



Treatment-Resistant Depression (TRD)

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Disclosures (lifetime): Maurizio Fava, MD

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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?

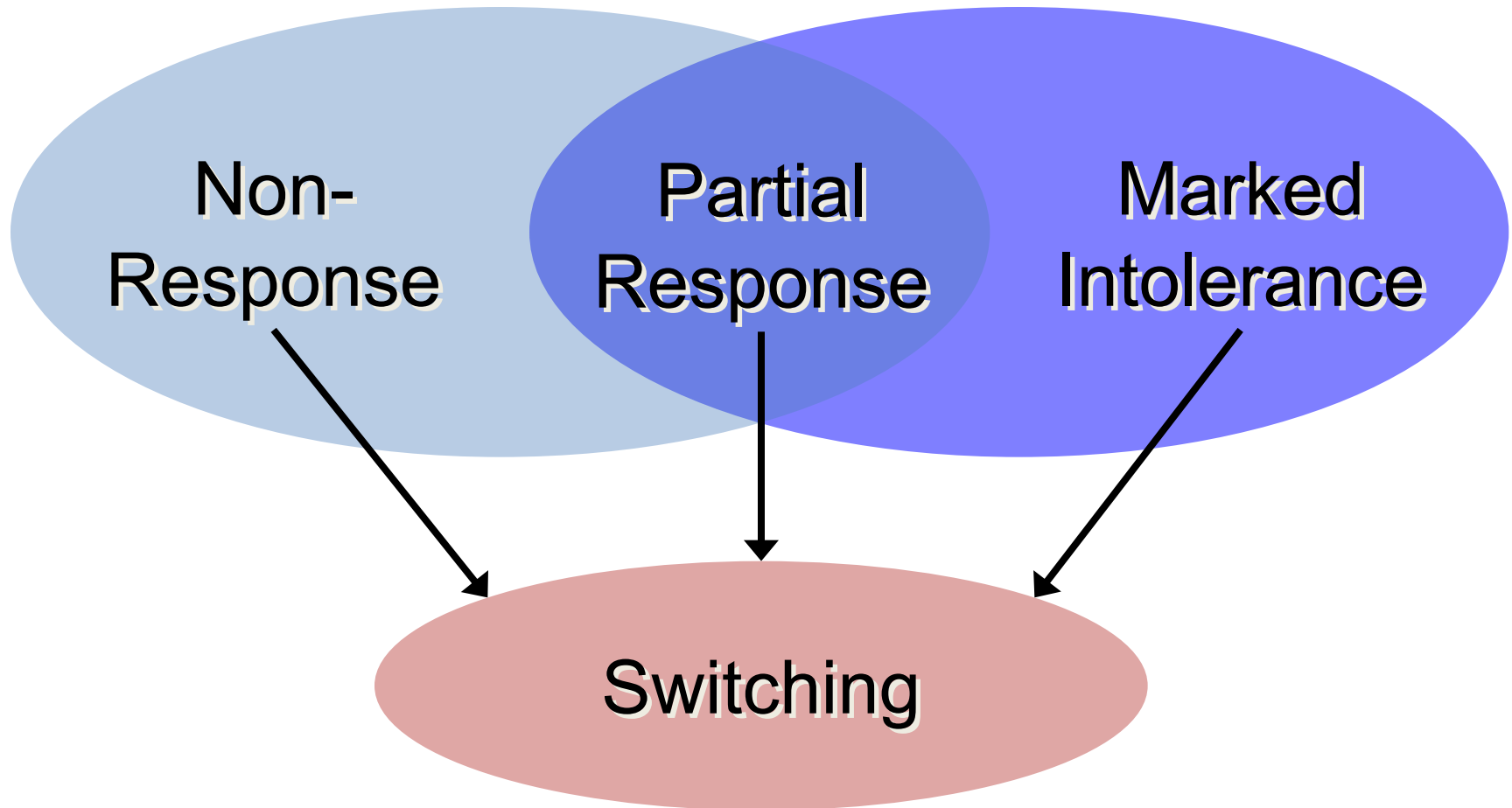
Contributing Factors to TRD

- 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

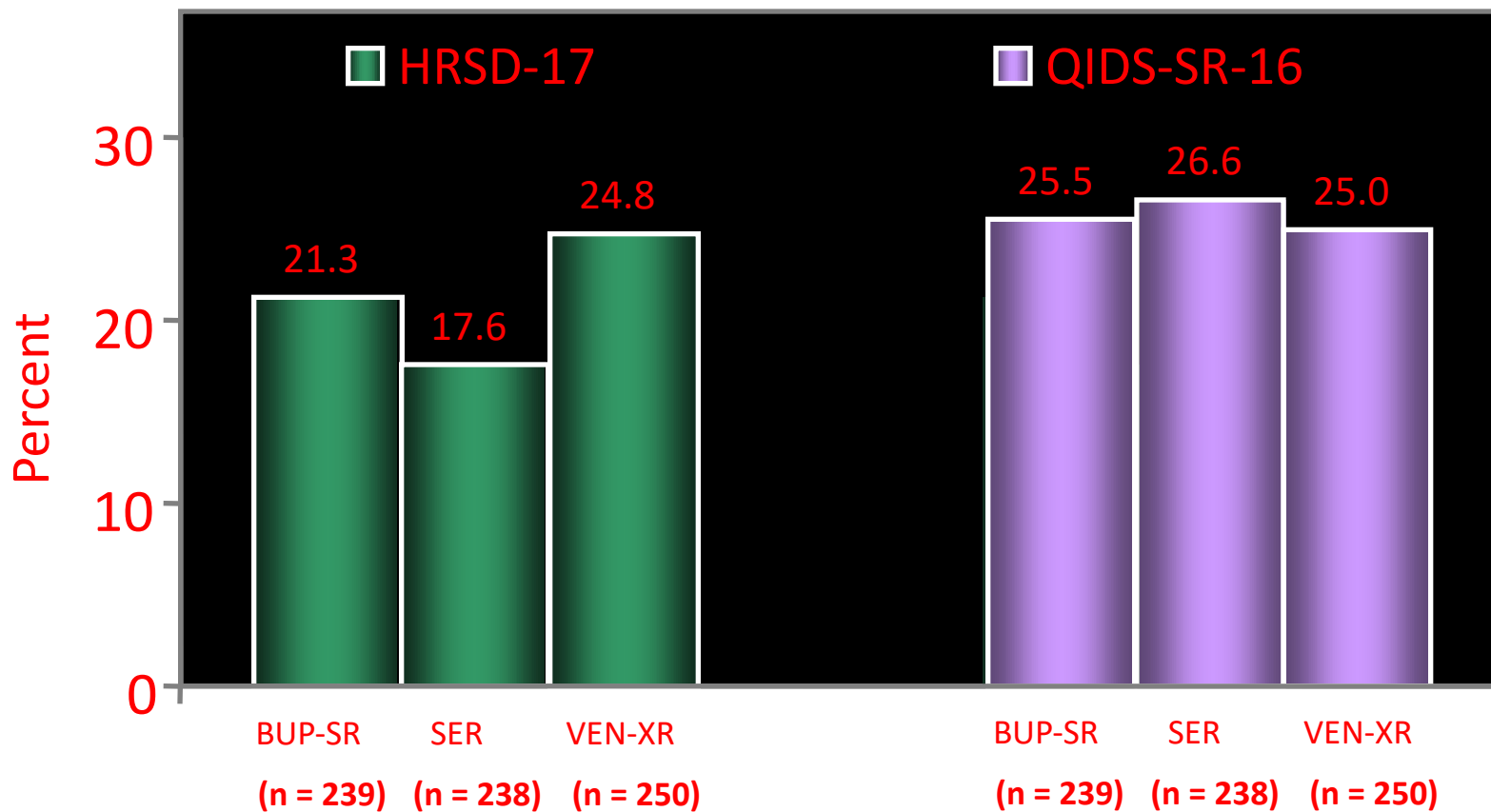
Switching Treatments: For Whom?



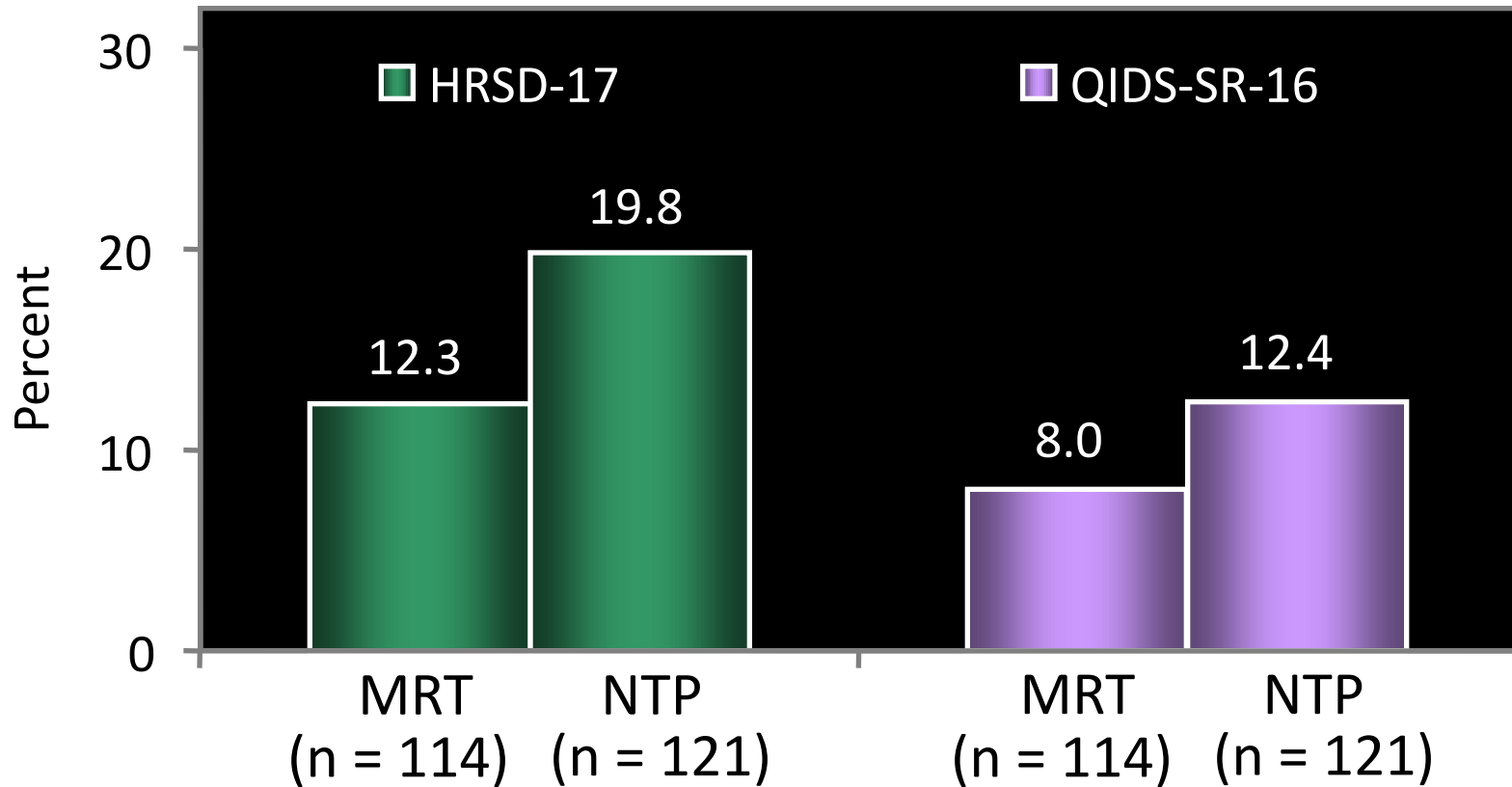
Switches: Rationales

- 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

Percent of Remission in STAR*D L-2 Switch



Percent of Remission in STAR*D L-3 Switch



Switching: Practical Approaches

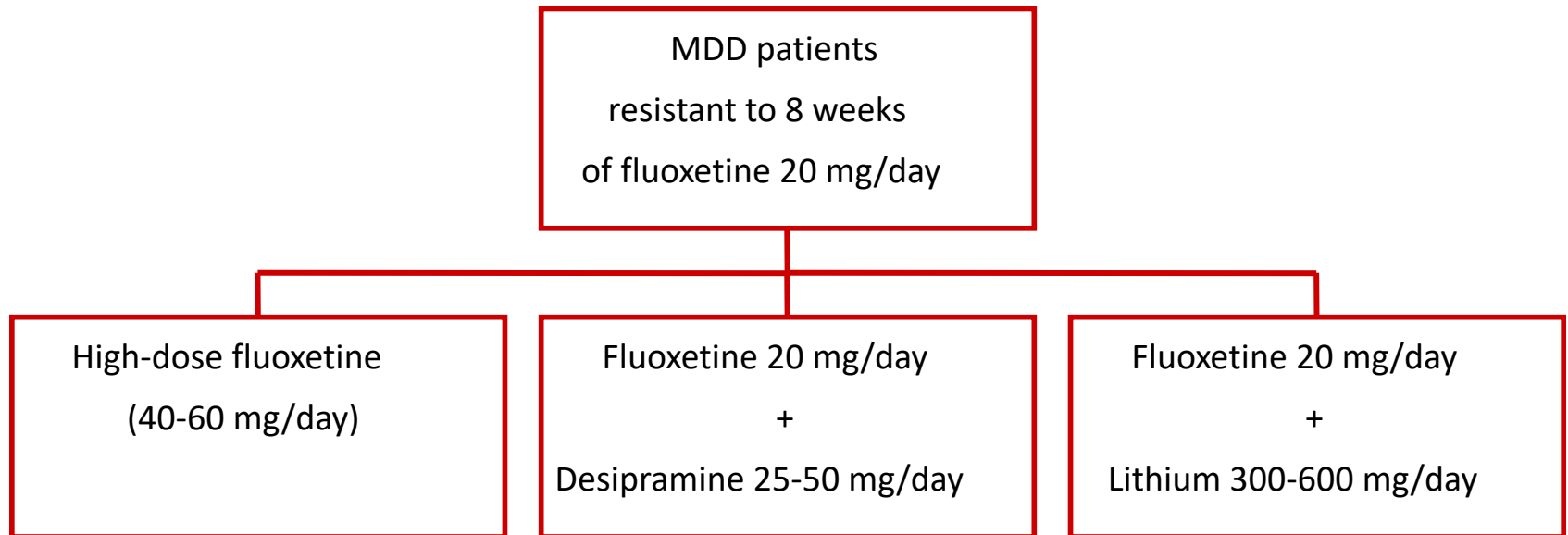
- Gradual tapering the first agent while starting the new one
 - Side effects of the new drug may be intensified by the concurrent presence of the first agent
 - “Start low and go slow” with the new agent
 - Consider possible drug-drug interactions
- Abrupt replacement with within class-switches
- Wash-outs 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

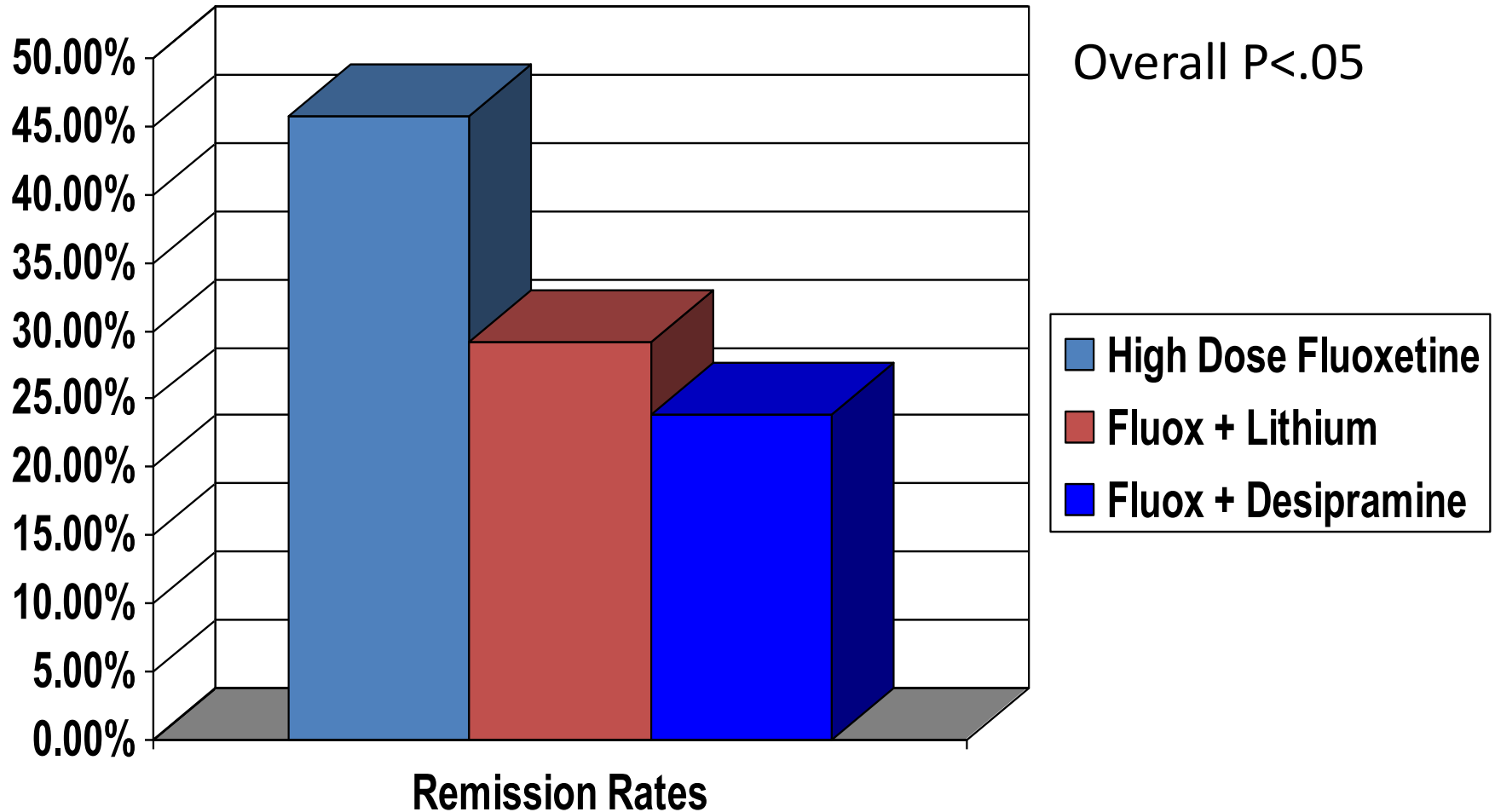
Trial Design



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 and 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

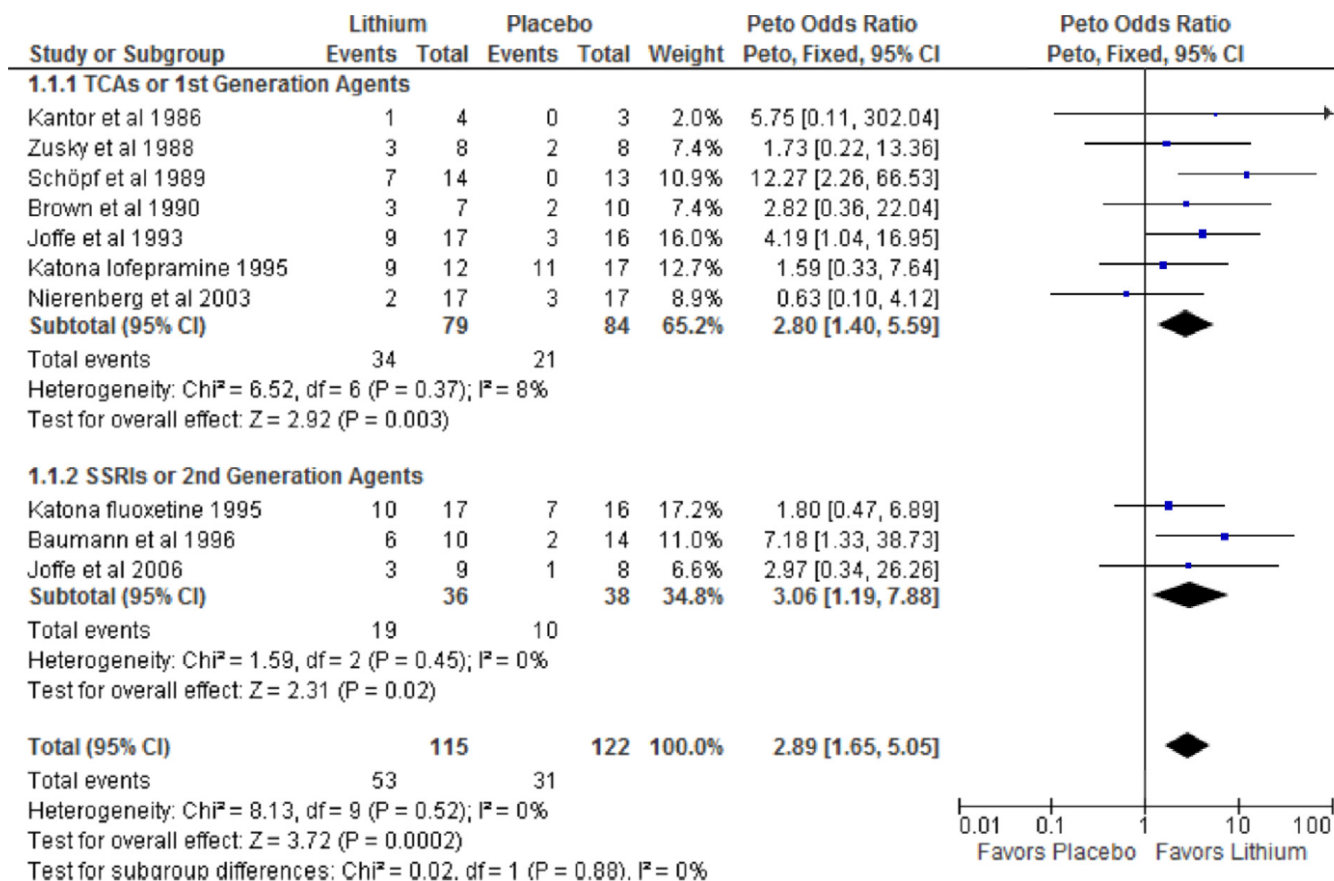
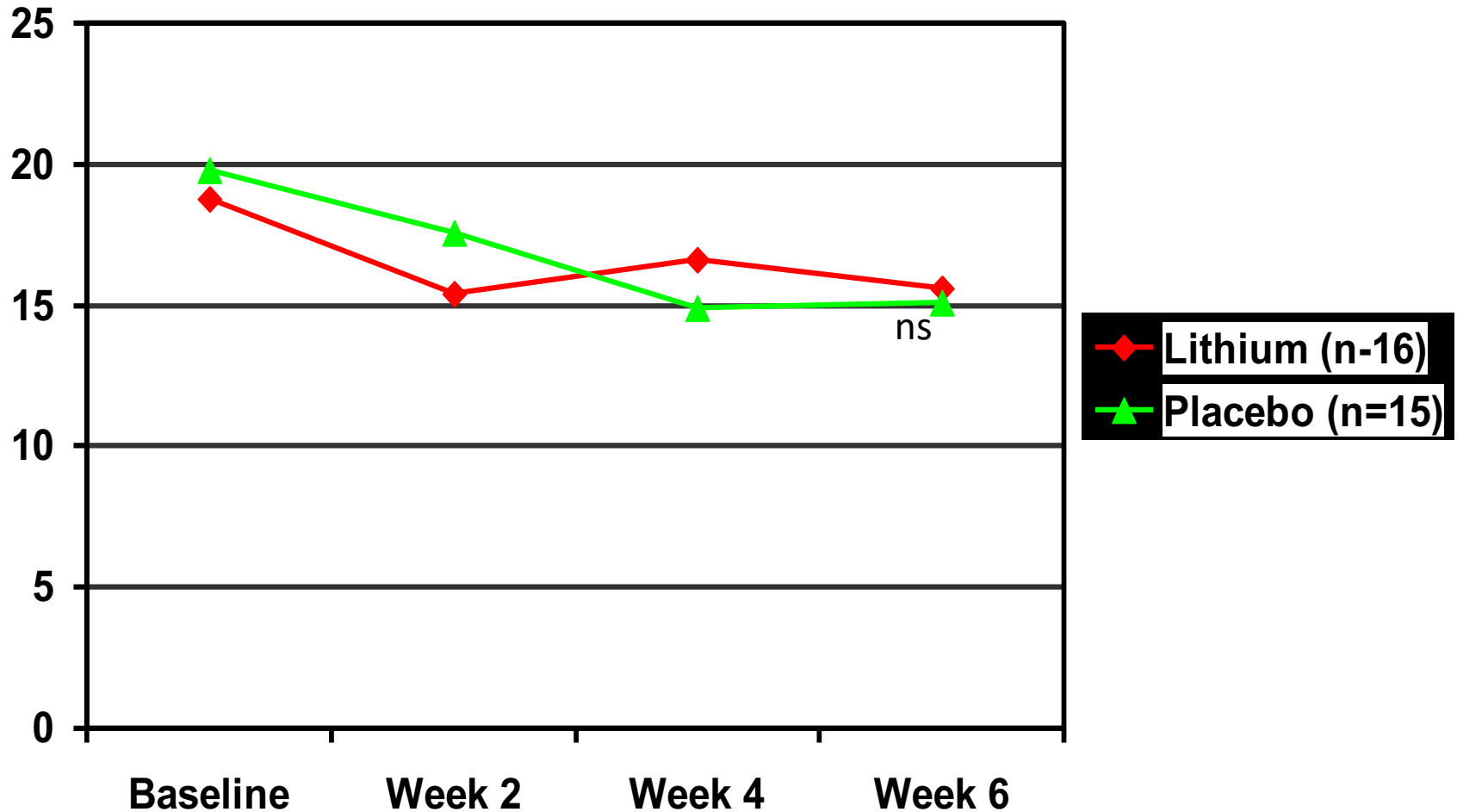
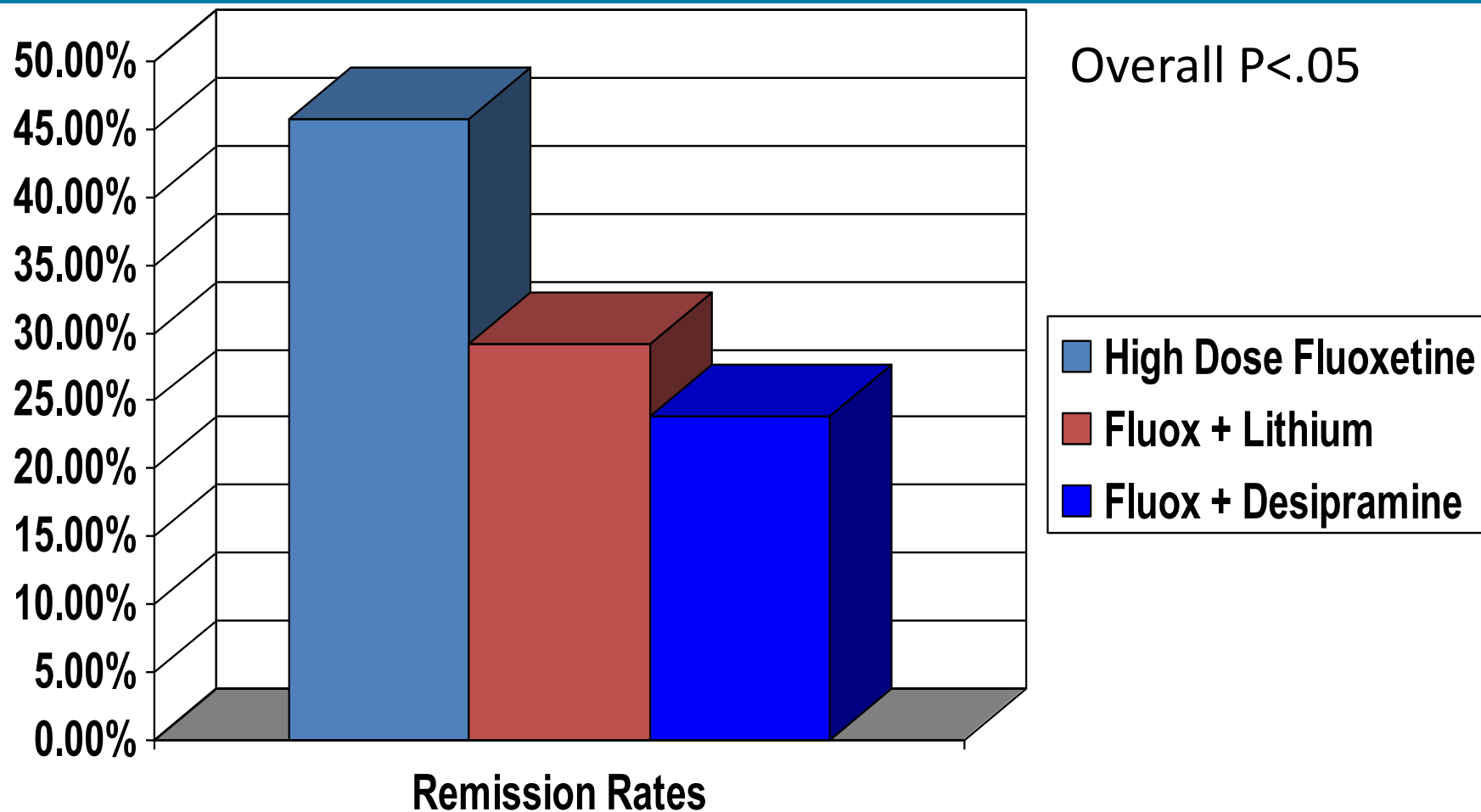


