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Master Class for Neuroscience Professional Development

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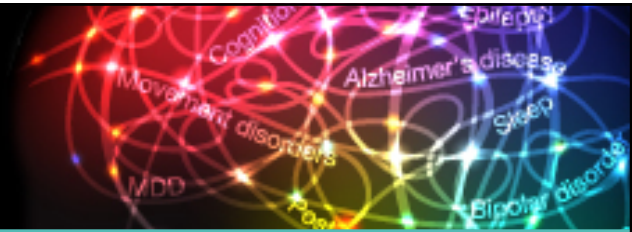
Mania, Depression and Mixed Episodes: The Spectrum of Bipolar Disorder

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Disclosures



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- **Disclosure Declaration:** Mayo Clinic has a financial interest in AssureRX and the technology referenced in this publication/presentation

Learning Objective 1

Initiate management strategies for the acute symptoms in bipolar disorder that focus on relapse prevention, functional recovery, and achieving remission

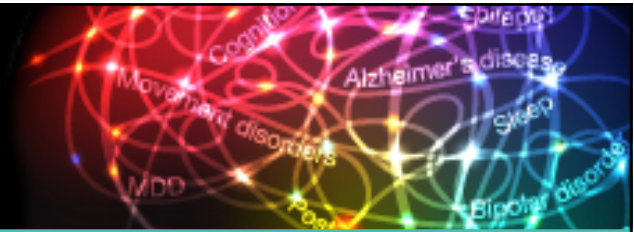


Learning Objective 2

Select treatment strategies for bipolar disorder that reduce the risk of adverse metabolic consequences

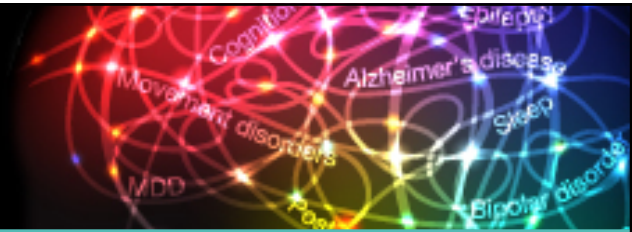


Spectrum Outline



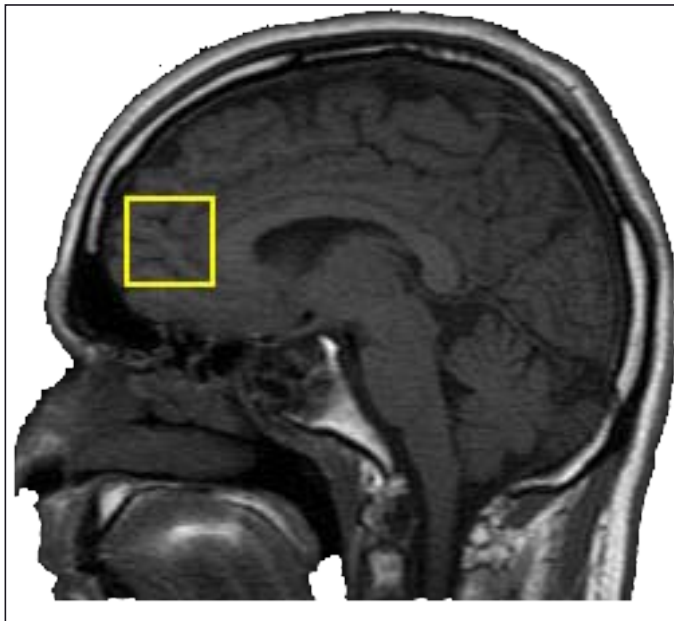
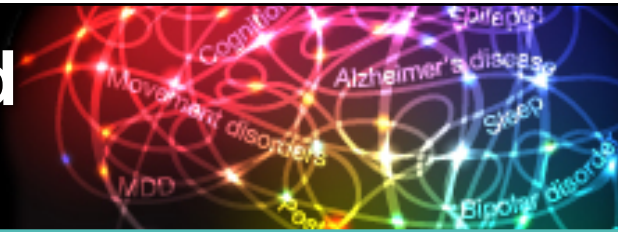
- Acute Mania
 - FDA approved
 - Adjunctive lorazepam
 - Biomarkers
- Acute Bipolar Depression
 - FDA approved
 - Off label
 - Antidepressant Induced Mania (AIM+)
- Mixed Specifier
 - DSM5 addition
- Maintenance

FDA Indications: Acute Mania

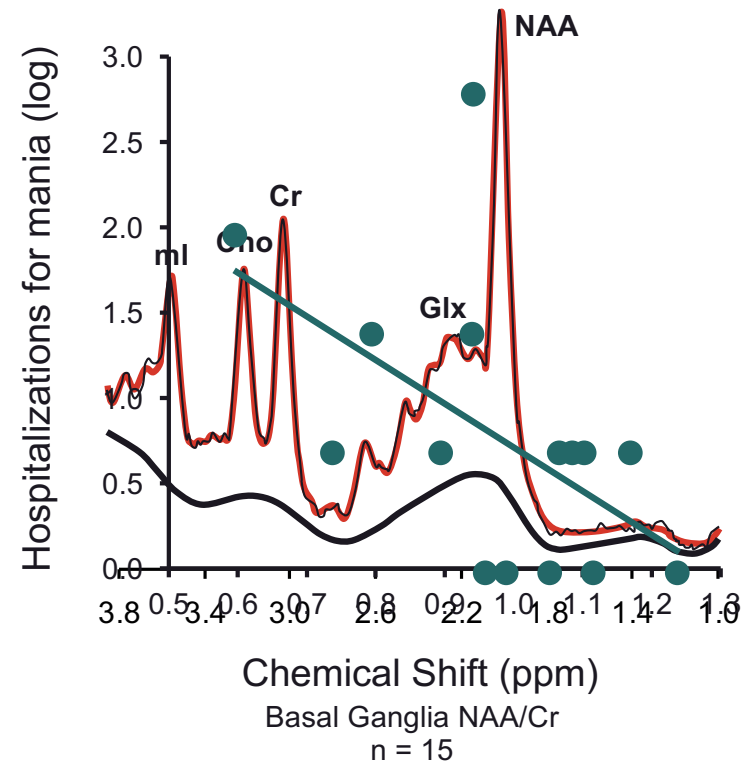


- Aripiprazole, asenapine, olanzapine, risperidone, quetiapine, ziprasidone, cariprazine (dopamine D2/D3 receptor partial agonist), chlorpromazine
- Carbamazepine ER and divalproex sodium
- Lithium
- Inhaled loxapine is approved for acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults

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 cm³)

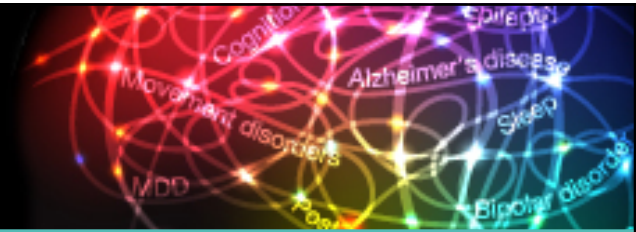


NAA-/Cr = N- acetylaspartate /creatine

Frye MA, et al. *Psychiatry Res.* 2007;154(3):259-265; Tsai G, et al. *Prog Neurobiol* 1995;46(5):531-540.

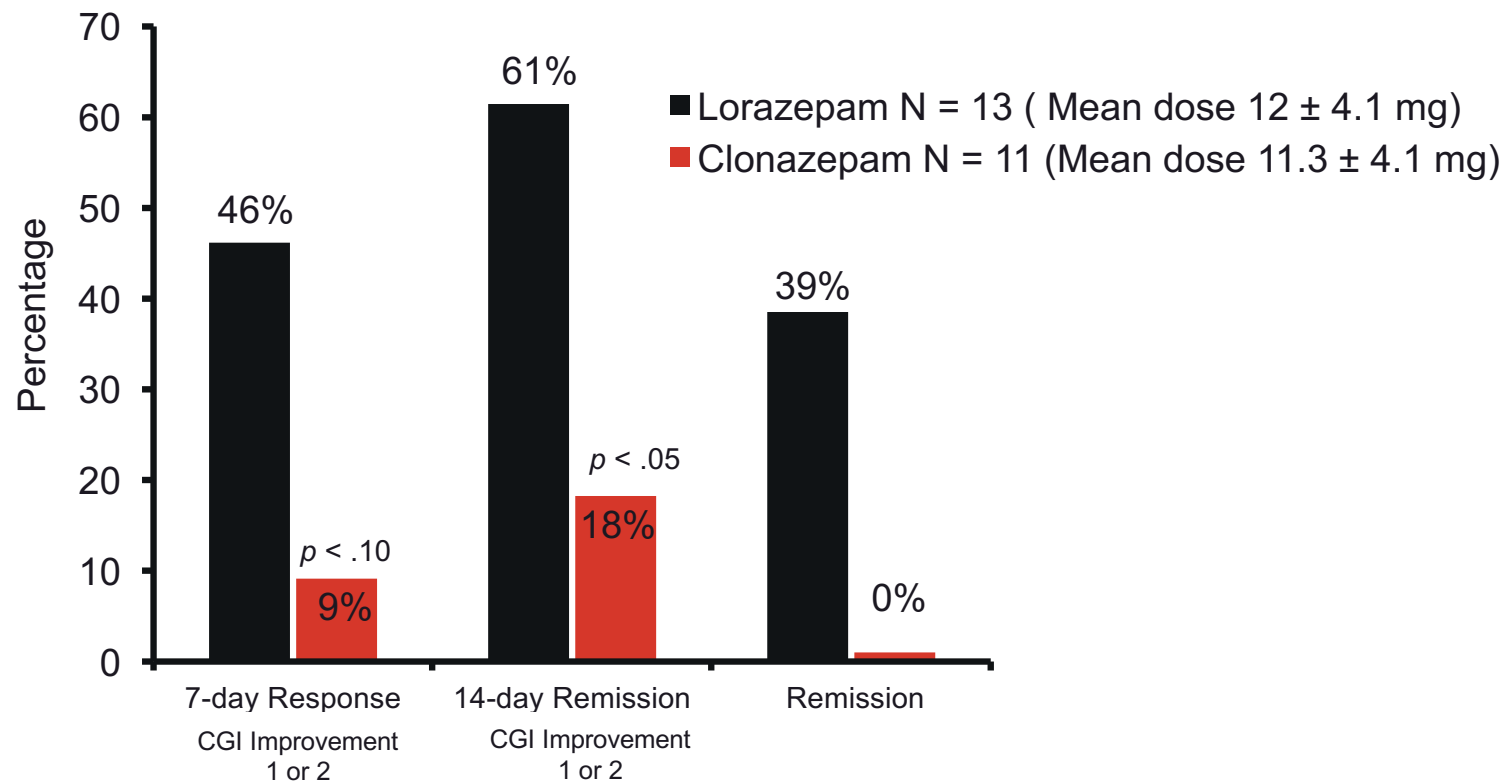
Altshuler LL. *Biol Psychiatry.* 1993;33(8-9):563-565.

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 Monotherapy in Acute Mania



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

FDA Approved Bipolar Disorder Treatments*

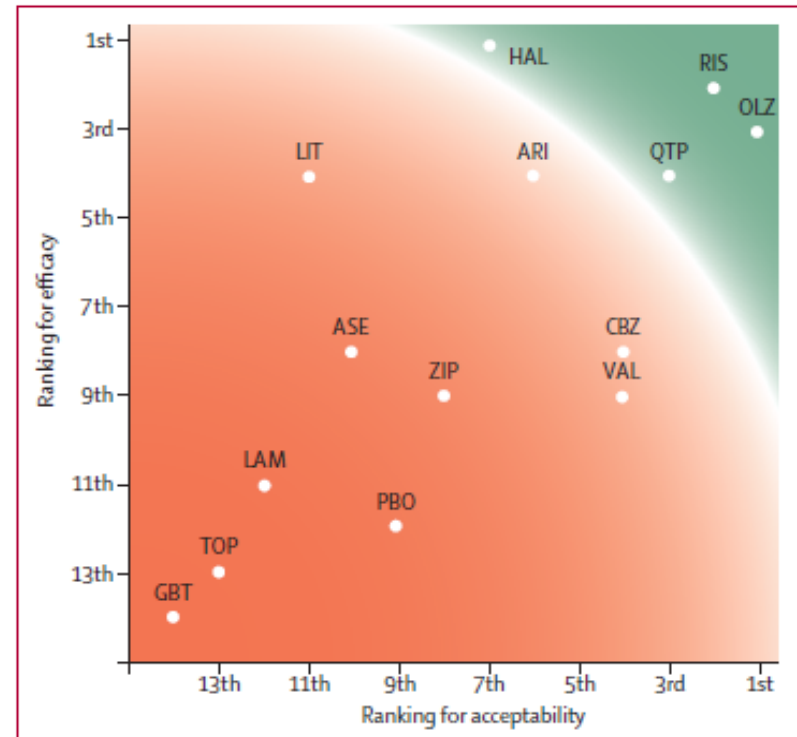
Agent	Manic	Mixed	Depression	Maintenance
Aripiprazole (Oral/IM)**	+	+	–	+ _(oral/IM)
Asenapine**	+	+	–	–
Cariprazine	+	+	–	–
Lurasidone*	–	–	+	–
Olanzapine**	+	+	–	+
Olanzapine/Fluoxetine	–	–	+	–
Quetiapine/XR**	+	+	+	+
Risperidone (Oral/IM) **	+	+	–	+ _(IM)
Ziprasidone*	+	+	–	+
Chlorpromazine	+	–	–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

*Monotherapy and adjunct to Li or DVPX and with / without psychosis; +Adolescent and/or pediatric indication.

