#CHAIR2019

11TH ANNUAL

CHAIR SUMMIT

CME Outfitters

Master Class for Neuroscience Professional Development

February 7-9, 2019 | The Westin Fort Lauderdale | Florida

Provided by

CME Outfitters

Receptor Pharmacology in Bipolar Depression

Mark A. Frye, MD
Professor & Chair
Department of Psychiatry & Psychology
Stephen & Shelly Jackson Family Professorship in Individualized Medicine
Mayo Clinic, Rochester, MN

Learning Objective 1

Formulate personalized treatment plans for patients with bipolar depression that consider mechanism of action, safety, efficacy, and dosing strategies

Receptor Pharmacology of Bipolar Depression

- FDA-approved
  - Olanzapine/fluoxetine (OFC)
  - Quetiapine monotherapy
  - Lurasidone mono & adjunct therapy
- Maximize the mood stabilizer
- Bipolar Depression
  - Limited pharmacopeia
  - Trial design considerations – modafinil/armodafi
  - Dopamine compounds
- Antidepressants FDA off-label
  - Do they work? Are they safe?
- Psychotherapy & Novel treatments

The Old Guitarist Pablo Picasso 1903
The Blue Period

FDA off-label – antidepressants are not indicated for treatment of bipolar depression. Modafinil/armodafinil are not FDA-approved for bipolar depression.

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Bipolar Disorder — A Focus on Depression

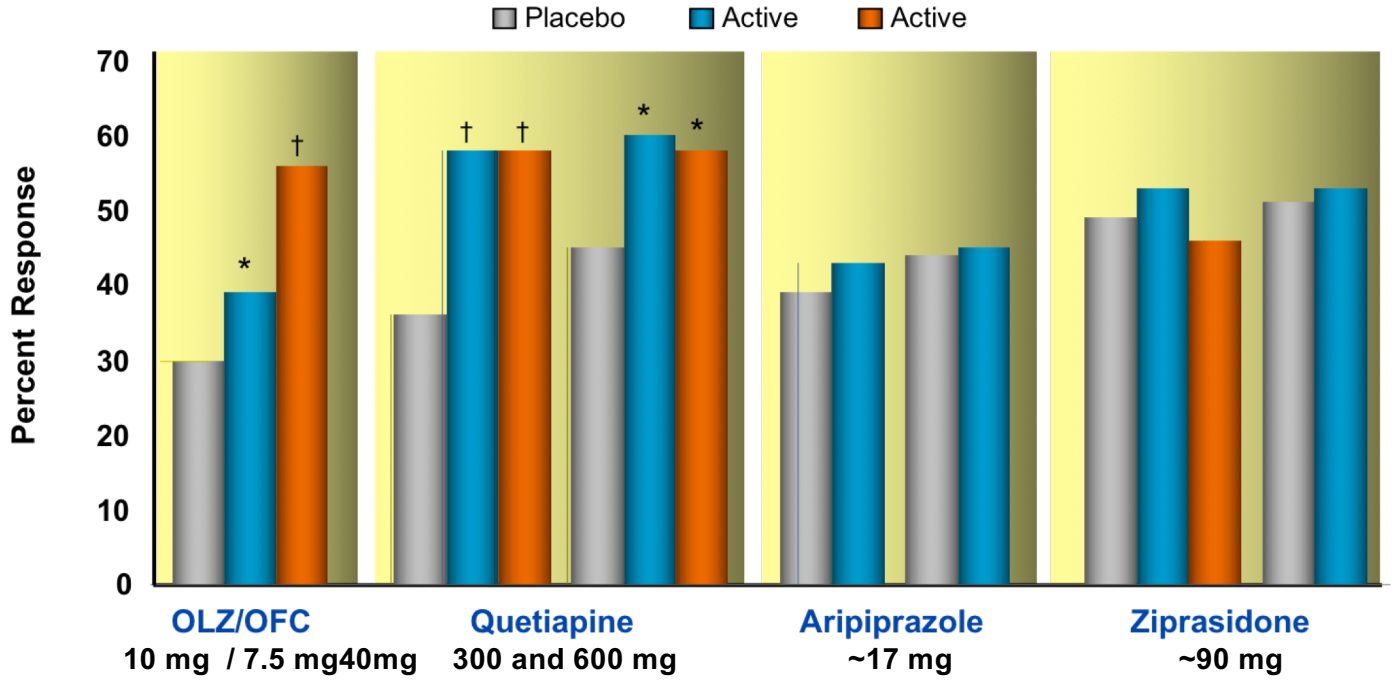
Mark A. Frye, M.D.

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. *NEJM*. 2011;364(1):51-59.

