Recent Pharmacotherapy Advances in Bipolar Disorder

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Disclosure

Entity	Role
Allergan	Speakers bureau
American Psychiatric Publishing, Inc	Royalties
BioXCel	Consultant
Neurocrine	Consultant, speakers bureau
Otsuka	Consultant, speakers bureau
SAGE Pharmaceuticals	Consultant
Sunovion	Consultant, speakers bureau
WebMD	Consultant

Objectives

- To understand the clinical significance of recent pharmacotherapy trial findings using newer second generation antipsychotics (SGAs) across phases of bipolar disorder

- To differentiate failed from negative randomized trials and issues of statistical underpowering in recent trials of innovative compounds for bipolar depression

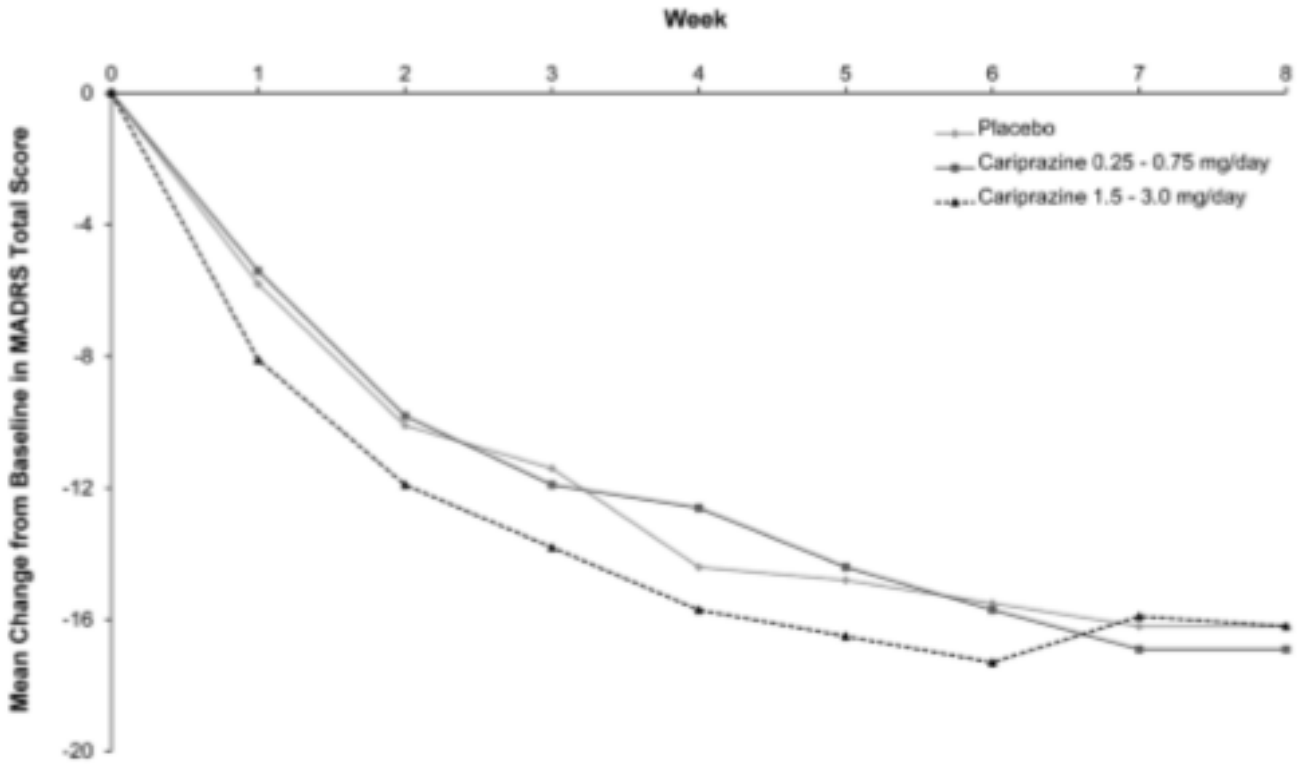
Cariprazine Phase 2 RCT in Bipolar Depression

- Phase 2 trial in BP I and BP II depression conducted 2009-2010

- Low-dose (0.25-0.5 mg; n=75) vs. high dose (1.5-3.0 mg; n=75) cariprazine vs. placebo (n=75)

