MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Bipolar Depression Evidence and Controversies

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Disclosure Statement

Employee Of	Massachusetts General Hospital
Consultant For	Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Bristol-Myers Squibb, Cephalon, Clexio, Clintara, Corcept, Eli Lilly & Co., Forest, Genaissance, Genentech, Ginger, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Lundbeck, Medavante, Merck, Myriad, Novartis, PamLabs, PGx Health, Pfizer, Roche,Sage, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, Teva
Stockholder In	Appliance Computing, Inc. (MindSite); Brain Cells, Inc., Medavante
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Honoraria From	MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly,, Shire, Wyeth-Ayerst), No speaker bureaus since 2003

Andrew A. Nierenberg, MD
Disclosure Statement

Other Income	MBL Publishing for past services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Editor of Psychiatric Annals; Assoc Editor Depression and Anxiety; Editorial Board, Mind Mood Memory, Belvior Publications
Patents and Copyrights	Copyright joint ownership with MGH for Structured Clinical Interview for MADRS and Clinical Positive Affect Scale
Additional Honoraria	ADURS, Brain and Behavior Foundation Colvin Prize, University of :Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England and Harold Grinspoon Charitable Foundation and Eli Lilly and AstraZeneca, American Society for Clinical Psychopharmacology and Zucker Hillside Hospital and Forest and Janssen, Brandeis University, International Society for Bipolar Disorder

Baldessarini *et al. Int J Bipolar Disord* (2020) 8:1
https://doi.org/10.1186/s40345-019-0160-1

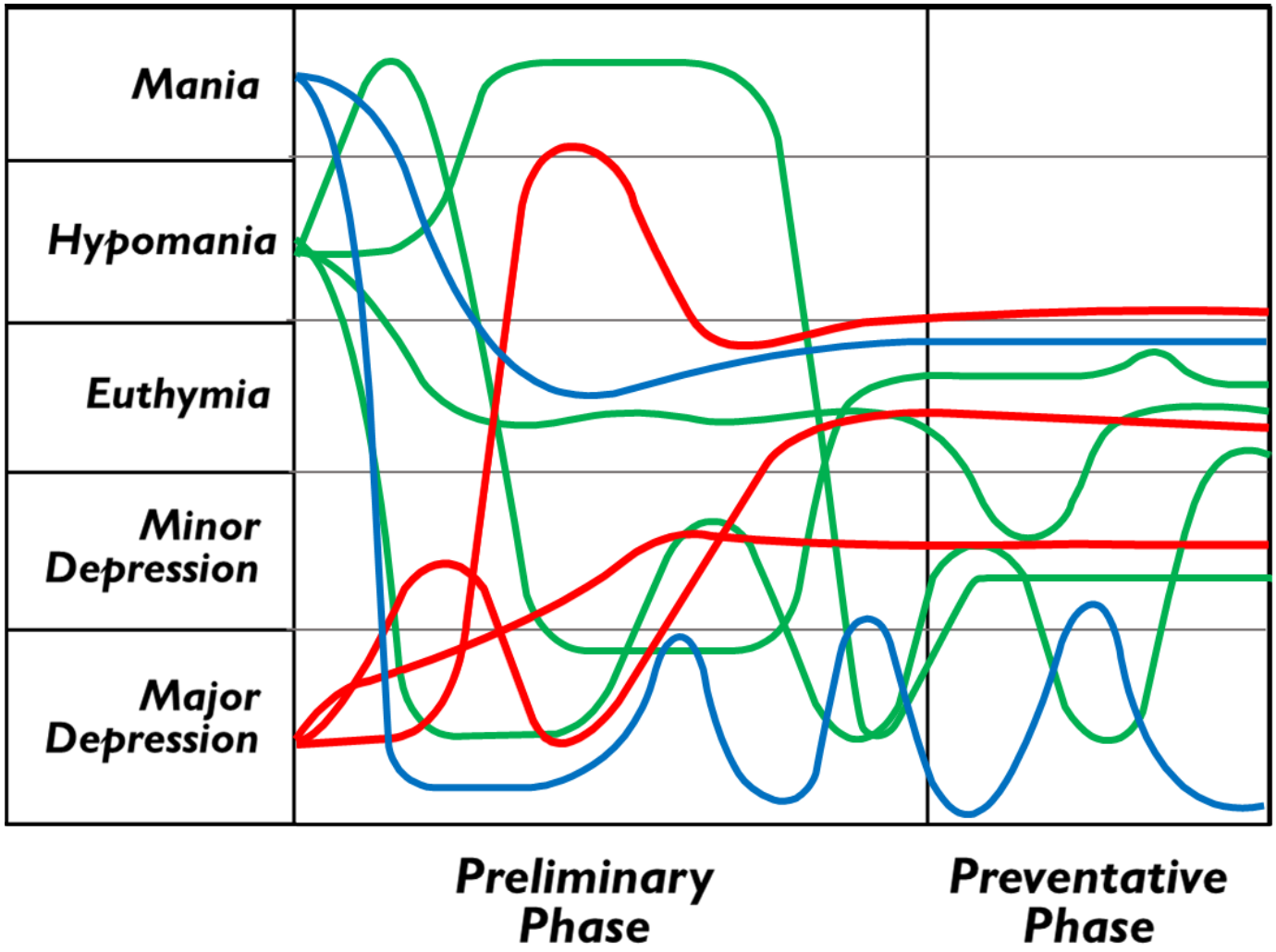
International Journal of Bipolar Disorders

REVIEW Open Access

Bipolar depression: a major unsolved challenge

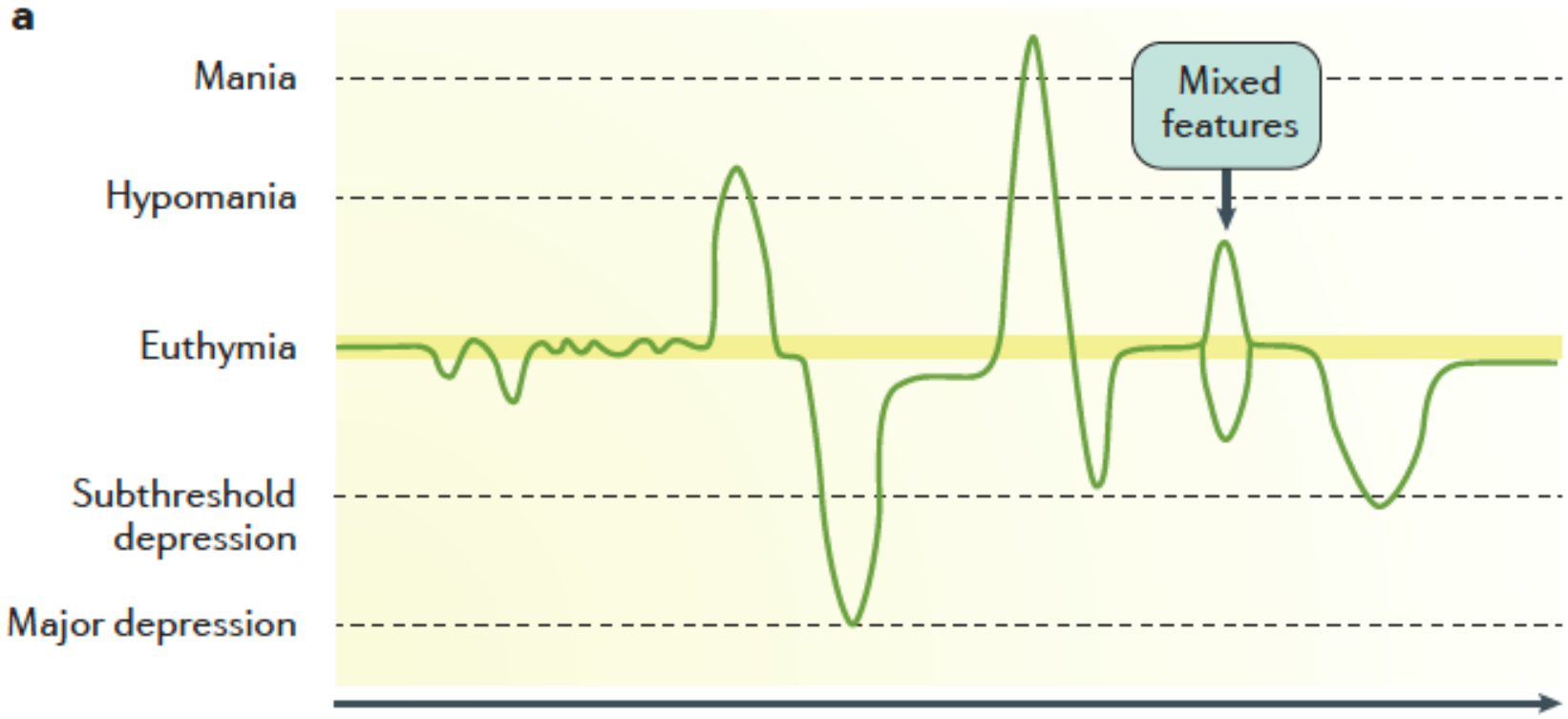
Ross J. Baldessarini[1,2*], Gustavo H. Vázquez[2,3] and Leonardo Tondo[1,2,4]

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



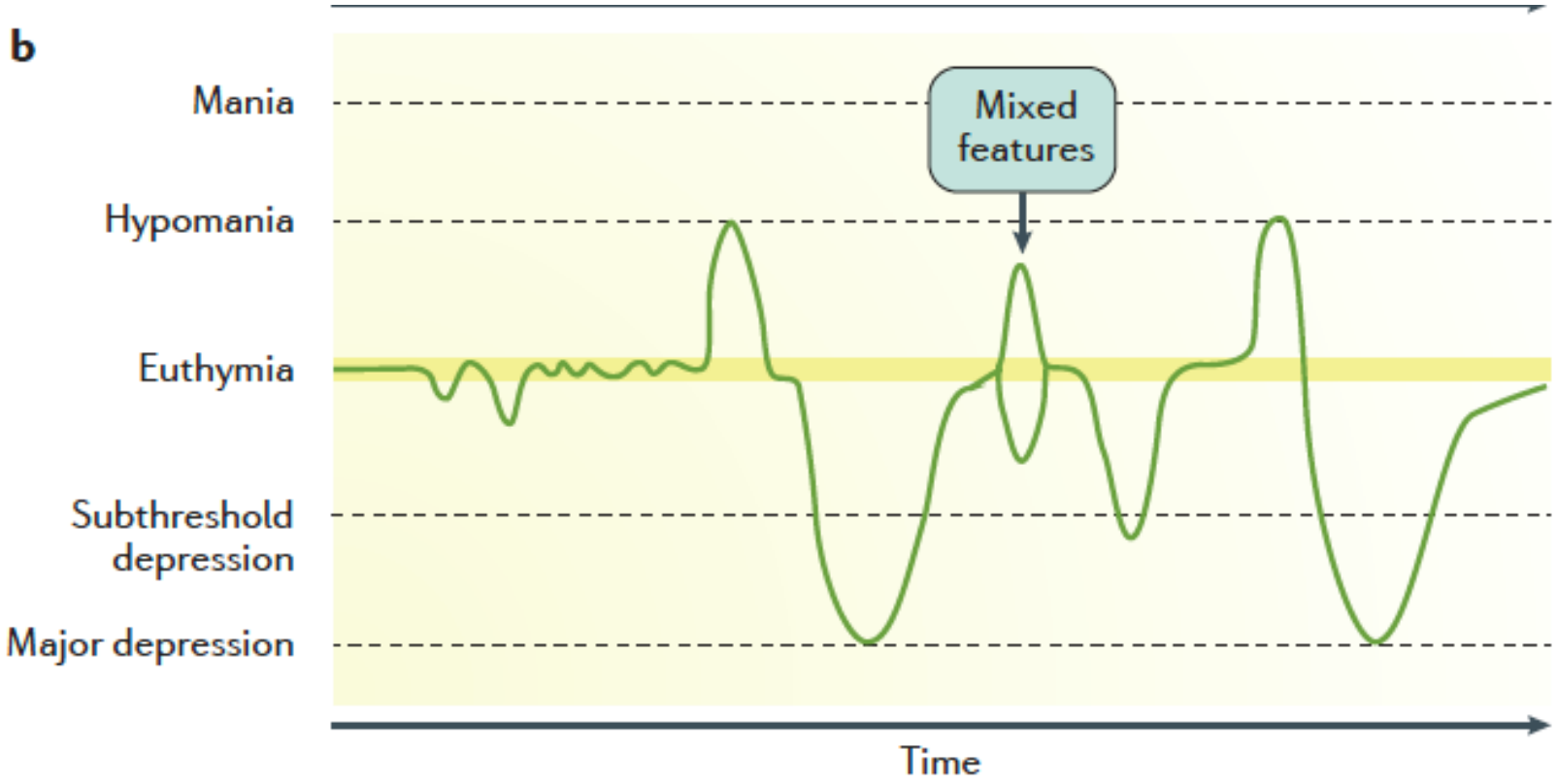
[1]Frank E, et al. *Biol Psychiatry.* 2000;48(6):593-604.

