MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Pharmacological Approaches to Treatment-Resistant Depression (TRD)

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Disclosures (lifetime): Maurizio Fava, MD

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Stock/Other Financial Options	Equity Holdings: Compellis; PsyTherapeutics. Royalty/patent, other income: Patents for Sequential Parallel Comparison Design (SPCD) (US_7840419, US_7647235, US_7983936, US_8145504, US_8145505); and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD), licensed by MGH to Biohaven. Patents for pharmacogenomics of Depression Treatment with Folate (US_9546401, US_9540691). Copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), and SAFER; Lippincott, Williams & Wilkins; Wolkers Kluwer; World Scientific Publishing Co. Pte.Ltd.

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?

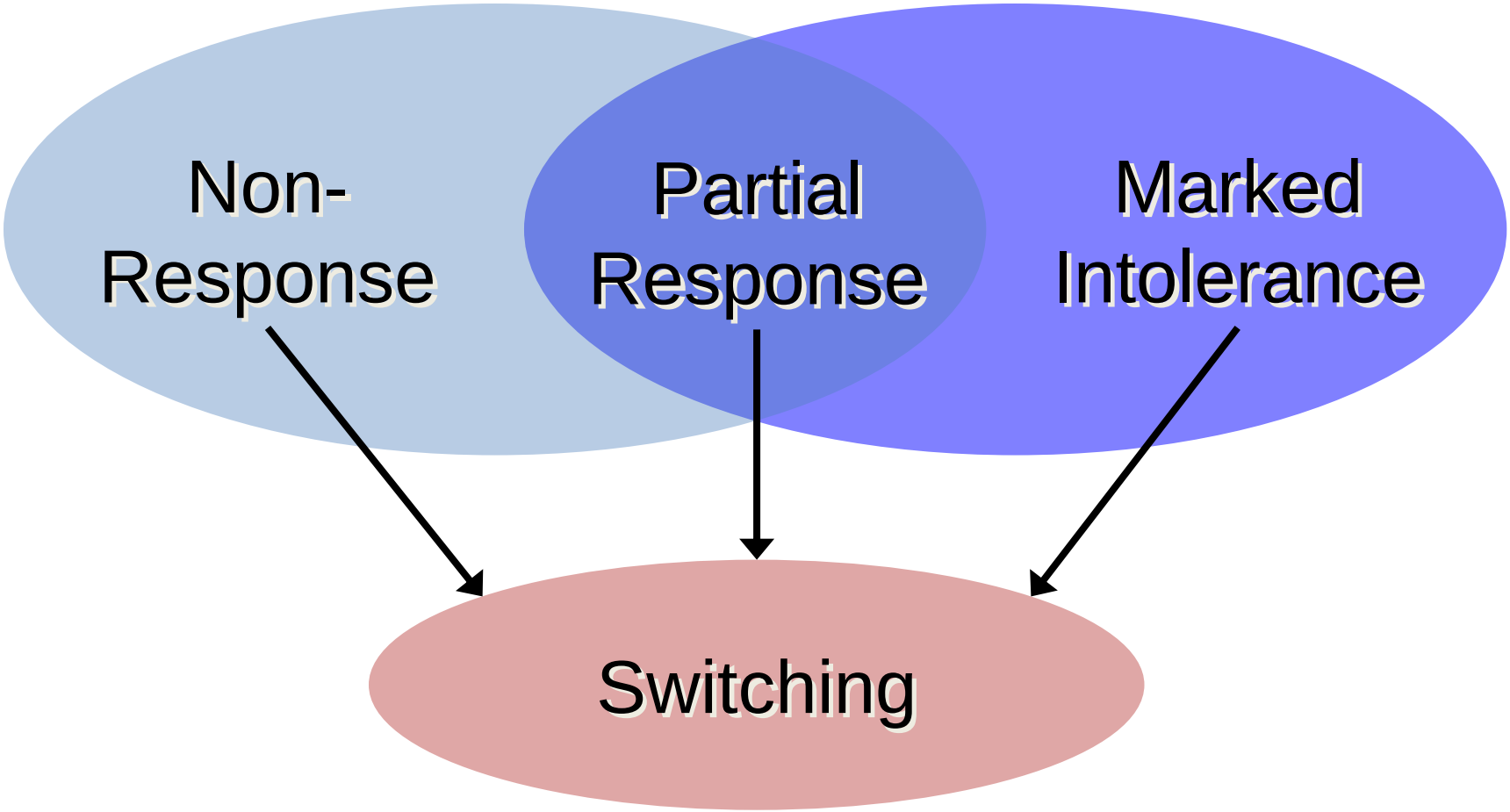
Contributing Factors to TRD

- 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

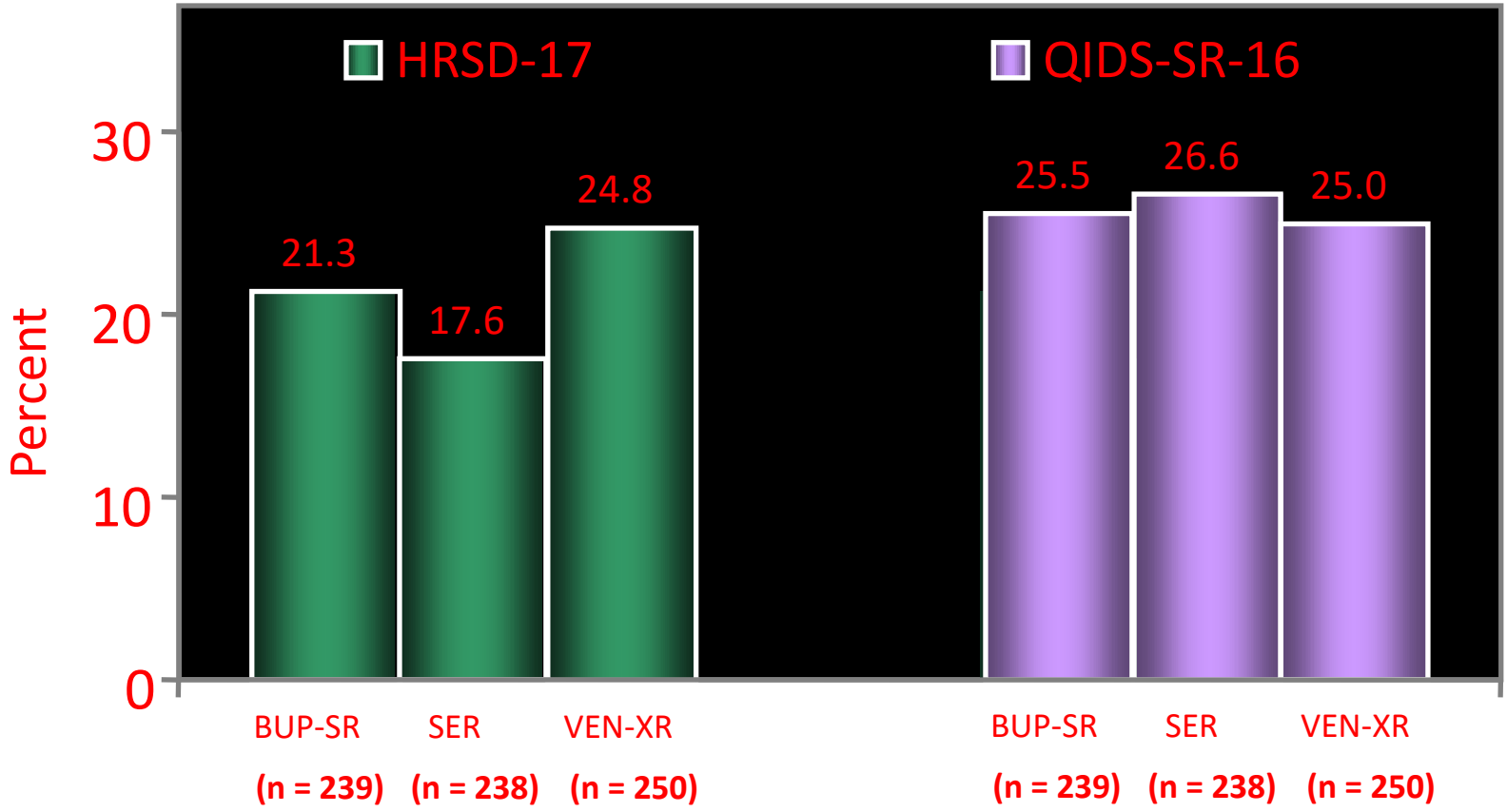
Switching Treatments: For Whom?



Switches: Rationales

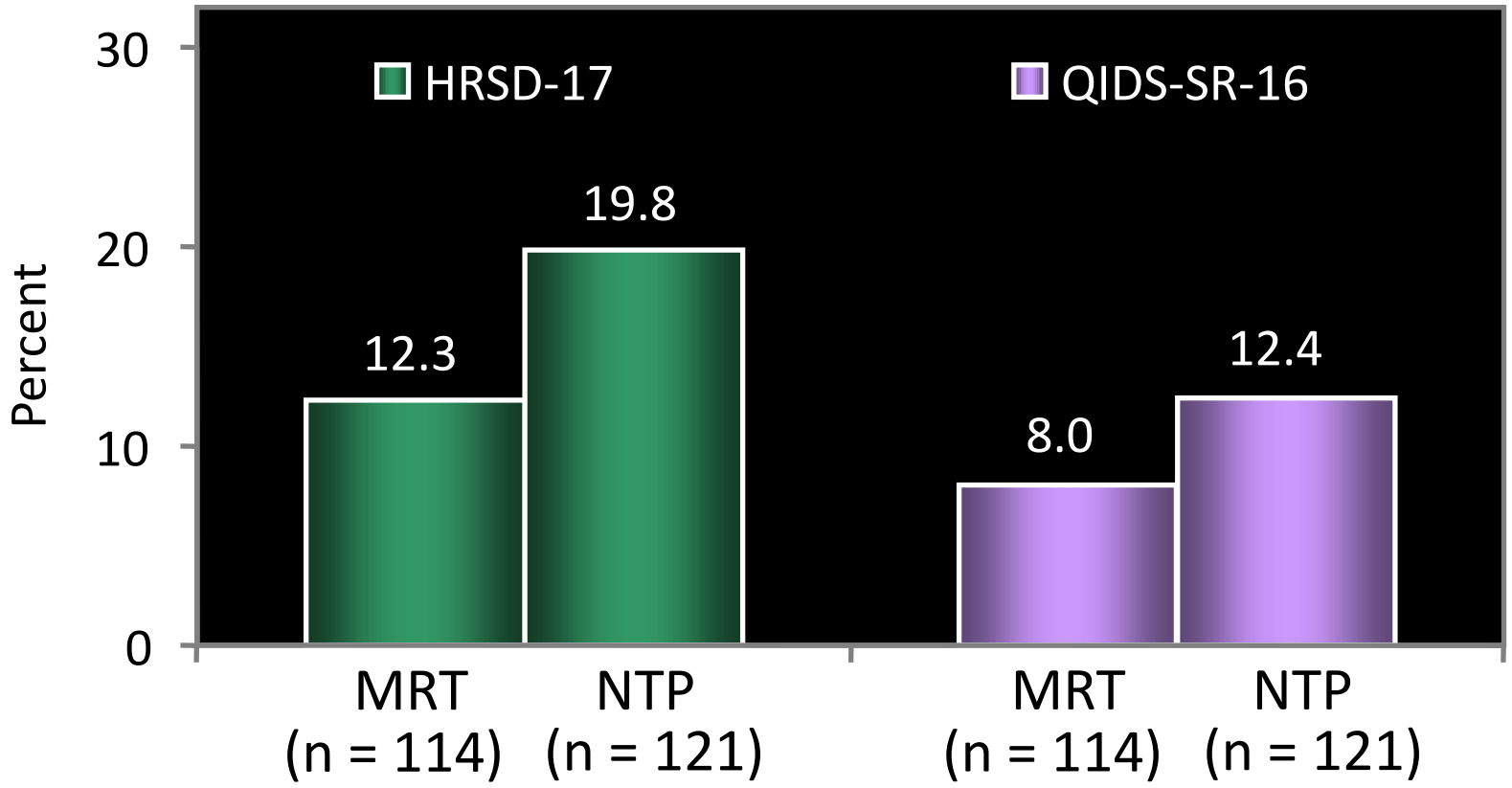
- Switch within Class:
  - There may be some differences across agents within the same class in pharmacological properties in vitro or in vivo (e.g., relatively greater uptake inhibition of other neurotransmitters such as norepinephrine or dopamine)
- Switch to a Different Class:
  - To obtain a different 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



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

Percent of Remission in STAR*D L-3 Switch



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

Switching: Practical Approaches

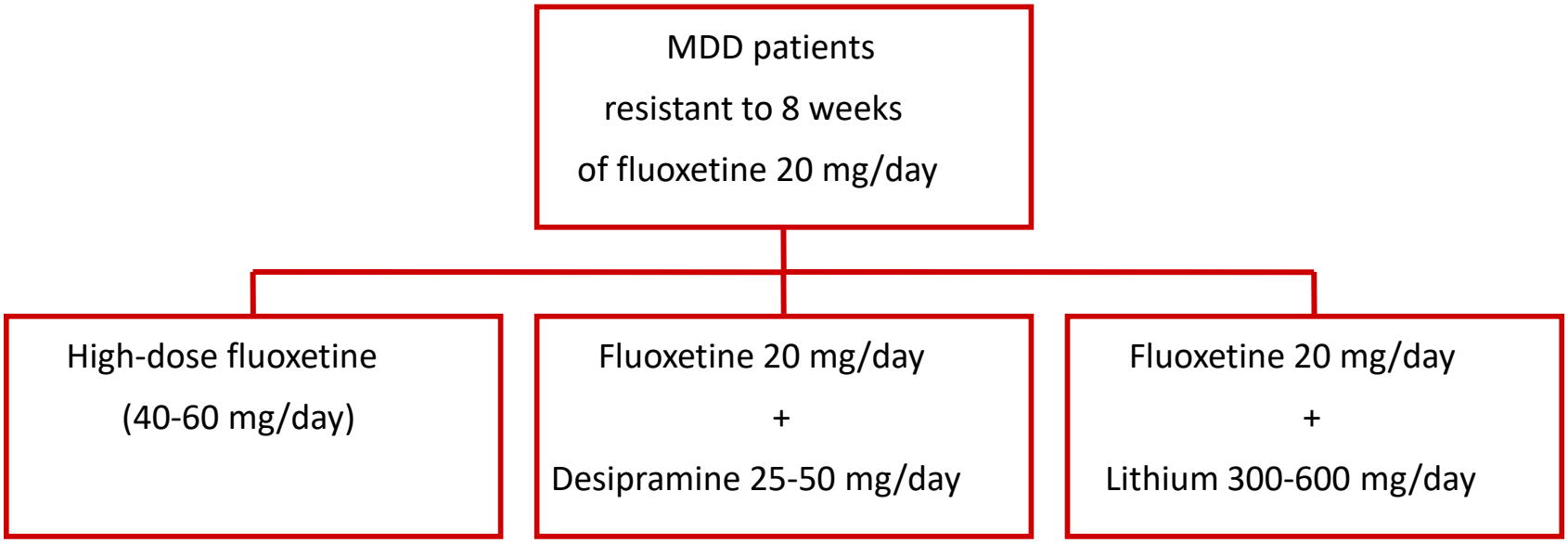
- Gradual tapering the first agent while starting the new one
  - Side effects of the new drug may be intensified by the concurrent presence of the first agent
  - "Start low and go slow" with the new agent
  - Consider possible drug-drug interactions
- Abrupt replacement with within class-switches
-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

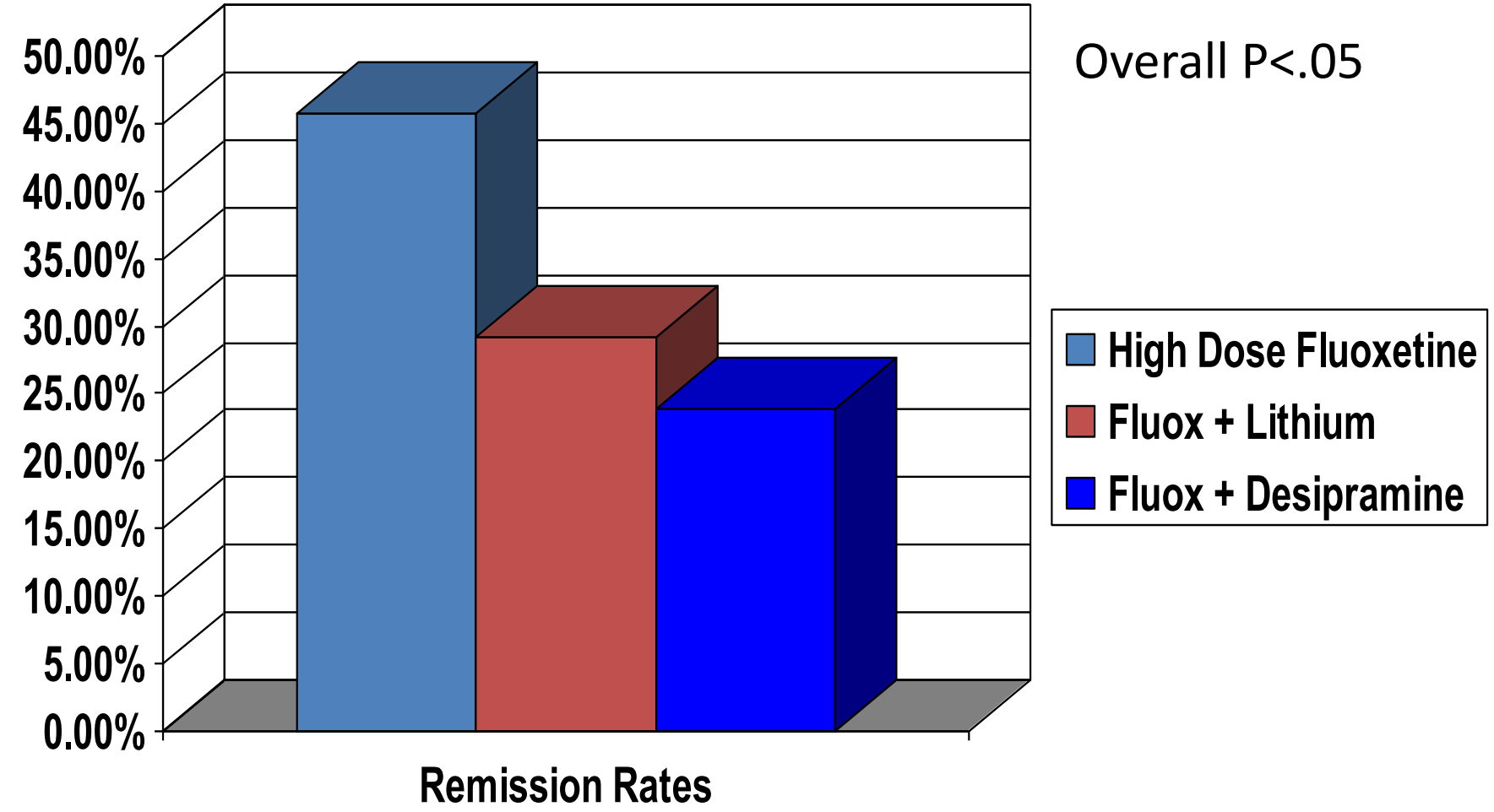
Double-Blind Study of High-Dose Fluoxetine vs. Lithium or Desipramine: Augmentation of Fluoxetine in Partial & Non-Responders to Fluoxetine

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

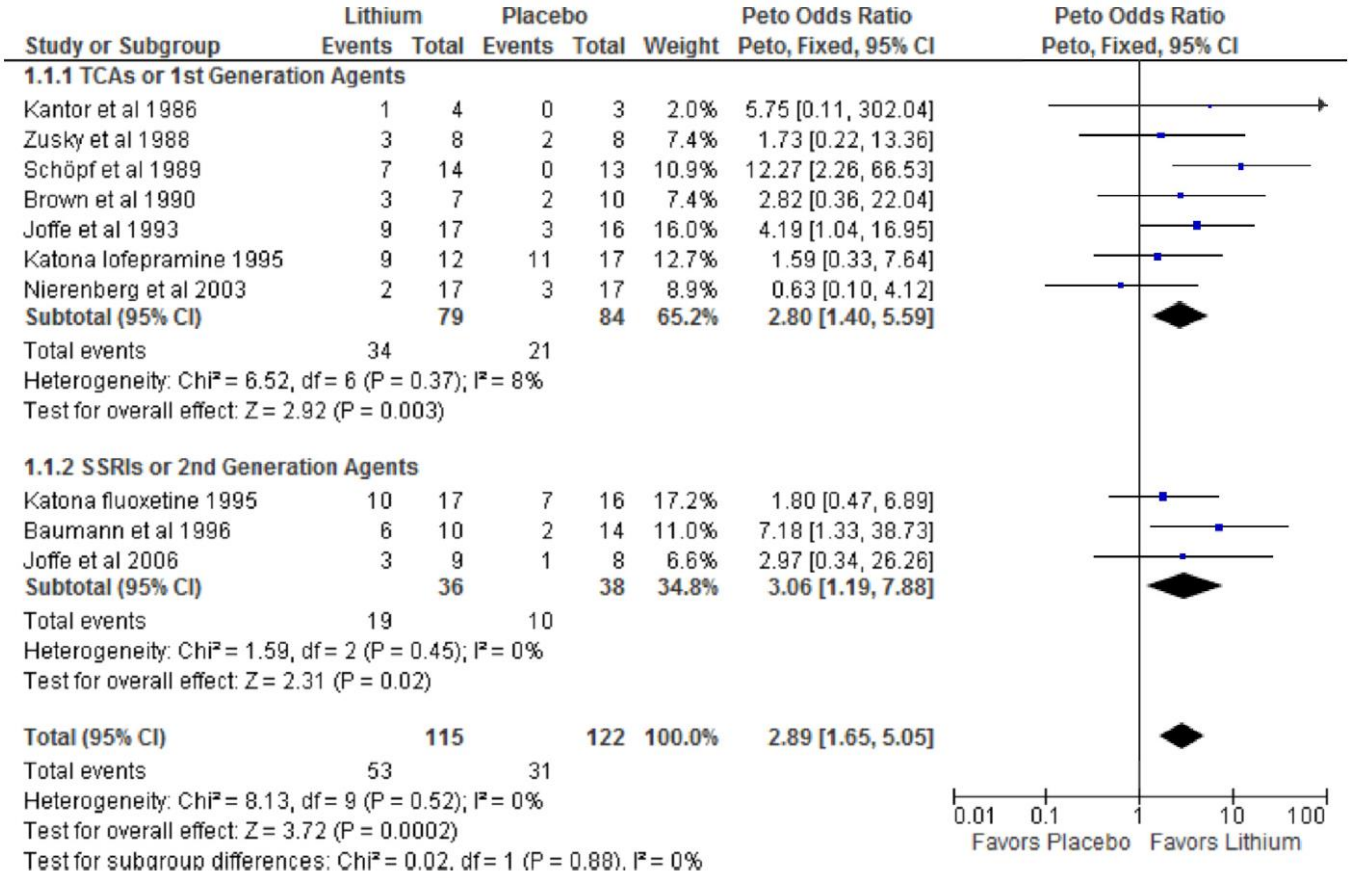
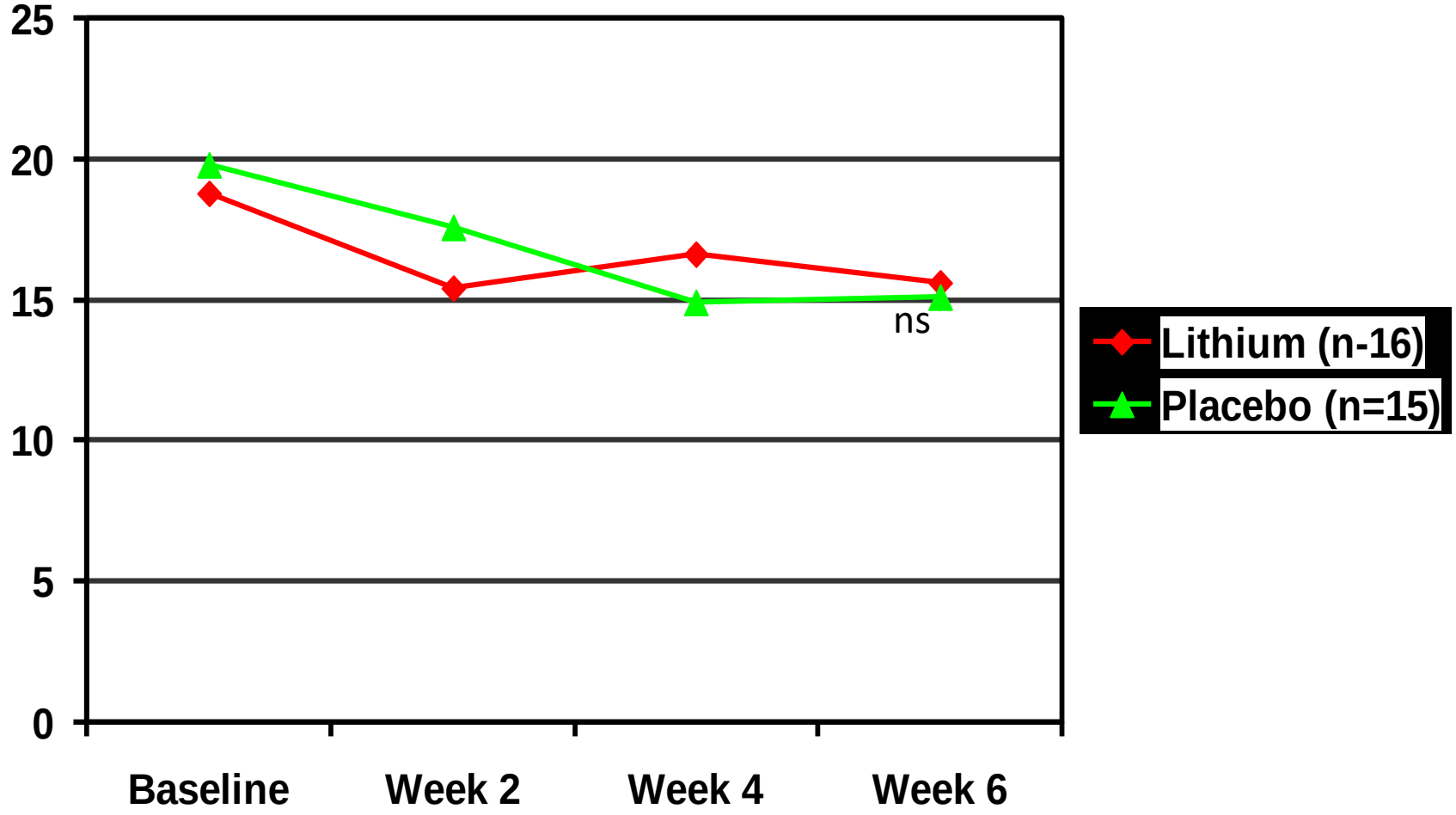


Fig. 2. Meta-analysis of 9 randomized placebo-controlled lithium augmentation trials in depression with 10 contrasts grouped by the type of antidepressant augmented.