- *Neither group differed from placebo*

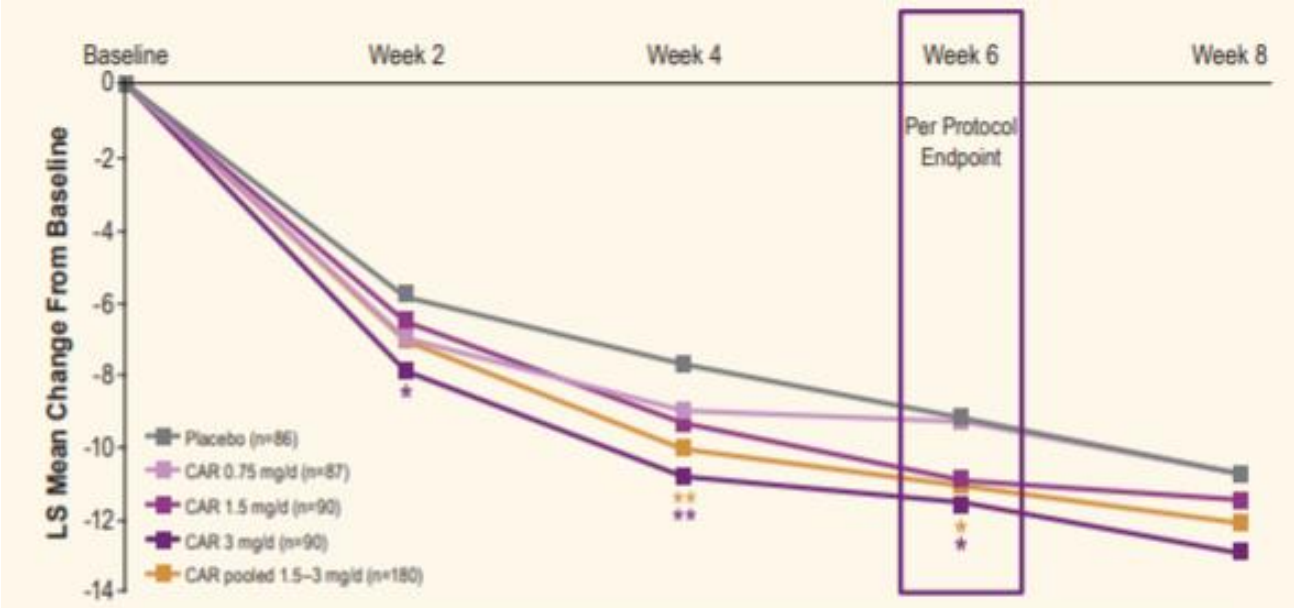
- When excluding placebo responders (post hoc) both cariprazine dosage groups had lower 4-6 week MADRS scores than did placebo ($p<.05$)



Yatham et al., *Int Clin Psychopharmacol* 2020; 35: 147-156

Recent Post Hoc/Secondary Analyses of Cariprazine FDA Registration Trial Data in Bipolar Depression

Bipolar depression with mixed features



Week 6 (MMRM)	CAR 0.75 mg/d	CAR 1.5 mg/d	CAR 3 mg/d	CAR 1.5–3 mg/d
LSMD (95% CI) vs PBO	-0.2 (-2.4, 2.1)	-1.7 (-4.0, 0.5)	-2.4 (-4.6, -0.1)	-2.0 (-4.0, -0.1)

*P<.05, **P<.01 versus placebo.
CAR, cariprazine; CI, confidence interval; $HAMD_{17}$, 17-item Hamilton Depression Rating Scale; LS, least squares; LSMD, LS mean difference; MMRM, mixed-effects model for repeated measures; PBO, placebo.

Stahl et al., Poster presented at the American College of Neuropsychopharmacology (ACNP), Palm Springs, CA; Dec 3-7, 2017

Recent Post Hoc/Secondary Analyses of Cariprazine FDA Registration Trial Data in Bipolar Depression

Subgroup with baseline HAM-A score ≥18 (n=529)

Outcome	1.5 mg cariprazine
Δ MADRS	-2.4 (p=.002)
MADRS Remission	32% cariprazine 21% placebo p=.0172, NNT=9
Δ HAM-A	-1.9 (p=.0105)

Outcomes for 3 mg/day dosing were superior to placebo in the non-anxious subgroup (n=423)

Yatham et al., presentation at APA Annual Meeting, Philadelphia, PA, May 25-29, 2020

Lurasidone for Bipolar Relapse Prevention

- Open label lurasidone (20-80 mg/day, mean dose=52.3 mg/day) + lithium or valproate stabilization for up to 20 weeks

- Then up to 28 weeks of lurasidone (mean dose= 54.4 mg/day) + lithium or valproate (n=246) or placebo + lithium or valproate (n=250)

- Time to depressive recurrence: HR=0.71 (95% CI=0.49-1.34, p=ns)
Time to manic/mixed recurrence: HR=0.57 (95% CI=0.28-1.16, p=ns)

