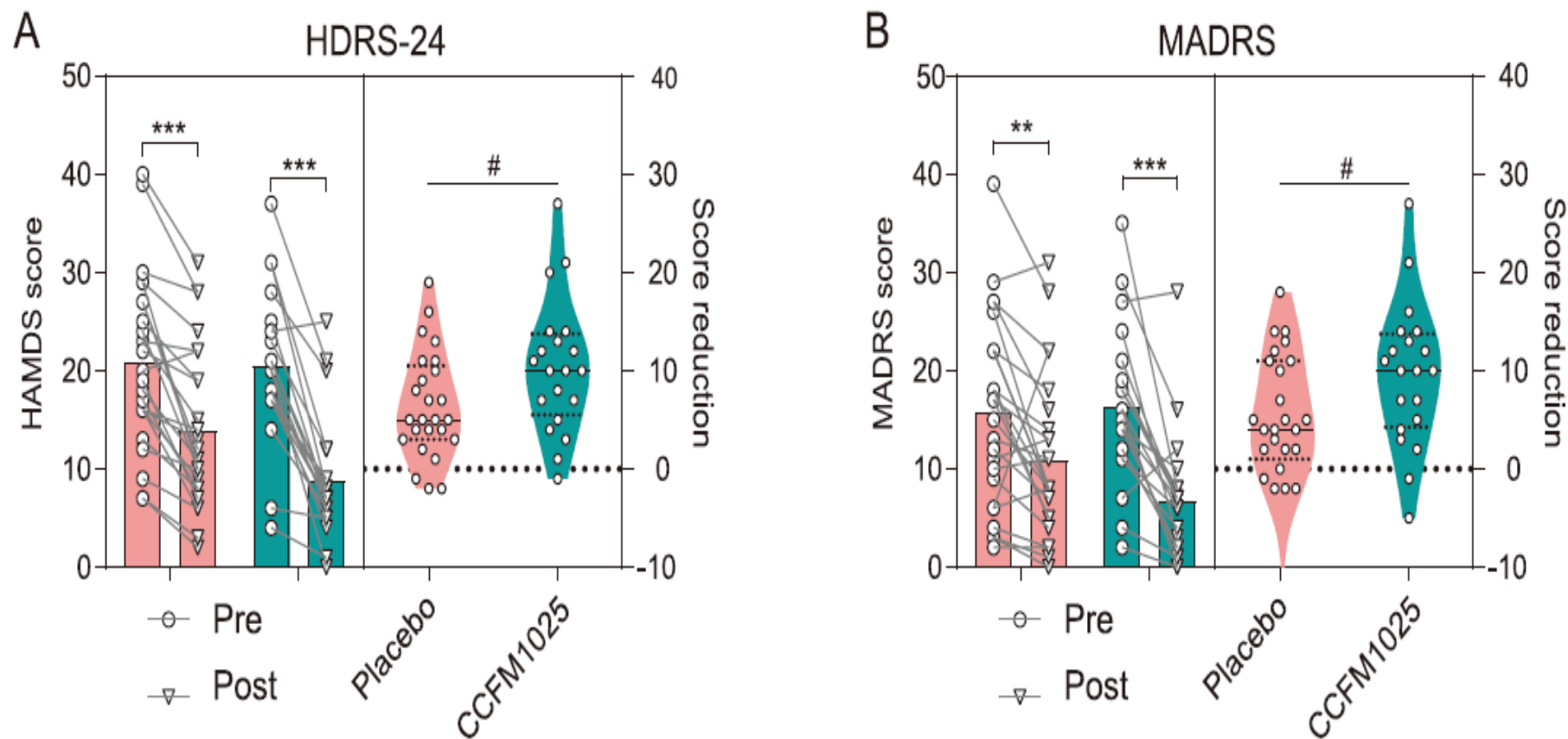


Fig. 2. *B. breve* CCFM1025's effect on alleviating depression symptoms. (A) The rating score change of the Hamilton Depression Rating scale-24 Items (HDRS-24). (B) The rating score changes of the Montgomery-Asberg Depression Rating Scale (MADRS). (C) The rating score changes of the Brief Psychiatric Rating Scale (BPRS). (D) Factor analysis of BPRS. (E) The rating score changes on the Gastrointestinal Symptom Rating Scale (GSRS). (F) Factor analysis of GSRS. In Figures A, B, C & E, a line connects each participant between day 0 (pre) and day 28 (post), and the reductions are represented as a histogram in the right panel. Colours distinguish groups. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ in Sidak's multiple comparisons test post two-way ANOVA. # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ in the unpaired t-tests.

Tian et al, Brain Behavior and Immunity 100 (2022) 233–241

Switching: Practical Approaches

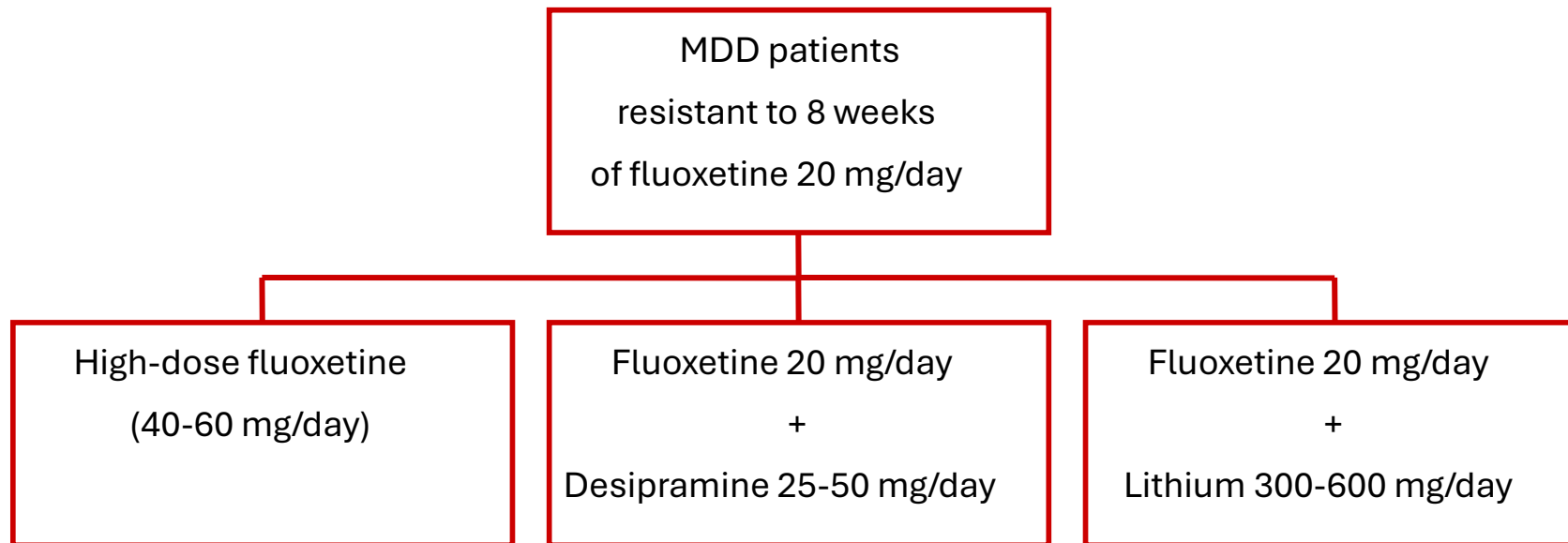
- Gradual tapering the first agent while starting the new one
 - Side effects of the new drug may be intensified by the concurrent presence of the first agent
 - “Start low and go slow” with the new agent
 - Consider possible drug-drug interactions
- Abrupt replacement with within class-switches
- Wash-outs are necessary with MAOIs (either when you start them or when you stop them)

Dose Increase

- Definition:
 - The use of doses higher than those considered standard for a given antidepressant
- Rationale:
 - To increase the chance of obtaining adequate blood levels in rapid metabolizers
 - To obtain a different neurochemical effect (e.g., going from a relatively selective serotonergic effect at lower doses to a dual-action effect at higher doses)

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

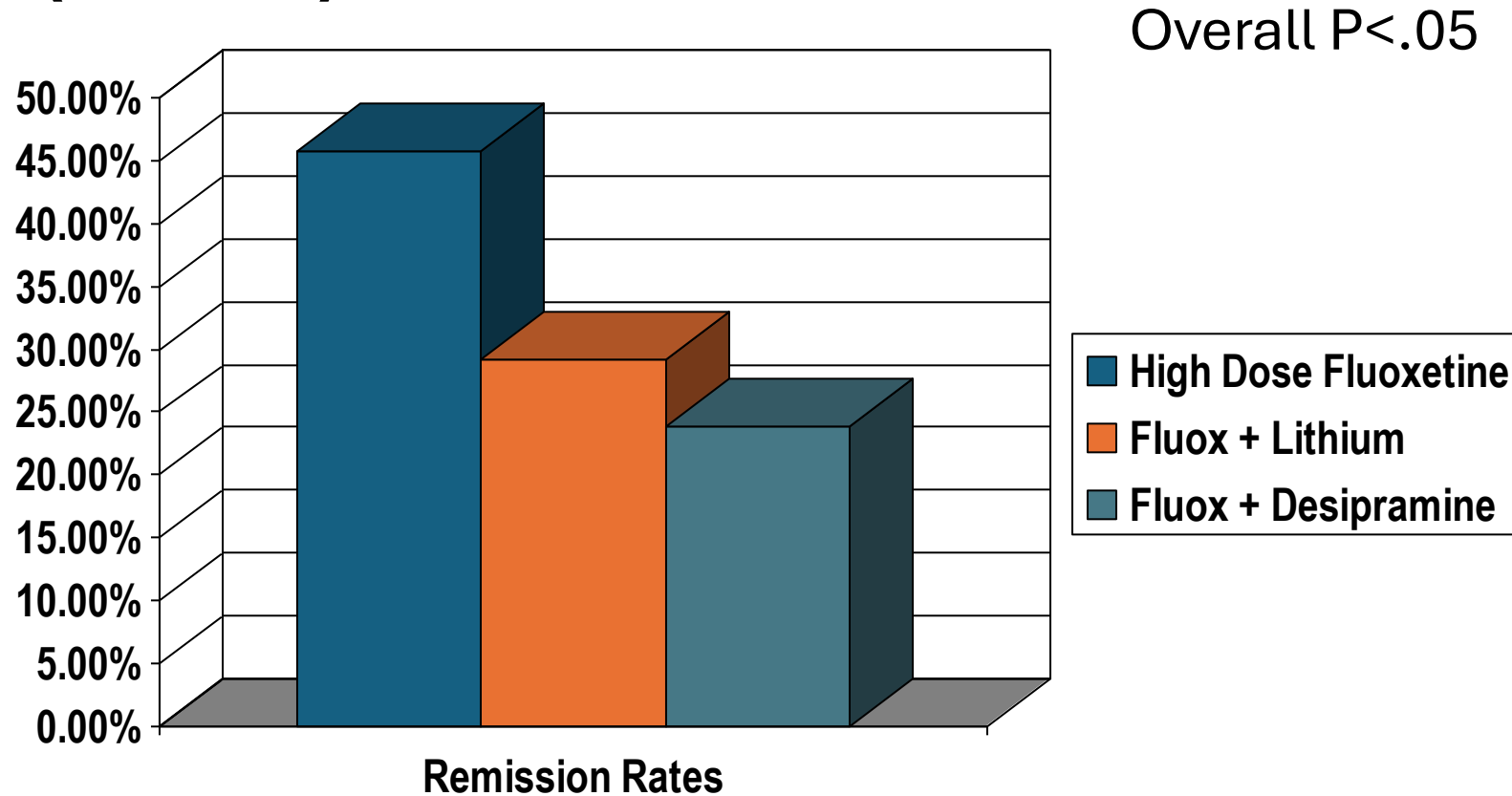
Trial Design



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

Fava M. *J Clin Psychopharmacol*. 2002 Aug;22(4):379-387.

Double-Blind Studies of High-Dose Fluoxetine vs. Fluoxetine Augmentation with Lithium or Desipramine (n = 142)



Data pooled from Fava M, et al. *Am J Psychiatry*. 1994 Sep;151(9):1372-4.
Fava M, et al. *J Clin Psychopharmacol*. 2002 Aug;22(4):379-87.

Dose Increase: Practical Approaches

- Gradual increasing the dose by 50-100%
- Wait at least 4 weeks before deciding whether this strategy helps
- If no side effects are present, consider increasing the dose further
- Blood levels may be informative (even with SSRIs or other newer antidepressants)

Augmentation

- Definition: the use of a psychotropic agent (without per se an indication for depression) to enhance the effect of an antidepressant
- Rationale:
 - To obtain a different neurochemical effect by adding an agent affecting different neurotransmitter systems
 - To broaden the therapeutic effect (e.g., by adding an anti-anxiety agent to an antidepressant)
 - To combine agents with different mechanisms of action and/or indications

Lithium Augmentation

- Lithium augmentation (> 600 mg/day) of TCAs, MAOIs, and SSRIs

Bauer M, Dopfmer S. *J Clin Psychopharmacol*. 1999 Oct;19(5):427-34.

- **Disadvantages:**

- Relatively low response rates in most recent studies

Fava M, et al. *J Clin Psychopharmacol*. 2002 Aug;22(4):379-87.

Nierenberg AA, et al. *J Clin Psychopharmacol*. 2003 Feb;23(1):92-5.

- Risk of toxicity

Salama AA, Shafey M. *Am J Psychiatry*. 1989 Feb;146(2):278.

- Need for blood monitoring

- **Advantage:** The pooled odds ratio (from 9 studies) of response during lithium augmentation compared with placebo is 3.31 (95% confidence interval: 1.46-7.53)

Bauer M, Dopfmer S. *J Clin Psychopharmacol*. 1999 Oct;19(5):427-34.

Meta-Analysis of Lithium Augmentation of Tricyclic and Second Generation Antidepressants in MDD

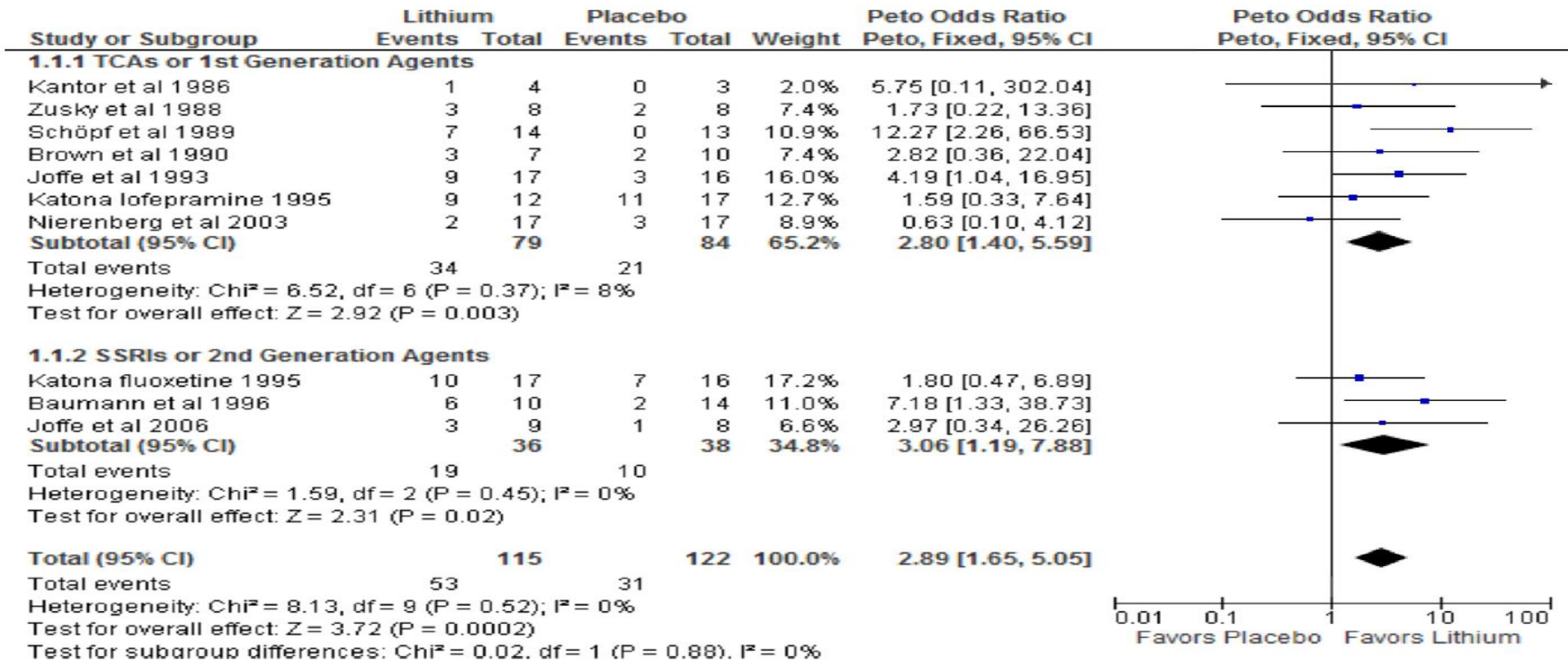
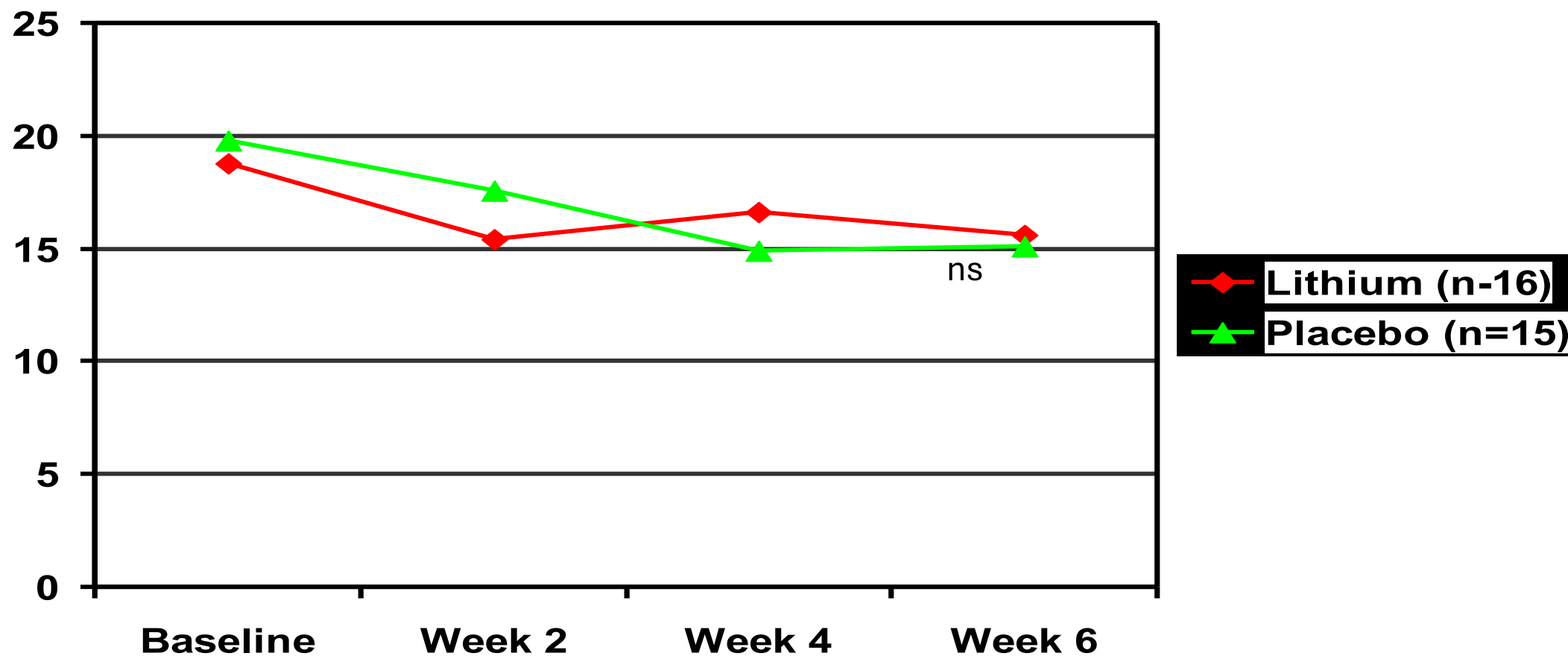


Fig. 2. Meta-analysis of 9 randomized placebo-controlled lithium augmentation trials in depression with 10 contrasts grouped by the type of antidepressant augmented.

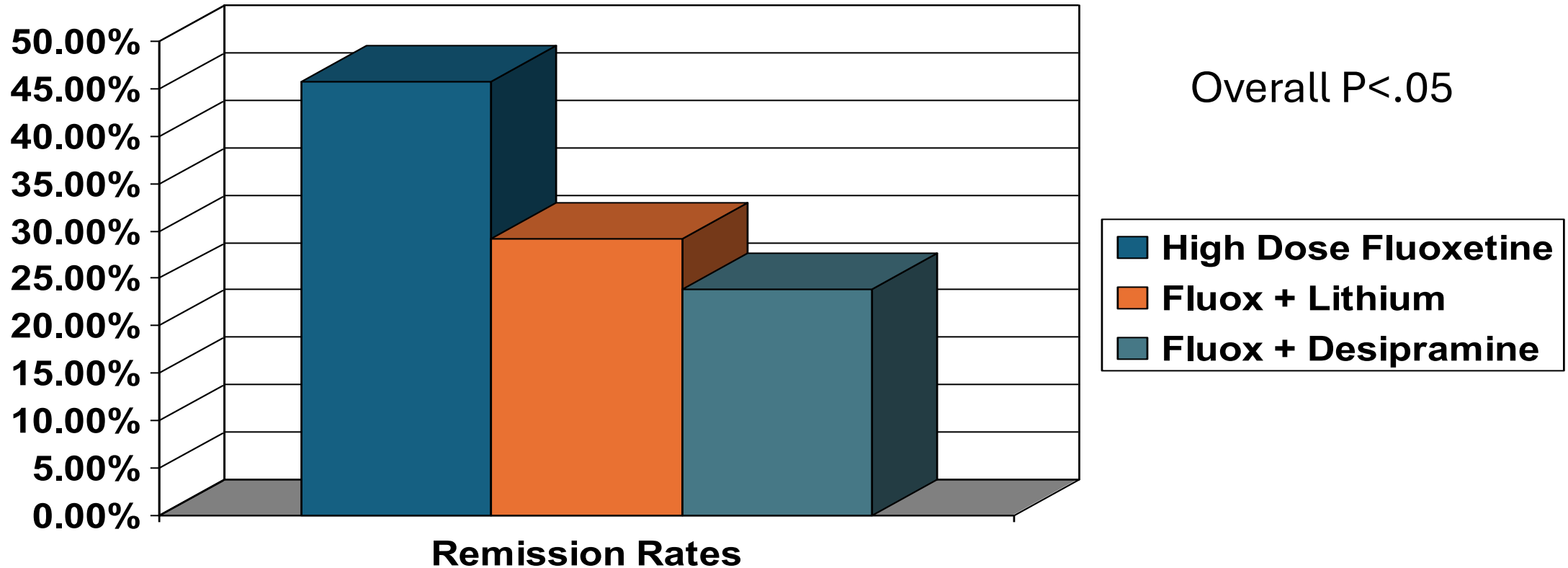
Nelson, et al. *Journal of Affective Disorders*. 168(2014)269–275.

Double-Blind, Placebo-Controlled Study of Lithium Augmentation of Nortriptyline (n=31)



Nierenberg AA, et al. *J Clin Psychopharmacol*. 2003 Feb;23(1):92-5.

Double-Blind Studies of High-Dose Fluoxetine vs. Fluoxetine Augmentation with Lithium or Desipramine (n = 142)



Data pooled from Fava M, et al. *Am J Psychiatry*. 1994 Sep;151(9):1372-4.
Fava M, et al. *J Clin Psychopharmacol*. 2002 Aug;22(4):379-87.

Lithium Augmentation Versus Citalopram Combination in Imipramine-Resistant Major Depression: A 10-Week Randomized Open-Label Study (n=104)

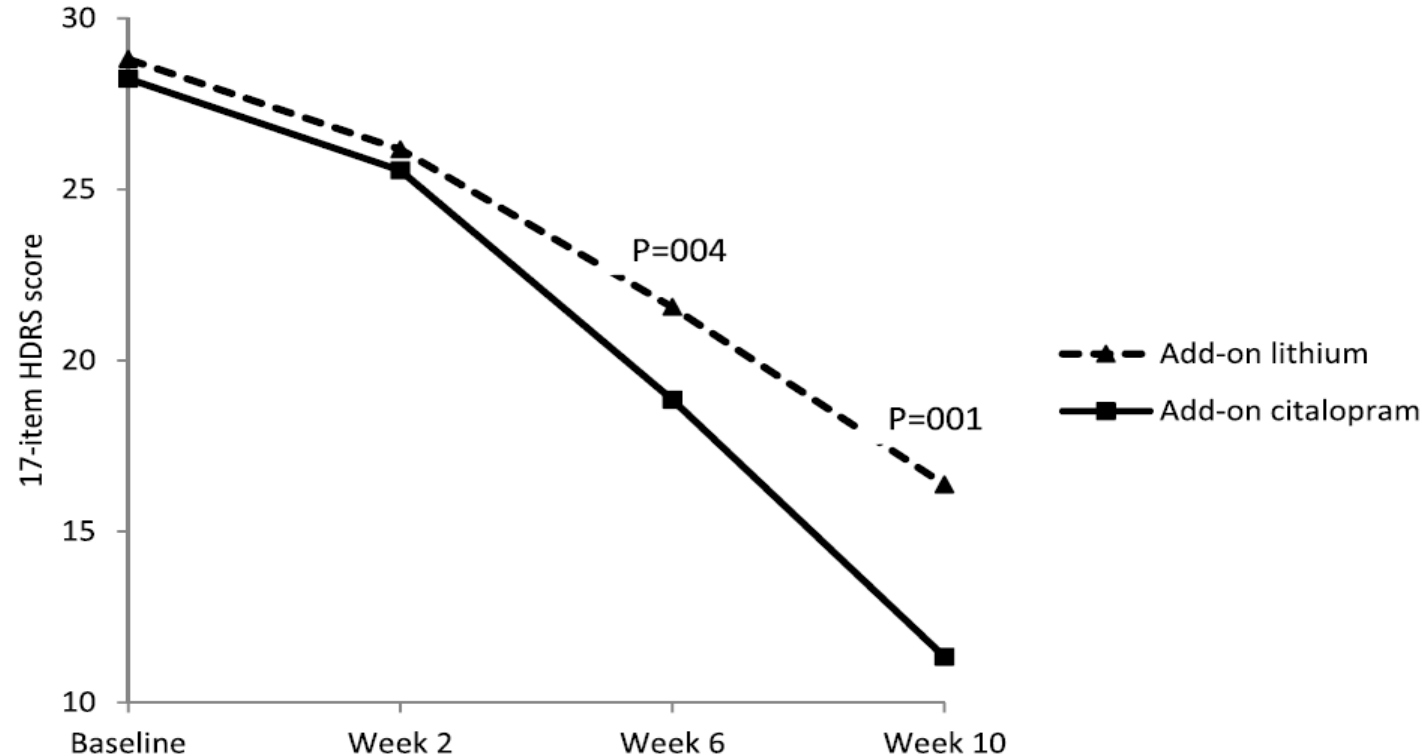


FIGURE 1. Repeated measures to compare efficacy of add-on lithium and add-on citalopram. Values represent means. *P* values show the result of the independent *t* test comparing HDRS scores between the 2 groups from baseline to each time point. NS indicates nonsignificant.

Navarro, et al. *J Clin Psychopharmacol.* 2019;39: 254–257.

Lithium versus Quetiapine Augmentation for Treatment-Resistant Depression: a Pragmatic, Open-label, Parallel-group, Randomized controlled superiority trial in the UK (n=212)

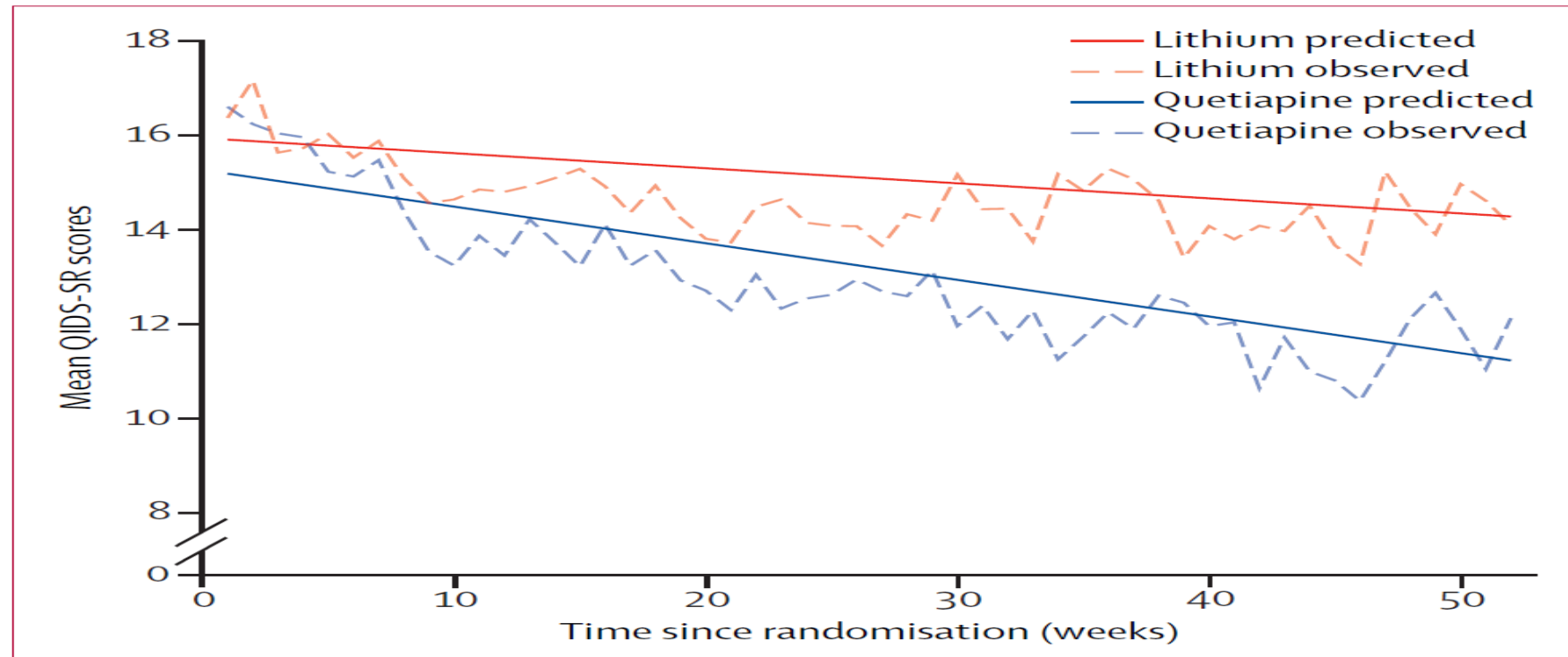


Figure 2: Observed and predicted weekly QIDS-SR scores in the intention-to-treat population

QIDS-SR=Quick Inventory of Depressive Symptomatology.