Comparative Efficacy and Acceptability of Antimanic Drugs in Acute Mania: A Multiple-Treatments Meta-Analysis

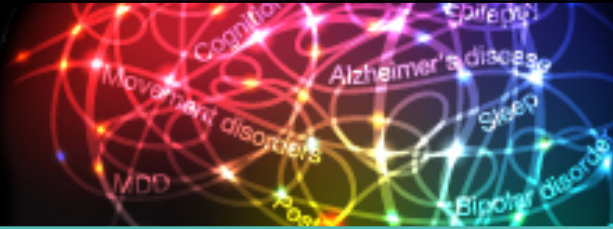


- Data are from a systematic review of 68 randomized trials of pharmacotherapy for acute mania in adults (16,073 patients)
- Any-cause early discontinuation is proxy for “acceptability”
- Multiple treatments meta-analysis (accounts for direct and indirect comparisons)

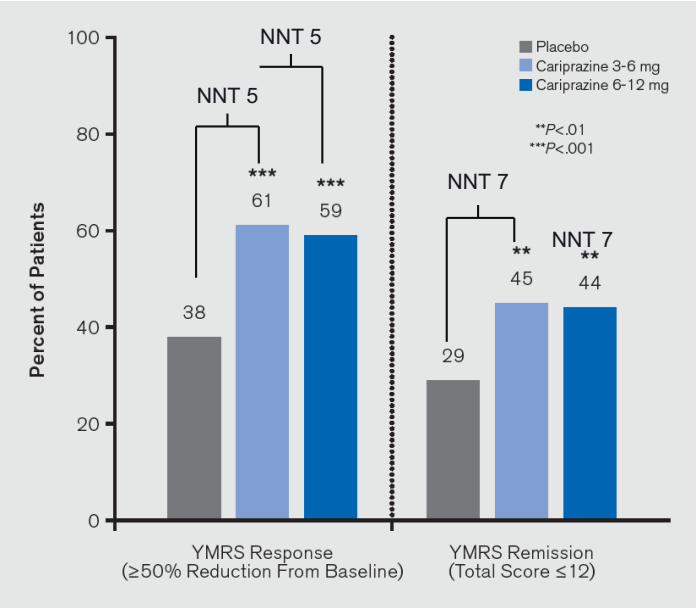
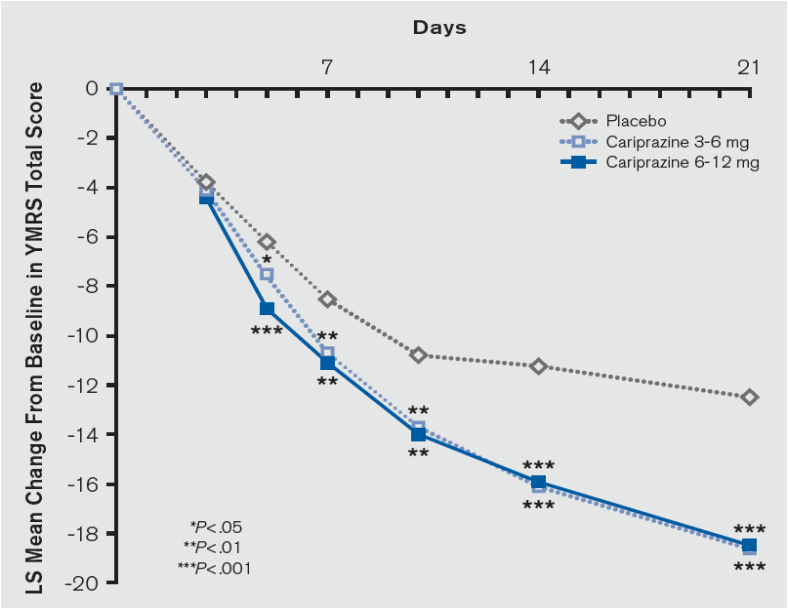


Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcomes) and dropout rate

Cariprazine for Acute Mania Associated With Bipolar I Disorder

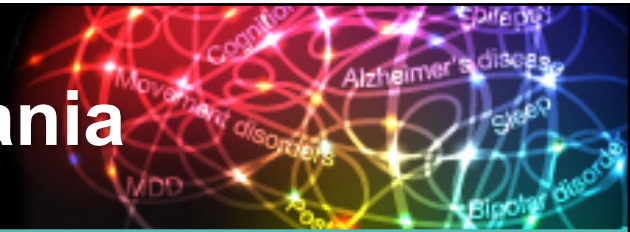


- Randomized, DB, PLC-controlled trial (2010-2011); cariprazine 3-6 mg/d vs cariprazine 6-12 mg/d vs PLC over 3 weeks; 497 patients with BP-I manic or mixed episodes; primary endpoint – change YMRS total score; secondary endpoints – response, remission



DB = double blind; PLC = placebo.
 Calabrese JR, et al. *J Clin Psychiatry* 2015;76(3):284-292.

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

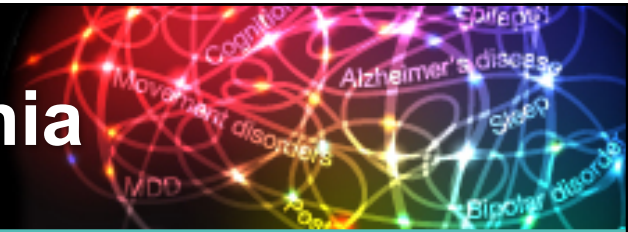
- Tardive dyskinesia, neuroleptic malignant syndrome
- Weight gain, related dysmetabolic effects

TD = tardive dyskinesia; EPS = extrapyramidal symptoms.

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

Yildiz A, et al. *Neuropsychopharmacology.* 2011;36(2):375-389.

Typical Antipsychotics in Acute Mania

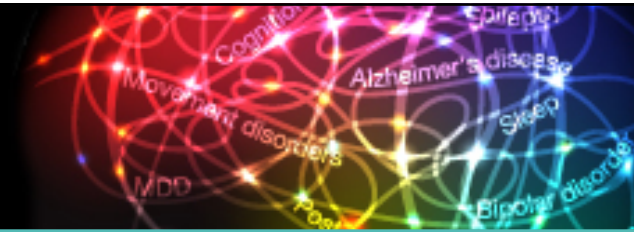


- Pros
 - Efficacious for acute mania
 - Haloperidol* may be more rapidly efficacious than olanzapine, quetiapine, ziprasidone
- Cons/adverse effects
 - Acute EPS, tardive dyskinesia, akathisia, neuroleptic malignant syndrome
- Negative impact on course of illness
 - ↑ post-mania depressive symptom severity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

*Not FDA approved for bipolar disorder

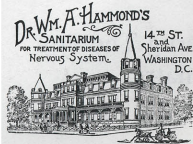
Vietta E, et al. *J Psychopharmacol*. 2010;24(4):547-558; Muralidharan K, et al. *J Affect Disord*. 2013;150(2):408-414; Goikolea JM, et al. *Eur Neuropsychopharmacol*. 2013;23(4):305-316; Kane JM. *J Clin Psychiatry* (60 Suppl 5).1999;60(Suppl 5):43-47.

Lithium in Acute Mania



Buffalo Lithia Water.

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



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 LITHAEMIA, and that unless this condition is removed, a cure is very often frustrated, and not infrequently entirely prevented. It is quite common to find cases that in CEREBRAL CONGESTION, producing INSOMNIA, NERVOUS PROSTRATION, resulting from overmental work or such emotional disturbance, and in epilepsy (by my reading 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 LITHAEMIA 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."

Its especial value in Nervous Prostration and other Nervous Diseases complicated with Lithaemia. 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.

"Several years ago, however, I began to treat such cases with BUFFALO LITHIA WATER, with a result that was so 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 feed him, as it were, with the water, making him drink a gallon, or even more, in the twenty-four hours. By this course the stagnant, morbid irritability of the patient disappears, the tongue becomes clean, the wandering pains in the head are subdued, 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, NEURALGIA, 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.

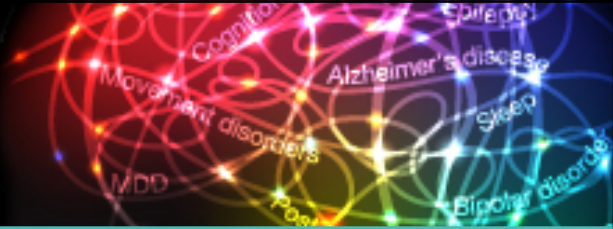
THOMAS F. GOODE,
Buffalo Lithia Springs,
Virginia.

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

*Not FDA approved for acute mania.

Frye MA, et al. *J Clin Psychopharmacol*. 1998;18(6):461-464; Goodwin FK, et al. *JAMA*. 1990;264(8):950-954; APA Practice Guidelines. American Psychiatric Press. Arlington, VA 2002.; Bowden CL, et al. *JAMA*. 1994;271:918-924.

Variable Lithium Response Rate



Based on Bipolar Subtype

Poor Response 30%	} Rapid Cycling	Mixed Mania	Substance Abuse	(-) Family History	>3 Episodes	DMI Pattern
<hr/>						
Good Response 70%	} Nonrapid Cycling	Euphoric Mania	No Substance Abuse	(+) Family History	Few Lifetime Episodes	MDI Pattern

DMI = Depression mania euthymic interval; MDI = Mania depression euthymic interval
 Frye MA, et al. *J Affect Disord.* 1998;48(2):91-104.

ConLi⁺Gen

The international Consortium on Lithium Genetics

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



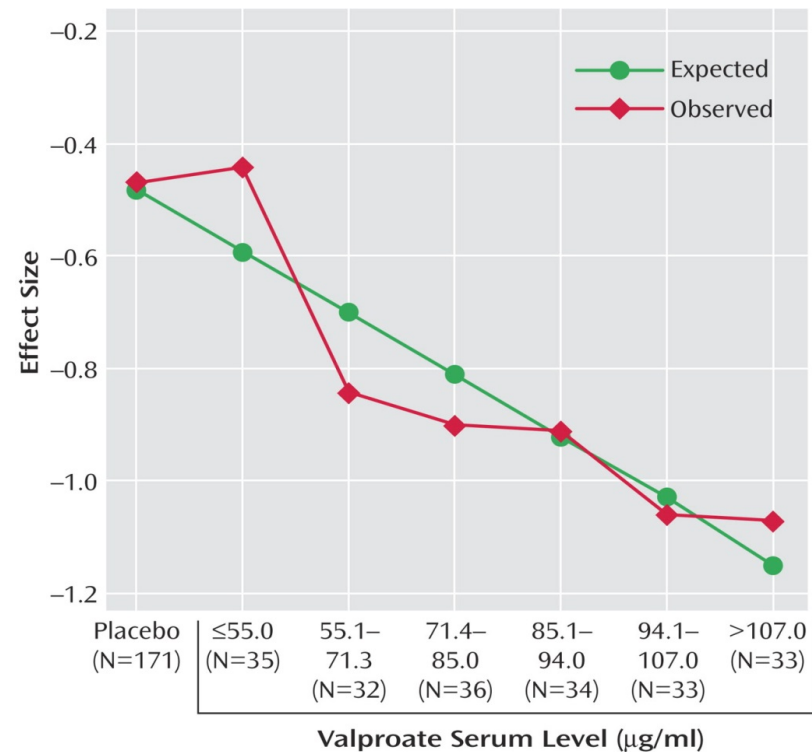
- 4 linked SNPs chromosome 21 associated with lithium response
 - (rs79663003, $p=1.37 \times 10^{-8}$; rs78015114, $p = 1.31 \times 10^{-8}$; rs74795342, $p=3.31 \times 10^{-9}$; and rs75222709, $p = 3.50 \times 10^{-9}$)
- Replicated prospective study (n = 73) lithium monotherapy X 2 yrs
 - ($p = .03268$, 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

SNP = single nucleotide polymorphism.
Hou L, et al, *Lancet* 2016;387(10023):1085-1093.

Valproate for Mania: Dose-Response Effect

374 manic patients stratified into 6 groups based on VPA serum level ranges

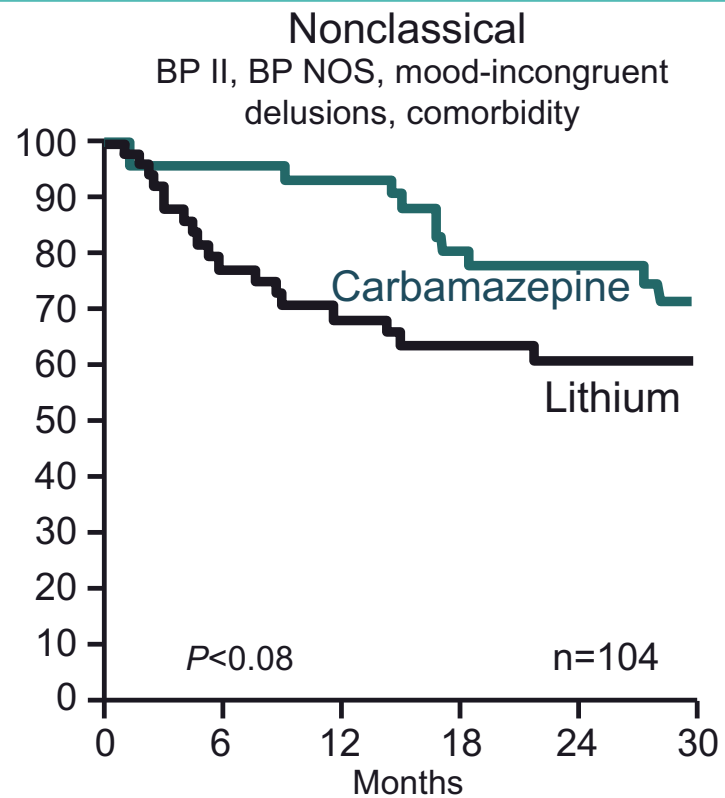
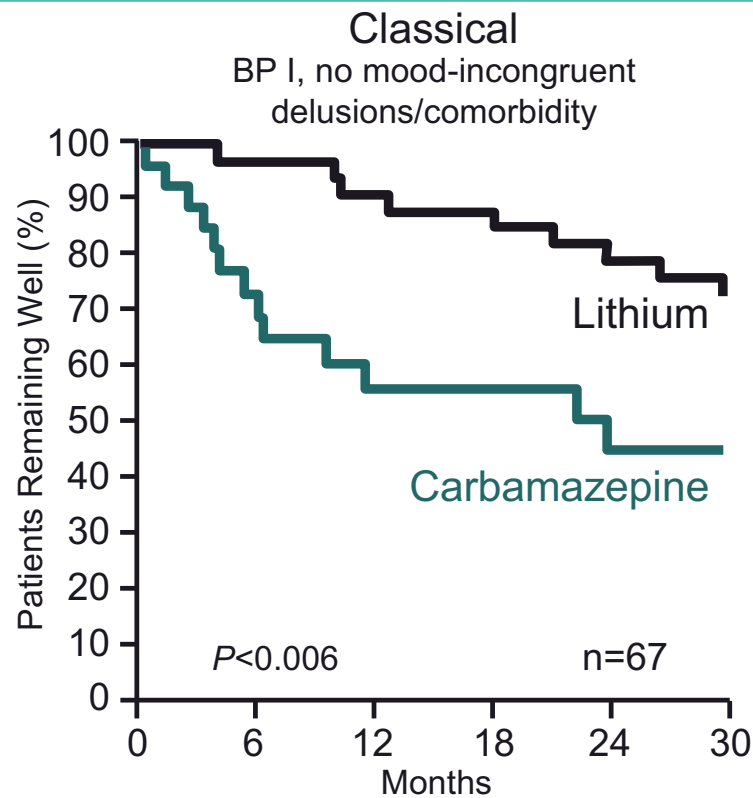
- Linear relationship between VPA serum level and therapeutic response
- Efficacy significantly > PLC beginning at 71.4-85.0 mcg/mL (consistent at all higher VPA concentrations)
- ES was associated with highest VPA serum levels (>94 mcg/mL)



VPA = valproate serum level; ES = effect size.

