CME Outfitters

Advances in Diagnosis, Neurobiology, and Treatment of Mood Disorders

June 13 - 14, 2016

Field House Coral Gables
University of Miami
Coral Gables, FL

CIAP

CURSO INTERAMERICANO DE ACTUALIZACIÓN EN PSIQUIATRÍA

Optimal Treatment of Bipolar Disorder

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CME Outfitters

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Disclosures

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

Learning Objectives

- Review the diagnosis and clinical management of mania in bipolar disorder.
- Differentiate bipolar depression from unipolar depression.
- Integrate the evidence-based, best-practice options for the pharmacological and non-pharmacological management of patients with bipolar disorder.

Audience Response

How confident are you in using the latest evidence in treating patients with bipolar disorders?

A. Extremely confident
B. Confident
C. Somewhat confident
D. Not confident at all

Audience Response

In the treatment of bipolar depression, which is the most commonly prescribed medication?

A. Antidepressants

B. Divalproex

C. Atypical antipsychotics

D. Stimulants

Optimal Treatment

- Diagnosis & Epidemiology of Bipolar Disorder
- Mania
- Depression
- Maintenance
- Conclusion

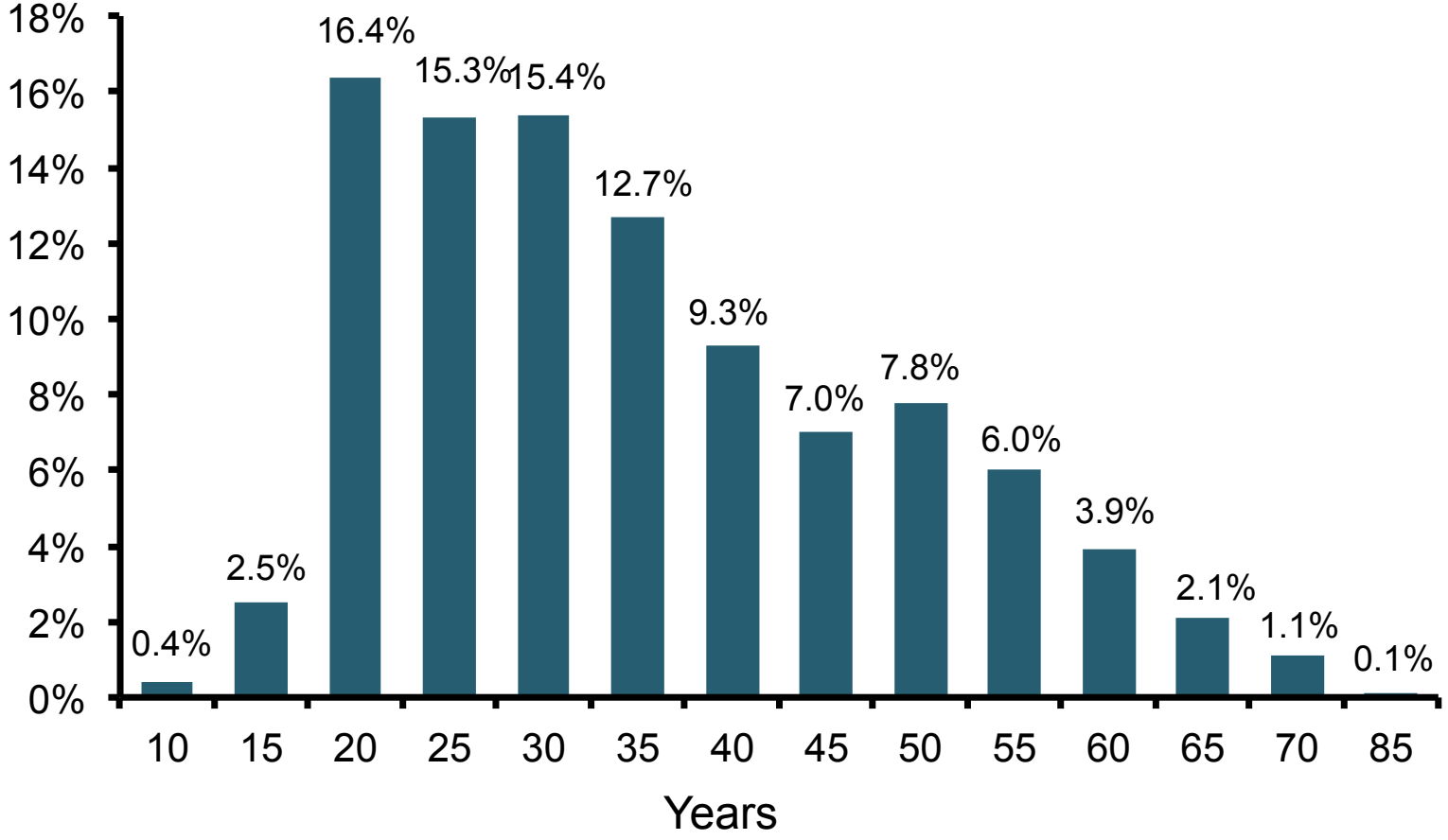
Epidemiology of Bipolar Disorder

Bipolar Disorder	
Bipolar I (M / D)	1% of US population
Bipolar II (m / D)	1-2% of US population
Sex	Equal distribution
Onset (average)	First impairment (age 15-19)
	First treatment (age 20-24)
	First hospitalization (age 25)
Recurrence	Average 2.7-9 years
Suicide	~35% attempt, ~9% succeed
Predominant phase of illness	Depression

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.

M = mania
M = hypemania
D = depression

Bipolar Diagnosis Across the Age Spectrum



Kraepelin, Emil (1921) *Manic-depressive Insanity and Paranoia* ISBN 0-405-07441-7.

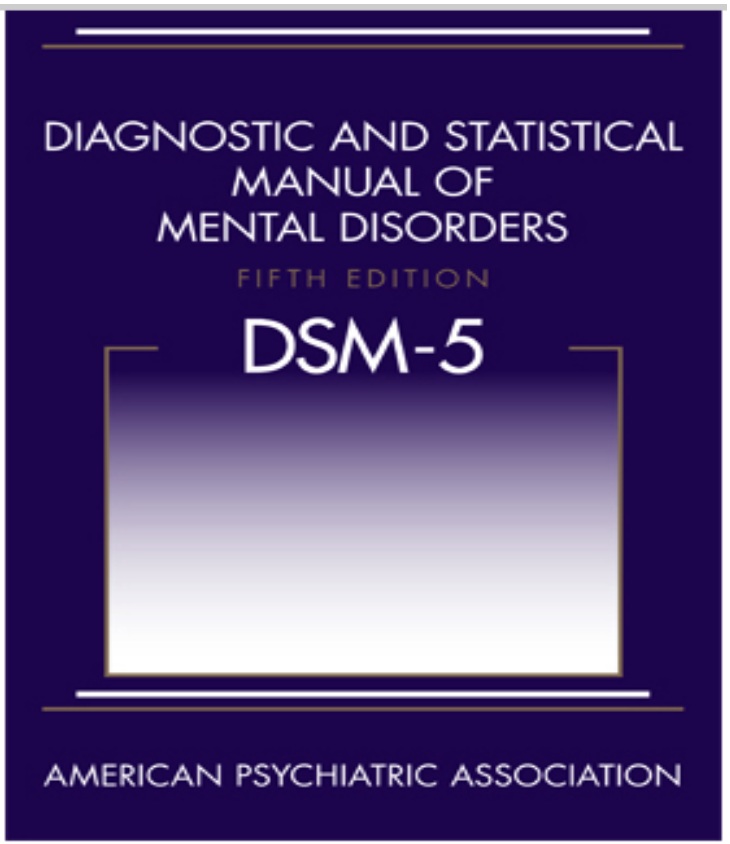
Young and Bipolar

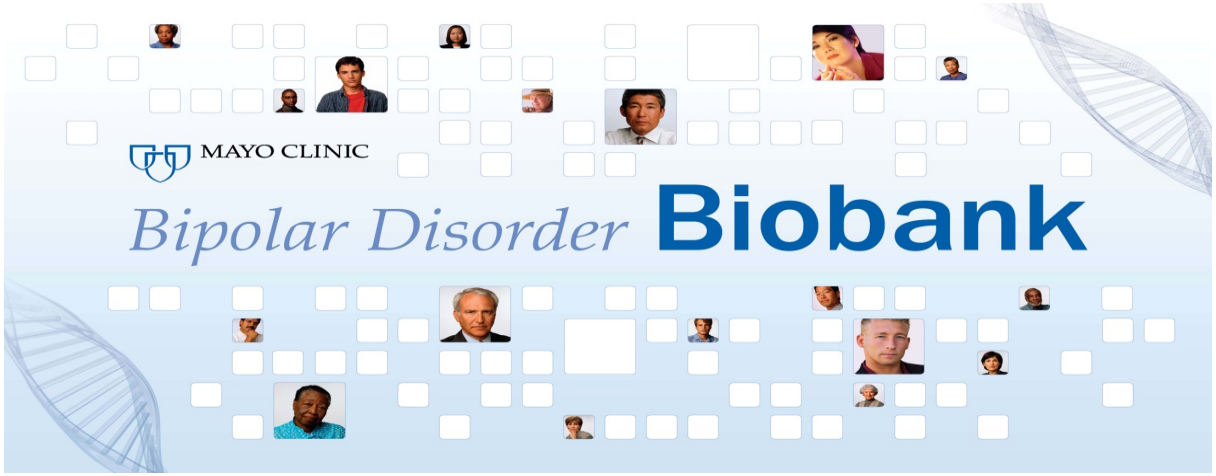
Time 2002, August 19.

Disruptive Mood Dysregulation Disorder (DMDD)

Time 2002, August 19.


AUGUST 19, 2002
TIME
THE SKINNY ON THE ANTI-FAT HORMONE
Inside the Volatile World of the
YOUNG AND BIPOLAR
Why are so many kids being diagnosed with the disorder once known as MANIC DEPRESSION?
Ian Palmer, 9, is being treated for bipolar disorder
www.time.com AOL Keyword: TIME

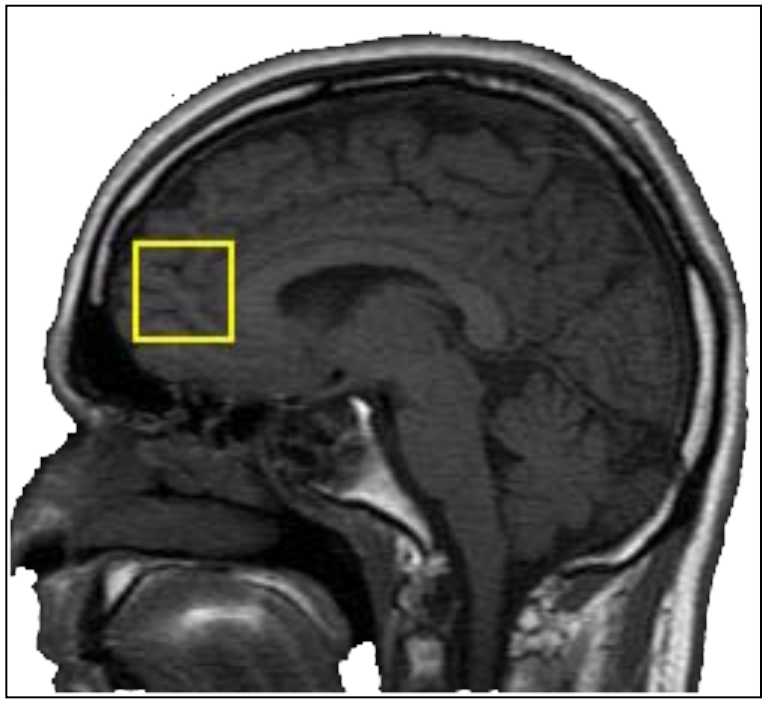

DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS
FIFTH EDITION
DSM-5
AMERICAN PSYCHIATRIC ASSOCIATION


MAYO CLINIC
Bipolar Disorder Biobank

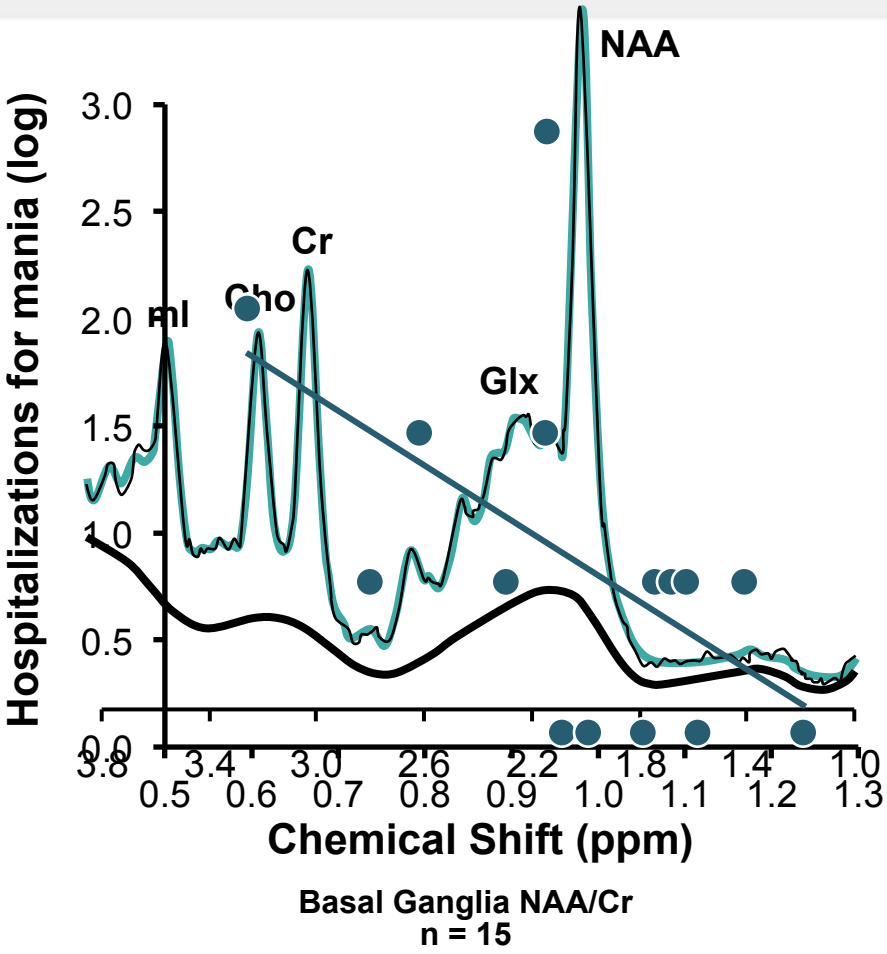
FDA Indications: Acute Mania

- 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 FDA approved for mania
- 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)

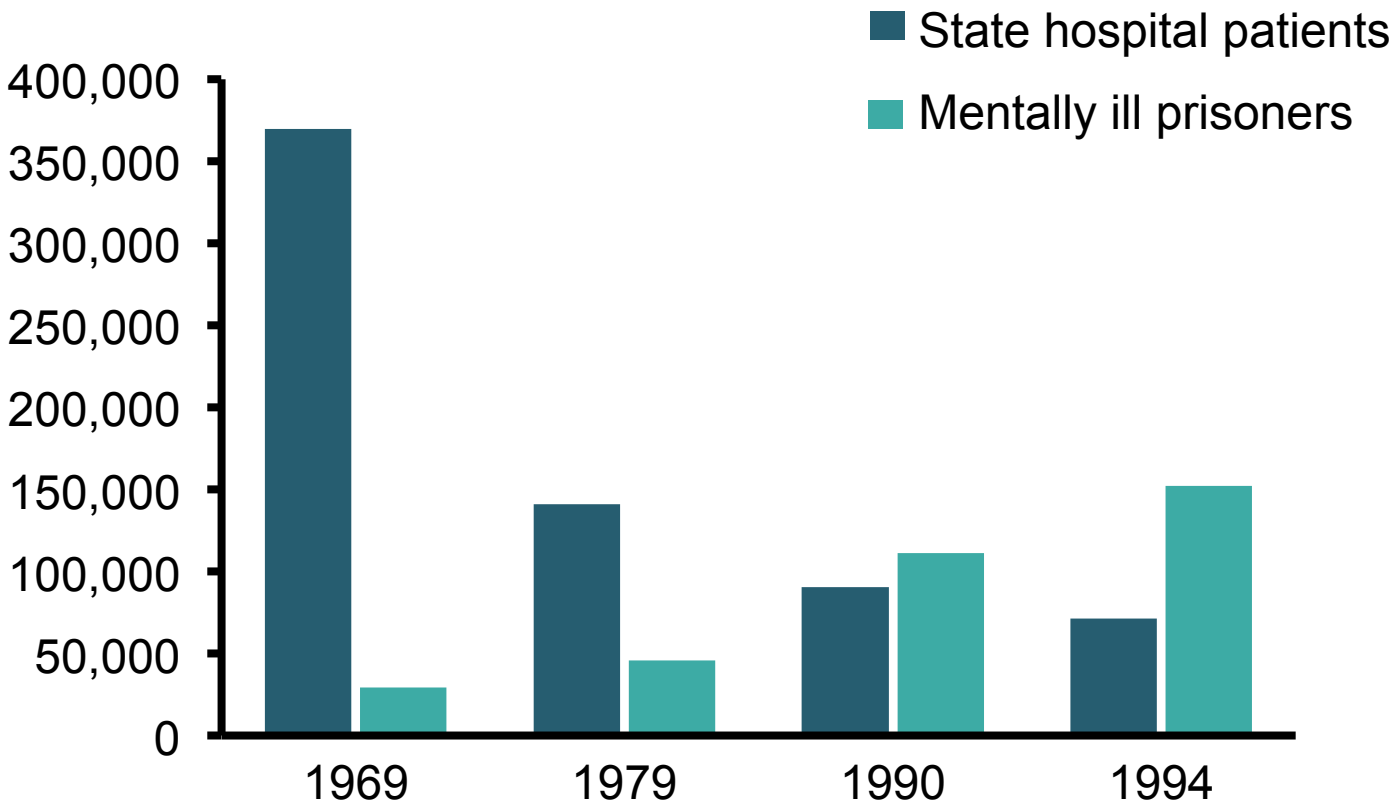


Basal Ganglia NAA/Cr
n = 15

NAA-/Cr = N- acetylaspartate /creatine

Frye MA, et al, *Psychiatry Res*. 2007;154(3):259-265.; TsaiG, et al. *Prog Neurobiol* 1995;46(5):531-540;. Altshuler LL. *Biol Psychiatry*. 1993;33(8-9):563-565.

