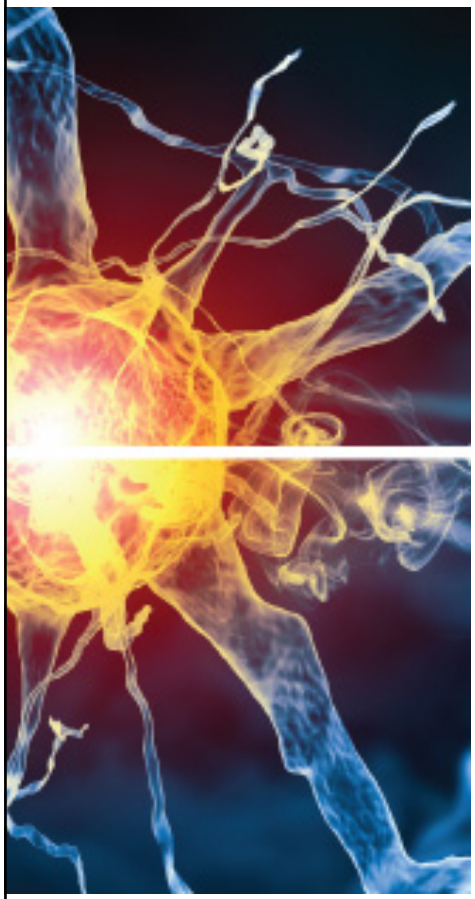
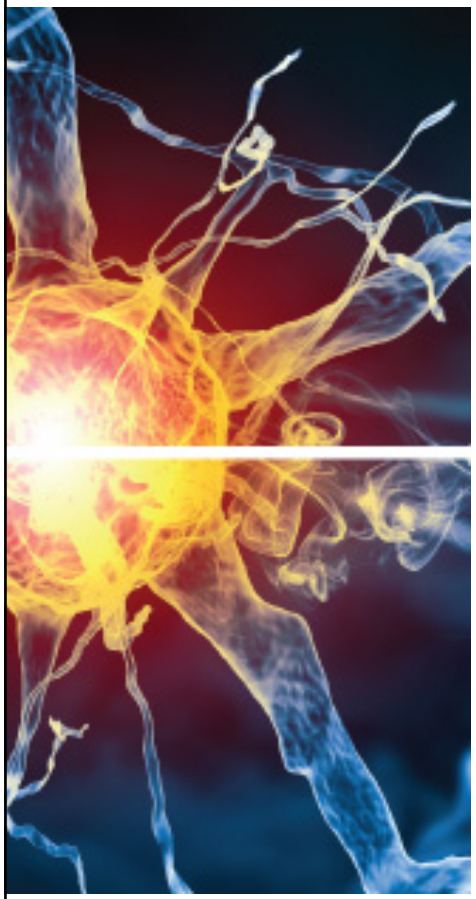


Optimal Management of Bipolar Disorder



Mark A. Frye, MD

Professor and Chair
Department of Psychiatry & Psychology
Stephen & Shelly Jackson Family Professorship in Individualized Medicine
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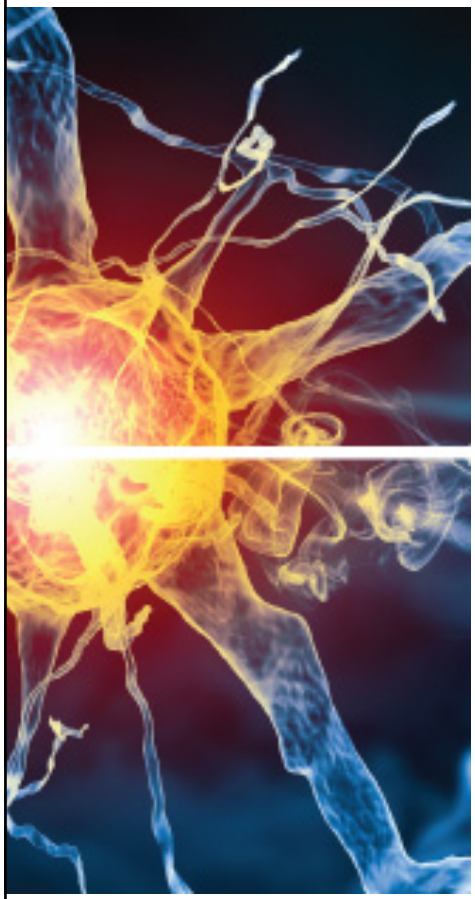
Rochester, MN

Mark A. Frye, MD

Disclosures

- ***Research/Grants***: AssureRX Health Inc.; Janssen Research & Development, LLC; Mayo Foundation for Medical Education and Research; Myriad Genetics; National Institute on Alcohol Abuse and Alcoholism (NIAAA); National Institute of Mental Health (NIMH); Pfizer Inc.
- ***Consultant***: Janssen Research & Development, LLC; Mitsubishi Tanabe Pharma Corporation; Myriad Genetics; Neuralstem Inc.; Sunovion Pharmaceuticals Inc.; Supernus Pharmaceuticals, Inc.; Teva Pharmaceuticals USA
- ***Other Financial Interest***: Mayo Clinic has a financial interest in AssureRX and the technology referenced in this publication/presentation



1 Learning Objective

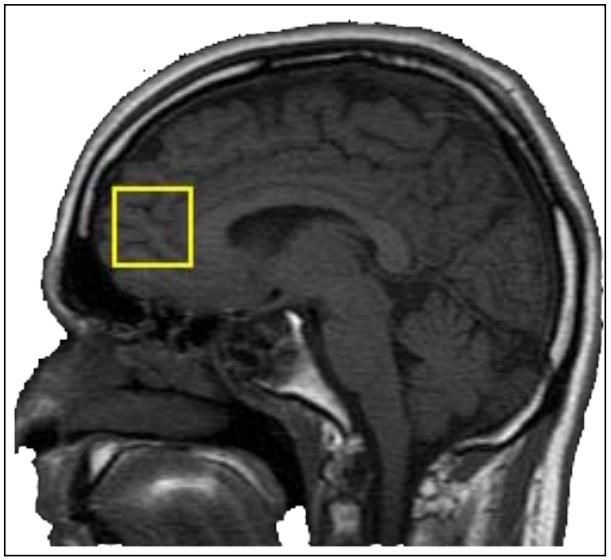
Integrate the evidence-based, best-practice options for the pharmacological and non-pharmacological management of patients with bipolar disorder.

Agents FDA-Approved for Acute Mania

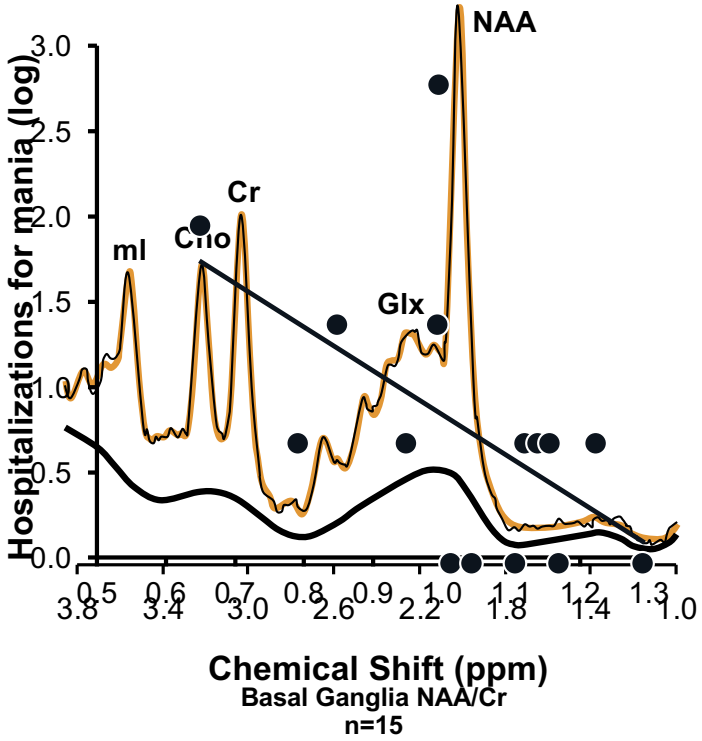
- Aripiprazole, Asenapine, Olanzapine, Risperidone Quetiapine, Ziprasidone, Cariprazine (dopamine D2/D3 receptor partial agonist), Chlorpromazine all FDA approved for mania
- Carbamazepine ER and Divalproex Sodium all FDA approved for mania
- Lithium all FDA approved for mania
- Adasuve® (inhaled loxapine) is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults

[Package Inserts]. Drugs@FDA Website.

Mania Matters
Episodes Associated With Neuroanatomic Change?



T1-weighted sagittal MRI anterior cingulate/medial prefrontal cortex
PRESS 1H-MRS (TR/TE = 3s/30ms voxel size 3x3x3 cm^3)

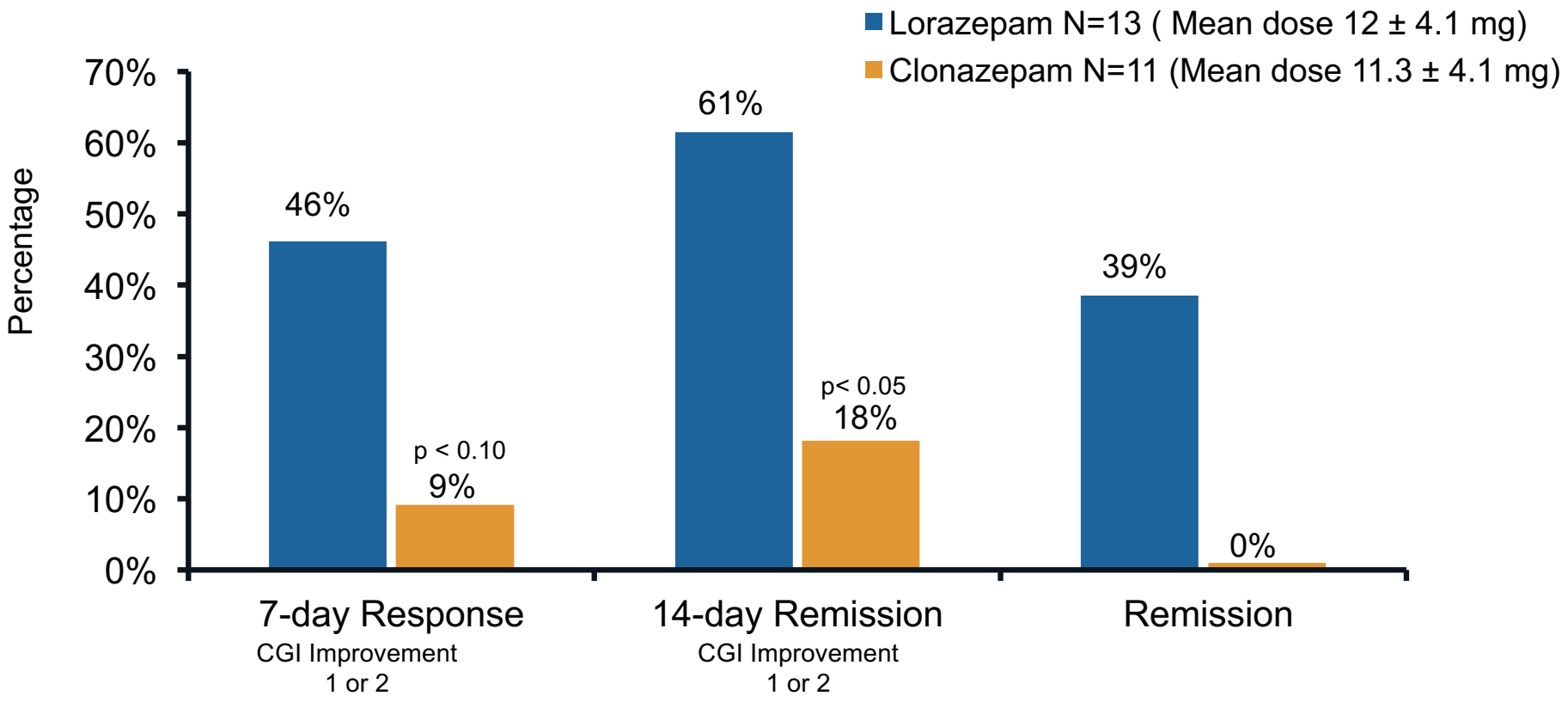


Frye M, et al. *Psychiatry Res*. 2007;154(3):259-65.; Tsai G, et al. *Prog Neurobiol* 1995;46(5):531-40.; Altshuler LL. *Biol Psychiatry*. 1993;33(8-9):563-5.

Mania is an EMERGENCY

- Need rapid, safe stabilization
- Reduction of behavioral agitation
- Sleep restoration and management of withdrawal from drugs and alcohol
- Antimanic treatment based on
  - Manic episode (mixed vs. manic)
  - Rapid cycling or psychotic symptoms
  - Patient's medication history
  - Presence of comorbidities
  - Willingness to accept therapy

Double-Blind Comparison of Clonazepam vs Lorazepam in Acute Mania (Monotherapy 14 days, N = 24)



Lorazepam and clonazepam are not FDA approved for bipolar mania.

Bradwejn J, et al. *J Clin Psychopharmacol.* 1990;10(6):403-408.