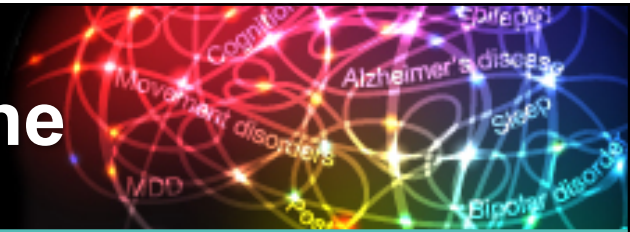
Allen MH, et al. *Am J Psychiatry*. 2006;163(2):272-275.

Maintenance Treatment of Bipolar Disorder: Differential Response to Lithium and Carbamazepine*



*Not FDA approved for bipolar disorder; BP I=bipolar I disorder; BP II=bipolar II disorder; BP NOS=bipolar disorder not otherwise specified.
Greil W, et al. *J Clin Psychopharmacol*. 1998;18(6):455-460.

FDA Alert 12/12/2007: Carbamazepine



- HLA-B*1502 allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians
- Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting carbamazepine
- If positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions

Divalproex and Carbamazepine in Acute Mania



● Pros

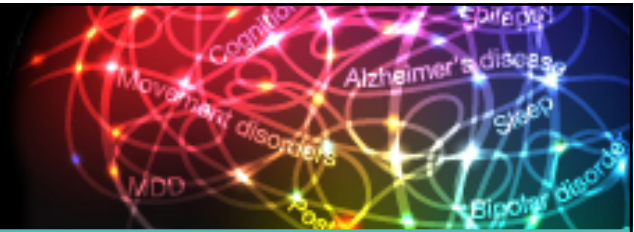
- Effective in manic and mixed episodes
- Effective in alcohol withdrawal & relapse prevention
- Several effective in migraine prevention

● Cons

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

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):126-132; Jiang B, et al. *Med Hypotheses*. 2009;73(6):996-1004.

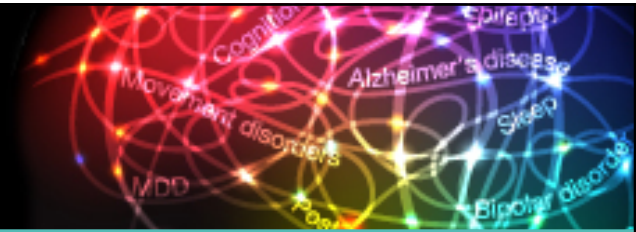
Other Anticonvulsant Drugs



- 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

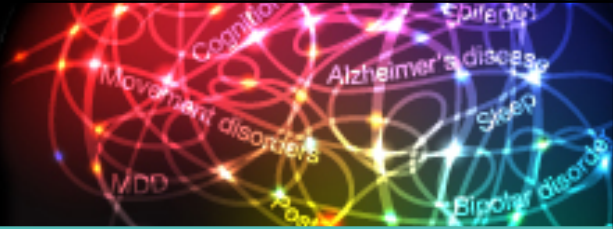
Wagner KD, et al. *Am J Psychiatry*. 2006;163(7):1179-1186; Rosa AR, et al. *CNS Neurosci Ther*. 2011;17(3):167-177; Pande AC, et al. *Bipolar Disord*. 2000;2(3 Pt 2):249-55; Kushner SF, et al. *Bipolar Disord*. 2006;8(1):15-27.

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

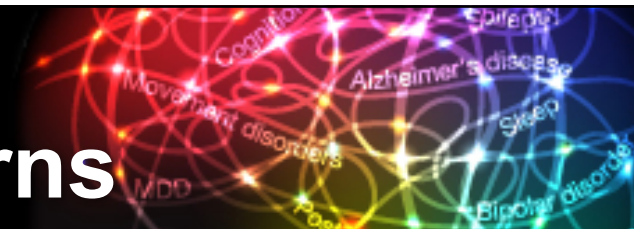
Target Dose Range for Acute Mania



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 Stabilizer Safety and Tolerability Concerns



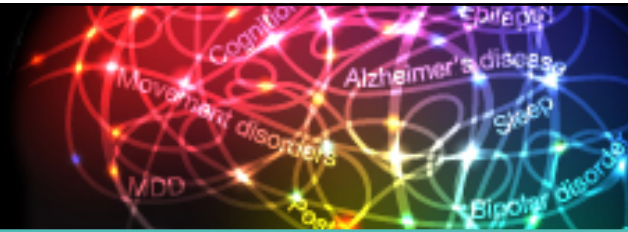
Lithium	Valproate	Carbamazepine	Lamotrigine
Gastrointestinal	Gastrointestinal	Gastrointestinal	Gastrointestinal
Weight gain	Weight gain	Rash	Rash
Neurotoxicity	Tremor	Neurotoxicity	Headache
Renal toxicity	Hepatotoxicity	Hepatotoxicity	Dizziness
Thyroid toxicity	Thrombocytopenia	Thyroid changes	Pruritis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

= boxed warning in prescribing information; (?) = recent alert

All Mood Stabilizers Have at Least One Boxed Warning

In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005; *Physician's Desk Reference*. 2008.

Antipsychotic Safety and Tolerability Concerns



First-Generation
Depression
Akathisia
Acute dystonia
Tardive dyskinesia^a
Weight gain
Sedation
Anticholinergic
Cardiac, Orthostasis
Hyperprolactinemia
Neuroleptic malignant^a

Cardiac/pneumonia in older adults^a

Second-Generation
Weight gain
Sedation
Hyperglycemia, Diabetes^b
Suicidality in age ≤ 24 ^c
Akathisia
Hyperprolactinemia
Cerebrovascular in elderly^d
Cardiac, Orthostasis
Tardive dyskinesia^a
Neuroleptic malignant^a

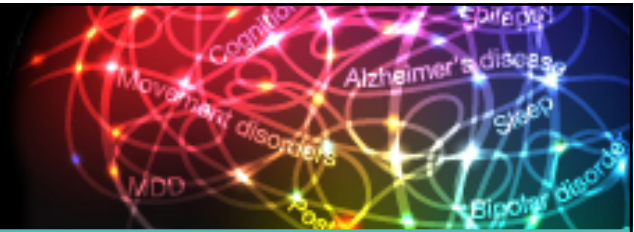
Cardiac/pneumonia in older adults^a

Warnings - boxed; ^a antipsychotic class warning; ^b Second generation antipsychotic class warning;
^c aripiprazole, quetiapine, olanzapine + fluoxetine combination (antidepressant class warning); ^d risperidone, olanzapine, aripiprazole

All Antipsychotics Have at Least One Boxed Warning

In: Ketter TA (ed). *Advances in the Treatment of Bipolar Disorder*. 2005. *Physician's Desk Reference*. 2008.

Kraepelinian Mixed States

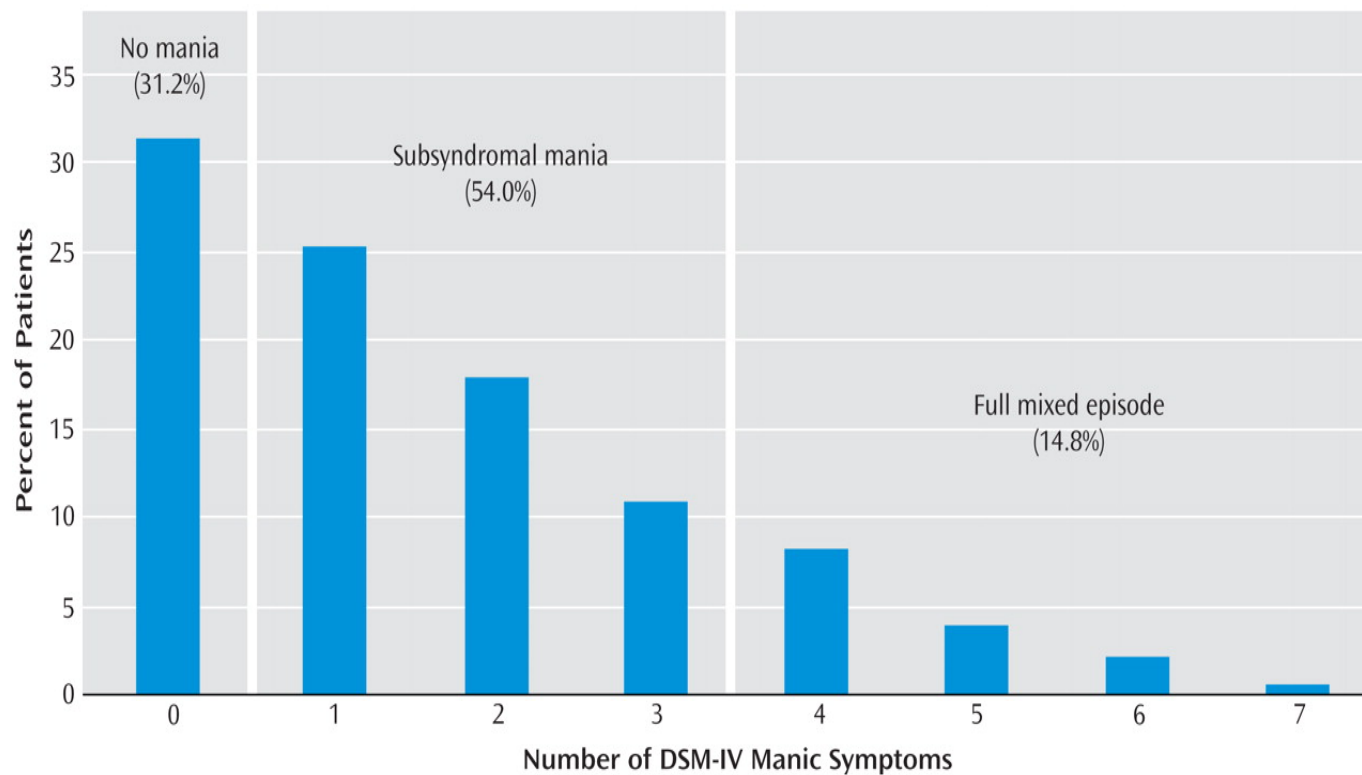


- Orthodox mania
- Depressive or anxious mania
- Excited depression
- Mania with poverty of thought
- Orthodox depression
- Manic stupor
- Depression with flight of ideas
- Inhibited mania



Kraepelin E. *Manic-Depressive Insanity and Paranoia*; 1921.

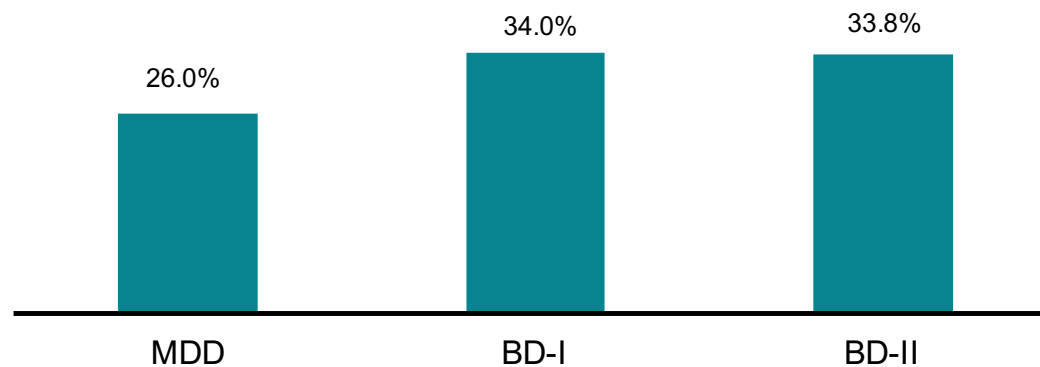
DSM-IV Mood Elevation Symptoms in STEP-BD Bipolar Depressive Episodes



N = 1,380

Goldberg JF, et al. *Am J Psychiatry*. 2009;166:173-181.

Mixed Features in Major Depressive AND Bipolar Disorder: The International Mood Disorders Collaborative Project

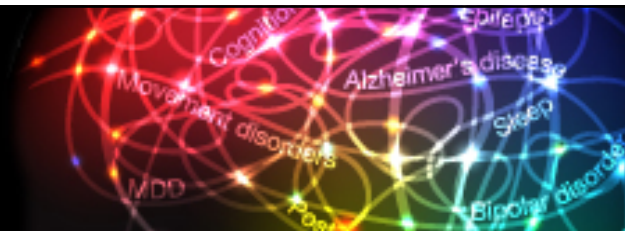


*Post hoc analysis of participants who met criteria for a current mood episode as MDD ($n = 506$) or BD (BD-I: $n = 216$, BD-II: $n = 130$).

Mixed features specifier (MFS) was operationalized as a score ≥ 1 on 3 or more select items on the Young Mania Rating Scale (YMRS) or ≥ 1 on 3 select items of the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D-17).

McIntyre RS, et al. *J Affect Disord.* 2015;172:259-264.