Fig. 2. Meta-analysis of 9 randomized placebo-controlled lithium augmentation trials in depression with 10 contrasts grouped by the type of antidepressant augmented.

Double-Blind, Placebo-Controlled Study of Lithium Augmentation of Nortriptyline



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 and 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

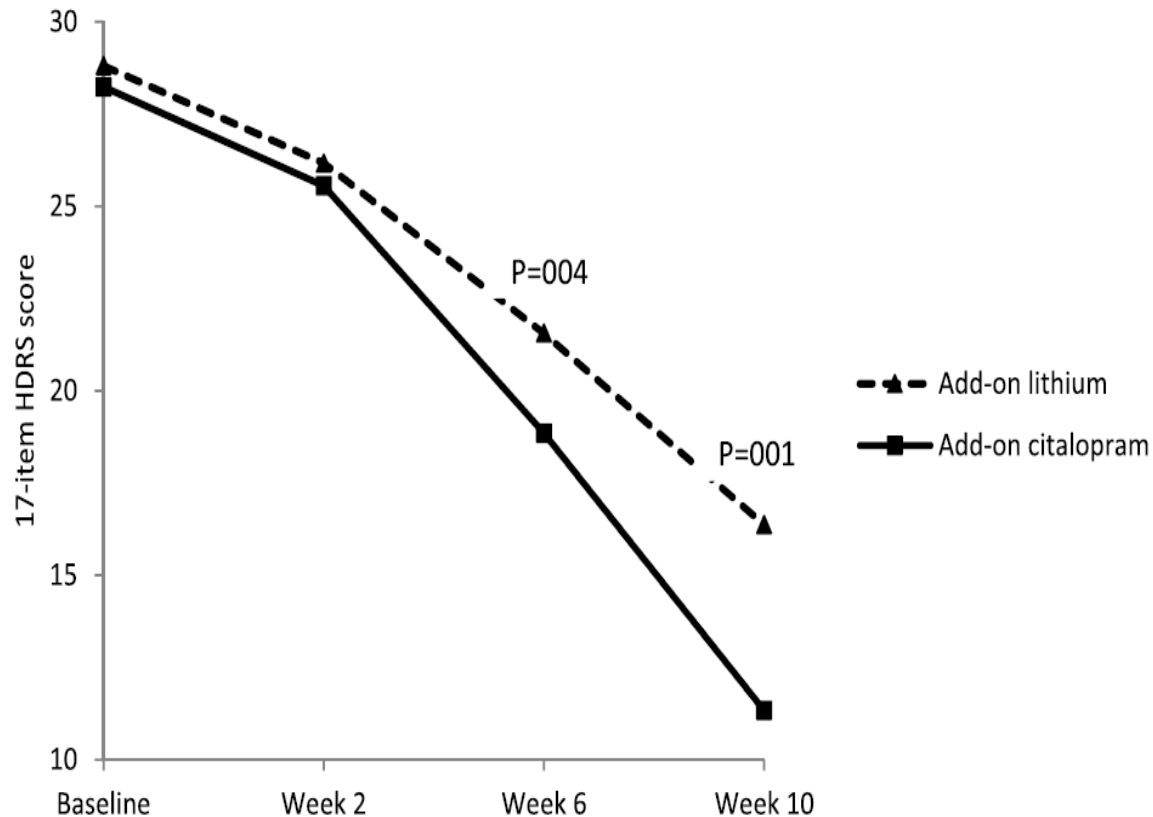
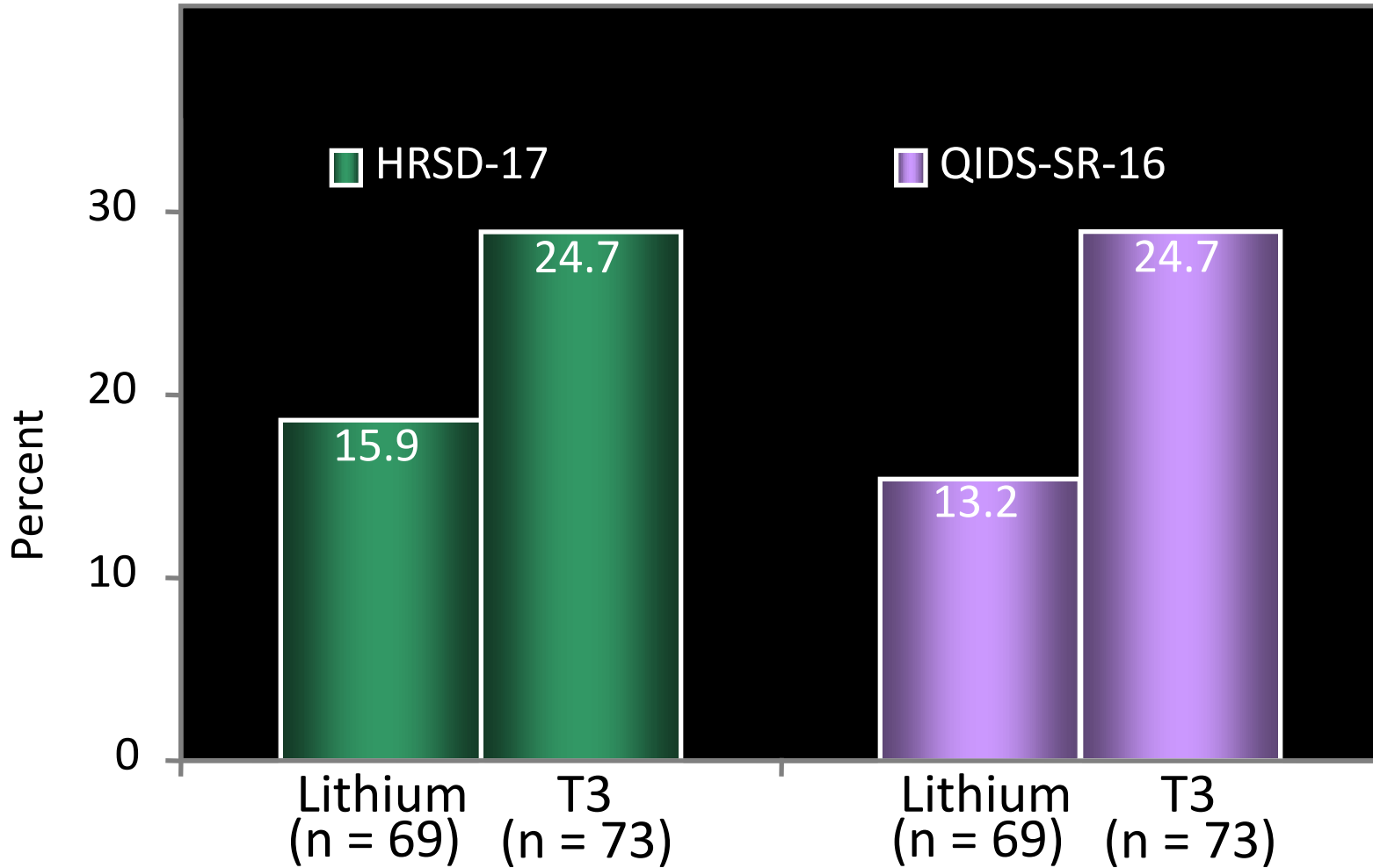


FIGURE 1. Repeated measures to compare efficacy of add-on lithium and add-on citalopram. Values represent means. *P* values show the result of the independent *t* test comparing HDRS scores between the 2 groups from baseline to each time point. NS indicates nonsignificant.

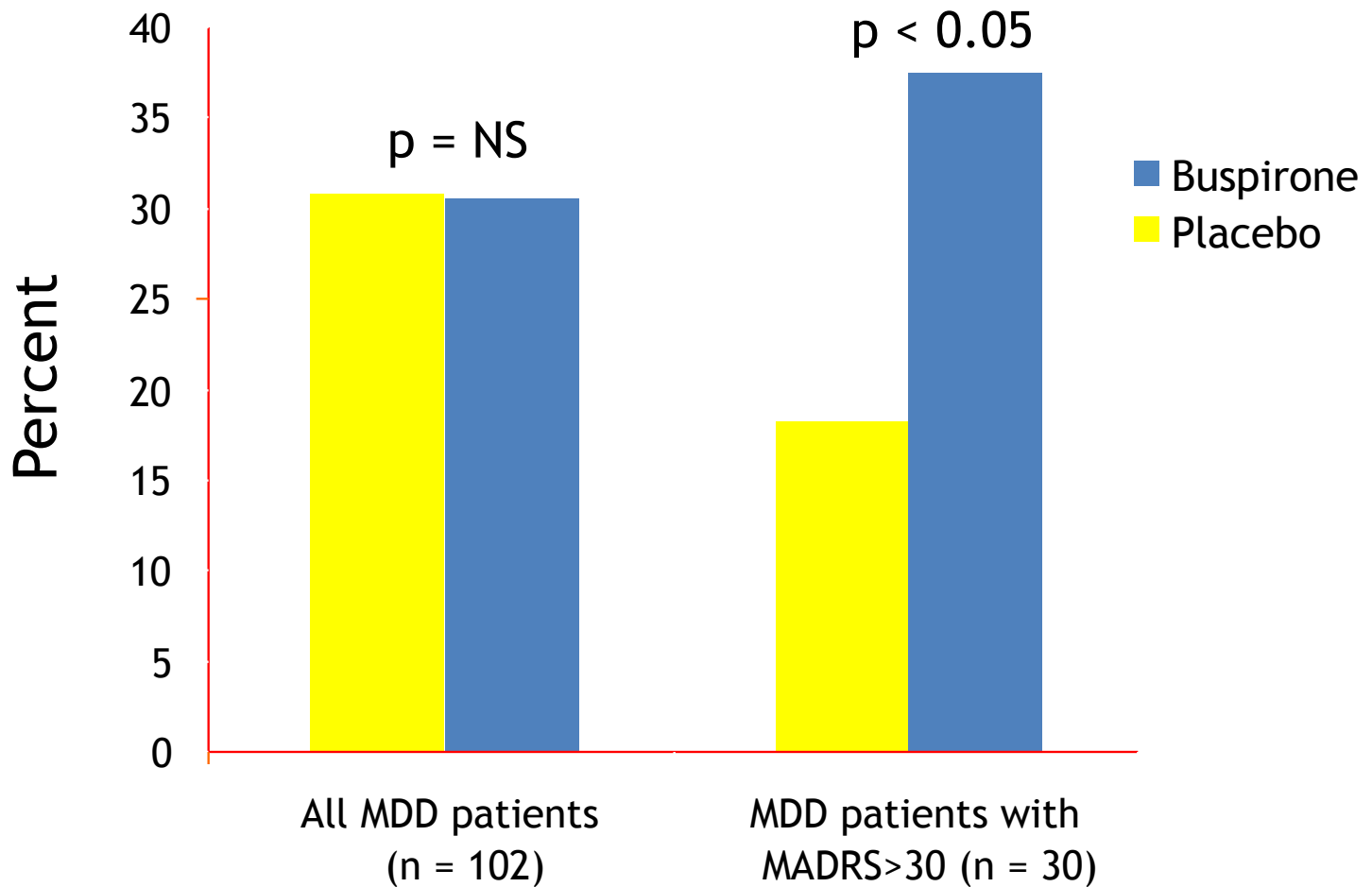
Thyroid Augmentation

- **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; Iosifescu 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.)

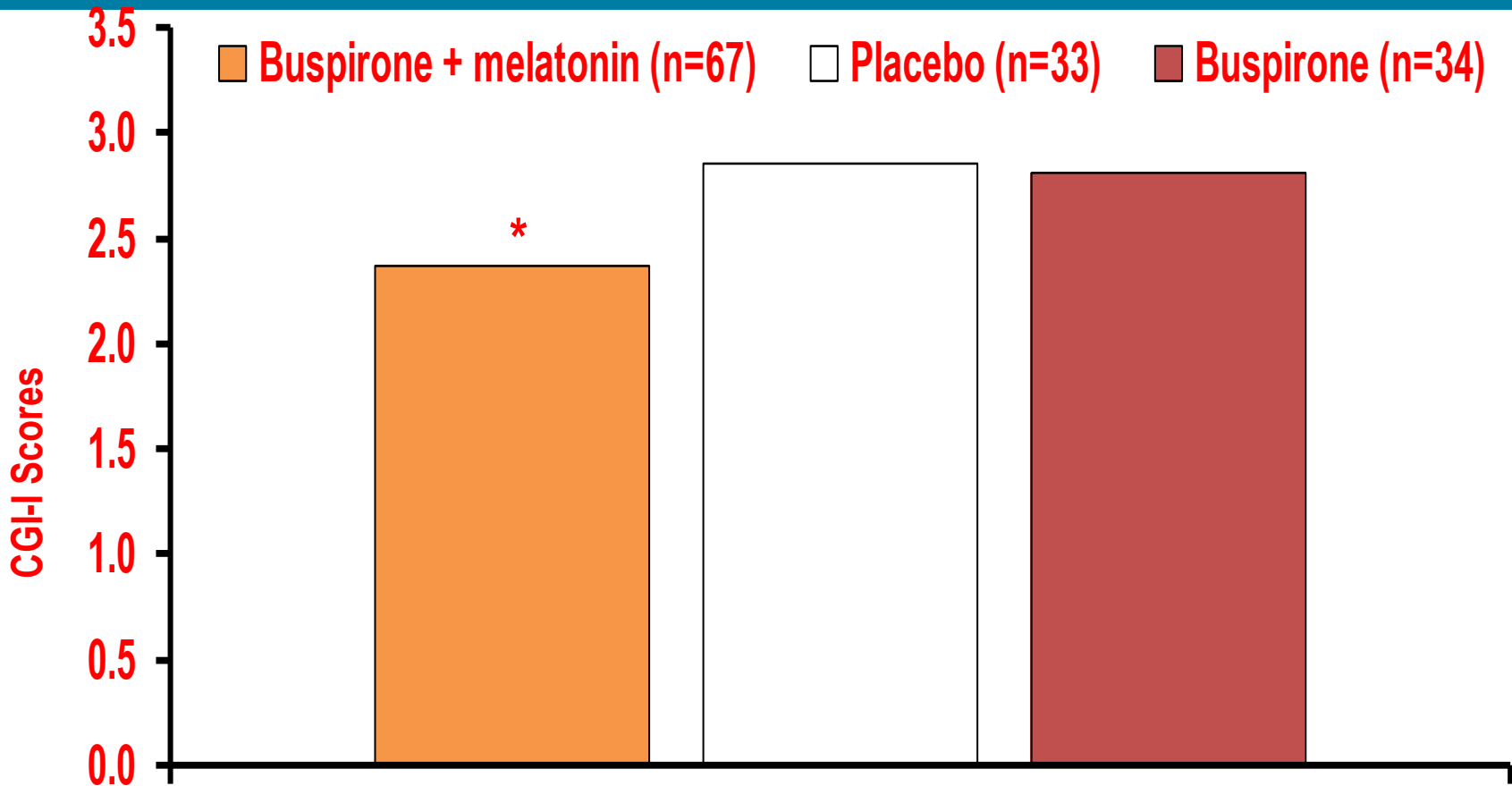
Percent of Remission in STAR*D L-3 Augmentation



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



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

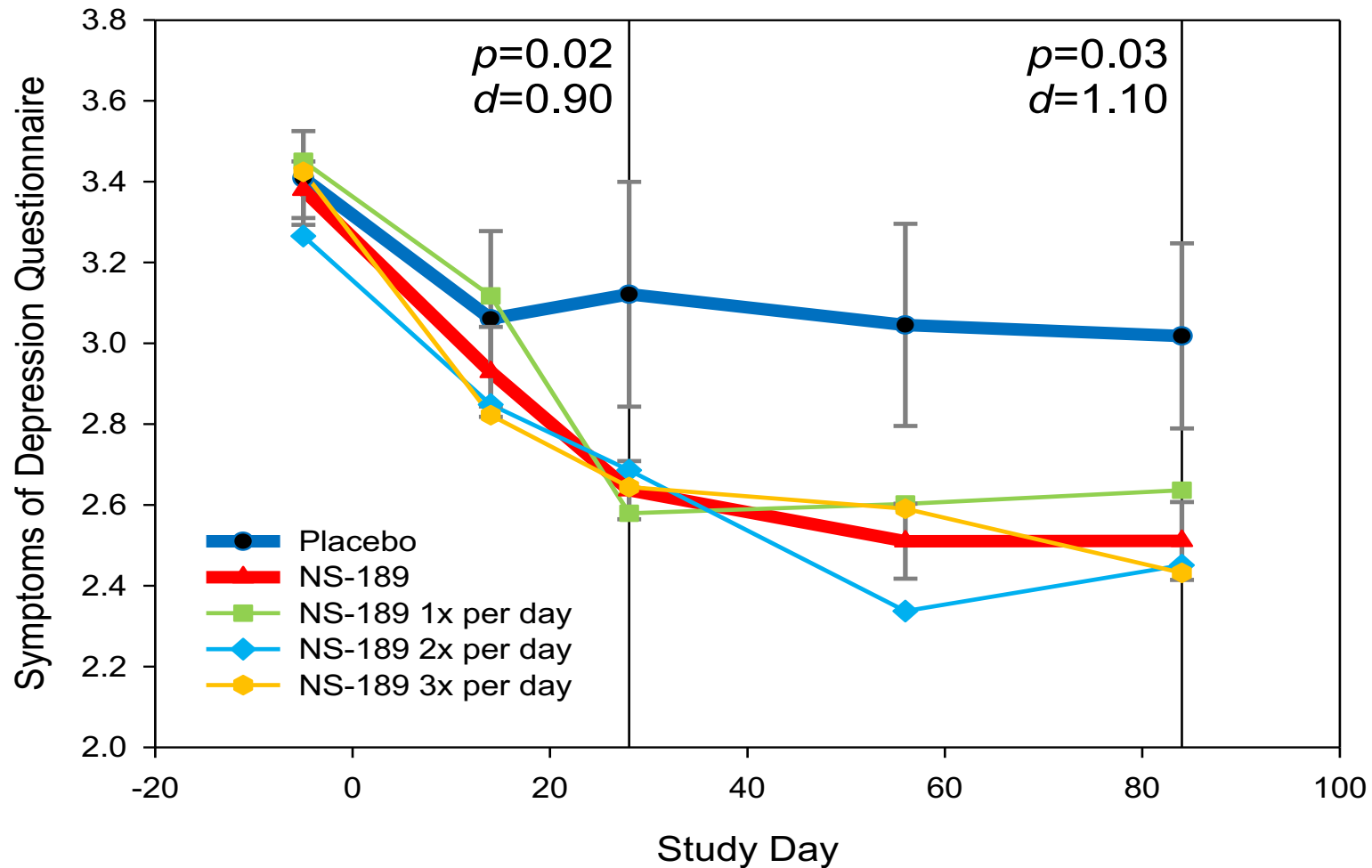


*p<.05 combination vs placebo and buspirone alone.

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

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

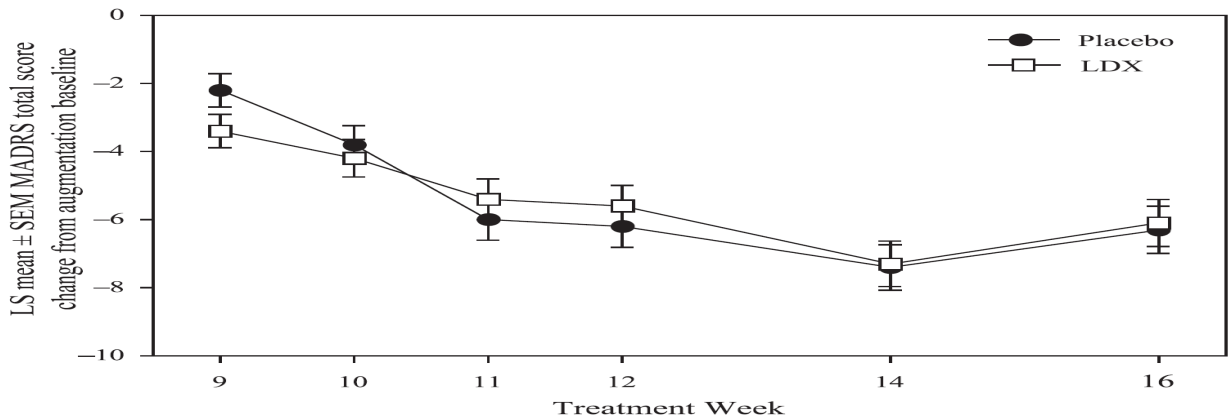
Targeting Neurogenesis: The Neurogenesis-Promoting Agent NSI-189 for the Treatment of MDD



Fava et al, Mol Psychiatry. 2016 Oct;21(10):1483-4.