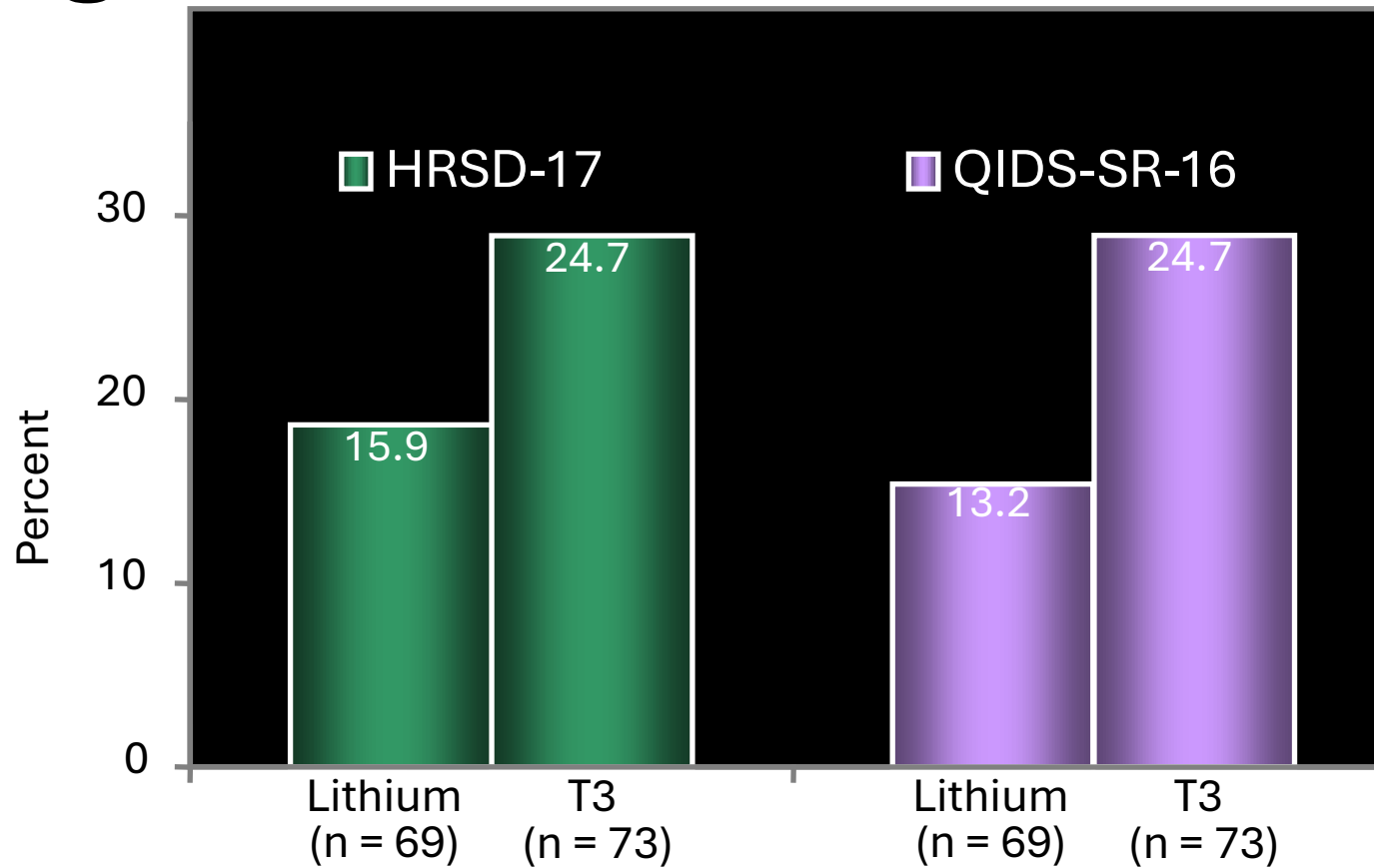
Cleare et al, Lancet Psychiatry 2025; 12: 276–88

Thyroid Augmentation

- Thyroid hormone augmentation (25-50 mcg/day)
Aronson R, et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.
- L-triiodothyronine (T3) has been used in preference and has been thought to be superior to thyroxine (T4)
Joffe RT, Singer W. Psychiatry Res. 1990 Jun;32(3):241-51.
- **Disadvantages:**
 - All published controlled studies concern TCAs
Aronson R, et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.
and only uncontrolled studies pertain to SSRIs
Agid O. Int J Neuropsychopharmacol. 2003 Mar;6(1):41-49.
Losifescu D, et al. J Clin Psychiatry. 2005 Aug;66(8):1038-42).
- **Advantage:** Among the four randomized, double-blind studies, pooled effects were not significant (relative response: 1.53; 95% CI: 0.70-3.35; $p = .29$)
Aronson R, et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.

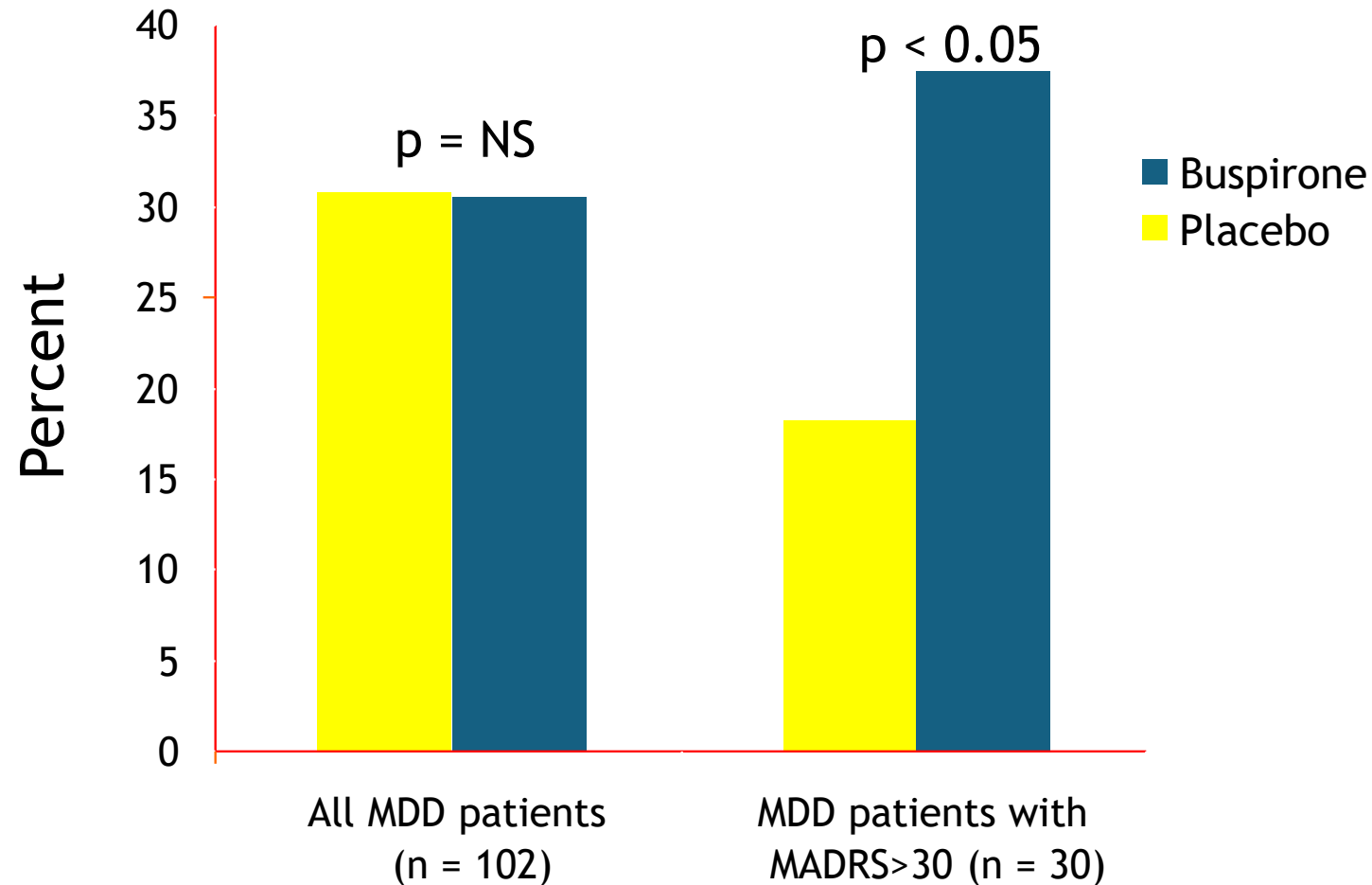
Remission Rates in STAR*D

Level 3 Augmentation: Lithium vs. T3



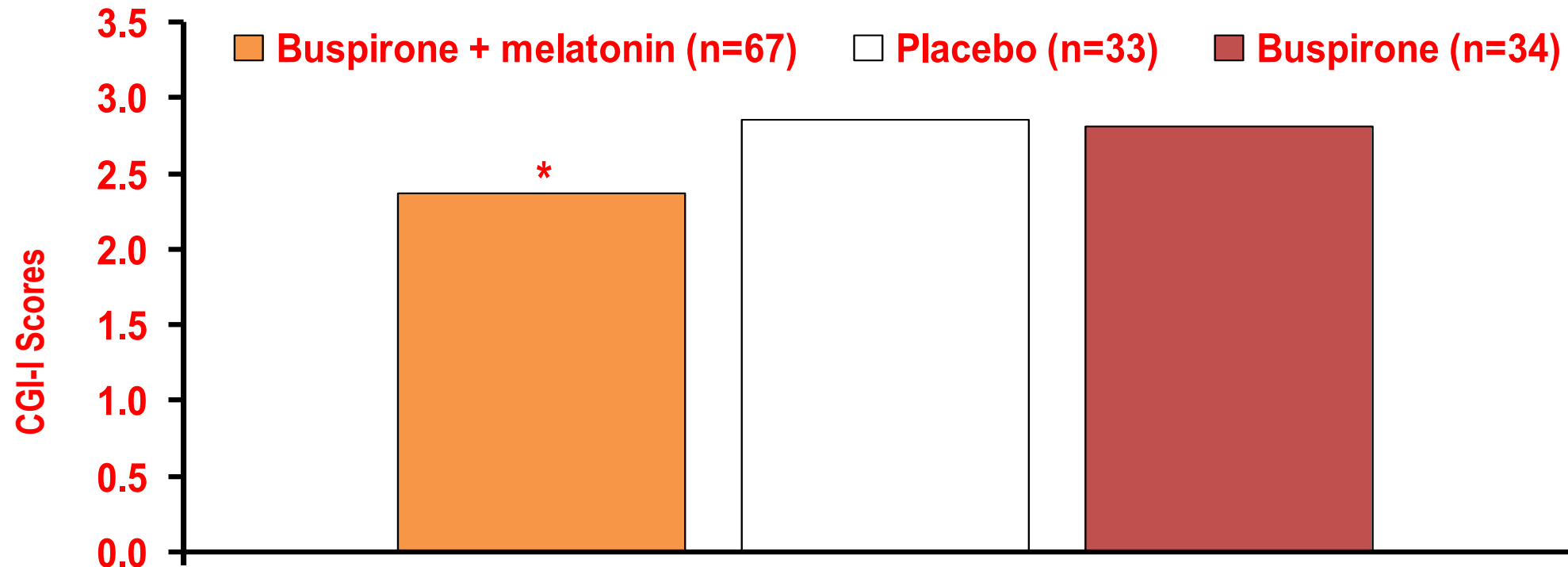
Nierenberg, et al. *Am J Psychiatry*. 2006;163:1519-1530.

Percentage Reduction in MADRS Scores with Buspirone vs. Placebo Augmentation of SSRIs



Appelberg BG, et al. *J Clin Psychiatry*. 2001;62:448-452.

Low-Dose Combination of Buspirone (15 mg/day) and Melatonin (3 mg qhs), Stimulating Hippocampal Neurogenesis, in MDD (n=134)



*p<.05 combination vs. placebo and buspirone alone.

This information includes a use that has not been approved by the US FDA.

Fava, et al. *J Psychiatr Res.* 2012 Dec;46(12):1553-63.

Lisdexamfetamine Dimesylate Augmentation for MDD with Inadequate Response to Antidepressant Monotherapy: Results from 2 Phase 3 Studies* (n=826)

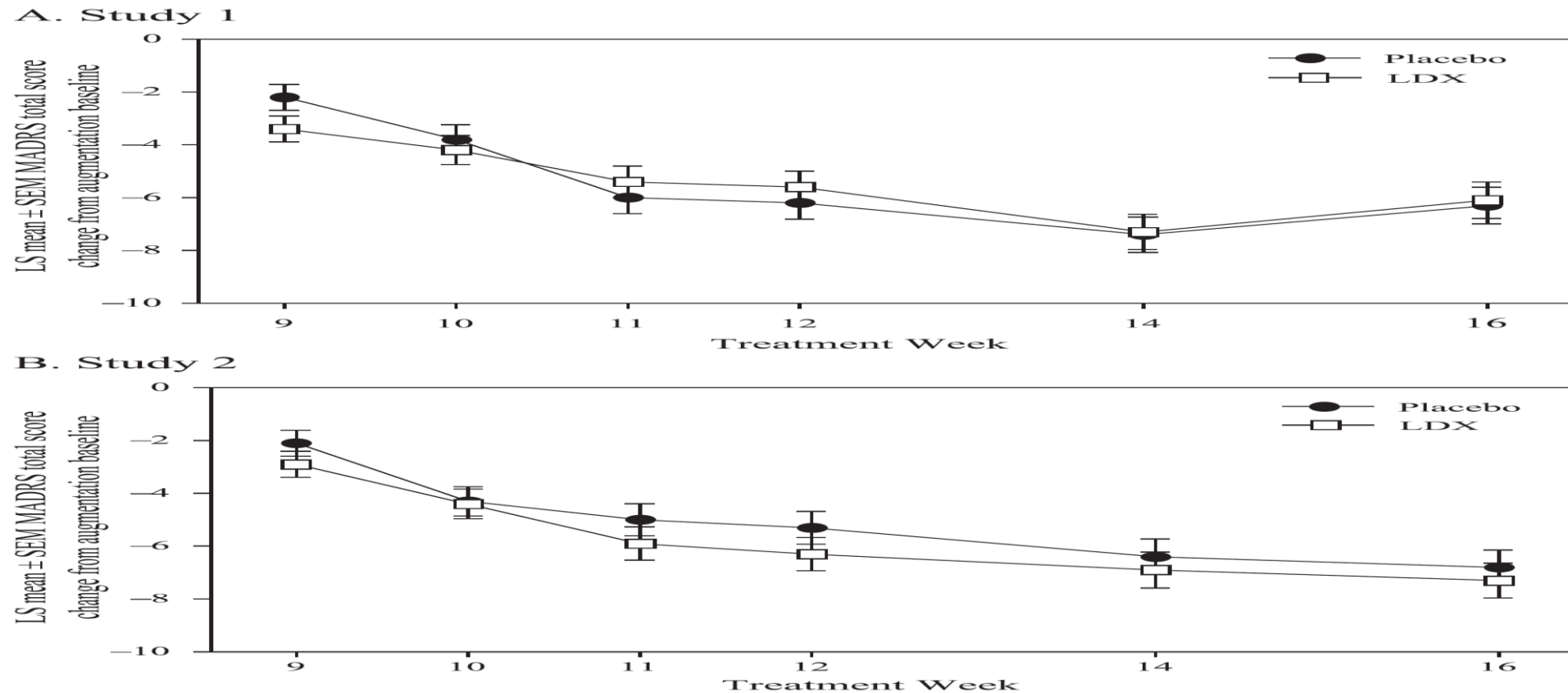


Fig. 3. Change in MADRS total score during double-blind treatment (full analysis set) for Study 1 (A) and Study 2 (B). LDX=lisdexamfetamine; dimesylate MADRS=Montgomery-Åsberg Depression Rating Scale.

*TRD assessed with ATRQ by site rater prior to enrollment into the prospective lead-in period Data derived from ClinicalTrials.gov.

Richards, et al. *Journal of Affective Disorders*. 2016;206:151–160.

Pooled Analysis of Studies on Modafinil (200 mg/day) Augmentation in SSRI Partial Responders with MDD and Persistent Fatigue and Sleepiness (n=348)

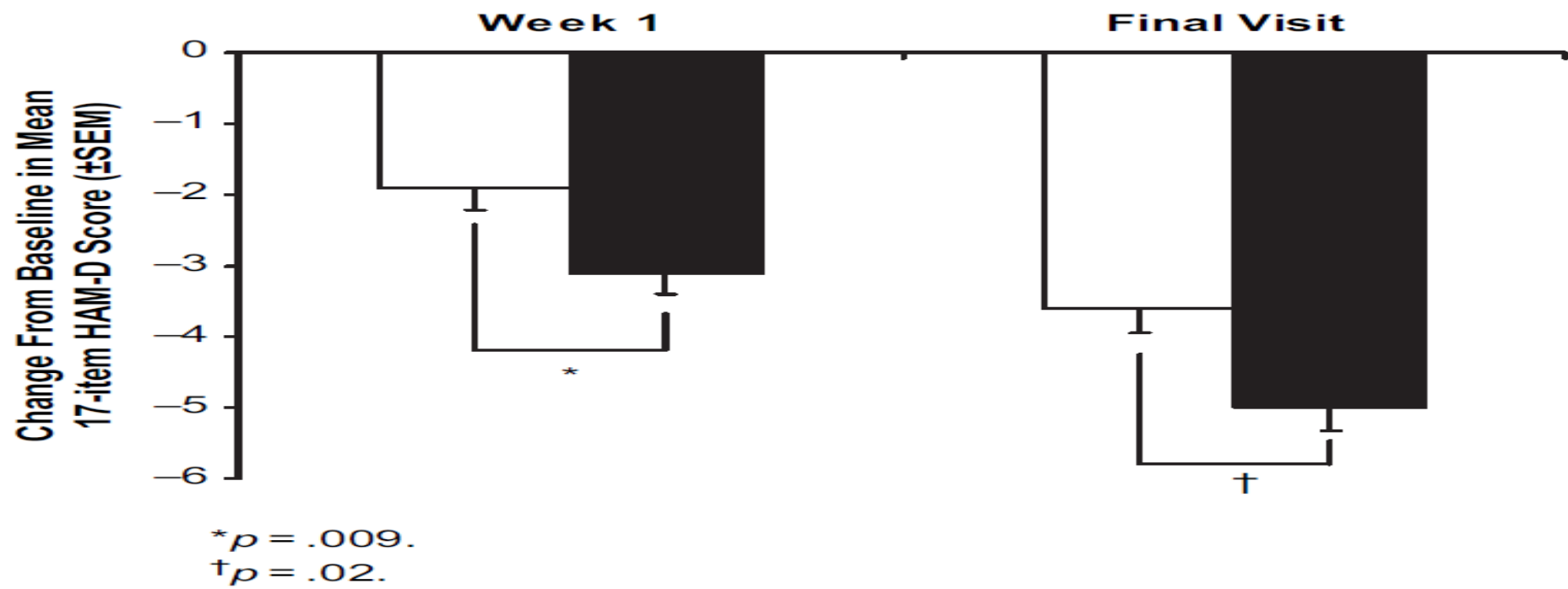
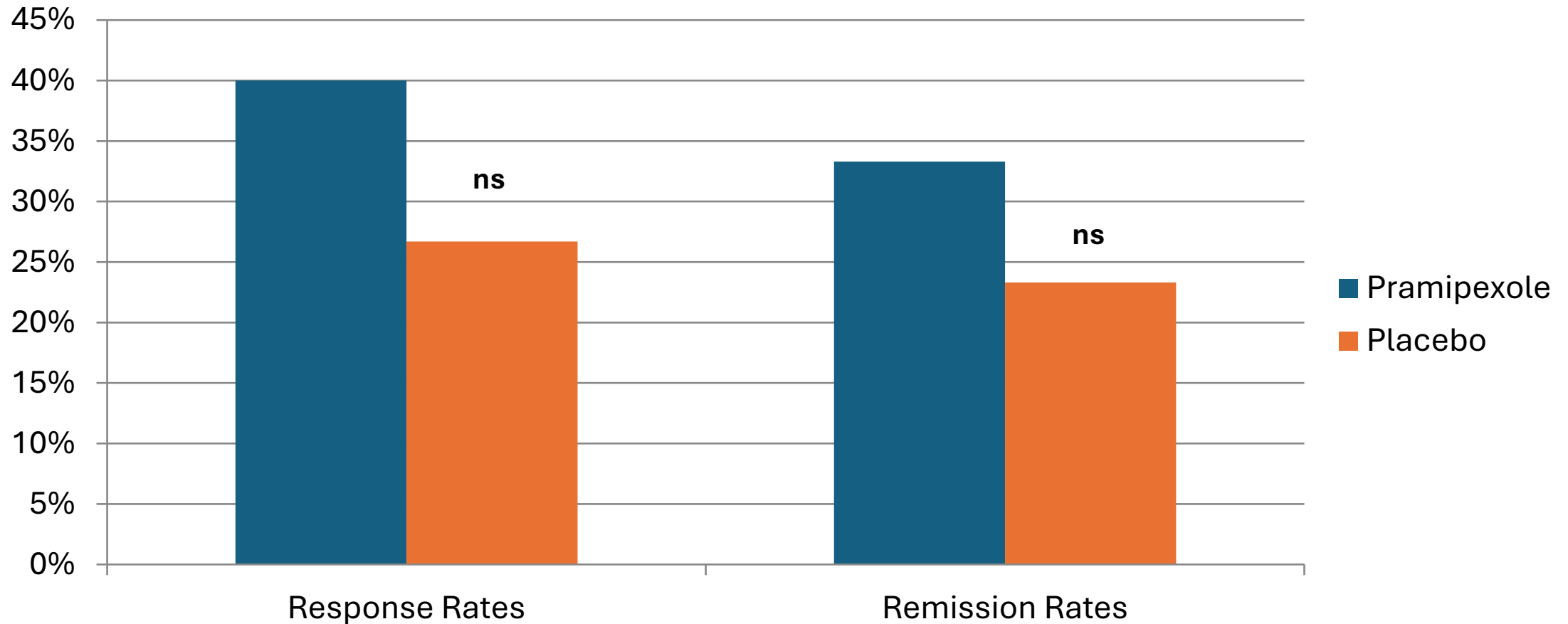


Figure 4 Mean ($\pm$ SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

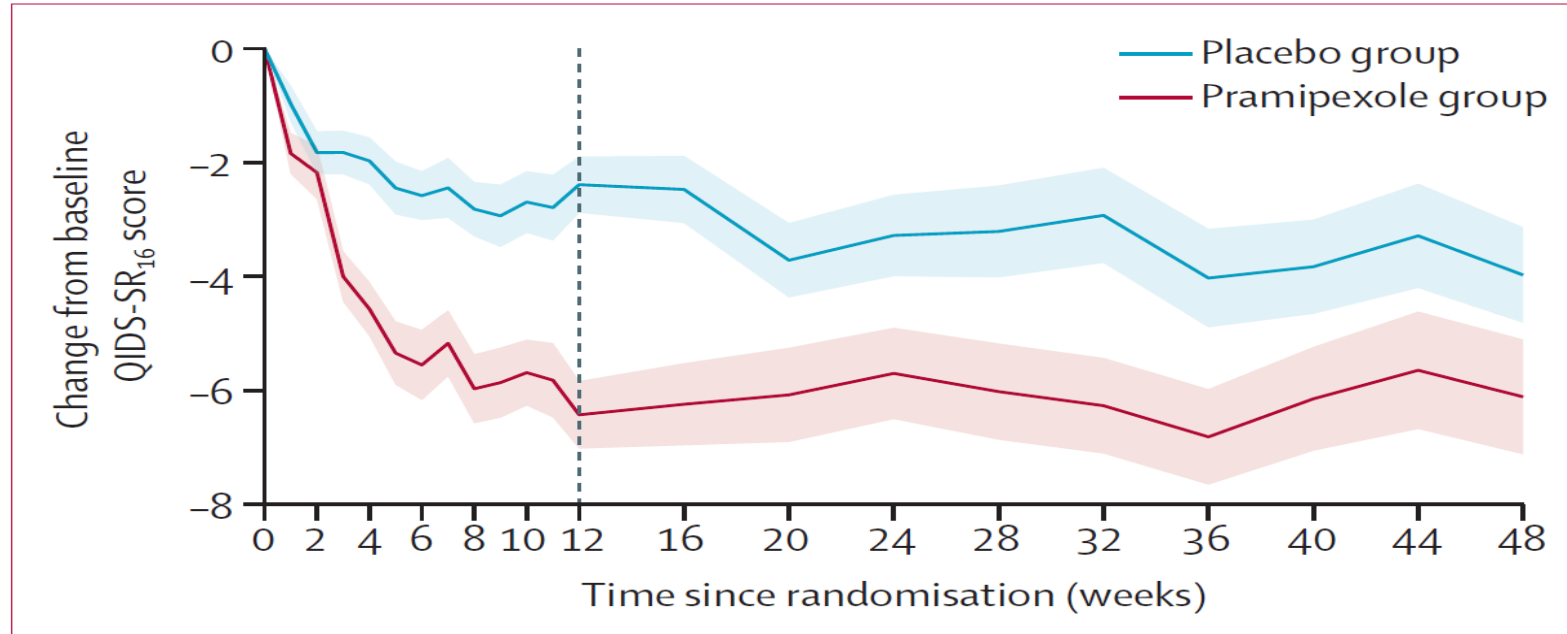
Fava, et al. *Annals of Clinical Psychiatry*. 2007;19[3]:153–159.

Double-Blind, Placebo-Controlled Study of Pramipexole (up to 1.5 mg bid) in Treatment Resistant Depression (n=60)



Cusin, et al. *J Clin Psychiatry*. 2013 Jul;74(7):e636-41.

Double-Blind, Placebo-Controlled Study of Pramipexole (up to 1.5 mg bid) in Treatment Resistant Depression (n=150)

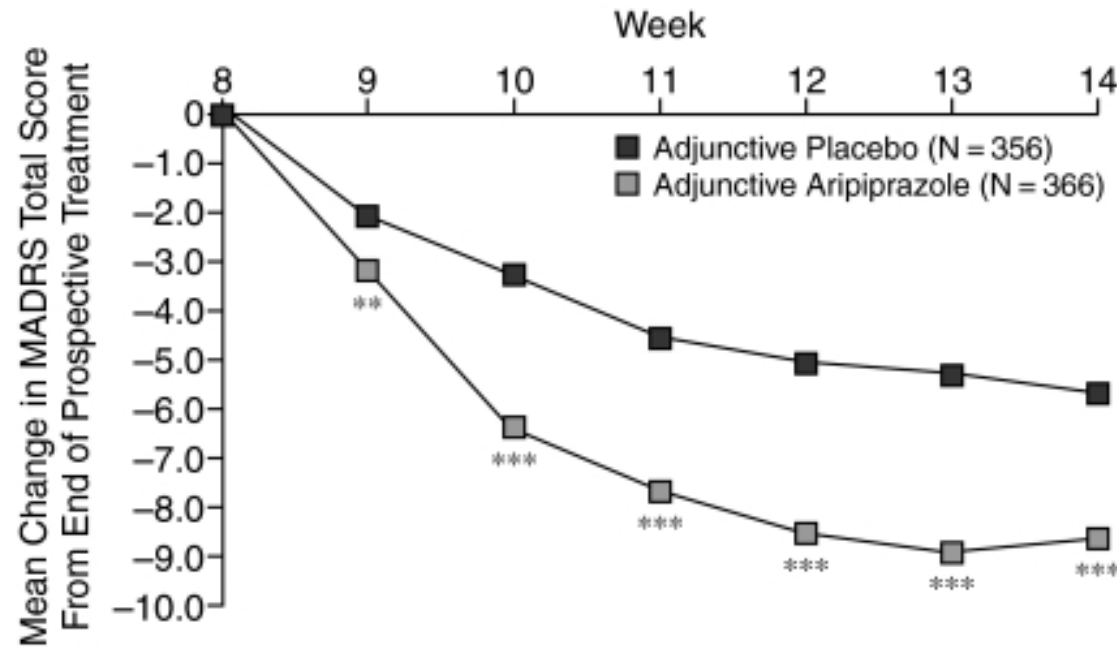


Browning et al, Lancet Psychiatry.
2025 Aug;12(8):579-589.

Figure 2: Primary efficacy assessment of change from baseline in QIDS-SR₁₆ total score at week 12

Data were obtained from all randomly assigned, eligible participants. Mean change in observed score is presented, and shaded areas show SE. The dashed line is the timepoint of the primary outcome. QIDS-SR₁₆=Quick Inventory of Depressive Symptomology, 16-item, self-report version.

Three Double-Blind Studies of Adjunctive Aripiprazole to ADT in TRD – Two Pooled Studies and a Single Study*

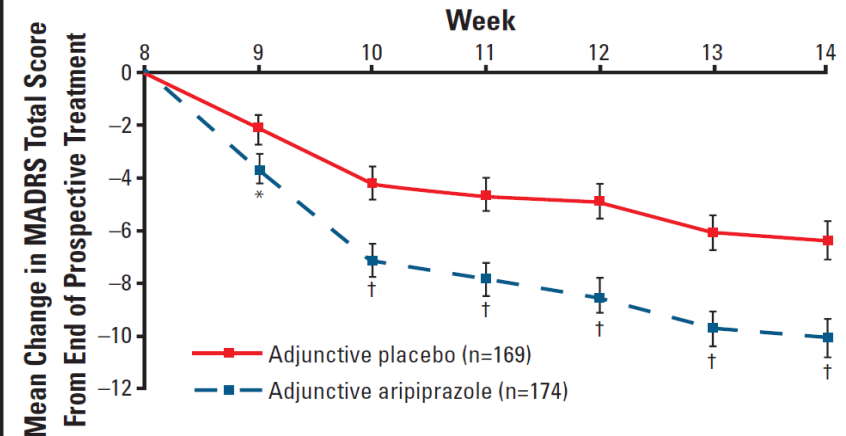


Two pooled studies: Thase, et al. *Prim Care Comp J Clin Psych*. 2008;10(6):440-7.