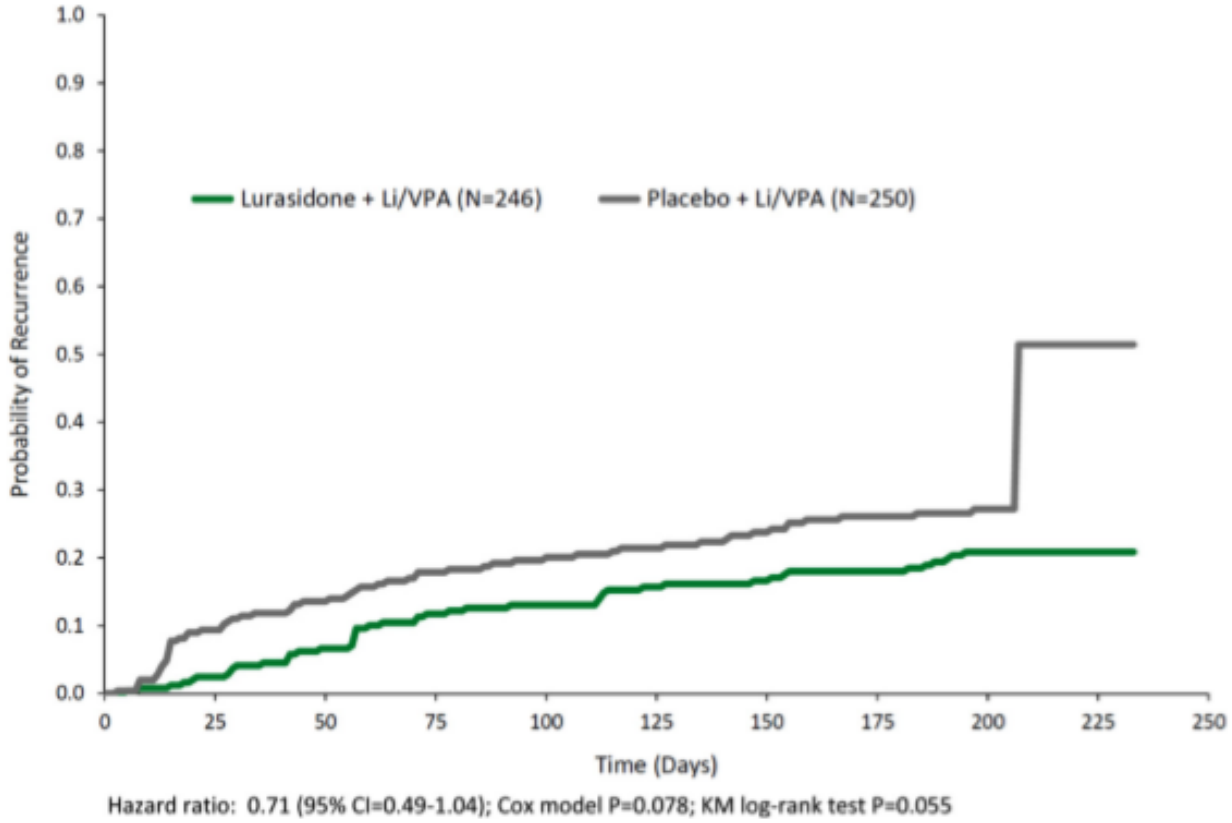


Figure 2 Kaplan-Meier curve: time to recurrence of any mood episode (primary efficacy analysis, total sample).

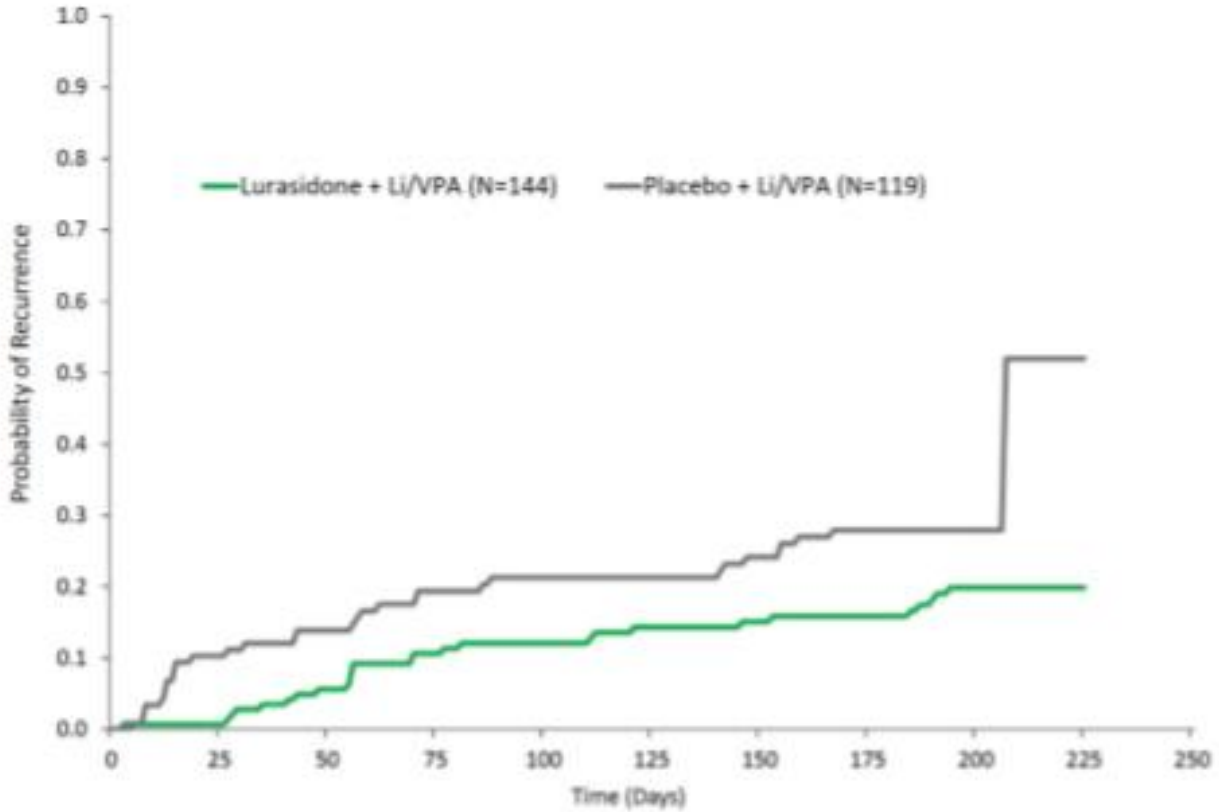
Calabrese et al., Eur Neuropsychopharmacol 2017; 27: 865-878