International Mood Disorders Collaborative Project

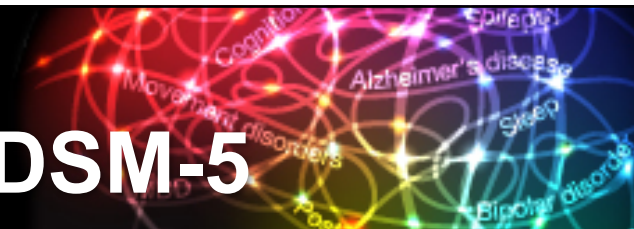


- UP (N = 506), BPI/BPII (N = 216/130, total 346)
- MFS = Index major depression & YMRS ≥ 1 on 3 or more YMRS items

Mixed Feature Specifier	UP	BPII	BPI
Depression with ≥ 1 on at least 3 YMRS items	26.0% (n = 149)	33.8% (n = 49)	34.0% (n = 65)
Mania/hypomania with ≥ 1 on at least 3 MADRS or HAMD items	NA	5.1% (n = 8)	20.4% (n = 52)

BPI = bipolar I disorder; BPII = bipolar II disorder; HAMD = Hamilton Depression Rating Scale; MADRS = Montgomery-Åsberg Depression Rating Scale; YMRS = Young Mania Rating Scale.
 McIntyre RS, et al. *J Affect Disord.* 2014;172C:259-264.

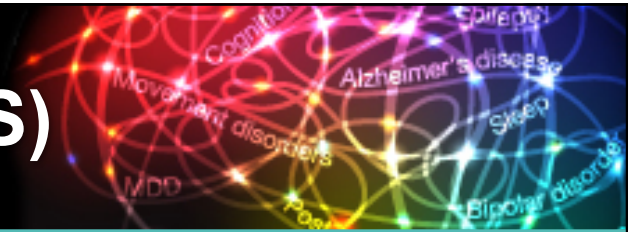
Conceptualization of Pure and Mixed States in DSM-IV-TR and DSM-5



	Core symptoms Manic Depressive	Elevated mood ≥3 <5	Elevated mood + depressed mood or loss of interest ≥3 ≥5	Depressed mood or loss of interest <3 ≥5	
DSM-IV-TR		Manic (Euphoric)	Mixed Mania	Depressive	
DSM-5		Manic	Manic with mixed features	Depressive with mixed features	
	Core symptoms Manic Depressive	Elevated mood + energy ≥3 <5	Elevated mood + energy ≥3 >3	Depressed mood or loss of interest ≥3 ≥5	Depressed mood or loss of interest <3 ≥5

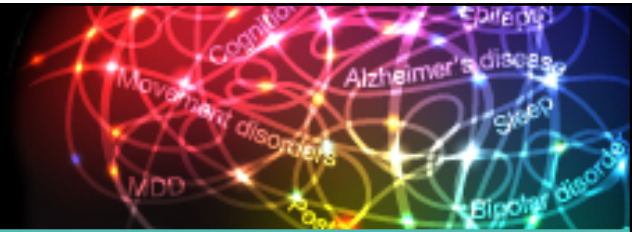
American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. APA Press, 1994.
 American Psychiatric Association. DSM-5. American Psychiatric Publishing; 2013.

DSM-5 Mixed Feature Specifier (MFS)



- Dimensional diagnostic criteria
- Syndromal episode +
 - ≥ 3 non-overlapping symptoms of opposite polarity
- Manic/Hypomanic episode
 - depressed mood, anhedonia, guilt, suicidality symptoms
- Depressive episode
 - \uparrow self-esteem, flight of ideas, \downarrow sleep need / \uparrow energy symptoms

Bipolar Depression: Best Practices



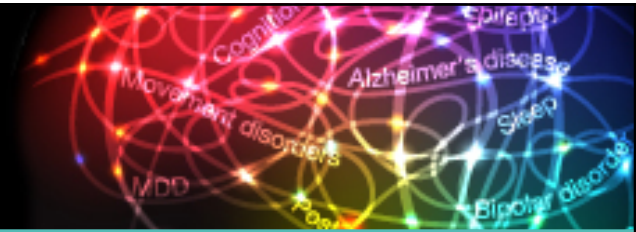
- FDA approved agents
 - Olanzapine Fluoxetine (OFC)
 - Quetiapine monotherapy
 - Lurasidone monotherapy & adjunct therapy
- Maximize the mood stabilizer
- Antidepressants FDA off-label*
 - Do they work? Are they safe?
- Psychotherapy
- Novel Treatment



The Old Guitarist Pablo Picasso 1903
The Blue Period

*Antidepressants are not indicated by US FDA for treatment of bipolar depression.

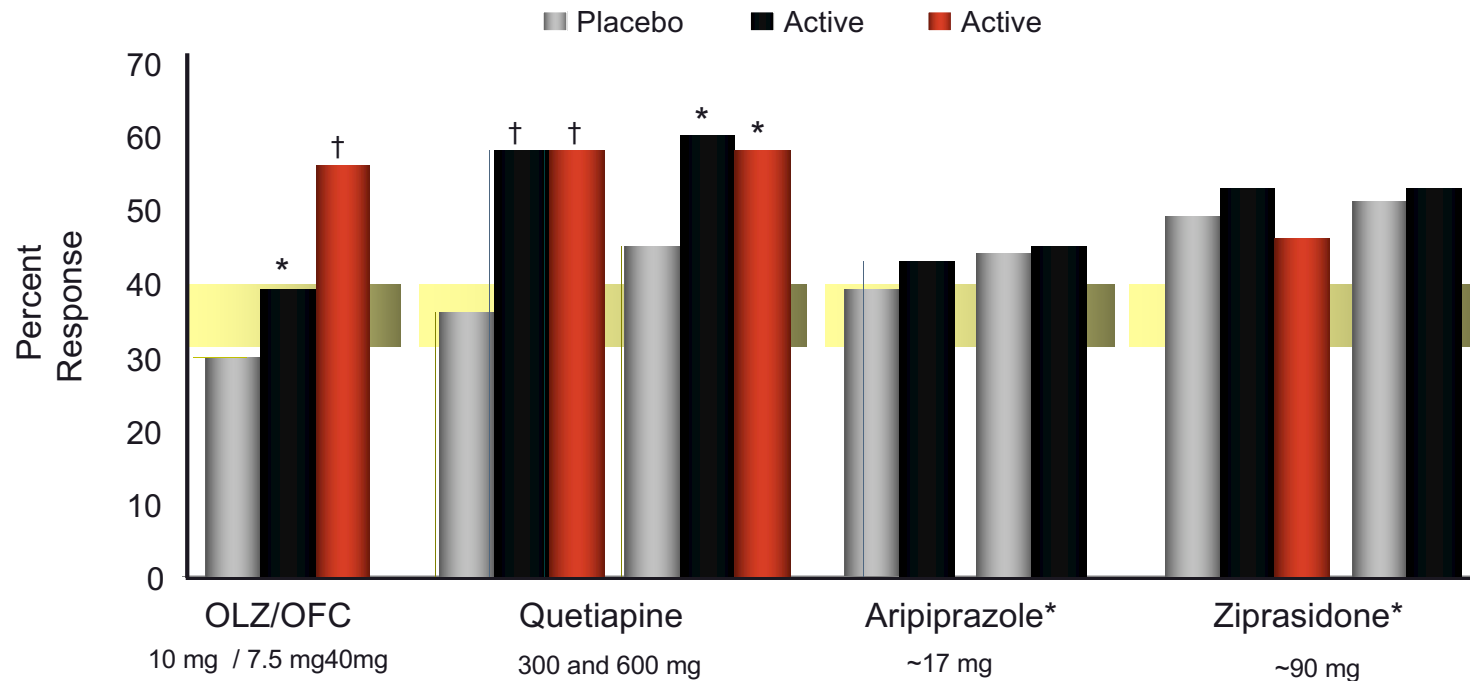
Epidemiology



- 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.

Response Rates of Atypical Antipsychotics in Bipolar Depression

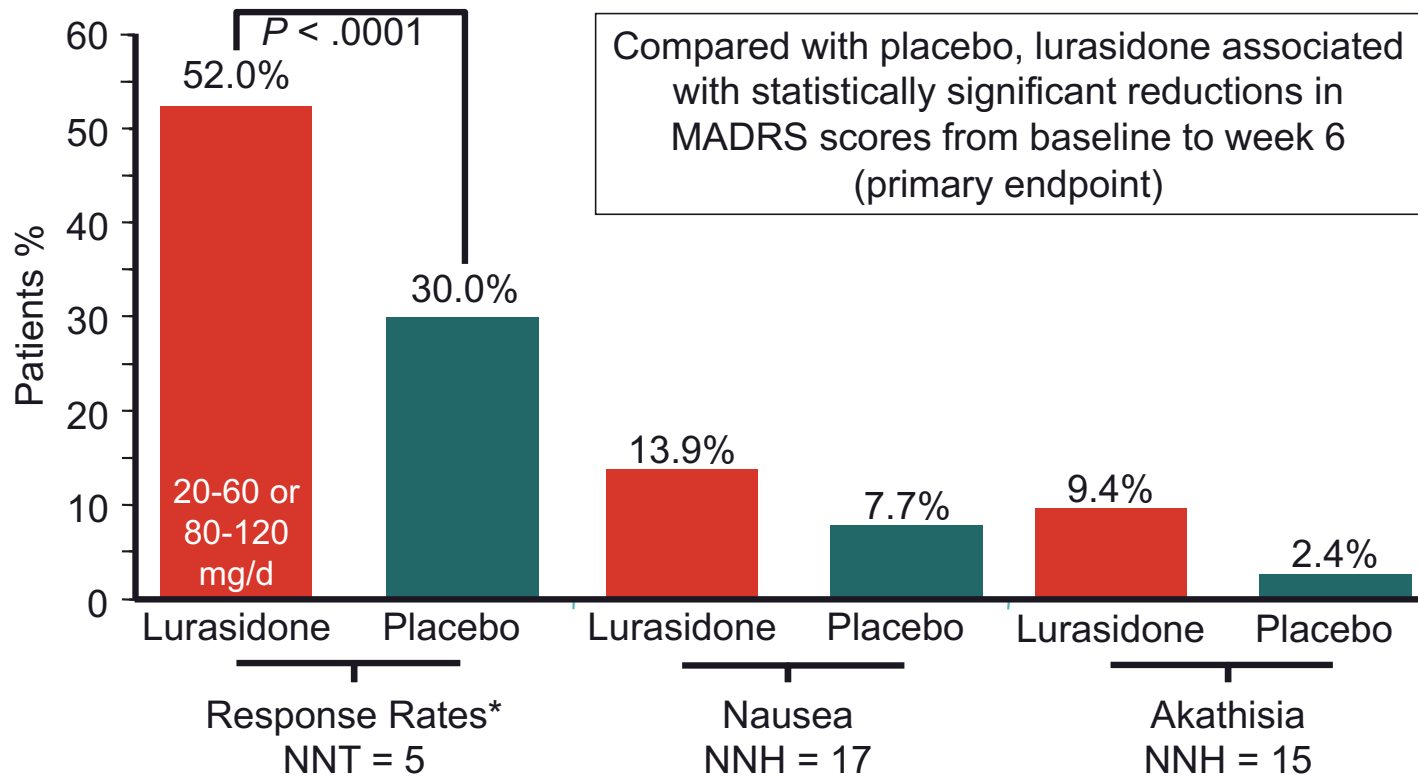


OFC = olanzapine/fluoxetine combination. * $P < 0.05$; † $P < 0.001$ vs placebo

*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

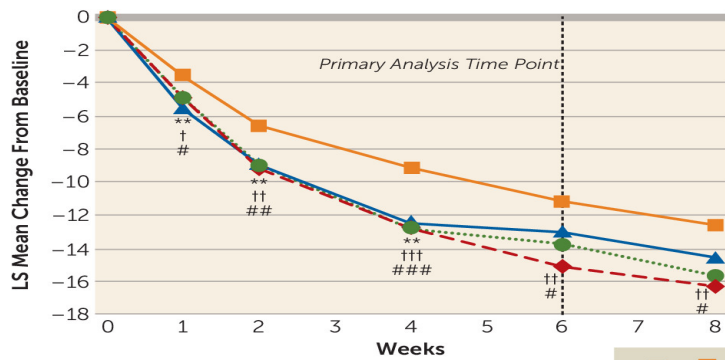


*Response: $\geq 50\%$ MADRS decrease.

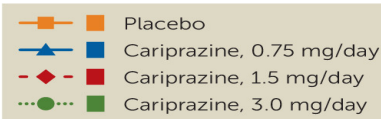
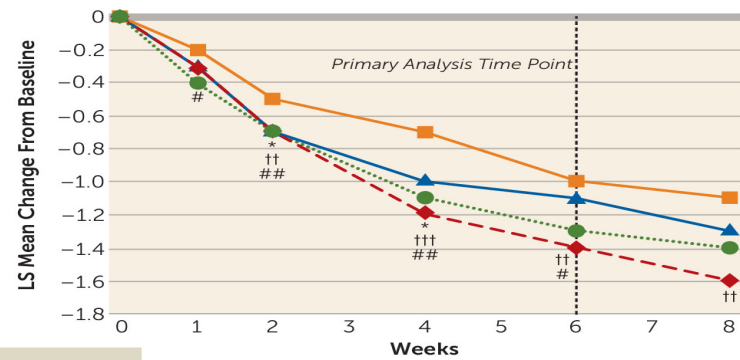
Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160-168; Loebel A, et al. *Am J Psychiatry*. 2014;171(2):169-177.

