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neuroscience CME

Master Class for Neuroscience Professional Development

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

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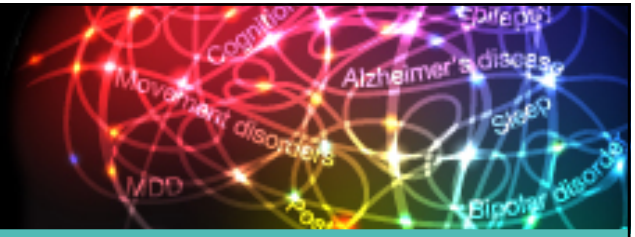
Disclosures



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

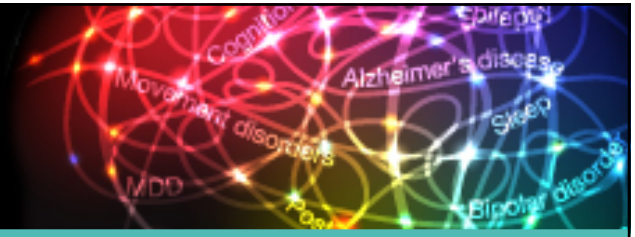
Learning Objective 1

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

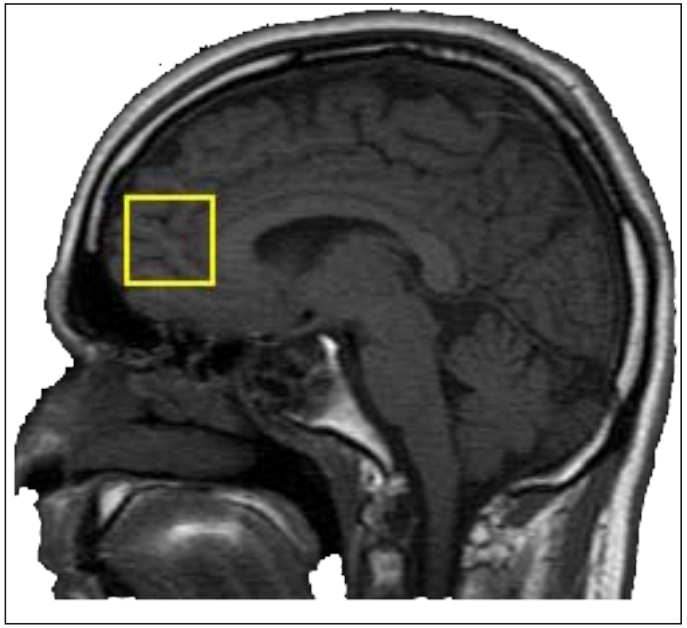


- Acute Mania
  - FDA approved
  - Adjunctive lorazepam
  - Biomarkers
- Acute Bipolar Depression
  - FDA approved
  - Off label
  - Antidepressant Induced Mania (AIM+)
- Mixed Specifier
  - DSM5 addition
- Maintenance

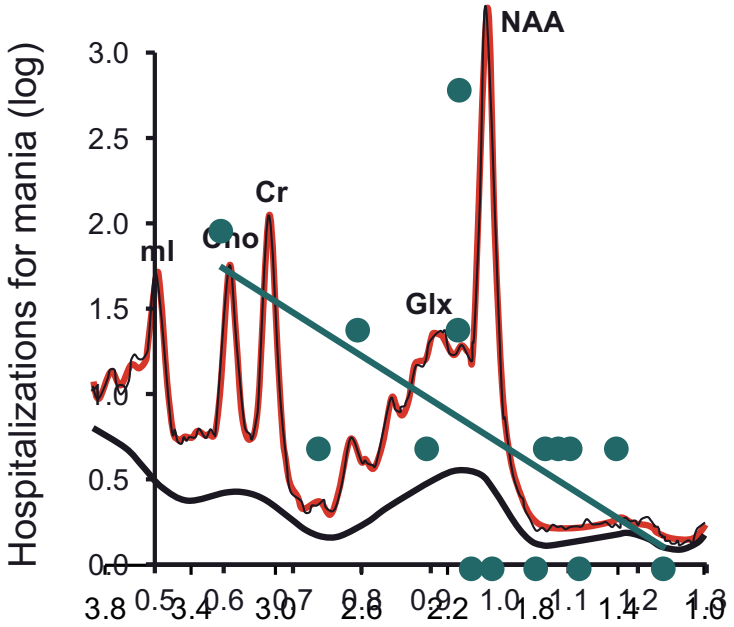
FDA Indications: Acute Mania

- 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 cm^3)

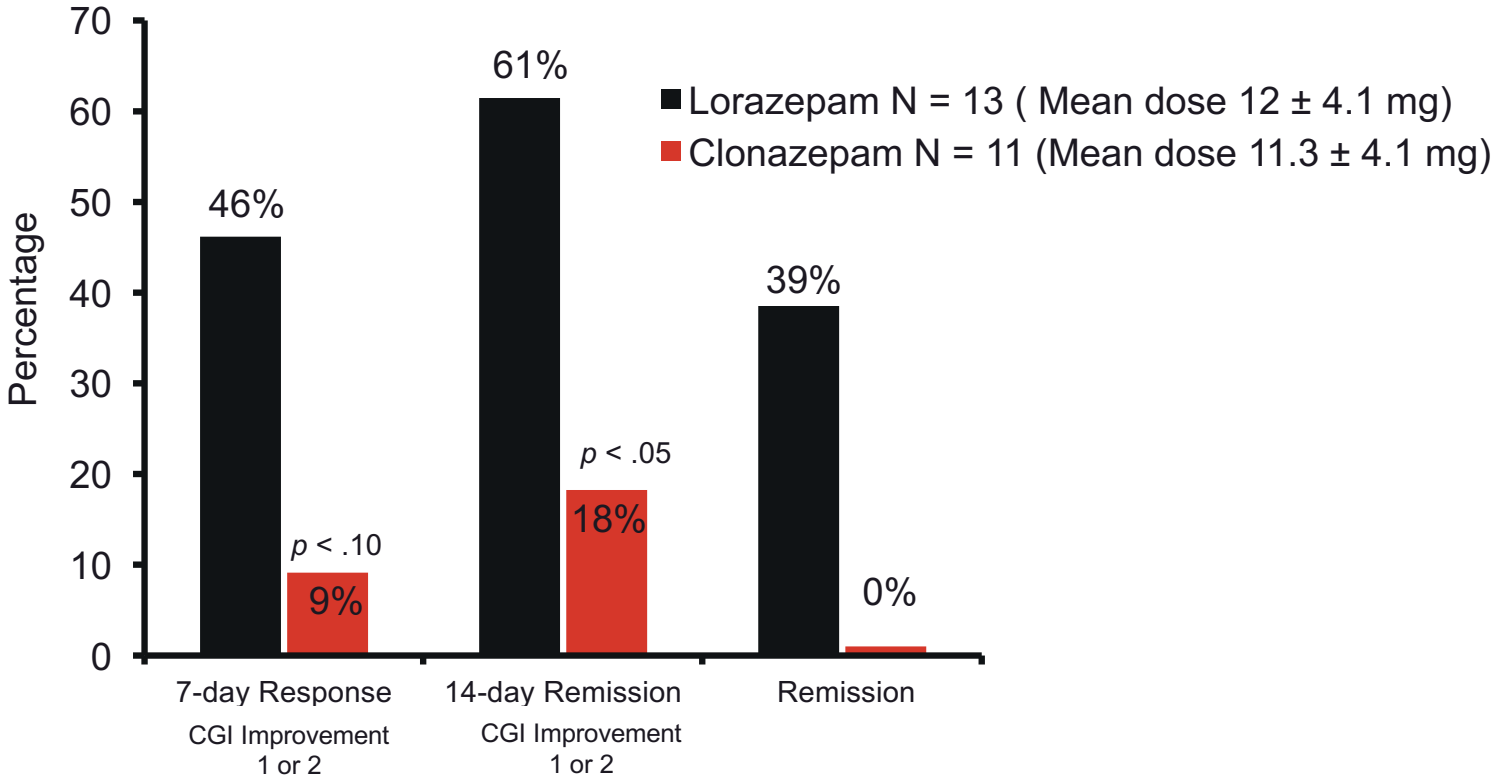


Basal Ganglia NAA/Cr
n = 15

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.

Double-Blind Comparison of Clonazepam vs. Lorazepam Monotherapy in Acute Mania



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

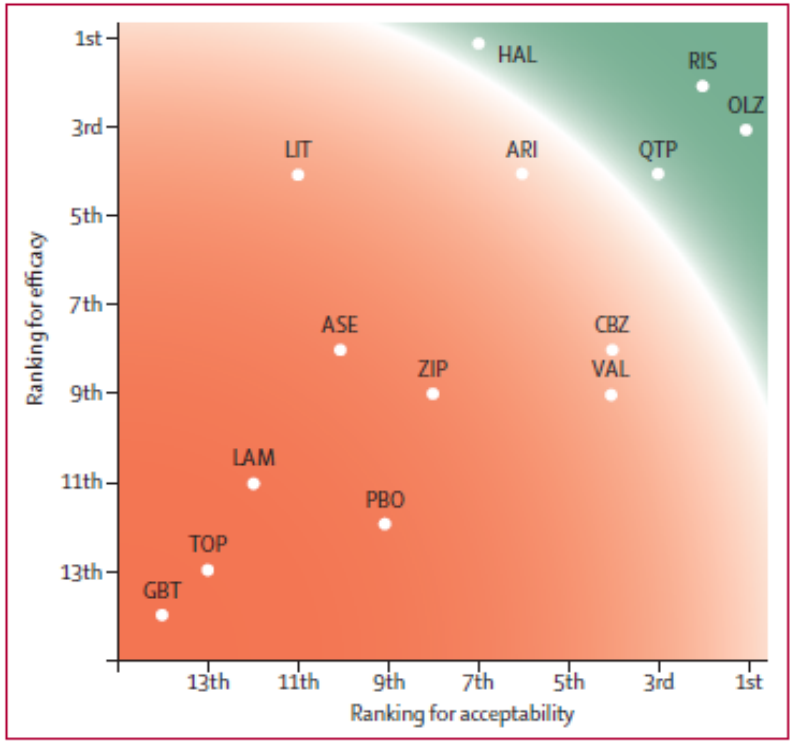
FDA Approved Bipolar Disorder Treatments*