Lisdexamfetamine Dimesylate Augmentation for MDD with Inadequate Response to Antidepressant Monotherapy: Results from 2 phase 3 Studies*

A. Study 1



B. Study 2

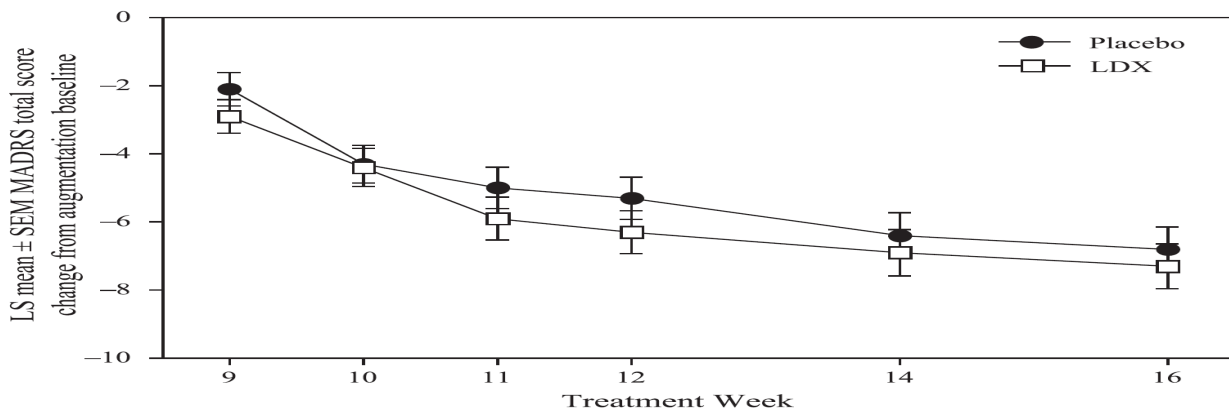


Fig. 3. Change in MADRS total score during double-blind treatment (full analysis set) for Study 1 (A) and Study 2 (B). LDX=lisdexamfetamine; dimesylate MADRS=Montgomery-Åsberg Depression Rating Scale.

Richards et al, Journal of Affective Disorders 206(2016): 151–160

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

Data derived from ClinicalTrials.gov

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

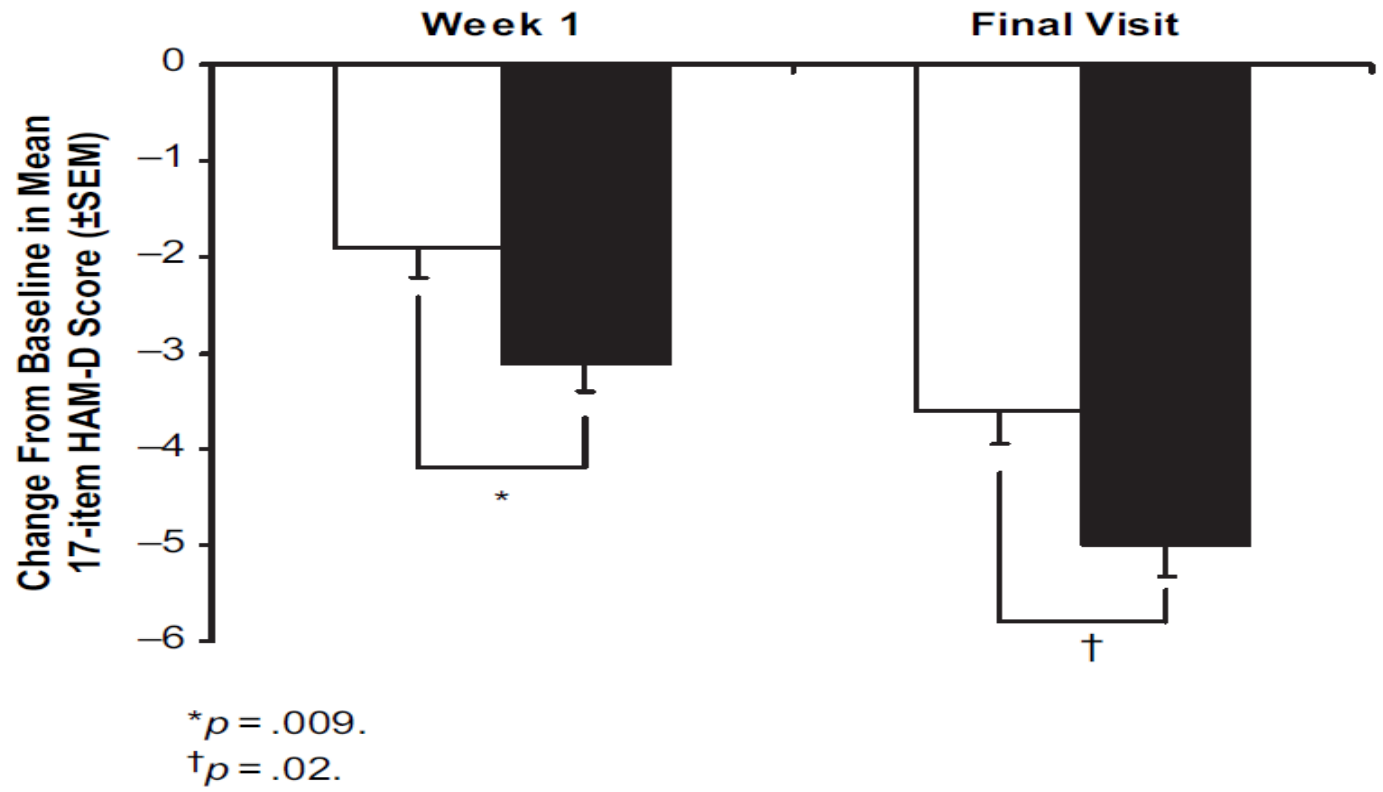
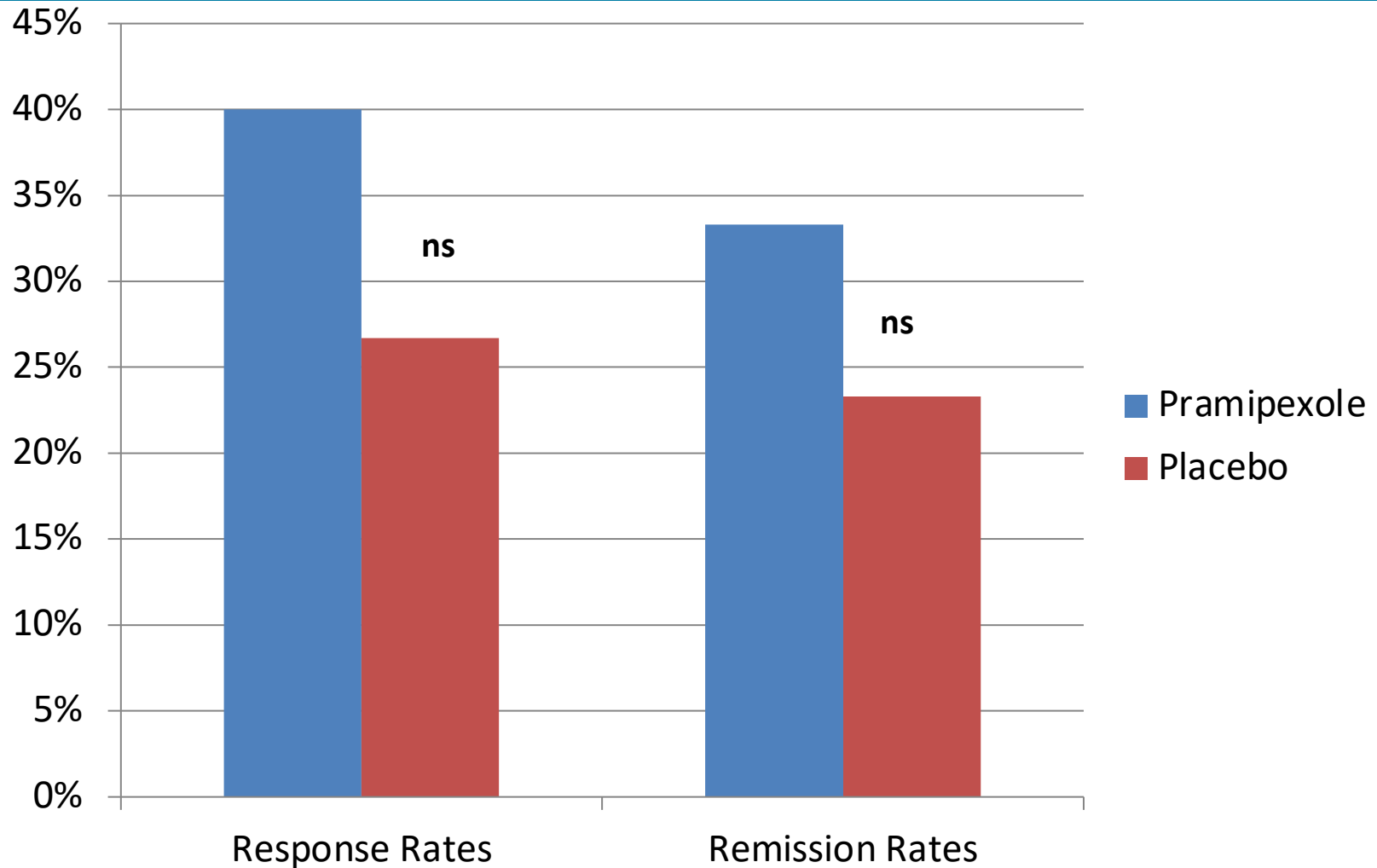


Figure 4 Mean (± SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

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

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



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

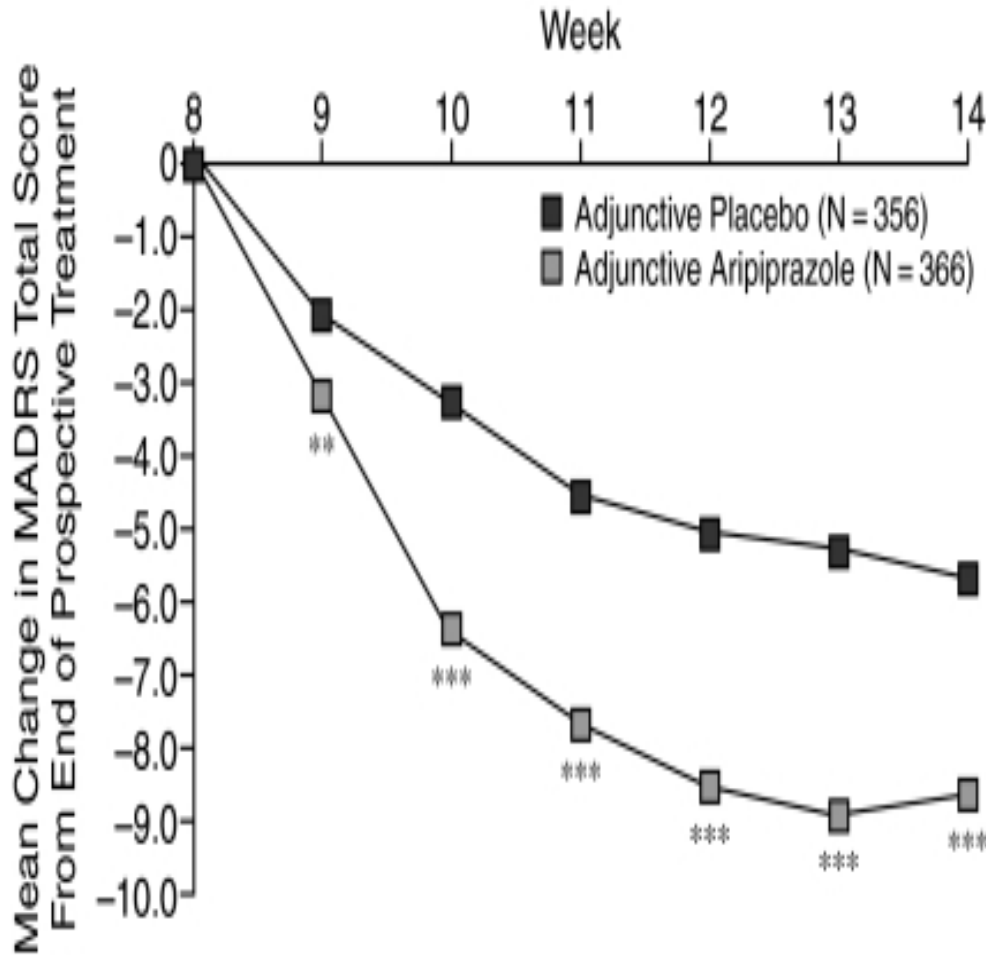
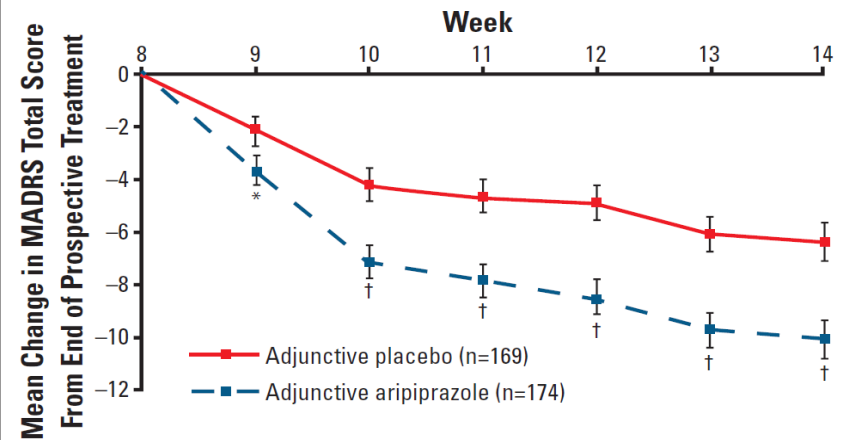


FIGURE 2. Change in mean (\pm SE) MADRS Total score during the randomized, double-blind treatment phase (LOCF)



* $P < .05$ 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.

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,

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

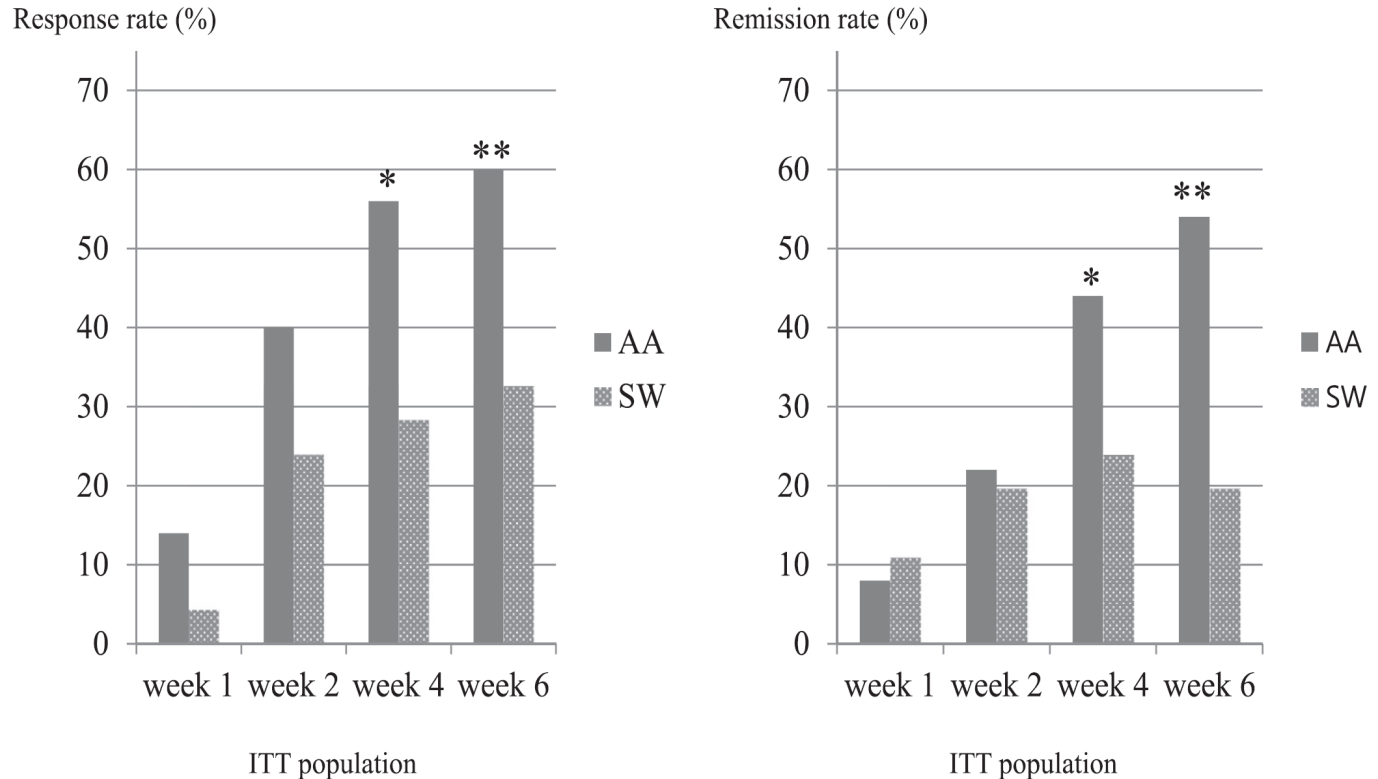
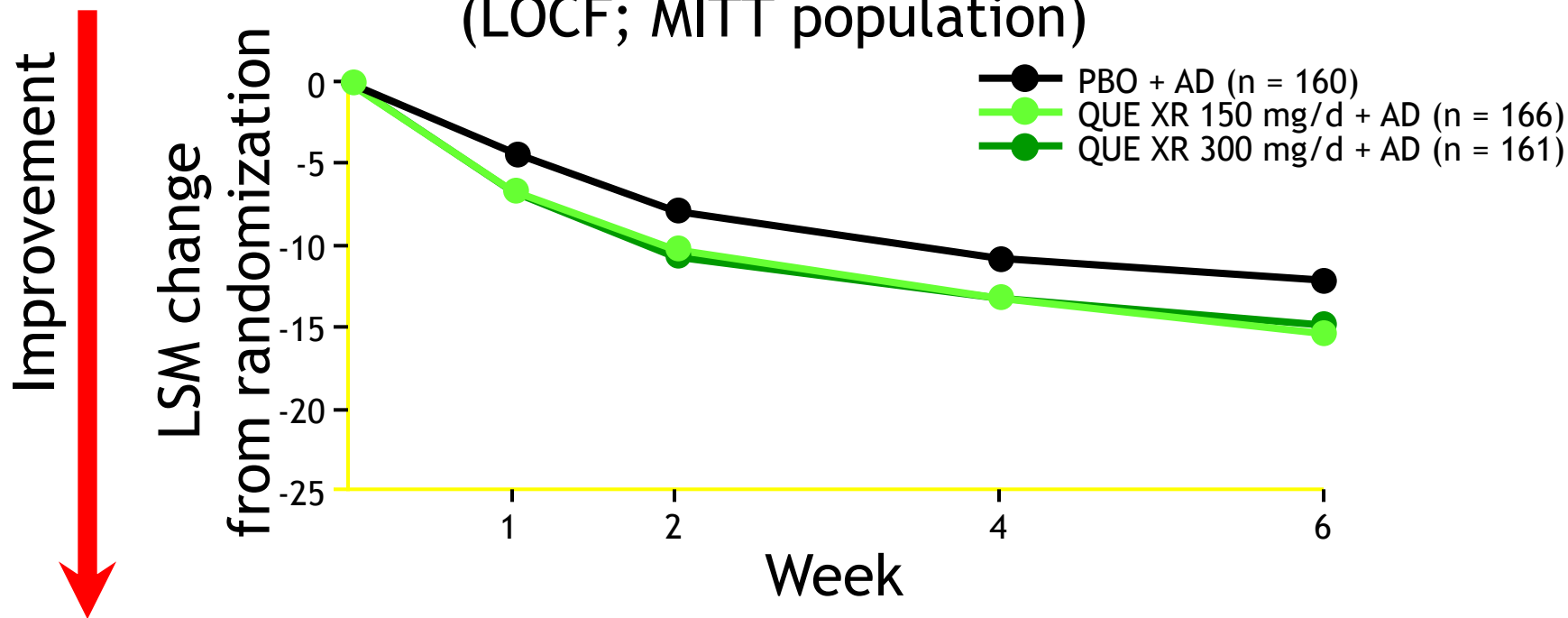


Fig. 3. The responder and remission rates between the two treatment groups during the study Annotation: ITT, intent-to-treat; AA, aripiprazole augmentation switching; *P = 0.0080 and **P = 0.0086 for response analysis; *P = 0.0408 and **P = 0.0005 for remission analysis.