Response Rates of Atypical Antipsychotics in BP Depression

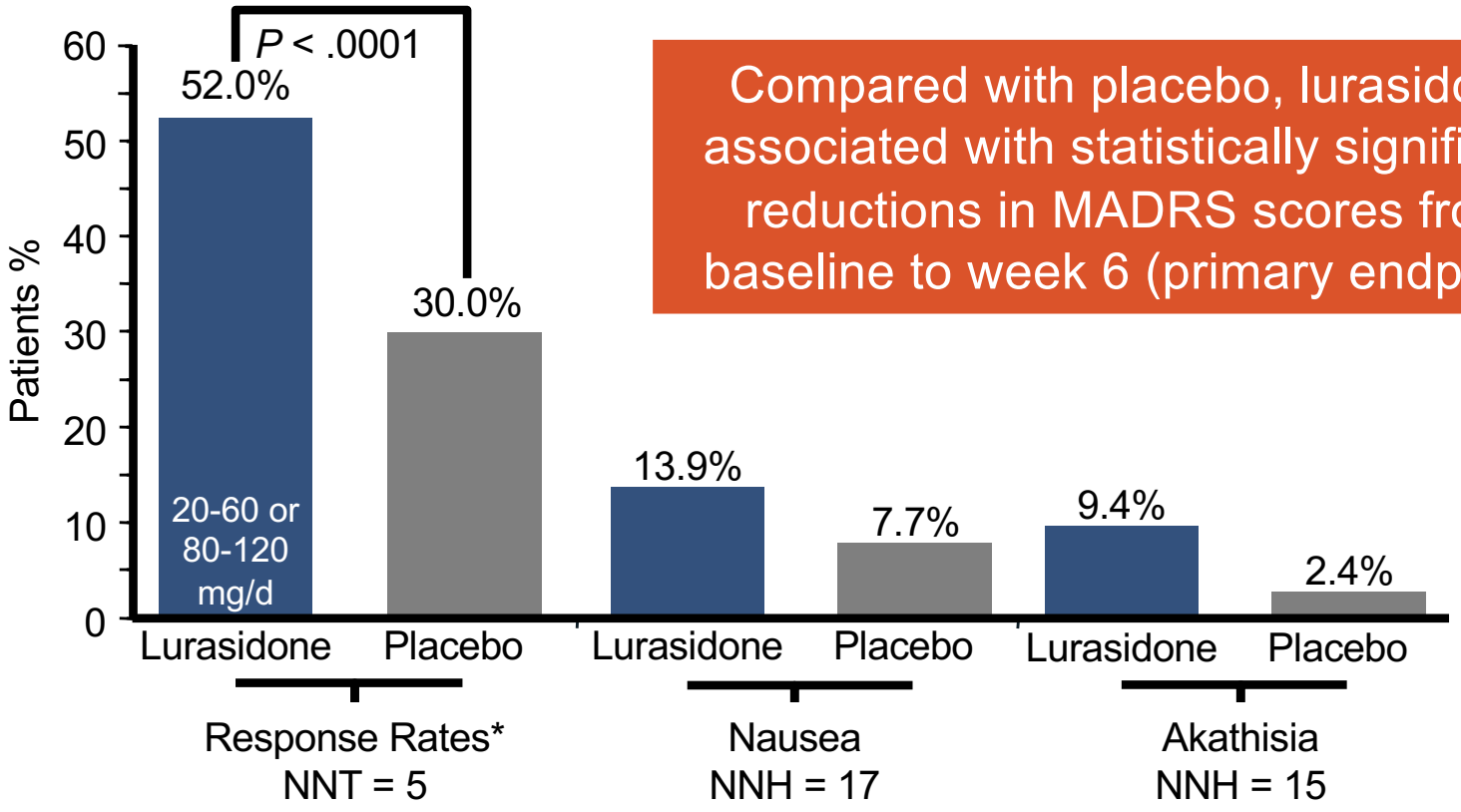


OFC = olanzapine/fluoxetine combination. *$p < 0.05$; †$p < 0.001$ vs placebo

*Aripiprazole and ziprasidone are 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