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

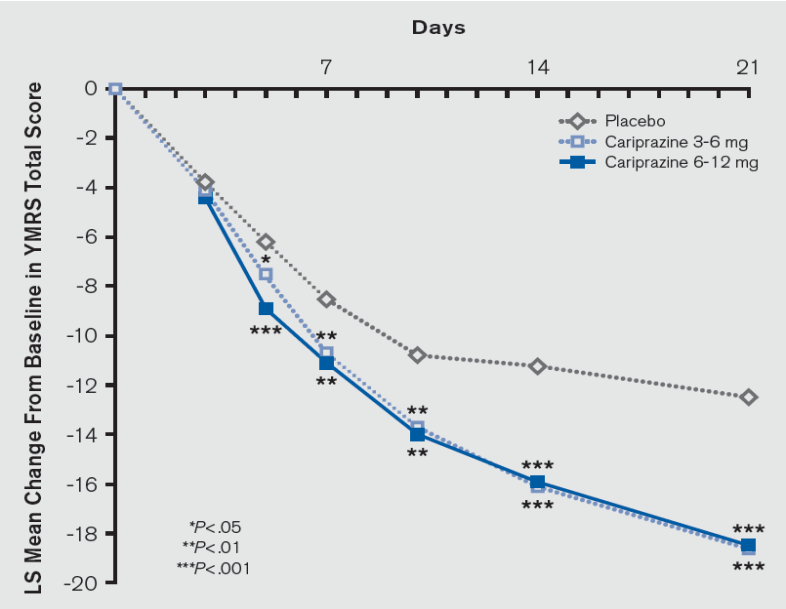


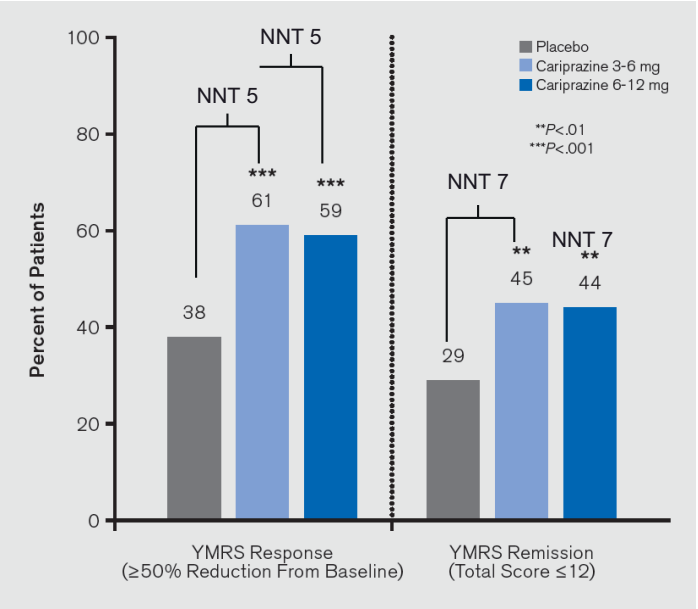
Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcomes) and dropout rate

Cipriani A, et al. *Lancet.* 2011;378(9799):1306-1315.

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.

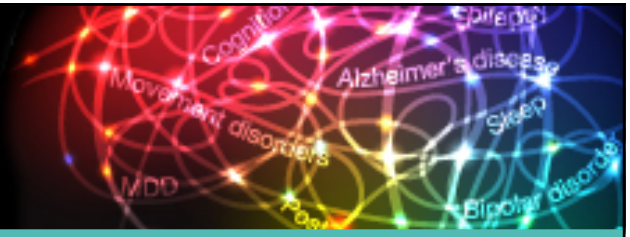
Typical Antipsychotics in Acute Mania

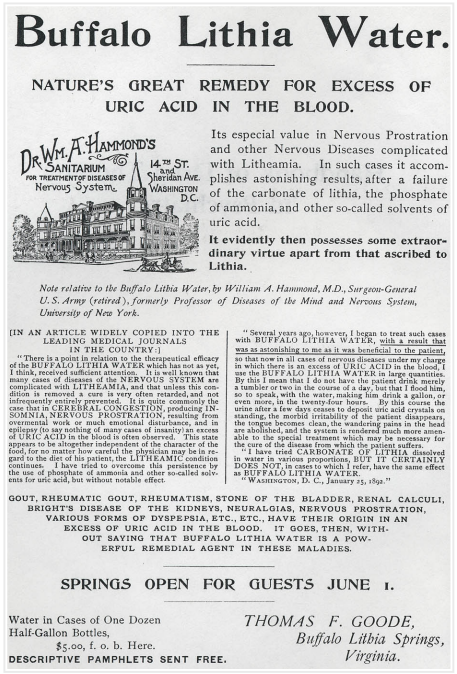
- Pros
  - Efficacious for acute mania
  - Haloperidol* may be more rapidly efficacious than olanzapine, quetiapine, ziprasidone
- Cons/adverse effects
  - Acute EPS, tardive dyskinesia, akathisia, neuroleptic malignant syndrome
- Negative impact on course of illness
  - ↑ post-mania depressive symptom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

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.

THOMAS F. GOODE, Buffalo Lithia Springs, Virginia.

DESCRIPTIVE PAMPHLETS SENT FREE.

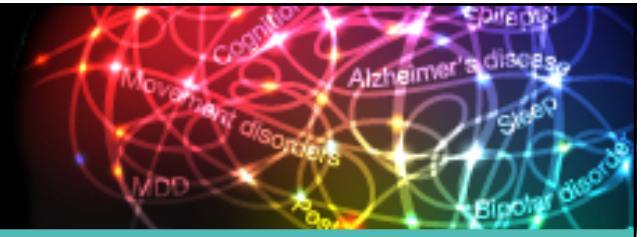
Advertisement from *Harper's New Monthly Magazine*, 1892, from the author's collection

- 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

*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):9501990; 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
Good Response 70%	Nonrapid Cycling	Euphoric Mania	No Substance Abuse	(+) Family History	Few Lifetime Episodes	MDI Pattern

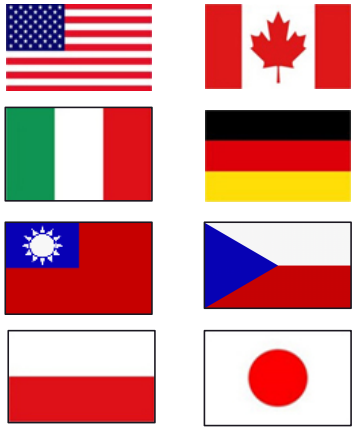
DMI = Depression mania euthymic interval; MDI = Mania depression euthymic interval

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 × 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 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

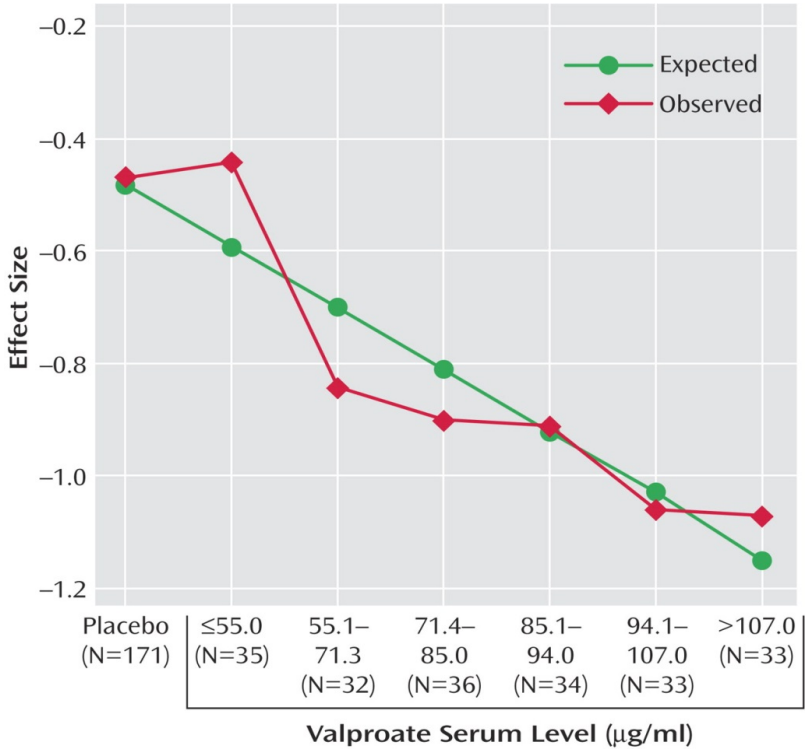
SNP = single nucleotide polymorphism.

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

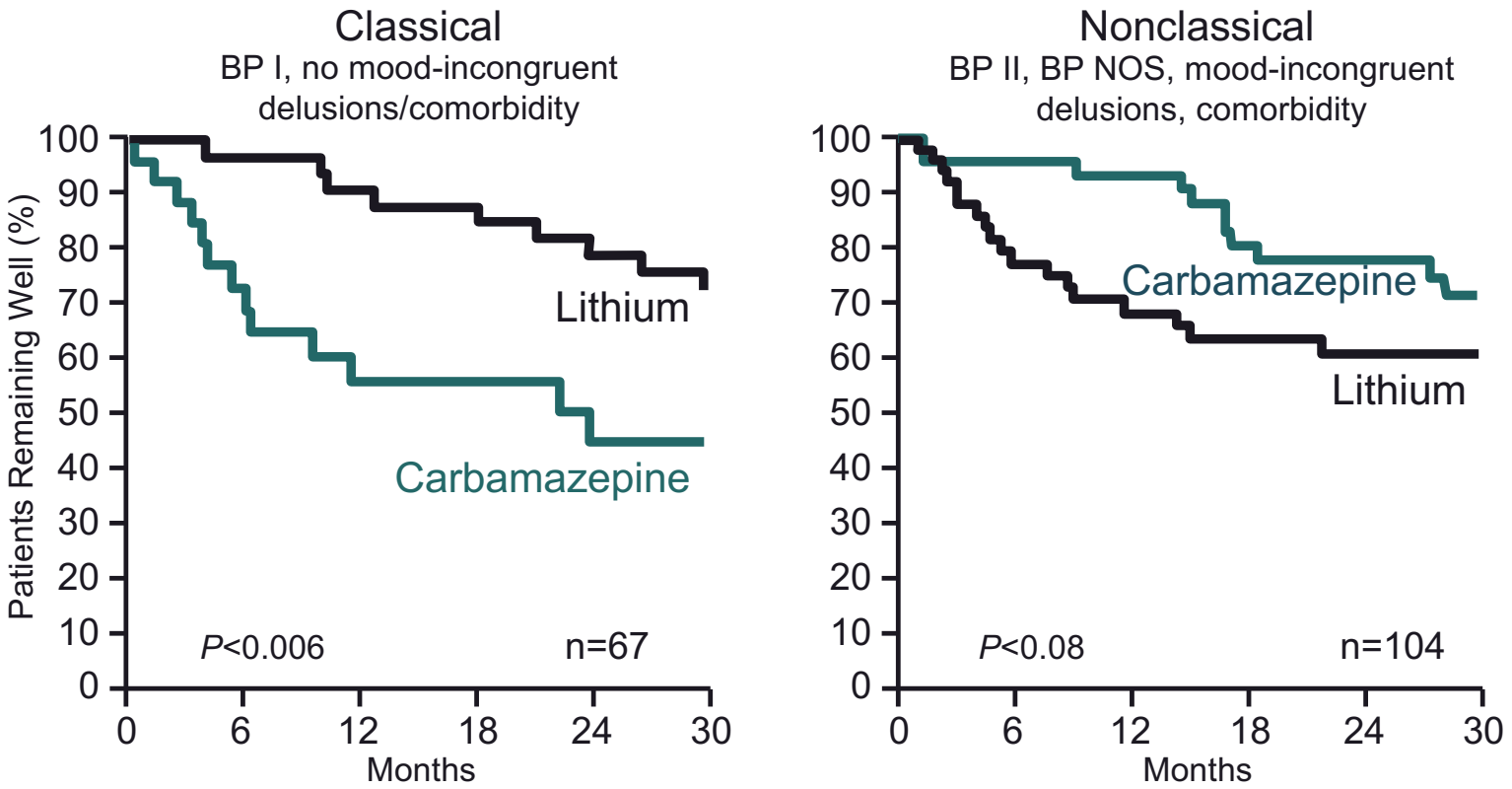
- Linear relationship between VPA serum level and therapeutic response
- Efficacy significantly > PLC beginning at 71.4-85.0 mcg/mL (consistent at all higher VPA concentrations)
- ES was associated with highest VPA serum levels (>94 mcg/mL)



VPA = valproate serum level; ES = effect size.

