

# Bipolar Disorder

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## Disclosure Statement

Employee Of	Massachusetts General Hospital
Consultant For	Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Bristol-Myers Squibb, Cephalon, Clintara, Corcept, Eli Lilly & Co., Forest, Genaissance, Genentech, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals, Lundbeck, Medavante, Merck, Myriad, Novartis, PamLabs, PGx Health, Pfizer, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, Teva
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## Disclosure Statement

Other Income	MBL Publishing for past services as Editor-in-chief of CNS Spectrums; Slack Inc. for services as Associate Editor of Psychiatric Annals; 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
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“...from the brain, and from the brain only, arise our pleasures, joy, laughter and jests, as well as our sorrows, pains, griefs, and tears.”

Hippocrates Circa 400 BCE

N A T I O N A L   B E S T S E L L E R

AN  
UNQUIET  
MIND

A MEMOIR OF MOODS AND MADNESS

Kay Redfield Jamison

"An invaluable memoir of manic depression,  
at once medically knowledgeable, deeply  
human and beautifully written...at times  
poetic, at times straightforward,  
always unashamedly honest."

—*The New York Times Book Review*



# Bipolar Disorder Fast Facts

- Among top 10 causes of disability worldwide
  - 50% with onset before the age of 25
    - Costs \$200 billion per year

# Bipolar Disorder Fast Facts

- Types
  - Type I with manic episodes
  - Type II with hypomanic episodes
- 90% have other problems
  - Substance use disorders
  - Anxiety disorders
- 1.5 to 2.1 times more likely to have chronic physical conditions
- Loss of 8 – 25 years of life

# DSM-V Bipolar I Disorder Epidemiology

- Lifetime prevalence 2.1%
  - ~4,884,000
- 12-month prevalence 1.5%
  - ~3,679,000



# Phenomenology

# Major Depressive Episodes: Psychological Symptoms

- Depressed mood
- Irritability
- Anxiety/nervousness
- Reduced concentration
- Lack of interest/motivation
- Inability to enjoy things
- Lack of pleasure
- Hypersensitivity to rejection/criticism
- Perfectionism/ Obsessiveness
- Indecisiveness
- Pessimism/hopelessness
- Feelings of helplessness
- Cognitive distortions
- Feeling stressed
- Low self-esteem/feelings of worthlessness
- Excessive guilt
- Thoughts of death or suicide
- Thoughts of hurting other people

**Adapted from: Cassano P, Fava M. *J Psychosom Res.* 2002;53(4):849-857.**

# Major Depressive Disorder: Behavioral Symptoms

- Crying spells
- Interpersonal friction/confrontation
- Anger attacks/outbursts
- Avoidance of anxiety-provoking situations
- Reduced productivity
- Social withdrawal
- Avoidance of emotional and sexual intimacy
- Reduced leisure-time activities
- Development of rituals or compulsions
- Workaholic behaviours
- Substance use/abuse
- Self-sacrifice/victimisation
- Self-cutting/mutilation
- Suicide attempts/gestures
- Violent/assaultive behaviour

**Adapted from: Cassano P, Fava M. *J Psychosom Res.* 2002;53(4):849-857.**

# Major Depressive Disorder: Common Somatic/Physical Symptoms

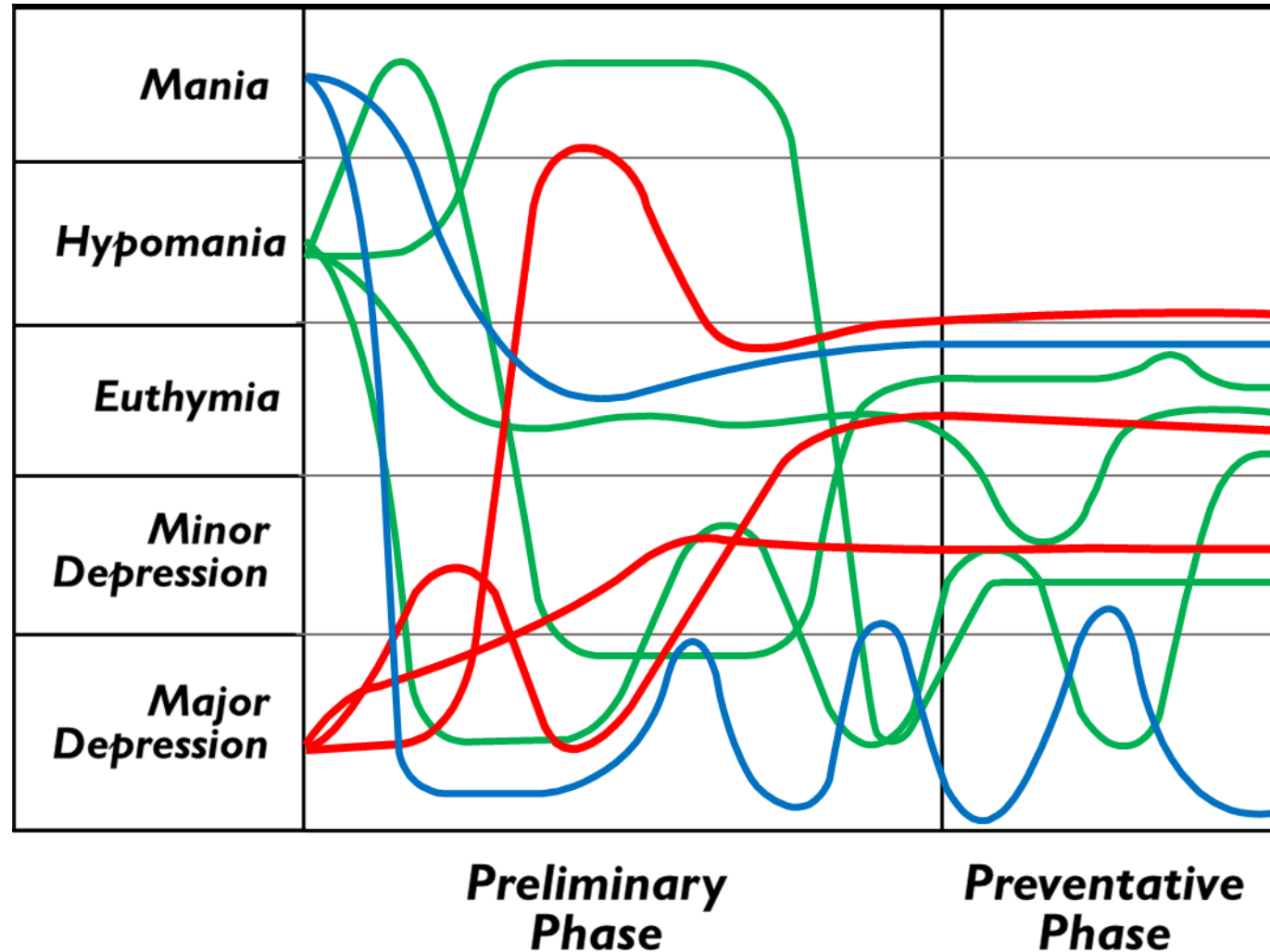
- Fatigue
- Leaden feelings in arms or legs
- Sleeping too little/insomnia
- Sleeping too much/hypersomnia
- Decreased appetite
- Weight loss
- Increased appetite
- Weight gain
- Reduced libido/arousal difficulties
- Erectile dysfunction
- Delayed orgasm/inability to achieve orgasm
- Headaches
- Muscle tension
- Gastrointestinal upset
- Heart palpitations
- Burning or tingling sensations

**Adapted from: Cassano P, Fava M. *J Psychosom Res.* 2002;53(4):849-857.**

# Bipolar Disorder: Manic/Hypomanic Symptoms

- Increased energy
- Euphoria
- Grandiosity
- Irritability/Decreased frustration tolerance
- Racing thoughts
- Rapid speech
- Decreased need for sleep
- Unconcerned with consequences
- Impulsive
- Cognitive impairment
- Poor judgement
- Unrealistic optimism
- Increased libido
- Hallucinations or delusions
- Disorganized thinking
- Decreased productivity
- Increased productivity
- Sharper, clearer thinking
- Increased creativity
- Entrepreneurial

