

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
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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

Bipolar Depression

Sorrowing Old Man

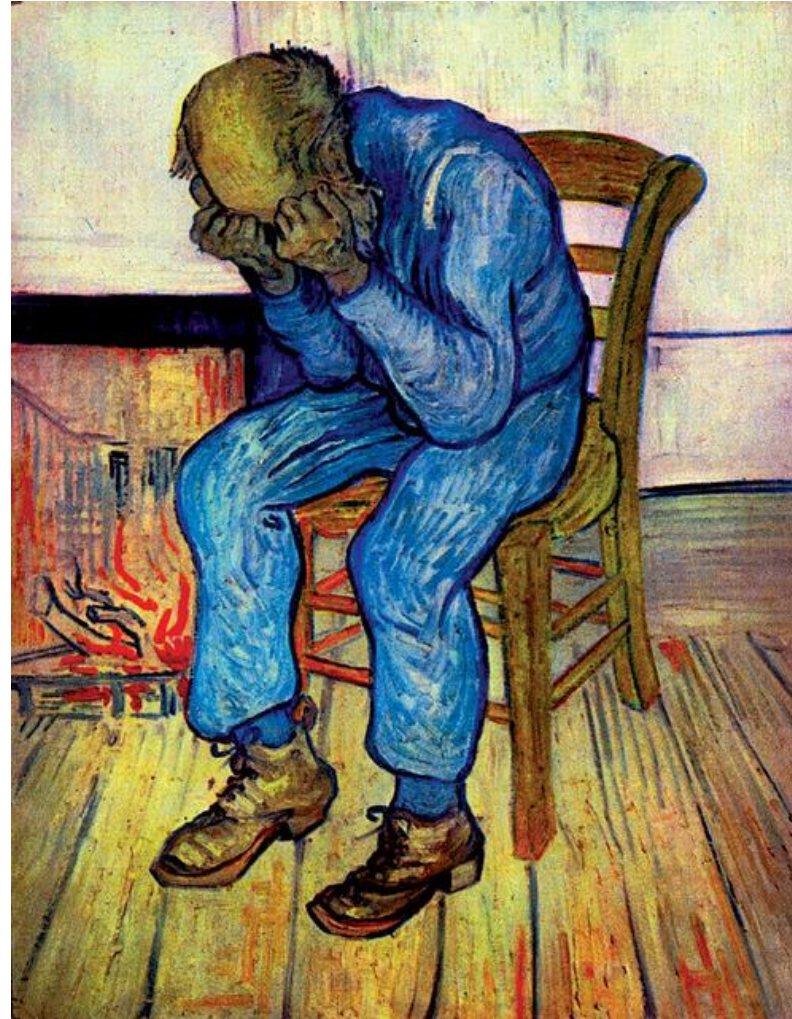
('At Eternity's Gate')

(Dutch: *Op de drempel der eeuwigheid*).

Vincent Van Gogh

Painted May 1890, at

Saint-Rémy-de-Provence, shortly before he left the asylum there and moved to Auvers-sur-Oise, where he died from suicide two months later.



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

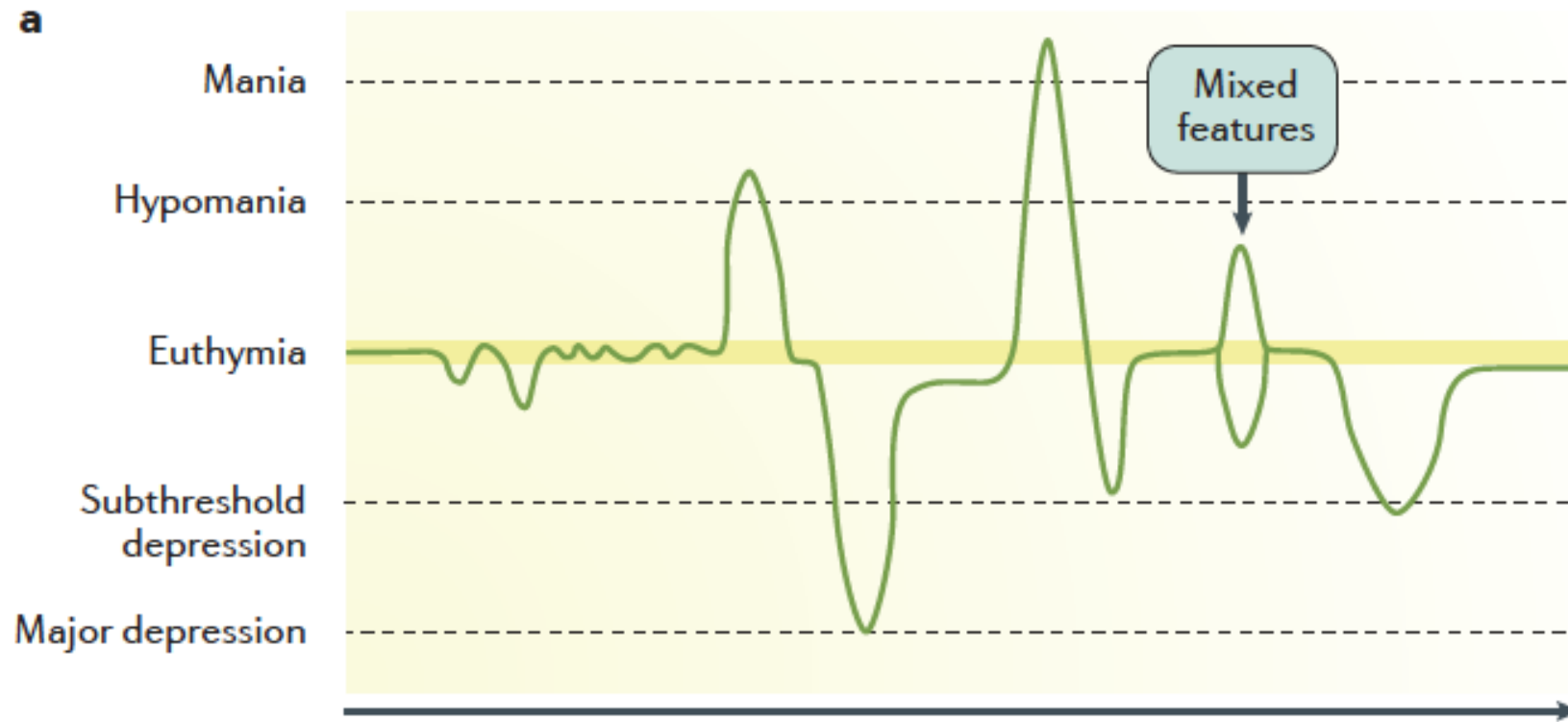
Open Access

Bipolar depression: a major unsolved challenge



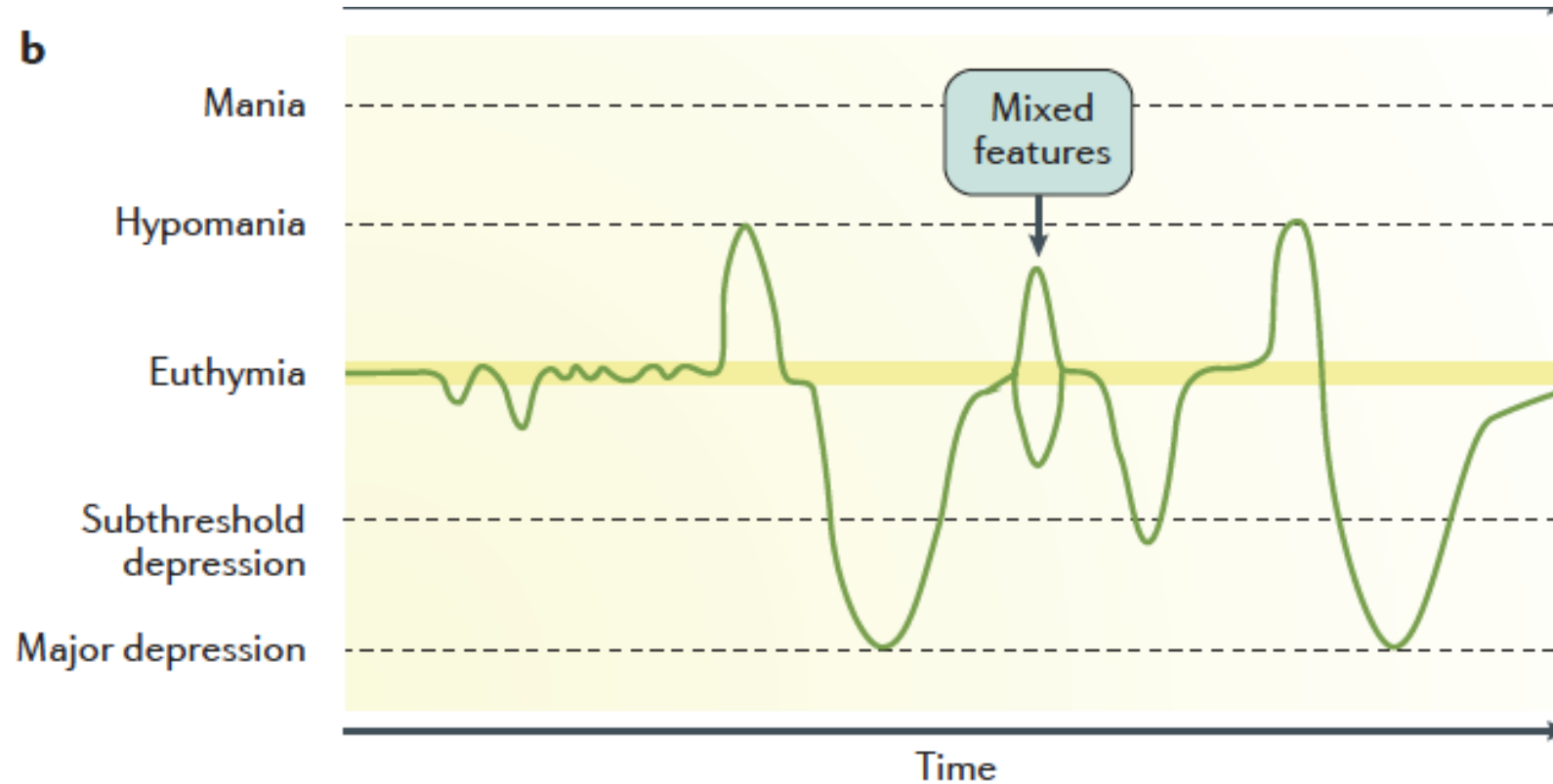
Ross J. Baldessarini^{1,2*} , Gustavo H. Vázquez^{2,3} and Leonardo Tondo^{1,2,4}

Bipolar I



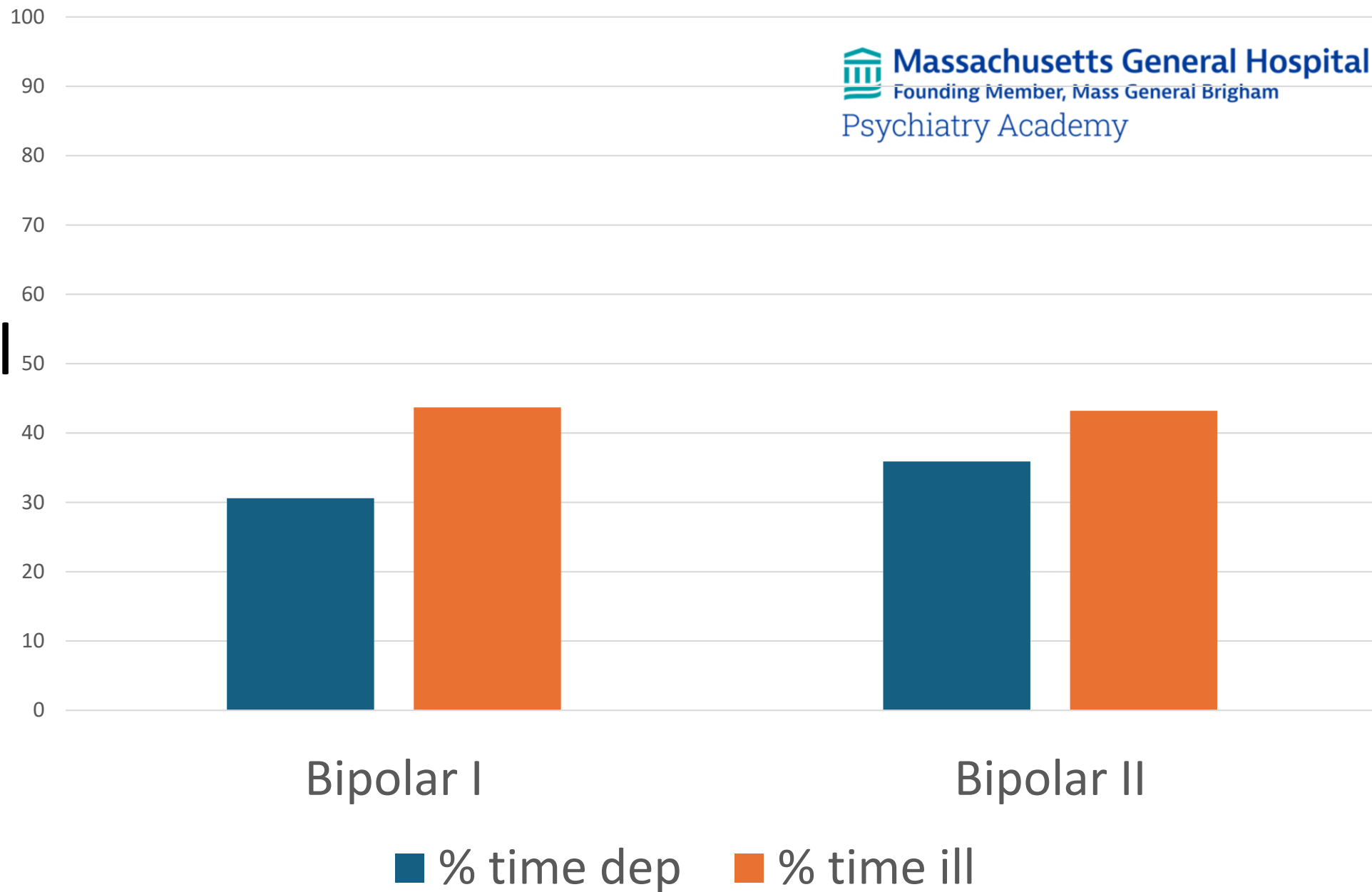
Vieta et al. Nature Reviews Disease Primer 2018