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

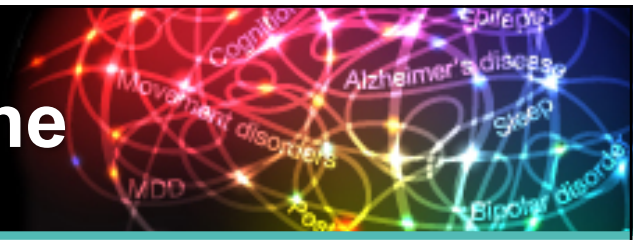
Maintenance Treatment of Bipolar Disorder: Differential Response to Lithium and Carbamazepine*



*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

FDA. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm

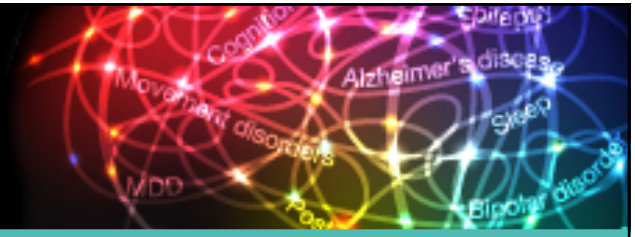
Divalproex and Carbamazepine in Acute Mania

- 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.

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

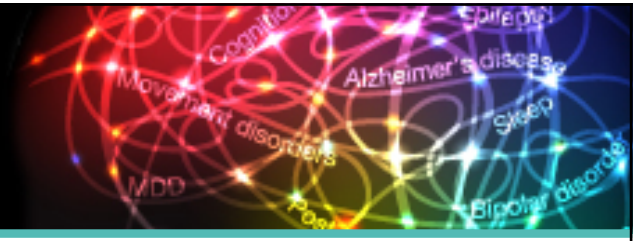
First-Generation	Second-Generation
Depression	Weight gain
Akathisia	Sedation
Acute dystonia	Hyperglycemia, Diabetes[b]
Tardive dyskinesia[a]	Suicidality in age ≤ 24[c]
Weight gain	Akathisia
Sedation	Hyperprolactinemia
Anticholinergic	Cerebrovascular in elderly[d]
Cardiac, Orthostasis	Cardiac, Orthostasis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

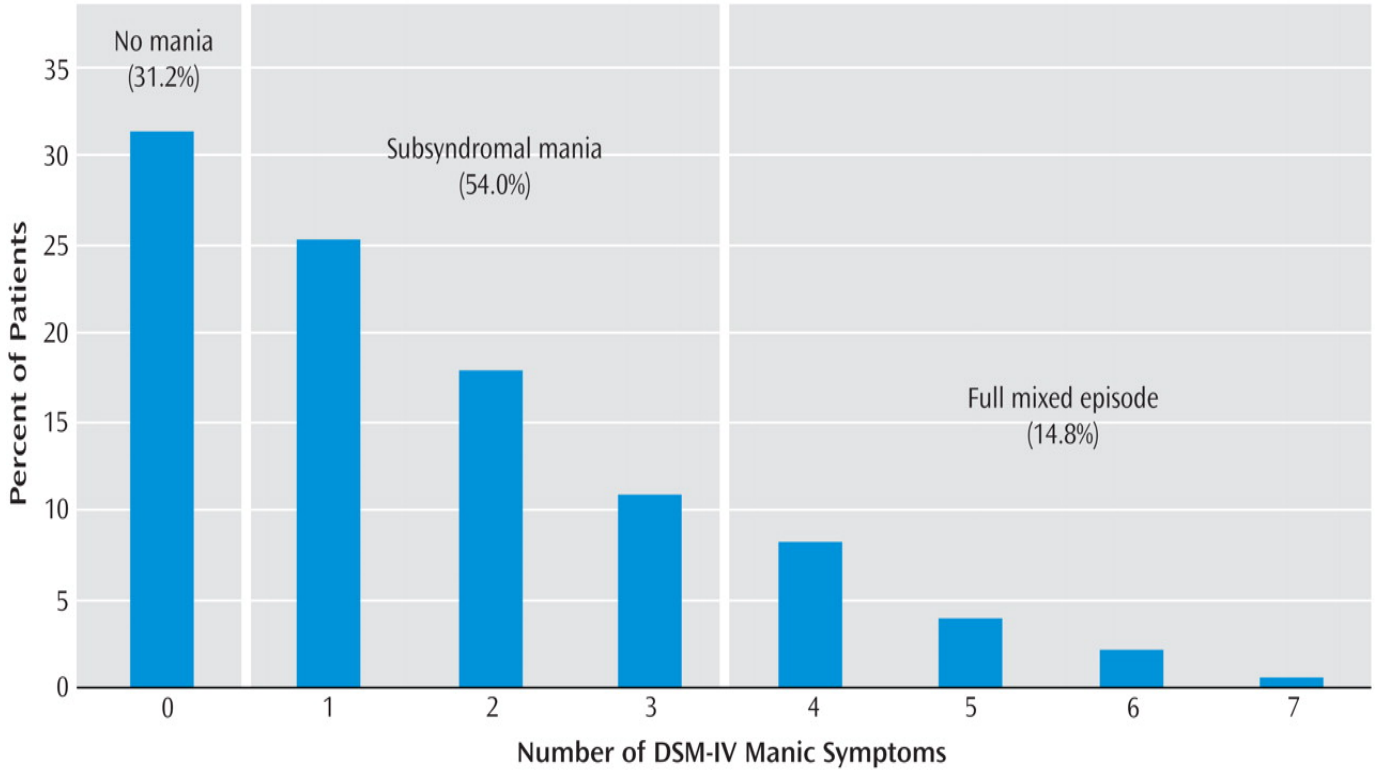
Kraepelinian Mixed States



- 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.

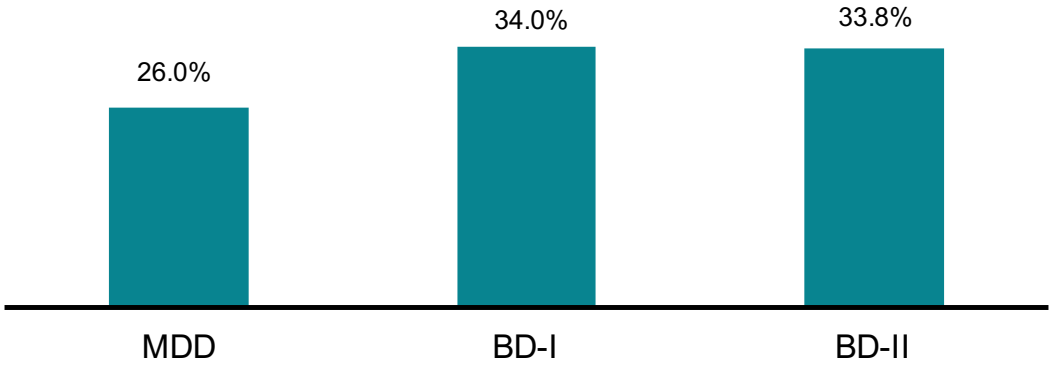
DSM-IV Mood Elevation Symptoms in STEP-BD Bipolar Depressive Episodes



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 (HAMD-17).

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

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

Core symptoms	Elevated mood	Elevated mood + depressed mood or loss of interest	Depressed mood or loss of interest
Manic	≥3	≥3	<3
Depressive	<5	≥5	≥5

DSM-IV-TR: Manic (Euphoric) | Mixed Mania | Depressive

DSM-5: Manic | Manic with mixed features | Depressive with mixed features | Depressive

Core symptoms	Elevated mood + energy	Elevated mood + energy	Depressed mood or loss of interest	Depressed mood or loss of interest
Manic	≥3	≥3	≥3	<3
Depressive	<5	>3	≥5	≥5

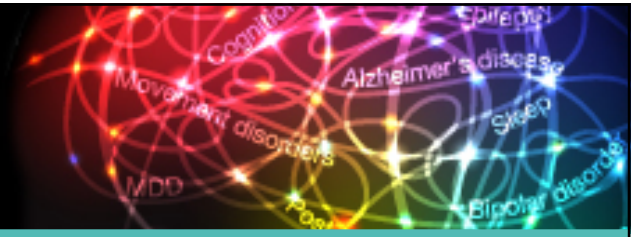
American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision. APA Press, 1994.
American Psychiatric Association. DSM-5. American Psychiatric Publishing; 2013.

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
  - ↑self-esteem, flight of ideas,↓ sleep need / ↑energy symptoms

McIntyre RS, et al. *J Affect Disord*. 2014;172C:259-264; Perugi G, et al. *J Clin Psychiatry*. 2015;76(3):e351-e358; Tohen M, et al. *J Affect Disord*. 2014;168:136-41.