Lurasidone for Bipolar Relapse Prevention: Index Episode=Depressed (n=263)

If index episode polarity=manic/ hypomanic/mixed:

HR=0.82 (95% CI=0.47-1.45, p=ns) for Mania relapse

HR=0.83 (95% CI=0.35-2.00, p=ns) for Depression relapse



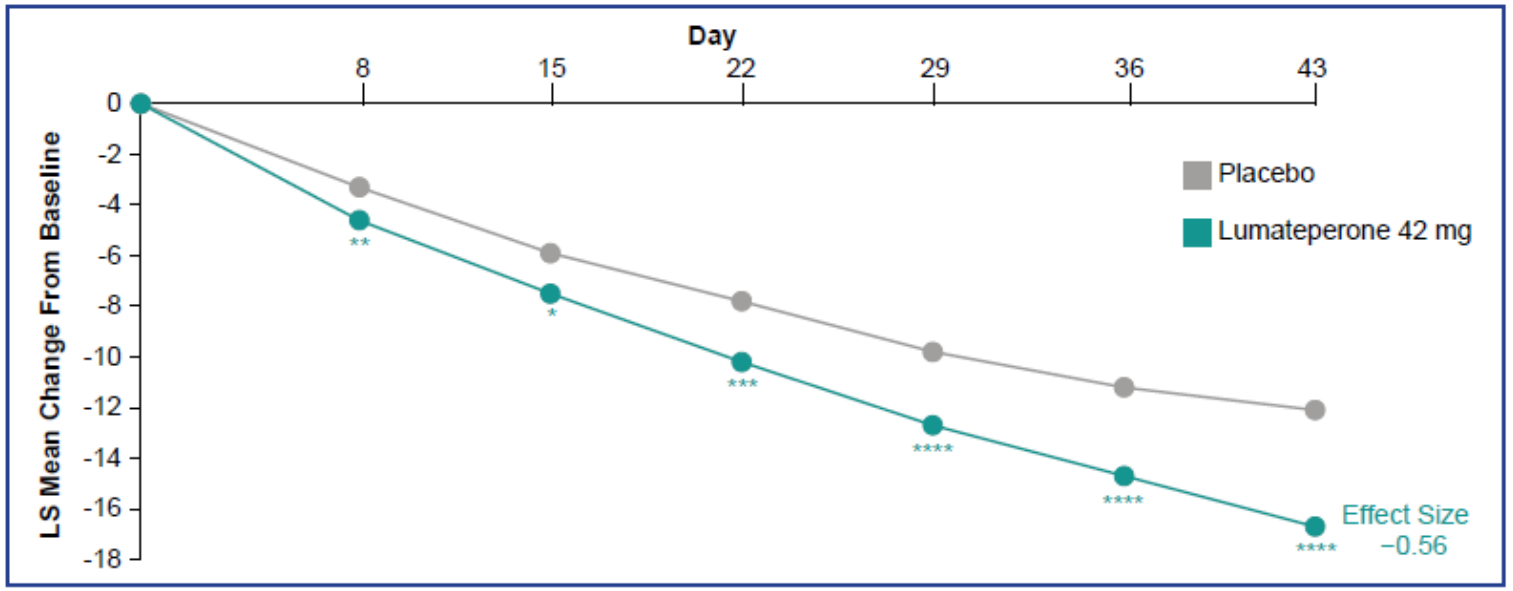
Hazard ratio: 0.57 (95% CI=0.34-0.97); Cox model P=0.039; KM log-rank test P=0.068

Figure 4 Kaplan-Meier curve: time to recurrence of any mood episode for patients with an index episode of depression.