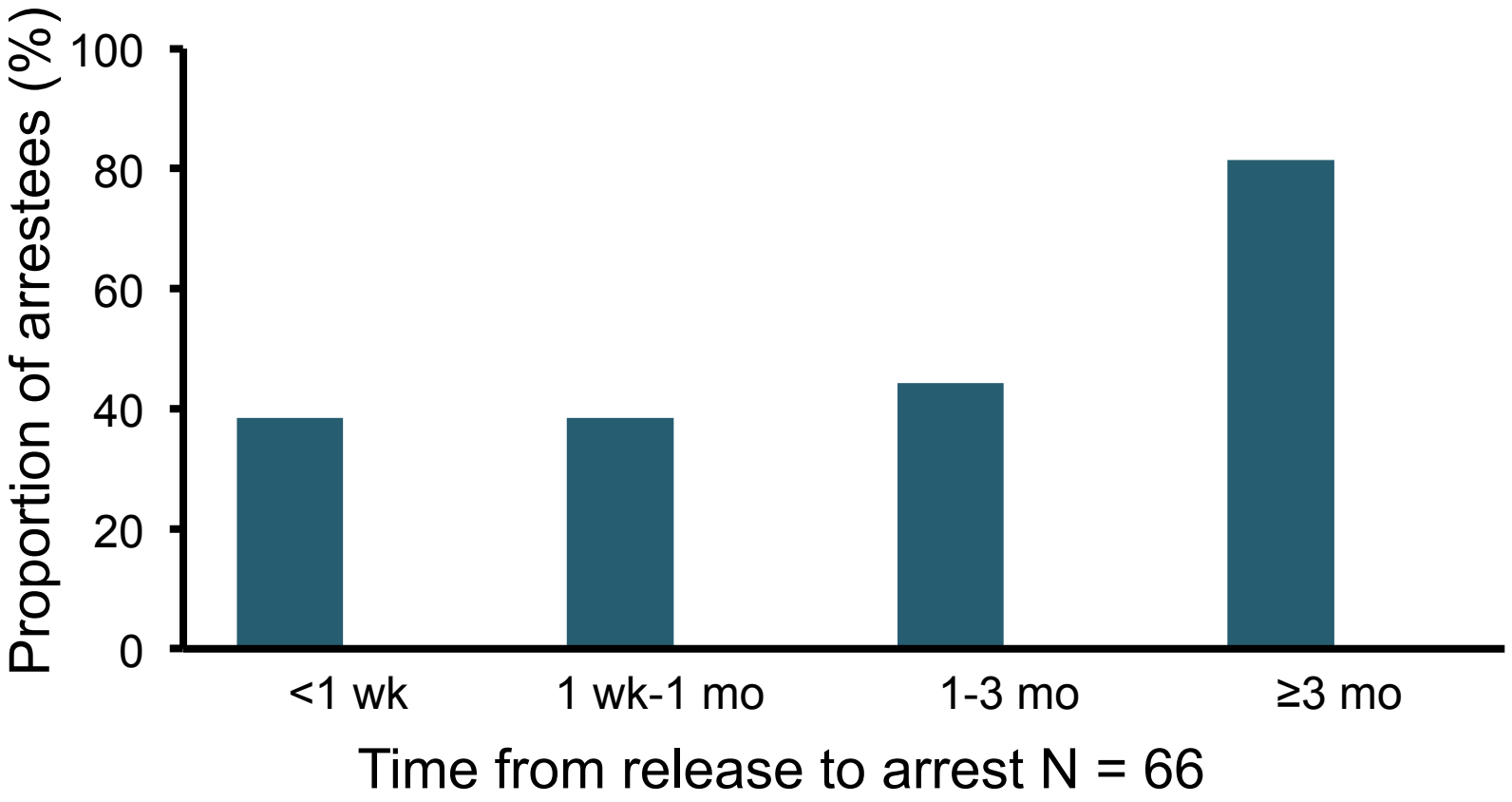
Jail / Prison Have Replaced State Hospitals



Mandersheid RW, Sonnenschen MA, eds. Mental Health, United States, 1996
Washington DC: US Government Printing Office; 1996. DHHS Publication SMA 99-3285.

Mania Discharge and Subsequent Arrest

Los Angeles Community Hospitals



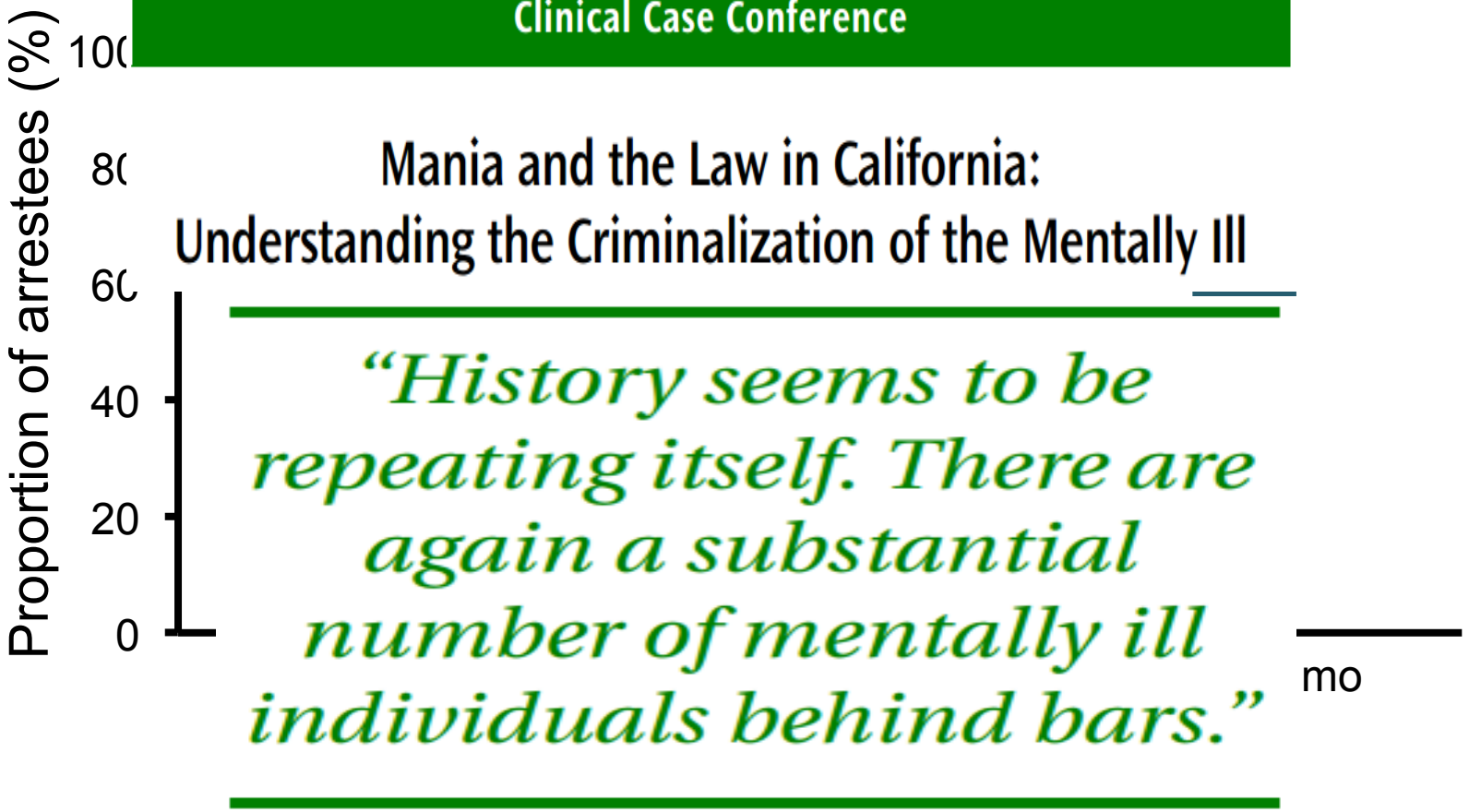
Quanbeck C, Frye MA, et al. *Am J Psychiatry.* 2003;160(7):1245-1250.

Mania Discharge and Subsequ

Los Angeles

THE AMERICAN JOURNAL OF PSYCHIATRY

Clinical Case Conference



Quanbeck C, Frye MA, et al. *Am J Psychiatry.* 2003;160(7):1245-1250.

Mania is an EMERGENCY

- Need rapid, safe stabilization
  - Reduction of behavioral agitation
  - Sleep restoration
  - Management of withdrawal from drugs & alcohol
- Antimanic treatment based on
  - Manic episode (euphoric or mixed specifier)
  - Rapid cycling
  - Psychotic symptoms
  - Medication history
  - Medical comorbidities
  - Patient expectations or shared decision making

Acute Management of Agitated Patient

- Agitation mild to moderate, cooperative, non-psychotic
  - Oral lorazepam* 1-2 mg, repeat 1-2 mg Q 30-60 min until calm (or max dose 10-15 mg)
- Agitation mild to moderate, cooperative, (+) evidence of psychosis*
  - Oral olanzapine (SOT or ODO) 5-10 mg
  - Oral risperidone* 0.5-2.0 mg
  - Oral quetiapine* 25-100 mg
  - Oral haloperidol 1-5 mg (anticholinergic is antipsychotic-naïve or EPS sensitive)

* Not FDA approved for agitation; SOD = standard olanzapine-coated tablet; ODO = orally disintegrating olanzapine

* Use **lorazepam** if suspected catatonia, NMS, or significant EPS.

Wilson MP, et al. *West J Emerg Med.* 2012(1):26-34. PMID: 2246191; Gardner DM, et al. *Am J Psychiatry*. 2010;167(6):686-693

Acute Management of Agitated Patient

- Agitation moderate to severe, uncooperative, with or without psychosis
  - Haloperidol 5-10 mg IM + lorazepam 1-2 mg IM (anticholinergic if neuroleptic naïve or EPS sensitive)
  - Ziprasidone 10-20 mg IM (repeat Q 2-4 hours as needed until calm, or max dose 40 mg/24 hours)
  - Olanzapine 10 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)
  - Aripiprazole 9.75 mg IM (repeat after 2 hours until calm, or max dose 30 mg/day)

Gardner DM, et al. *Am J Psychiatry*. 2010;167(6):686-693.; Bosanac P, et al. *Australas Psychiatry*. 2013;21(6):554-562.; Gonzalez D, et al. *Curr Med Res Opin*. 2013;29(3):241-250.; DeFilippis M, et al. *Pharmacotherapy* 2013;(2):433-445.; Zimbroff D, et al. *J Clin Psychopharmacol*. 2007; Apr;27(2): 171-176.

Short-acting Injectable Antipsychotic Drugs: Comparative Safety and Efficacy in Treating Agitation

Pooled analysis of 9 RCT, effect sizes reported as NNT (vs. PLC) for positive response to treatment; no direct head-to-head comparisons		
Medication	Number needed to treat (NNT) vs. PLC	95% Confidence Interval
Ziprasidone IM, 10-20 mg	3	2 to 4
Olanzapine IM, 10 mg	3	2 to 3
Aripiprazole IM, 9.75 mg	5	4 to 8

Citrome L. *J Clin Psychiatry*. 2007;68(12):1876-1885.

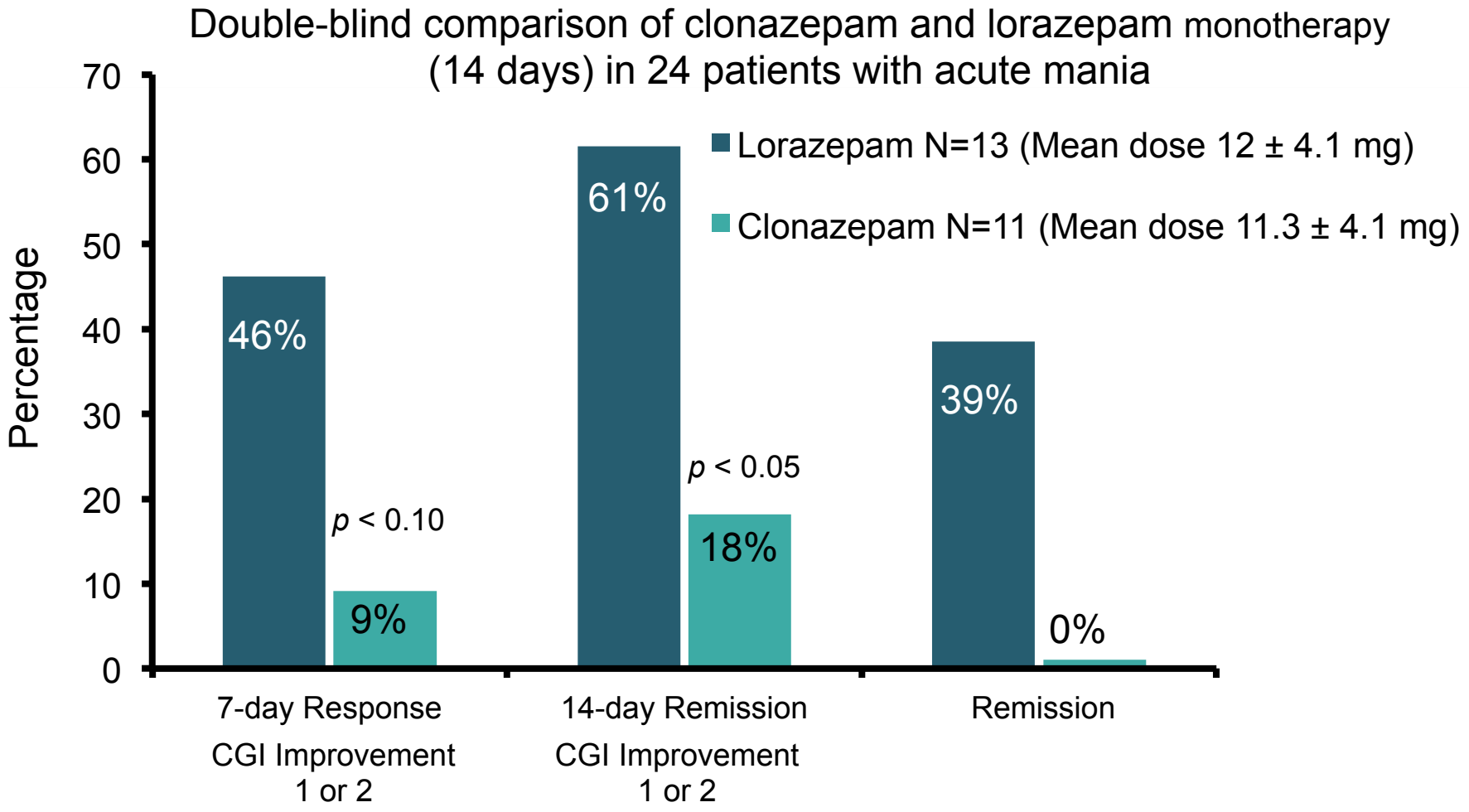
Orally Inhaled Loxapine Powder

- **Dosing**: 10 mg single inhaled dose (1/24 hrs)
- **Pooled analysis** of two Phase III randomized trials (one study in patients with schizophrenia, one study in patients with BP-I)
- NNT (vs. PLC) for positive response:
  - Loxapine 5 mg, NNT 4
  - Loxapine 10 mg, NNT 3
- NNT (vs. PLC) for requiring only one dose of study drug without rescue medication:
  - Loxapine 5 mg, NNT – n.s.
  - Loxapine 10 mg, NNT 7

Citrome L. *Int J Clin Pract*. 2012; 66(3):318-325.

Approved by the FDA 2012

Double-Blind Comparison of Clonazepam* vs Lorazepam* in Acute Mania



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

*Not FDA approved for mania

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	+	–	–	+

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

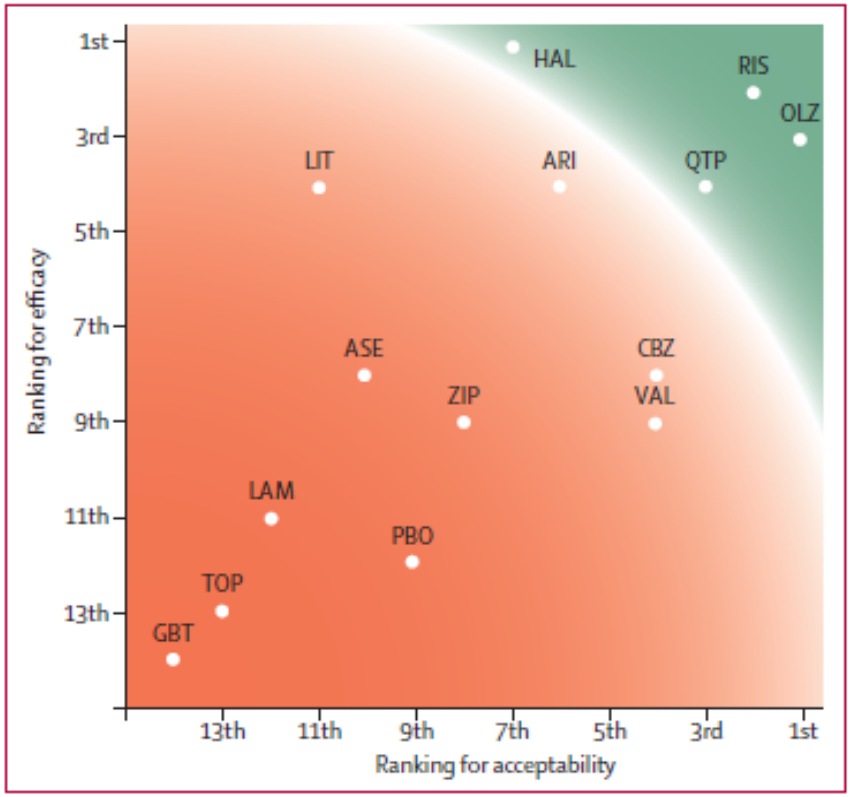
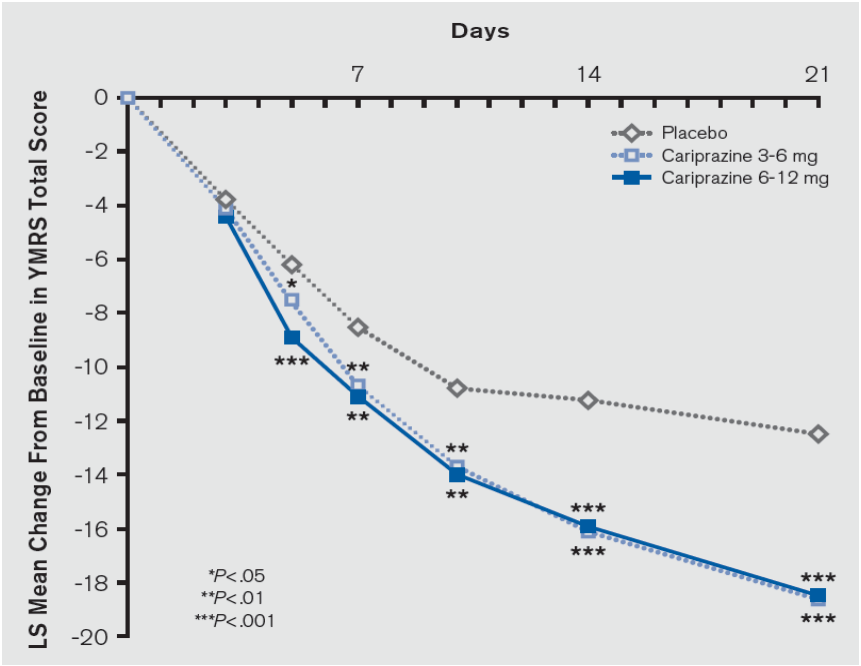


