Neuroscience Education Institute

IN THE RED: OPTIMIZING TREATMENT FOR BIPOLAR I DISORDER

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Learning Objectives

- Improve recognition of bipolar I disorder early in the disease process to increase likelihood of successful treatment
- Compare treatments for bipolar I disorder based on their mechanisms of action, efficacy, and tolerability to determine which is most appropriate for an individual patient
- Implement evidence-based treatments for bipolar I disorder that best meet the individual needs of the patient to increase adherence and improve patient outcomes

Impact of Delayed Diagnosis and Treatment Initiation in Bipolar Disorder

Median duration from illness onset to diagnosis = 6.7 years [1]

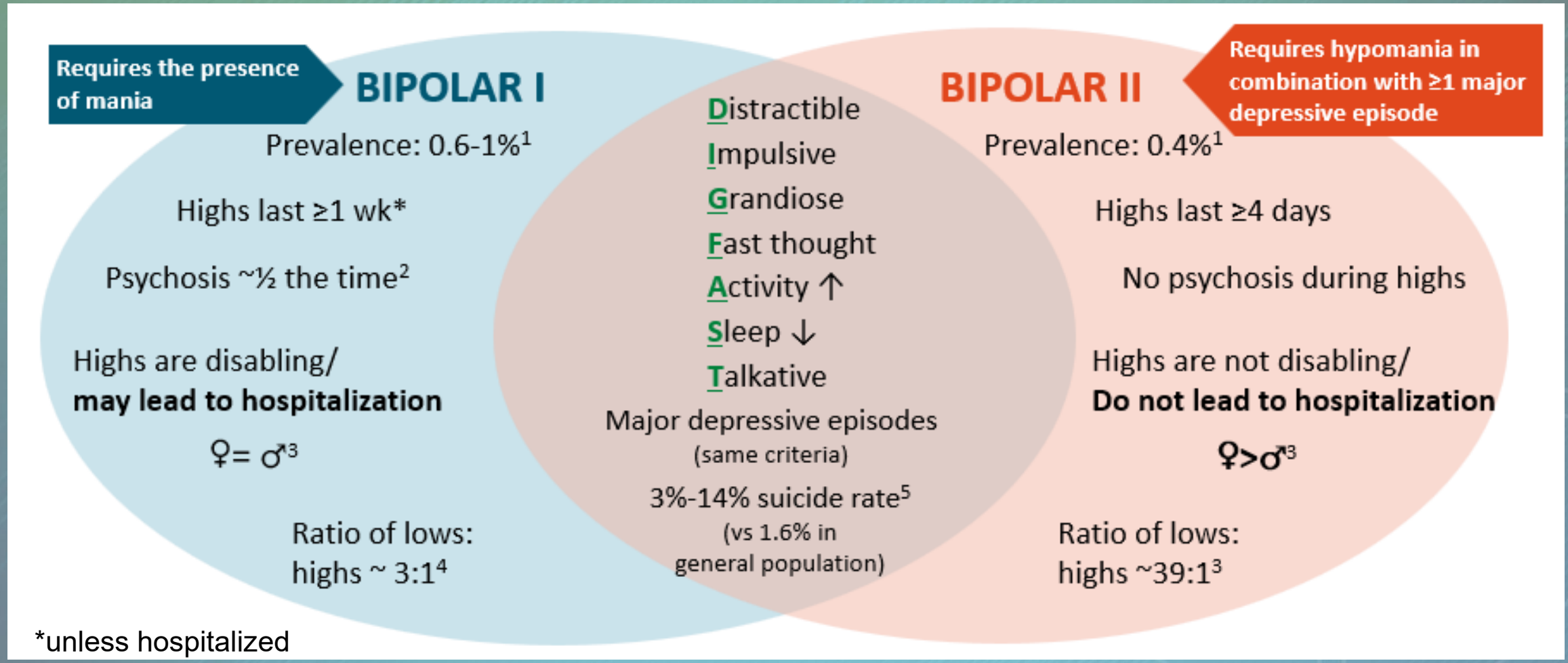
Longer duration of untreated illness in bipolar disorder associated with:

- more hospitalizations, more manic and depressive episodes, poorer functioning [2]
- more suicide attempts [3,4]
- more comorbid personality disorders [5]

Pharmacotherapy for bipolar disorder may be more effective when begun early in the course of illness [6]

[1] Scott J et al. Acta Psychiatr Scand 2022;146(5):389-405; [2] Altamura AC et al. J Affect Disord 2015;182:70-5; [3] Altamura AC et al. Eur Arch Psychiatry Clin Neurosci 2010;260(5):385-91; [4] Goldberg JF, Ernst CL. J Clin Psychiatry 2002;63(11):985-91; [5] Murru A et al. J Affect Disord 2015;188:319-23; [6] Joyce K et al. Int J Bipolar Disord 2016;4(1):19.

Phenomenology of Bipolar Disorder

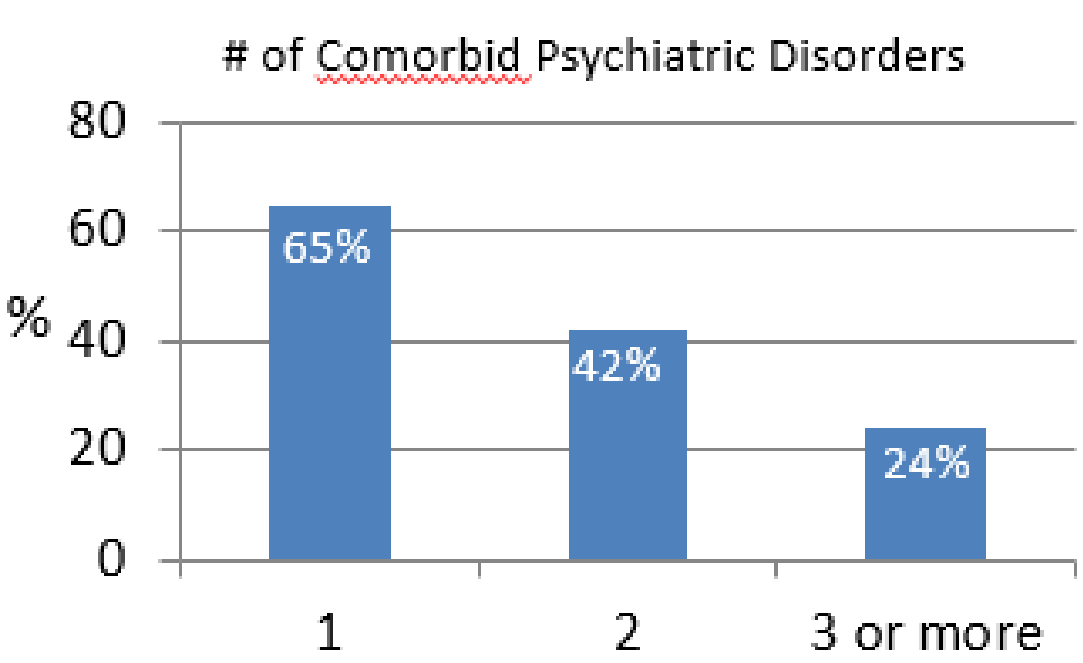


*unless hospitalized

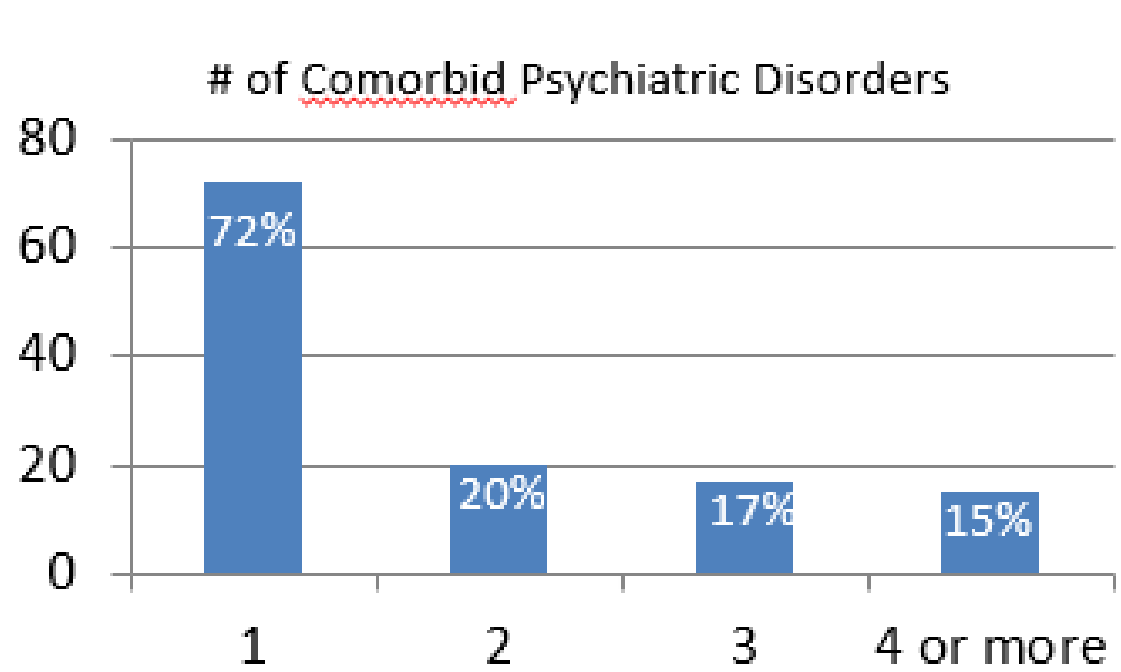
[1] Merikangas KR et al. Arch Gen Psychiatry 2011;68(3):241-51; [2] Keck PE Jr et al. Compr Psychiatry 2003;44(4):263-9; [3] Altshuler LL et al. Am J Psychiatry 2010;167(6):708-15; [4] Judd LL et al. Arch Gen Psychiatry 2002;59(6):530-7; [5] Pompili M et al. Bipolar Disord 2013;15(5):457-90.

Psychiatric Comorbidites Are Common in Bipolar Disorder

N=288 bipolar subjects in Stanley Bipolar Cohort [1]



N=656 bipolar subjects in STEP-BD [2]



Most common: anxiety disorder and substance use disorders

[1] McElroy SL et al. Am J Psychiatry 2001;158(3):420-6; [2] Simon NM et al. J Clin Psychopharmacol 2004;24(5):512-20.

Screening for Bipolar Disorder

RMS[1]

1. ≥6 periods of deep depression in 2 weeks
2. Depression before the age of 18
3. Irritability or hyperactivity from antidepressant
4. Period of ≥1 week spent more talkative or with thoughts racing
5. Period of ≥1 week spent unusually happy, outgoing, or energetic
6. Period of ≥1 week needing much less sleep

PPV	NPV	Sensitivity	Specificity
0.80	0.88	0.88	0.80

MDQ[2]

1. A period of time where you were **not yourself and**:

• Felt unusually good or hyper (with consequences)	• Had much more energy
• Were unusually irritable (shouting, starting fights)	• Were much more active
• Much more self-confident	• Were much more social/outgoing
• Required much less sleep	• Much more interested in sex
• Were much more talkative or had much faster speech	• Had unusual or risky behavior
• Had racing thoughts	• Were excessively spending
• Were easily distractable	

2. Several of the above during the same period

3. How much of a problem did any of these cause?

PPV	NPV	Sensitivity	Specificity
0.78	0.86	0.86	0.78

[1] McIntyre RS et al. Curr Med Res Opin 2021;37(1):135-44. [2] Hirschfeld RM et al. Am J Psychiatry 2000;157(11):1873-5.

Bipolar Screening and Its Limitations

Mood Disorders Questionnaire (MDQ): 13-item self-report measure; scores ≥7=casehood [1]

Meta-analysis of 23 studies with 6730 subjects: [2]

Sensitivity	Specificity	PPV	NPV
61.3%	87.5%	58.0%	88.9%

Better sensitivity for BP I (66.3%) than BP II disorder (38.6%)

Table 3. Operating Characteristics of the Mood Disorders Questionnaire Scored According to Hirschfeld and Colleagues' Algorithm in Studies of the General Population, General Psychiatric Outpatients, and Patients with Mood Disorders

Sample	Number of studies	*n*	Prevalence of bipolar disorder (%)	Sensitivity[a] (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
General population	3	1875	5.8	25.9	97.9	43.1	95.6
Psychiatric outpatients	3	943	14.7	64.7	82.3	38.8	93.1
Mood disorder patients	10	2052	39.1	64.7	81.1	68.7	78.2

[a]Sensitivity for all bipolar disorders.