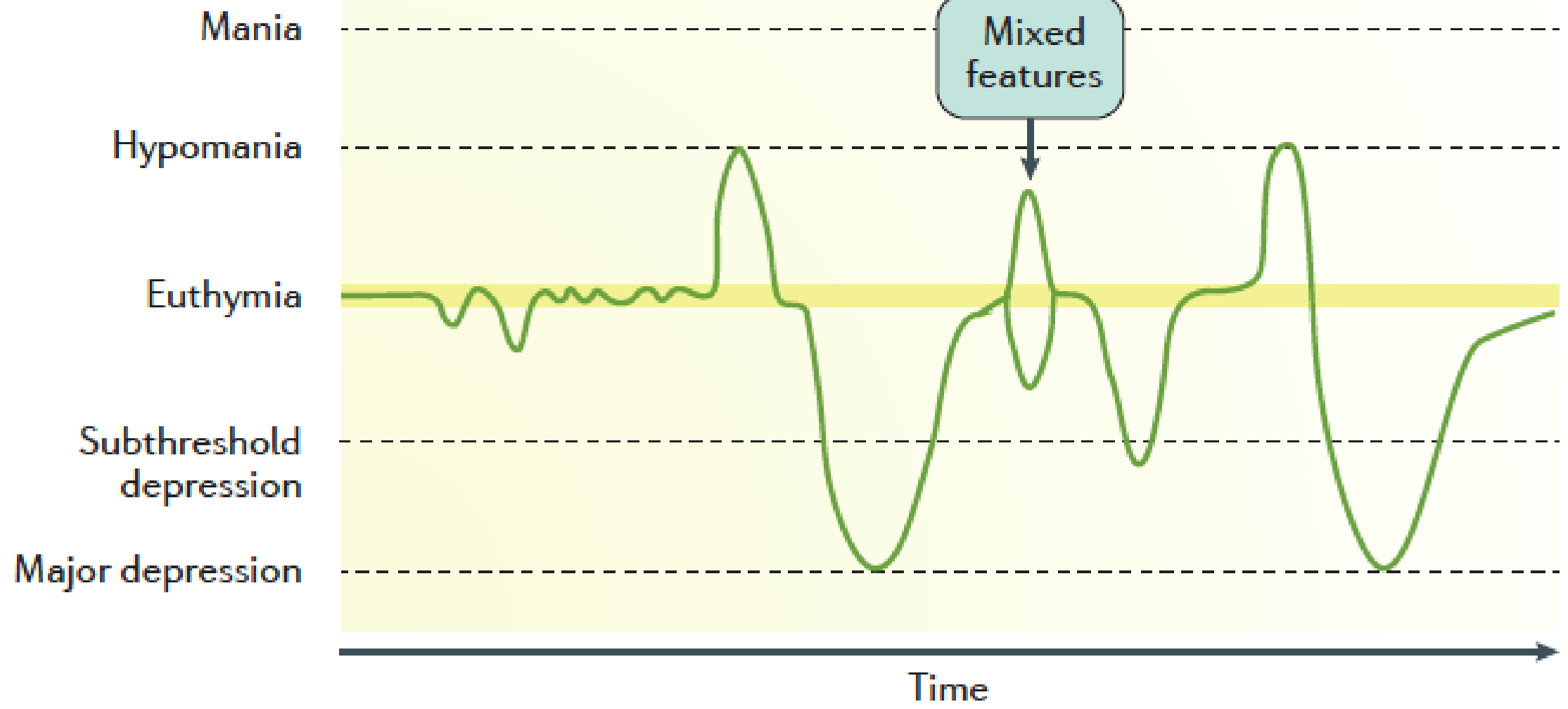
# Response, Remission, Recovery, Relapse, Recurrence: Phases of Treatment of Bipolar Disorder