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

FIGURE 2.

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



* $P < .05$ vs placebo.

† $P < .001$ vs placebo.

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

Berman RM, Fava M, Thase ME, et al. *CNS Spectr*. Vol 14, No 4. 2009.

Aripiprazole Augmentation versus Antidepressant Switching for Patients with TRD: A 6-Week, Randomized, Rater-Blinded, Prospective Study (n=101)

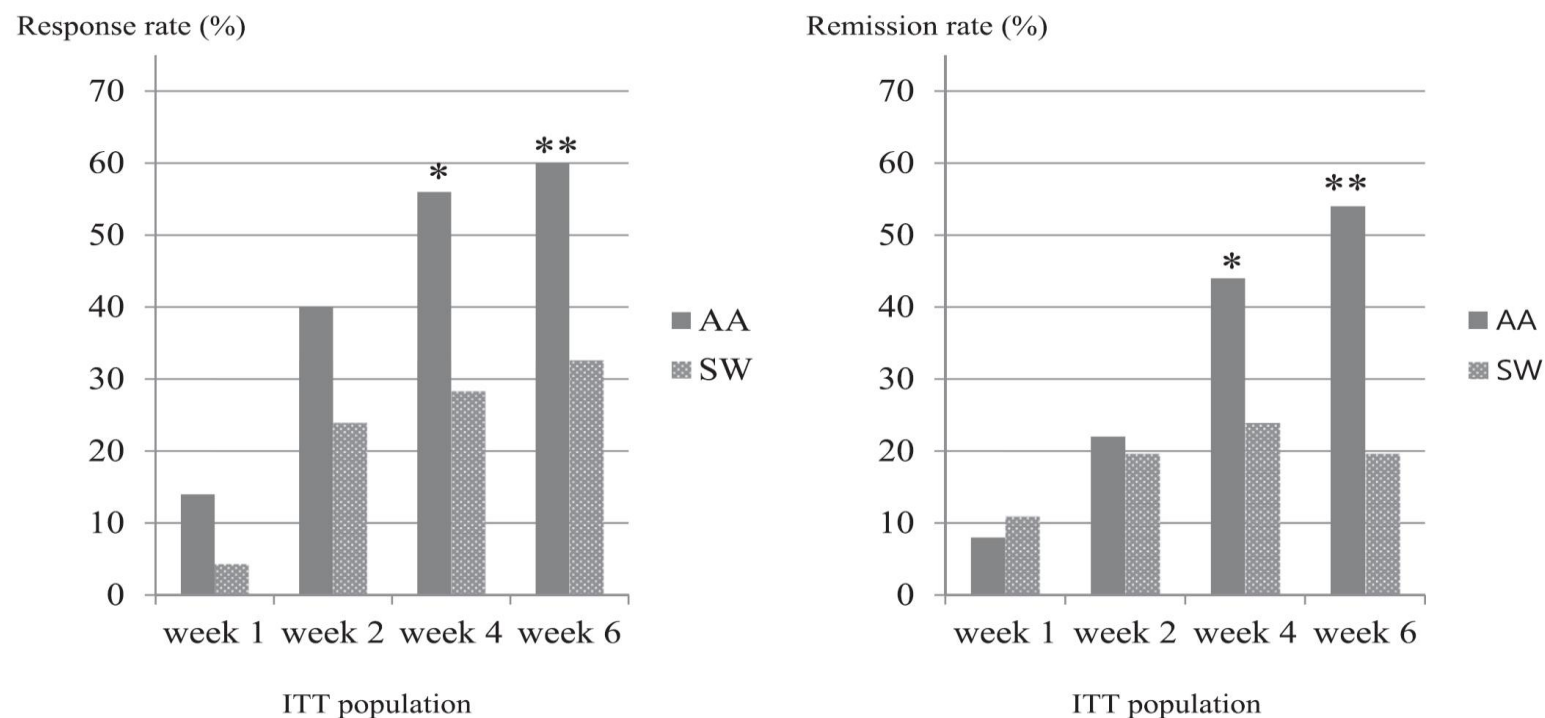
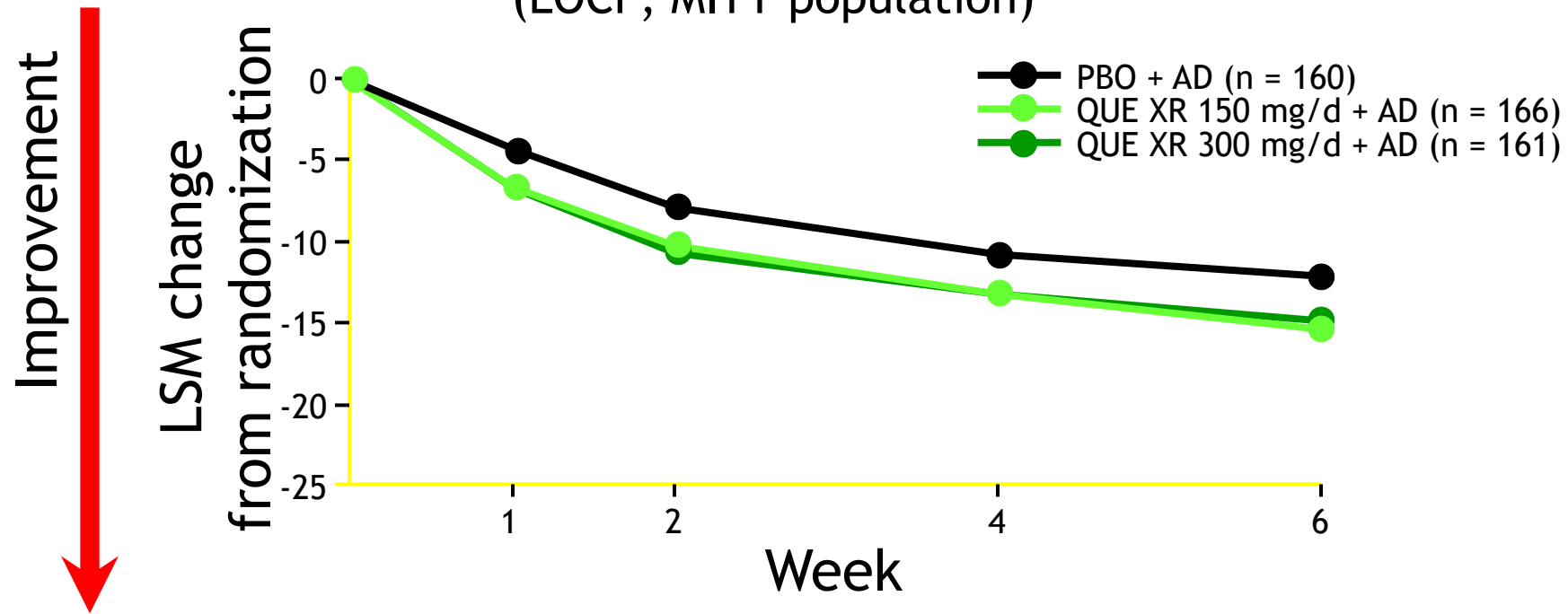


Fig. 3. The responder and remission rates between the two treatment groups during the study Annotation: ITT, intent-to-treat; AA, aripiprazole augmentation; *P = 0.0080 and **P = 0.0086 for response analysis; *P = 0.0408 and **P = 0.0005 for remission analysis.

Han, et al. *Journal of Psychiatric Research*. 2015;66-67;84-94.

Double-Blind, Placebo-Controlled Study of Quetiapine Augmentation in TRD

Change in MADRS total score from randomization over time
(LOCF; MITT population)

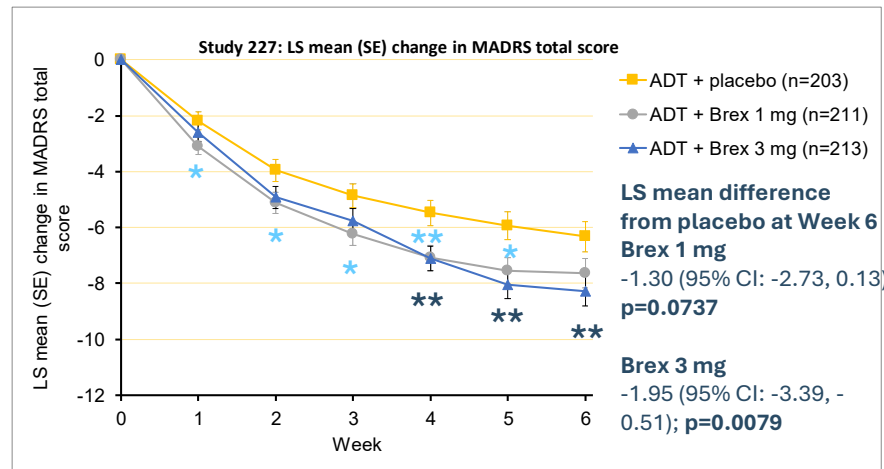


p value active treatment vs. placebo + antidepressant:

QUE XR 150 mg/d + AD	< 0.001	< 0.01	< 0.05	< 0.01
QUE XR 300 mg/d + AD	< 0.001	< 0.001	< 0.05	< 0.01

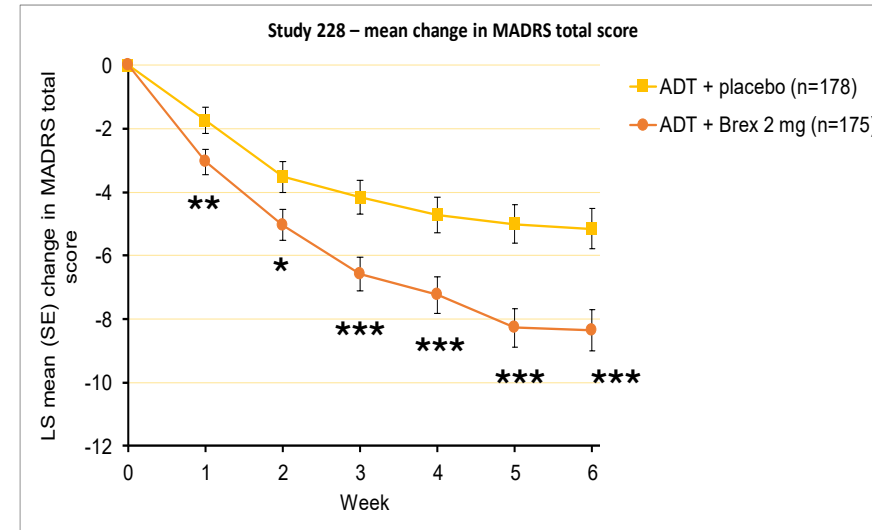
Bauer M, et al. *J Clin Psychiatry*. 2009;70:540-549.

Double-Blind Study of Adjunctive Brexpiprazole to ADT in TRD – Studies 227* and 228*



*p<0.05, **p<0.01 vs placebo

MMRM analysis; MADRS baseline: ADT + placebo 26.5, ADT + Brex 1 mg 26.9, ADT + Brex 3 mg 26.5
Study 227 CSR – Thase, et al. *J Clin Psychiatry*. 2015 Sep;76(9):1232-40.



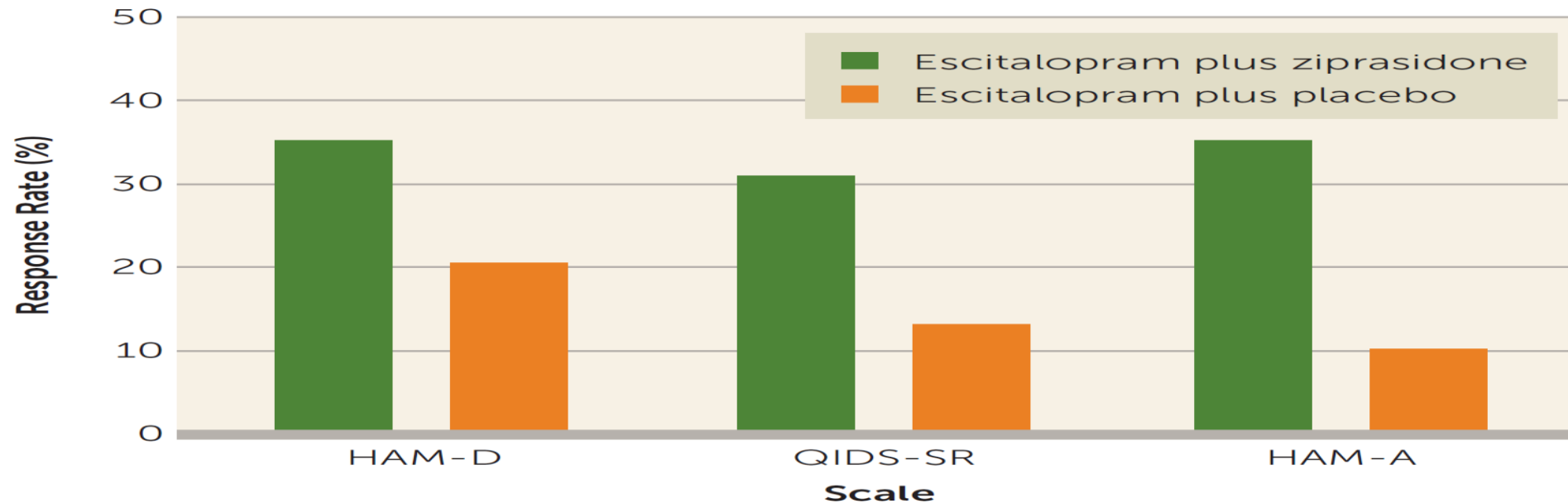
*p<0.05, **p<0.01, ***p<0.001 vs placebo

MMRM analysis; MADRS baseline: ADT + placebo 27.3, ADT + Brex 26.9
Study 228 CSR – Thase, et al. *J Clin Psychiatry*. 2015 Sep;76(9):1224-31.

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

Double-Blind Study of Adjunctive Ziprasidone to Escitalopram in TRD (n=139)

FIGURE 1. Response Rates, by Clinical Scale, Among Patients With Major Depression Receiving Escitalopram Plus Ziprasidone or Placebo^a

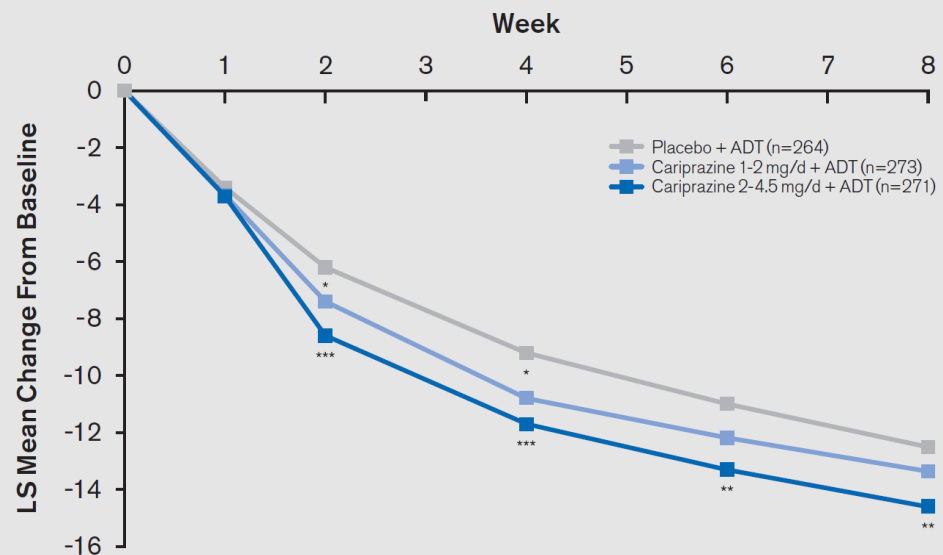


^a HAM-D=Hamilton Depression Rating Scale (17-item); QIDS-SR=Quick Inventory of Depressive Symptoms–Self-Rated (16-item); HAM-A=Hamilton Anxiety Rating Scale. According to the mixed-effects model with repeated-measures analyses, the p values were 0.04, 0.03, and <0.001 for the HAM-D, the QIDS-SR, and the HAM-A, respectively.

Papakostas, et al. *Am J Psychiatry*. 2015;172:1251-1258.

Two Double-Blind, Randomized, Placebo-Controlled Trials of Cariprazine As Adjunctive Therapy in TRD* (n=1,599)

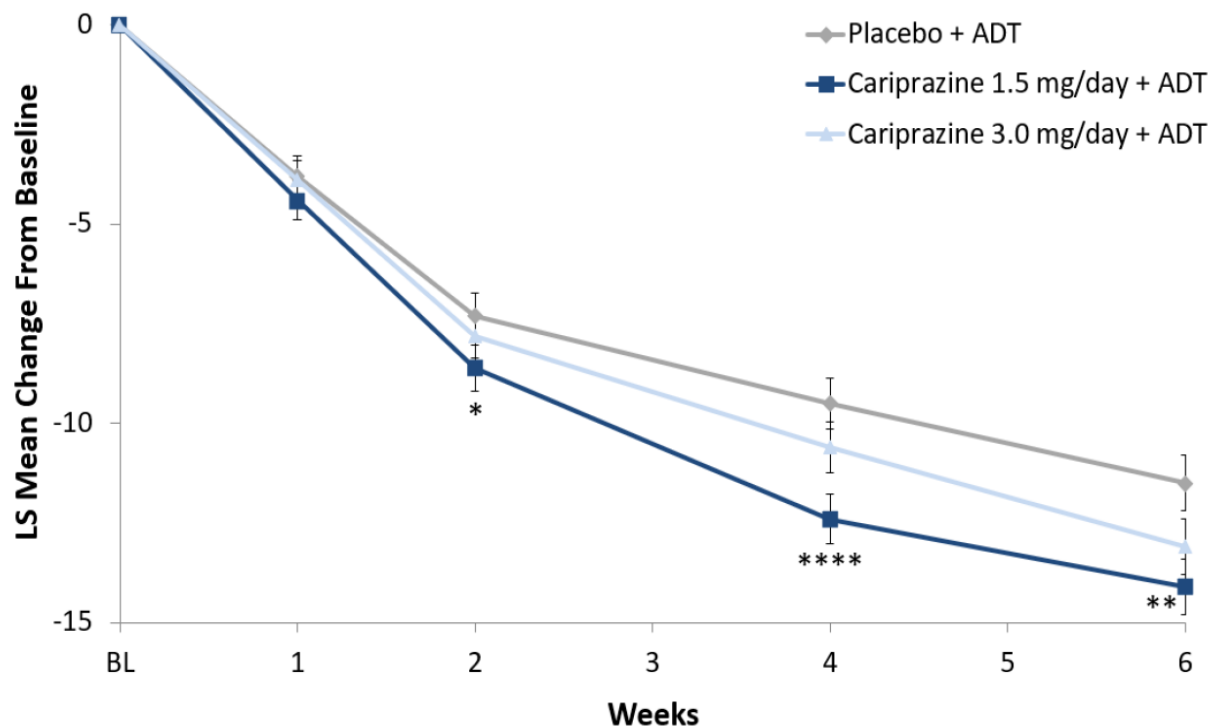
Figure 1. Mean Change From Baseline to Week 8 in MADRS Total Score (ITT Population, MMRM)



* $P < .05$; ** $P < .01$; *** $P < .001$ vs placebo; P values represent pairwise comparisons and were not adjusted for multiple comparisons. ADT indicates antidepressant treatment; ITT, intent-to-treat; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

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

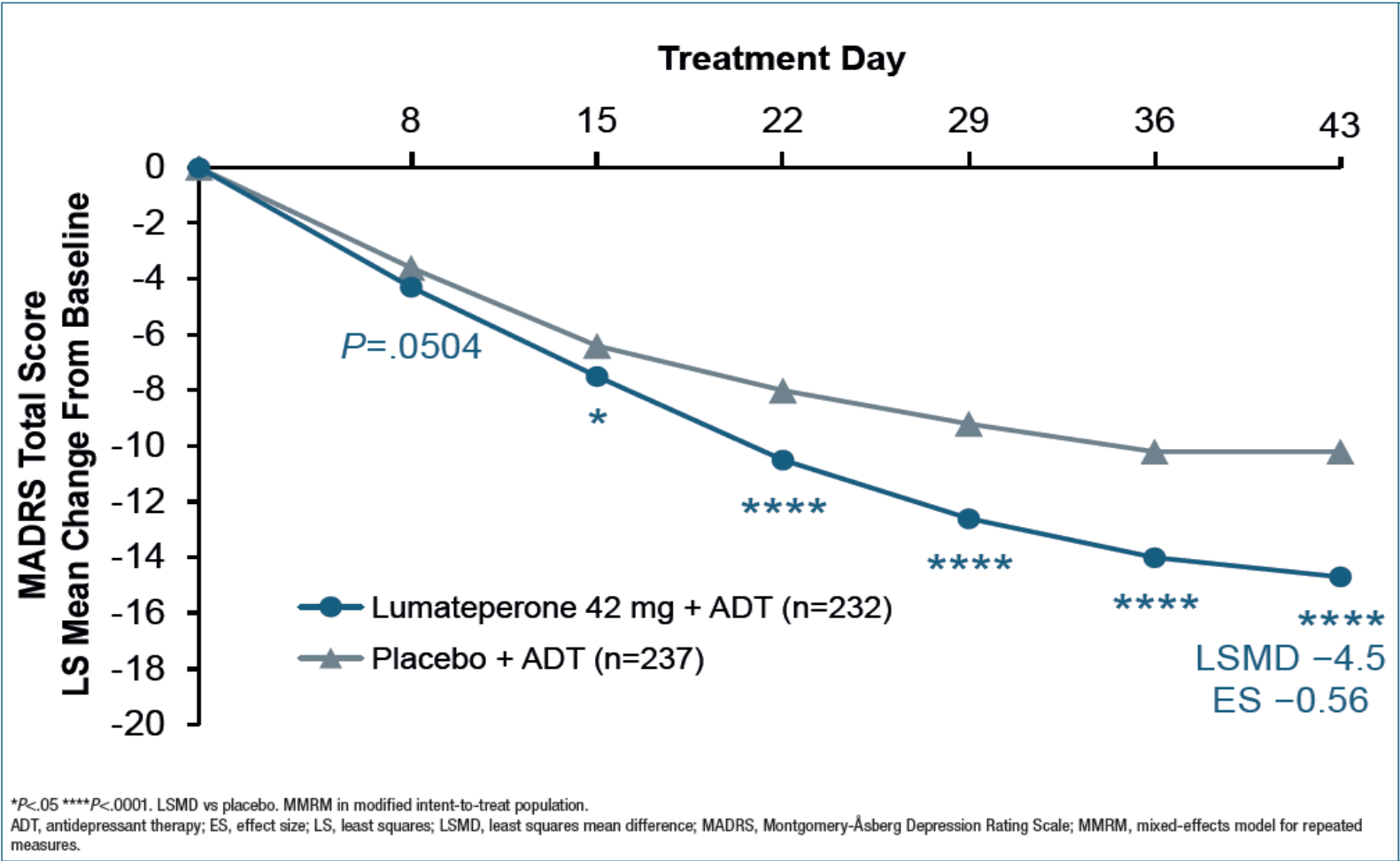
A. MADRS Total Score



Sachs G, et al. *Am J Psychiatry*. 2023 Mar;180(3):241-251.

Double-Blind, Randomized, Placebo-Controlled Trial of Lumateperone As Adjunctive Therapy in TRD*

Figure 1. LS Mean Change From Baseline in MADRS Total Score



Earley et al, ASCP Annual Meeting, 2025

A Randomized Trial of Aripiprazole Augmentation vs rTMS Augmentation vs Switch to Venlafaxine in Treatment Resistant Depression (ASCERTAIN-TRD) (n=278)



Fig. 2 Model adjusted change in MADRS scores. MADRS Montgomery Asberg Depression Rating Scale, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

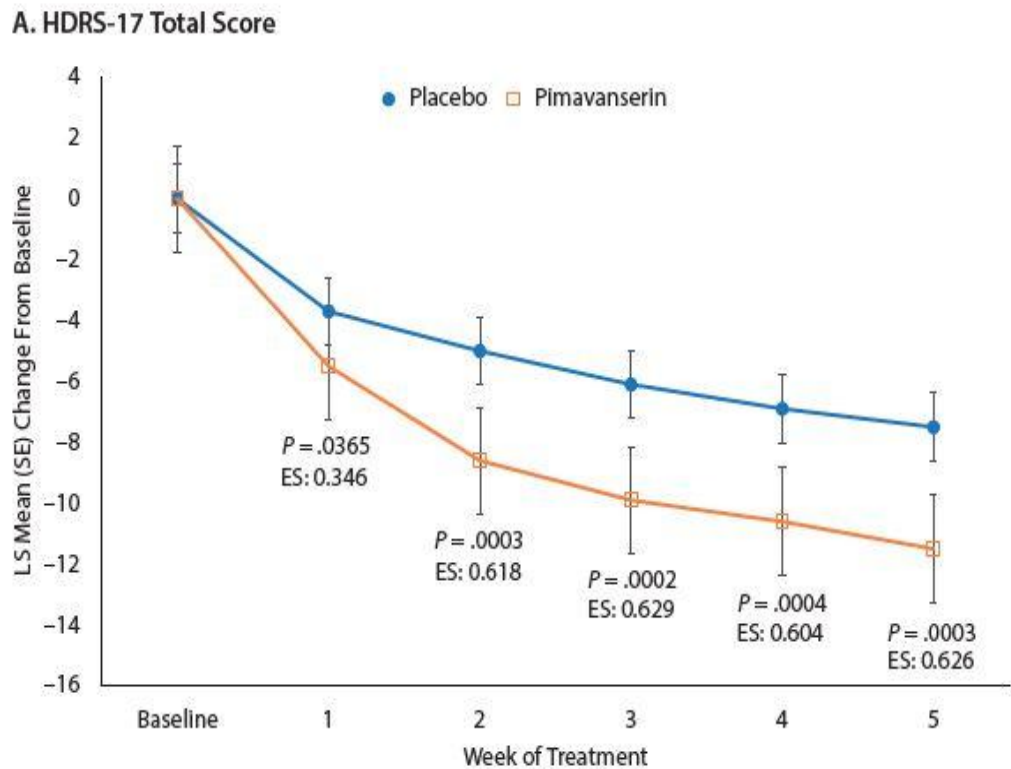


Fig. 3 Model adjusted change in SDQ scores. SDQ Symptoms of Depression Questionnaire, rTMS Repetitive Transcranial Magnetic Stimulation. Alpha = 0.025.

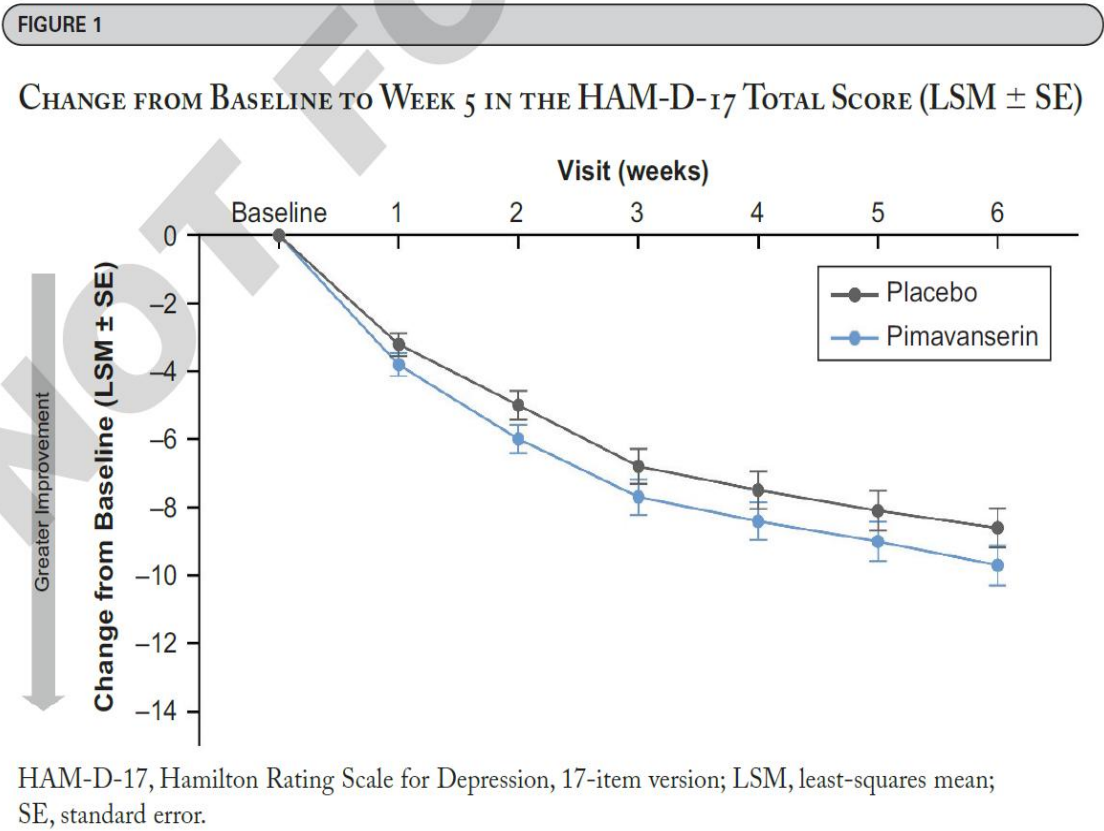
Papakostas et al, Mol Psychiatry. 2024 Aug;29(8):2287-2295.