Calabrese et al., Eur Neuropsychopharmacol 2017; 27: 865-878

Lumateperone in Acute Bipolar Depression

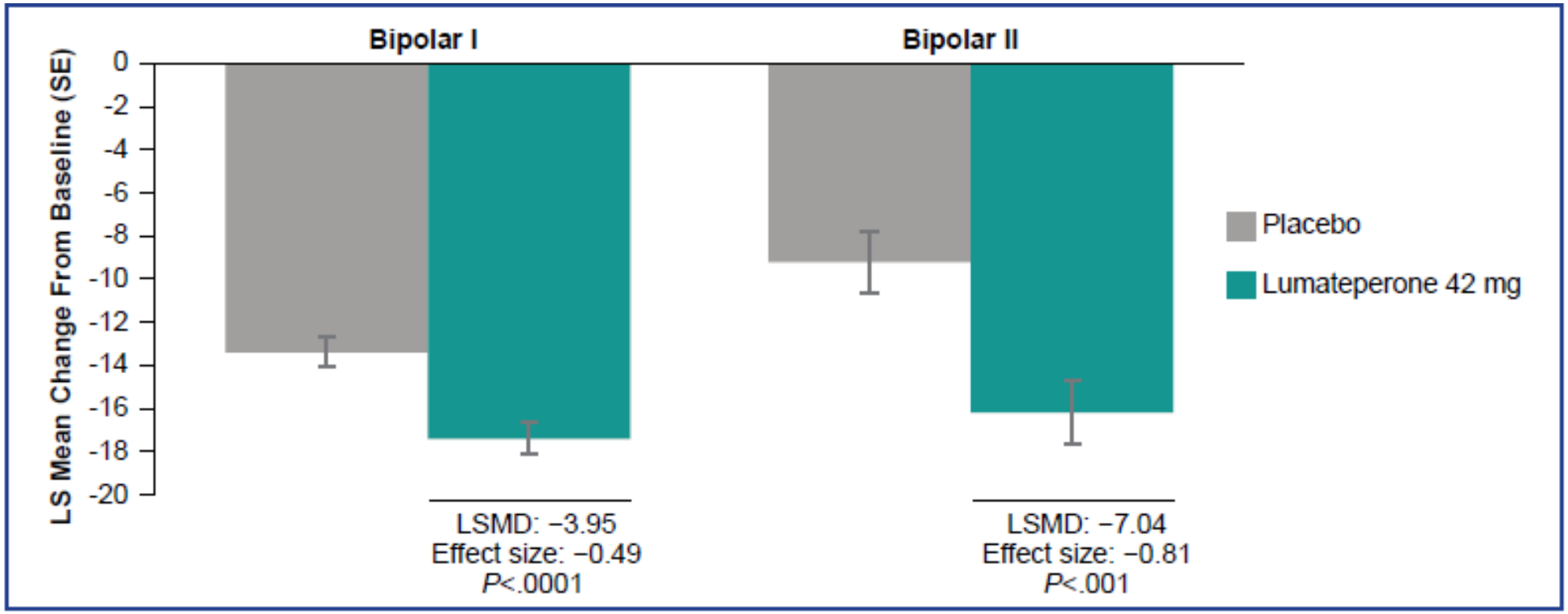
Six-week randomized study of 381 bipolar depressed subjects comparing lumateperone 42 mg/day or placebo



* $P < .05$, ** $P < .01$, *** $P < .001$, **** $P < .0001$ LSMD vs Placebo. MMRM in the ITT population.
Effect size calculated as LSMD/pooled estimate of within subject error standard deviation.
ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures.