Bipolar I



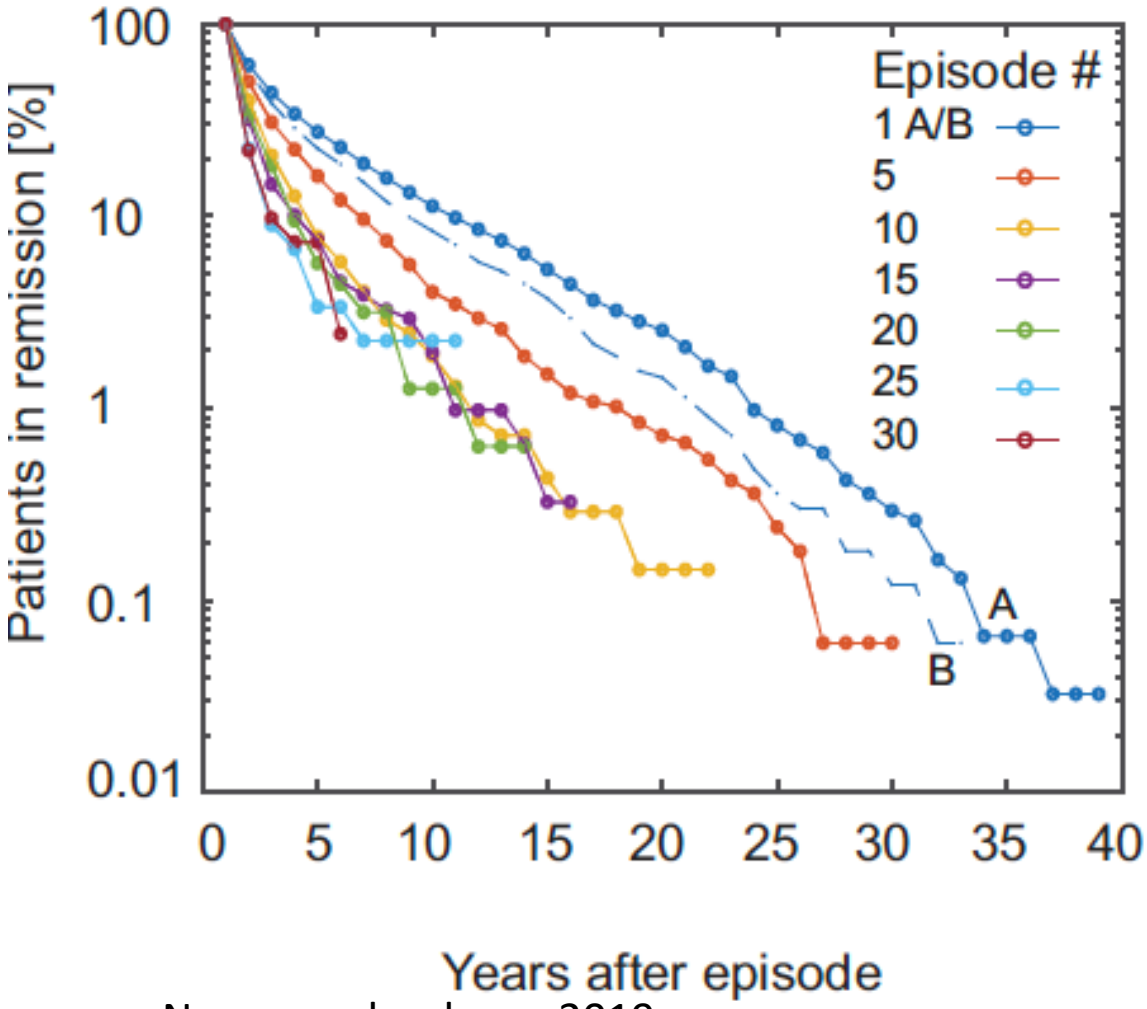
Vieta et al. Nature Reviews Disease Primer 2018

Bipolar II



Vieta et al. Nature Reviews Disease Primer 2018

Bipolar Highly Recurrent



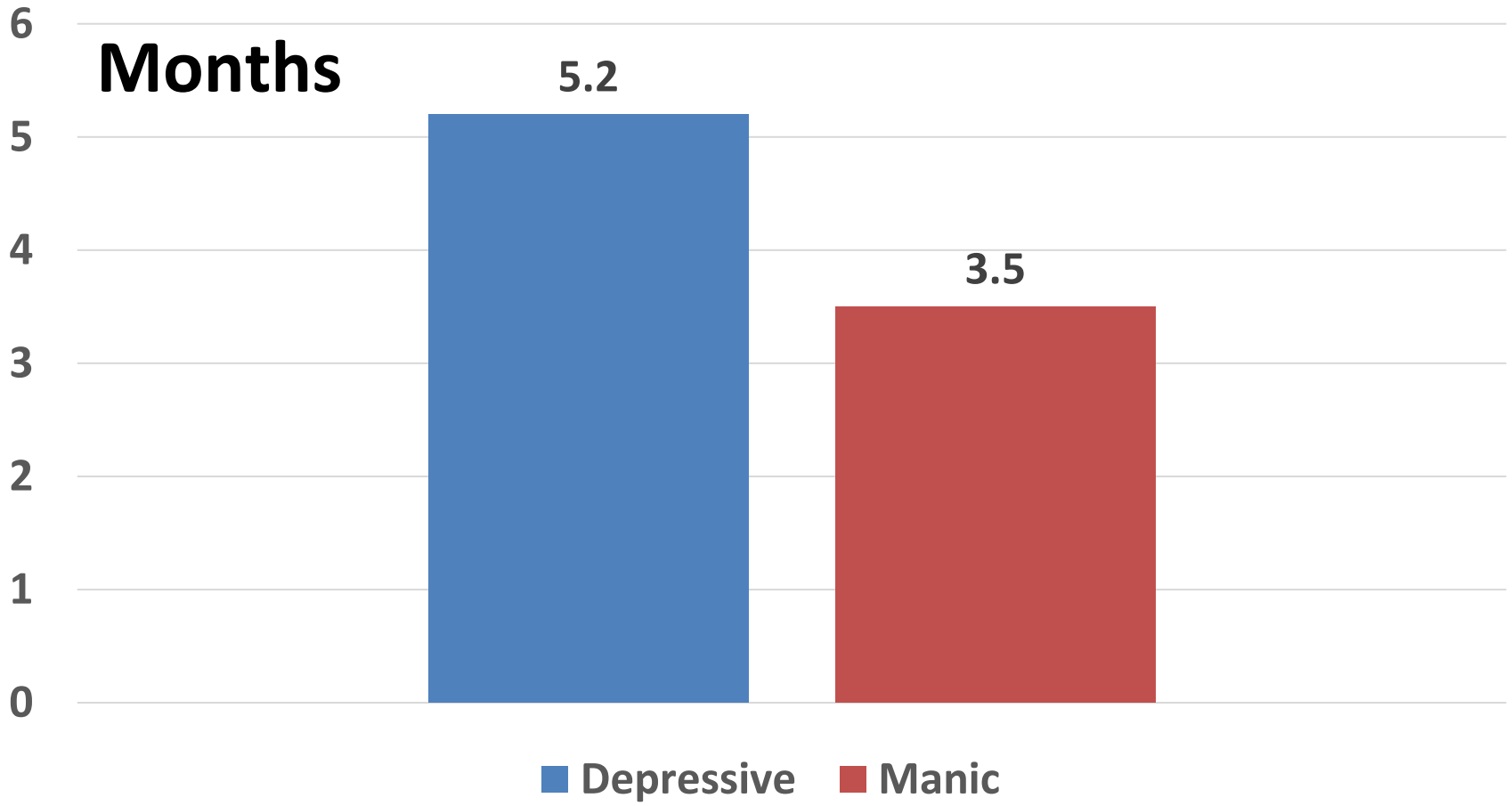
Smedler et al. European Neuropsychopharm 2019

Table 1 Depressive morbidity in clinically treated bipolar disorder subjects. Data adapted from Forte et al. (2015), based on systematic review of studies involving adult patients treated by community standards

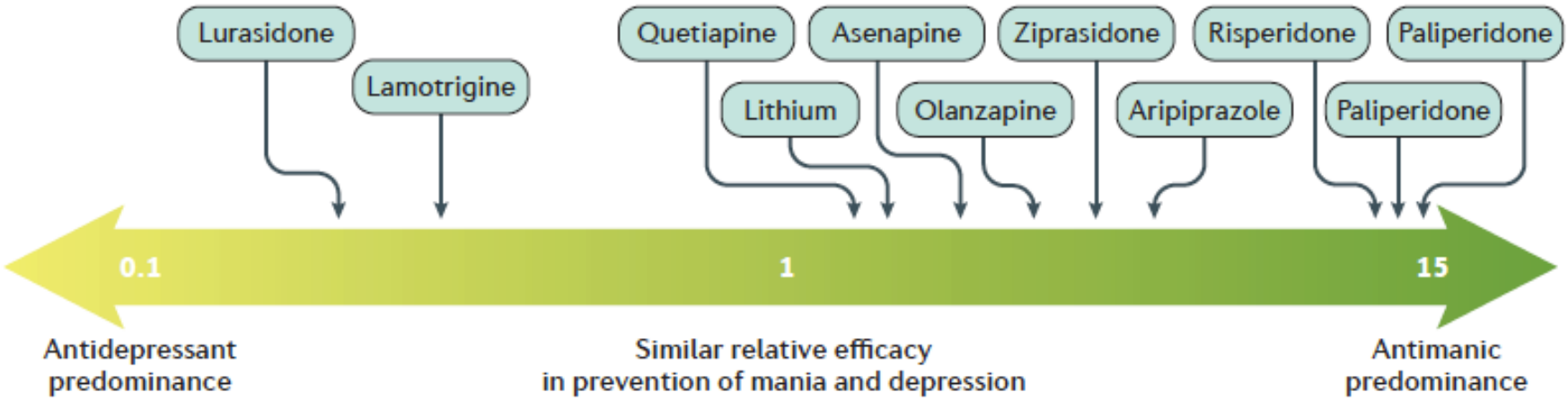
Measure	Bipolar I	Bipolar II	All bipolar
Studies	12	8	15
Subjects	2760	822	3582
Exposure (years)	7.78 [3.53–12.0]	8.28 [2.18–14.4]	7.89 [5.47–12.6]
%-Time depressed	30.6 [23.9–37.3]	35.9 [23.1–48.7]	31.8 [23.7–39.9]
Total %-time ill	43.7 [37.5–49.4]	43.2 [35.2–51.1]	43.6 [37.0–49.8]
%-of illness depressed	69.6 [60.4–78.9]	81.2 [71.3–91.0]	72.3 [62.9–81.7]

Data are means with 95% confidence intervals [CI]. Depression includes major episodes plus dysthymia

Depression lasts longer than Mania



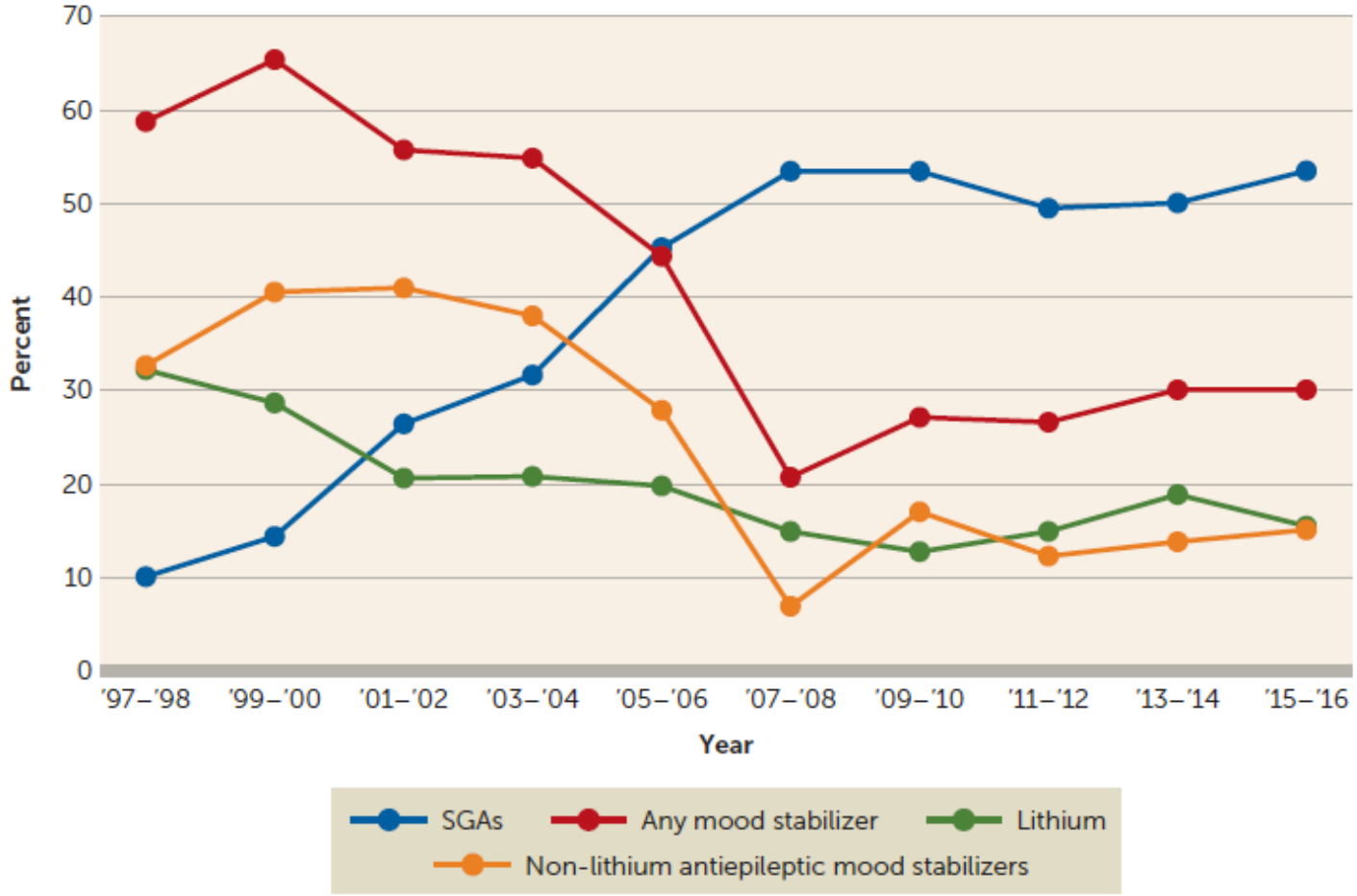
Tondo, Vasquez, Baldessarini. Current Neuropharmacology, 2017, 15, 353-358