FDA Approved Bipolar Disorder Treatments*

Agent	Manic	Mixed	Depression	Maintenance
Aripiprazole	+	+	–	+
Asenapine	+	+	–	–
Cariprazine	+	+	–	–
Lurasidone	–	–	+	–
Olanzapine	+	+	–	+
Olanzapine/Fluoxetine	–	–	+	–
Quetiapine/XR	+	+	+	+
Risperidone (Oral / IM)	+	+	–	+ (IM)
Ziprasidone	+	+	–	+
Chlorpromazine	+	–	–	–
Carbamazepine ER	+	+	–	–
Divalproex DR/ER	+	+	–	–
Lamotrigine	–	–	–	+
Lithium	+	–	–	+

*Aripiprazole, Asenapine, Olanzapine, Quetiapine, Risperidone indication as monotherapy and adjunct to Li or DVPX and with / without psychosis

Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: a Multiple-treatments Meta-analysis

- Systematic review of 68 randomized trials of pharmacotherapy for acute mania in adults (16,073 patients)
- Any-cause early discontinuation is proxy for "acceptability"
- Multiple treatments meta-analysis (accounts for direct and indirect comparisons)

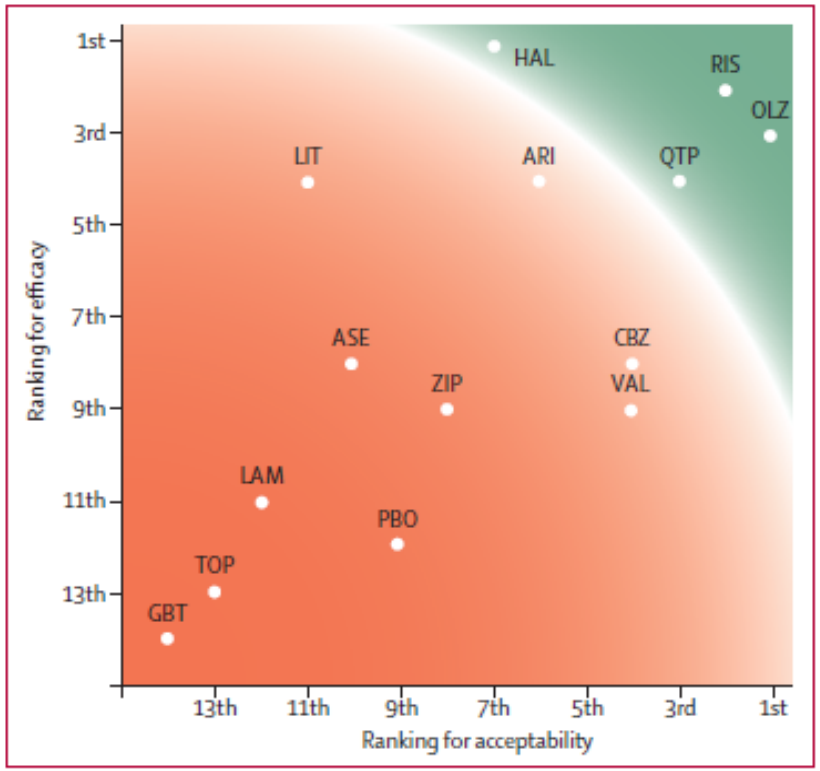
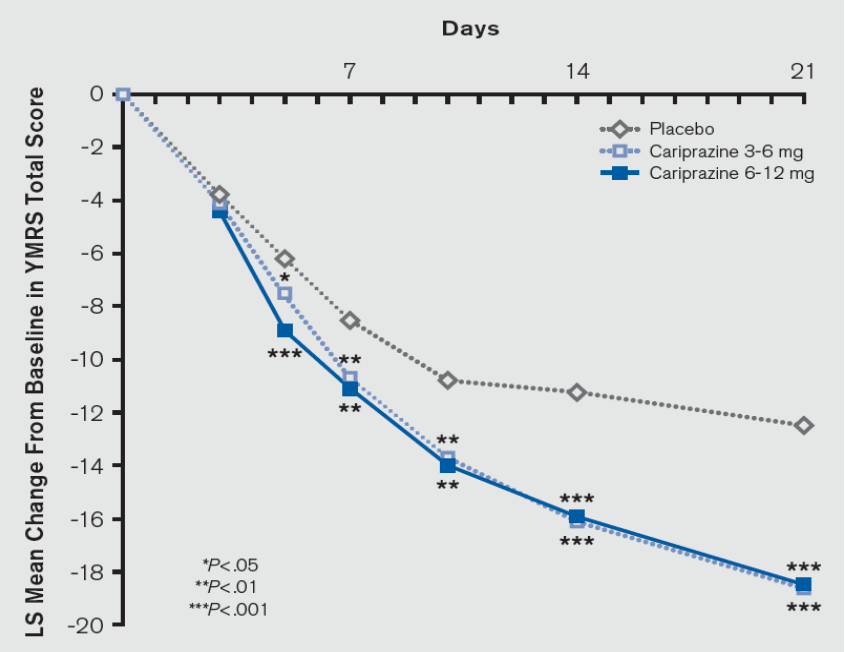


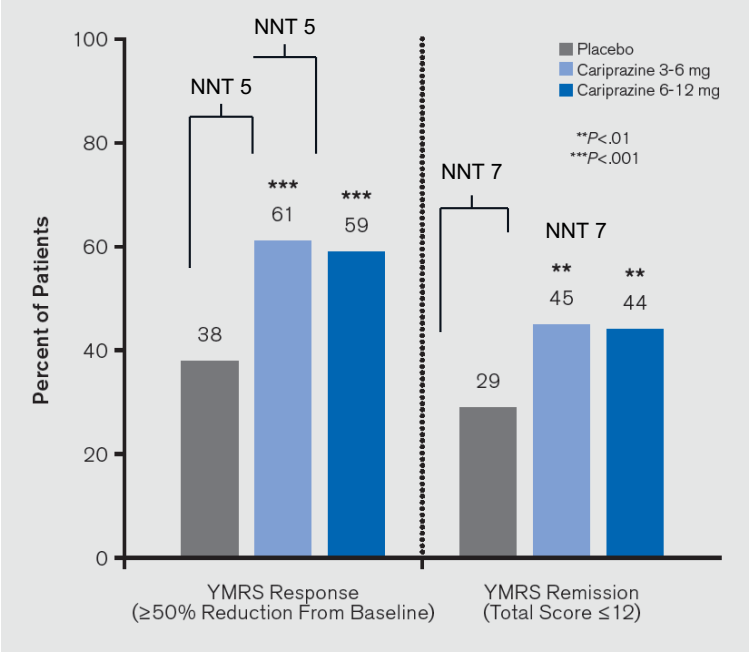
Figure 6: **Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate**

Cipriani A, et al. *Lancet* 2011;378(9799):1306-15.

Cariprazine for Acute Mania Associated With Bipolar I Disorder

Randomized, DB, PLC-controlled trial (2010-2011); cariprazine 3-6 mg/d vs. cariprazine 6-12 mg/d vs. PLC over 3 weeks; 497 patients with BP-I manic or mixed episodes; primary endpoint – change YMRS total score; secondary endpoints – response, remission

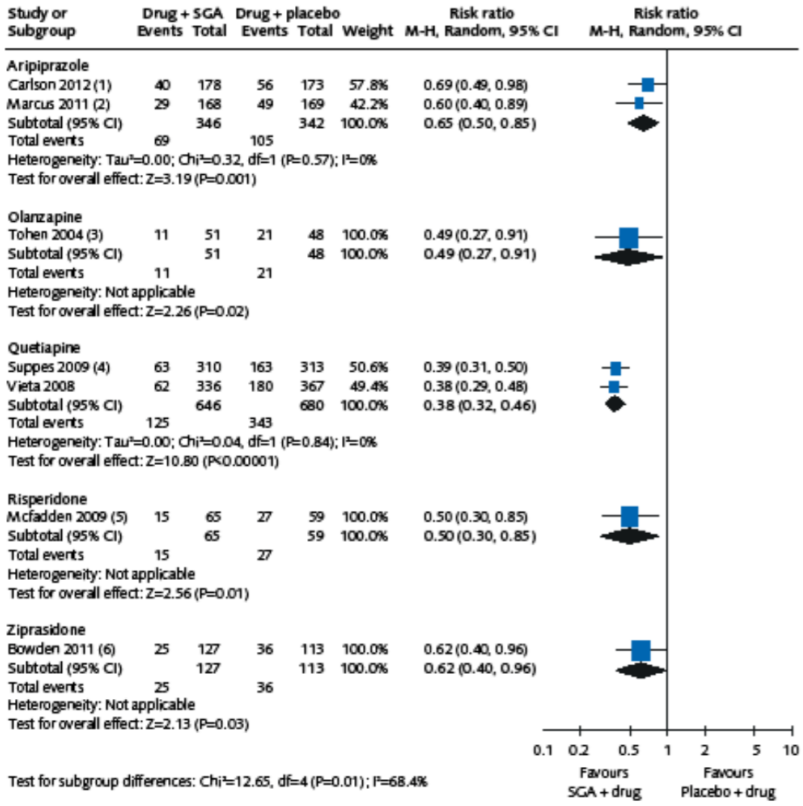




Calabrese JR, et al. *J Clin Psychiatry.* 2015;76(3):284-292.

Meta-analysis Prophylaxis with Add-on SGAs

- Prevented Relapse to any mood episode:
  - Aripiprazole (RR 0.65, 95% CI 0.50-0.85)
  - Quetiapine (RR 0.38, 95% CI 0.32-0.46)
  - Ziprasidone (RR 0.62, 95% CI 0.40-0.96)
- Prevented Relapse to depression:
  - Quetiapine (RR 0.38, 95% CI 0.29- 0.49)
  - Prevented Relapse to mania:
  - Aripiprazole ((RR 0.46, 95% CI 0.26-0.80)
  - Quetiapine (RR 0.39, 95% CI 0.30-0.52)



Lindstrom L, et al. *Journal of Affective Disorders*. 2017;213:138-150.

Atypical Antipsychotics in Acute Mania

Pros

- As a class, effective in acute mania and mixed episodes
- Rapid control of acute mania/mixed, rapid cycling, psychosis/no psychosis
- Sustained improvement of symptoms

Cons

- Tardive dyskinesia, neuroleptic malignant syndrome
- Weight gain, related dysmetabolic effects

Tarr GP, et al. *J Affect Disord*. 2011;134(1-3):14-19.

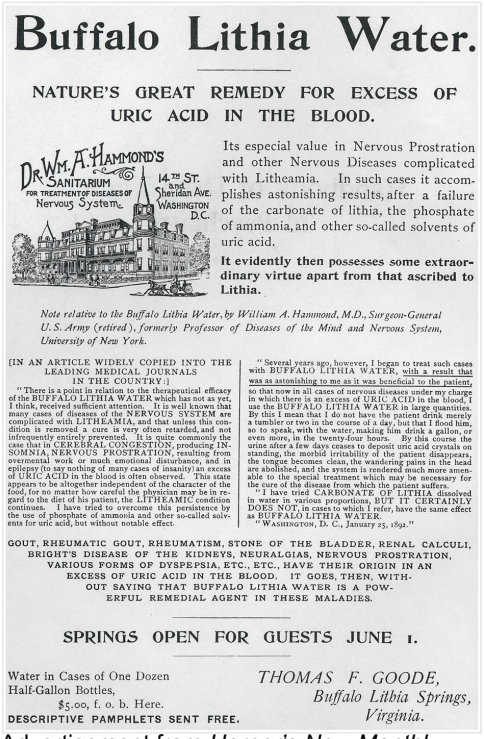
Yildiz A, et al. *Neuropsychopharmacology*. 201136(2):375-389.

Typical Antipsychotics in Acute Mania

- Pros
  - Efficacious for acute mania
  - Haloperidol may be more rapidly efficacious than olanzapine, quetiapine, ziprasidone
- Cons/adverse effects
  - Acute EPS, tardive dyskinesia, akathisia, neuroleptic malignant syndrome
- Negative impact on course of illness
  - ↑ post-mania depressive symptom severity
  - ↑ frequency of major depressive episodes

Vieta E. *J Clin Psychiatry.* 2010;71(10):e26.; Muralidharan K, et al. *J Affect Disord*. 2013;150(2):408-14.; Goikolea M, et al. *Eur Neuropsychopharmacol*. 2013;23(4):305-16.; Kane JM. *J Clin Psychiatry.* 1999;60 Suppl 5:43-7.

Lithium in Acute Mania



Buffalo Lithia Water.

NATURE'S GREAT REMEDY FOR EXCESS OF URIC ACID IN THE BLOOD.

DR. WM. A. HAMMOND'S SANITARIUM FOR TREATMENT OF DISEASES OF Nervous System. 14TH ST. and Sheridan Ave. WASHINGTON D.C.

Its especial value in Nervous Prostration and other Nervous Diseases complicated with Litheamia. In such cases it accomplishes astonishing results, after a failure of the carbonate of lithia, the phosphate of ammonia, and other so-called solvents of uric acid.

It evidently then possesses some extraordinary virtue apart from that ascribed to Lithia.

Note relative to the Buffalo Lithia Water, by William A. Hammond, M.D., Surgeon-General U.S. Army (retired), formerly Professor of Diseases of the Mind and Nervous System, University of New York.

[IN AN ARTICLE WIDELY COPIED INTO THE LEADING MEDICAL JOURNALS IN THE COUNTRY:]

"There is a point in relation to the therapeutical efficacy of the BUFFALO LITHIA WATER which has not as yet, I think, received sufficient attention. It is well known that many cases of diseases of the NERVOUS SYSTEM are complicated with LITHEAMIA, and that unless this condition is removed a cure is very often retarded, and not infrequently entirely prevented. It is quite commonly the case that in CEREBRAL CONGESTION, producing INSOMNIA, NERVOUS PROSTRATION, resulting from overmental work or much emotional disturbance, and in epilepsy (to say nothing of many cases of insanity) an excess of URIC ACID in the blood is often observed. This state appears to be altogether independent of the character of the food, for no matter how careful the physician may be in regard to the diet of his patient, the LITHEAMIC condition continues. I have tried to overcome this persistence by the use of phosphate of ammonia and other so-called solvents for uric acid, but without notable effect.

"Several years ago, however, I began to treat such cases with BUFFALO LITHIA WATER, with a result that was as astonishing to me as it was beneficial to the patient, so that now in all cases of nervous diseases under my charge in which there is an excess of URIC ACID in the blood, I use the BUFFALO LITHIA WATER in large quantities. By this I mean that I do not have the patient drink merely a tumbler or two in the course of a day, but that I flood him, so to speak, with the water, making him drink a gallon, or even more, in the twenty-four hours. By this course the urine after a few days ceases to deposit uric acid crystals on standing, the morbid irritability of the patient disappears, the tongue becomes clean, the wandering pains in the head are abolished, and the system is rendered much more amenable to the special treatment which may be necessary for the cure of the disease from which the patient suffers.

"I have tried CARBONATE OF LITHIA dissolved in water in various proportions, BUT IT CERTAINLY DOES NOT, in cases to which I refer, have the same effect as BUFFALO LITHIA WATER.

"WASHINGTON, D. C., January 25, 1892."

GOUT, RHEUMATIC GOUT, RHEUMATISM, STONE OF THE BLADDER, RENAL CALCULI, BRIGHT'S DISEASE OF THE KIDNEYS, NEURALGIAS, NERVOUS PROSTRATION, VARIOUS FORMS OF DYSPEPSIA, ETC., ETC., HAVE THEIR ORIGIN IN AN EXCESS OF URIC ACID IN THE BLOOD. IT GOES, THEN, WITHOUT SAYING THAT BUFFALO LITHIA WATER IS A POWERFUL REMEDIAL AGENT IN THESE MALADIES.

SPRINGS OPEN FOR GUESTS JUNE 1.

Water in Cases of One Dozen Half-Gallon Bottles, $5.00, f. o. b. Here.

DESCRIPTIVE PAMPHLETS SENT FREE.