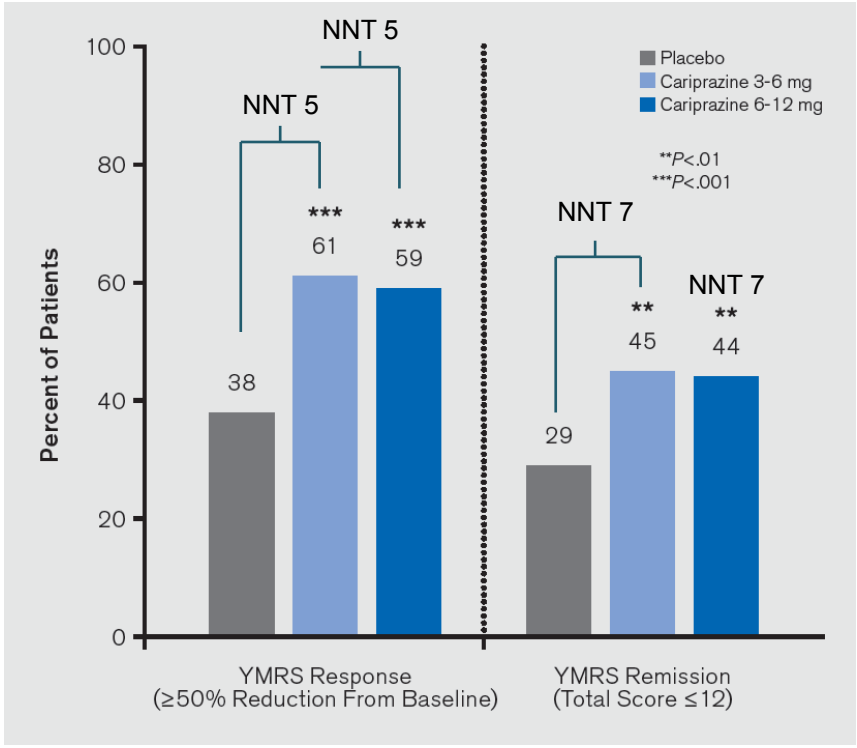
Figure 6: Ranking of antimanic drugs according to primary outcomes: efficacy (as continuous outcome) and dropout rate

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

Cariprazine for Acute Mania Associated With Bipolar I Disorder

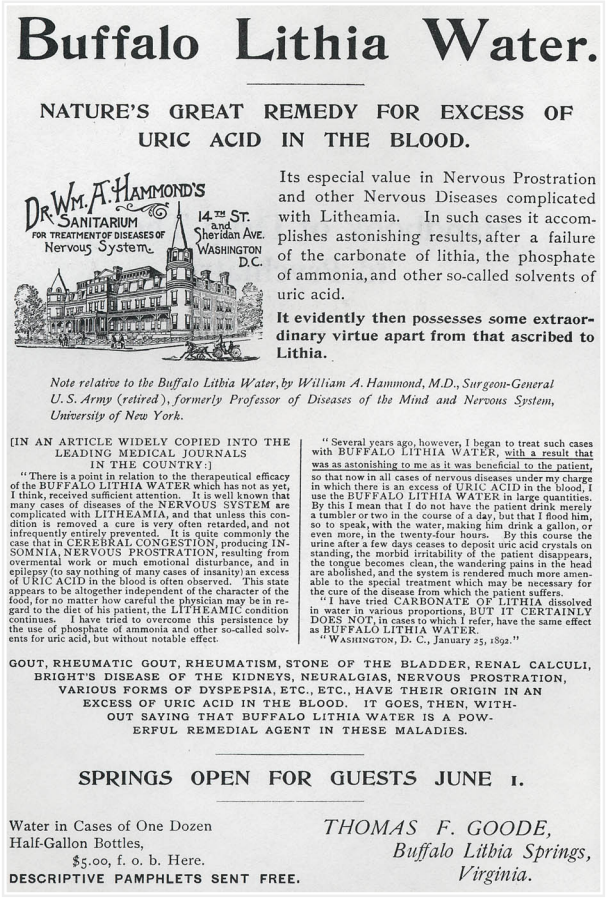
- Randomized, DB, PLC-controlled trial (2010-2011); cariprazine 3-6 mg/d vs. cariprazine 6-12 mg/d vs. PLC over 3 weeks; 497 patients with BP-I manic or mixed episodes; primary endpoint – change YMRS total score; secondary endpoints – response, remission





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

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

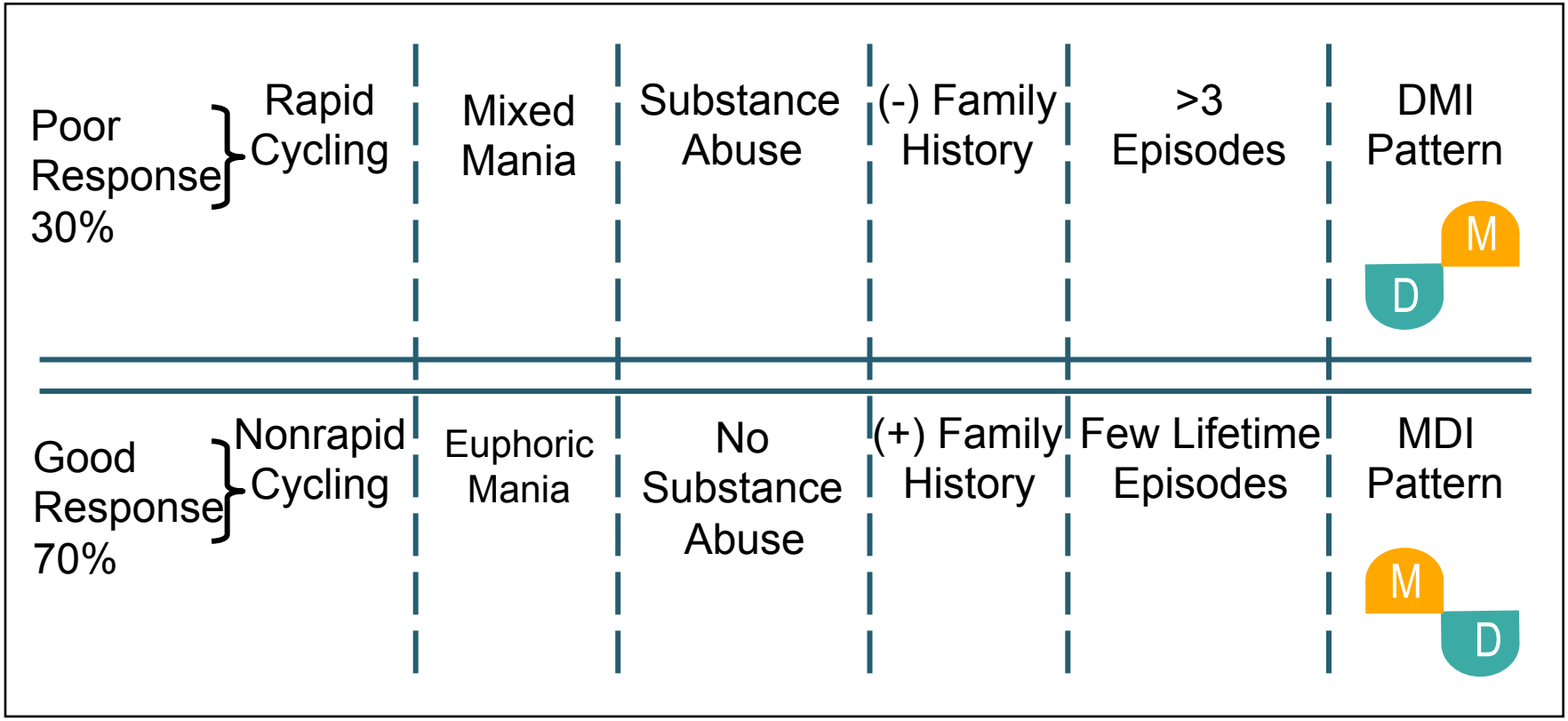
- Gold standard – benchmark
- Lithium non-response differs from other mood stabilizers
- Clinical predictors account for <50% of variance, suggesting genetic factors
- Prophylactic response familial
- Numerous side effects, narrow therapeutic index
- Believed to reduce suicide rates via unknown mechanism

*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



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

Frye MA et al. *J Affect Disord*. 1998;48(2):91-104.

ConLi+Gen

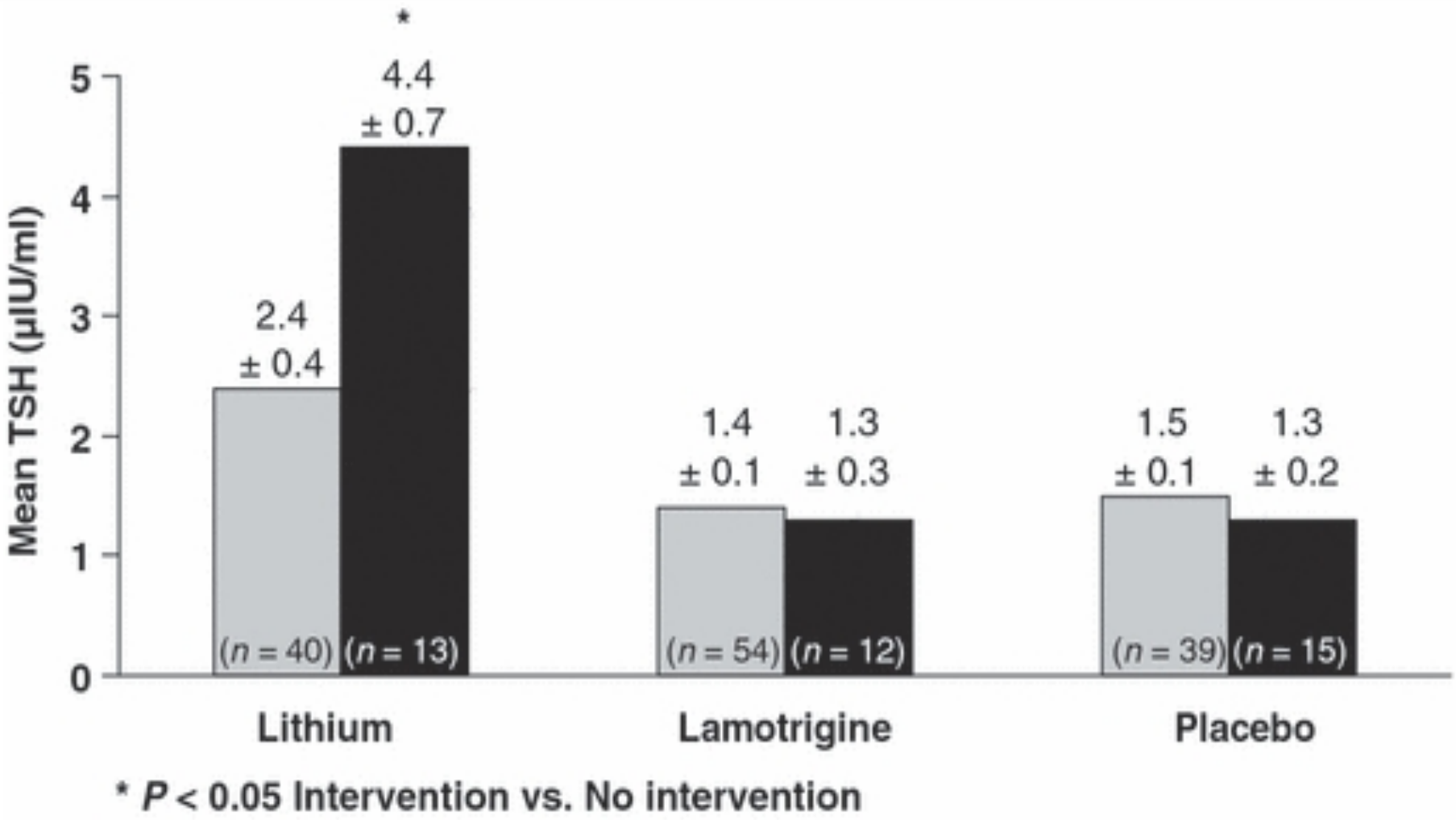
The international Consortium on Lithium Genetics

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 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

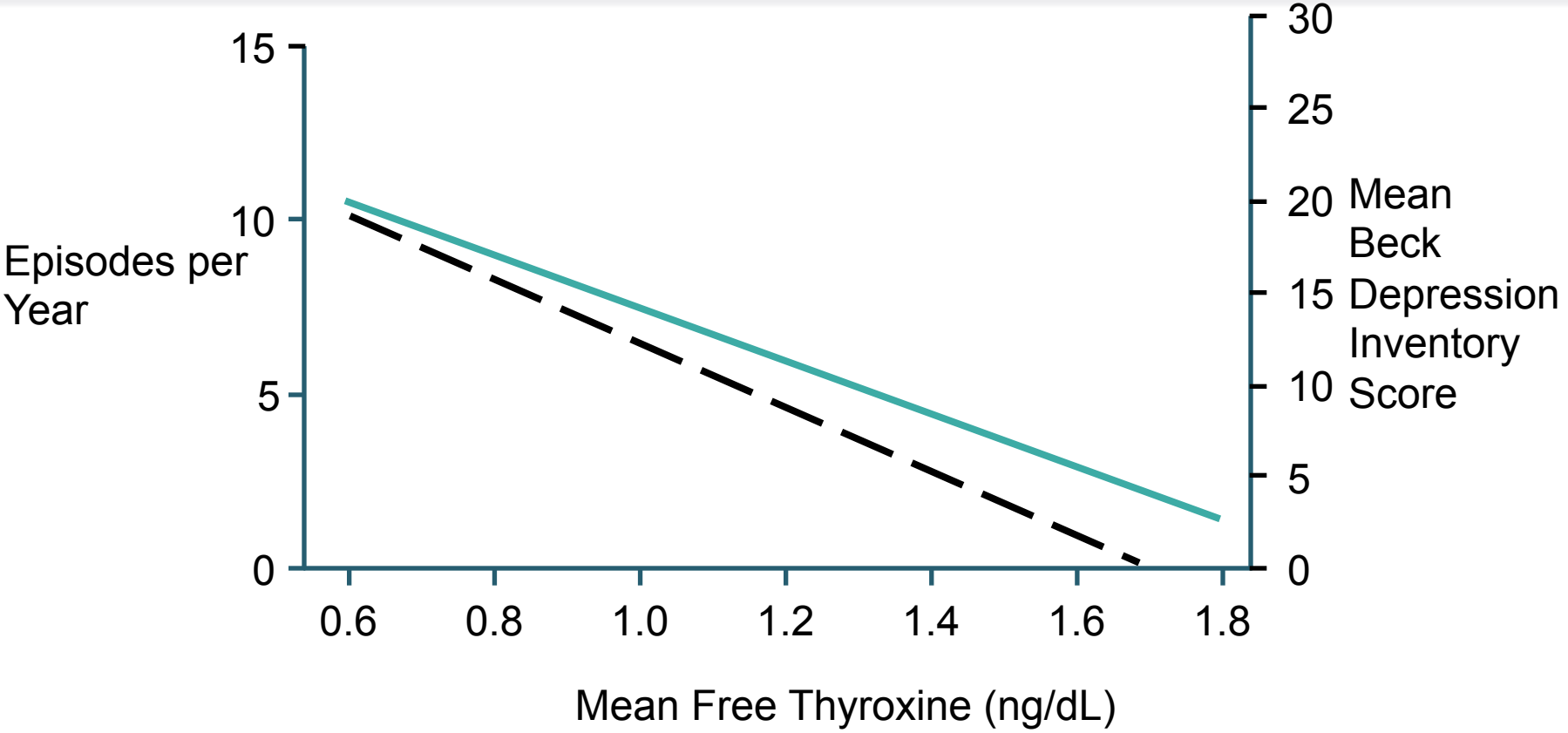
HouL, et al., *Lancet* 2016;387(10023):1085-1093.

↑ TSH and with Depressive Relapse in Lithium Maintained Bipolar Patients



Frye MA, et al., *Acta Psychiatrica* 2009;120:10-13.

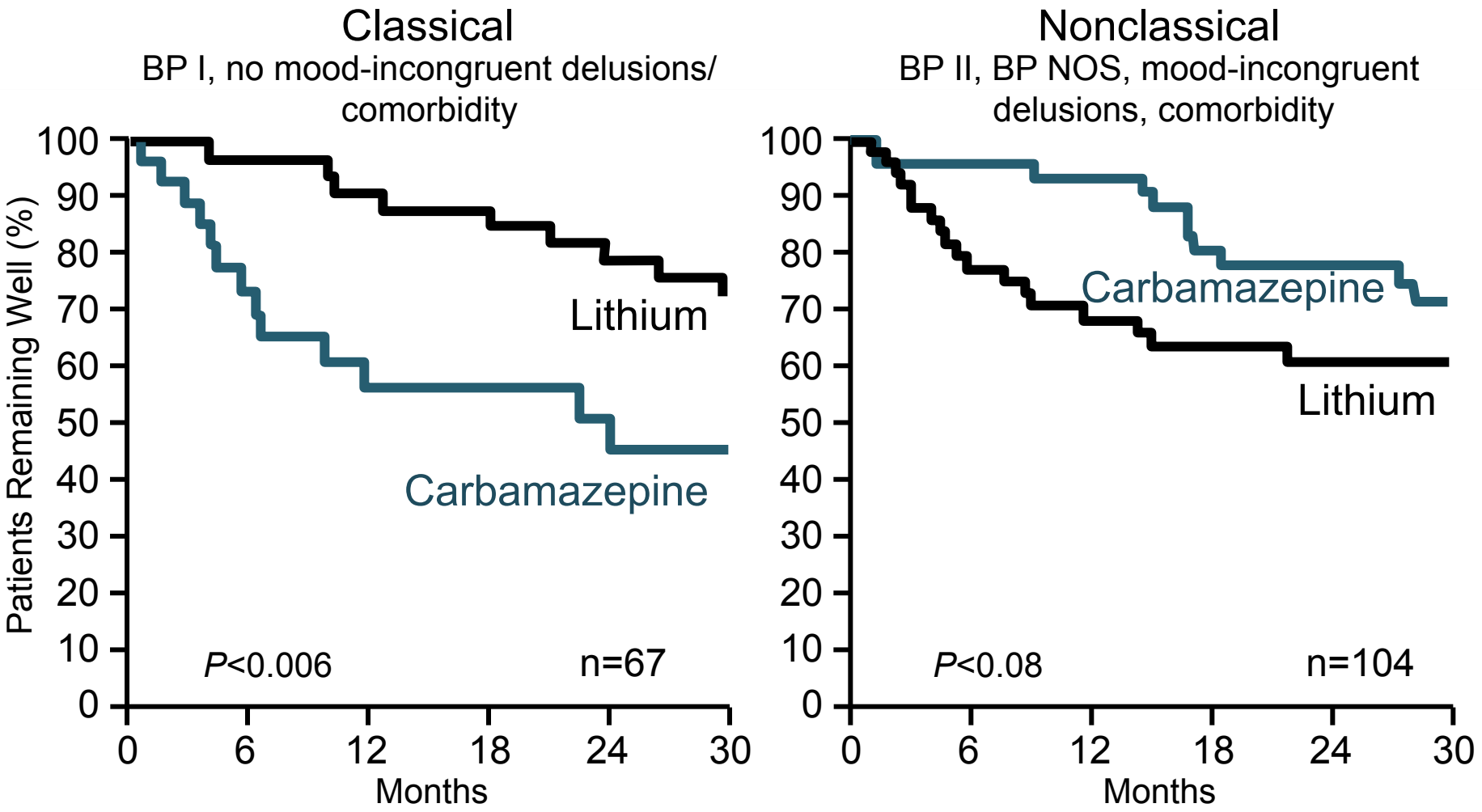
Free T4 & Depressive Severity in Lithium Maintenance



P < 0.01; Beck Depression Inventory 10-16 = mild depression

Frye MA et al. *Am J Psychiatry*. 1999;156(12):1909-1914.