Bipolar Depression: Best Practices

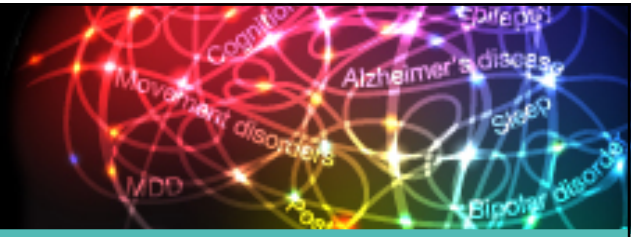


- FDA approved agents
  - Olanzapine Fluoxetine (OFC)
  - Quetiapine monotherapy
  - Lurasidone monotherapy & adjunct therapy
- Maximize the mood stabilizer
- Antidepressants FDA off-label*
  - Do they work? Are they safe?
- Psychotherapy
- Novel Treatment

The Old Guitarist Pablo Picasso 1903
The Blue Period

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

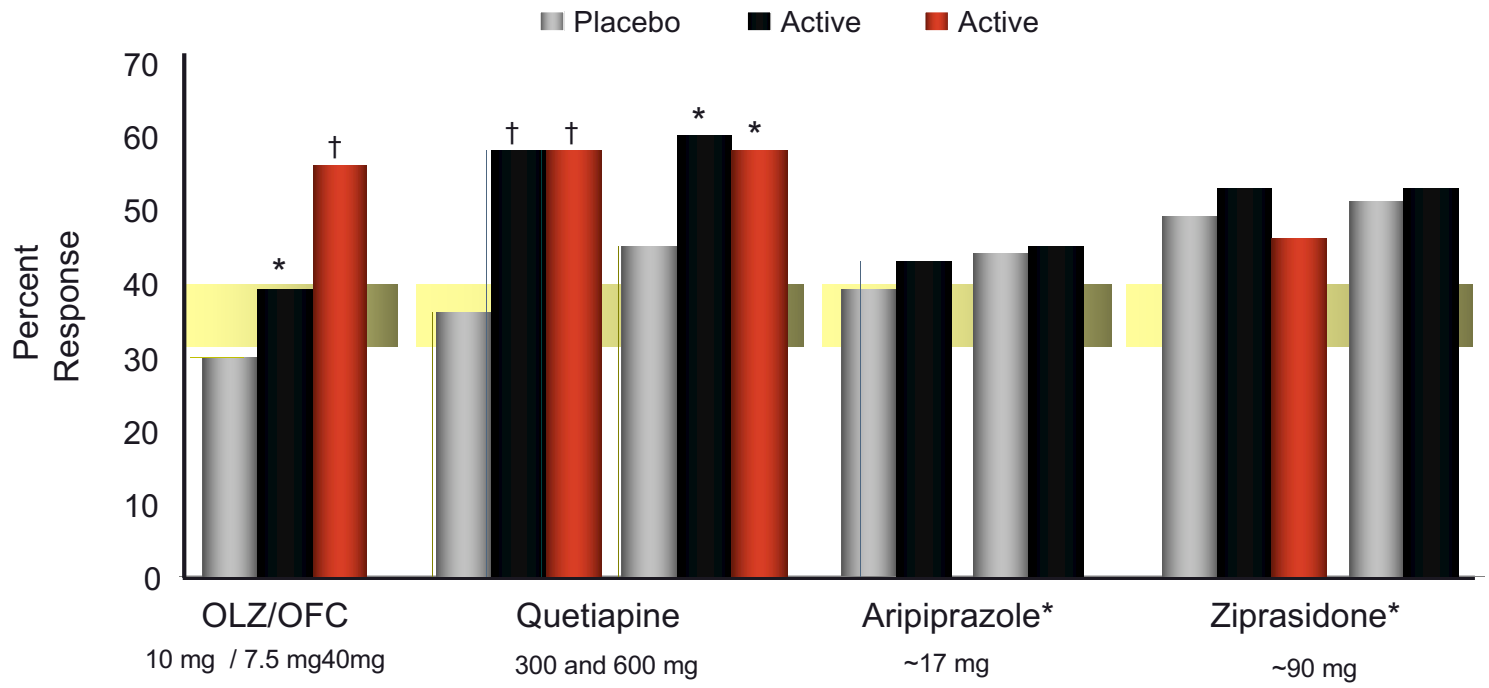
Epidemiology



- 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.

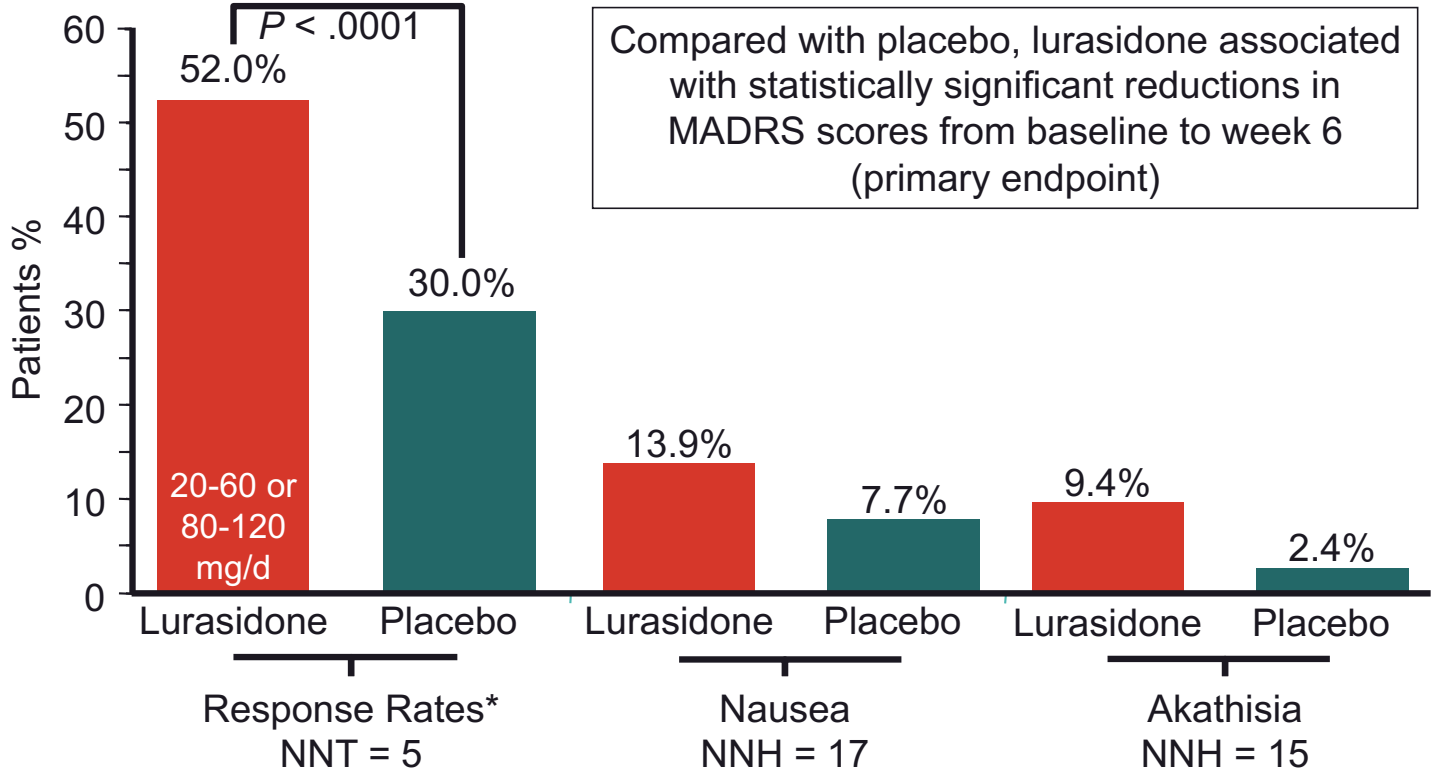
Response Rates of Atypical Antipsychotics in Bipolar Depression



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

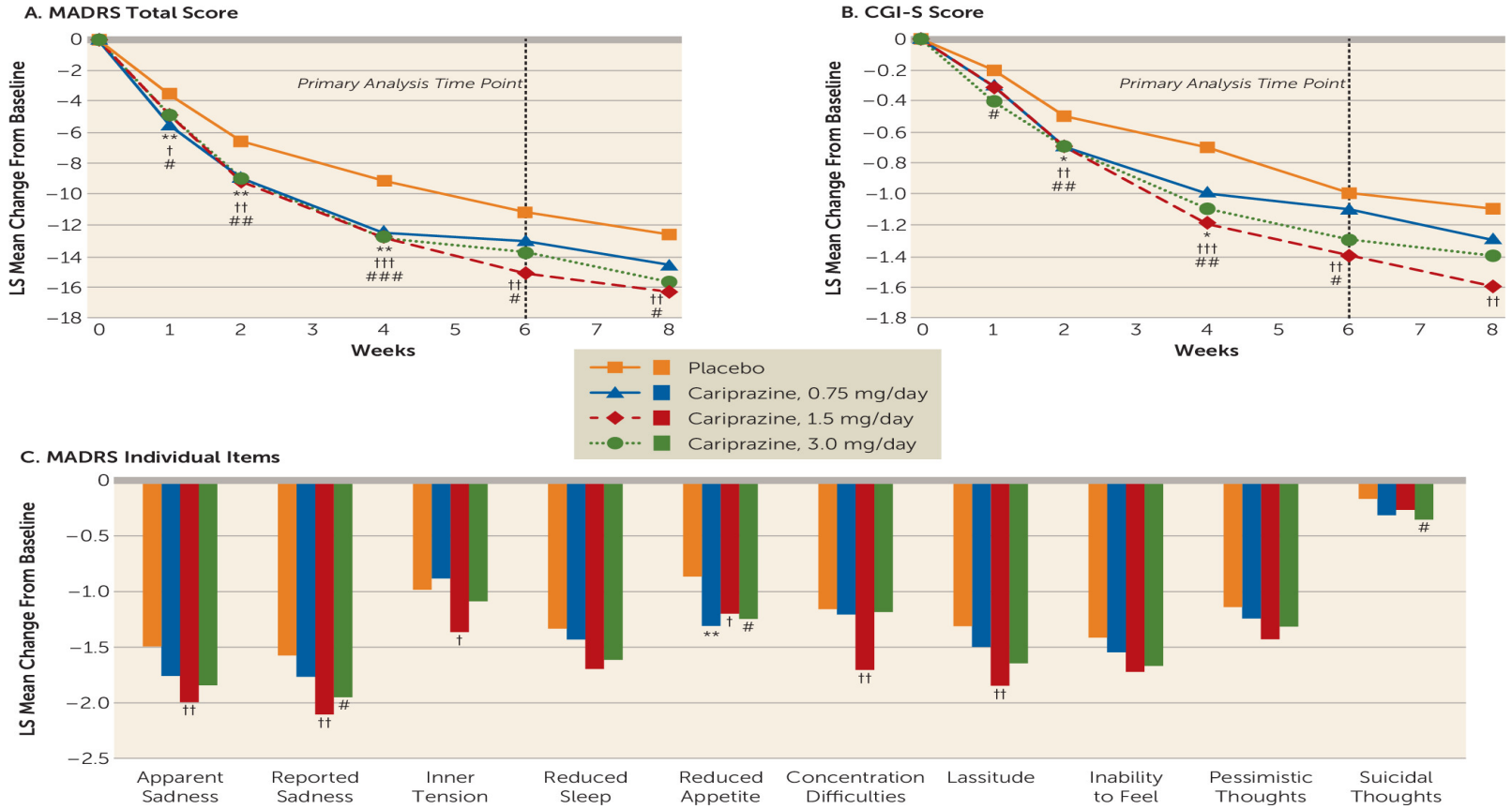


Compared with placebo, lurasidone associated with statistically significant reductions in MADRS scores from baseline to week 6 (primary endpoint)

*Response: ≥ 50% MADRS decrease.