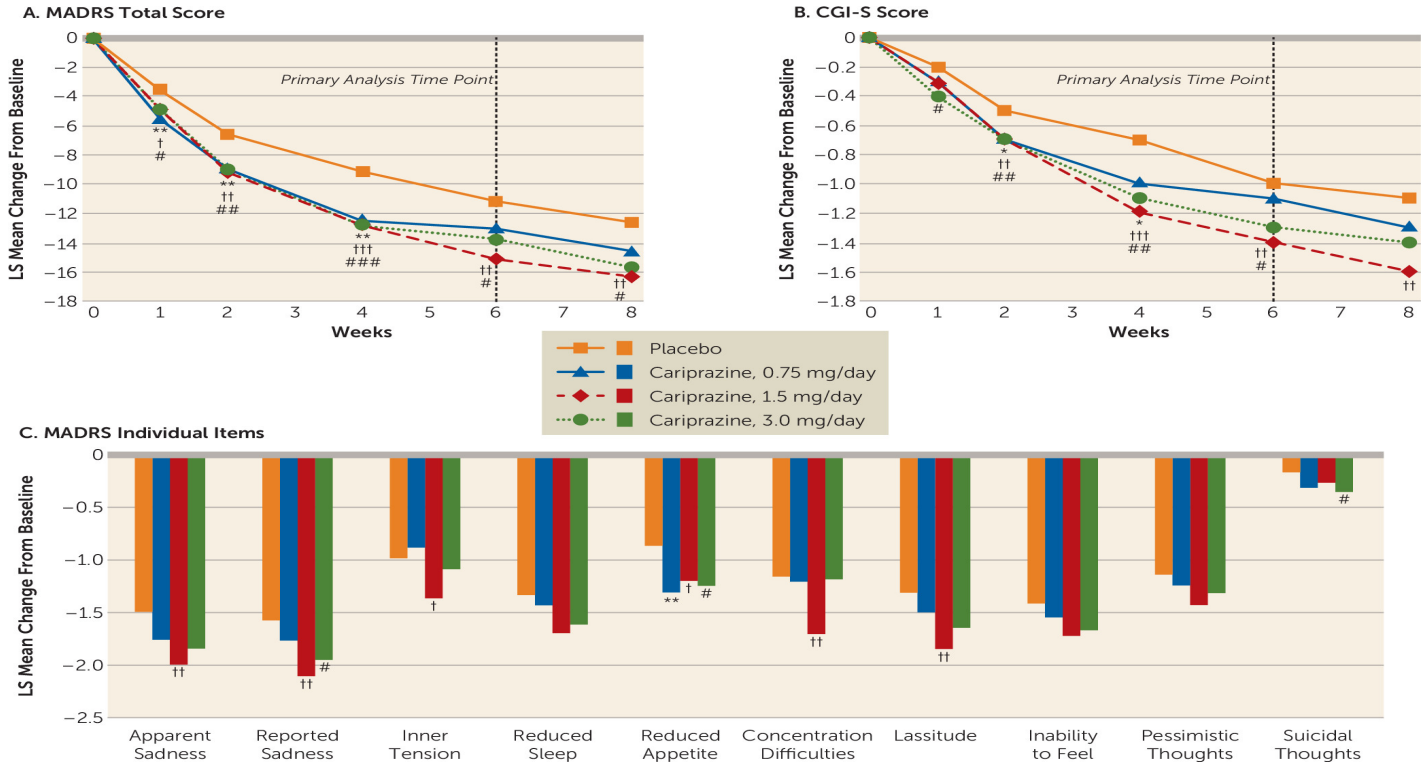


Compared with placebo, lurasidone associated with statistically significant reductions in MADRS scores from baseline to week 6 (primary endpoint)