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

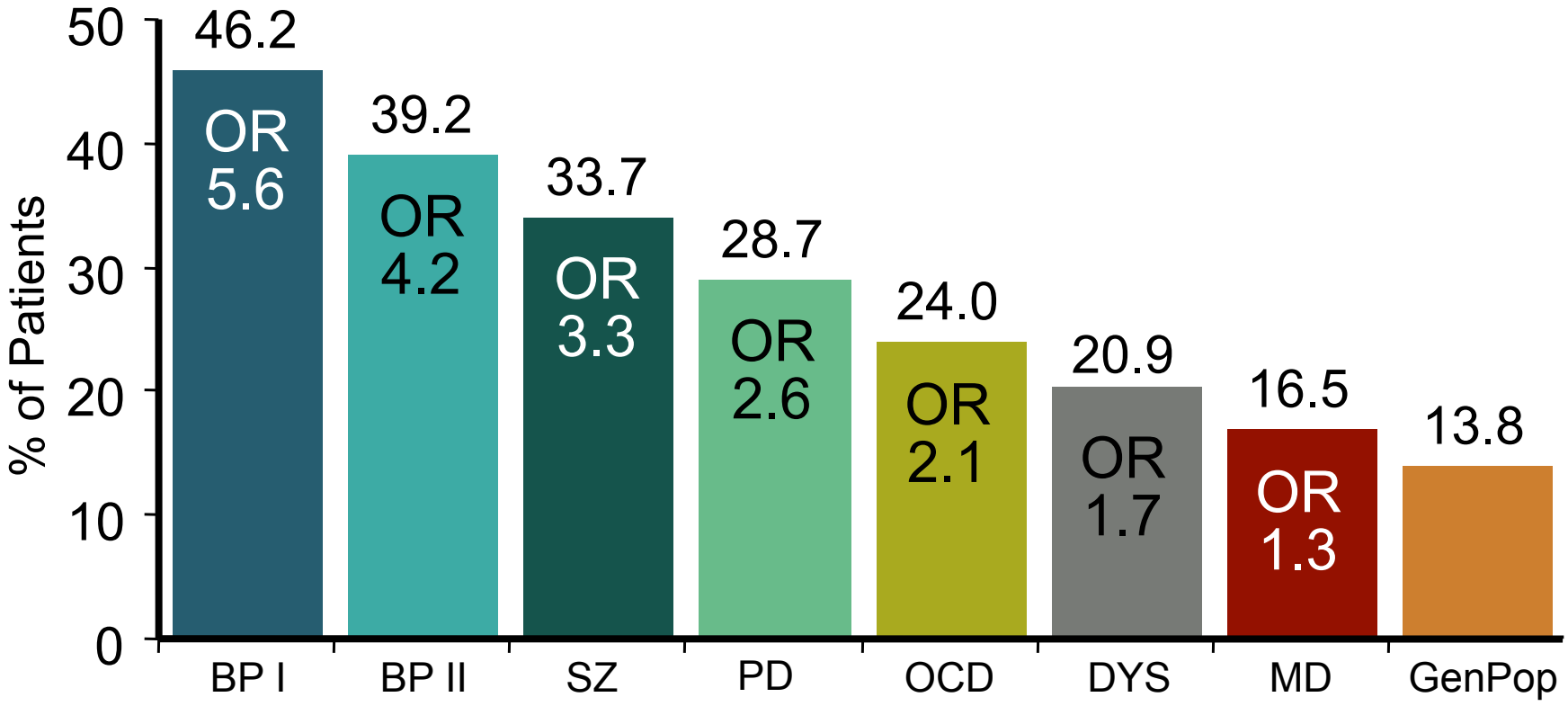


BP I=bipolar I disorder; BP II=bipolar II disorder; BP NOS=bipolar disorder not otherwise specified.

Greil W, et al. *J Clin Psychopharmacol.* 1998;18(6):455-460.

*Not FDA approved for bipolar disorder

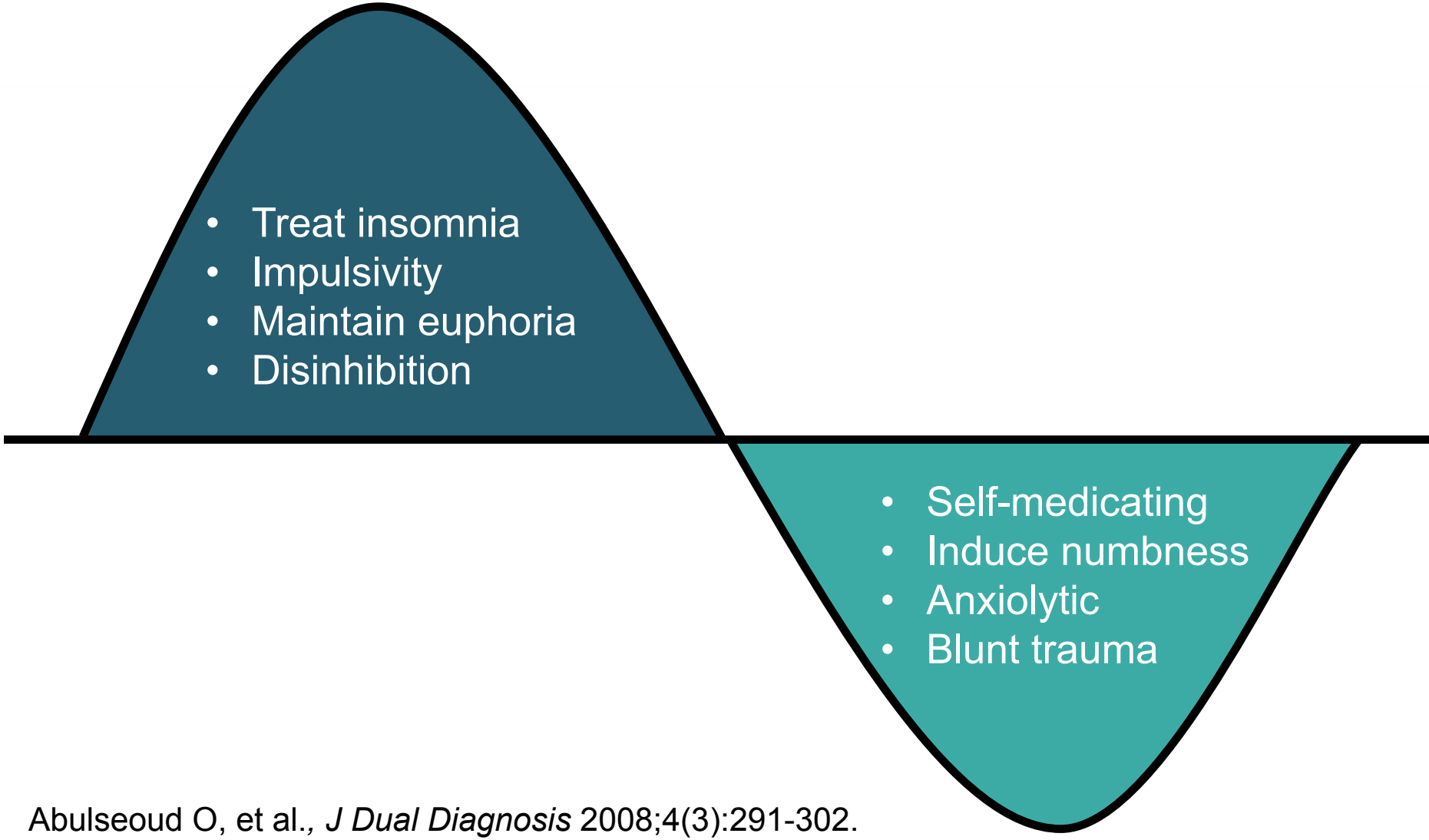
Lifetime Prevalence of Alcohol Use Disorders*



*Use = abuse or dependence; OR = Odds ratio

Regier DA, et al. *JAMA*.1990;264(19):2511-2518.

Why Do Patients Drink?



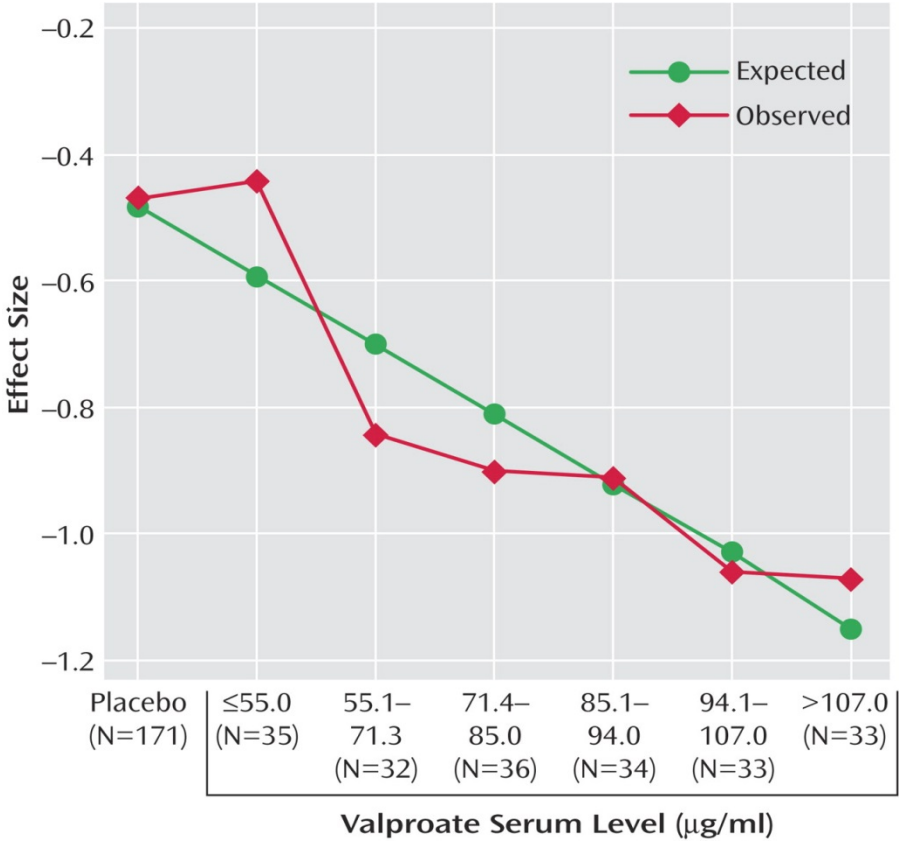
Abulseoud O, et al., *J Dual Diagnosis* 2008;4(3):291-302.

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.

Carbamazepine* Levels: Correlation with Improvement

- Anticonvulsant serum levels (4-12 mcg/mL)
- Mood stabilization serum levels unclear
  - Plasma carbamazepine (n=10, r=0.21, ns)
  - Plasma-10, 11 epoxide (n=10, r=0.62, p<0.06)
  - CSF carbamazepine (n=10, r=0.23, ns)
  - CSF-10, 11 epoxide (n=10,r=0.67, p<0.01)
- Induction of CYP450 3A3/4
  - Decreases serum concentrations of many medications
  - Autoinduction 3-5 weeks (ie after hospital discharge) with need to adjust dose

Centorrino F, et al., *Bipolar Disord*. 2003;5(5):370-374.; Bowden C*L. J Clin Psychiatry* 1996[1996;57 Suppl 13:4-9; Post R, et al. *Am J Psychiatry*. 1983;140(12):1602-1604.

*Not FDA approved for bipolar disorder

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

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.

*Not FDA approved for bipolar disorder

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*. 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.

*Not FDA approved for mania bipolar disorder

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

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.

*Not FDA approved for bipolar disorder

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.

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

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.

*Not FDA approved for bipolar disorder

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.

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.

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

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

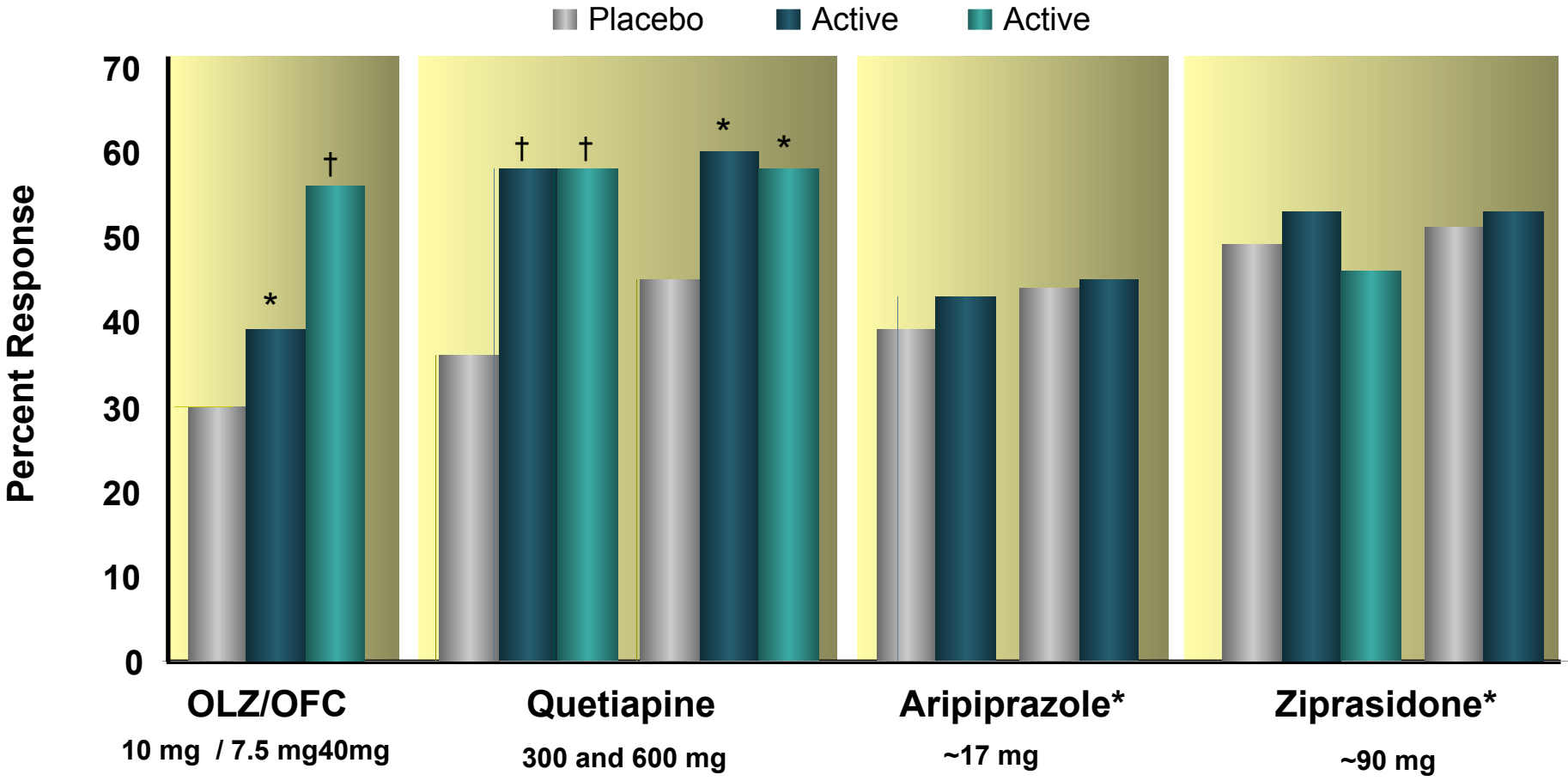
The Old Guitarist Pablo Picasso 1903
The Blue Period

Epidemiology Bipolar Disorder – Focus Depression

- 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.

Antipsychotics



OFC = olanzapine/fluoxetine combination. **P* < .05; †*P* < .001 vs. placebo.

Calabrese J, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.; Thase ME,et al. *J Clin Psychopharmacol*. 2009;29(1):38.; Tohen et al. Arch Gen Psychiatry. 2003;60(11):1079-1088.; J Clin Psychopharmacol. 2008;;28(1):13-20.; Sachs et al., *J Clin Psychiatry*. 201;72(10):1413-1422.