Loebel A, et al. *Am J Psychiatry*. 2014;171(2):160168; Loebel A, et al. *Am J Psychiatry*. 2014;171(2):169-177.

Cariprazine* vs. Placebo in Bipolar I Depression

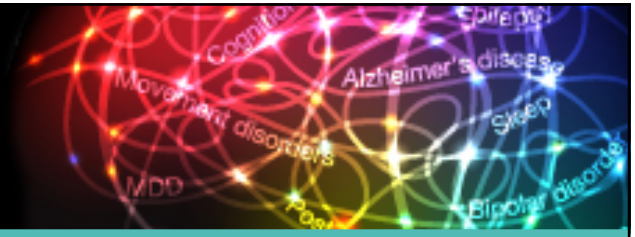


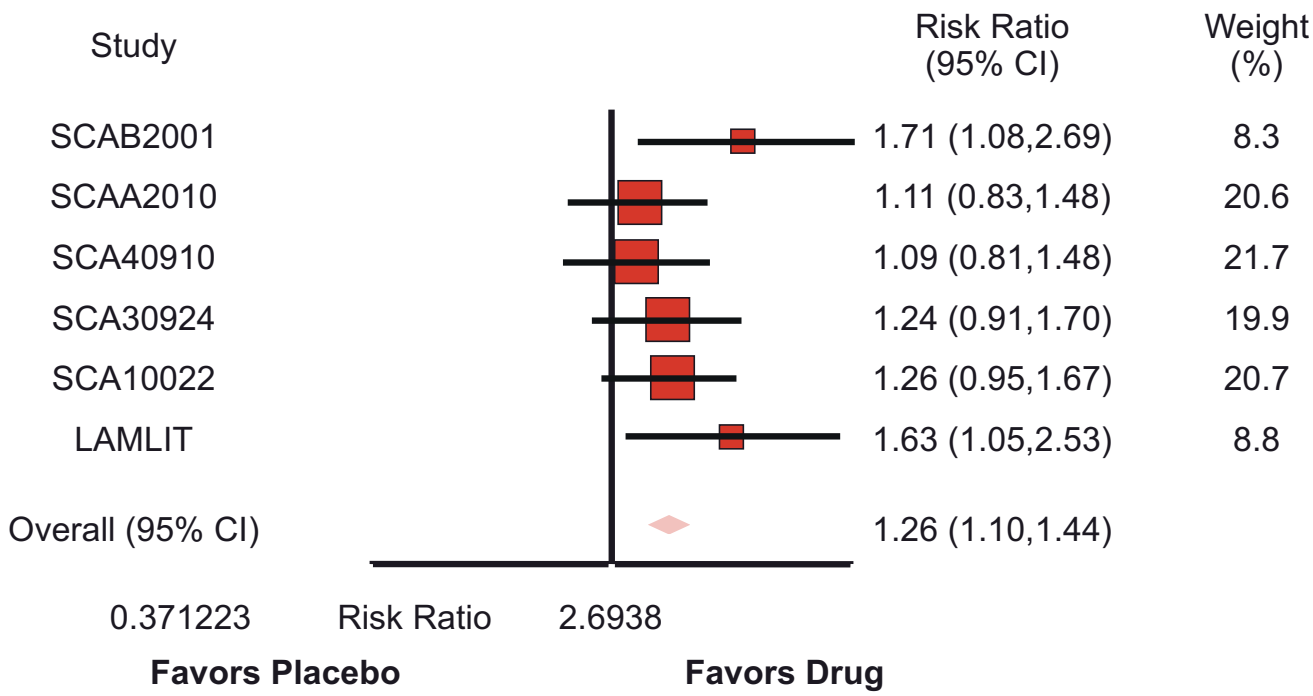
*Not approved by the FDA for treatment of bipolar depression.

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.

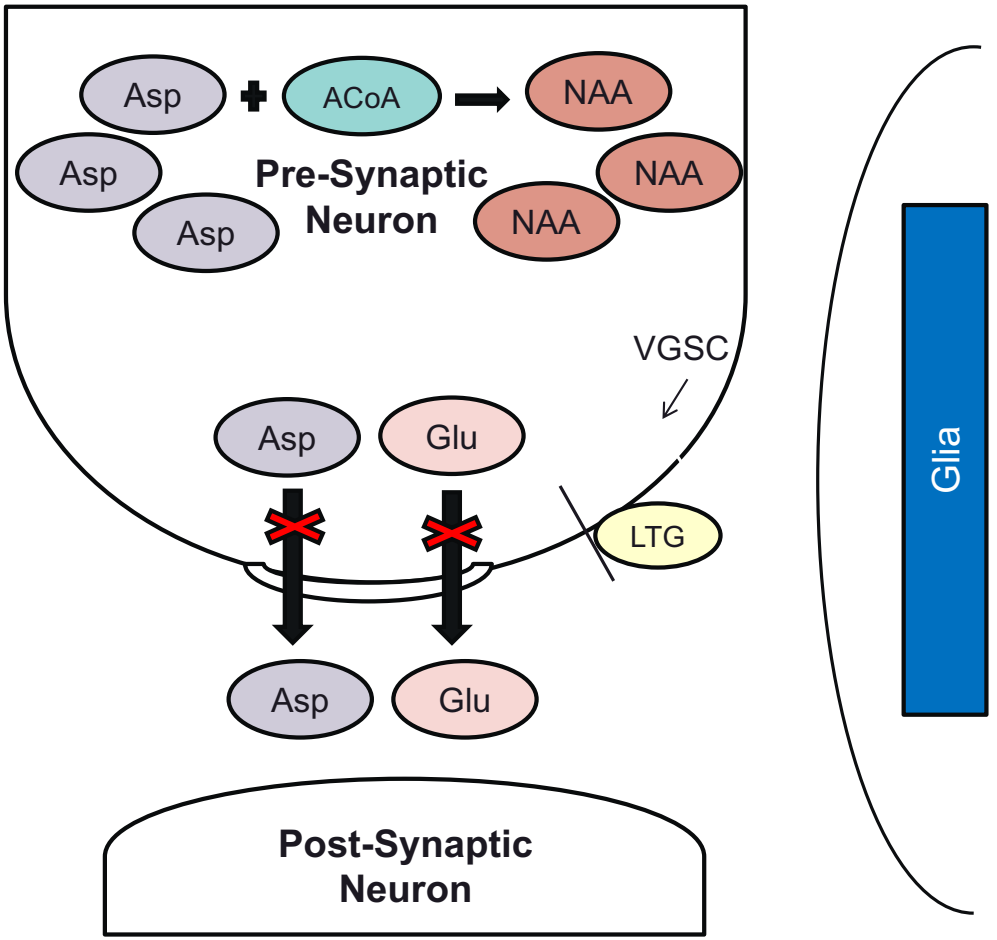
Meta-Analysis of Lamotrigine* in Acute Bipolar Depression





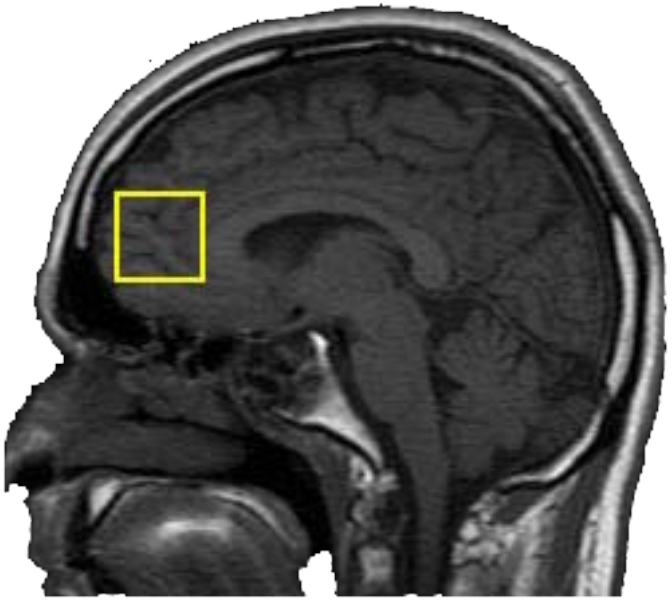
*Not FDA approved for bipolar depression

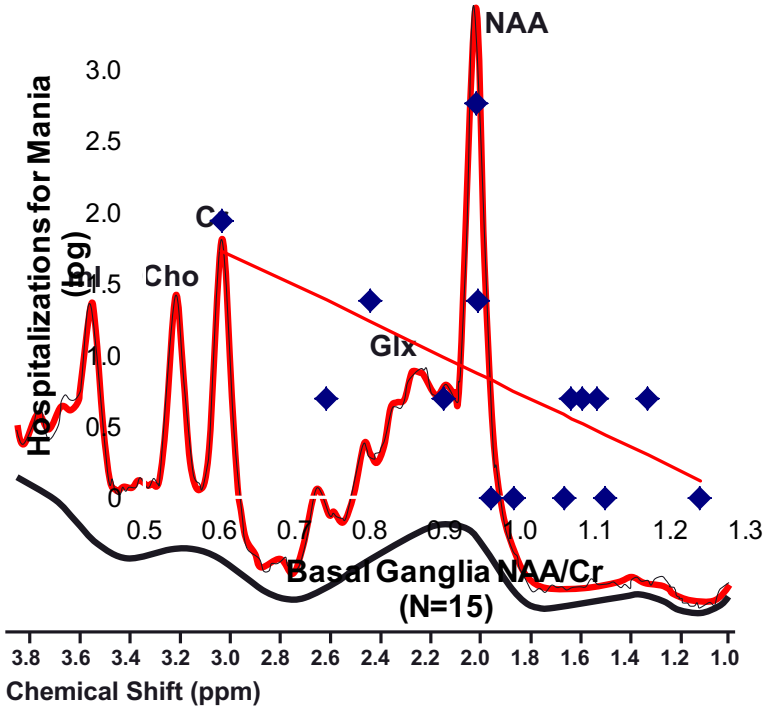
Geddes JR. *Br J Psychiatry*. 2009;194(1):4-9; Van der Loos ML, et al. *J Clin Psychiatry*. 2009;70(2):223-231.



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

Can NAA Stage Disease?

