MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Bipolar Depression Update 2020

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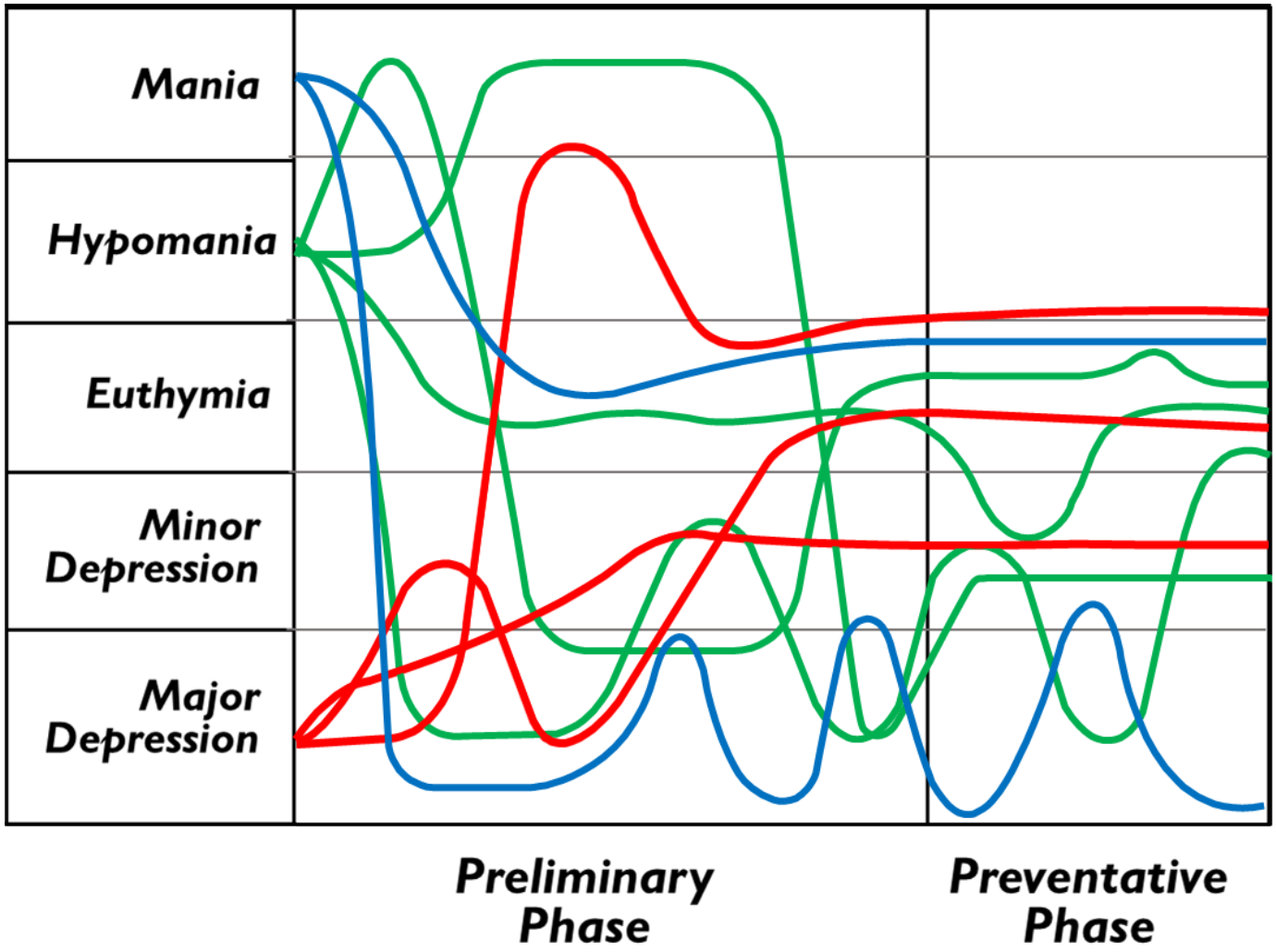
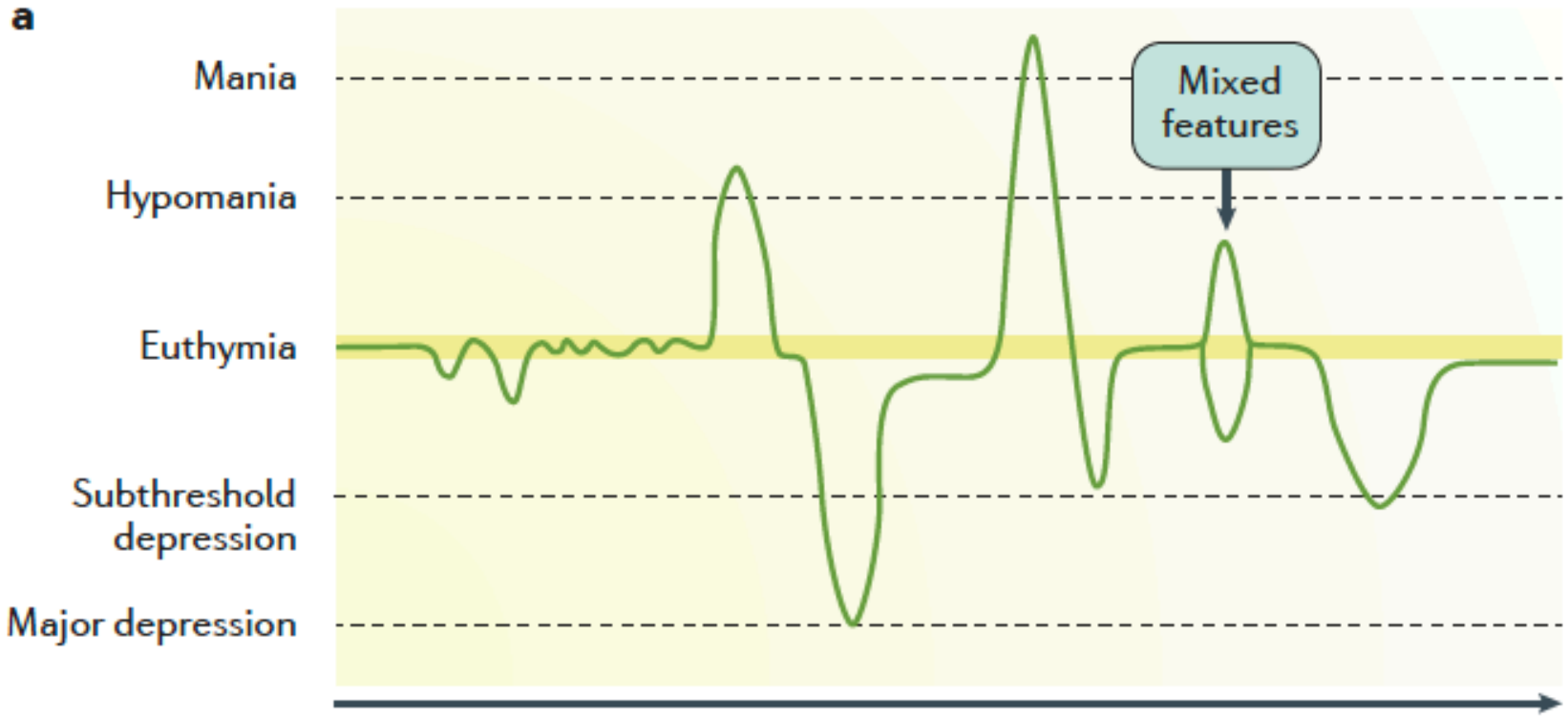
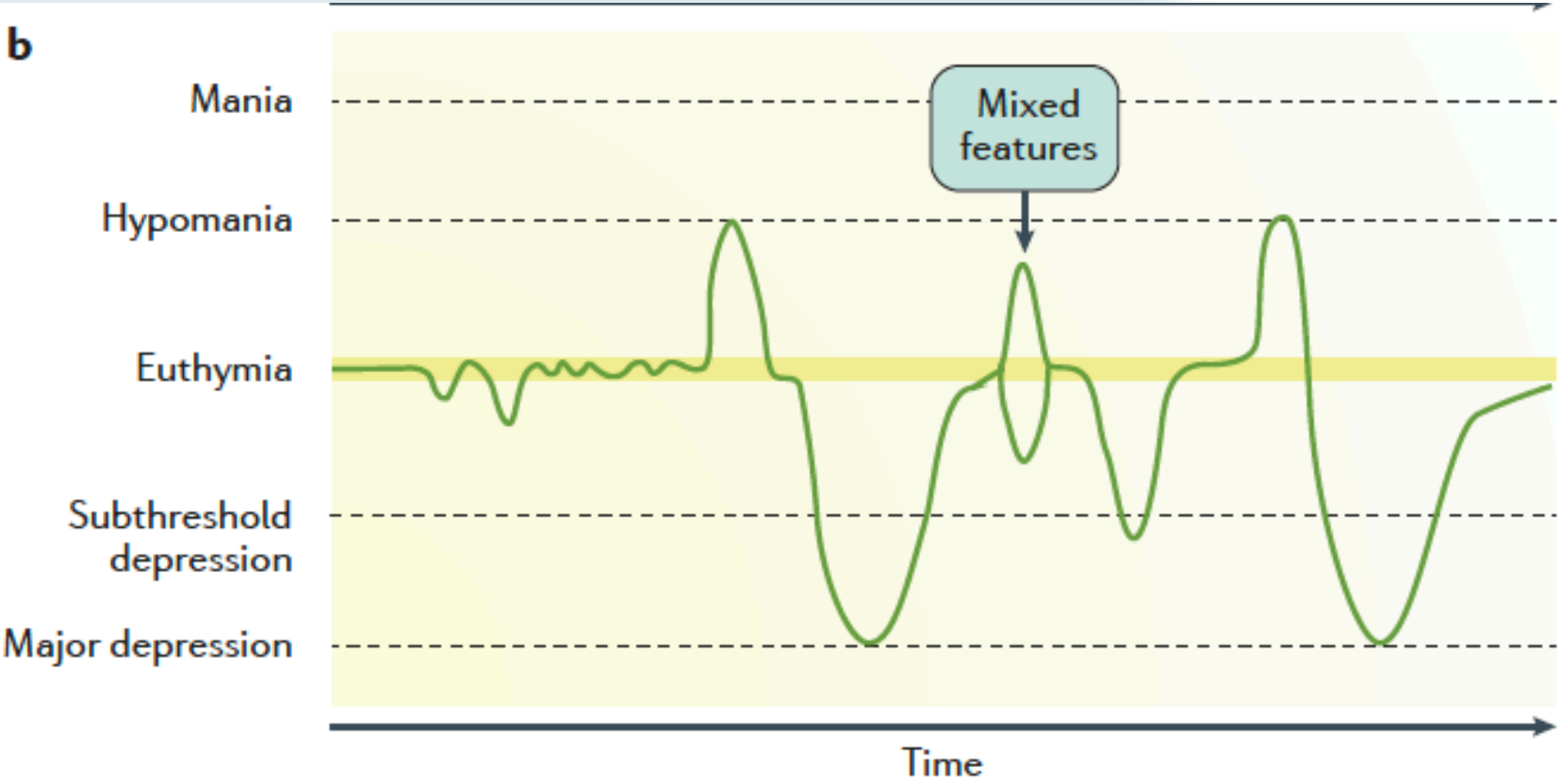
Response, Remission, Recovery, Relapse, Recurrence:
Phases of Treatment of Bipolar Disorder



[1]Frank E, et al. *Biol Psychiatry*. 2000;48(6):593-604.