[1] Hirschfeld RM et al. Am J Psychiatry 2000;157(11):1873-5; [2] Zimmerman M, Galione JN. Harv Rev Psychiatry 2011;19(5):219-28.

Bipolarity Index

A corroborator—not a proxy—for diagnosis

	Points	Most points for
Episode characteristics	Up to 20	DSM-5 mania, fewer for hypomania
Family history	Up to 20	1st degree relatives
Age at onset of depression	Up to 20	Ages 15–19; fewer for earlier or later
Course of illness	Up to 20	Highly recurrent episodes
Response to treatment	Up to 20	Recovery with a mood stabilizer or manic switch with an antidepressant; possible loss of antidepressant response; very rapid antidepressant response

Cut-off score = **50**; sensitivity=0.91, specificity=0.90

Aiken CB et al. J Affect Disord 2015;177:59-64.

Polypharmacy in Bipolar Disorder Is Common But Not Necessarily Rationale-Based

33% of bipolar patients take ≥3 psychotropic medications

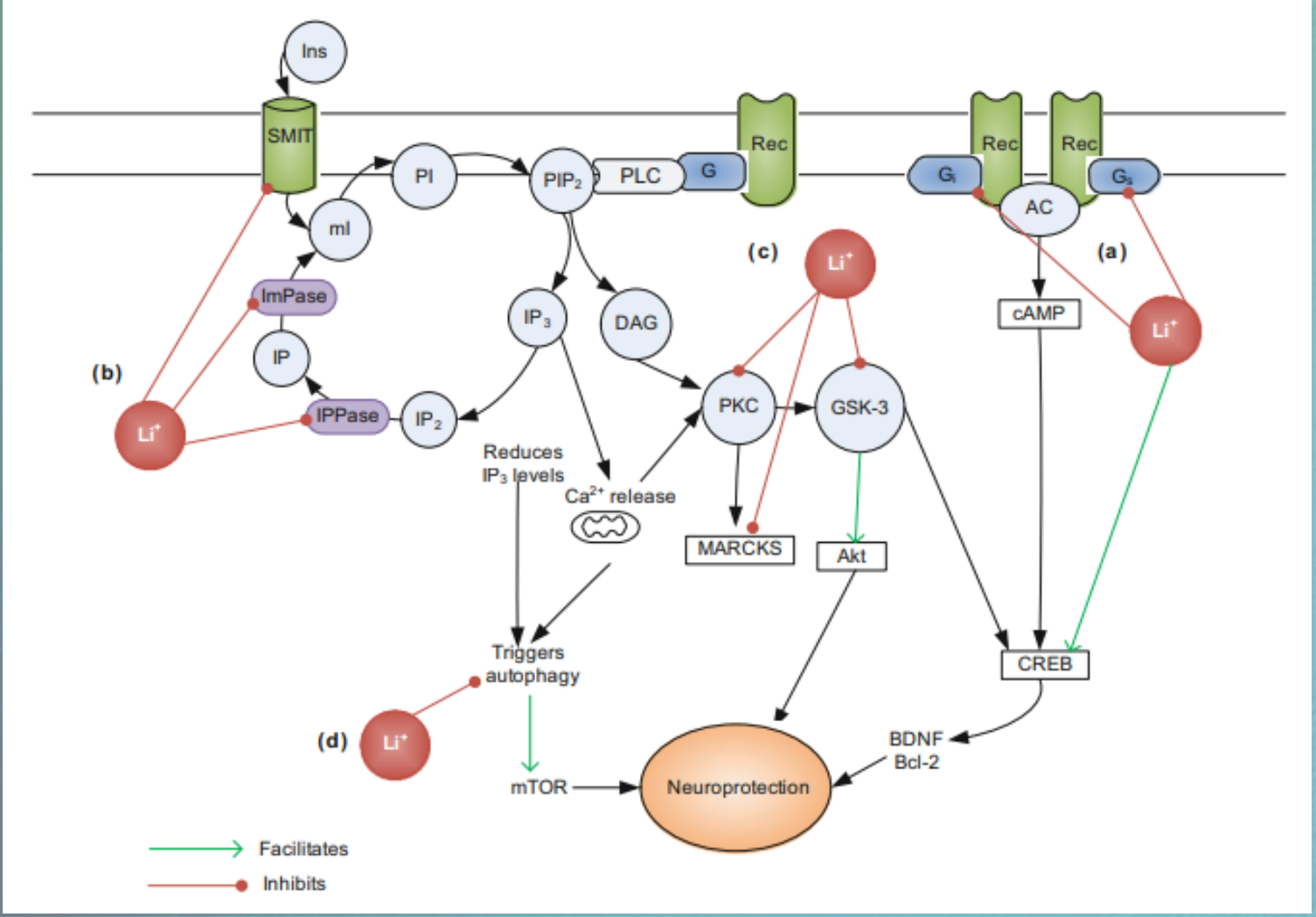
- Complex polypharmacy more likely in women, whites, age >50 years, history of psychosis, low dosages, poor adherence, more suicide attempts [1]
- Extensive polypharmacy often driven by the burden of depressive illness [2]
- Trends over past 20 years: [2]
  Second-generation antipsychotic use has risen 39%, mood stabilizer use has declined 36%, antidepressant use has risen by 23%

[1] Kim AM et al. J Clin Psychiatry 2021;82(3):20r13263; [2] Goldberg JF et al. J Clin Psychiatry 2009;70(2):155-62;
[3] Rhee TG et al. Am J Psychiatry 2020;177(8):706-15.

FDA-Approved Treatments for Bipolar Disorder

Mania	Mania	Depression	Maintenance
Lithium	√		√
Divalproex	√		
Carbamazepine	√		
Lamotrigine			√
Chlorpromazine	√		
Loxapine (inhaled)	√		
Risperidone	√		√ (LAI)
Quetiapine	√	√	√
Olanzapine	√		√
Olanzapine-fluoxetine combination		√	
Ziprasidone	√		√
Aripiprazole	√		√
Asenapine	√		
Cariprazine		√	
Lurasidone		√	
Lumateperone		√	

Putative Mechanisms of Action of Lithium Carbonate

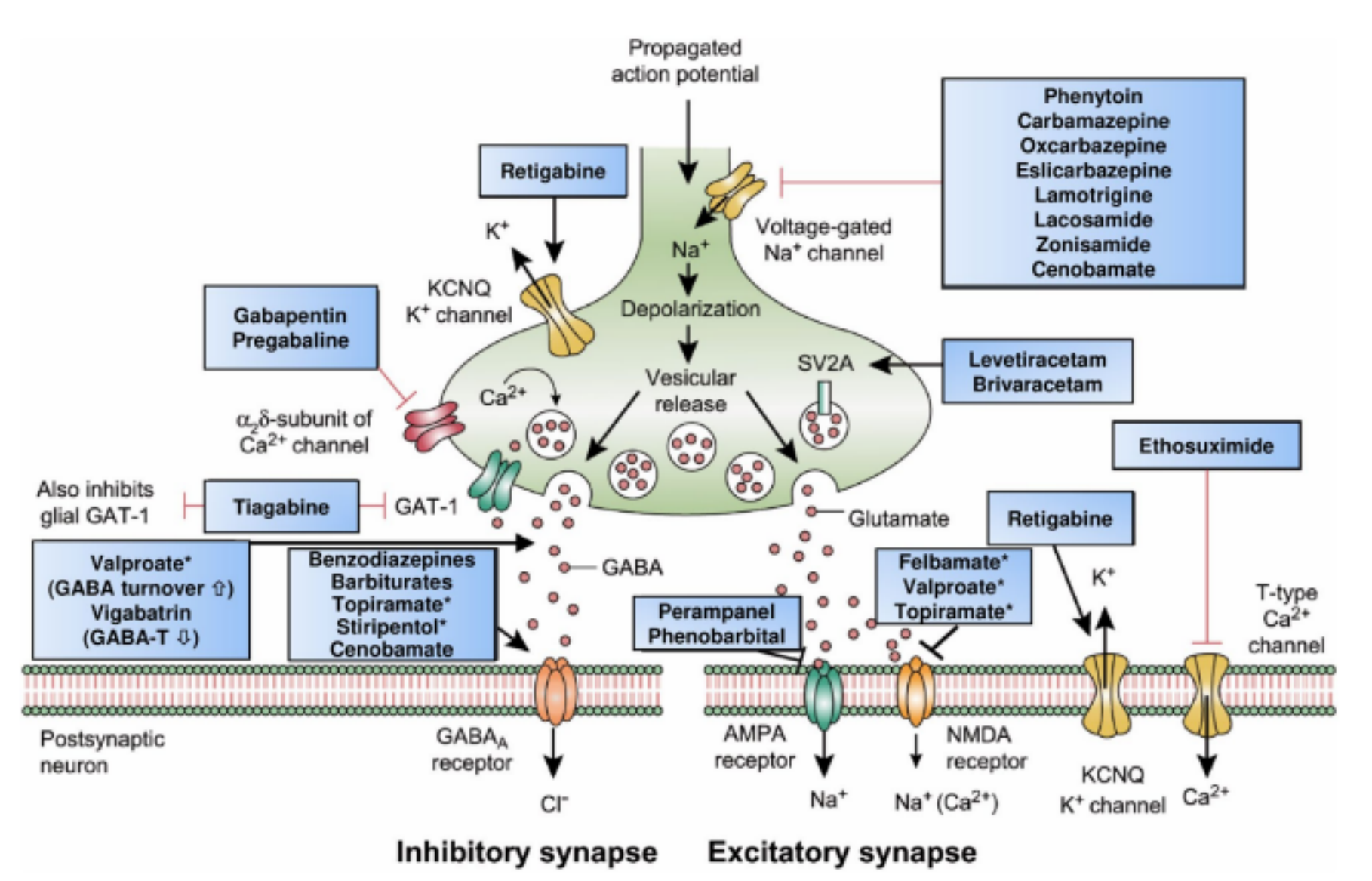


Abbreviations:

- Akt=protein kinase B
- Bcl-2=b-cell lymphoma 2
- BDNF=brain-derived neurotrophic factor
- CREB=cAMP response element binding transcription factor
- GSK-3= glycogen synthase kinase-3
- IMPase=inositol monophosphatase-1 phosphatase
- MARCKS=myristoylated alanine-rich C-kinase substrate
- PI=phosphatidyl inositol
- PIP2=phosphatidyl inositol bisphosphate
- PKC=protein kinase C
- SMIT=sodium myoinositol transporter

Malhi GS et al. CNS Drugs 2013;27(2):135-53.

Putative Mechanisms of Anticonvulsants



Löscher L, Klein P. CNS Drugs 2021;35(9):935-63.

Putative Mood Stabilizer Mechanisms of Action

Mechanism	Lithium	Divalproex	Carbamazepine	Lamotrigine	SGAs	Antidepressants
PKC inhibition	√	√				
BDNF upregulation	√	√	√	√	√	√
Bcl-2 upregulation	√	√	√	√		
GSK-3β inhibition	√	√				
MARCKS downregulation	√	√				
GABA upregulation	√	√	√			
Glutamate downregulation	√	√	√	√		
Na^+ channel blockade	√	√	√	√		√
Ca^{++} channel blockade		√	√	√		
5HT2A antagonism					√	√
5HT1A partial agonism					√	√
5HT1B antagonism					√	
D2 antagonism	√	√	√		√	

Goldberg JF. FOCUS (Am Psychiatr Publ) 2019;17:218-31.