**a**

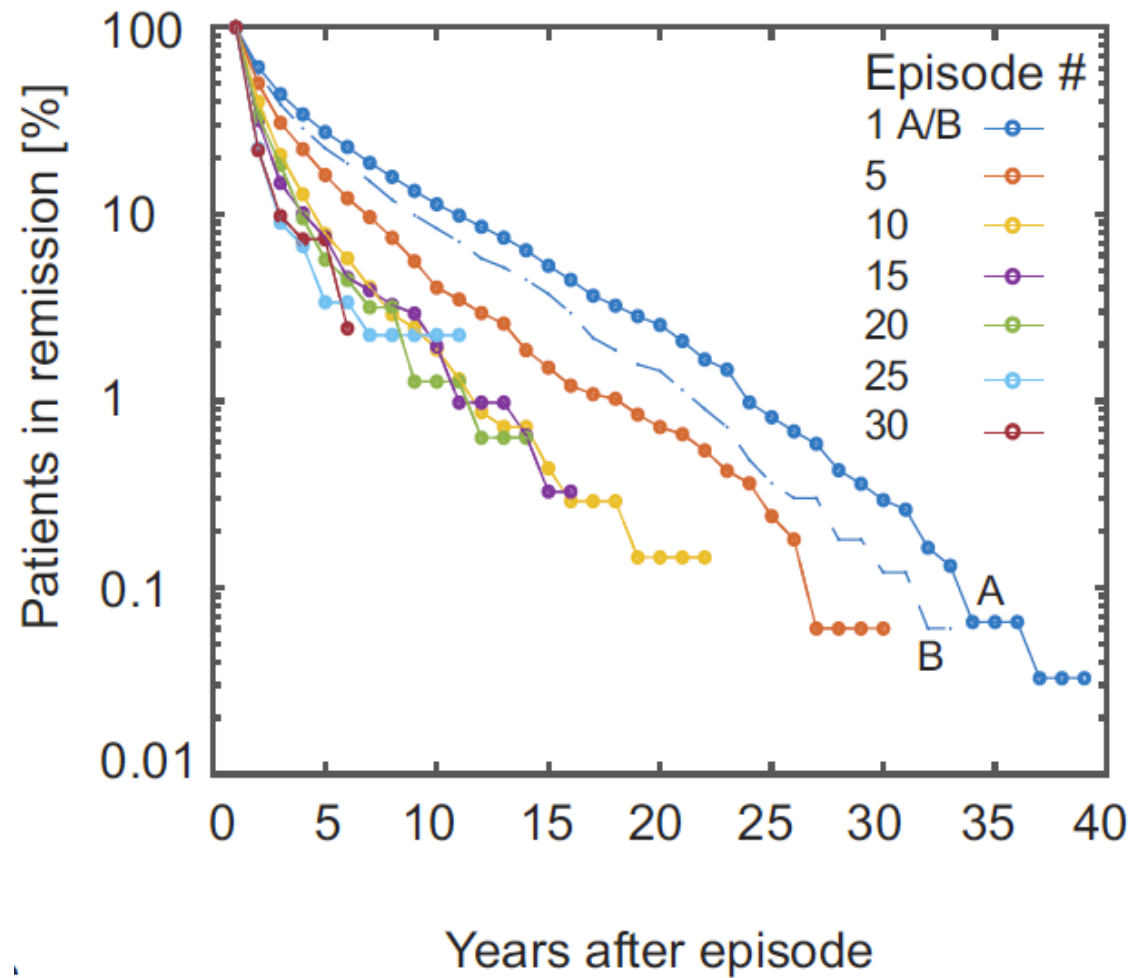


**b**



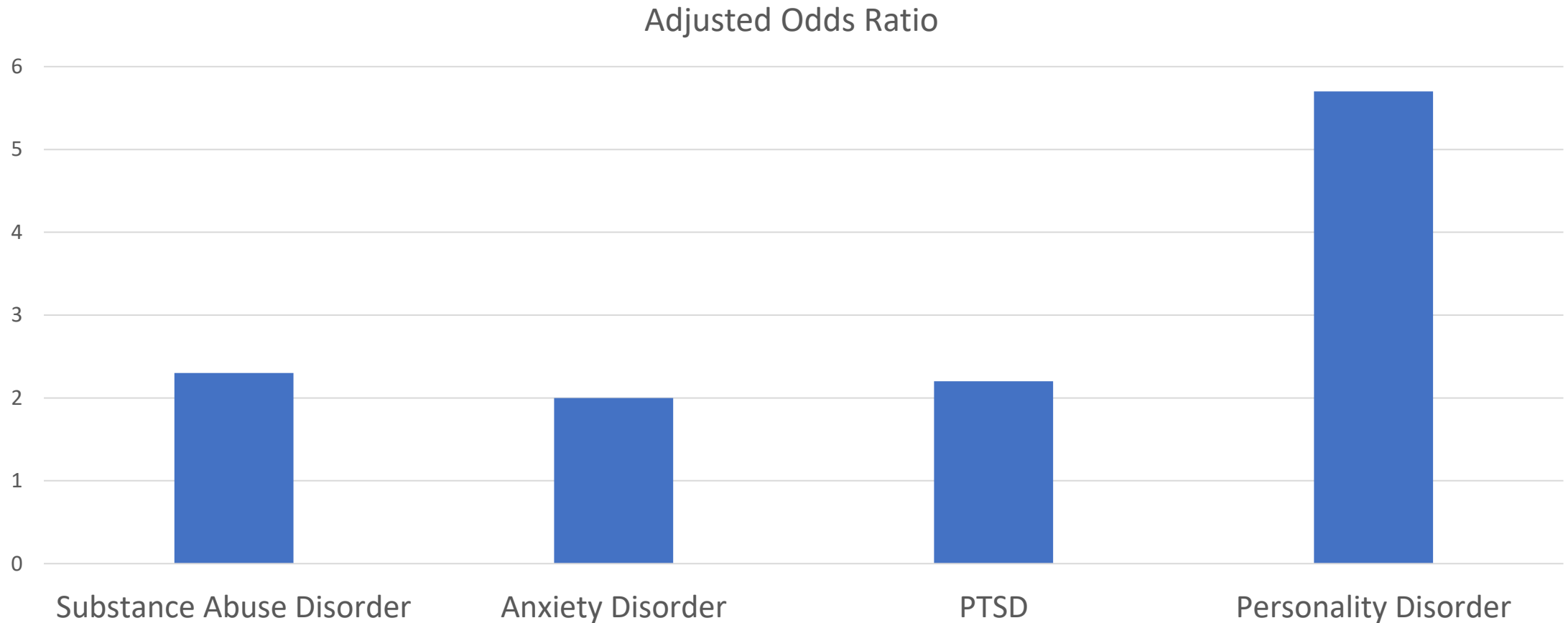


# Bipolar: Real World - Highly Recurrent



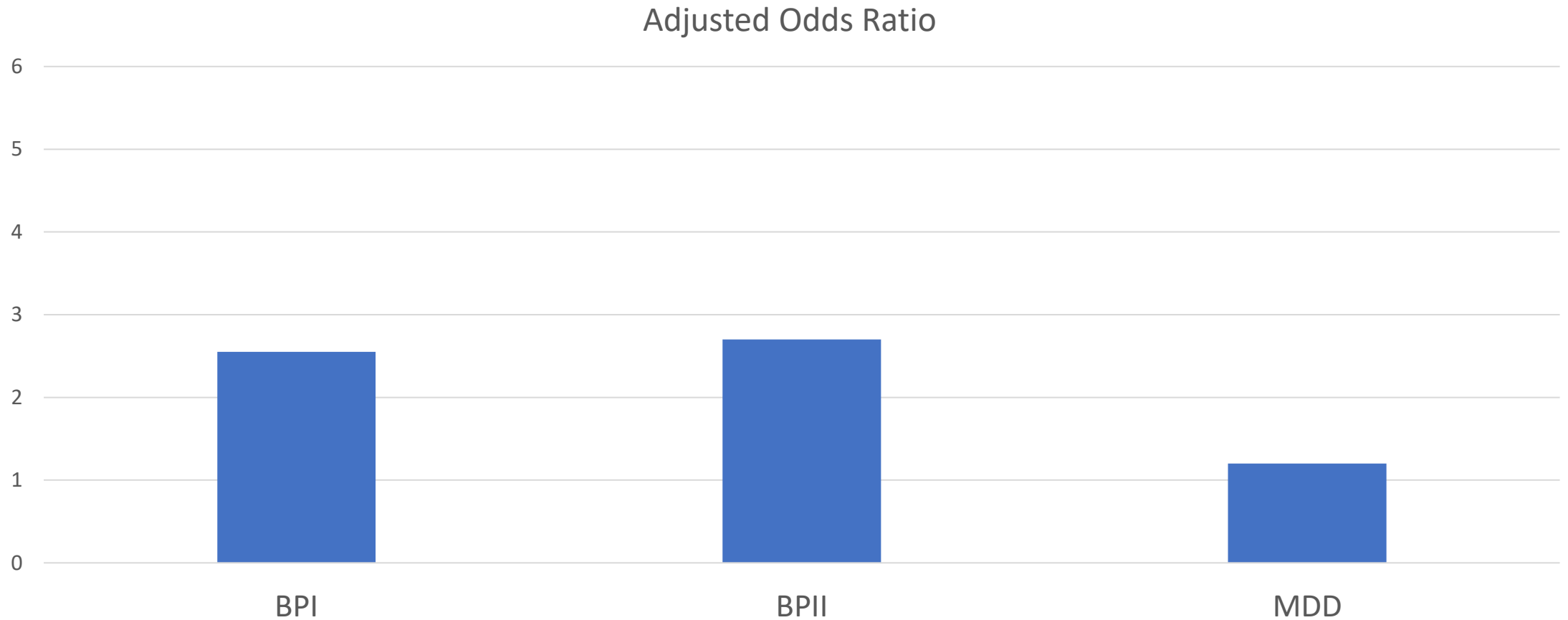
- N = 3074
- 1A all subjects
- 2B those with at least five inpatient episodes.