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

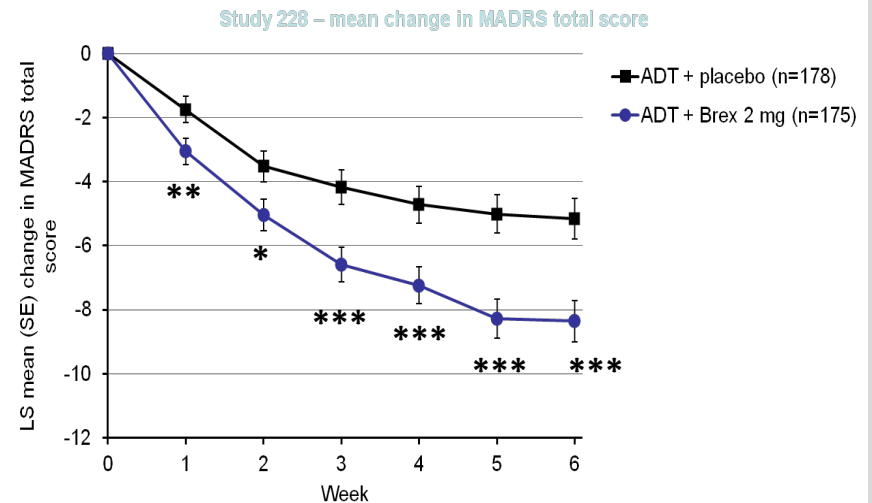
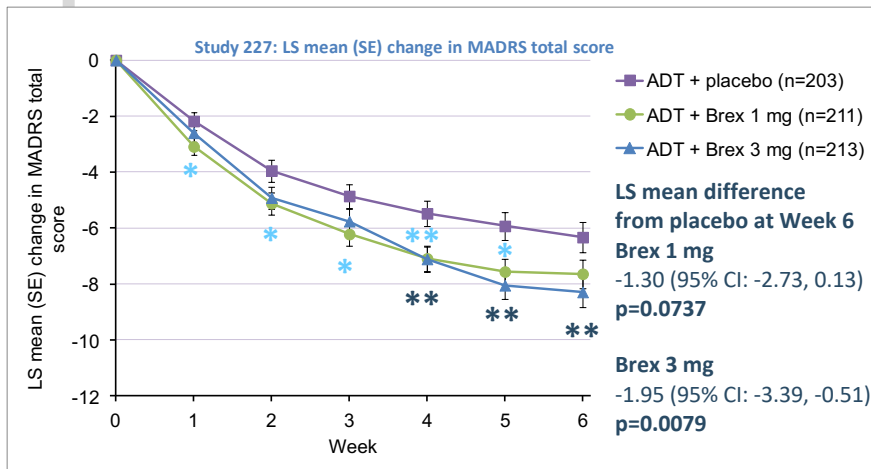
Change in MADRS total score from randomization over time (LOCF; MITT population)



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

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

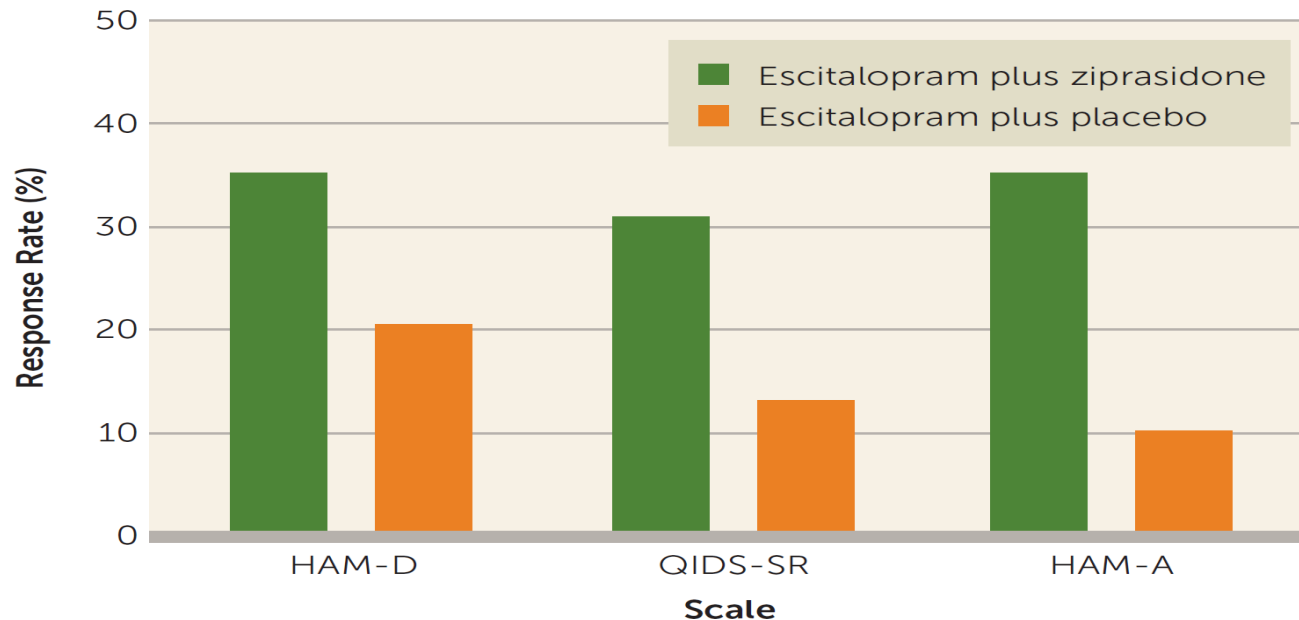
MMRM analysis; MADRS baseline: ADT + placebo 27.3, ADT + Brex 26.9

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)

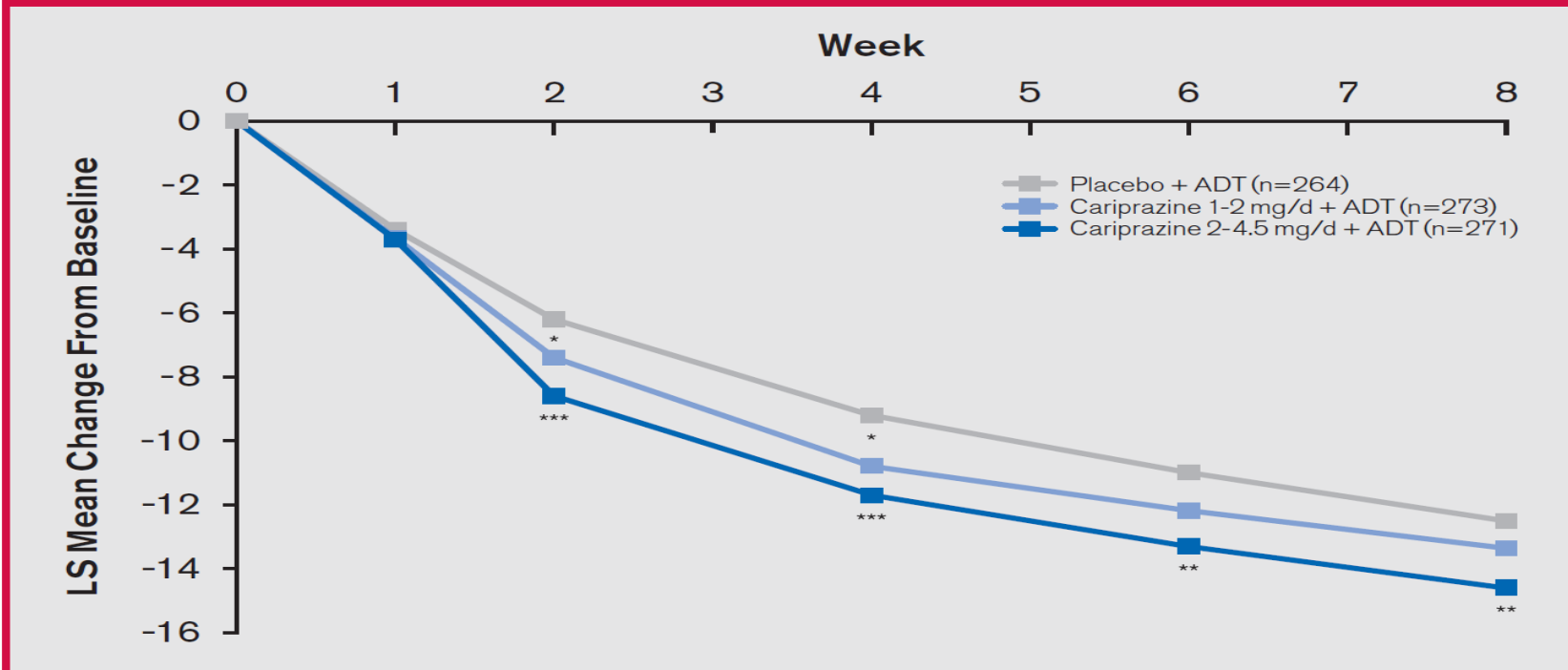
FIGURE 1. Response Rates, by Clinical Scale, Among Patients With Major Depression Receiving Escitalopram Plus Ziprasidone or Placebo^a



^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.

A Double-Blind, Randomized, Placebo-Controlled Study of Cariprazine as Adjunctive Therapy in TRD*

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



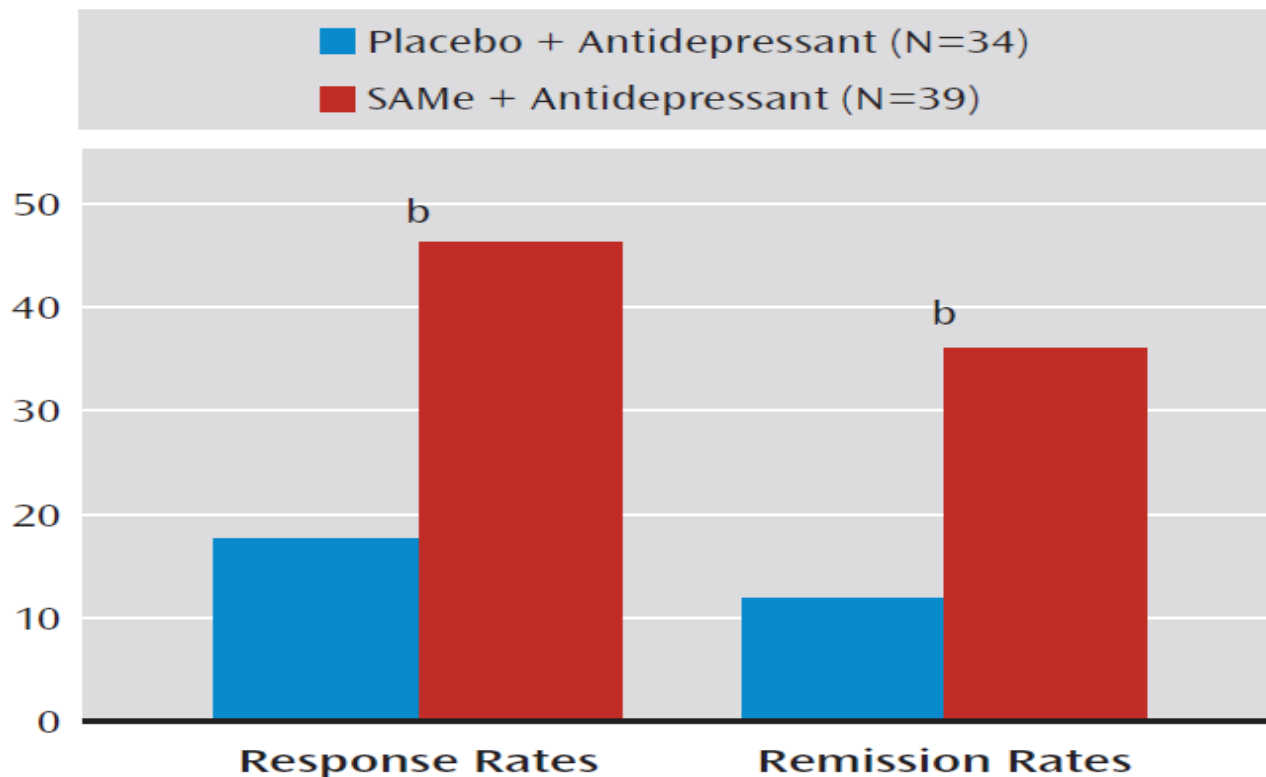
* $P < .05$; ** $P < .01$; *** $P < .001$ vs placebo; P values represent pairwise comparisons and were not adjusted for multiple comparisons. ADT indicates antidepressant treatment; ITT, intent-to-treat; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for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

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

*Treatment resistance assessed with the ATHF by site rater (resistance rating ≥ 3 ; ATHF global confidence score ≥ 3)

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

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

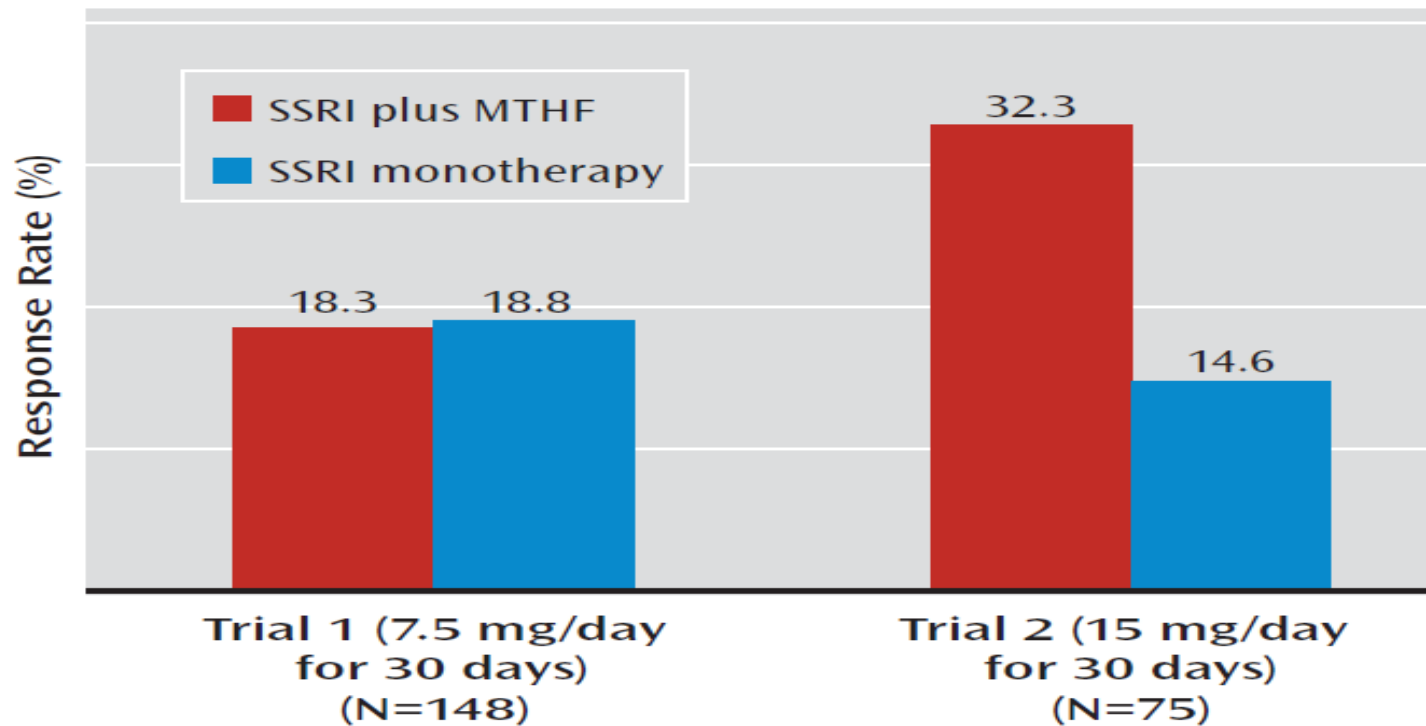


^a Data depict last observation carried forward (LOCF) for all patients randomly assigned.

^b Significant difference between groups ($p < 0.05$, Fisher's exact test).

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).

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

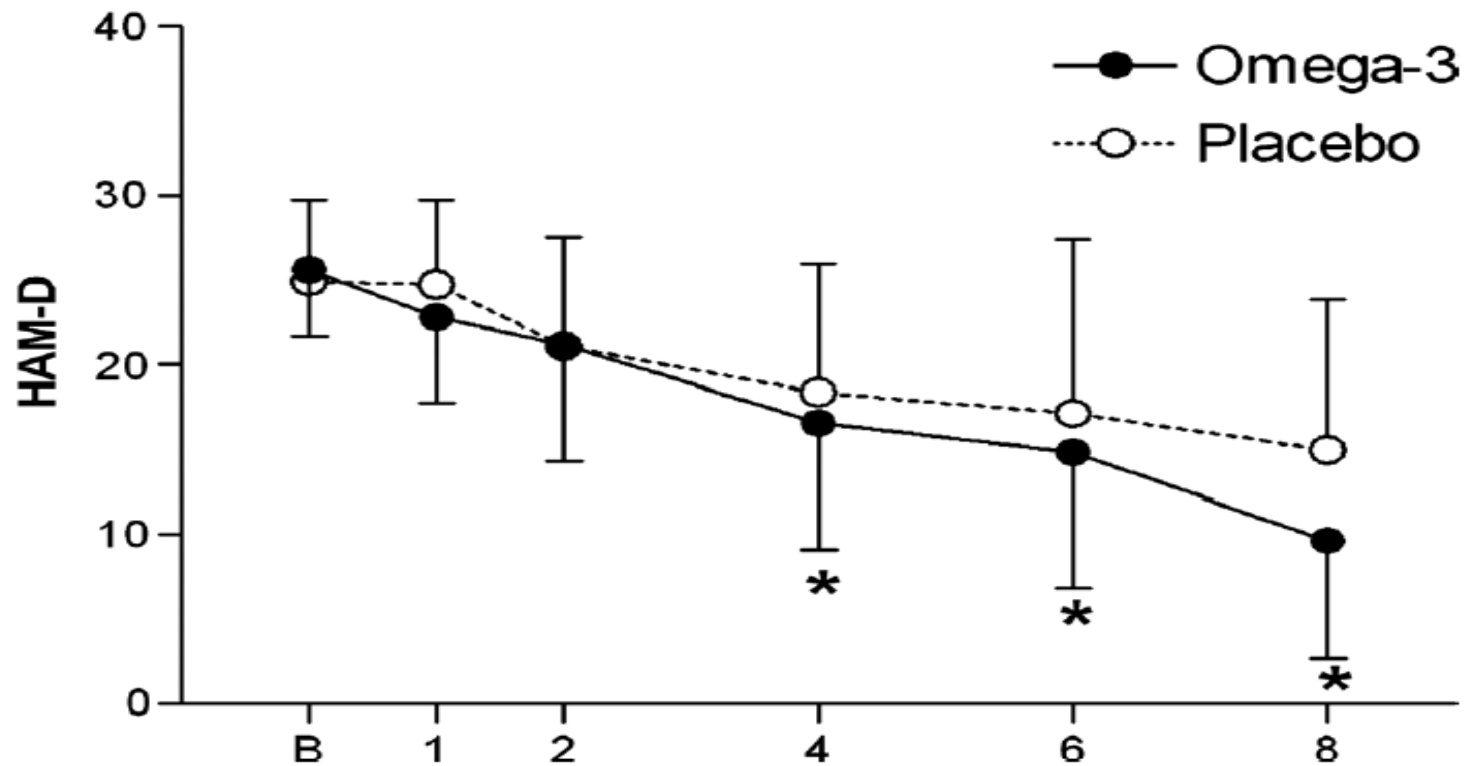
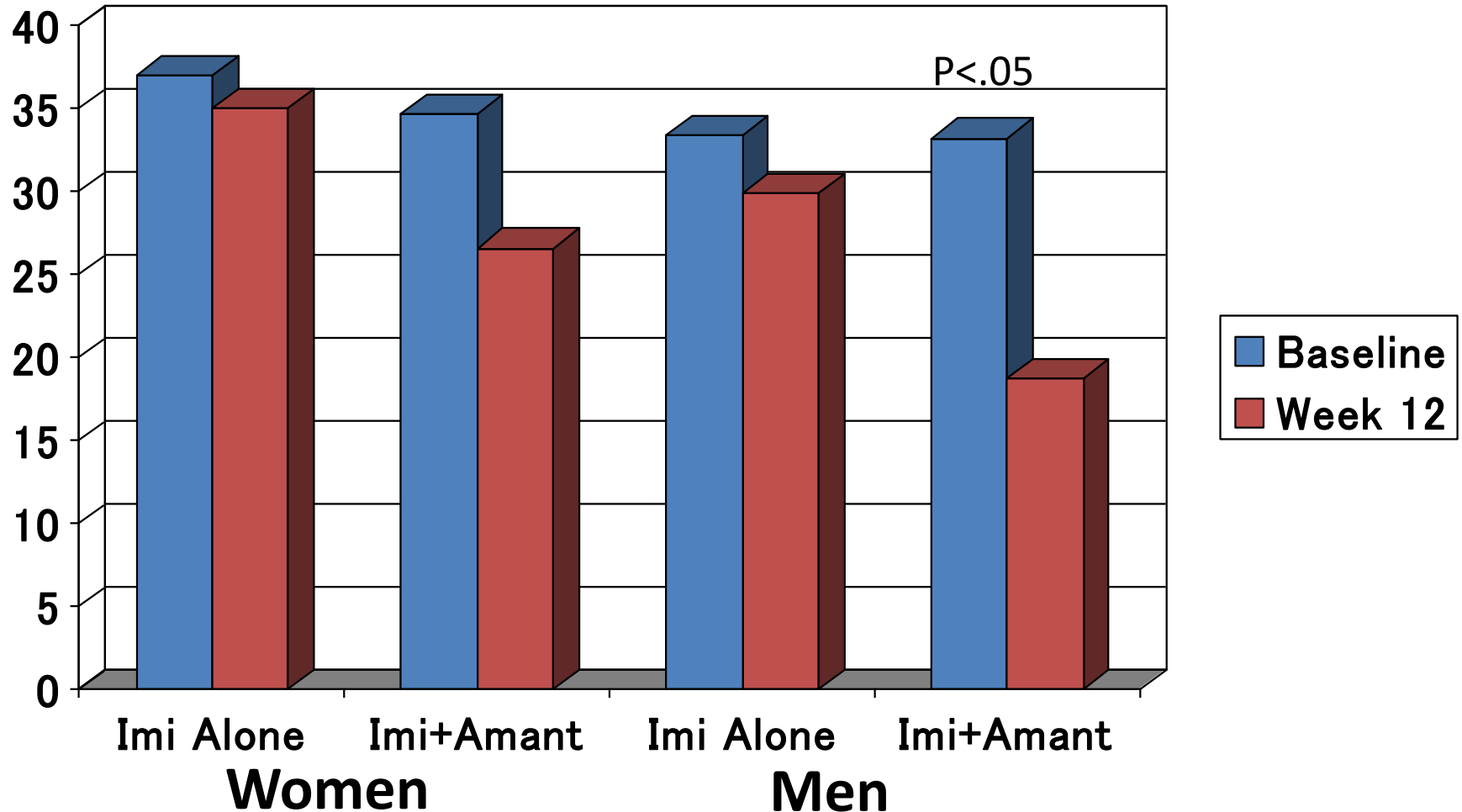


FIGURE 1. Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean \pm SD (* $P < 0.05$, computed via regression modeling).

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



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

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

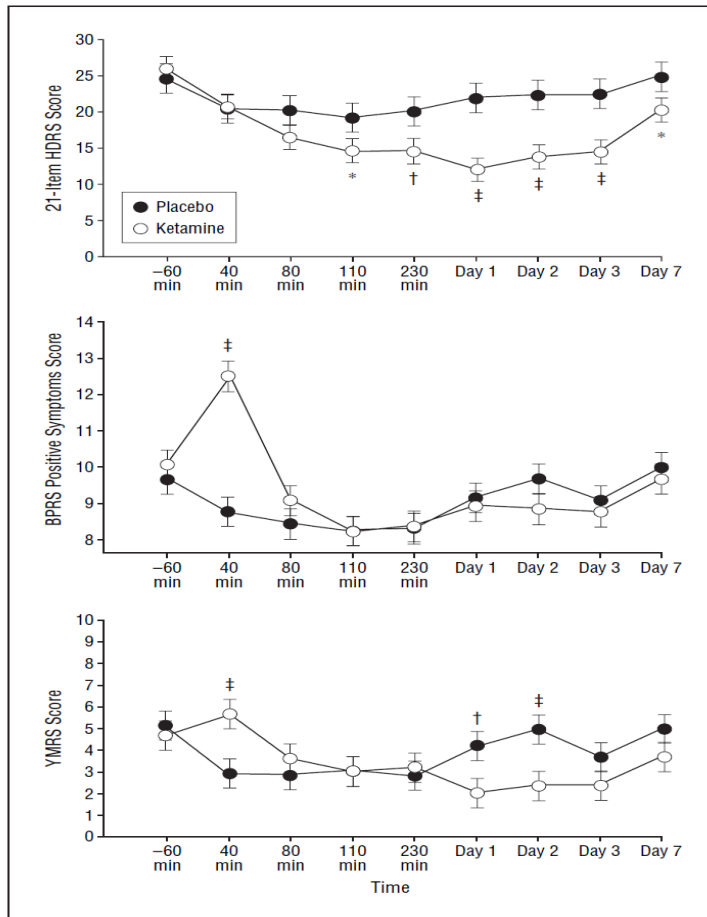


Figure 2. Change in the 21-item Hamilton Depression Rating Scale²⁸ (HDRS), Brief Psychiatric Rating Scale³¹ (BPRS) positive symptoms subscale, and Young Mania Rating Scale³² (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the completer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