Profile of Lithium-Responsive Bipolar Mania

- Mania polarity-proneness [1,2]
- Mania as initial episode [2]
- Later age at onset [1]
- Few episodes [3,4]
- Absence of mixed features [5]
- Absence of rapid cycling [6]
- Absence of psychosis [2]

- Absence of comorbid OCD or alcohol/substance use disorders [2]
- Family history of bipolar disorder [2,7]
- Positive family history of lithium responsivity [8]
- Hyperthymic temperament [9]
- Absence of anxiety [9]

[1] Kleindeinst N et al. Bipolar Disord 2005;7(5):404-17; [2] Scott J et al. Acta Psychiatr Scand 2020;141(6):522-33; [3] Gelenberg AJ et al. N Engl J Med 1989;321(22):1489-93; [4] Swann AC et al. Am J Psychiatry 1999;156(8):1264-6; [5] Swann AC et al. Arch Gen Psychiatry 1997;54(1):37-42; [6] Dunner DL, Fieve RR. Arch Gen Psychiatry 1974;30(2):229-33; [7] Nivoli AMA et al. Neuropsychobiology 2010;62(1):27-35; [8] Grof P et al. J Clin Psychiatry 2002;63(10):942-7; [9] Rybakowski JK et al. J Affect Disord 2013;145(2):187-9.

Lithium: Additional Points

- Lithium is a better preventative than acute drug
  - Lithium has stronger antimanic (RR=0.62, overall relapse rate=14%) than antidepressant (RR=0.72, overall relapse rate=25%) preventative efficacy [1]
- Beware of low Na^+ intake as driver of high lithium levels
- NSAIDs raise serum lithium levels by about 20%
- Suspected lithium toxicity: tremor, GI distress
  - EKG changes: T wave inversion, sinus bradycardia, SA block, PR prolongation, QT prolongation, ventricular tachycardia [2]
  - Hold lithium; IV hydration; dialysis if serum [Li+]>4 mEq/L w/renal dysfunction [3]
- Risk of developing Cr >1.5 ng/dl after 20 years = 1.2% [4]
- After OD, lithium can remain in bone and brain long after serum level is zero
- (Nontoxic) postural lithium tremor manageable with propranolol or primidone

[1] Geddes JR et al. Am J Psychiatry 2004;161(2):217-22; [2] Mehta N, Vannozzi R. Clin Cardiol 2017;40(12):1363-7 ; [3] Decker BS et al. Clin J Am Soc Nephrol 2015;10(5):875-87; [4] Bendz H et al. Kidney Int 2010;77(3):219-24.

Profile of Divalproex-Responsive Bipolar Mania

- Multi-episode presentations
- Utility of rapid oral loading
- Mania-prone > depression-prone
- Mixed or pure manias
- Impulsivity/aggression
- Presence or absence of rapid cycling
- Presence or absence of comorbid alcohol/substance use disorders
- Avoid in sexually active women of reproductive potential

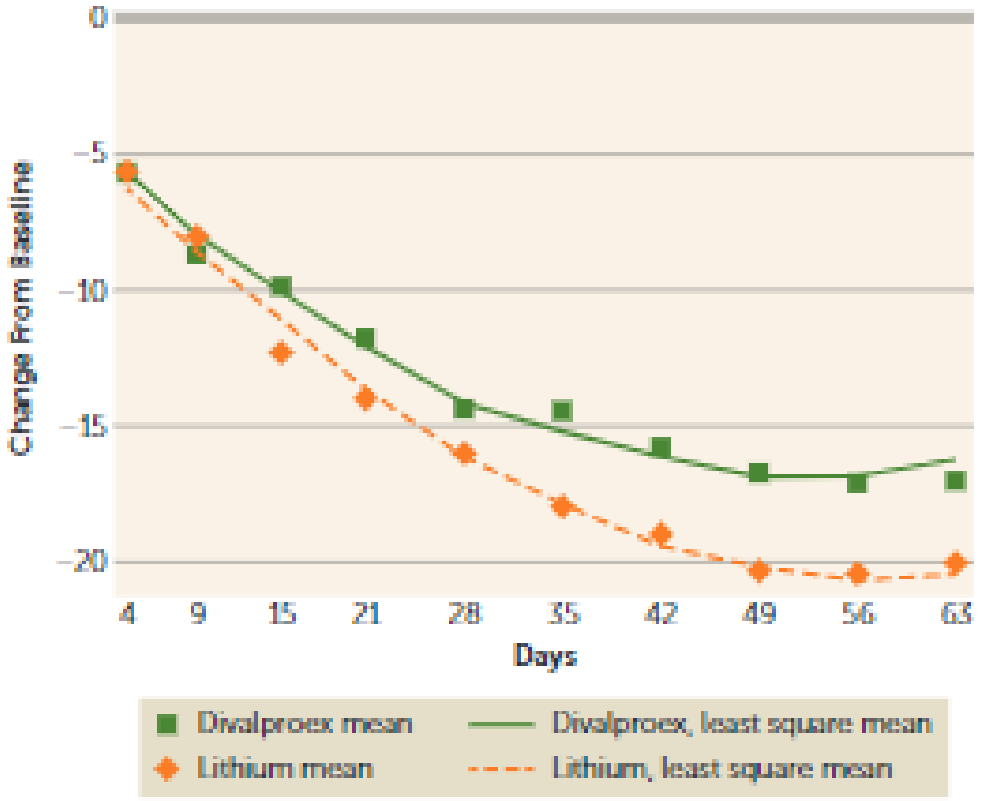
Goldberg JF, Stahl SM. Practical Psychopharmacology, Cambridge Univ. Press, 2021.

Lithium or Divalproex in Geriatric Mania

N=224 manic inpatients
Treated over 9 weeks

Maximum daily dosing:
lithium=780 mg
(serum [Li+]=0.76 mEq/l;
divalproex=1200 mg/day)
(serum [valproate]= 74 µg/ml)

FIGURE 2. Change From Baseline in Young Mania Rating Scale Score in a Trial of Lithium and Divalproex for the Treatment of Mania in Older Patients With Bipolar Disorder[a]



[a] Least square means are from mixed models of change from baseline in YMRS score.

Comparable 9-week response rates with lithium (79%) or divalproex (73%)

Young RC et al. Am J Psychiatry 2017;174(11):1086-93.

Divalproex in Bipolar Disorder With Active Alcohol Use Disorder Comorbidity

52 bipolar I patients with active alcohol dependence
24-week randomized trial of divalproex + TAU vs placebo + TAU

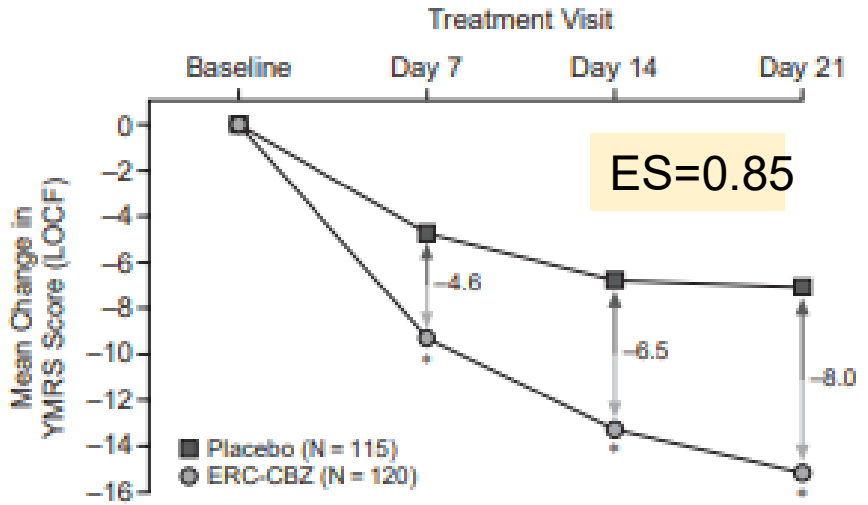
	Placebo (n=30)	Divalproex (n=29)	p
Proportion of any drinking days	0.240	0.168	0.080
Proportion of heavy drinking days	0.186	0.093	0.021
# drinks/heavy drinking day	10.2	5.6	0.018
# drinks/day	8.9	5.1	0.022

Salloum IM et al. Arch Gen Psychiatry 2005;62(1):37-45.

Carbamazepine in Bipolar Disorder

- FDA approval of extended release in mania
- Dosing begins at 200 mg PO BID, increase by 200 mg/day to max of 1600 mg/day
- Mean dose= 643 ± 349 mg/day
- No established therapeutic relevance of serum drug levels
- No maintenance data
- Marked P450 induction
- Benign leukopenia in about 10% of patients in first 3–6 months
- Aplastic anemia in 1/200,000
- Teratogenicity

Figure 1. Change in YMRS Total Scores From Baseline at Each Week by Treatment Group Using LOCF Analysis for the Intent-to-Treat Population[a]



[a]In the ERC-CBZ group, YMRS scores were 28.46 at baseline and 13.38 at end point; in the placebo group, scores were 27.93 at baseline and 20.82 at end point.
*p < .0001 compared with placebo following analysis of covariance with baseline score as covariate.
Abbreviations: ERC-CBZ = extended-release carbamazepine capsules, LOCF = last observation carried forward, YMRS = Young Mania Rating Scale.

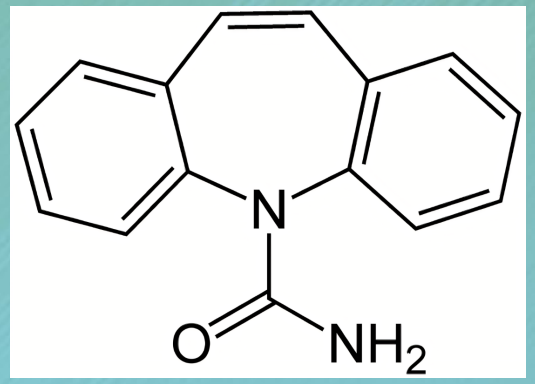
Most common adverse effects: dizziness, somnolence, nausea, ataxia

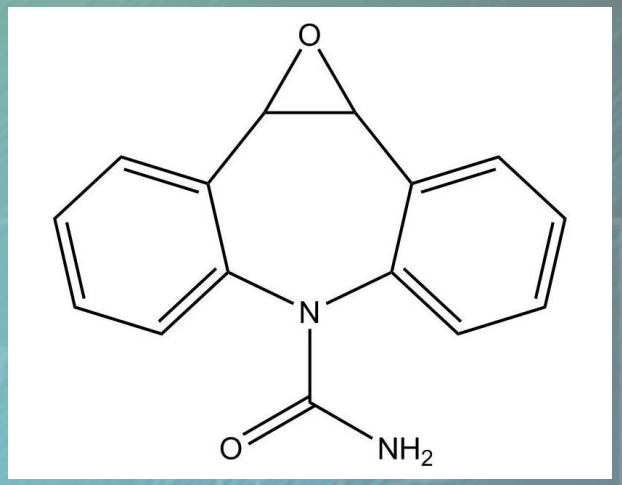
Weisler RH et al. J Clin Psychiatry 2005;66(3):323-30.

What About Oxcarbazepine in Bipolar Disorder?