Durgam et al., ACNP Ann Meeting 2019

Lumateperone in Acute Bipolar Depression

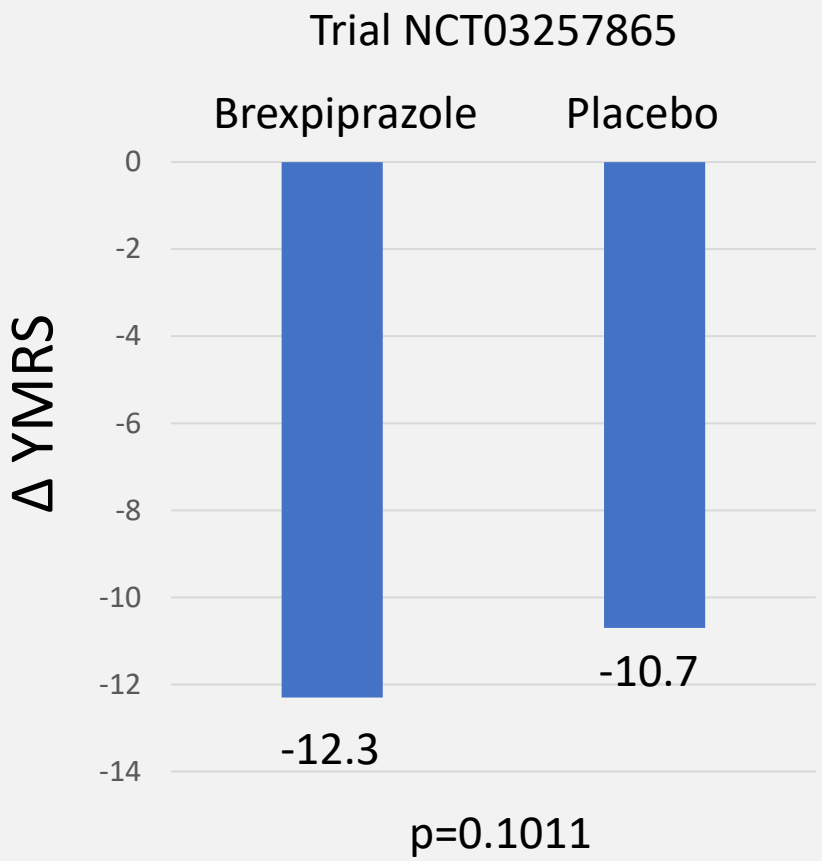


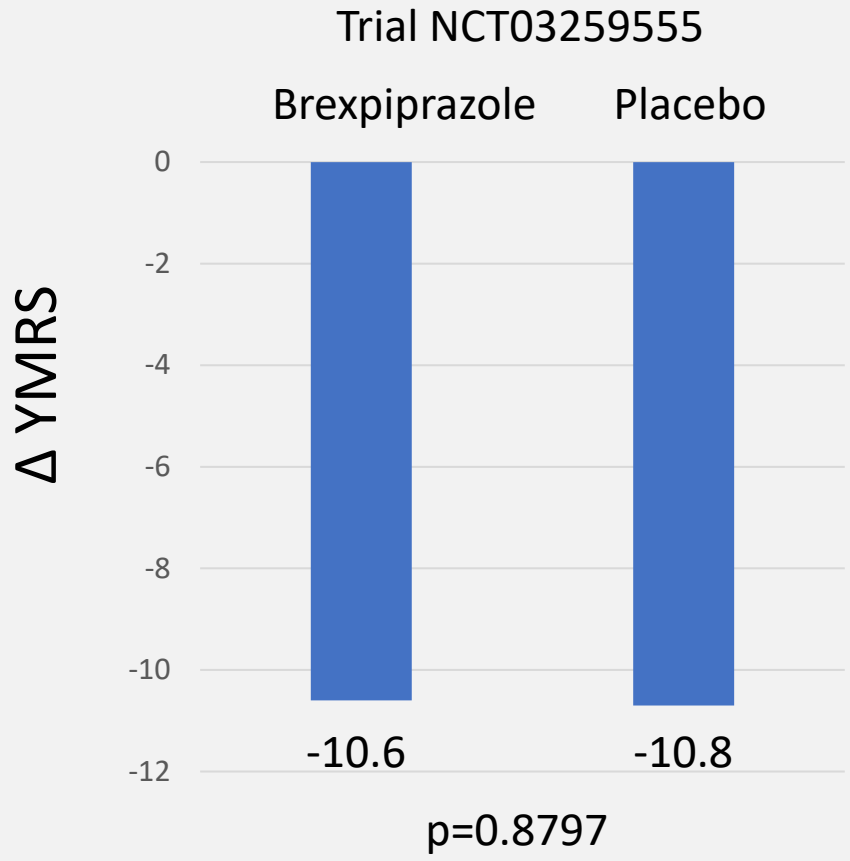
LSMD vs Placebo. MMRM. Effect size calculated as LSMD/pooled estimate of within subject error standard deviation.
ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; SE, standard error.