# DSM-V Bipolar I Psychiatric Comorbid Conditions



Blanco et al., Journal of Psychiatric Research 84 (2017) 310e317

# DSM-IV Bipolar I Cardiovascular Comorbid Conditions

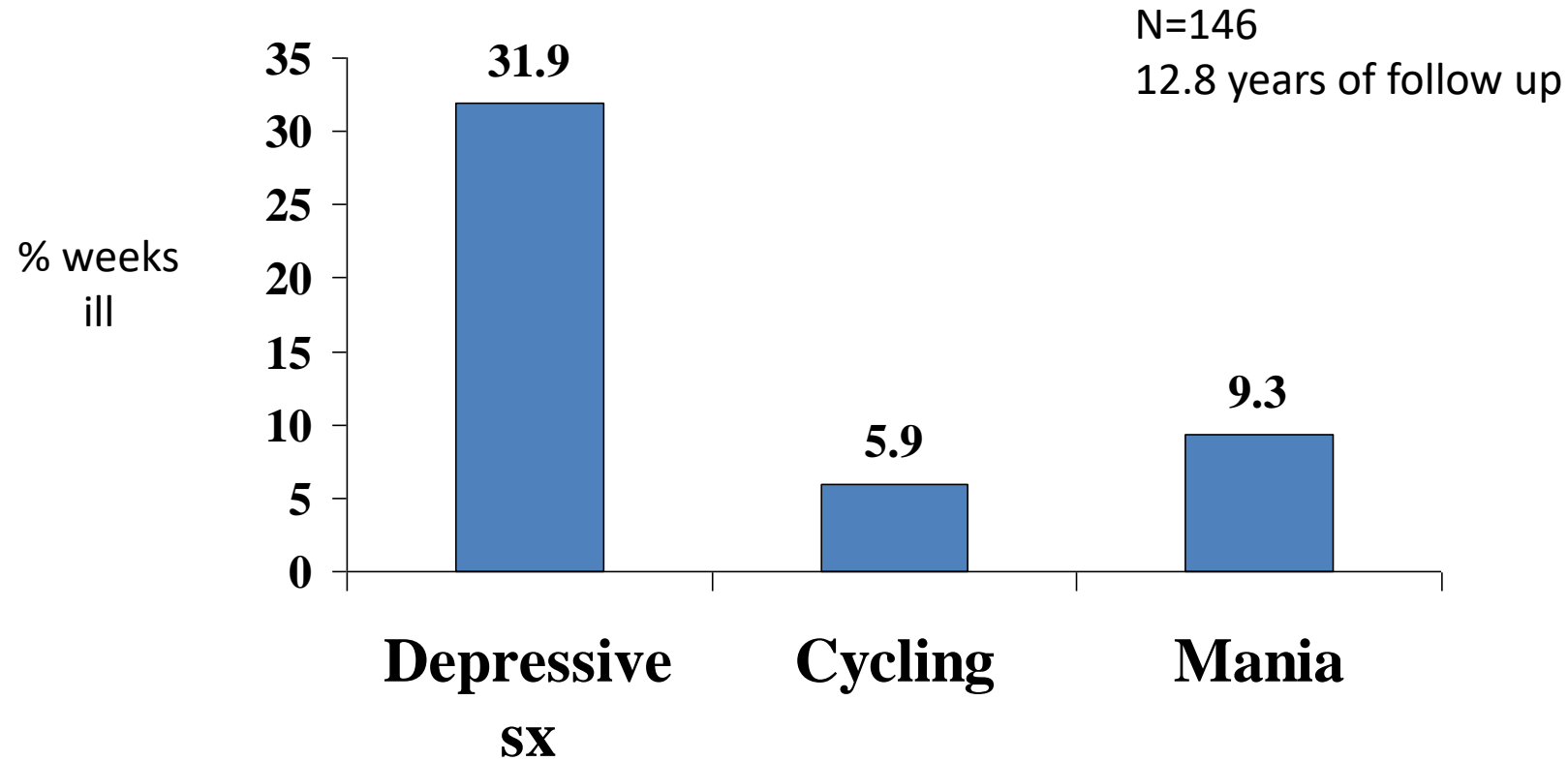


*Goldstein et al., J Clin Psychiatry 2015;76(2):163–169*

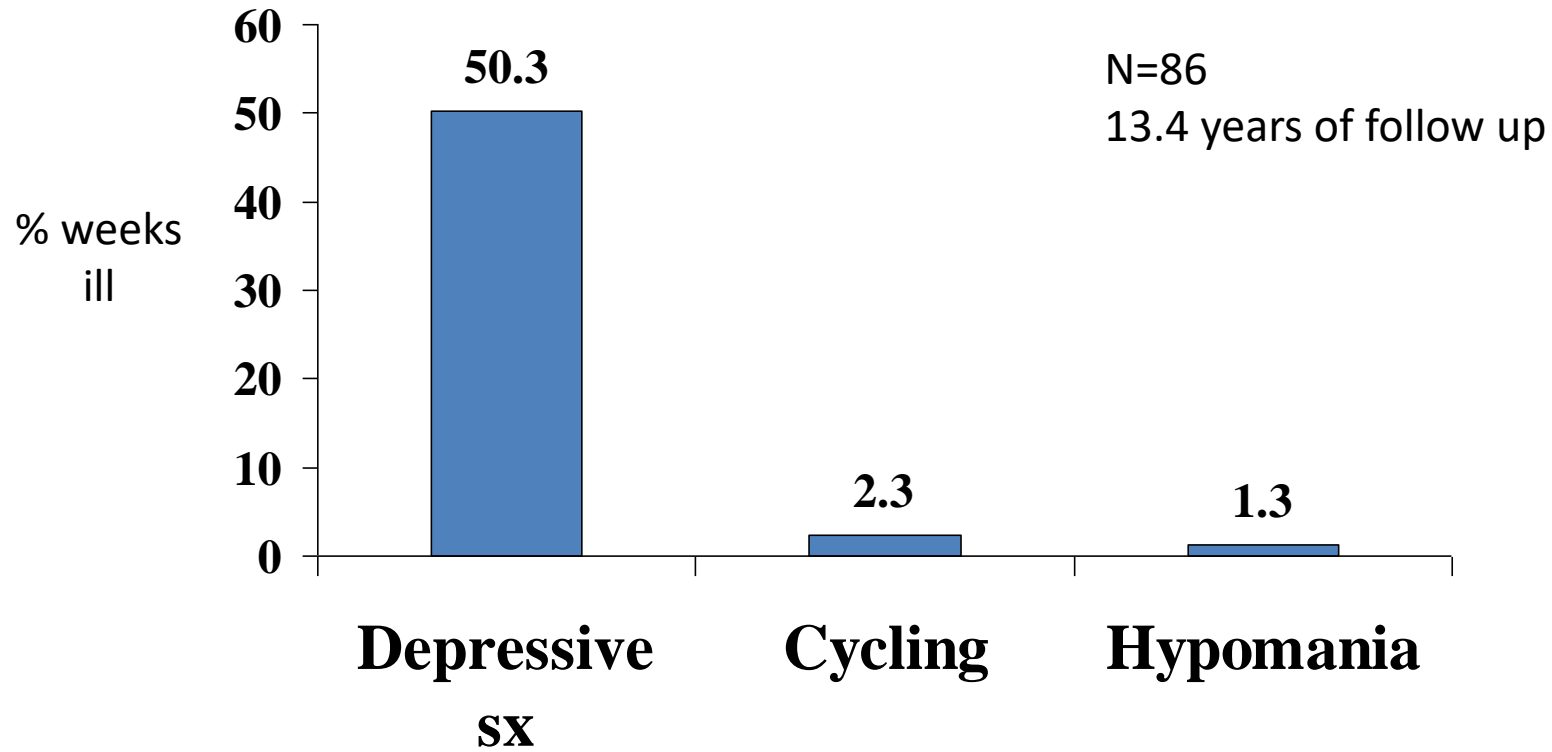


<http://www.theguardian.com/commentisfree/2015/mar/04/bipolar-disorder-wouldnt-want-to-fix-mind>

# Depressive Symptoms Predominate in BPI



# Depressive Symptoms Predominate in BP II



# Suicide



Jimi Hendrix



Kurt Cobain



David Foster Wallace

Men: 36.6 per 100,000  
Women: 21.7 per 100,000

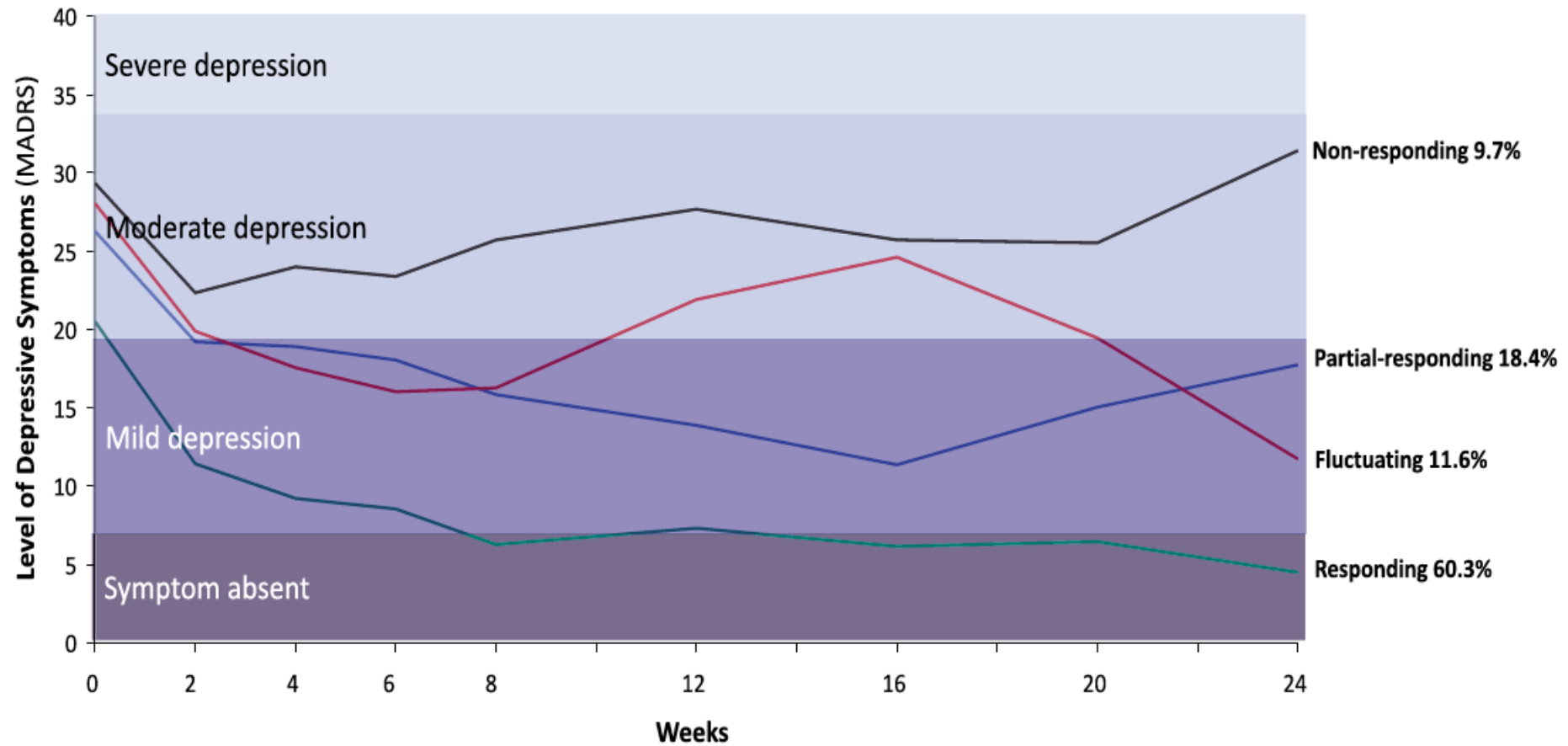
# Bipolar vs Unipolar Depression

- Early age of onset
- More episodes (> 5)
- Probably Myth
  - More atypical symptoms
  - Hyperphagia and hypersomnia
- Probably True:
  - More psychosis; More frequently postpartum;
  - More psychomotor retardation

Mitchell et al. The British Journal of Psychiatry (2011) 199, 303–309.