Vieta et al. Nature Reviews Disease Primer 2018

More antipsychotics, less mood stabilizers

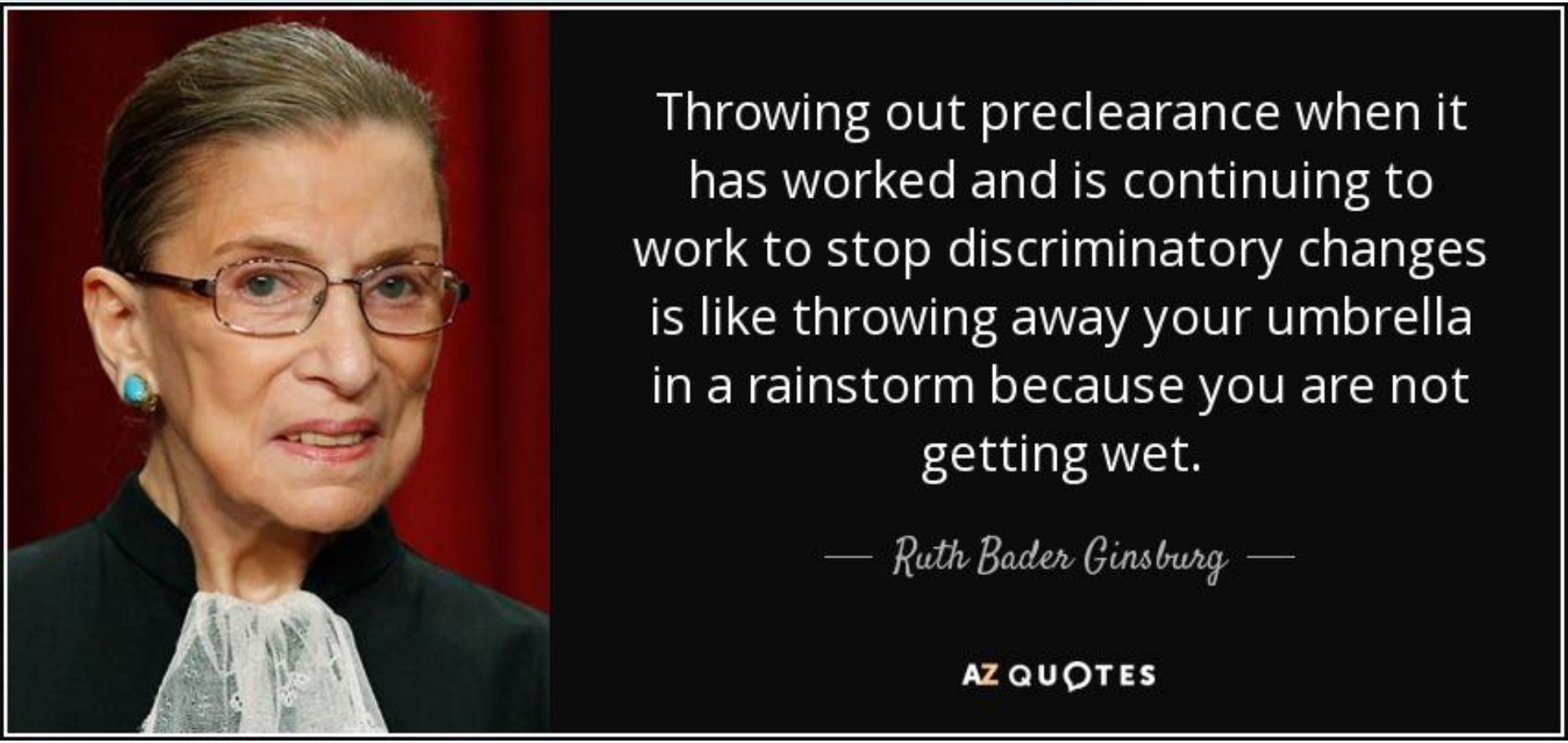
FIGURE 1. Prescribing trends for second-generation antipsychotics (SGAs) and mood stabilizers in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]



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

Rhee, Olfson, Nierenberg, Wilkerson. AJP 2020

Stopping meds while feeling well…



FDA Approved Treatments for Bipolar Depression

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

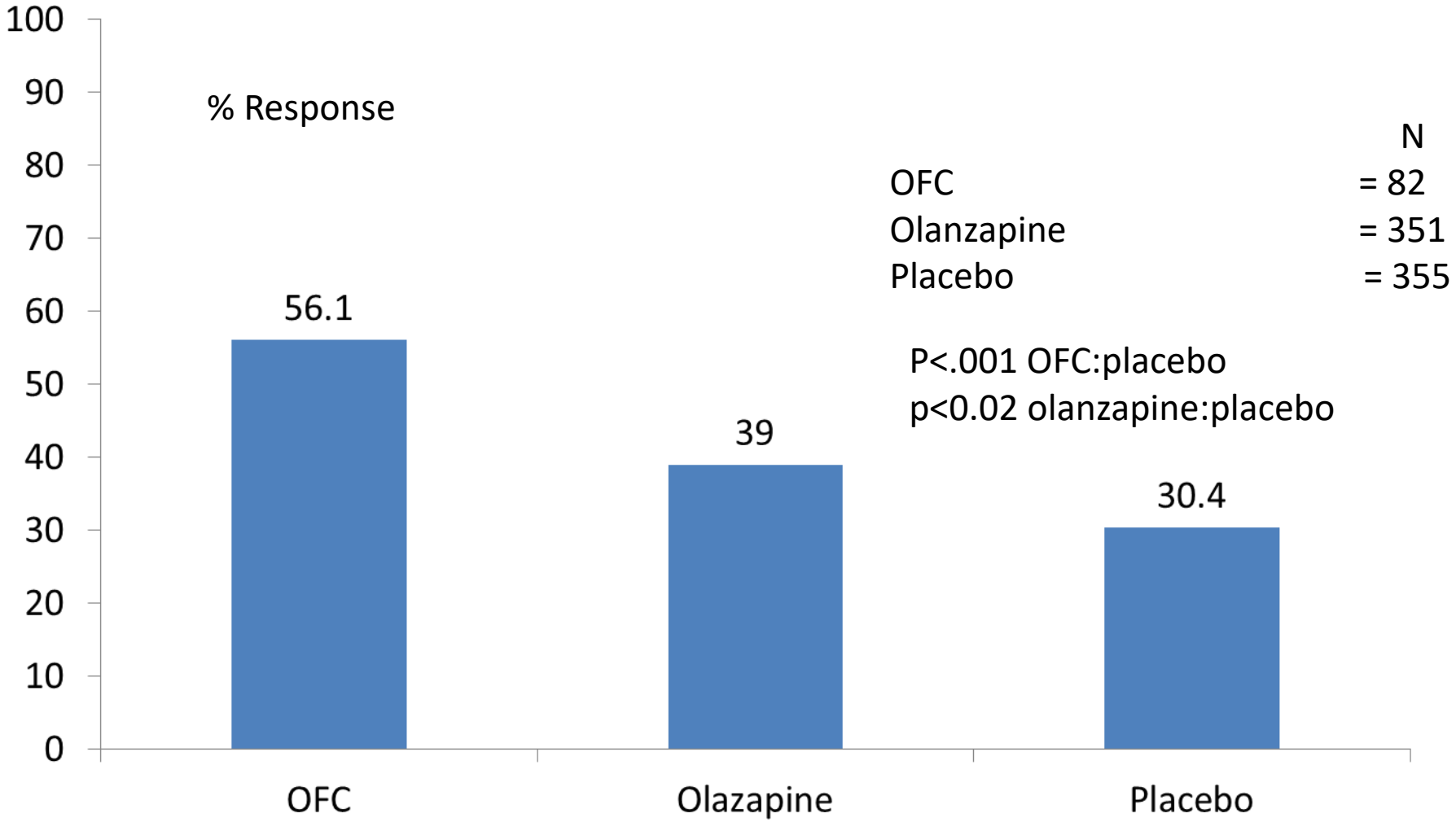
Receptor	Action	Result
Alpha 1	Antagonist	Increase NE
D1	Antagonist	Decrease DA
H1	Antagonist	Decrease Histamine
5HT2A	Antagonist	Increase 5HT
Muscarinic	Antagonist	Decrease Acetylcholine
D2	Antagonist	Mixed effects
D3	Antagonist	Increase DA
NE Reuptake	Inhibition	Increase NE
5HT1A	Agonism	Increase 5HT

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

FDA and not so 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

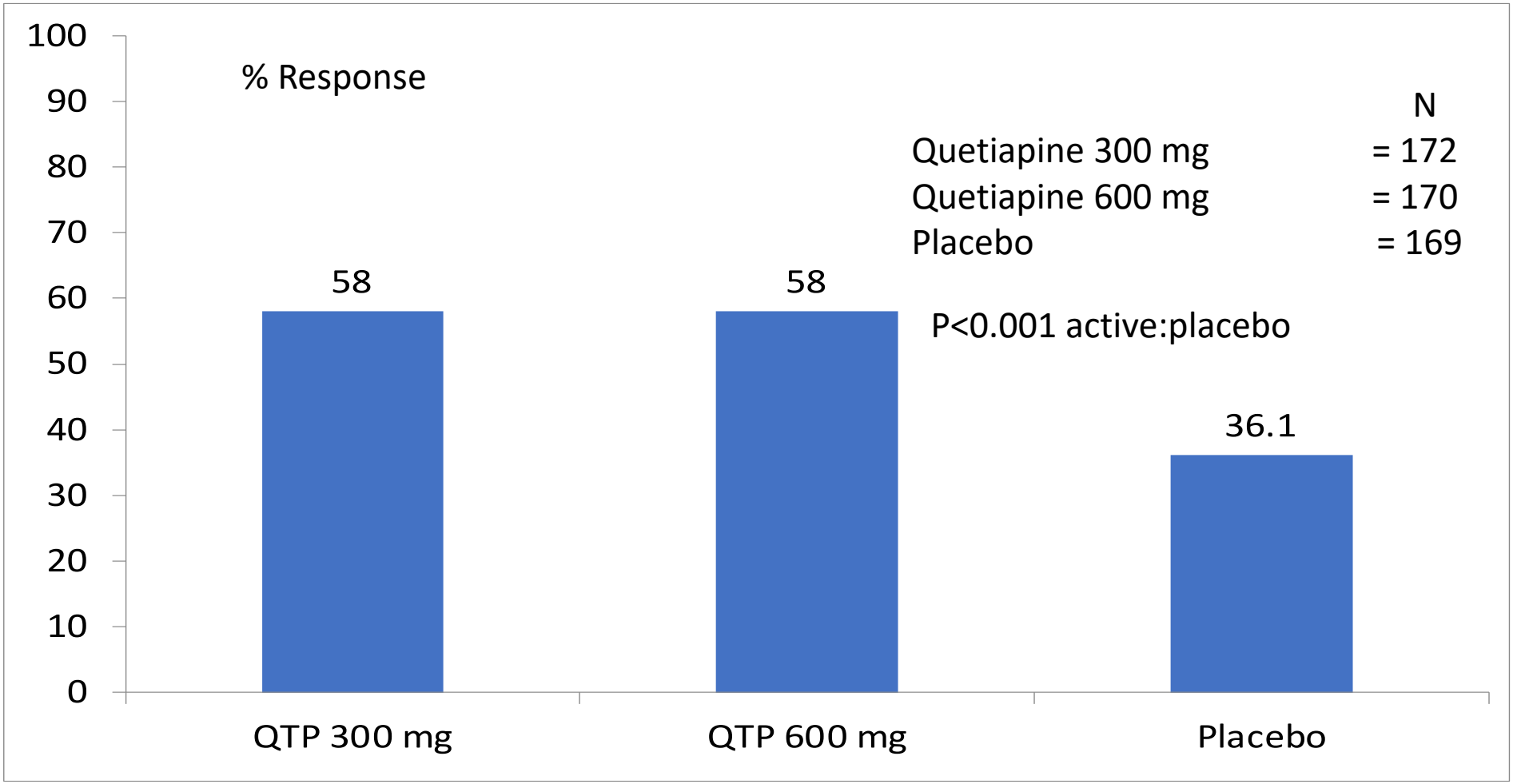
S. Koch et al. Neuropharmacology 46 (2004) 232–242; He et al. Psychoneuroendocrinology (2014) 42, 153—164; Weston-Green et al. CNS Drugs (2013) 27:1069–1080

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?