Bipolar II



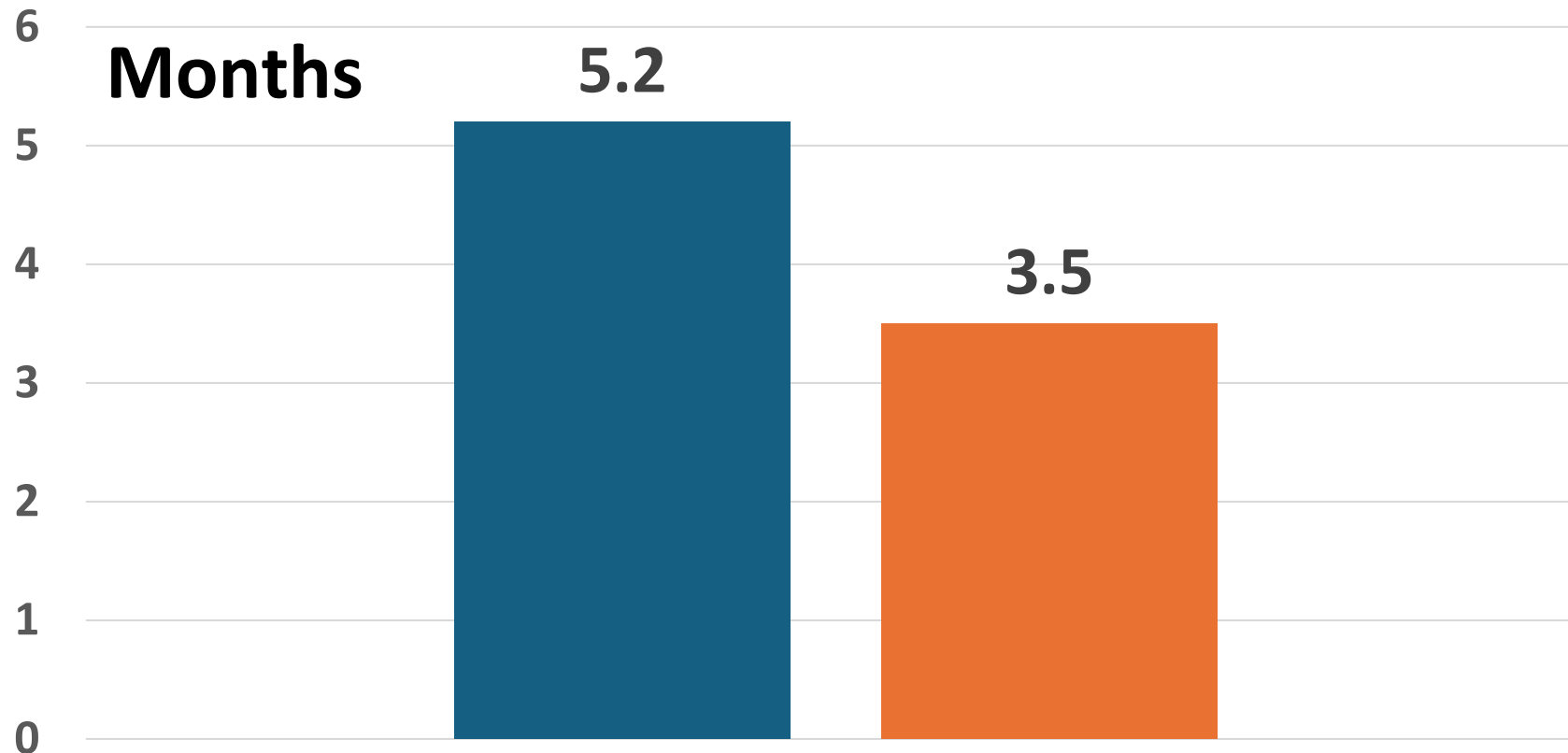
Vieta et al. Nature Reviews Disease Primer 2018

~80% of
total time ill
is bipolar
depression



Forte et al. 2015

Depression lasts longer than Mania



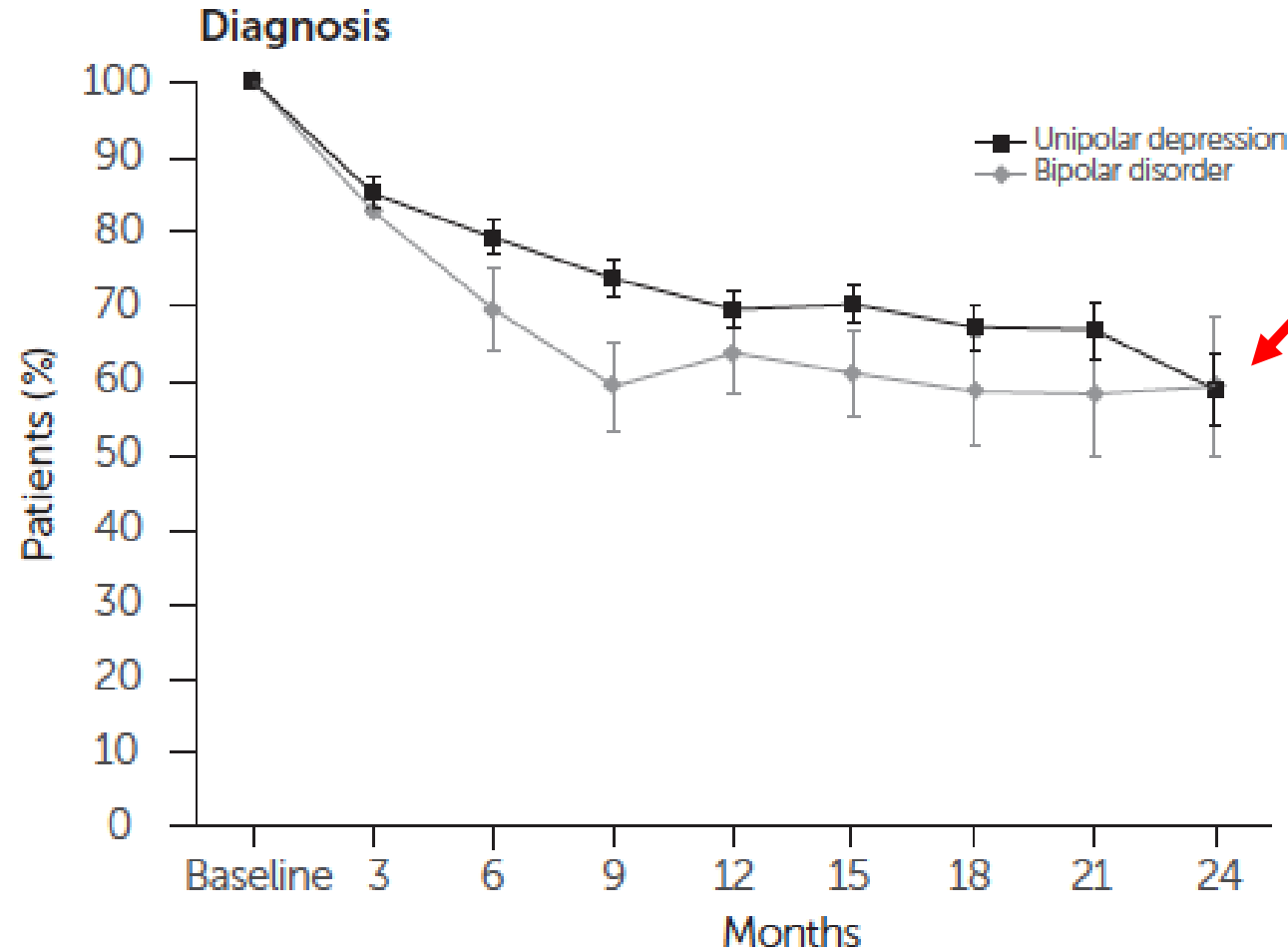
Tondo, Vasquez, Baldessarini.
Current Neuropharmacology, 2017, 15, 353-358

■ Depressive ■ Manic

Bipolar Depression Results

National Network
Depression Centers
Mood Outcomes Program

Proportion of
patients
With PHQ-9 ≥ 10



**60% still
depressed
after 24
months of
treatment**

Zandi et al., Psychiatric Services 71:5, May 2020

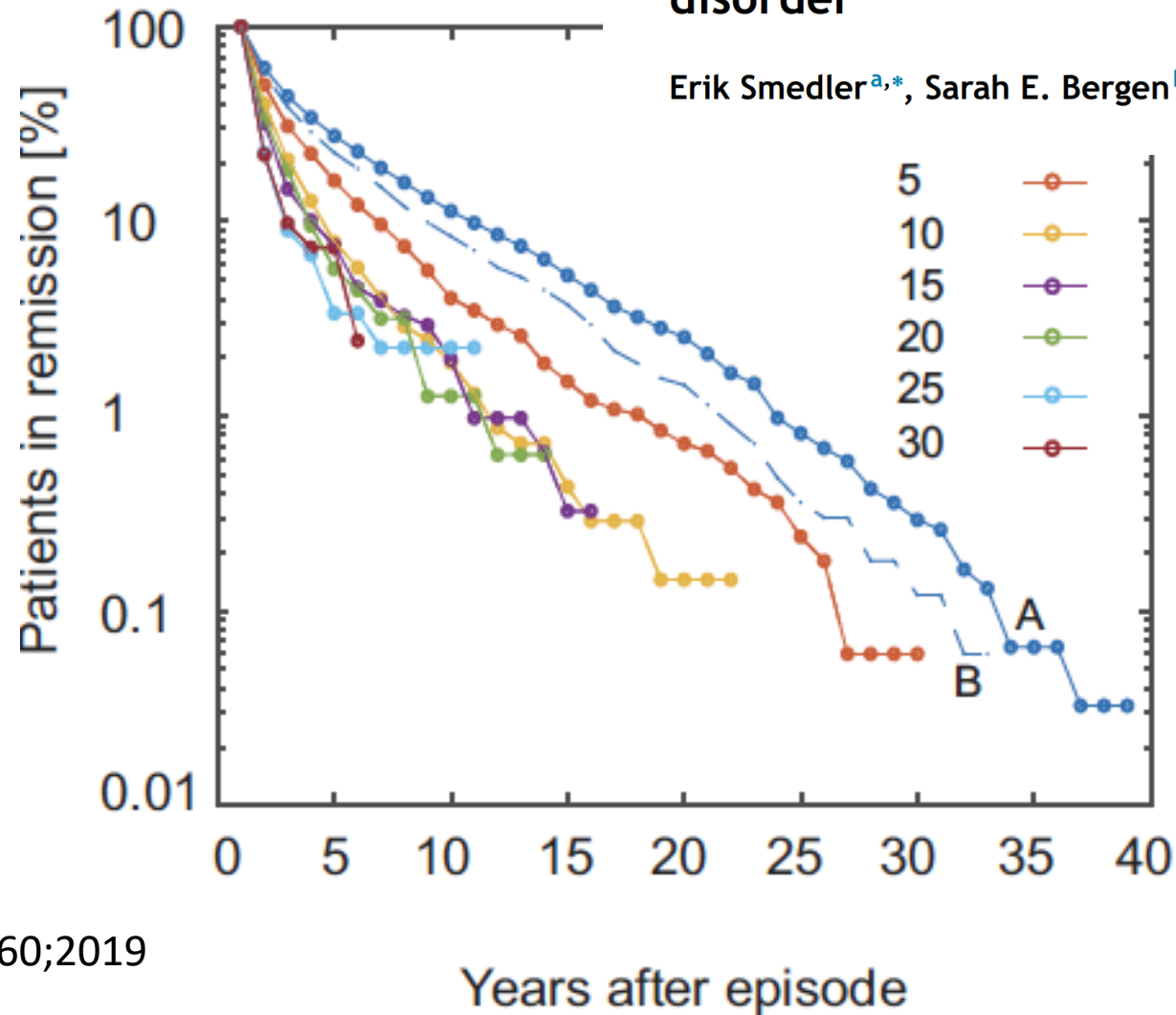
Bipolar Highly Recurrent

Genes, biomarkers, and clinical features associated with the course of bipolar disorder



Erik Smedler^{a,*}, Sarah E. Bergen^b, Jie Song^b, Mikael Landén^{a,b}

N=3074



Smedler et al. European
Neuropsychopharm 29:1152-1160;2019

Co-occurring Conditions

Approximately 65% of individuals with BD meet criteria for at least one psychiatric comorbidity

Psychiatric Comorbidities

Anxiety disorders: 70–90%

GAD	14.4%
Panic disorder	16.8%
Social anxiety disorder	14.4%
Specific phobia	10.8%
Agoraphobia	7.8%