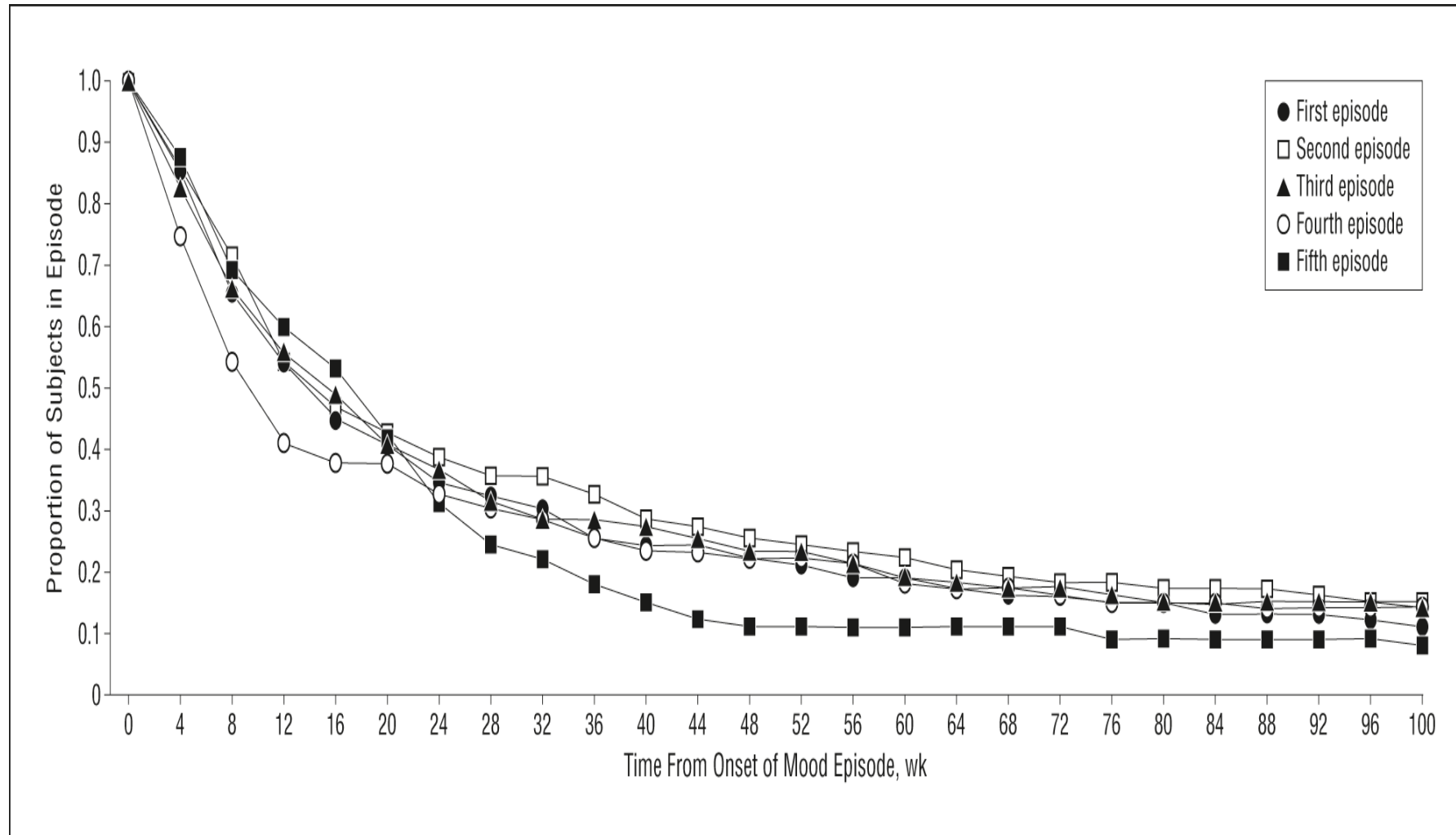


# Real World Outcomes

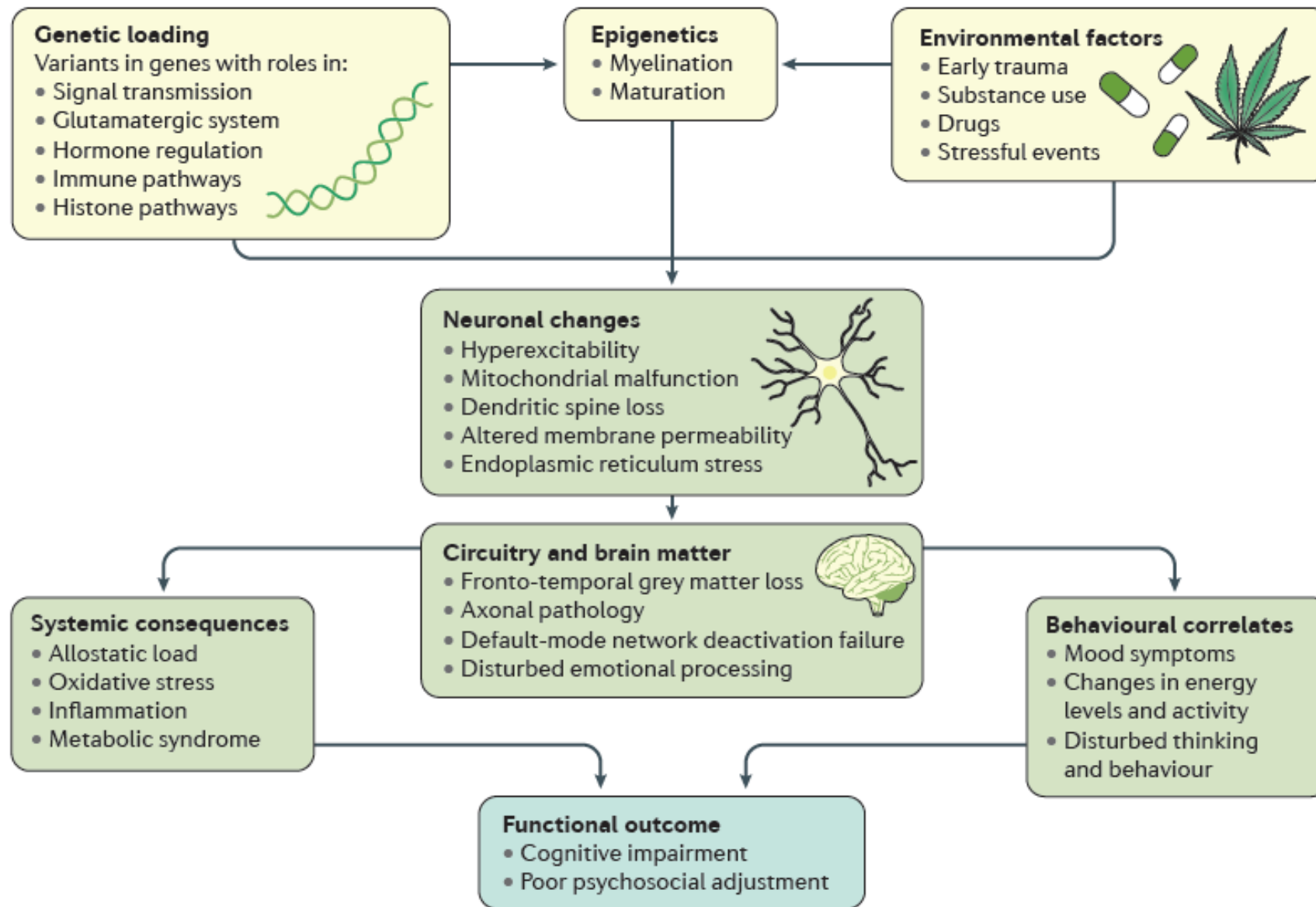


Behrendt-Møller et al. Bipolar Disorders. 2019;21:350–360.