Quetiapine for Bipolar I or II Depression



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

Quetiapine

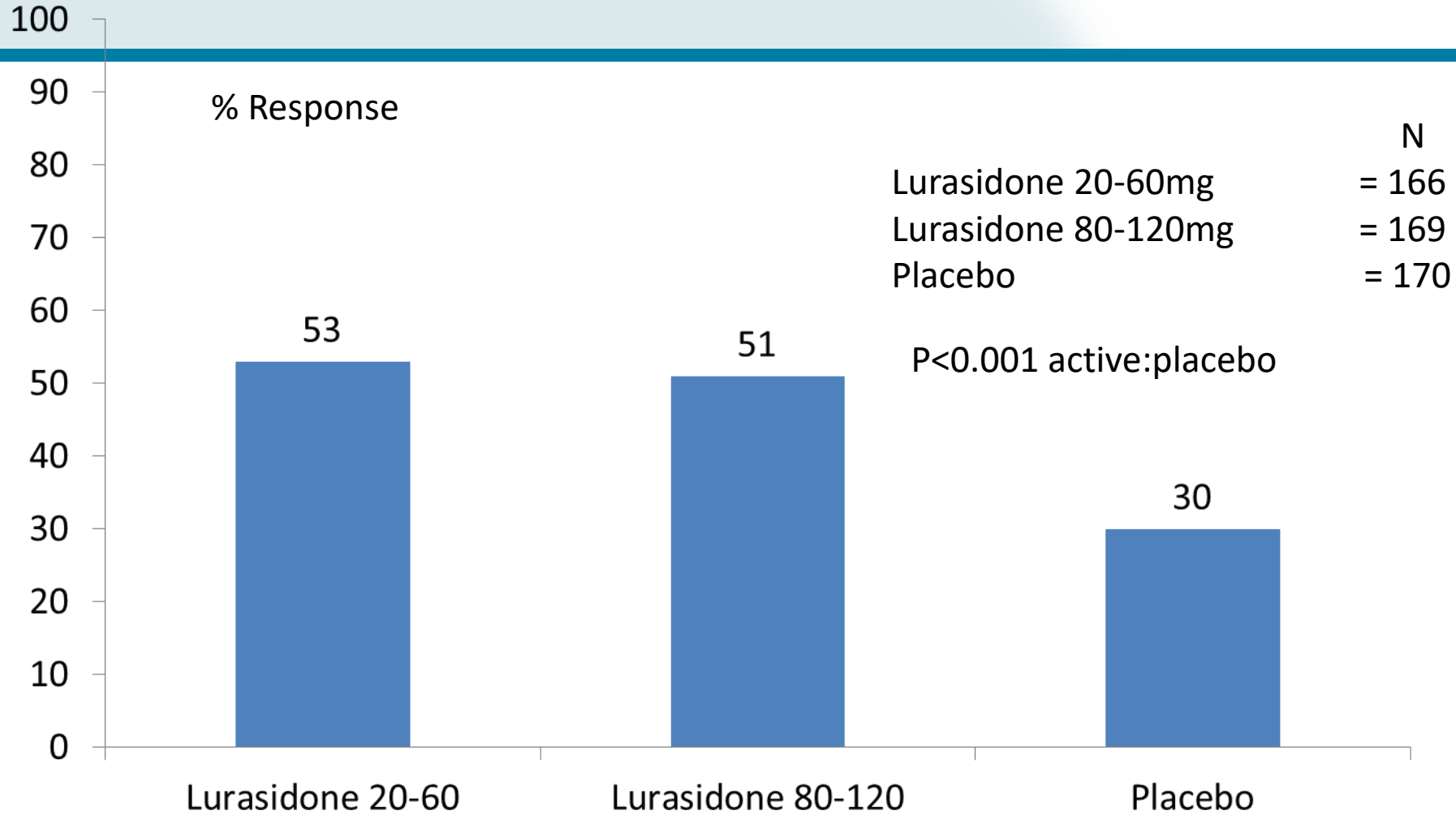
- Pharmacodynamic profile
  - D2 antagonist
  - 5-HT 2a antagonist
  - 5-HT 1A partial agonist
  - Alpha 2c adrenergic agonist
  - Alpha 1 adrenergic antagonist
  - Histaminergic antagonist
  - Muscarinic antagonist
- Metabolized through CYP450 3A4
- t½ 6 hours

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

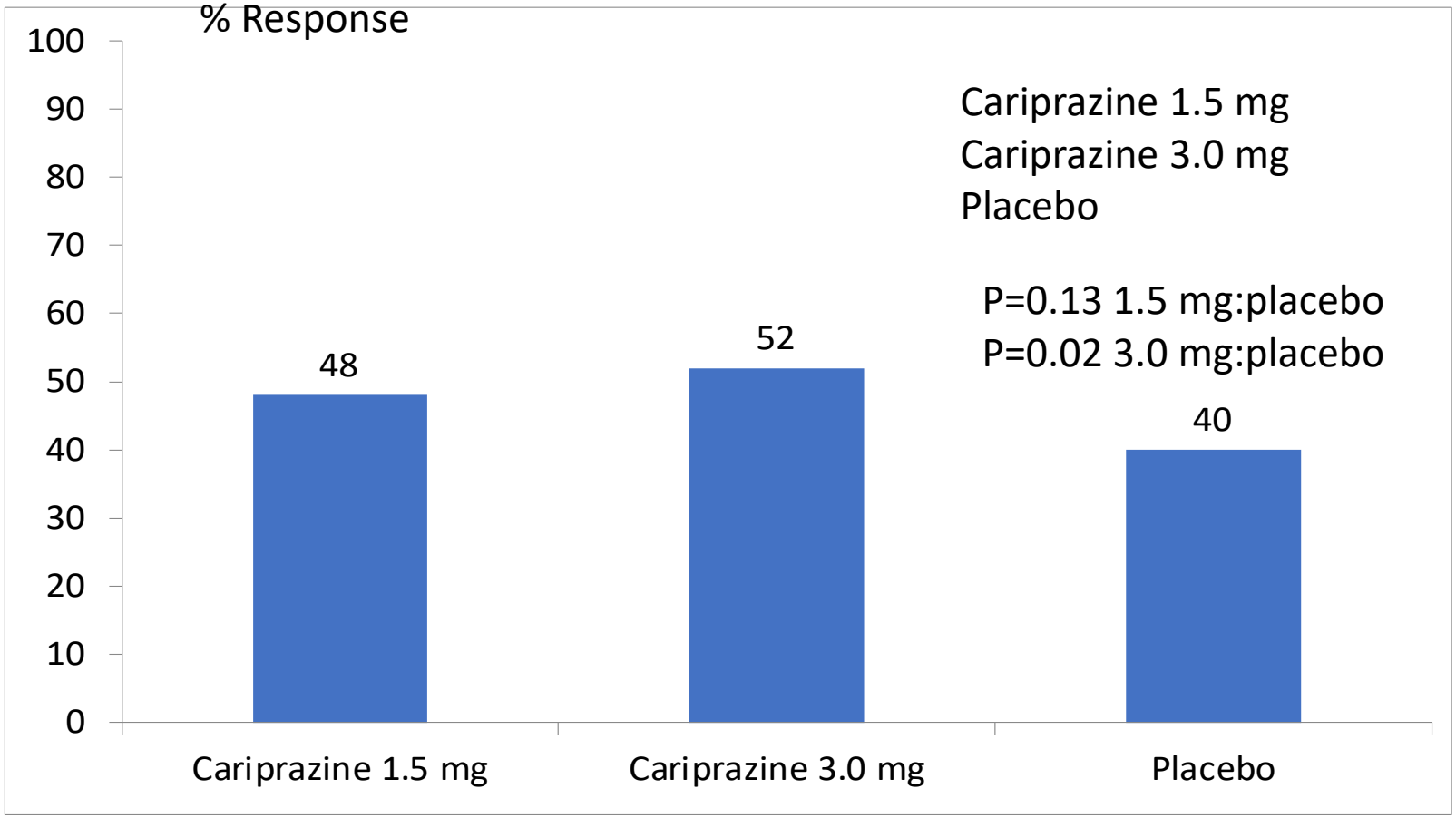
- Pharmacodynamic profile
  - D3/D2 partial antagonist
  - 5-HT 1A partial agonist
  - 5-HT 2a antagonist
  - No affinity for histaminergic or muscarinic receptors
- Metabolized through CYP3A4 and to a lesser extent by CYP2D6
- t½ 2-5 days; steady state in 7 days

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

Cariprazine for Bipolar I Depression

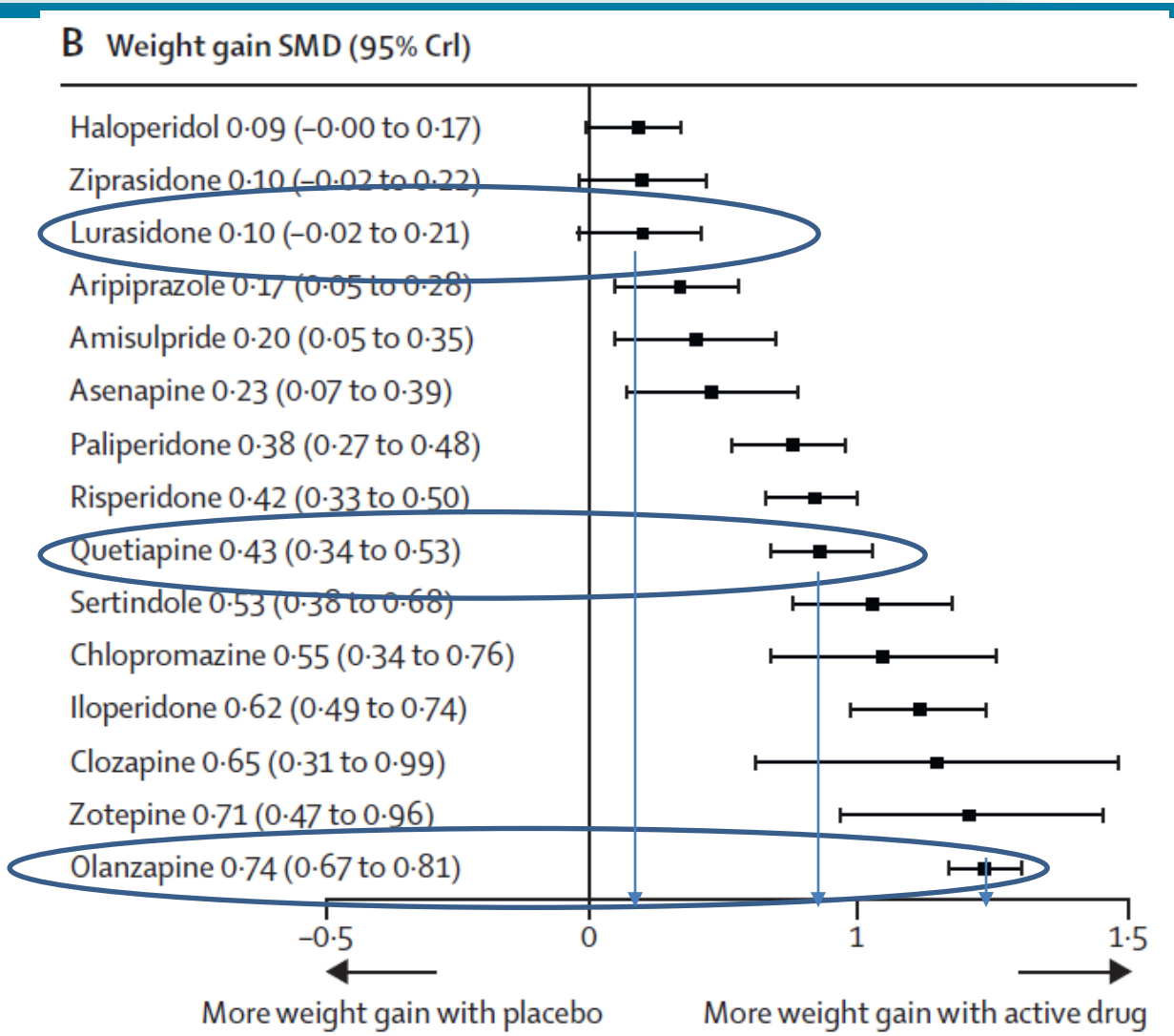
- Monotherapy
- Side effects
  - Restlessness, akathisia, extrapyramidal symptoms, somnolence, vomiting, dyspepsia
- Discontinuation rates (6 week studies)
  - 2.5% placebo;
  - 4.5% lurasidone 20 to 60 mg
  - 5.5 % lurasidone 80-120 mg