Substance use disorders: 56%

Tobacco smoking	45%
Alcohol use disorder	30%–50%
Substance use disorder	30%–50%

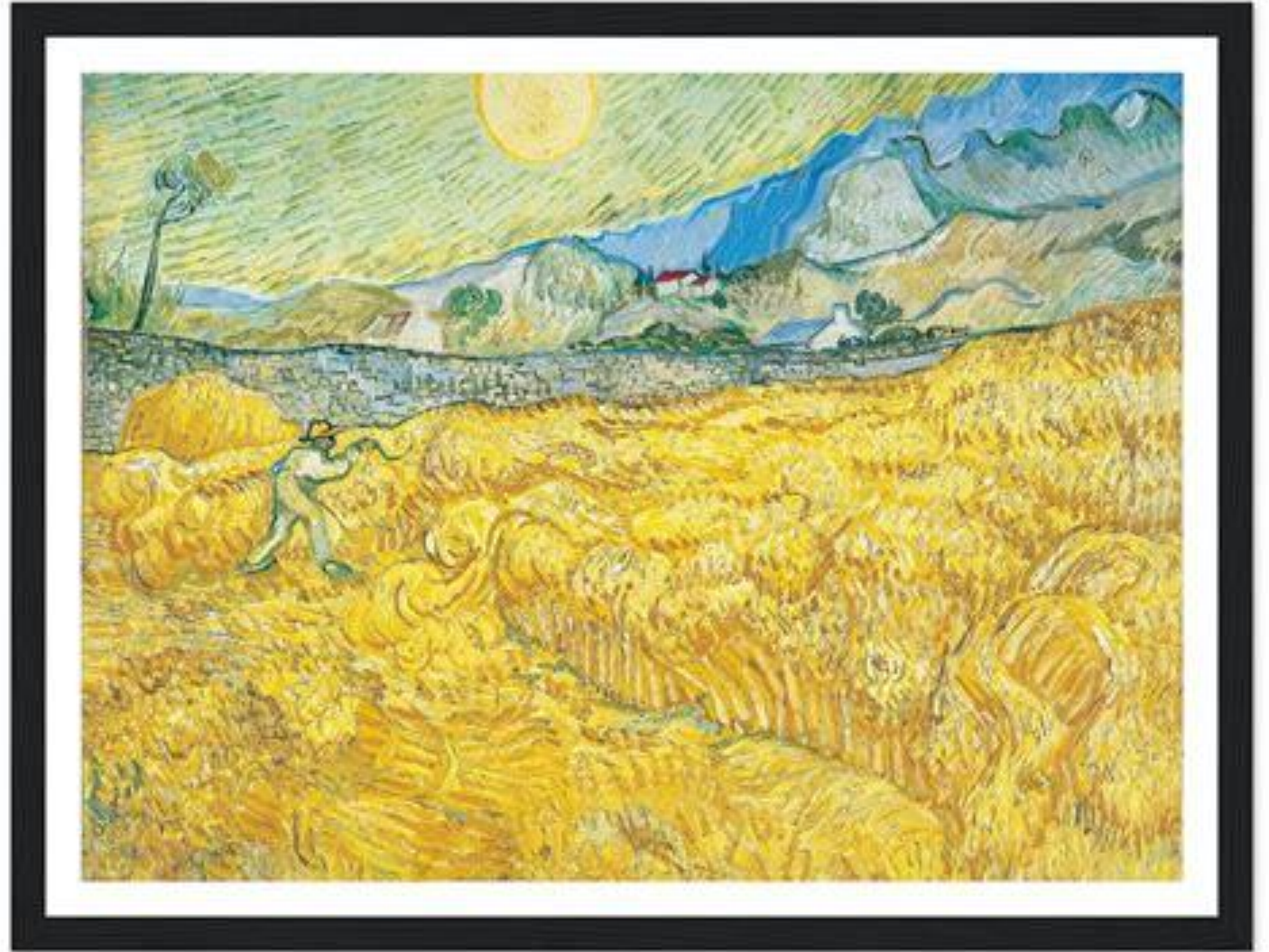
Other psychiatric disorders

ADHD	10%–20%
Personality disorders	20%–40%
Eating disorders	10%–20%



Soliman et al., Am J Psychiatry 183:3, March 2026

Vincent Van Gogh
Wheat Field behind Saint-
Paul with Reaper,
September 1889



Vincent Van Gogh
Wheatfield with Crows

(Dutch: *Korenveld met kraaien*)

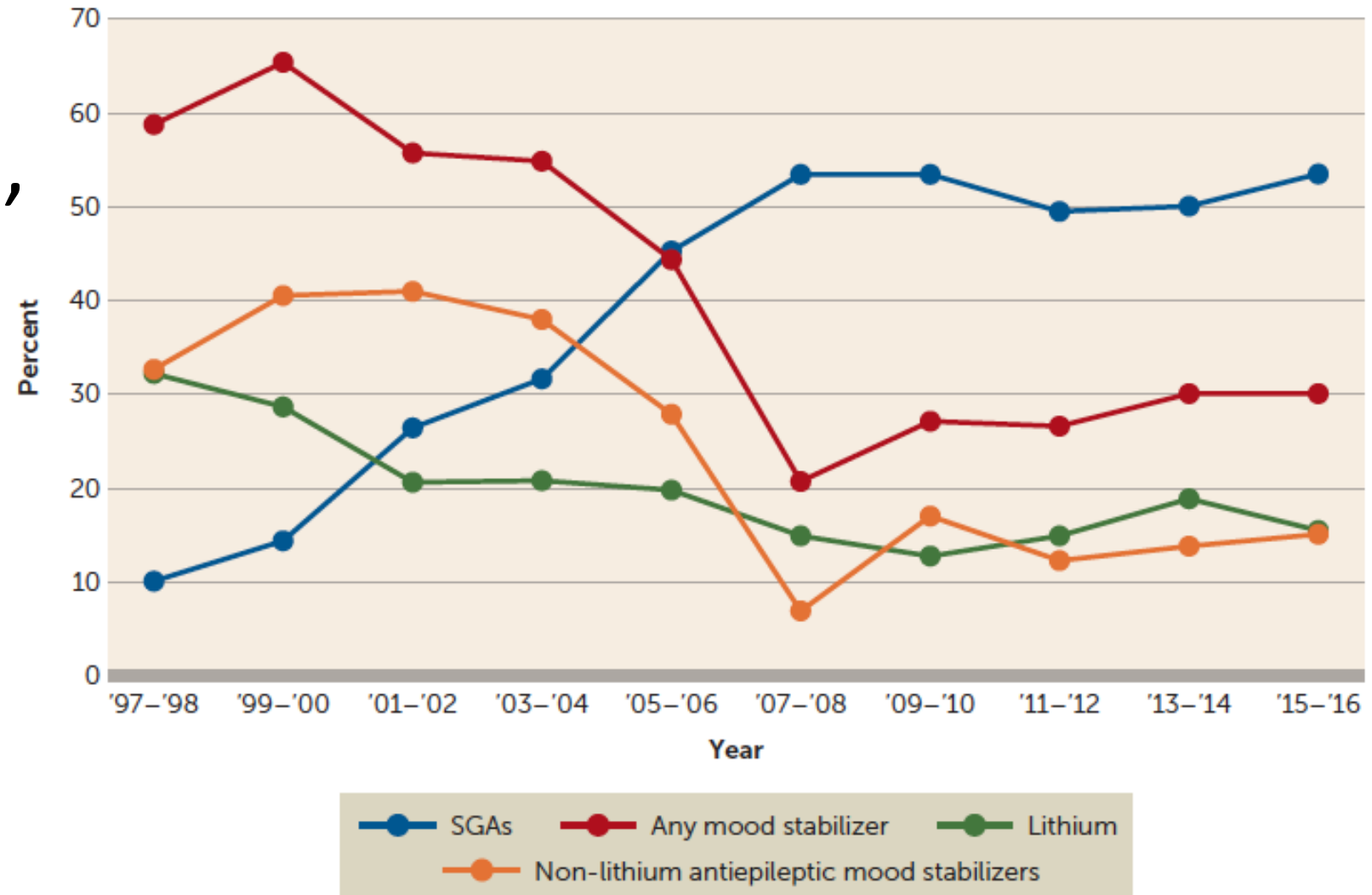
July 1890



Treatment

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



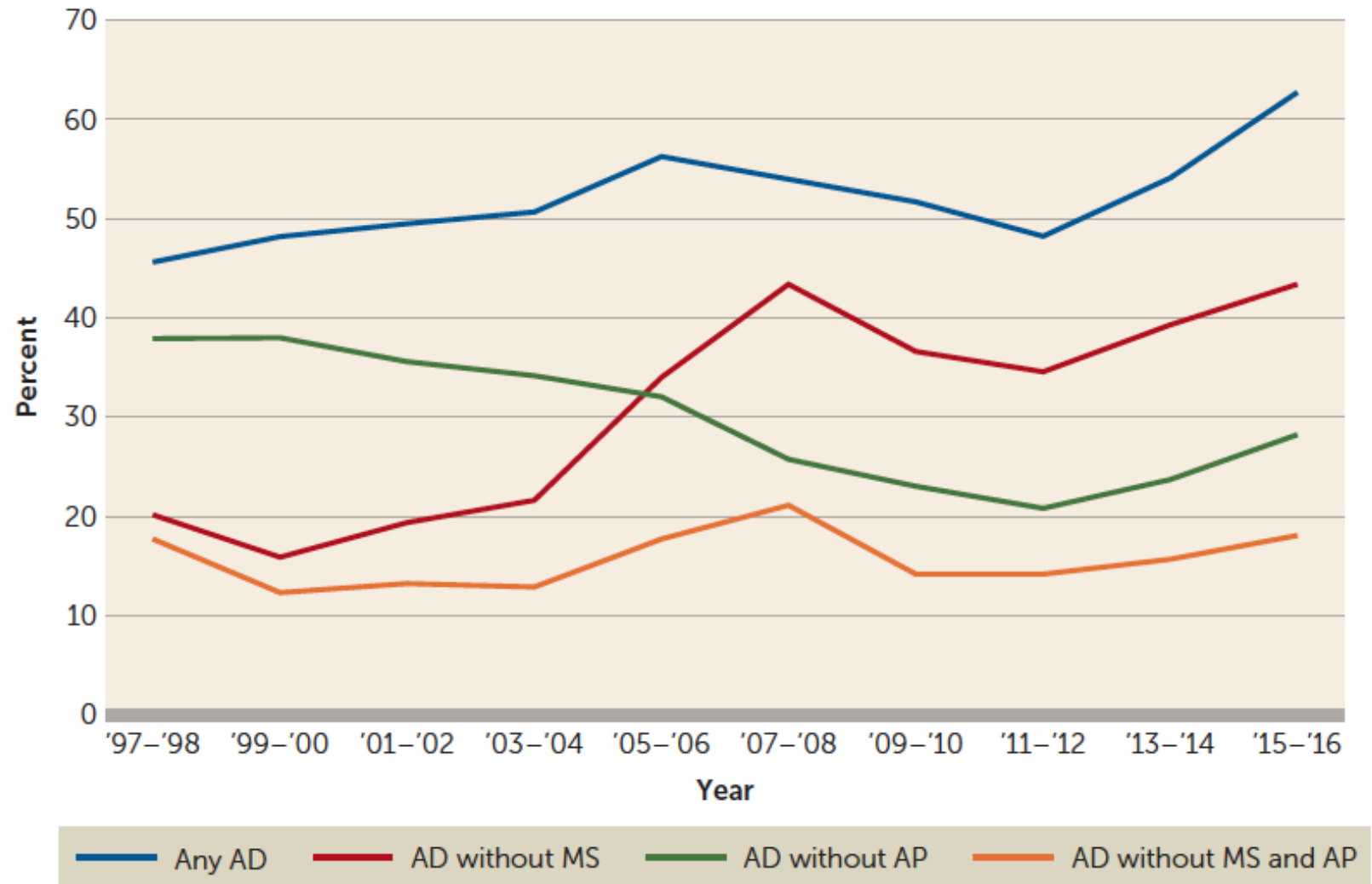
Rhee, Olfson,
Nierenberg,
Wilkerson.
AJP 2020

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

Antidepressants Persist

Rhee, Olfson,
Nierenberg,
Wilkerson.
AJP 2020

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.

Algorithms may be
too brittle for complex
Problems.



"I know of no one who combines theory and observation—intellectual rigor and painstaking observation of the real world—so brilliantly and gracefully as Gary Klein."
Malcolm Gladwell, author of *Outliers* and *Blink*

GARY KLEIN



Streetlights and Shadows

Searching for the Keys
to Adaptive
Decision Making

Massachusetts General Hospital
Founding Member, Mass General Brigham
Psychiatry Academy

ACUTE bipolar I depression

First-line (hierarchical order)

1. Quetiapine (300 mg/day)
2. Lurasidone + lithium or divalproex (lurasidone 20–120 mg/day)
3. Lithium (600–1,800 mg/day [target serum level, 0.8–1.2 mEq/L])
4. Lamotrigine (100–400 mg/day [slow titration])
5. Cariprazine (1.5–3 mg/day)
6. Lurasidone (adjunctive) (20–120 mg/day)

Note: Lurasidone should be taken with ≥ 350 calories for absorption. Lamotrigine requires slow titration.

Second-line (hierarchical order)

1. Divalproex (750–2,500 mg/day)
2. SSRIs/bupropion (adjunctive) (standard antidepressant dosages)
3. ECT
4. Olanzapine-fluoxetine (olanzapine 6–12 mg/day, fluoxetine 25–50 mg/day)
5. Lumateperone (42 mg/day)



Am J Psychiatry 183:3, March 2026

Acute bipolar II depression

First-line

- Quetiapine (300 mg/day)

Second-line

- Bupropion (adjunctive; standard dosages)
- ECT
- Lithium (600–1,800 mg/day [target serum level, 0.8–1.2 mEq/L])
- Lamotrigine (100–400 mg/day)
- Lumateperone (42 mg)
- Sertraline or venlafaxine (standard dosages)



Am J Psychiatry 183:3, March 2026

FDA Approved Treatments for Bipolar Depression

FDA and not FDA approved

Olanzapine/Fluoxetine
Combination (OFC)

Quetiapine

Lurasidone

Cariprazine

Lumateperone

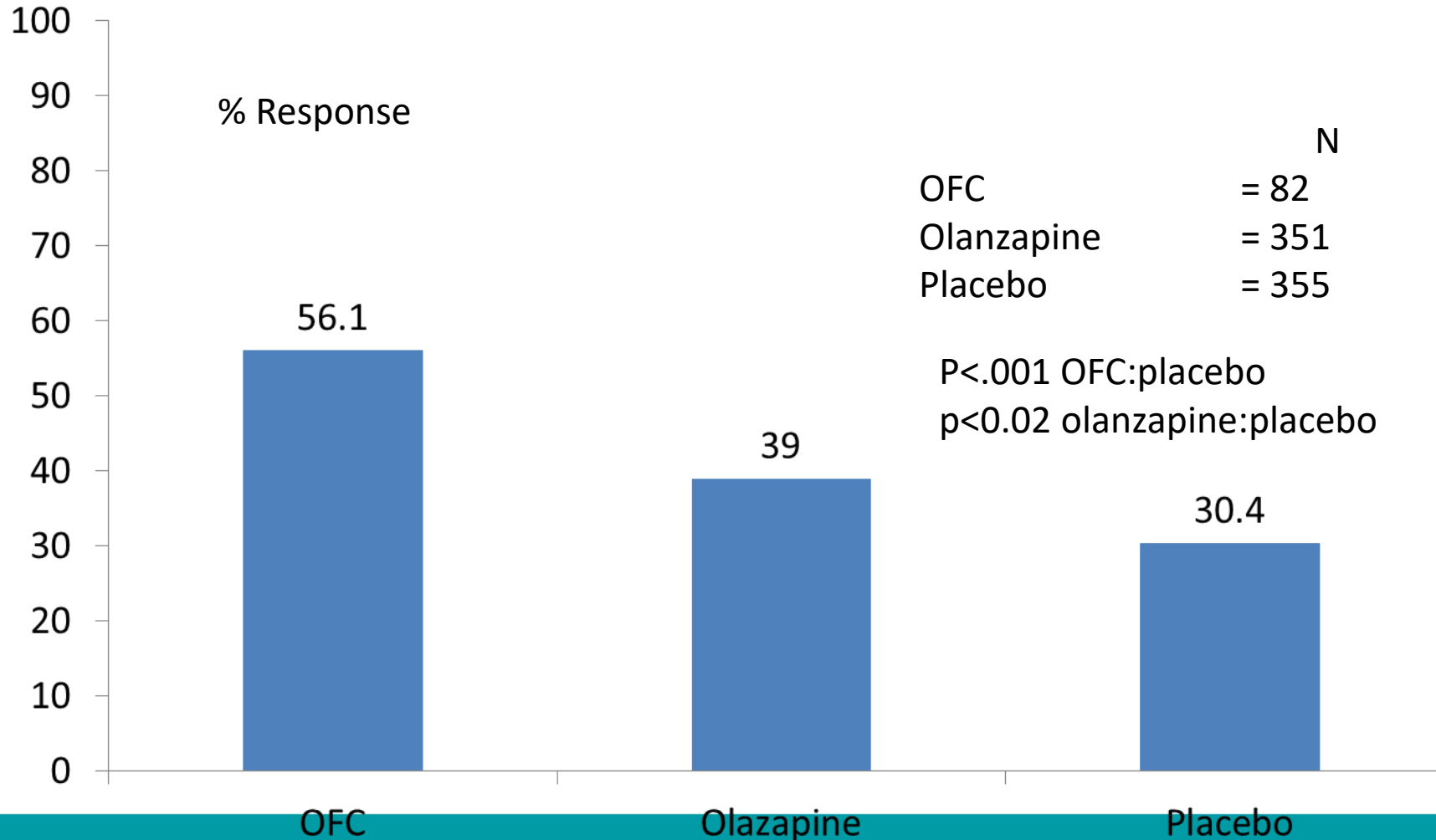
(Lamotrigine)
Not FDA Approved for
Acute Bipolar
Depression