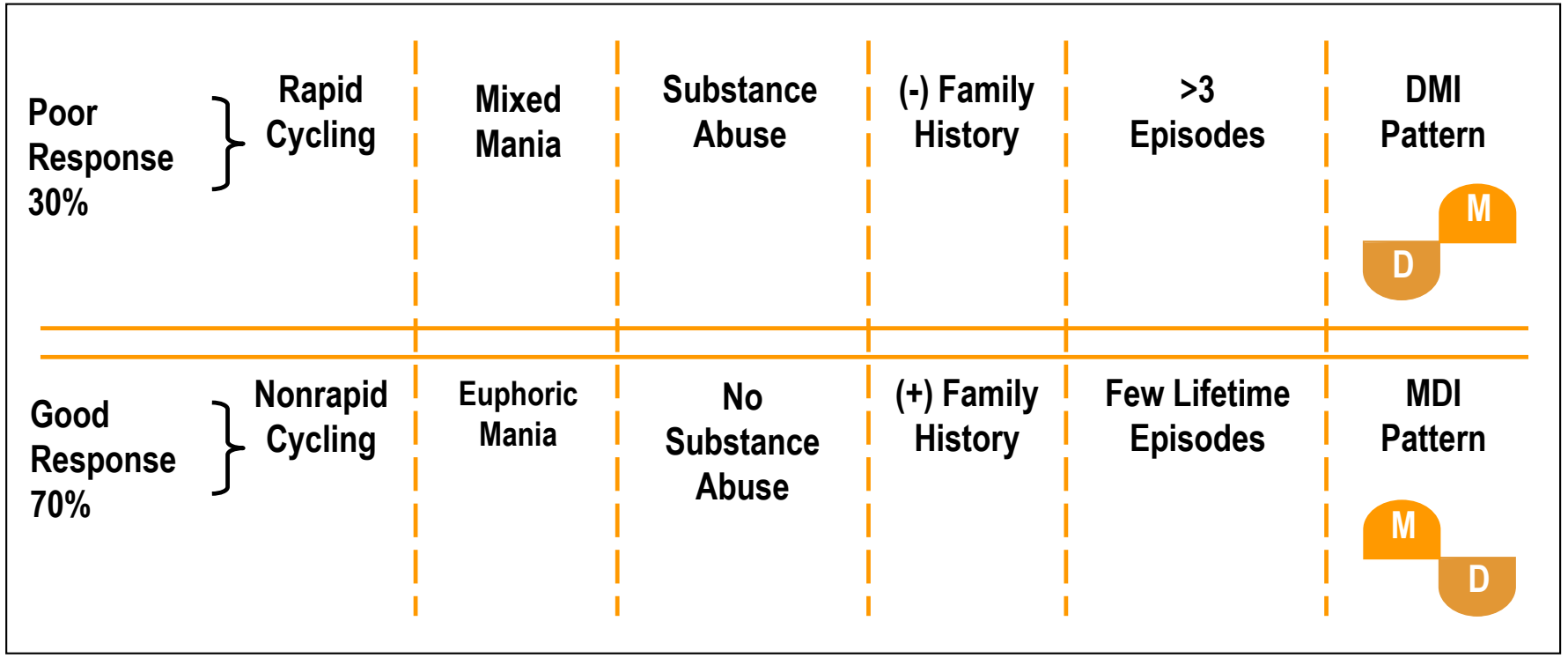
THOMAS F. GOODE, Buffalo Lithia Springs, Virginia.

Advertisement from *Harper's New Monthly Magazine*, 1892, from the author's collection

- Gold standard – benchmark
- Lithium non-response differs from other mood stabilizers
- Clinical predictors account for <50% of variance, suggesting genetic factors
- Prophylactic response familial
- Numerous side effects, narrow therapeutic index
- Believed to reduce suicide rates via unknown mechanism

Frye MA, et al. *J Clin Psychopharmacol.* 1998;18(6):461-464.; Goodwin FK, et al. *Manic Depressive Illness.* New York: Oxford University Press. 1990.; Bowden CL, et al. *JAMA.* 1994;271:918–92.

Variable Lithium Response Rate Based on Bipolar Subtype



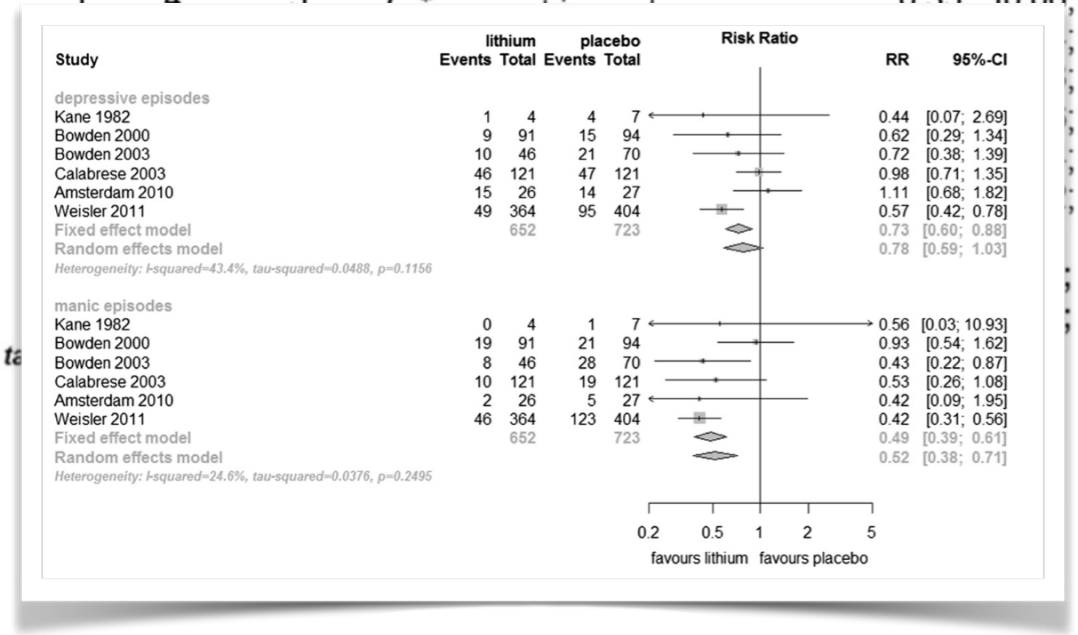
DMI = Depression → mania → euthymic interval; **MDI** = Mania → depression → euthymic interval

Frye MA et al. *J Affect Disord*. 1998;48:91-104.

Meta-Analysis Lithium Preventing Any Mood Episode Seven Trials, (1,580 participants) Lithium More Effective than Placebo (Fixed Effect RR 0.61, 95% CI 0.54 to 0.68)

Lithium prevention of depressive/manic episodes
Depressive (RR 0.73, 95% CI 0.60 to 0.88)
Manic (RR 0.49, 95% CI 0.39 to 0.61)

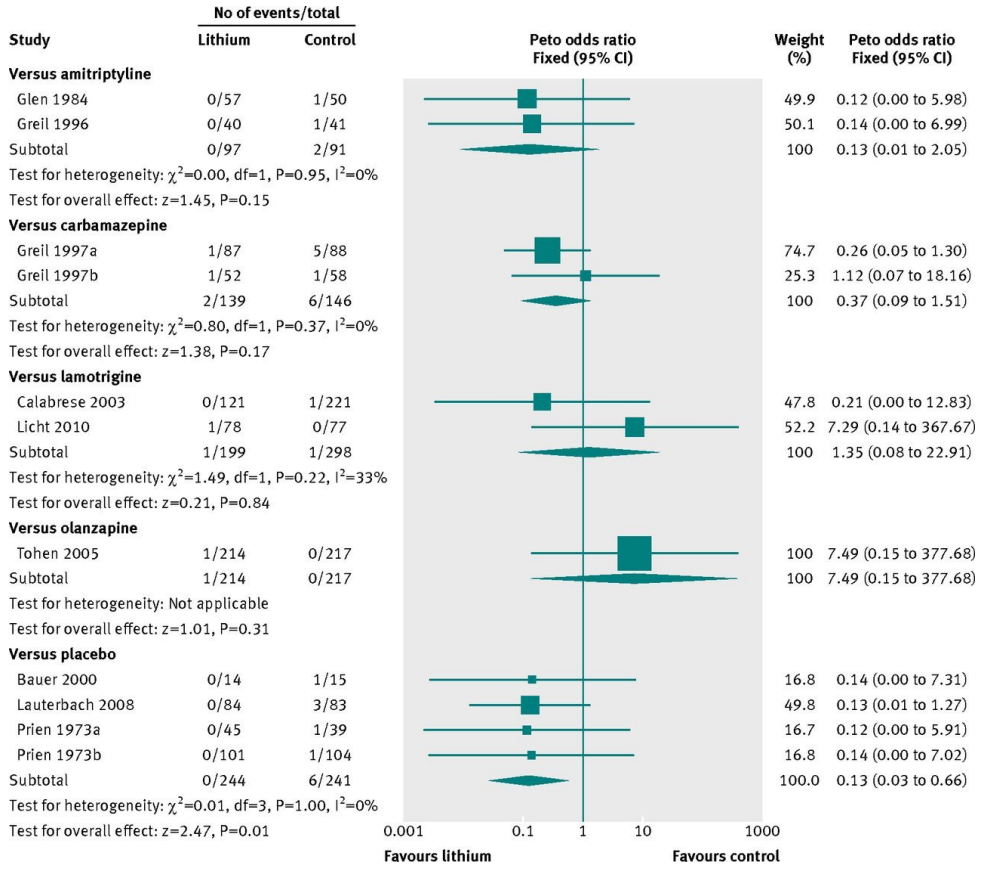
Study			W(fixed)	W(random)
Prien 1973		]	18.7%	18.5%
Kane 1982		2.04]	0.8%	1.5%
Bowden 2000		1.20]	8.0%	13.5%
Bowden 2003		0.83]	8.8%	13.7%
Calabrese 2003		1.09]	14.9%	18.3%
Amsterdam 2010		1.35]	4.2%	14.3%
Weisler 2011		0.62]	44.6%	20.1%
Fixed effect model		**0.68]**	**100%**	--
Random effects model		**0.82]**	--	**100%**
Heterogeneity: I-squared=68%, ta				



Severus E, et al. *Int J Bipolar Disord*. 2014;2:15.

Lithium and Suicidal Behavior

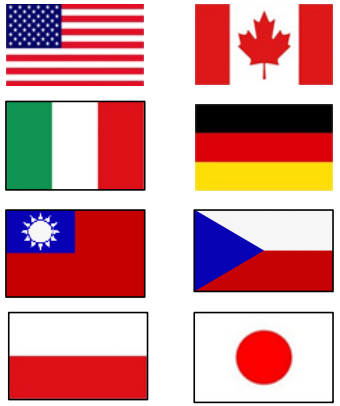
- 48 RCT (19 BD), (6674 participants)
- Mean duration 19.1 (SD 7.2) months (range 4-48 months)
- More effective than placebo (odds ratio 0.13, 95% CI 0.03 to 0.66)



Cipriani A, et al. *BMJ.* 2013;346:f3646.

ConLi+Gen

The international Consortium on Lithium Genetics



National Institute of Mental Health (NIMH) International Group for The Study of Lithium Treated Patients (IGSLI)

- 4 linked SNPs chromosome 21 associated with lithium response
  - (rs79663003, p = 1·37 × 10-8; rs78015114, p = 1·31 × 10-8; rs74795342, p = 3·31 × 10-9; and rs75222709, p = 3·50 × 10-9)
- Replicated prospective study (n=73) lithium monotherapy X 2 years
  - (p = 0·03268, hazard ratio 3·8, 95% CI 1·1-13·0)
- Response-associated region-2 genes for long, non-coding RNAs (lncRNAs) increasingly recognized regulators of gene expression
  - AL157359.3 and AL157359

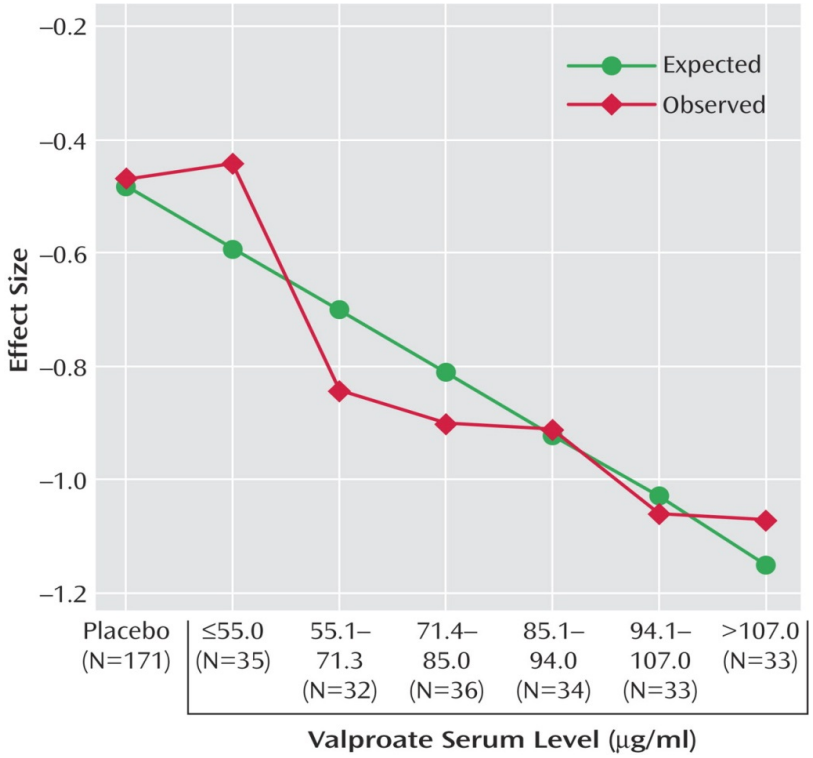
Hou L, et al. *Lancet.* 2016;387(10023):1085-1093.

Valproate for Mania: Dose-Response Effect

Prospective study of 374 patients with acute mania stratified into 6 groups based on VPA serum level ranges (lowest level ≤ 55.0 mcg/mL)

Results

- Linear relationship between VPA serum level and therapeutic response
- Efficacy significantly > PLC beginning at 71.4-85.0 mcg/mL
- Efficacy was associated with highest VPA serum levels (>94 mcg/mL)



Allen MH, et al. *Am J Psychiatry* 2006;163(2):272-275.

Divalproex & Carbamazepine* in Acute Mania

Pros

- Effective in manic and mixed episodes
- Effective in alcohol withdrawal & relapse prevention
- Several effective in migraine prevention

Cons

- Ineffective in acute mania (LTG, TPX, GBP)
- P450 3A/4 heteroinduction
- Weight gain & endocrine disturbances (VAL)
- Teratogenicity (VAL, CBZ)
- Rash risk

*Not FDA approved for bipolar disorder

CBZ = carbamazepine; VAL = valproate; LTG = lamotrigine; GBP = gabapentin; OLZ = olanzapine. DVPX = divalproex; TPX = topiramate

Novick D, et al. *Pharmacopsychiatry*. 2009;42(4):145-152.; Goodwin GW, et al: *Psychopharmacol*. 2009;23(4):346-388.; Frye MA, et al. *J Clin Psychiatry*. 2006;67(11):1721-1728.; Harden CL, et al. *Neurology*. 2009;73(2):126-32.; Jiang B, et al. *Med Hypotheses*. 2009;73(6):996-1004.

Other Anticonvulsant Drugs

- Oxcarbazepine*
  - One negative randomized, DB, PLC-controlled trial
  - No PLC-controlled studies in adults
- Lamotrigine
  - Two unpublished negative trials
- Gabapentin*
  - Negative PLC-controlled add-on study (LI, VPA)
- Topiramate*
  - Four negative PLC-controlled trials

*Not FDA approved for bipolar disorder

Wagner KD, et al. *Am J Psychiatry*. 2006t;163(10):1843.; Rosa AR, et al. *CNS Neurosci Ther*. 2011;17(3):167-177.; Pande et al. *Bipolar Disord.* 2000;2(3 Pt 2):249-255.; Kushner SF, et al. *Bipolar Disord.* 2006; Feb;8(1):15-27.

ECT for Acute Mania

- Electroconvulsive therapy (ECT) is a mood stabilizer
- 2 controlled studies of acute mania
  - ECT vs lithium
  - ECT vs lithium + haloperidol
- ECT reported significant benefits for acute mania

Mukherjee S, et al. *Convuls Ther.* 1988;4(1):74-80.
Small JG, et al. *Arch Gen Psychiatry* 1988;45(8):727-732.