*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

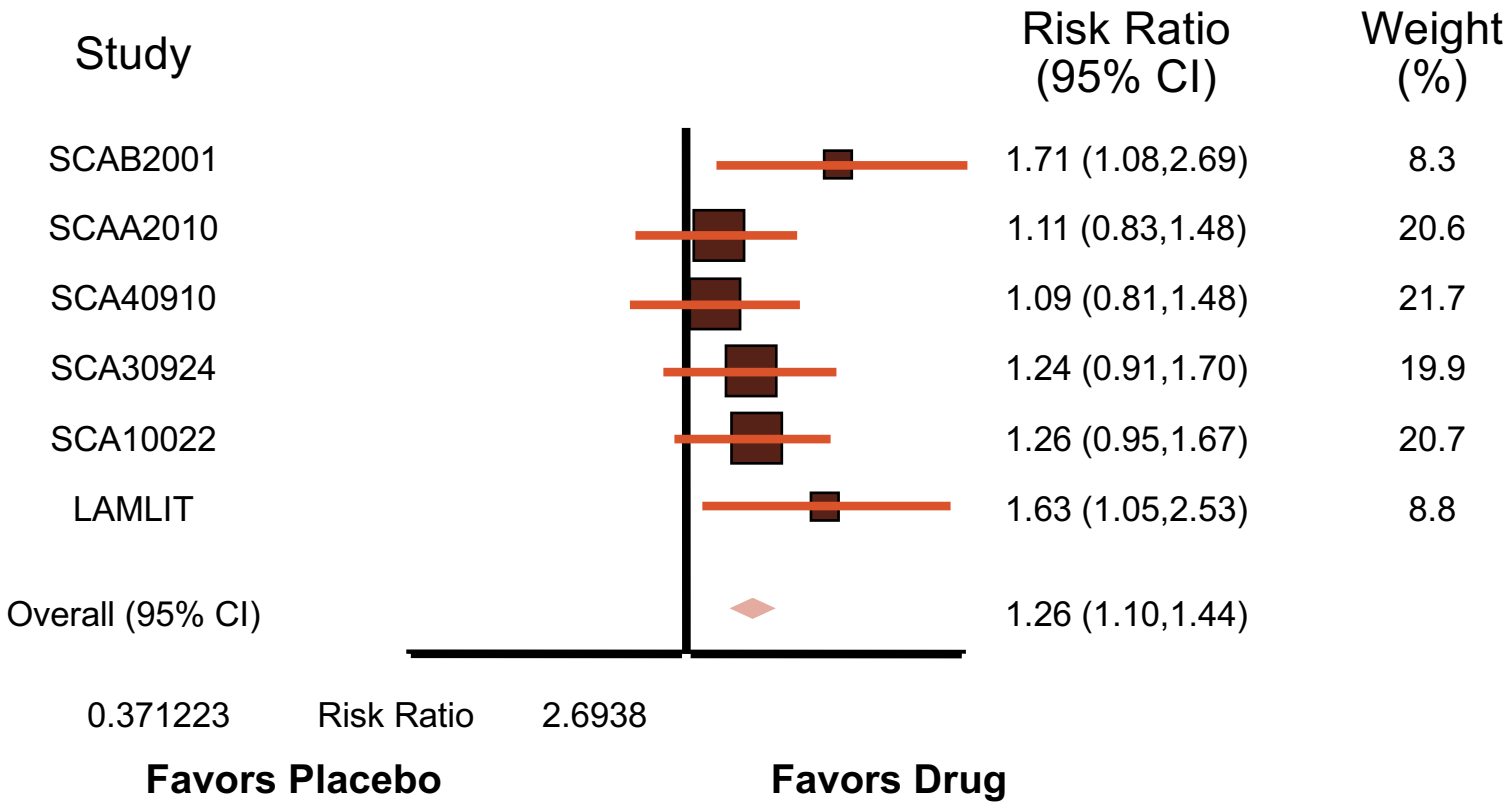


*Not approved by the FDA for treatment of bipolar depression.

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.

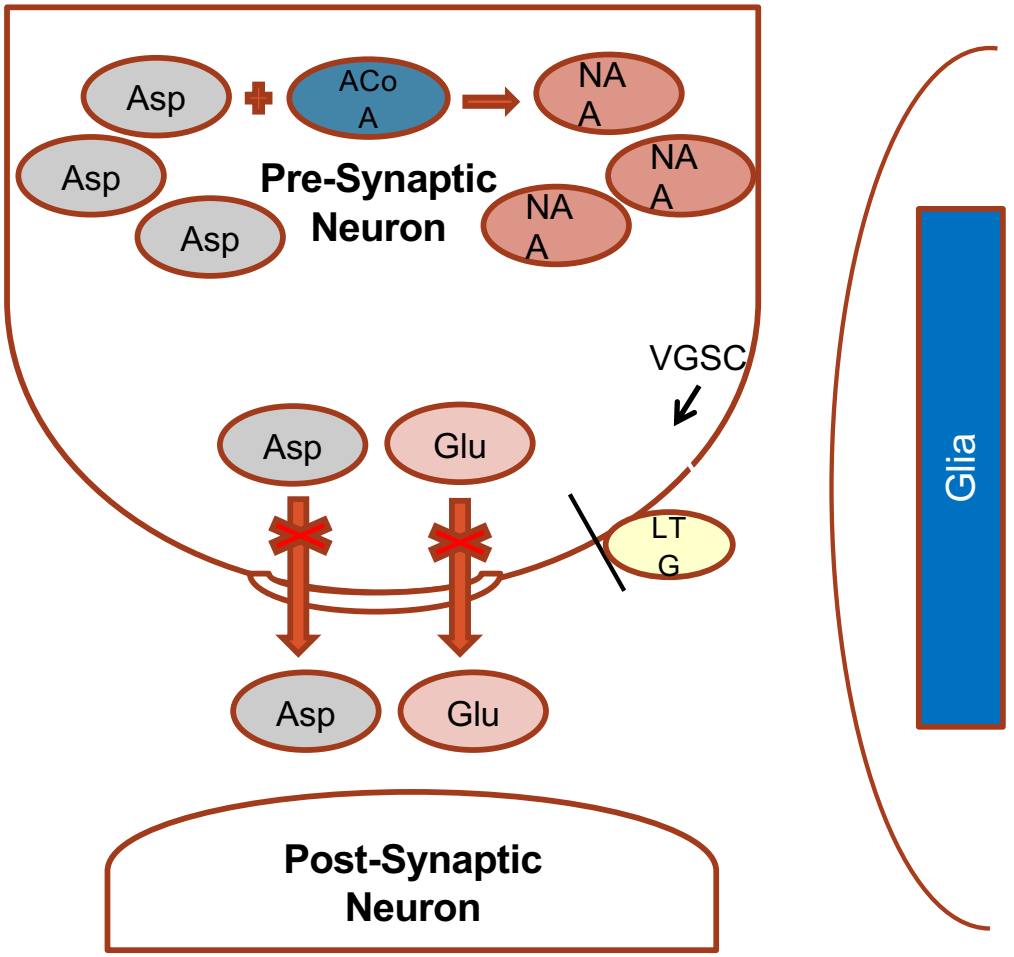
Durgam S, et al. *Am J Psychiatry*. 2016;173(3):271-281.