Mechanisms of Action

[illegible]

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 $t_{1/2}$ 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

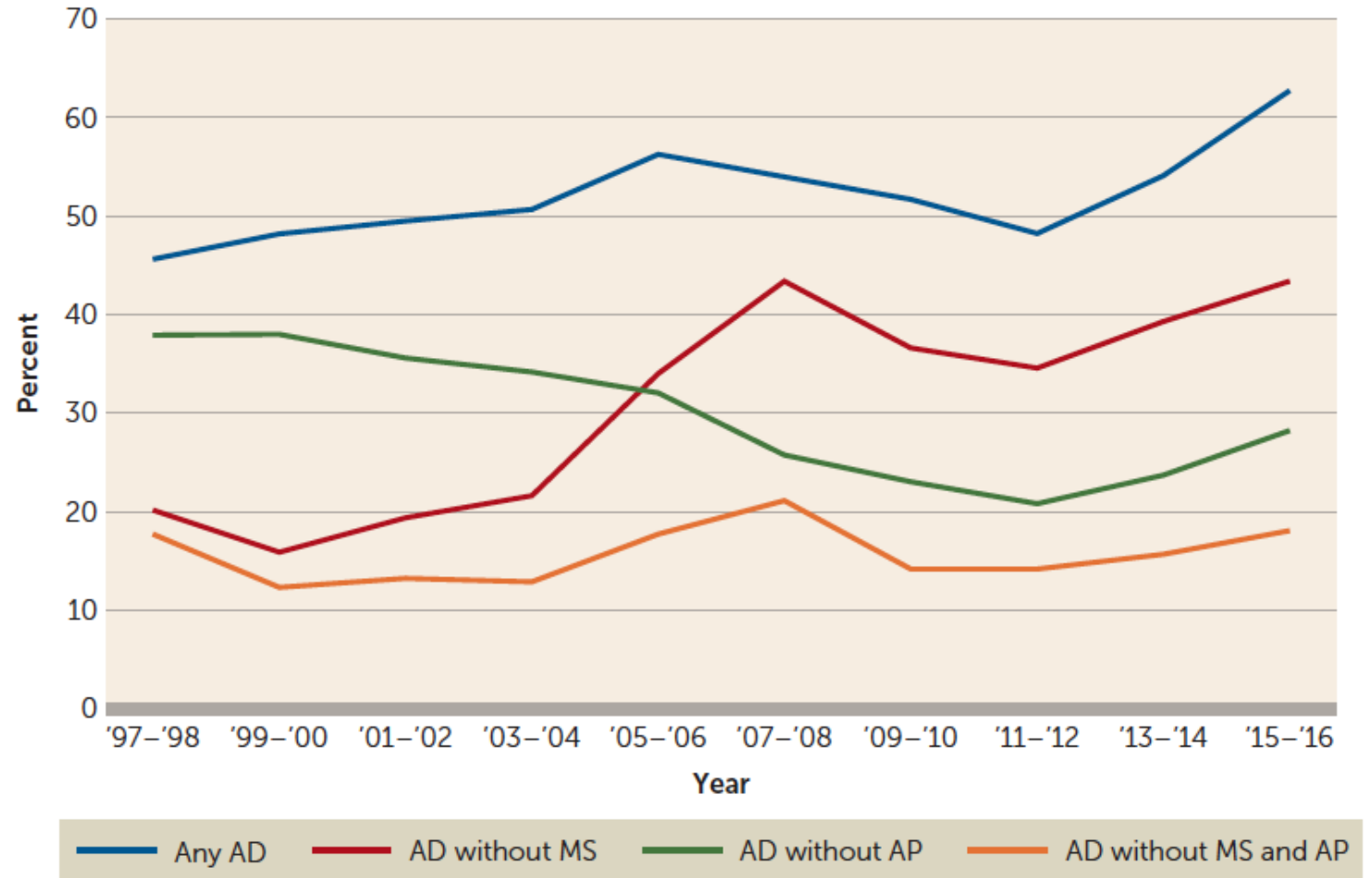
OFC for Bipolar I Depression

- 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 antidepressant 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.

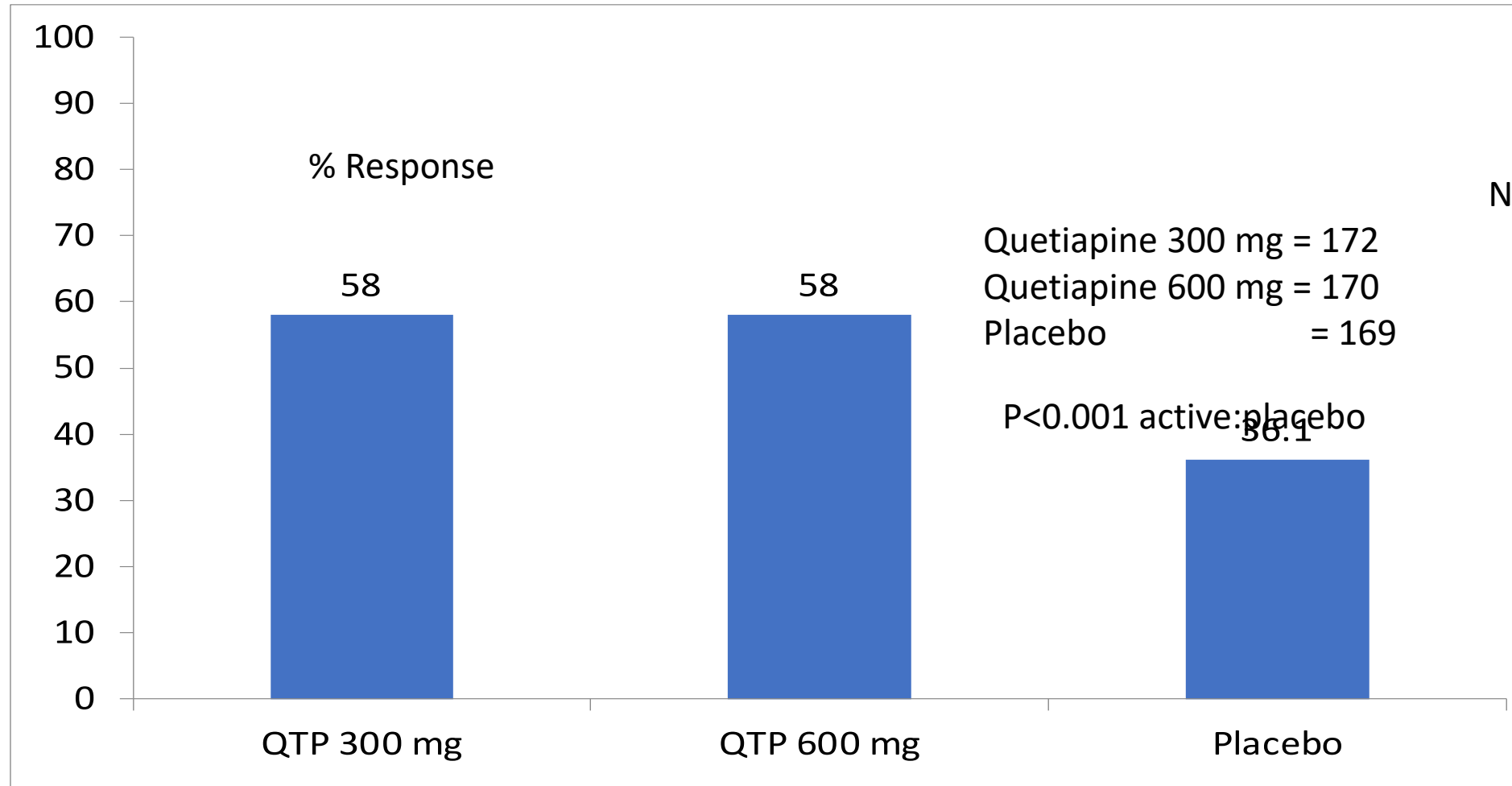
Rhee, Olfson,
Nierenberg,
Wilkerson.
AJP 2020

Meta-analysis: AD for BP Depression Not superior to Placebo

...53.7% chance that a person picked at random from the treatment group would have a higher change in their depressive symptoms rating scale than a person picked at random from the control group. Clinically, this difference is insignificant...

Hu et. al, Psychiatry Research 311; 2022

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
- $t_{1/2}$ 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

Vincent Van Gogh

Wheatfield Under Thunderclouds

(in Dutch, *Korenveld onder onweerslucht*)

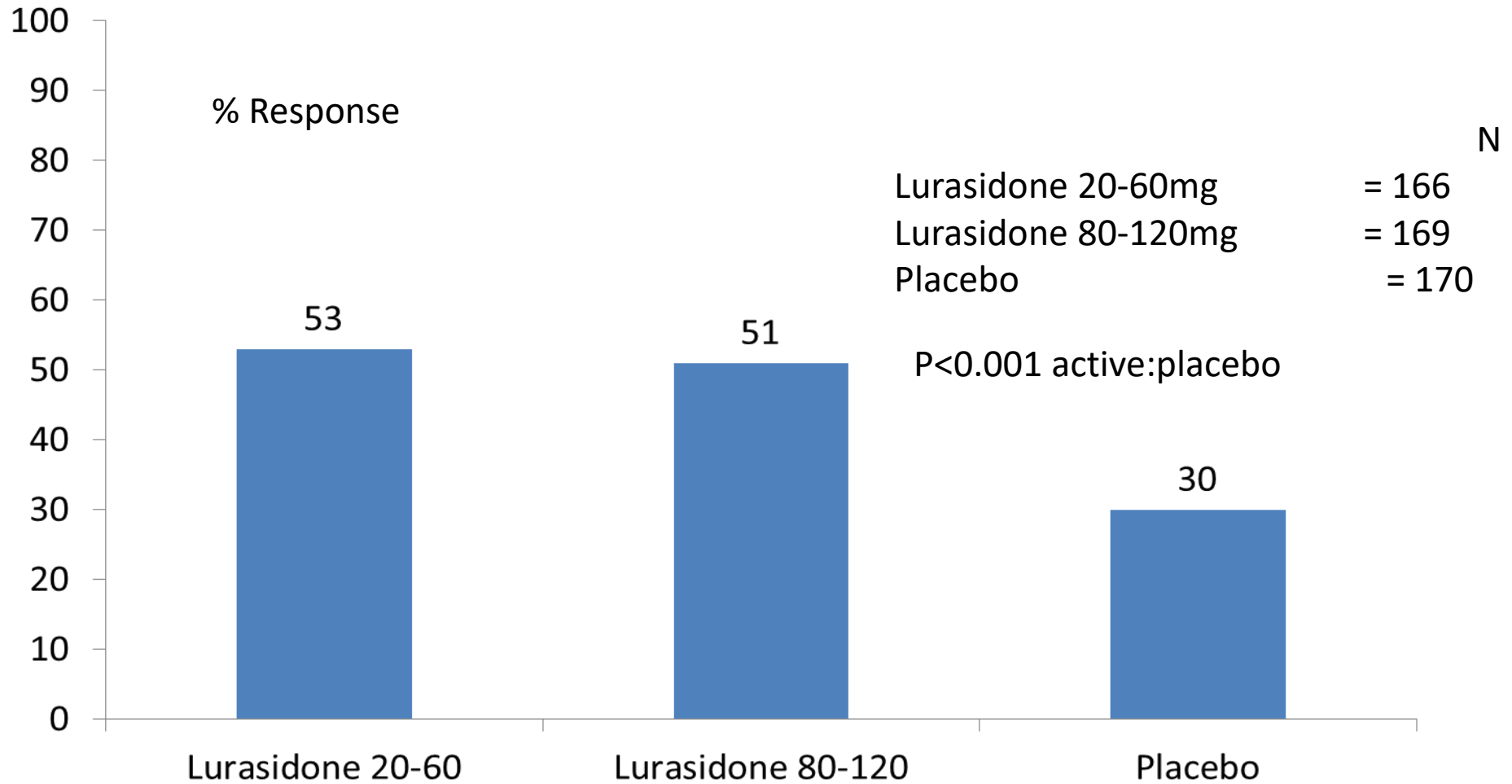
July 1890

"trying to express
sadness, extreme
loneliness"