Adjunctive Pimavanserin in Patients with Major Depressive Disorder: A Phase 2, Double-Blind, Placebo-Controlled Trial (n=207) and the Combined Results from Two Randomized, Double-Blind, Placebo-Controlled Phase 3 Studies (n=298)

Figure 2. Least Squares (LS) Mean Change From Baseline to Week 5 in (A) HDRS-17 Total Score and (B) SDS Score, and (C) Response and Remission Rate During Stage 1



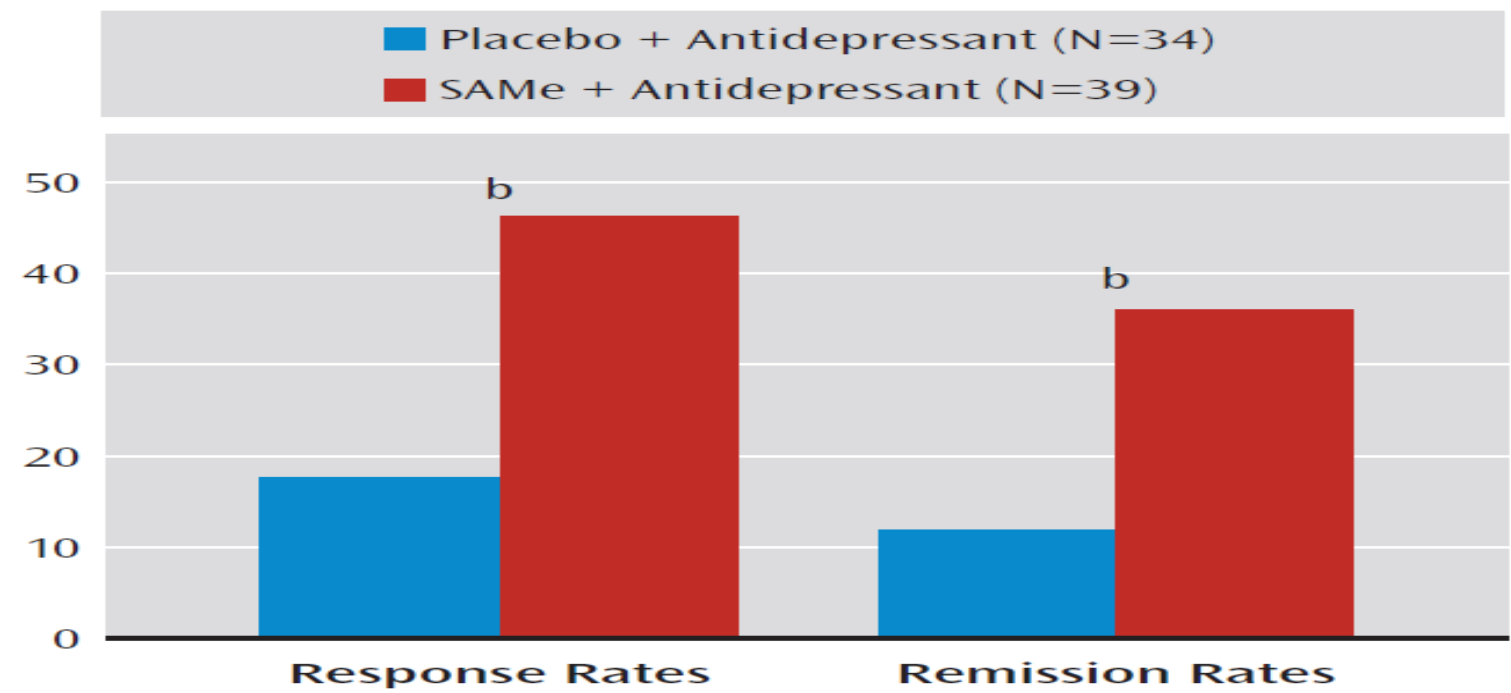
Fava, et al. *J Clin Psychiatry*. 2019 Sep 24;80(6):19m12928.



Dirks, et al. *Psychopharmacology Bulletin*. 2022;52(4):8-30.

Double-Blind Study of SAME (1600 mg/d) Augmentation in SSRI-Resistant Depressed Patients (n=73)

FIGURE 2. HAM-D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAME) or Placebo^a

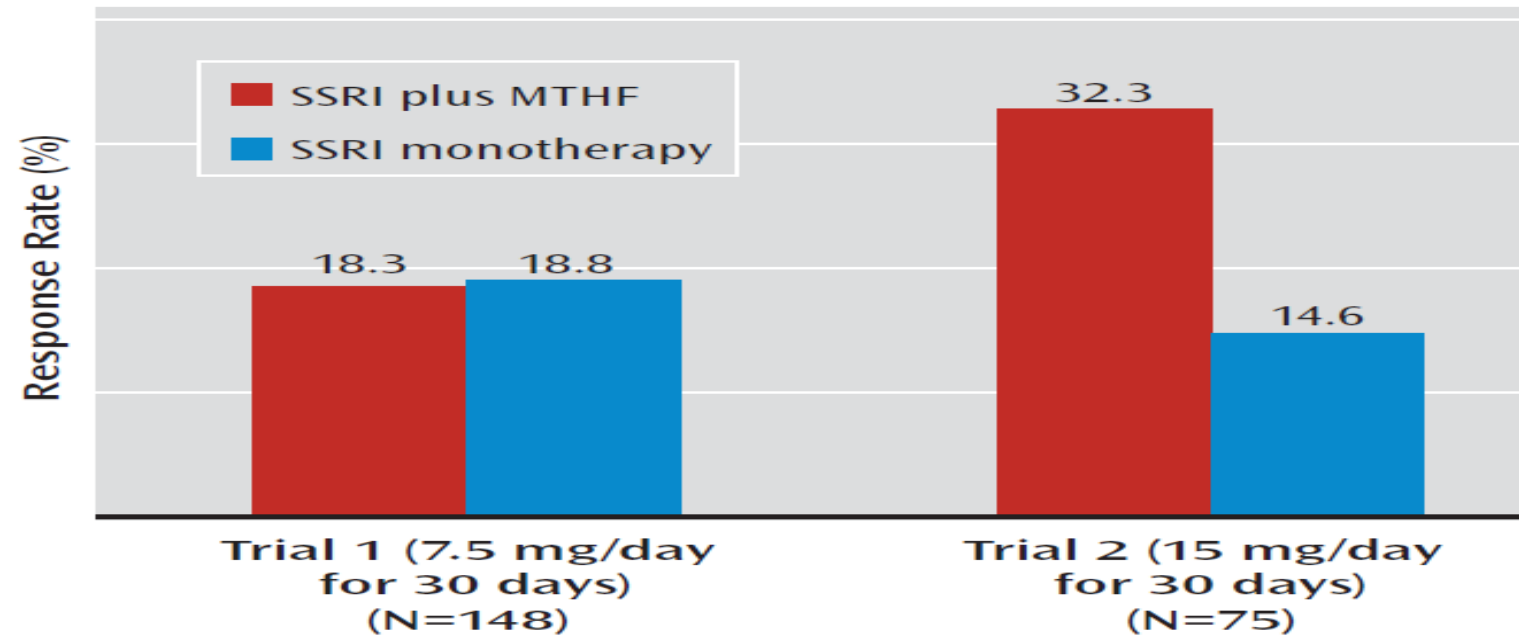


^a Data depict last observation carried forward (LOCF) for all patients randomly assigned.
^b Significant difference between groups ($p < 0.05$, Fisher's exact test).

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

Double-Blind Study of L-Methylfolate (L-MTHF) Augmentation of SSRIs in TRD—Sequential Parallel Comparison Design (SPCD)

FIGURE 1. Pooled Response Rates in Two Trials of L-Methylfolate (MTHF) Compared With Placebo as an Adjunct to SSRIs in Patients With SSRI-Resistant Depression^a



^a Response was defined as a reduction of $\geq 50\%$ 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. (25).

Papakostas, et al. *Am J Psychiatry*. 2012 Dec 1;169(12):1267-74.

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

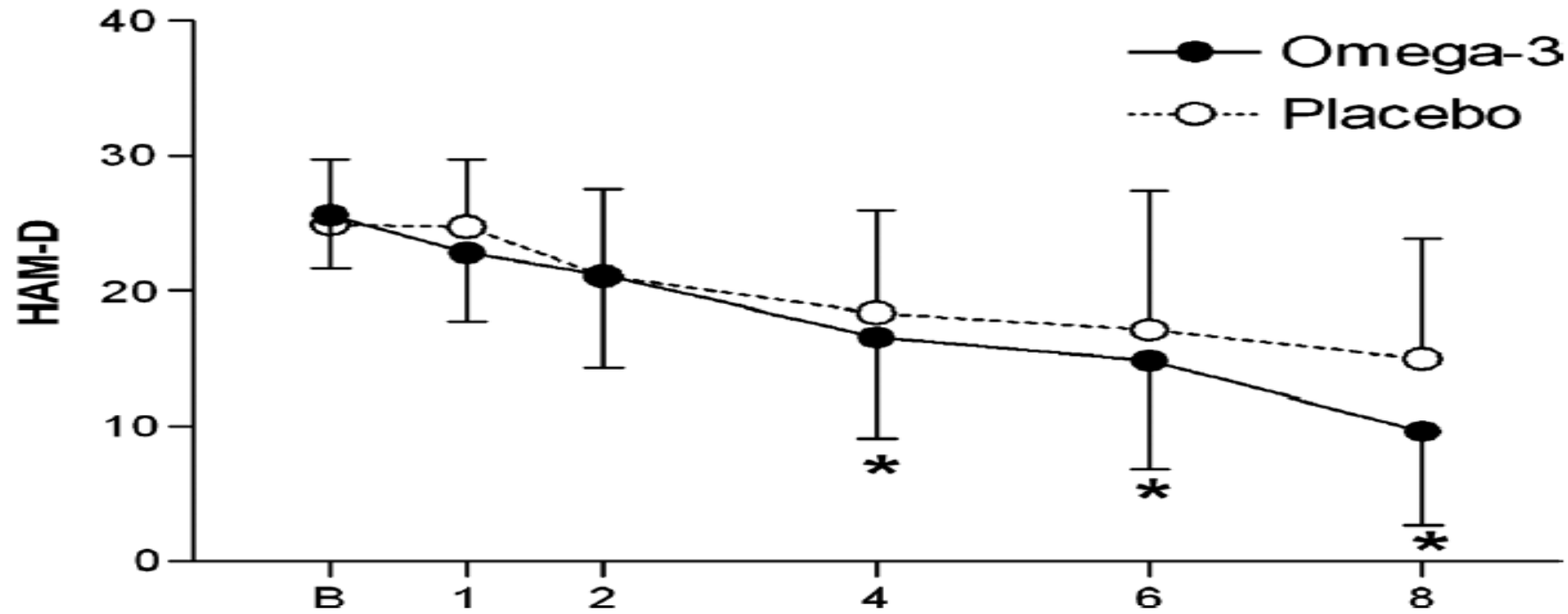


FIGURE 1. Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean $\pm$ SD (* $P < 0.05$, computed via regression modeling).

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

Double-Blind, Placebo-Controlled, Crossover Study of i.v. Ketamine, a Selective NMDA Receptor Antagonist, in TRD (n=18)

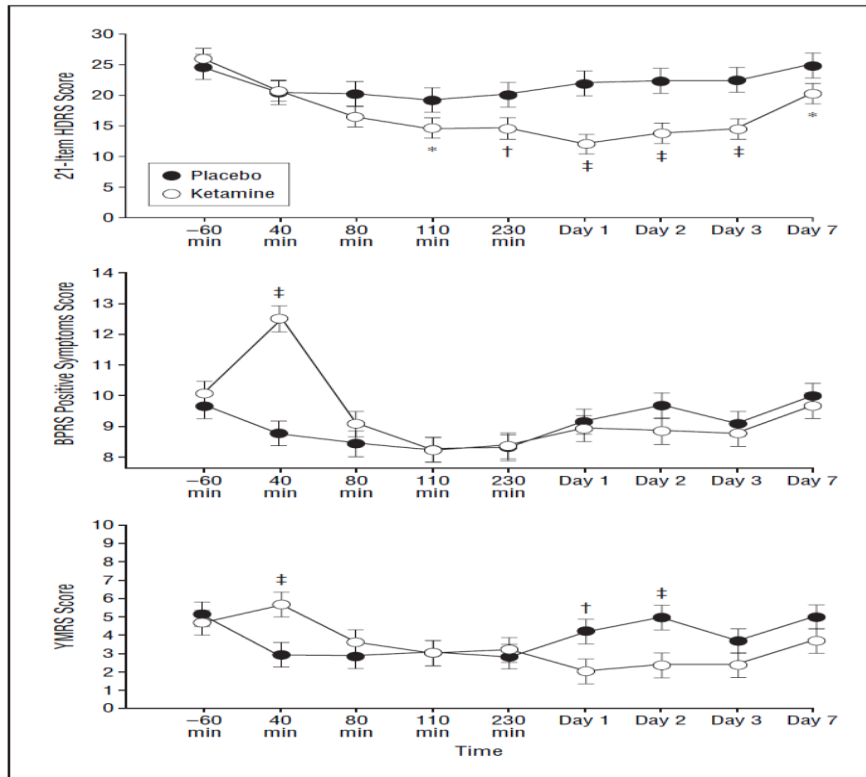


Figure 2. Change in the 21-item Hamilton Depression Rating Scale²⁸ (HDRS), Brief Psychiatric Rating Scale³¹ (BPRS) positive symptoms subscale, and Young Mania Rating Scale³² (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the completers analysis. * indicates $P < .05$; †, $P < .01$; ‡, $P < .001$.

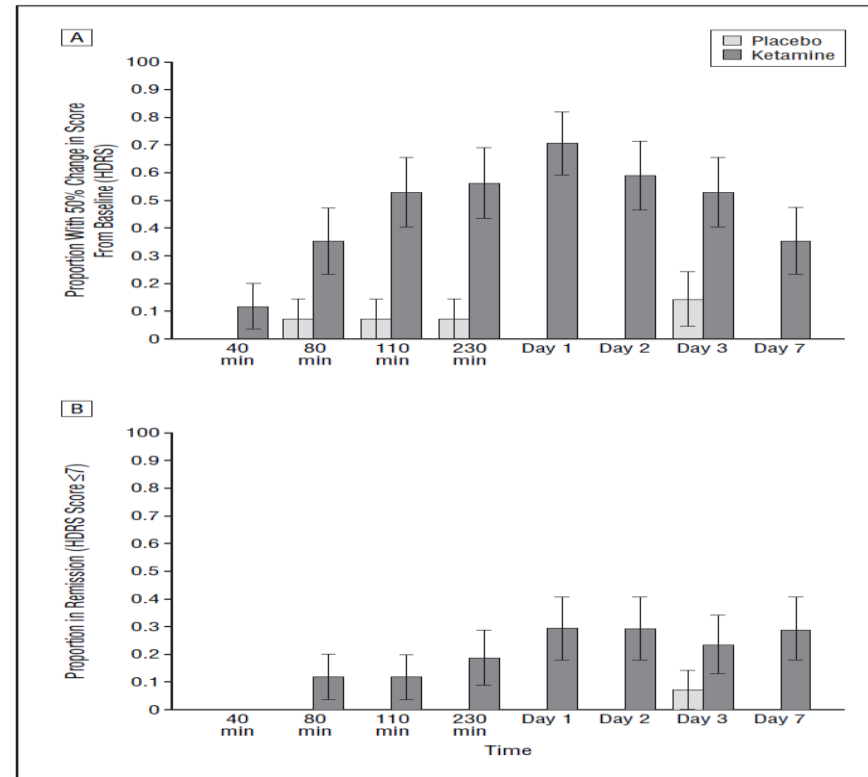
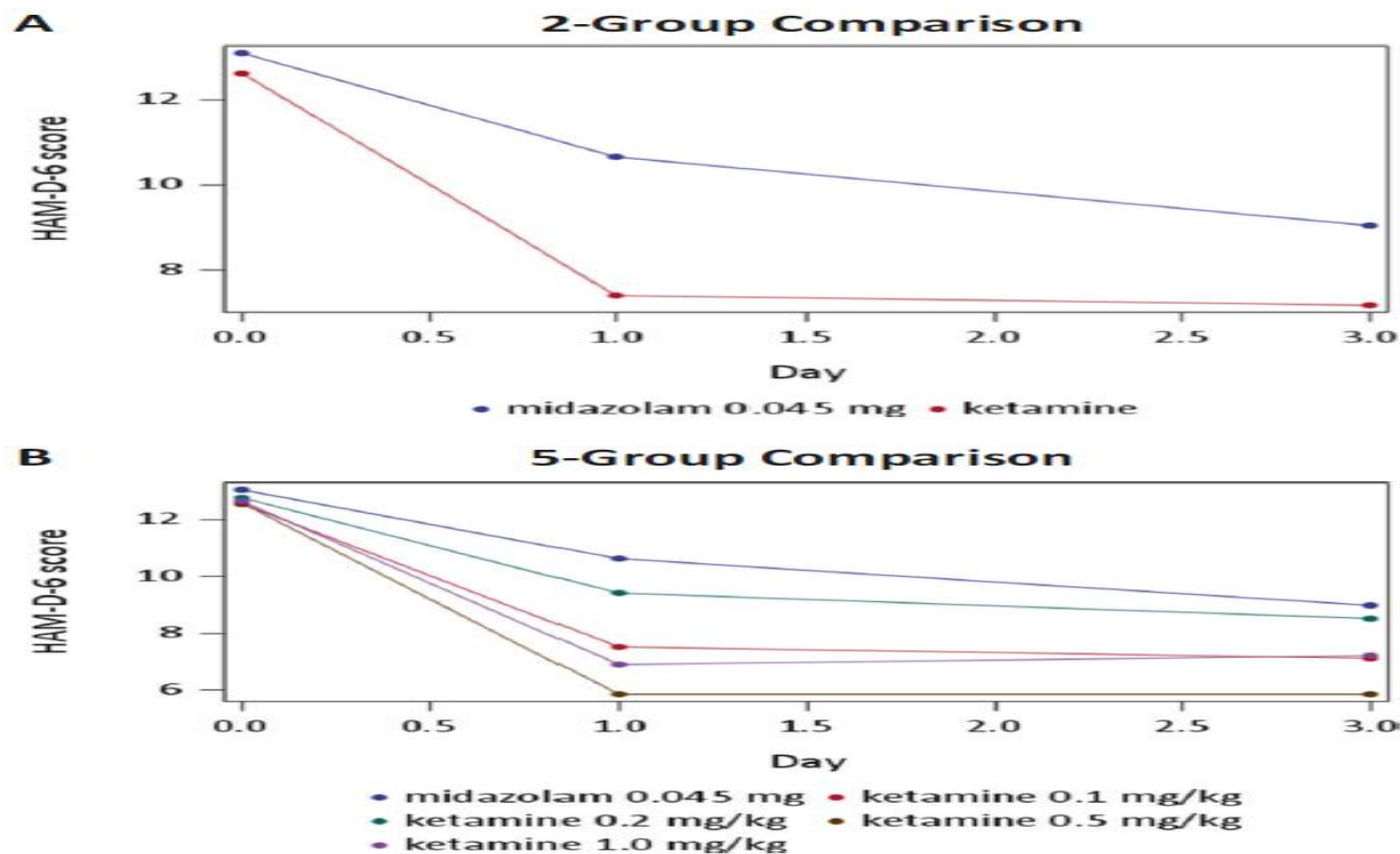


Figure 3. A, Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale²⁸ [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B, Proportion of remitters (HDRS score ≤ 7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18).

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

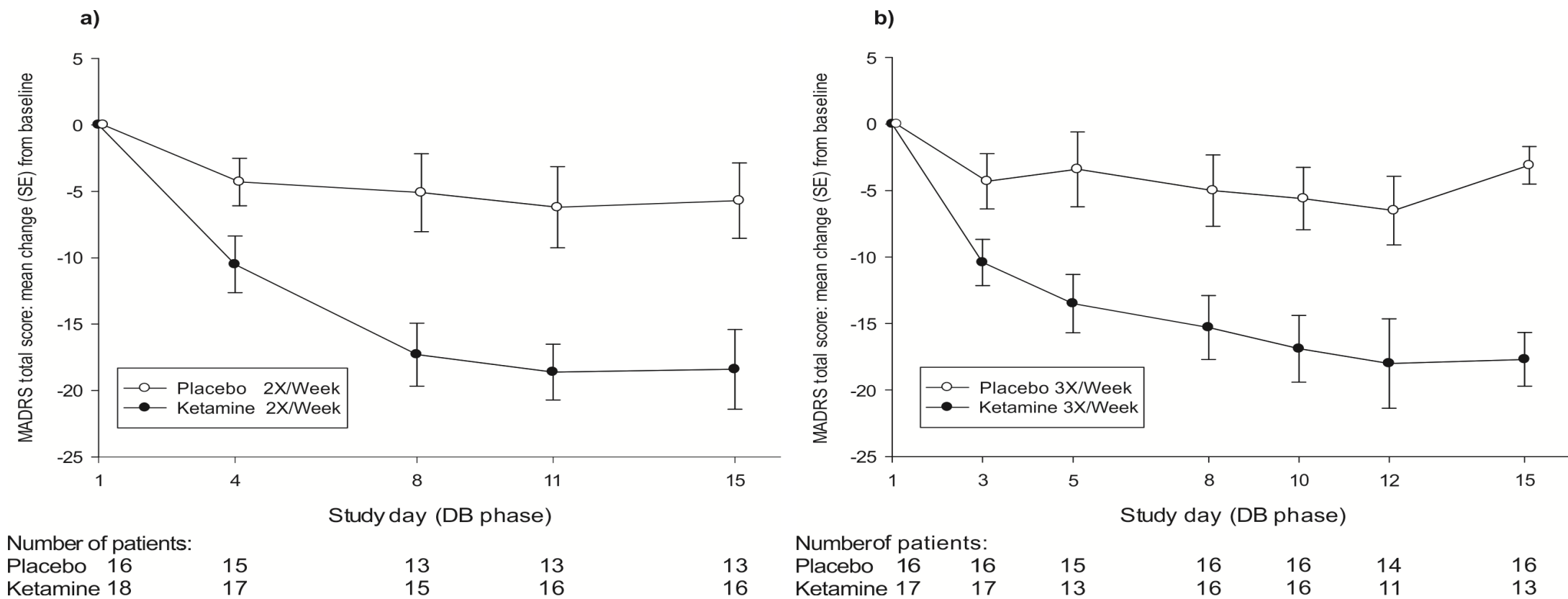
Double-Blind, Placebo-Controlled, Dose-Ranging Trial of Intravenous Ketamine As Adjunctive Therapy in Treatment-Resistant Depression (TRD) (n=99)



Fava et al
Mol Psychiatry 2020 Jul;25(7):1592-1603.

Fig. 2 HAM-D-6 scores over the first 72 h of treatment; Fig. 2A reports the 2-group analysis; Fig. 2B reports the 5-group analysis;

Intravenous Ketamine in Adult Patients with Treatment-Resistant Depression: A Dose-Frequency Study* (n=67)



*TRD assessed with ATRQ by SAFER rater

Singh, et al. *Am J Psychiatry*. 2016 Aug 1;173(8):816-26.

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression (n=403)

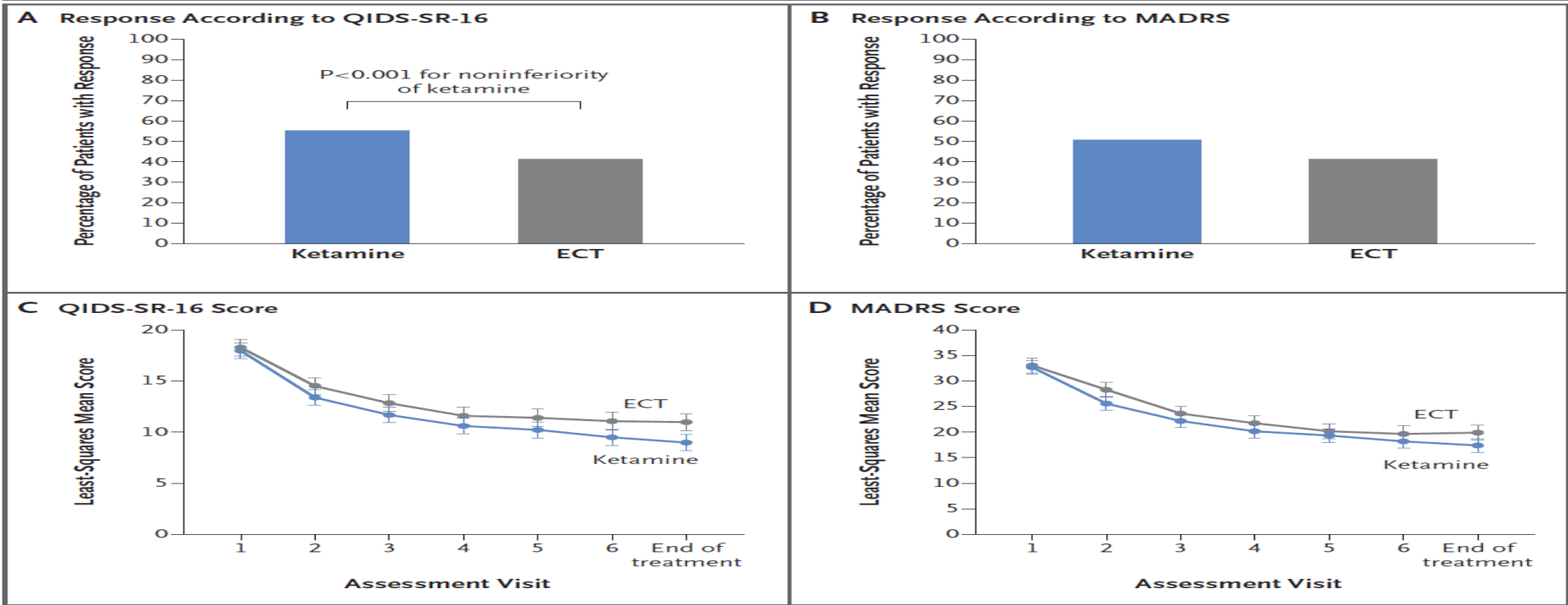
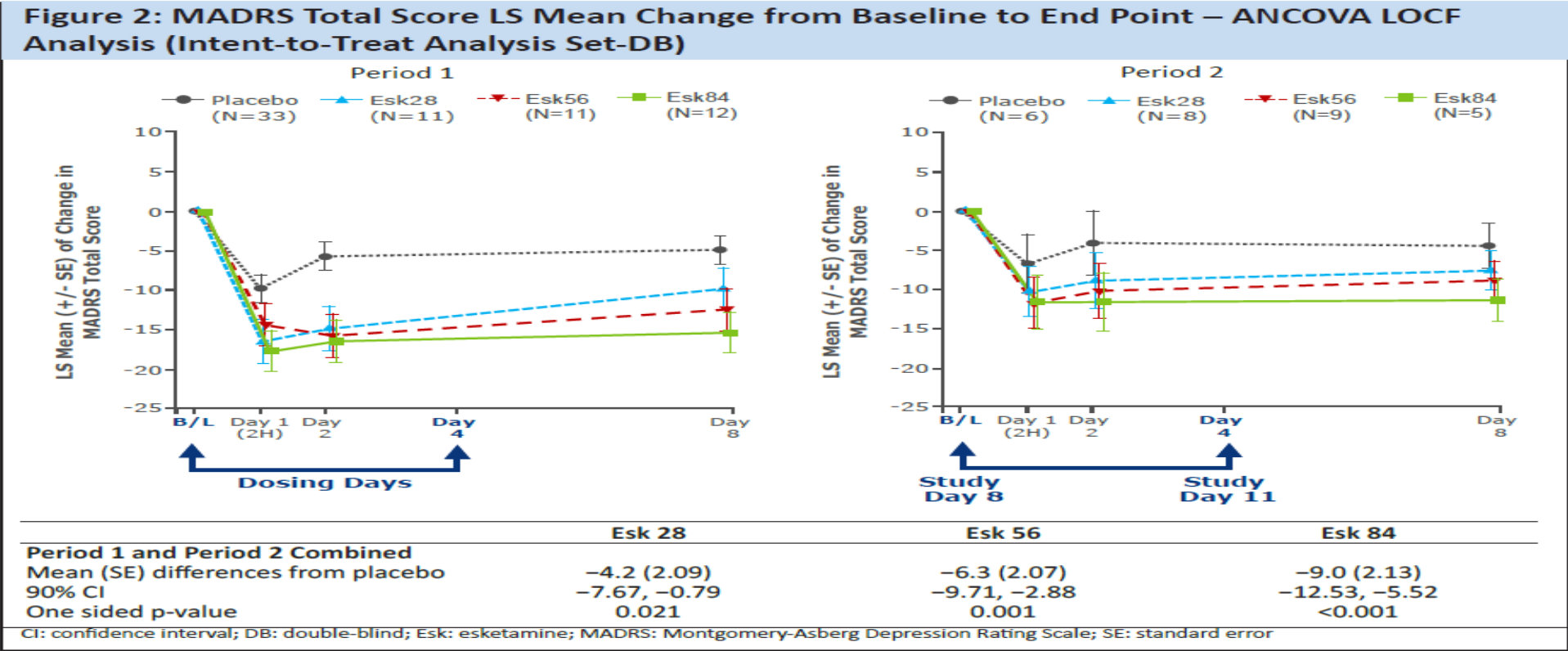


Figure 1. Response to Ketamine and ECT According to the QIDS-SR-16 and MADRS during the Initial 3-Week Treatment Phase.
Shown are the percentages of patients who had a response to ketamine or electroconvulsive therapy (ECT) according to the scores on the Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16, Panel A) and the Montgomery–Åsberg Depression Rating Scale (MADRS, Panel B) at the end-of-treatment visit, as well as the least-squares mean QIDS-SR-16 scores (Panel C) and the mean MADRS scores (Panel D) at the assessment visits during the initial 3-week treatment phase. Analyses were performed in the modified intention-to-treat population, which included all the patients who had completed at least one treatment session and had at least one QIDS-SR-16 measurement. Scores on the QIDS-SR-16 range from 0 to 27, with higher scores indicating greater depression. Scores on the MADRS range from 0 to 60, with higher scores indicating greater depression. The I bars in Panels C and D represent 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

Anand, et al. *N Engl J Med* 2023;388:2315-25.