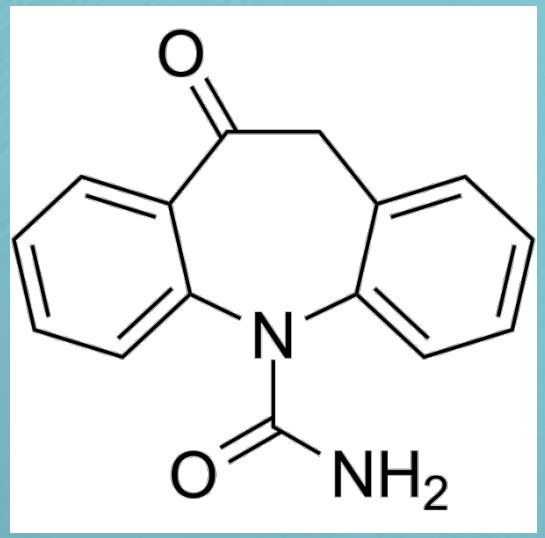
- Keto analogue of carbamazepine
- Spares formation of the epoxide metabolite of carbamazepine

carbamazepine

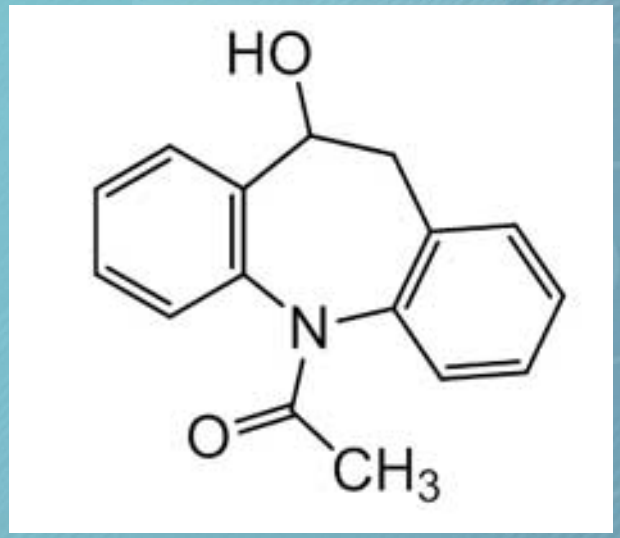




oxcarbazepine



Monohydroxy derivative oxcarbazepine

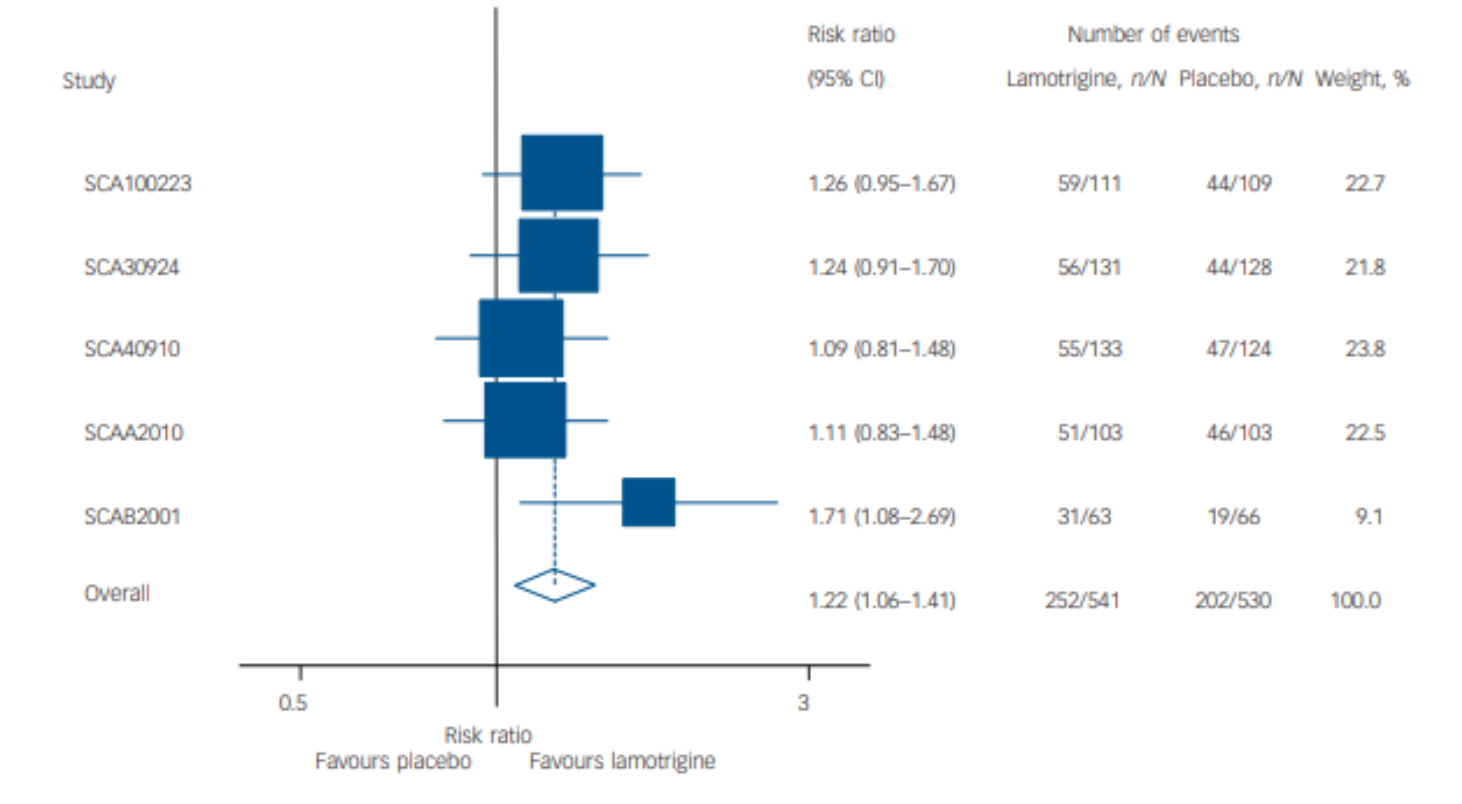


NO (+) PLACEBO-CONTROLLED TRIALS IN MANIA

Lamotrigine

- Inhibits voltage-sensitive Na^+ channels, thereby decreasing excitatory neurotransmitter release (glutamate, aspartate)
- No known efficacy in acute mania
- Off-label dosing in acute depression:
  - 25 mg/day x 2 weeks then 50 mg/day x 2 weeks then 100 mg/day x 1 week then 200 mg/day
- No known therapeutic relevance of serum drug levels
- Metabolized by glucuronidation, therefore levels double in presence of divalproex

Why Lamotrigine Failed in Trials for Acute Bipolar Depression



Pooled analysis of five lamotrigine RCTs in acute bipolar depression [1]

	Moderate Baseline Severity	High Baseline Severity
Lamotrigine Response Rate	48%	45%
Placebo Response Rate	45%	30%

[1] Geddes JR et al. Br J Psychiatry 2009;194(1):4-9.

Non-Mood Stabilizer Anticonvulsants

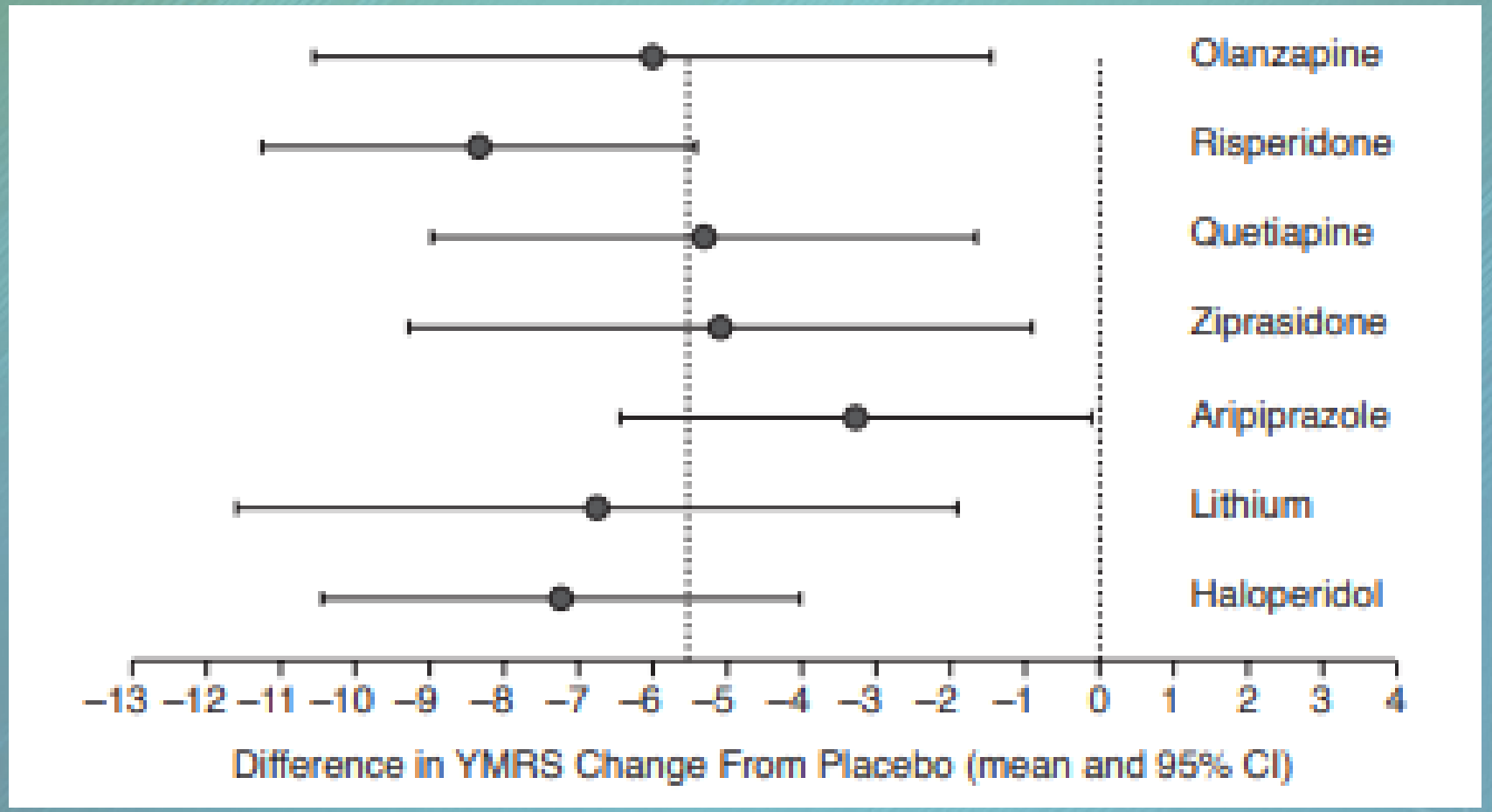
	GAD	Social Anxiety*	Neuropathic Pain	Migraine	Insomnia*	RLS	Weight Loss/Binge Eating	Alcohol Use Disorder
Gabapentin	√ *	√ *	√	√ *	√ *	√		
Pregabalin	√ *	√ *	√					
Topiramate				√			√ *	√ *
Zonisamide							√ *	
Levetiracetam	?							

Abbreviation: RLS=restless legs syndrome

Goldberg JF, Stahl SM. Practical Psychopharmacology, Cambridge Univ. Press, 2021.

Atypical Antipsychotics in Acute Mania

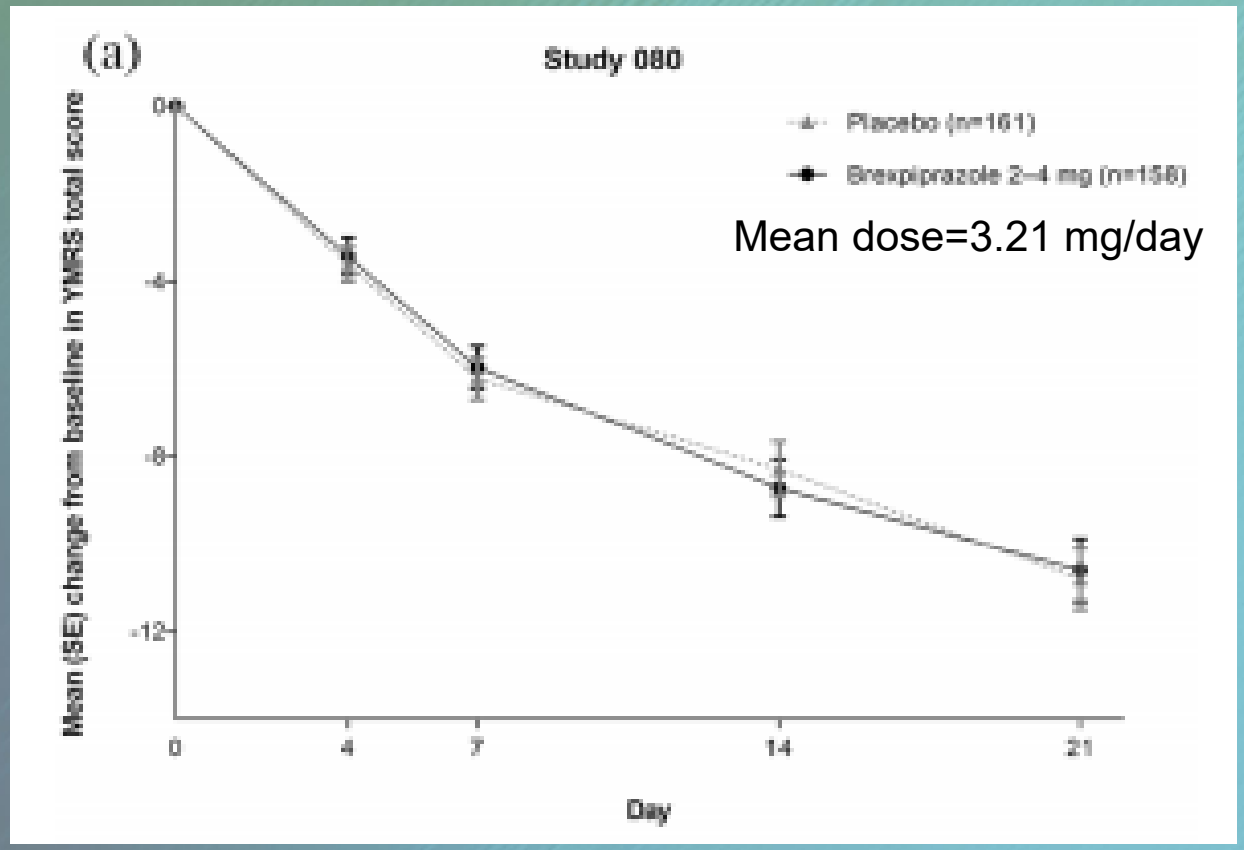
Overall, no significant differences in magnitude of antimanic effects among second-generation antipsychotics