# Duration of Mood Episodes

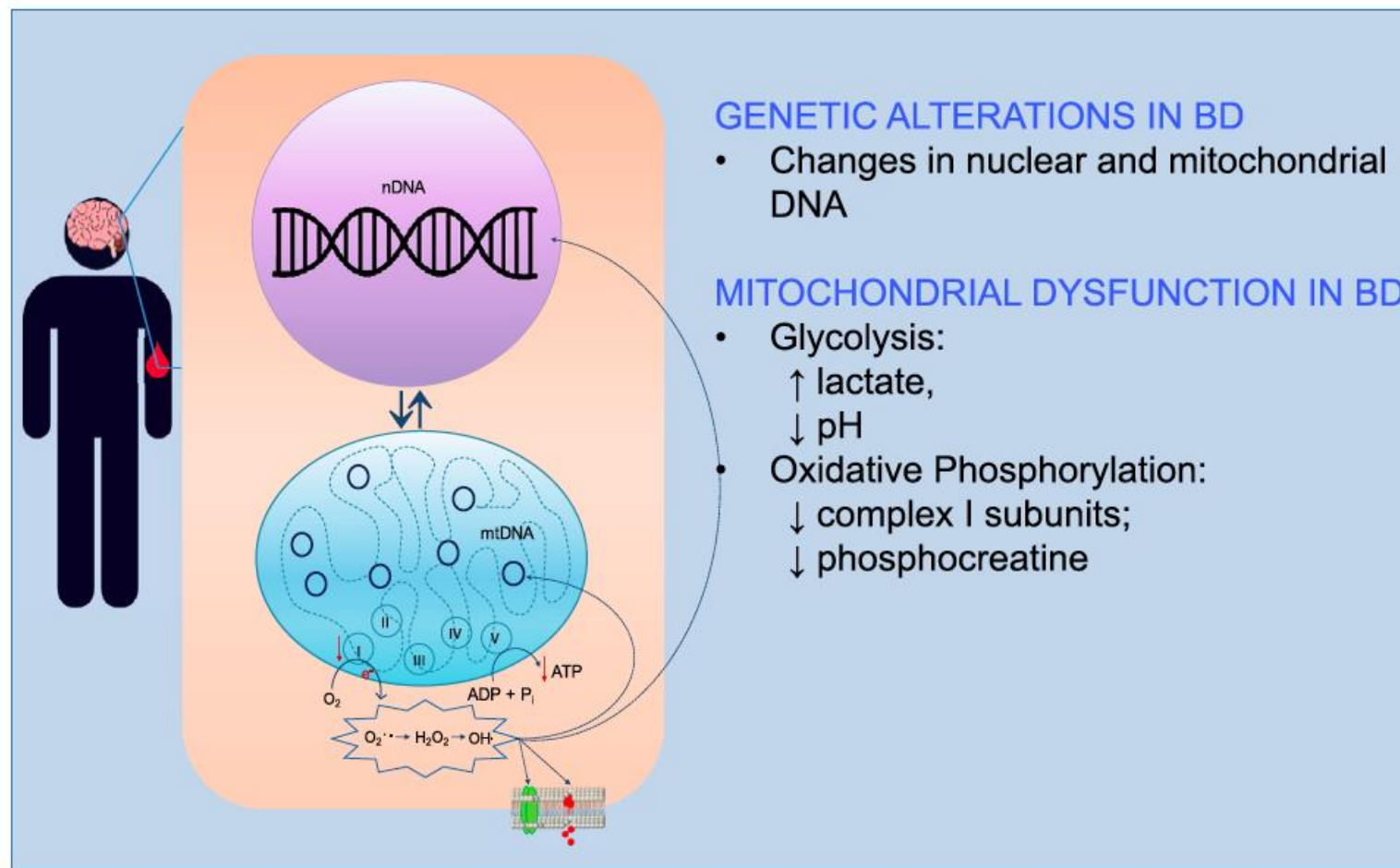


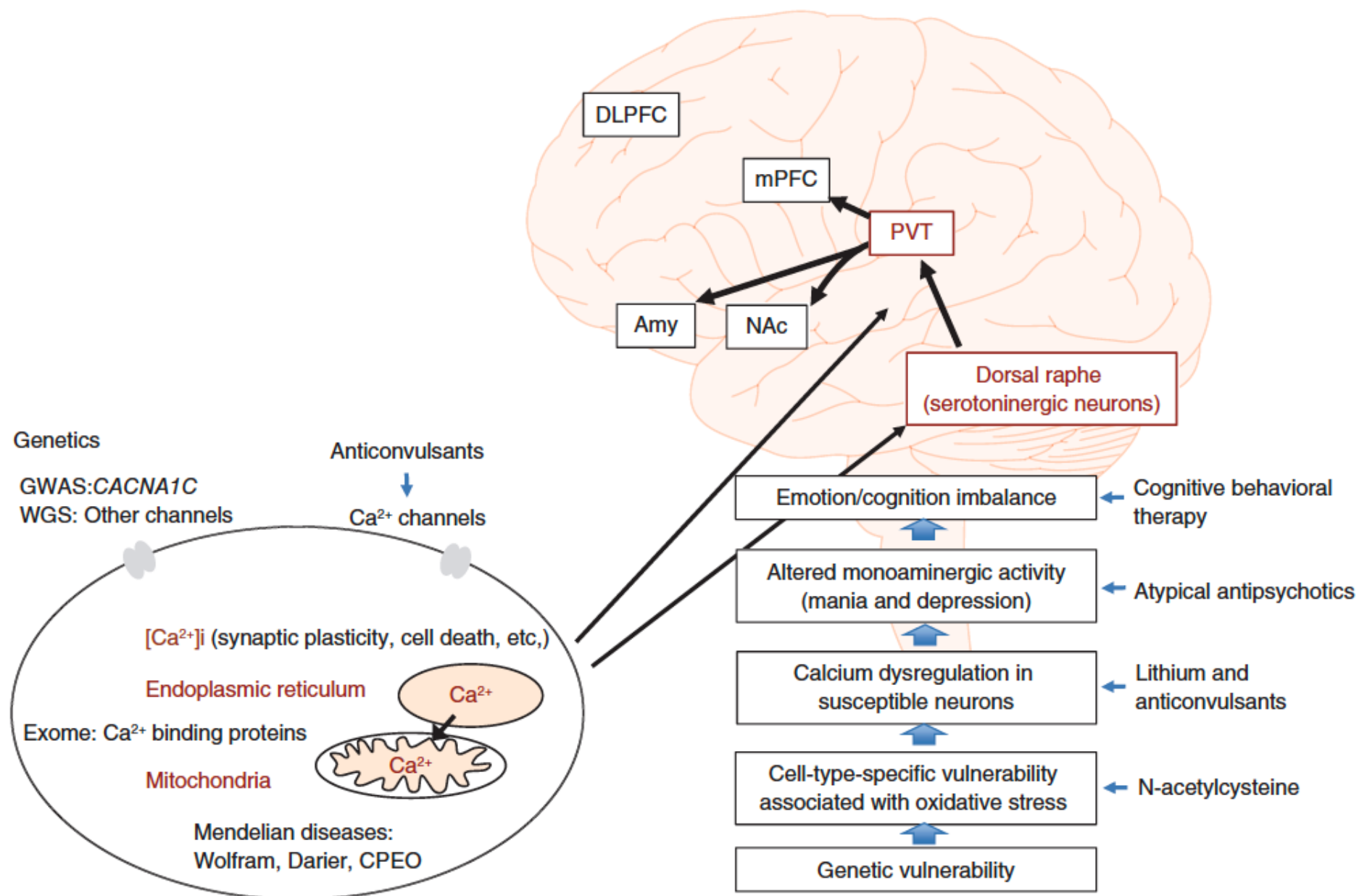
Solomon et al. Arch Gen Psychiatry. 2010 Apr;67(4):339-47.



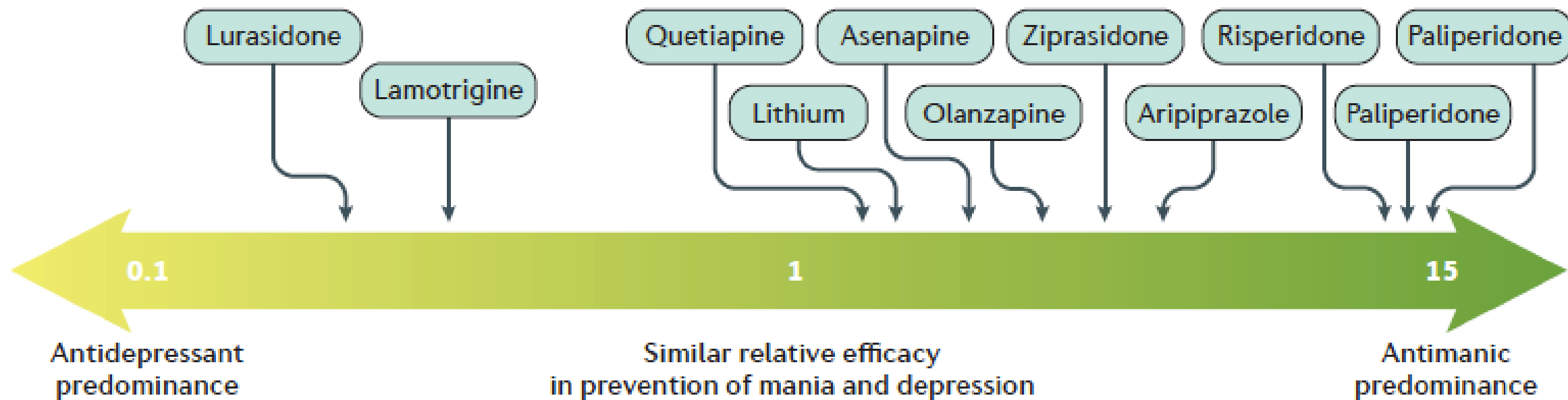
## Bipolar Disorder as a Mitochondrial Disease