Target Dose Range for Acute Mania

Agent	Monotherapy
Lithium	0.8 – 1.2 mmol/L
Divalproex	90 – 125 mg/L
Carbamazepine*	4-12 mcg/ml vs. 800 mcg
Asenapine	10 mg bid sublingual
Olanzapine	10 – 20 mg/d
Risperidone	4 – 5 mg/d
Quetiapine	600 – 800 mg/d
Ziprasidone	80 – 120 mg/d
Aripiprazole	15 – 30 mg/d
Clozapine*	150 – 450 mg
Cariprazine	3 – 6 mg/d

*Not FDA approved for bipolar disorder

Frye M, et al., *Am J Psychiatry*. 2009;166(2):164-172.; Novick DM, et al. *Bipolar Disord.* 2010;12(1):1-9.; Bostwick JM, et al. *Am J Psychiatry*. 2000;157(12):1925-1932.

Mood Stabilizers: Safety and Tolerability Concerns

Lithium	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis
Hair Loss	Hair Loss	Blood dyscrasias	Dream abnormality
Cardiac toxicity	Pancreatitis	Cardiac toxicity	
Acne, Psoriasis	PCOS	Hyponatremia	
Teratogen	Teratogen	Teratogen	Teratogen
	Suicidality	Suicidality	Suicidality

All mood stabilizers have at least one boxed warning.

[Package Insert]. Drugs@FDA Website.; In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005.

Antipsychotic Safety and Tolerability Concerns

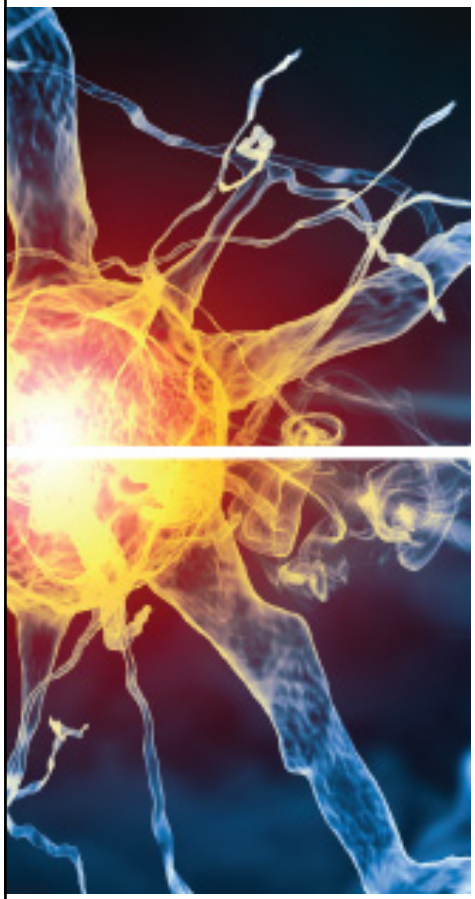
First-Generation	Second-Generation
Depression	Weight gain, Sedation
Akathisia	Hyperglycemia, Diabetes[b]
Acute dystonia	Suicidality in age ≤ 24[c]
Tardive dyskinesia[a]	Akathisia
Weight gain, Sedation	Hyperprolactinemia
Anticholinergic	Cerebrovascular in elderly[d]
Cardiac, Orthostasis	Cardiac, Orthostasis
Hyperprolactinemia	Tardive dyskinesia[a]
Neuroleptic malignant[a]	Neuroleptic malignant[a]
Leukopenia, Neutropenia,	Leukopenia, Neutropenia,
Agranulocytosis[a]	Agranulocytosis[a]
Cardiac/pneumonia in older adults[a]	Cardiac/pneumonia in older adults[a]

All Antipsychotics Have at Least One Boxed Warning

In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005.; [Package Insert]. Drugs@FDA Website.

Mania Matters

- Treat the illness
  - Short term high dose benzodiazepine, sleep restoration, containment
- Individualize treatment
  - Right medication to the right patient
- Improve psychoeducation
- Enhance treatment adherence and minimize side effect burden



Bipolar Depression

Bipolar Depression: Best Practices

- FDA approved
  - Olanzapine Fluoxetine (OFC)
  - Quetiapine monotherapy
  - Lurasidone mono & adjunct therapy
- Maximize the mood stabilizer
- Antidepressants FDA off-label*
  - Do they work? Are they safe?
- Psychotherapy
- Novel treatment

The Old Guitarist Pablo Picasso
1903 The Blue Period

FDA off-label – antidepressants are not indicated for treatment of bipolar depression

Epidemiology

- Lifetime prevalence rate 4.5 %
  - 1% for BPI, 1.1% BPII, 2.4% subthreshold
- Suicide
  - 25% attempt, 15% succeed (5% never hospitalized)
- Comorbid anxiety and substance use disorders
  - Greater risk suicidality and treatment emergent mania
- Work days lost/ ill worker/ year
  - BP > UP, driven by depression, not mania
- Subsyndromal depression
  - Functional disability & subsequent relapse

Merikangas KR, et al, *Arch Gen Psychiatry*. 2007;64(5):543-552.; Levander GS, et al, *J Affect Disord*. 2007;101(1-3):211-217.; Frye MA, et al. *Am J Psychiatry*. 2003;160(5):883-889.; Ostacher et al, *Am J Psychiatry*. 2010;167(3):289-297.; Gitlin MJ, et al, *J Clin Psychiatry*. 2011;72(5):692-697.; Kessler RC, et al. *Am J Psychiatry*. 2006;163(9):1561-1568.; Altshuler et al, *J Clin Psychiatry*. 2009;70(4):450-457.; Frye MA, et al, *J Clin Psychiatry*. 2006;67(11):1721-1728.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Bipolar Disorder — A Focus on Depression

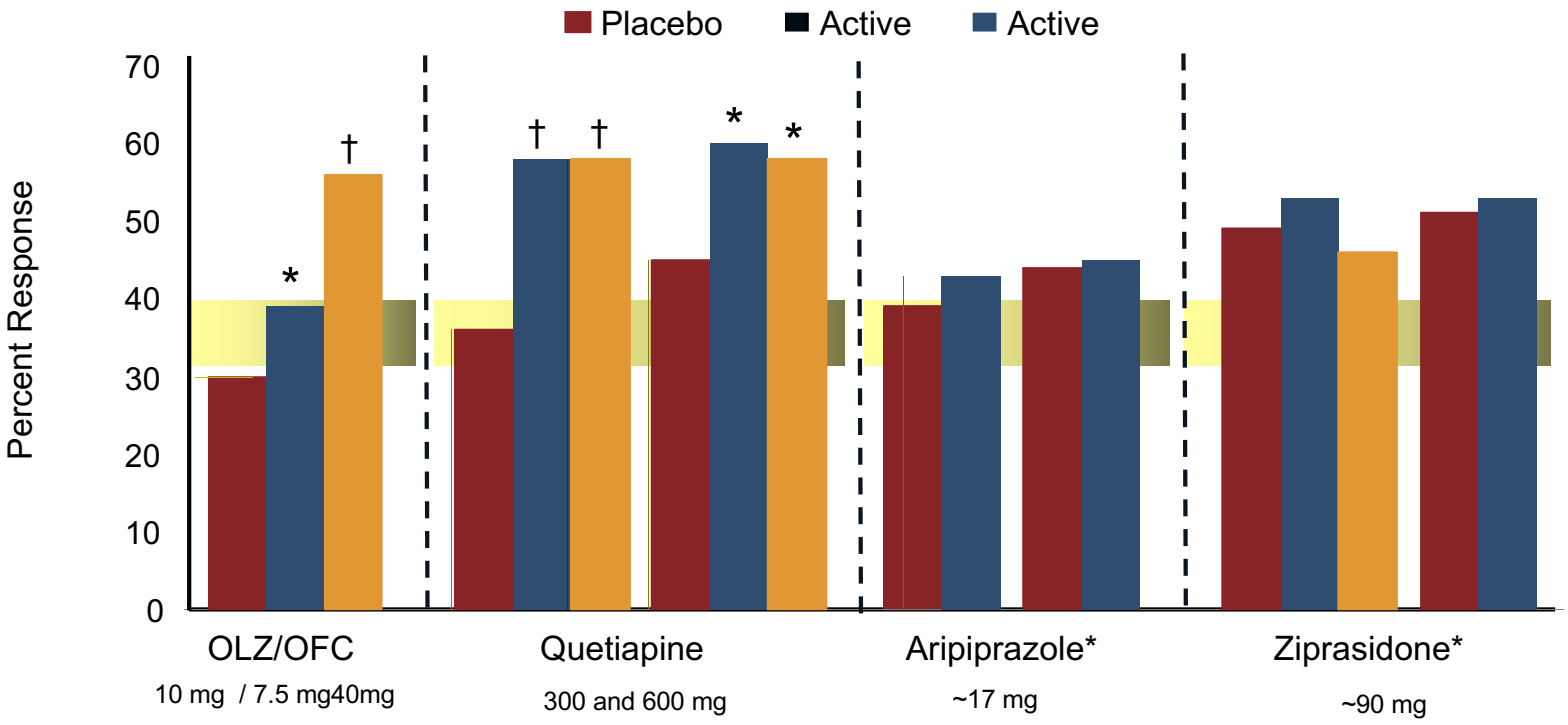
Mark A. Frye, M.D.

This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

A 26-year-old businesswoman seeks evaluation for a pattern of "hibernating away" each winter; this pattern began when she was in high school. Her current symptoms include excessive sleeping, a 20-lb (9-kg) weight gain related to an increased intake of sweets and excessive alcohol use, anhedonia, lack of motivation, negative ruminations, and decreased productivity at work. She reports a history of several-week periods in college when she had less need for sleep, with associated increases in mood, energy, and libido. During the last episode, she exceeded her credit-card limit and was evaluated at an emergency department for alcohol intoxication. How should she be evaluated and treated?

Frye MA. *N Engl J Med*. 2011;364(1):51-59.

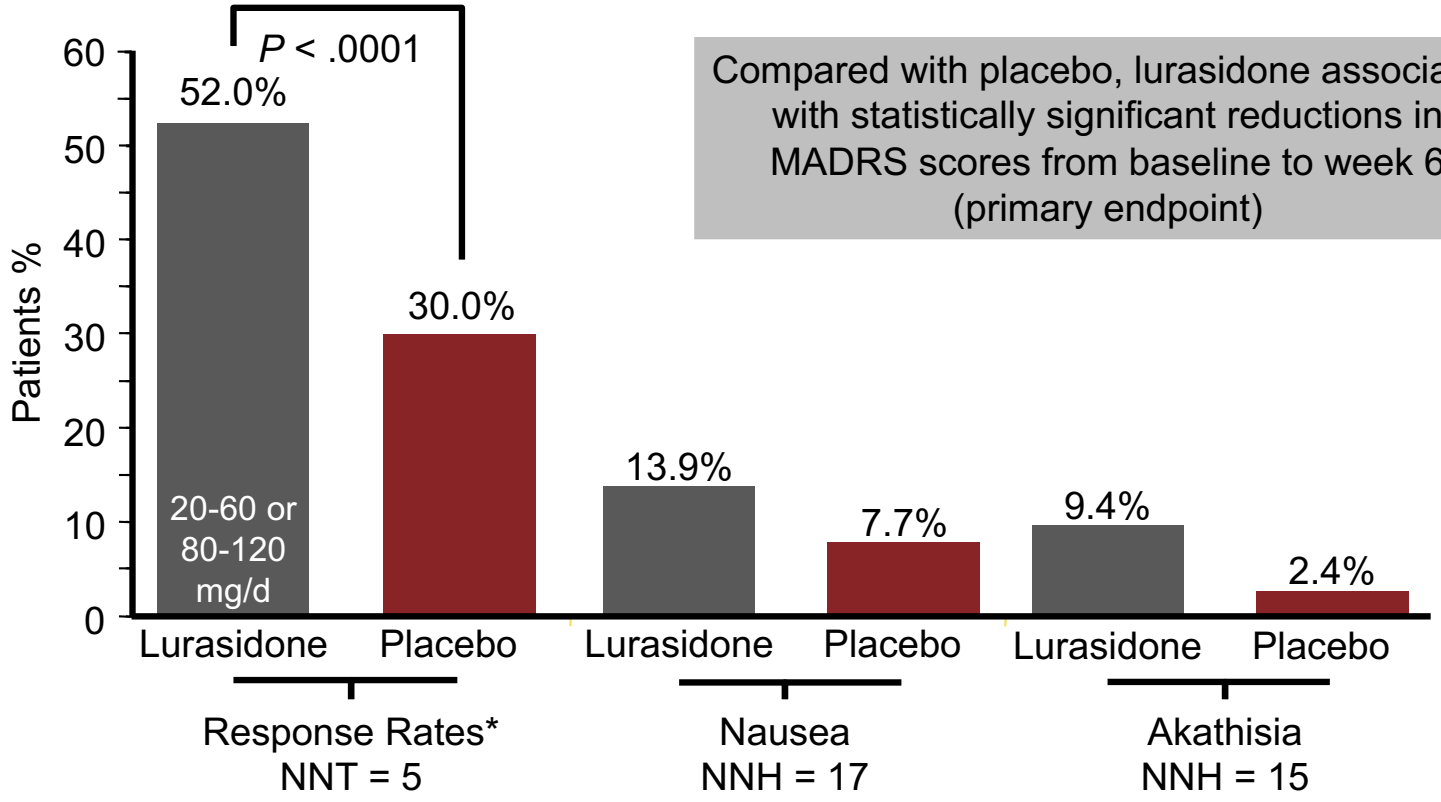
Response Rates of Atypical Antipsychotics in BP Depression



OFC = olanzapine/fluoxetine combination. *$P < 0.05$; †$P < .001$ vs. placebo
*Agent not approved by FDA for bipolar depression.

Calabrese J, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.; Thase ME, et al. *J Clin Psychopharmacol*. 2009;29(1):38.; Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.; *J Clin Psychopharmacol*. 2008;28(1):13-20.; Sachs G, et al., *J Clin Psychiatry*. 2001;72(10):1413-1422.