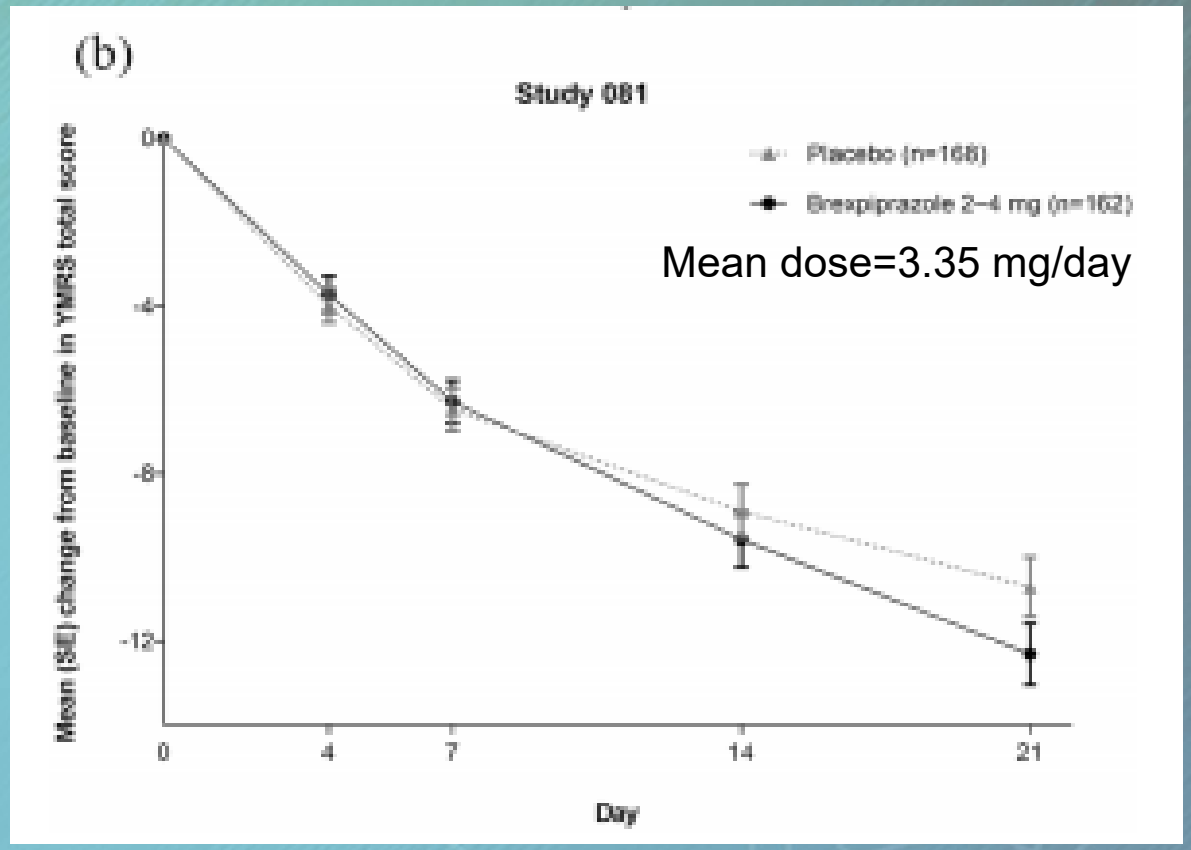


Perlis RH et al. J Clin Psychiatry 2006;67(4):509-16.

Not All Antipsychotics Treat Mania

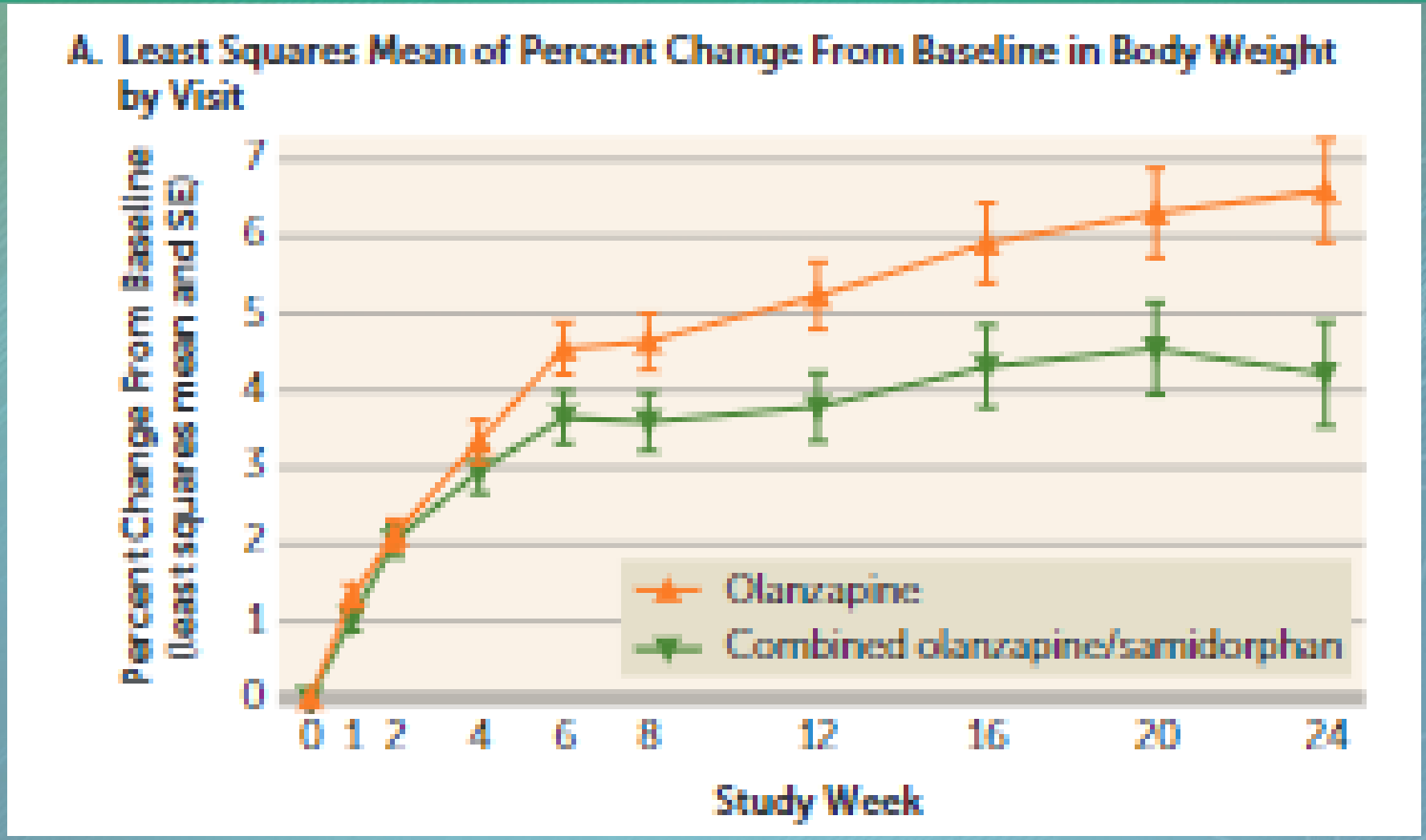
Brexpiprazole: Two Negative Randomized Trials in Bipolar Mania





Vieta E et al. J Psychopharmacol 2021;35(8):971-82.

Tolerability: Olanzapine/Samidorphan in Bipolar I Mania or Maintenance Therapy



6.59%

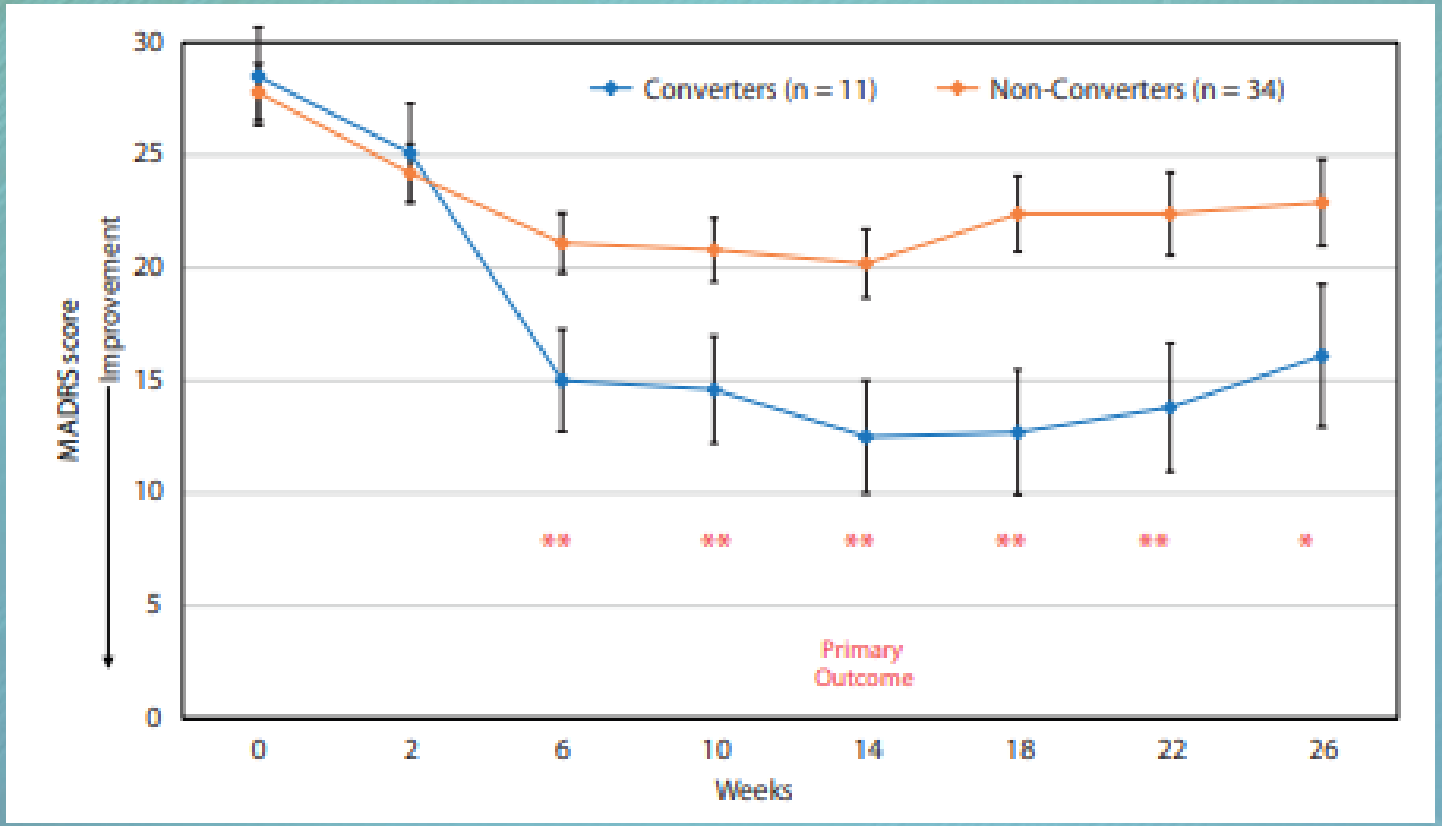
4.21%

Correll CU et al. Am J Psychiatry 2020;177(12):1168-78.