Durgam et al., ACNP Ann Meeting 2019

Brexpiprazole in Acute Bipolar Mania

- 2 (-) Phase III 3-week RCTs, n=650, brexpiprazole 2-4 mg/day

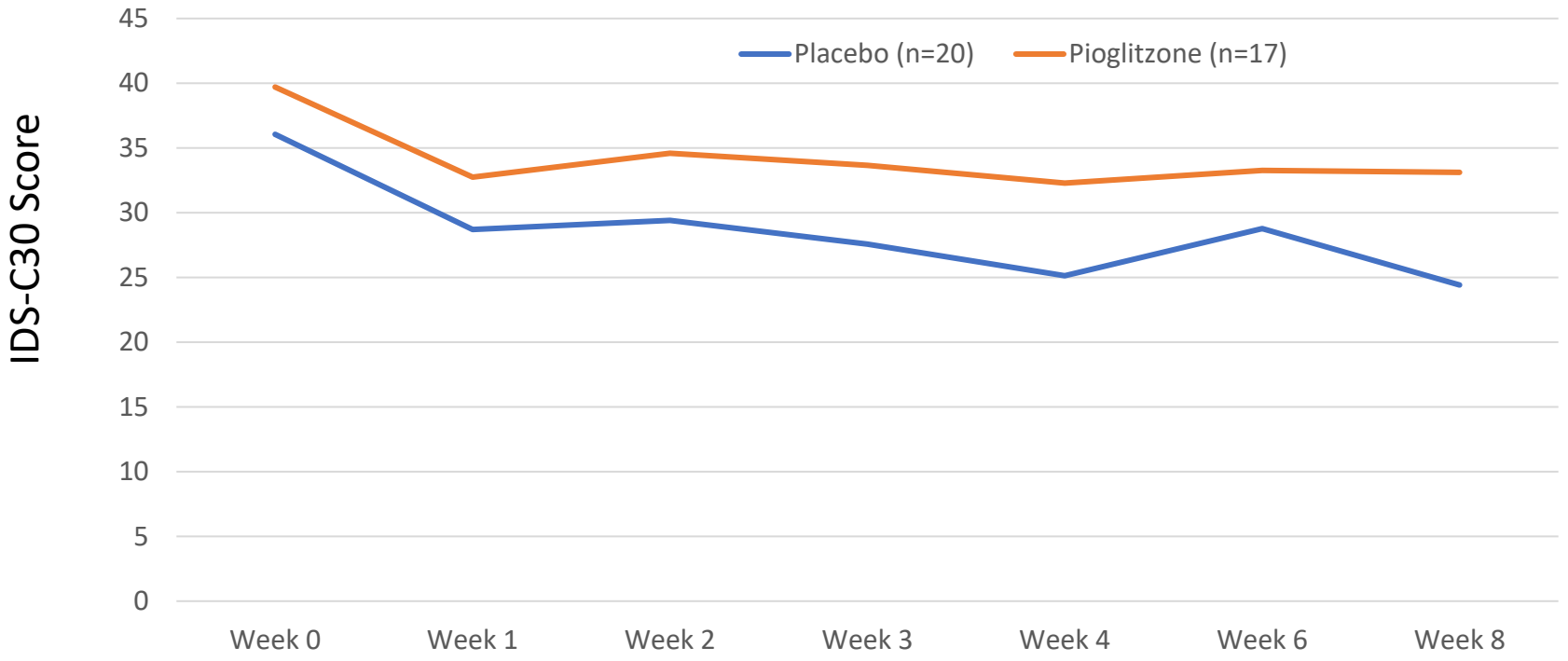




Data on file, Lundbeck

Pioglitazone vs. Placebo in Acute Bipolar Depression

Pioglitazone (15-45 mg/day) may have antidepressant properties by lowering insulin resistance



Mixed effect model: p=0.056 in favor of **placebo**

Δ Leptin scores correlated with Δ IDS (r=0.67, p=0.047)

Aftab et al., *J Affect Disord* 2019; 245: 957-964

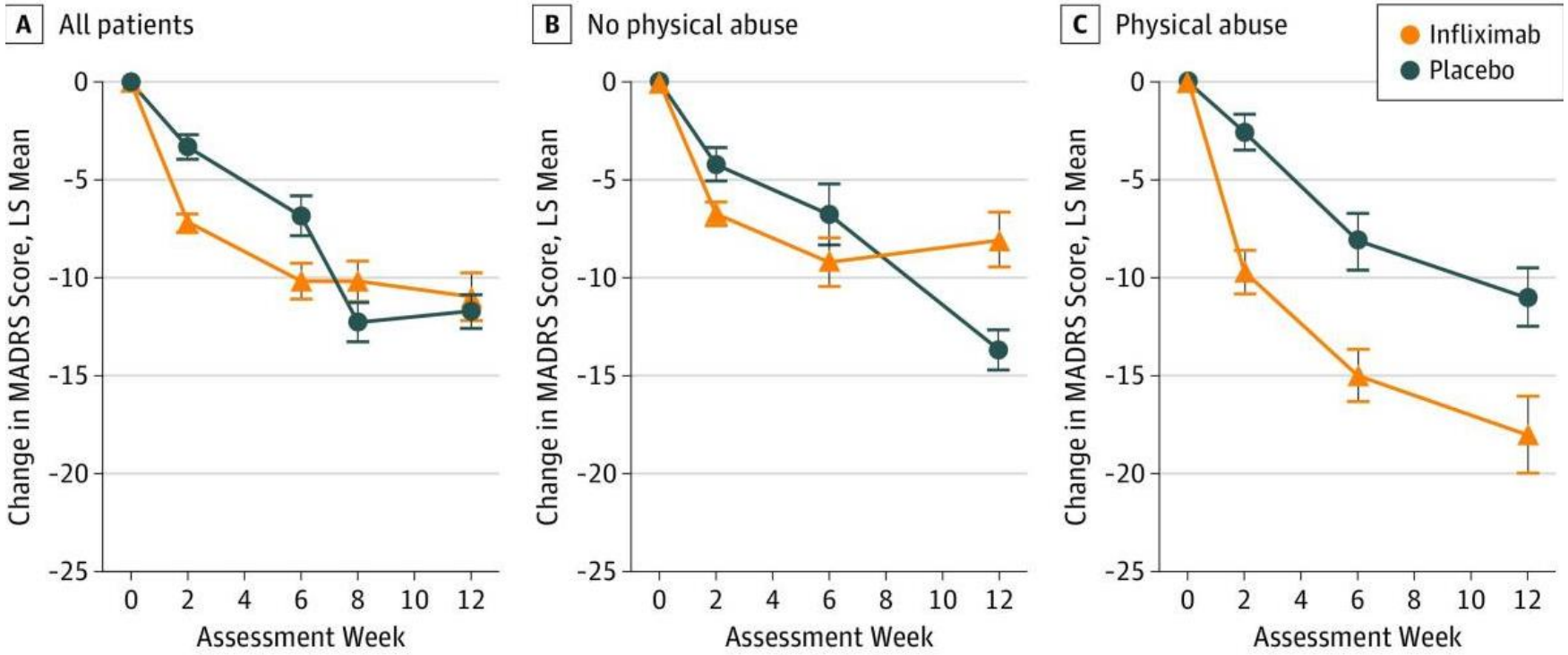
Infliximab vs. Placebo in Bipolar I/II Depression

12-week RCT of infliximab (n=29) or placebo (n=31)