Cariprazine* vs. Placebo in Bipolar I Depression

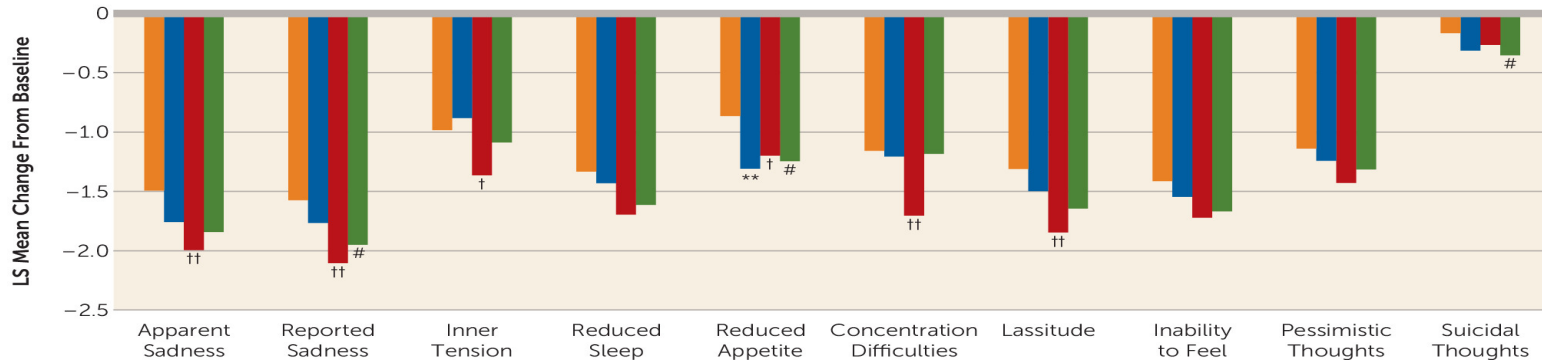
A. MADRS Total Score



B. CGI-S Score



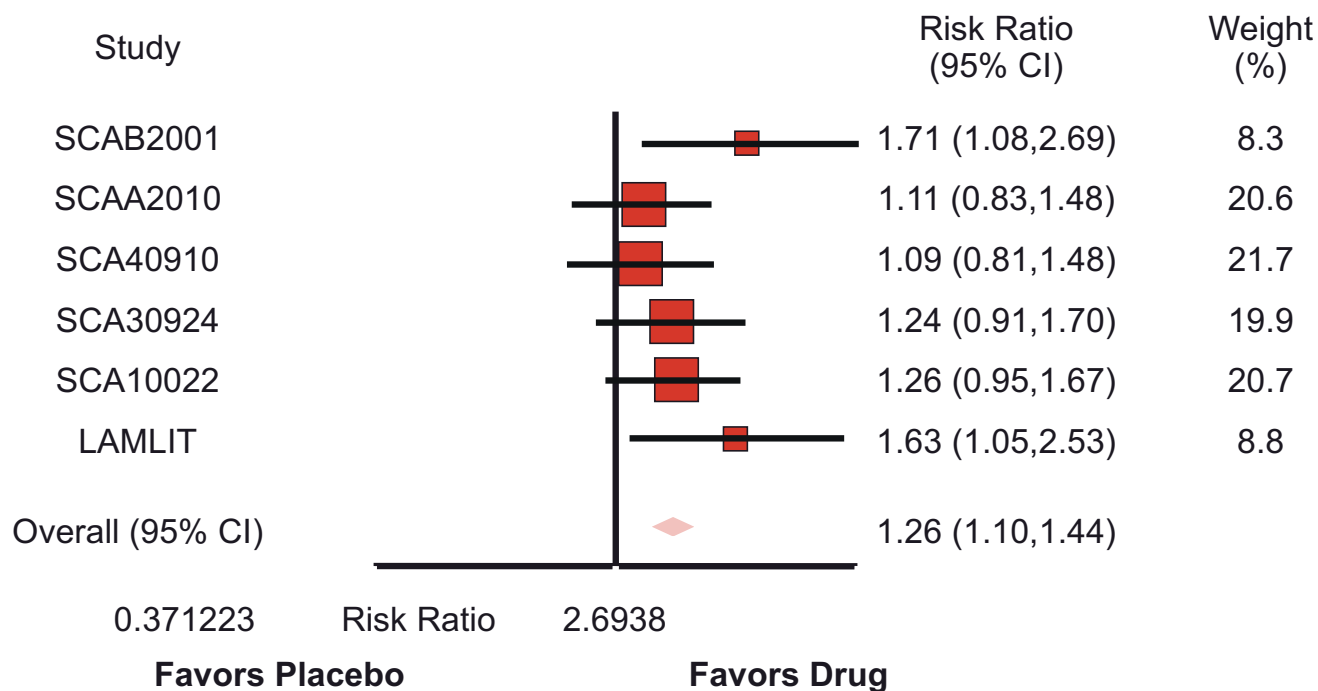
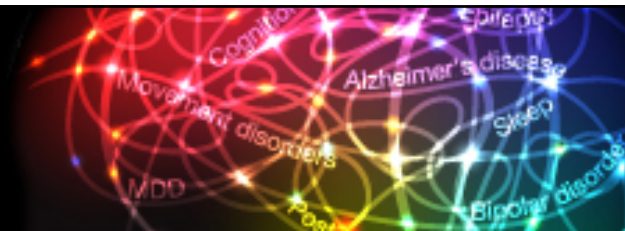
C. MADRS Individual Items



*Not approved by the FDA for treatment of bipolar depression.

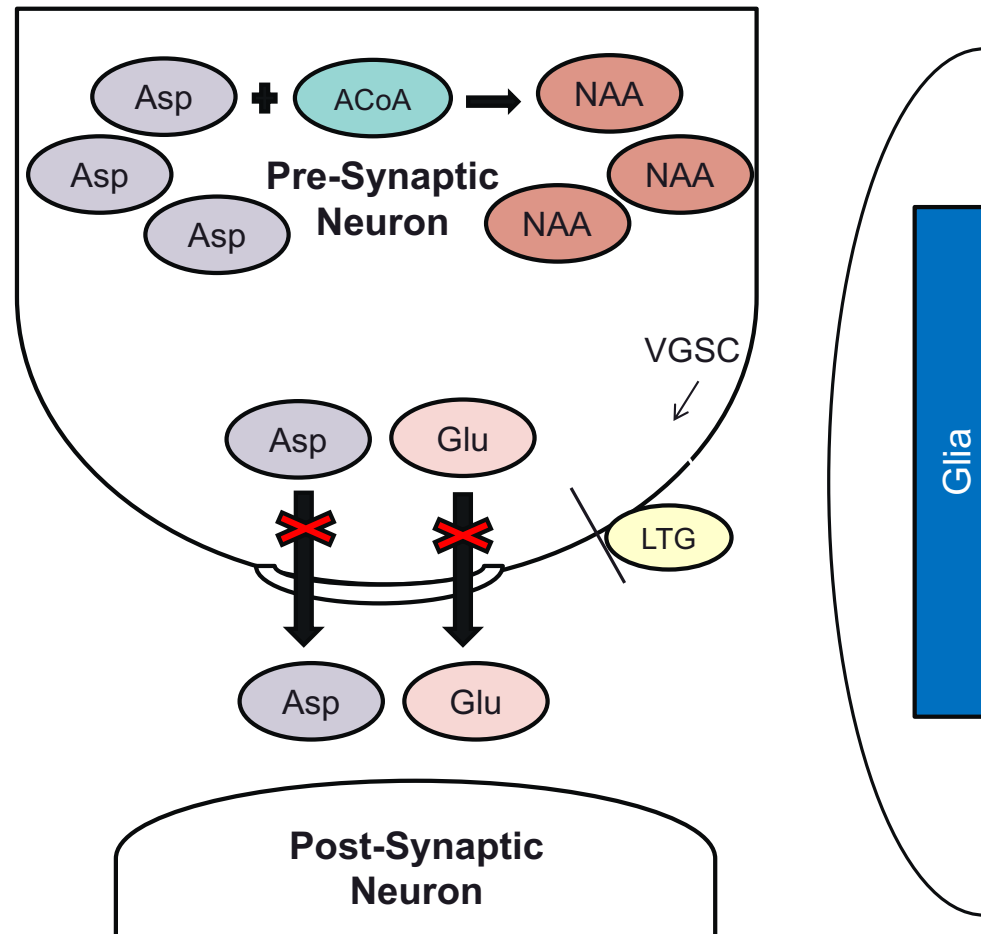
Mixed-effects model for repeated measures, intent-to-treat population; p values were not adjusted for multiple comparisons. Cariprazine 0.75 mg/day compared with placebo: * $p < .05$; ** $p < .01$; *** $p < .001$. Cariprazine 1.5 mg/day compared with placebo: † $p < .05$; †† $p < .01$; ††† $p < .001$. Cariprazine 3.0 mg/day compared with placebo: # $p < .05$; ## $p < .01$; ### $p < .001$. Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-281.

Meta-Analysis of Lamotrigine* in Acute Bipolar Depression



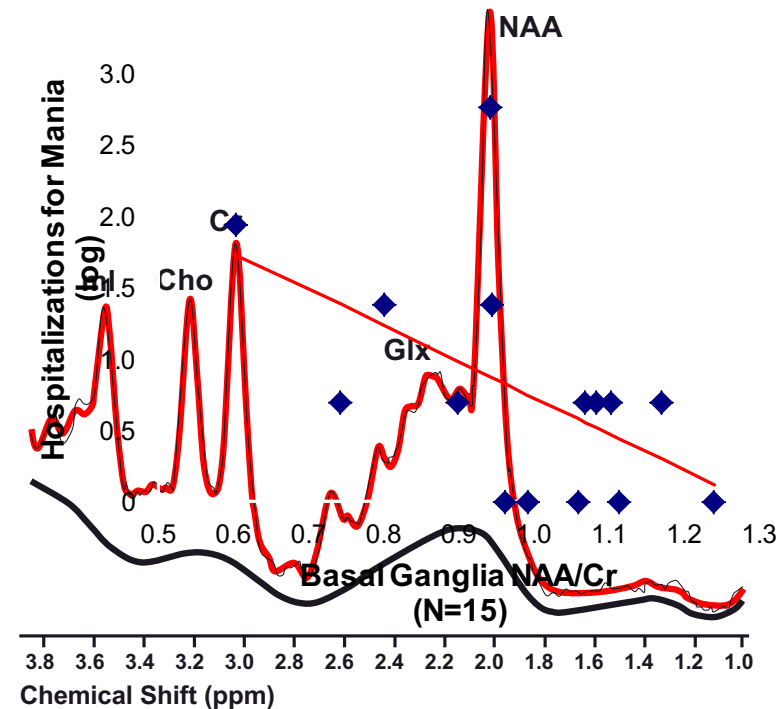
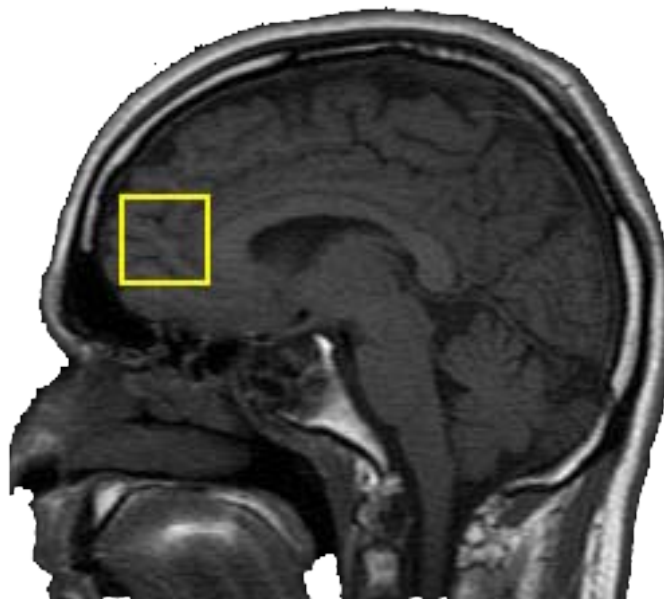
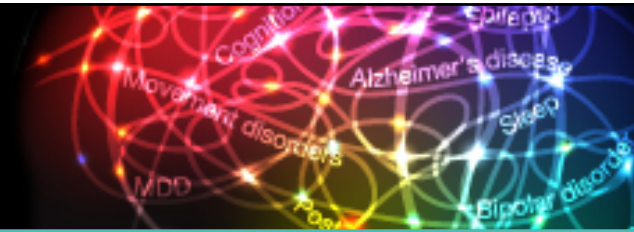
*Not FDA approved for bipolar depression

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



VGSC = voltage gated sodium channel, Glu = glutamate, ASP = aspartate.
 Croarkin PE, et al. *Bipolar Disord.* 2015;17(4):450-457.

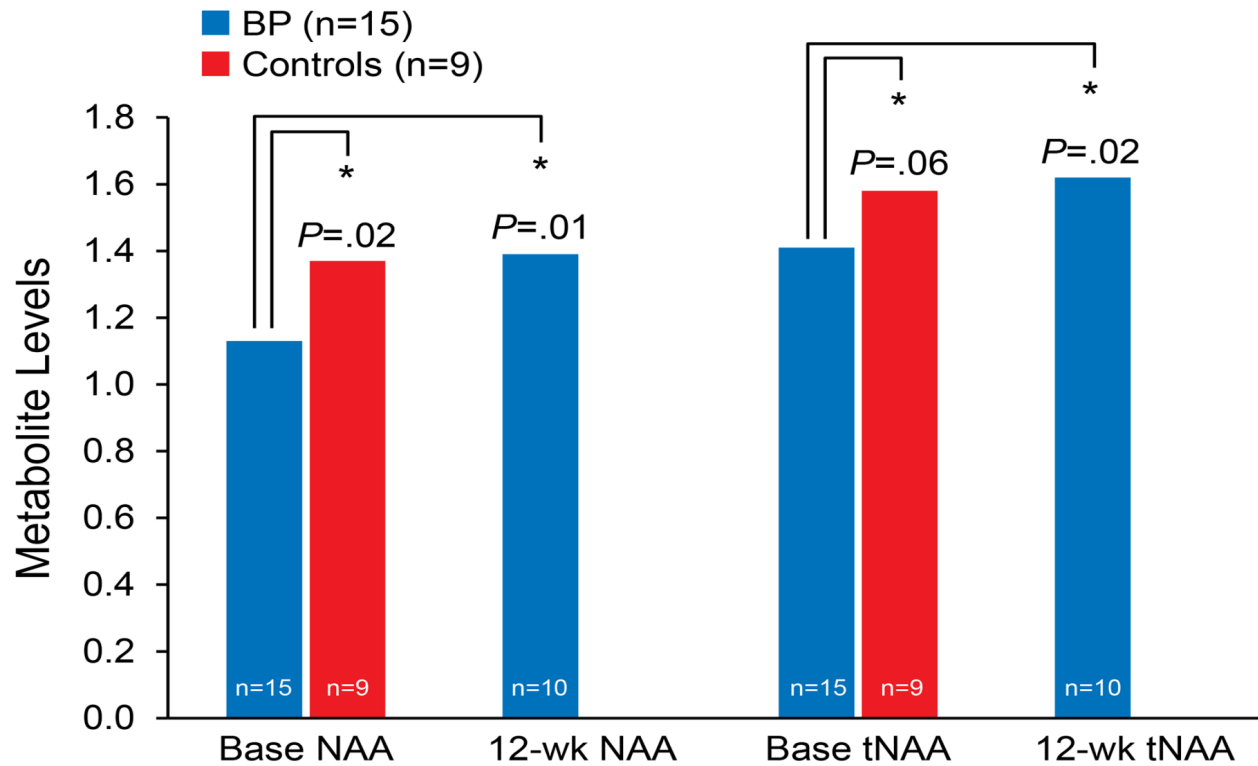
Can NAA Stage Disease?