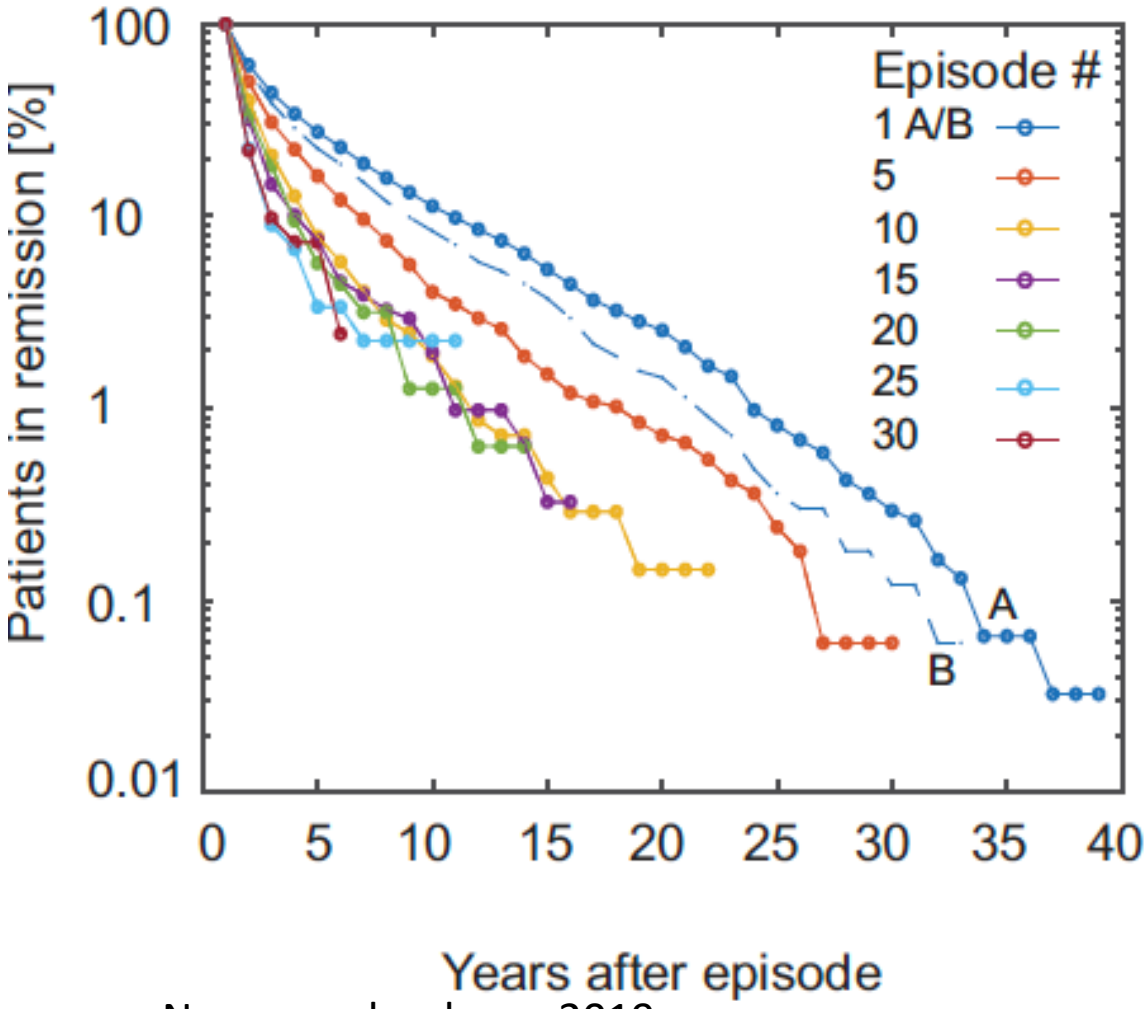


Vieta et al. Nature Reviews Disease Primer 2018



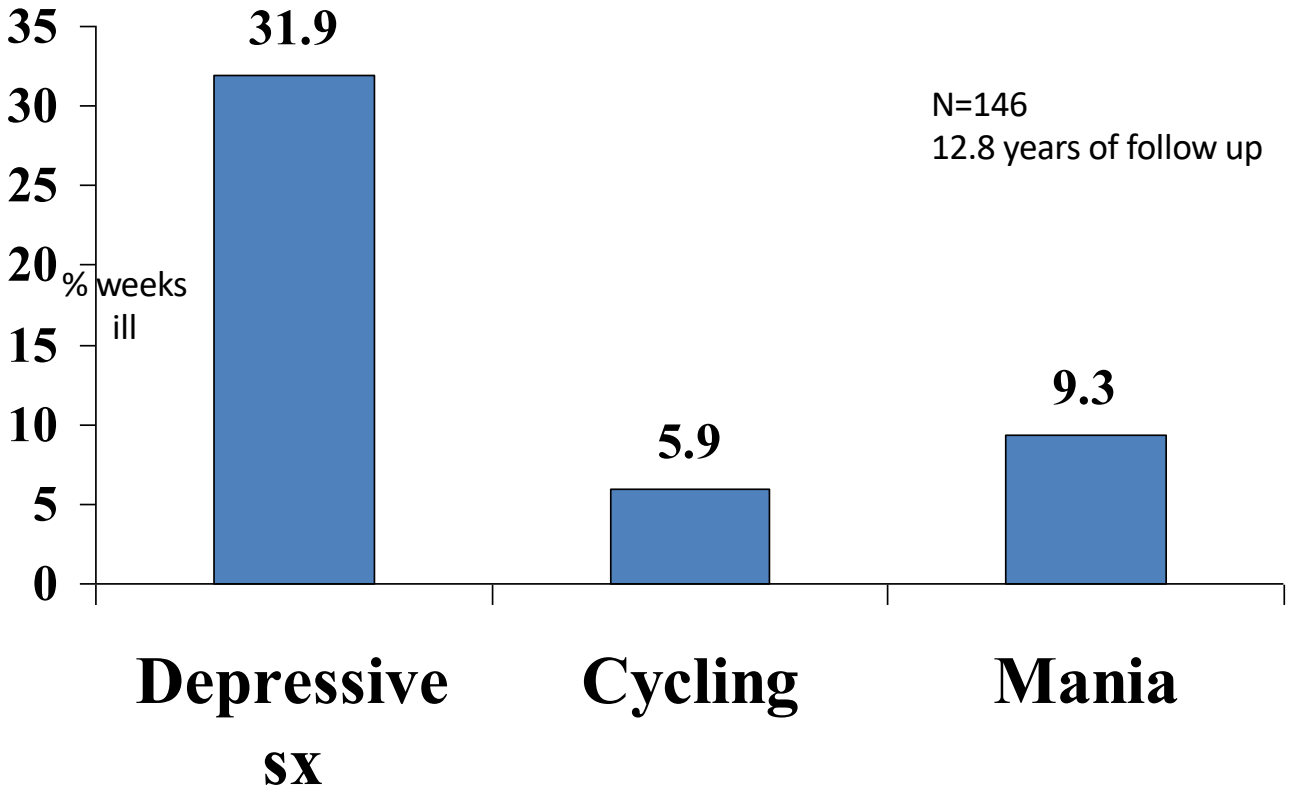
Vieta et al. Nature Reviews Disease Primer 2018

Bipolar Highly Recurrent



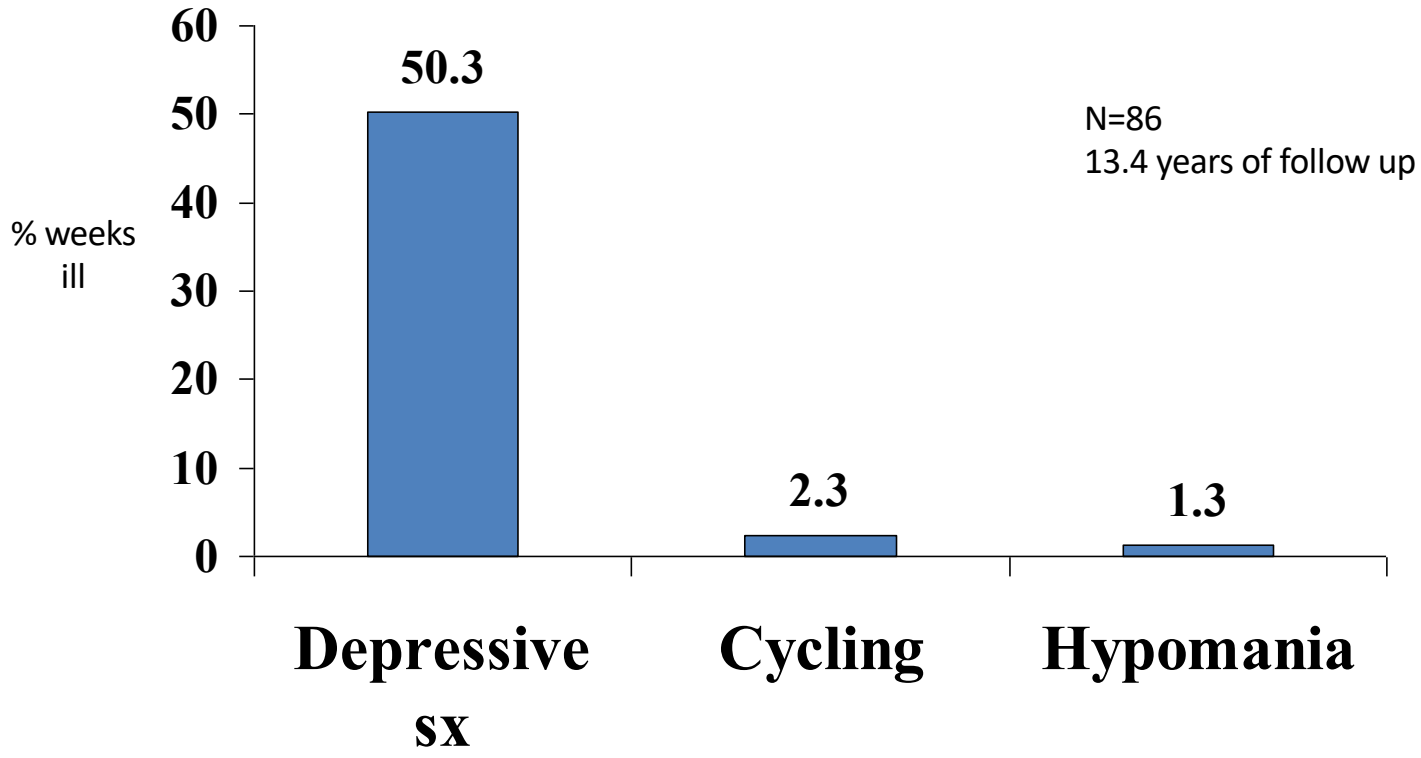
Smedler et al. European Neuropsychopharm 2019

Depressive Symptoms Predominate in BPI

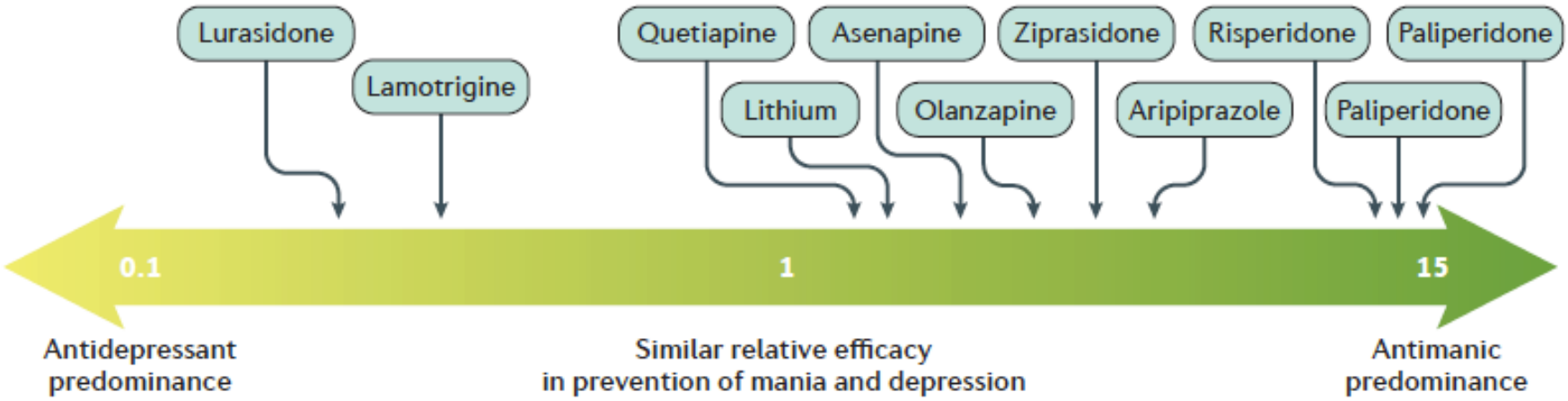


Judd et al. Arch Gen Psych 59:530-537, 2002

Depressive Symptoms Predominate in BPII



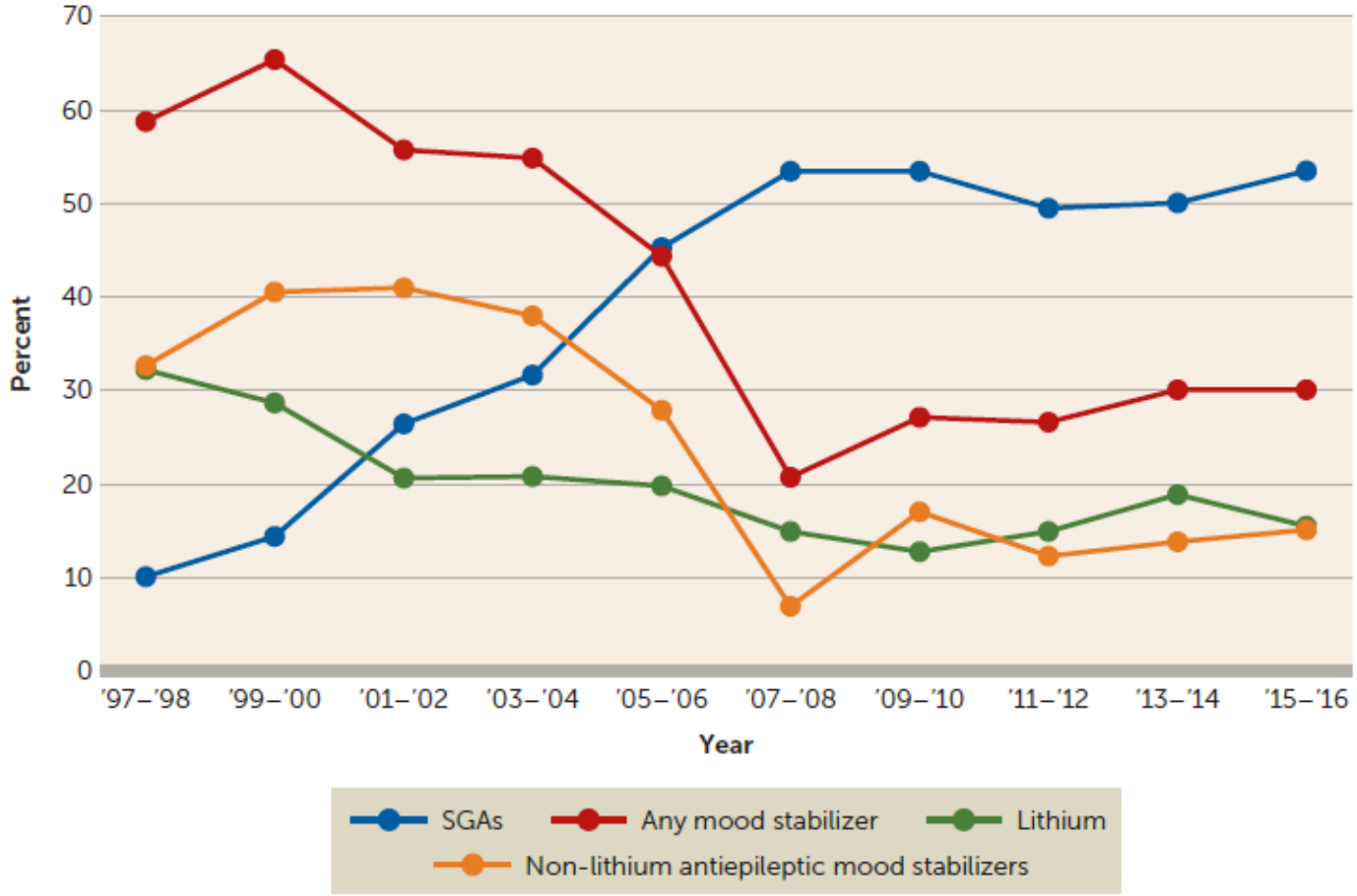
Judd et al. Arch Gen Psych 60:261-269, 2003



Vieta et al. Nature Reviews Disease Primer 2018

More antipsychotics, less mood stabilizers

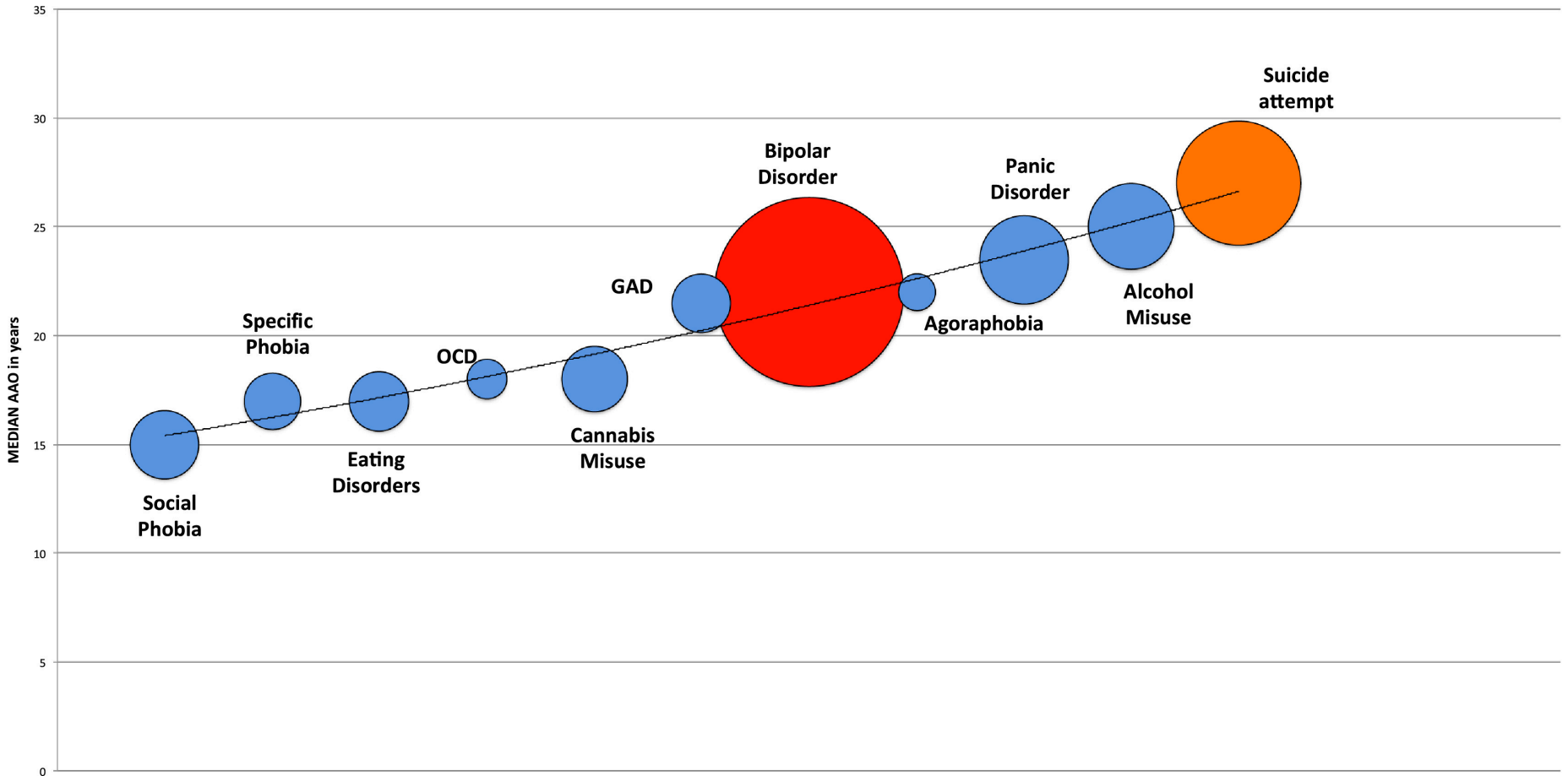
FIGURE 1. Prescribing trends for second-generation antipsychotics (SGAs) and mood stabilizers in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]



[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016.