Letter of around 10 July 1890,
to his brother Theo and
sister-in-law Jo



Lurasidone for Bipolar I Depression



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

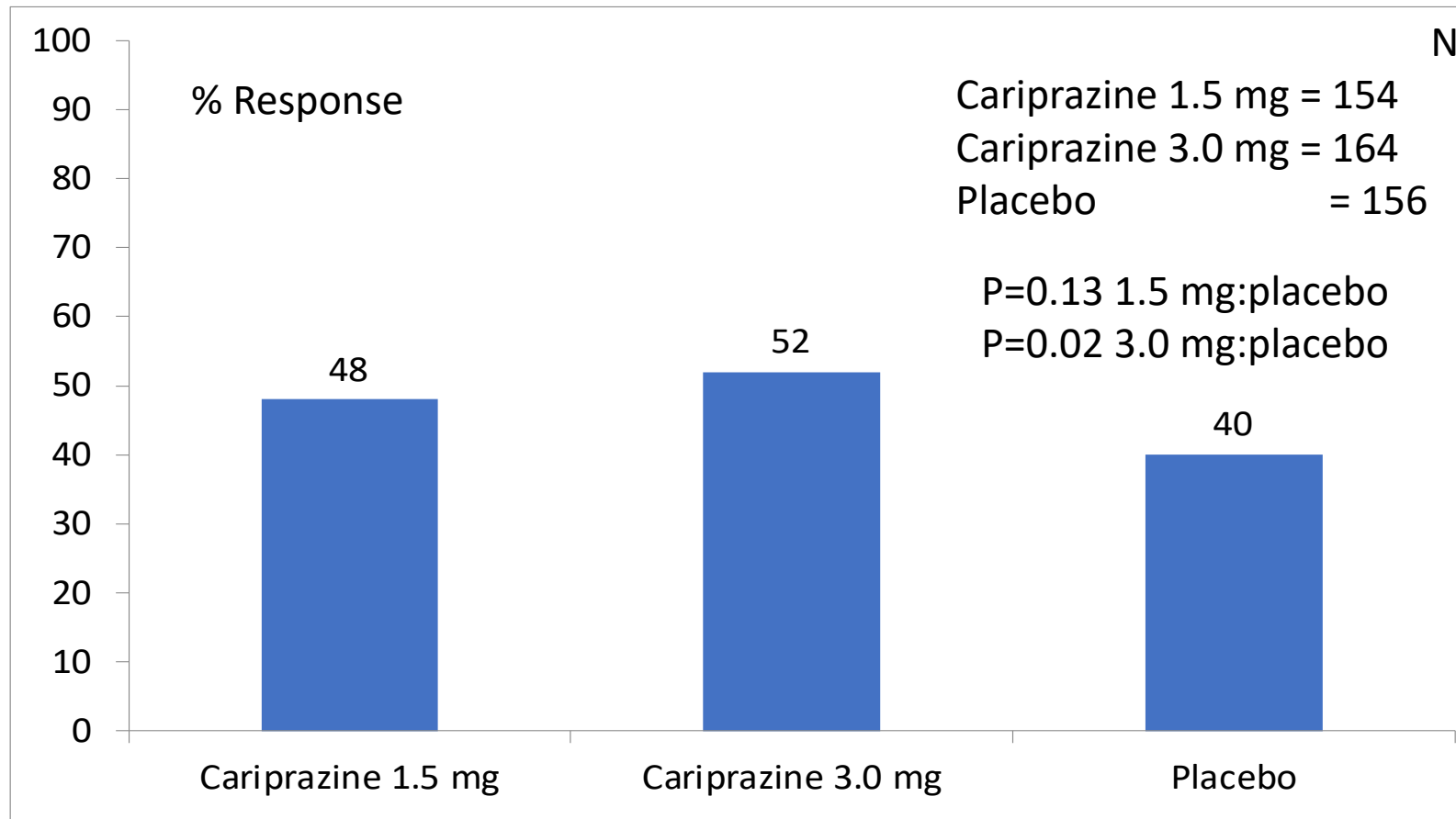
Lurasidone

- 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
- $t_{1/2}$ 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 for Bipolar I Depression



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

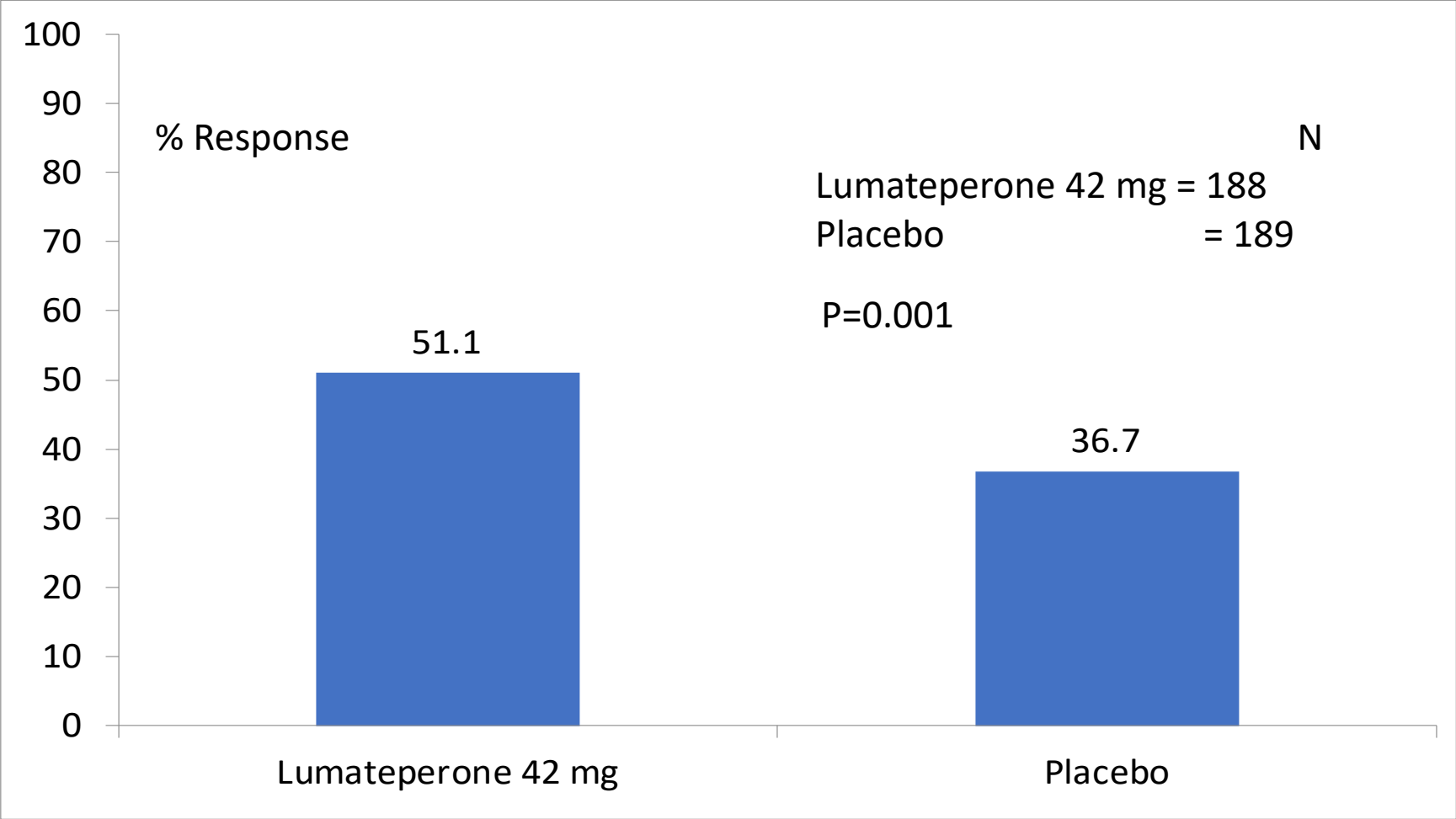
Cariprazine

- 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
- $t_{1/2}$ 2-5 days; steady state in 7 days

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% cariprazine 1.5 mg
 - 5.5 % cariprazine 3.0 mg

Lumateperone for Bipolar I and II Depression



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

Lumateperone

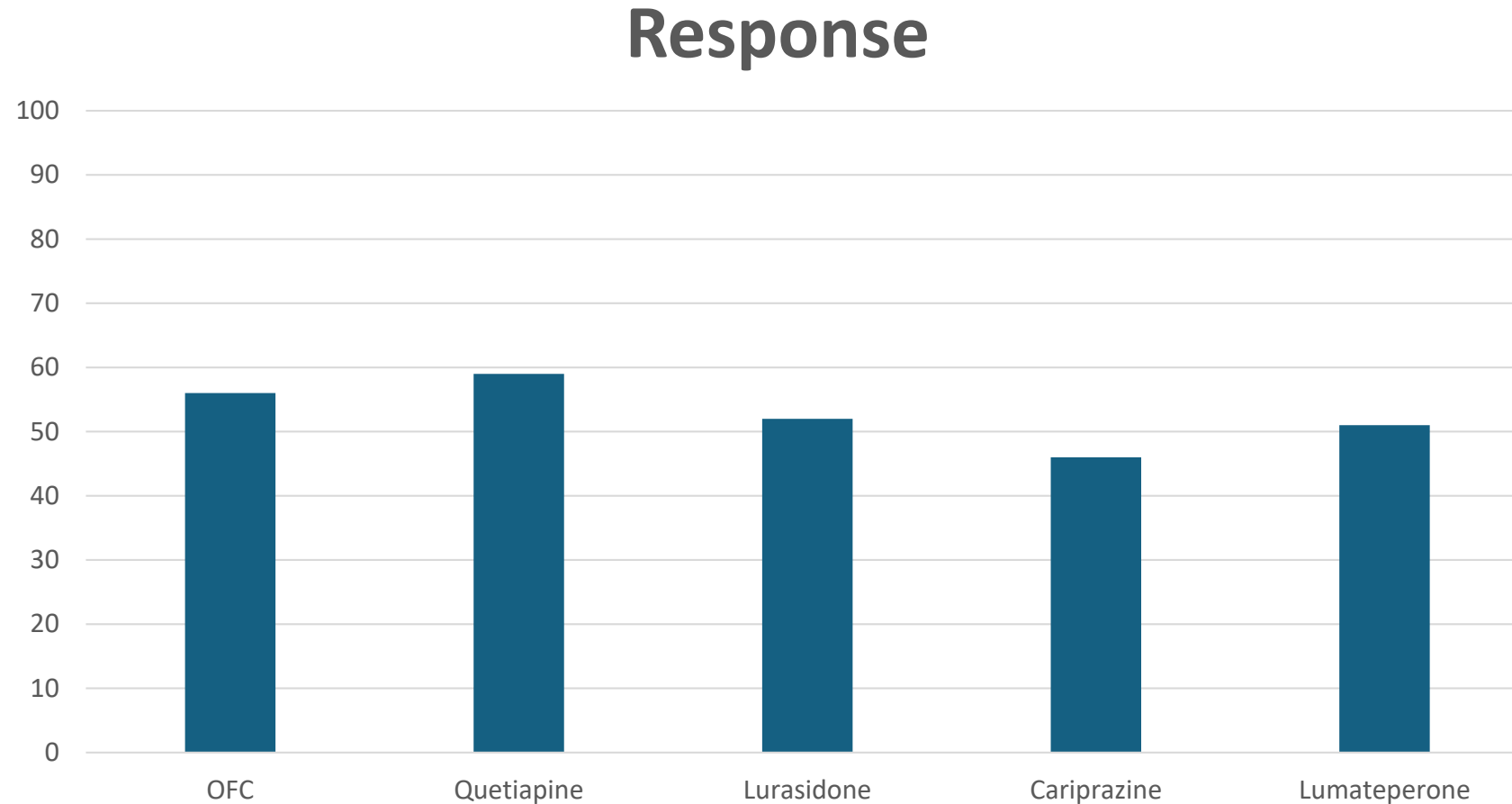
Pharmacodynamic profile

- serotonin 5-HT_{2A} antagonist
- 5-HT receptor inhibition
- D₂ presynaptic partial agonist
- D₂ postsynaptic antagonist
- D₁ receptor-dependent indirect modulator of glutamatergic N-methyl-d-aspartate GluN_{2B} receptors

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

FDA Approved Treatments Bipolar Depression

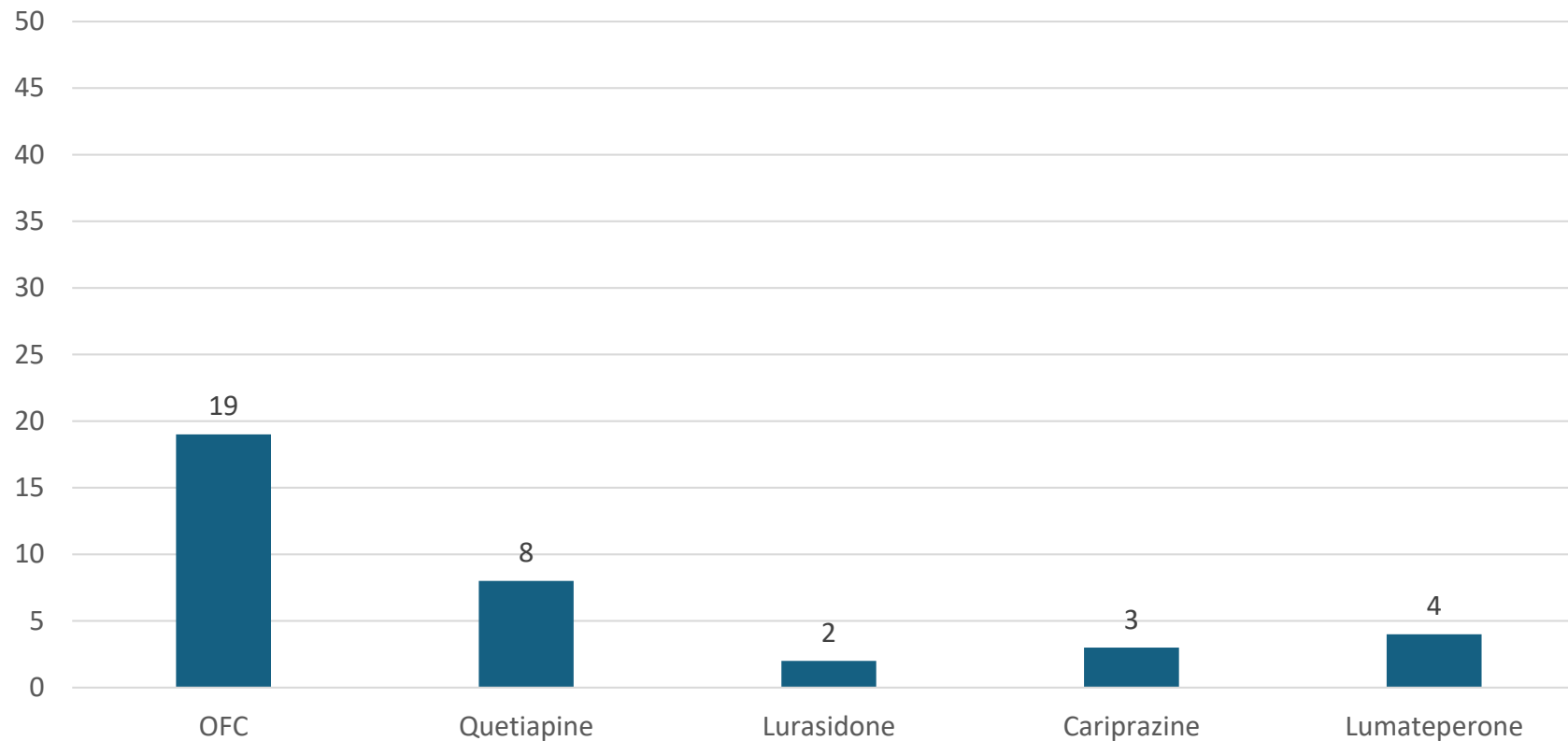


Adopted from: Citrome. Journal of Clinical Psychopharmacology • Volume 40, Number 4, July/August 2020
Ritvij et al. J Clin Psychopharmacology 42: 495–499; 2022; Calabrese et al., Am J Psychiatry 178:12, 2021