T1-weighted sagittal MRI location for anterior cingulate/medial prefrontal cortex single-voxel, water-suppressed (Haase 1985) PRESS (Bottomley 1987); 1H-MRS (TR/TE = 3s/30ms, number of averages = 256, voxel size 3x3x3 cm³).

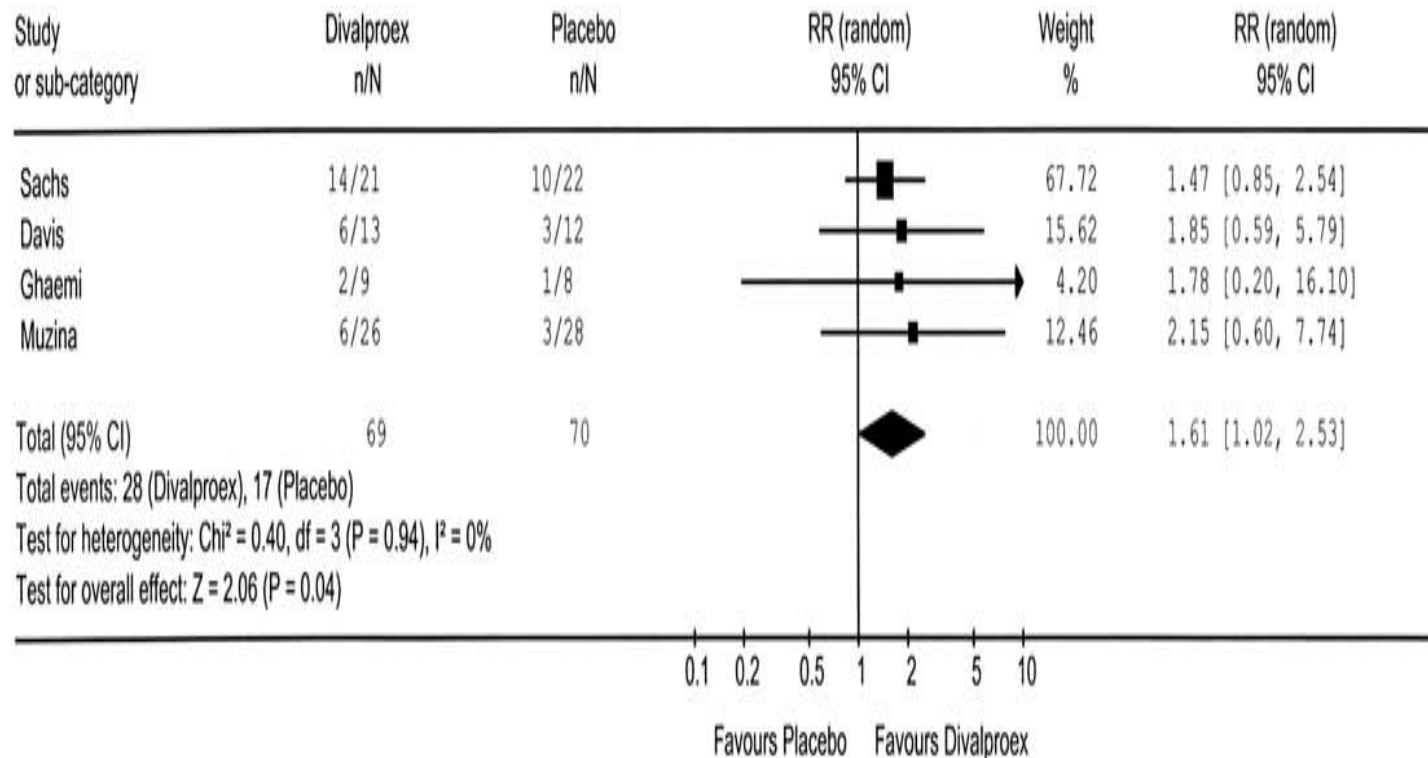
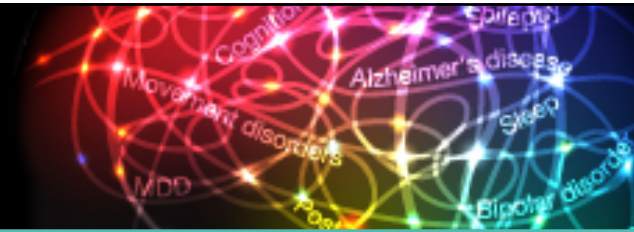
Frye MA, et al. *Psychiatry Res.* 2007;154:259–265; Tsai G, et al. *Prog Neurobiol.* 1995;46:531–540; Altshuler LL. *Biol Psychiatry.* 1993;33:563–565.

NAA Normalization After Lamotrigine



NAA and tNAA Levels at Baseline and After 12 Weeks of Lamotrigine Treatment. Base indicates baseline; BP, bipolar depression; NAA, *N*-acetylaspartate; tNAA, total *N*-acetylaspartate

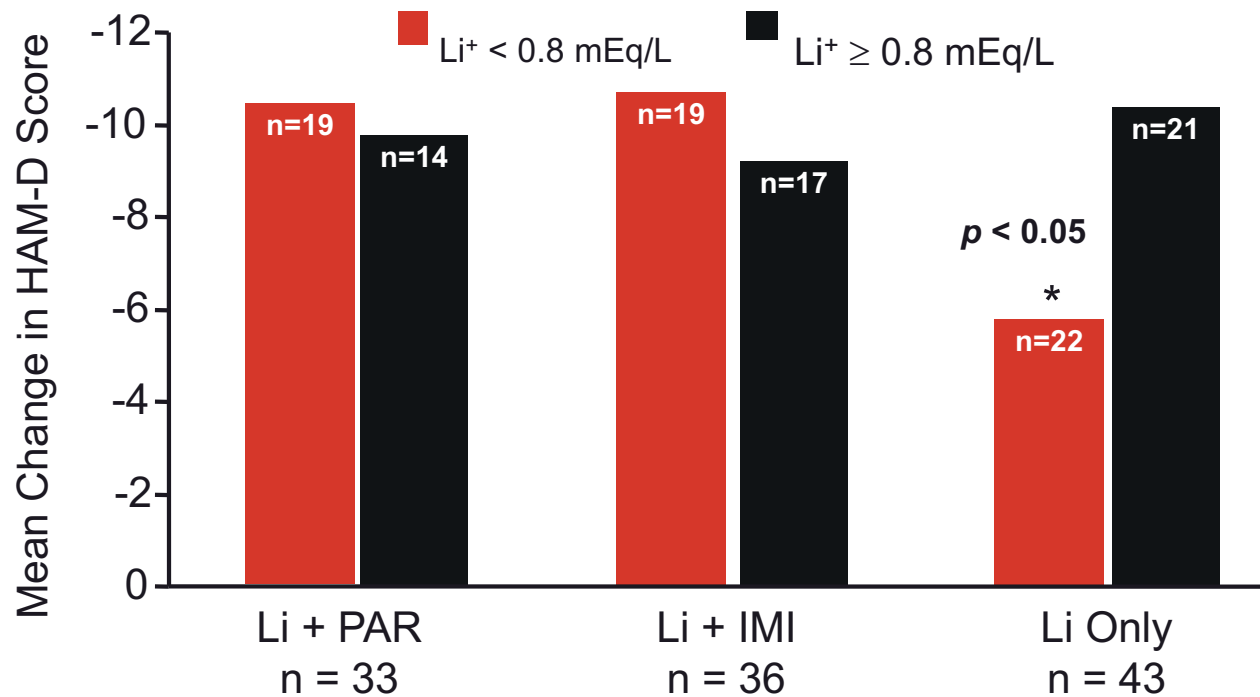
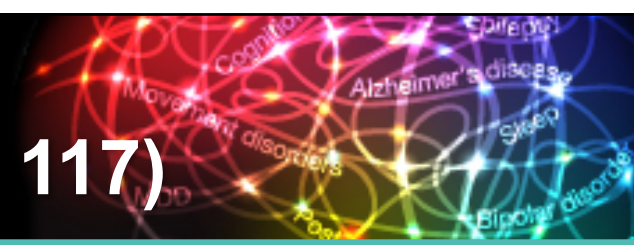
Meta-Analysis: Divalproex in Acute BP Depression



Relative risk of remission in patients treated with divalproex versus placebo

Muzina DJ, et al. *J Clin Psychiatry*. 2011;72(6):813-819. Davis J, et al. *Affect Disord*. 2005; 85(3):259-66; Ghaemi SN, et al. *J Clin Psychiatry*. 2007;68(12):1840-1844.

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

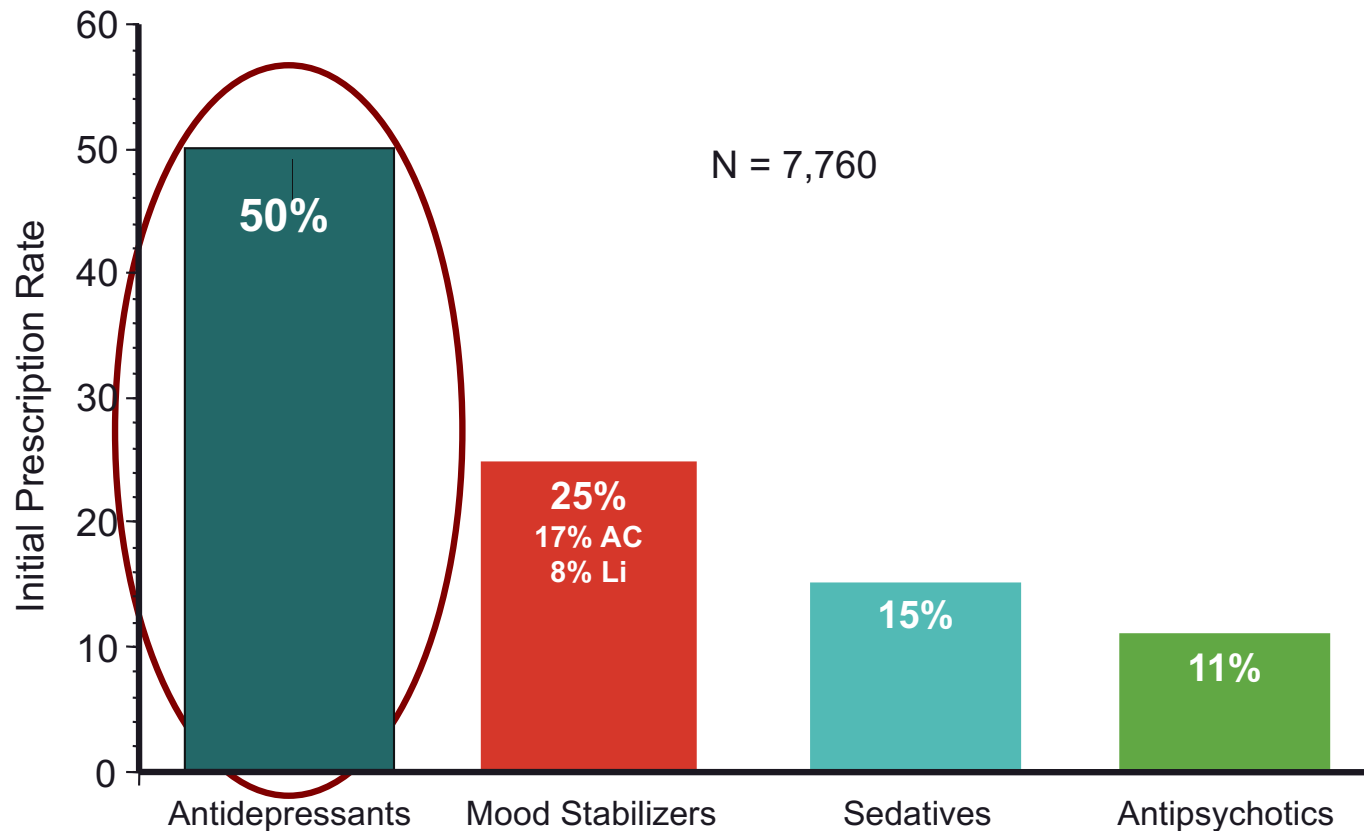


*Not FDA approved for bipolar depression.

Li = lithium, IMI = imipramine, PAR = paroxetine

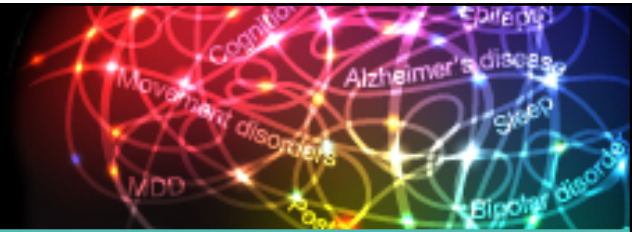
Nemeroff CB, et al. *Am J Psychiatry*. 2001;158(6):906-912.

Antidepressants Most Common Initial Treatment for Bipolar Disorder Patients in US in 2002-2003



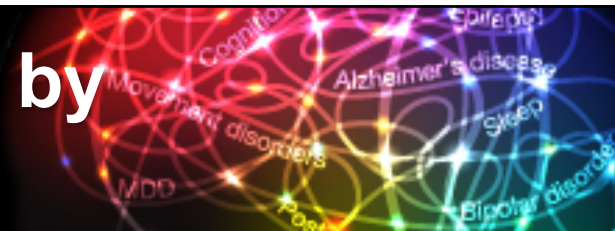
Baldessarini RJ, et al. *Psychiatr Serv.* 2007;58(1):85-91.