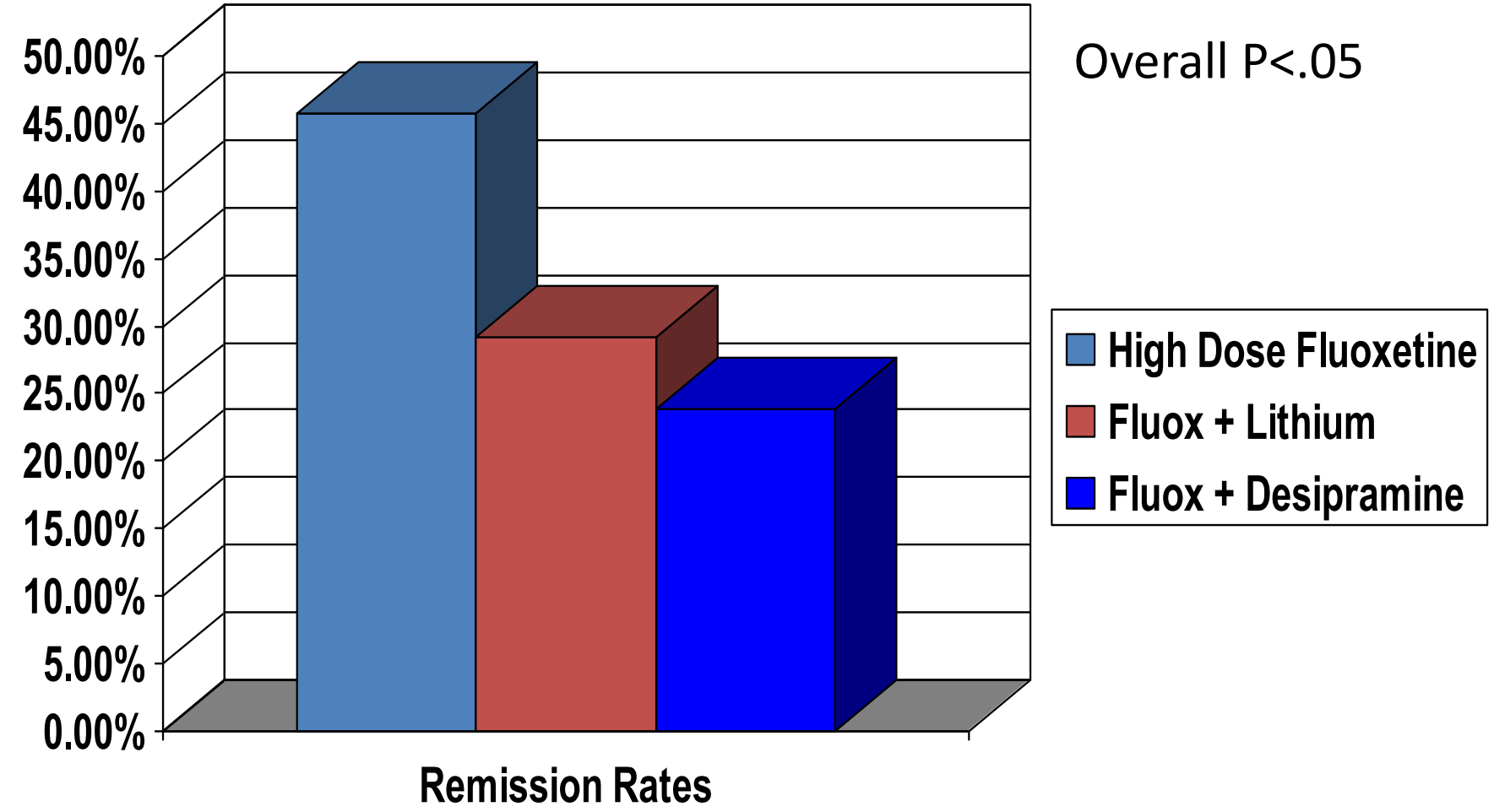
Nelson et al, Journal of Affective Disorders 168(2014)269–275

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



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 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

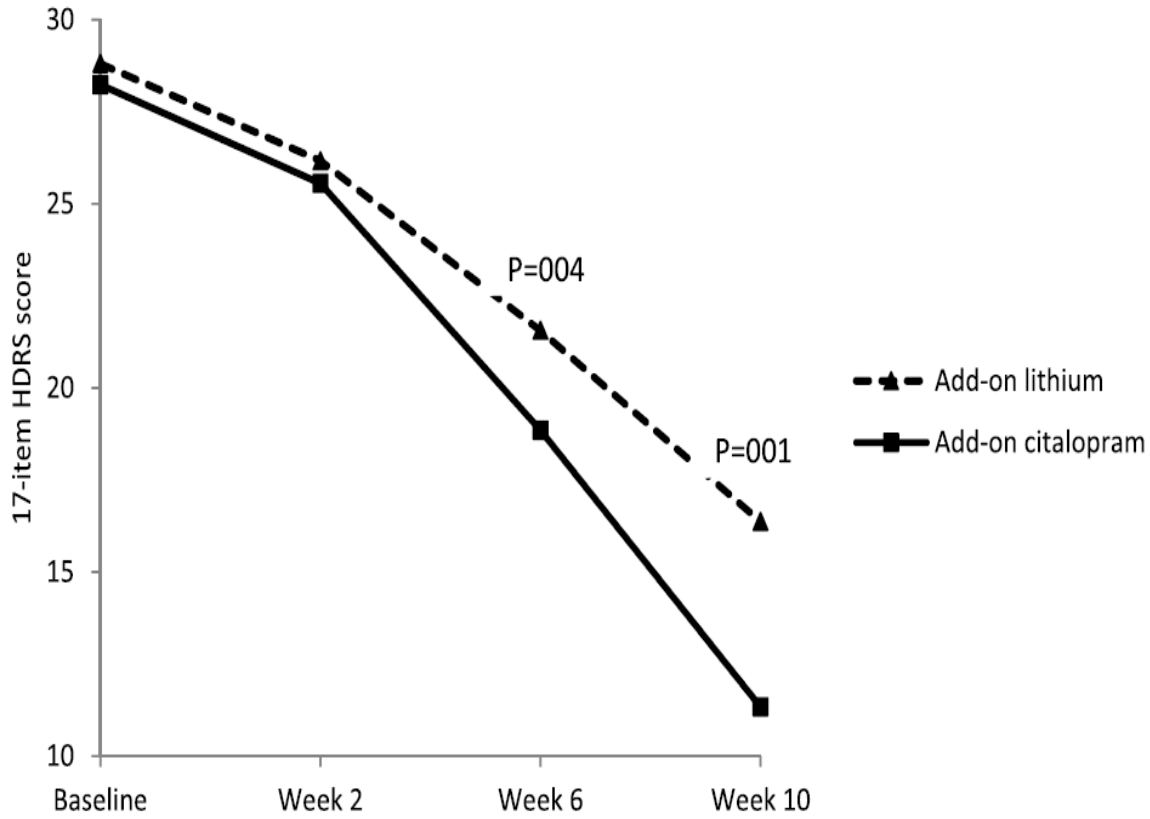


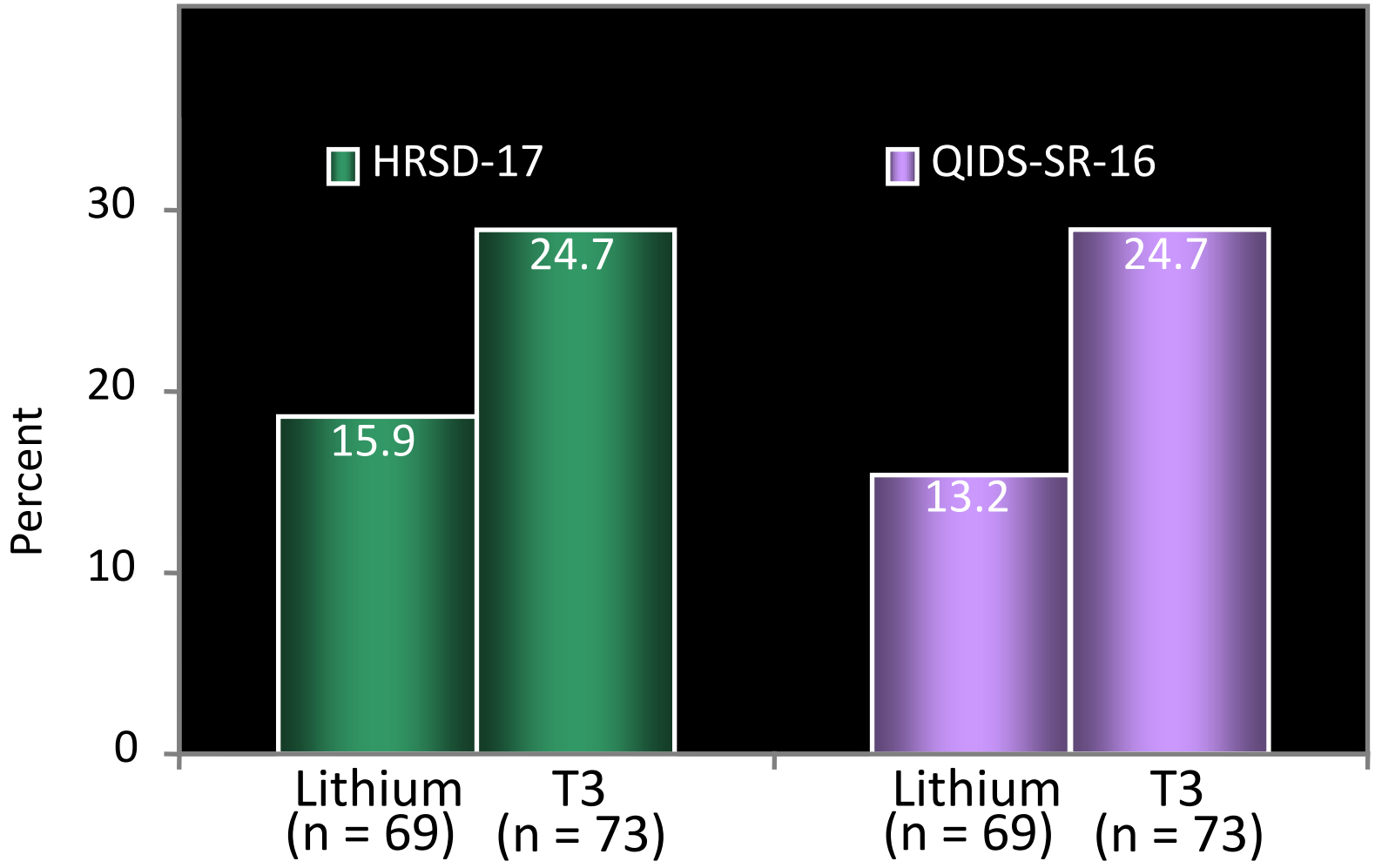
FIGURE 1. Repeated measures to compare efficacy of add-on lithium and add-on citalopram. Values represent means. *P* values show the result of the independent *t* test comparing HDRS scores between the 2 groups from baseline to each time point. NS indicates nonsignificant.

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

Thyroid Augmentation

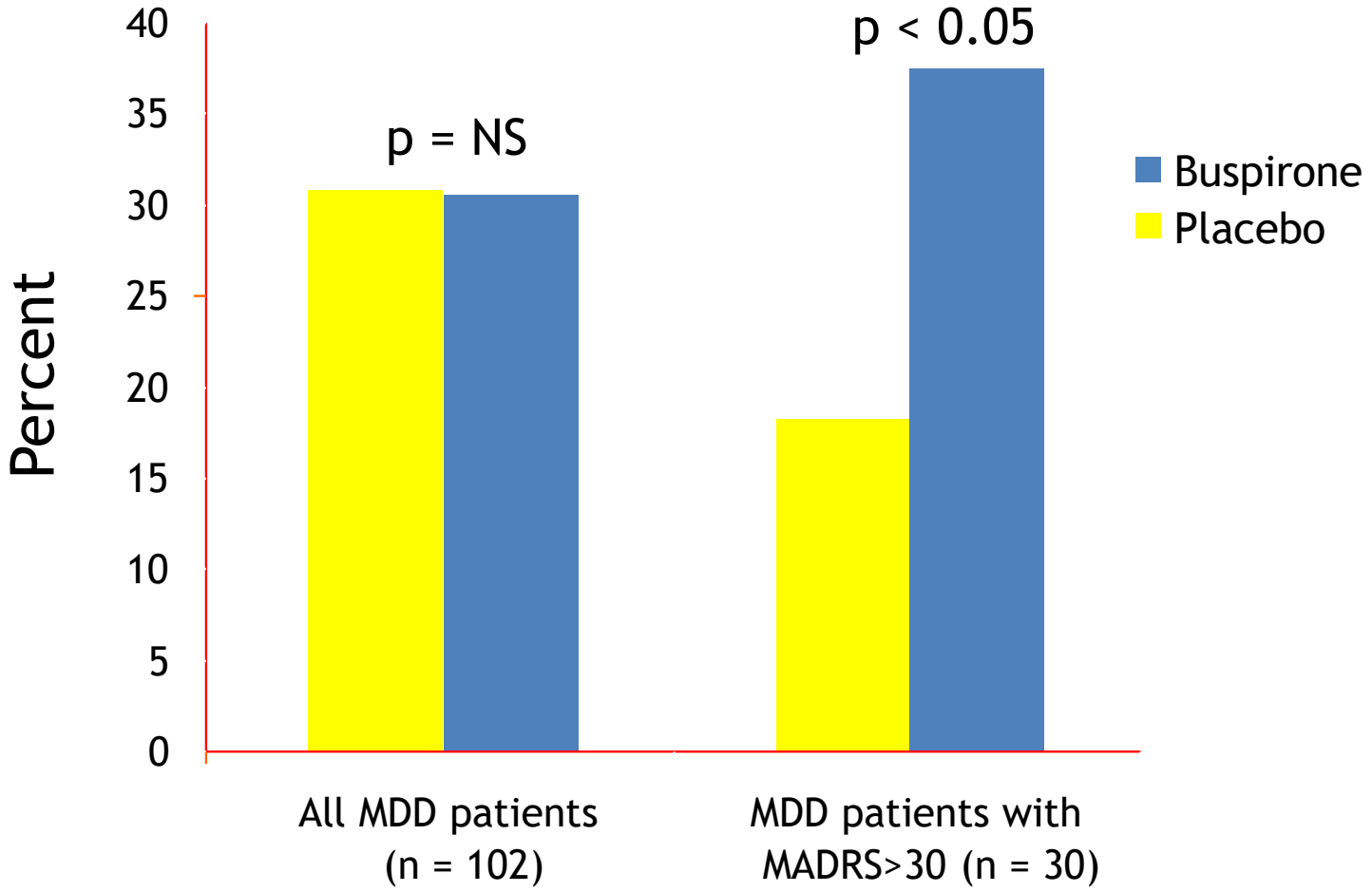
- Thyroid hormone augmentation (25-50 mcg/day) (Aronson R et al. Arch Gen Psychiatry. 1996 Sep;53(9):842-8.)
- L-triiodothyronine (T3) has been used in preference and has been thought to be superior to thyroxine (T4) (Joffe RT, Singer W. Psychiatry Res. 1990 Jun;32(3):241-51.)
- Disadvantages:
  - All 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



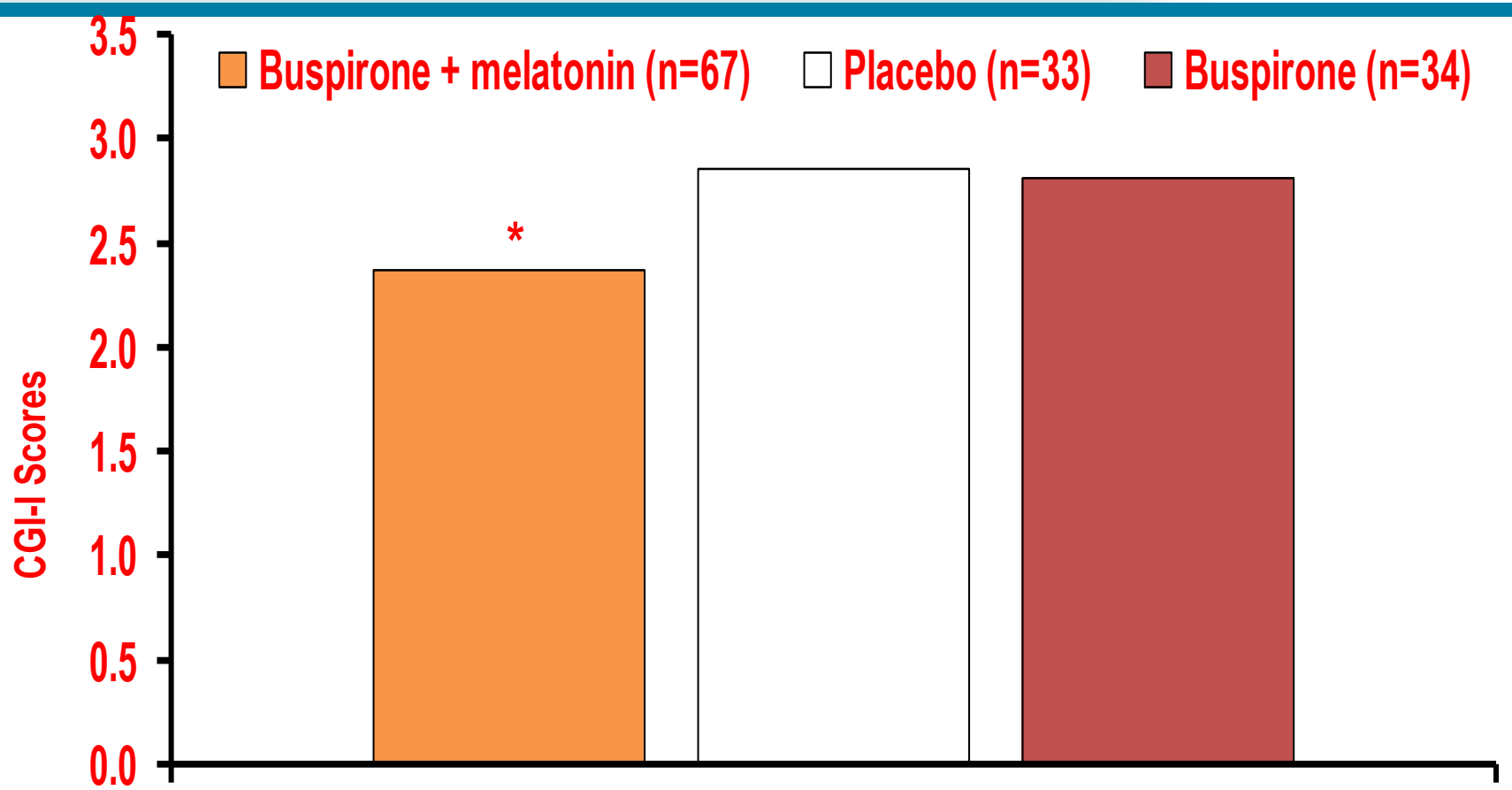
Nierenberg et al. Am J Psychiatry. 2006;163:1519-1530.

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

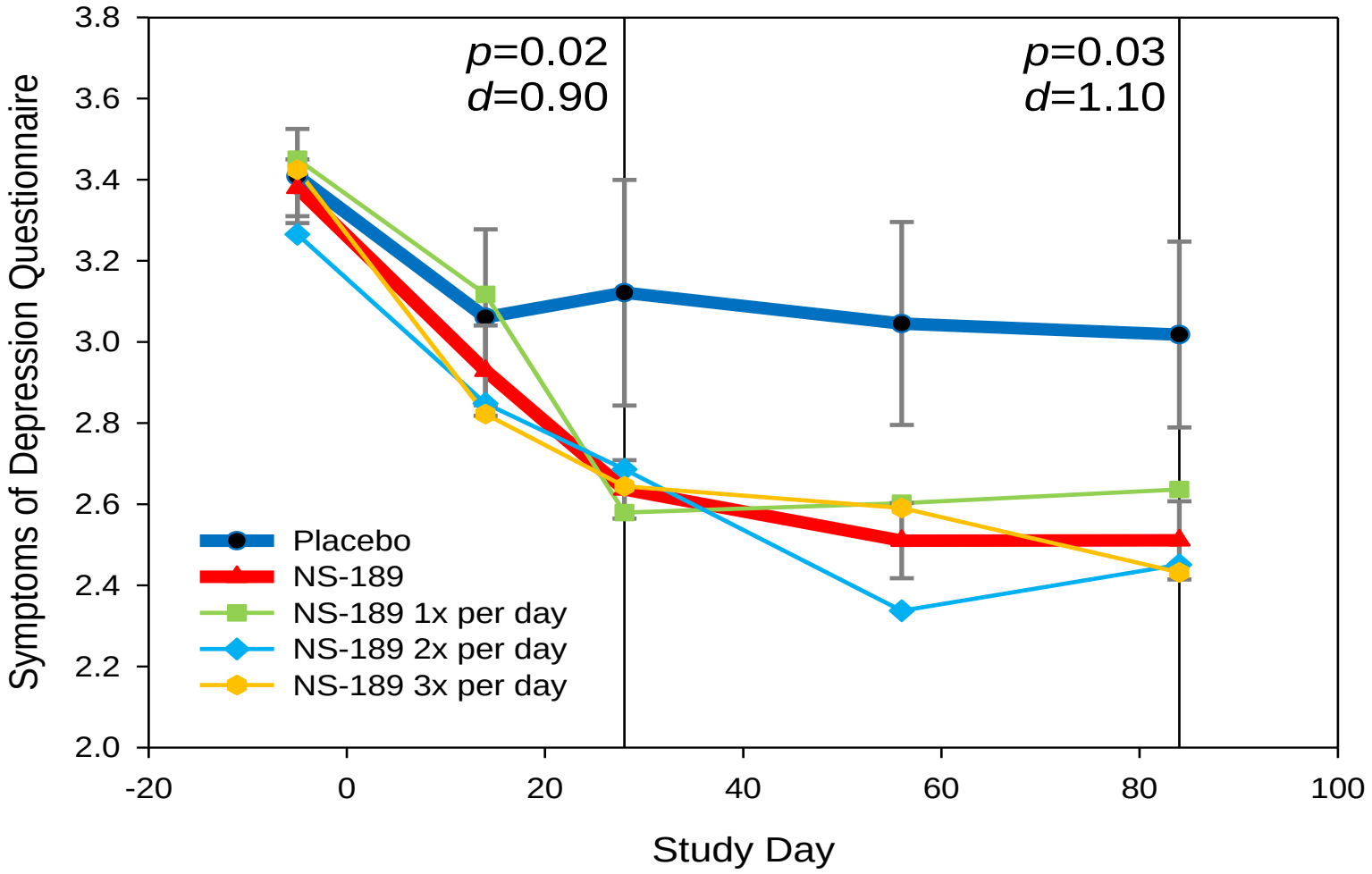


*p<.05 combination vs placebo and buspirone alone.