FDA Approved Treatments Bipolar Depression

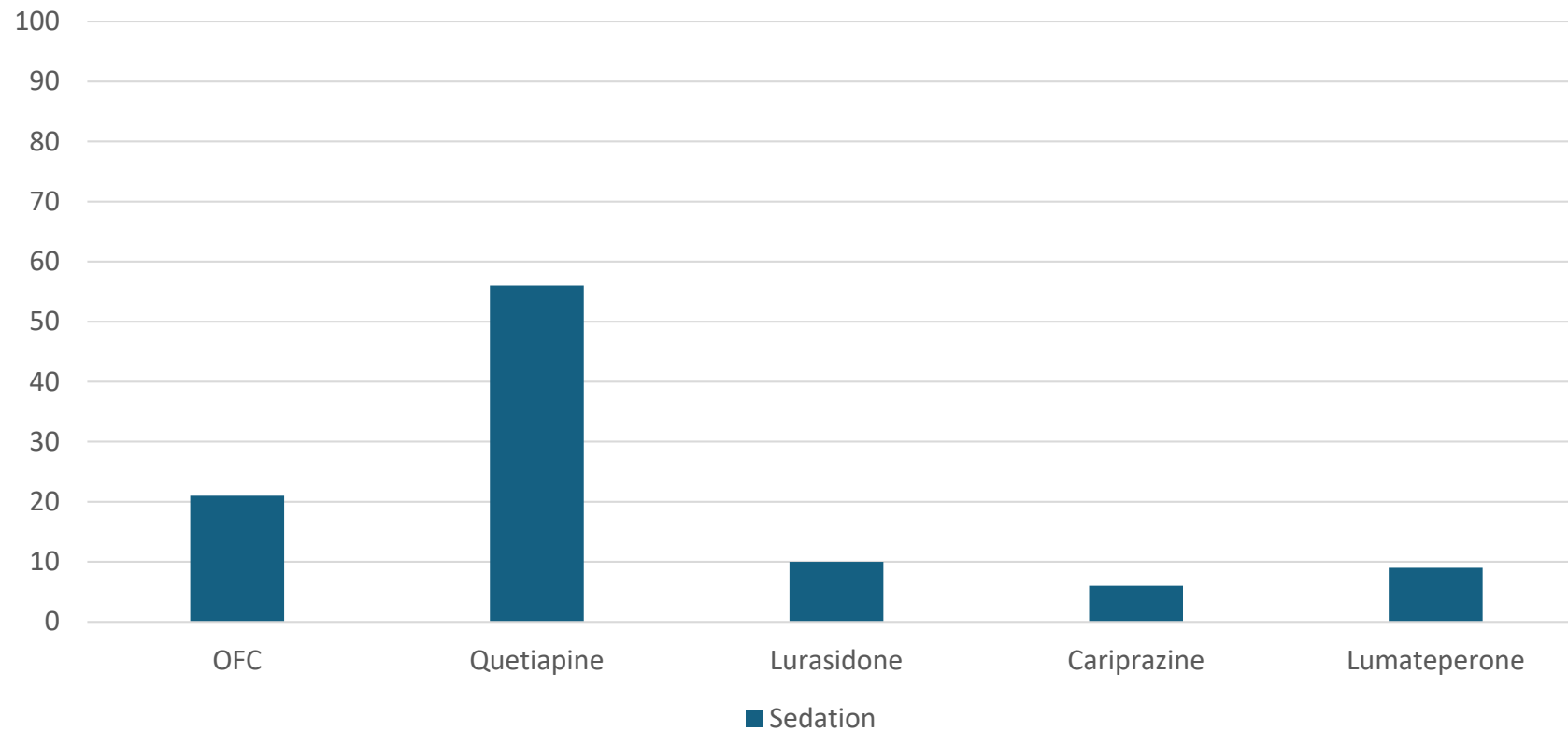
% with > 7% increase in weight

Weight Gain



FDA Approved Treatments Bipolar Depression

Sedation



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

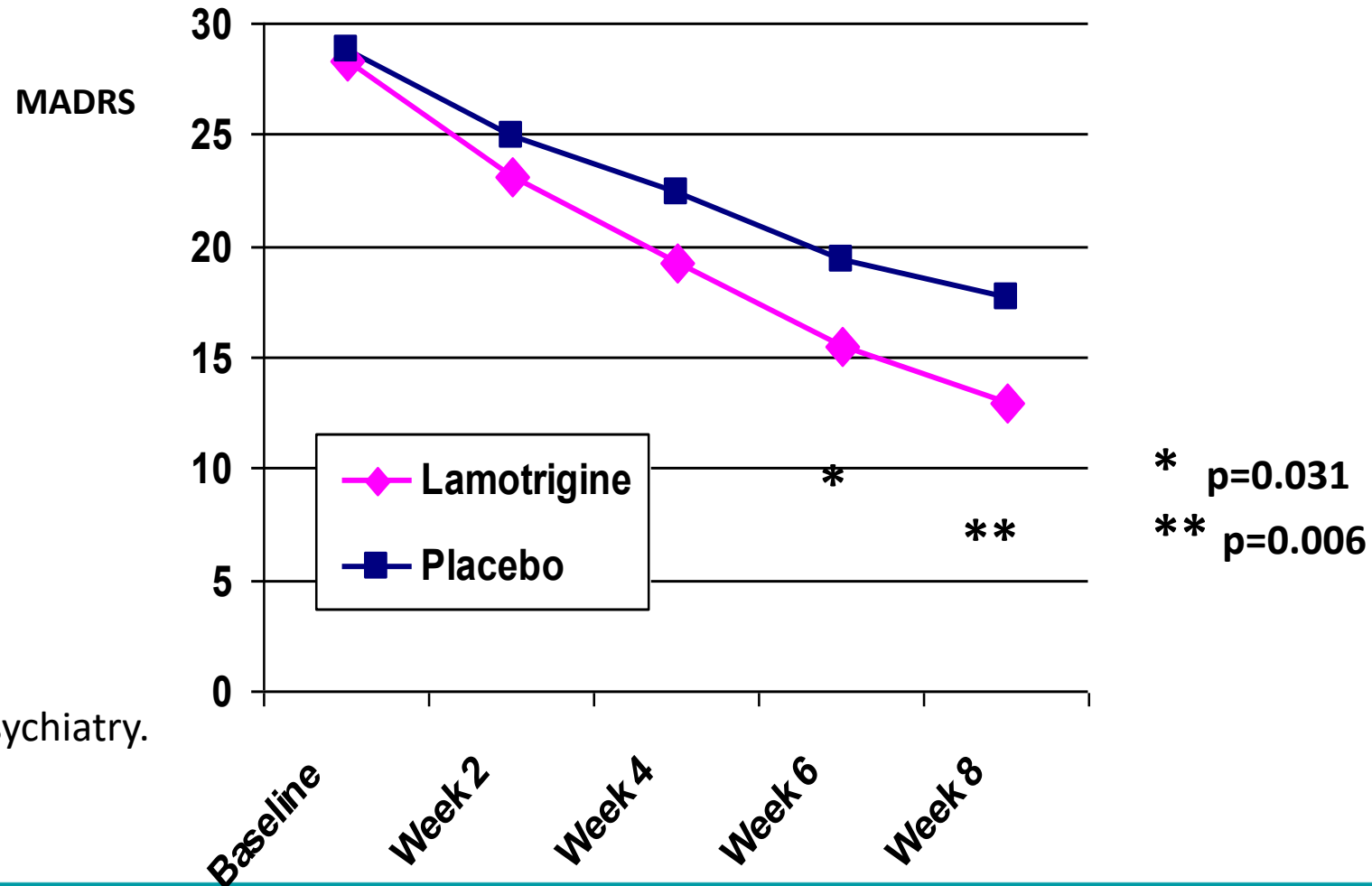
- Pharmacodynamic profile
 - Desensitization of the terminal 5HT_{1B} autoreceptors
 - Increase 5HT_{1a} activity
 - Inhibit glutamate release
 - decreased glutamate transmission in the dentate gyrus
 - No affinity for histaminergic or muscarinic receptors
- Metabolized through CYP450 3A4 (increased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

Lamotrigine plus Lithium



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

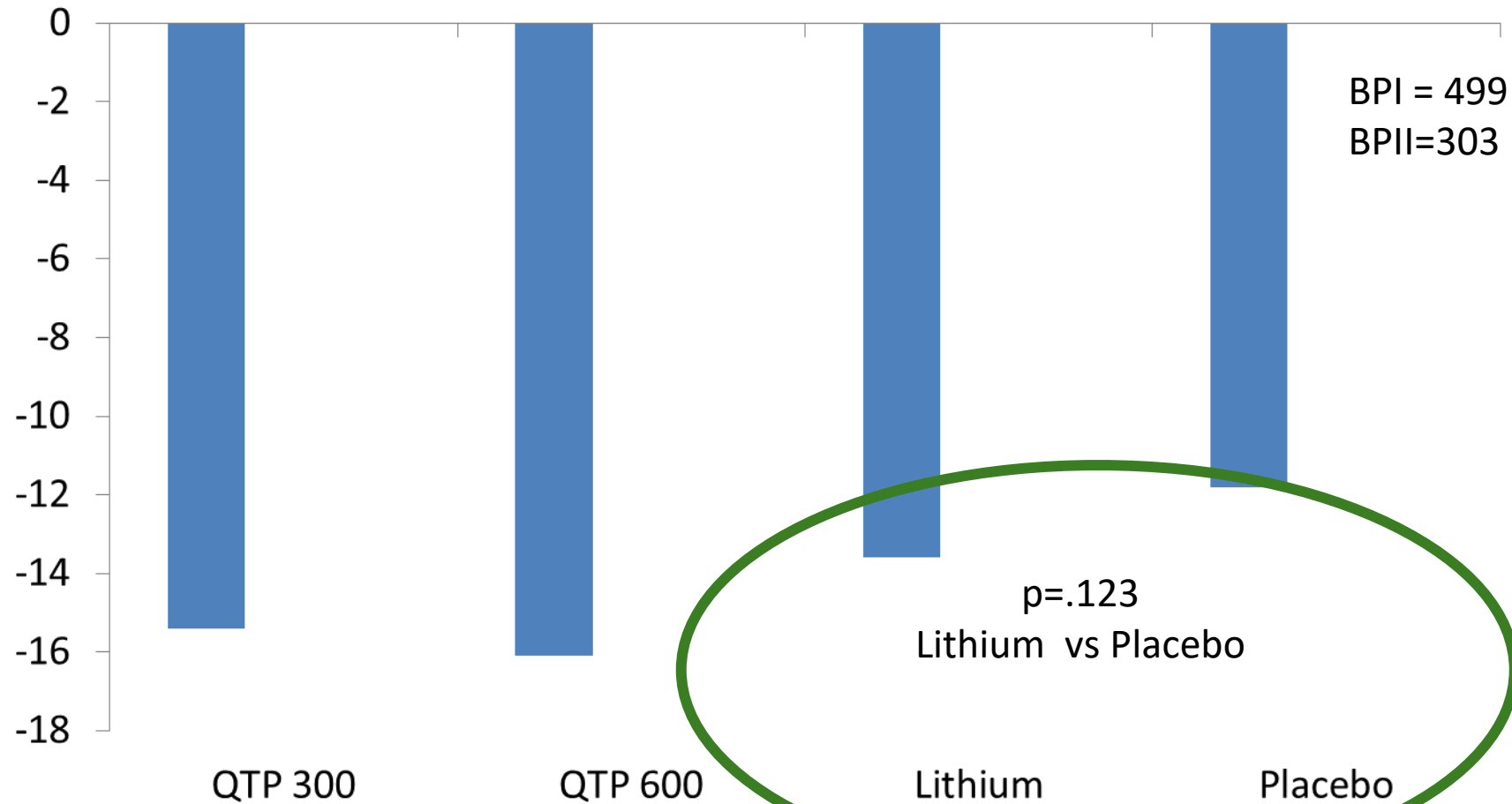
Mechanisms of Action

[illegible]

Lithium for bipolar depression?