Meta-Analysis of Lamotrigine* in Acute Bipolar Depression



*Not FDA approved for bipolar depression

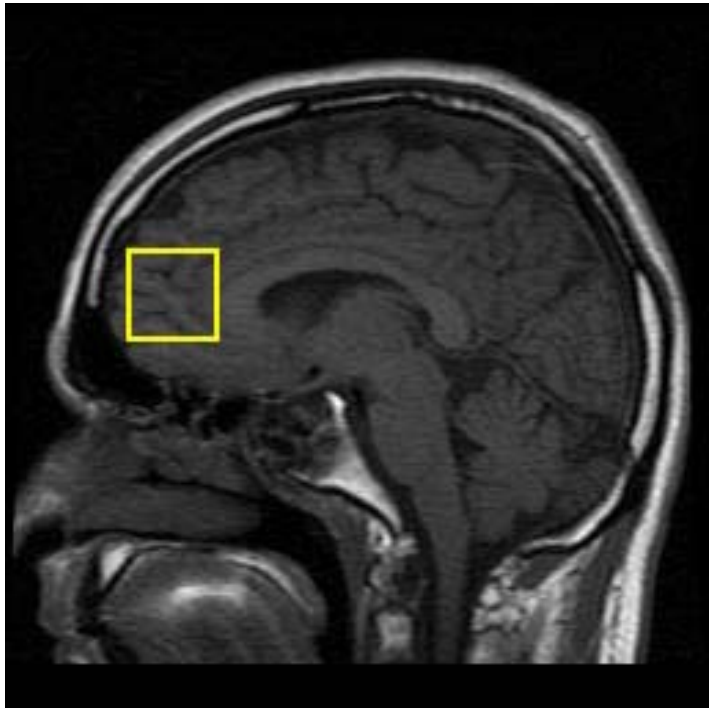
Geddes JR. *Br J Psychiatry*. 2009;194(1):4-9; Van der Loos ML, et al. *J Clin Psychiatry*. 2009;70(2):223-231.

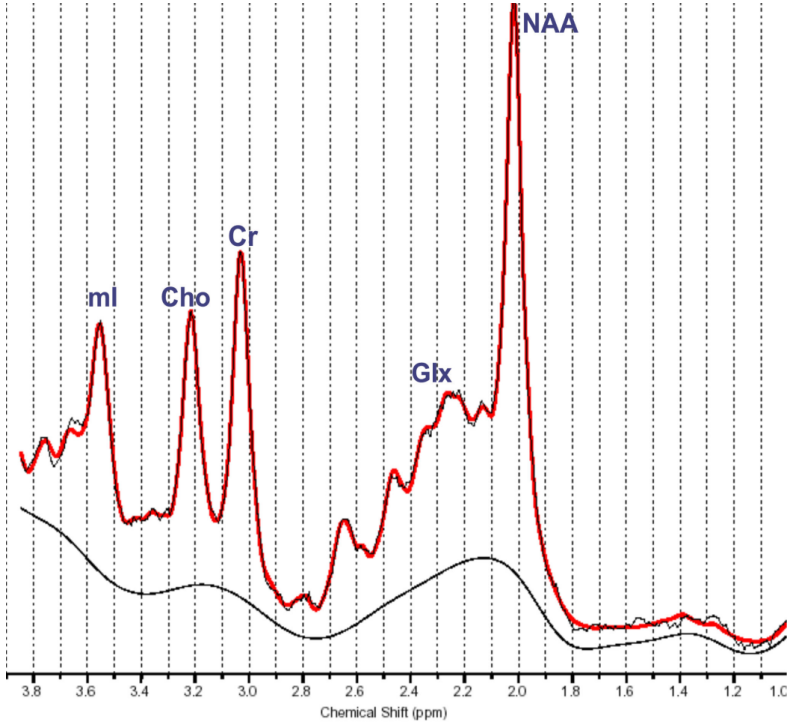


VGSC = voltage gated sodium channel, Glu = glutamate, ASP = aspartate.

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

N- Acetylaspartate (NAA) Normalization in Bipolar Depression after Lamotrigine Treatmen