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*

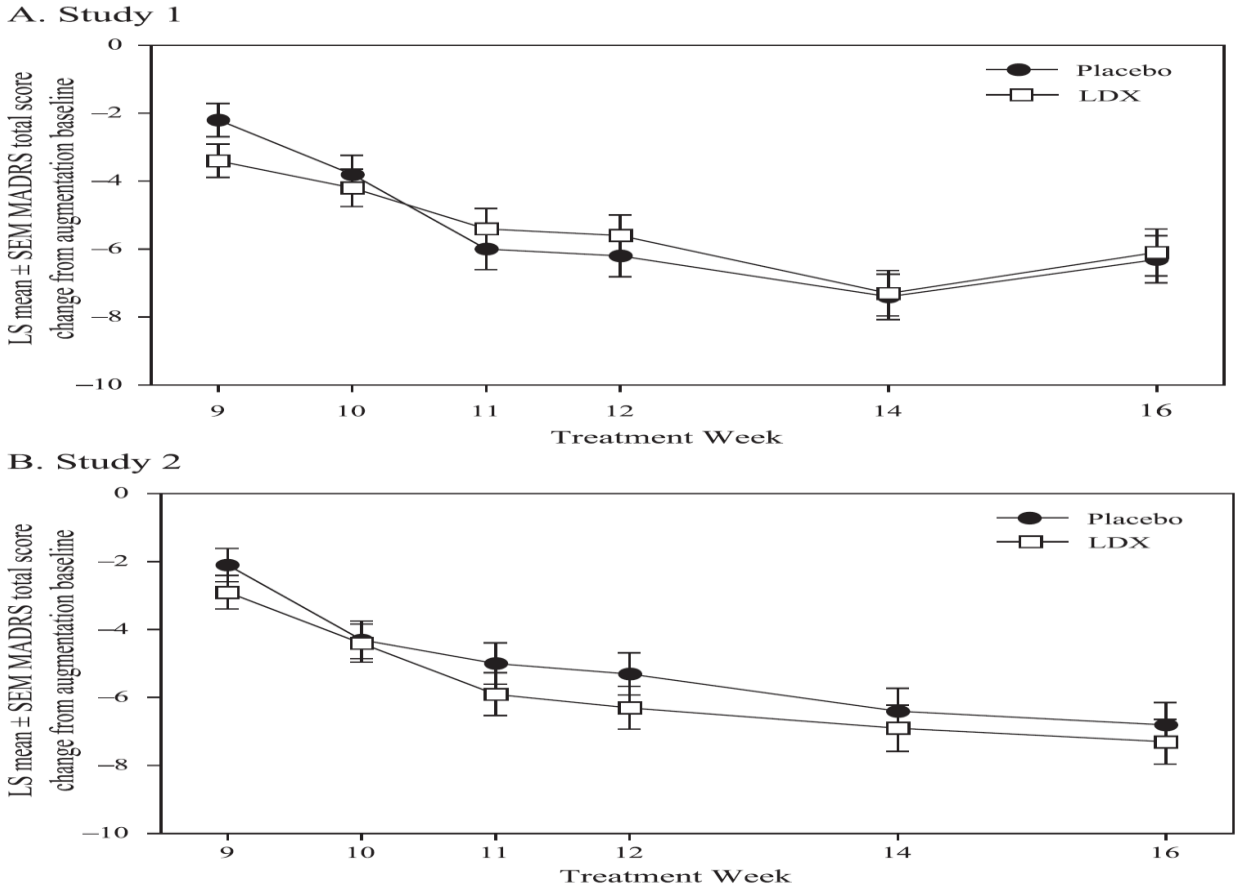


Fig. 3. Change in MADRS total score during double-blind treatment (full analysis set) for Study 1 (A) and Study 2 (B). LDX = lisdexamfetamine; dimesylate MADRS = Montgomery-Åsberg Depression Rating Scale.

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)

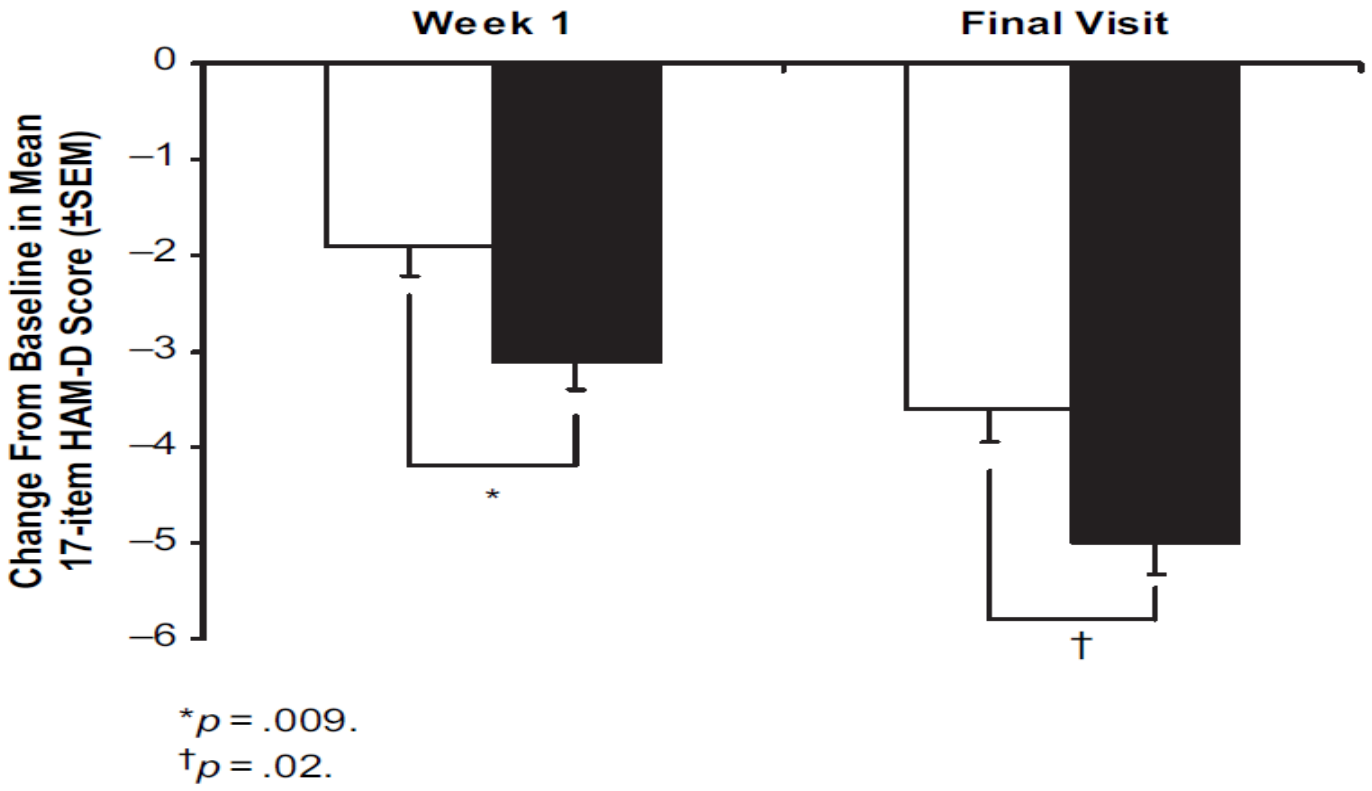
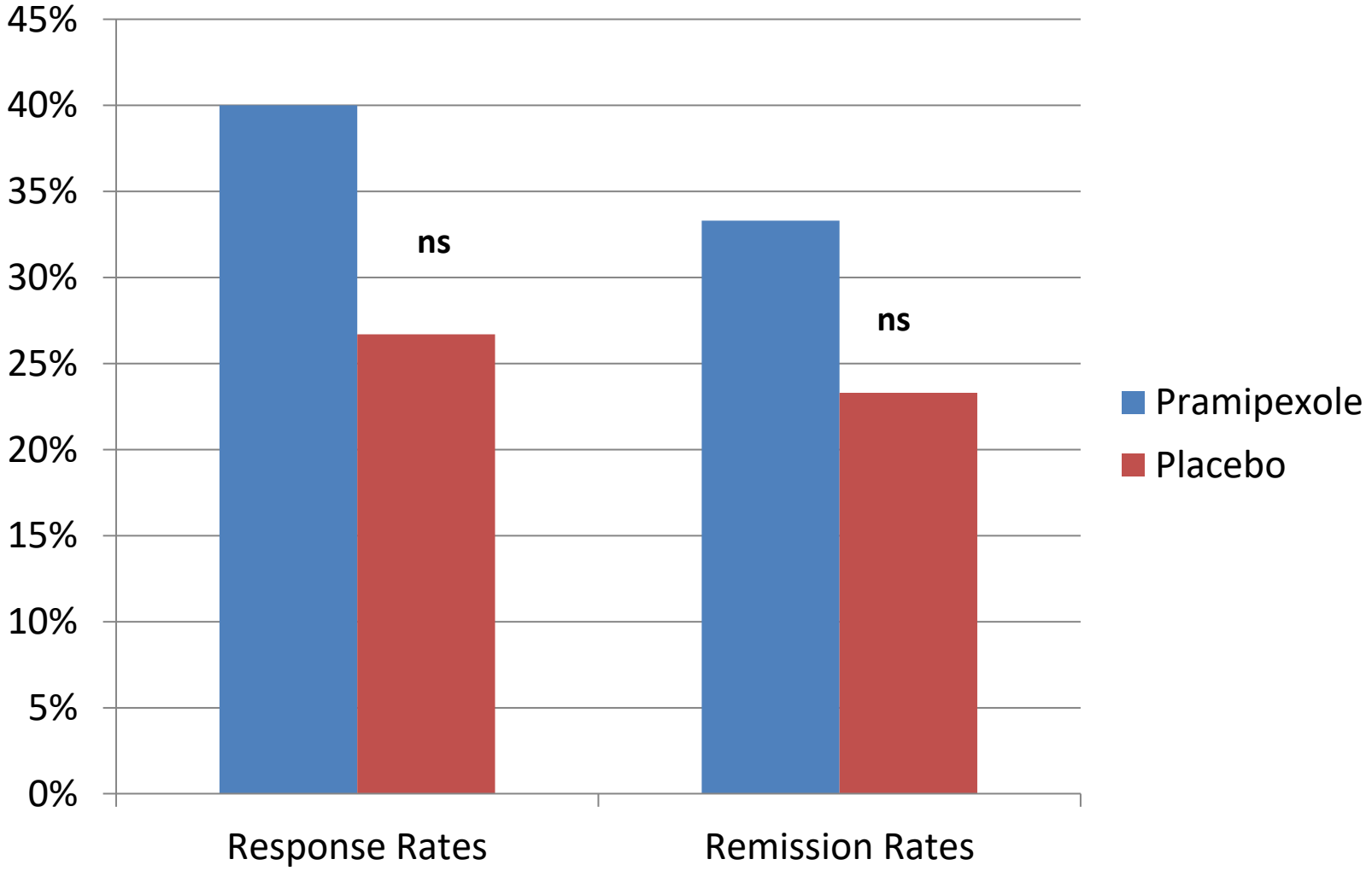


Figure 4 Mean (± SEM) Changes from Baseline in 17-item Hamilton Depression Scale (17-item HAM-D) Scores between Placebo and Modafinil (All Patients).

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)



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

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

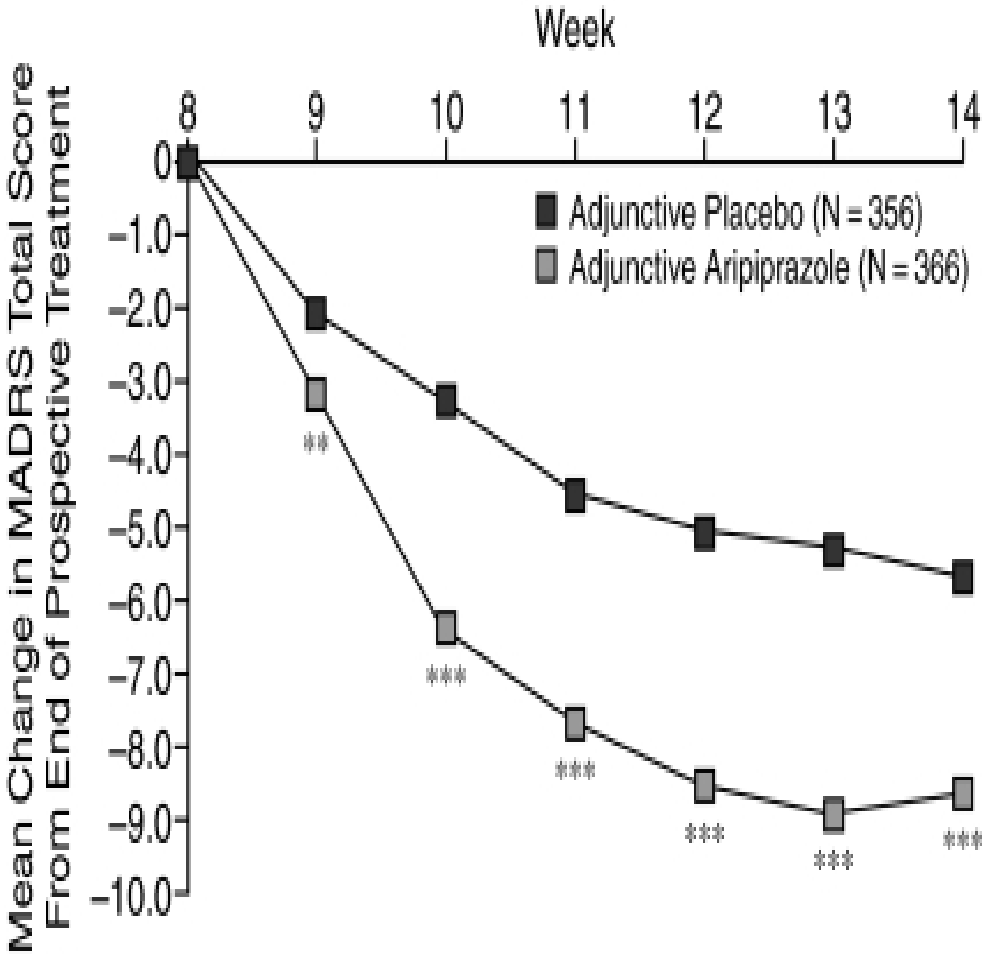
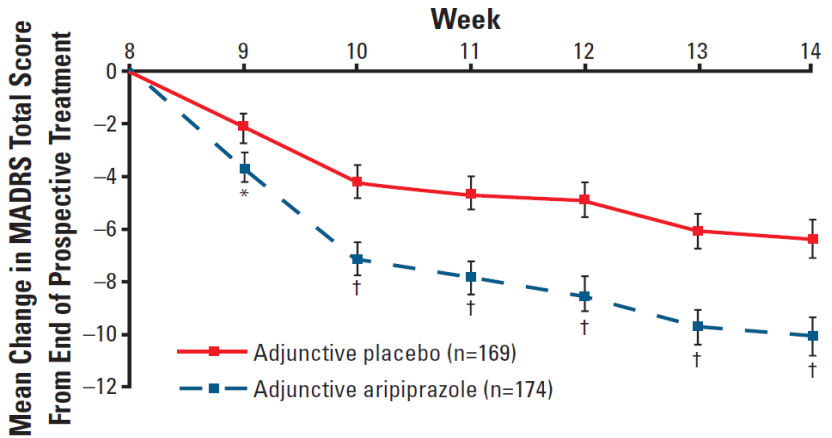


FIGURE 2.
Change in mean (±SE) MADRS Total score during the randomized, double-blind treatment phase (LOCF)



* *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)

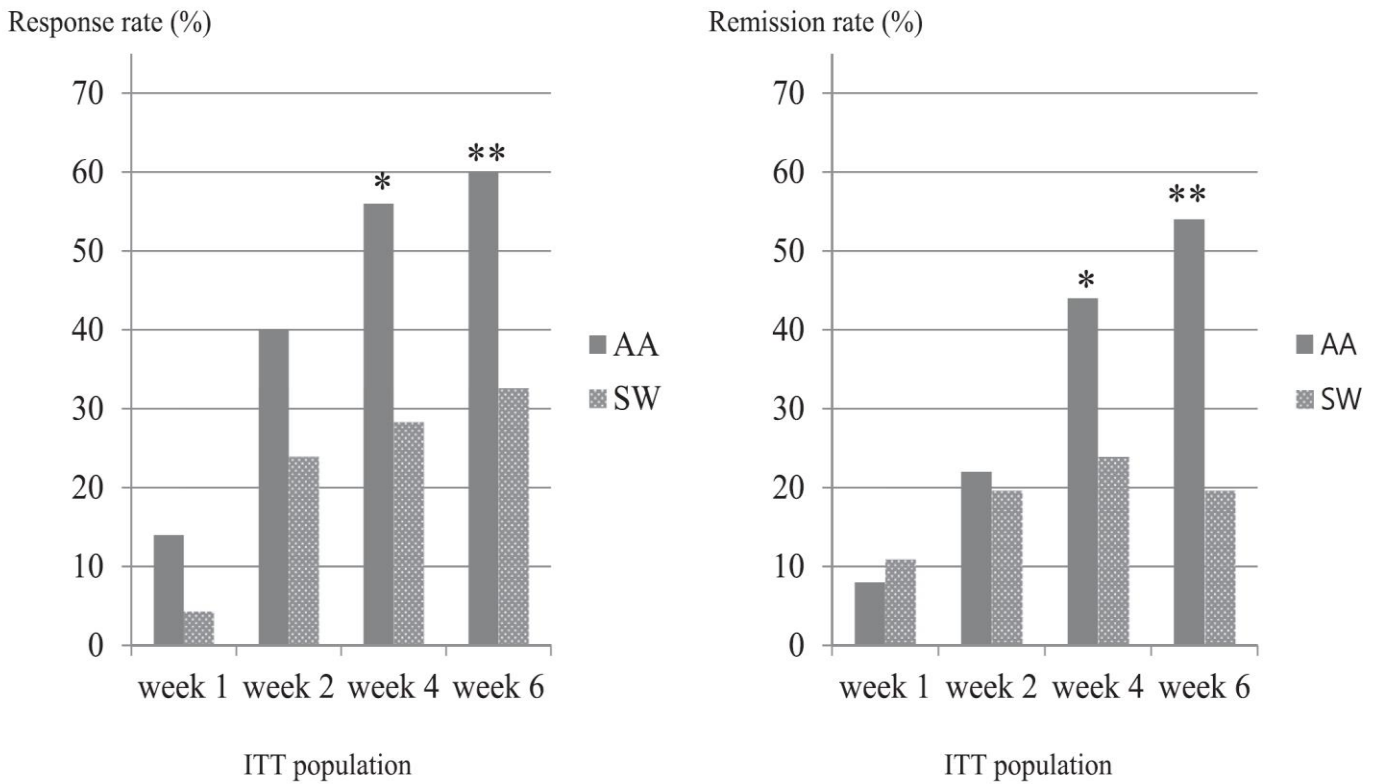
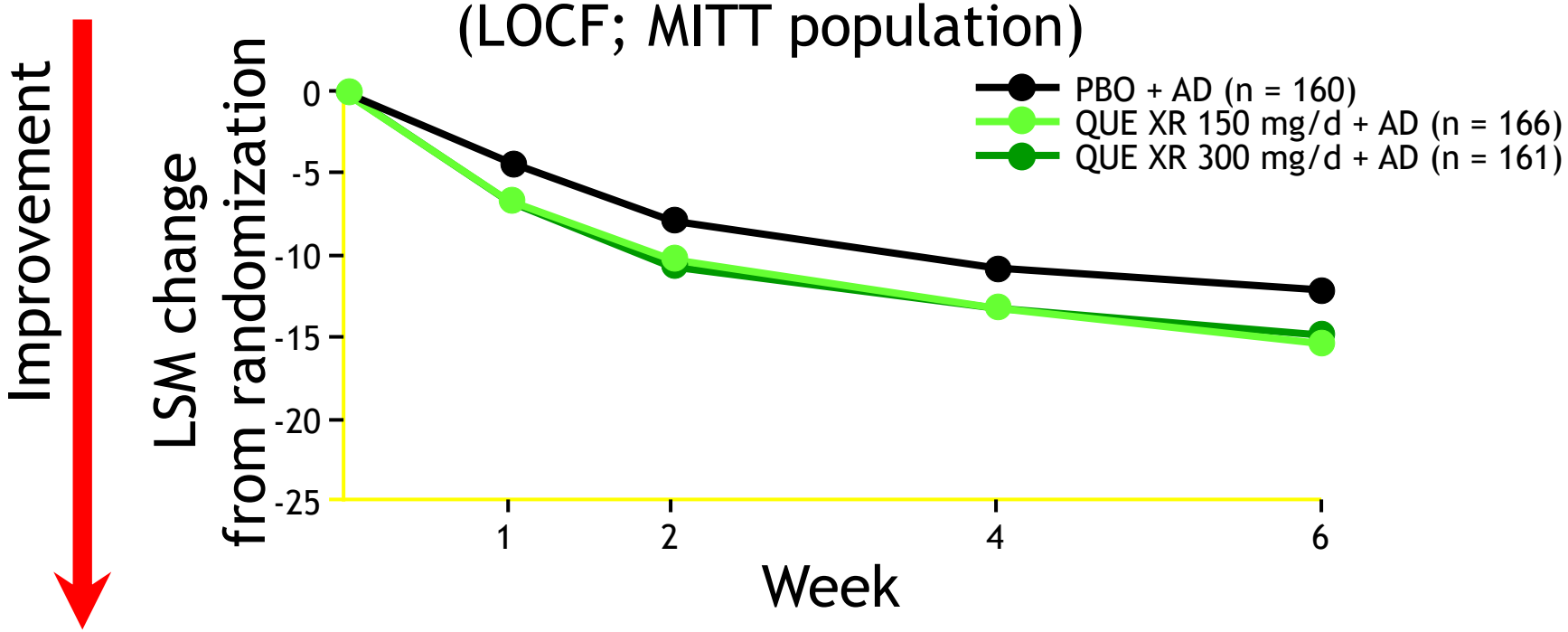


Fig. 3. The responder and remission rates between the two treatment groups during the study Annotation: ITT, intent-to-treat; AA, aripiprazole augmentatic switching; *P = 0.0080 and **P = 0.0086 for response analysis; *P = 0.0408 and **P = 0.0005 for remission analysis.

Han et al, Journal of Psychiatric Research 66-67 (2015) 84-94

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

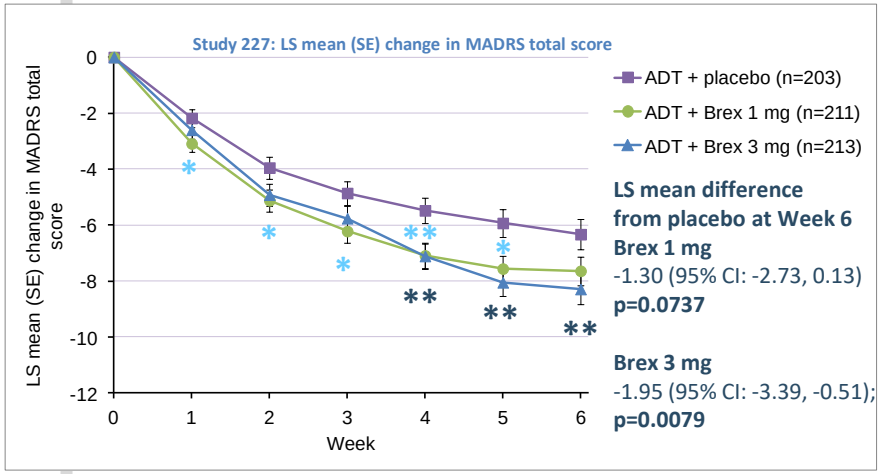
Change in MADRS total score from randomization over time (LOCF; MITT population)

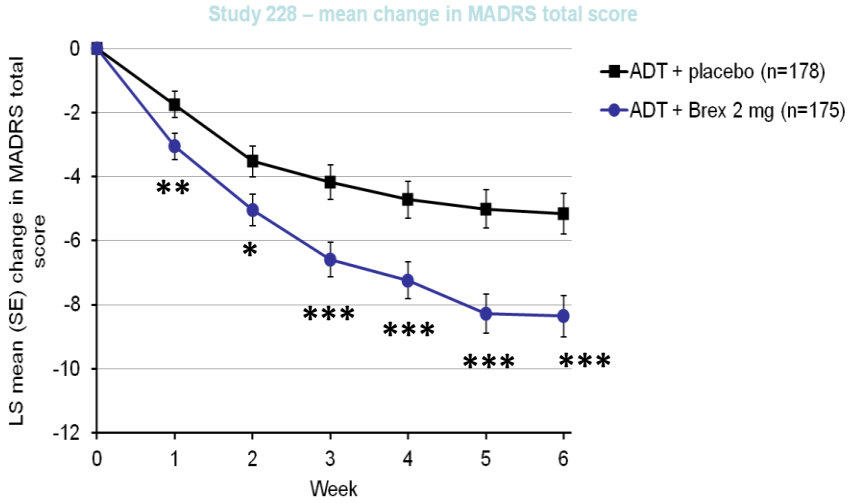


p value active treatment vs. placebo + antidepressant:				
QUE XR 150 mg/d + AD	< 0.001	< 0.01	< 0.05	< 0.01
QUE XR 300 mg/d + AD	< 0.001	< 0.001	< 0.05	< 0.01

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

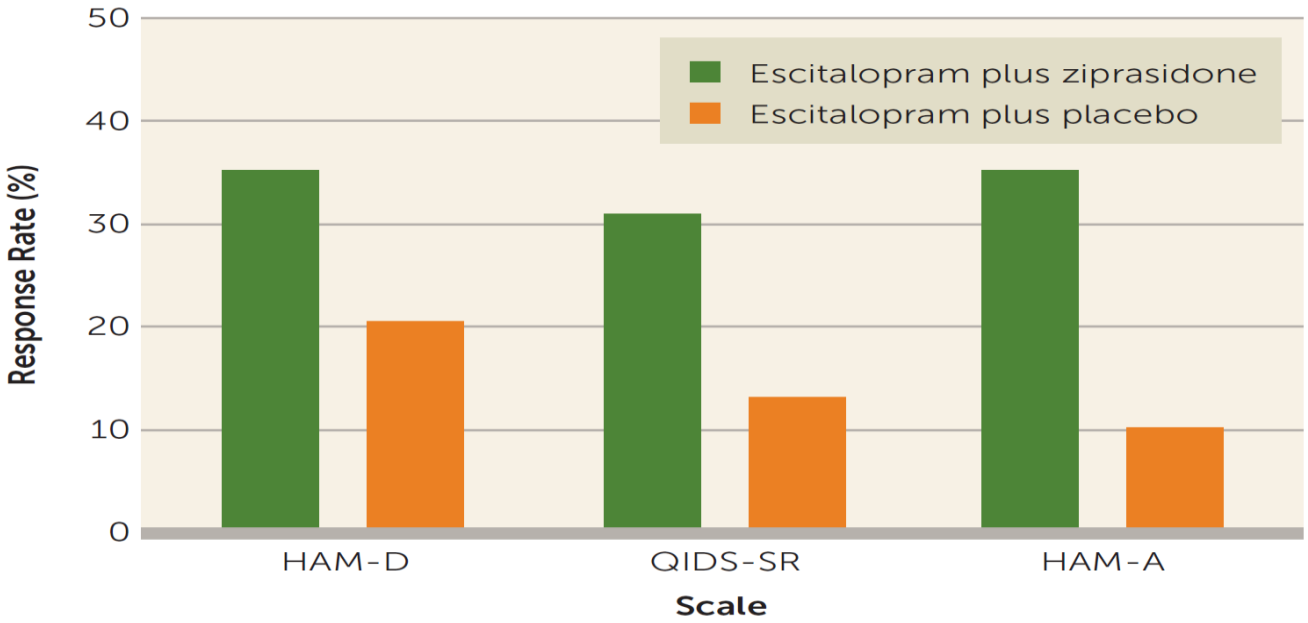
MMRM analysis; MADRS baseline: ADT + placebo 27.3, ADT + Brex 26.9