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



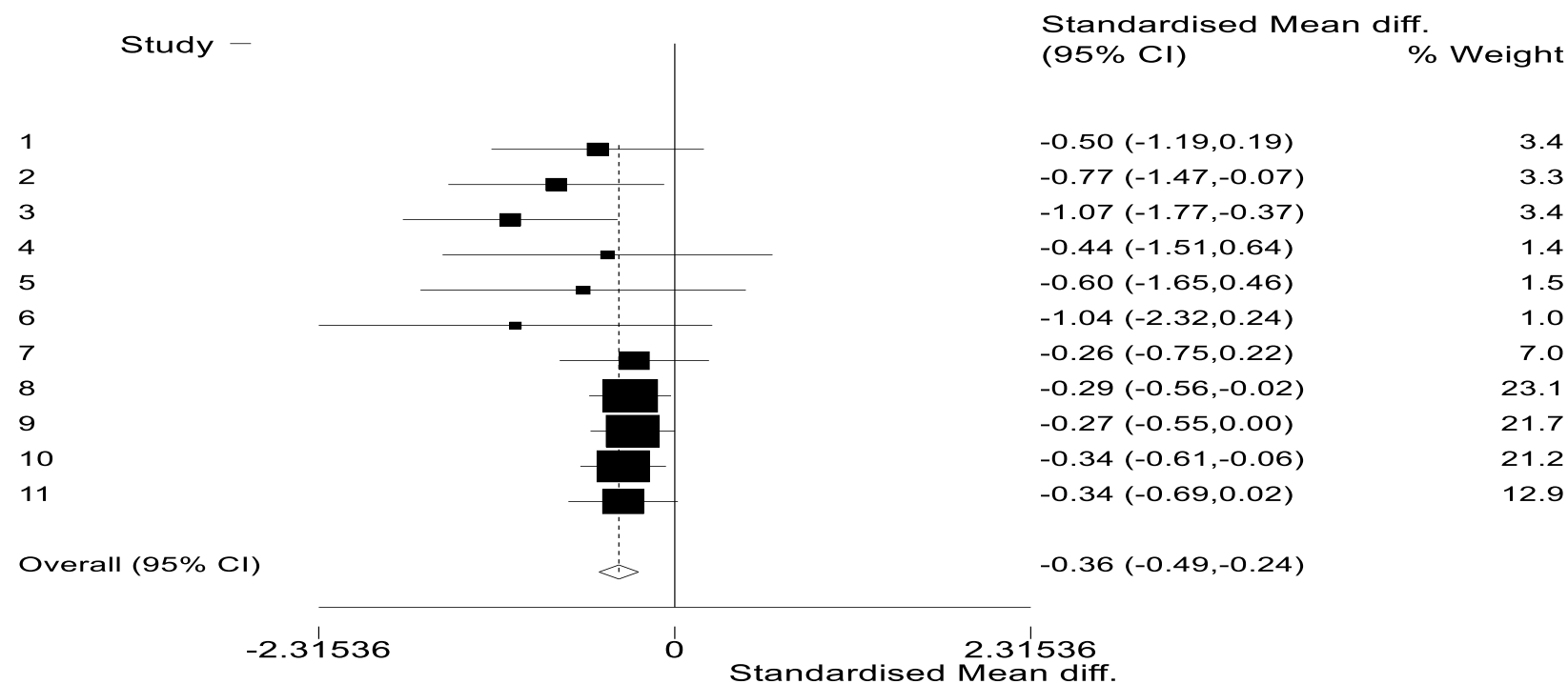
- Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ

Singh, et al. *Biol Psychiatry*. 2016 Sep 15;80(6):424-31.

Meta-Analysis of Esketamine Augmentation in TRD Studies

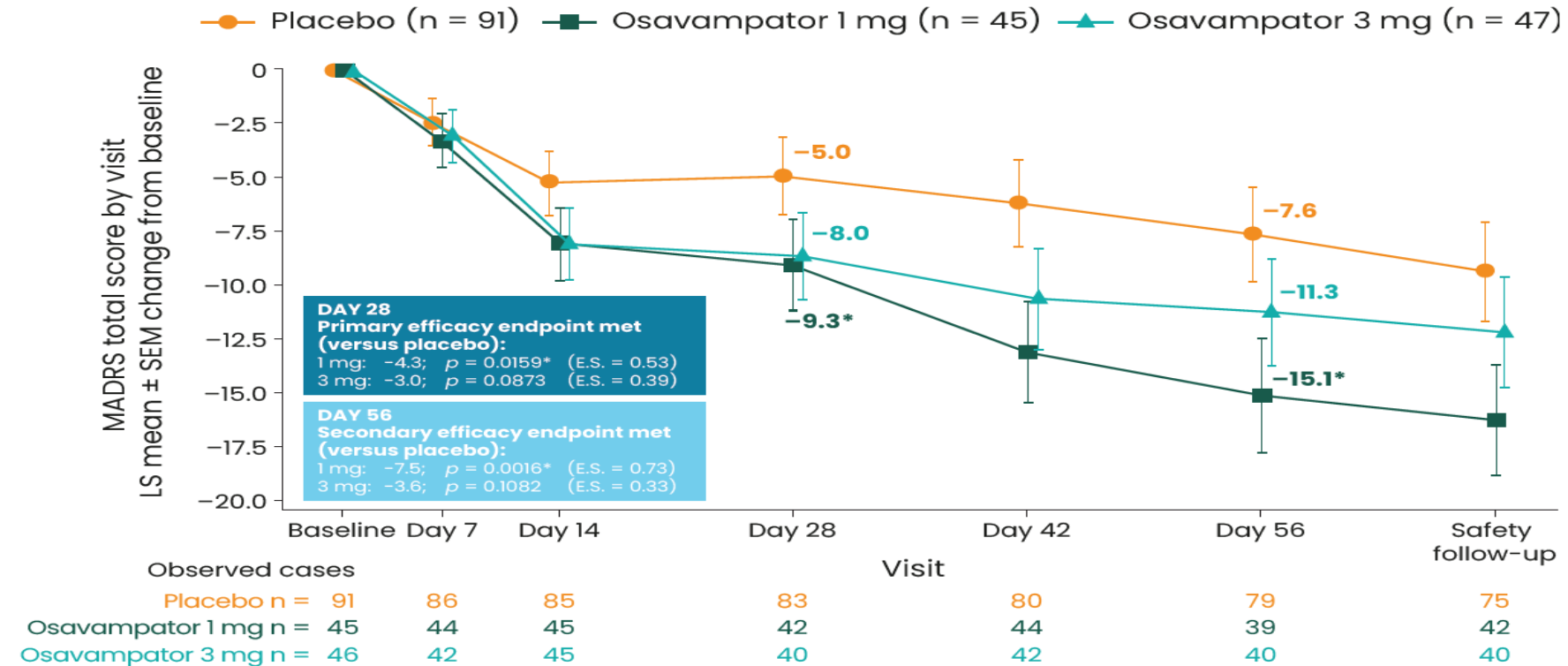
Figure 1: Forest Plot of SMD in change in primary outcome scores between adjunctive esketamine and placebo



Papakostas, et al. *J Clin Psychiatry*. 2020 May 26;81(4):19r12889. doi: 10.4088/JCP.19r12889.

Double-Blind, Placebo-Controlled Trial of Osavampator (PAM of AMPA Receptors) Augmentation in MDD

Figure 2. LS mean (SEM) change from baseline in MADRS total score by visit (FAS).



Observed data. * $p < 0.05$ versus placebo.

E.S., effect size; FAS, full analysis set; LS, least-squares; MADRS, Montgomery-Åsberg Depression Rating Scale; n, number of participants; SEM, standard error of the mean.

Singh et al, Psych Congress, San Diego, CA, 2025

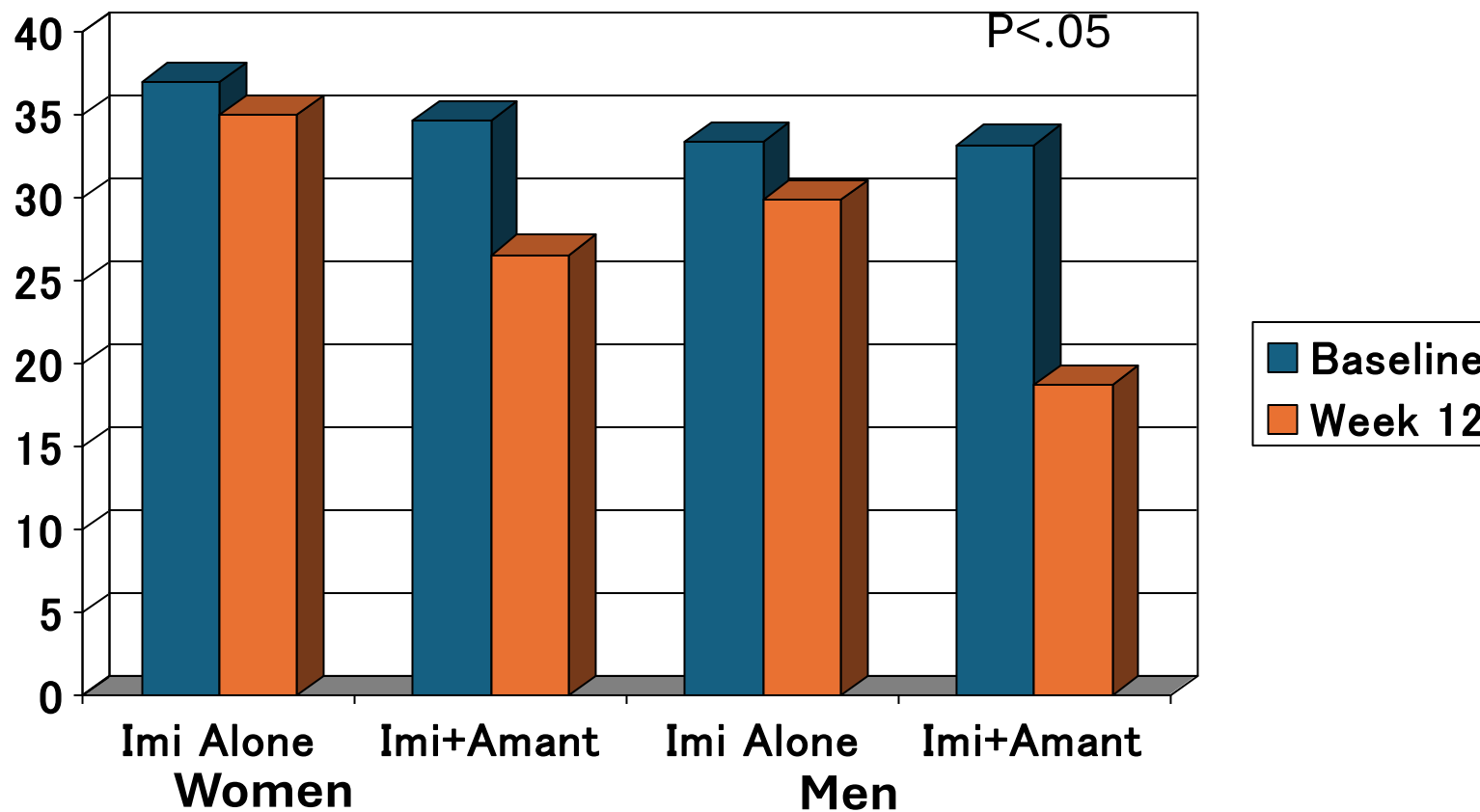
Retrospective study of Adjunctive Pregabalin (75-300 mg/day) (Pregabalin Increases the Activity of the Neuronal Glutamate Transporter Type 3 [EAAT3]) in Partial Responders with Major Depressive Disorder and Residual Anxiety (n=20)

TABLE 2. Clinical Outcomes at Week 9 and After Pregabalin Augmentation at Week 17

Variable	Week 9	Week 17	<i>P</i>
HDRS-17 scores	13.5 ± 3.1	9.1 ± 2.9	<0.000
HDRS-AS scores	6.3 ± 2	3.6 ± 1.7	<0.000
HDRS total – AS scores	7.2 ± 2.3	5.5 ± 1.9	0.003
Responders, n (%)	0	13 (65)	
Remitters, n (%)	0	7 (35)	

Vitali, et al. *J Clin Psychopharmacol*. 2013 Feb;33(1):95-8.

Double-Blind Study of the Anti-Viral and Dopaminergic (plus NMDA Antagonist) Amantadine (150 mg/day) Augmentation of Imipramine in TRD Patients (n=50)



Rogoz Z, et al. *Pharmacol Rep.* 2007;59(6):778-784.

Effect of Memantine (20 mg/day), a Low-Affinity Voltage-Dependent Uncompetitive Antagonist at Glutamatergic NMDA Receptors, Combination Therapy on Symptoms in Patients with Moderate-to-Severe Depressive Disorder: Randomized, Double-Blind, Placebo-Controlled Study N(n=66)

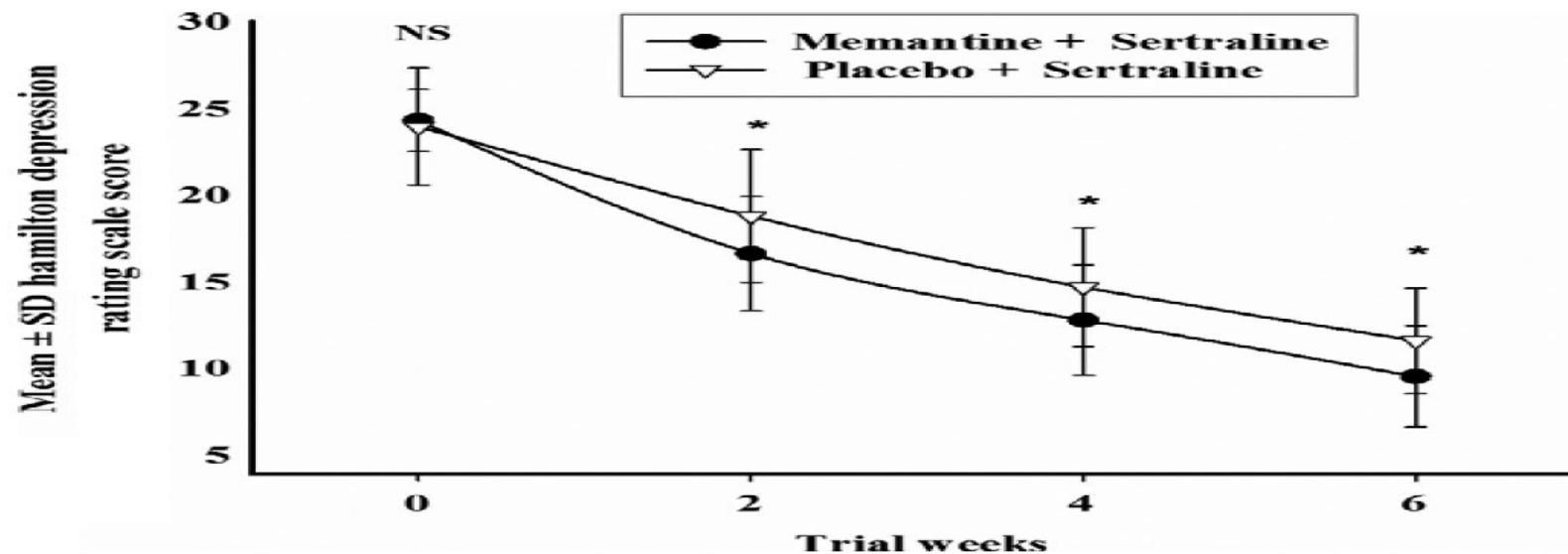
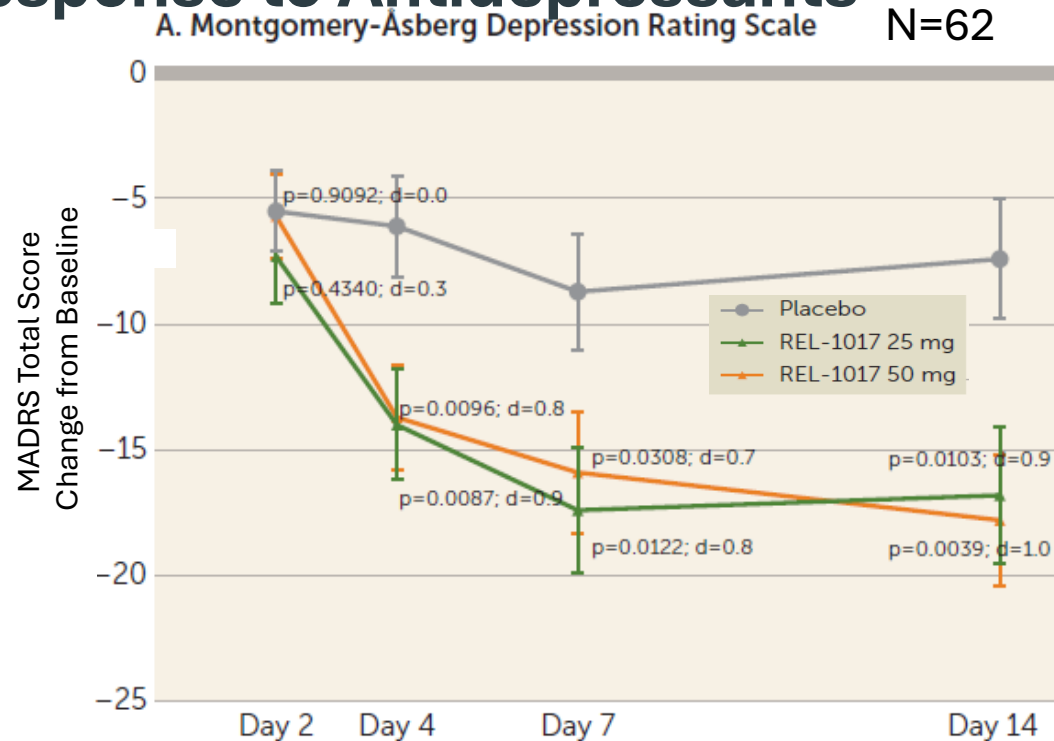


Fig. 2. Repeated measures for comparison of the effects of two treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean $\pm$ standard deviation. *P*-values show the result of the independent *t*-test comparing HDRS scores between the two groups at each time point. NS indicates non-significant; *, *P* < 0.05.

Amidfar, et al. *Journal of Clinical Pharmacy and Therapeutics*. 2017;42:44–50.

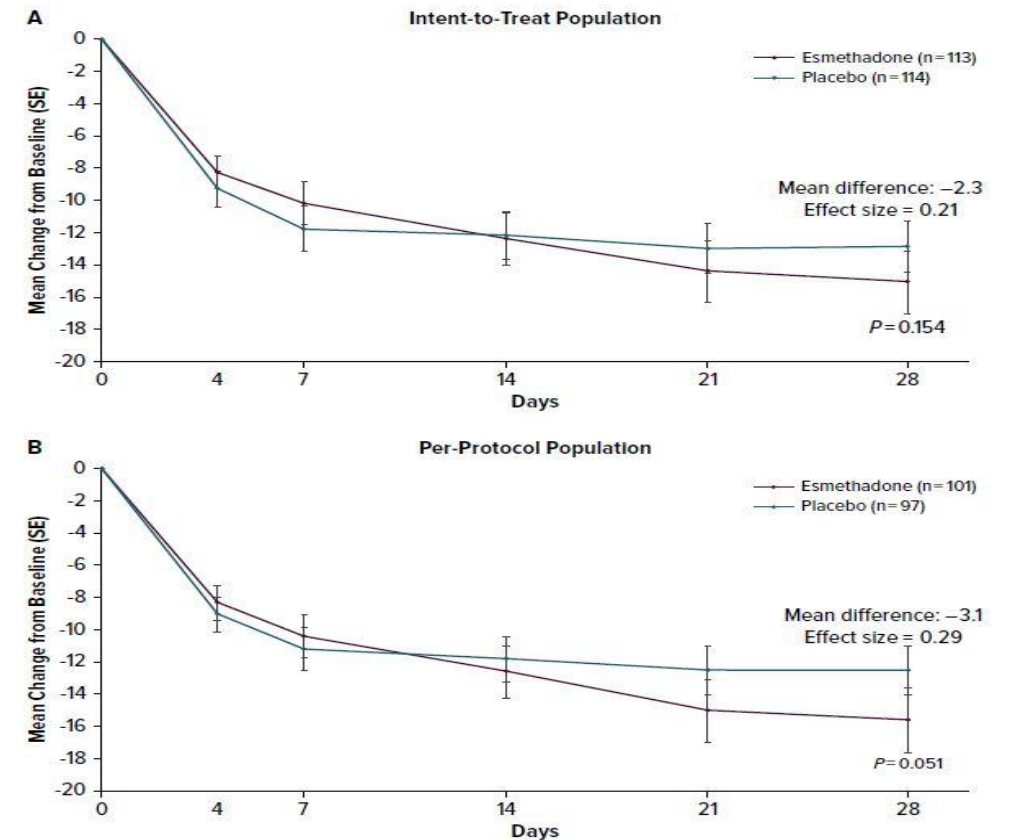
Double-Blind Trials of Esmethadone (REL-1017; NMDA receptor antagonist) As Adjunctive Treatment in MDD Patients with Inadequate Response to Antidepressants



*Trial not powered for efficacy detection; p-values and effect size calculations were performed for efficacy measures, with no adjustments for multiple comparisons. LS Mean, least-squares mean; MADRS, Montgomery-Åsberg Depression Rating Scale.

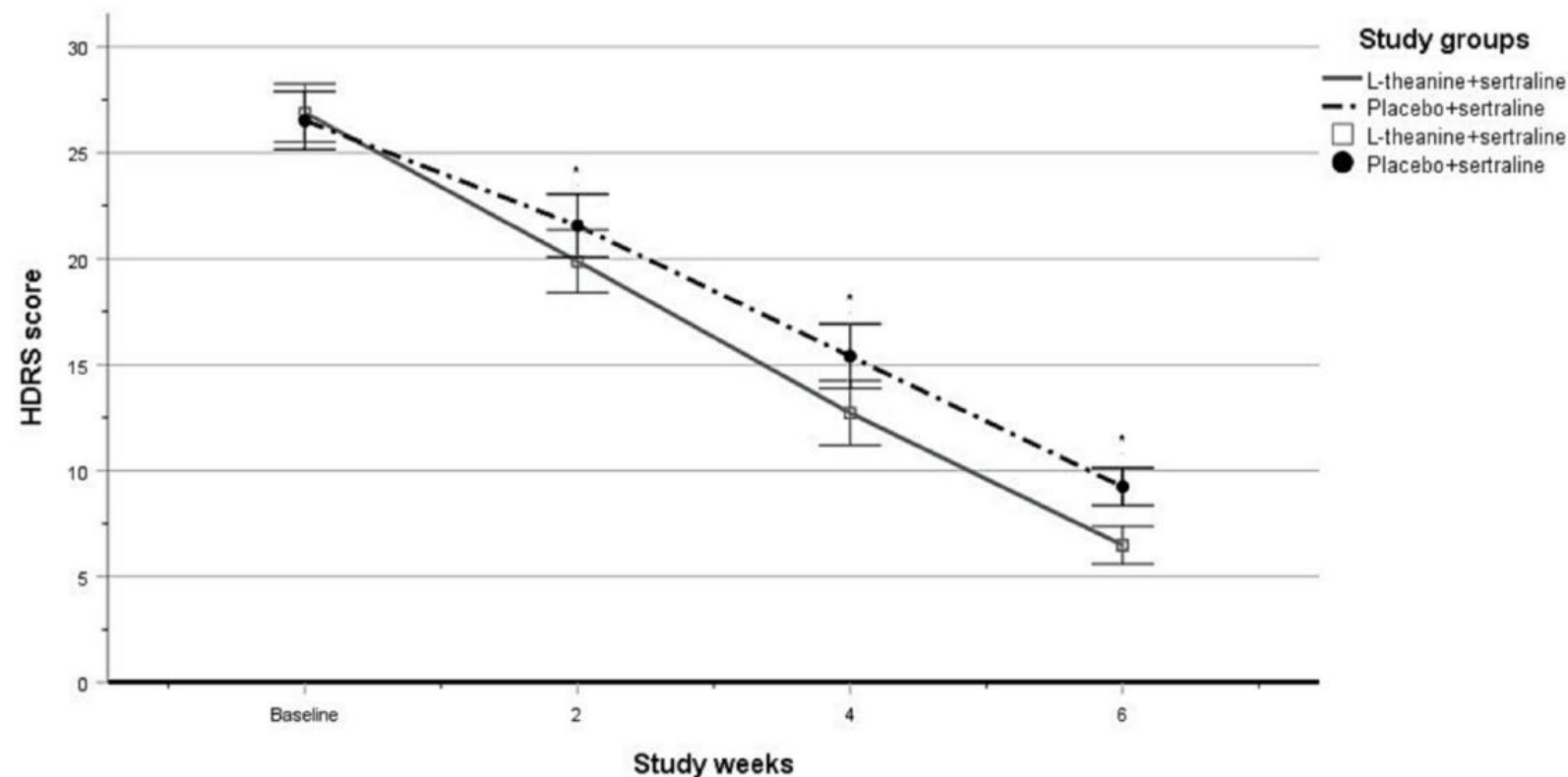
Fava et al, Am J Psychiatry. 2022 Feb;179(2):122-131.

Figure 2. Mean Change From Baseline to Day 28 for Montgomery-Åsberg Depression Rating Scale (MADRS) Total Score for the Primary Efficacy Analysis in the Intent-to-Treat (A) and Per-Protocol (B) Populations and Response and Remission Rates (C)*



Fava et al. J Clin Psychiatry. 2024 Jun 17;85(3):24m15265. doi: 10.4088/JCP.24m15265

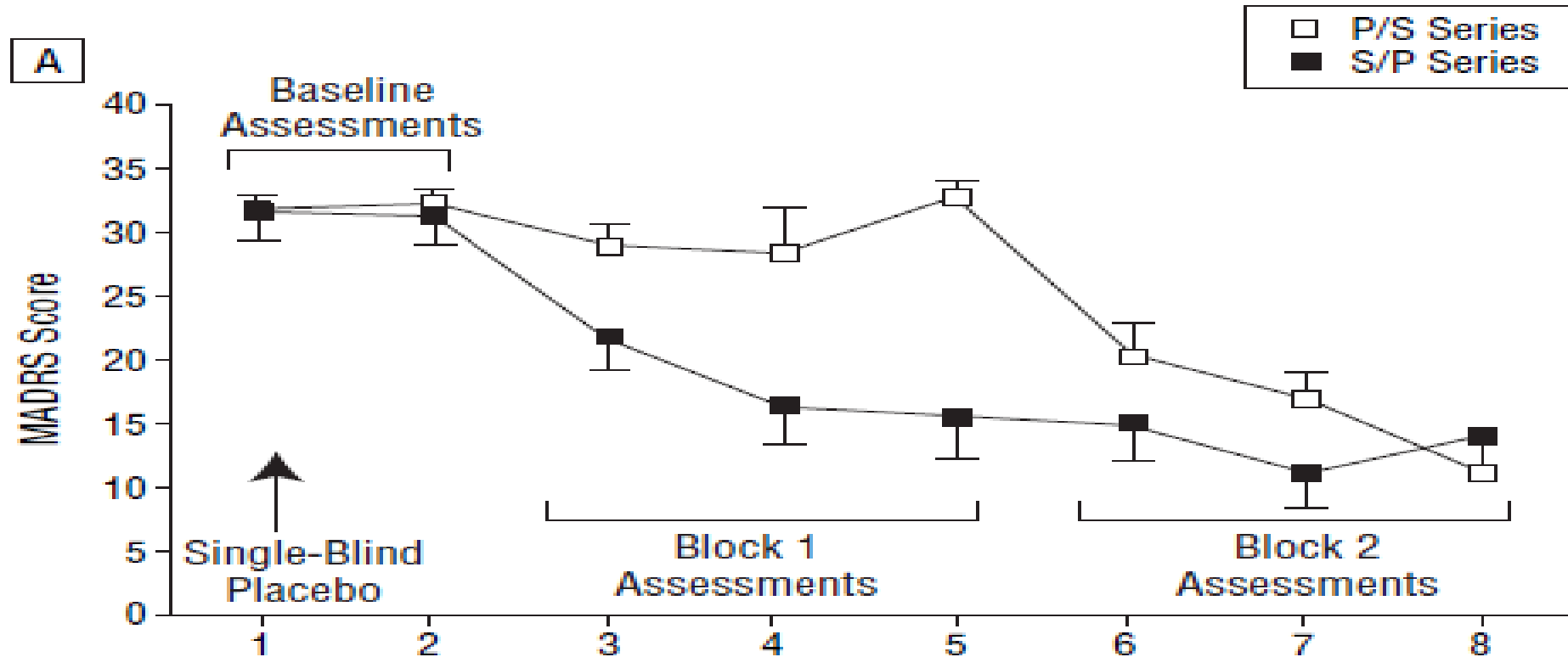
L-Theanine, a Glutamate Modulator, Adjunct to Sertraline for MDD: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial (n=60)



Shamabadi et al, Journal of Affective Disorders 333 (2023) 38–43

Fig. 2. Repeated measure analysis for comparison of effects of the two treatments on the Hamilton depression rating scale (HDRS) scores. Error bars represent ± 2 standard errors. * shows a significant p -value obtained from the independent sample t -test comparing the score change from baseline to each time point between the two groups.