Cariprazine for Bipolar I Depression



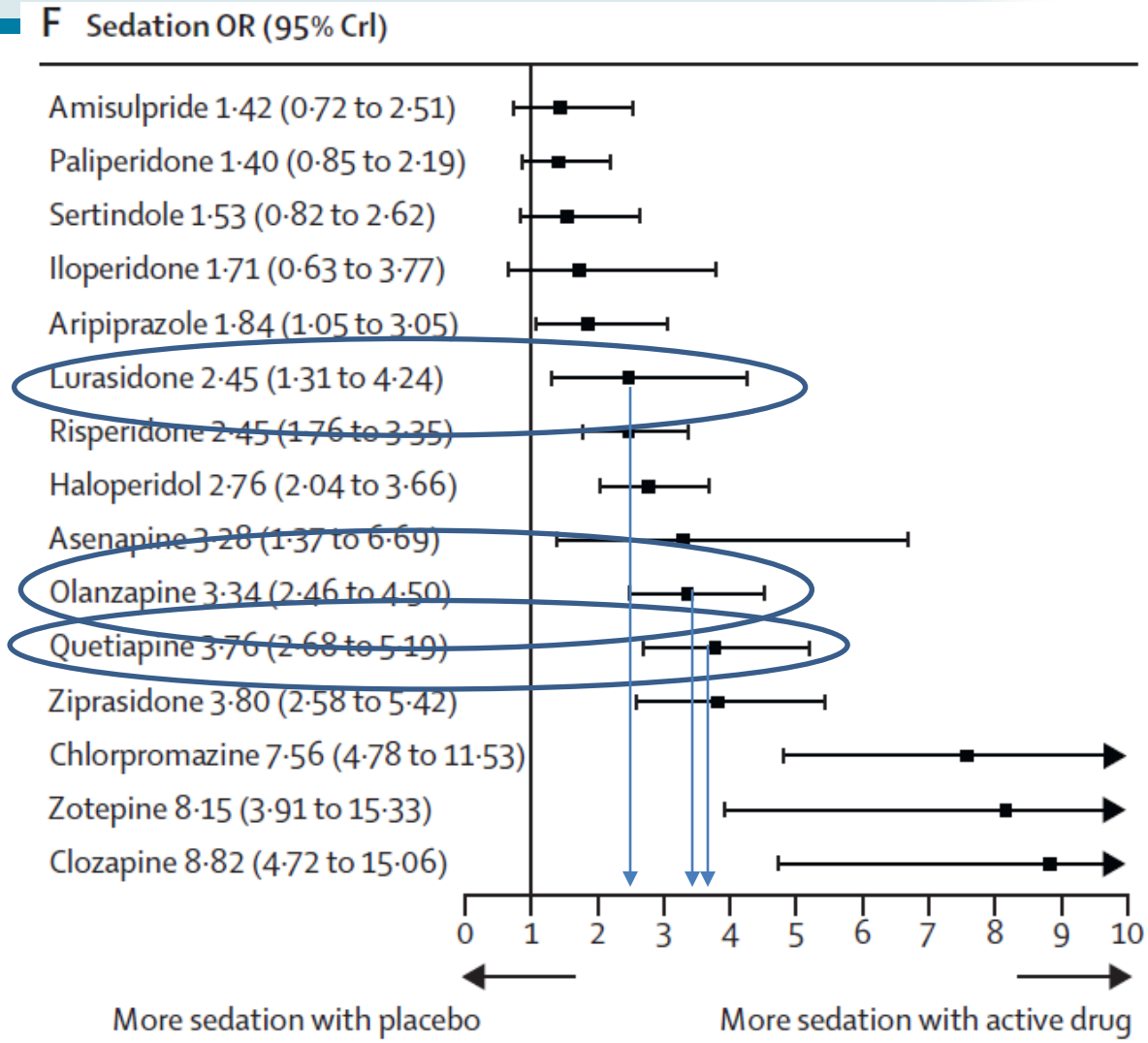
Early et al. AmJPsychiatry 2019; 176:439–448

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

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)

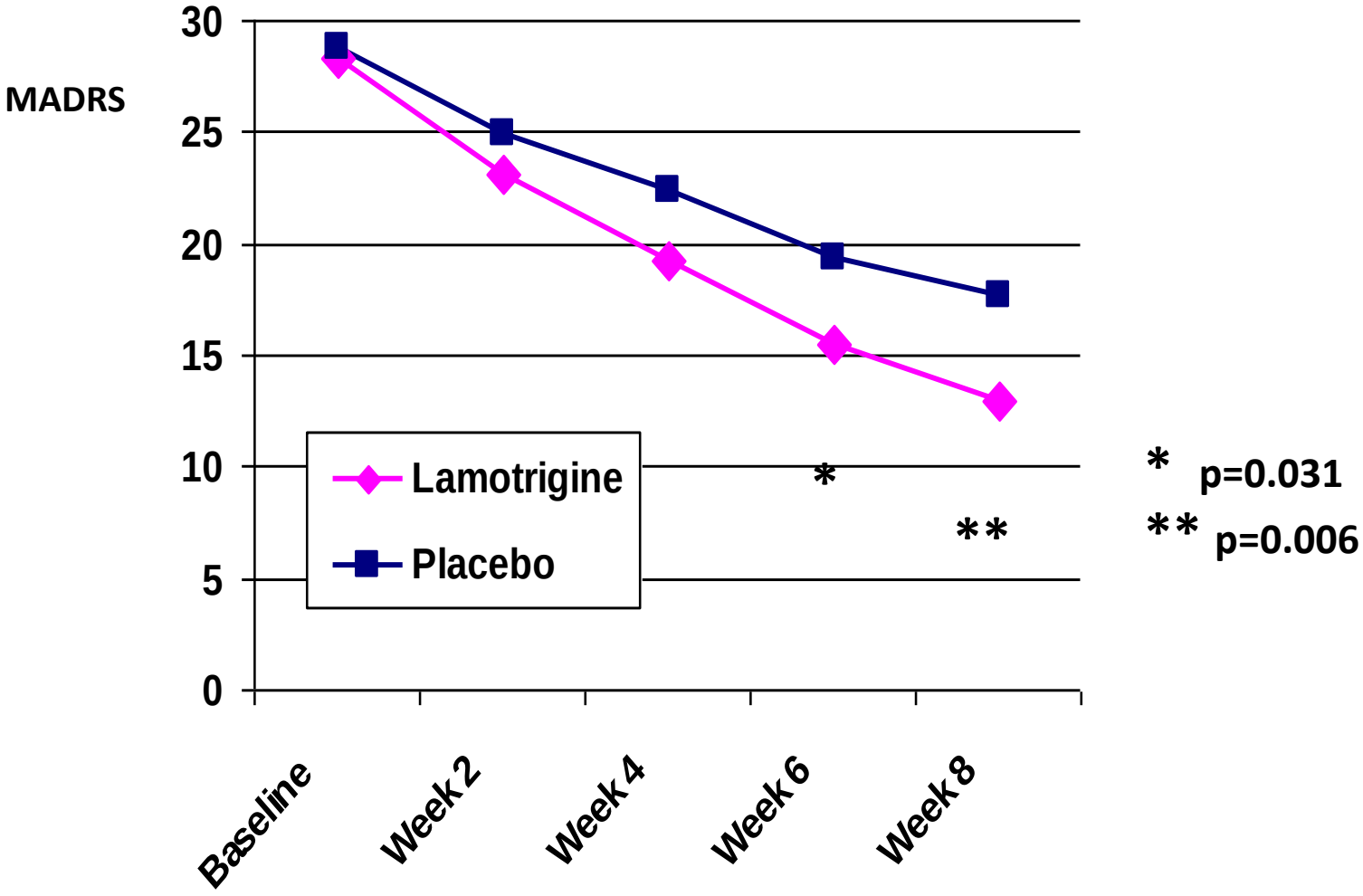
Shim et al. J Pharmacol Exp Ther 347:487–496, November 2013

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

Lamotrigine plus Lithium



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

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

Receptor	Action	Result
Alpha 1	Antagonist	Increase NE
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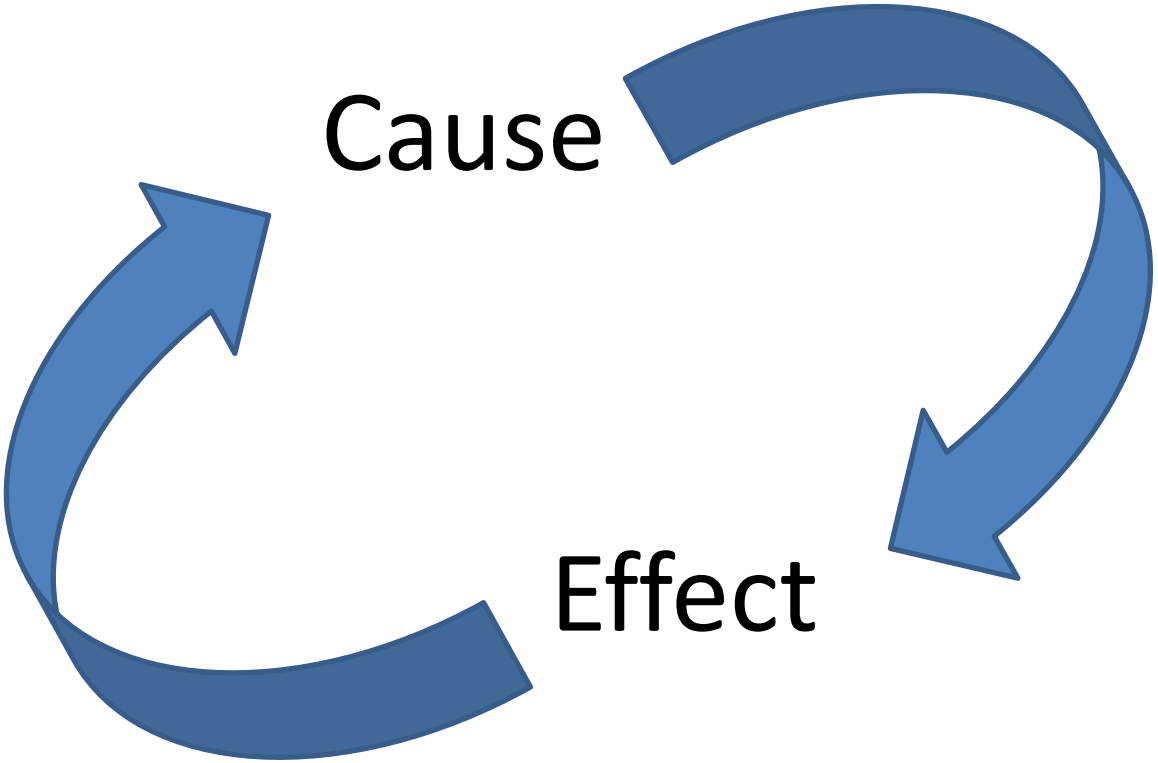
D3	Antagonist	Increase DA
NE Reuptake	Inhibition	Increase NE
5HT1A	Agonism	Increase 5HT

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?