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]

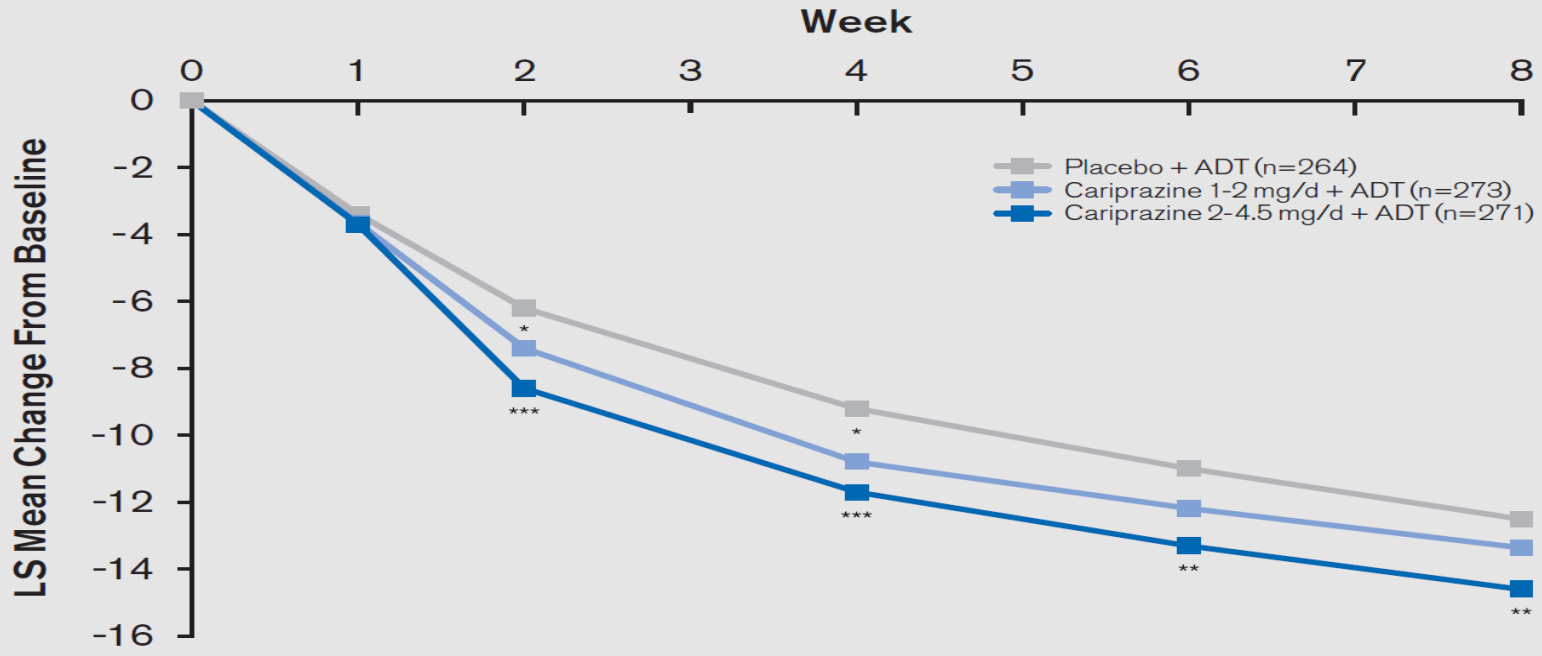


[a] HAM-D=Hamilton Depression Rating Scale (17-item); QIDS-SR=Quick Inventory of Depressive Symptoms—Self-Rated (16-item); HAM-A=Hamilton Anxiety Rating Scale. According to the mixed-effects model with repeated-measures analyses, the p values were 0.04, 0.03, and <0.001 for the HAM-D, the QIDS-SR, and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

Papakostas et al, Am J Psychiatry 2015; 172:1251–1258

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)



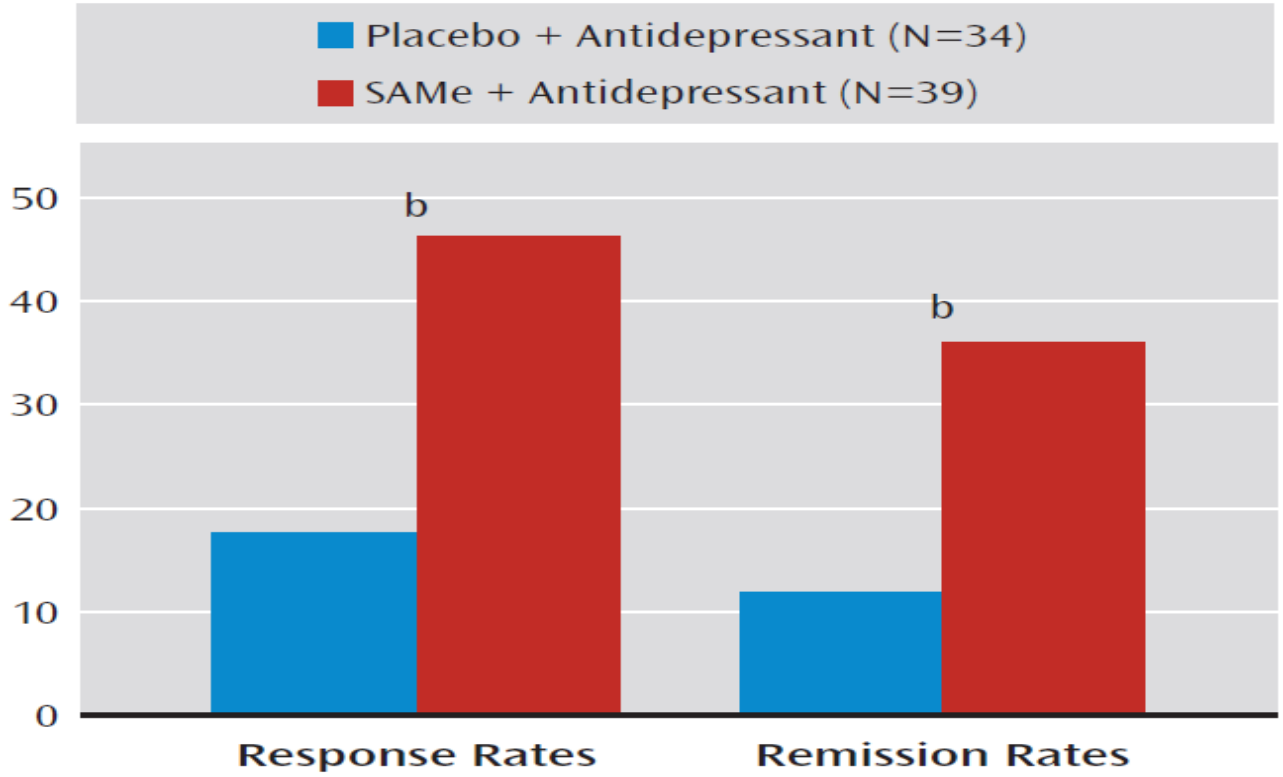
*P<.05; **P<.01; ***P<.001 vs placebo; P values represent pairwise comparisons and were not adjusted for multiple comparisons. ADT indicates antidepressant treatment; ITT, intent-to-treat; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

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]

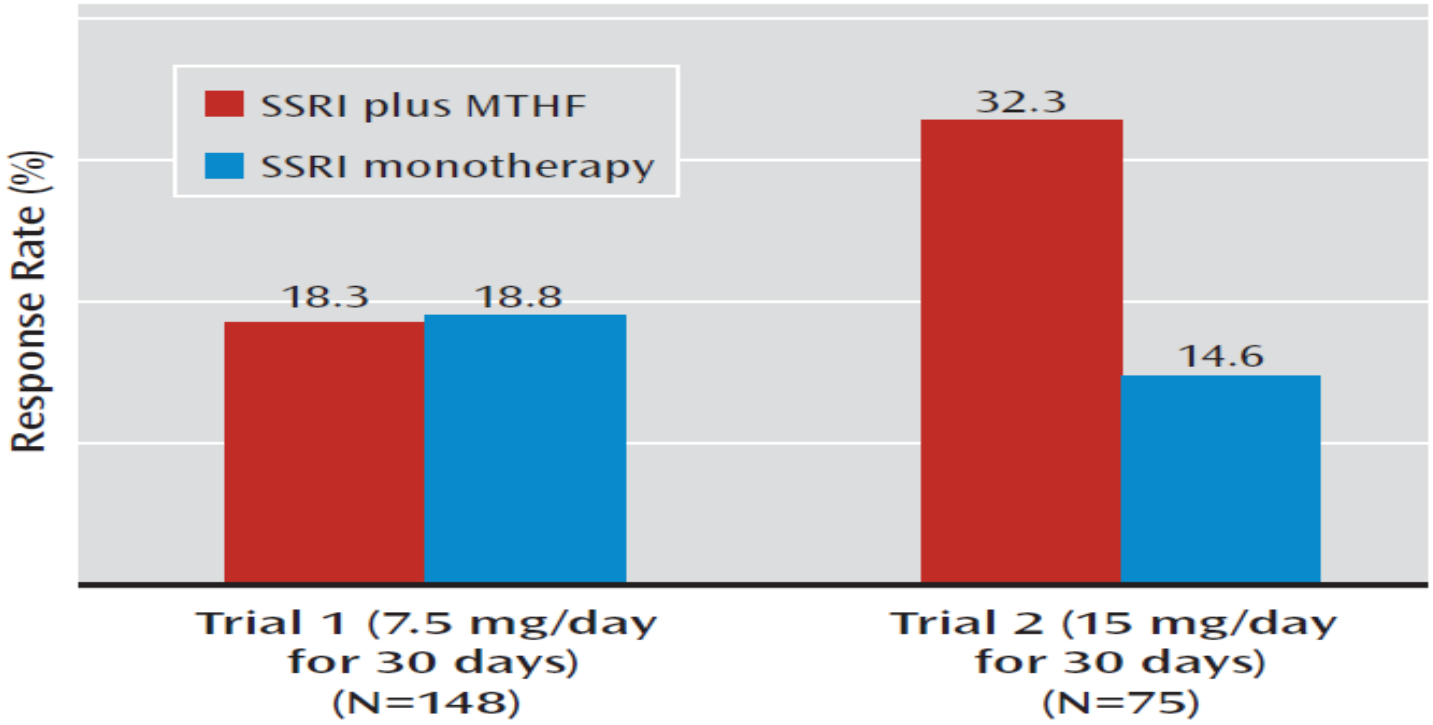


[a] Data depict last observation carried forward (LOCF) for all patients randomly assigned.
[b] Significant difference between groups ($p<0.05$, Fisher's exact test).

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 ≥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)

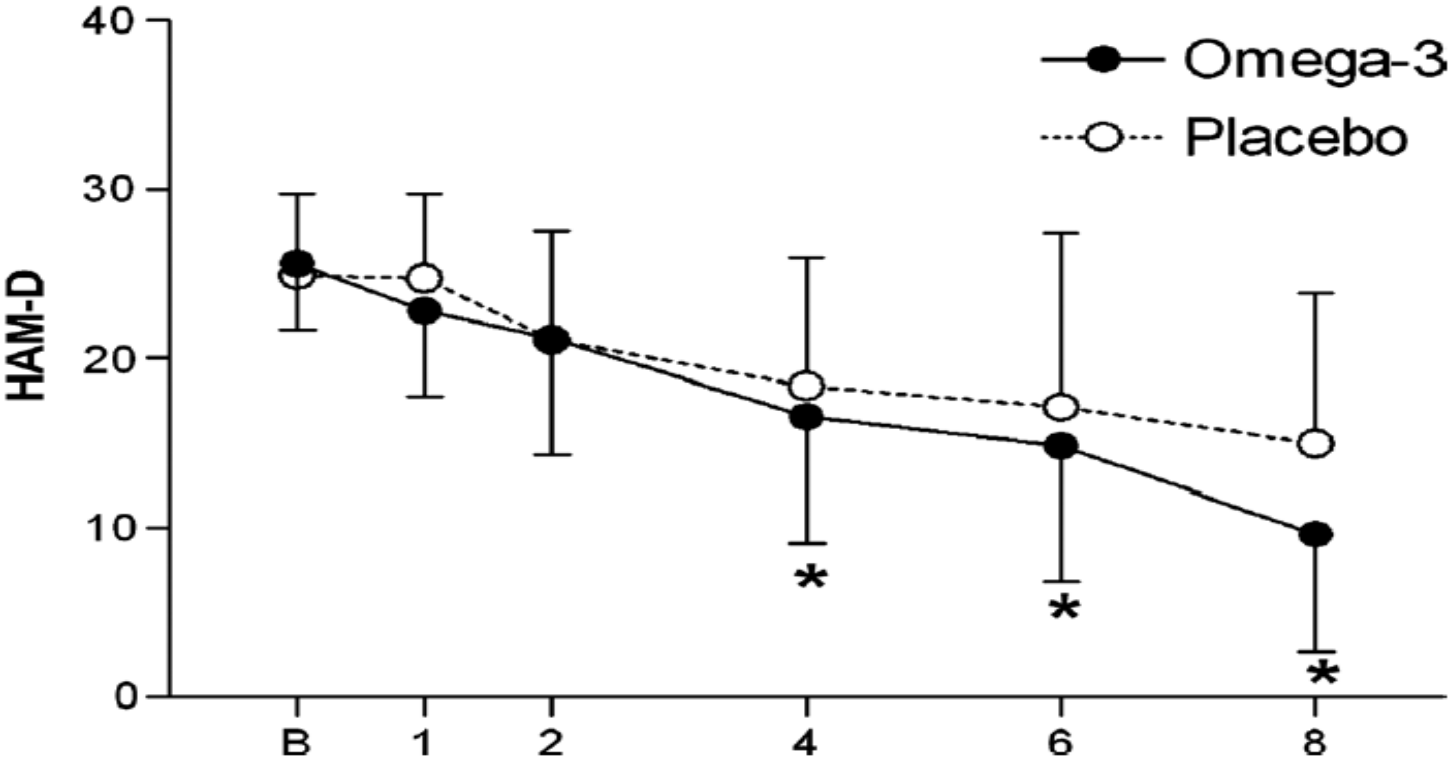
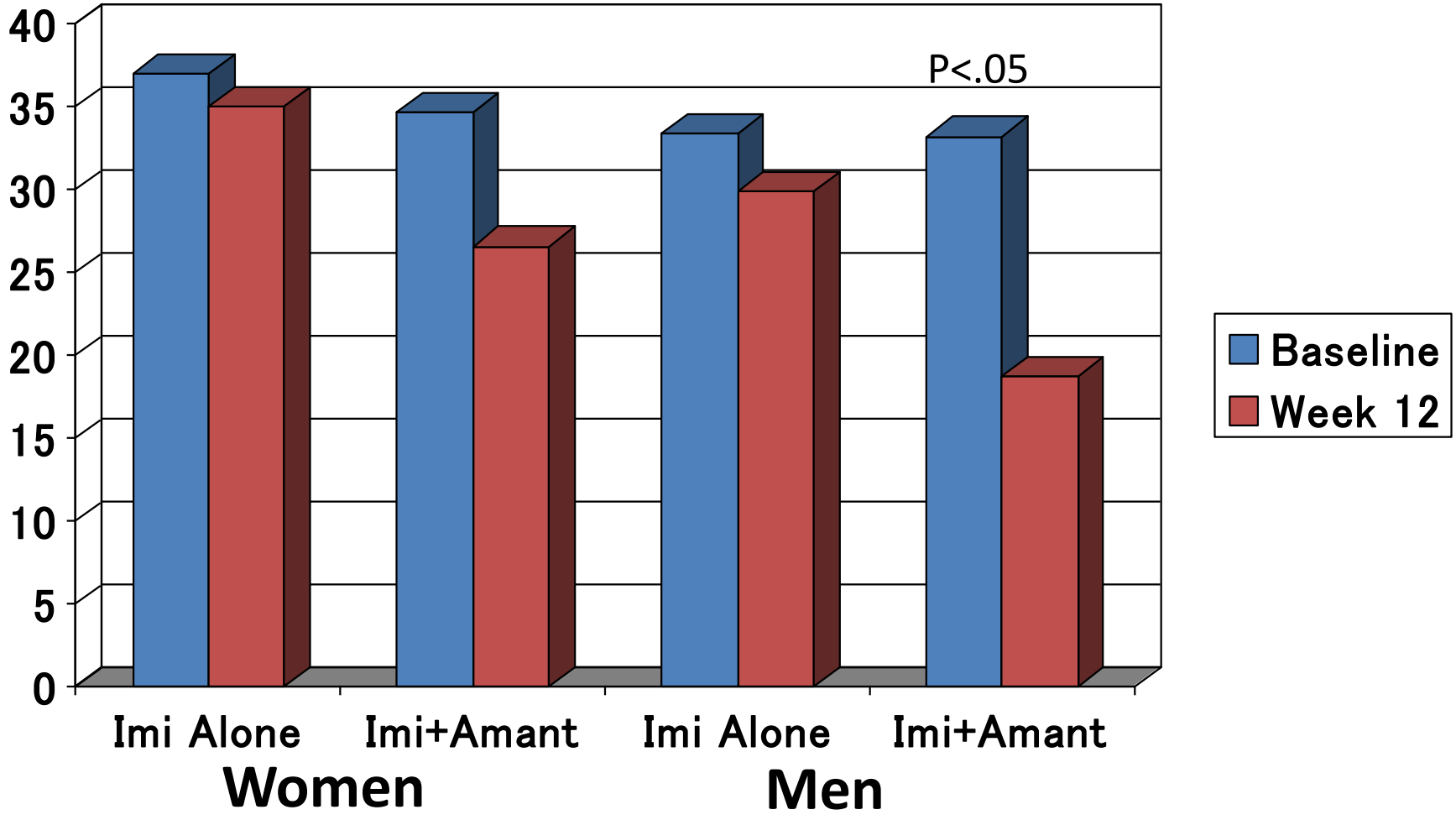


FIGURE 1. Hamilton Depression Rating Scale measures of depressive symptoms for subjects treated with citalopram + placebo or citalopram + omega-3 supplements over the 8 weeks of study, mean ± SD (*$P < 0.05$, computed via regression modeling).

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

Double-Blind Study of the Anti-Viral and Dopaminergic 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)

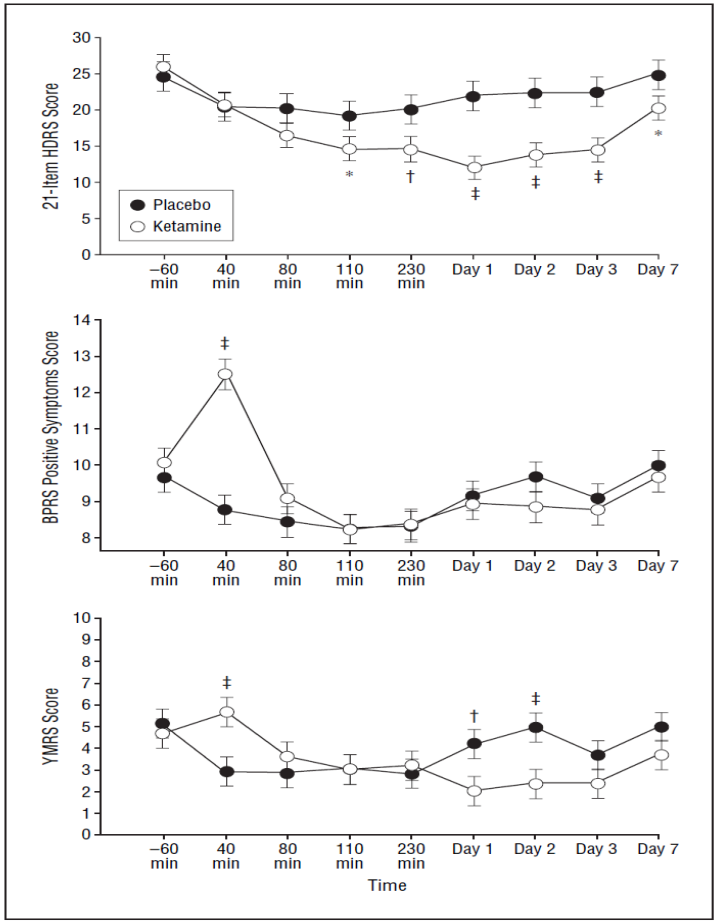


Figure 2. Change in the 21-item Hamilton Depression Rating Scale[28] (HDRS), Brief Psychiatric Rating Scale[31] (BPRS) positive symptoms subscale, and Young Mania Rating Scale[32] (YMRS) scores over 1 week (n=18). Values are expressed as generalized least squares means and standard errors for the completer analysis. * indicates $P<.05$; †, $P<.01$; ‡, $P<.001$.

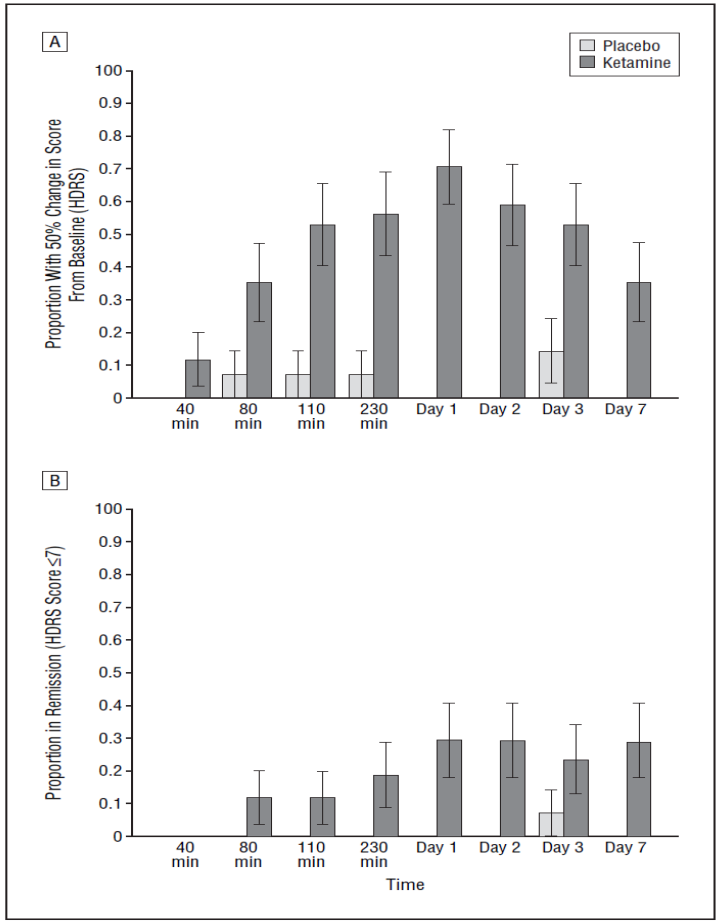


Figure 3. A, Proportion of responders (50% improvement on 21-item Hamilton Depression Rating Scale[28] [HDRS]) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (n=18). B, Proportion of remitters (HDRS score ≤7) to ketamine and placebo treatment from minute 40 to day 7 postinfusion (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)