Double-Blind Study of i.v. Scopolamine (4 µg/kg intravenously) in TRD (n=18)

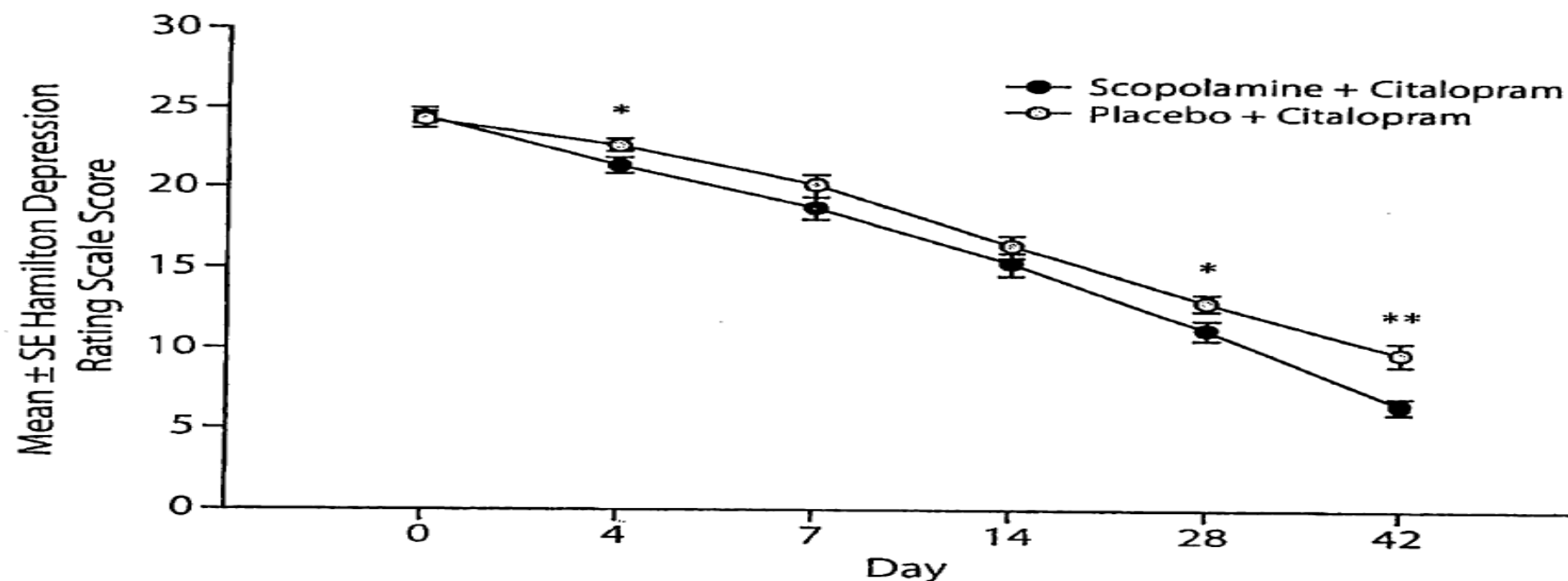


Mean Montgomery-Asberg Depression Rating Scale (MADRS) (A) scores for the placebo/scopolamine hydrobromide (P/S) group and the scopolamine/placebo (S/P) group across 8 assessments. Two baseline, 3 block 1, and 3 block 2 assessments are identified in each panel. Error bars represent SE. For each scale, there are significant group x assessment interactions ($P < .001$).

Furey and Drevets. *Arch Gen Psychiatry*. 2006;63:1121-1129.

Double-Blind Study of Oral Scopolamine (1 mg/day) Augmentation on Citalopram in MDD (n=40)

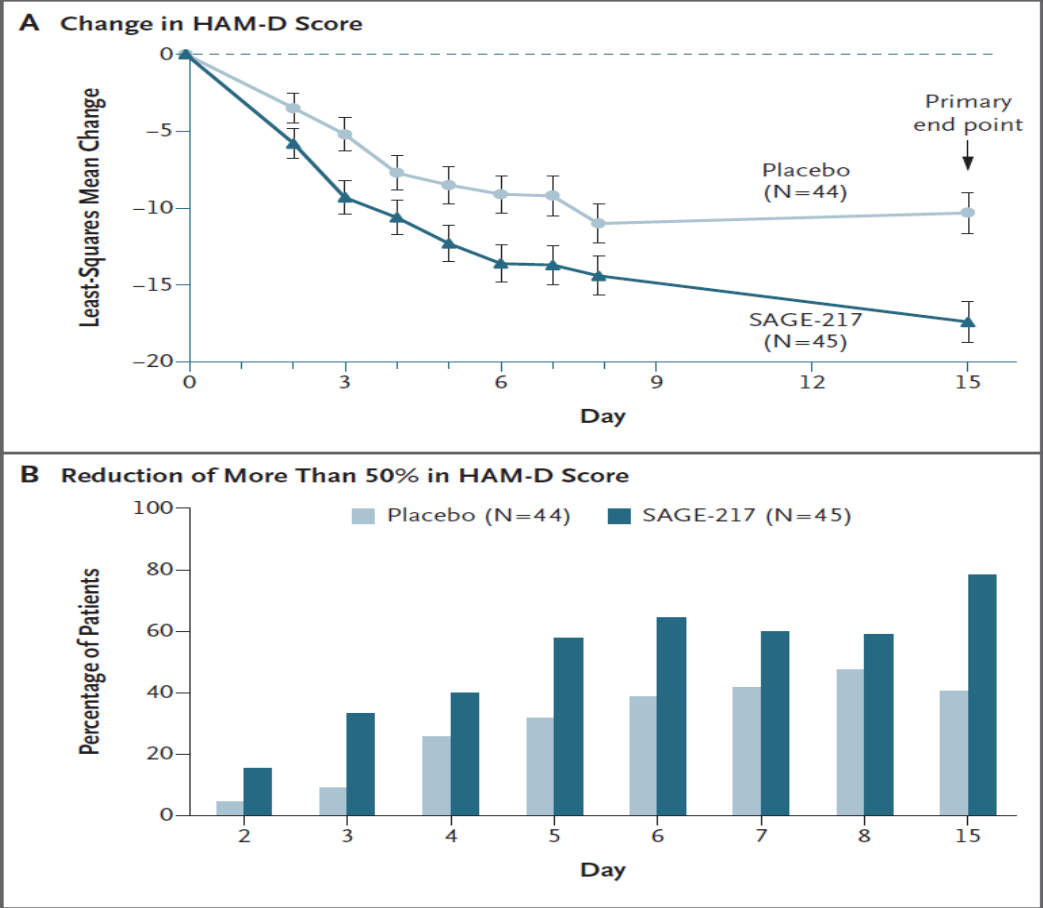
Figure 2. Results of 2-Factor Repeated-Measures Analysis of Variance



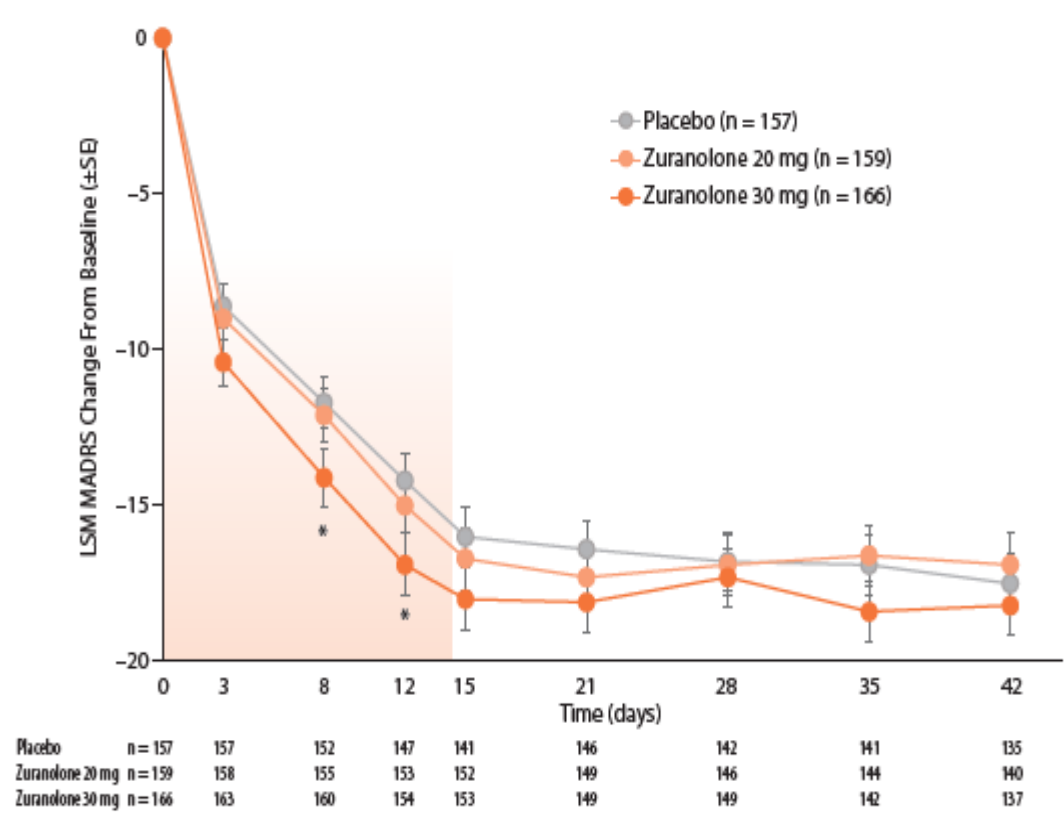
* $P < .05$, ** $P < .01$.

Khajavi, et al. *J Clin Psychiatry*. 2012;73:1428-1433.

Double-Blind, Placebo-Controlled Trials of SAGE-217 (Zuranolone), a Next Generation Positive Allosteric Modulator of GABA, in MDD (n=89 and n=482)



B. CFB MADRS Total Score Over Time^b

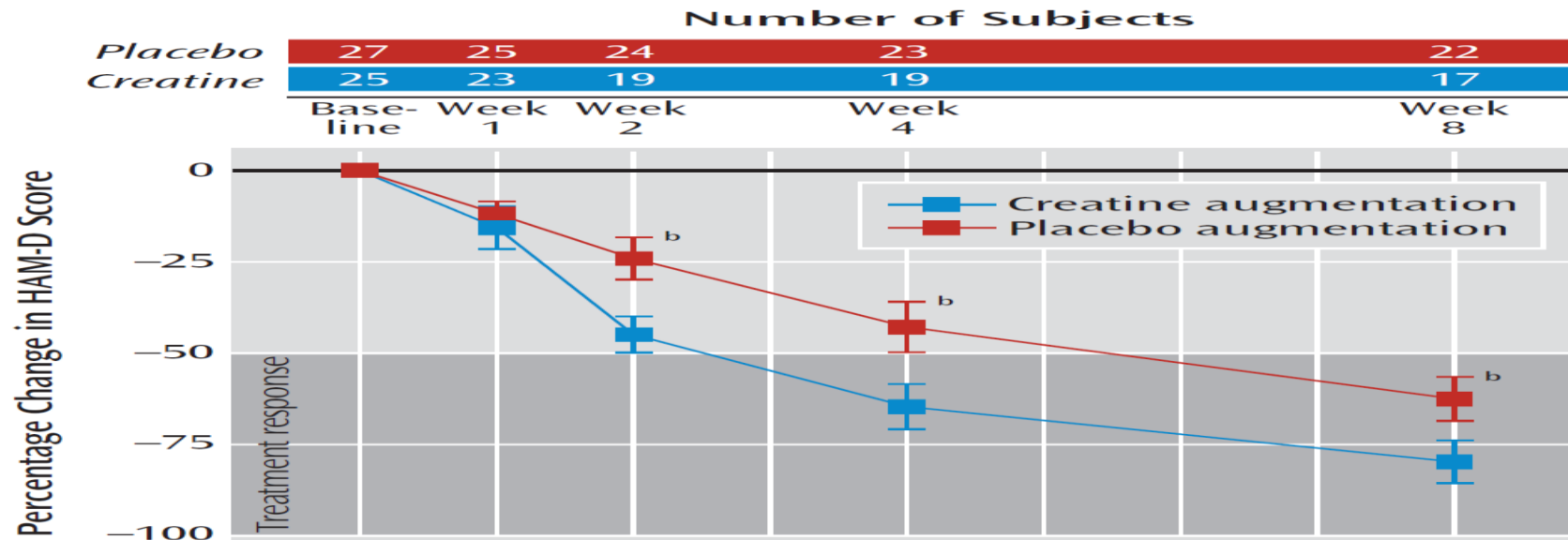


Gunduz-Bruce, et al. *N Engl J Med*. 2019;381:903-11.

Clayton et al, *J Clin Psychiatry*. 2023 Feb 20;84(2):22m14445. doi: 10.4088/JCP.22m14445

Double-Blind, Placebo-Controlled Creatine (5 gr/day) Augmentation of SSRIs in Women with MDD (n=52)

FIGURE 2. Percentage Change in Hamilton Depression Rating Scale (HAM-D) Score for Women With Major Depressive Disorder Assigned to Creatine Monohydrate or Placebo Augmentation of SSRI^a



^a Mean changes in total score with 95% confidence intervals are shown. Changes in depression score were analyzed by using mixed-effects model repeated-measures analysis. Main effects for treatment group, visit, and their interaction were included in the model. Age and baseline HAM-D score were also included as covariates in the model.

^b Significant difference between groups in intent-to-treat analysis ($p < 0.001$).

Lyoo, et al. *Am J Psych*. 2012 Sep;169(9):937-945.

Minocycline (200 mg/day) (an Anti-Inflammatory and Neuroprotective Agent) as an Adjunct for Treatment-Resistant Depressive Symptoms

N=41

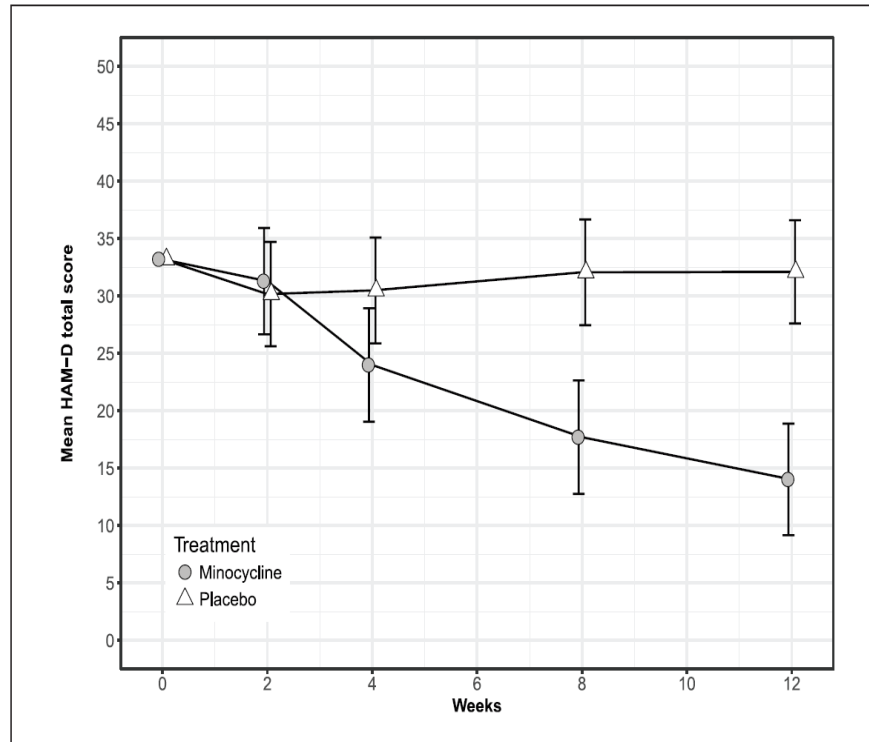
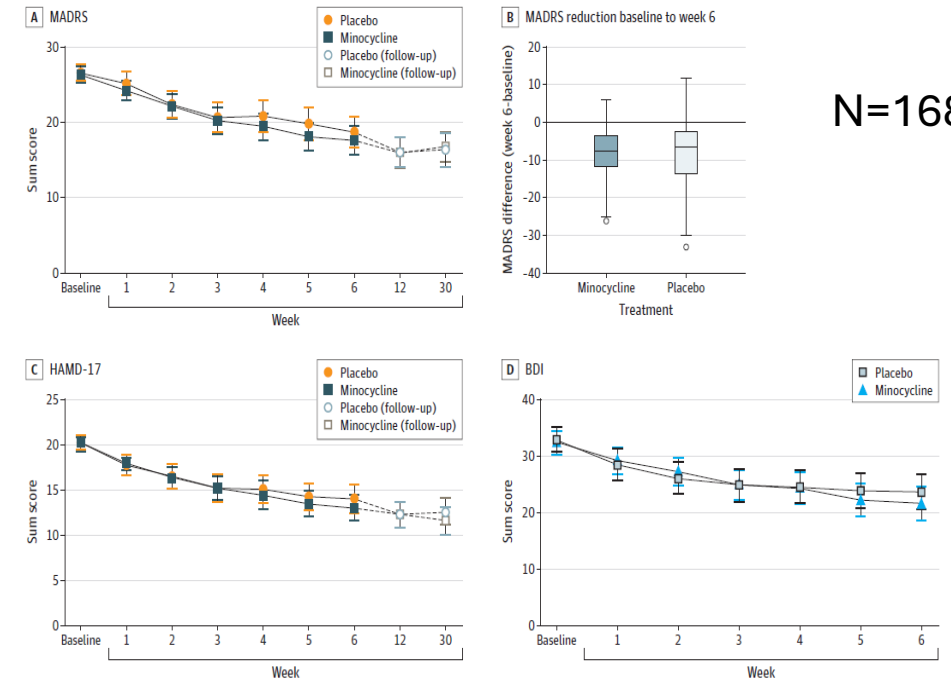


Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socioeconomic status class participants (most frequent class).

Husain, et al. *J Psychopharmacol.* 2017 Sep;31(9):1166-1175.

Figure 2. Time Course of Depression Severity



N=168

BDI indicates Beck Depression Inventory; HAM-D-17, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale. Error bars in panels A, C, and D indicate 95% CIs. Box plots in panel B were created by the Tukey method; horizontal line indicates median; upper and lower border of the box indicates 75th / 25th percentile; error bars in panel B indicate upper and lower values as calculated by the Tukey method.

Hellmann-Regen, et al. *JAMA Network Open.* 2022;5(9):e2230367.
doi:10.1001/jamanetworkopen.2022.30367 (Reprinted).

A 12-week, Randomized, Placebo-Controlled Trial of 2,000 mg/day Adjunctive NAC for MDD (n=269)

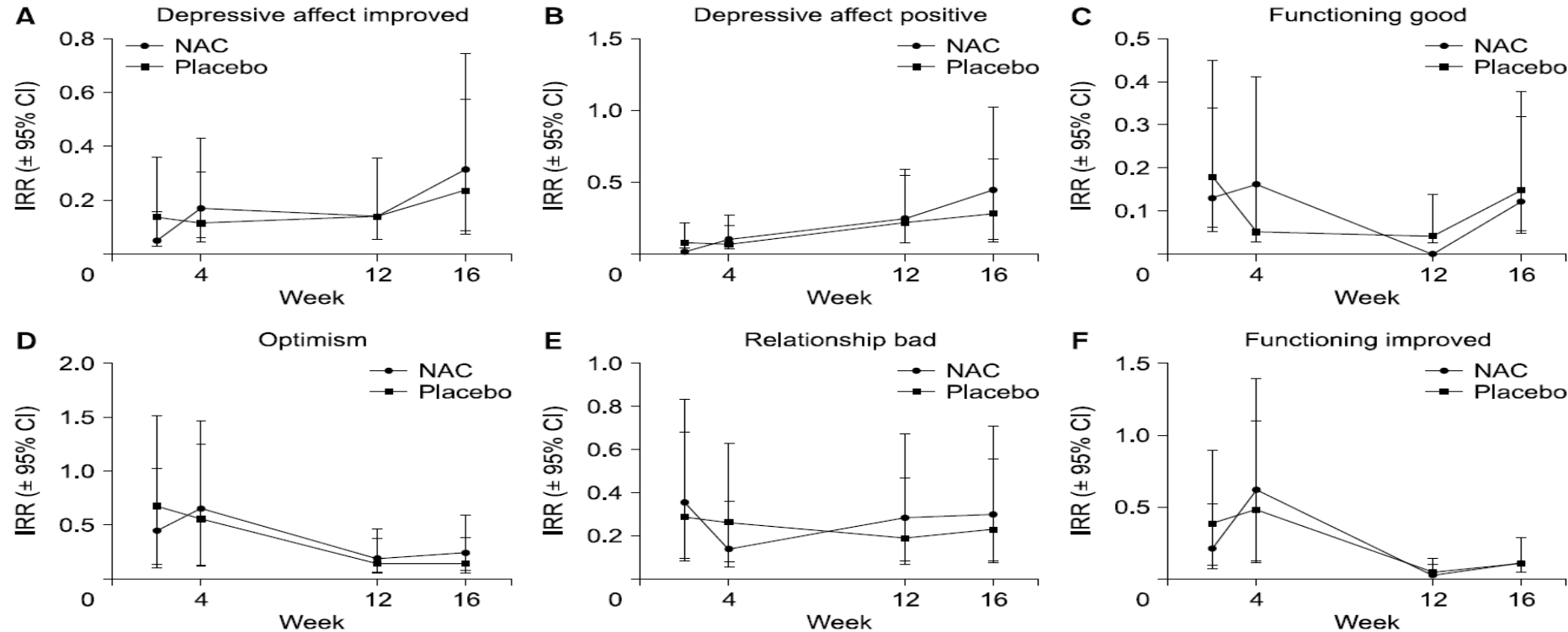
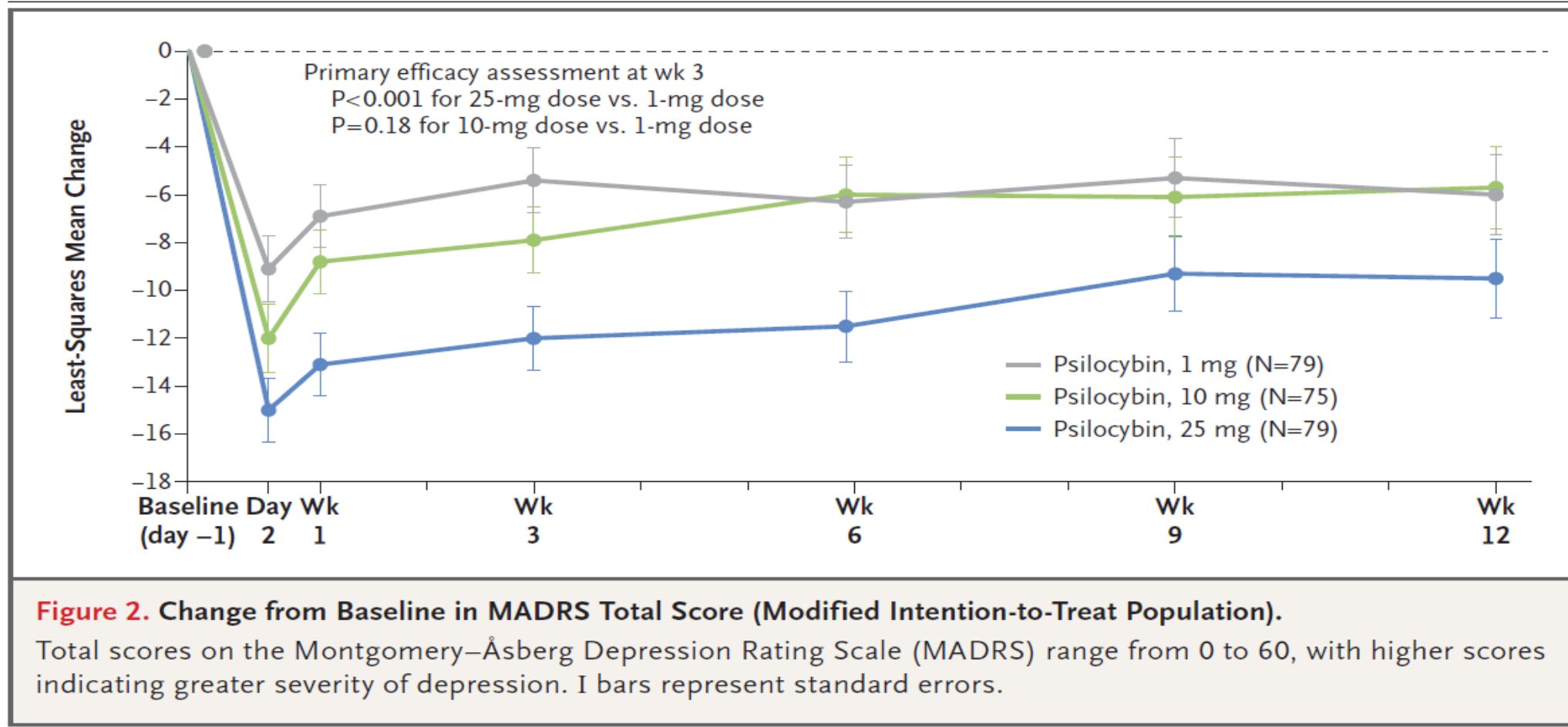


Fig. 1. Incidence rate ratio (IRR) and 95% confidence intervals (95% CIs) from the per protocol analysis. Presented are the main effects for time and group allocation and the time by group interaction were tested for each outcome using log-linked, generalised linear models for Poisson distributed dichotomous outcomes. The statistically significant themes are displayed; depressive affect improved (A), depressive affect positive (B), functioning good (C), optimism (D), relationship bad (E), functioning improved (F), over the course of the 12 weeks of treatment and 4 weeks after discontinuation. NAC, *N*-acetylcysteine.

Change in depressive symptoms, as measured by the MADRS, did not significantly differ for NAC in comparison to placebo at week 12, but was in favor of the NAC group at week 16 ($p = 0.036$)

Russell, et al. *Clinical Psychopharmacology and Neuroscience*. 2023;21(2):320-331.

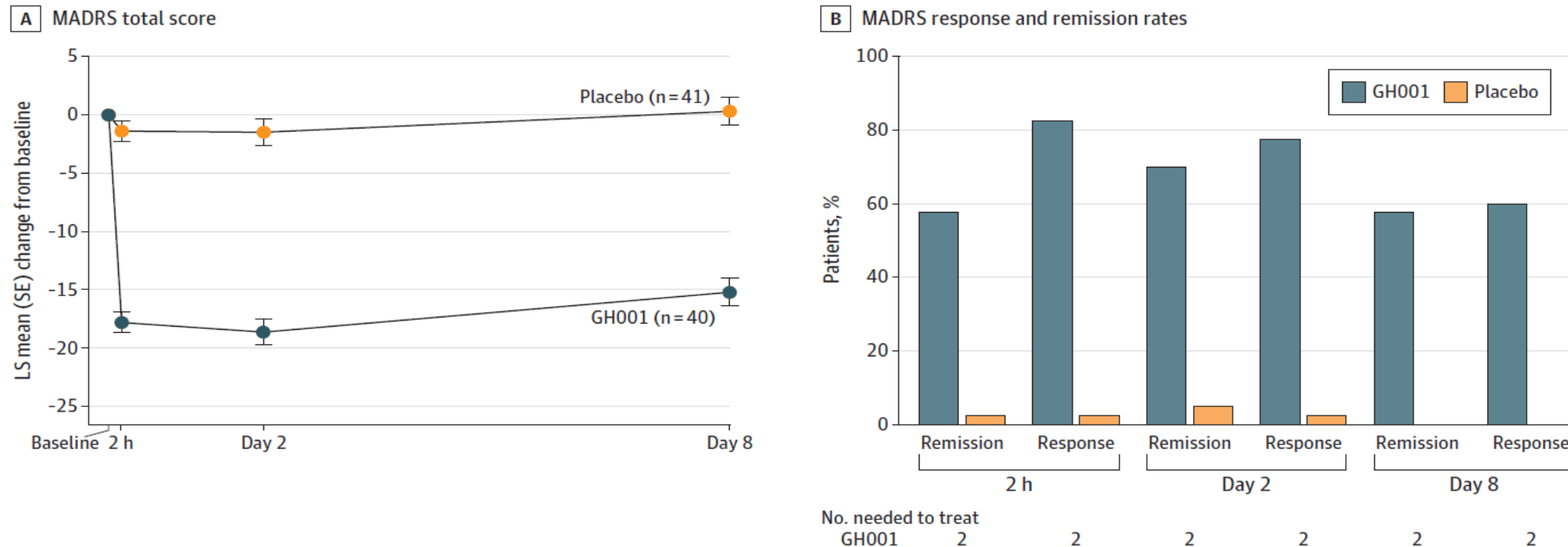
Psilocybin in TRD



Goodwin, et al. *N Engl J Med*. 2022;387:1637-48. DOI: 10.1056/NEJMoa2206443.

Mebutofotenin in Treatment-Resistant Depression

Figure 2. Dot Plot and Bar Graph Showing Efficacy in Part 1

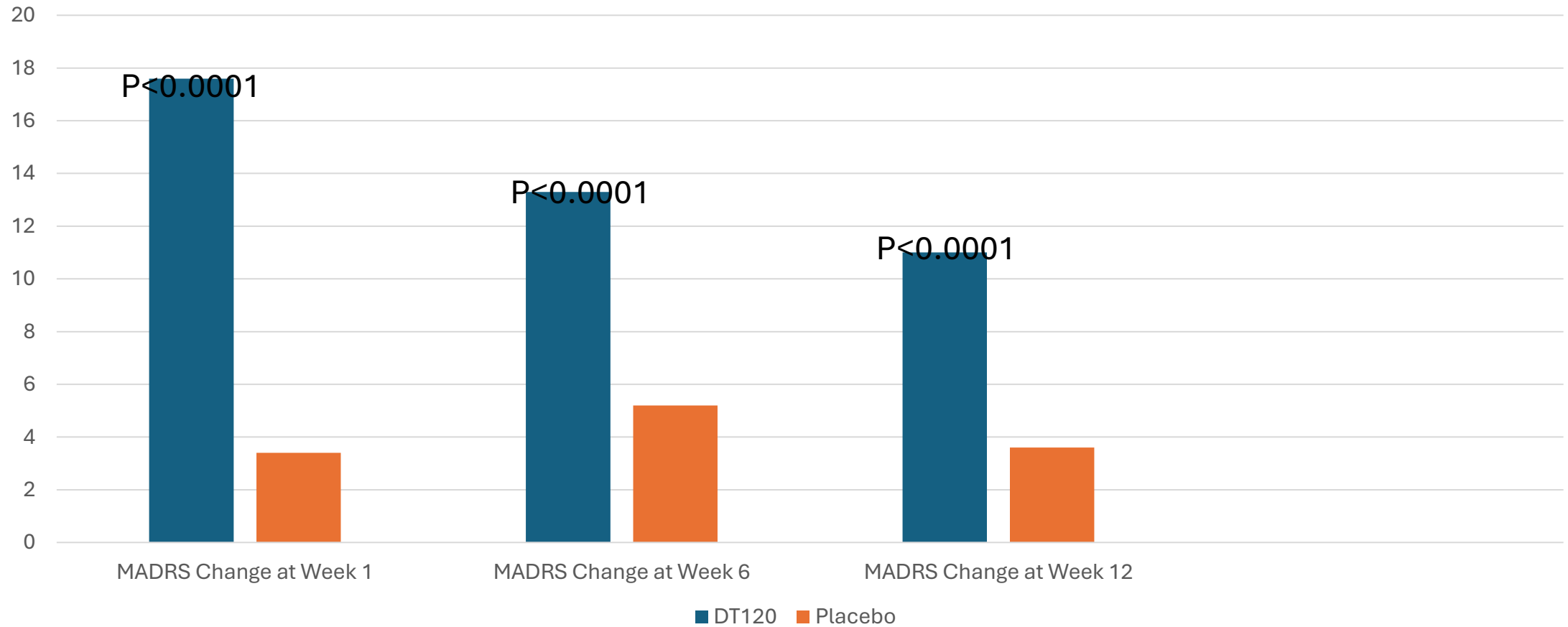


A, Change in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (primary end point) (least squares [LS] mean difference vs placebo: -15.5; $P < .001$; effect size: Cohen d , -2.0). B, MADRS response ($\geq 50\%$ reduction

from baseline) and remission (total score ≤ 10) rates; number needed to treat for remission and for response.