Ana C. Andreazza, Angela Duong, and L. Trevor Young



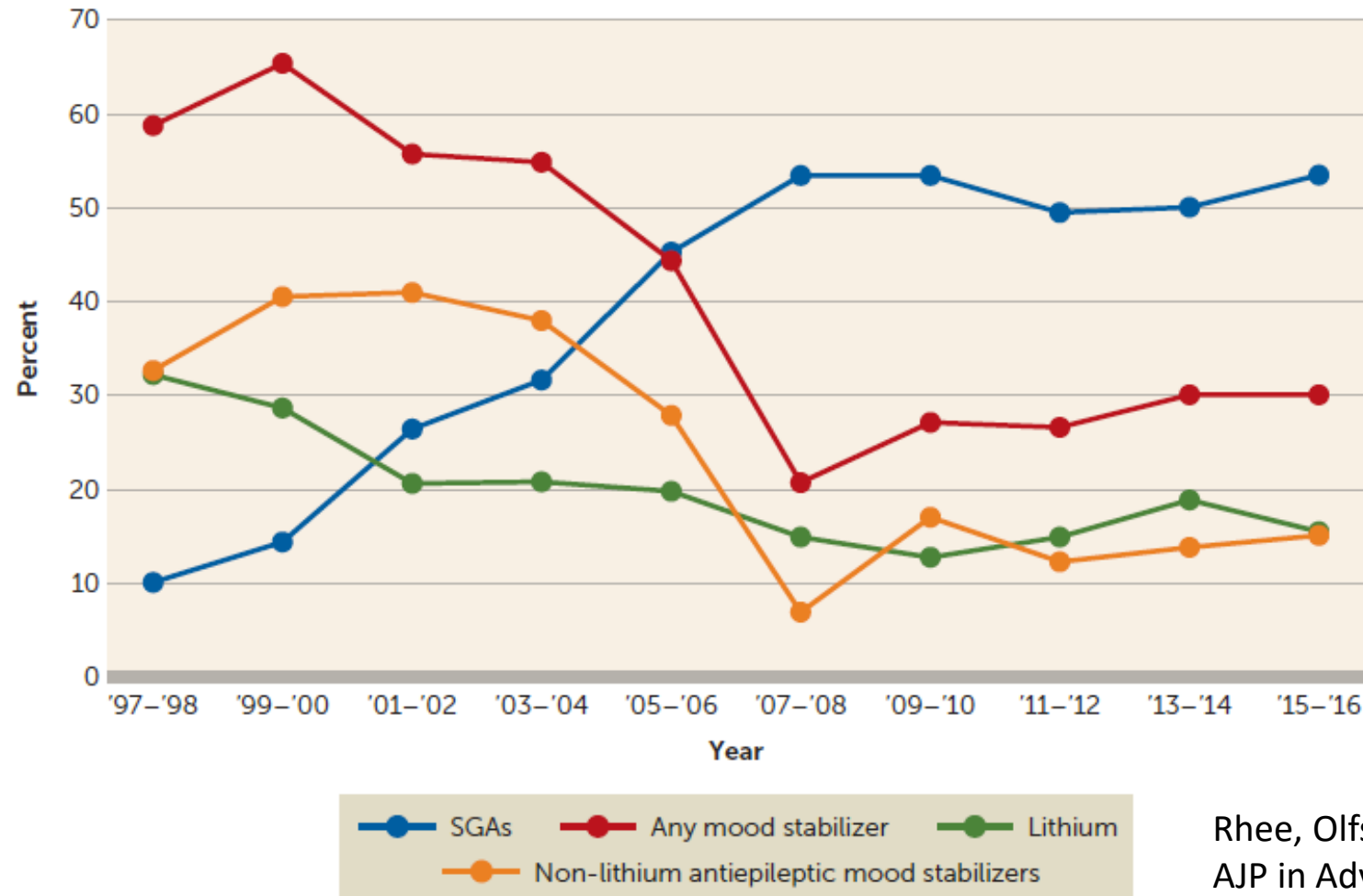


# Bipolar Treatment



# 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<sup>a</sup>



<sup>a</sup>Data are from the National Ambulatory Medical Care Survey, 1997–2016.

Rhee, Olfson, Nierenberg, Wilkerson.  
AJP in Advance  
(doi: 10.1176/appi.ajp.2020.19091000)



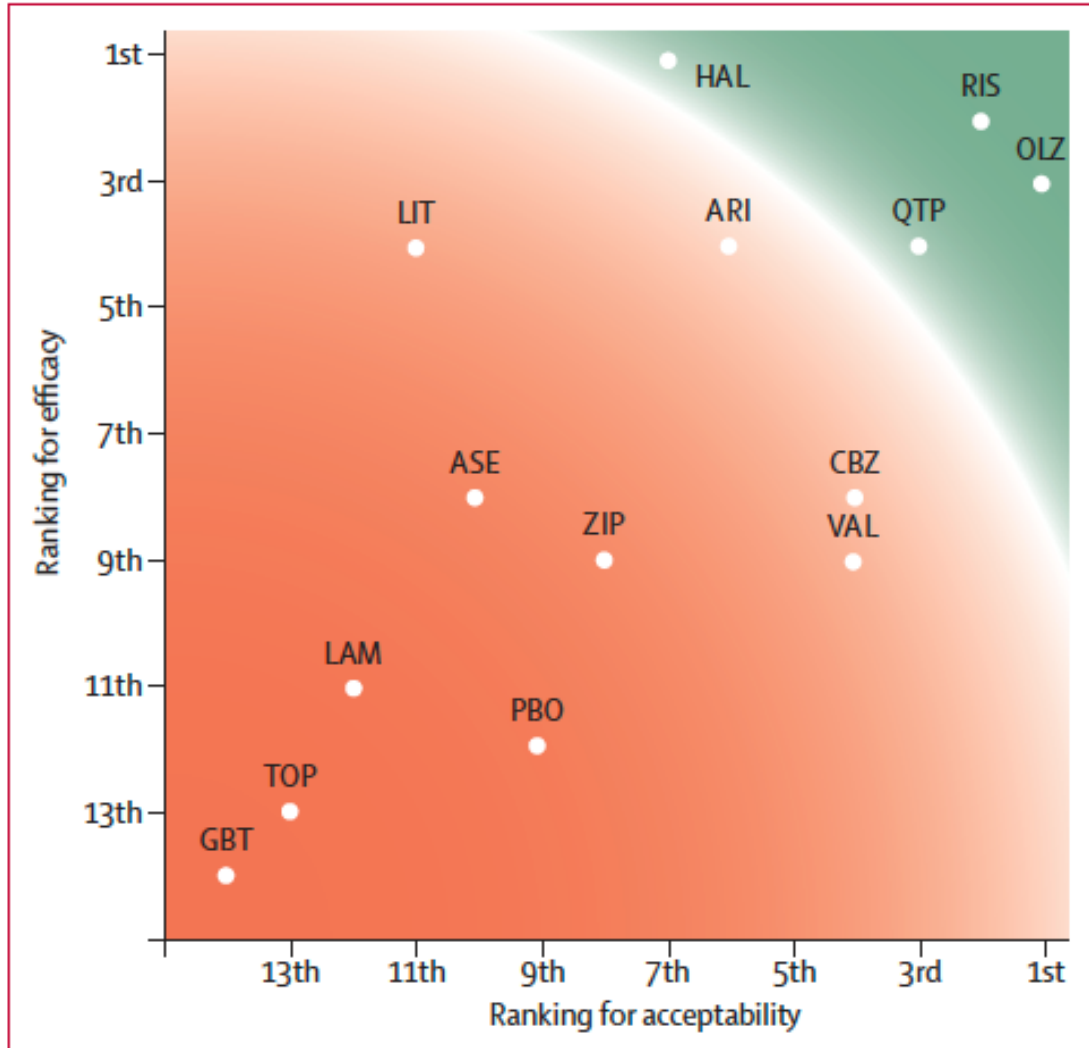
# Anti-manic Agents

**Table 1** Meta-analyses of randomized, placebo-controlled trials in mania

Drug	Trials	Subjects	Mean Dose (mg/day)	Response (RR [95% CI])	Dropout (RR [95% CI])
Risperidone	4	976	3.50 ± 0.00	2.66 [1.86–3.81]	0.60 [0.38–0.93]
Carbamazepine	2	427	700 ± 80.0	2.64 [1.60–4.30]	0.88 [0.51–1.56] <sup>a</sup>
Haloperidol	9	1663	9.45 ± 5.65	2.47 [1.89–3.25]	0.74 [0.53–1.04] <sup>a</sup>
Cariprazine	4	1198	7.12 ± 1.89	2.33 [1.56–3.53]	1.04 [0.63–1.73] <sup>a</sup>
Olanzapine	10	2031	13.4 ± 1.92	2.33 [1.82–3.02]	0.47 [0.35–0.63]
Aripiprazole	8	1982	22.5 ± 4.74	2.07 [1.56–2.77]	0.68 [0.48–0.96]
Quetiapine	6	1306	612 ± 118	2.05 [1.49–2.85]	0.63 [0.41–0.94]
Valproate	7	1299	1431 ± 954	2.05 [1.48–2.87]	0.67 [0.47–0.97]
Lithium	14	1981	1260 ± 251	1.92 [1.49–2.49]	0.94 [0.69–1.29] <sup>a</sup>
Paliperidone	5	1157	7.50 ± 3.87	1.72 [1.08–2.74]	0.60 [0.33–1.06] <sup>a</sup>
Asenapine	4	841	18.3 ± 0.14	1.61 [1.03–2.54]	0.88 [0.51–1.53] <sup>a</sup>
Ziprasidone	4	839	124 ± 7.21	1.47 [1.06–2.04]	0.93 [0.61–1.41] <sup>a</sup>

**Table 2** Controlled trials of treatment types for mania

Treatment type	Trials ( <i>n</i> )	Response rates (%) [95% CI]
Antipsychotics	37	49.7 [47.0–52.5]
Lithium carbonate	7	49.1 [42.8–55.3]
Anticonvulsants	8	48.4 [40.2–56.6]
All drugs	52	49.5 [47.3–51.7]
Placebo	60	31.6 [29.3–33.8]
Overall drug/placebo RR	52	1.57 [1.50–1.64]