Rhee, Olfson, Nierenberg, Wilkerson. AJP 2020

Bipolar and age of onset of comorbid conditions



Loftus et al. Journal of Affective Disorders 267 (2020) 258–263

FDA Approved Treatments for Bipolar Depression

Mechanisms of Action Differentiates Effective from Non-Effective Treatments for BP Depression

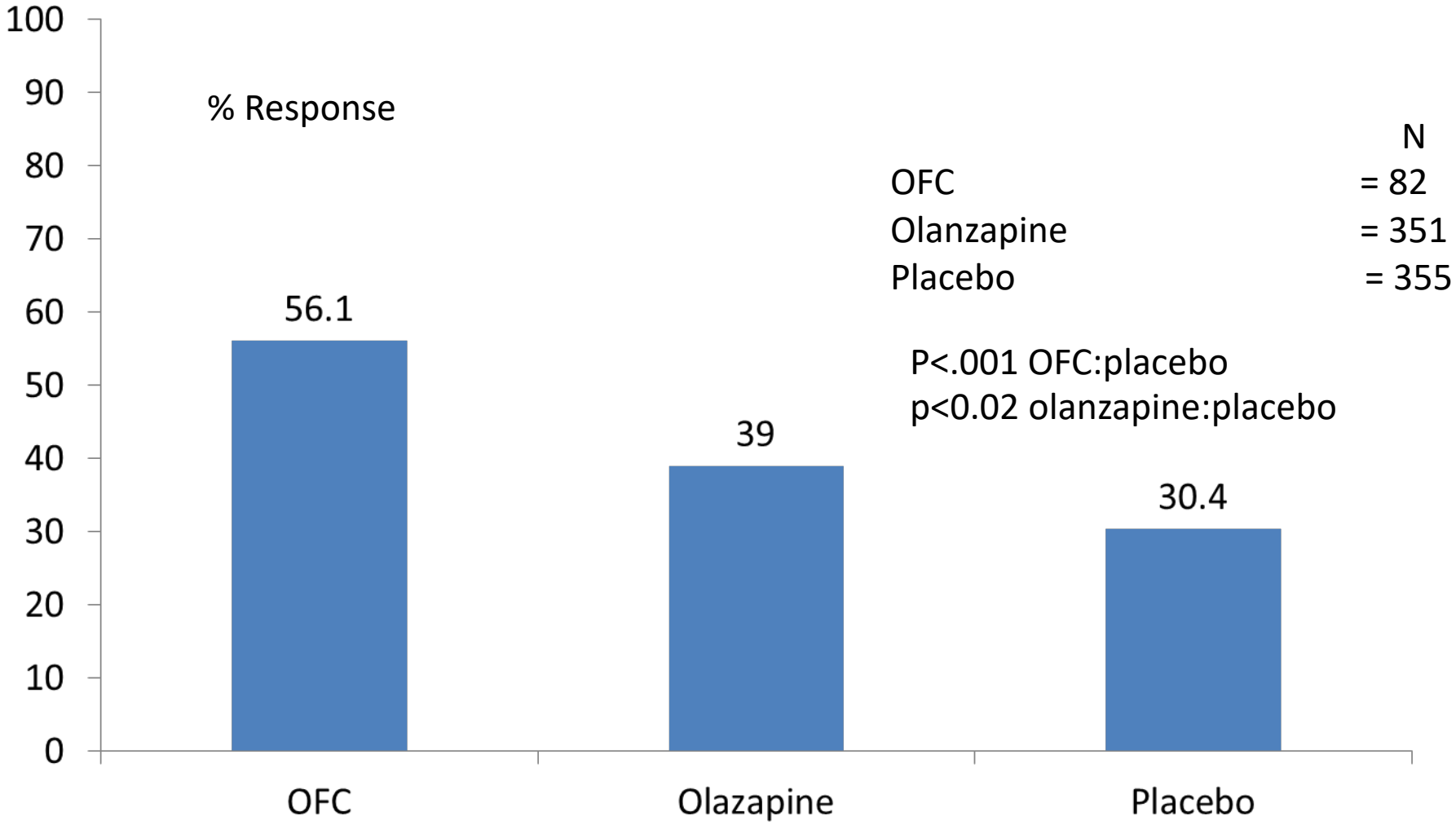
Receptor	Action	Result
Alpha 1	Antagonist	Increase NE
D1	Antagonist	Decrease DA
H1	Antagonist	Decrease Histamine
5HT2A	Antagonist	Increase 5HT
Muscarinic	Antagonist	Decrease Acetylcholine
D2	Antagonist	Mixed effects
D3	Antagonist	Increase DA
NE Reuptake	Inhibition	Increase NE
5HT1A	Agonism	Increase 5HT

Fountoulakas et al. Journal of Affective Disorders 138 (2012) 222–238

FDA Approved

- Olanzapine/Fluoxetine Combination (OFC)
- Quetiapine
- Lurasidone
- Cariprazine
- (Lamotrigine)

OFC for Bipolar I Depression



Tohen M et al. Arch Gen Psychiatry 60:1079-1088. 2003.

Olanzapine Fluoxetine Combination

- Pharmacodynamic profile
  - 5-HT 2c antagonist that increases DA and NE
    - Prefrontal cortex and hypothalamus
  - Histaminergic antagonist decreases energy expenditure
  - Muscarinic 3R antagonist decreases insulin secretion
- Metabolized through CYP450 3A4
- Olanzapine t½ 30 hours
- Fluoxetine/NorFluox 2 to 4 days

S. Koch et al. Neuropharmacology 46 (2004) 232–242; He et al. Psychoneuroendocrinology (2014) 42, 153—164; Weston-Green et al. CNS Drugs (2013) 27:1069–1080

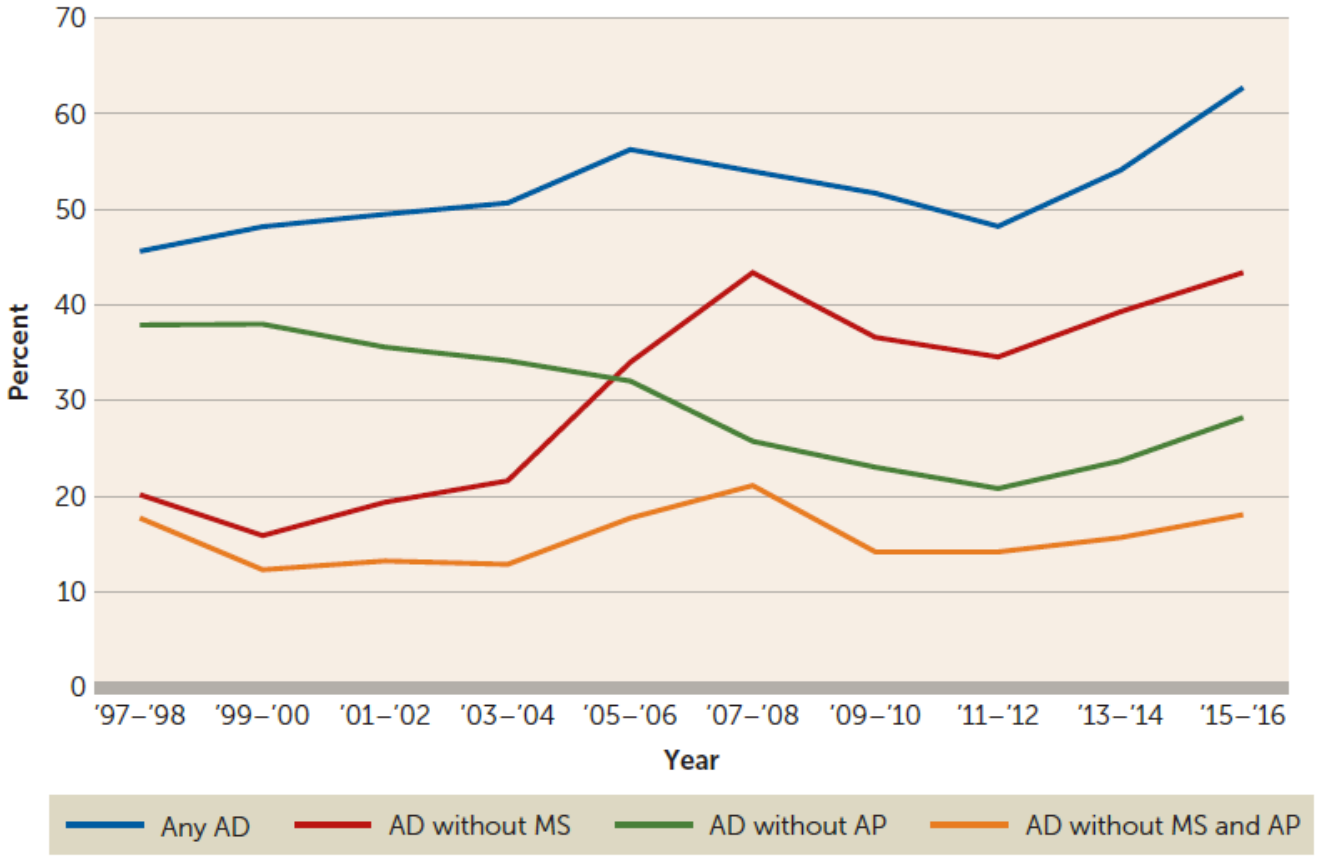
OFC for Bipolar I Depression

- Adjunctive with lithium or valproate
- Side effects
  - Weight gain, dry mouth, asthenia, diarrhea
  - Metabolic syndrome
- Discontinuation rates (8 week study)
  - 61.5% placebo; 51.6% olanzapine, 36% OFC

DOES OFC GENERALIZE TO ANY ANTIPSYCHOTIC/ANTIDEP COMBINATION?

Antidepressants Persist

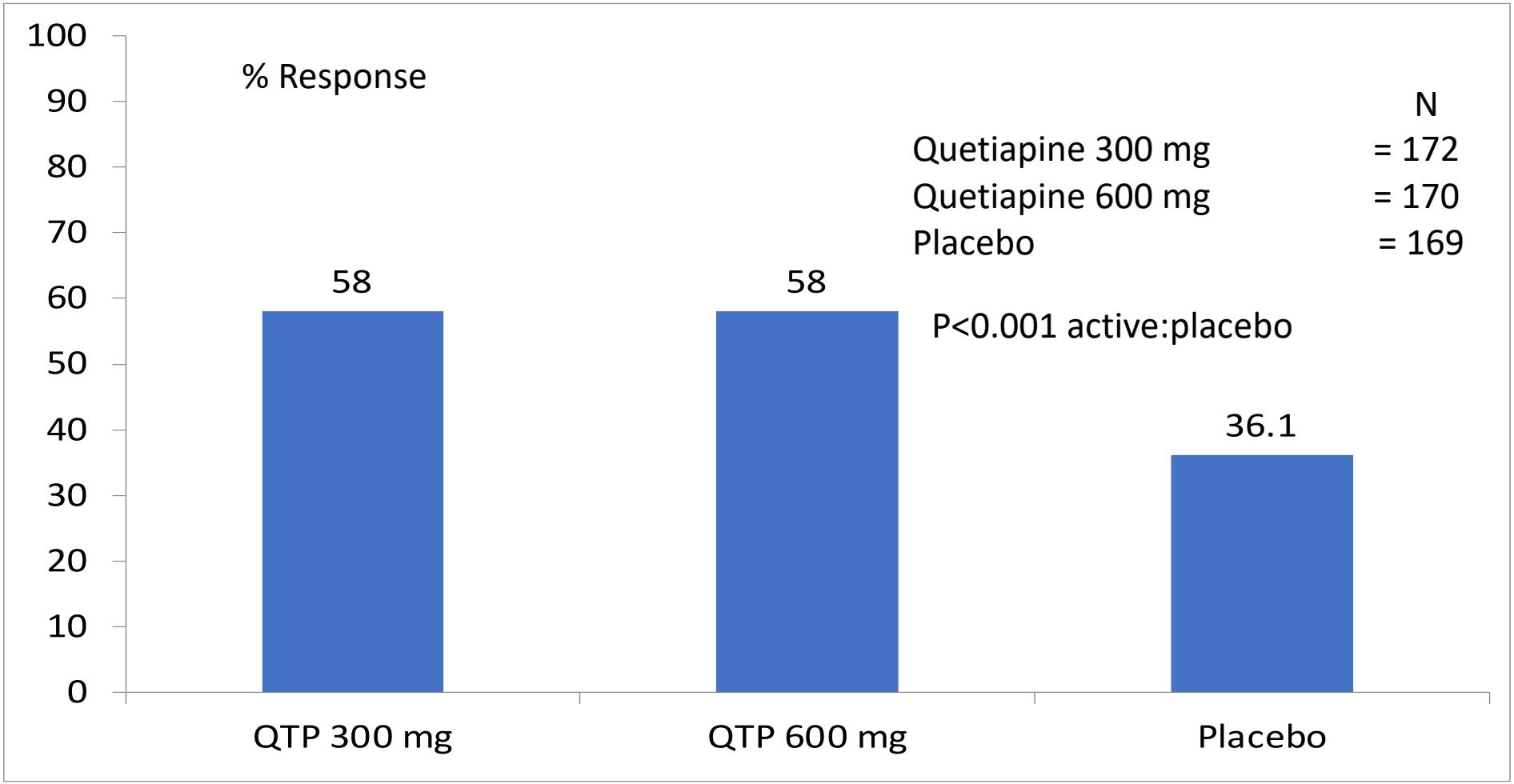
FIGURE 2. Prescribing trends for antidepressants in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]



[a] Data are from the National Ambulatory Medical Care Survey, 1997–2016. AD=antidepressant; AP=antipsychotic; MS=lithium and antiepileptic mood stabilizers.