Lurasidone in Bipolar I depression: PREVAIL 2

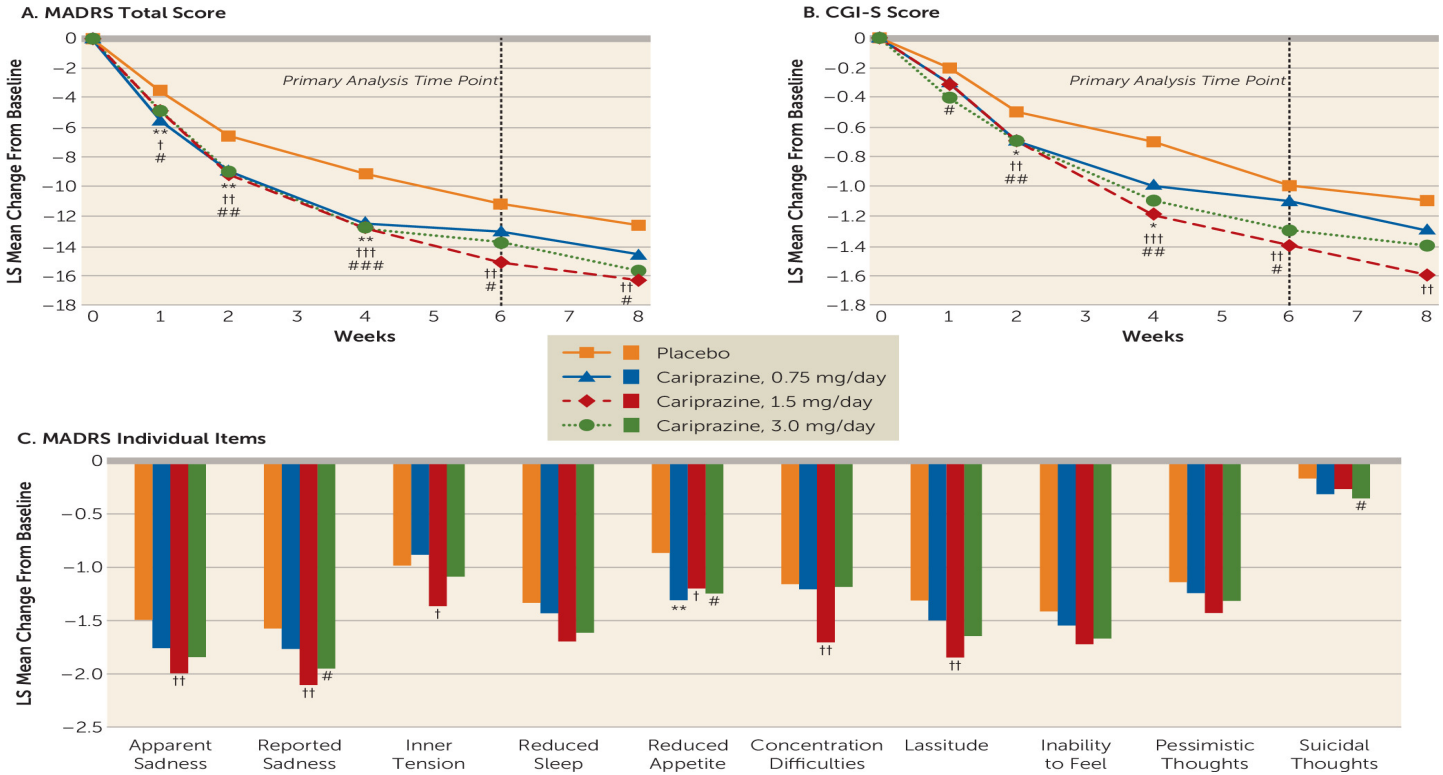


Compared with placebo, lurasidone associated with statistically significant reductions in MADRS scores from baseline to week 6 (primary endpoint)

*Response: ≥ 50% MADRS decrease.

Loebel A, et al. *Am J Psychia*try. 2014;171(2):160-168.; Loebel A, et al. *Am J Psychiatry*. 2014;171(2):169-177.

Cariprazine* vs. Placebo in Bipolar I Depression



a Mixed-effects model for repeated measures, intent-to-treat population; p values were not adjusted for multiple comparisons. Cariprazine 0.75 mg/day compared with placebo: *$p < .05$; **$p < .01$; ***$p < .001$. Cariprazine 1.5 mg/day compared with placebo: †$p < .05$; ††$p < .01$; †††$p < .001$. Cariprazine 3.0 mg/day compared with placebo: #$p < .05$; ##$p < .01$; ###$p < .001$.

Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-81

*Not approved by the FDA for treatment of bipolar depression

Pros and Cons of Atypical Antipsychotics in Bipolar Depression

Pros

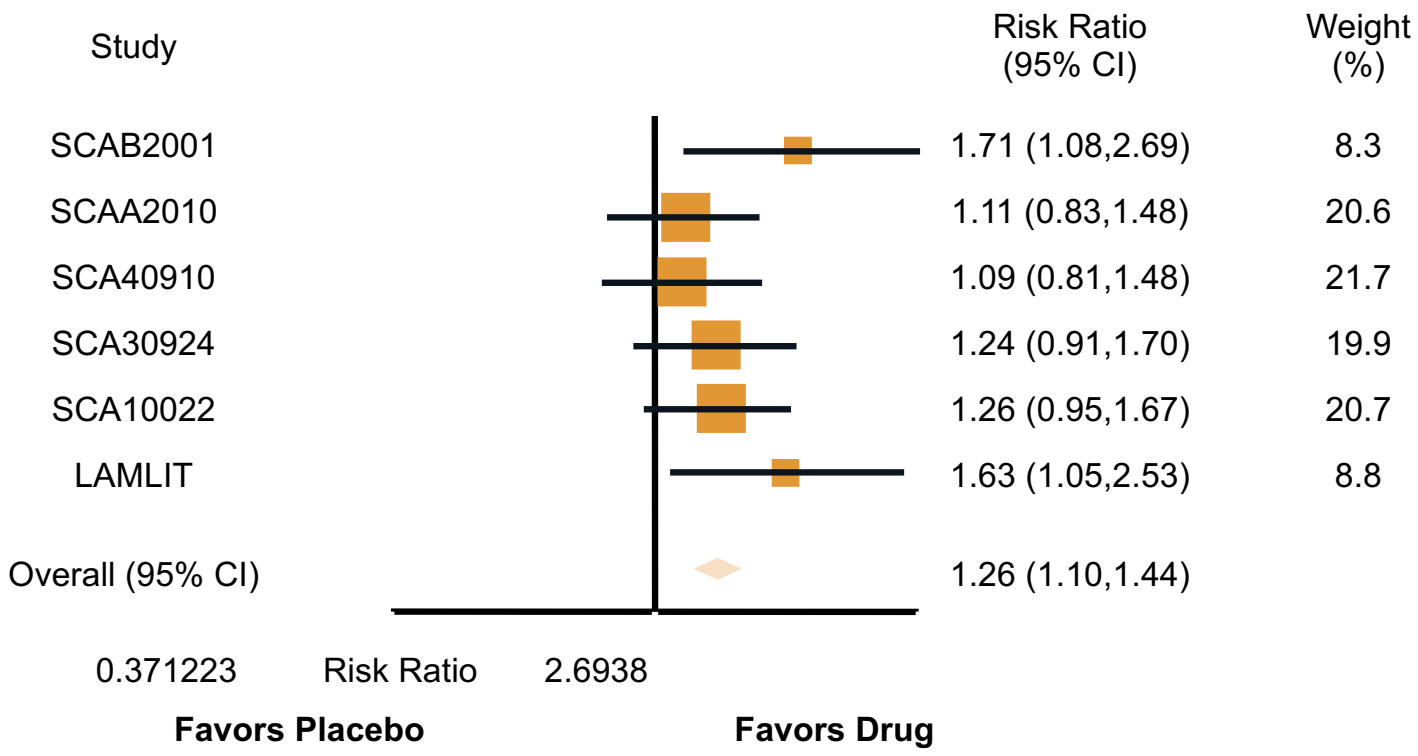
- As a class, effective in acute mania
- Rapid control of acute mania/mixed, rapid cycling, psychosis/no psychosis
- Sustained improvement of symptoms

Cons

- Tardive dyskinesia, neuroleptic malignant syndrome
- Weight gain

Lyoo IK, et al. *Bipolar Disord*. 2006;8(1):65-74.

Meta-Analysis of Lamotrigine* in Acute Bipolar Depression

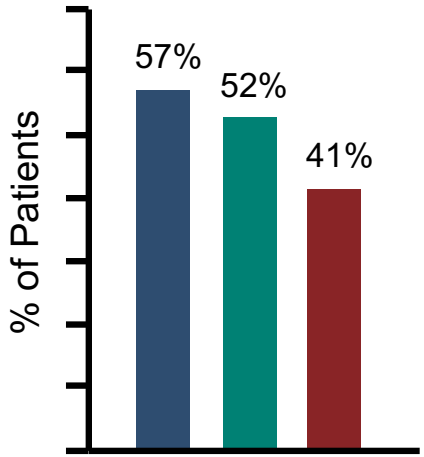


*Not FDA approved for bipolar depression

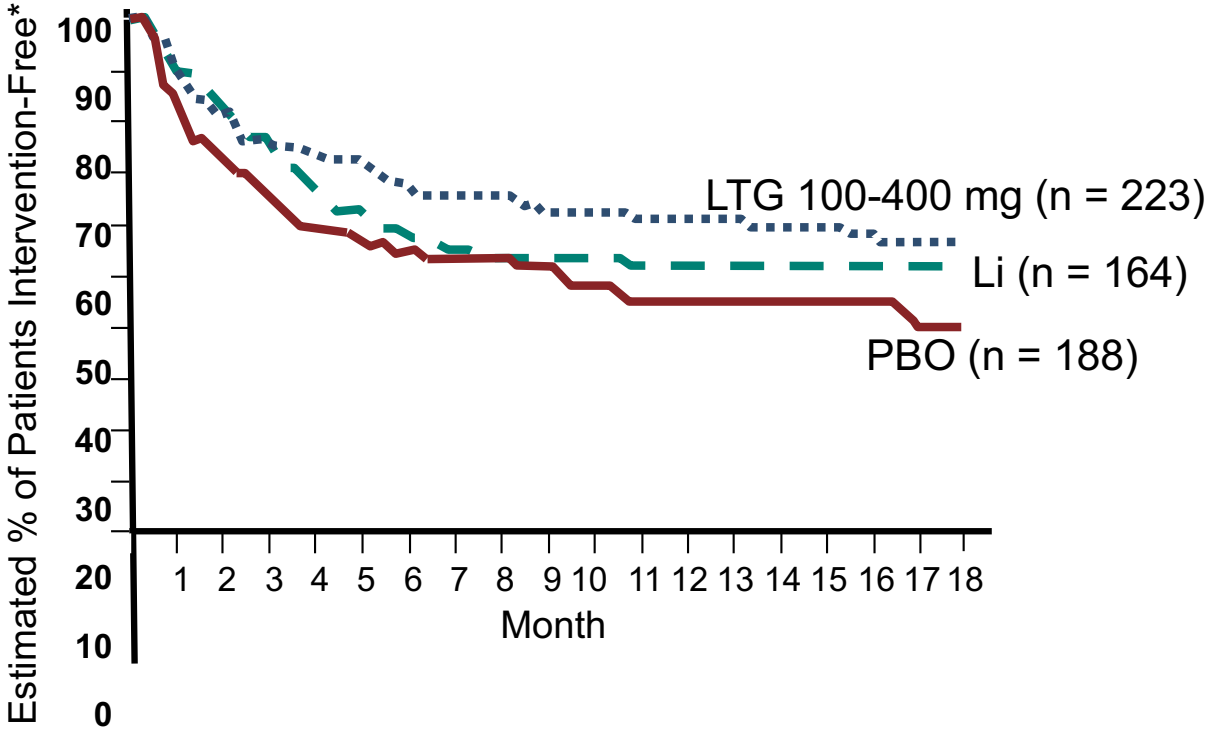
Geddes JR. *Br J Psychiatry*. 2009;194(1):4-9.; Van der Loos ML, et al. *J Clin Psychiatry*. 2009;70(2):223-231.

Lamotrigine in Maintenance Treatment of Bipolar Disorder: Delayed Time to Intervention for a Depressive Episode

Combined Data (Bowden 2003, Calabrese 2003)



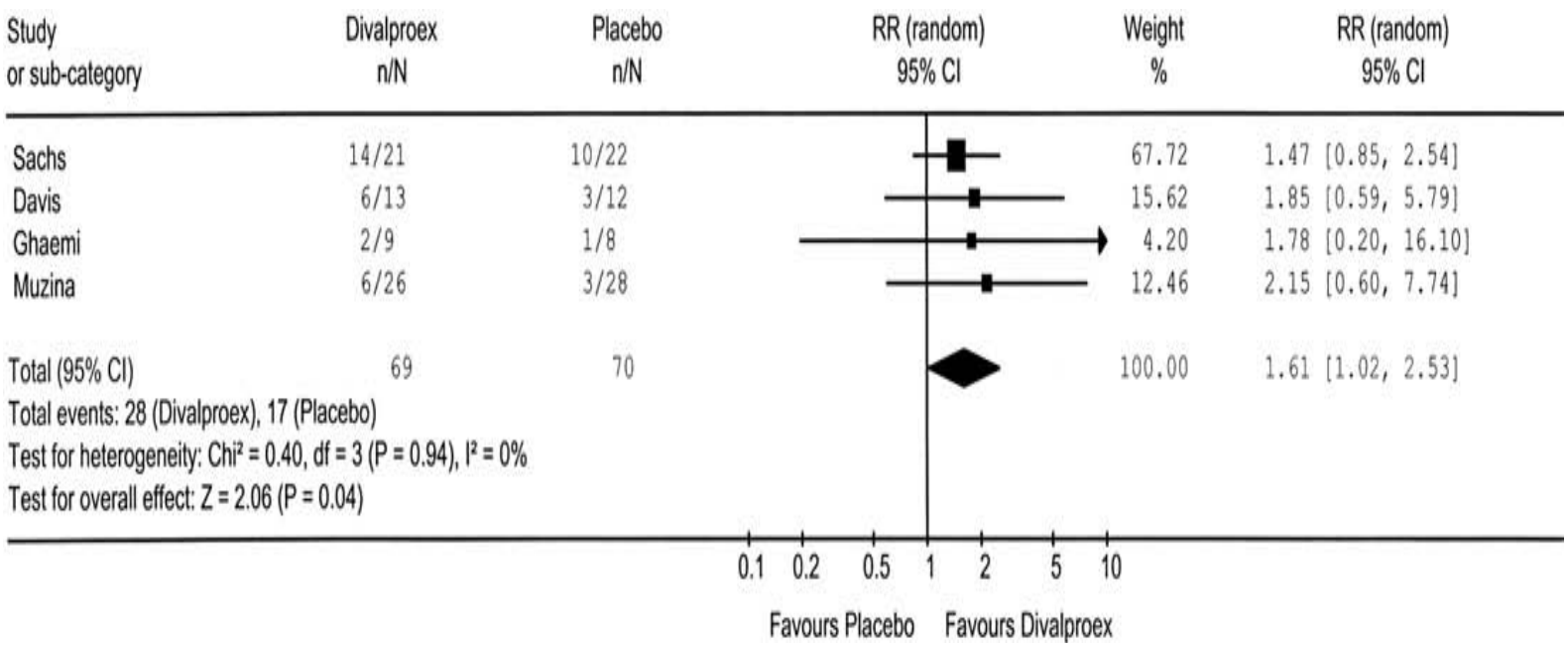
***p* = .009, LTG vs. PBO**
***p* = .120, Li vs. PBO**
***p* = .325, LTG vs. Li**



*Some patients considered intervention-free for depressive episodes could have had intervention for manic episodes.

Goodwin GM, et al. *J Clin Psychiatry.* 2004;65(3):432-441.

Meta-Analysis Divalproex* in Acute BP Depression



Relative risk of remission in patients treated with divalproex versus placebo

*Not FDA approved for bipolar depression

Muzine et al. *J Clin Psychiatry*. 2011;72(6):813-819.; Davis LL, et al. J Affect *Disord*. 2005;85(3):259-266.; Ghaemi SN, et al. *J Clin Psychiatry*. 2007;68(12):1840-4.