EMBOLDEN I: Li not better than Pbo

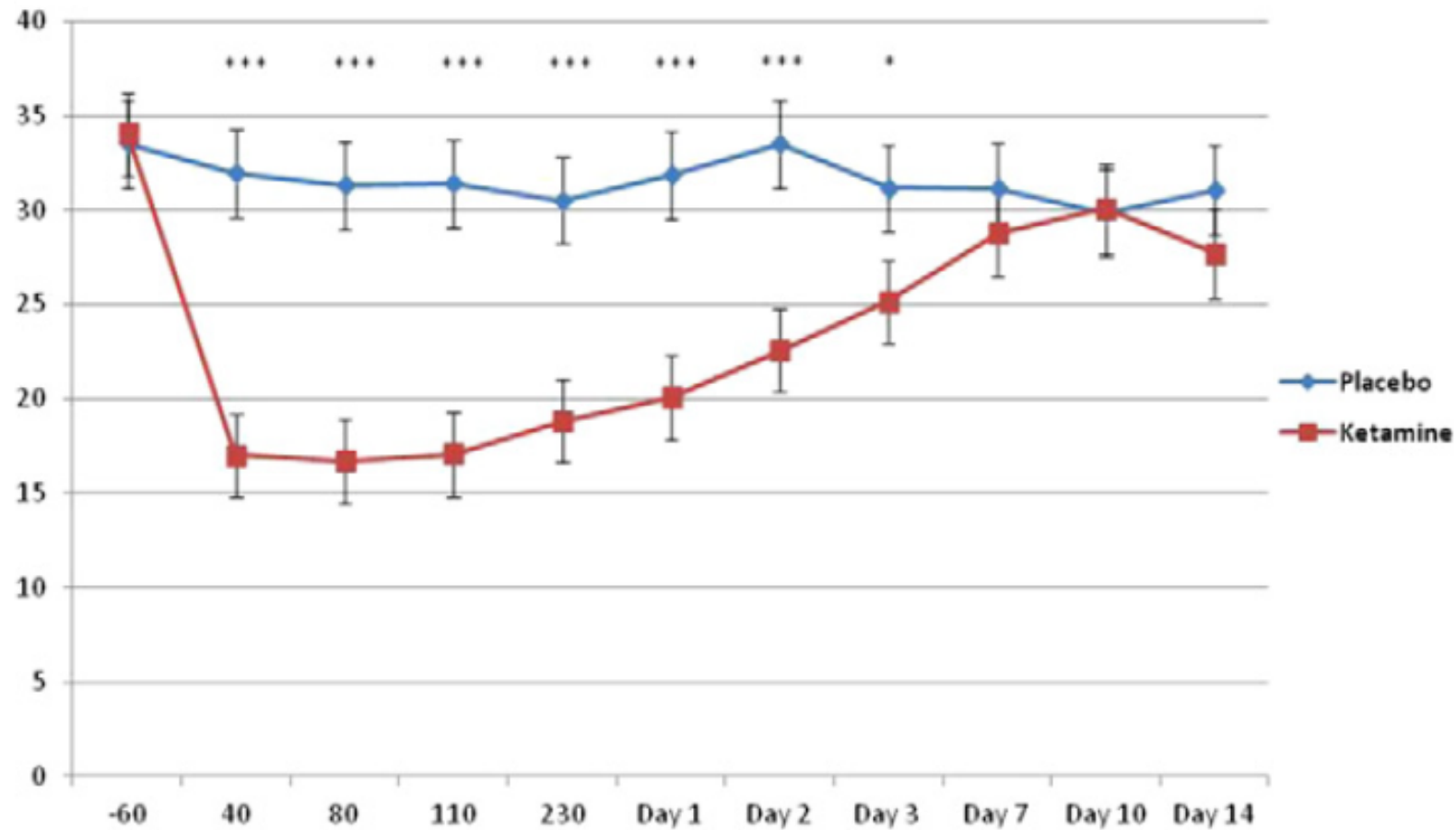
Decrease in MADRS



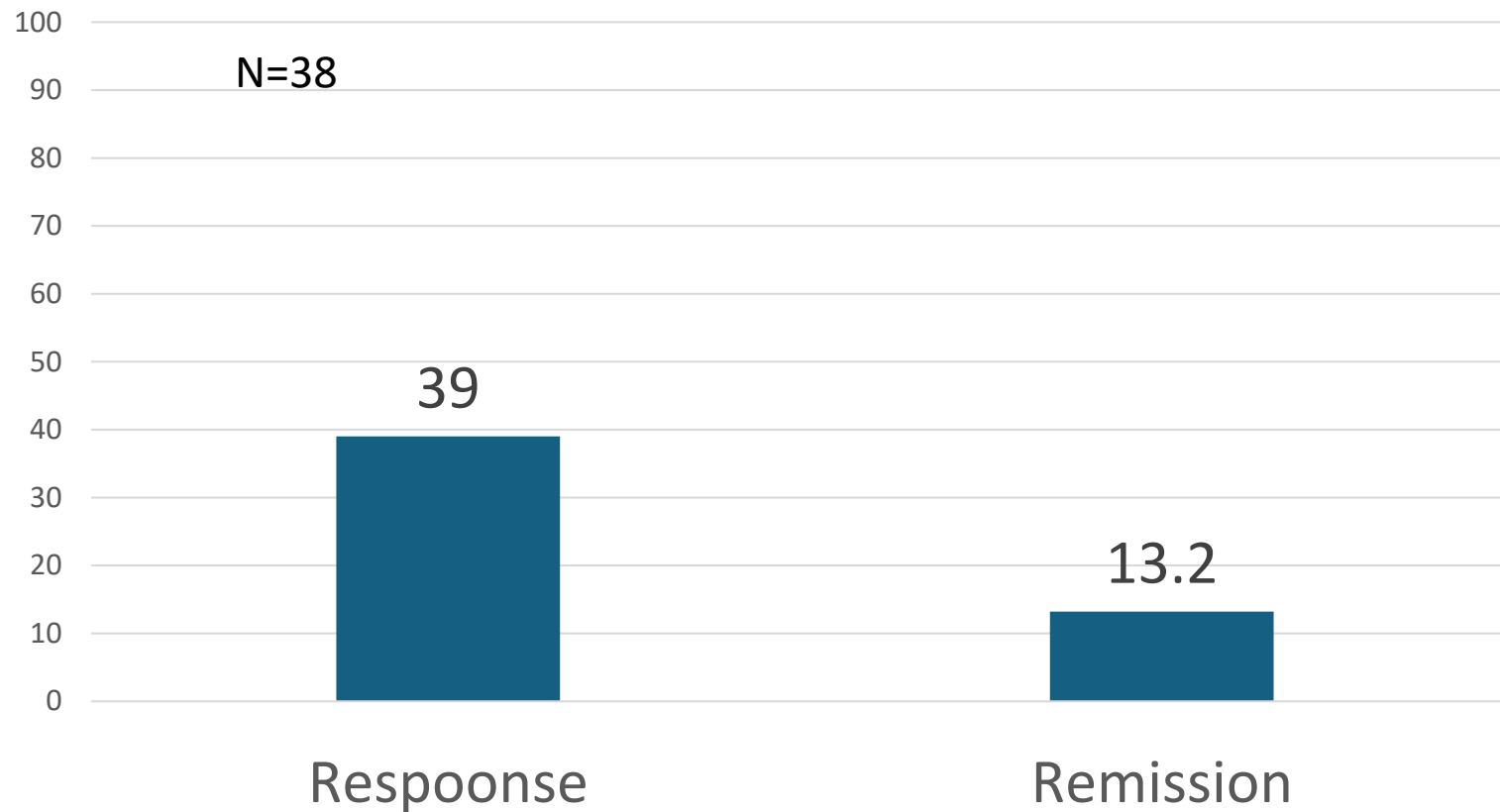
Potential treatments for bipolar depression

- Ketamine
- Esketamine (not approved for bipolar depression)
- ECT
- rTMS (not approved for bipolar depression)

Ketamine for Bipolar Depression



Ketamine/Esketamine for BD Depression



Ketamine: Remission from Suicidal Ideation

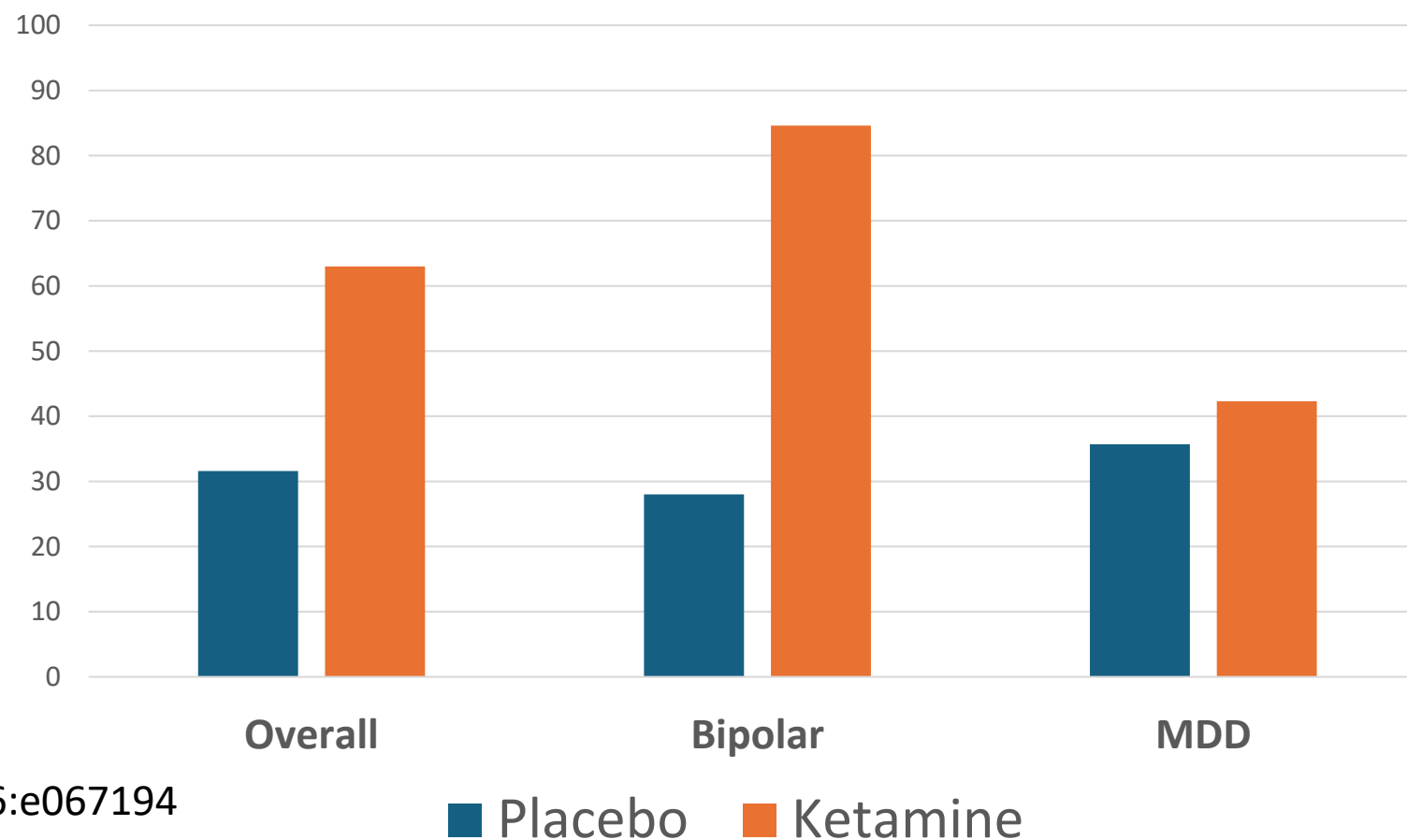
Ketamine 0.5 mg/kg added to current treatment