*Not FDA approved for bipolar depression

PREVAIL 2 Trial

6-week randomized double-blind trial of lurasidone monotherapy for acute bipolar I depression

- N = 505
- Bipolar I depression
- MADRS ≥ 20

R

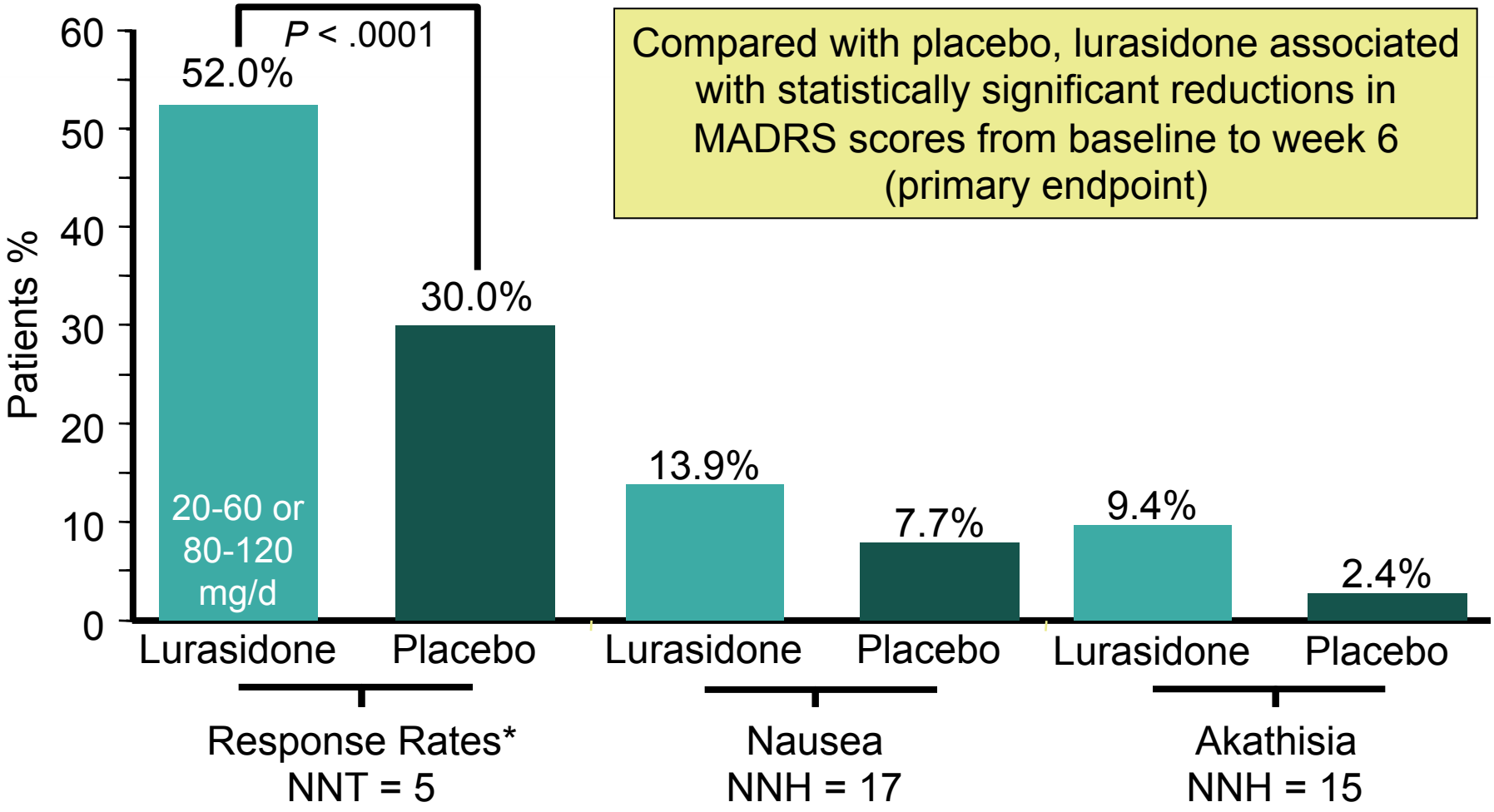
Lurasidone
20-60 mg/day
n = 166

Lurasidone
80-120 mg/day
n =169

Placebo
n = 170

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

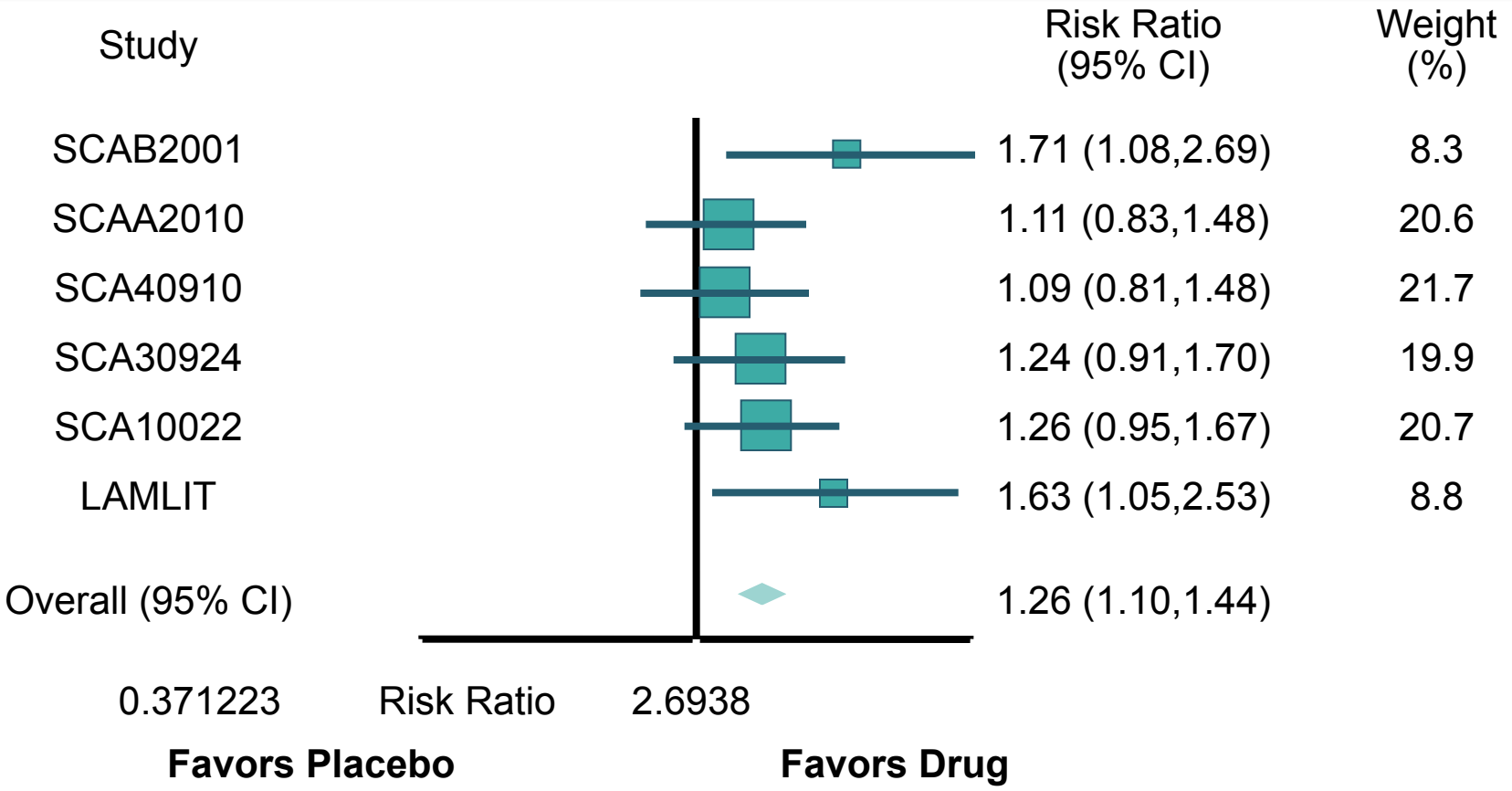
PREVAIL 2: Results



*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.

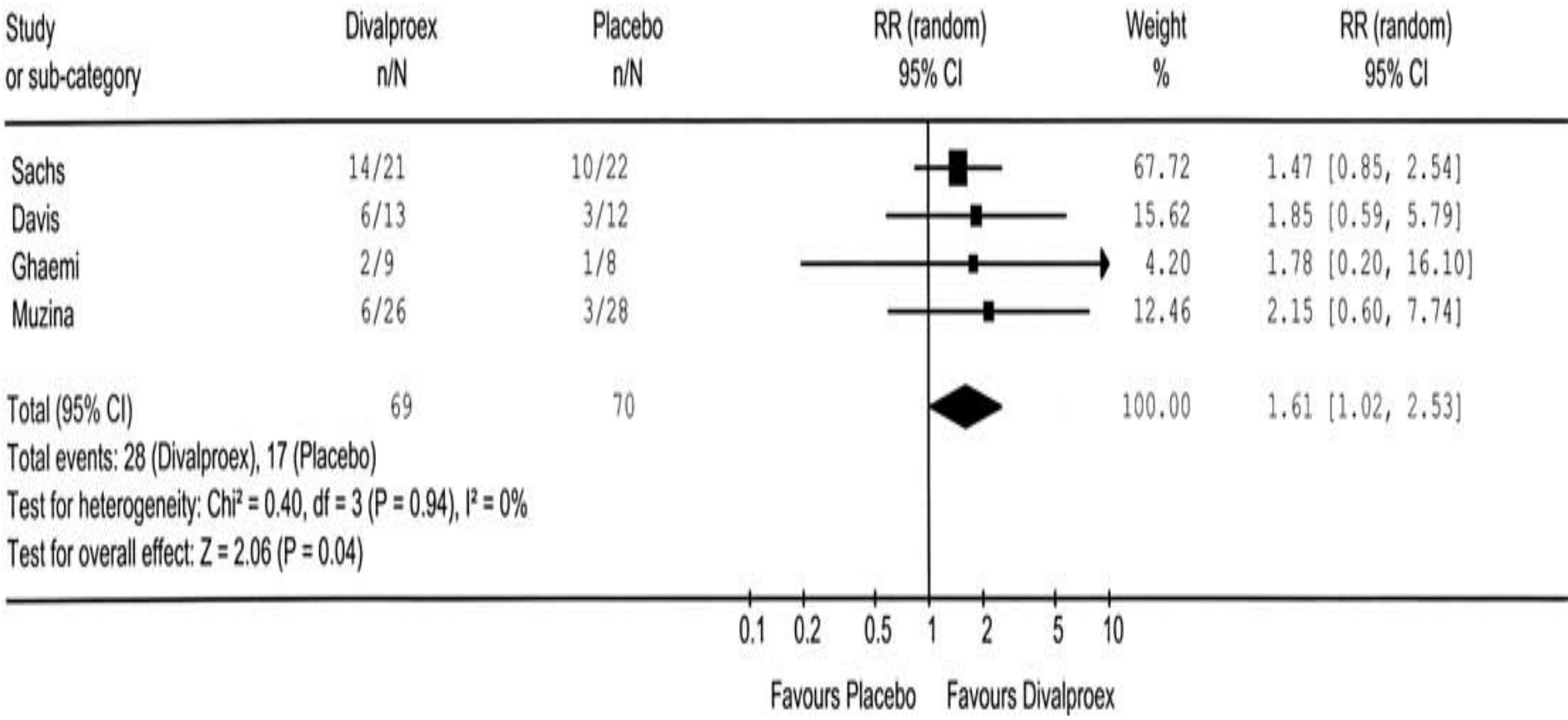
Meta-Analysis Lamotrigine* in Acute BP Depression



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

*Not FDA approved for bipolar depression

Meta-Analysis Divalproex* in Acute BP Depression

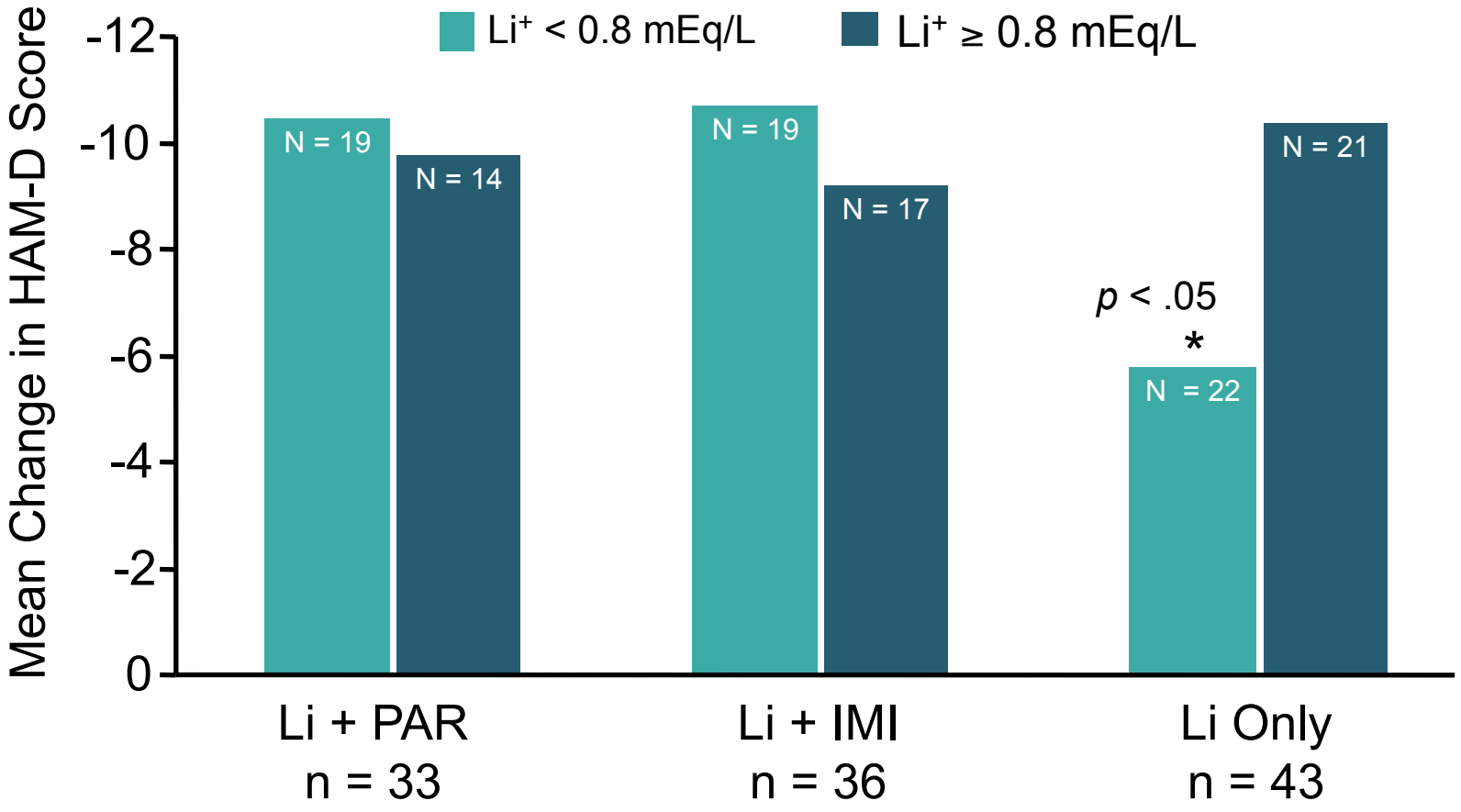


Relative risk of remission in patients treated with divalproex vs. placebo.

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.