Rhee, Olfson, Nierenberg, Wilkerson. AJP 2020

Quetiapine for Bipolar I or II Depression



Calabrese et al., Am J Psychiatry. 2005 Jul;162(7):1351-60.

Quetiapine

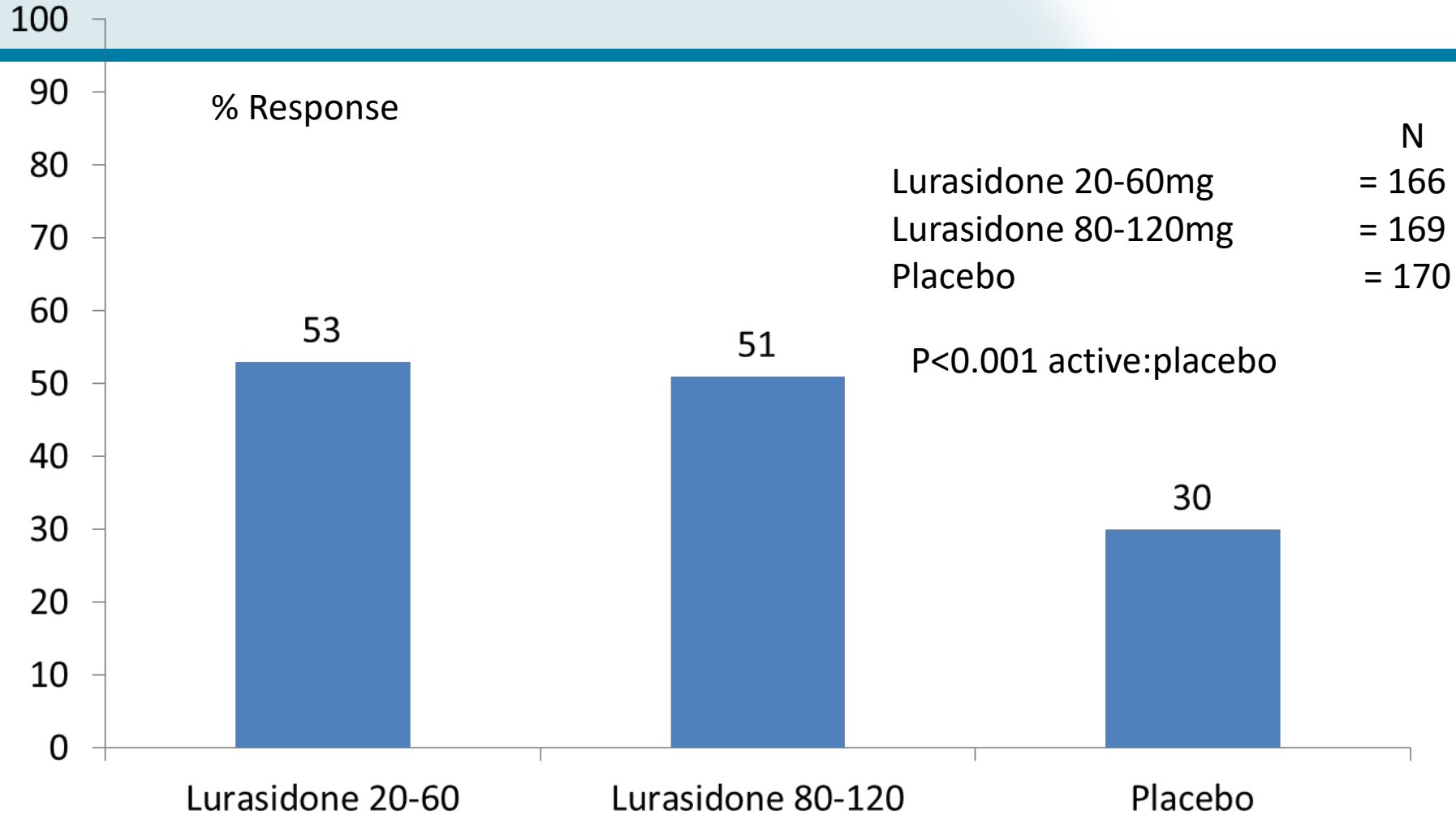
- Pharmacodynamic profile
  - D2 antagonist
  - 5-HT 2a antagonist
  - 5-HT 1A partial agonist
  - Alpha 2c adrenergic agonist
  - Alpha 1 adrenergic antagonist
  - Histaminergic antagonist
  - Muscarinic antagonist
- Metabolized through CYP450 3A4
- t½ 6 hours

Quetiapine

- Monotherapy or adjunctive
- Side effects
  - Dry mouth, sedation, somnolence, dizziness, fatigue, constipation, headache, nausea
  - Metabolic syndrome
- Discontinuation rates (8 week study)
  - Placebo 40.1%;
  - QTP 300 mg 33.1%;
  - QTP 600 mg 45.5%

Calabrese et al. Am J Psychiatry 2005; 162:1351–1360

Lurasidone for Bipolar I Depression



Lobel A, et al. Am J Psychiatry. 2014 Feb;171(2):160-8..

Lurasidone

- Pharmacodynamic profile
  - D2 antagonist
  - 5-HT 2a, 5-HT7 antagonist
  - Alpha 2c adrenergic agonist
  - 5-HT 1A partial agonist
  - Alpha 2a adrenergic antagonist
  - No affinity for histaminergic or muscarinic receptors
- Metabolized through CYP450 3A4
- t½ 18 hours; steady state in 7 days

Lurasidone for Bipolar I Depression

- Monotherapy (Take with food 350 calories)
- Adjunctive with lithium or valproate
- Side effects
  - akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety
- Discontinuation rates (6 week studies)
  - 6.5% placebo;
  - 6.6% lurasidone 20 to 60 mg
  - 5.9 % lurasidone 80-120 mg

Cariprazine

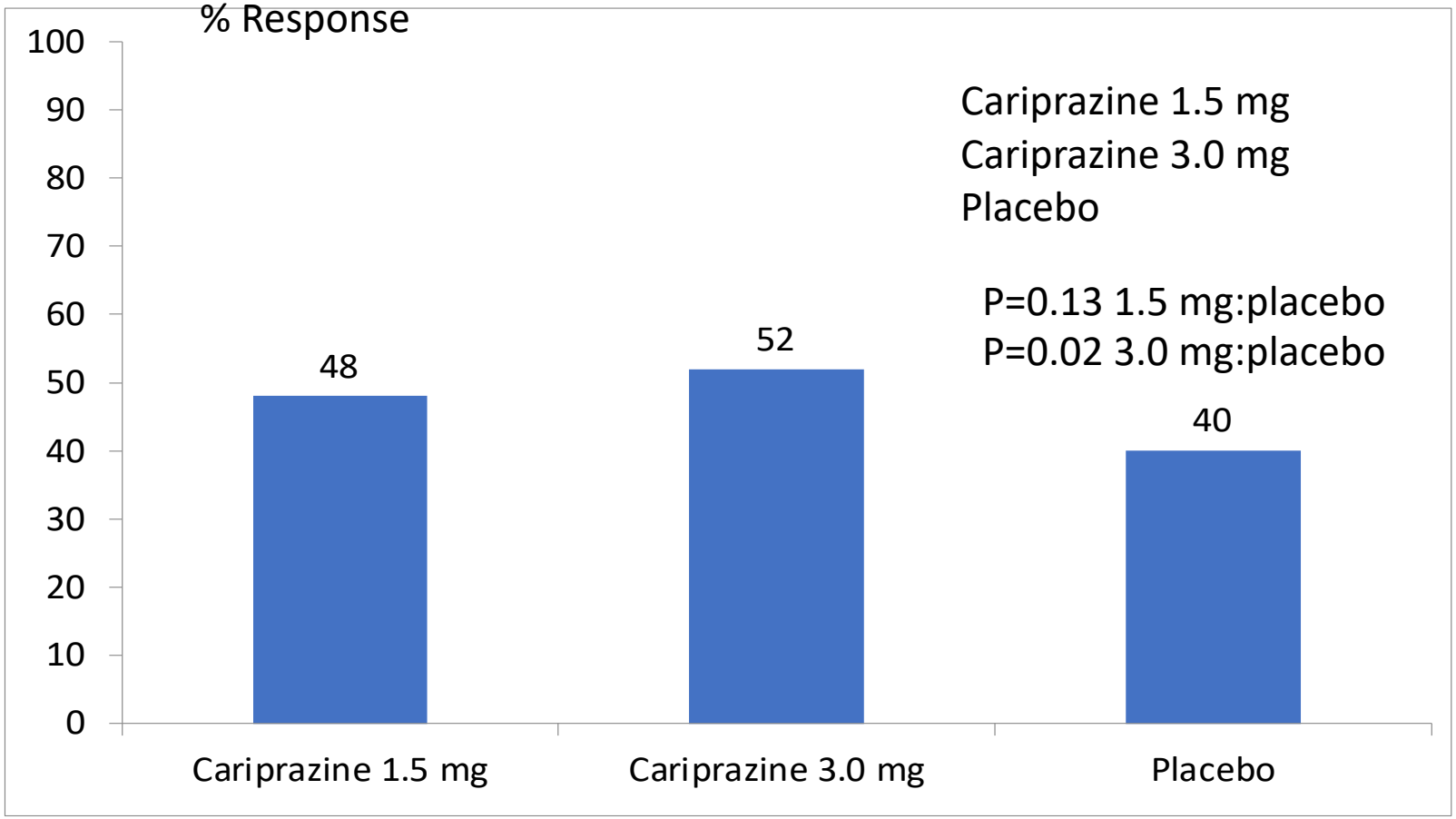
- Pharmacodynamic profile
  - D3/D2 partial antagonist
  - 5-HT 1A partial agonist
  - 5-HT 2a antagonist
  - No affinity for histaminergic or muscarinic receptors
- Metabolized through CYP3A4 and to a lesser extent by CYP2D6
- t½ 2-5 days; steady state in 7 days

Early et al. AmJPsychiatry 2019; 176:439–448

Cariprazine for Bipolar I Depression

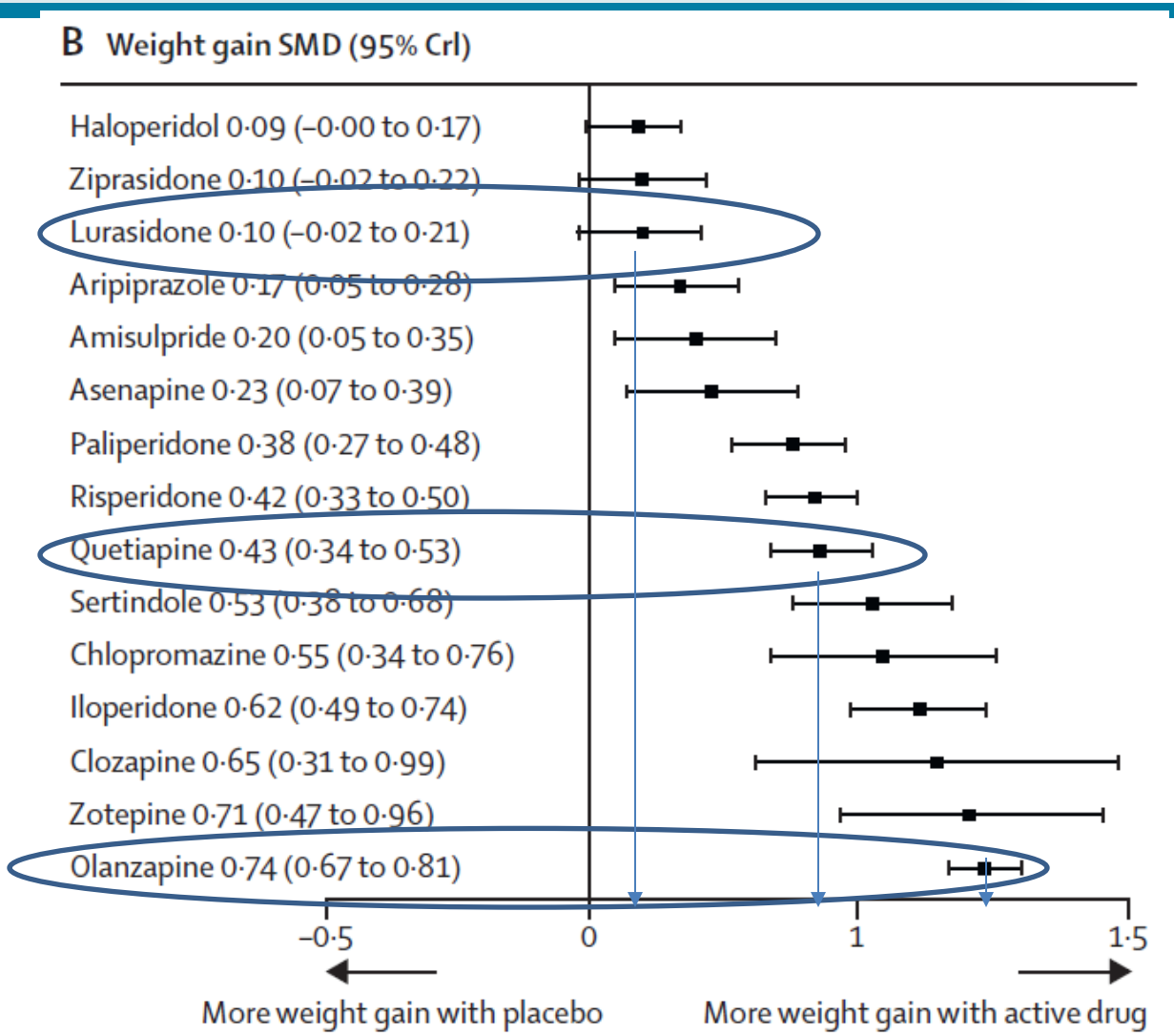
- Monotherapy
- Side effects
  - Restlessness, akathisia, extrapyramidal symptoms, somnolence, vomiting, dyspepsia
- Discontinuation rates (6 week studies)
  - 2.5% placebo;
  - 4.5% lurasidone 20 to 60 mg
  - 5.5 % lurasidone 80-120 mg