2 infusions 24hr apart

Remission on day 3 days

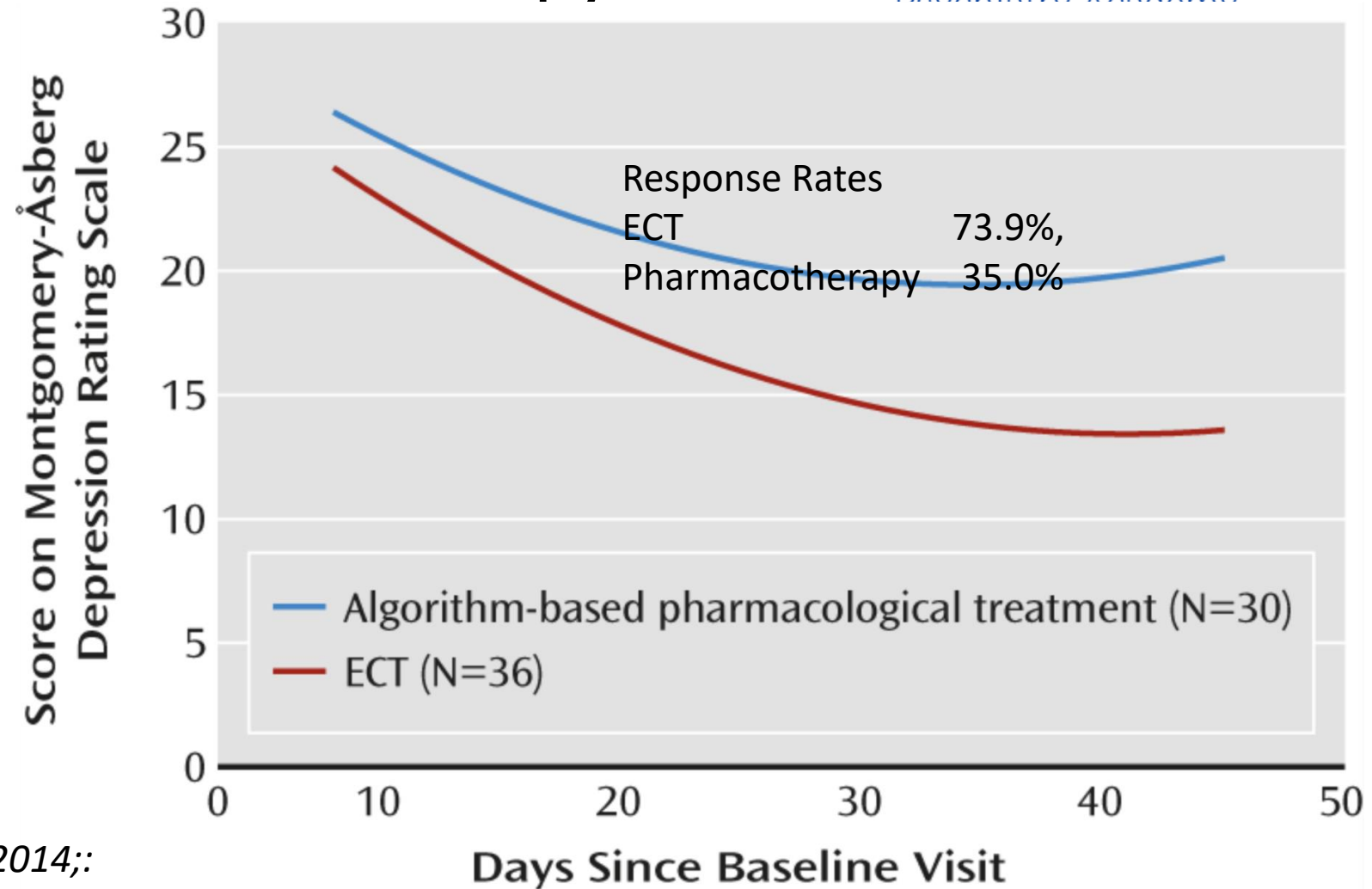
Bipolar N=51

MDD N= 54



Abbar et. al., BMJ 2022;376:e067194
| doi: 10.1136/bmj-2021-067194

ECT Superior to Pharmacotherapy



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

Bipolar Disorders

WILEY

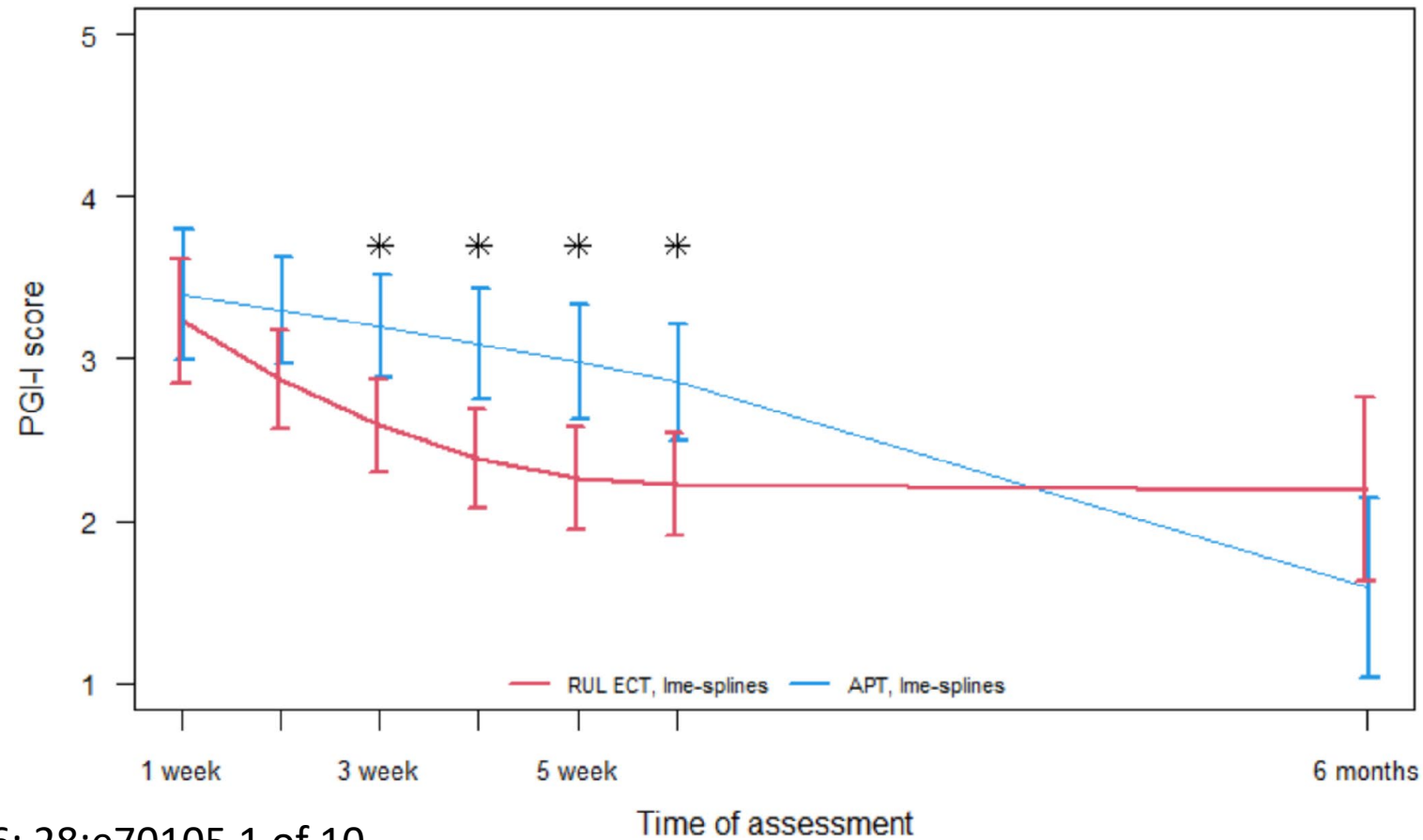
BIPOLAR DISORDERS
AN INTERNATIONAL JOURNAL OF PSYCHIATRY AND NEUROSCIENCES

ORIGINAL ARTICLE

Patient-Reported Outcomes From a Randomized Controlled Trial Comparing Right Unilateral Electroconvulsive Therapy With Algorithm-Based Pharmacological Treatment in Bipolar Depression, With Long-Term Follow-Up on Pharmacological Treatment

Jeanette Bjørke^{1,2,3} | Helle Schøyen¹ | Arne Vaaler^{4,5} | Bjørn Auestad^{1,6} | Ulrik Malt⁷ | Gunnar Morken^{4,5}  | Ketil Joachim Oedegaard^{3,8} | Ole Andreas Andreassen^{7,9} | Per Bergsholm¹⁰ | Ute Kessler^{3,8}

Right Unilateral ECT Faster than Algorithm Based Pharmacotherapy



Bipolar Disorders, 2026; 28:e70105 1 of 10
<https://doi.org/10.1111/bdi.70105>

rTMS for Bipolar Depression

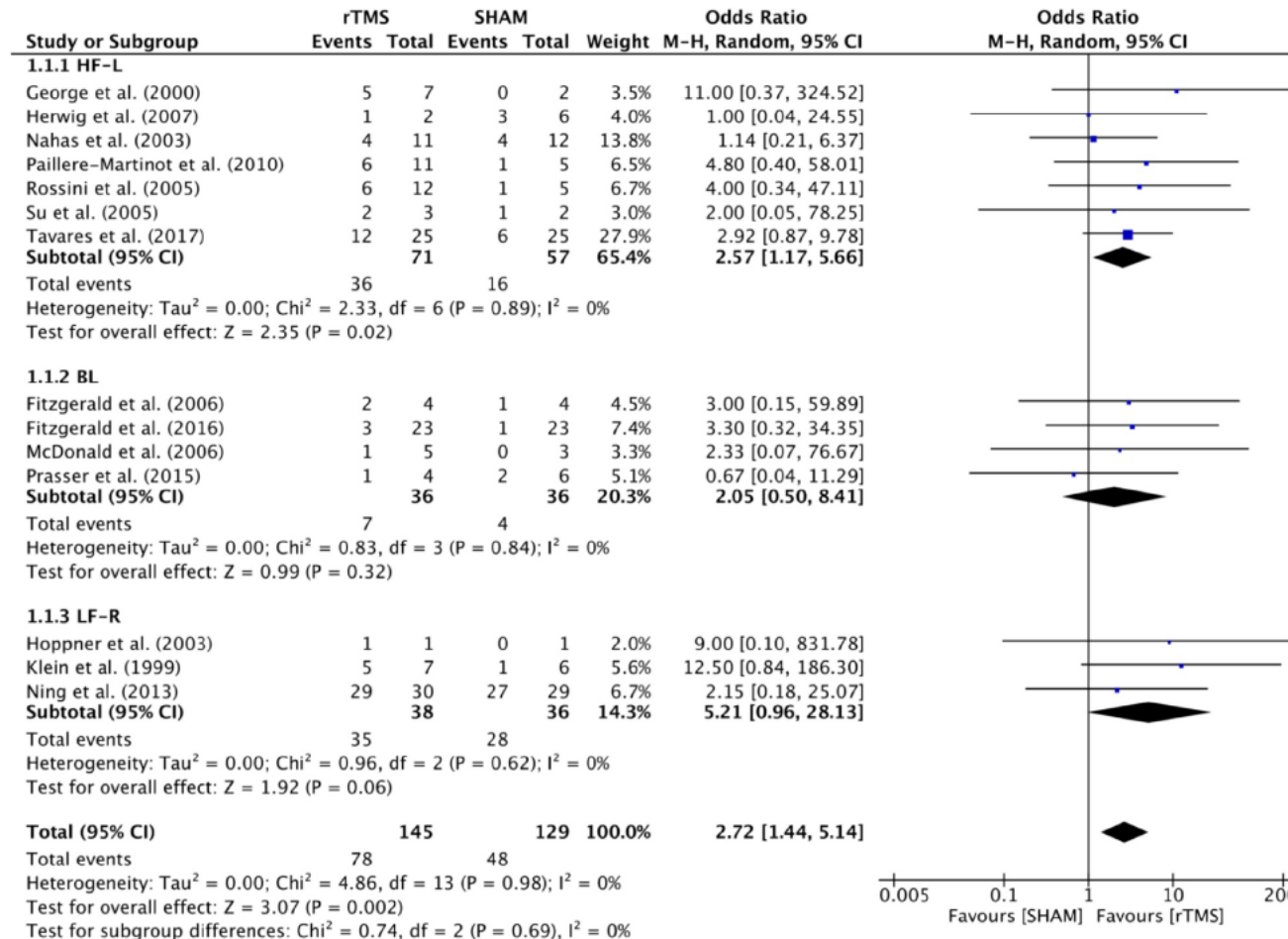


Fig. 2. Forest plot of response rates. Note: rTMS=repertive transcranial magnetic stimulation; M-H=Mantel-Haenszel; CI=confidence interval; HF-L=high frequency stimulation – left-sided; BL=bilateral stimulation; LF-R=low frequency stimulation – right-sided.

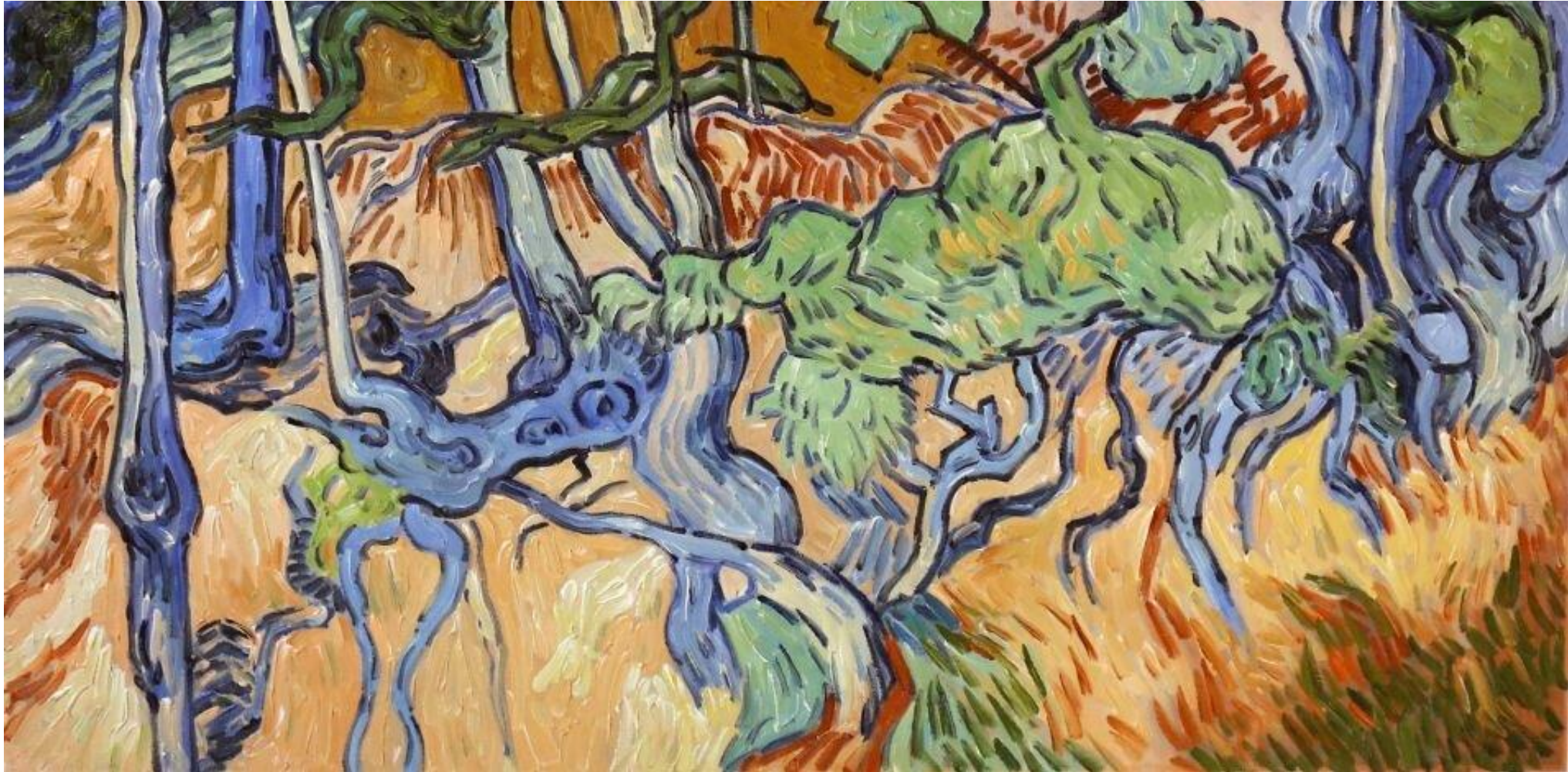
Nguyen, et al.,
 Journal Affective Disorders,
 279;250-255:2021

Investigational Treatment	Mechanism of Action	Phase / Design	Status	Sponsor
Azetukalner	Neuronal Kv7 (KCNQ2/3) potassium channel opener	Phase 3 Randomized, double-blind vs. placebo	Recruiting	Xenon Pharmaceuticals
Lacosamide	Voltage-gated sodium channel modulator (slow inactivation)	Phase 3 Randomized, double-blind vs. placebo	Recruiting	University of São Paulo
Psilocybin-assisted therapy (Bipolar II)	5-HT2A receptor agonist (psychedelic) + psychotherapy	Phase 3 Randomized vs. 1mg active-placebo microdose	Not yet recruiting	University of British Columbia
Icalciprant	κ-opioid receptor antagonist	Phase 2 Randomized, vs. placebo	Recruiting	
N-methyl amisulpride	Dopamine D2 and D3 receptor antagonist, as well as a serotonin 5-HT2B and 5-HT7	Phase 2 Randomized, blind vs. placebo	Recruiting	LB Pharmaceuticals Inc.
Alto-100	Neurogenesis stimulant and indirect brain-derived neurotrophic factor modulator	Phase 2 Randomized, blind vs. placebo	Recruiting	Alto Pharmaceuticals

Tree Roots

Vincent Van Gogh
27 July 1890

Died by suicide
29 July 1990
Age 37





37. — Auvers-sur-Oise — Rue Daubigny

Summary

- Bipolar depression: Basics
- FDA Approved Treatments
- Other treatments