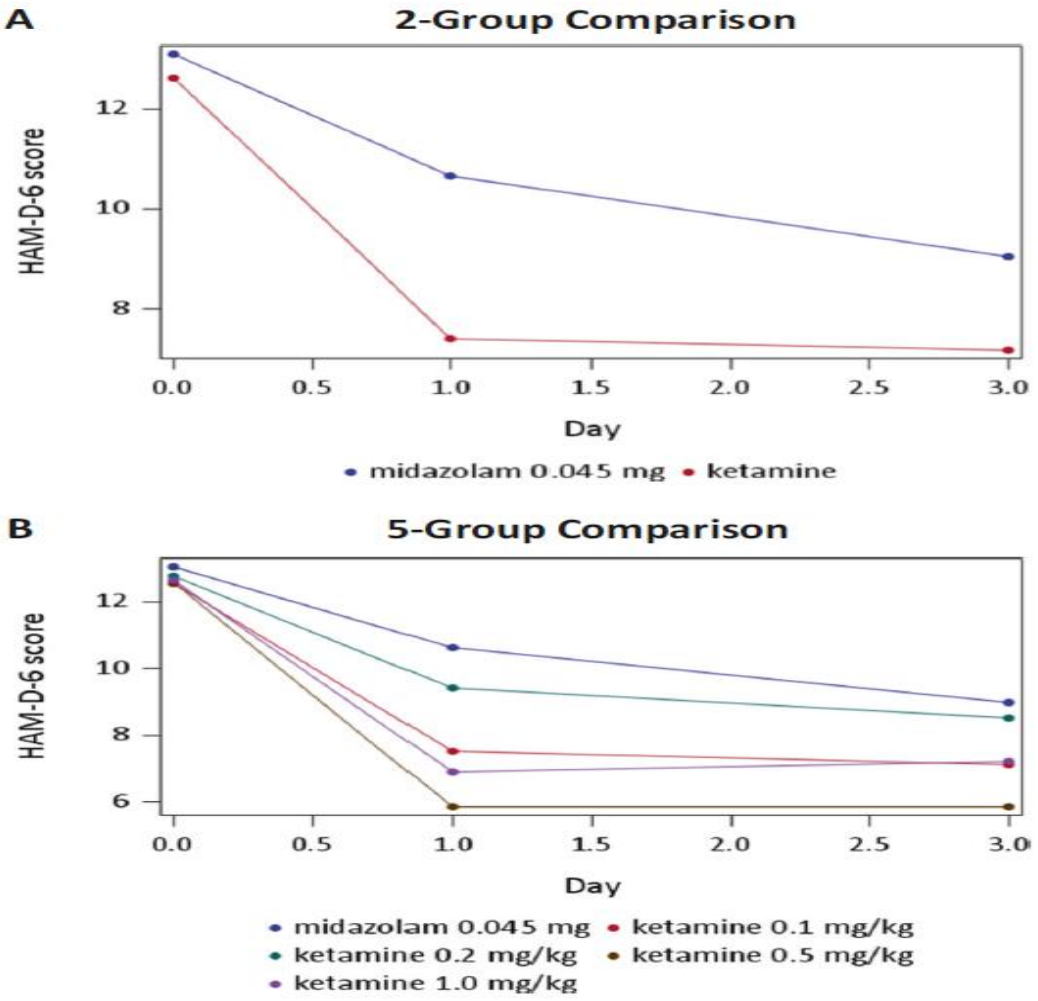
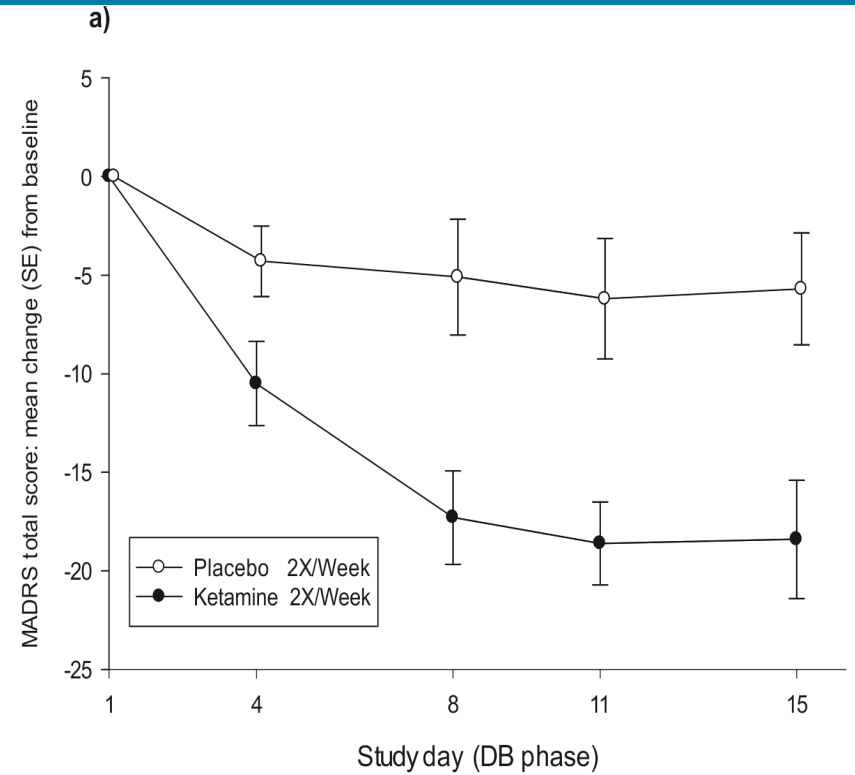


Fig. 2 HAM-D-6 scores over the first 72 h of treatment; Fig. 2A reports the 2-group analysis; Fig. 2B reports the 5-group analysis;

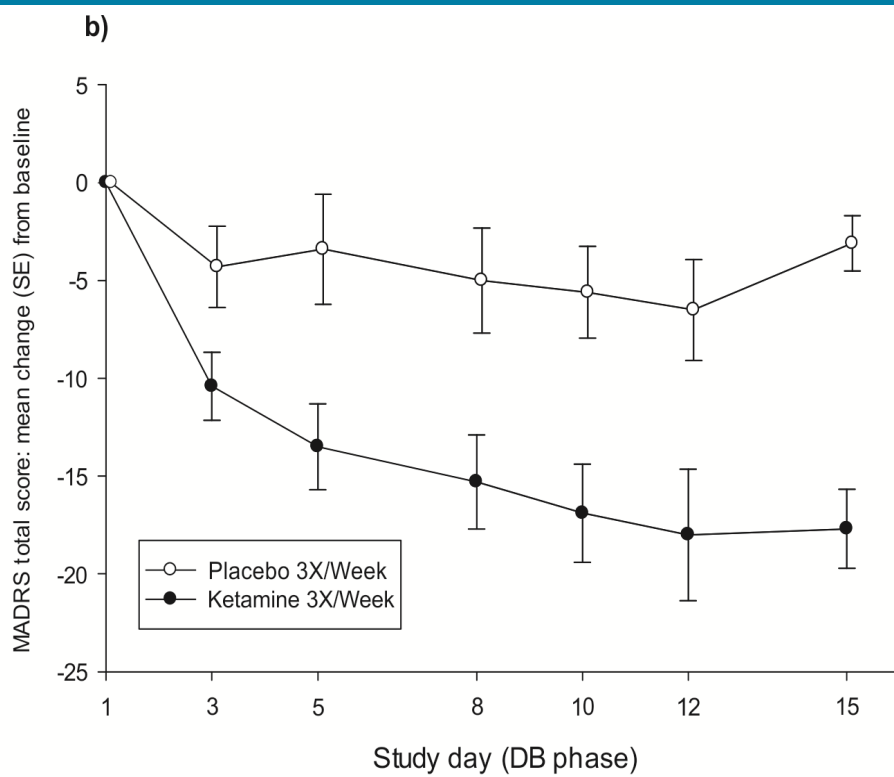
Fava et al
Molecular Psychiatry
https://doi.org/10.1038/s41380-018-0256-5

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



Numberof patients:

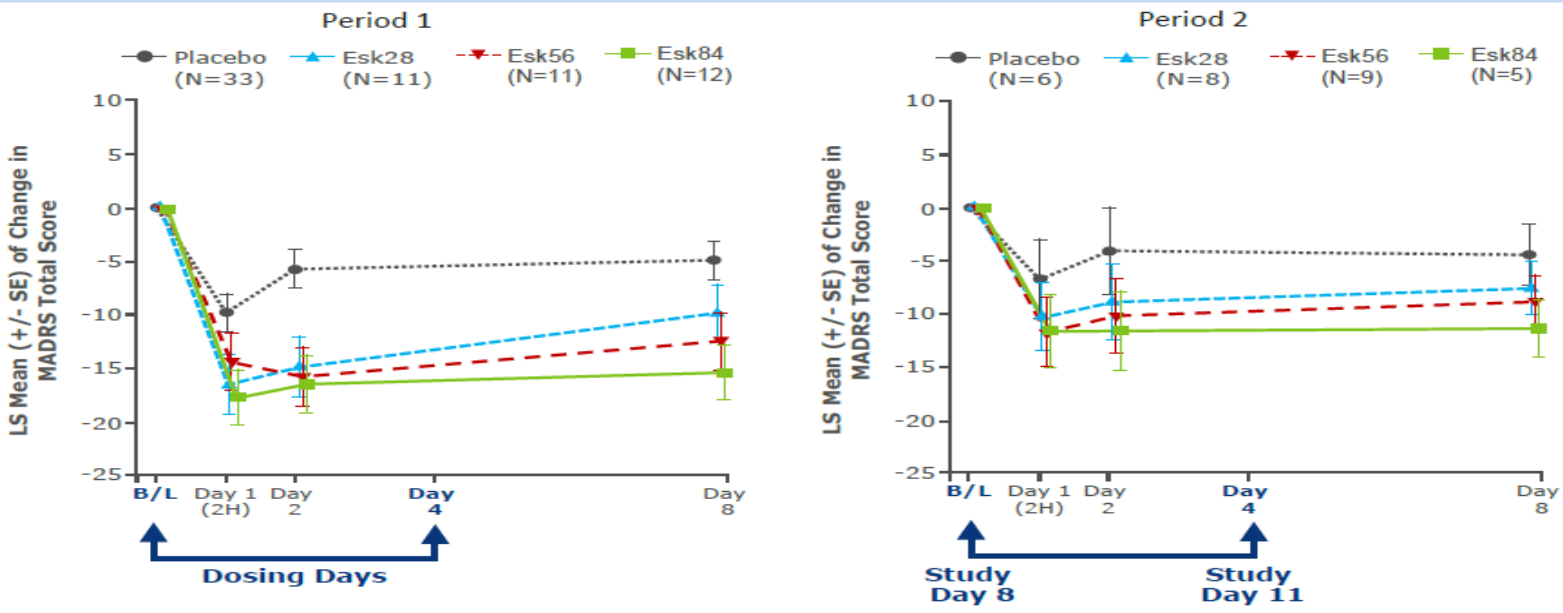
Placebo	16	16	15	16	16	14	16
Ketamine	17	17	13	16	16	11	13

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

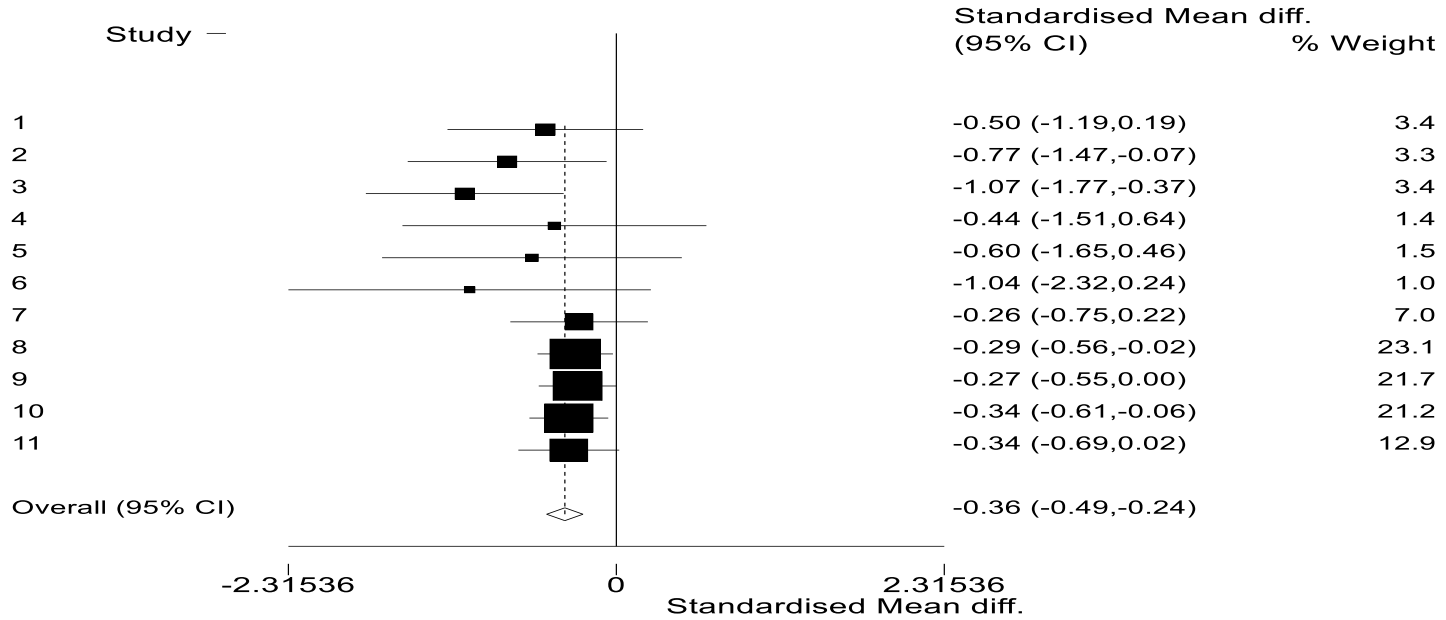
- Assuming equal variance across treatments and periods, the effect size combining both periods ranged from 0.52 for 28 mg, 0.92 for 56 mg, and 1.20 for 84 mg esketamine

*TRD assessed with the ATRQ

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

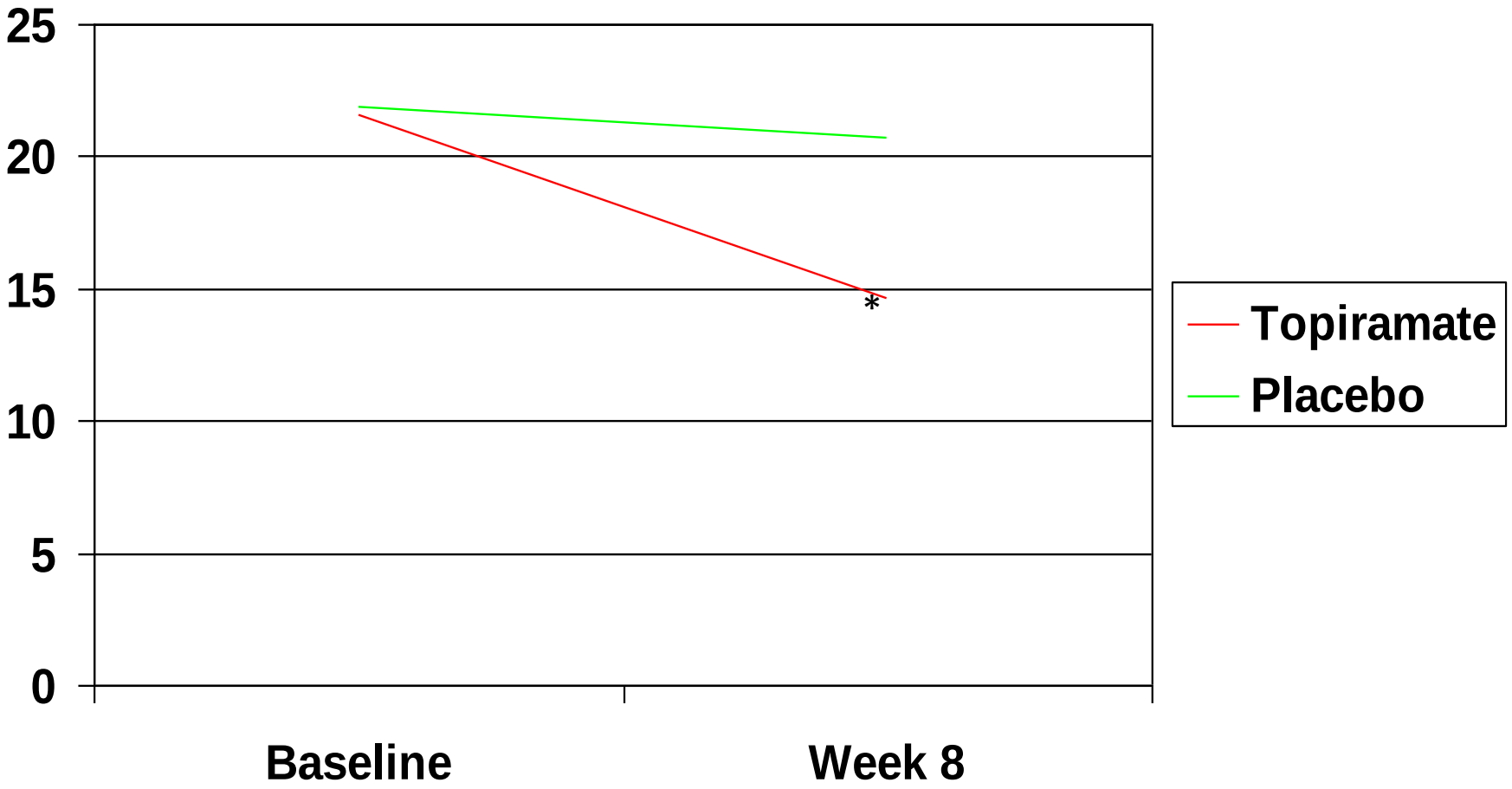
Meta-Analysis of Esketamine Augmentation in TRD Studies

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.

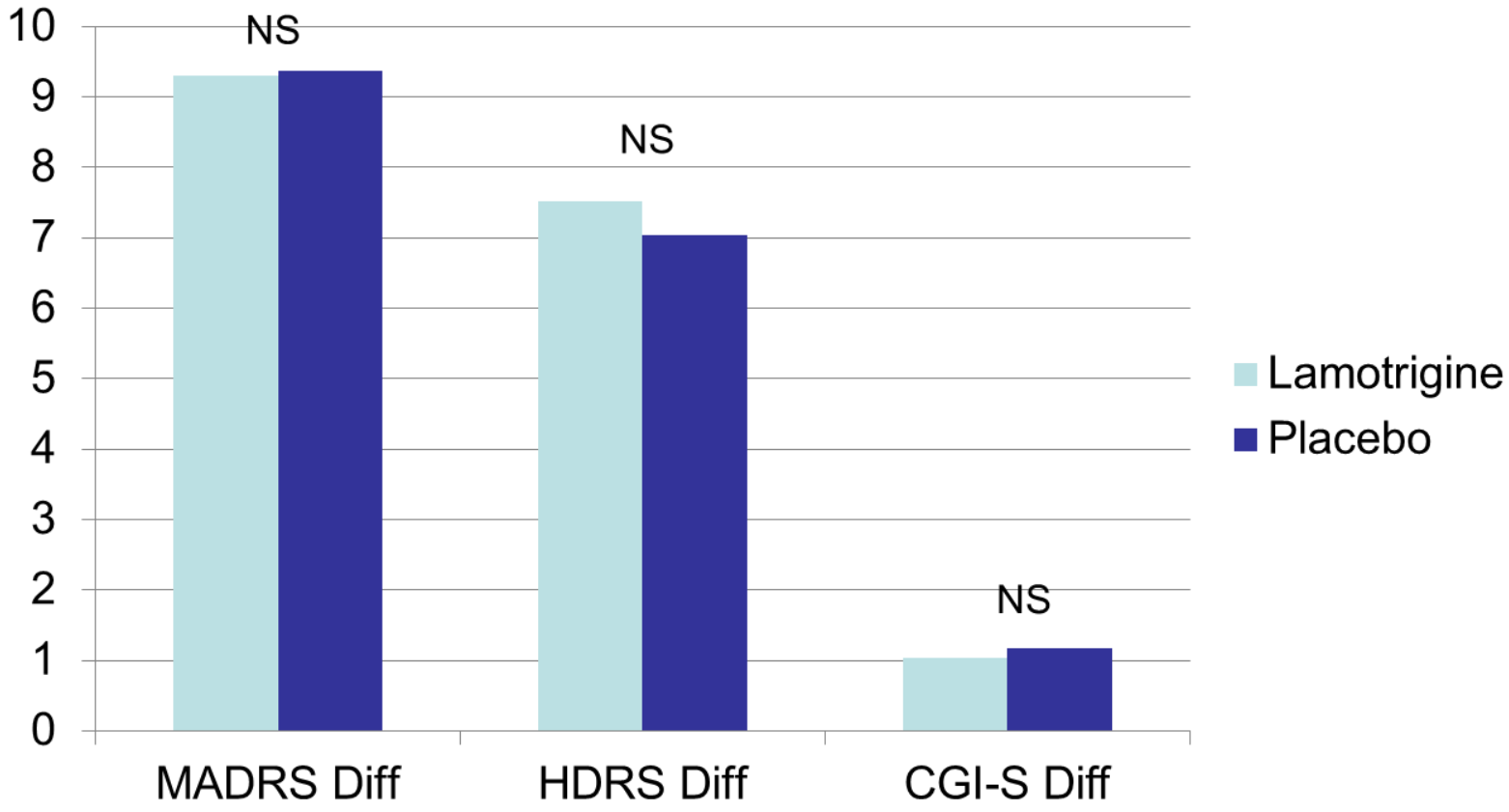
HAM-D Scores in Double-Blind Study of the Kainate (Glutamate) Receptor Antagonist Topiramate (100-200 mg/day) Augmentation in TRD (n=53)



•p<.000

Mowla and Kardeh, Progress in Neuro-Psychopharm & Biol Psychiatry 35 (2011) 970–973

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



Barbee et al, J Clin Psychiatry 2011; 72(10):1405-1412

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	*P*
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.

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

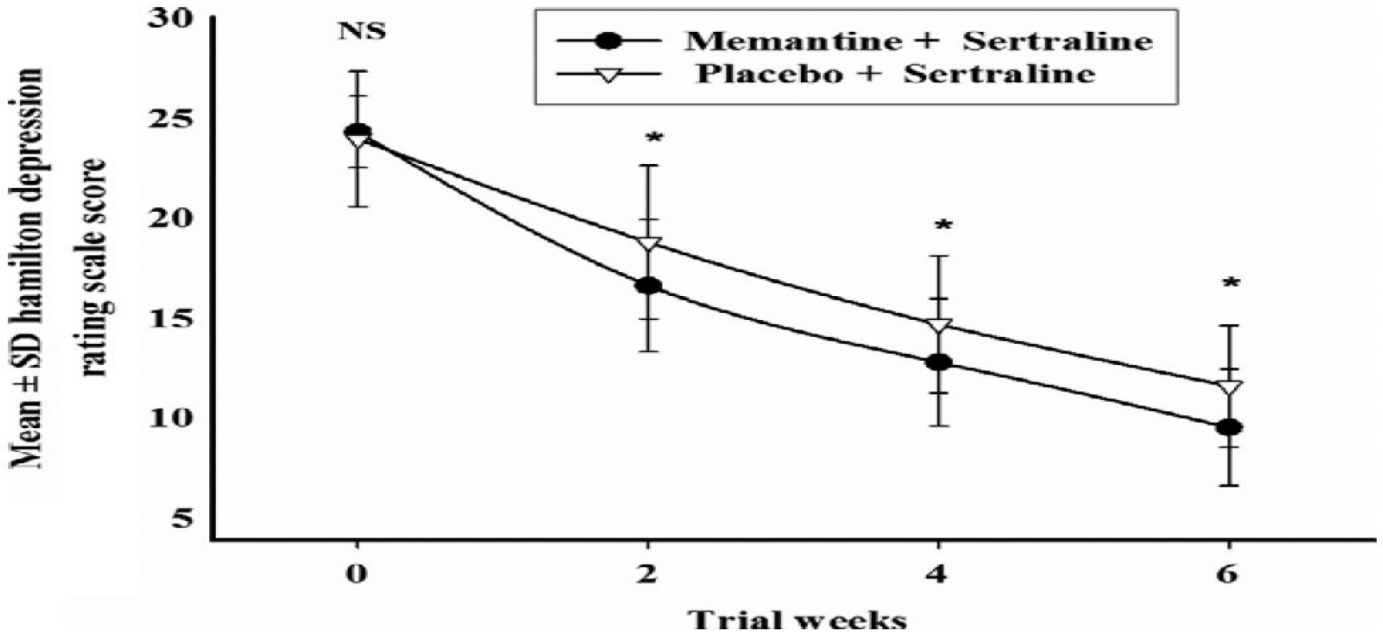
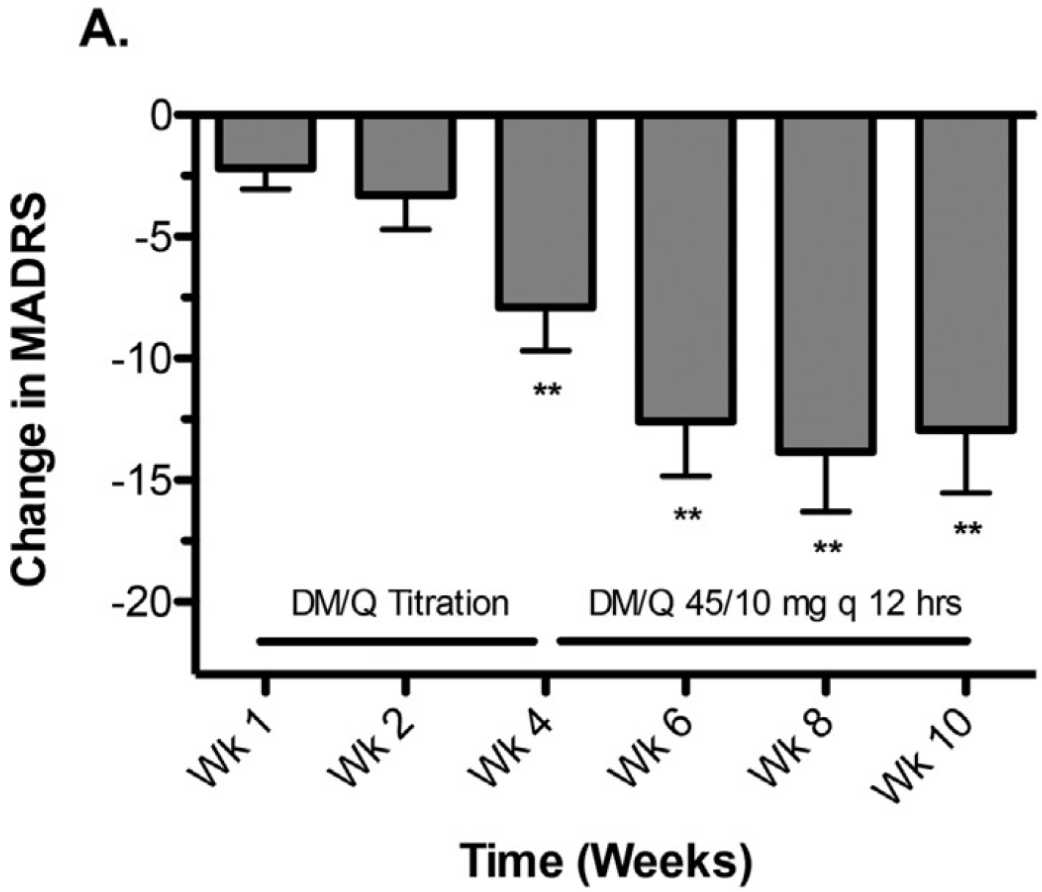


Fig. 2. Repeated measures for comparison of the effects of two treatments on Hamilton Depression Rating Scale (HDRS). Values represent mean ± standard deviation. *P*-values show the result of the independent *t*-test comparing HDRS scores between the two groups at each time point. NS indicates non-significant; *, $P < 0{\cdot}05$.