Cariprazine for Bipolar I Depression



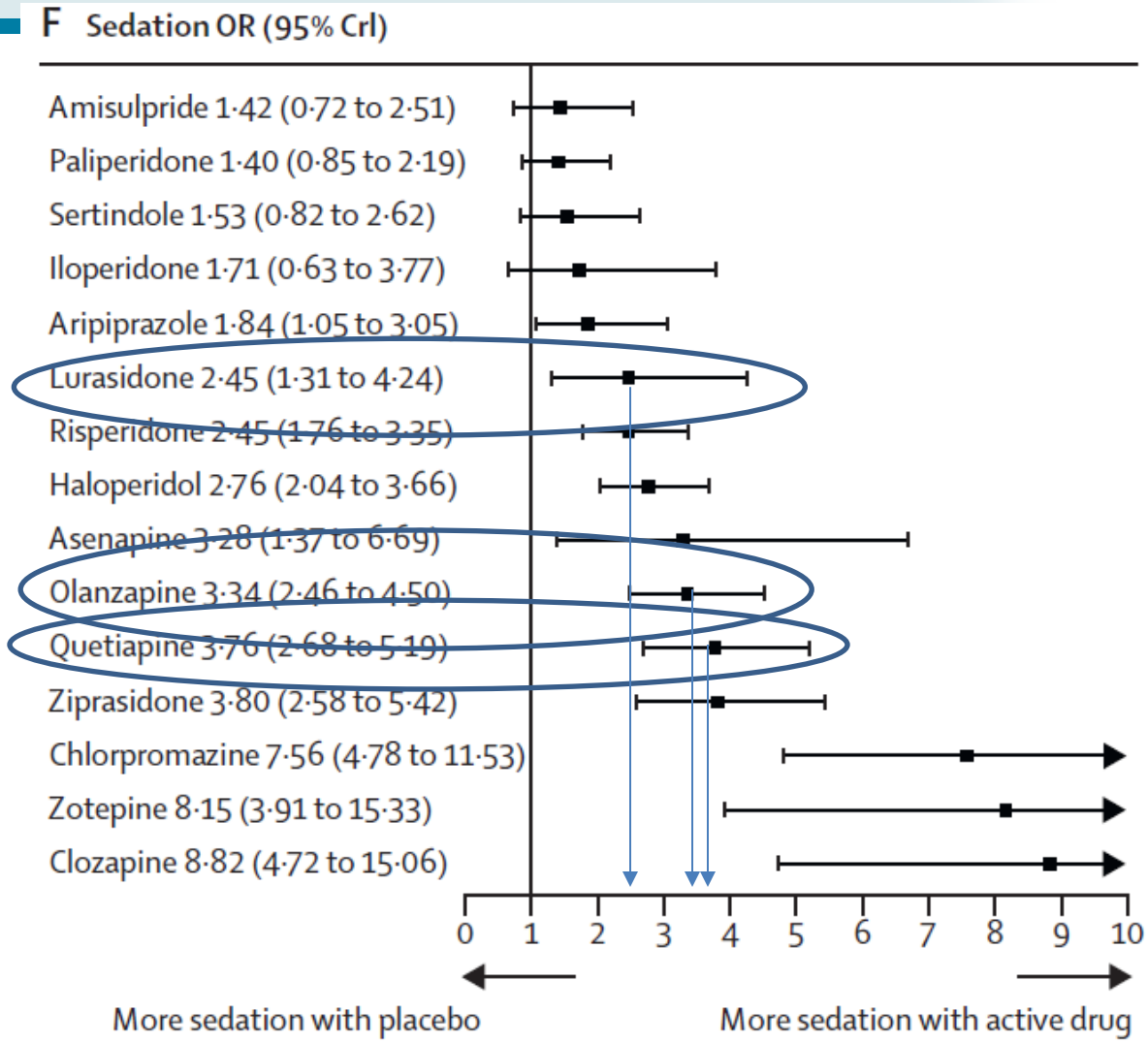
Early et al. AmJPsychiatry 2019; 176:439–448

Comparative Weight Gain (Schizophrenia)



Leucht et al. *Lancet 2013; 382: 951–62*

Comparative Sedation



Leucht et al. *Lancet 2013; 382: 951–62*

FDA Approved Bipolar Depression Treatments

	Response	Weight Gain	Sedation
OFC	56%	19%	21%
Quetiapine	59%	8%	56%
Lurasidone	52%	2%	10%
Cariprazine	46%	3%	6%

Citrome. Journal of Clinical Psychopharmacology • Volume 40, Number 4, July/August 2020

Likelihood to be Helped or Harmed (LHH)

The LHH of 1.5 for response versus weight gain can be interpreted that "acute olanzapine-fluoxetine combination treatment is 1.5 times as likely to help (therapeutic response) versus harm (weight gain)."

Citrome. Journal of Clinical Psychopharmacology • Volume 40, Number 4, July/August 2020

Likelihood to be Helped or Harmed

TABLE 2. LHH for Selected Outcomes for Olanzapine-Fluoxetine Combination, Quetiapine Immediate and Extended Release, Lurasidone Monotherapy, and Cariprazine

	Olanzapine-Fluoxetine Combination	Quetiapine Immediate and Extended Release	Lurasidone	Cariprazine
Response vs				
Discontinuation because of adverse event	NC	1.7	NC	10.0
Weight gain ≥7% from baseline	1.5	2.7	11.6	5.0
Adverse event somnolence	3.0	0.5	5.0	4.0
Adverse event akathisia	NC	5.7	3.0	1.7
Remission vs				
Discontinuation because of adverse event	NC	1.7	NC	9.1
Weight gain ≥7% from baseline	1.2	2.7	8.3	4.5
Adverse event somnolence	2.4	0.5	3.6	3.6
Adverse event akathisia	NC	5.7	2.1	1.5

NC, not calculable or interpretable as the corresponding NNH value was a negative number, or data not available (not in product label or in published study report).

Citrome. Journal of Clinical Psychopharmacology • Volume 40, Number 4, July/August 2020

Lamotrigine

- Approved for the prevention of mood episodes
- Not approved for acute treatment of bipolar depression
  - 5 trials
  - 4 could not distinguish LTG from placebo
  - Modest effect size in meta-analysis
  - But clinicians use LTG anyway

Geddes J R et al. BJP 2009;194:4-9

Lamotrigine

- Pharmacodynamic profile
  - Desensitization of the terminal $5HT_{1B}$ autoreceptors
  - Increase 5HT1a activity
  - Inhibit glutamate release
  - decreased glutamate transmission in the dentate gyrus
  - No affinity for histaminergic or muscarinic receptors
- Metabolized through CYP450 3A4 (increased with VPA)

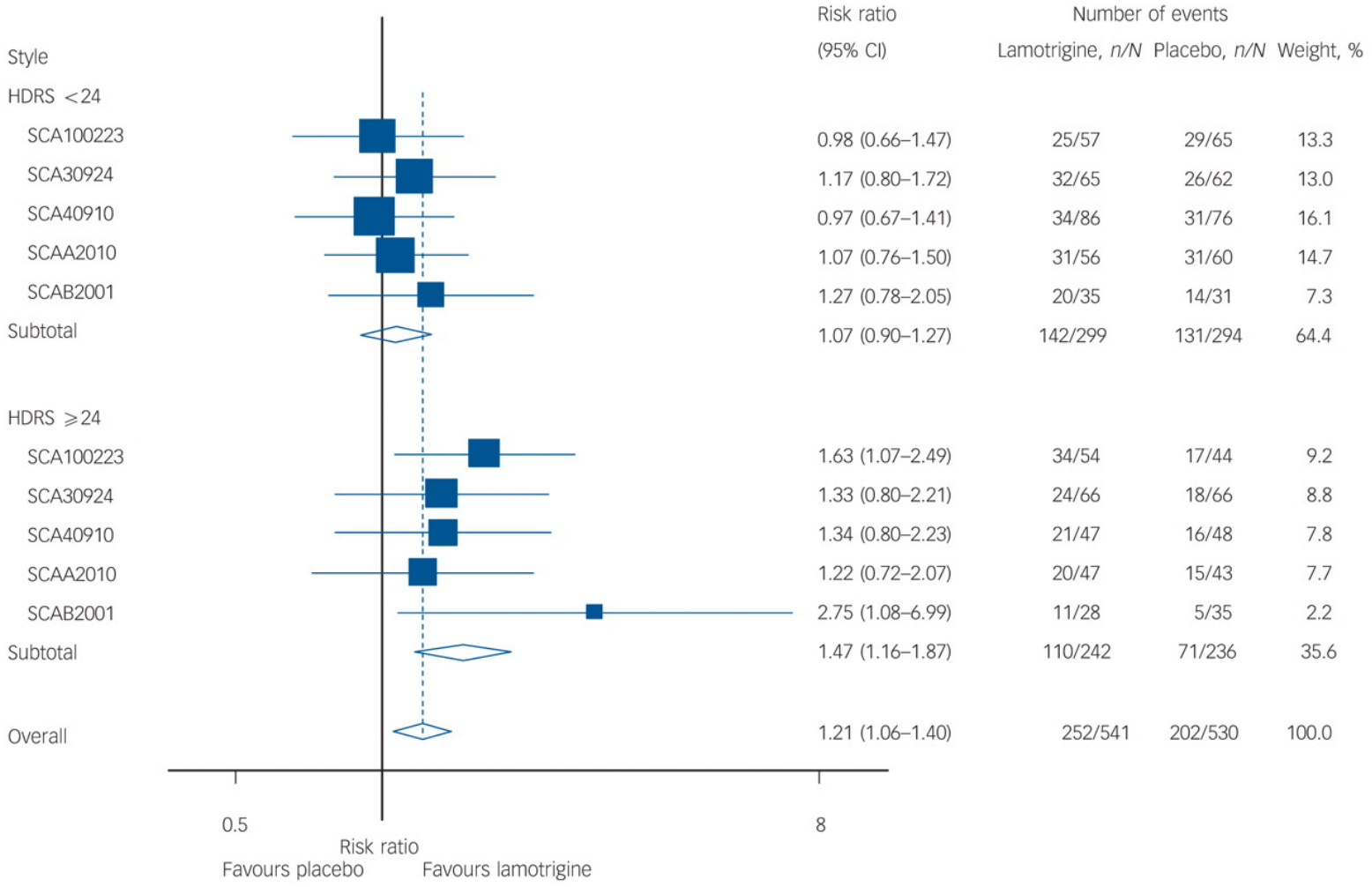
Shim et al. J Pharmacol Exp Ther 347:487–496, November 2013

Lamotrigine

- Side effects
  - Benign rash 8.3% and 6.4% in lamotrigine- and placebo-treated patients
  - Stevens Johnson Syndrome (toxic epidermal necrosis)
    - 0% with lamotrigine, 0.1% (N = 1) with placebo, and 0% with comparators.
    - 13.1% overall rate of rash with serious rash, 0.1%
    - Decrease risk with slow titration
  - Headache, nausea, dizziness, infection

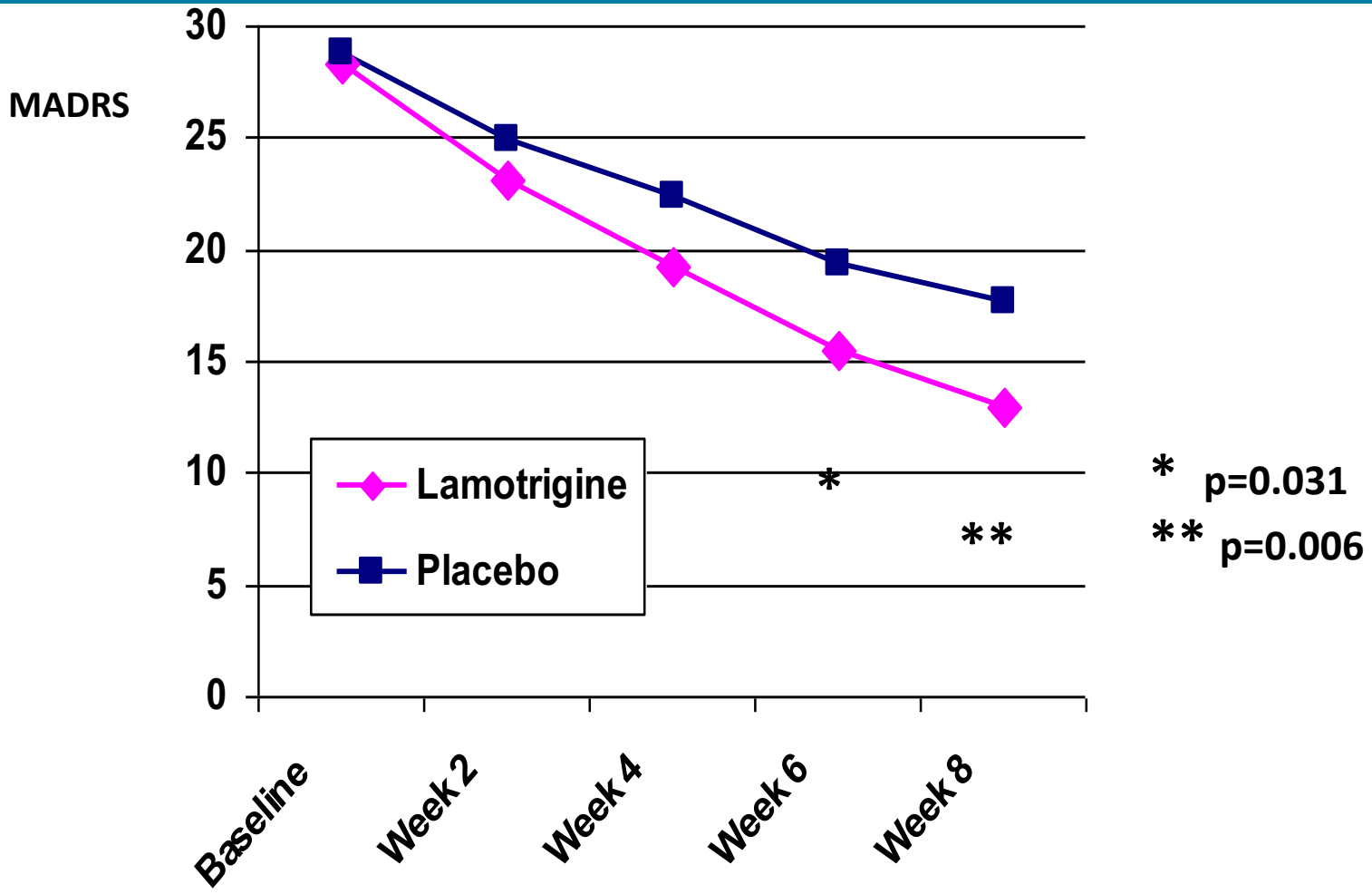
Calabrese et al. J Clin Psychiatry 2002;63(11):1012-101
Bowden et al. Drug Safety 2004; 27 (3): 173-184

Bigger effect size for more severe bipolar depression.