Cubala et al, JAMA Psychiatry. 2026 Mar 25:e260096. doi: 10.1001/jamapsychiatry.2026.0096. Online ahead of print

Double-blind, Placebo-controlled Trial of a single dose of DT120 (lysergide) ODT 100 µg in adults with MDD (n=149)



Definium Therapeutics Announces Positive Topline Results from Phase 3 Emerge Study of DT120 Orally Disintegrating Tablet (ODT) in Major Depressive Disorder :: Definium Therapeutics (DFTX)

Palmitoylethanolamide (600 mg bid), with Anti-Inflammatory and Endocannabinoid Effects, As Adjunctive Therapy in MDD (n=58)

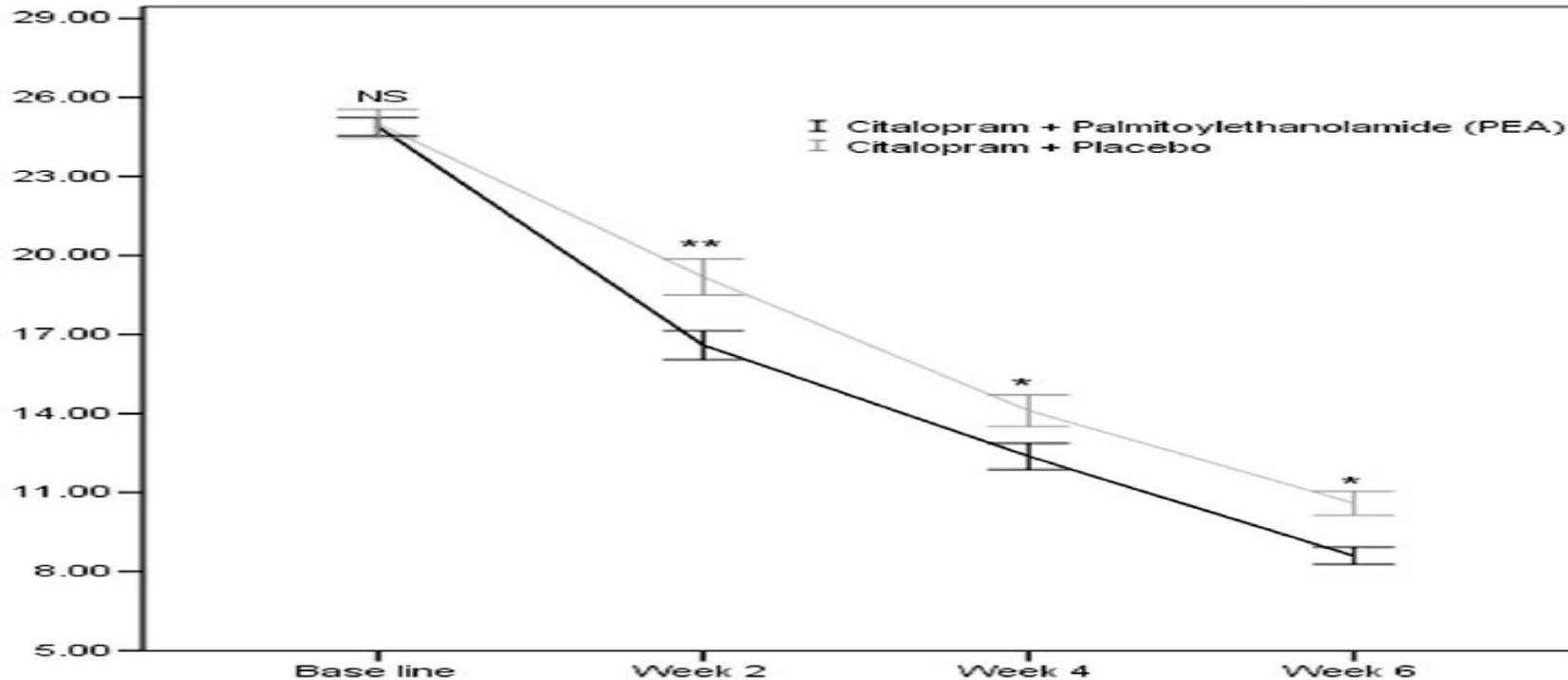
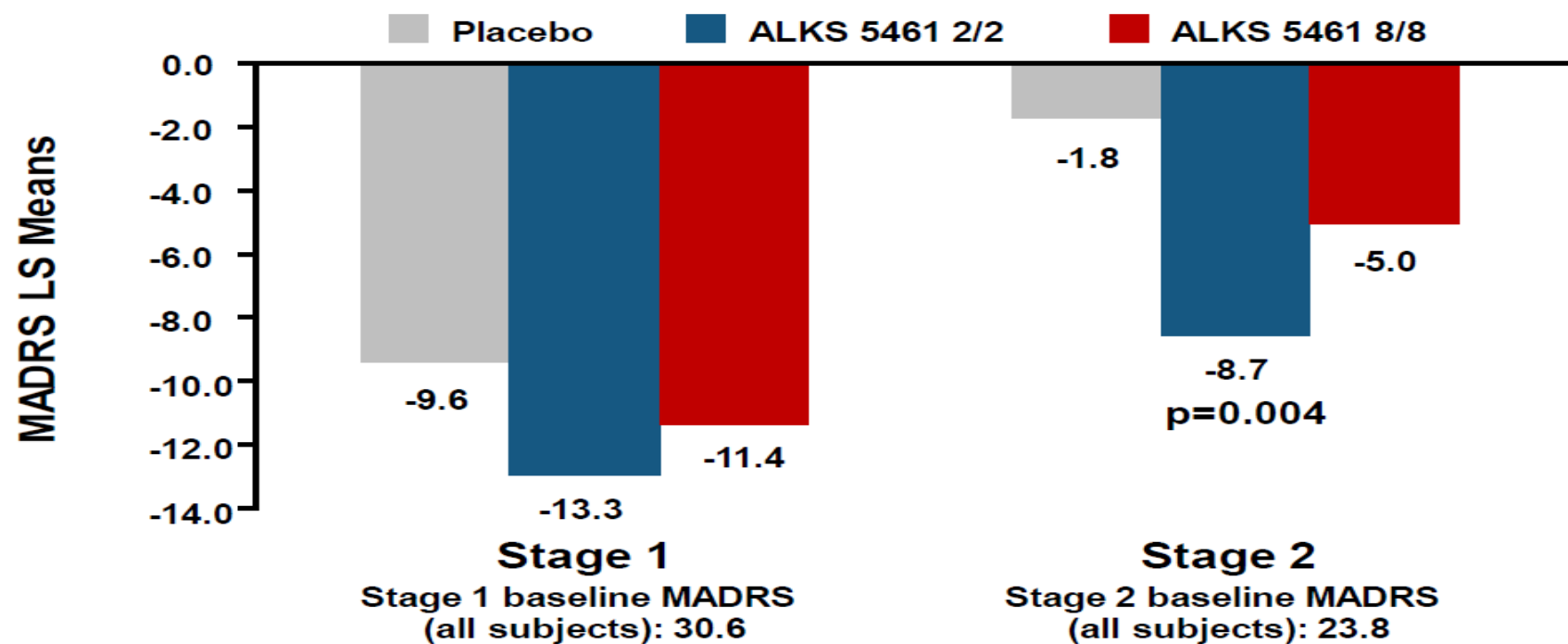


Fig. 2. Repeated measure analysis for comparison of the effects of two treatments on the Hamilton depression rating scale (HDRS) scores. Values represent mean $\pm$ SEM (standard error of mean). P values show the result of the independent sample *t*-test for comparison of the score change from the baseline between the two groups at each time point. NS non-significant. * $p \leq .05$; *** $p \leq .01$.

Ghazizadeh-Hashemi, et al. *Journal of Affective Disorders*. 2018;232:127-133.

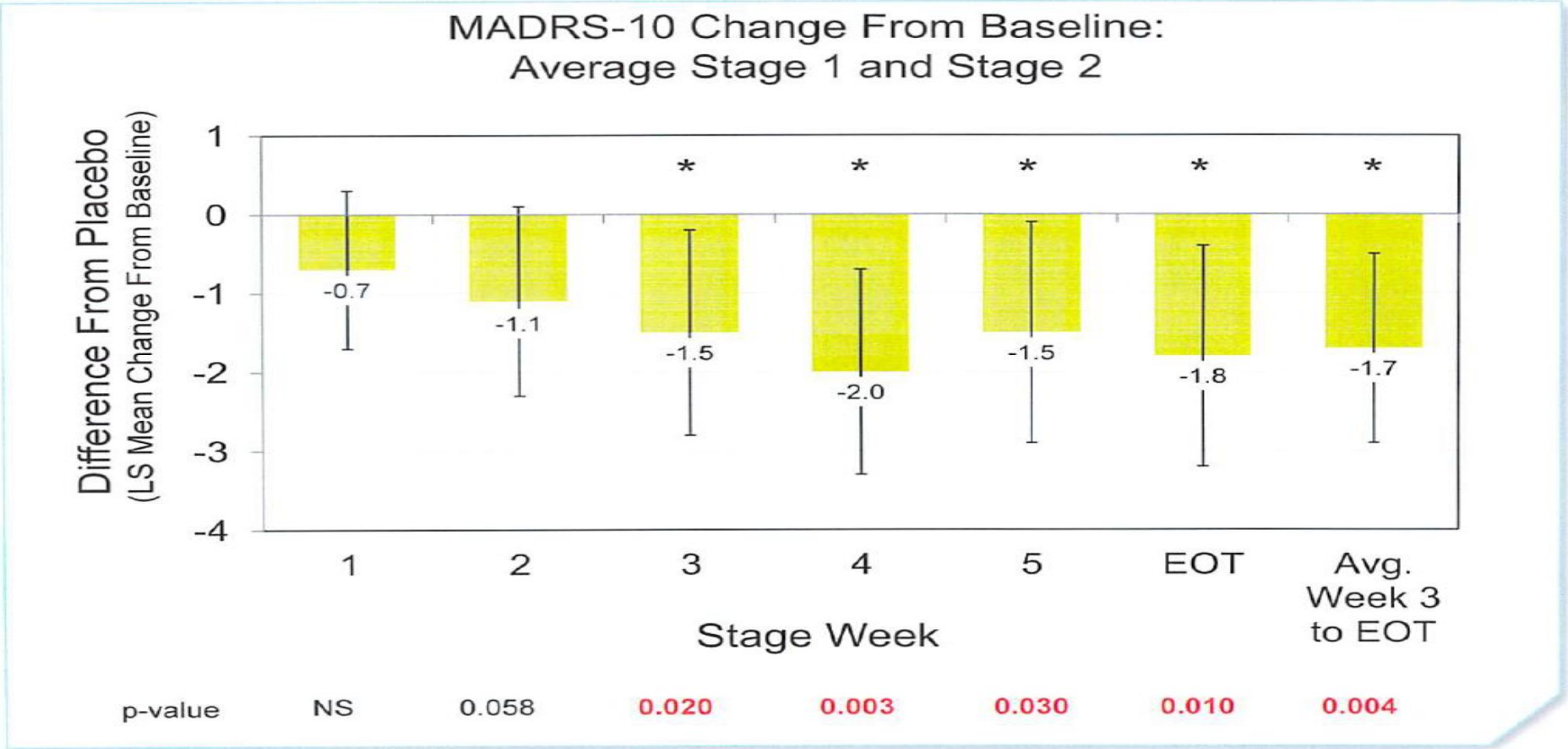
Double-Blind, SPCD Study of ALKS 5461 (Buprenorphine Plus the mu Antagonist samidorphan) vs. Placebo (n=141)

Figure 4: MADRS Change from Baseline at Week 4



Fava, et al. *Am J Psychiatry*. 2016 May 1;173(5):499-508.

Pooled Analysis of the FORWARD-4 and FORWARD-5 SPCD Studies of ALKS 5461 (n=792)



95% confidence interval

Fava, et al. *Mol Psychiatry*. 2018 Oct 29. doi: 10.1038/s41380-018-0284-1. [Epub ahead of print]

A Randomized Proof-of-Mechanism Trial Applying the 'Fast-Fail' Approach to Evaluating the κ -opioid Antagonist Aticaprant As a Treatment for Anhedonia (n=89)

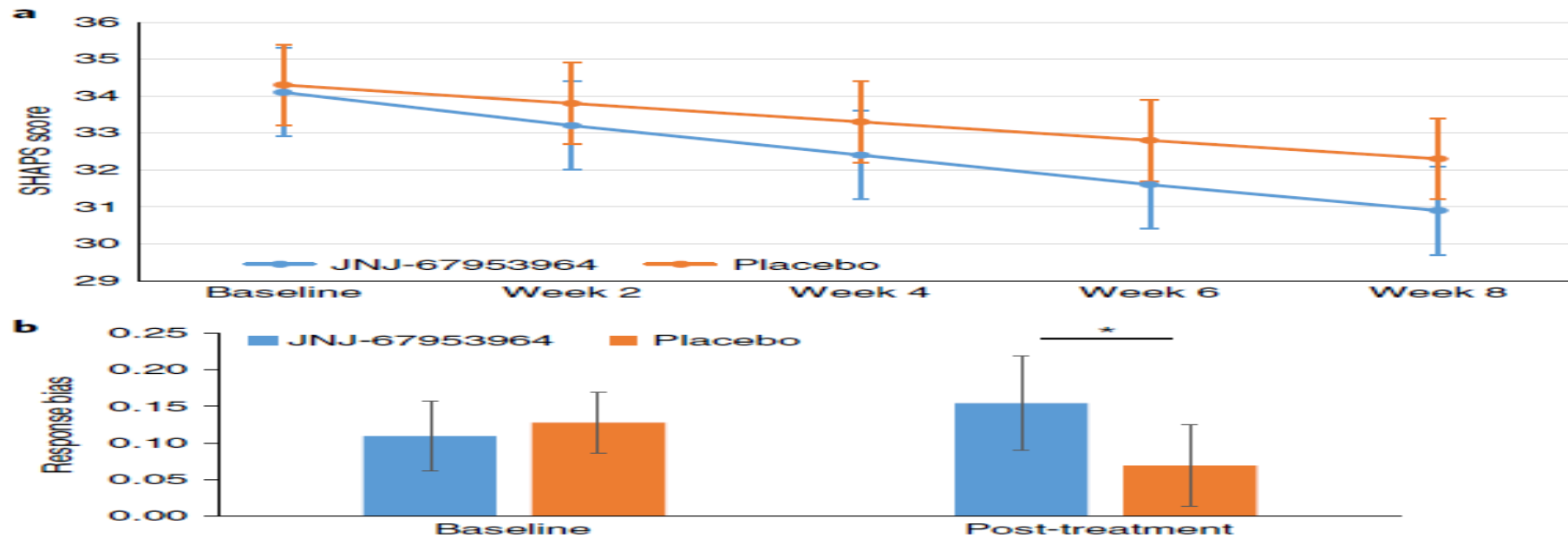


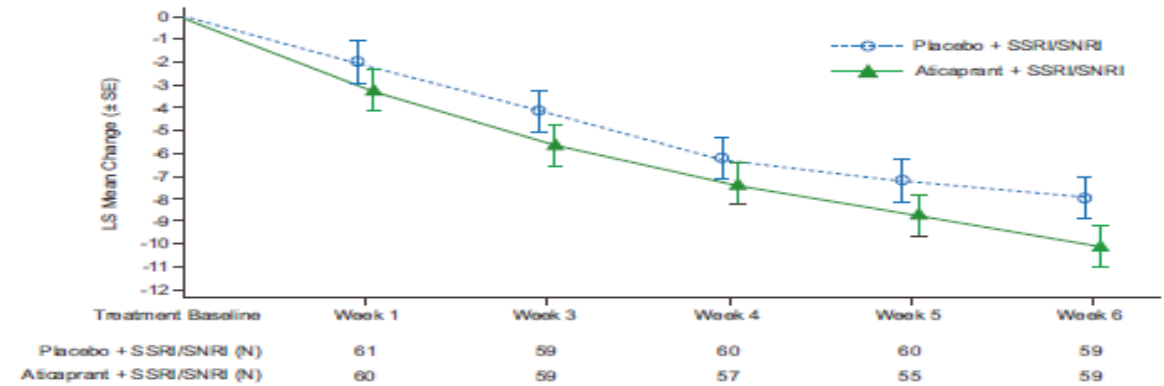
Fig. 3 | SHAPS and PRT results. a, Effects of study drug versus placebo on mean SHAPS score (ITT population). Error bars represent the 95% confidence intervals around the means. **b**, Effects of study drug versus placebo on mean PRT response bias (ITT population). Error bars represent standard errors. * $P < 0.05$. Mixed-effects model analysis was carried out in the ITT population including mean centered baseline value, age, study site and sex as covariates.

Krystal, et al. *Nature Medicine*. 2020 May;26764:760-768.



A Phase 2 Randomized, Double-blind, Placebo-controlled Study of Aticaprant, a Kappa Receptor Antagonist, Adjunctive to Oral SSRI/SNRI Antidepressant in MDD (n=166)

a. eITT Analysis Dataset



b. fITT Analysis Dataset

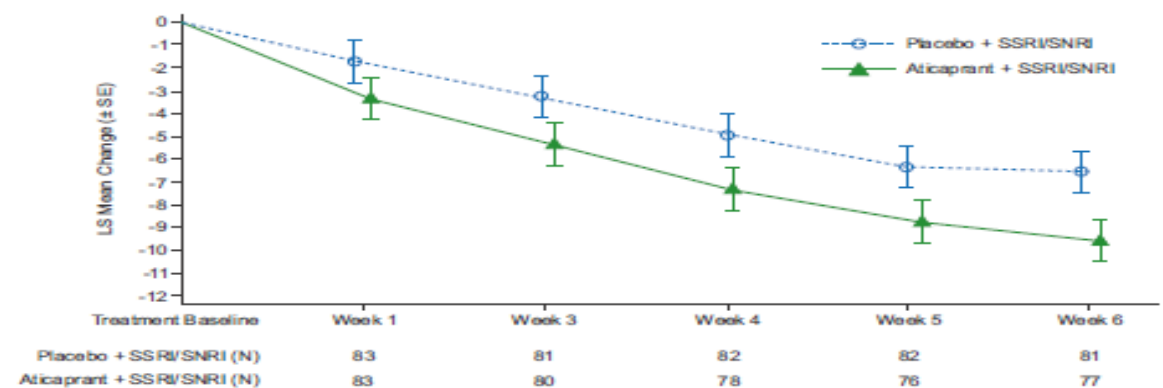
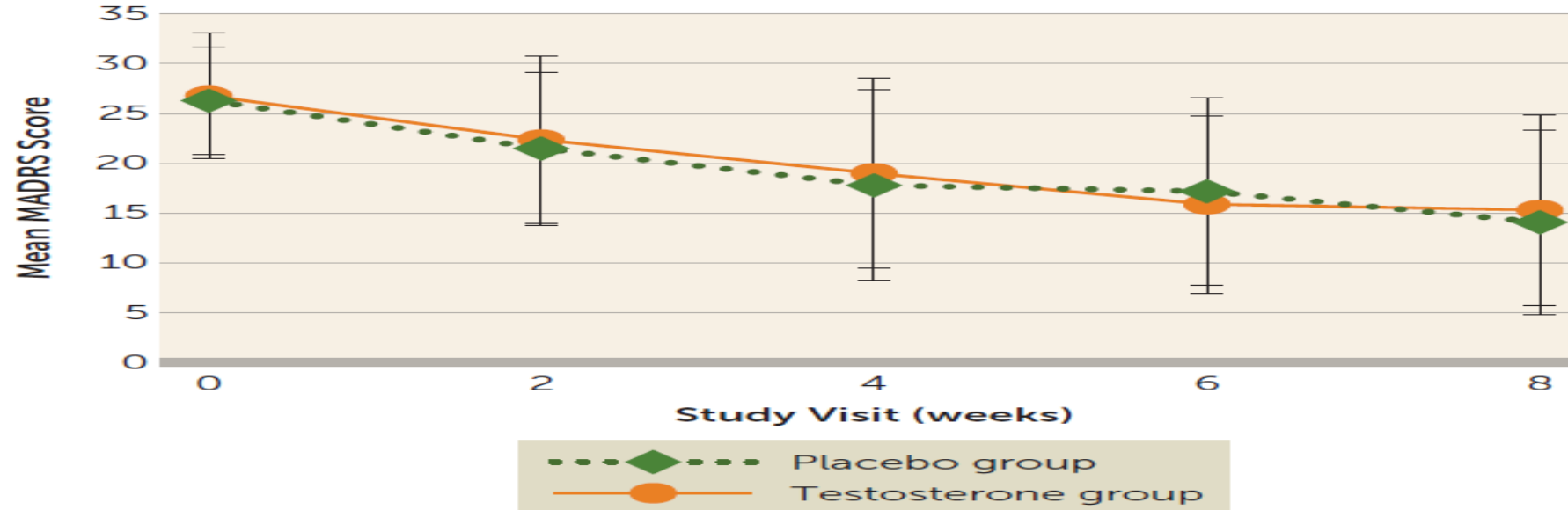


Fig. 1 MADRS total score: LS mean change from baseline (±SE) over 6 weeks. eITT enriched intent-to treat, fITT full intent-to-treat, LS least squares, MADRS Montgomery–Åsberg Depression Rating Scale, SE standard error, SNRI serotonin-norepinephrine reuptake inhibitor, SSRI selective serotonin reuptake inhibitor. Note: MADRS total score ranges from 0 to 60; a higher score indicates a more severe condition. Negative change in score indicates improvement. Negative difference favors aticaprant.

Schmidt et al., Neuropsychopharmacology. 2024 Aug;49(9):1437-1447.

Low-Dose Testosterone Augmentation for Antidepressant-Resistant Major Depressive Disorder in Women: An 8-Week Randomized Placebo-Controlled Study (n=101)

FIGURE 1. Depression severity over time, as assessed by mean MADRS score, in a study of low-dose testosterone augmentation for antidepressant-resistant major depression in women^a



^a MADRS=Montgomery-Åsberg Depression Rating Scale. There was no significant difference between the testosterone and placebo groups. Error bars indicate standard deviation.

Dichtel, et al. *AJP*. 2020 Oct 1;177(10):965-973. doi: 10.1176/appi.ajp.2020.19080844.

A Cross-over, Placebo-Controlled Trial of Inhaled Nitrous Oxide, an NMDA Receptor Antagonist, for TRD (Nagele et al) and a Parallel Trial of Inhaled Nitrous Oxide in TRD (Liu et al)

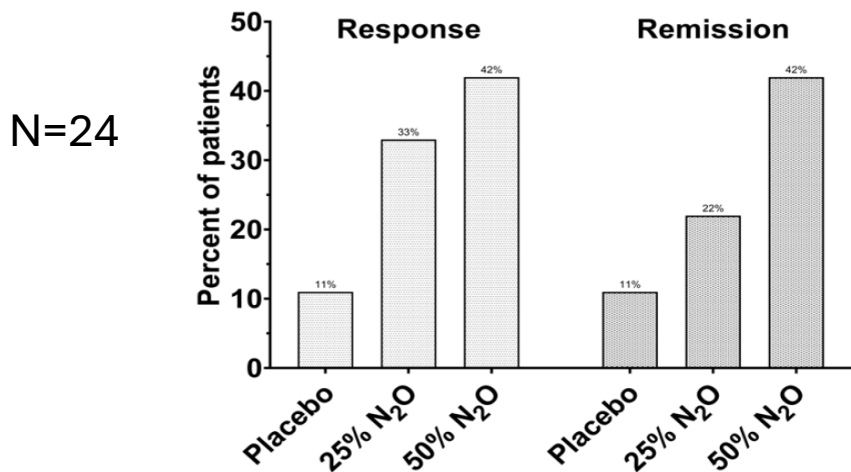
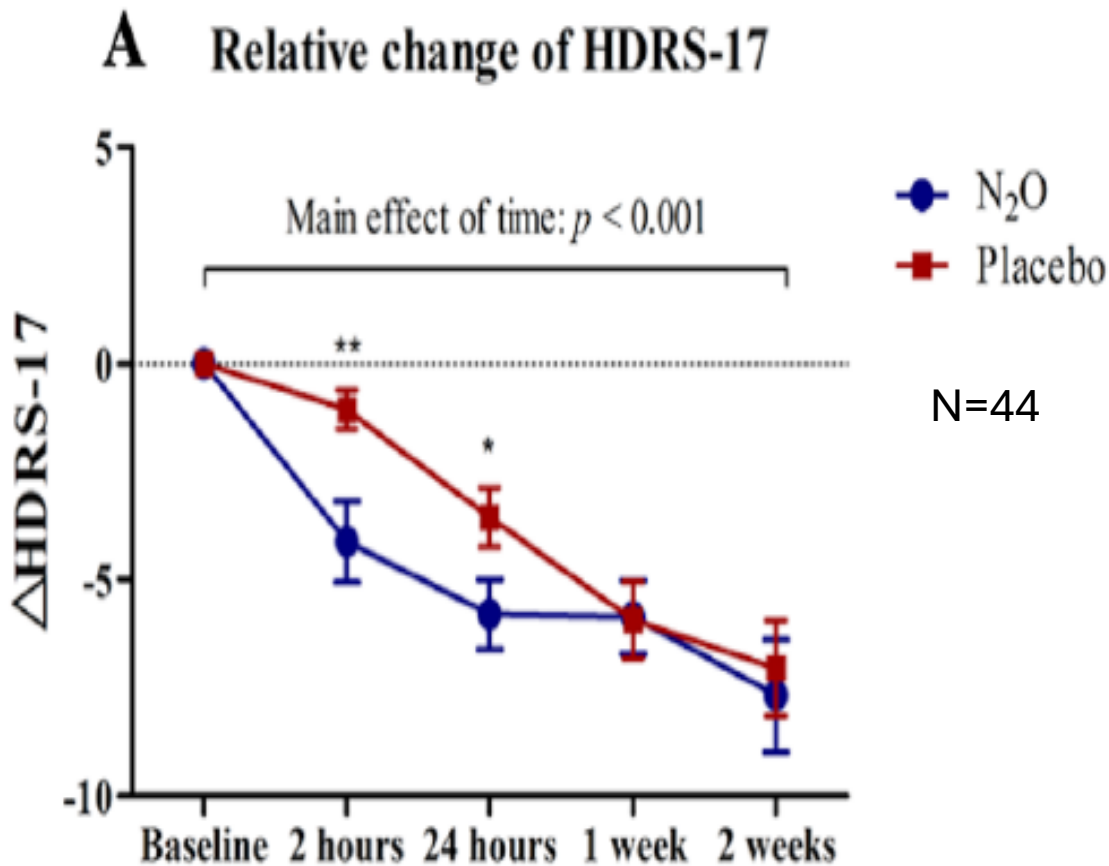


Fig. 3. Proportion of patients who experienced response or remission after treatment with 50% nitrous oxide, 25% nitrous oxide, and placebo. In this analysis, we only included treatments where the pretreatment HDRS-21 score was ≥19. Differences between categorical outcomes (response and remission) were tested by Fisher’s exact test; RR and 95% CIs were calculated using the Koopman asymptotic score. After placebo treatment, one of nine patients had a treatment response (11.1%) and one of nine was in remission (11.1%). After 25% nitrous oxide, three of nine patients had a treatment response (33.3%; RR, 2.50; 95% CI, 0.43 to 16.30) and two of nine were in remission (22.2%; RR, 1.82; 95% CI, 0.27 to 12.84). After 50% nitrous oxide, 5 of 12 patients had a treatment response (41.7%; RR, 2.94; 95% CI, 0.57 to 18.02) and 5 of 12 were in remission (41.7%; RR, 2.94; 95% CI, 0.57 to 18.02).

Nagele, et al. *Sci Transl Med.* 13, eabe1376 (2021) 9 June 202.