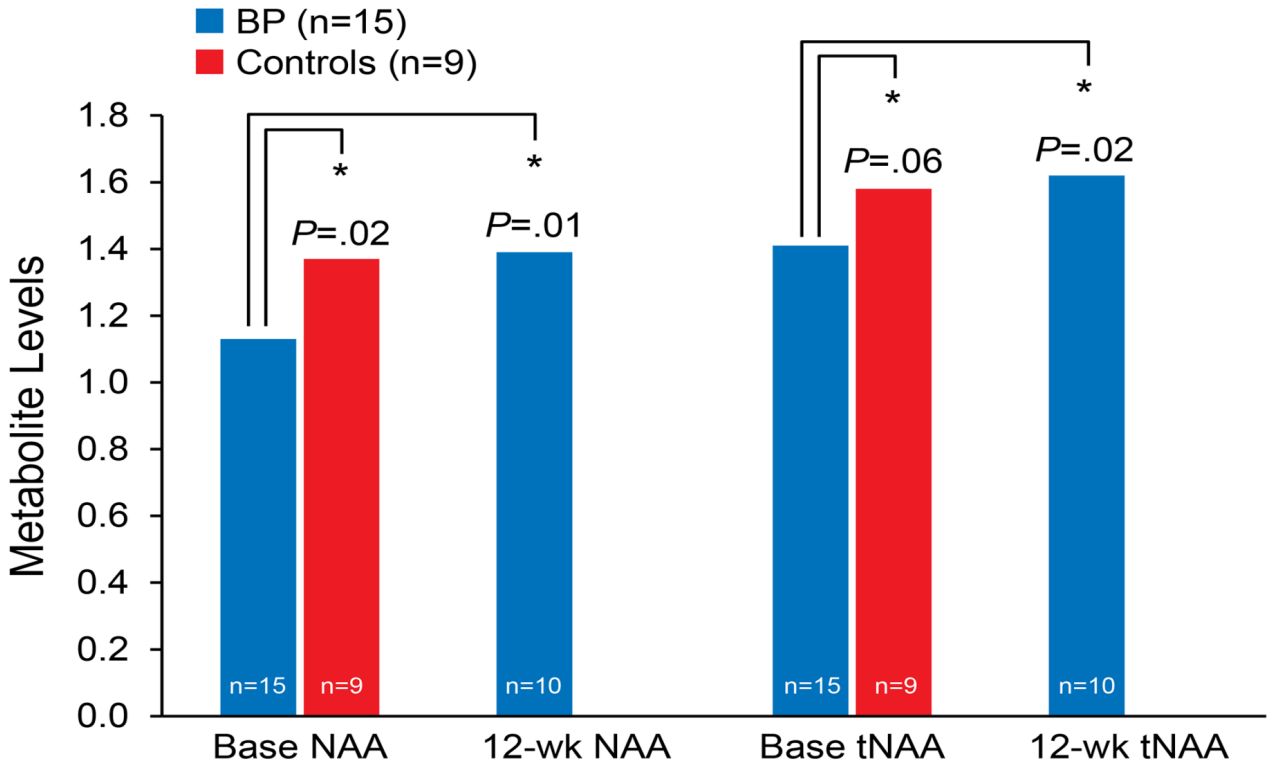




T1-weighted sagittal MRI location for anterior cingulate/medial prefrontal cortex single-voxel, water-suppressed (Haase 1985) PRESS (Bottomley 1987); 1H-MRS (TR/TE = 3s/30ms, number of averages = 256, voxel size 3x3x3 cm^3.

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.

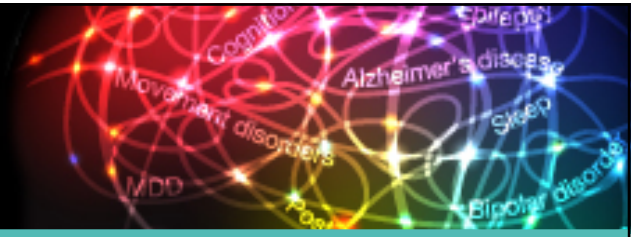
NAA Normalization After Lamotrigine

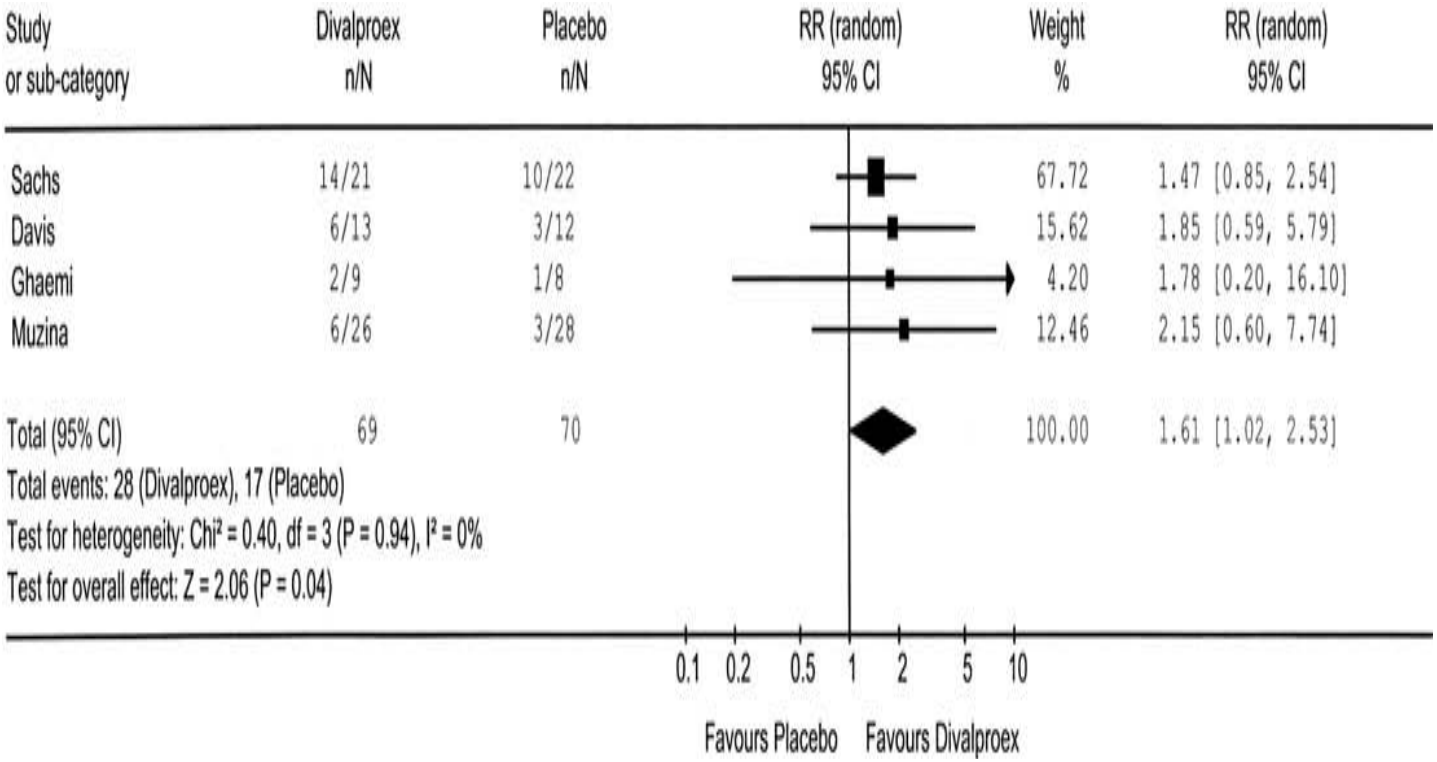


NAA and tNAA Levels at Baseline and After 12 Weeks of Lamotrigine Treatment. Base indicates baseline; BP, bipolar depression; NAA, *N*-acetylaspartate; tNAA, total *N*-acetylaspartate

Croarkin PE, et al. *Bipolar Disord*. 2015;17(4):450-457.

Meta-Analysis: Divalproex in Acute BP Depression

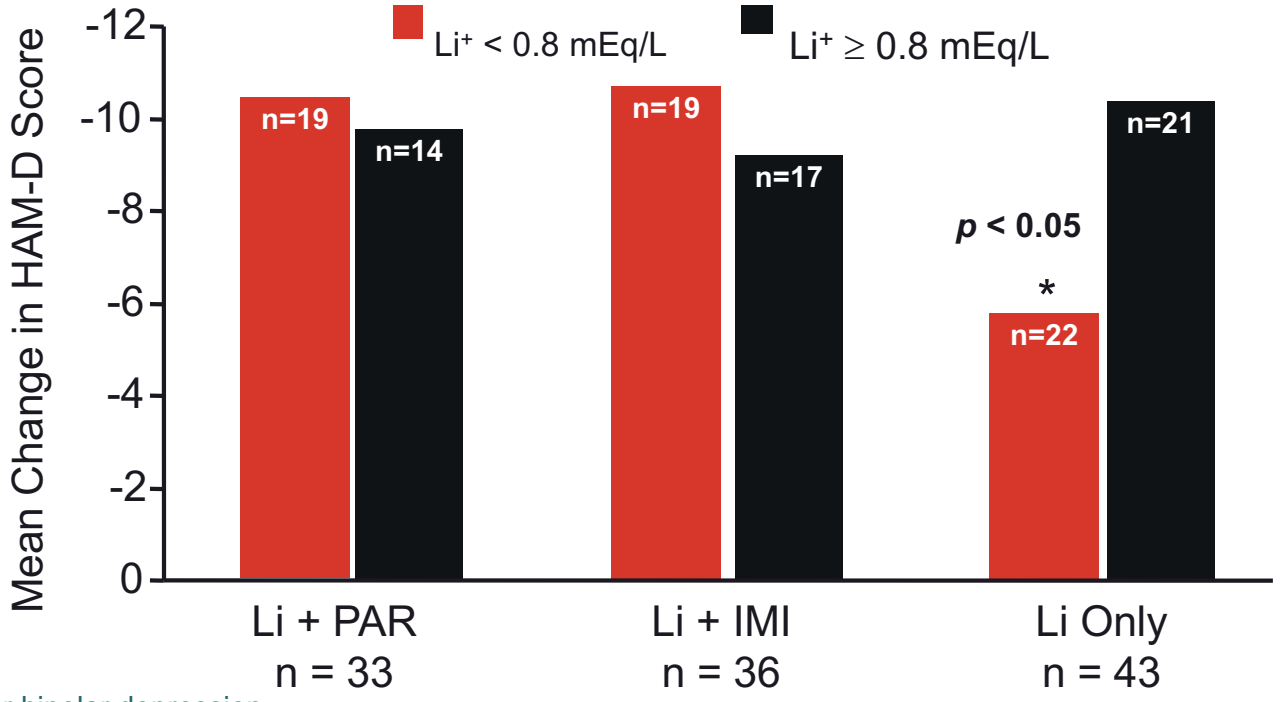




Relative risk of remission in patients treated with divalproex versus placebo

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 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

Sidor MM, MacQueen GM, *J Cln Psychiatry*. 2011;72(2):156-67.