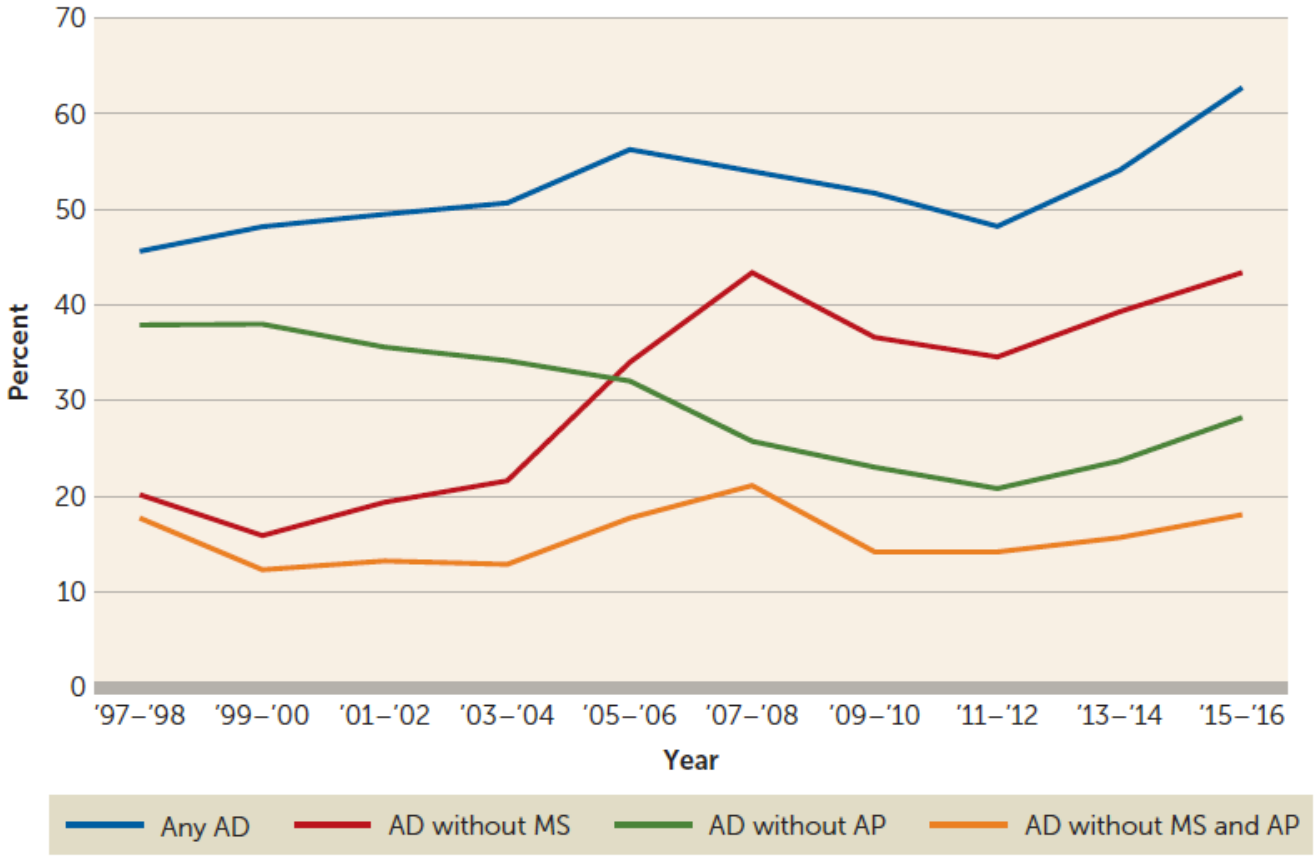


Post hoc ergo proptor hoc.

"After this, therefore, because of this."

Antidepressants Persist

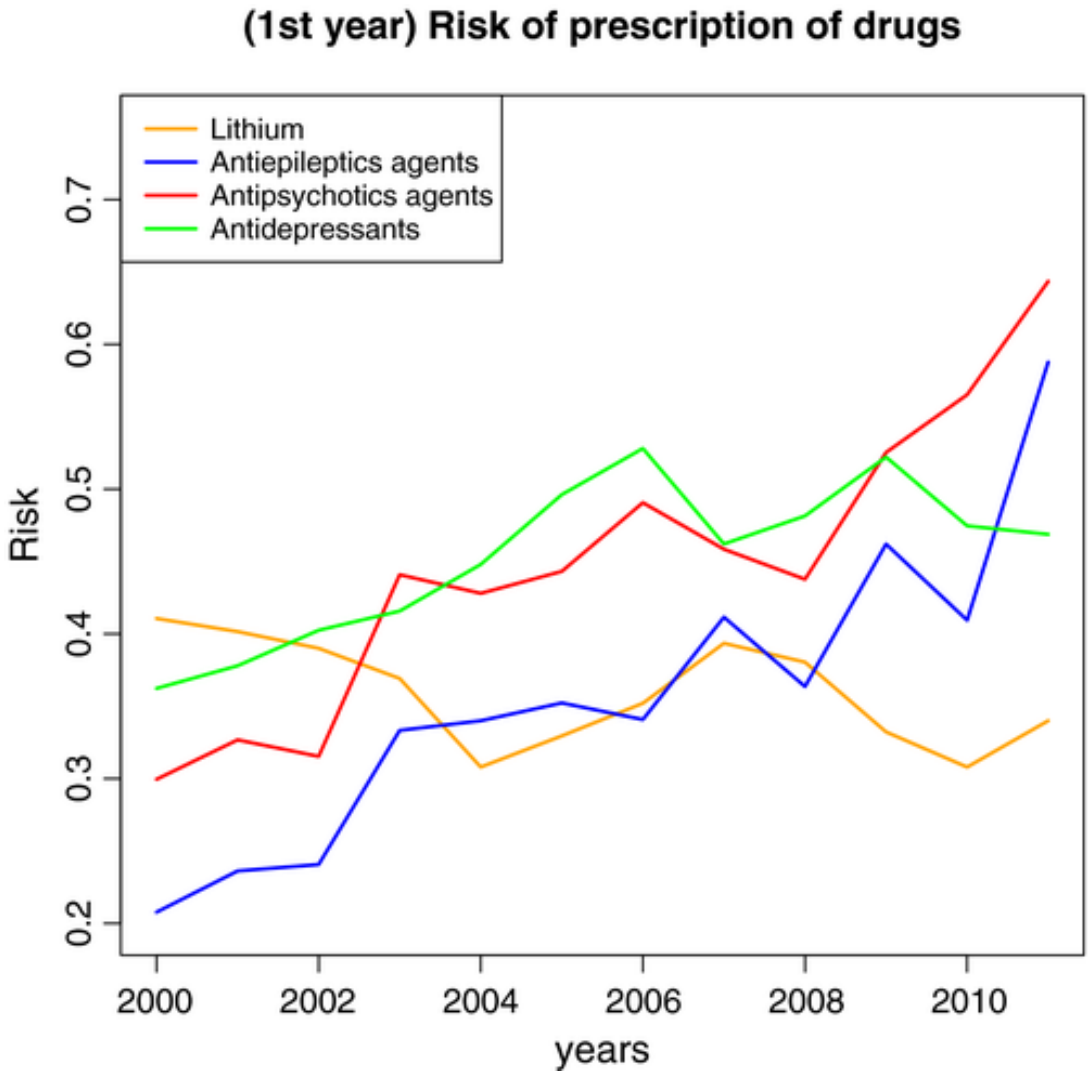
FIGURE 2. Prescribing trends for antidepressants in the treatment of bipolar disorder in office-based visits to psychiatrists, 1997–2016[a]



[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

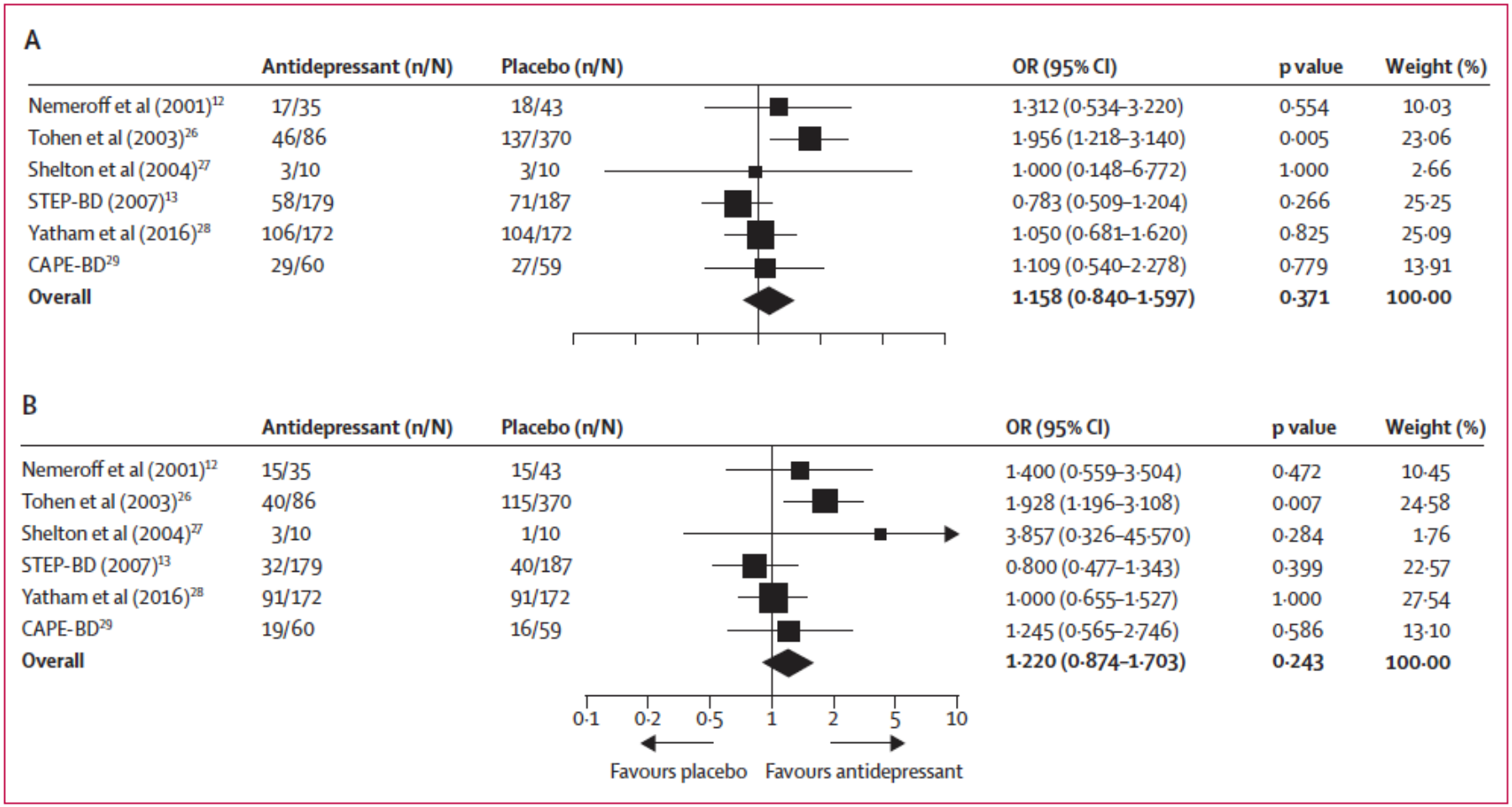
Secular Trends in Bipolar Meds



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

What is evidence?

Minimal advantage AD over Placebo



A

	Antidepressant (n/N)	Placebo (n/N)	OR (95% CI)	p value	Weight (%)
Nemeroff et al (2001)[12]	17/35	18/43	1·312 (0·534–3·220)	0·554	10·03
Tohen et al (2003)[26]	46/86	137/370	1·956 (1·218–3·140)	0·005	23·06
Shelton et al (2004)[27]	3/10	3/10	1·000 (0·148–6·772)	1·000	2·66
STEP-BD (2007)[13]	58/179	71/187	0·783 (0·509–1·204)	0·266	25·25
Yatham et al (2016)[28]	106/172	104/172	1·050 (0·681–1·620)	0·825	25·09
CAPE-BD[29]	29/60	27/59	1·109 (0·540–2·278)	0·779	13·91
Overall			**1·158 (0·840–1·597)**	**0·371**	**100·00**

B

	Antidepressant (n/N)	Placebo (n/N)	OR (95% CI)	p value	Weight (%)
Nemeroff et al (2001)[12]	15/35	15/43	1·400 (0·559–3·504)	0·472	10·45
Tohen et al (2003)[26]	40/86	115/370	1·928 (1·196–3·108)	0·007	24·58
Shelton et al (2004)[27]	3/10	1/10	3·857 (0·326–45·570)	0·284	1·76
STEP-BD (2007)[13]	32/179	40/187	0·800 (0·477–1·343)	0·399	22·57
Yatham et al (2016)[28]	91/172	91/172	1·000 (0·655–1·527)	1·000	27·54
CAPE-BD[29]	19/60	16/59	1·245 (0·565–2·746)	0·586	13·10
Overall			**1·220 (0·874–1·703)**	**0·243**	**100·00**

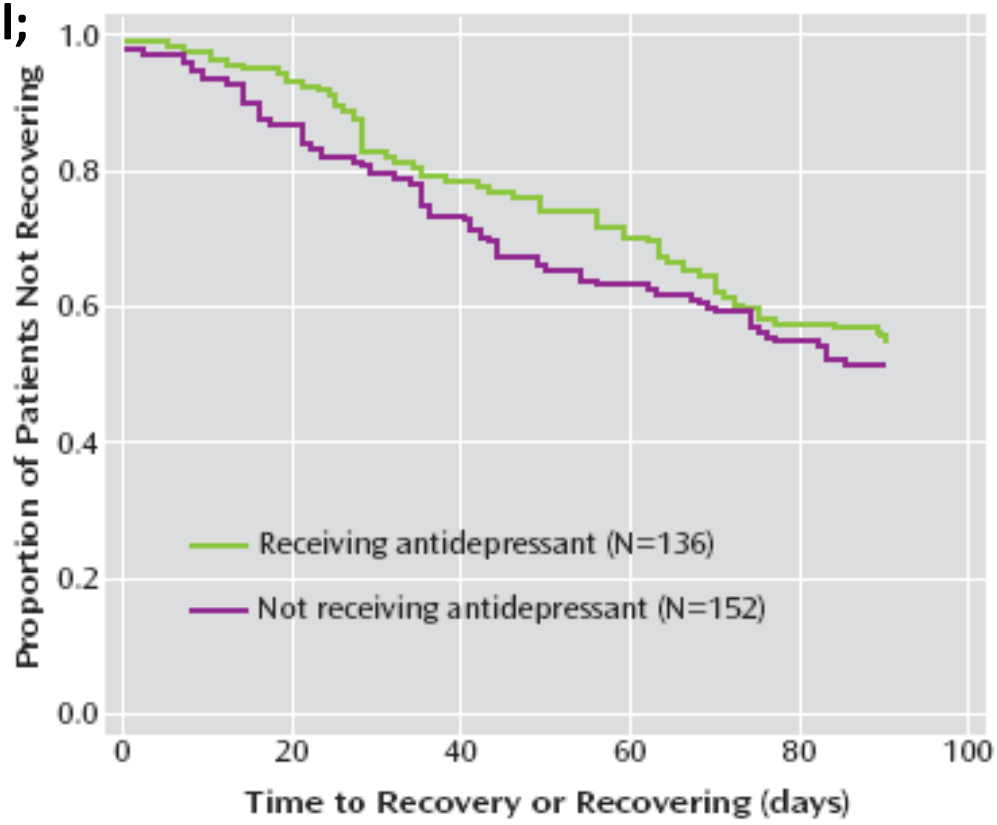
Figure 3: **(A) Clinical response and (B) clinical remission**
OR=odds ratio.