Adjunctive Metformin Improves Insulin Resistance and Depressive Symptoms

TRIO-BD Study: 45 bipolar patients randomized to metformin (titrated to 1000 mg twice a day) or placebo for 14 weeks

Half of metformin recipients no longer met criteria for insulin resistance



Calkin CV et al. J Clin Psychiatry 2022;83(2):21m13022.

Higher Risk for Post-Mania Depression With First-Generation Antipsychotics

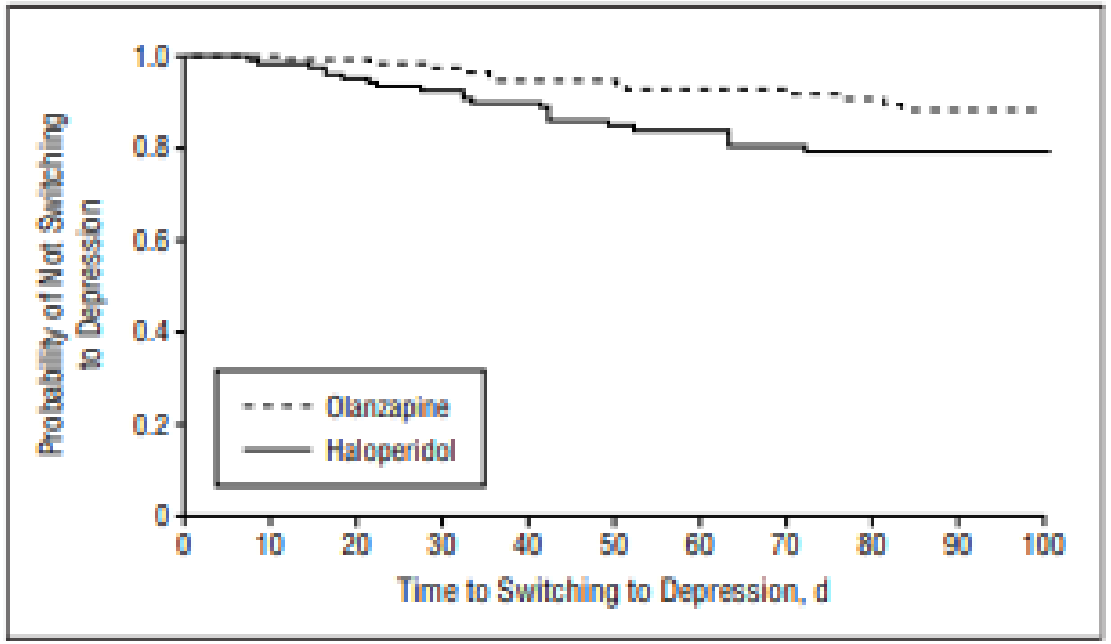


Figure 2. Time to switch to depression for patients who were not clinically depressed at baseline (21-item Hamilton Rating Scale for Depression [HAMD-21] score ≤8). Time to switch into depression (HAMD-21 score ≥15) was significantly longer (log-rank test $\chi^2_1=4.1$, $P=.04$) for the olanzapine group (dashed line) compared with the haloperidol group (solid line). During the 12-week period, 22 haloperidol- and 12 olanzapine-treated patients switched into depression. The number of patients who experienced a switch to depression by days 15, 30, and 60 were 3, 9, and 18 for the haloperidol group and 1, 3, and 8 for the olanzapine group, respectively.

Tohen M et al. Arch Gen Psychiatry 2003;60(12):1218-26.

FDA-Approved Treatments for Bipolar Depression

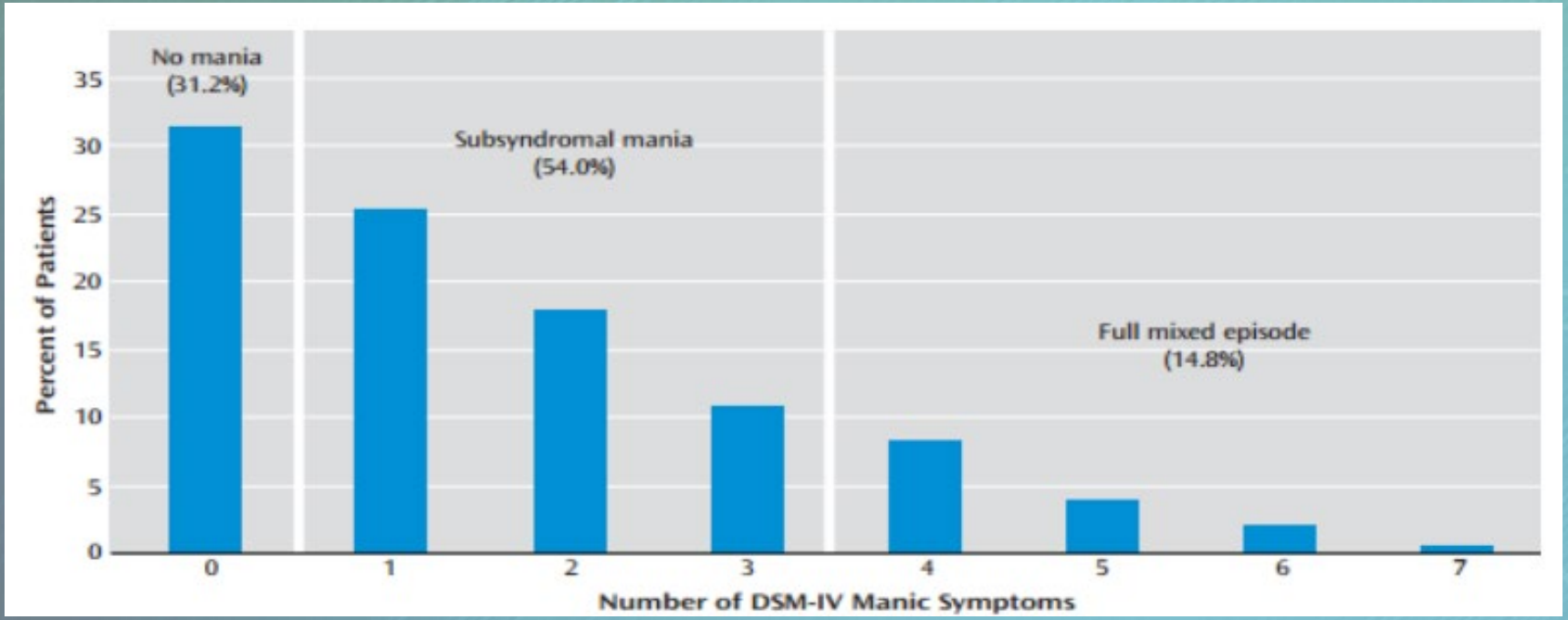
Medication	Dosing	Bipolar I	Bipolar II	NNT (Response)	NNT (Remission)*	Maintenance Data?
Olanzapine-fluoxetine combination	6/25, 6/50 or 12/25, 12/50 mg/day	Yes	No	4	5	No
Quetiapine (IR or XR)	300 or 600 mg/day	Yes	Yes	6	6	Yes
Lurasidone	20–120 mg/day	Yes	No	5	7	No
Cariprazine	1.5 or 3 mg/day	Yes	No	10	11	No
Lumateperone	42 mg/day	Yes	Yes	7	16	No

* remission = score ≤ 10 for cariprazine or ≤ 12 others

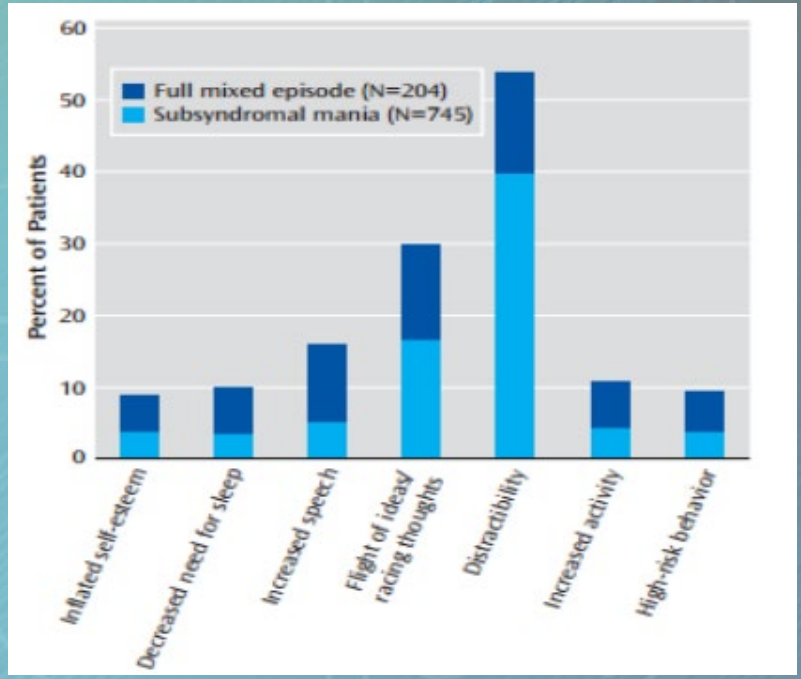
Citrome L. Int J Clin Pract 2019;73(10):e13397; and calculated from Calabrese JR et al. Am J Psychiatry 2021;178(12):1098-106.

Most Syndromally Depressed Bipolar Patients Have Subthreshold Mixed Features

DSM-IV manic symptoms during an index bipolar depressive episode: STEP-BD (n=1380)