Pros and Cons of Antiepileptics (Divalproex*, Carbamazepine*) in Bipolar Depression

Pros

- Effective in manic and mixed episodes
- Effective in alcohol withdrawal & relapse prevention
- Several effective in migraine prevention

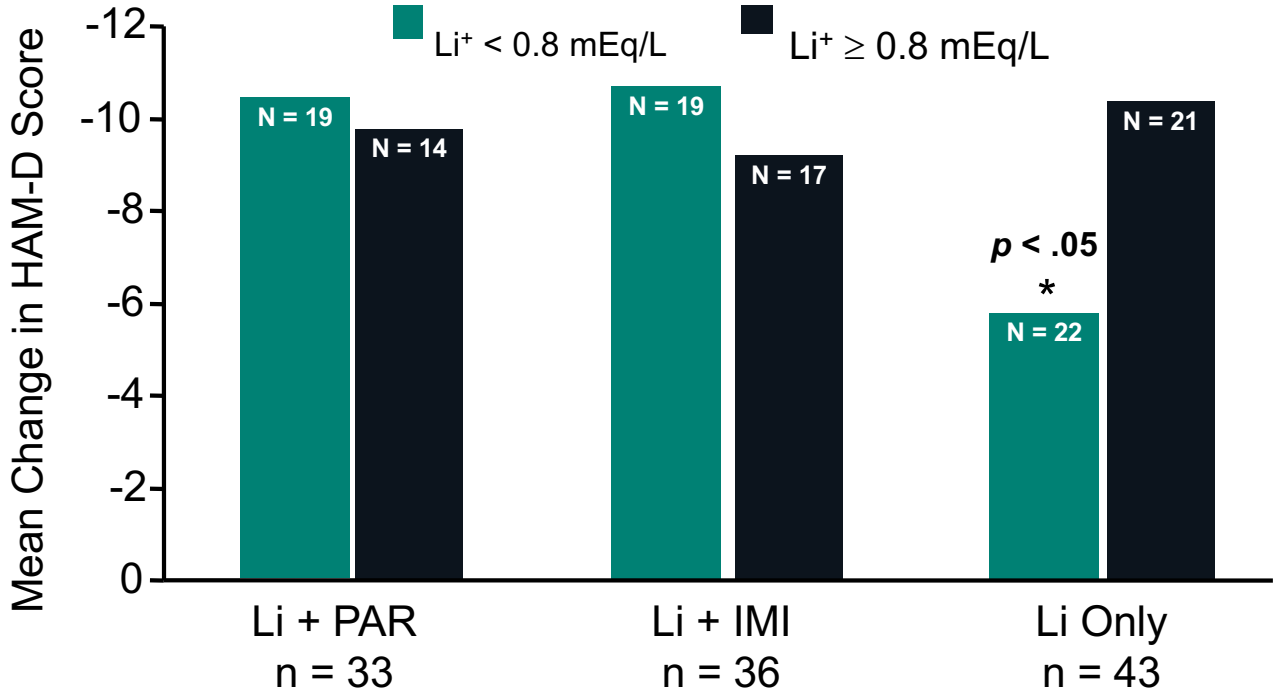
Cons

- Ineffective in acute mania (LTG, TPX, GBP)
- P450 3A/4 heteroinduction
- Weight gain & endocrine disturbances (VAL)
- Teratogenicity (VAL, CBZ)
- Rash risk

CBZ = carbamazepine; VAL = valproate; LTG = lamotrigine; GBP = gabapentin; OLZ = olanzapine. DVPX = divalproex; TPX = topiramate

Novick D, et al. *Pharmacopsychiatry*. 2009;42(4):145-152.; Frye MA, et al. *J Clin Psychiatry.* 2006;67(11):1721-1728.; Goodwin GW, et al: Psychopharmacol. 2009;23(4):346-388.; Harden C, et al. *Neurology.* 2009;73:126-132., Jiang B, et al. *Med Hypotheses.* 2009;73(6):996-1004.

Maximize the Mood Stabilizer and Lithium* in Bipolar Depression (N = 117)



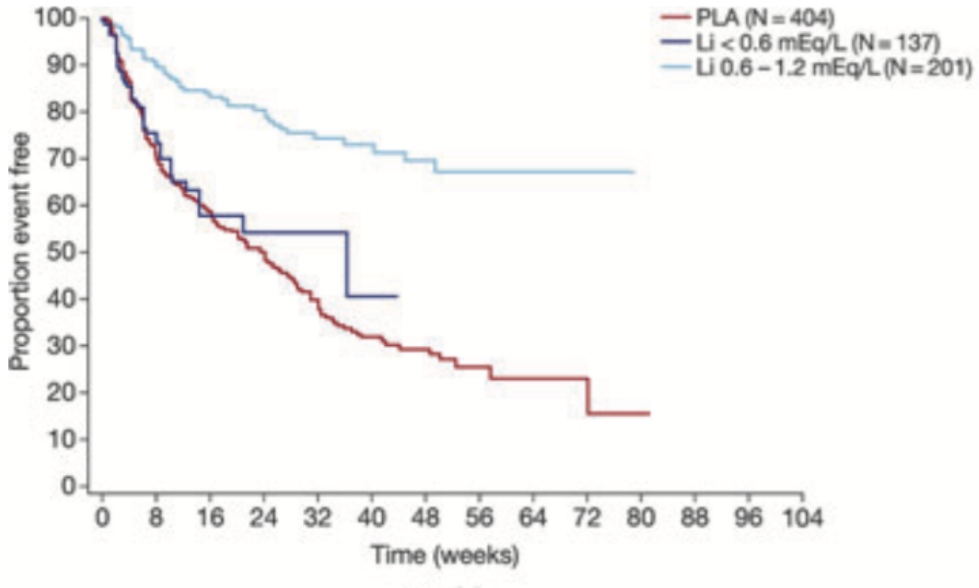
*Not FDA approved for bipolar depression

Li = lithium, IMI = imipramine, PAR = paroxetine

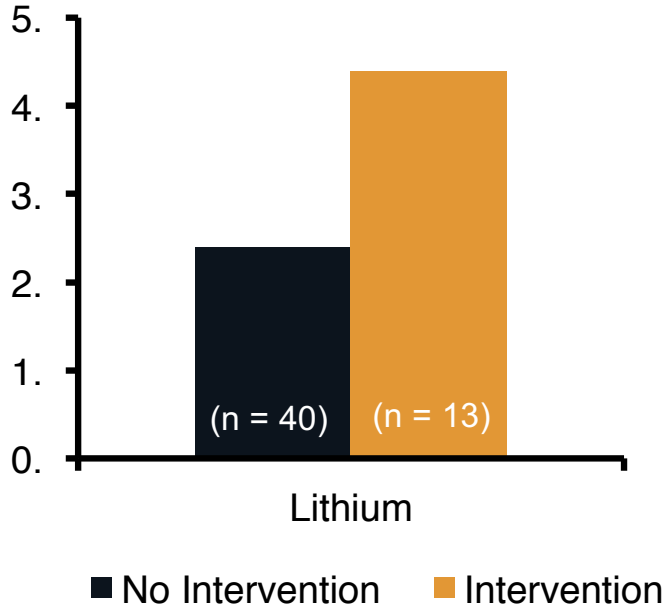
Nemeroff CB, et al. Am J Psychiatry. 2001;158(6):906-912.

Li and Depressive Relapse: Watch for Optimum Levels and Thyroid Function

Recurrence of any Mood Episode Significantly Longer Li 0.6–1.2 mEq/l Group

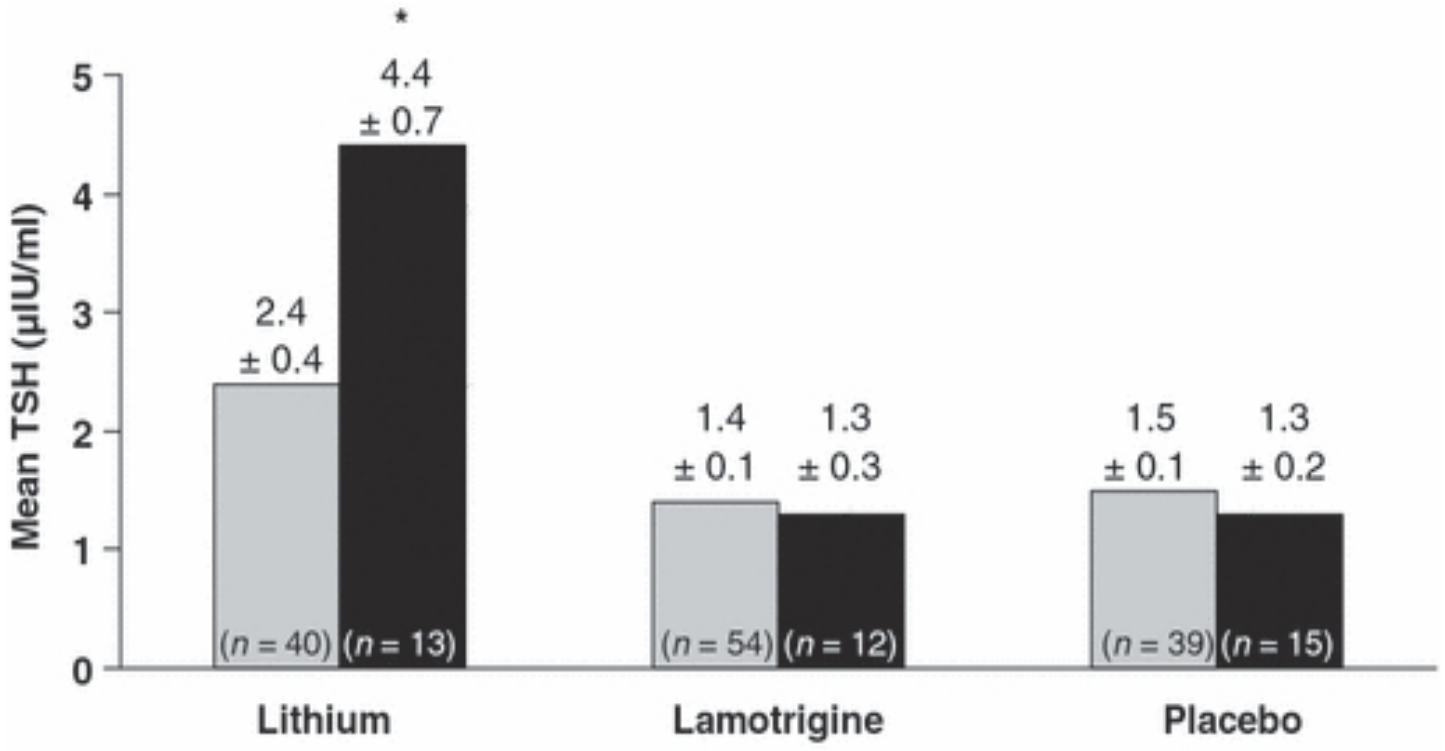


TSH Change and Depression Relapse in Bipolar I Treated with Lithium



Nolen WA, Weisler RH. *Bipolar Disord*. 2013;15(1):100-109.; Frye MA, et al. *Acta Psychiatr Scand*. 2009;120(1):10-13.

↑ TSH Associated with Depressive Relapse in Lithium-Maintained Bipolar Patients



* P < .05 Intervention vs. No Intervention

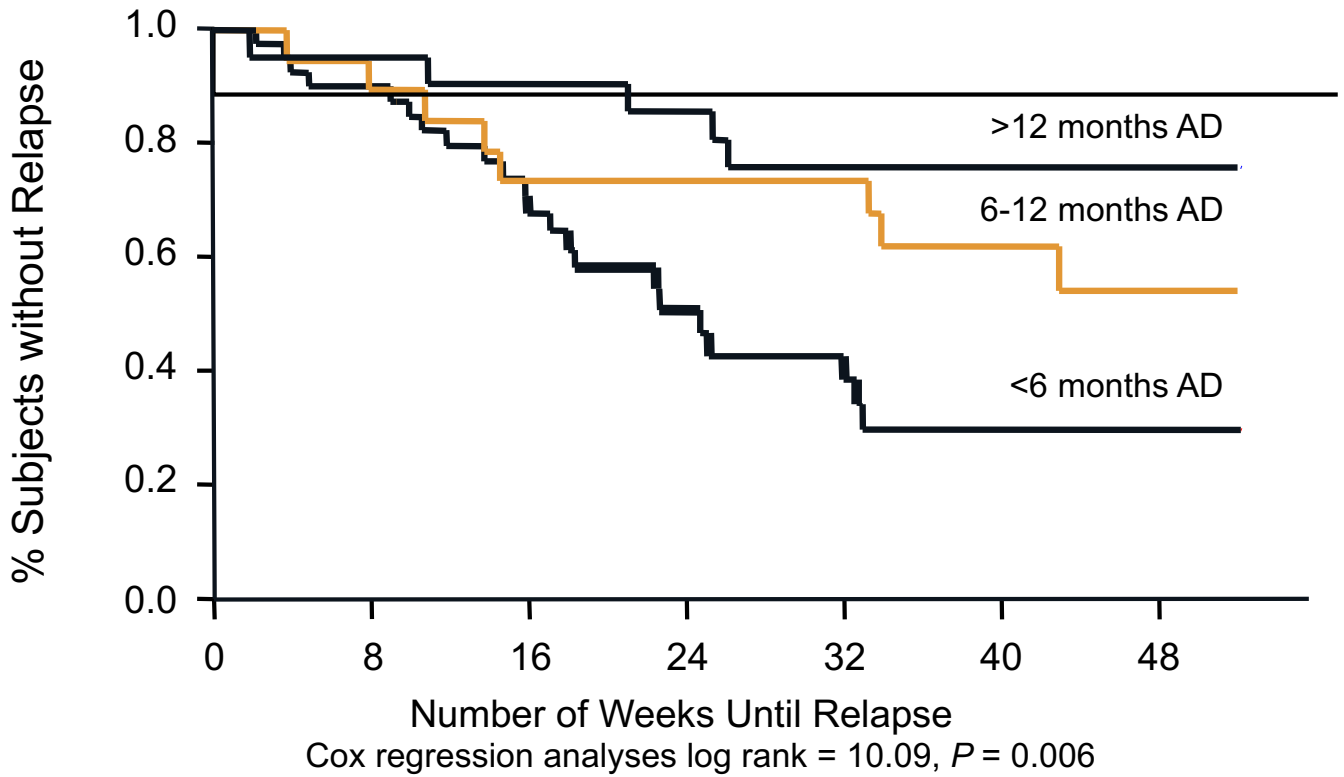
Frye MA, et al. *Acta Psychiatr Scand*. 2009;120(1):10-13.

Antidepressants (AD) Not Effective for Bipolar Depression

- Meta-analysis 16 studies acute AD Rx vs. placebo or active comparator in BPI / II depressed patients (n = 3113)
- The pooled treatment estimates
  - Clinical response (RR = 1.17, 95% CI, 0.88-1.57; *p* = .28)
  - Clinical remission (RR = 1.14, 95% CI, 0.90-1.45; *p* = .28)
- Pooled treatment estimates for 1000 patients
  - No increase risk of switch
- In smaller analysis
  - 43% TCA, 15% venlafaxine, 7% SSRI, 5% bupropion

Sidor MM, et al. *J Clin Psychiatry*. 2011;72(2):156-167.
Sidor MM, et al. *Curr Psychiatry Rep*. 2012;14(6):696-704.

Depressive Episode Relapse with AD Discontinuation



Cox regression analyses log rank = 10.09, *P* = 0.006

AD = antidepressant

Altshuler L, et al. *Am J Psychiatry*. 2003;160(7):1252-1262.