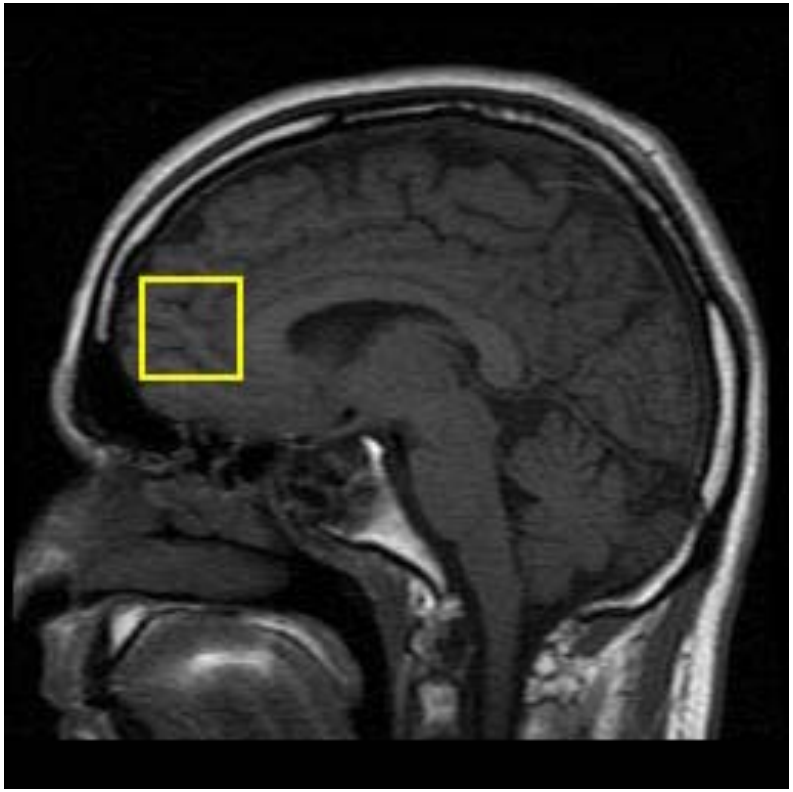


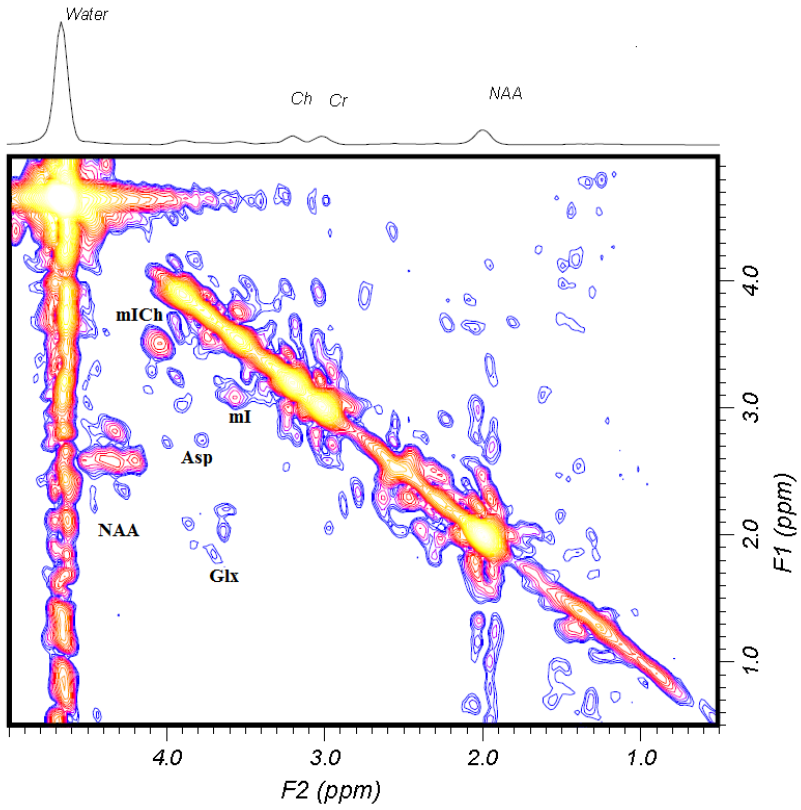
T1-weighted sagittal MRI location for anterior cingulate/medial prefrontal cortex single-voxel, water-suppressed (Haase et al 1985) PRESS (Bottomley 1987) ^{1}HMRS (TR/TE= 3s/30ms, number of averages= 256, voxel size 3x3x3 cm^3

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.