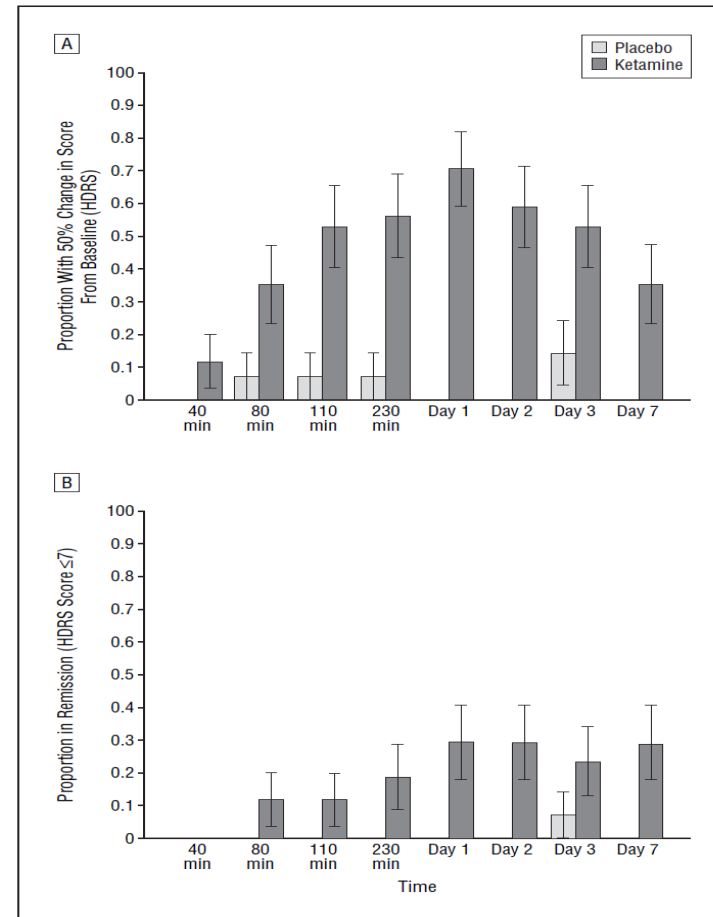
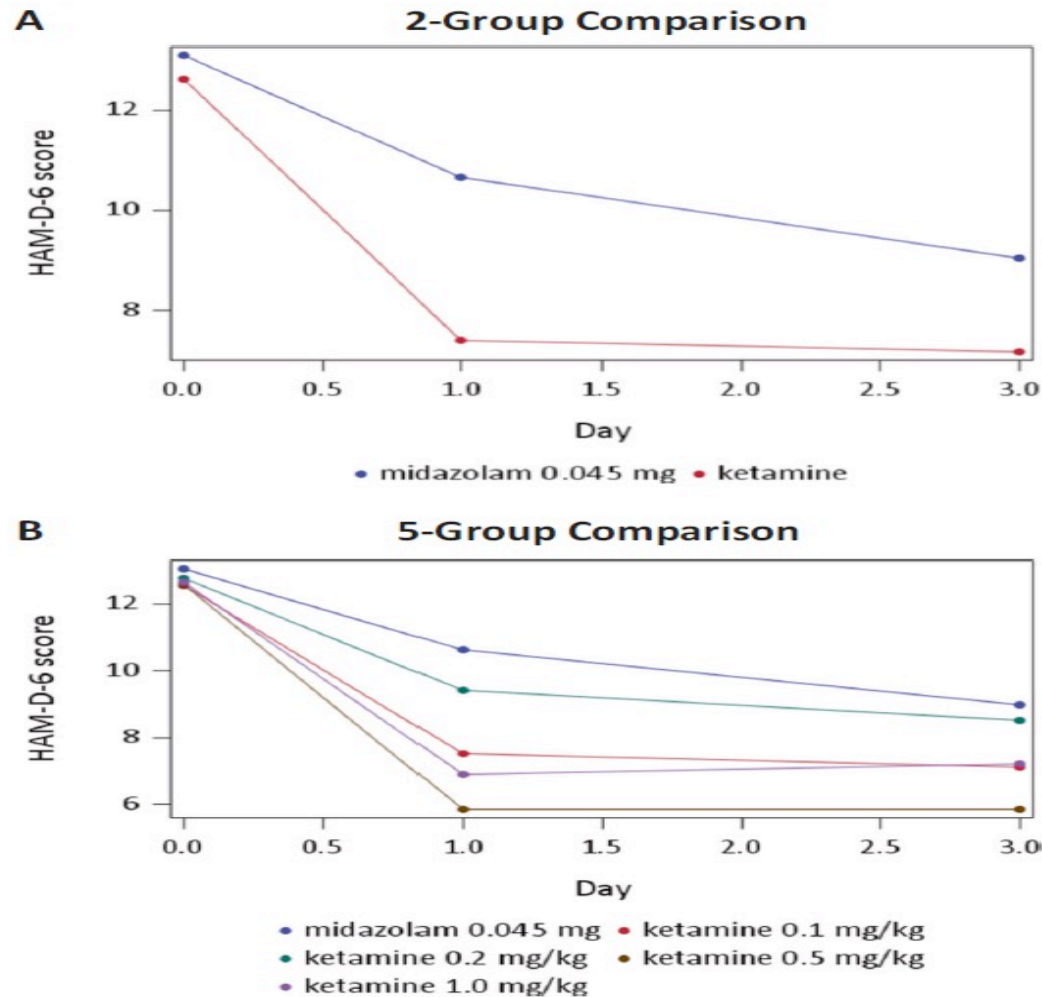


Figure 3. A, Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale²⁸ [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B, Proportion of remitters (HDRS score ≤ 7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion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

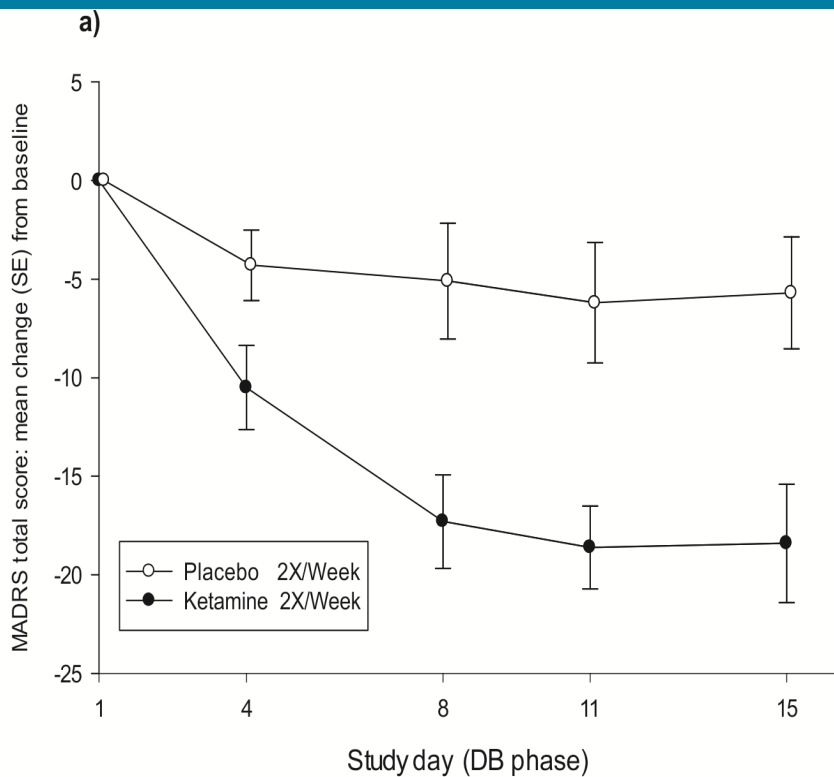
Double-blind, Placebo-controlled, Dose-ranging Trial of Intravenous Ketamine as Adjunctive Therapy in Treatment-Resistant Depression (TRD)



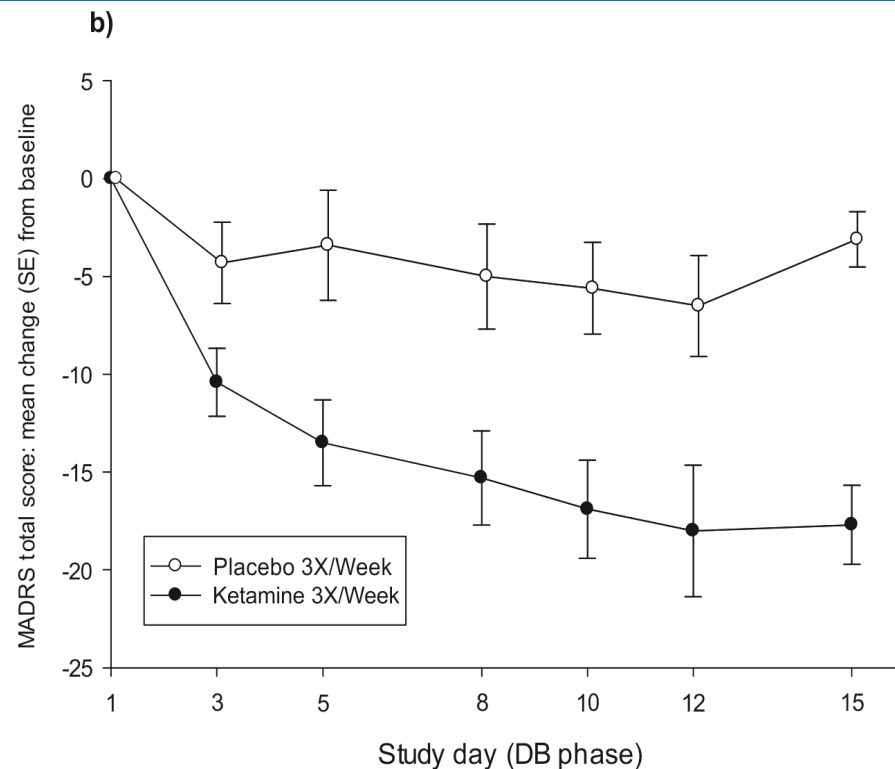
Fava et al
Molecular Psychiatry
<https://doi.org/10.1038/s41380-018-0256-5>

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*



Number of patients:		1	4	8	11	15
Placebo	16	15	13	13	13	13
Ketamine	18	17	15	16	16	16



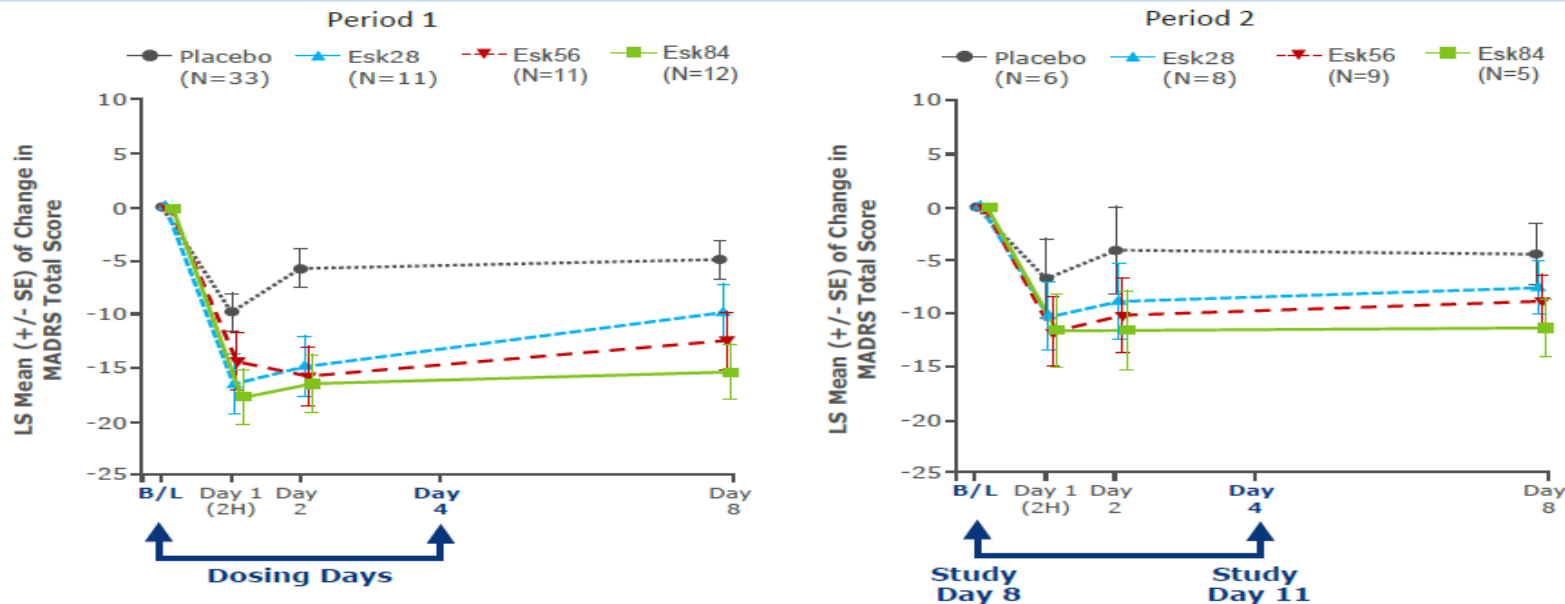
Number of patients:		1	3	5	8	10	12	15
Placebo	16	16	16	15	16	16	14	16
Ketamine	17	17	17	13	16	16	11	13

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

*TRD assessed with ATRQ by SAFER rater

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

Figure 2: MADRS Total Score LS Mean Change from Baseline to End Point – ANCOVA LOCF Analysis (Intent-to-Treat Analysis Set-DB)



	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

CI: confidence interval; DB: double-blind; Esk: esketamine; MADRS: Montgomery-Asberg Depression Rating Scale; SE: standard error

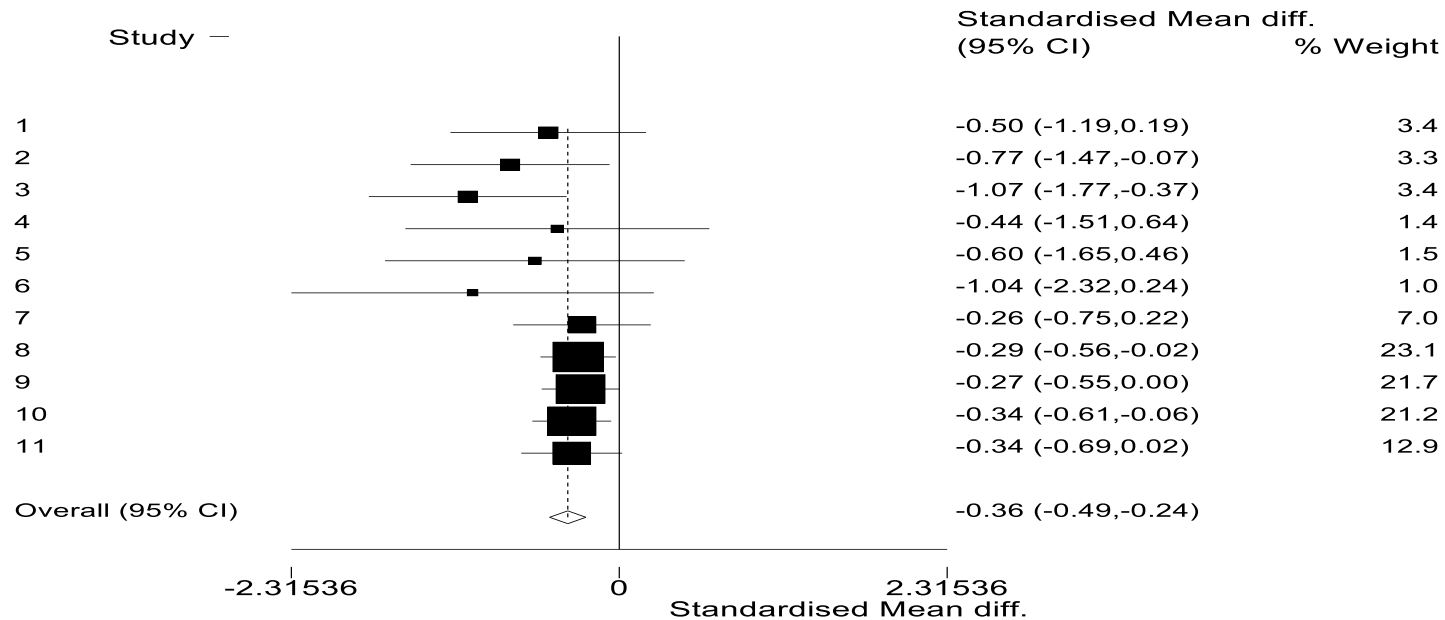
- Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ

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

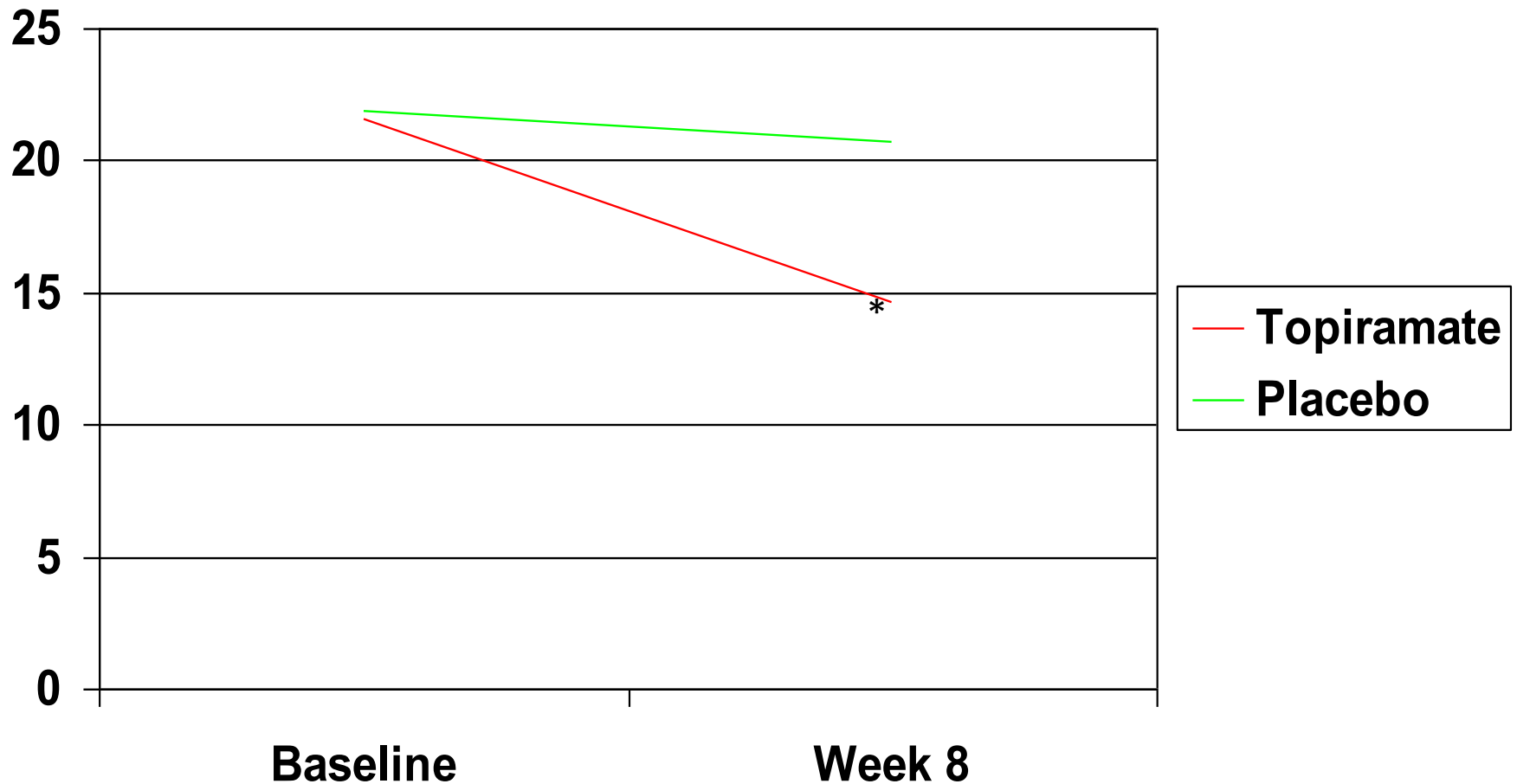
Meta-Analysis of Esketamine Augmentation in TRD Studies

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



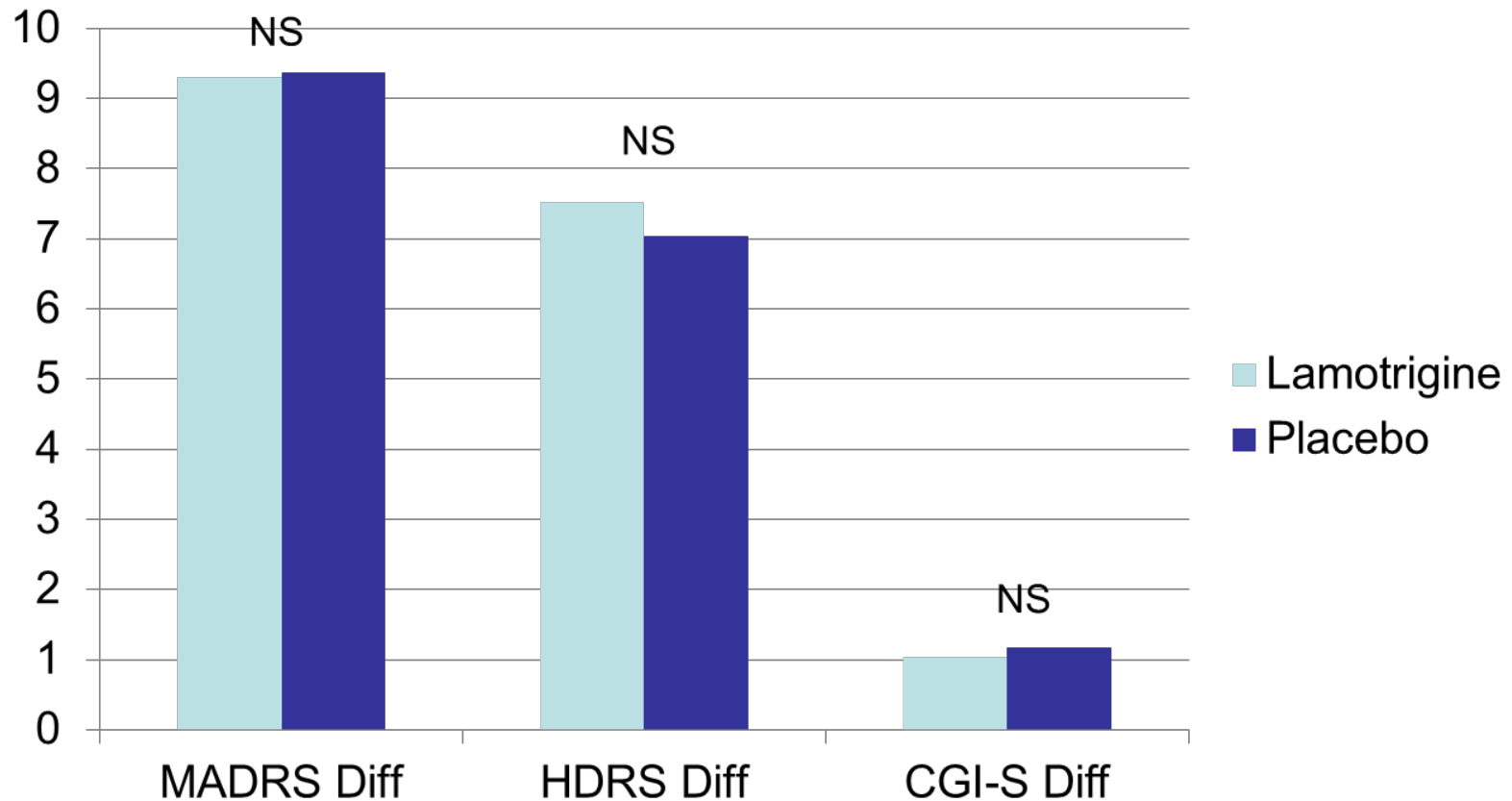
Papakostas et al, J Clin Psychiatry. 2020 May 26;81(4):19r12889. doi: 10.4088/JCP.19r12889.