Antidepressants 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=0.28)
 - Clinical remission (RR = 1.14, 95% CI, 0.90-1.45; p=0.28)
- Pooled treatment estimates for 1000 patients
 - No increase risk of switch
- In smaller analysis
 - 43% TCA, 15% venlafaxine, 7% SSRI, 5% bupropion

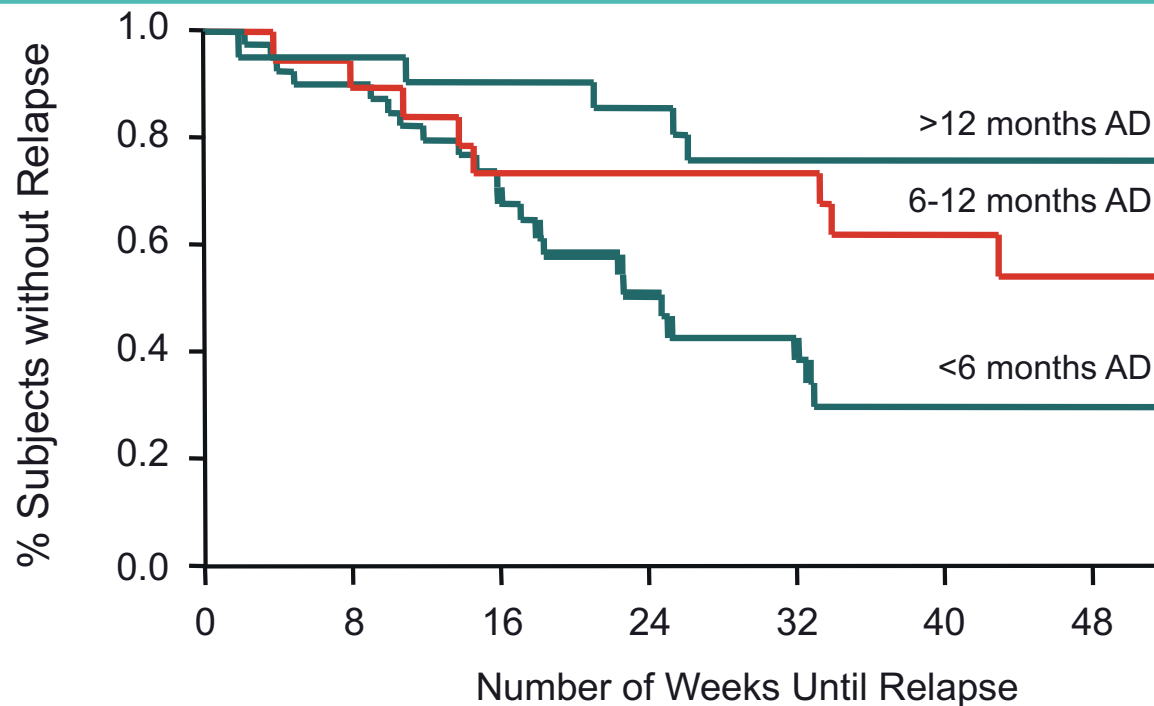
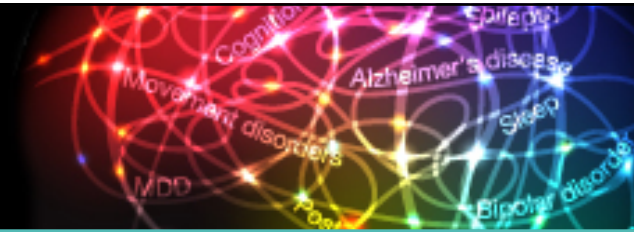
Switching and Response Outcomes by Treatment Group



	Lithium (n = 49)	Sertraline (n = 45)	Combination (n = 48)	<i>p value</i>
Switch into hypomania	14%	17%	10%	0.78
Antidepressant response during study	67%	73%	48%	0.09

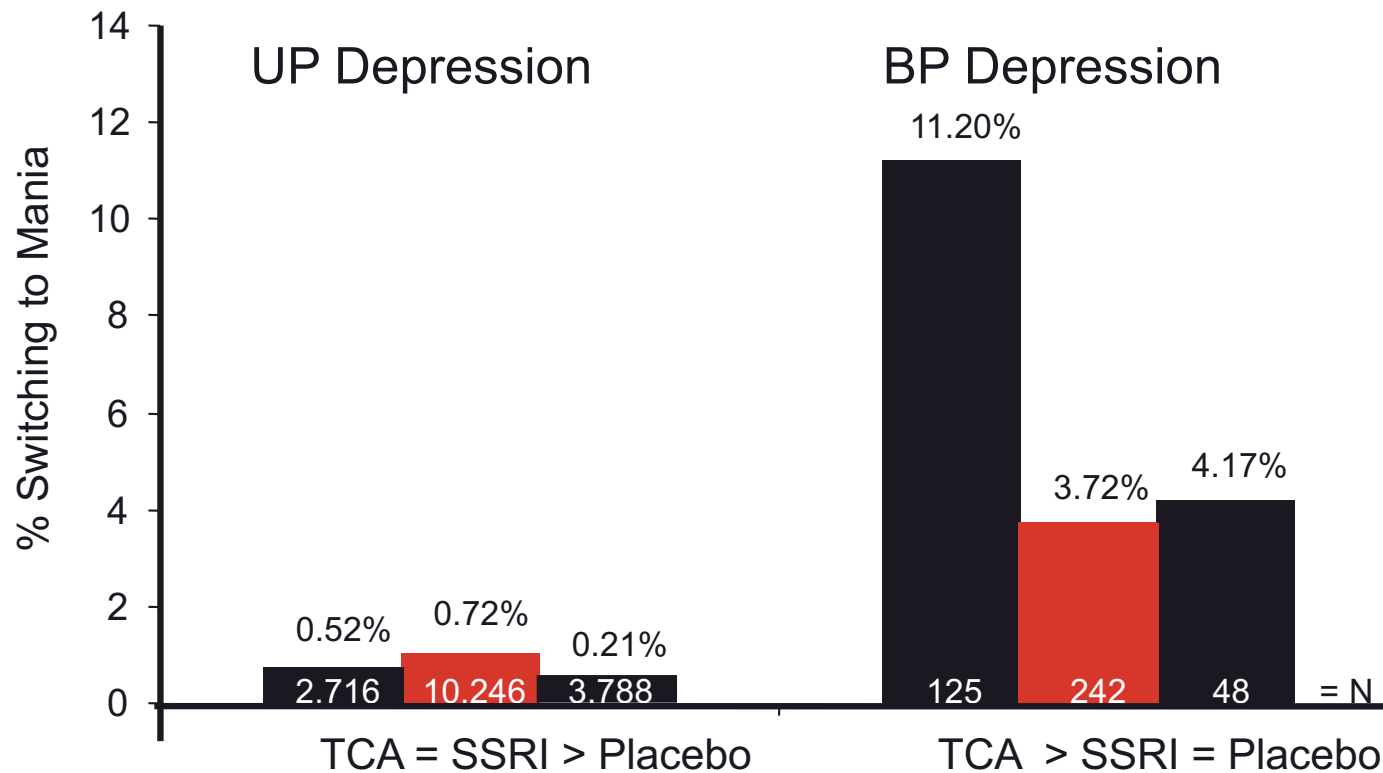
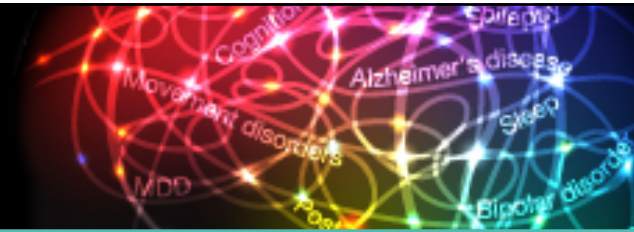
- Primary: No differences in rate of switch
- Secondary: No difference in treatment response
- Secondary: Drop out rate higher for combination than for lithium alone or sertraline alone

Depressive Episode Relapse with Antidepressant Discontinuation



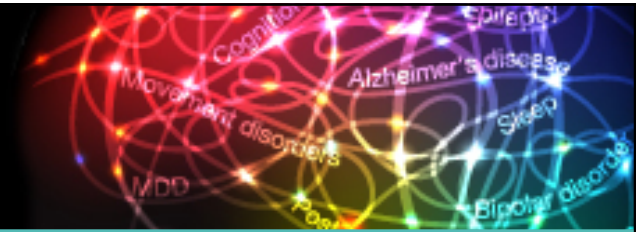
Cox regression analyses log rank = 10.09, $p = .006$

Meta-Analysis of Antidepressant Induced Mania (AIM+)



SSRI = fluoxetine, fluvoxamine, paroxetine, or sertraline
Peet M. *Br J Psychiatry*. 1994;164(4):549-550.

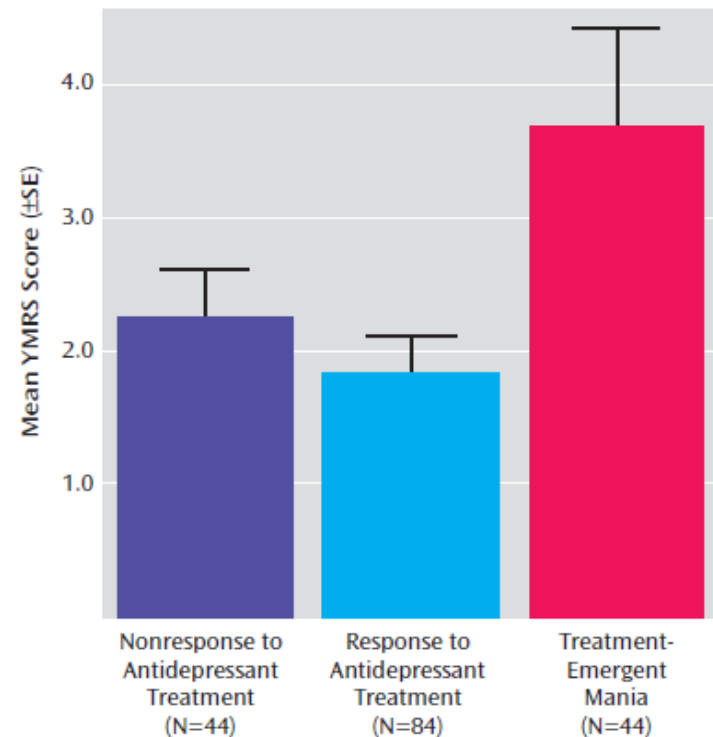
Risk Factors for Switch



- 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

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 ($F(2,169) = 3.99, p = .02$)



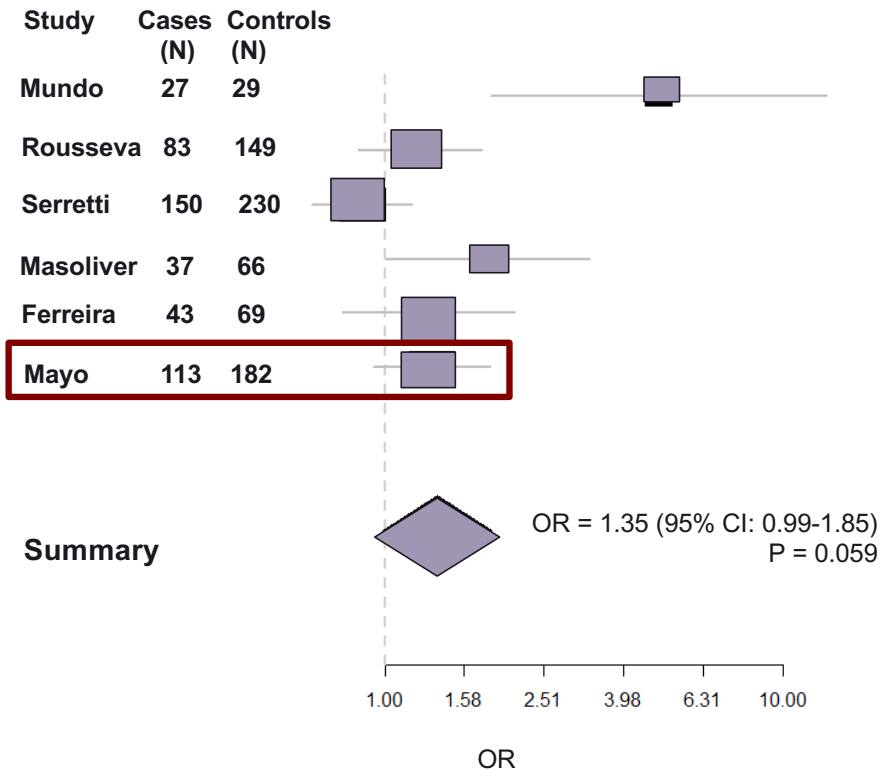
YMRS = Young Mania Rating Scale, TEM = Treatment Emergent Mania
Frye MA, et al. *Am J Psychiatry*. 2009;166(2):164-172.