Infusions at baseline and weeks 2 and 6

No *overall* significant difference at week 12

No significant treatment interaction by CRP



X^2=12.20, p=.02

Higher response rate (p=0.04)

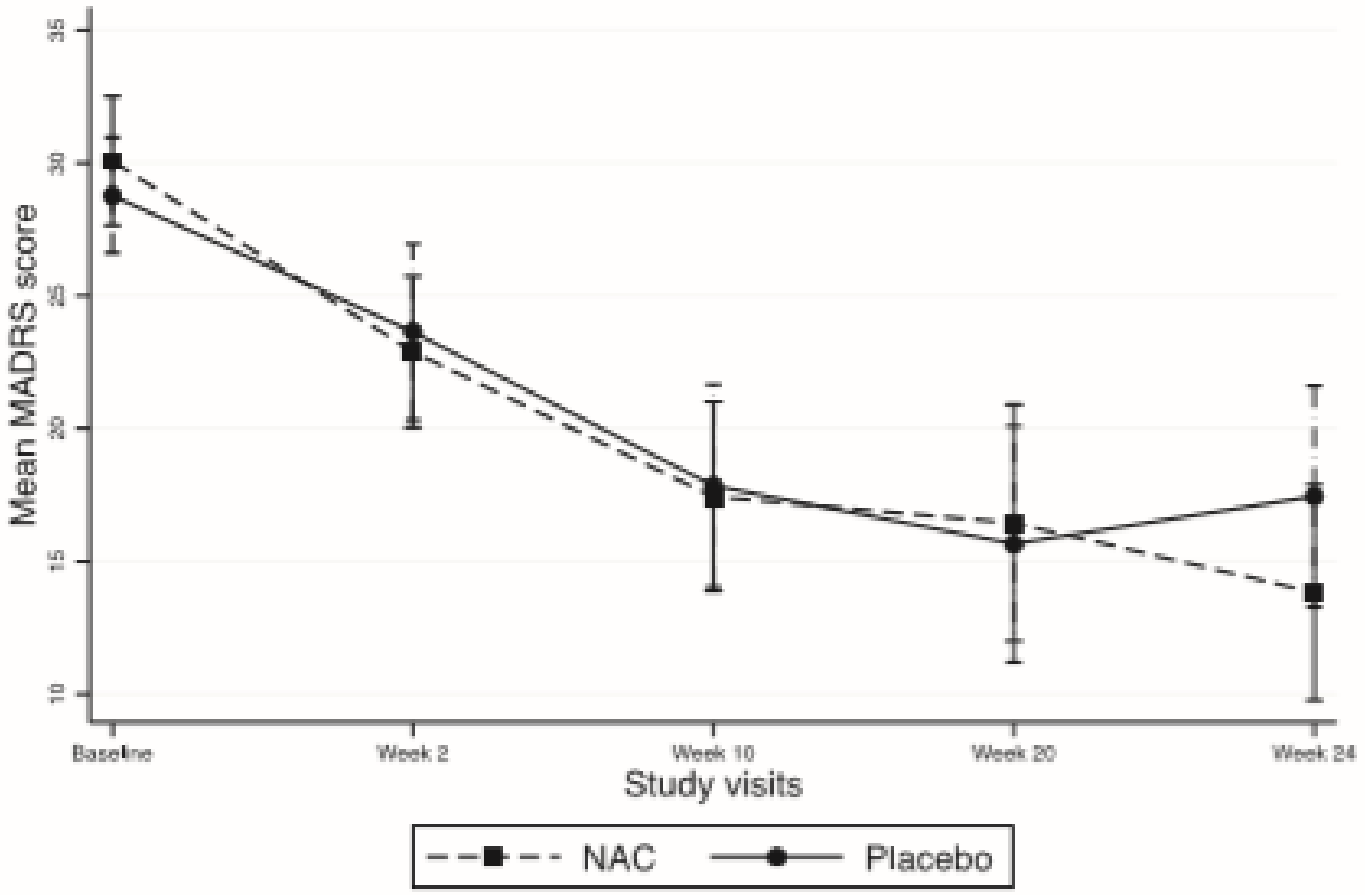
McIntyre et al., *JAMA Psychiatry* 2019; 76: 783-790

Adjunctive N-Acetylcysteine in Bipolar Depression

20-week RCT of NAC (3 gms/day; N=80) or placebo (n=80)

No significant difference in MADRS scores by mixed regression

Placebo response rate=**55.6%**



Ellegaard et al., J Affect Disod 2019; 245: 1043-1051

Summary

- Broadening data on breadth of spectrum with some SGAs (i.e.,lumateperone in bipolar depression; cariprazine in bipolar depression with mixed features and probable (low) dose-related efficacy in anxious bipolar depression)
- Lack of evidence for maintenance efficacy with lurasidone may (?) reflect lack of enrichment for index polarity of depression, possible better efficacy against depressive than mania recurrences
- Preliminary negative trials in bipolar depression with novel pharmacotherapies involving anti-inflammatory mechanisms may reflect methodological shortcomings (underpowering, elevated placebo response)