HAM-D Scores in Double-Blind Study of the Kainate (Glutamate) Receptor Antagonist Topiramate (100-200 mg/day) Augmentation in TRD (n=53)



• $p < .000$

Double-Blind Study of the Glutamate Release Inhibitor Lamotrigine (up to 400 mg/day) Augmentation of Paroxetine in TRD Patients (n=96)



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

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)	

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

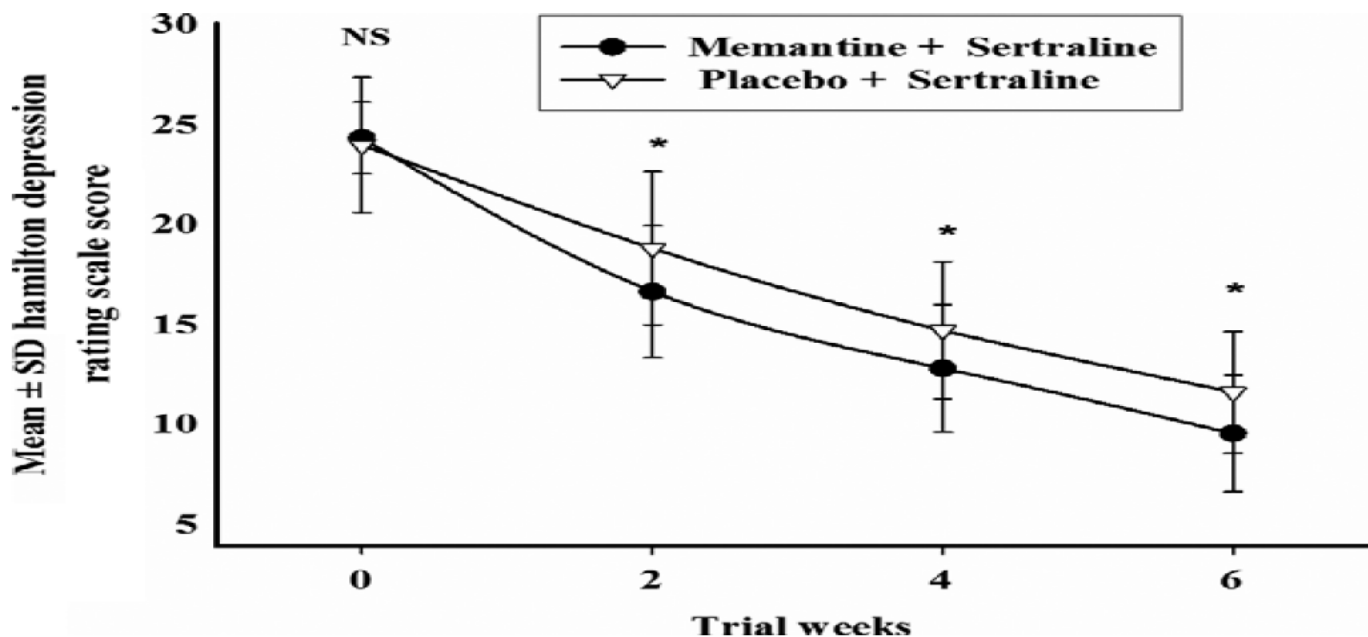
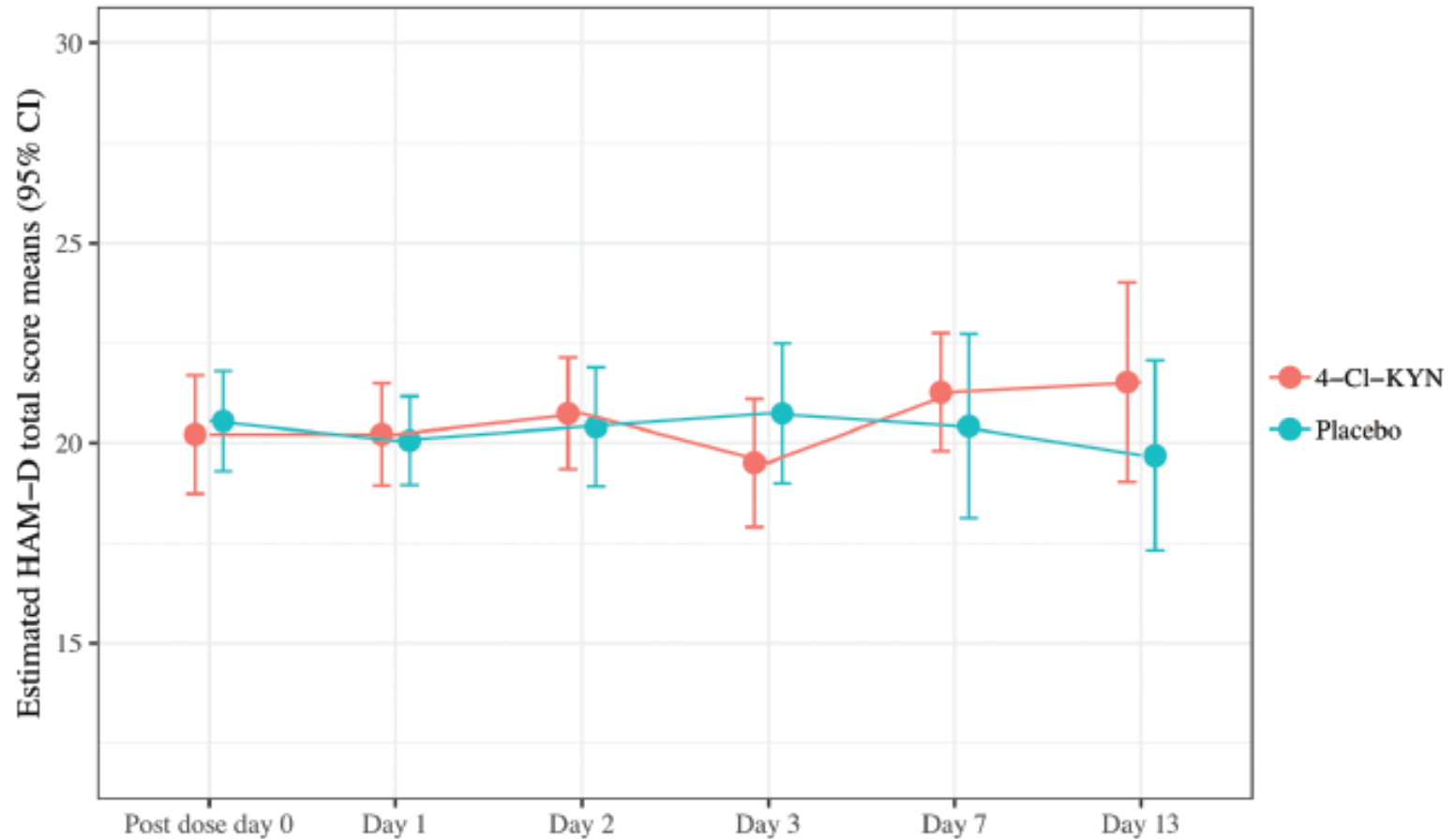


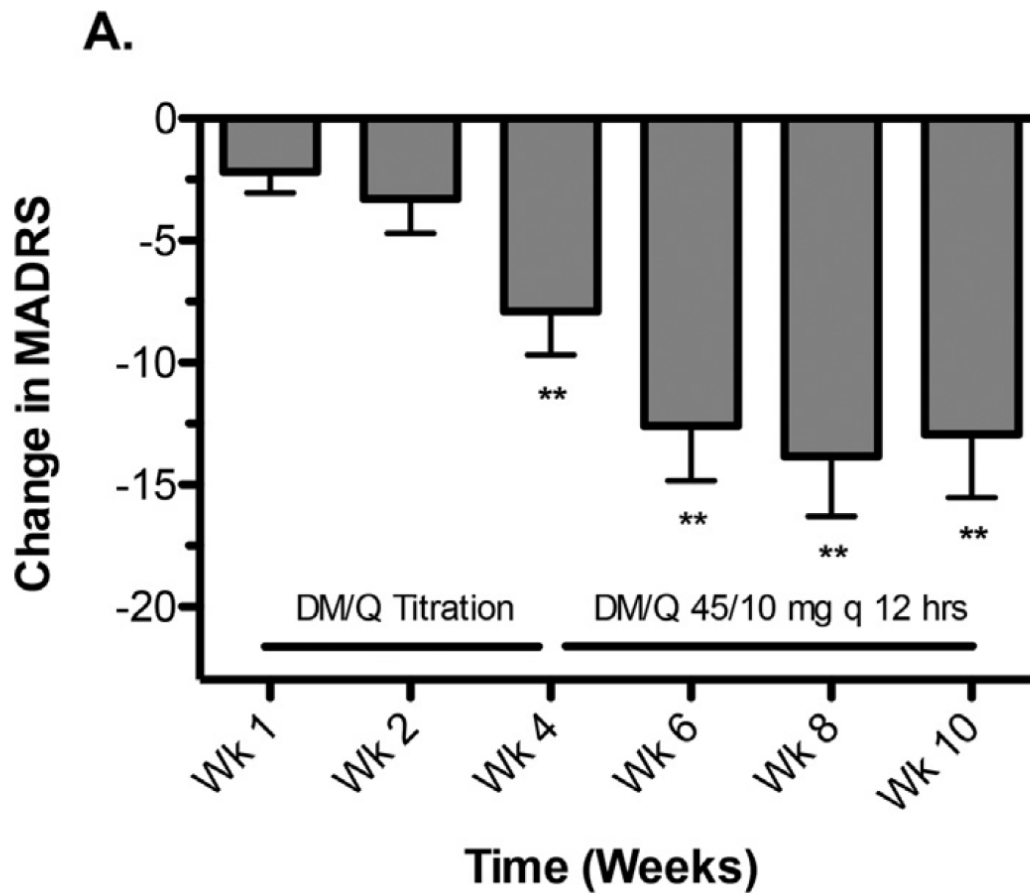
Fig. 2. Repeated measures for comparison of the effects of two treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean \pm standard deviation. *P*-values show the result of the independent *t*-test comparing HDRS scores between the two groups at each time point. NS indicates non-significant;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

A Randomized Trial of the N-Methyl-d-Aspartate Receptor Glycine Site Antagonist Prodrug 4-Chlorokynurenine (4-Cl-KYN) in Treatment-Resistant Depression



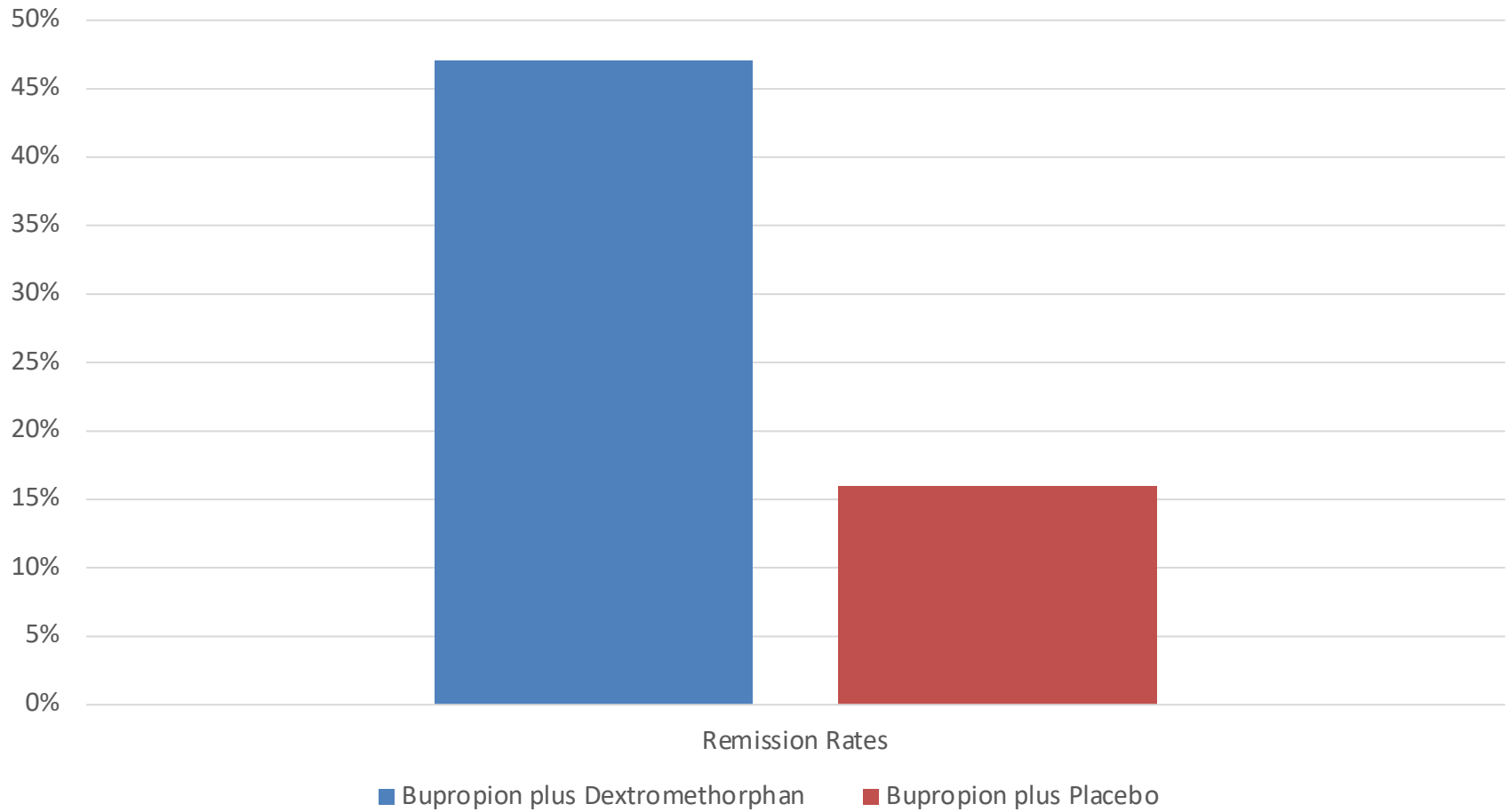
Park et al, International Journal of Neuropsychopharmacology (2020) 23(7): 417–425

Dextromethorphan/Quinidine (45/10 mg/day) (Dextromethorphan is an NMDA receptor Antagonist) Pharmacotherapy in Patients with TRD: A Proof of Concept, Open Clinical Trial



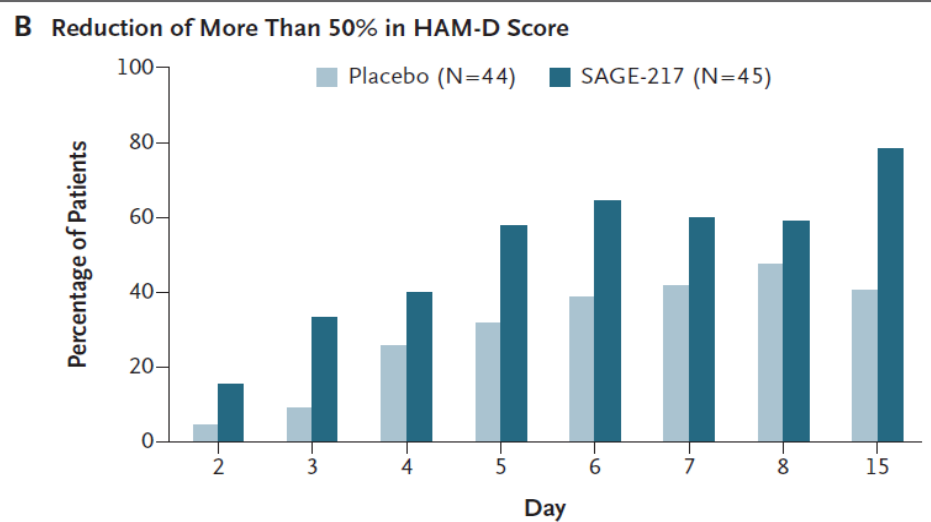
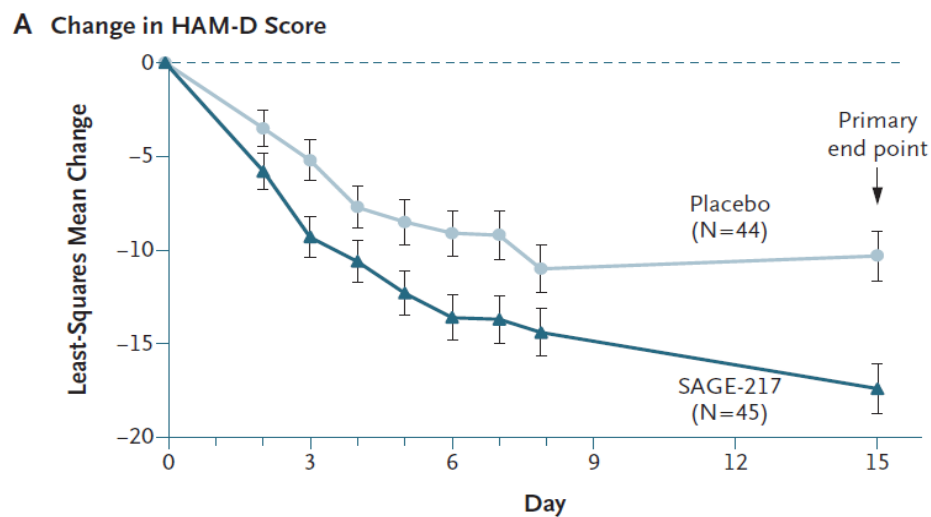
Murrough et al, Journal of Affective Disorders 218 (2017) 277–283

Double-blind Study in Moderate to Severe MDD of AXS-05 (45 mg Dextromethorphan/105 mg Bupropion) vs. Bupropion (105 mg), Twice Daily for 6 Weeks (n=80)



[https://axsometherapeuticsinc.gcs-web.com/news-releases/news-release-details/axsome-therapeutics-announces-axs-05-achieves-primary-endpoint?field_nir_news_date_value\[min\]=2019](https://axsometherapeuticsinc.gcs-web.com/news-releases/news-release-details/axsome-therapeutics-announces-axs-05-achieves-primary-endpoint?field_nir_news_date_value[min]=2019)

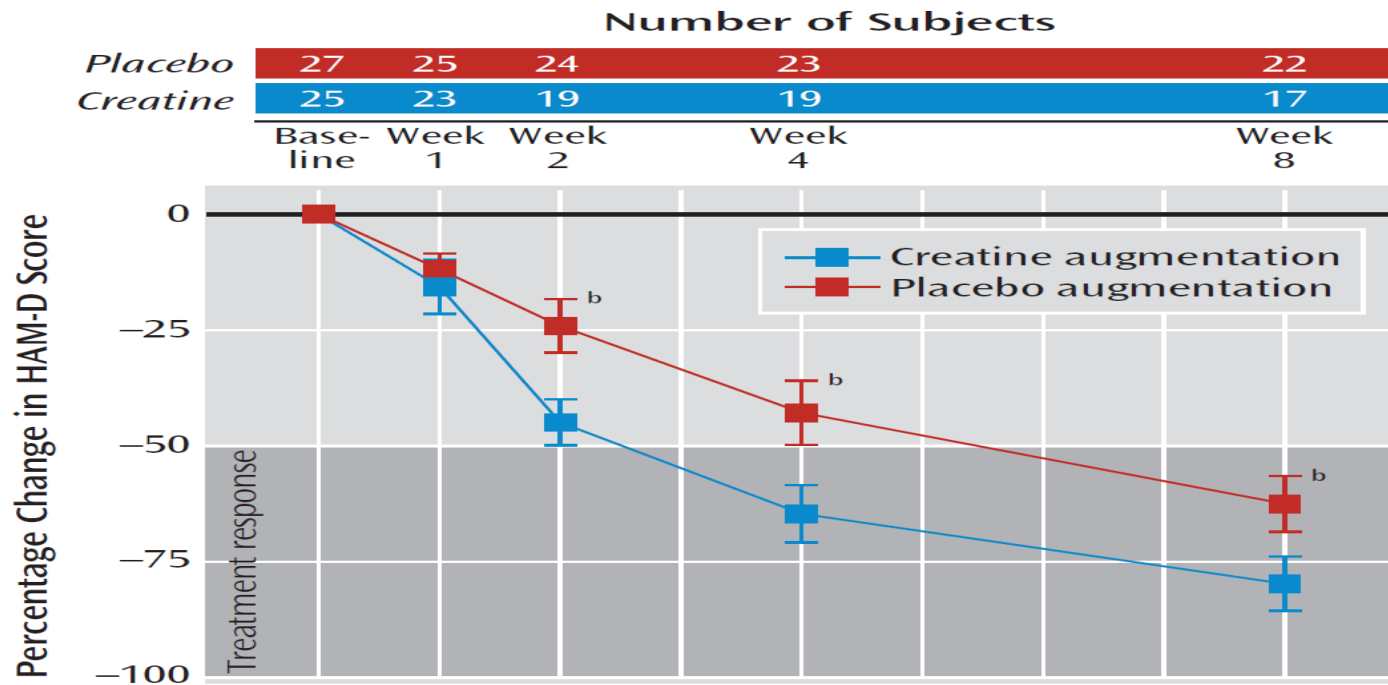
Double-Blind, Placebo-Controlled Study of SAGE-217, a Next Generation Positive Allosteric Modulator of GABA, in MDD (n=89)



Gunduz-Bruce et al, N Engl J Med
2019;381:903-11.
DOI: 10.1056/NEJMoa1815981

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
epub

A Double-Blind Study of the Phosphodiesterase Inhibitor Pentoxifylline, an Inhibitor of IL-6 and TNF- α synthesis, as a Novel Adjunct to Antidepressants in MDD Patients

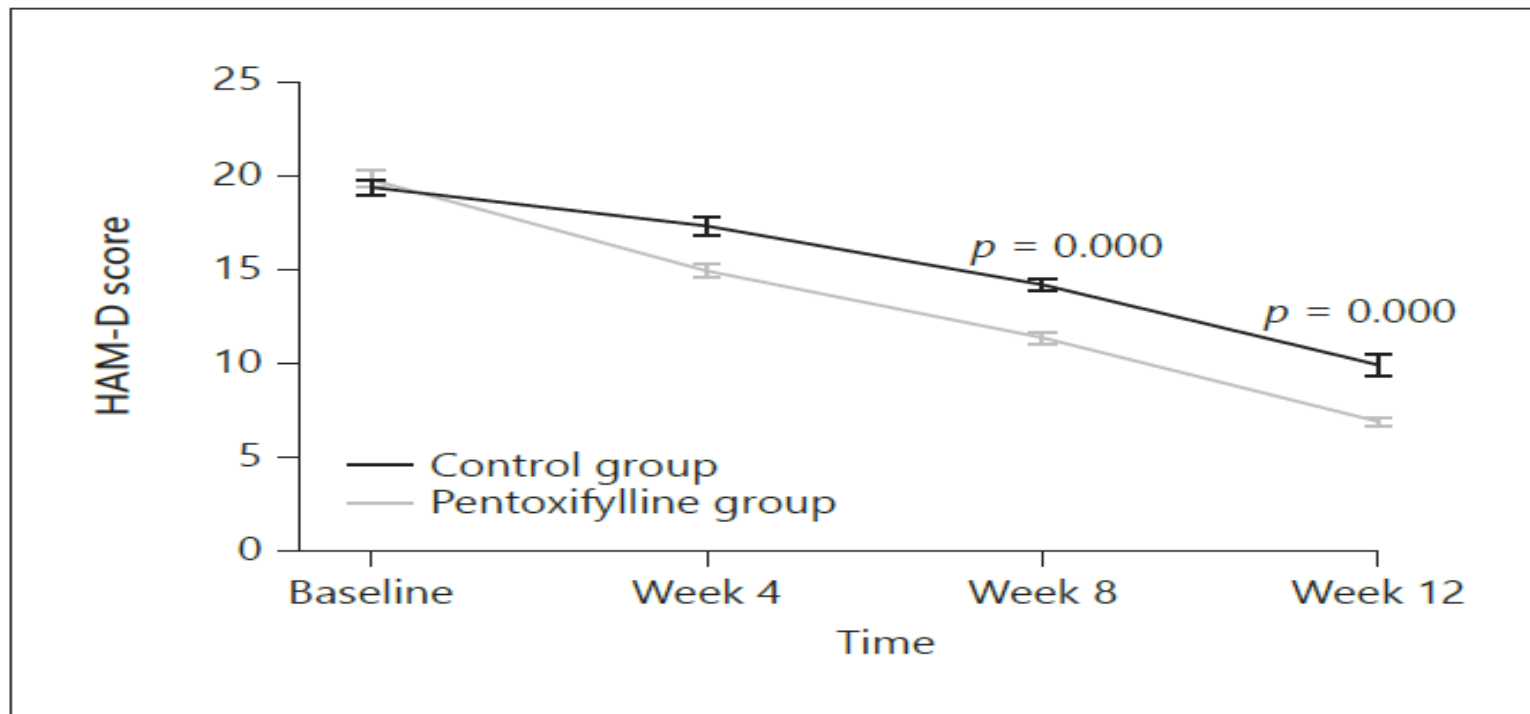


Fig. 2. Changes in Hamilton Depression Rating Scale (HAM-D) total score from baseline to week 12. Data are presented as mean and 95% confidence interval.