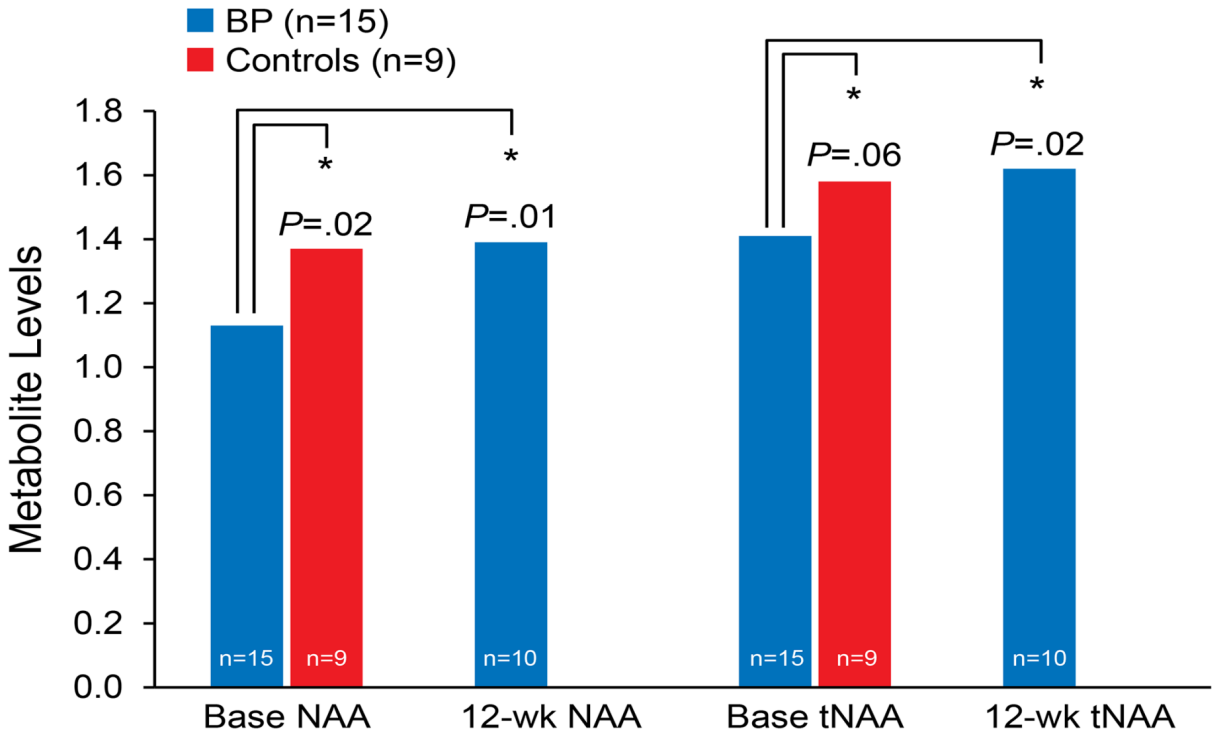
N- Acetylaspartate (NAA) Normalization in Bipolar Depression after Lamotrigine Treatmen





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.

NAA Normalization After Lamotrigine

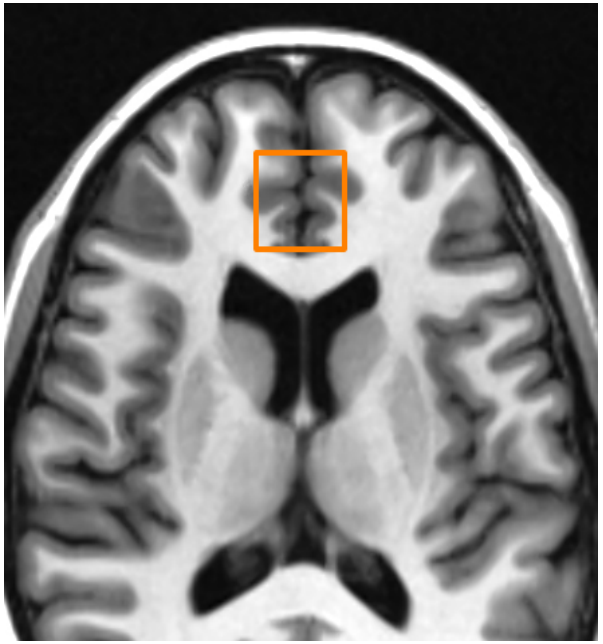


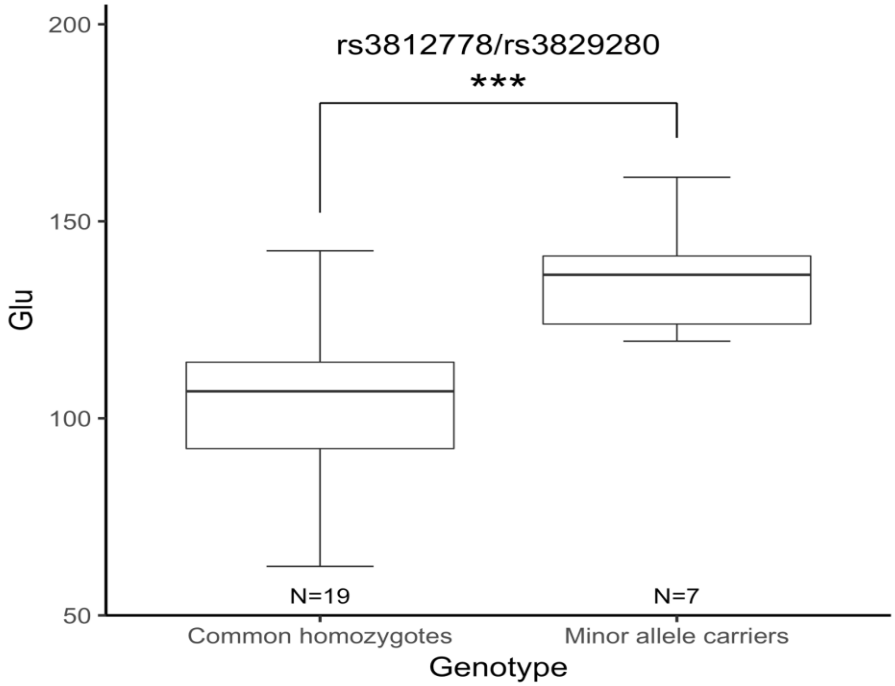
NAA and tNAA Levels at Baseline and After 12 Weeks of Lamotrigine Treatment. Base indicates baseline; BP, bipolar depression; NAA, *N*-acetylaspartate; tNAA, total *N*-acetylaspartate