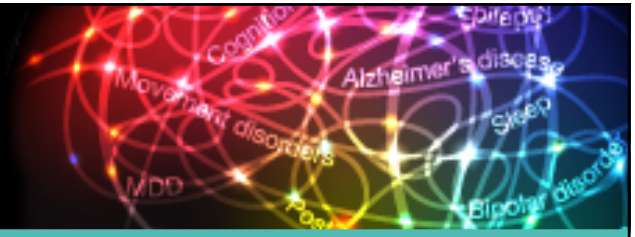
Switching and Response Outcomes by Treatment Group

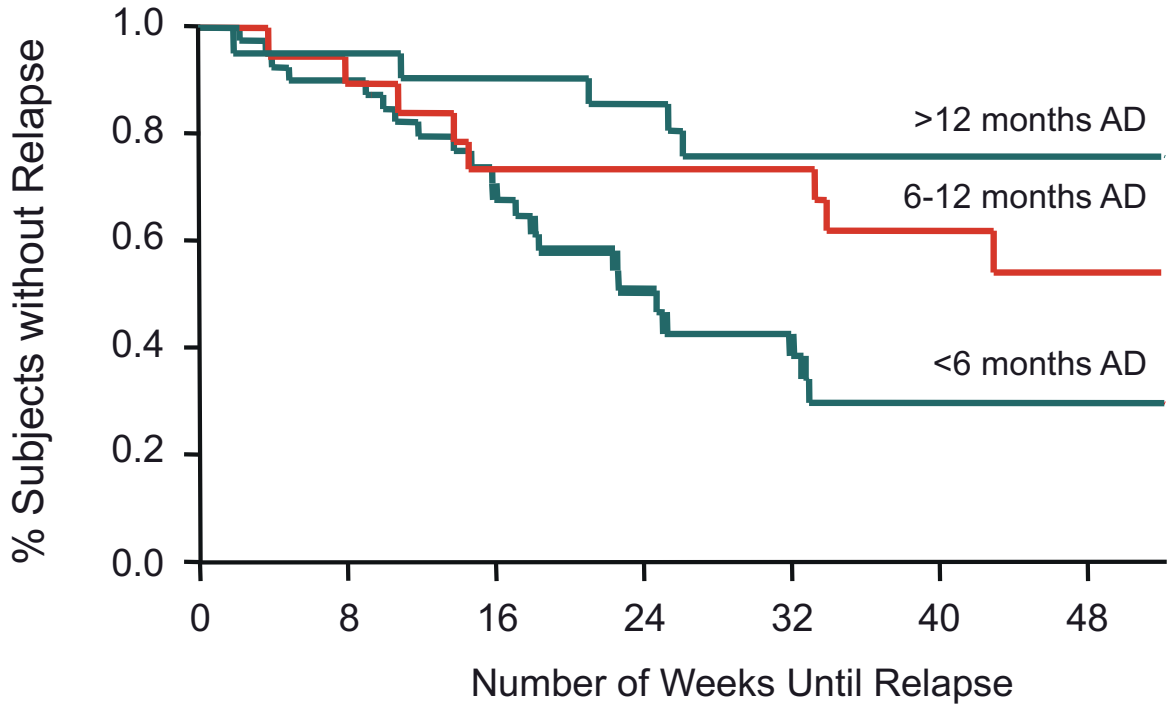
	Lithium (n = 49)	Sertraline (n = 45)	Combination (n = 48)	*p value*
Switch into hypomania	14%	17%	10%	0.78
Antidepressant response during study	67%	73%	48%	0.09

- 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

Altshuler L, et al. *Am J Psychiatry*. 2017;174(3):266-276.

Depressive Episode Relapse with Antidepressant Discontinuation

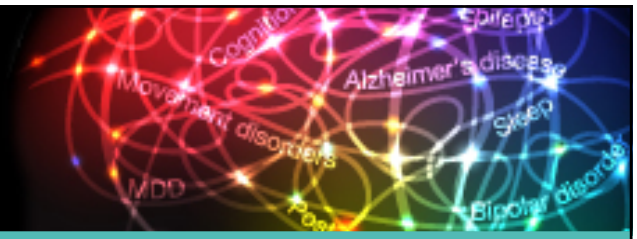




Cox regression analyses log rank = 10.09, p = .006

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

Risk Factors for Switch

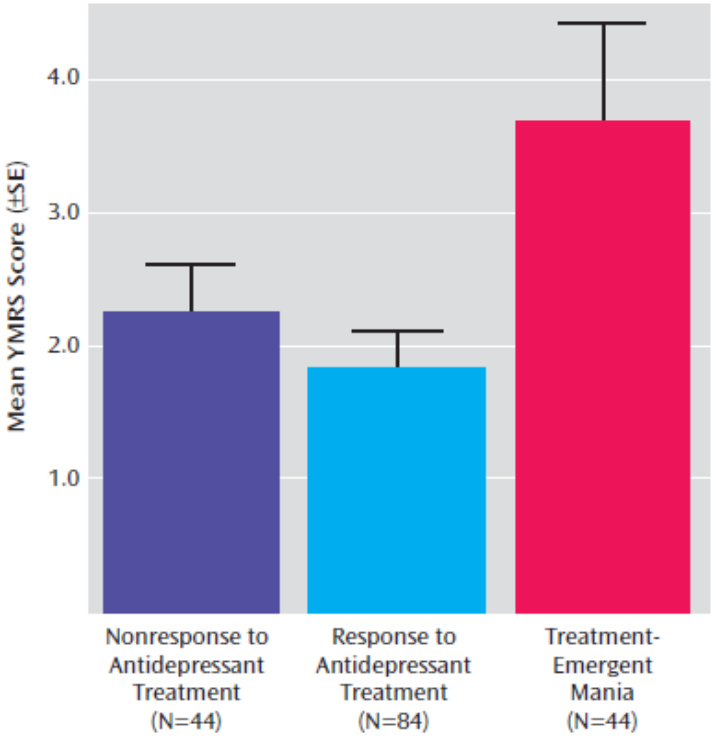


- Mixed Depression
- Tricyclic antidepressants (TCA) vs. SSRI/SNRI
- History of antidepressant-induced mania (AIM)
- Absence of antimanic mood stabilizer
  - First 3 months associated with greatest liability
- Low thyroid stimulating hormone (with TCAs)
- Polymorphism (s/s or s/l) at 5-HTTLPR
- Hyperthymic 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 ($F(2,169) = 3.99$, $p = .02$)



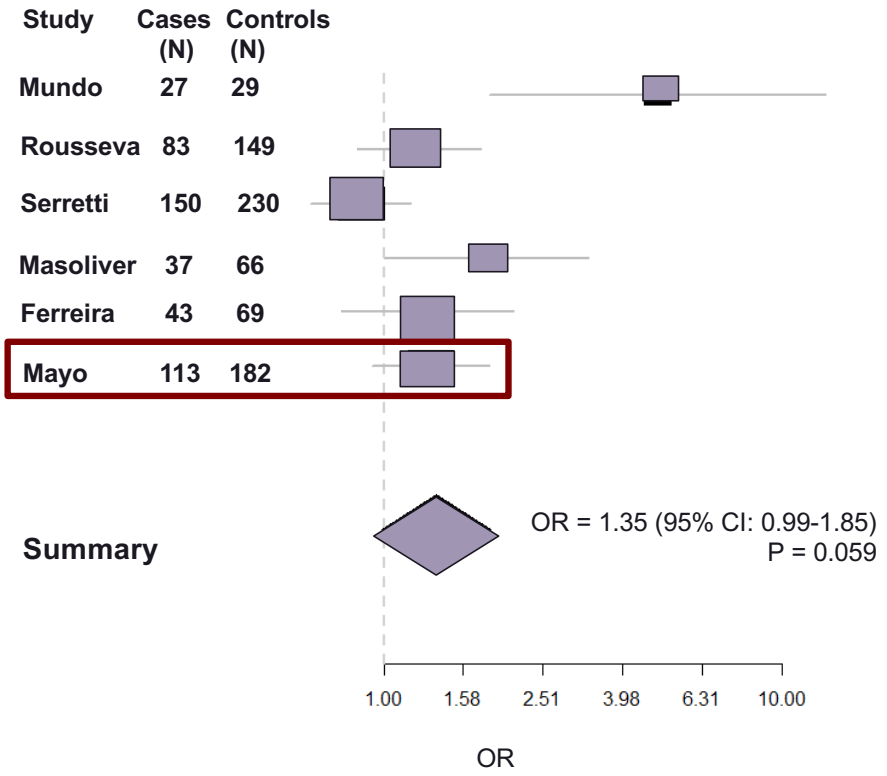
Baseline Manic Symptom Severity Prior to Antidepressant Treatment

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

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

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.

Pharmacogenomic Haplotype Analysis: L-A-Protective

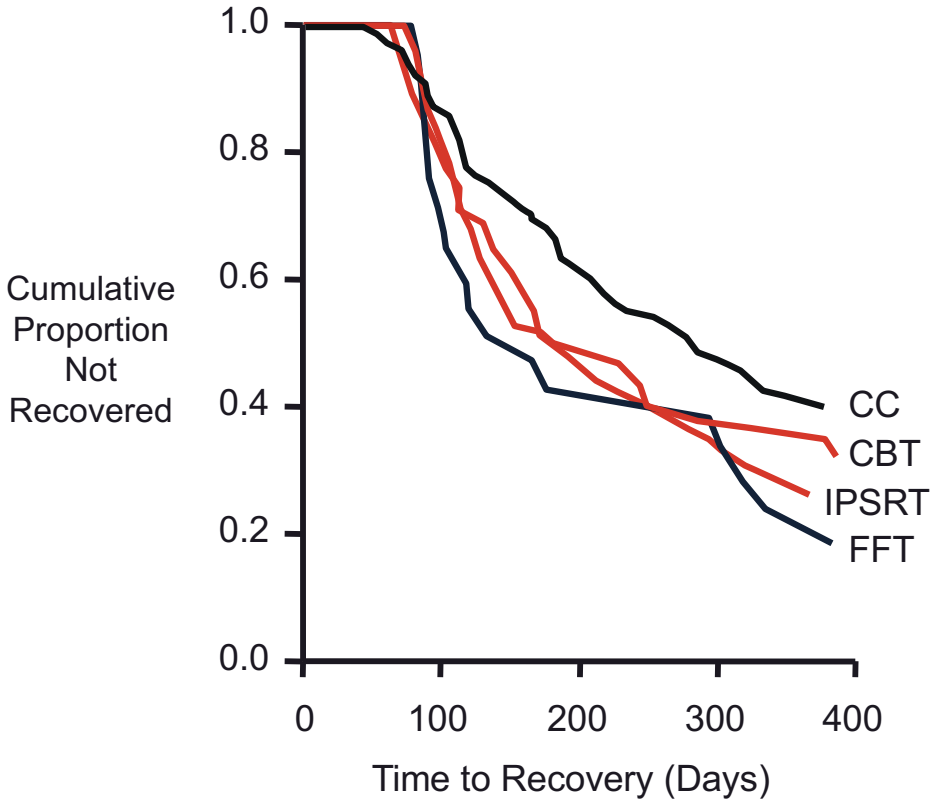
Haplotype	Freq.	Score	Sim p	Max stat sim p	Global sim p
L-A-10	**0.344**	**-2.448**	**0.012**	**0.047**	**0.020**
L-G-12	0.027	-1.555	0.14	–	
S-A-10	0.214	0.144	0.86	–	
L-A-12	0.136	0.965	0.31	–	
S-A-12	0.225	1.034	0.28	–	

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.