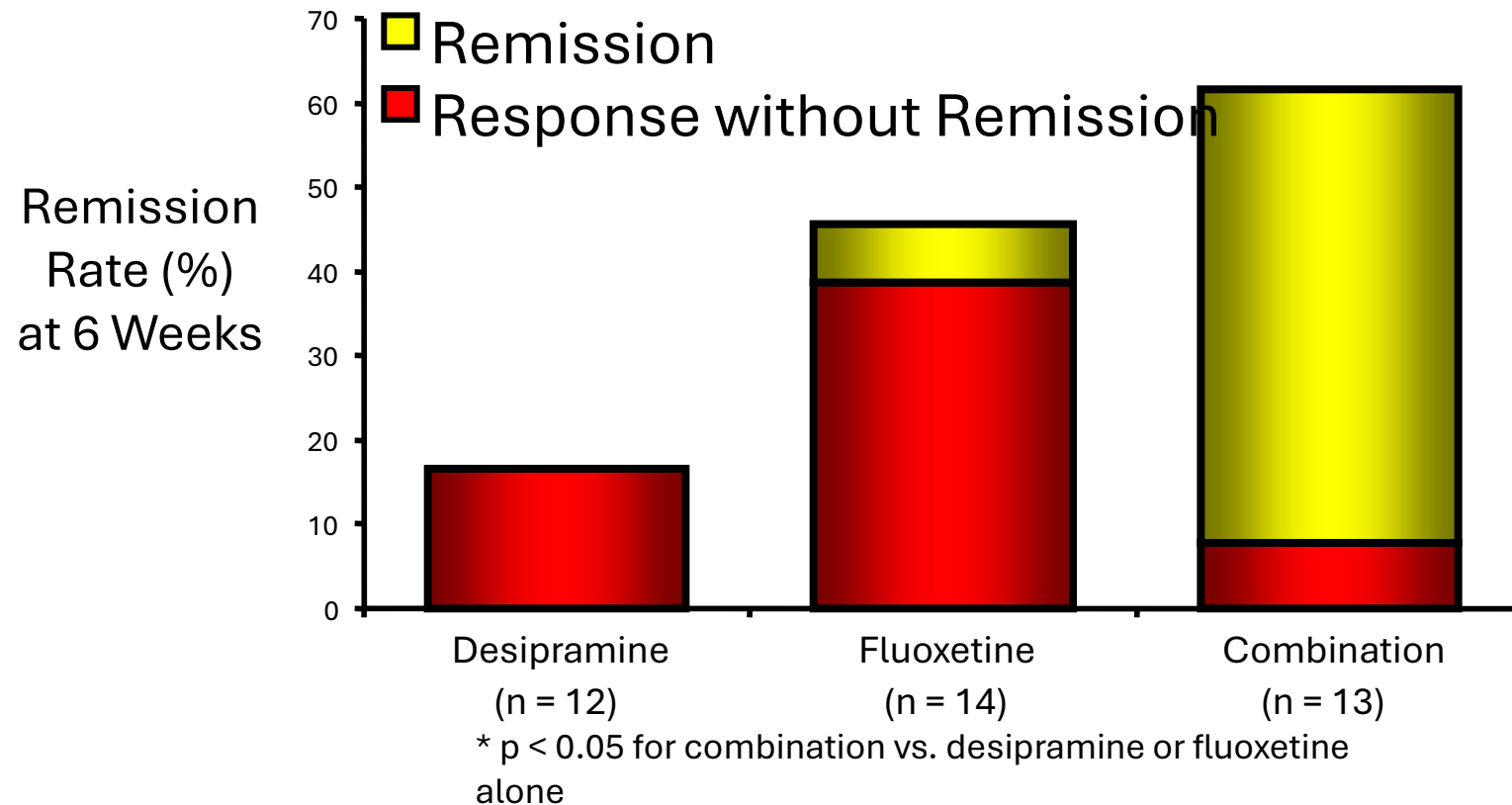


Liu et al, *Psychiatry Research* 326 (2023) 115326

Combination

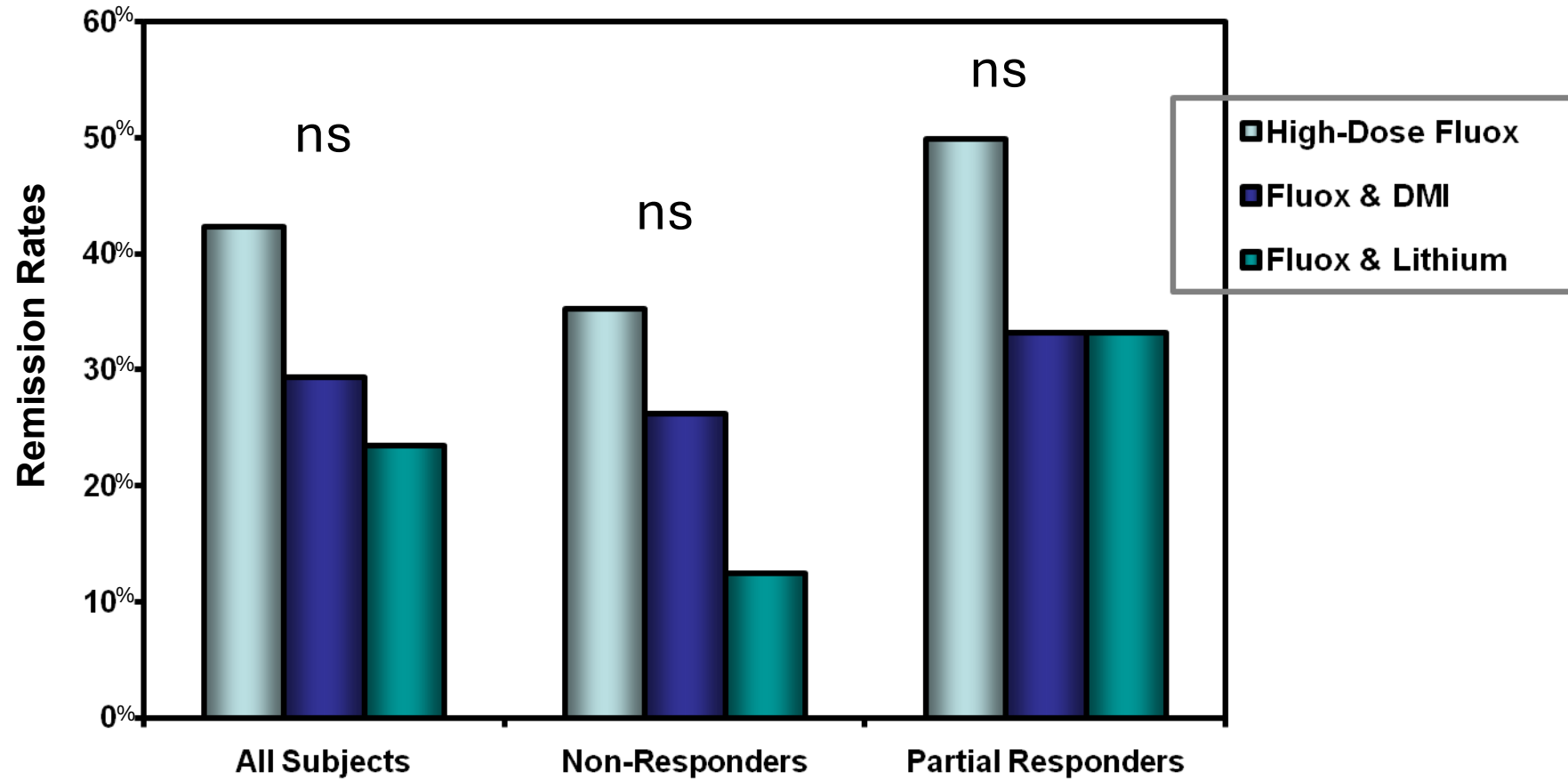
- Definition: The concomitant use of two antidepressants to enhance their therapeutic effect
- Rationale:
 - To obtain a different neurochemical effect by combining antidepressants affecting different neurotransmitter systems
 - To combine antidepressants with different mechanisms of action

Combination NE and 5-HT Reuptake Inhibition vs. Either Alone



Nelson JC, et al. *Biol Psychiatry*. 2004;55:296-300.

Double-Blind Study in 101 Non- and Partial Responders to an 8-Week Fluoxetine Trial: Remission ($\text{HAM-D-17} < 8$) Rates



Fava M. *J Clin Psychopharmacol.* 2002 Aug;22(4):379-387.

Lithium Augmentation Versus Citalopram Combination in Imipramine-Resistant Major Depression: A 10-Week Randomized Open-Label Study (n=104)

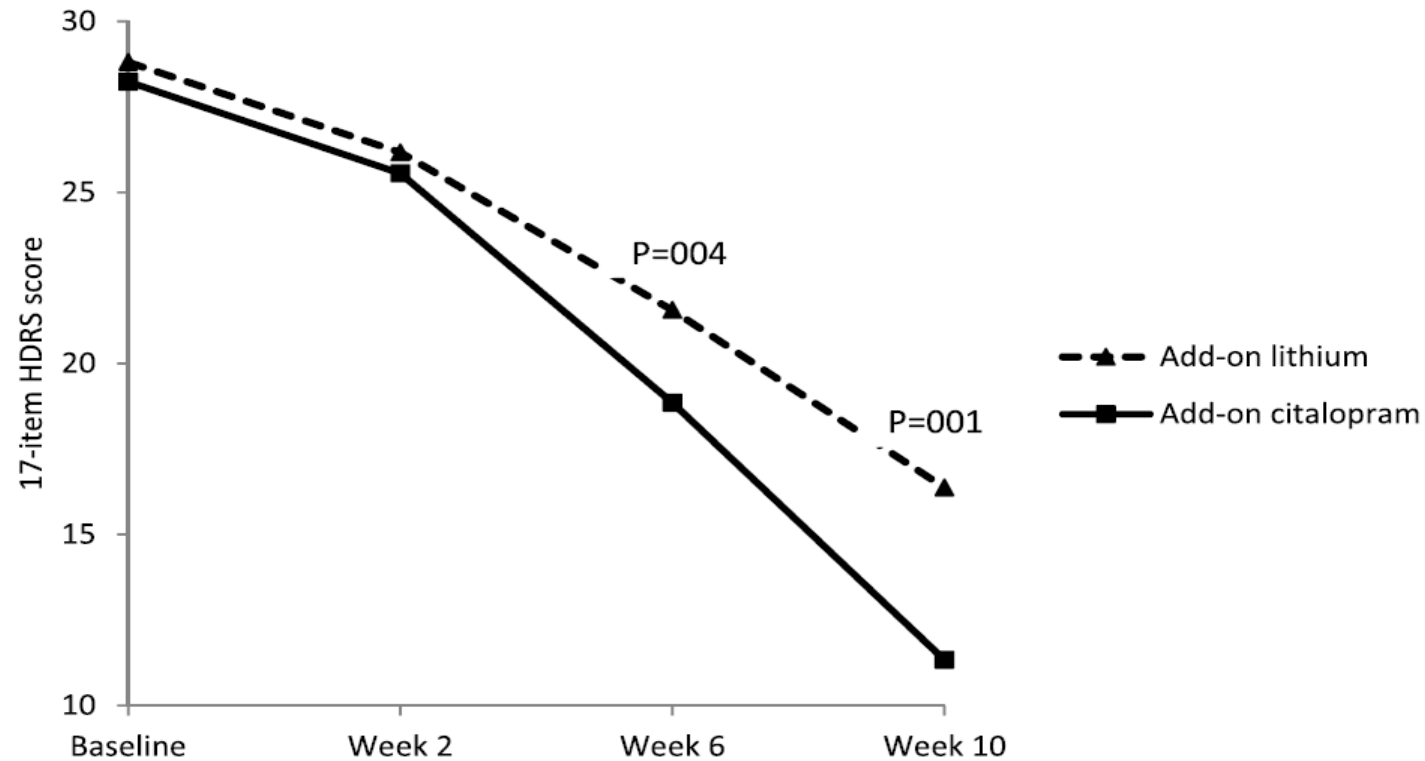


FIGURE 1. Repeated measures to compare efficacy of add-on lithium and add-on citalopram. Values represent means. *P* values show the result of the independent *t* test comparing HDRS scores between the 2 groups from baseline to each time point. NS indicates nonsignificant.

Navarro, et al. *J Clin Psychopharmacol.* 2019;39: 254–257.

Double-Blind Study of Atomoxetine Augmentation

Remission rates: open-label sertraline monotherapy and randomized combination-treatment phases.

Study phase/genotype class	Remission rate (%)	Between-group <i>P</i> value ^a	Versus S/S <i>P</i> value ^b
SRT open-label monotherapy		0.42	
S/S (<i>N</i> = 51)	21.6		
S/L (<i>N</i> = 128)	23.4		
L/L (<i>N</i> = 82)	30.5		
non-S/S (<i>N</i> = 210)	26.2		0.59
SRT + ATX randomized combination therapy		0.008	
S/S (<i>N</i> = 11)	81.8		
S/L (<i>N</i> = 31)	38.7		
L/L (<i>N</i> = 24)	25.0		
Non-S/S (<i>N</i> = 55)	32.7		0.005
SRT + PBO randomized combination therapy		0.47	
S/S (<i>N</i> = 14)	35.7		
S/L (<i>N</i> = 37)	43.2		
L/L (<i>N</i> = 16)	25.0		
Non-S/S (<i>N</i> = 53)	37.7		>0.99

Abbreviations: ATX = atomoxetine, L = 5-HTTLPR long variant, PBO = placebo, S = 5-HTTLPR short variant, SRT = sertraline.

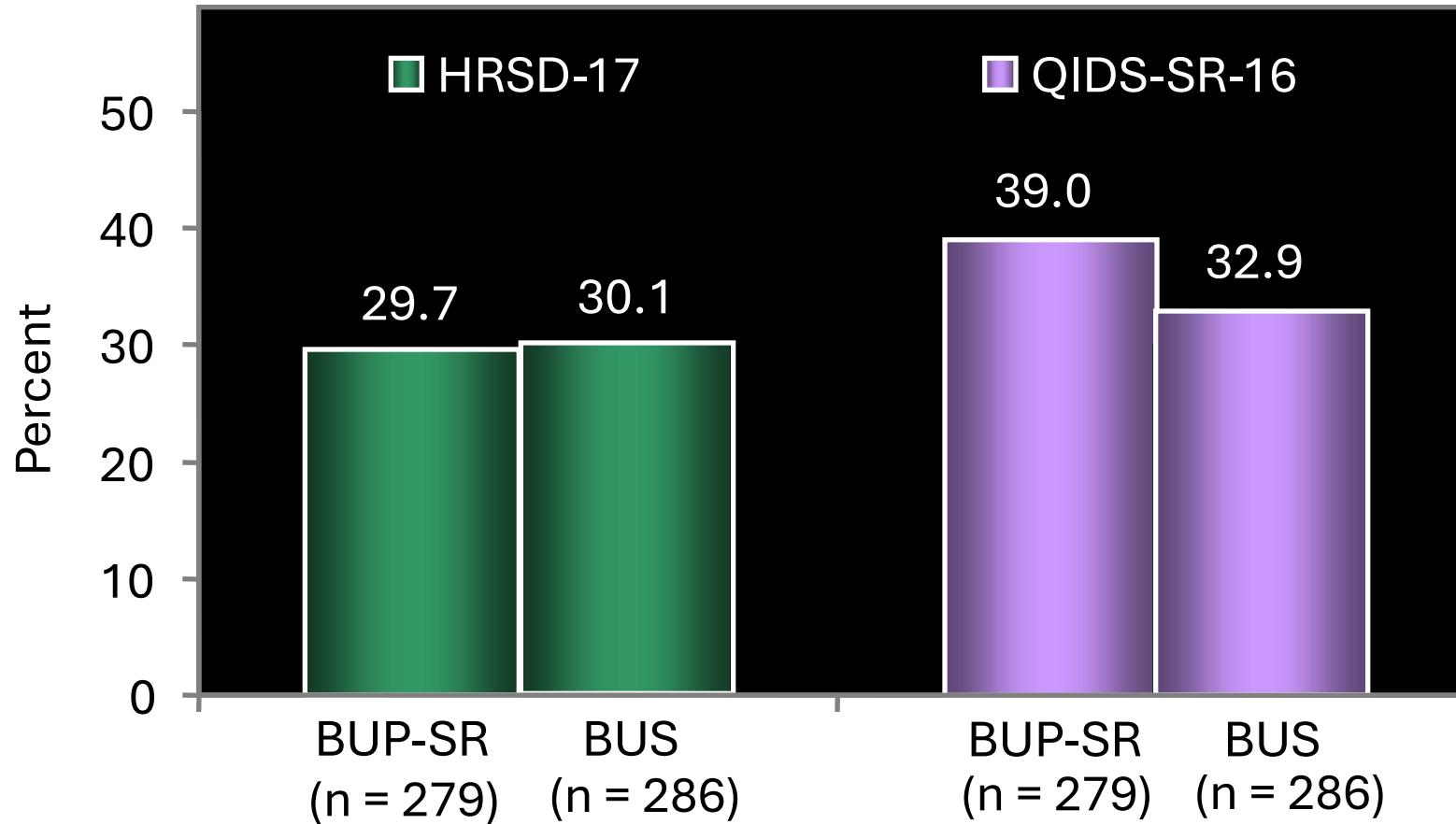
^a Significance of overall difference among all 3 subgroups.

^b Comparison of non-S/S versus S/S.

Reimherr F, et al. *Psychiatry Research*. 2010;175:67-73.

Percent of Remission in STAR*D L-2

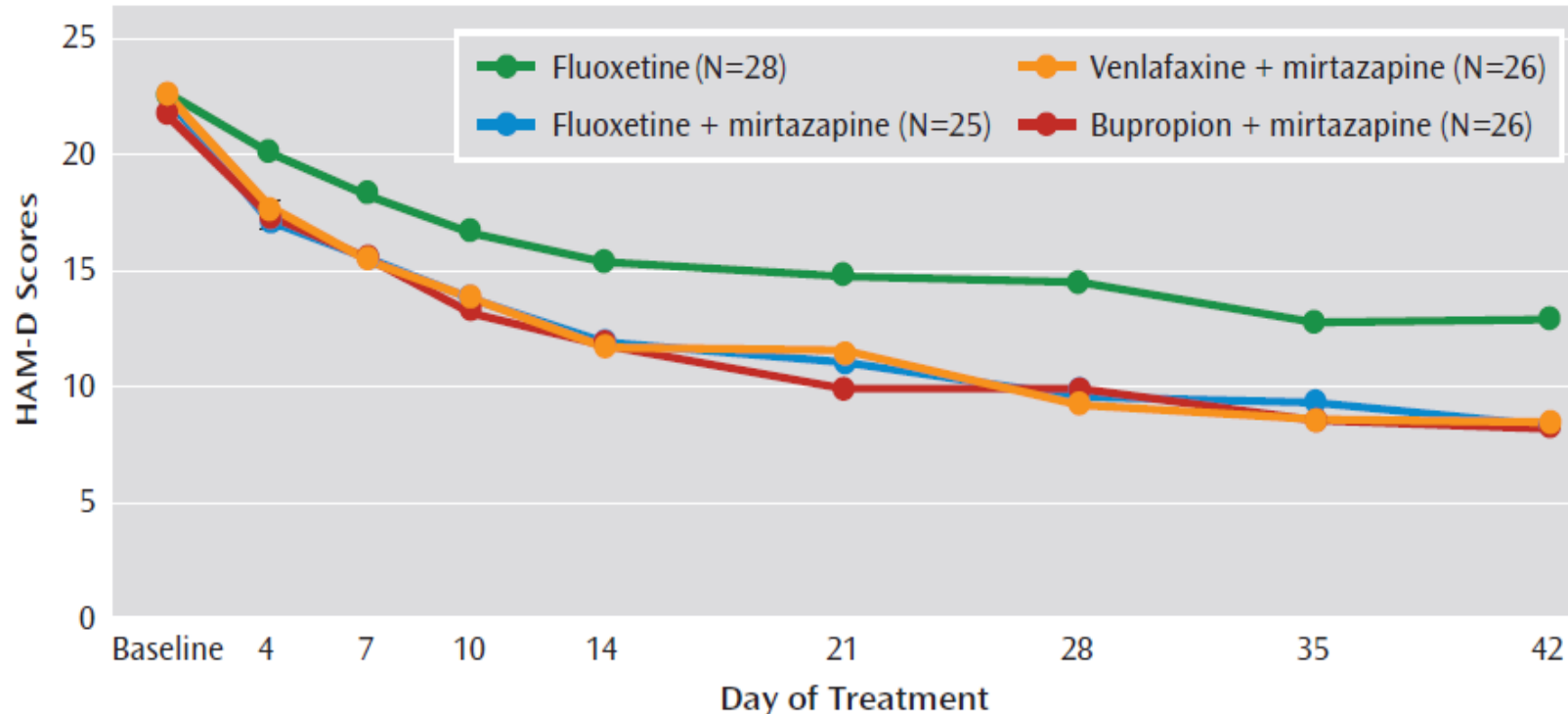
Augmentation: Bupropion-SR (BUP-SR) vs. Buspirone (BUS)



Trivedi, et al. *N Engl J Med*. 2006;354(12):1243-52.

Double-Blind Study of Mirtazapine Augmentation

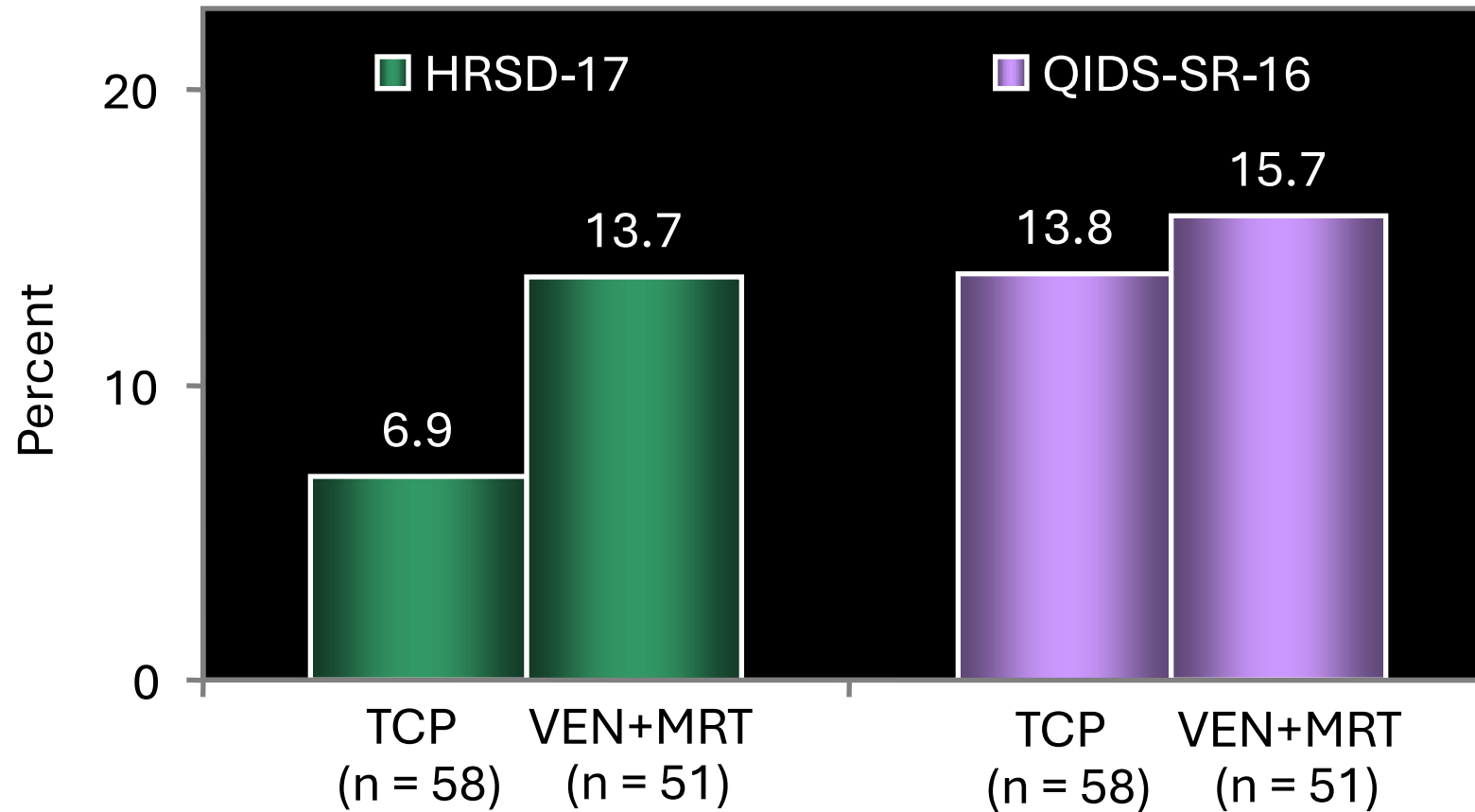
FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale (HAM-D), by Visit, for All Patients Treated (Last Observation Carried Forward) in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment^a



^a Statistically significant difference between fluoxetine monotherapy and all combination treatment groups ($F=3.87$; $df=3, 101$, $p=0.011$).

Blier P, et al. *Am J Psych*. 2010 Mar;167(3):281-8.

Percent of Remission in STAR*D L-4: Tranylcypromine (TCP) vs Venlafaxine plus Mirtazapine (VEN+MRT)



McGrath, et al. *Am J Psychiatry*. 2006;163:1531-1541.

Trazodone Plus Fluoxetine (n=37)

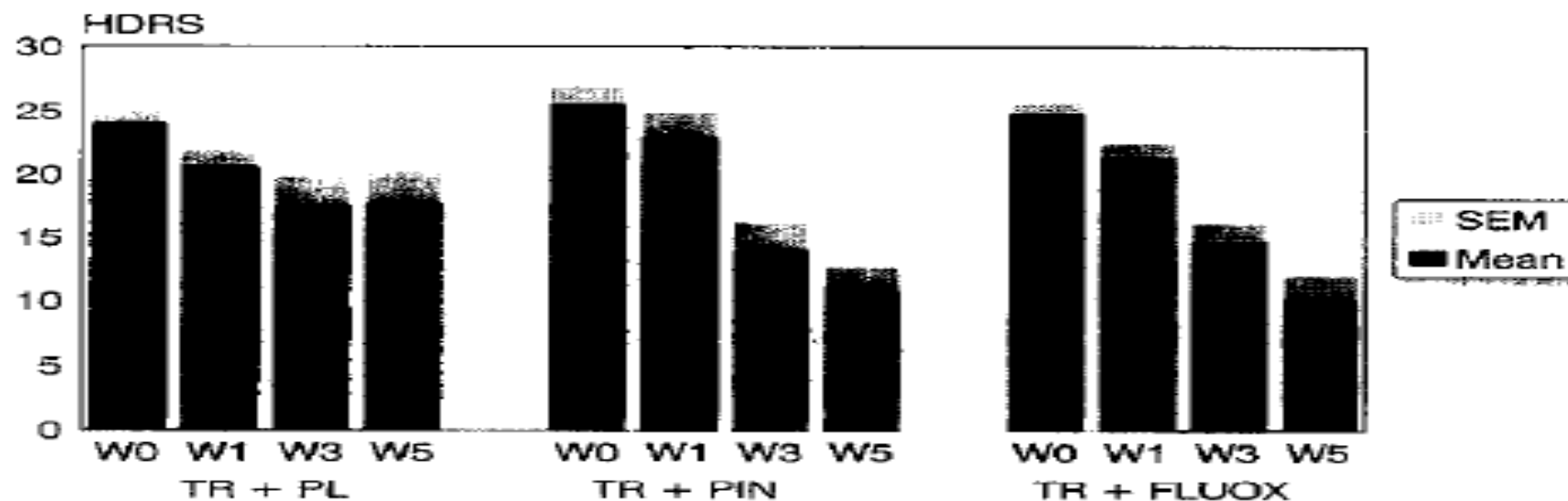


Fig. 1. Mean Hamilton Depression Rating Scale (HDRS) score at baseline (W0), 1 week after treatment with trazodone 100 mg/day (W1), and at weeks 3 (W3) and 5 (W5), after randomization of the patients (at W1) to receive trazodone 100 mg/day + placebo (TR + PL), trazodone 100 mg/day + pindolol 7.5 mg/day (TR + PIN), or trazodone 100 mg/day + fluoxetine 20 mg/day (TR + FLUOX).

Maes M, et al. *Journal of Affective Disorders*. 1996;41:201-210.

Double-Blind, Placebo-Controlled Trial of Combining Agomelatine with SSRIs/SNRIs (n=123)

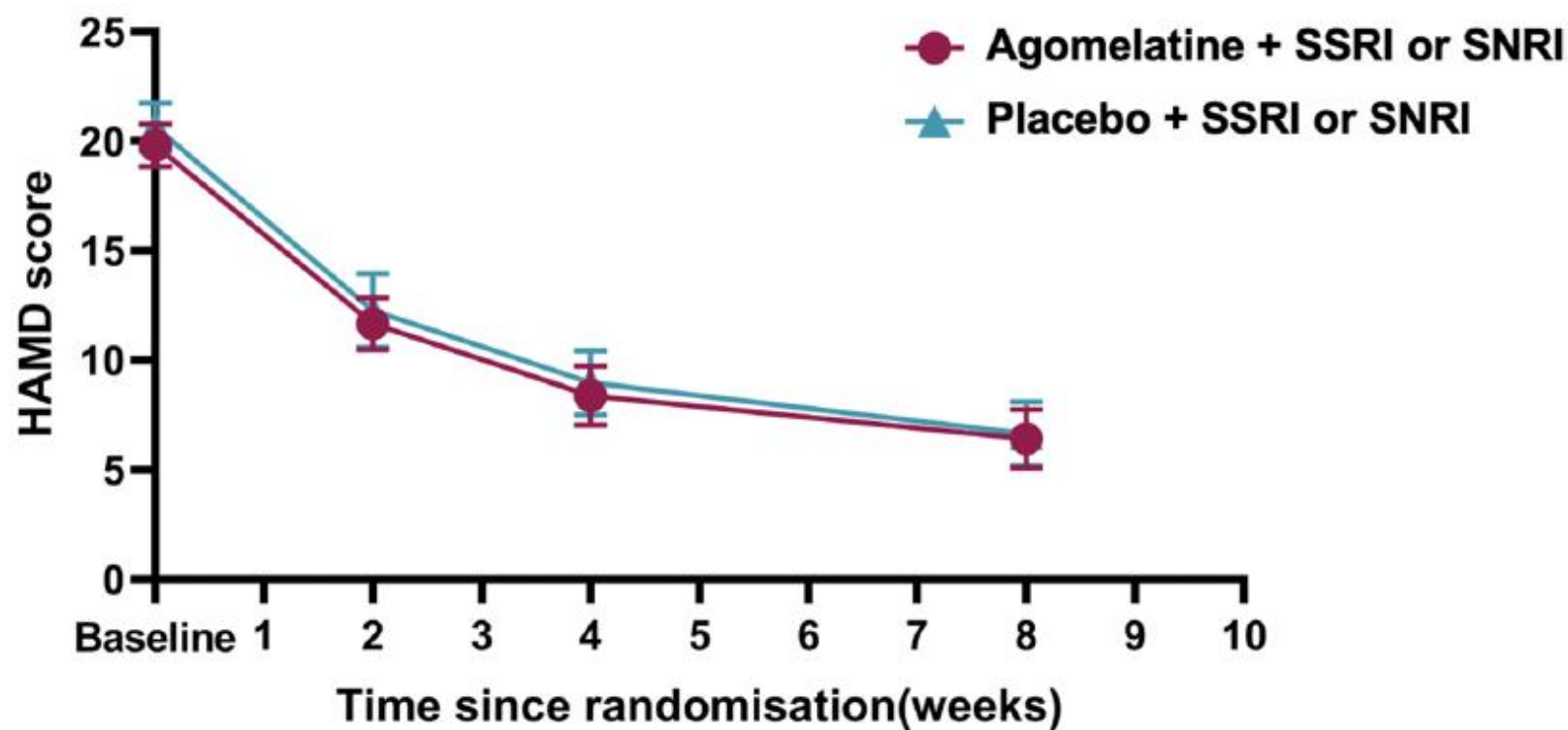


Fig. 2 Change on HAMD-17 from baseline to week 8

Ju et al, BMC Med. 2025 Mar 5;23(1):137.

Conclusions

- Treatment resistance is common in MDD
- Many strategies may be effective approaches for partial and non-responders to antidepressant treatment
- The potential loss of partial benefit from the failed trial may reduce the feasibility of switching strategies
- The presence of significant side effects from the antidepressant itself may reduce the acceptability of dose increase, augmentation and combination strategies