Cipriani et al.  
Lancet 2011; 378: 1306–15

**Figure 6: Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate**

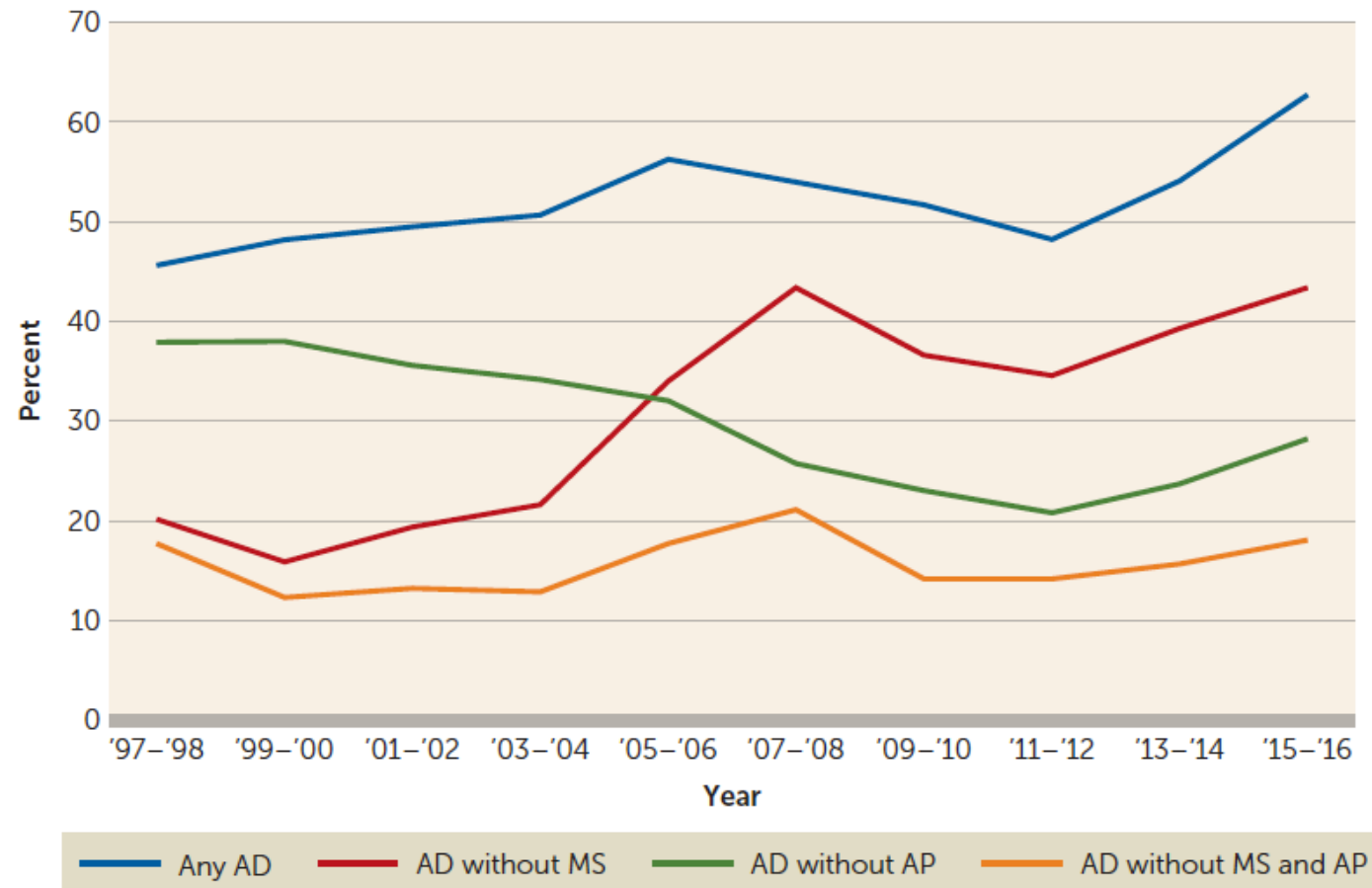
Red colour represents worst treatment and green represents best treatment in a qualitative approach. ARI=aripiprazole. ASE=asenapine. CBZ=carbamazepine. VAL=valproate. GBT=gabapentin. HAL=haloperidol. LAM=lamotrigine. LIT=lithium. OLZ=olanzapine, PBO=placebo. QTP=quetiapine. RIS=risperidone, TOP=topiramate. ZIP=ziprasidone.

# Bipolar Antidepressant Treatments

- Olanzapine/Fluoxetine Combination (OFC)
  - Zyprexa/Prozac
- Quetiapine - Seroquel
- Lurasidone – Latuda
- Cariprazine – Vraylar
- (Lamotrigine)
- (No antidepressants approved for bipolar depression)
- Electroconvulsive therapy
- Repetitive transcranial magnetic stimulation (rTMS)?

# Antidepressant prescriptions persist

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



<sup>a</sup> 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.

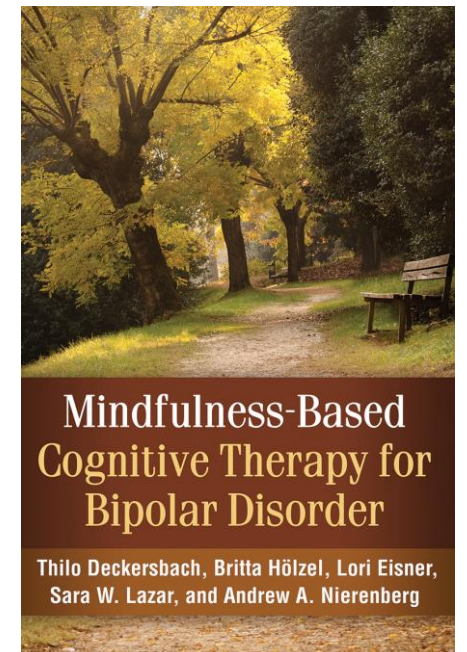
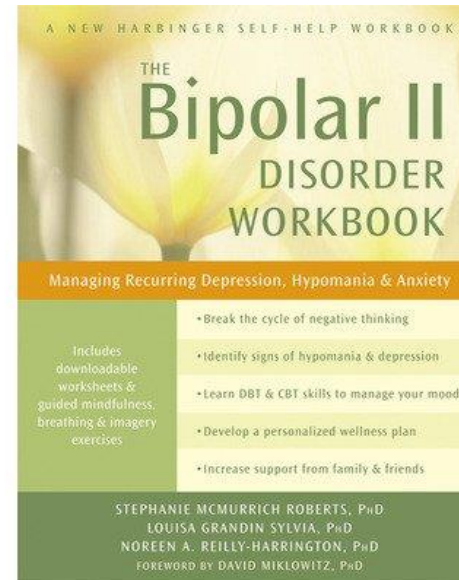
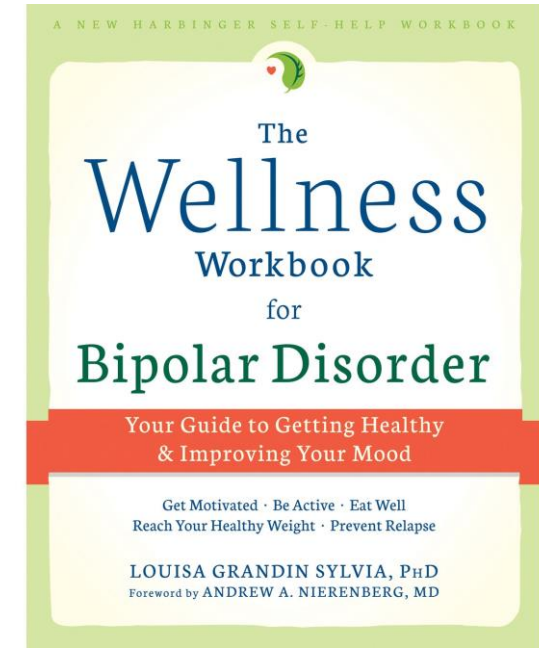
AJP in Advance  
(doi: 10.1176/appi.ajp.2020.19091000)

## 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

# Psychotherapy

- Cognitive behavioral therapy (CBT)
- Mindfulness based cognitive therapy (MBCT)
- Unified protocol for emotional regulation
- Dialectical behavioral therapy (DBT)
- Lifestyle interventions



# Potential new treatments

- Ketamine
- Pioglitazone
- Bezafibrate
- Minocycline
- N-acetylcysteine
- Pramipexole
- Nicotinamide riboside
- Candesartan



# Summary

- Bipolar disorder
  - Depressive and manic/hypomanic episodes
  - Complex chronic course
  - Comorbid conditions
  - Complex pathophysiology
- Treatments
  - Antimanic
  - Antidepressant
  - Maintenance