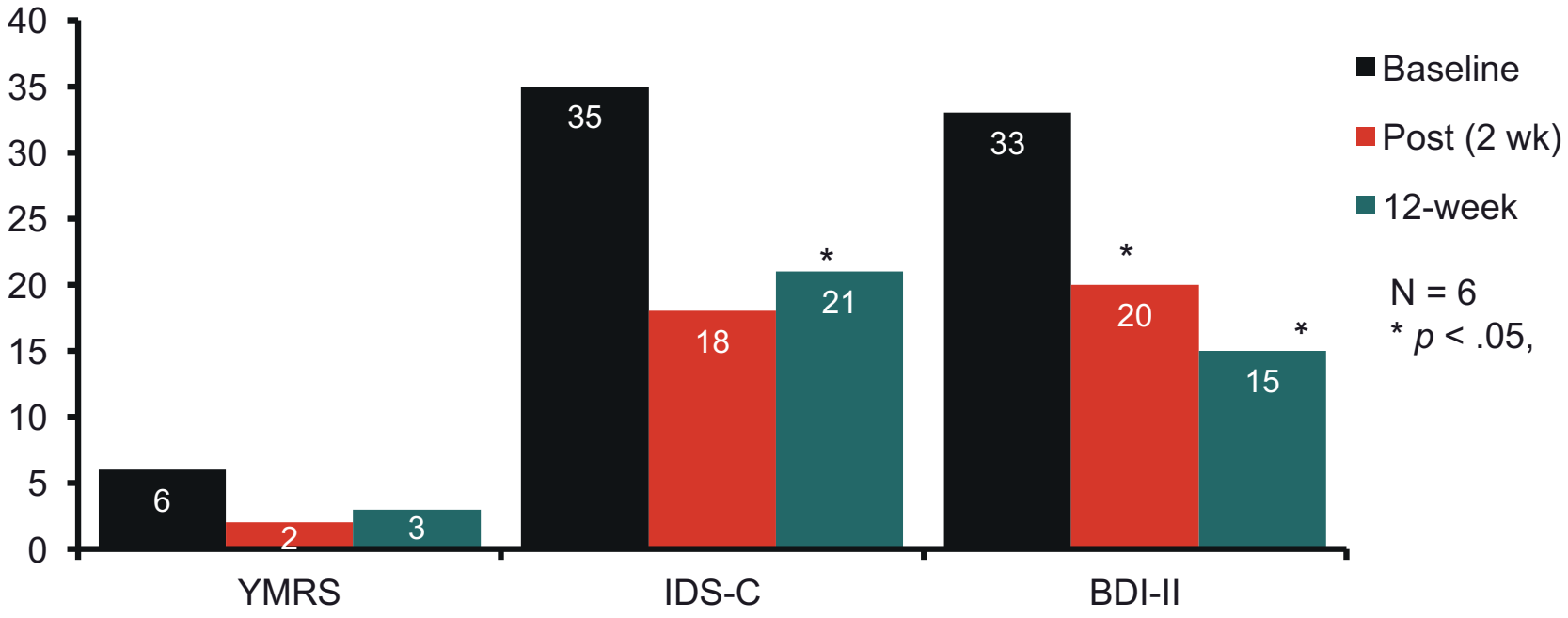
Intensive Psychotherapies Improve Bipolar Depression



- 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.

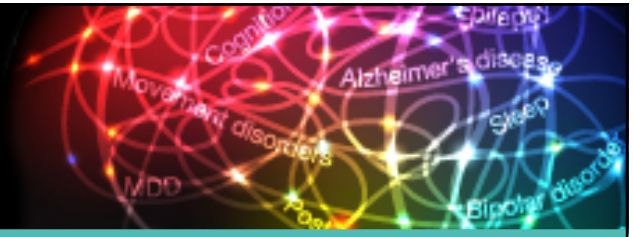
Maintenance of Antidepressant Response After Group IPSRT Group for Bipolar Disorder



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.

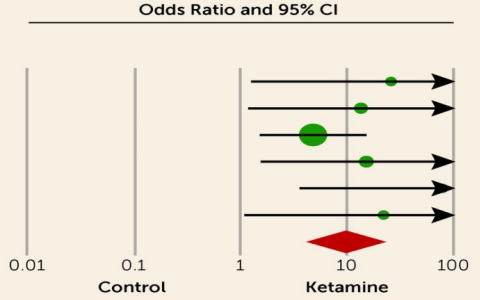
Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression



A

Statistics for Each Study

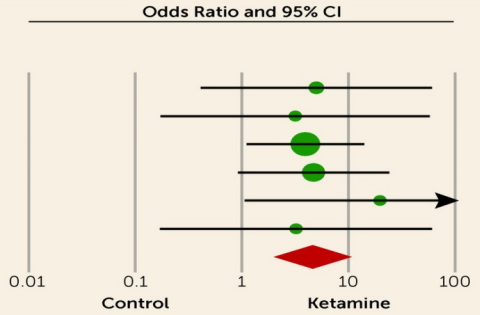
Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	26.053	1.359	499.339	2.164	0.030
Lapidus et al. (84)	13.600	1.238	149.455	2.134	0.033
Murrough et al. (87)	4.833	1.578	14.803	2.759	0.006
Sos et al. (91)	15.294	1.610	145.305	2.374	0.018
Zarate et al. (88)	79.545	3.762	1681.833	2.811	0.005
Zarate et al. (86)	22.176	1.133	434.158	2.042	0.041
	9.865	4.366	22.293	5.503	0.000



B

Statistics for Each Study

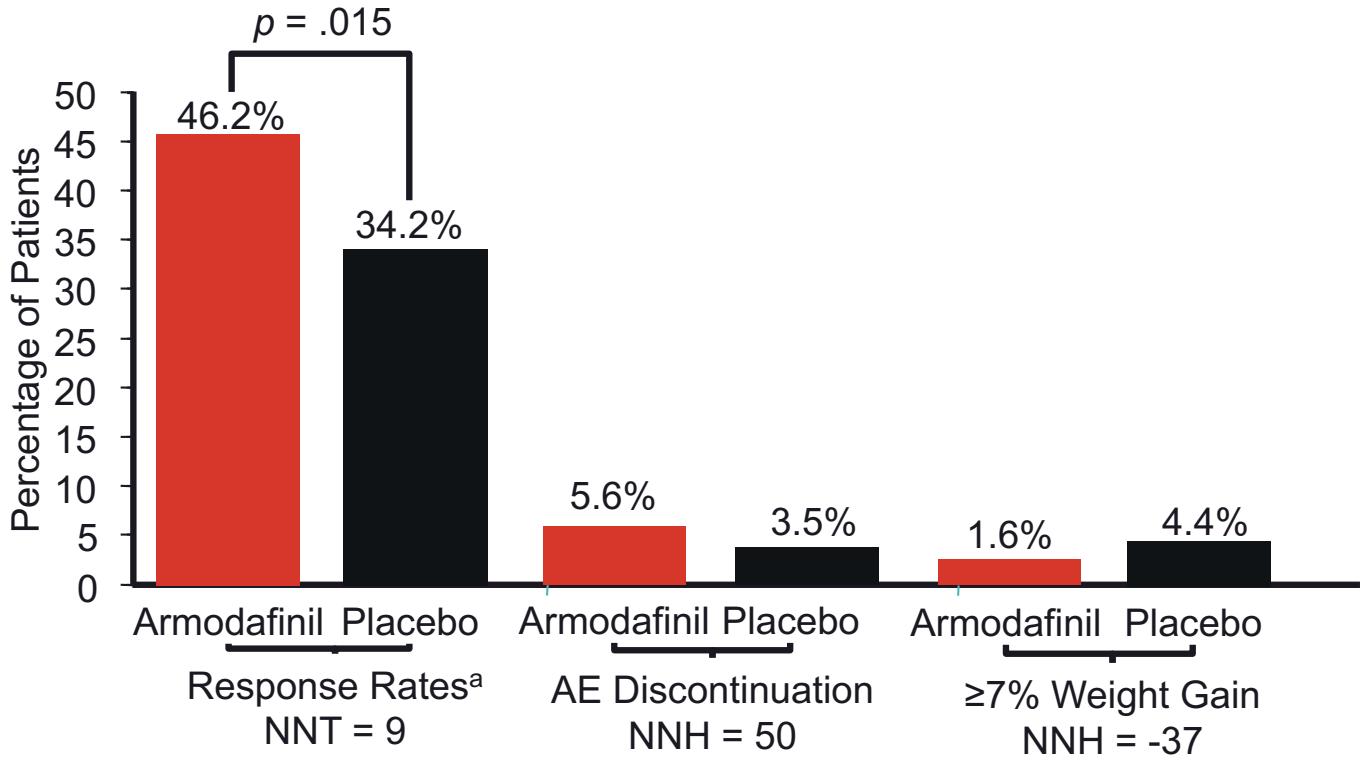
Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	1.999	0.046
Zarate et al. (86)	3.222	0.176	58.849	0.789	0.430
	4.610	2.076	10.236	3.754	0.000



a The A) top plot shows results one day after initiation of ketamine (heterogeneity: $\chi 2=4.27$, df=4, p=0.51, I2=0%). The B) bottom plot shows results one week after initiation of ketamine (heterogeneity: $\chi 2=1.14$, df=5, p=0.95, I2=0%).

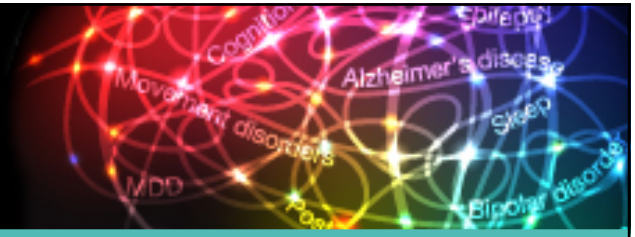
Newport DJ, et al. *Am J Psychiatry*. 2015;172(10):950-966.

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



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


MAYO
CLINIC

Questions & Answers

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