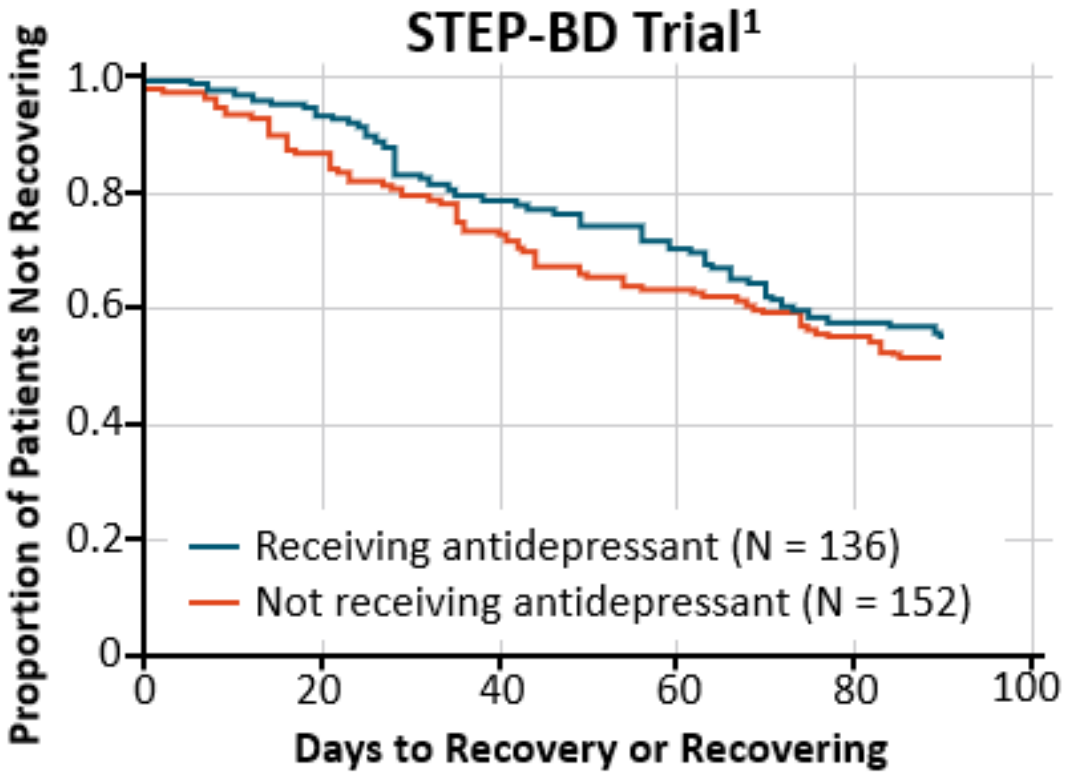


Specific mania symptoms during an index bipolar depressive episode

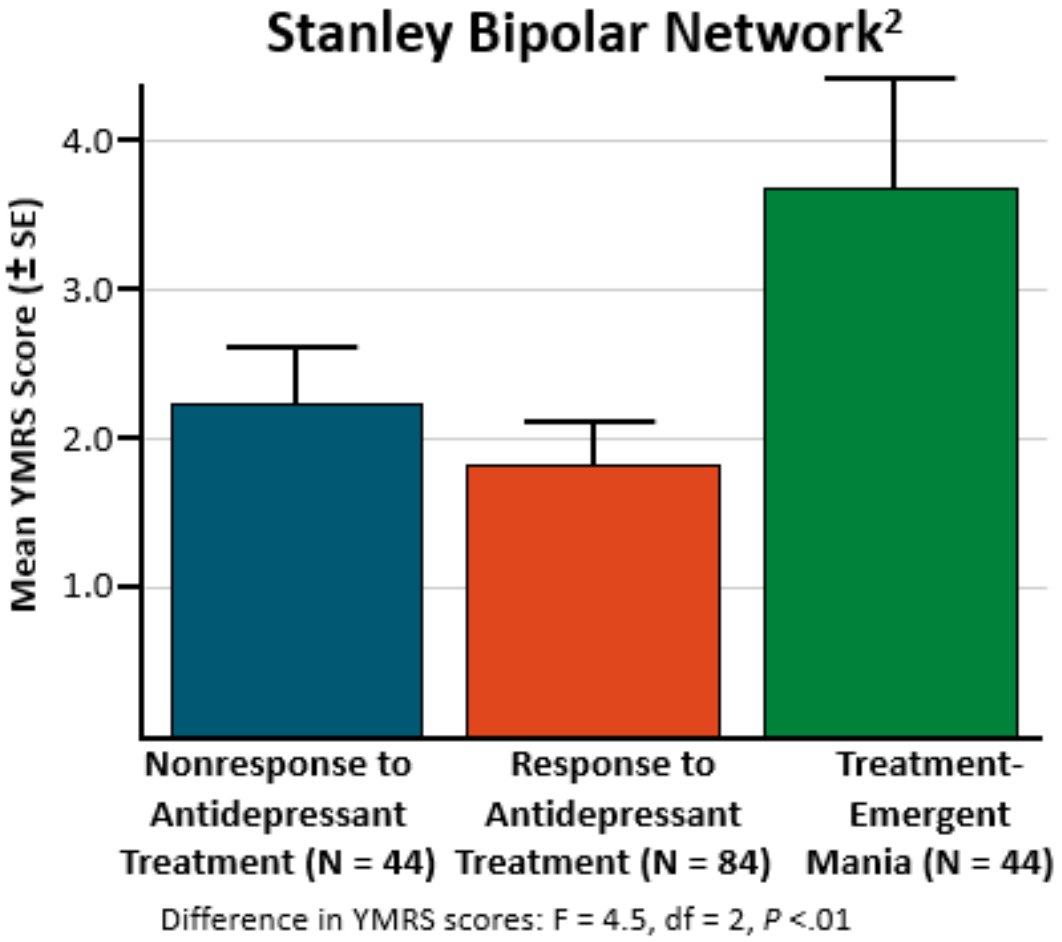


Goldberg JF et al. Am J Psychiatry 2009;166(2):173-81.

Antidepressants Exacerbate Low-Grade Mania Symptoms in Bipolar Depression



Interaction effect: antidepressant use × number of mania symptoms at baseline = higher YMRS score after 3 mo (P = .003)

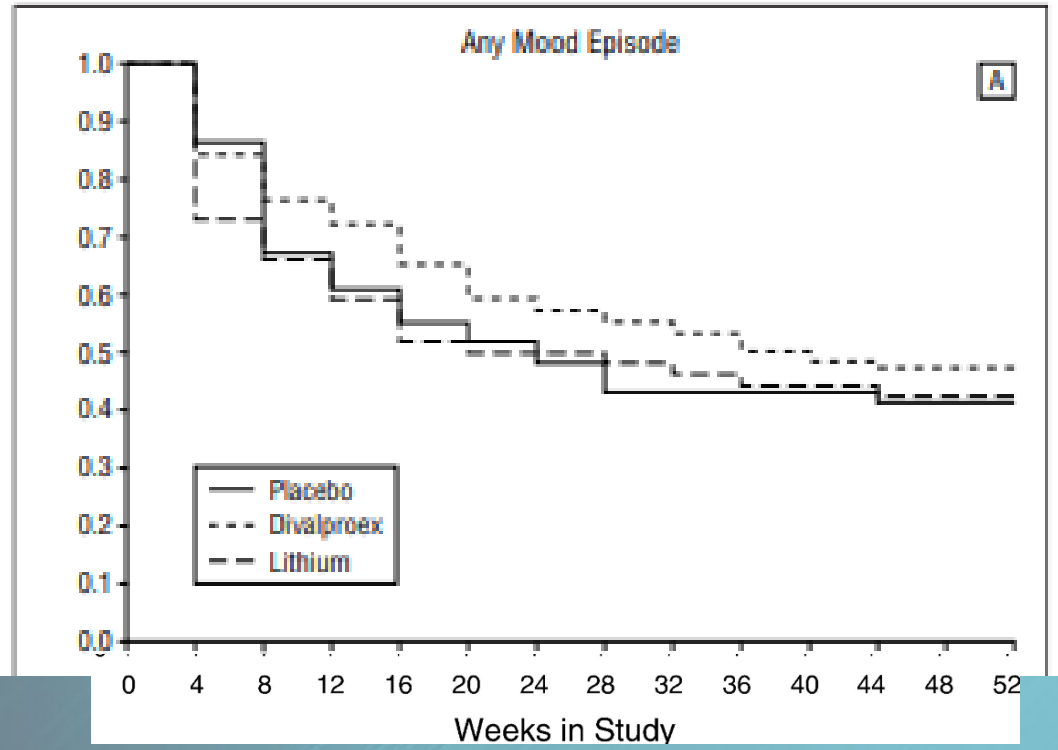


Difference in YMRS scores: F = 4.5, df = 2, P <.01

[1] Goldberg JF et al. Am J Psychiatry 2007;164(9):1348-55; [2] Frye MA et al. Am J Psychiatry 2009;166(2):164-72.

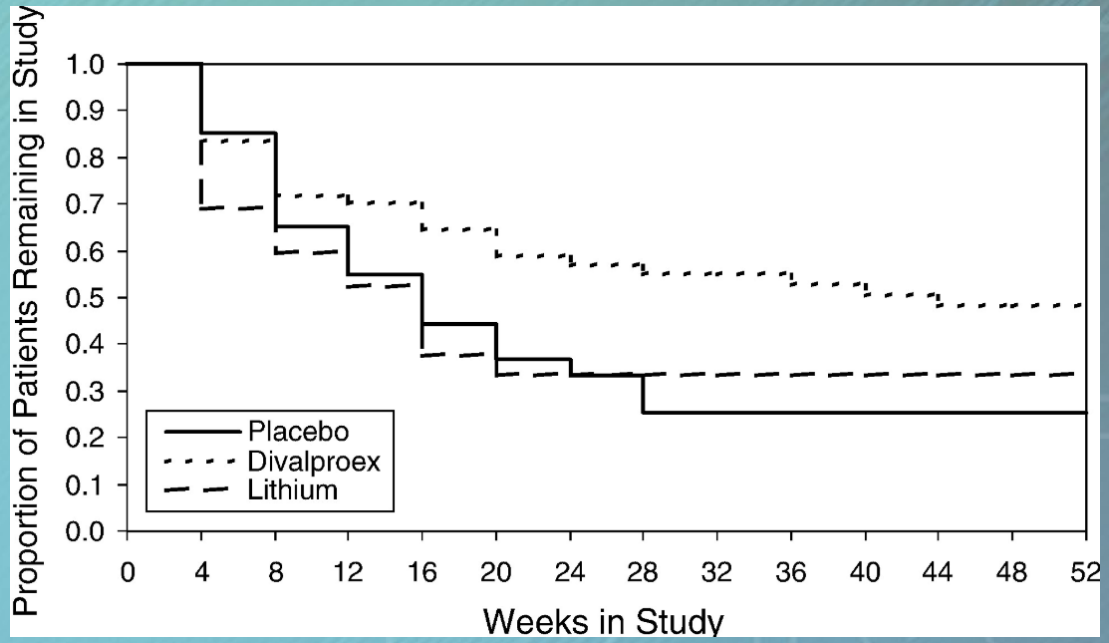
Divalproex Failed Maintenance Trial: Efficacy When Enriched for Acute Antimanic Response

All-comers independent of acute antimanic response [1]



Log rank test: divalproex vs. lithium: p=0.06
divalproex vs. placebo: p=0.33

Acute divalproex responders in acute mania [2]



Log rank test: divalproex vs. lithium: p=0.04
divalproex vs. placebo: p=0.05

[1] Bowden CL et al. Arch Gen Psychiatry 2000;57(5):481-9; [2] McElroy SL et al. J Affect Disord 2008;107(1–3):127-33.

Maintenance Pharmacotherapy

- BALANCE Study: 330 bipolar I patients randomized to open-label lithium, divalproex, or both for up to 24 months
- Primary outcome: time until intervention for a new mood episode:

	Combination	Lithium	Divalproex
New intervention for mood episode	54%	58%	69%
p-value	--	0.27	0.0023

	Combination	Lithium	Divalproex
New treatment for mania	27%	36%	45%
p-value	--	0.10	0.0034

	Combination	Lithium	Divalproex
New treatment for depression	35%	32%	45%
p-value	--	0.63	0.10

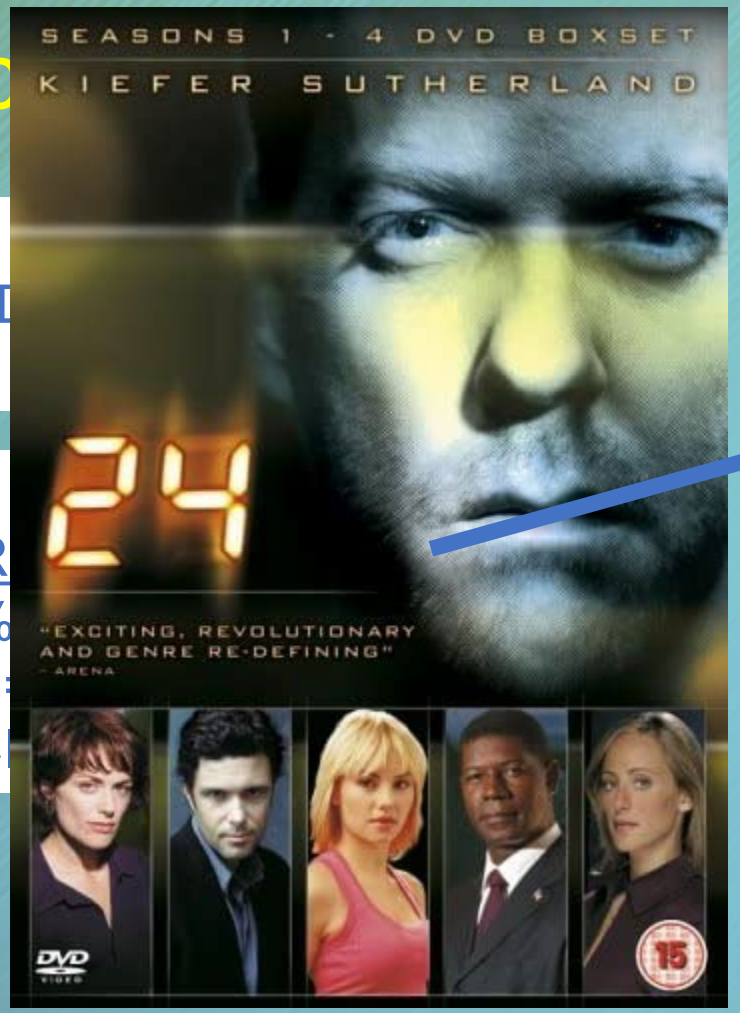
The Balance Investigators and Collaborators. Lancet 2010;375(9712):385-95.