Risk Factors for Switch

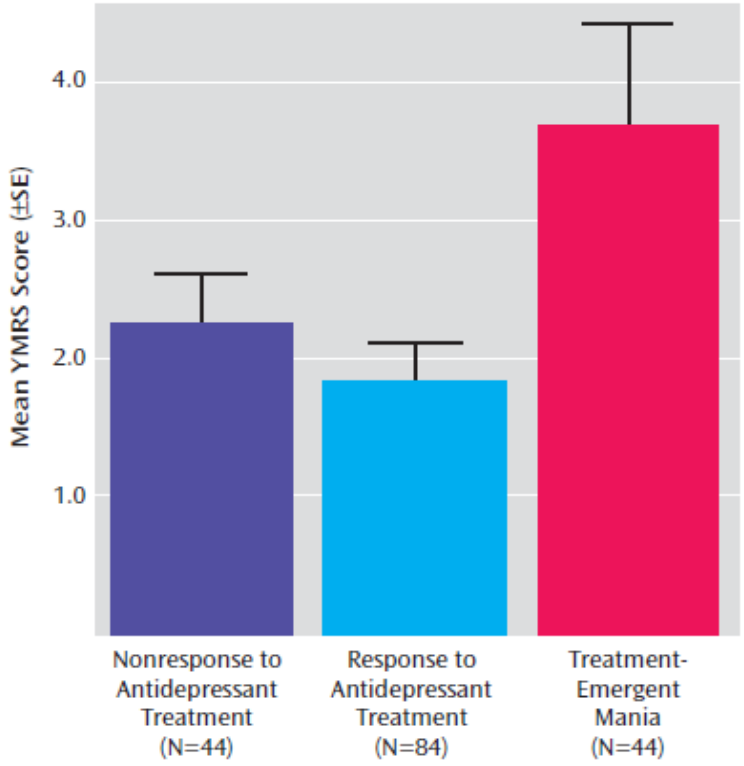
- **Mixed depression**
- Tricyclic antidepressants (TCA) vs. SSRI/SNRI
- History of antidepressant-induced mania (AIM)
- Absence of antimanic mood stabilizer
  - First 3 months associated with greatest liability
- Low thyroid stimulating hormone (with TCAs)
- **Polymorphism (s/s or s/l) at 5-HTTLPR**
- Hyperthymic temperament
- Comorbid alcoholism
- Female gender and comorbid anxiety disorder
- Age (peripubertal > adolescents)
- BP I > BP II

Viktorin A, et al. *Am J Psychiatry*. 2014;171(10):1067-1073.

Frye MA, et al. *Am J Psychiatry*. 2009;166(2):164-172.

Baseline Mixed Depression Associated with Treatment Emergent Mania (TEM)

- Prior to antidepressant treatment
- 3 YMRS items significantly higher in TEM
  - ↑ motor-energy
  - Speech
  - Thought content
- Factor analysis to identify clusters of YMRS items that covaried and analysis of variance only identified motor/verbal activation ($F(2,169) = 3.99$, $p = .02$)



Baseline Manic Symptom Severity Prior to Antidepressant Treatment

YMRS = Young Mania Rating Scale, TEM = Treatment Emergent Mania

Frye MA, et al. *Am J Psychiatry*. 2009;166(2):164-172.

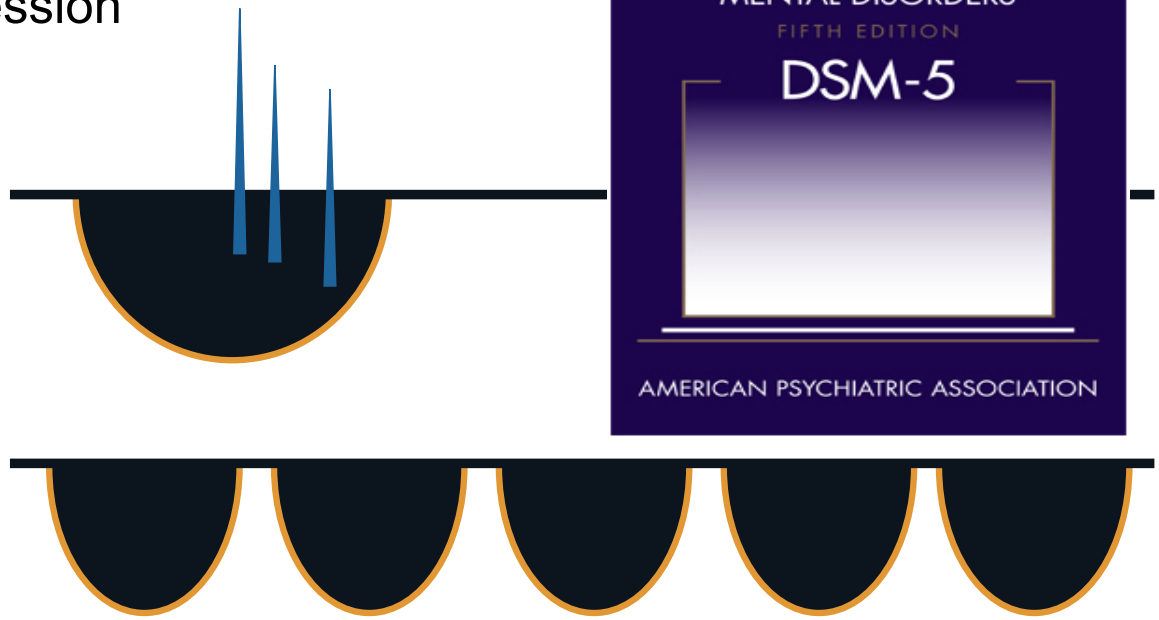
DSM-5 Mixed Specifier

Hyperthymic Temperament

BP-IV
Hyperthymia + Depression

Depressive Mixed State

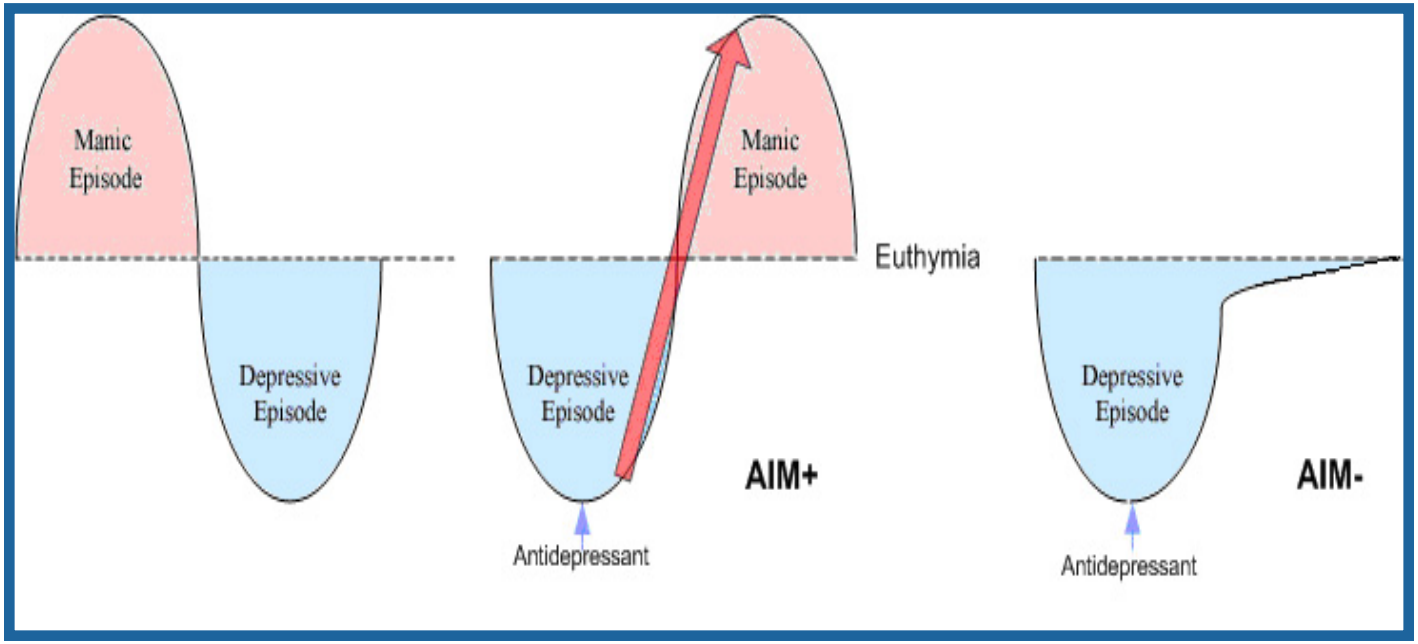
Recurrent "Unipolar"



Akiskal HS et al. *J Affect Disord*. 2000;59(Suppl 1):S5-S30.

Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (BP)

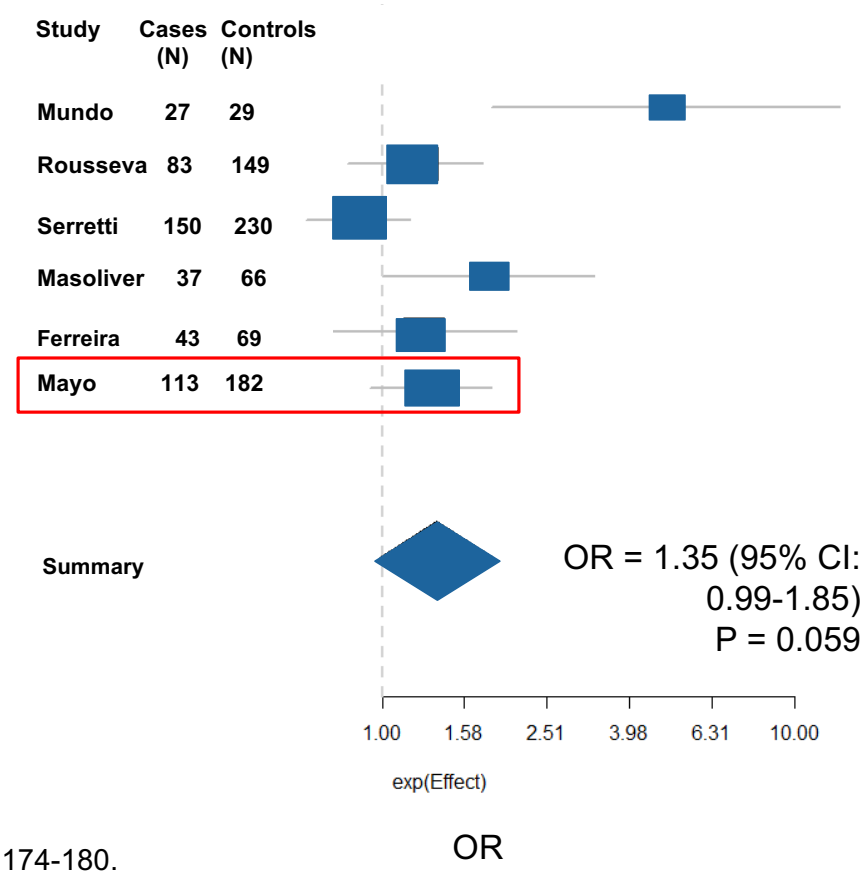
SLC6A4 polymorphism & Antidepressant Induced Mania



Nemeroff CB, et al. *Am J Psychiatry*. 2001;158(6):906-912.

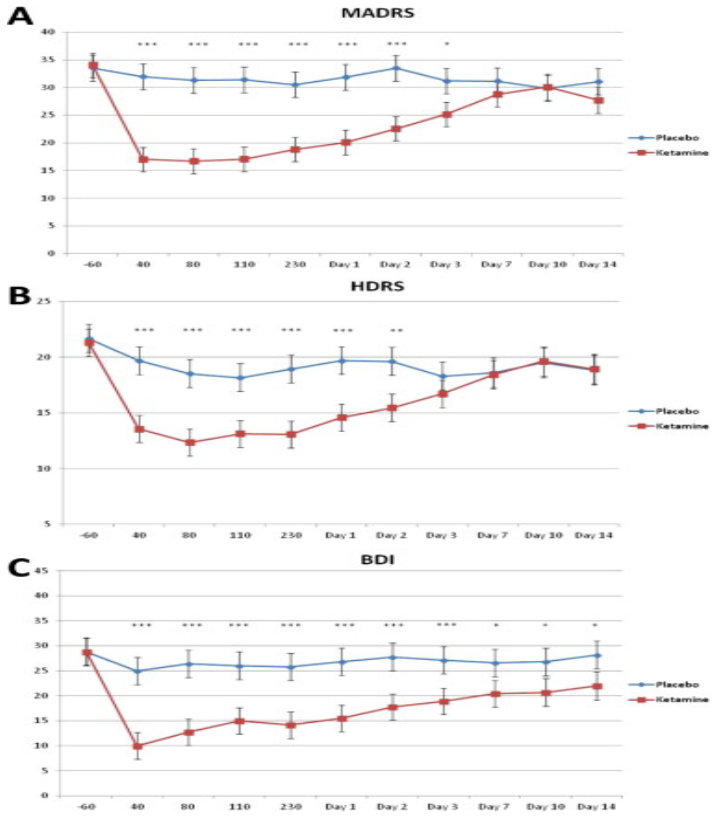
SLC6A4 S Allele and AIM: Meta-Analysis Results

Meta-analysis marginally significant evidence of association between S allele and AIM+ (p = .059)



Frye MA, et al. *J Clin Psychiatry.* 2015;76(2):174-180.

Ketamine* for Treatment Resistant Bipolar Depression-Replication

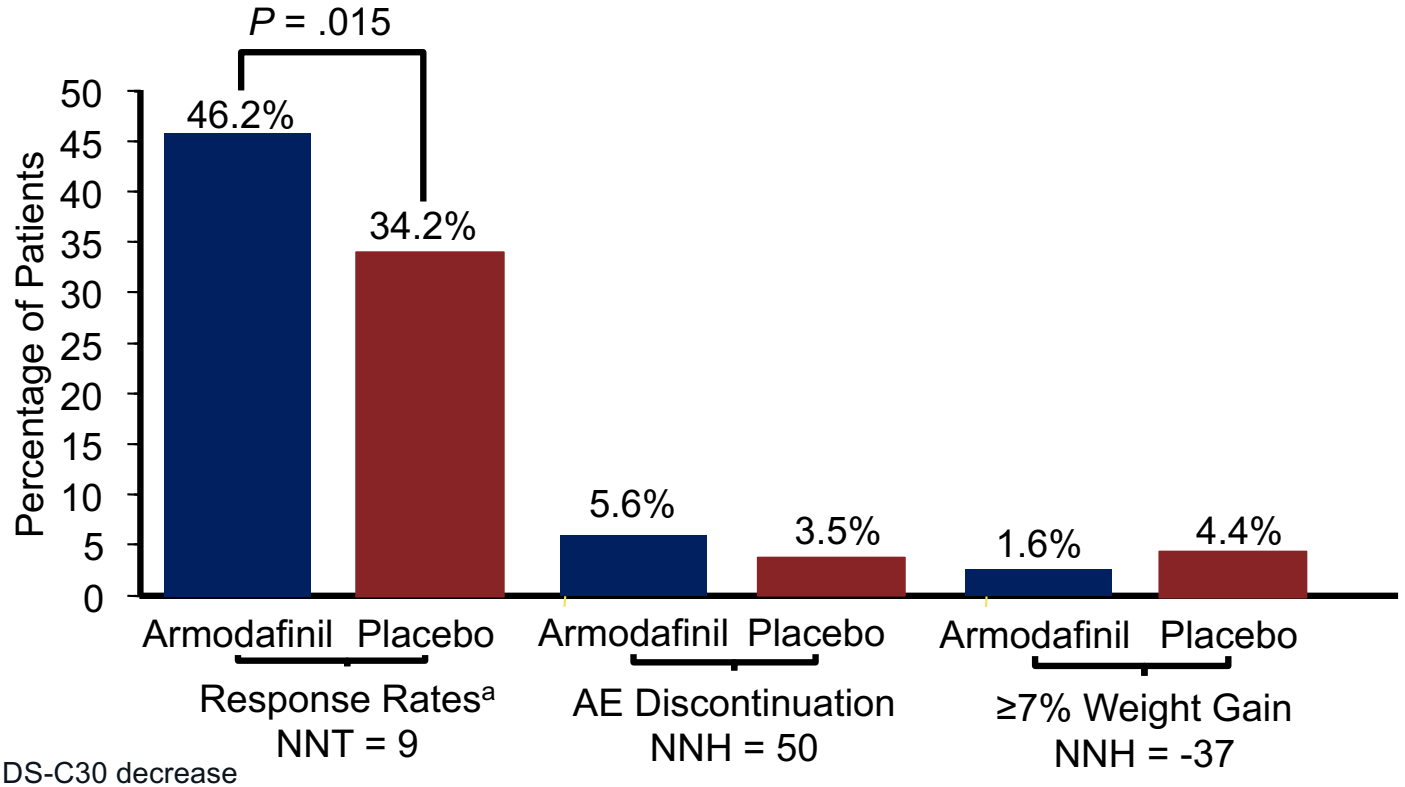


- Ketamine noncompetitive NMDA antagonist
- FDA approved as a general anesthetic
- 0.5 mg/kg over 40 minutes vs one infusion of saline placebo.
- Almost immediate reductions in depression rating scores.