Geddes J R et al. BJP 2009;194:4-9

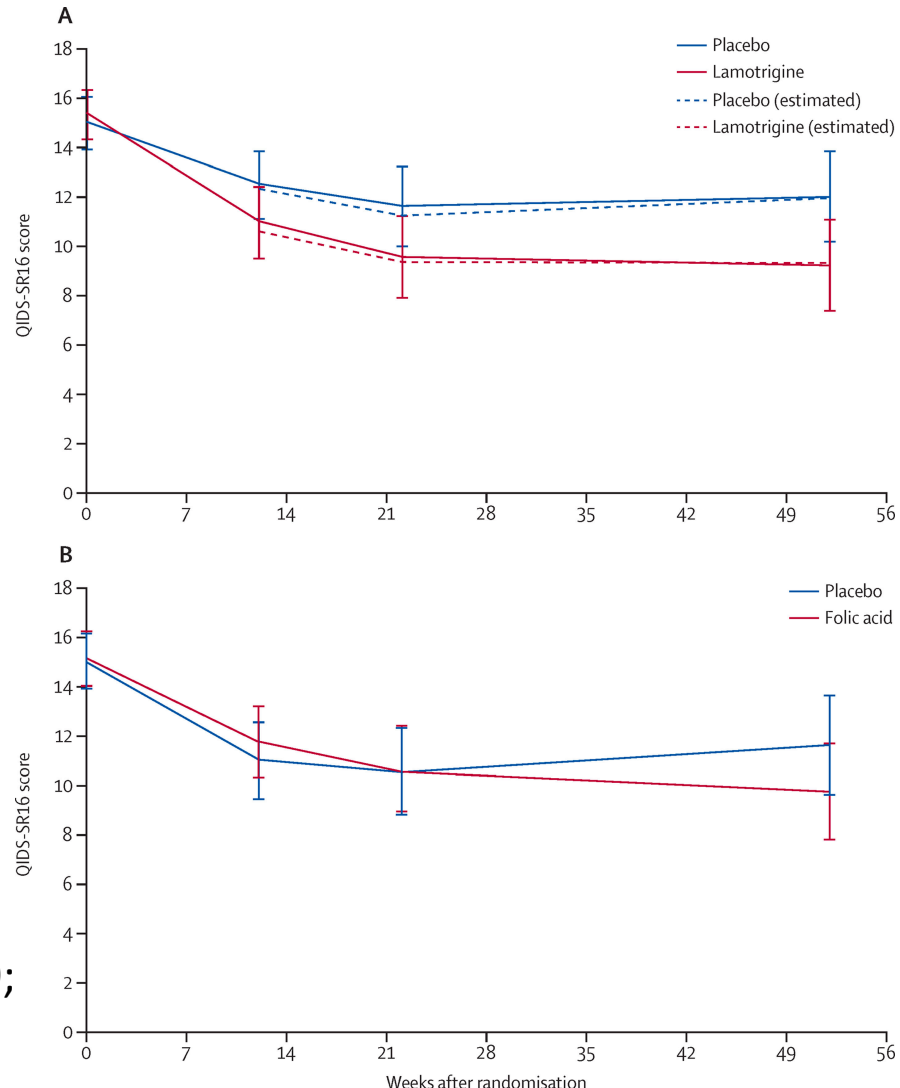
Lamotrigine plus Lithium



Van der Loos et al. J Clin Psychiatry. 2009 Feb;70(2):223-31. Epub 2008 Dec 30.

Lamotrigine added to Quetiapine

CEQUEL Trial



Geddes et al.
Lancet Psych 3:31-39; 2016

Mechanisms of Action Differentiates Effective from Non-Effective Treatments for BP Depression

Receptor	Action	Result
Alpha 1	Antagonist	Increase NE
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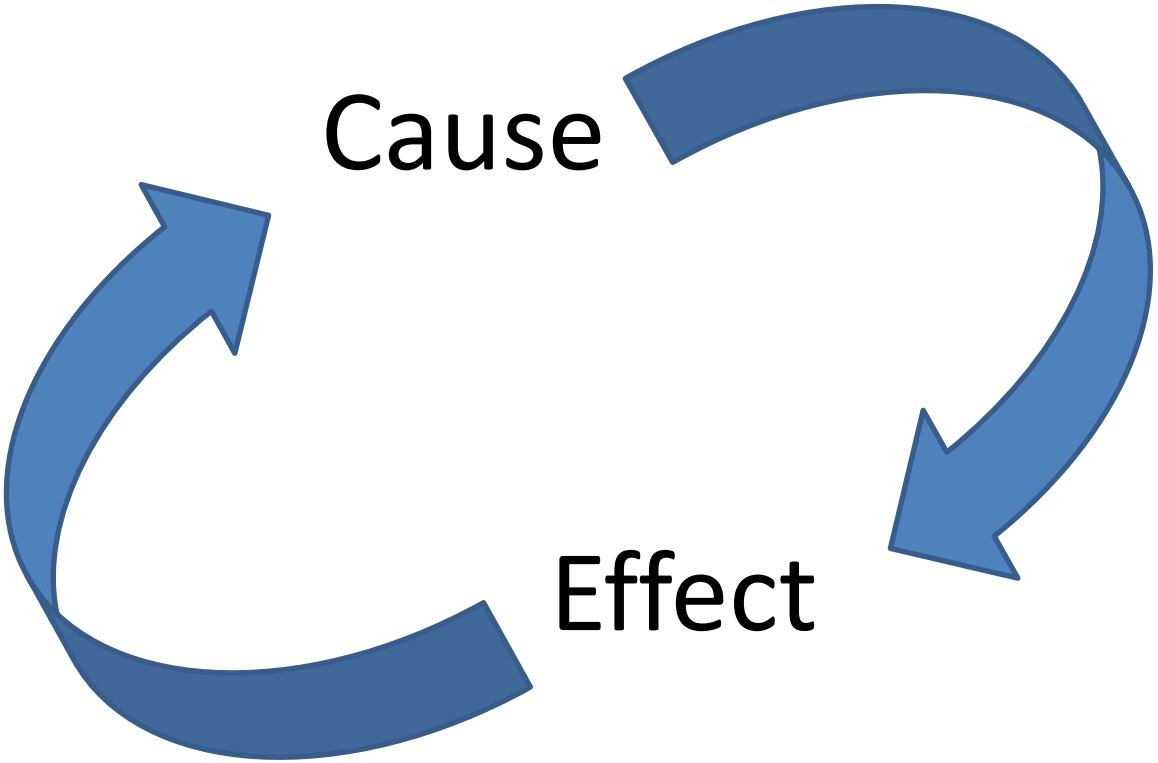
H1	Antagonist	Decrease Histamine
5HT2A	Antagonist	Increase 5HT
Muscarinic	Antagonist	Decrease Acetylcholine
D2	Antagonist	Mixed effects
D3	Antagonist	Increase DA
NE Reuptake	Inhibition	Increase NE
5HT1A	Agonism	Increase 5HT

Fountoulakas et al. Journal of Affective Disorders 138 (2012) 222–238

What's the problem with antidepressants?

- Widespread use.
- Efficacy?
- Safety?
- Long-term harm?

What's the problem?



Post hoc ergo proptor hoc.

"After this, therefore, because of this."

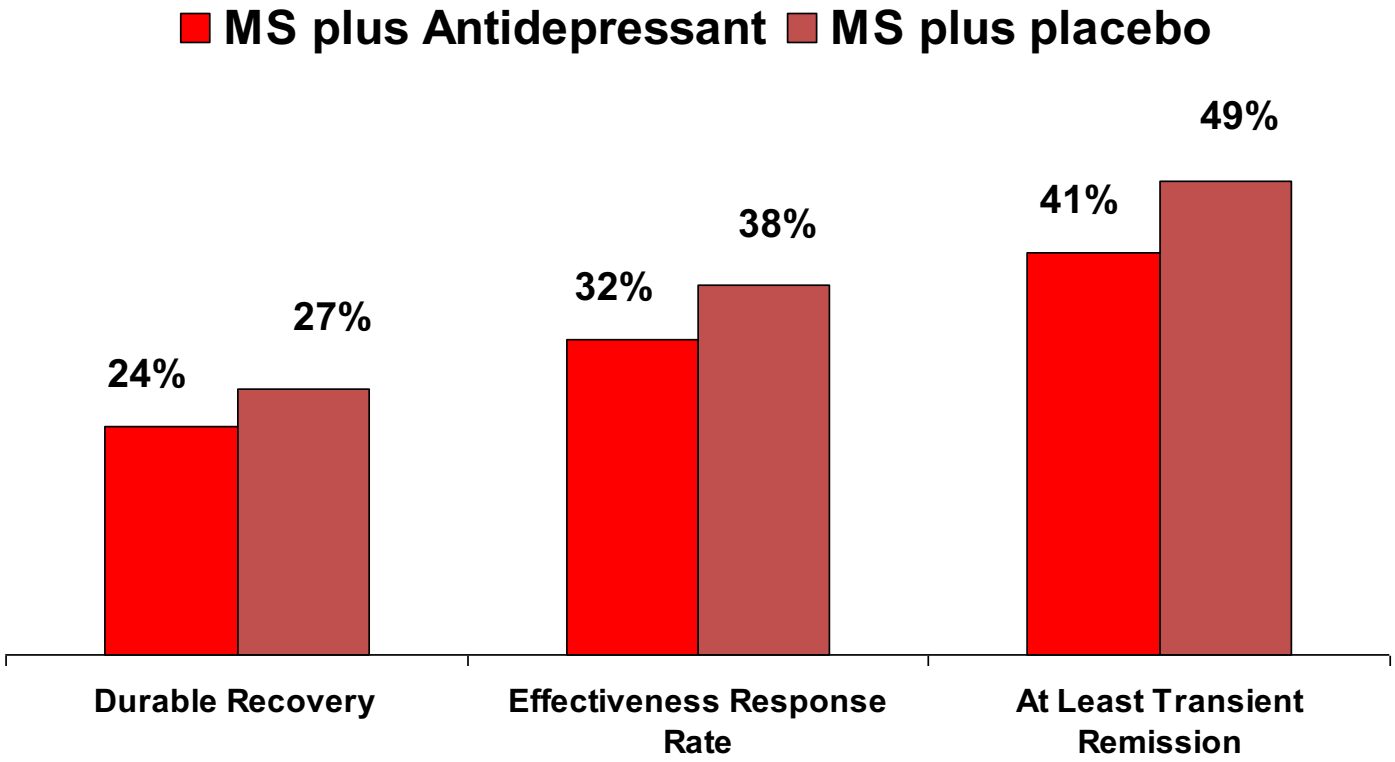
What is evidence?

Meta-analysis of Efficacy of Antidepressants for BP Depression

- 15 studies
- 2373 patients
- No superiority over placebo
- No increased risk of switch

Sidor and MacQueen. J Clin Psychiatry 2011 Feb;72(2):156-67. Epub 2010 Oct 5.

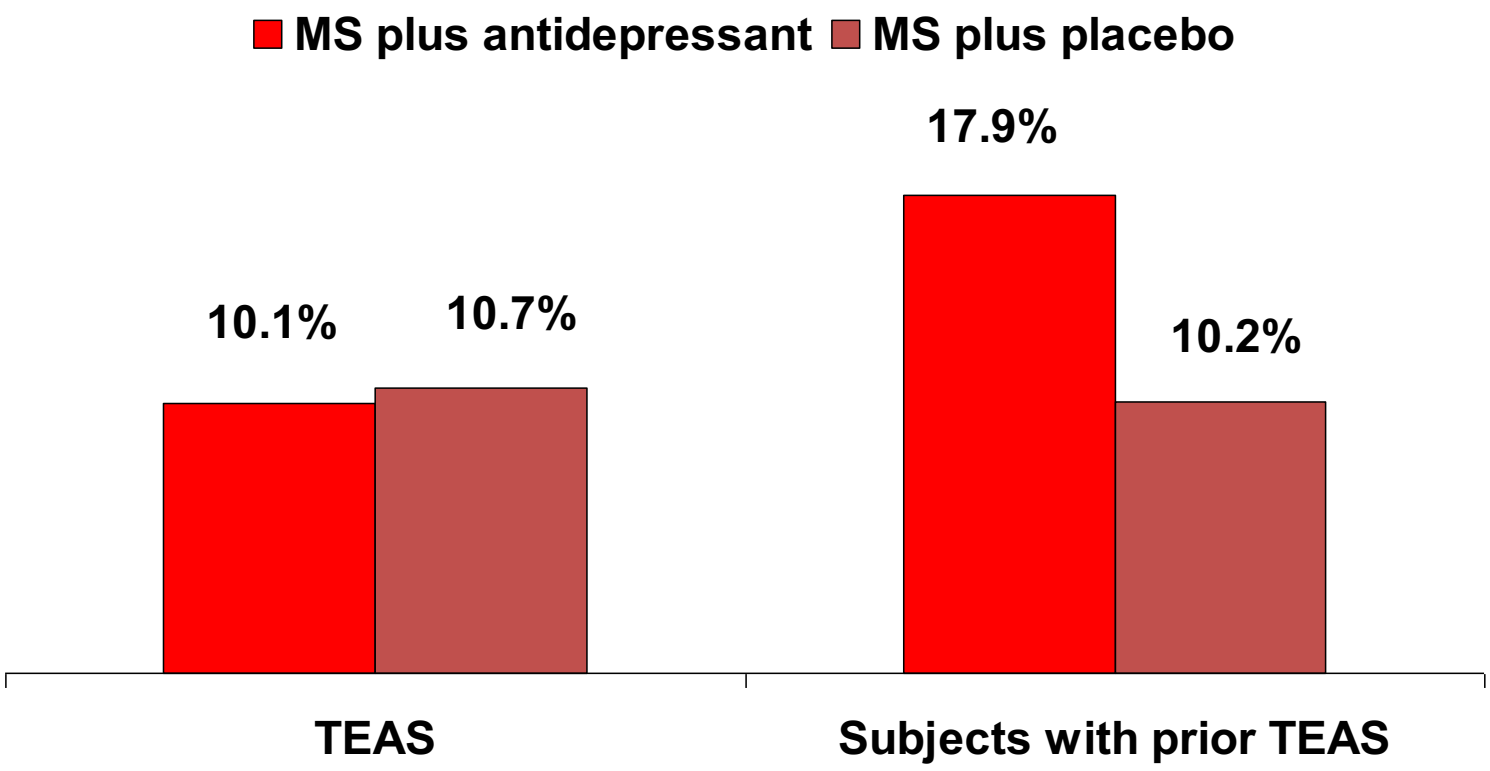
STEP-BD
Randomized Acute Bipolar Depression Study