*Not FDA approved for bipolar depression

Maximize the Mood Stabilizer Lithium* & BP Depression

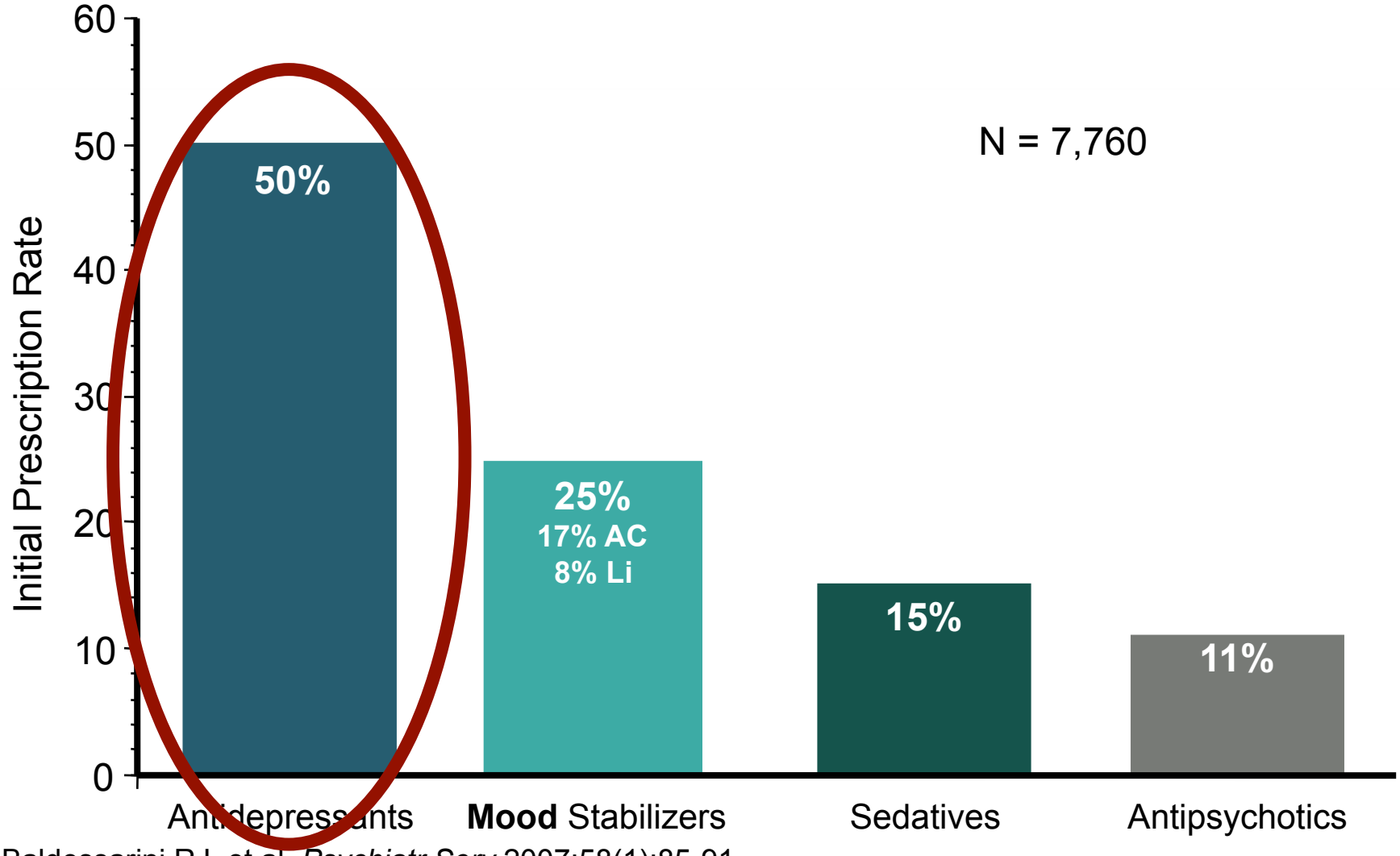


Li = lithium, IMI = imipramine, PAR = paroxetine

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

*Not FDA approved for bipolar depression

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



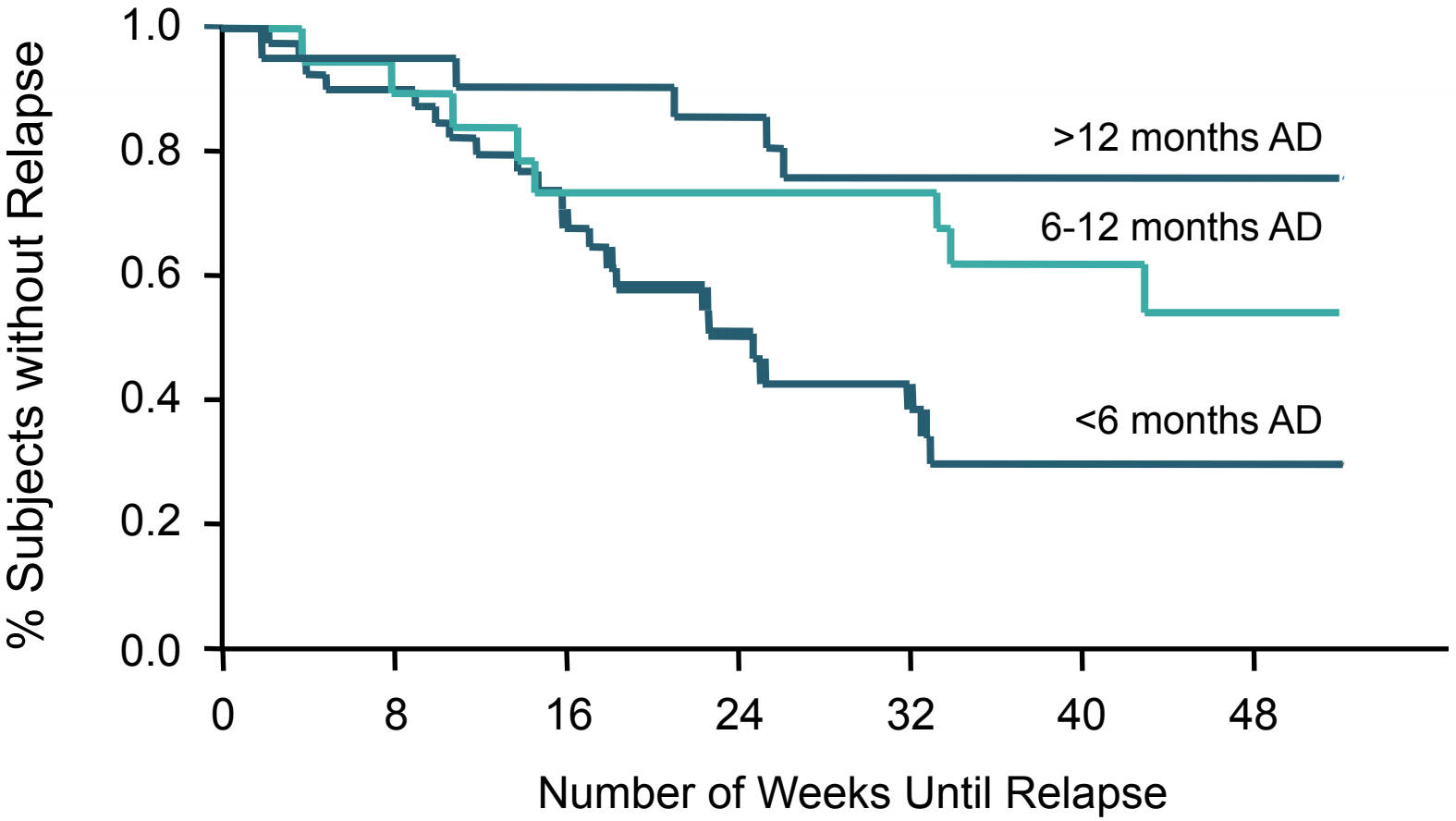
Baldessarini RJ, et al. *Psychiatr Serv* 2007;58(1):85-91.

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

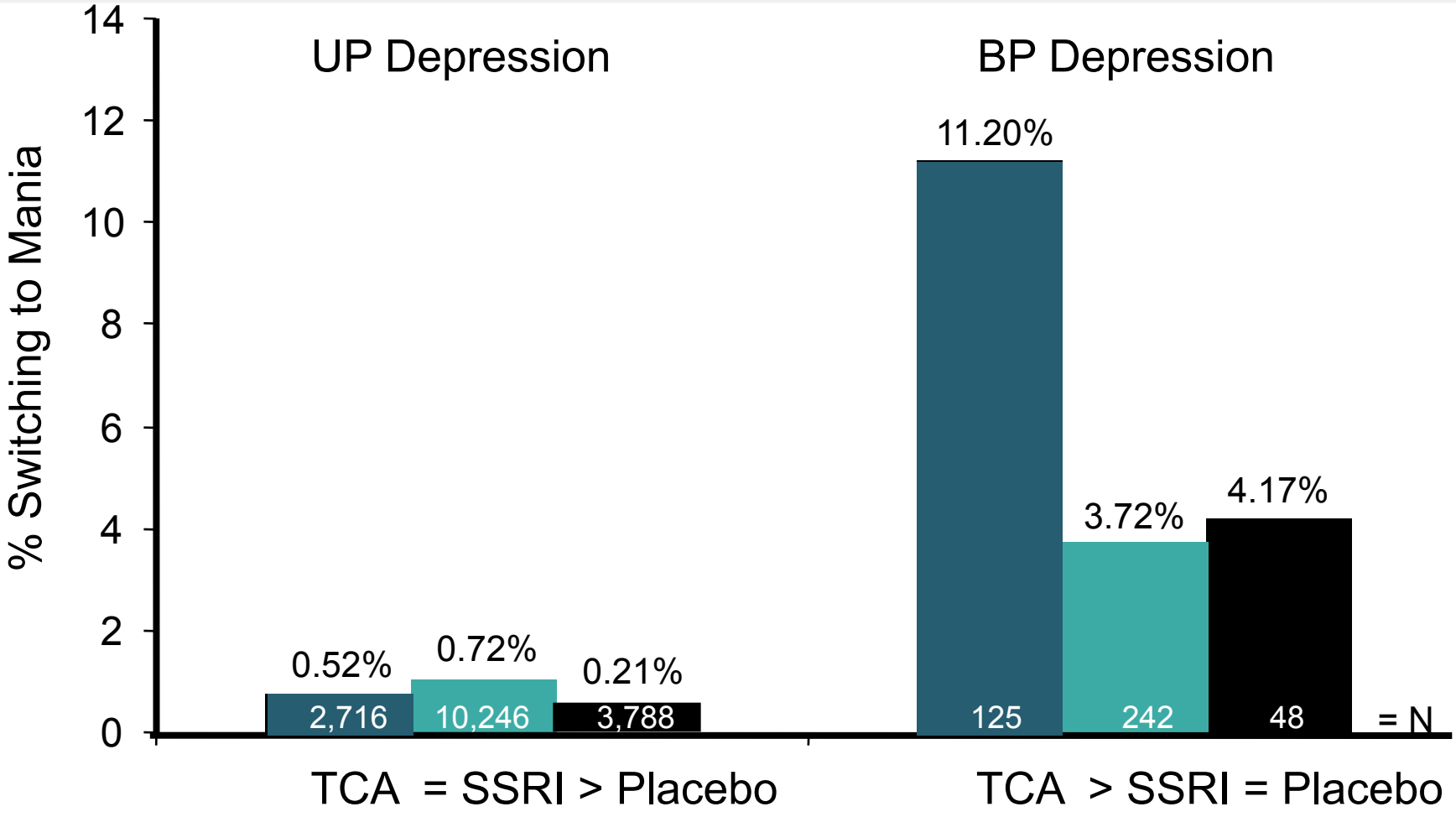
Depressive Episode Relapse with Antidepressant Discontinuation



Cox regression analyses log rank = 10.09, *P* = .006

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

Meta-Analysis of Antidepressant Induced Mania (AIM+)



SSRI = fluoxetine, fluvoxamine, paroxetine, or sertraline

Peet M. *Br J Psychiatry* 1994;164(4):549-550.

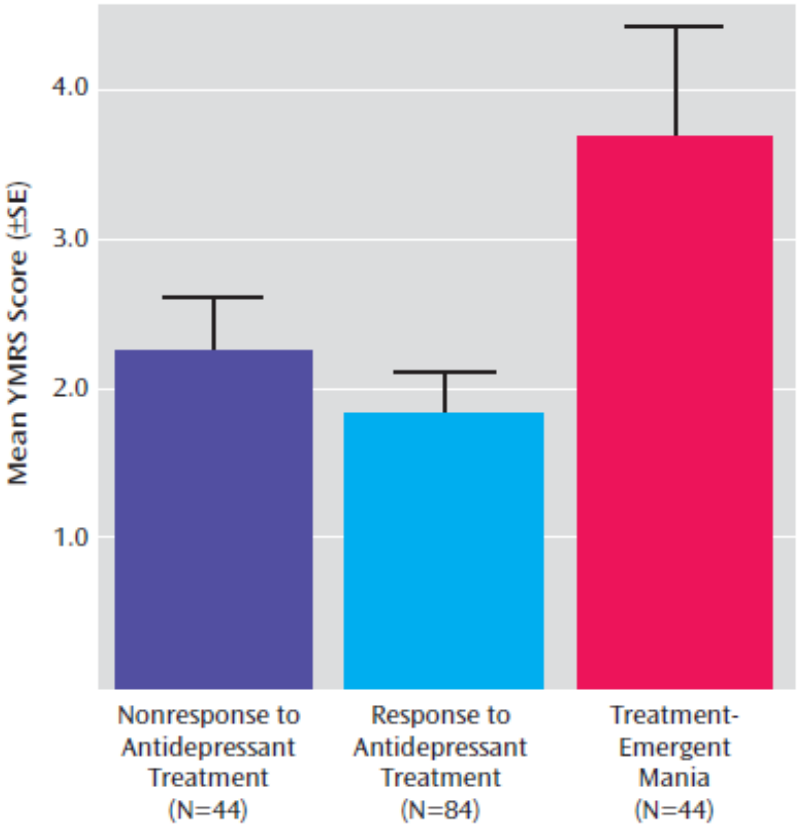
Risk Factors for Switch

- 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

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

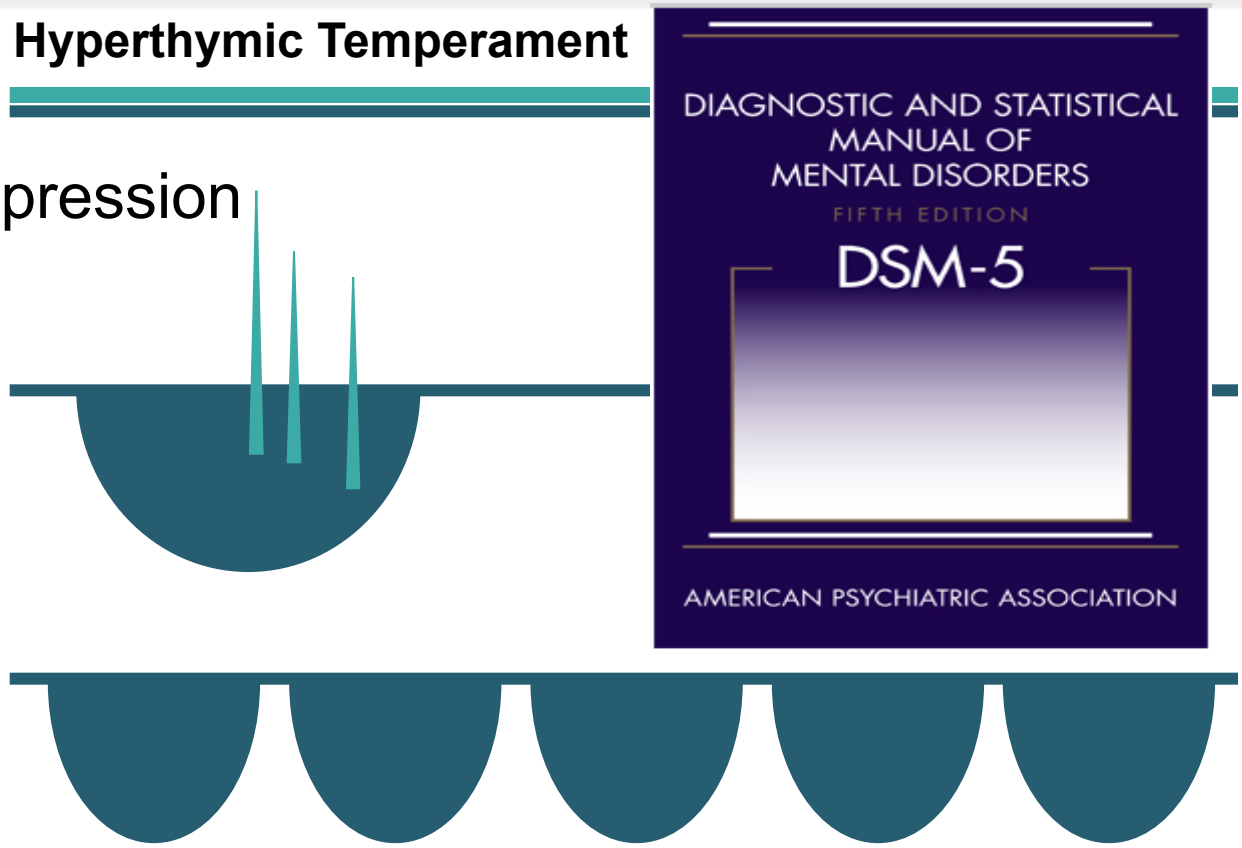
Frye MA, et al. *Am J Psychiatry*. 2009;166(2):164-172.

DSM-5 Mixed Specifier

BP-IV
Hyperthymia + Depression

Depressive Mixed State

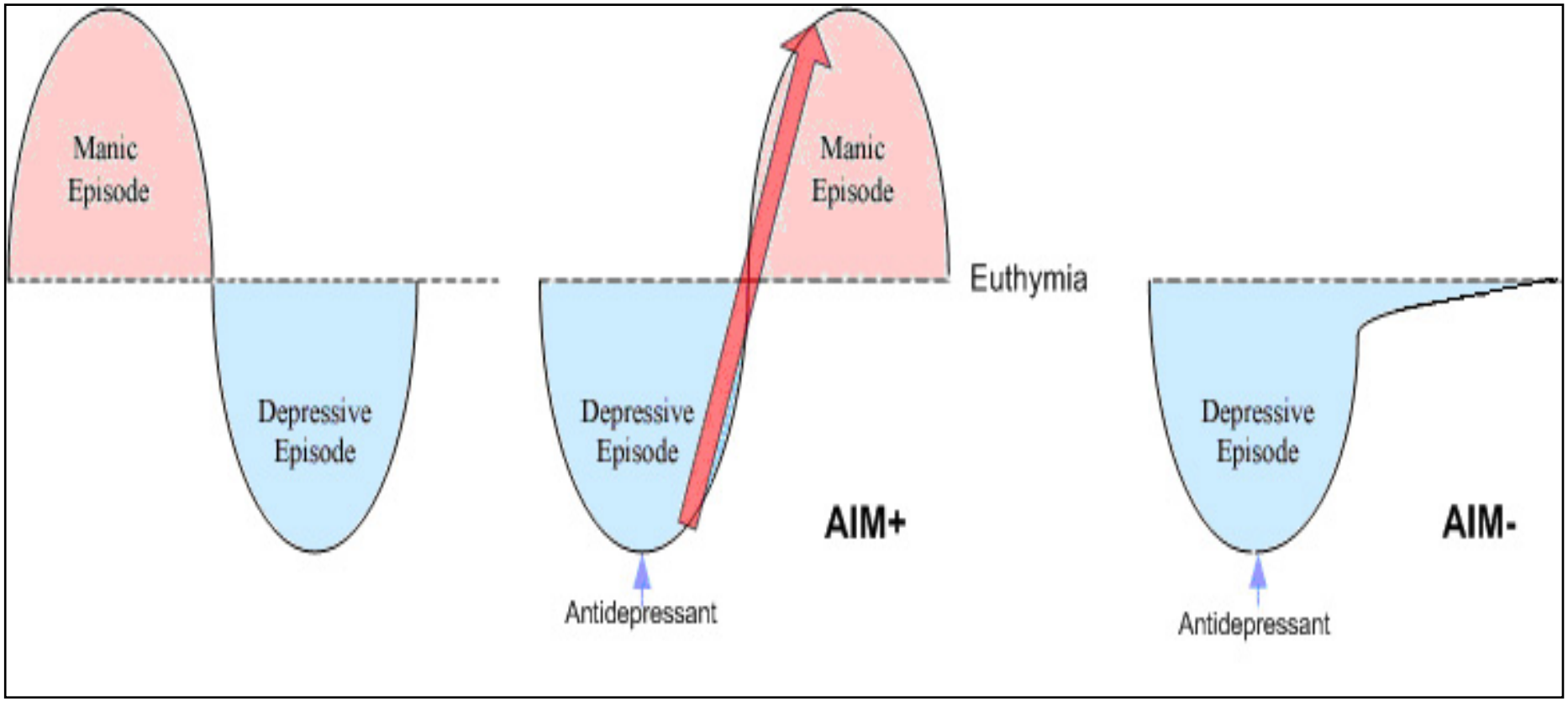
Recurrent "Unipolar"



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

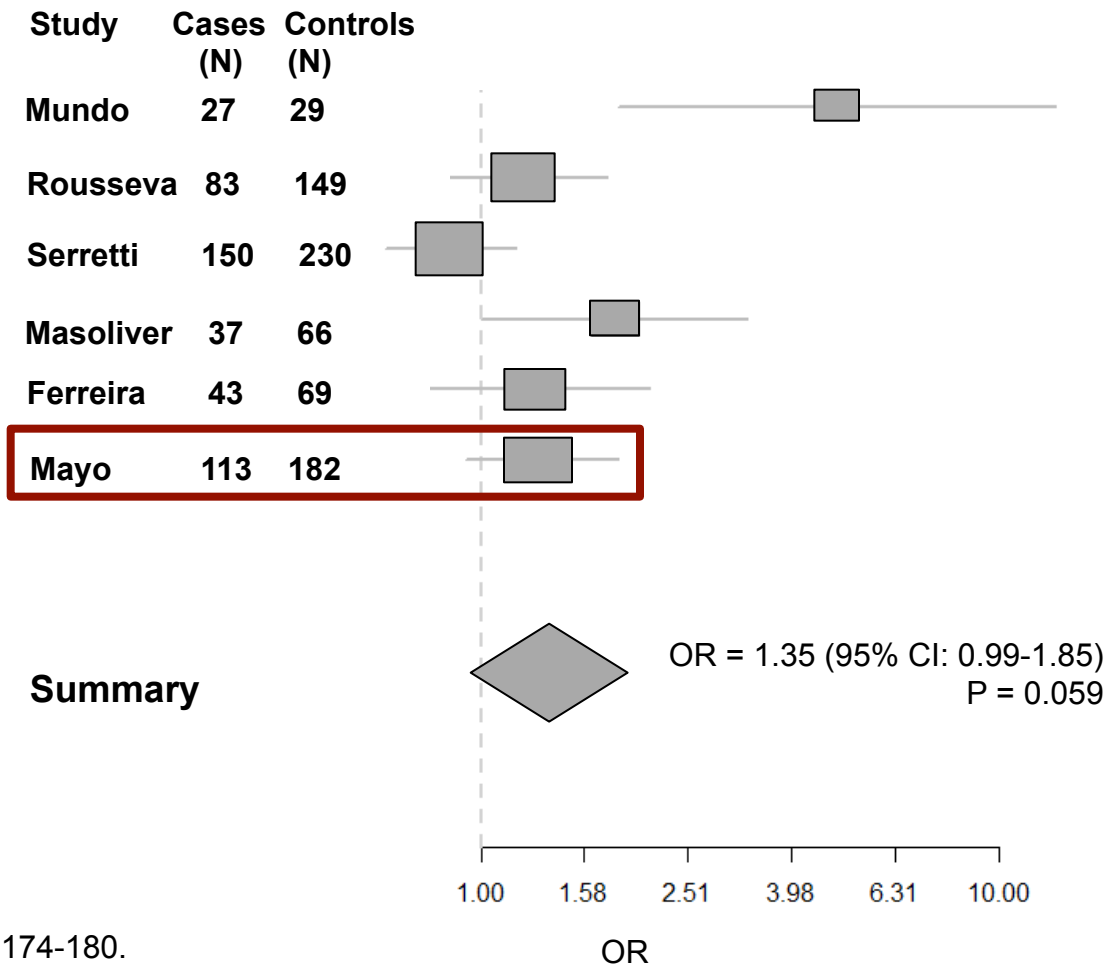
Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (BP)