McGirr et al. Lancet Psychiatry 2016;3: 1138–46

Practice Based Evidence

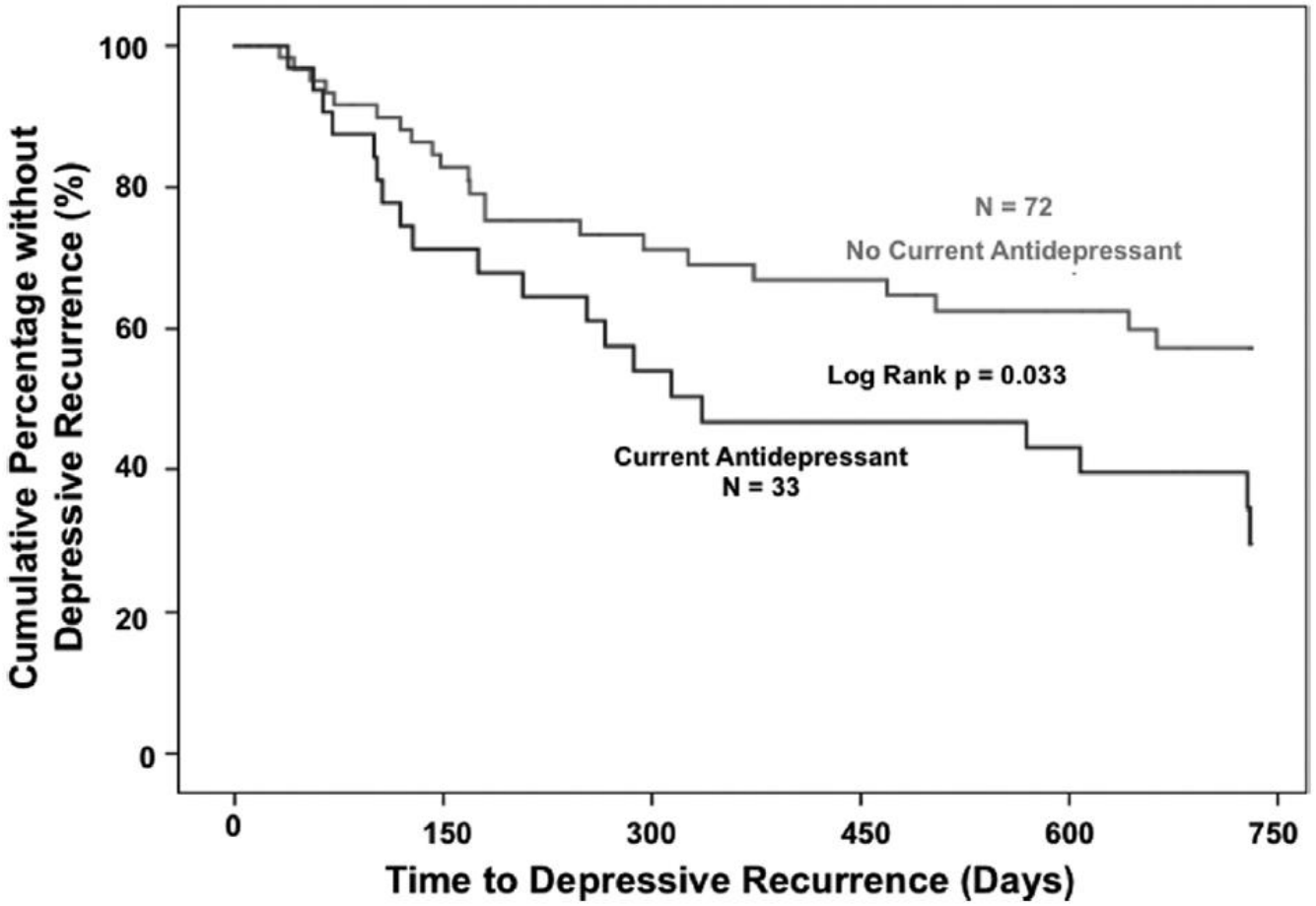
No benefit with antidepressants for bipolar depression with manic symptoms

Note: Observational; Not Randomized



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

Antidepressants Hastens Depressive Recurrence in Bipolar Disorder

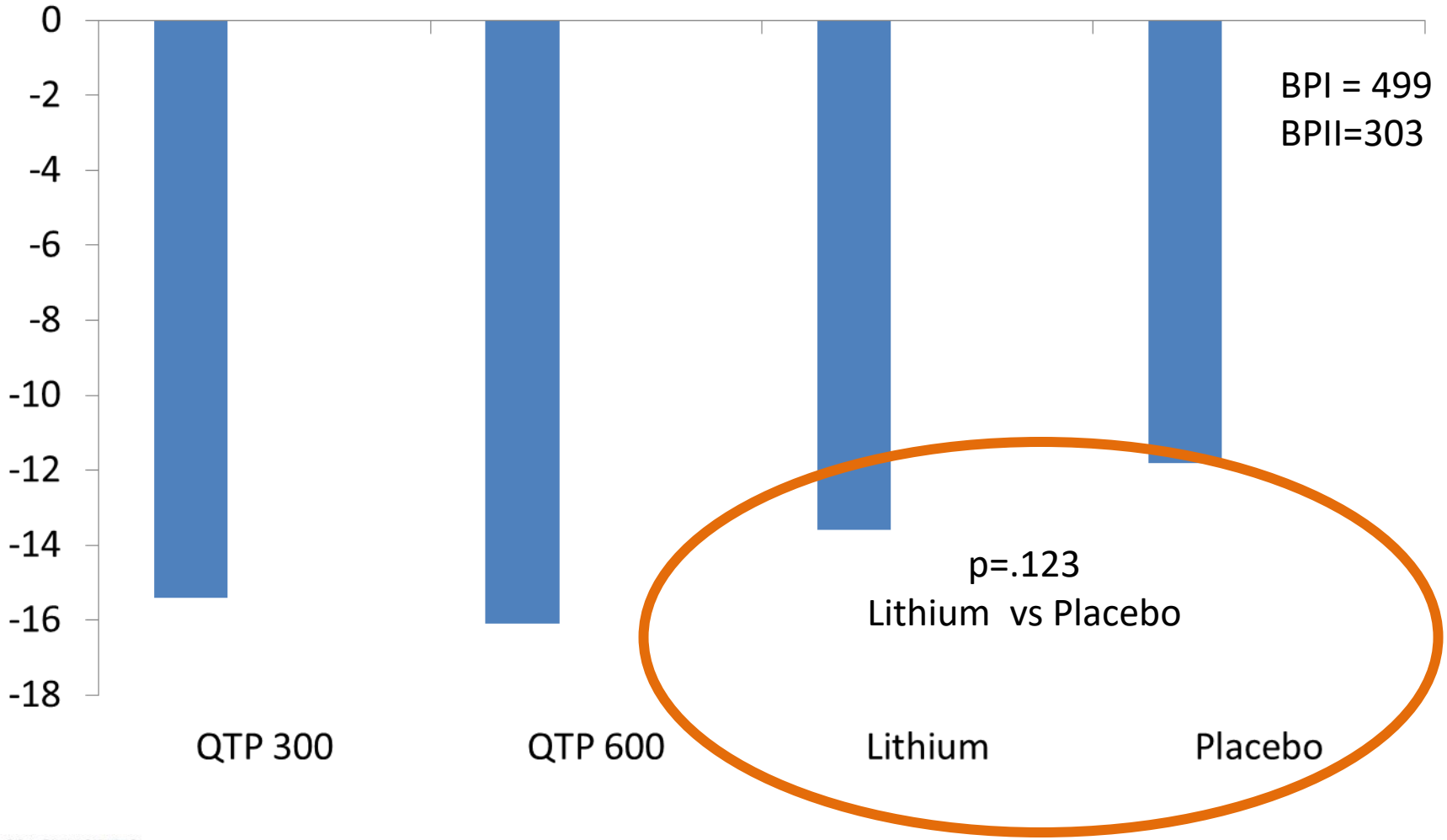


Hooshmand et al. Journal of Affective Disorders 246 (2019) 836–842

Lithium for bipolar depression?