Minocycline (200 mg/day) (an Anti-Inflammatory and Neuroprotective Agent) as an Adjunct for Treatment-Resistant Depressive Symptoms: A Pilot, Randomized Placebo-Controlled Trial

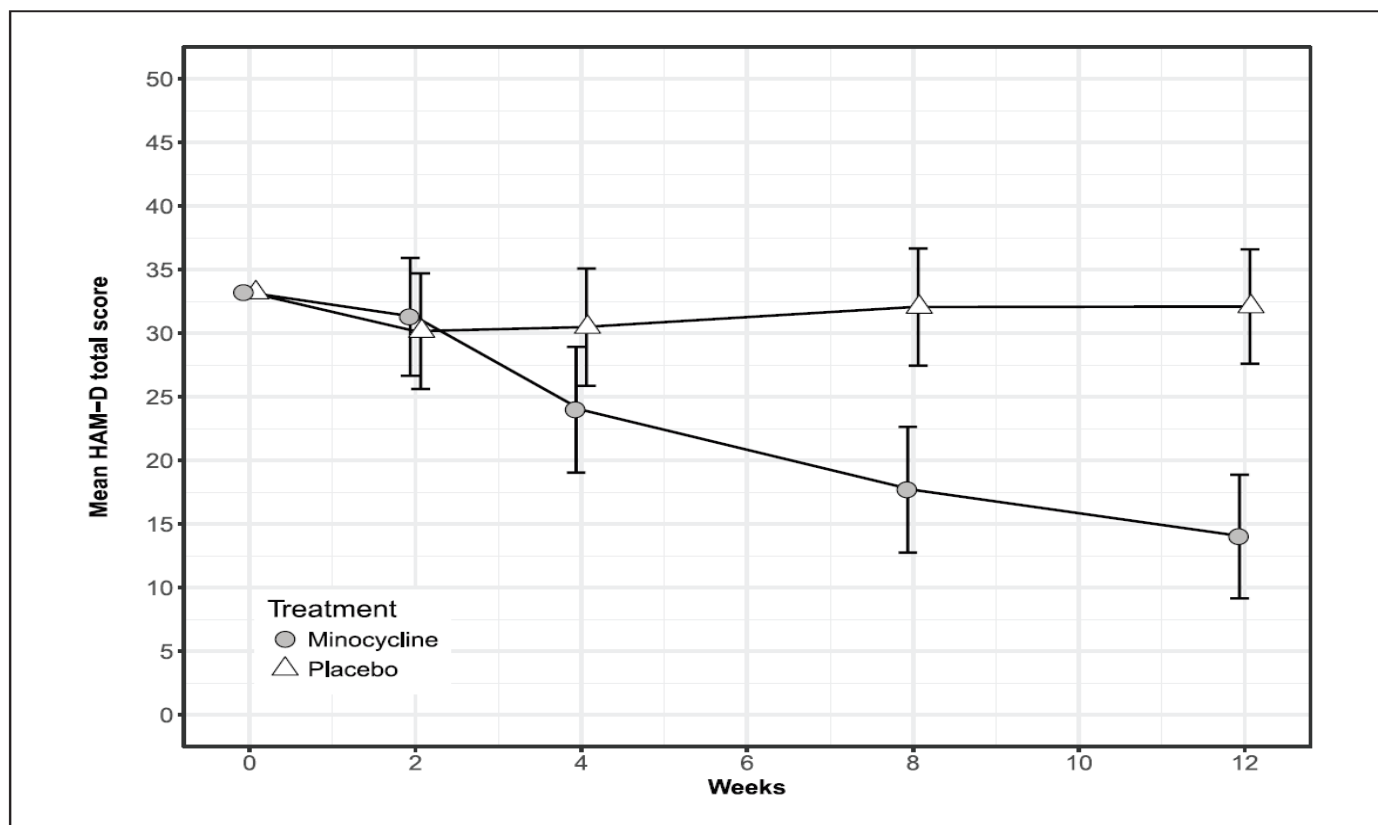
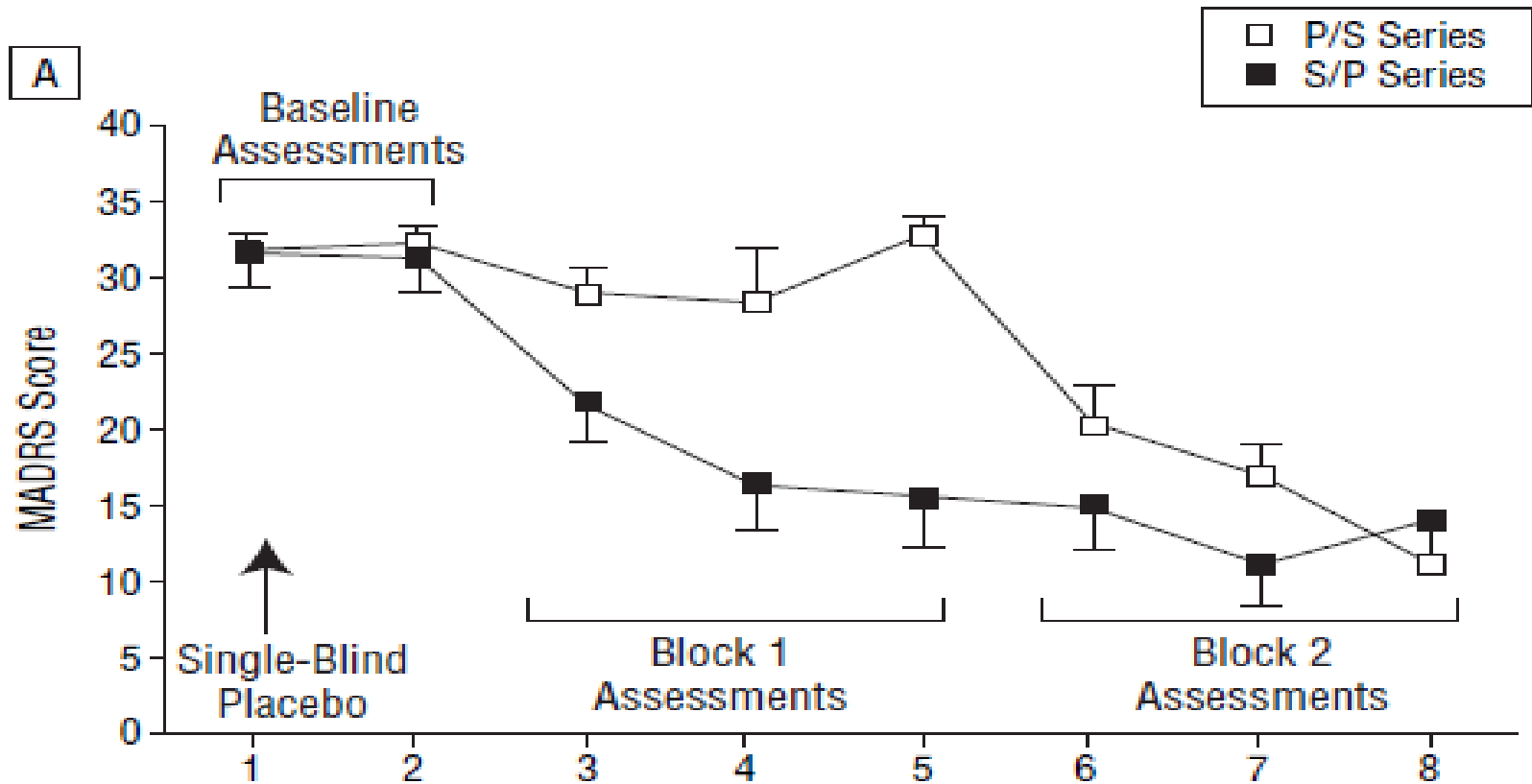


Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socio-economic status class participants (most frequent class).

Husain et al, J Psychopharmacol. 2017 Aug 1;269881117724352. doi: 10.1177/0269881117724352. [Epub ahead of print]

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

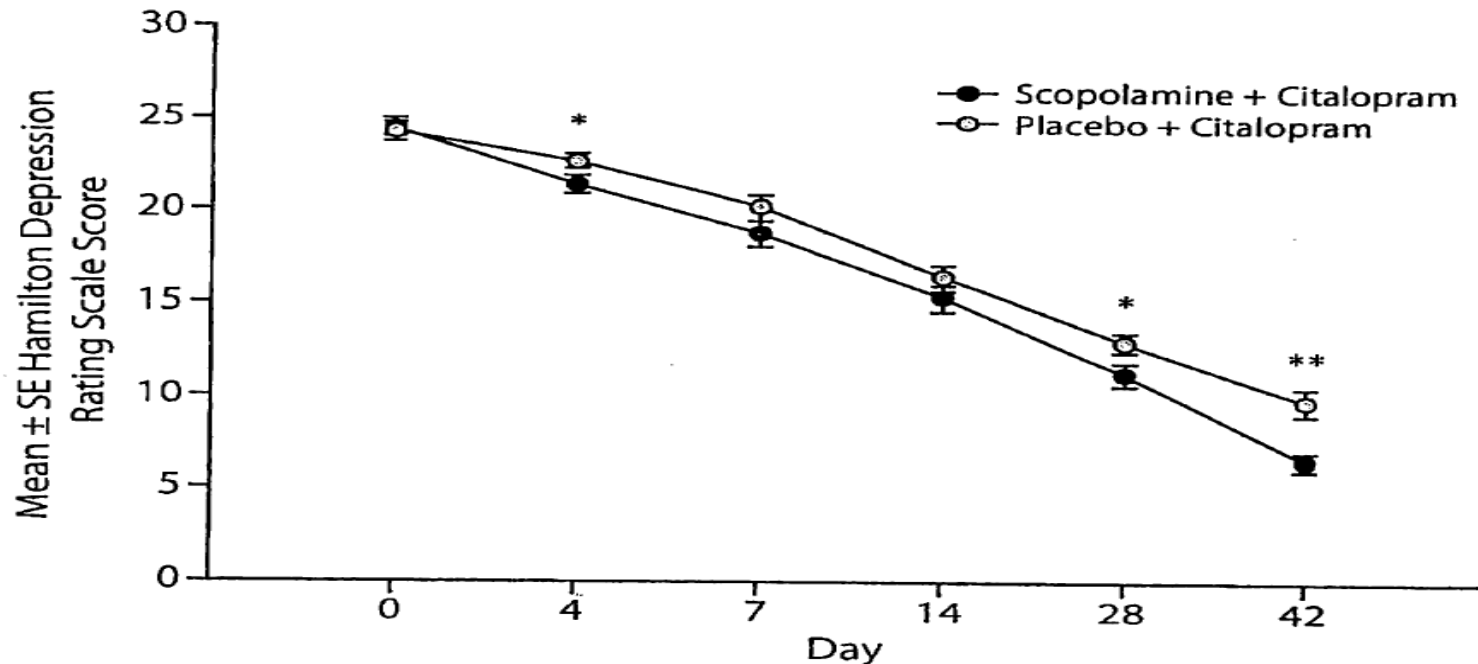


Mean Montgomery-Asberg Depression Rating Scale (MADRS) (A) scores for the placebo/scopolamine hydrobromide (P/S) group and the scopolamine/placebo (S/P) group across 8 assessments. Two baseline, 3 block 1, and 3 block 2 assessments are identified in each panel. Error bars represent SE. For each scale,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

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

The Effects of Intramuscular Administration of Scopolamine Augmentation in Moderate to Severe Major Depressive Disorder: A Randomized, Double-blind, Placebo-Controlled Trial

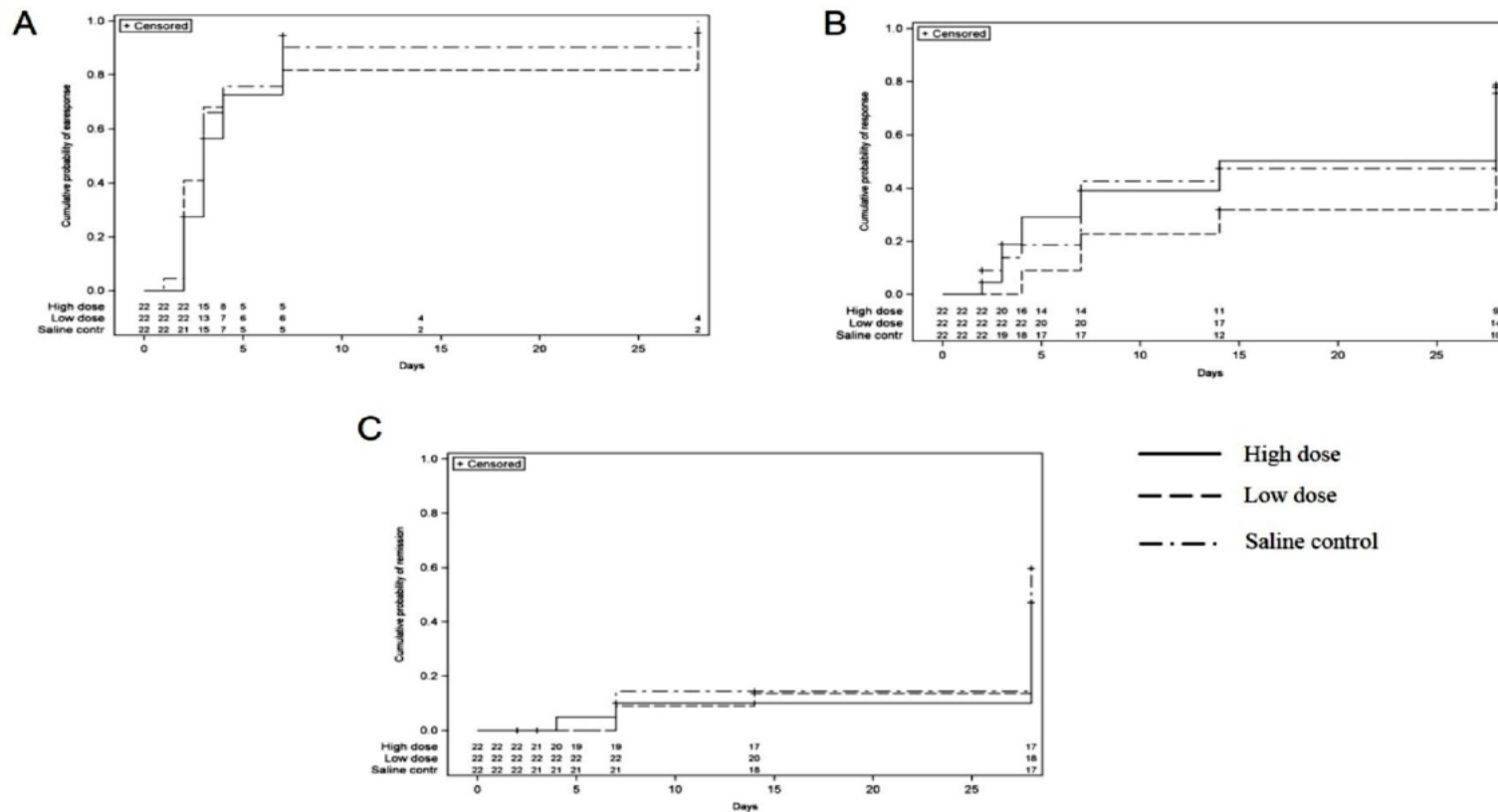


Figure 2. Time to early response, response and remission by Kaplan–Meier analysis. (a) Time to early response; (b) time to response (with number of subjects at risk); and (c) time to remission.

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

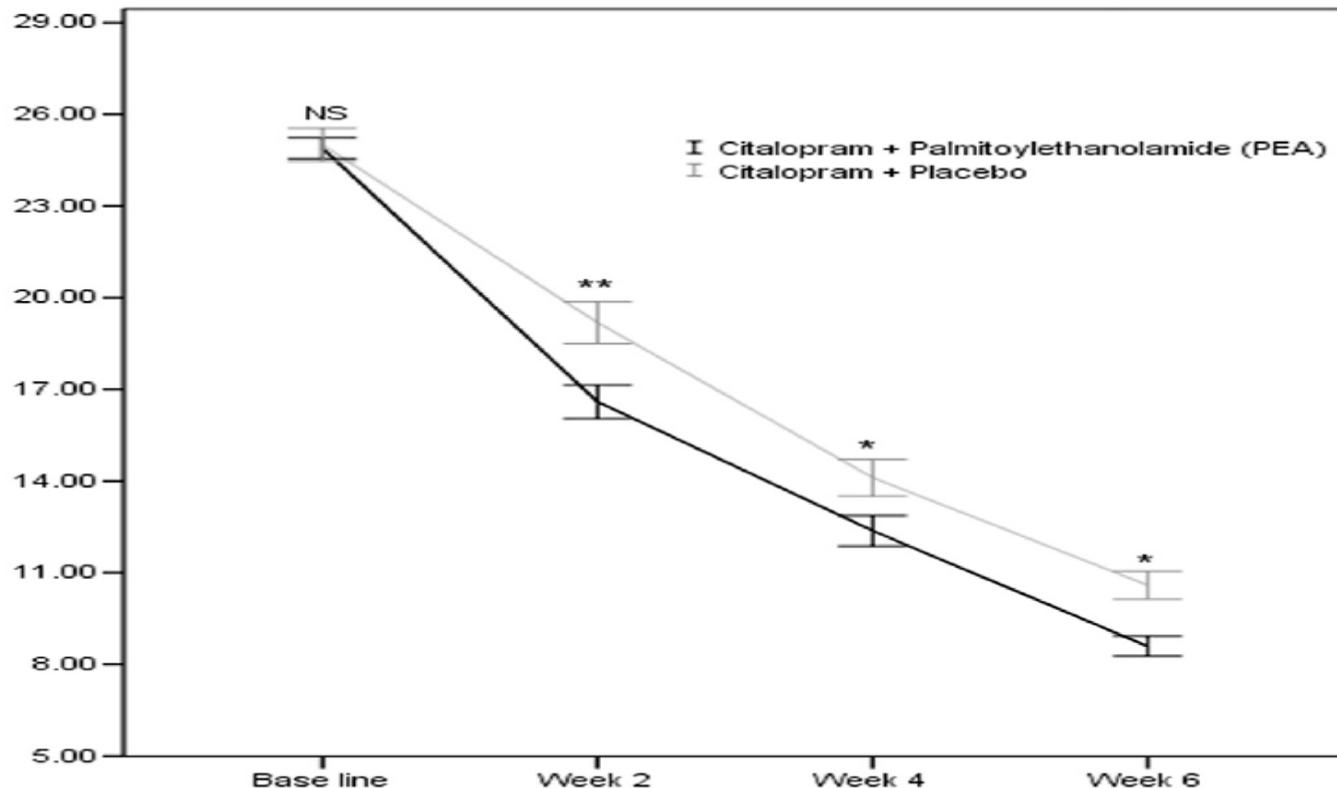
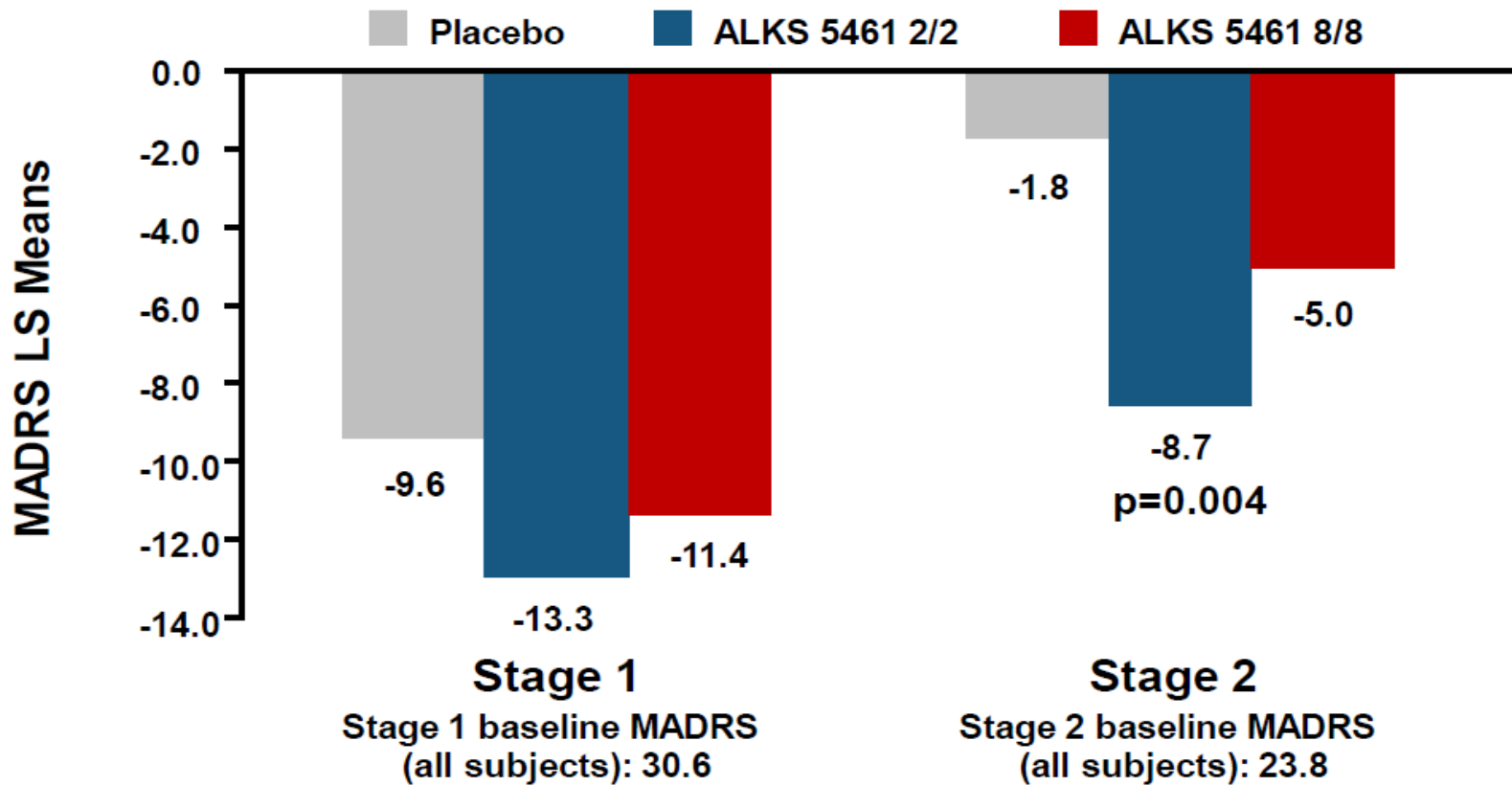


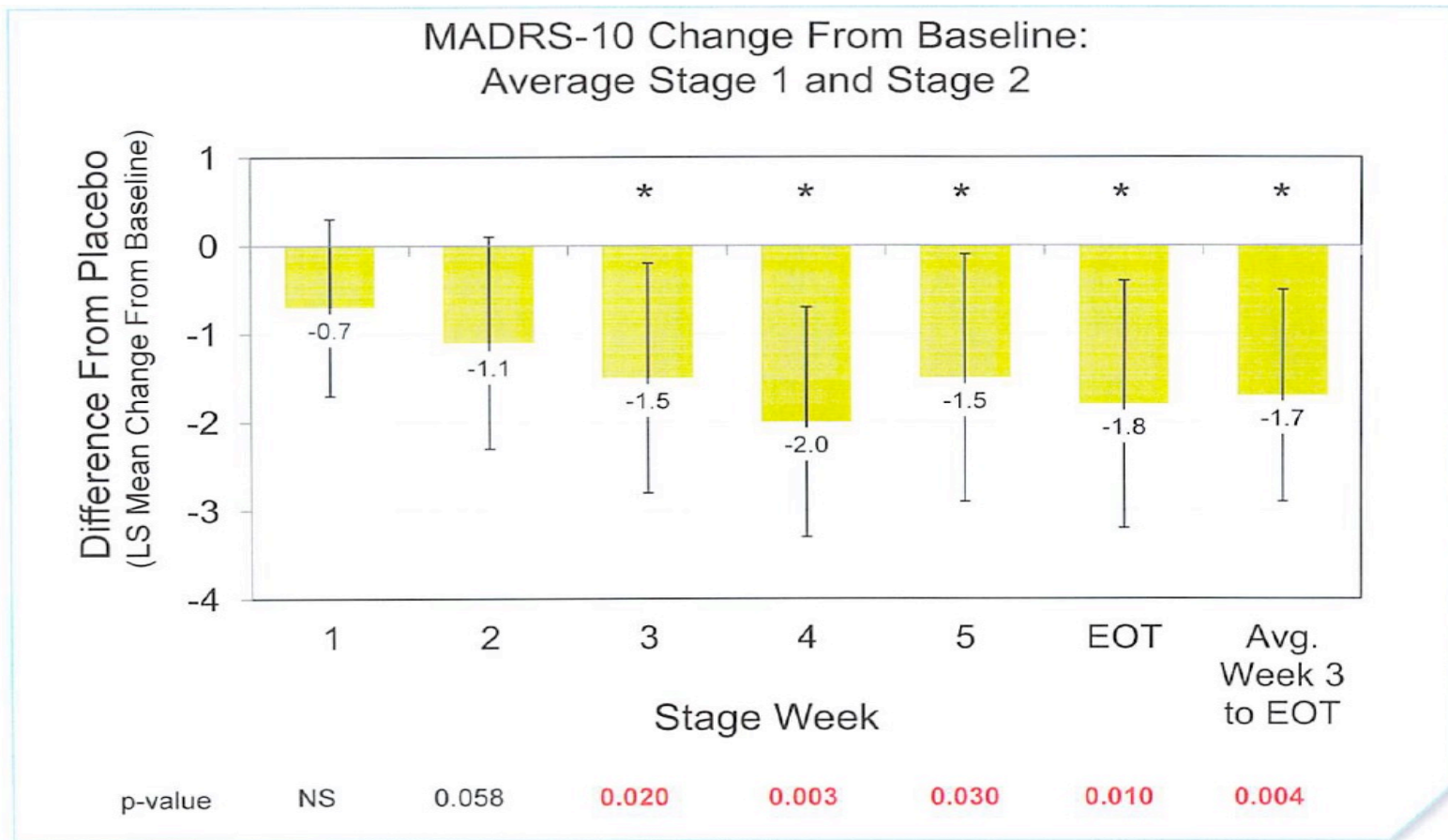
Fig. 2. Repeated measure analysis for comparison of the effects of two treatments on the Hamilton depression rating scale (HDRS) scores. Values represent mean \pm SEM (standard error of mean). P values show the result of the independent sample *t*-test for comparison of the score change from the baseline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

Double-Blind, SPCD Study of ALKS 5461 (buprenorphine plus the mu antagonist Alks 33) vs. Placebo