SLC6A4 polymorphism & Antidepressant Induced Mania



SLC6A4 S Allele and AIM: Meta-Analysis Results

Meta-analysis marginally significant evidence of association between S allele and AIM+ (p = 0.059)



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	--	

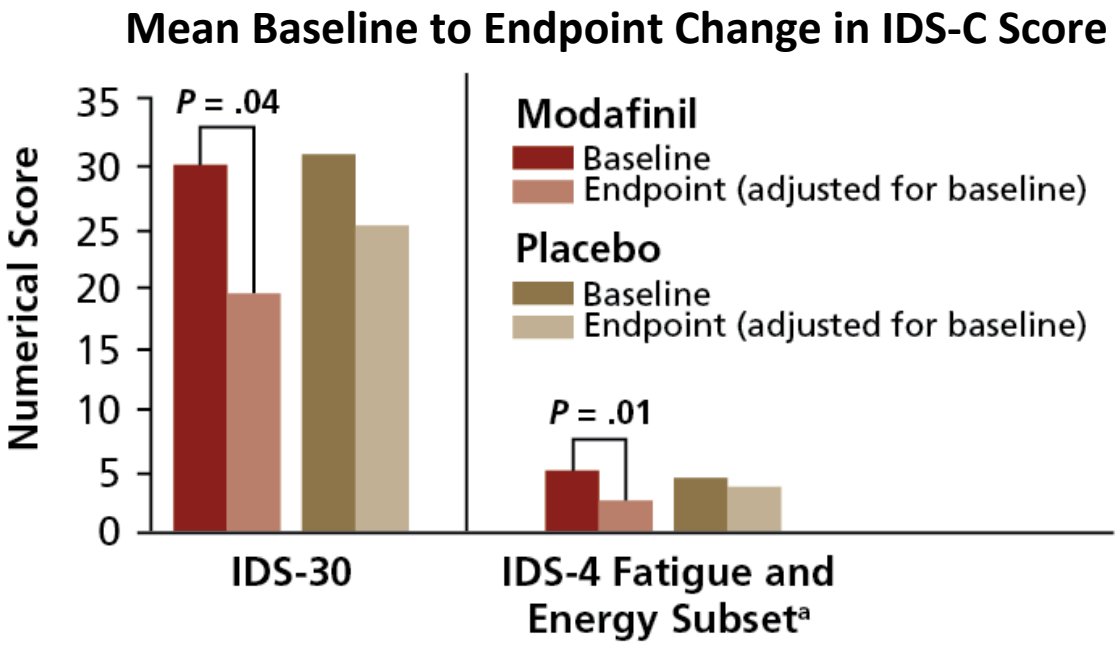
Cases N = 113; Controls N = 182

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.

6-Week, Randomized Placebo-Controlled Evaluation of Adjunctive Modafinil* for Bipolar Depression

- N = 85
- Bipolar I/II depression
- Inadequate response to mood stabilizers ± AD Rx



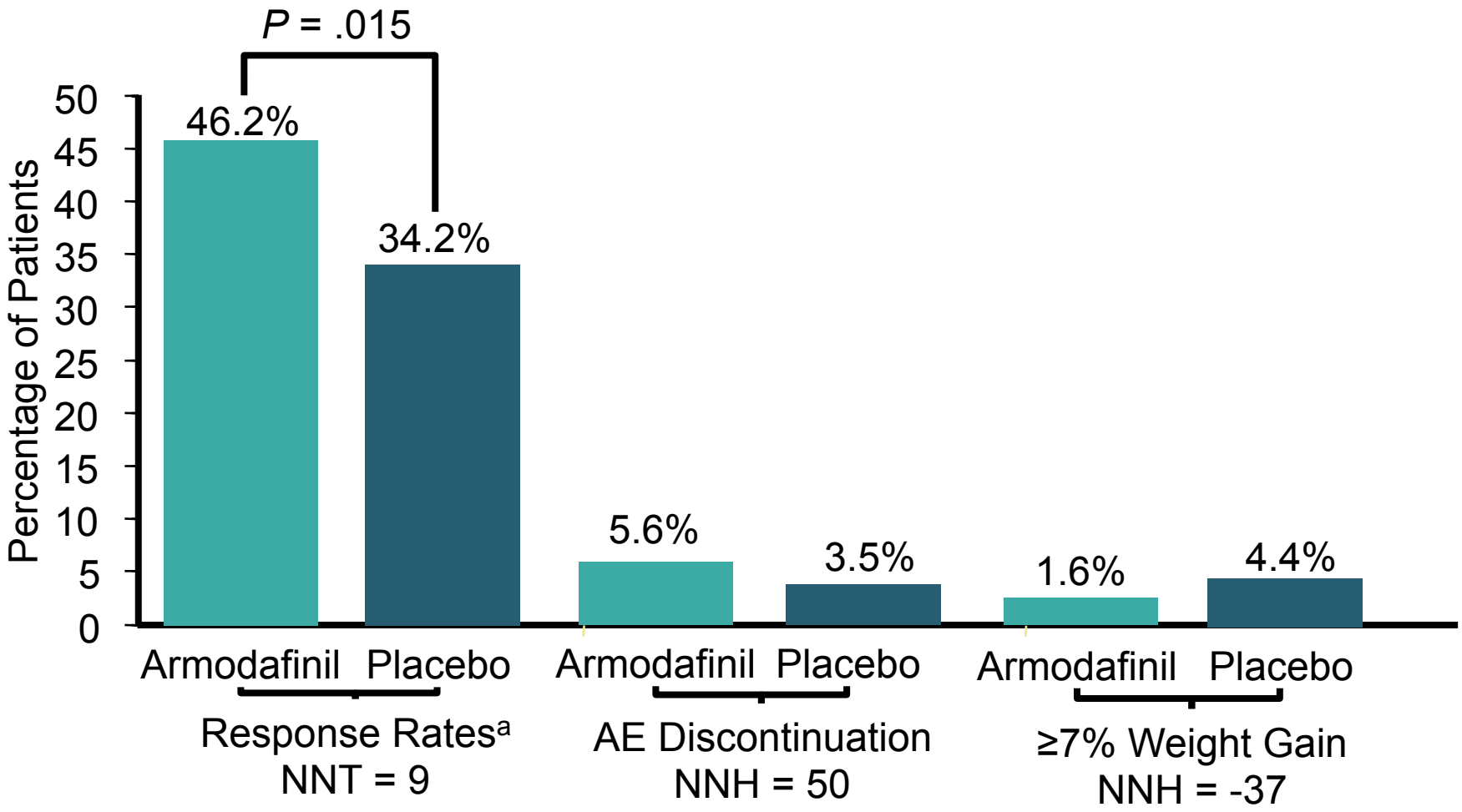
- Modafinil well tolerated; headache most common AE
- No difference (modafinil vs placebo) in weight gain or treatment-emergent mania

[a] hypersomnia, energy level, cognitive slowing, and leaden paralysis.
AD: antidepressant; IDS-C: Inventory for Depressive Symptomatology–Clinician.

Frye MA, et al. *Am J Psychiatry*. 2007;164(8):1242-1249.

*Not FDA approved for bipolar depression

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



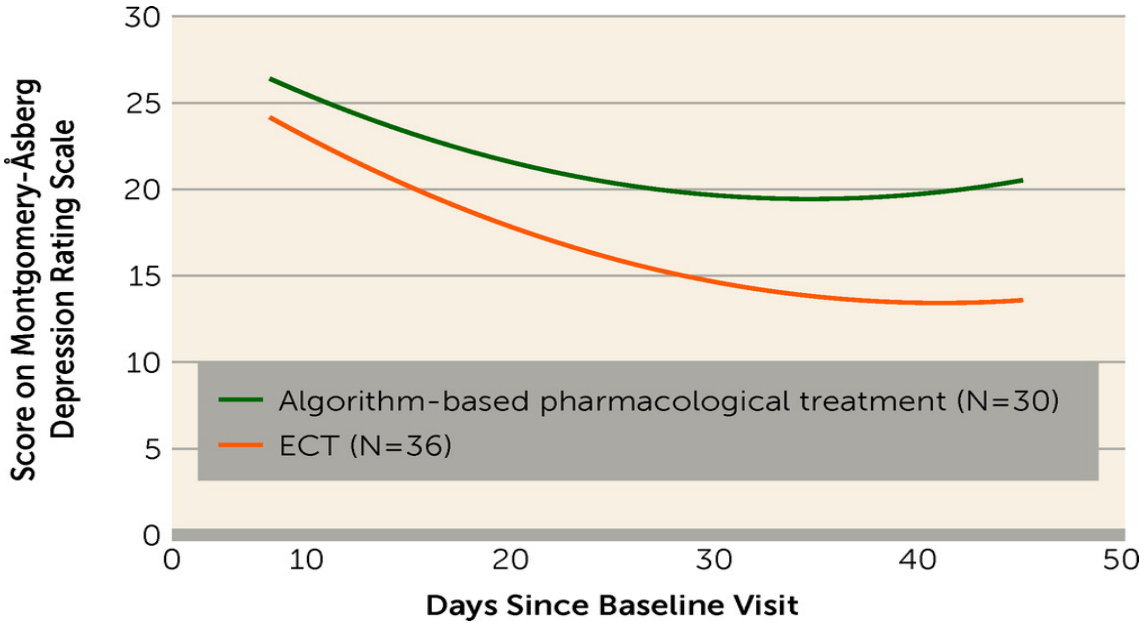
[a] Response: ≥50% IDS-C30 decrease

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

*Not FDA approved for bipolar depression

ECT Bipolar Depression

- 6-week, 6-site, randomized trial of 3X/week RUL ECT vs algorithm based pharmacological treatment (n = 73)
  - Response rate 74% (17/23) vs. 35% (7/20, *p* .01)



- Bitemporal generally acknowledge to have greater efficacy and side effects

Schoeyen HK, et al. *Am J Psychiatry*. 2015;172(1):41-51.; Tohen M, et al. *Am J Psychiatry*. 2015;172(1):3-5.; Kotzalidis GD, et al. *Am J Psychiatry*. 2015 1;172(3):294.

Transcranial Magnetic Stimulation (TMS) in Bipolar Depression

- Meta-analysis of 19 TMS studies in bipolar depression (n = 181)
  - Stimulation targets: left, right, bilateral DLPFC
  - High vs Low or sequential stimulation frequency
  - Response: TMS 44% (47/106) vs Sham 25% (19/75, $p < 0.01$)
- Bilateral sequential (1 Hz rDLPFC → 10 Hz lDLPFC) vs sham rTMS for 4 weeks (n = 49)
  - No significant difference in baseline to end point change, response or remission rates
- Substantial clinical trial design heterogeneity
  - Stimulation target
  - Laterality
  - High (10hz) vs low (1 Hz) stimulation

McGirr A, et al. *World Psychiatry*. 2016 Feb;15(1):85-86.
Fitzgerald PB, et al. *J Affect Disord*. 2016;198:158-162.

Archival Report

Biological Psychiatry

A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression

Darin D. Dougherty, Ali R. Rezai, Linda L. Carpenter, Robert H. Howland, Mahendra T. Bhati, John P. O'Reardon, Emad N. Eskandar, Gordon H. Baltuch, Andre D. Machado, Douglas Kondziolka, Cristina Cusin, Karleyton C. Evans, Lawrence H. Price, Karen Jacobs, Mayur Pandya, Timothey Denko, Audrey R. Tyrka, Tim Brelje, Thilo Deckersbach, Cynthia Kubu, and Donald A. Malone Jr.

ABSTRACT

BACKGROUND: Multiple open-label trials of deep brain stimulation (DBS) for treatment-resistant depression (TRD), including those targeting the ventral capsule/ventral striatum target, have shown encouraging response rates. However, no randomized controlled trials of DBS for TRD have been published.

METHODS: Thirty patients with TRD participated in a sham-controlled trial of DBS at the ventral capsule/ventral striatum target for TRD. Patients were randomized to active versus sham DBS treatment in a blinded fashion for 16 weeks, followed by an open-label continuation phase. The primary outcome measure was response, defined as a 50% or greater improvement on the Montgomery–Åsberg Depression Rating Scale from baseline.

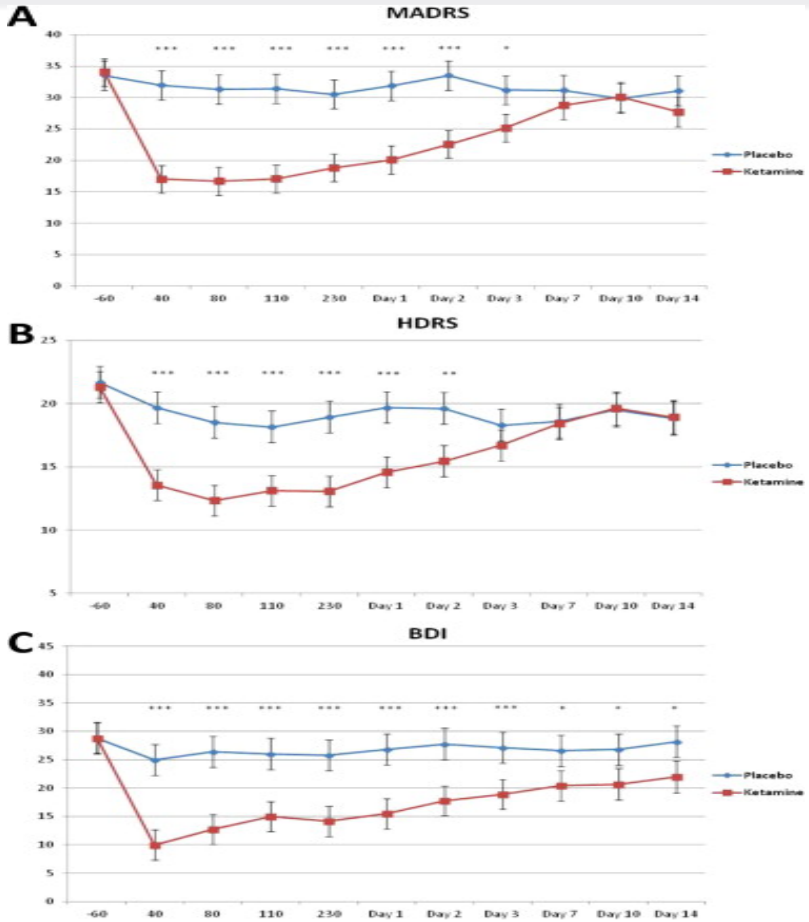
RESULTS: There was no significant difference in response rates between the active (3 of 15 subjects; 20%) and control (2 of 14 subjects; 14.3%) treatment arms and no significant difference between change in Montgomery–Åsberg Depression Rating Scale scores as a continuous measure upon completion of the 16-week controlled phase of the trial. The response rates at 12, 18, and 24 months during the open-label continuation phase were 20%, 26.7%, and 23.3%, respectively.

CONCLUSION: The results of this first randomized controlled study of DBS for the treatment of TRD did not demonstrate a significant difference in response rates between the active and control groups at the end of the 16-week controlled phase. However, a range of 20% to 26.7% of patients did achieve response at any time during the open-label continuation phase. Future studies, perhaps utilizing alternative study designs and stimulation parameters, are needed.

Keywords: Deep brain stimulation, DBS, Treatment resistant depression, TRD, Major depression, Ventral capsule/ventral striatum

Dougherty DD, et al. *Biol Psychiatry*. 2015;78(4):240-248.