EMBOLDEN I: Li not better than Pbo

Decrease in MADRS

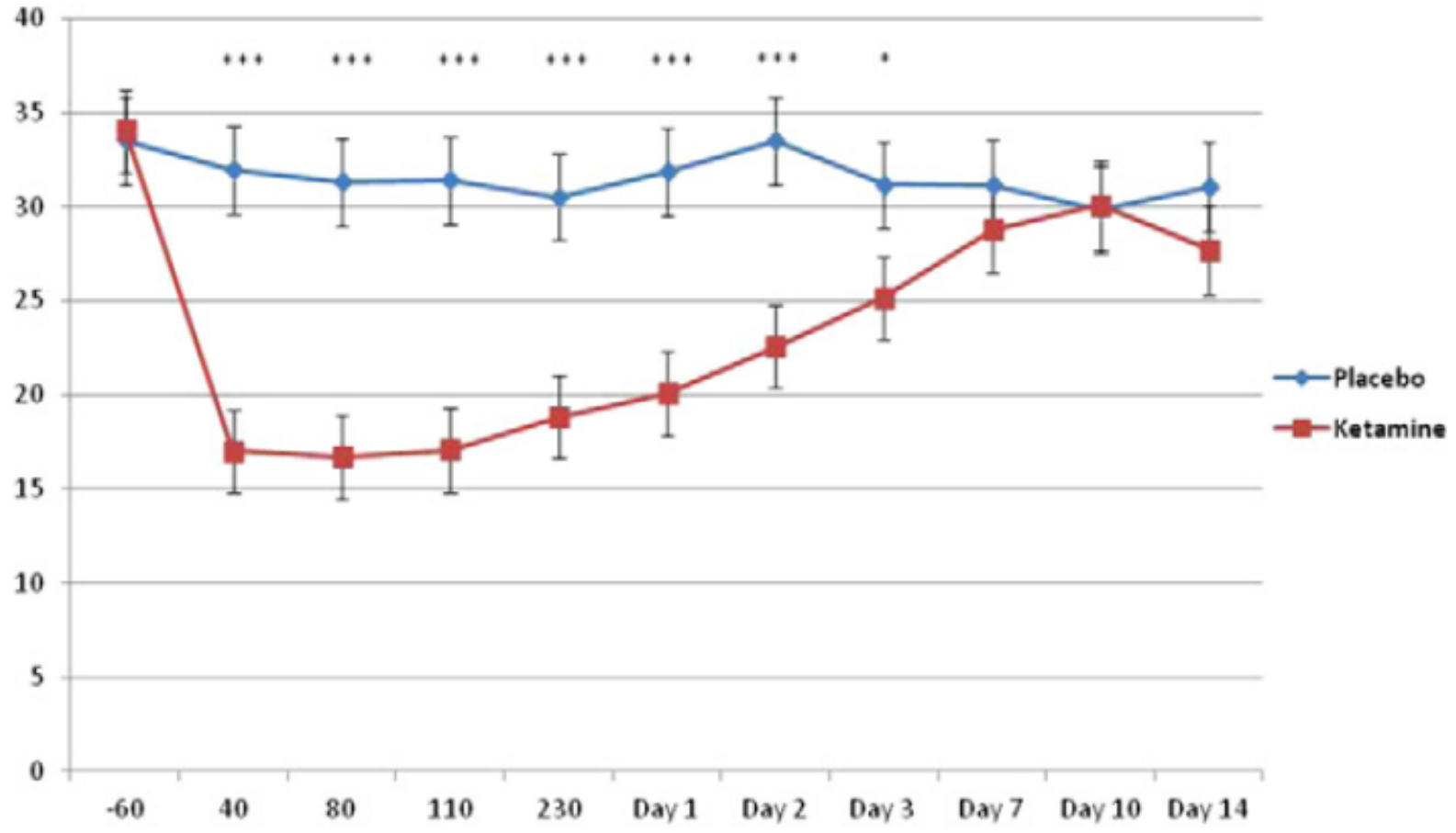


McElroy et al. J Clin Psychiatry 2010 Feb;71(2):163-74. Epub 2010 Jan 26

Potential treatments for bipolar depression

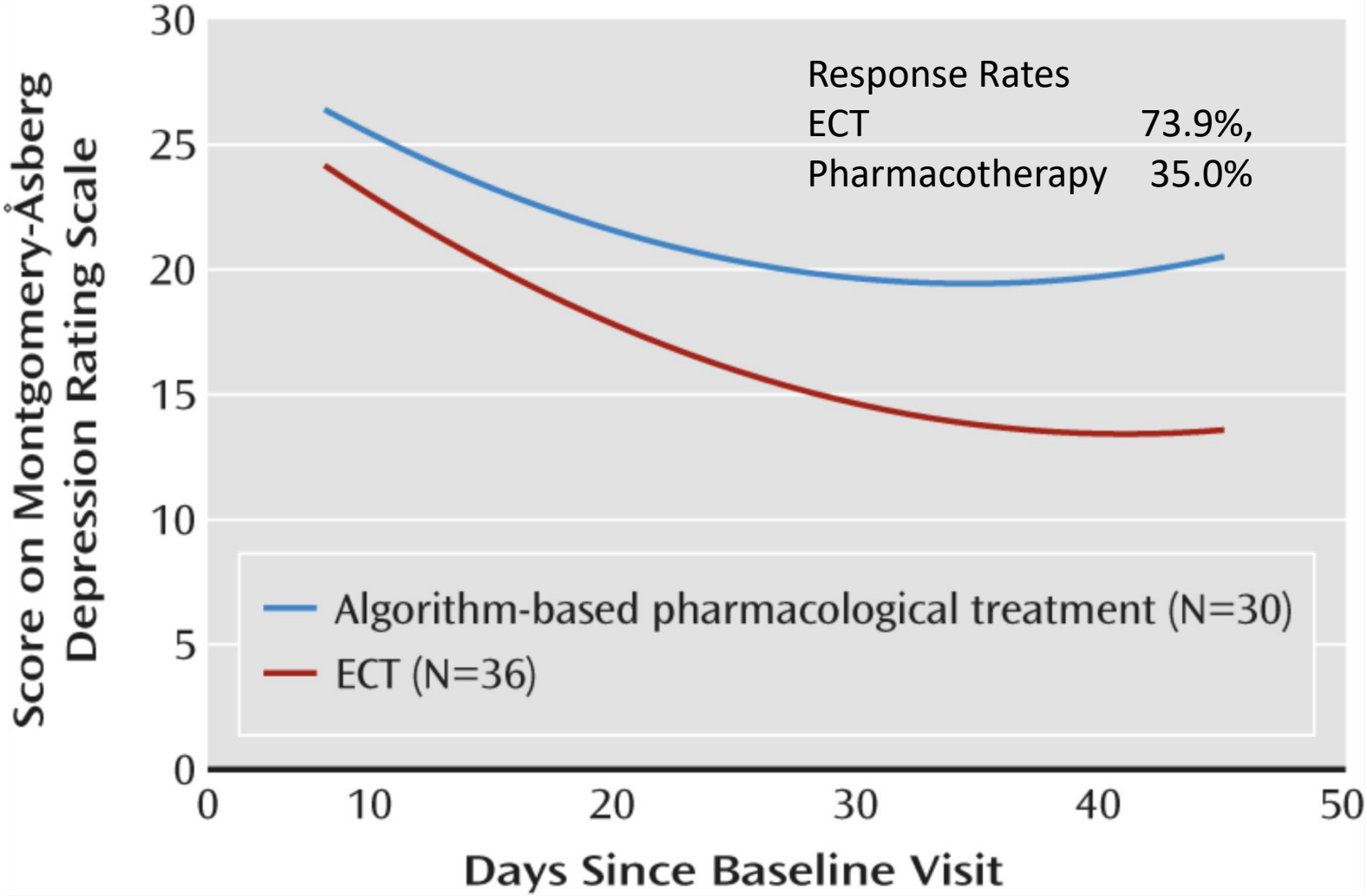
- Ketamine
- ECT
- rTMS
- Lumateperone?

Ketamine for Bipolar Depression



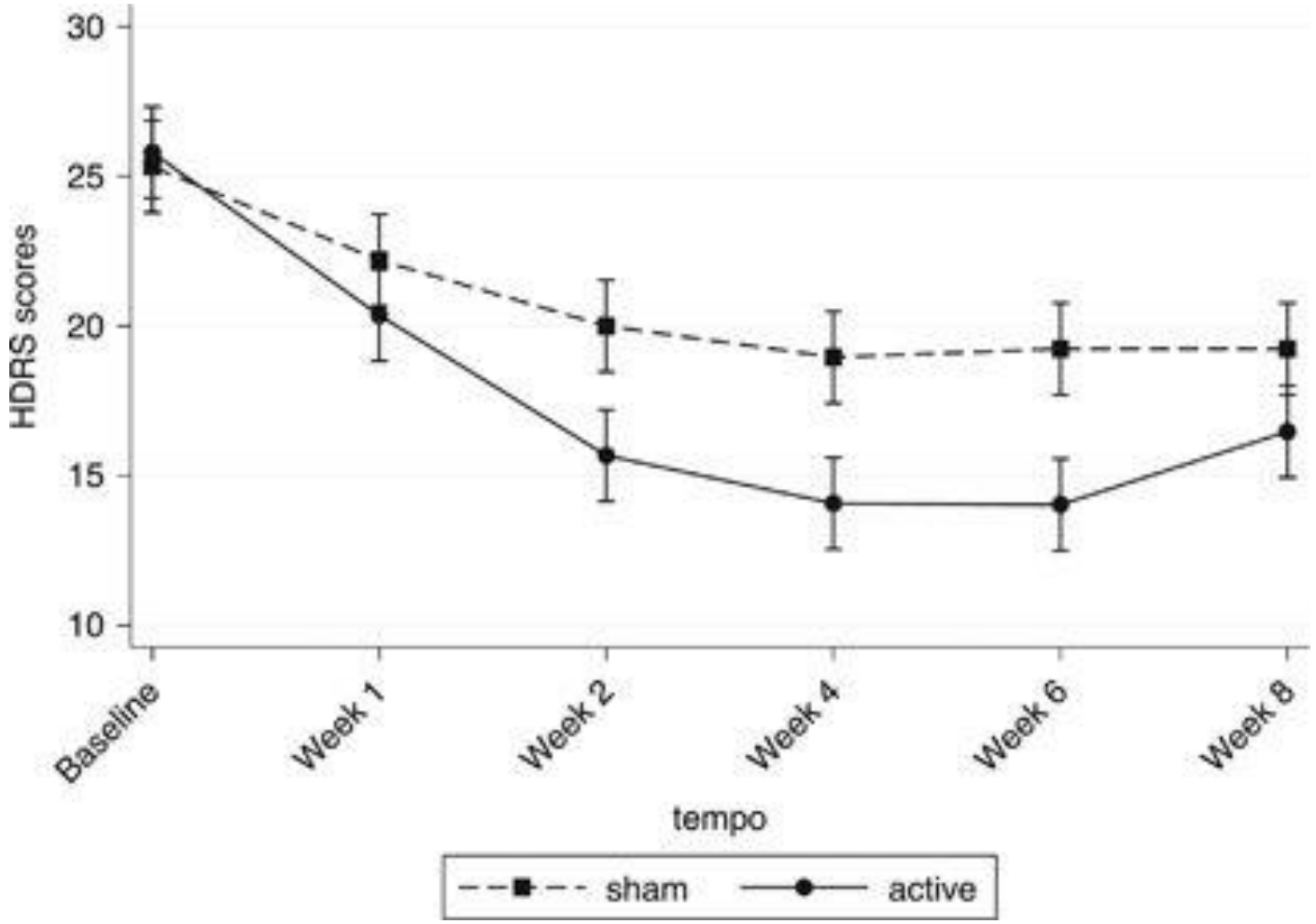
Zarate et al. BIOL PSYCHIATRY 2012;71:939–946

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

Lumateperone

- Not yet approved for bipolar depression
- Approved for schizophrenia

Lumateperone

Pharmacodynamic profile

- antagonistic activity at serotonin 5-HT2A receptors
- Inhibitor of serotonin transport
- Presynaptic partial agonist and a postsynaptic antagonist at dopamine D2 receptors
- Dopamine D1 receptor-dependent indirect modulator of glutamatergic N-methyl-d-aspartate GluN2B receptors

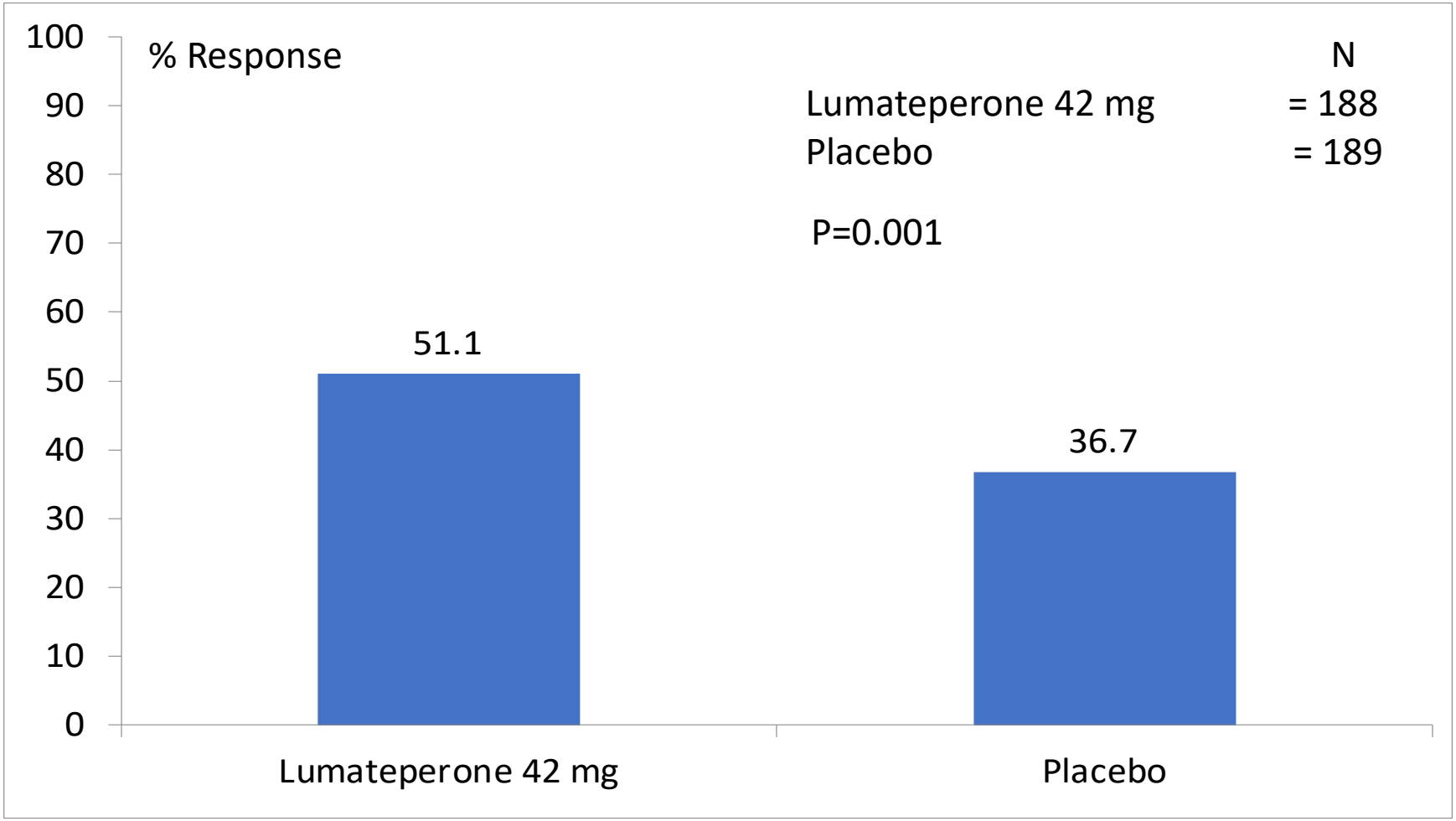
Vanover KE, Neuropsychopharmacology. 2019;44(3):598–605.

Lumateperone

- Side effects
- somnolence/sedation, nausea, dry mouth dizziness, increased creatine phosphokinase, fatigue, vomiting, increased hepatic transaminases and decreased appetite
- No weight gain
- No metabolic syndrome

Blair H. Drugs (2020) 80:417–423

Lumateperone for Bipolar I and II Depression



D'Souza et al. CNS Spectrums 2021 Apr;26(2):150.

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