Figure 4: MADRS Change from Baseline at Week 4



Pooled Analysis of the FORWARD-4 and FORWARD-5 SPCD Studies of ALKS 5461

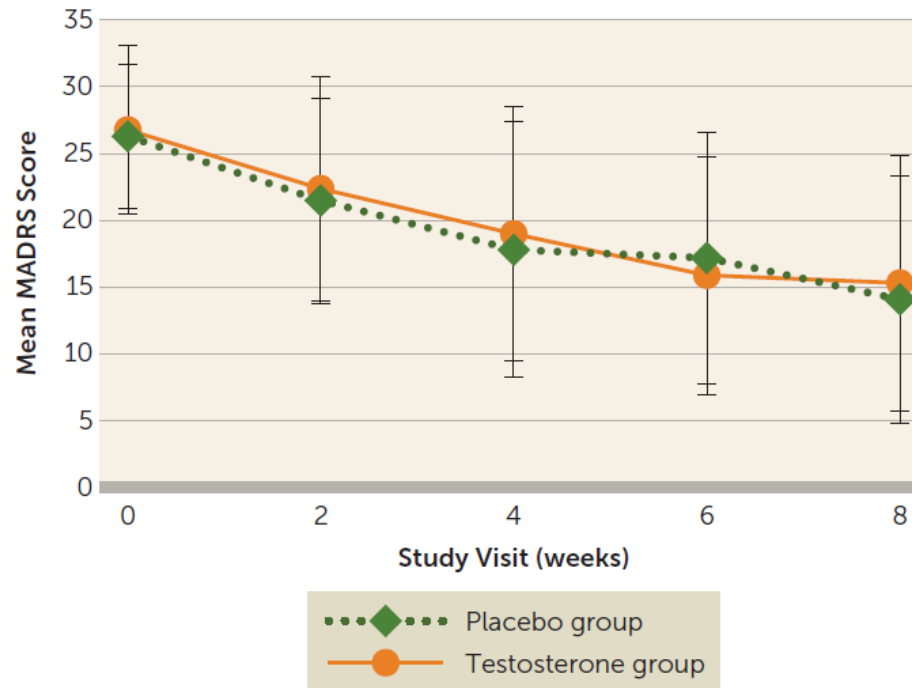


95% confidence interval

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

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

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

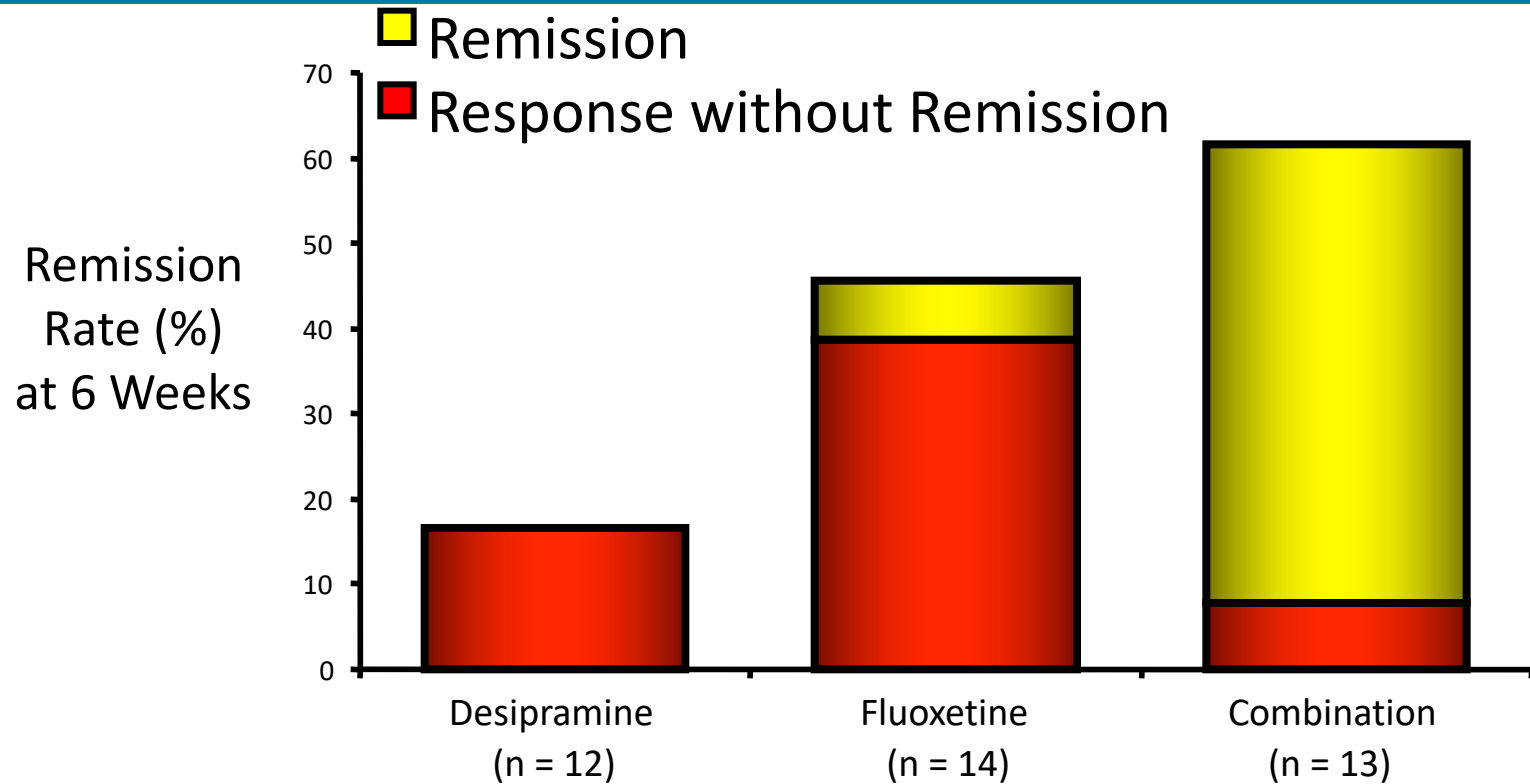


^a MADRS=Montgomery-Åsberg Depression Rating Scale. There was no significant difference between the testosterone and placebo groups. Error bars indicate standard deviation.

Combination

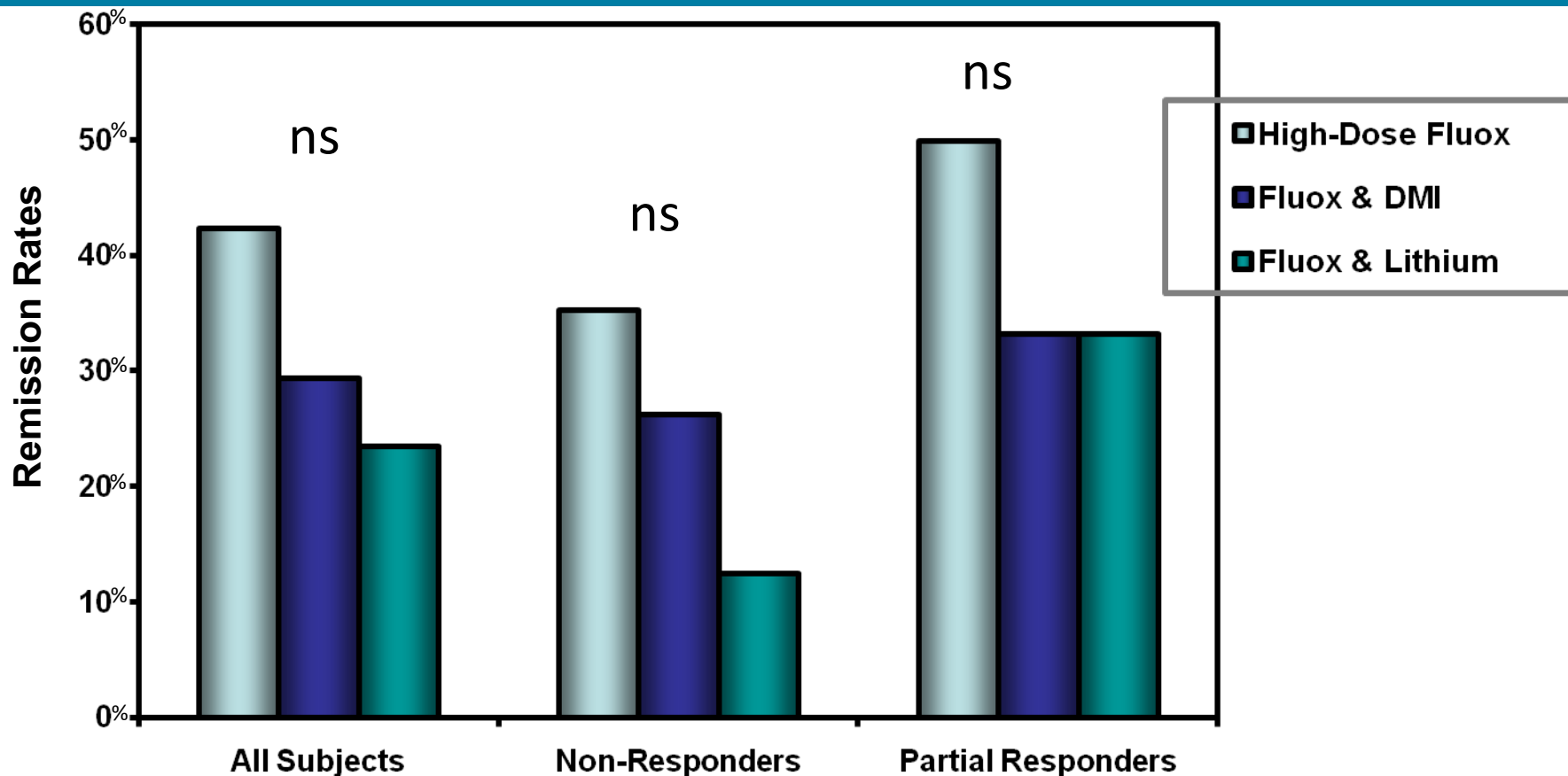
- Definition: The concomitant use of two antidepressants to enhance their therapeutic effect
- Rationale:
 - To obtain a different neurochemical effect by combining antidepressants affecting different neurotransmitter systems
 - To combine antidepressants with different mechanisms of action

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



* $p < 0.05$ for combination vs. desipramine or fluoxetine alone

Double-Blind Study in 101 Non- and Partial Responders to an 8-week Fluoxetine Trial: Remission (HAM-D-17 < 8) Rates



Double-Blind Study of Atomoxetine Augmentation

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

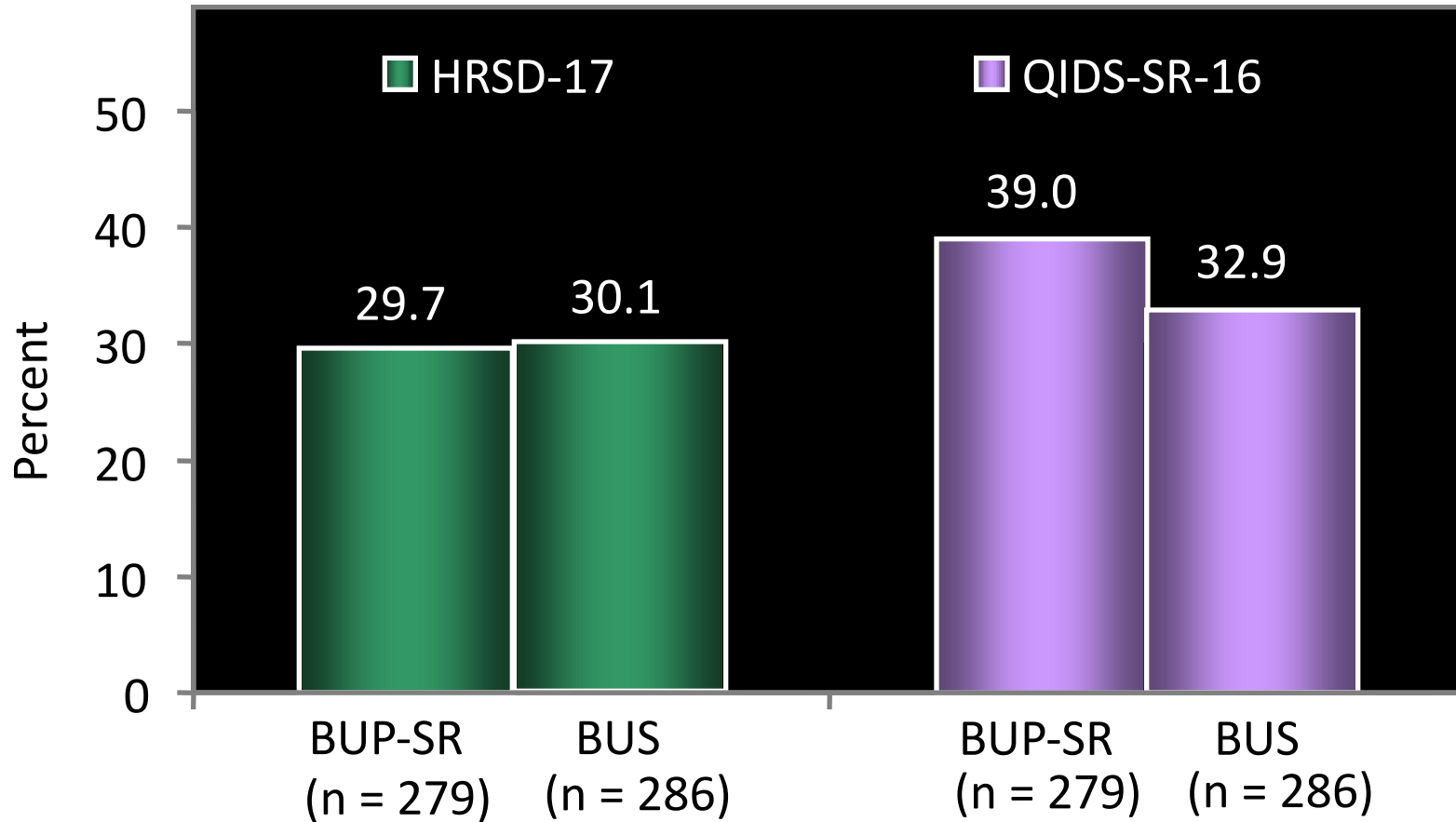
Study phase/genotype class	Remission rate (%)	Between-group P value ^a	Versus S/S P value ^b
SRT open-label monotherapy		0.42	
S/S (N = 51)	21.6		
S/L (N = 128)	23.4		
L/L (N = 82)	30.5		
non-S/S (N = 210)	26.2		0.59
SRT + ATX randomized combination therapy		0.008	
S/S (N = 11)	81.8		
S/L (N = 31)	38.7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

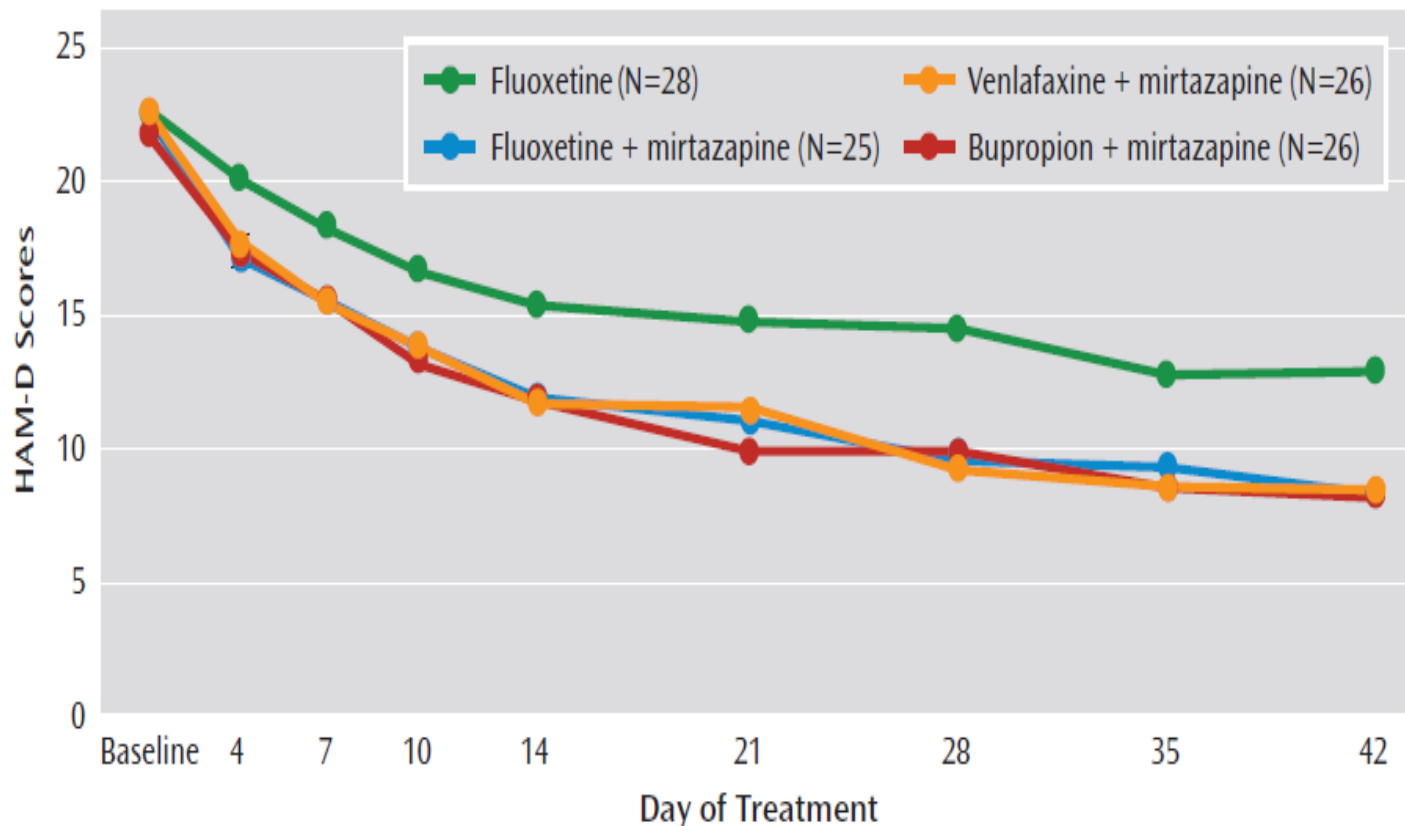
^b Comparison of non-S/S versus S/S.

Percent of Remission in STAR*D L-2 Augmentation



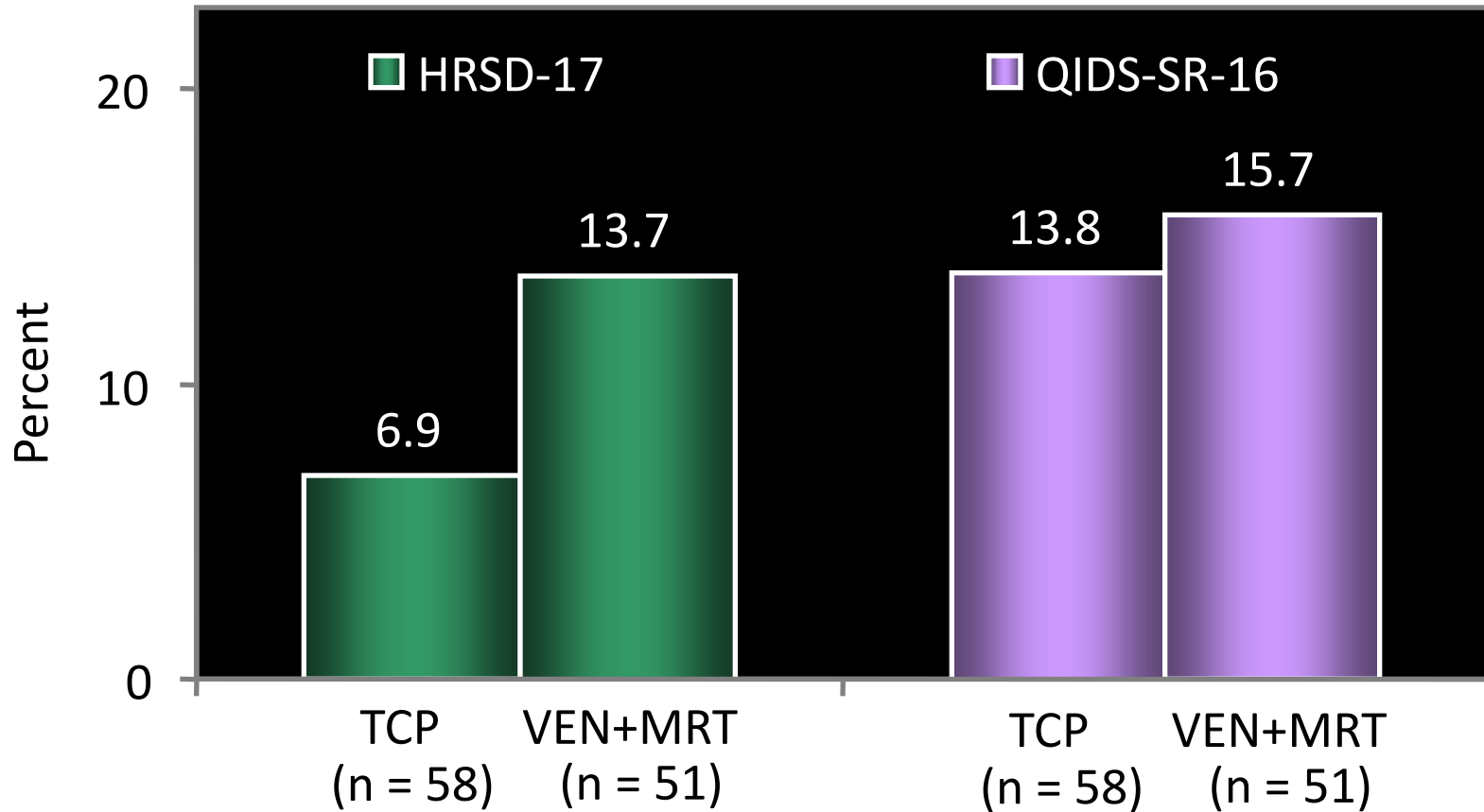
Double-Blind Study of Mirtazapine Augmentation

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 ($F=3.87$; $df=3, 101$, $p=0.011$).

Percent of Remission in STAR*D L-4



Trazodone plus SSRIs

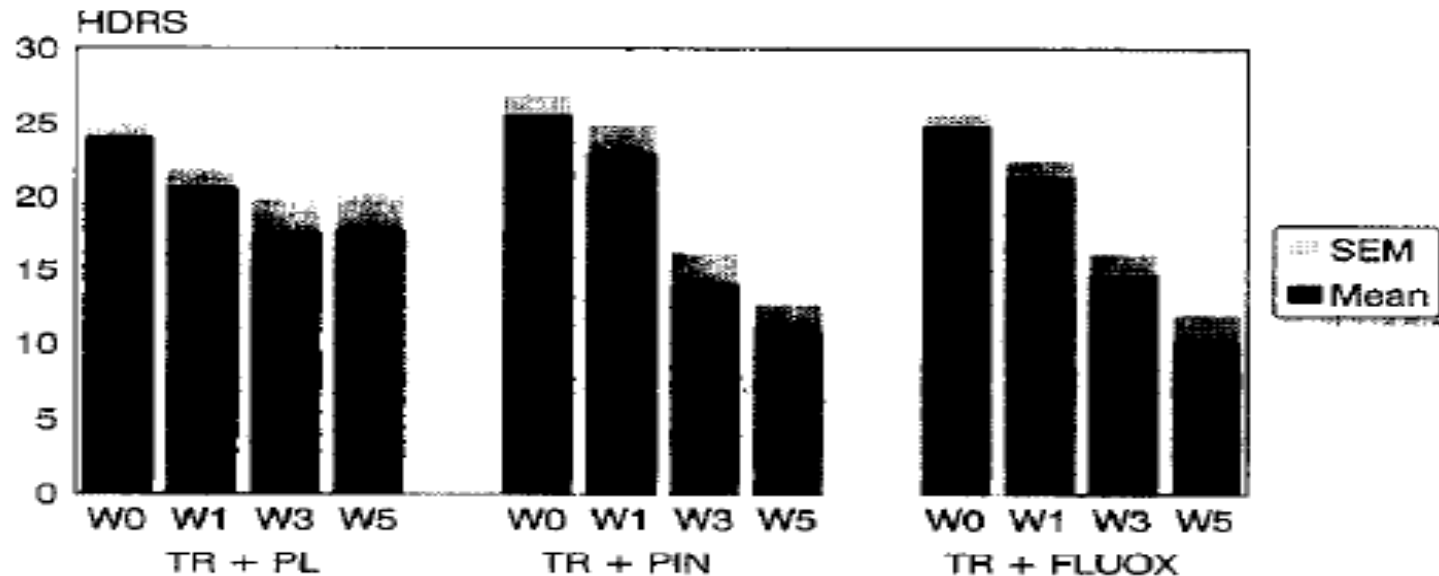


Fig. 1. Mean Hamilton Depression Rating Scale (HDRS) score at baseline (W0), 1 week after treatment with trazodone 100 mg/day (W1), and at weeks 3 (W3) and 5 (W5), after randomization of the patients (at W1) to receive trazodone 100 mg/day + placebo (TR + PL), trazodone 100 mg/day + pindolol 7.5 mg/day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

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