Ketamine* for Treatment Resistant Bipolar Depression- Replication

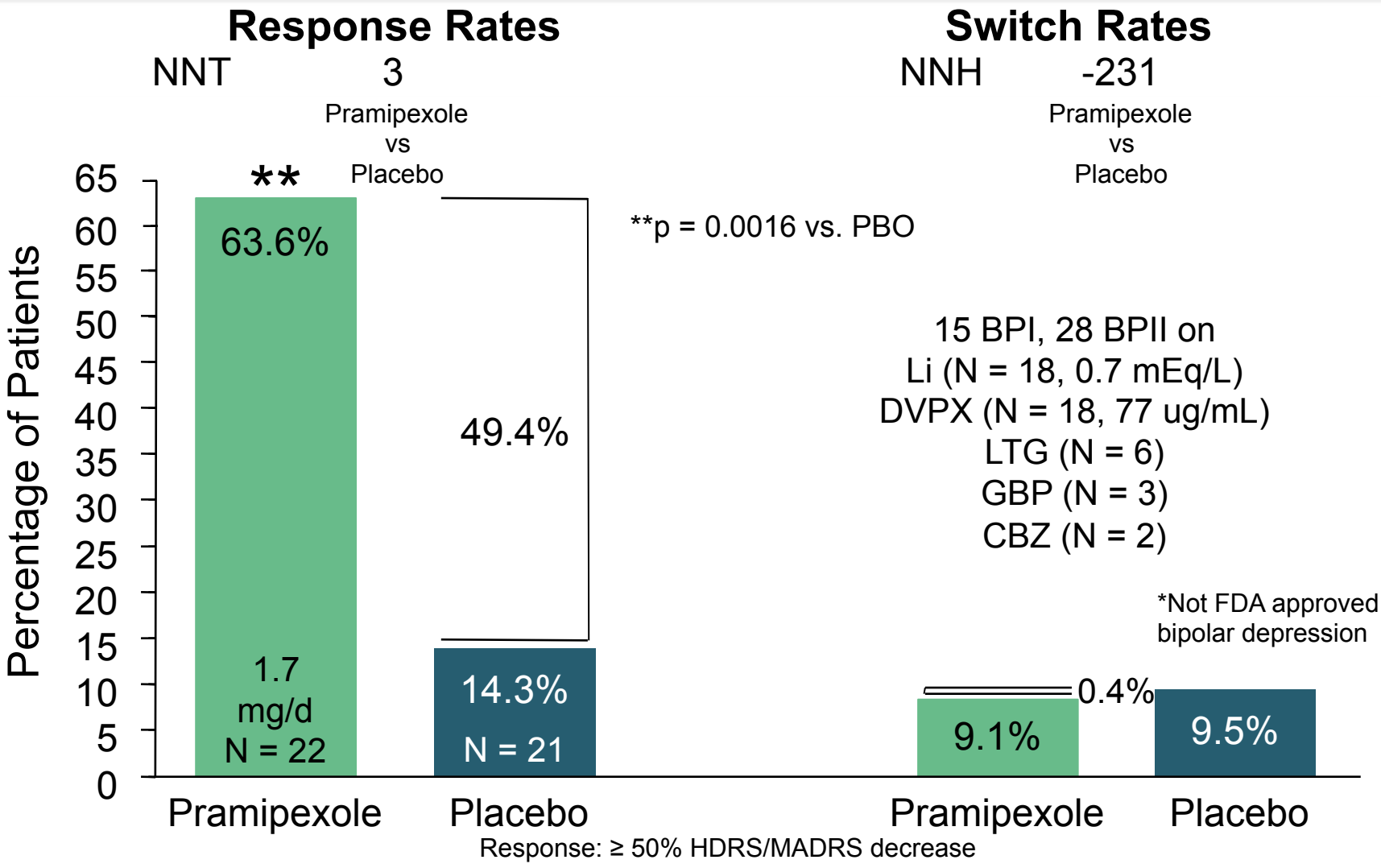


- Ketamine noncompetitive NMDA antagonist
- FDA approved as a general anesthetic
- 0.5 mg/kg over 40 minutes vs one infusion of saline placebo.
- Almost immediate reductions in depression rating scores.

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

*Not FDA approved for bipolar depression

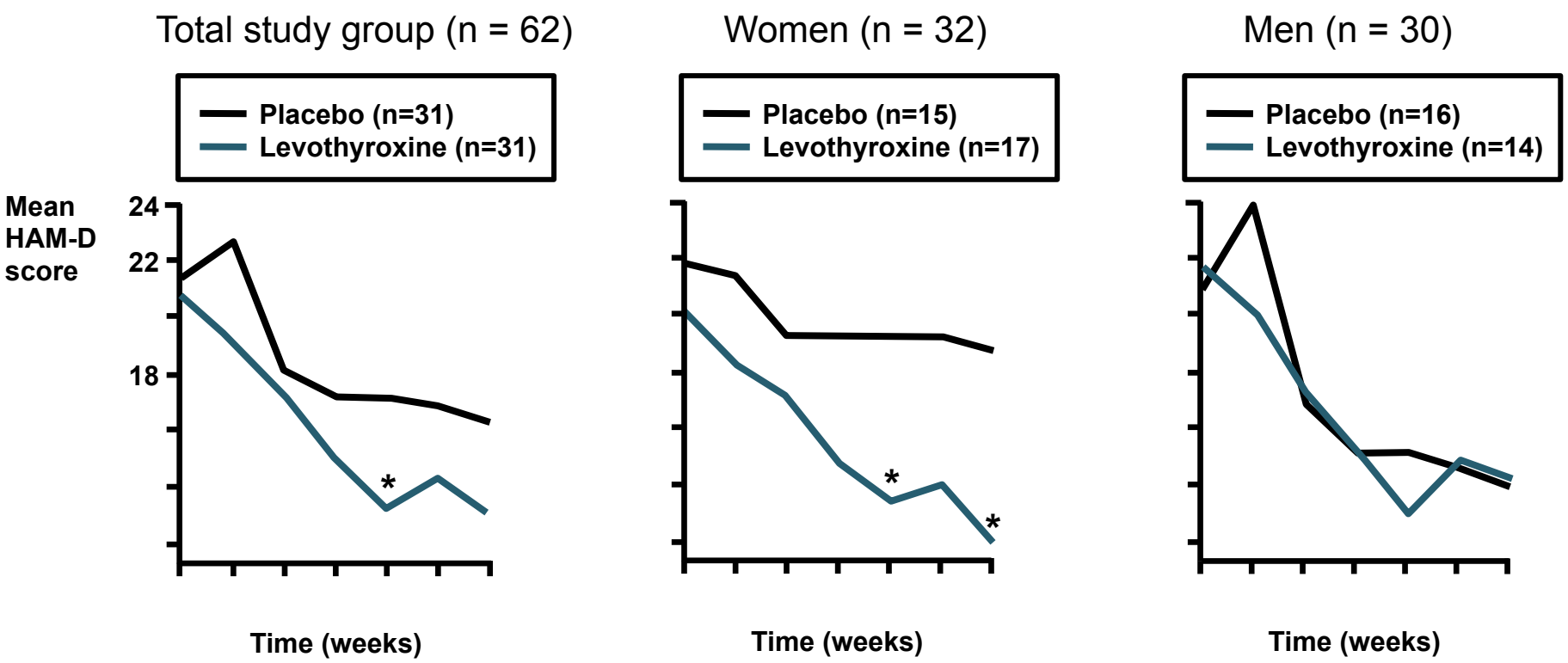
(Pooled) 6-week Randomized Double-Blind Adjunctive Pramipexole* in Acute Bipolar Depression



Response: ≥ 50% HDRS/MADRS decrease

Goldberg JF, et al. *Am J Psychiatry* 2004;161(3):564-566.; Zarate CA, et al. *Biol Psychiatry* 2004;56(1):54-60.

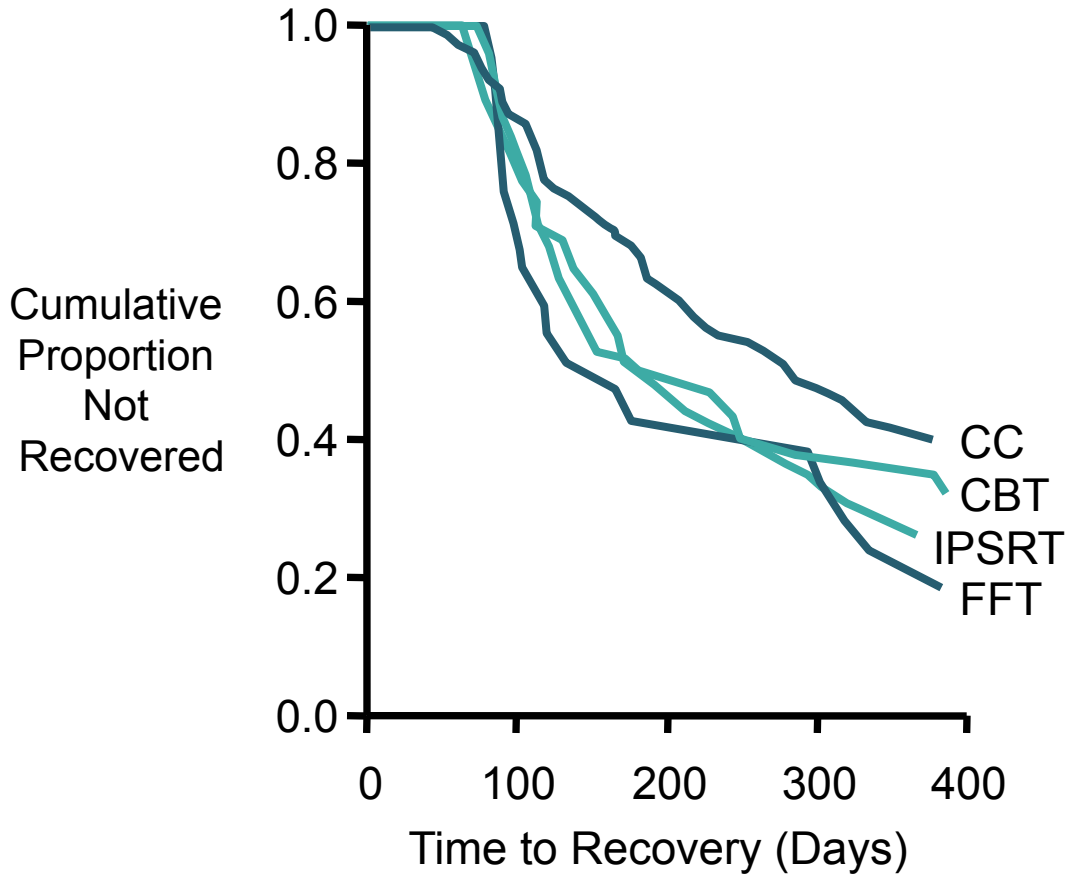
Adjunctive Levothyroxine in Bipolar Depression



*$p < 0.05$ vs placebo (ITT; LOCF)
Adjunctive levothyroxine (300 µg/day) or placebo in patients with bipolar I or II disorder
HAM-D, Hamilton rating scale for depression
Stamm TJ, et al. *J Clin Psychiatry.* 2014;75(2):162-168.

*Not FDA approved for bipolar depression

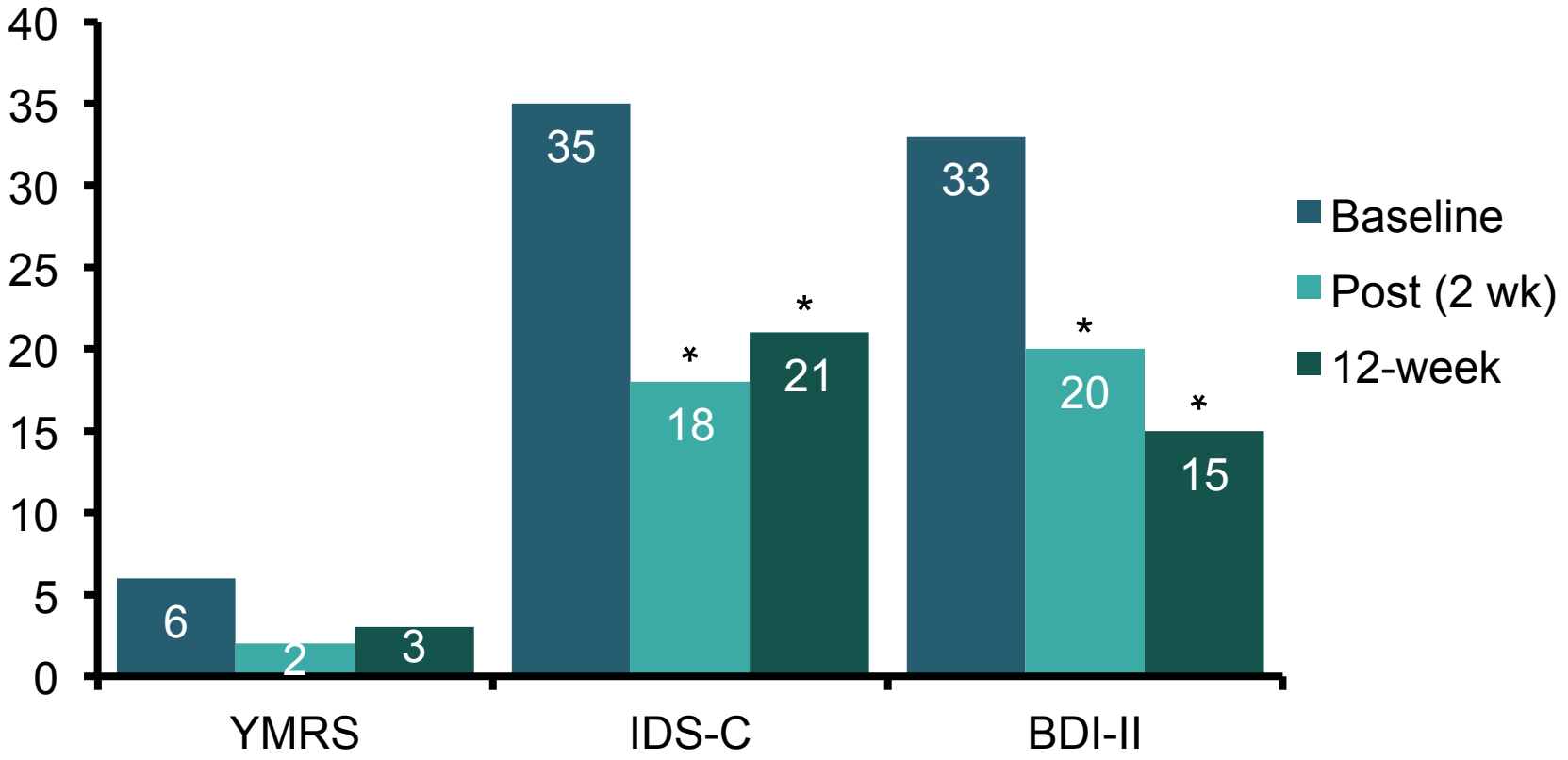
Intensive Psychotherapies Improve Bipolar Depression



- 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)

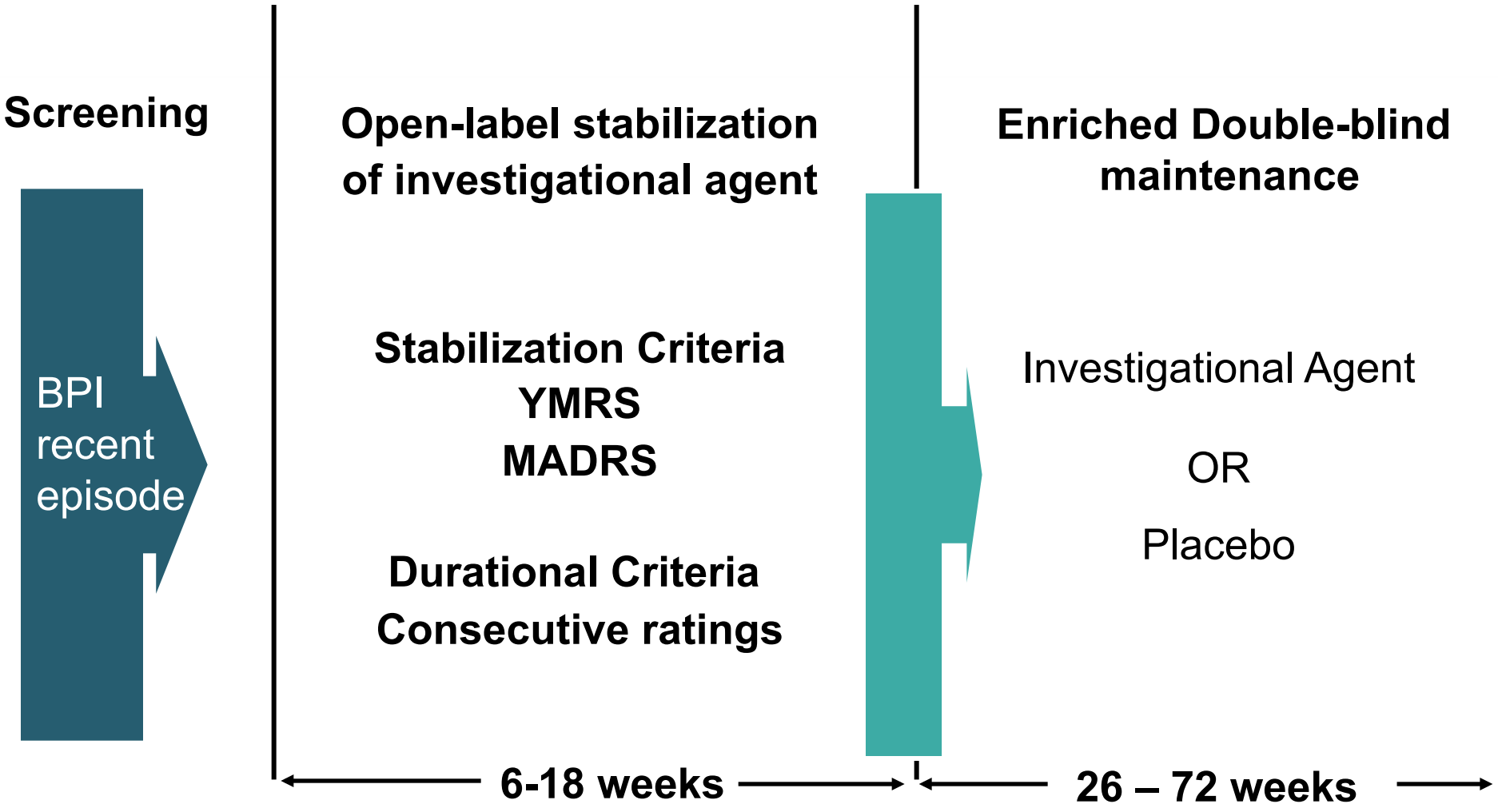
Hoberg AA, et al. *Perspect Psychiatr Care*. 2013;49(4):226-234.

FDA Language of Maintenance

- Lithium - "… prevents or diminishes the intensity of subsequent episodes"
- Lamotrigine - "to delay the time to occurrence of mood episodes in patients treated for an acute mood episode with standard therapy"
- Olanzapine - "maintaining monotherapy after achieving a responder status for an average of 2 weeks"
- Aripiprazole - "recent manic or mixed episode that had been stabilized and then maintained for at least 6 weeks"
- Quetiapine- "maintenance of bipolar I disorder as adjunct therapy to lithium or valproate"
- Risperidone long acting injectable - "as monotherapy or adjunct therapy to lithium or valproate for maintenance treatment of bipolar I disorder "
- Ziprasidone " adjunct to lithium or valproate for maintenance

Physicians' Desk Reference. 2016. Website: http://pdr.net

Maintenance Trial Design



Gitlin MJ, Frye MA, et al. *Curr Med Res Opin*. 2010;26(8):1835-1842. PMID: 20515320.

Goals of Maintenance Treatment in Bipolar Disorder

- Prevent recurrent mood episodes
- Decrease frequency and intensity of recurrent episodes
- Abolish/reduce interepisode/ subsyndromal symptoms
- Prevent Suicide
- Manage comorbidity
- Enhance/normalize functioning

Mania Matters

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

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%

Audience Response

How has this presentation improved your confidence in using the latest evidence in treating patients with bipolar disorders?

A. Extremely confident
B. More confident
C. Somewhat confident
D. Not confident at all

Audience Response

In the treatment of bipolar depression, which is the most commonly prescribed medication?

A. Antidepressants
B. Divalproex
C. Atypical antidepressants
D. Stimulants

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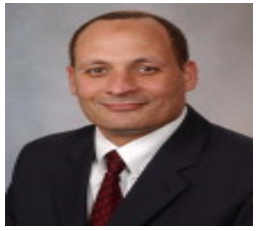
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