Amidfar et al, Journal of Clinical Pharmacy and Therapeutics, 2017, 42, 44–50

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, Placebo-Controlled Study of the NMDAR Antagonist Dextromethadone (REL-1017) as Adjunctive Treatment in MDD

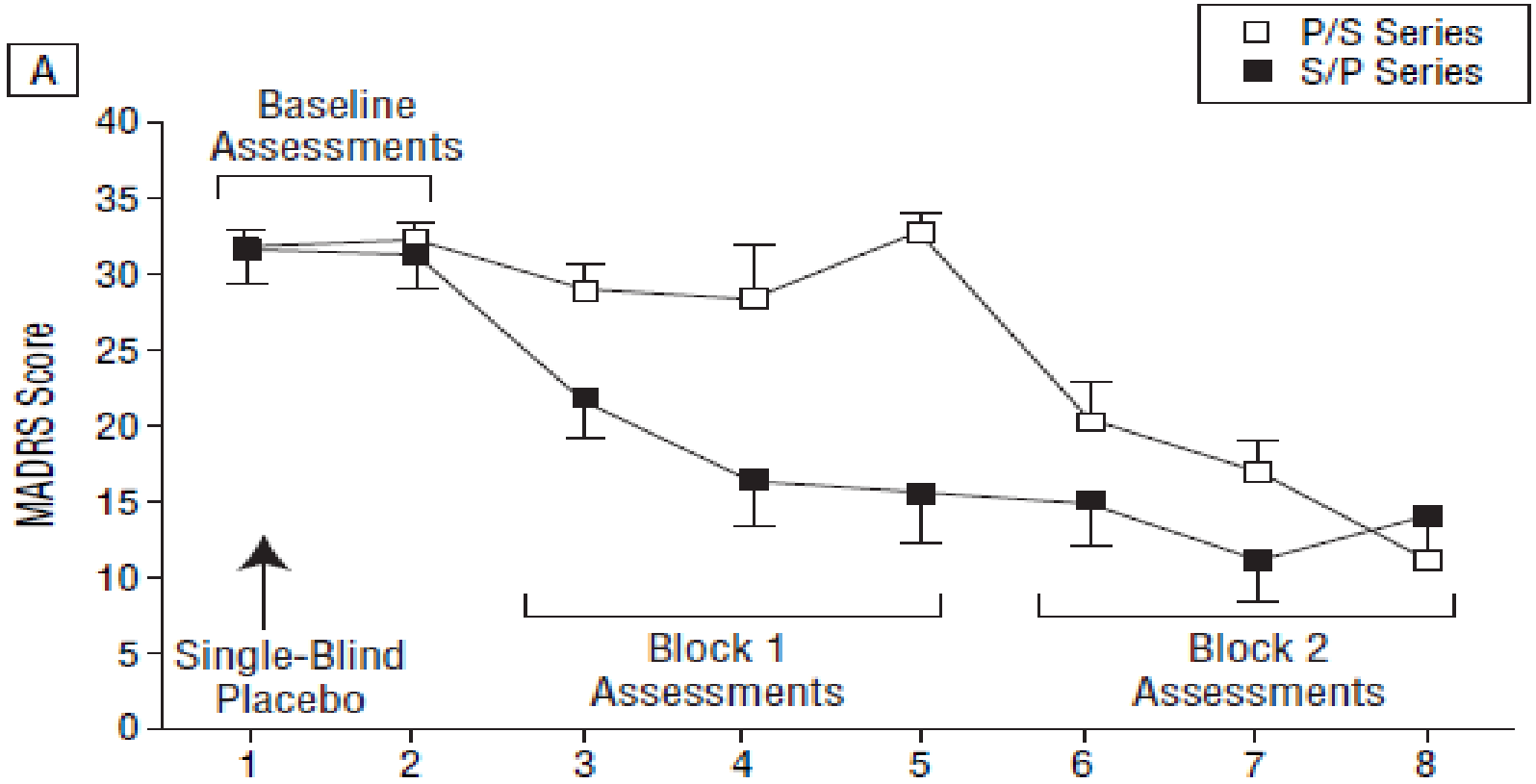
MADRS: Analysis of Change from Baseline to Day 7 and to Day 14 ITT Population

	Day 2			Day 4			Day 7			Day 14		
	LS Means Difference	P-value	d	LS Means Difference	P-value	d	LS Means Difference	P-value	d	LS Means Difference	P-value	d
REL-1017 25mg vs Placebo	-1.9	0.4340	0.3	-7.9	0.0087	0.9	-8.7	0.0122	0.8	-9.4	0.0103	0.9
REL-1017 50mg vs Placebo	-0.3	0.9092	0.0	-7.6	0.0096	0.8	-7.2	0.0308	0.7	-10.4	0.0039	1.0

LS = Least Squares; d = Cohen's effect size

https://www.relmada.com/news-events/press-releases/detail/200/relmada-therapeutics-announces-top-line-results-from

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

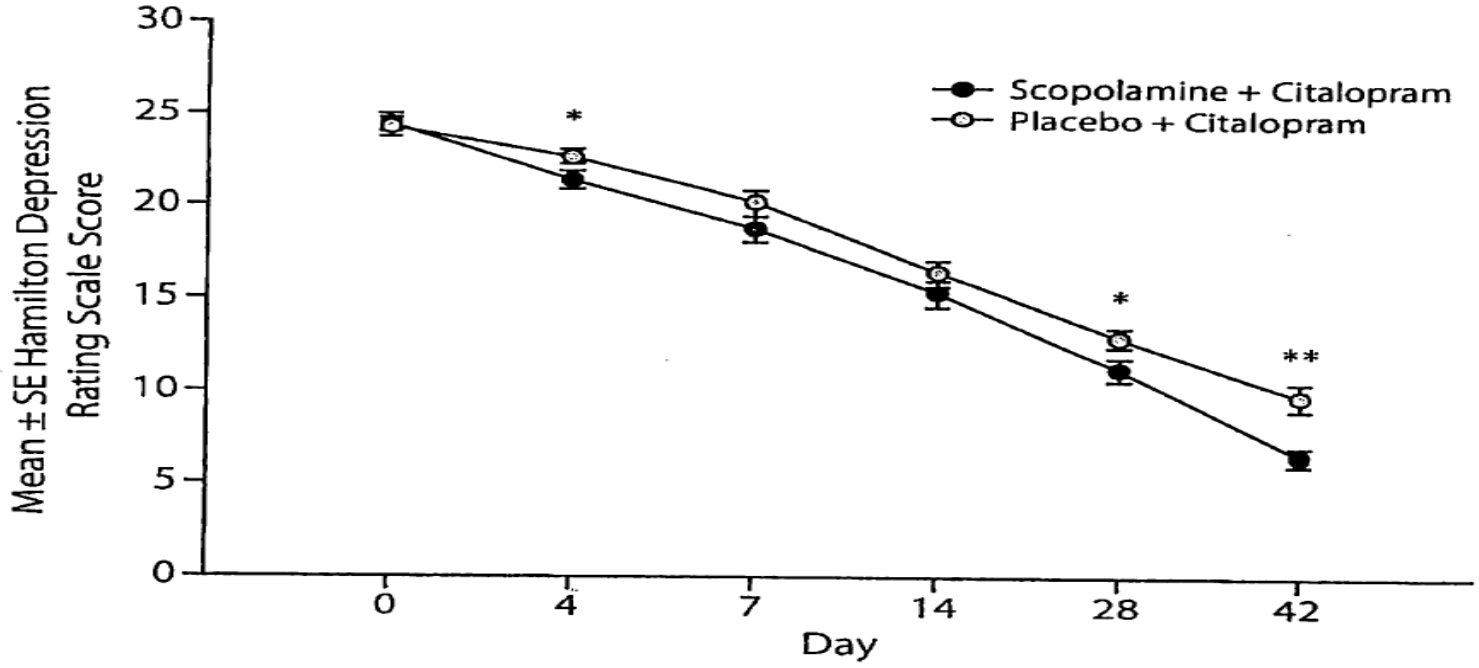


Mean Montgomery-Asberg Depression Rating Scale (MADRS) (A) scores for the placebo/scopolamine hydrobromide (P/S) group and the scopolamine/placebo (S/P) group across 8 assessments. Two baseline, 3 block 1, and 3 block 2 assessments are identified in each panel. Error bars represent SE. For each scale,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

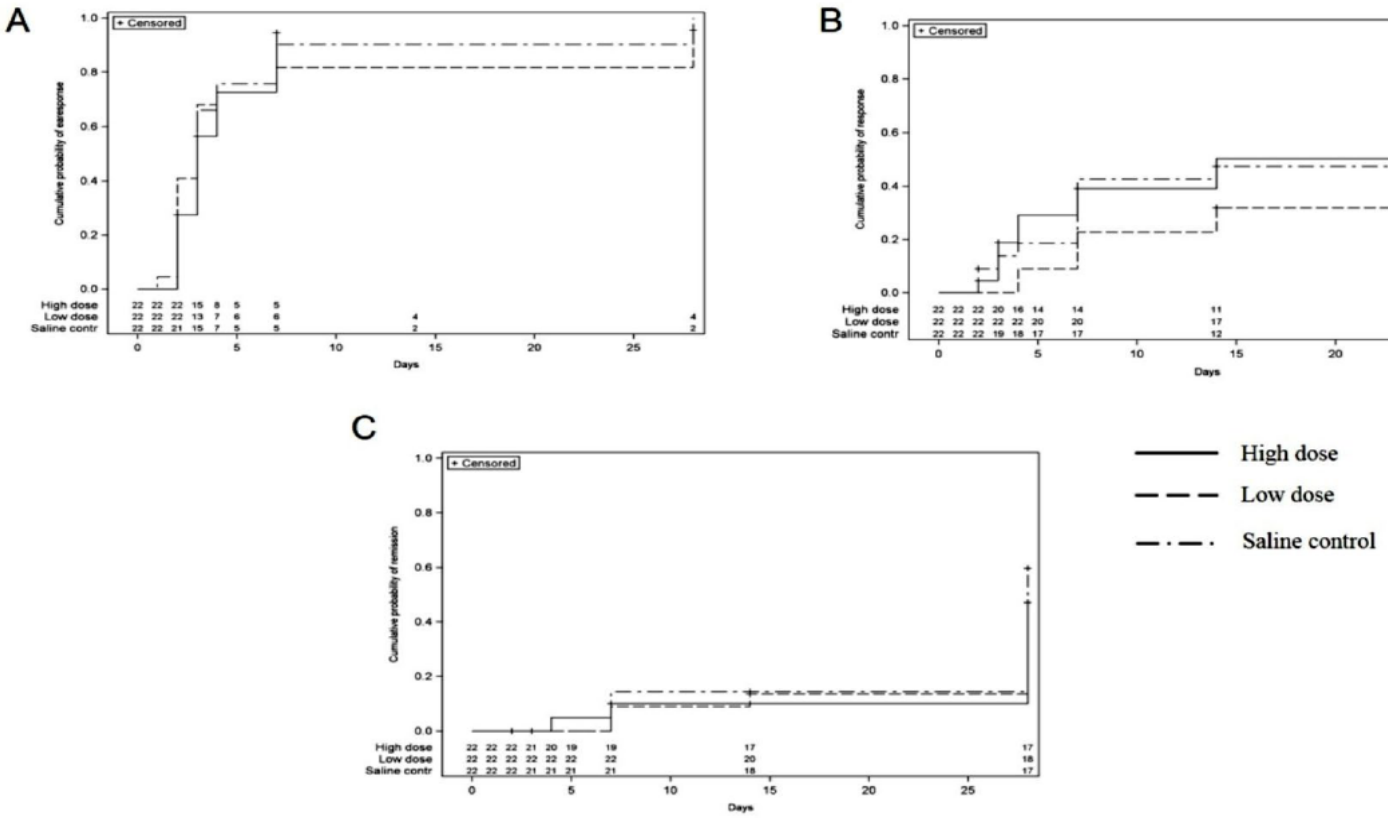
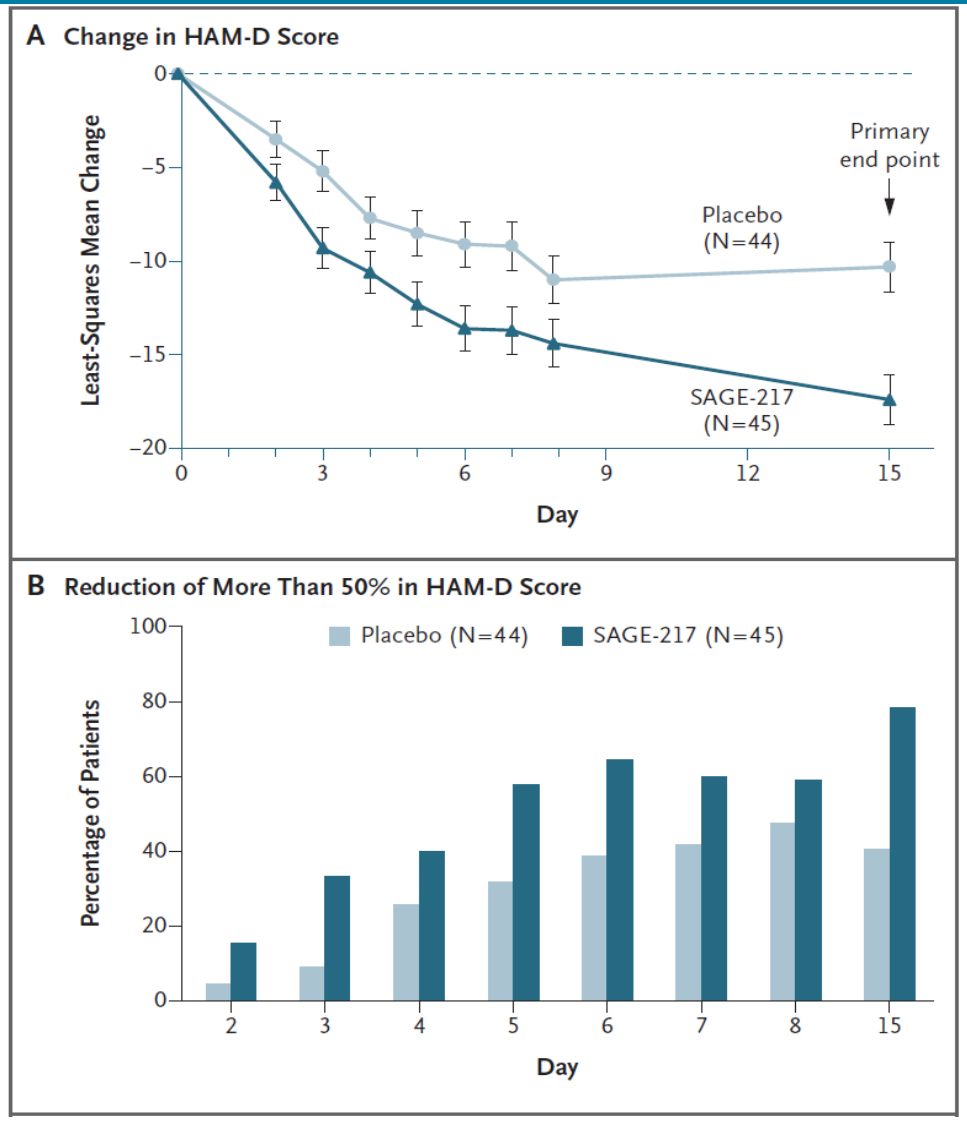


Figure 2. Time to early response, response and remission by Kaplan–Meier analysis. (a) Time to early response; (b) time to response (with number of subjects at risk); and (c) time to remission.

Zhou et al, Ther Adv Psychopharmacol 2020, Vol. 10: 1–11 DOI: 10.1177/2045125320938556

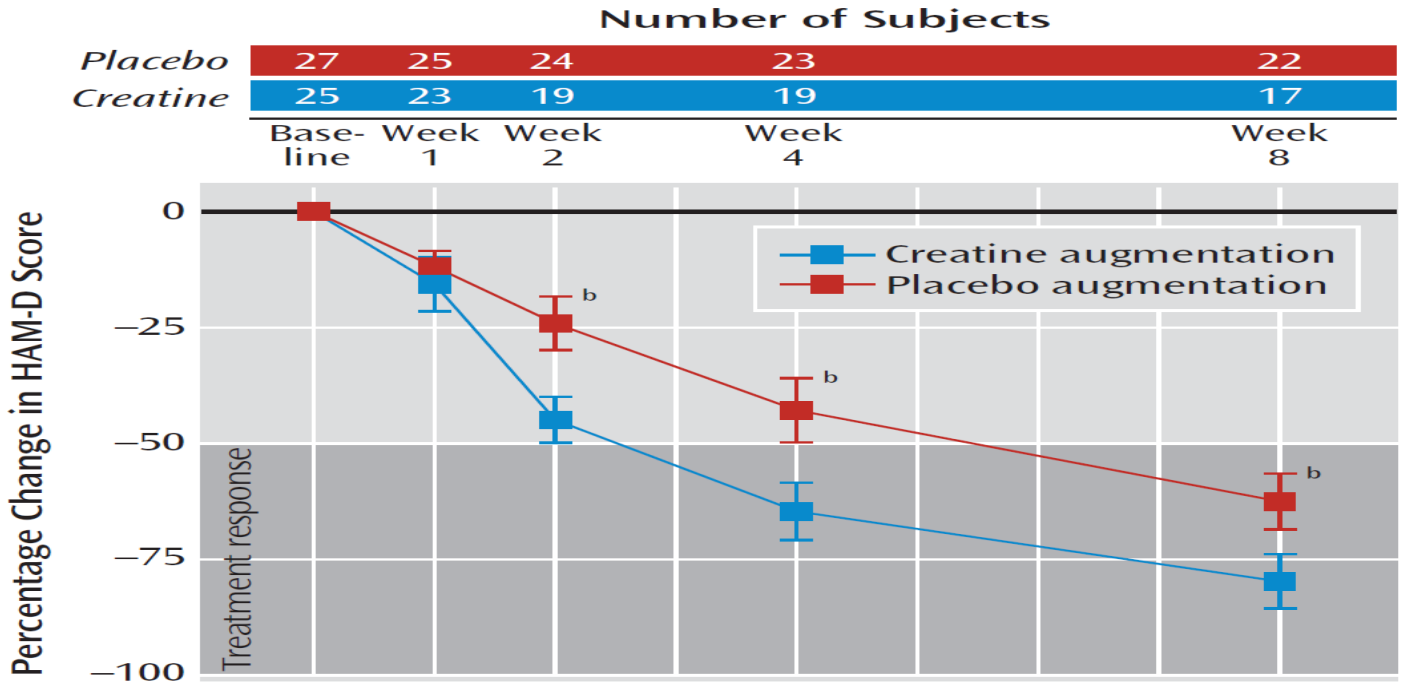
Double-Blind, Placebo-Controlled Study of SAGE-217, a Next Generation Positive Allosteric Modulator of GABA, in MDD (n=89)



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

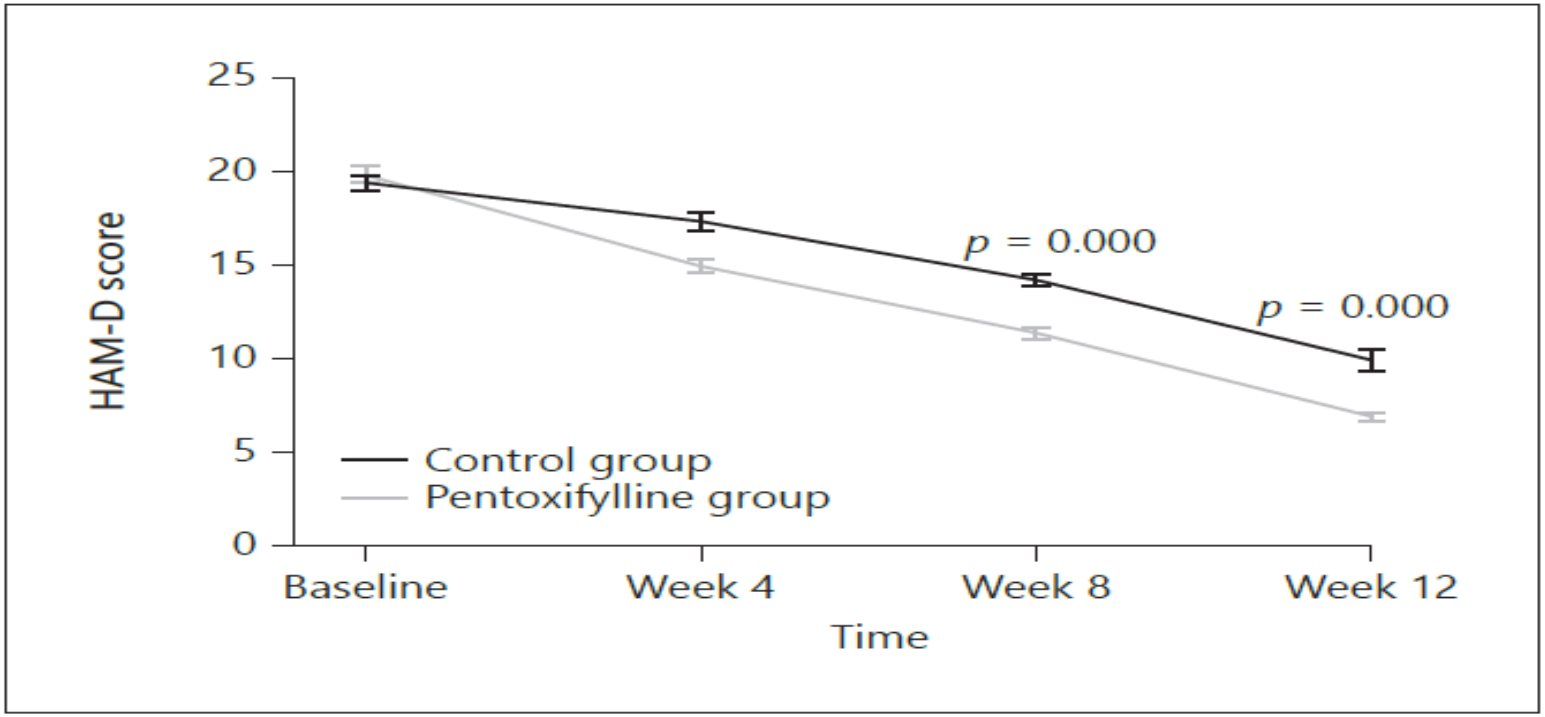


Fig. 2. Changes in Hamilton Depression Rating Scale (HAM-D) total score from baseline to week 12. Data are presented as mean and 95% confidence interval.

El-Haggar et al, Psychother Psychosom 2018;87:331–339

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

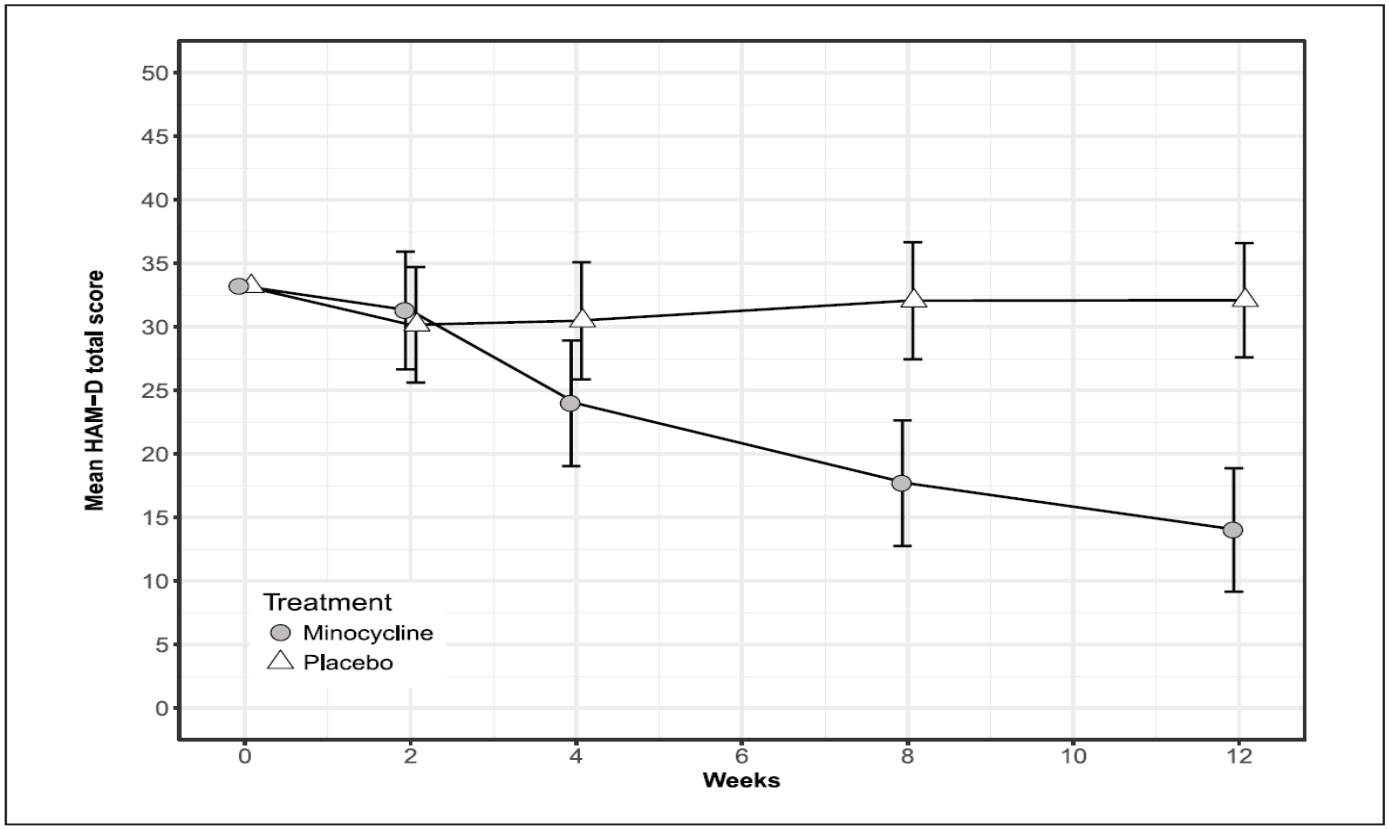


Figure 2. Predicted means and 95% confidence intervals for Hamilton Rating Scale total scores by treatment group and week for lower socio-economic status class participants (most frequent class).