>50% SUM-D reduction at week 6

No statistically significant differences, All p>.23

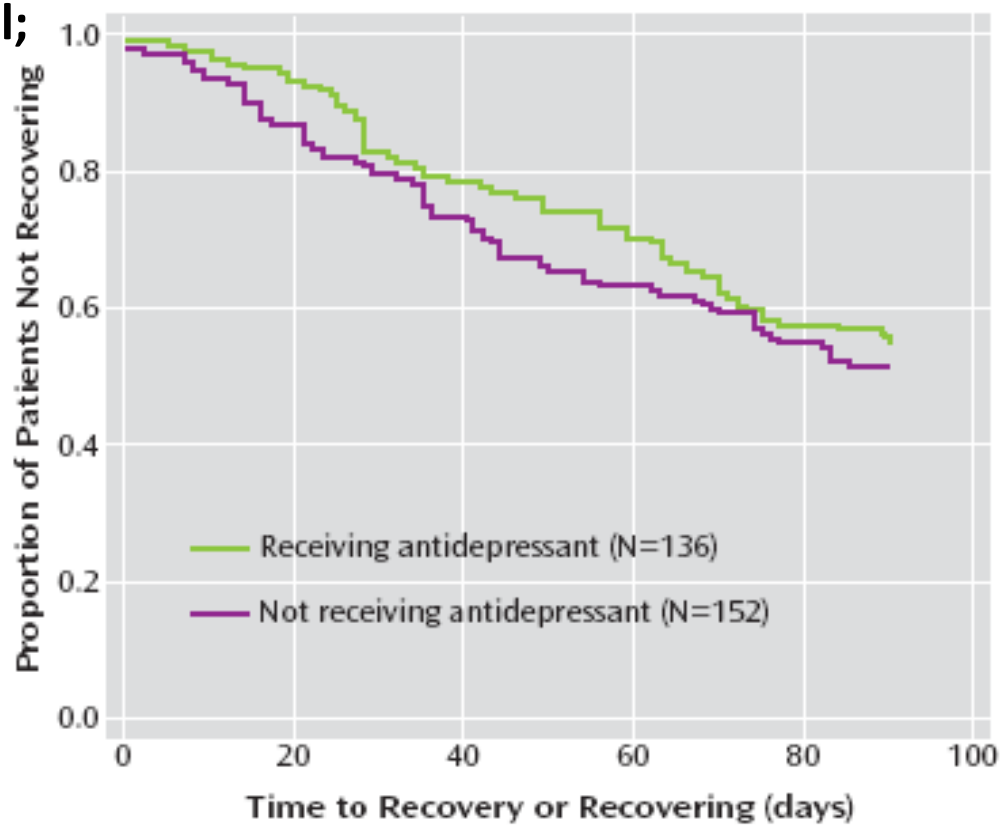
Treatment Emergent Affective Switch



Practice Based Evidence

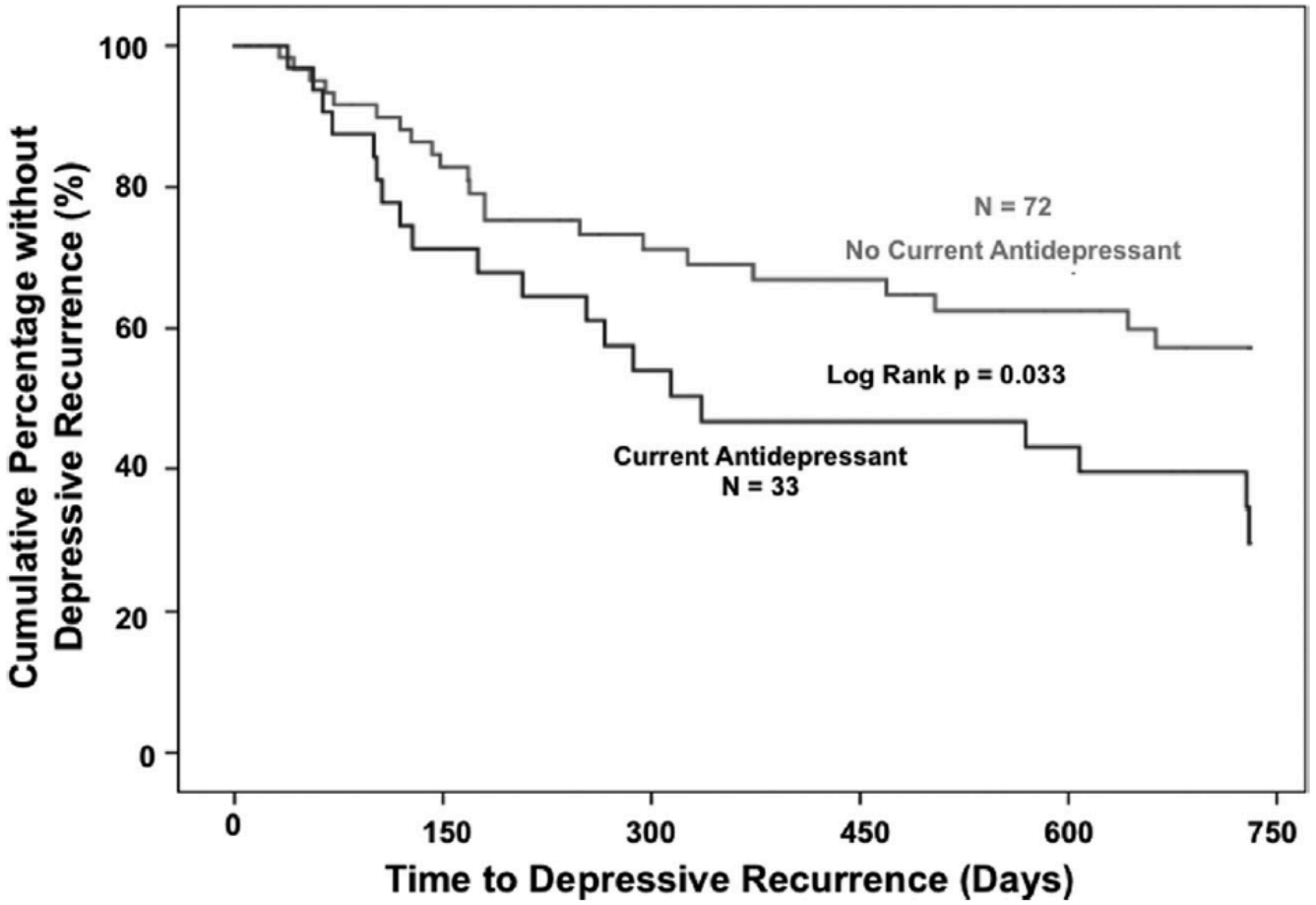
No benefit with antidepressants for bipolar depression with manic symptoms

Note: Observational; Not Randomized



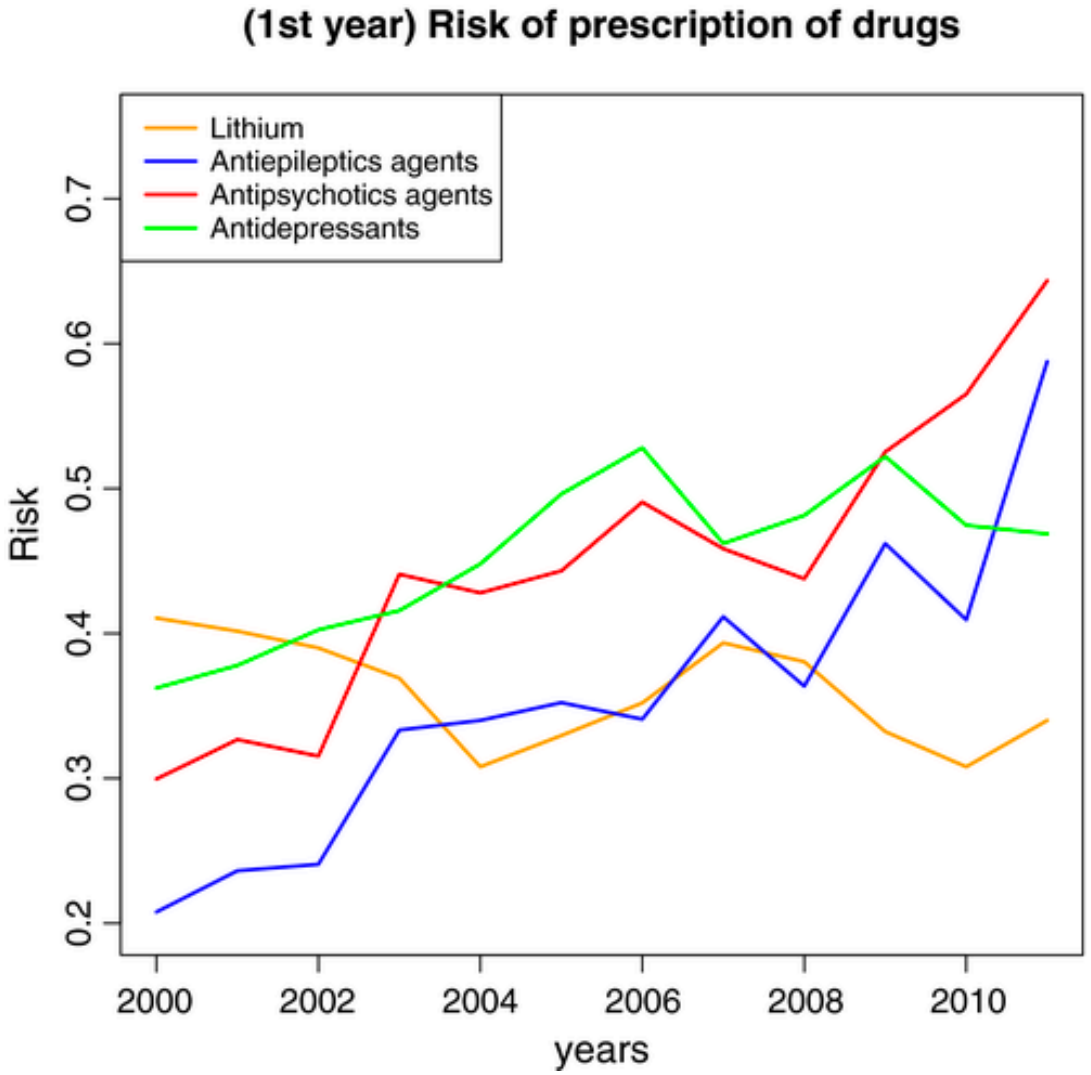
Goldberg et al. Am J Psychiatry 2007:164:1348-1355

Antidepressants Hastens Depressive Recurrence in Bipolar Disorder



Hooshmand et al. Journal of Affective Disorders 246 (2019) 836–842

Secular Trends in Bipolar Meds



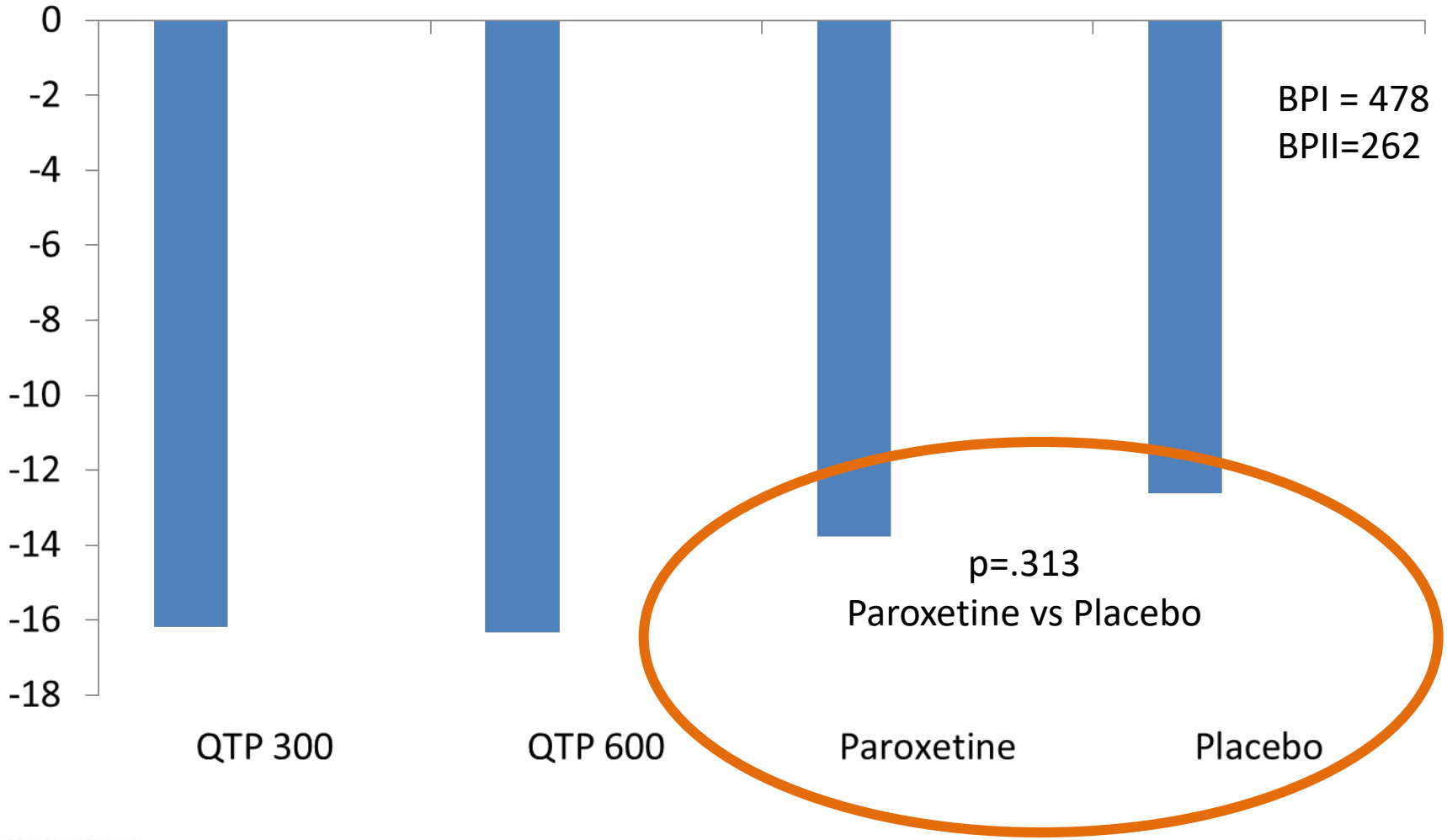
Kessing, Vradi, Anderson
Bipolar Disorders Volume18, Issue2
March 2016
Pages 174-182

Antidepressants and Bipolar Depression: Evidence for Efficacy

- MAOIs - old flawed literature
- TCAs - increased cycling
- SSRIs - mixed mostly negative studies
- SNRIs - increased cycling?
- Bupropion - no positive studies
- Lithium, valproate, carbamazepine?

EMBOLDEN II

Decrease in MADRS



McElroy et al. J Clin Psychiatry 2010 Feb;71(2):163-74. Epub 2010 Jan 26

International Society for Bipolar Disorders Clinical (ISBD) Recommendations for Antidepressant Use in Bipolar Disorders

Acute treatment

1. Adjunctive antidepressants may be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants.

2. Adjunctive antidepressants should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms in the presence of psychomotor agitation or rapid cycling.