Baseline Manic Symptom Severity Prior to Antidepressant Treatment

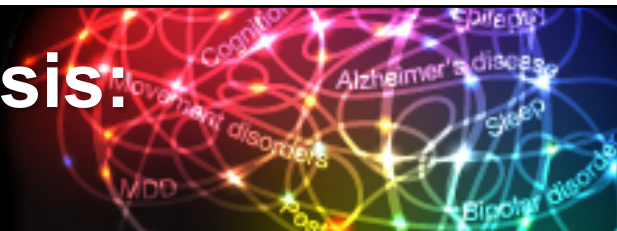
SLC6A4 S Allele and AIM: Meta-Analysis Results



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



Pharmacogenomic Haplotype Analysis: L-A-Protective



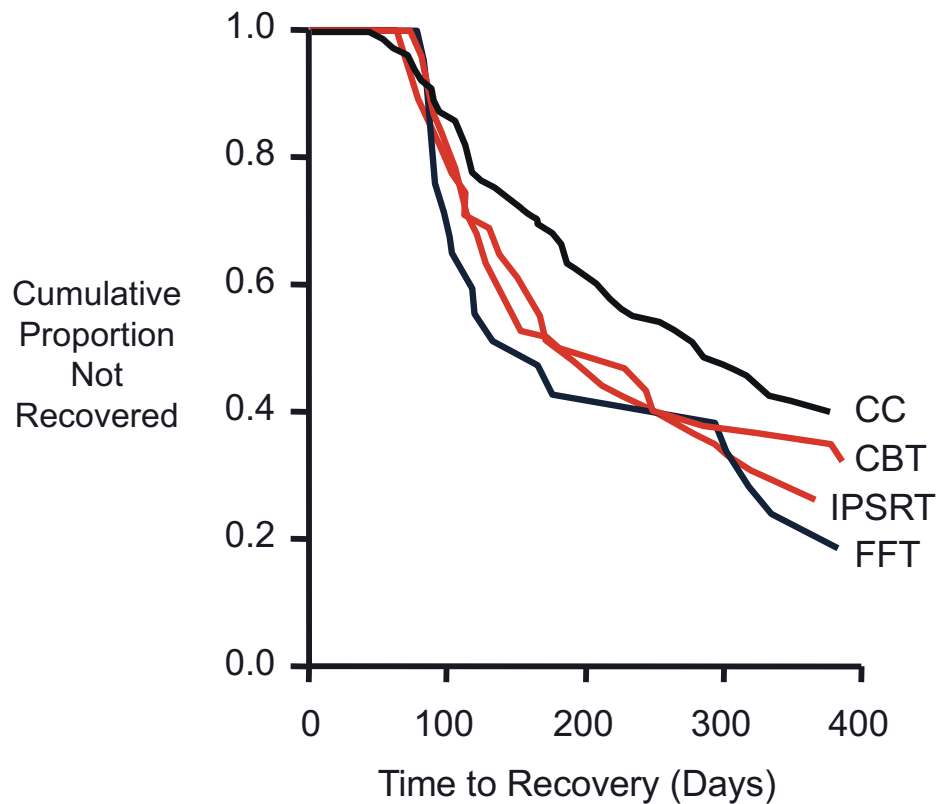
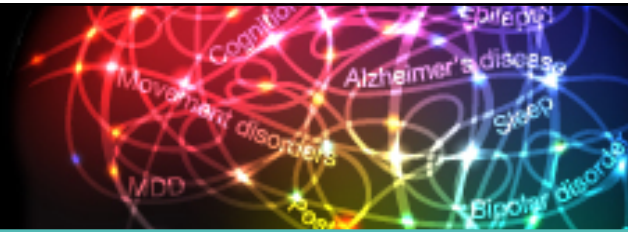
Haplotype	Freq.	Score	Sim p	Max stat sim p	Global sim p
L-A-10	0.344	-2.448	0.012	0.047	0.020
L-G-12	0.027	-1.555	0.14	–	
S-A-10	0.214	0.144	0.86	–	
L-A-12	0.136	0.965	0.31	–	
S-A-12	0.225	1.034	0.28	–	

Cases N = 113; Controls N = 182

Haplotype analysis suggests an association between AIM and haplotypes composed of the 5HTTLPR, rs25531, and the intron 2 VNTR in the SLC6A4 gene, with the L-A-10 haplotype being associated with reduced risk of AIM

Frye MA, et al. *J Clin Psychiatry*. 2015;76(2):1741-1780.

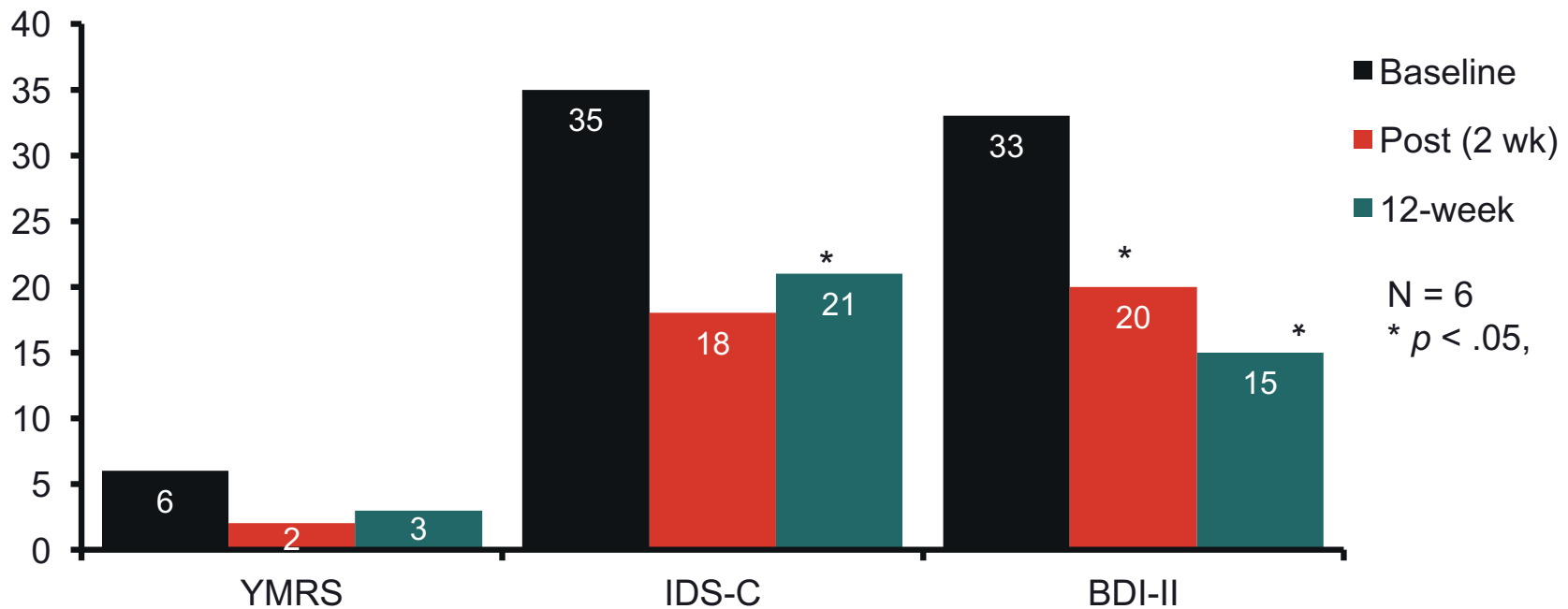
Intensive Psychotherapies Improve Bipolar Depression



- 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

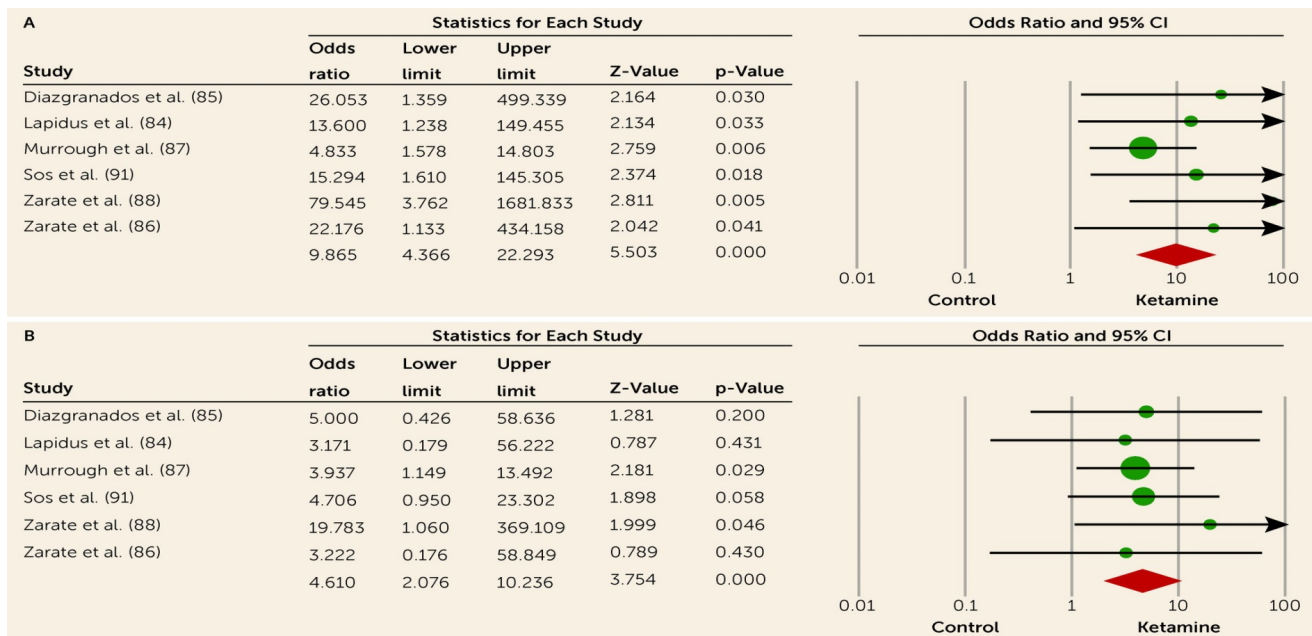
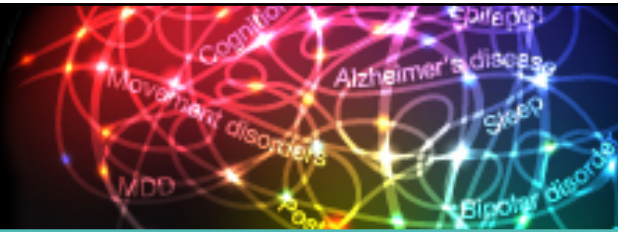
Miklowitz DJ et al. *Arch Gen Psychiatry*. 2007;64(4):419-426.

Maintenance of Antidepressant Response After Group IPSRT Group for Bipolar Disorder



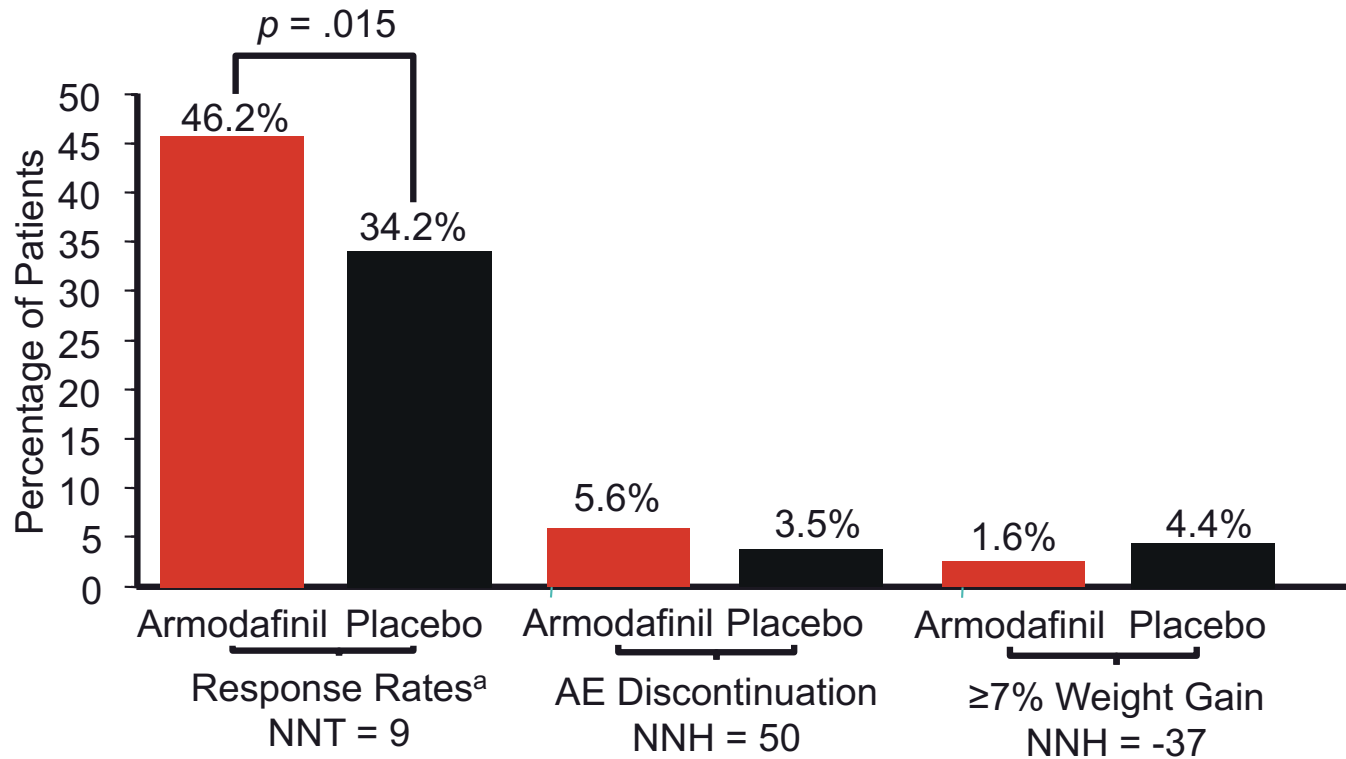
YMRS = Young Mania Rating Scale; IDS-C = Inventory of Depressive Symptomatology-Clinician Rated; BDI-II = Beck Depression Inventory-II
Hoberg AA, et al. *Perspect Psychiatr Care*. 2013;49(4):226-234.

Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression



a The A) top plot shows results one day after initiation of ketamine (heterogeneity: $\chi^2=4.27$, $df=4$, $p=0.51$, $I^2=0\%$). The B) bottom plot shows results one week after initiation of ketamine (heterogeneity: $\chi^2=1.14$, $df=5$, $p=0.95$, $I^2=0\%$).

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

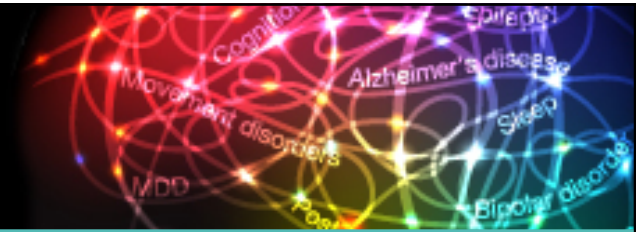


Response = $\geq 50\%$ IDS-C30 decrease

*Not FDA approved for bipolar depression

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

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)
 - Antisuiicidal or classic illness- lithium
- Antidepressants in BP depression
 - Evidence base does not support monotherapy use
 - Switch rate is not 0%



Questions & Answers

Don't forget to fill out your evaluations to collect your credit.