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

Augmentation Therapy with Minocycline in TRD Patients with Low-grade Peripheral Inflammation

Table 2. (A) HAM-D-17 and CRP descriptive statistics.

	Baseline	*n*	Week 4	*n*	Baseline vs Week 4 statistics (bootstrapped)
HAM-D-17, mean (SD)					
Minocycline	19.06 (3.45)	18	13.44 (5.17)	18	**$t = 3.74$ $p = 0.008$**
Placebo	17.00 (3.26)	21	14.10 (5.59)	21	**$t = 3.43$ $p = 0.003$**
CRP+/M	21.50 (2.59)	6	9.5 (5.32)	6	**$t = 4.55$ $p = 0.02$**
CRP+/P	16.08 (2.91)	12	12.58 (5.45)	12	**$t = 2.79$ $p = 0.03$**
CRP-/M	17.83 (3.24)	12	15.42 (3.36)	12	**$t = 2.61$ $p = 0.03$**
CRP-/P	18.22 (4.36)	9	16.11 (5.42)	9	$t = 1.94$ $p = 0.11$
hsCRP, mean (SD)					
Minocycline	3.13 (2.52)	18	3.30 (3.24)	17	$t = 0.41$ $p = 0.70$
Placebo	4.49 (5.20)	21	4.03 (3.53)	21	$t = 0.52$ $p = 0.61$
CRP+/M	5.68 (2.95)	6	5.13 (4.84)	6	All $p > 0.05$
CRP+/P	6.62 (6.11)	12	5.86 (3.72)	12	
CRP-/M	1.85 (0.72)	12	2.30 (1.39)	11	
CRP-/P	1.75 (0.62)	9	1.59 (0.58)	9	

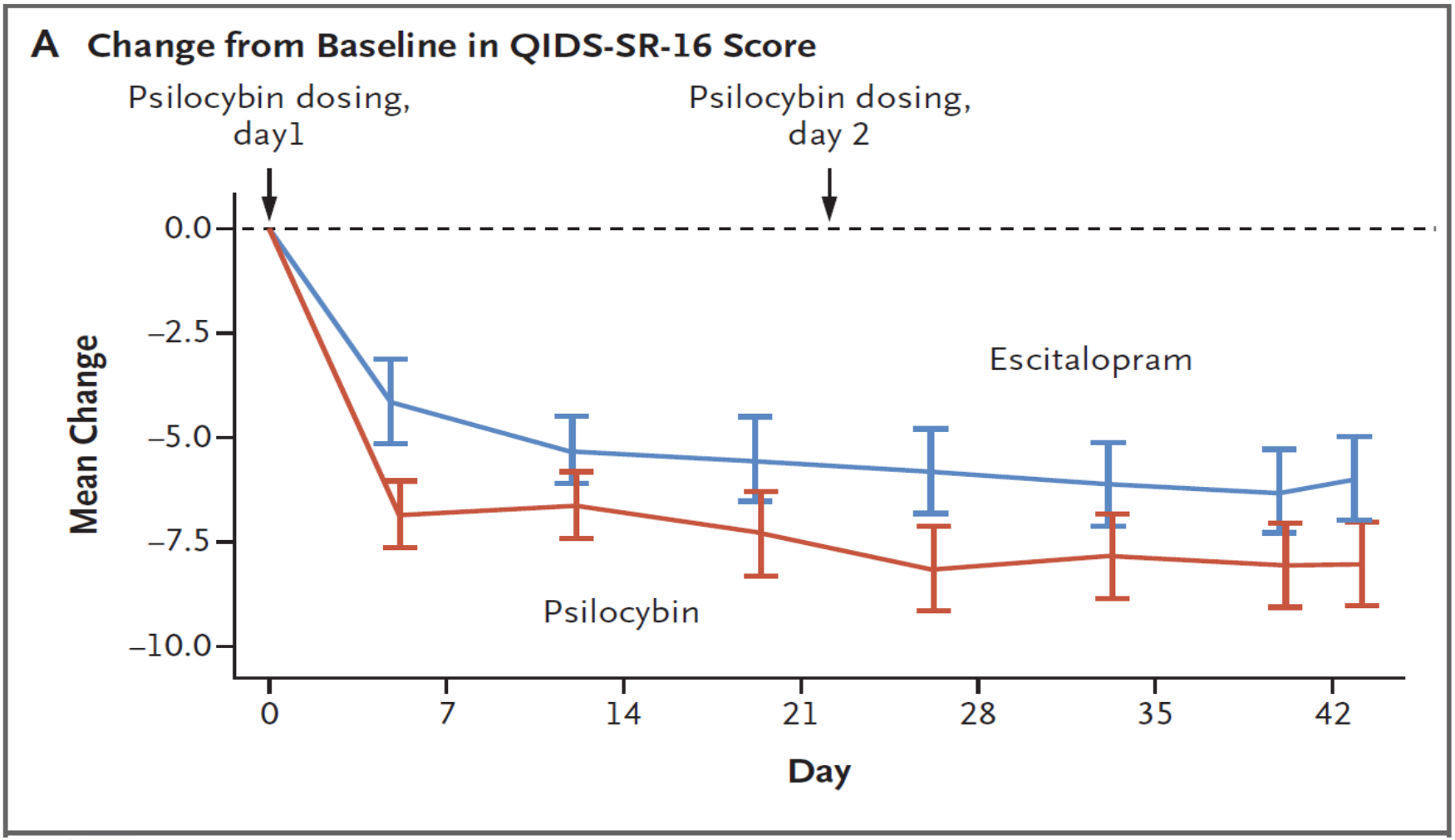
(B) Proportions of responders and non-responders by groups

	HAM-D-17 improvement <25%	*n*	HAM-D-17 improvement ≥25%	*n*	Statistics
CRP+/M	16.7%	1	83.3%	5	**$X^2 = 8.27$ $p = 0.04$**
CRP+/P	41.7%	5	58.3%	7	
CRP-/M	75.0%	9	25.0%	3	
CRP-/P	77.8%	7	22.2%	2	

HAM-D-17 Hamilton Depression Rating Scale, *hsCRP* high sensitivity C-reactive protein (analysis conducted with logarithmic CRP), *CRP*$^+$ baseline hsCRP levels ≥ 3 mg/L, *CRP*$^-$ baseline hsCRP levels < 3 mg/L, *M* Minocycline, *P* Placebo.
Bold means that the results are statistically significant.

Nettis et al Neuropsychopharmacology (2021) 46:939–948; https://doi.org/10.1038/s41386-020-00948-6

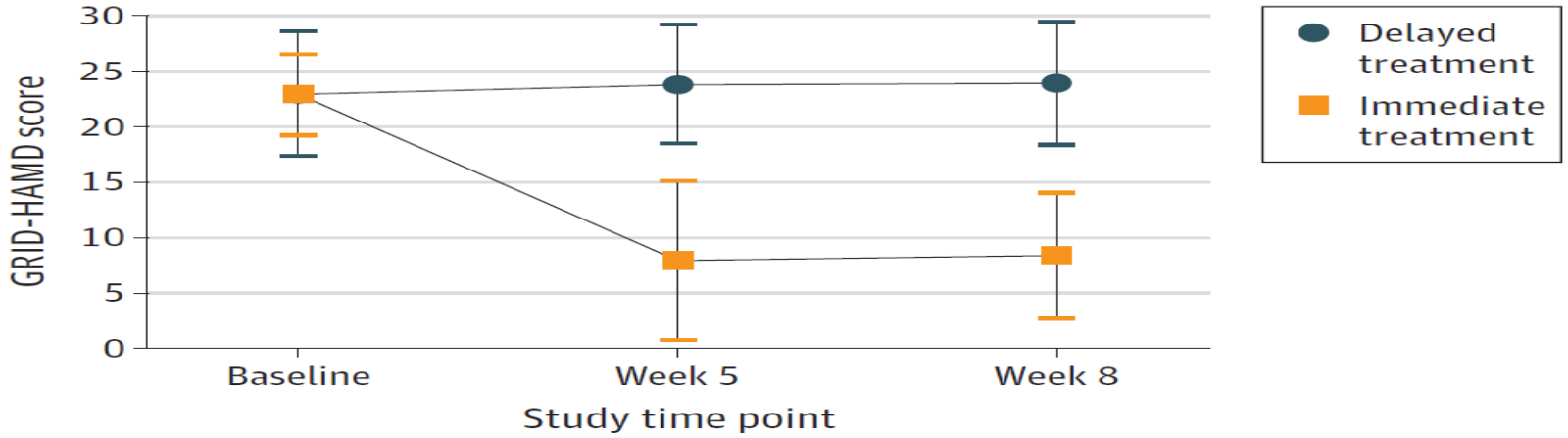
Trial of Psilocybin (25 mg) versus Escitalopram (10-20 mg) for Depression



Carhart-Harris et al, N Engl J Med 2021;384:1402-11. DOI: 10.1056/NEJMoa2032994

Effects of Psilocybin-Assisted Therapy (20-30 mg/70 kg) on Major Depressive Disorder: A Randomized Clinical Trial

Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups



Data points are presented as mean (SD). In the immediate treatment group (n = 13), weeks 5 and 8 correspond to weeks 1 and 4 after the psilocybin session 2. In the delayed treatment group (n = 11), weeks 5 and 8 are prepsilocybin assessments obtained during the delay period. Effect sizes (Cohen *d* with 95% CI) and *P* values reflect the results of a 2-sample *t* test between the 2 groups at week 5 (Cohen *d* = 2.5; 95% CI, 1.4-3.5; *P* < .001) and week 8 (Cohen *d* = 2.6; 95% CI, 1.5-3.7; *P* < .001).

Davis et al, JAMA Psychiatry. 2021;78(5):481-489. doi:10.1001/jamapsychiatry.2020.3285

Placebo-controlled Trial of Ayahuasca (adjusted to contain 0.36 mg/kg of N, N-DMT) in TRD

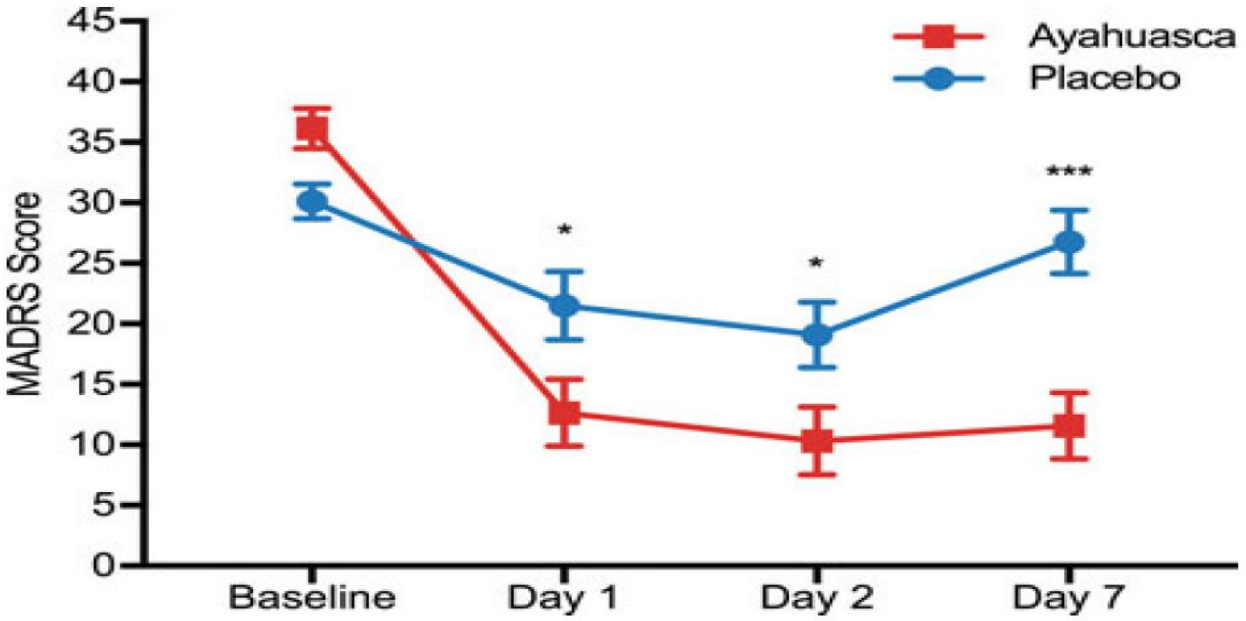


Fig. 3. MADRS scores as a function of time. Significant differences are observed between ayahuasca (squares) and placebo (circles) at D1 ($p = 0.04$), D2 ($p = 0.04$) and D7 ($p < 0.0001$). Between groups effect sizes are high at all time points after dosing: D1 (Cohen's $d = 0.84$), D2 (Cohen's $d = 0.84$), and D7 (Cohen's $d = 1.49$). Values are (mean ± S.E.M.). MADRS scores: mild depression (11–19), moderate (20–34), severe (⩾35). $^{*}p < 0.05$; $^{***}p < 0.0001$.

Palhano-Fontes et al, Psychological Medicine 49, 655–663.
https://doi.org/10.1017/S0033291718001356

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

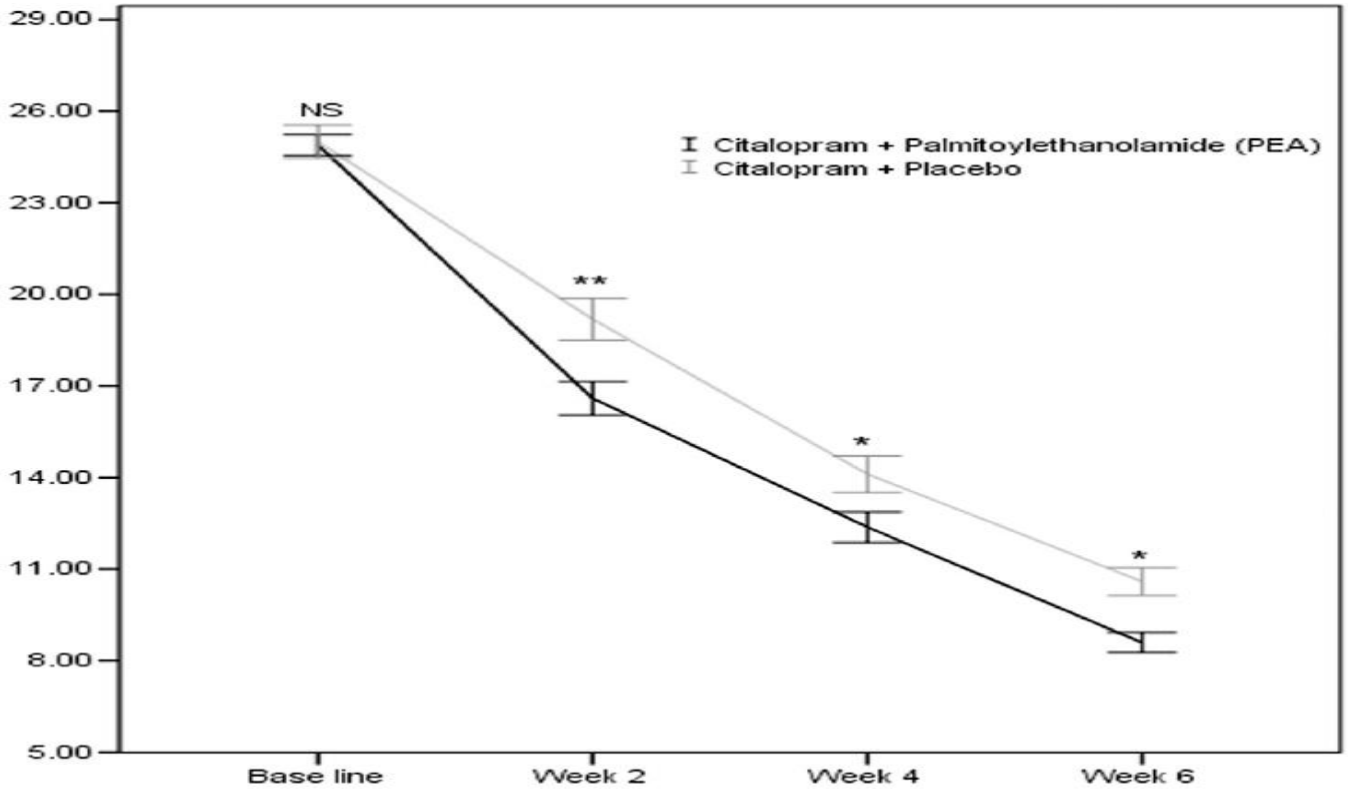
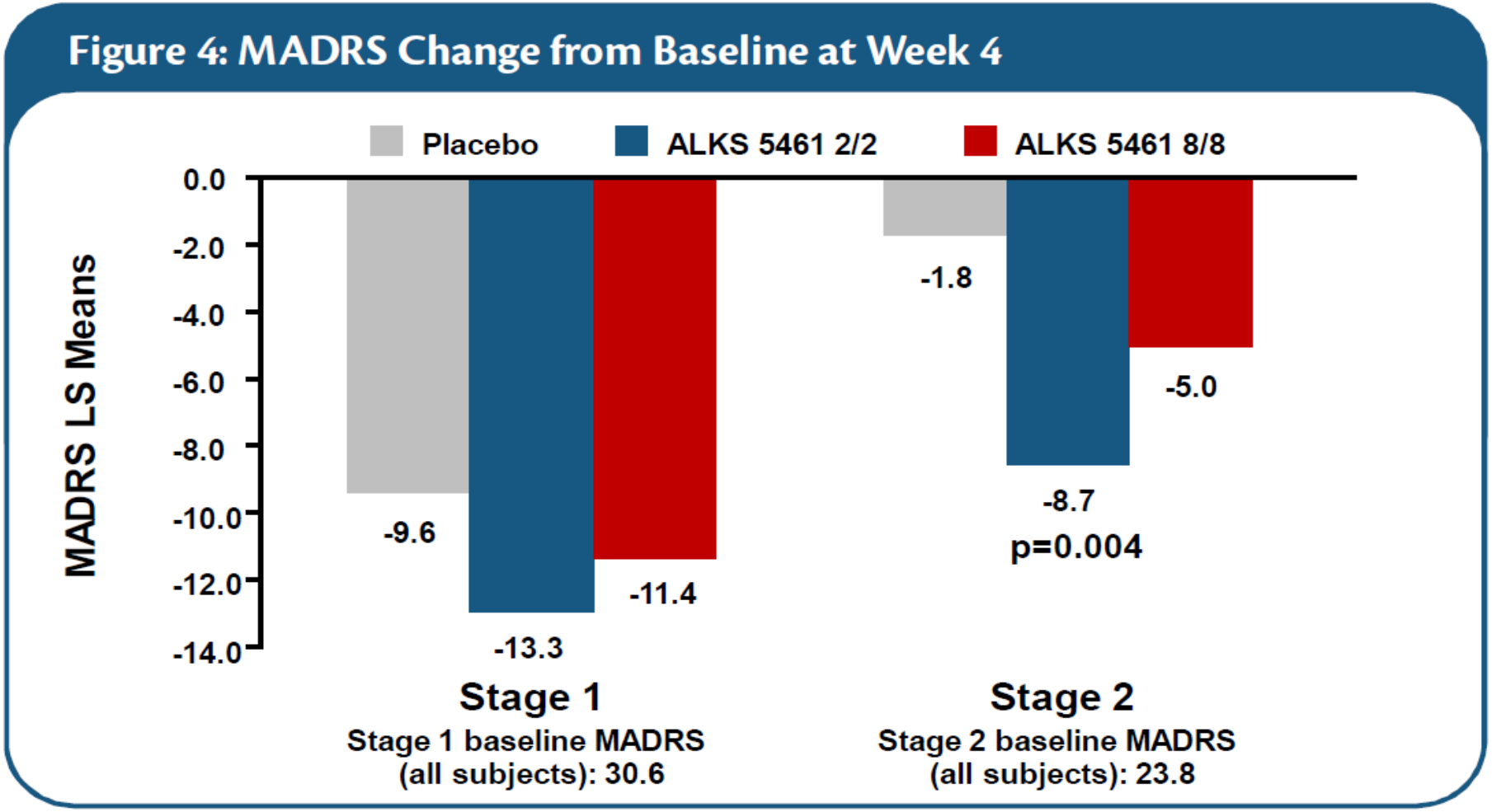


Fig. 2. Repeated measure analysis for comparison of the effects of two treatments on the Hamilton depression rating scale (HDRS) scores. Values represent mean ± SEM (standard error of mean). P values show the result of the independent sample *t*-test for comparison of the score change from the baseline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

Ghazizadeh-Hashemi et al, Journal of Affective Disorders 232 (2018) 127–133

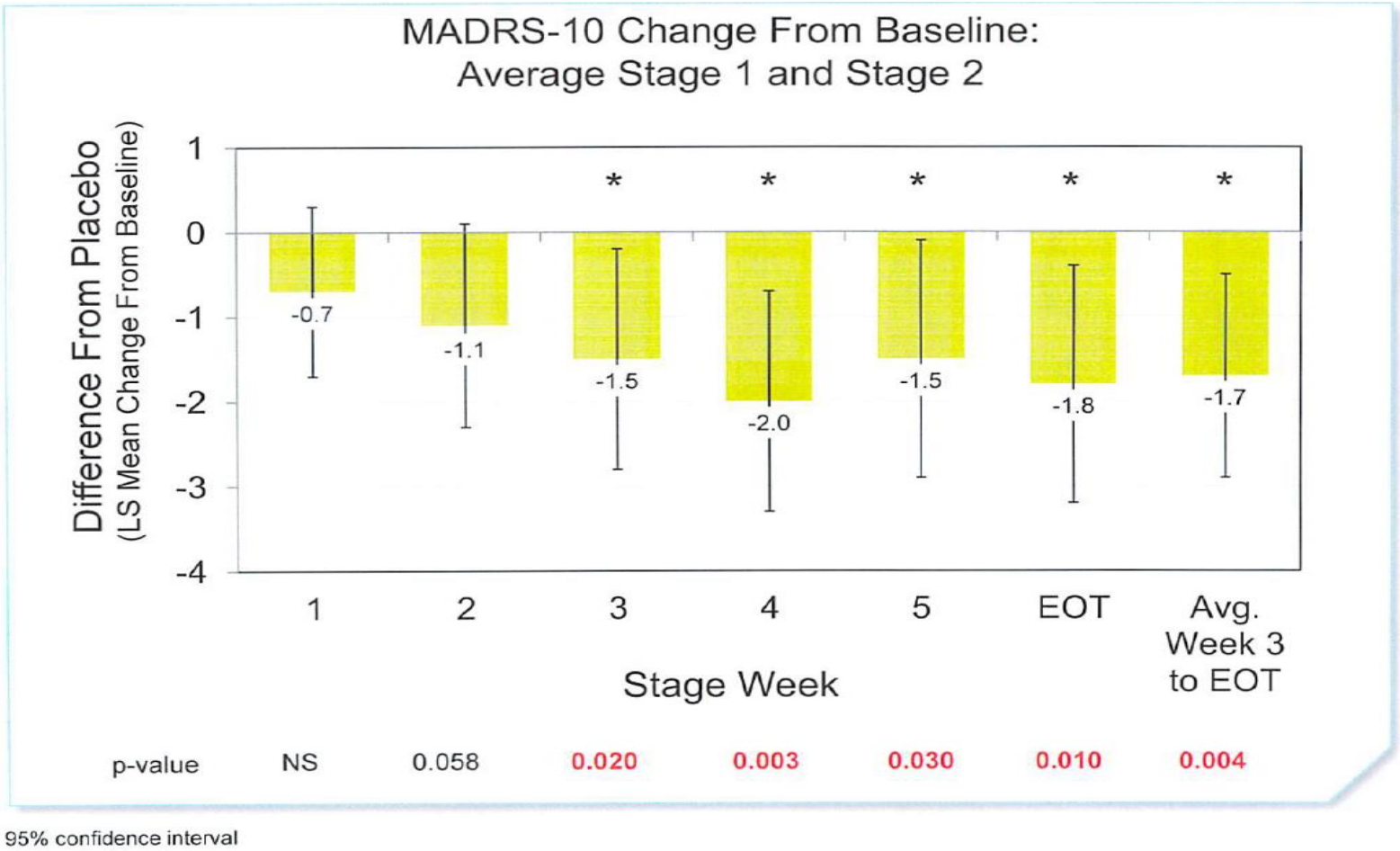
Double-Blind, SPCD Study of ALKS 5461 (buprenorphine plus the mu antagonist Alks 33) vs. Placebo



MASSACHUSETTS GENERAL HOSPITAL PSYCHIATRY ACADEMY

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

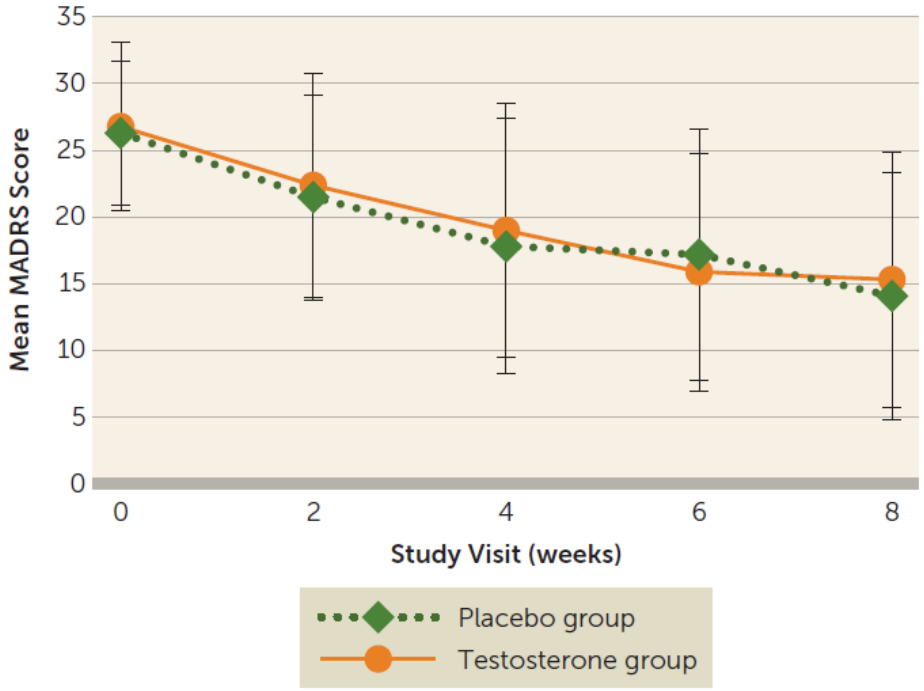
Pooled Analysis of the FORWARD-4 and FORWARD-5 SPCD Studies of ALKS 5461



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.