*Not FDA approved for bipolar depression

Zarate CA, et al. *Biol Psychiatry*. 2012;71(11):939-946.

8-Week Randomized Double-Blind Adjunctive Armodafinil* in Acute Bipolar I Depression: Results

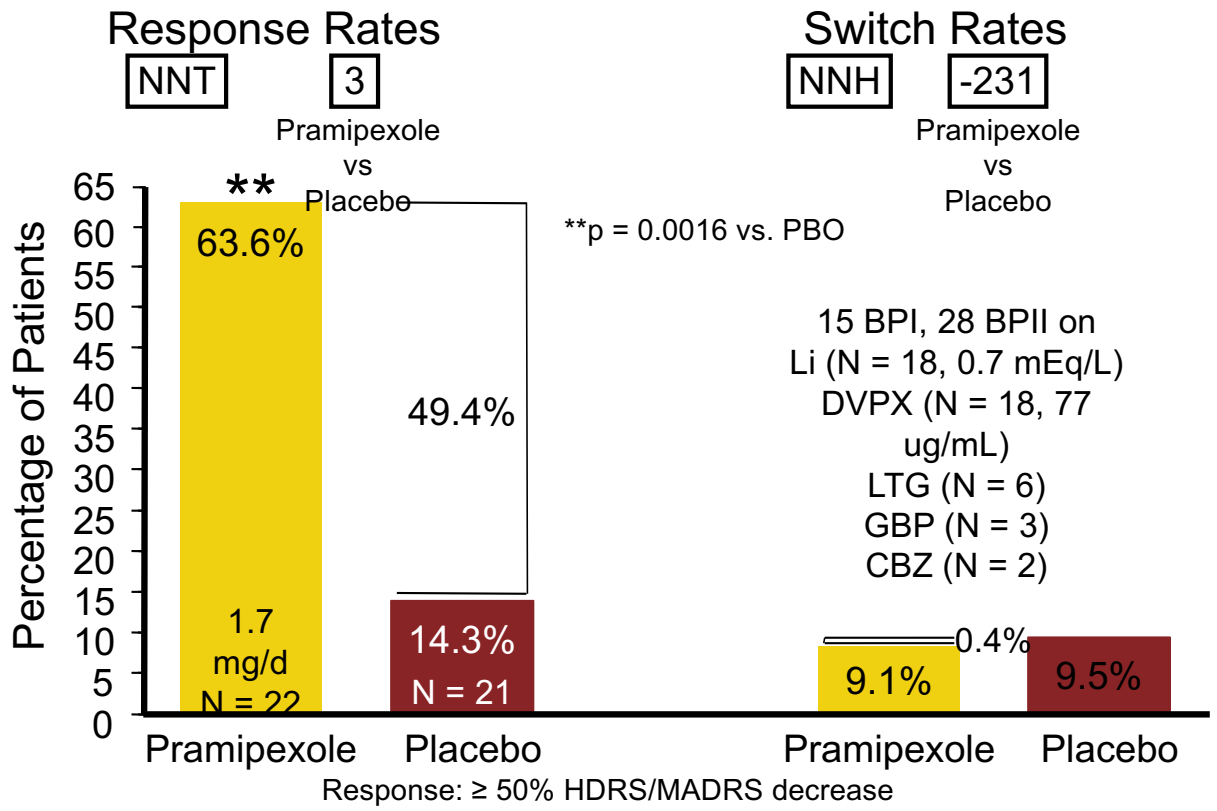


a Response: ≥50% IDS-C30 decrease

*Not FDA approved for bipolar depression

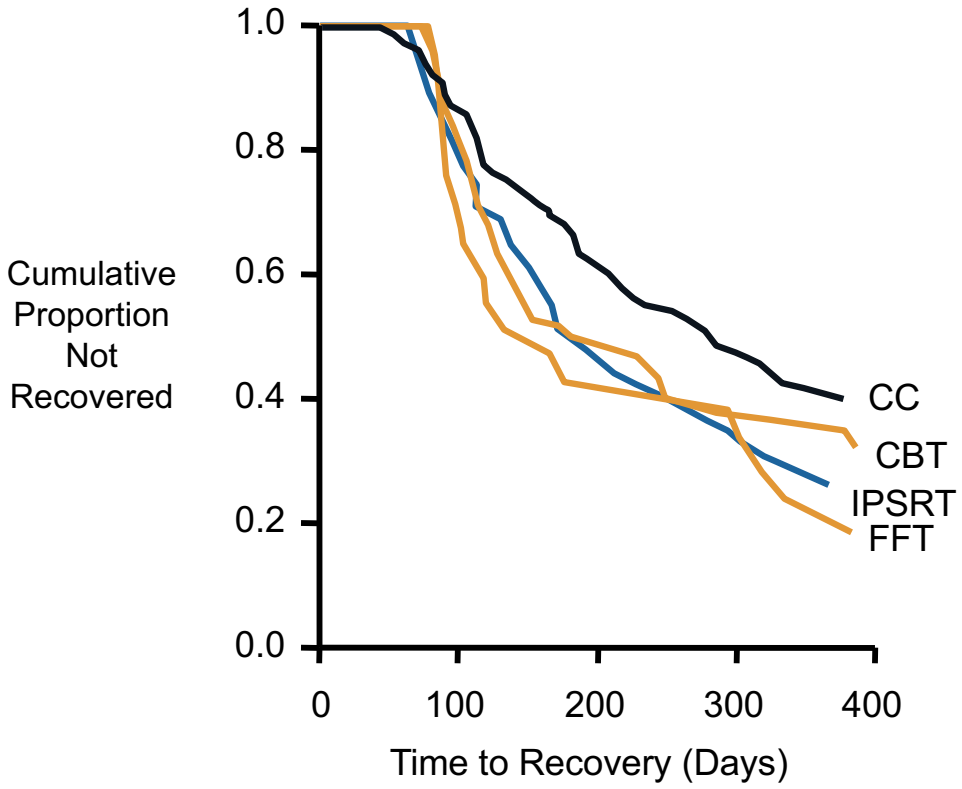
Calabrese J, et al. *J Clin Psychiatry* 2014;75(10):1054-1061.

(Pooled) 6-week Randomized Double-Blind Adjunctive Pramipexole in Acute Bipolar Depression



Goldberg JF, et al. *Am J Psychiatry* 2004;161:564-6; Zarate CA, et al. *Biol Psychiatry* 2004;56:54-60.

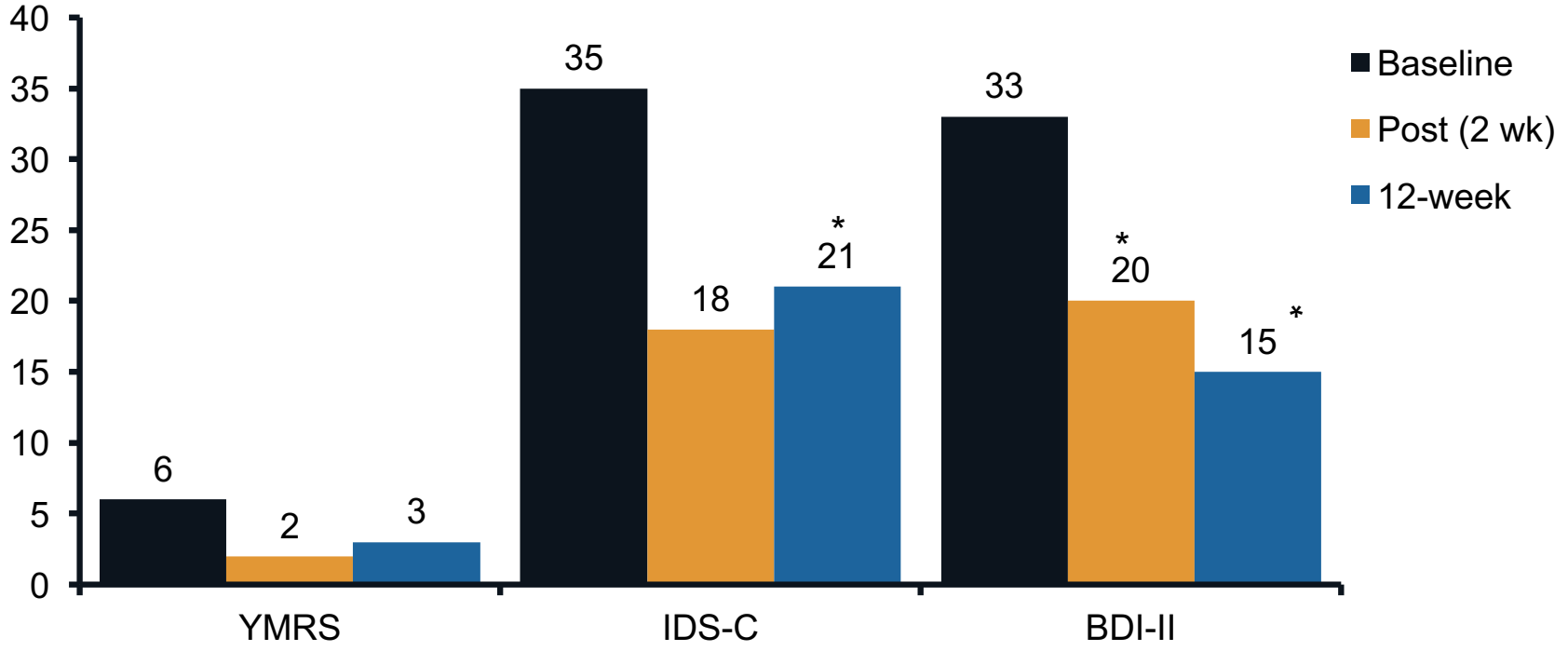
Intensive Psychotherapies Improve Bipolar Depression



- N = 293 bipolar depressed outpatients
- Protocol meds + 9 mos:
  - FFT (family-focused therapy)
  - IPSRT (interpersonal and social rhythm therapy)
  - CBT (cognitive behavior therapy)
  - CC (collaborative care)
- Intensive psychotherapies
  - Higher recovery rate
  - Shorter time to recovery
  - 1.6x more likely to be clinically well during any study month

Miklowitz DJ et al. *Arch Gen Psychiatry*. 2007;64(4):419-426.

Maintenance of Antidepressant Response After Group IPSRT Group for Bipolar Disorder



* $p < .05$, N=6, YMRS (Young Mania Rating Scale); IDS-C (Inventory of Depressive Symptomatology-Clinician Rated); BDI-II (Beck Depression Inventory-II)

Hoberg AA, et al. *Perspect Psychiatr Care*. 2013;49(4):226-234.

Evidence Base for Treatment of BP Depression

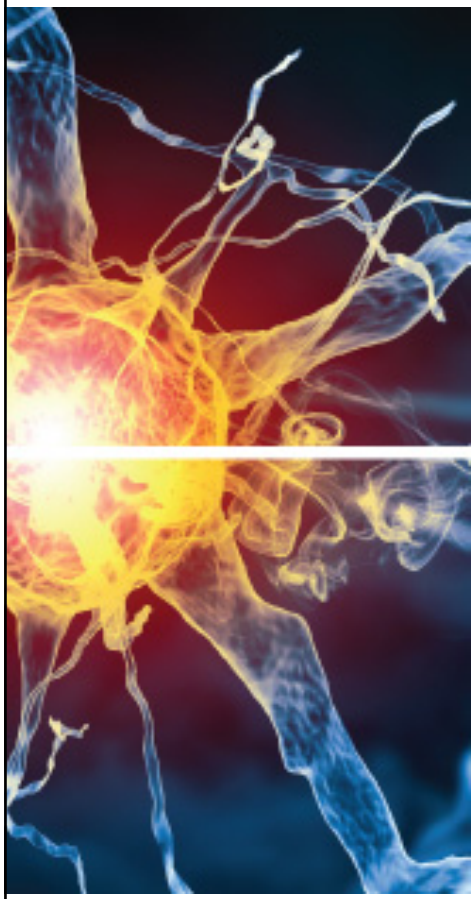
Drug	Evidence Base	Drug	Evidence Base
Quetiapine	++	Modafinil	+/-/-
Lurasidone	++	Aripiprazole	-
Fluoxetine	+	Ziprasidone	-
Lamotrigine	+	High dose thyroxine	+
Lithium	+	Sleep Dep/Pindolol	+
Olanzapine	+	ECT	+
Pramipexole	+	Clozapine	?
Valproate	+	TMS	?
Ketamine	+/+	DBS	?

++ = At least 1 fully powered, randomized, placebo-controlled, double-blind, parallel-group, positive trial with moderate-to-large effect-size; + = At least 1 positive randomized, controlled trial or small placebo-controlled, double-blind, parallel-group trial or small effect size; – = Controlled evidence of lack of efficacy; ? = No data.

Vieta E. *World J Biol Psychiatry*. 2009;10(2):82-84.; Zarate CA, et al. *Am J Psychiatry* 2004;161(1):169-171.; Diazgranados N, et al. *Arch Gen Psychiatry* 2010;67(8):793-802.;Goldberg JF, et al. *Am J Psychiatry* 2004;161(3):564-566.; Frye MA, et al. *Am J Psychiatry*. 2007;164(8):1242-1249.; Calabrese JR, et al. *J Clin Psychiatry* 2010;12(4):404-413.

Conclusions

- Evidence-based options
  - OFC, Quetiapine, Lamotrigine, Lurasidone
- Maximize the mood stabilizer
- Evidence base + Comorbidity
  - Psychotic depression or psychotic illness – AAP
  - Weight neutrality – ARI, LUR, ZIP, LTG
  - Migraine – valproate
  - Smoking cessation – bupropion (with MS)
  - Antisuicidal or classic illness- lithium
- Antidepressants in BP depression
  - Evidence base does not support monotherapy use
  - Switch rate is not 0%



Questions & Answers