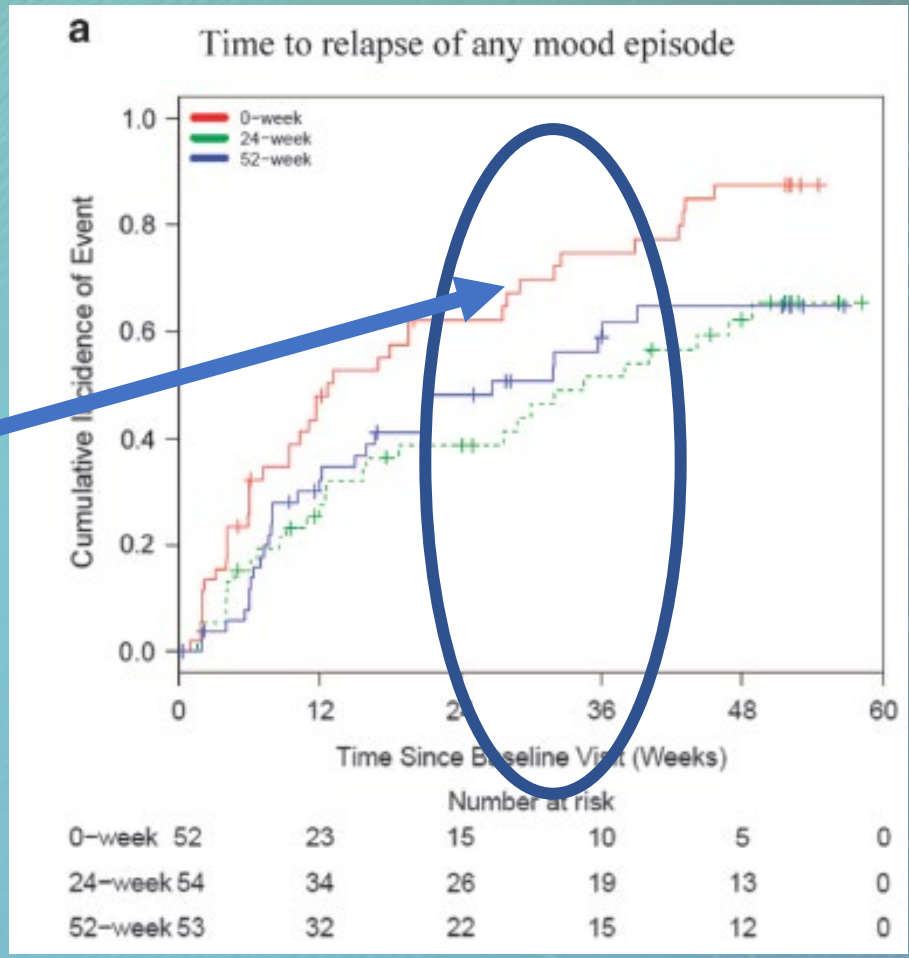
How Long to Continue an Adjunctive Second-Generation Antipsychotic After Acute Mania?

The magic

N=159 BP I manic
treated with Li+ or D
plus olanzapine or

After 24 weeks:
Relapse Hazard R
Overall=0.53 (95%
RIS=1.85 (95% CI
OLZ=0.48 (95% CI





Yatham LN et al. Mol Psychiatry 2016;21(8):1050-6.

Second-Generation Antipsychotics and Bipolar Maintenance

SGAs	Efficacy	Common Adverse Effects
Aripiprazole	Oral [1,2] or LAI [3] prevention of mania but not depression	Headache, nausea, akathisia, weight gain
Asenapine	1 (+) 26-week maintenance trial; prevented mania or depression [4]	Somnolence, akathisia, sedation
Lurasidone	1 (-) 28-week maintenance trial (post hoc: depression prophylaxis if index episode was depressive) [5]	Nausea, somnolence
Olanzapine	3 (+) RCTs (vs. placebo,[6] lithium,[7] or divalproex[8])	Weight gain, somnolence
Quetiapine	2 (+) adjunctive trials, comparable prevention of mania or depression [9]	Weight gain, sedation
Risperidone	LAI (prevention of mania but not depression) [10]	Weight gain
Ziprasidone	1 (+) adjunctive trial [11]	Tremor

[1] Keck PE Jr et al. J Clin Psychiatry 2007;68(10):1480-91; [2] Keck PE et al. J Affect Disord 2009;112(1-3):36-49; [3] Calabrese JR et al. J Clin Psychiatry 2017;78(3):324-31; [4] Szegedi A et al. Am J Psychiatry 2018;175(1):71-9; [5] Calabrese JR et al. Eur Neuropsychopharmacol 2017;27(9):865-76; [6] Tohen M et al. Am J Psychiatry 2006;163(2):247-56; [7] Tohen M et al. Am J Psychiatry 2005;162(7):1281-90; [9] Suppes T et al. Depress Anxiety 2013;30(11):1089-98; [10] Quiroz JA et al. Biol Psychiatry 2010;68(2):156-62; [11] Bowden CL et al. J Clin Psychiatry 2010;71(2):130-7.

Factors Associated With Medication Nonadherence in Bipolar Disorder

Present in 20–60% of individuals with bipolar disorder [1]

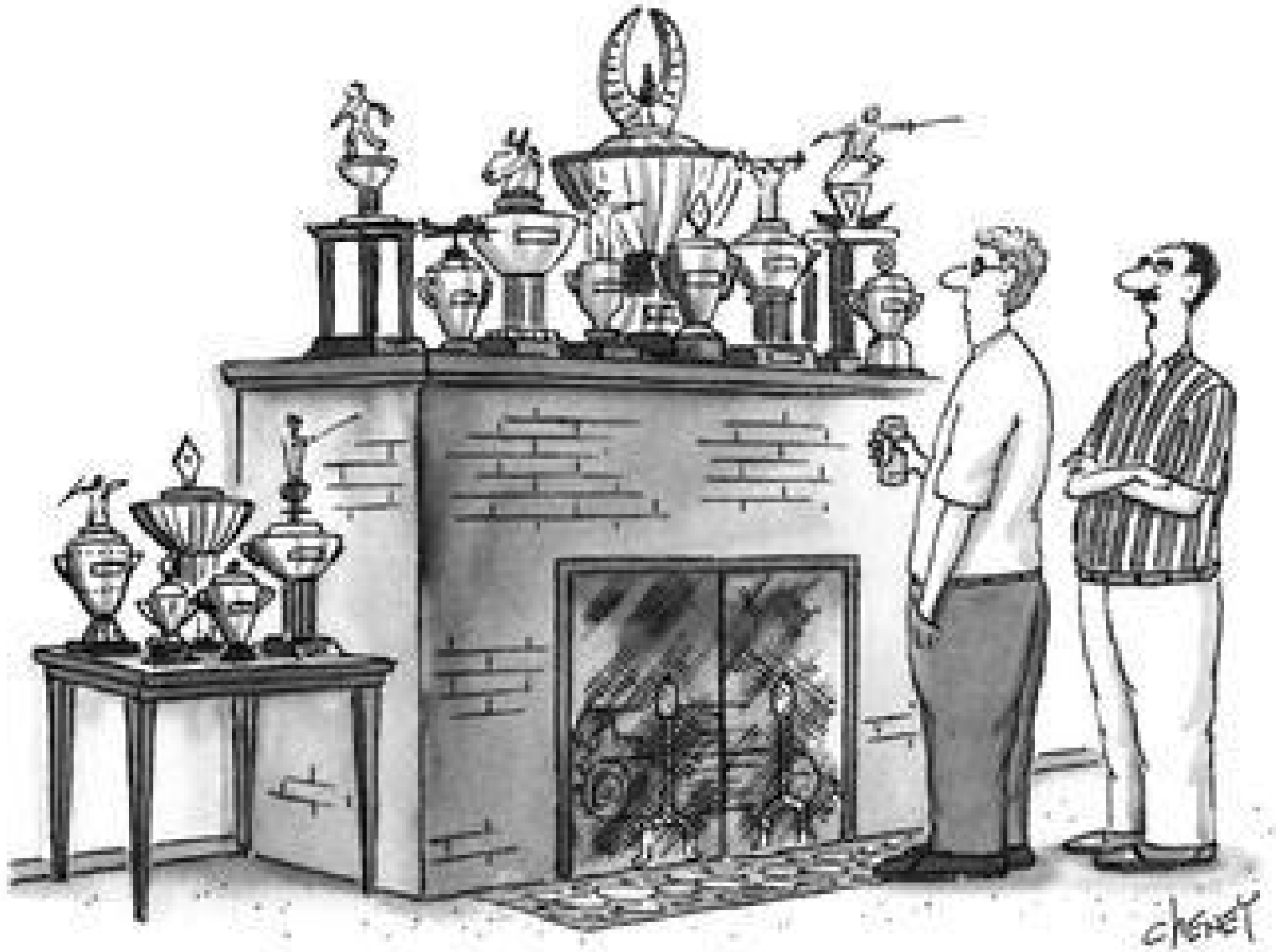
Factors associated with poor medication adherence: [2,3]

- Forgetting to take medications
- Ethnic/racial minorities
- Substance use comorbidity
- Fear of adverse effects
- Unsupportive social networks
- Skepticism about the need for treatment

[1] Sajatovic M et al. J Clin Psychiatry 2018;79(6):17m12036; [2] Sajatovic M et al. Compr Psychiatry 2011;52(3):280-7; [3] Clatworthy J et al. J Affect Disord 2009;116(1-2);51-5.

Summary

- Devote sufficient attention to making a clear diagnosis in mood disorder patients, and recognize factors that can cause delayed diagnoses or appropriate treatment initiation
- Lithium, anticonvulsant drugs, and second-generation antipsychotics vary in the extent to which they exert antimanic, antidepressant, or other psychotropic properties
- Recognize the evidence base supporting specific medications for distinct clinical roles in patients with bipolar disorder
- Devise clinical profiles for judging the likelihood of response to a given psychotropic agent for bipolar disorder patients, taking into account polarity prominence, episode number, comorbidities, past response, and tolerability of adverse effects



"Those? Oh, just a few souvenirs from my bipolar-disorder days."

Post-test Question 1

According to findings from the BALANCE study for maintenance pharmacotherapy of bipolar I disorder, which one of the following statements is true?

1. Valproate monotherapy is comparable to lithium monotherapy in preventing the time until any mood episode
2. Valproate monotherapy yielded higher relapse rates than did either lithium monotherapy or lithium plus valproate
3. Relapse into depression was more common with lithium or valproate monotherapy than with the combination of both
4. Lithium use in the elderly causes poor balance and therefore generally should be avoided

Post-test Question 2

Wanda is a 33-year-old woman diagnosed with bipolar II depression, now presenting with her third lifetime depression and one prior hypomania 8 years earlier. Which one of the following is an FDA-approved treatment for her current condition?

1. Lurasidone
2. Lumateperone
3. Cariprazine
4. Lamotrigine

Post-test Question 3

For a bipolar disorder patient with poor adherence related to concerns about weight gain from medications, which one of the following statements would be true?

1. Adding metformin can reverse insulin resistance in about half of bipolar patients with insulin resistance, which can in turn lead to improved mood
2. Adding samidorphan to olanzapine can cause an approximate 6.9% loss of initial body weight
3. Carbamazepine is a relatively weight-neutral FDA-approved maintenance pharmacotherapy for bipolar disorder
4. Stopping an adjunctive atypical antipsychotic within 3 months of an index manic episode can minimize weight gain without increasing risk for affective relapse