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 for TRD

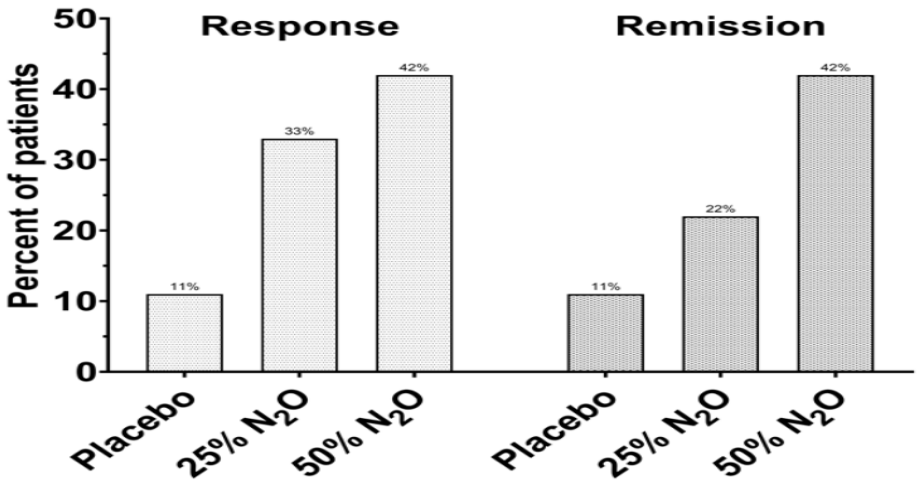


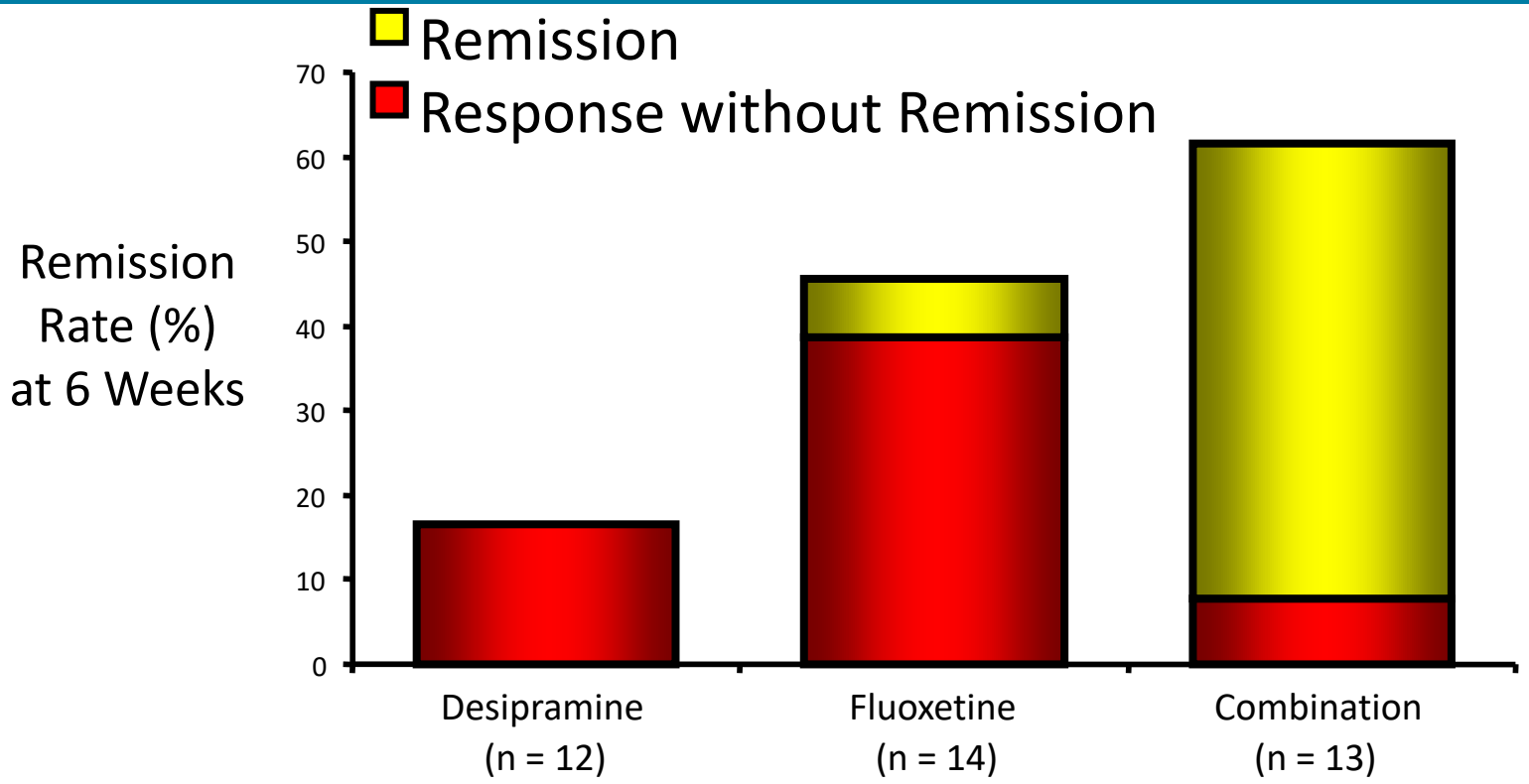
Fig. 3. Proportion of patients who experienced response or remission after treatment with 50% nitrous oxide, 25% nitrous oxide, and placebo. In this analysis, we only included treatments where the pretreatment HDRS-21 score was ≥19. Differences between categorical outcomes (response and remission) were 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

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

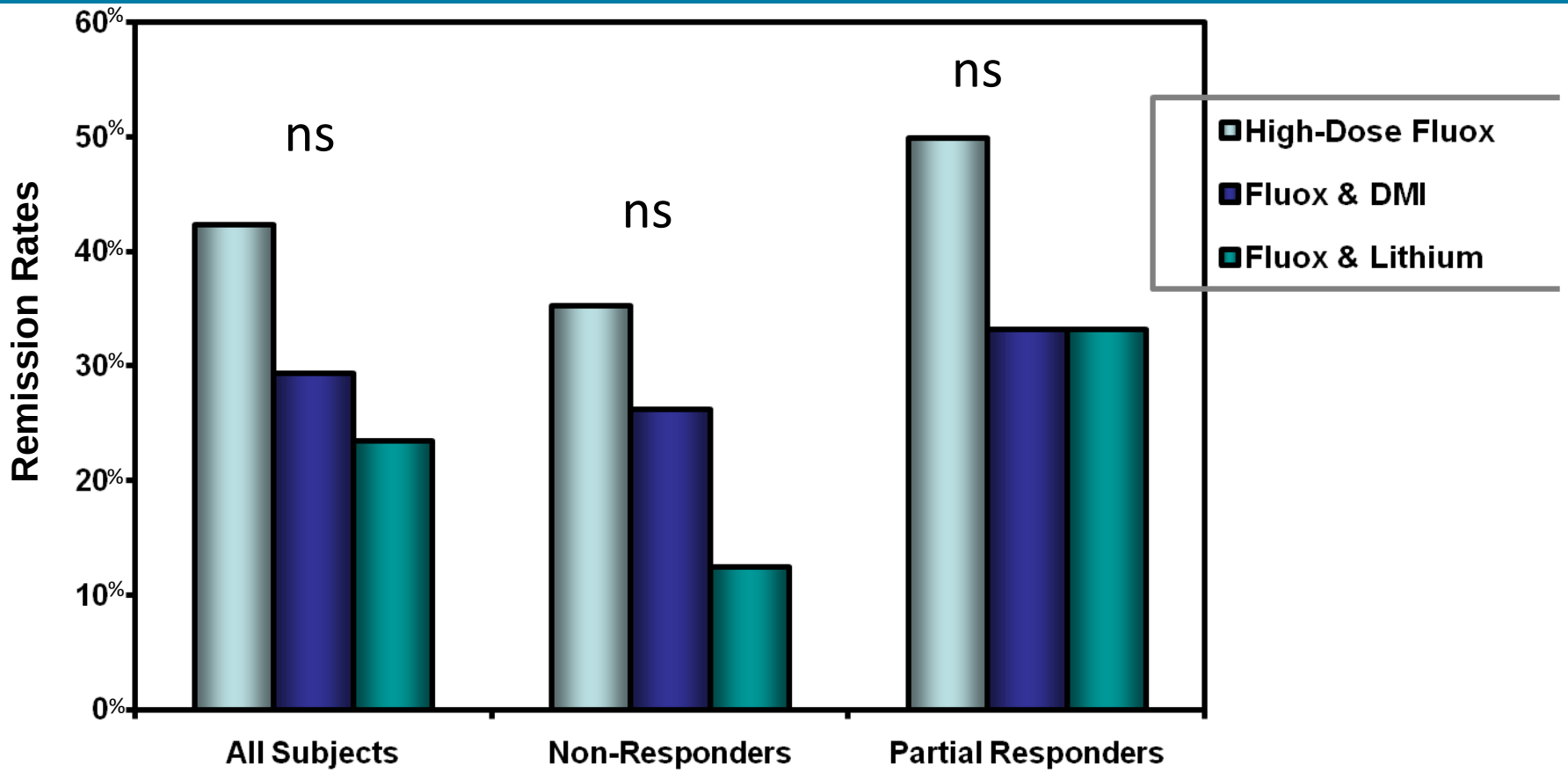
Combination NE and 5-HT Reuptake Inhibition vs. Either Alone



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

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 (HAM-D-17 < 8) Rates



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

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

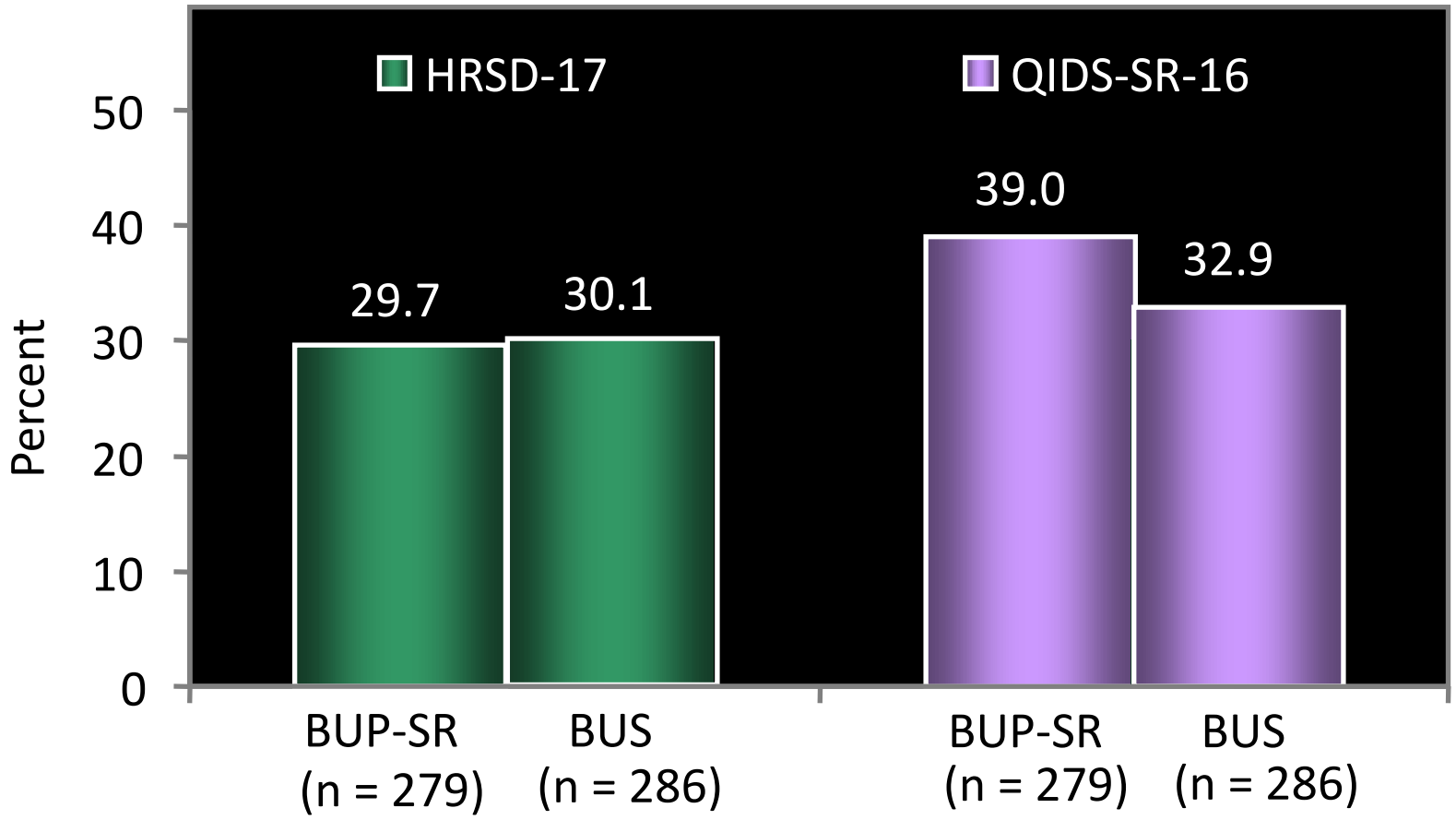
Abbreviations: ATX = atomoxetine, L = 5-HTTLPR long variant, PBO = placebo, S = 5-HTTLPR short variant, SRT = sertraline.

[a] Significance of overall difference among all 3 subgroups.

[b] Comparison of non-S/S versus S/S.

Reimherr F et al; Psychiatry Research 175 (2010) 67–73

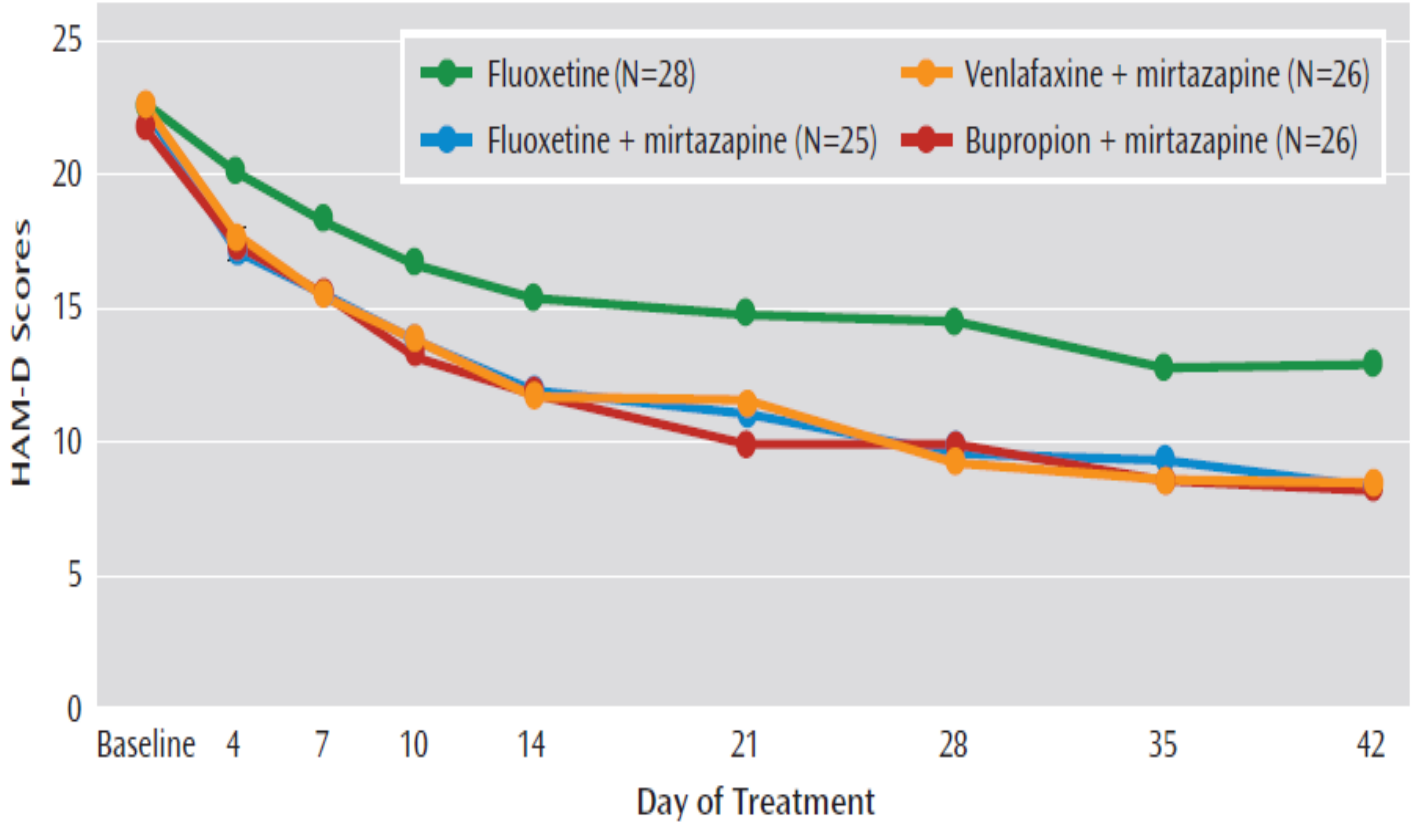
Percent of Remission in STAR*D L-2 Augmentation



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

Double-Blind Study of Mirtazapine Augmentation

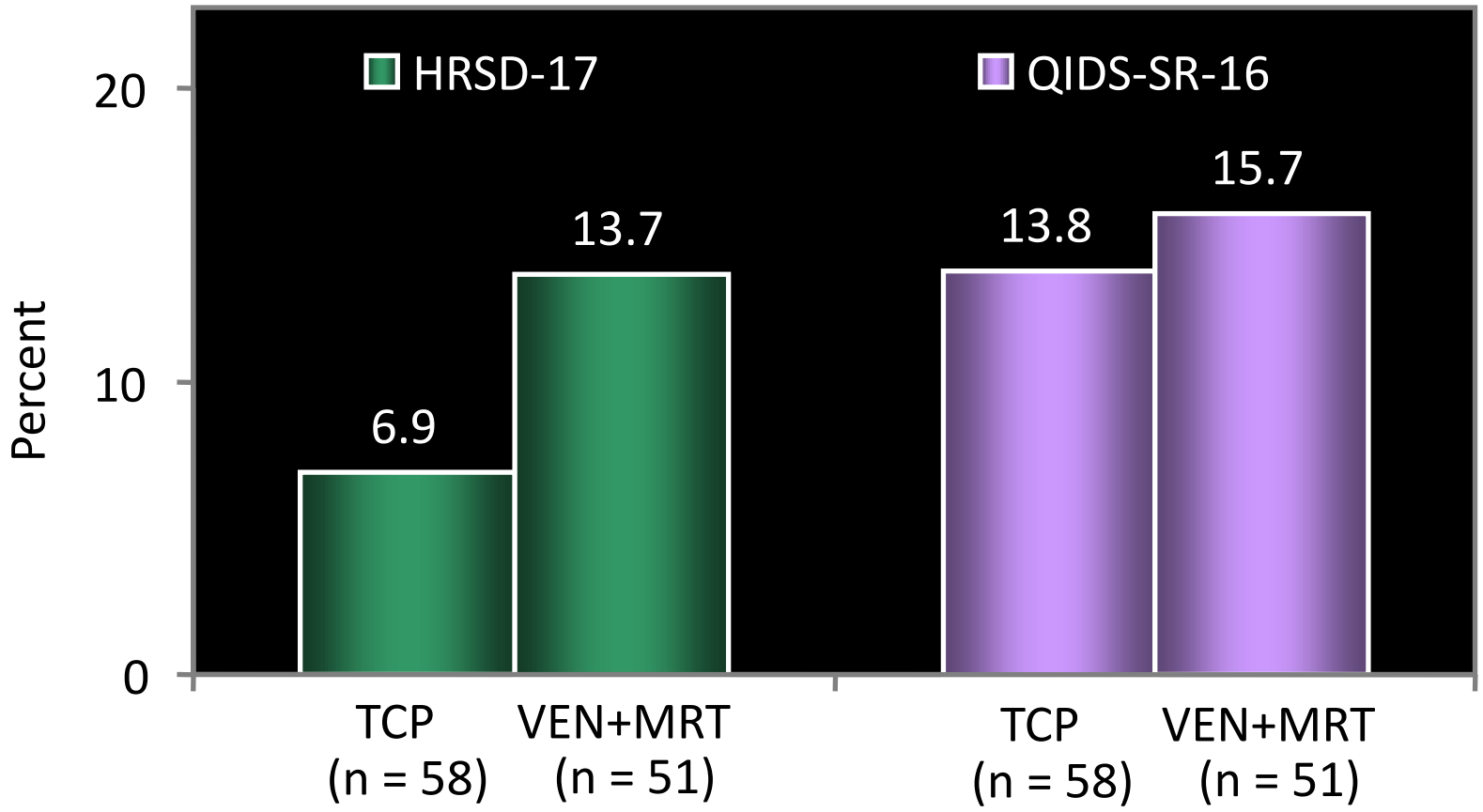
FIGURE 1. Mean Scores on the Hamilton Depression Rating Scale (HAM-D), by Visit, for All Patients Treated (Last Observation Carried Forward) in a Randomized Trial of Antidepressant Monotherapy or Combination Treatment[a]



[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



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

Trazodone plus SSRIs

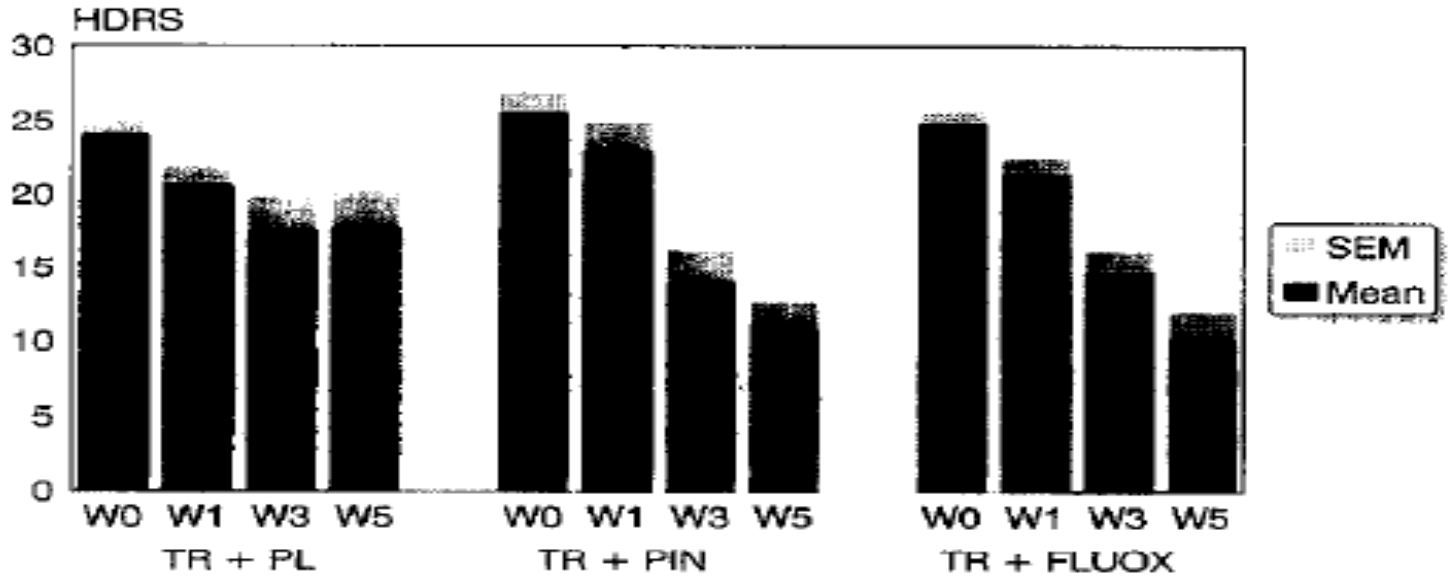


Fig. 1. Mean Hamilton Depression Rating Scale (HDRS) score at baseline (W0), 1 week after treatment with trazodone 100 mg/day (W1), and at weeks 3 (W3) and 5 (W5), after randomization of the patients (at W1) to receive trazodone 100 mg/day + placebo (TR + PL), trazodone 100 mg/day + pindolol 7.5 mg/day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

Maes M et al; Journal of Affective Disorders 41 (1996) 201-210

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