Am J Psychiatry Pacchiarotti et al.; AiA:1–14

International Society for Bipolar Disorders Clinical (ISBD) Recommendations for Antidepressant Use in Bipolar Disorders

Maintenance treatment

3. Maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy.

Monotherapy

4. Antidepressant monotherapy should be avoided in bipolar I disorder.

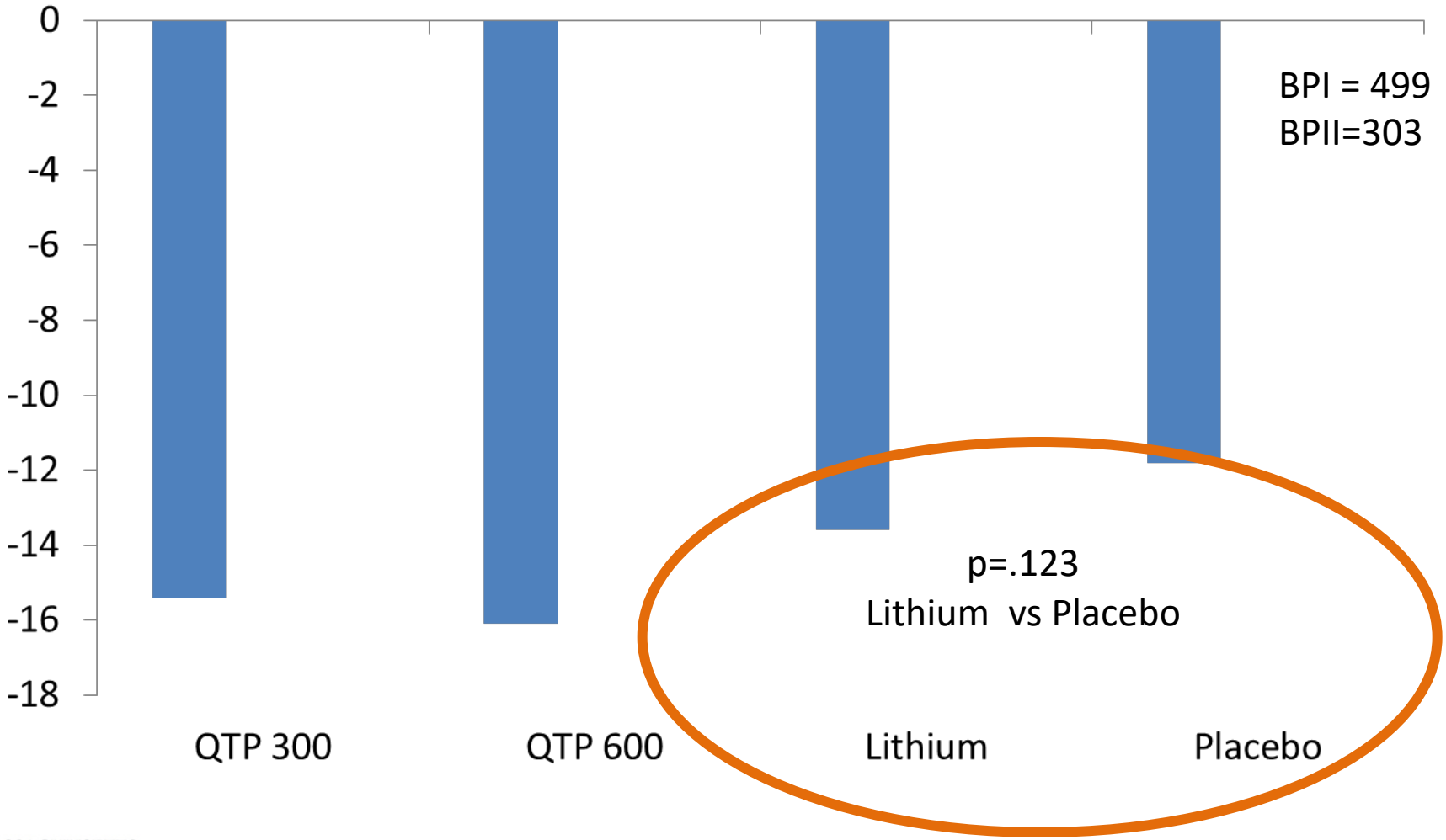
5. Antidepressant monotherapy should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms.

Am J Psychiatry Pacchiarotti et al.; AiA:1–14

Lithium for bipolar depression?

EMBOLDEN I: Li not better than Pbo

Decrease in MADRS

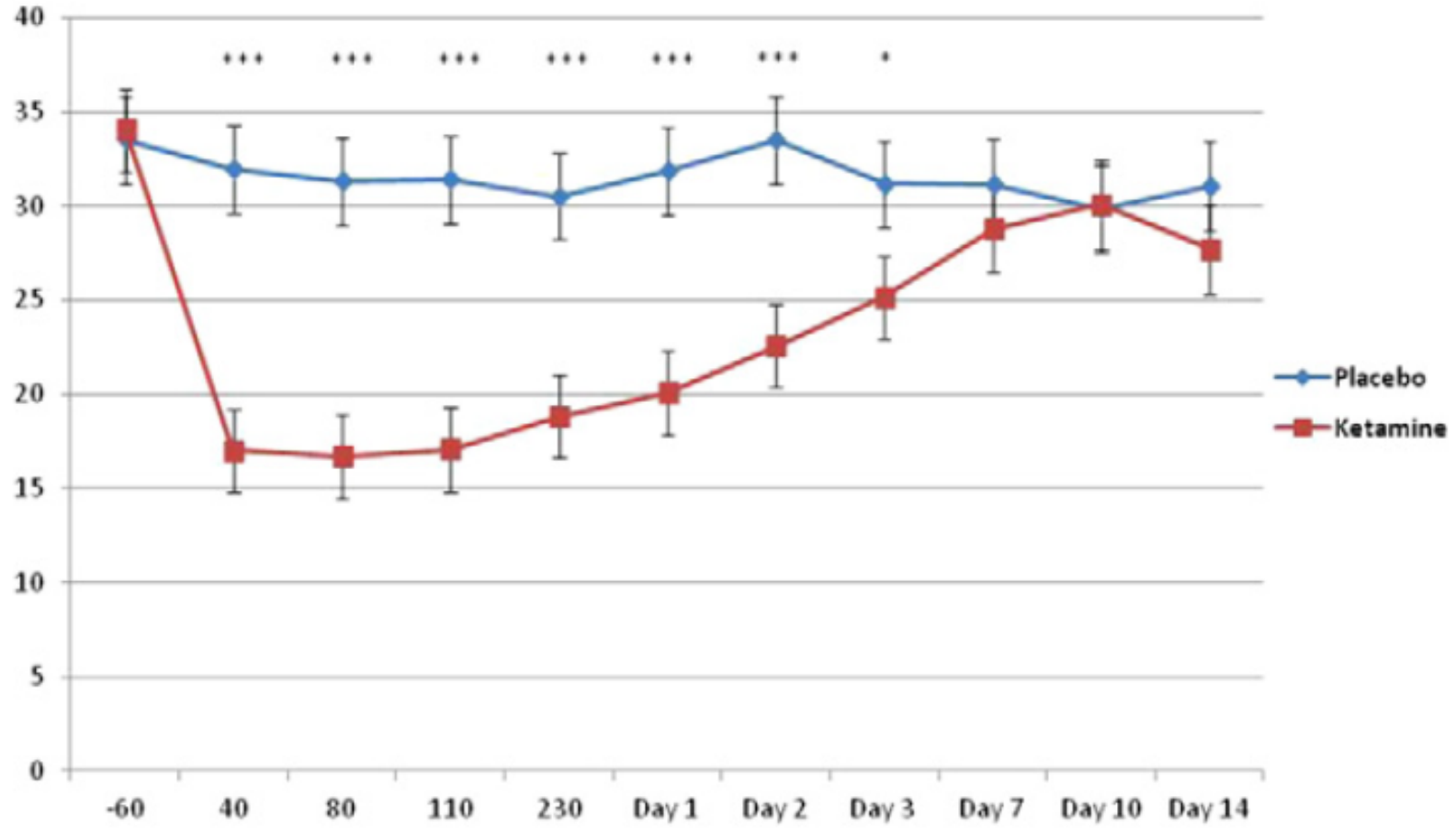


McElroy et al. J Clin Psychiatry 2010 Feb;71(2):163-74. Epub 2010 Jan 26

Potential treatments for bipolar depression

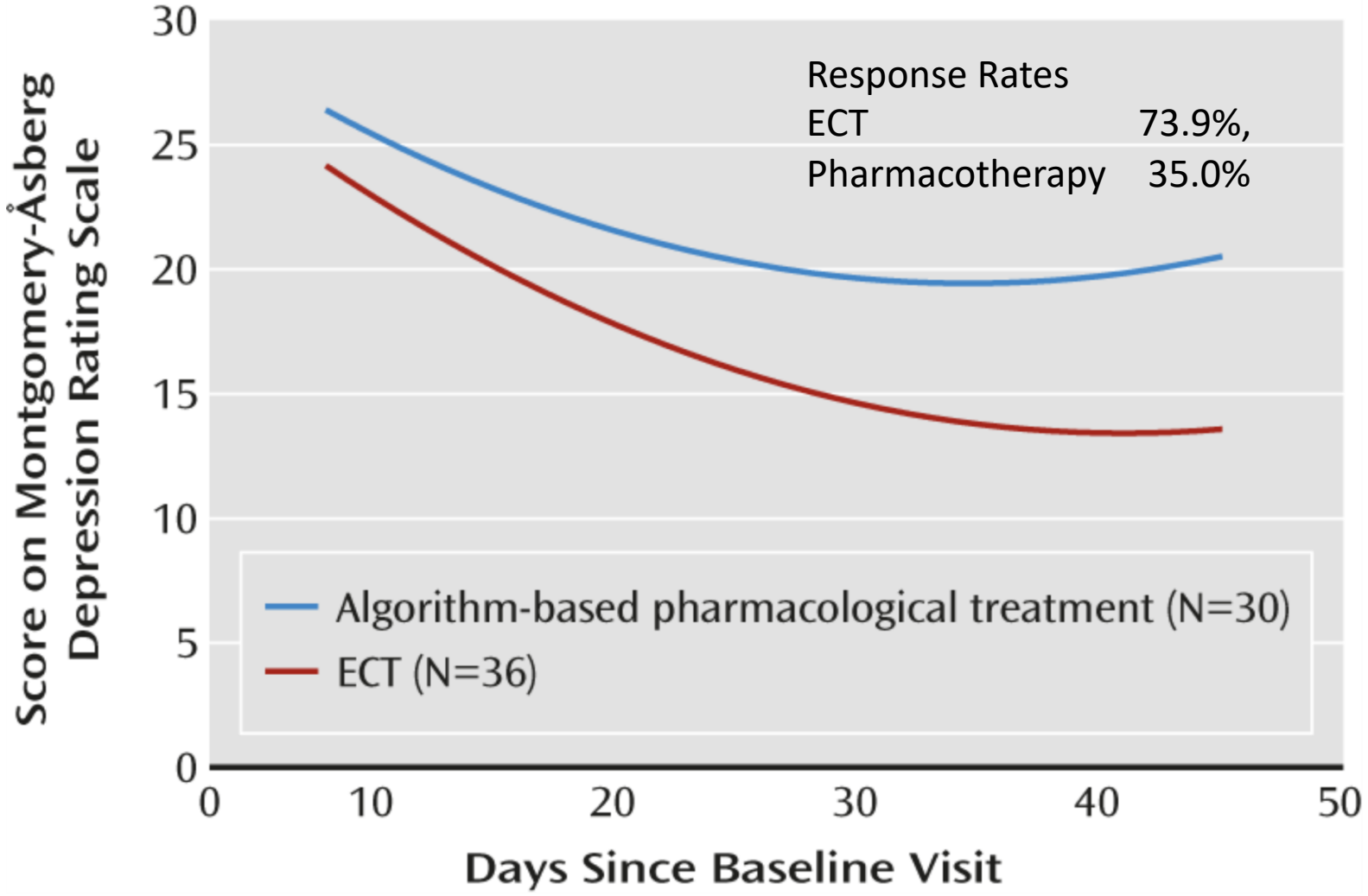
- Ketamine
- ECT
- rTMS

Ketamine for Bipolar Depression



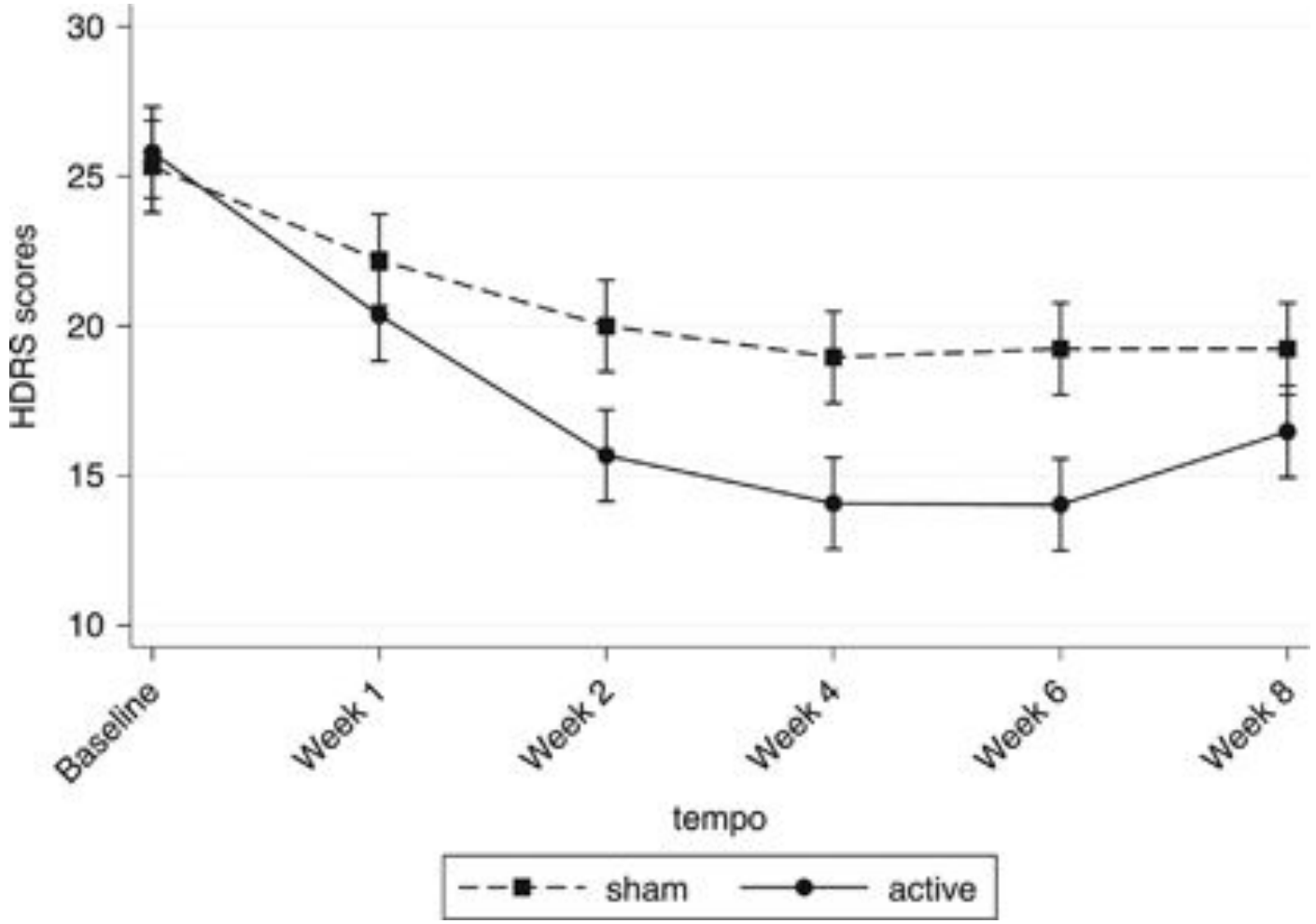
Zarate et al. BIOL PSYCHIATRY 2012;71:939–946

ECT Superior to Pharmacotherapy



Schoeyen et al. *Am J Psychiatry 2014;:.* doi:10.1176/appi.ajp.2014.13111517

Deep rTMS for Bipolar Depression



Taveres et al. *Neuropsychopharmacology* advance online publication 31 May 2017

Preliminary evidence….

- Pramipexole?
- Pioglitazone?
- Minocycline?
- N-acetylcysteine?
- Pimavanserin?
- Ebselen?

Fawcett et al. AJP 173:107-111;2016
Kemp DE et al. CNS Drugs. 28(6):571-81;2014
Soczynsak et al. Bipolar Dis 19:198-213;2017
Berk M et al. J Affect Dis 135:389-94;2011.

Summary

- Bipolar depression: Basics
  - Frequent problem
- FDA Approved Treatments
  - Olanzapine Fluoxetine Combination
  - Quetiapine
  - Lurasidone
  - (Lamotrigine)
- Antidepressants and other treatments