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

Increased Glutamate in Minor Allele Carriers for *SLC1A2* SNPs rs3812778 / rs3829280

Gene Encodes for Excitatory Amino Acid Transporter (EAAT2)

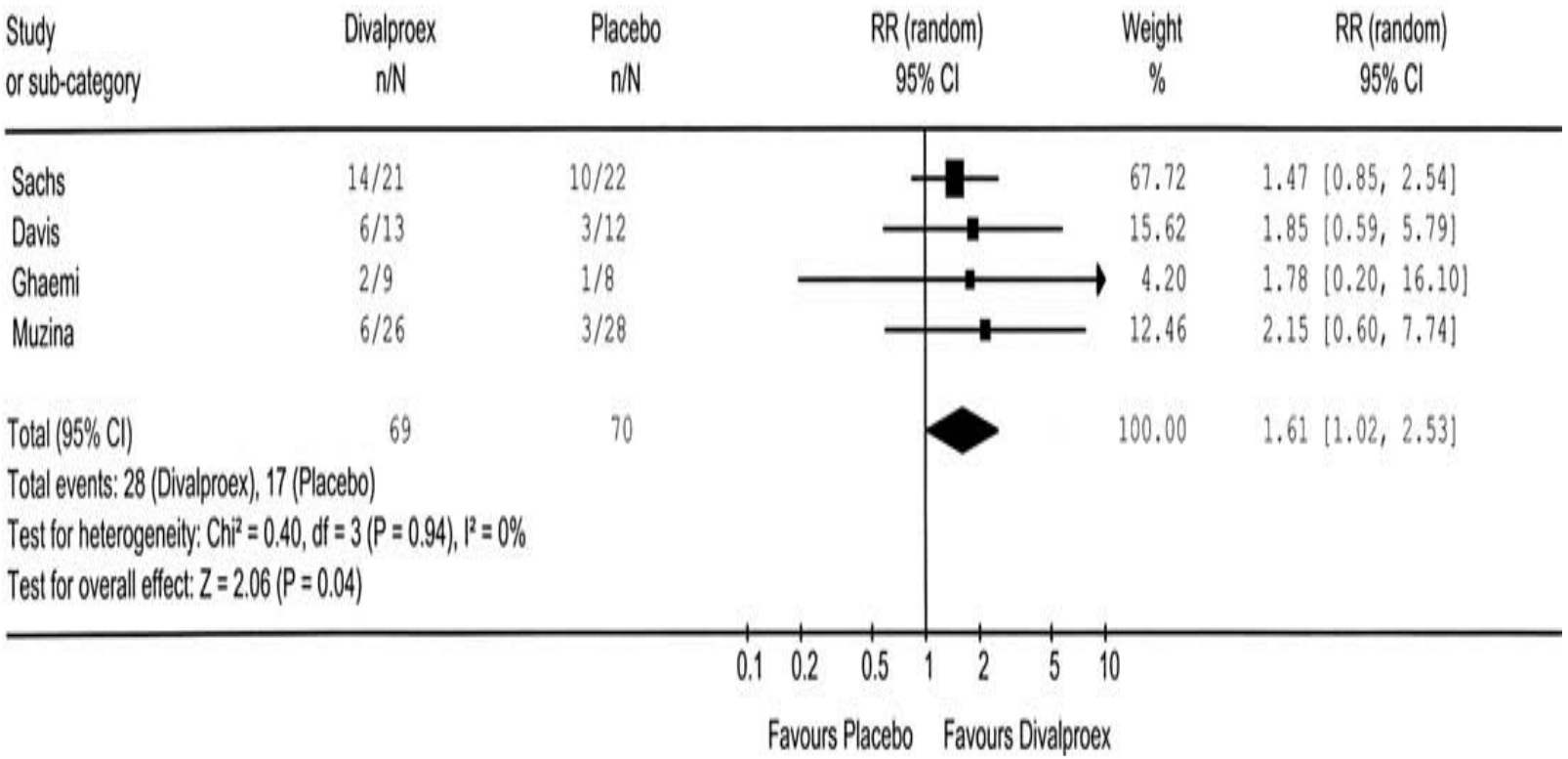




pregenual anterior cingulate cortex ^{1}H-MRS Voxel (2 x 2 x 2 cm)
*** rs3812778/rs3829280 homozygotes versus minor allele carriers, *p*=0.00078.

Veldic M, Millischer V, et al. Presented at the 6th Annual Molecular Biology Meeting, 2018.

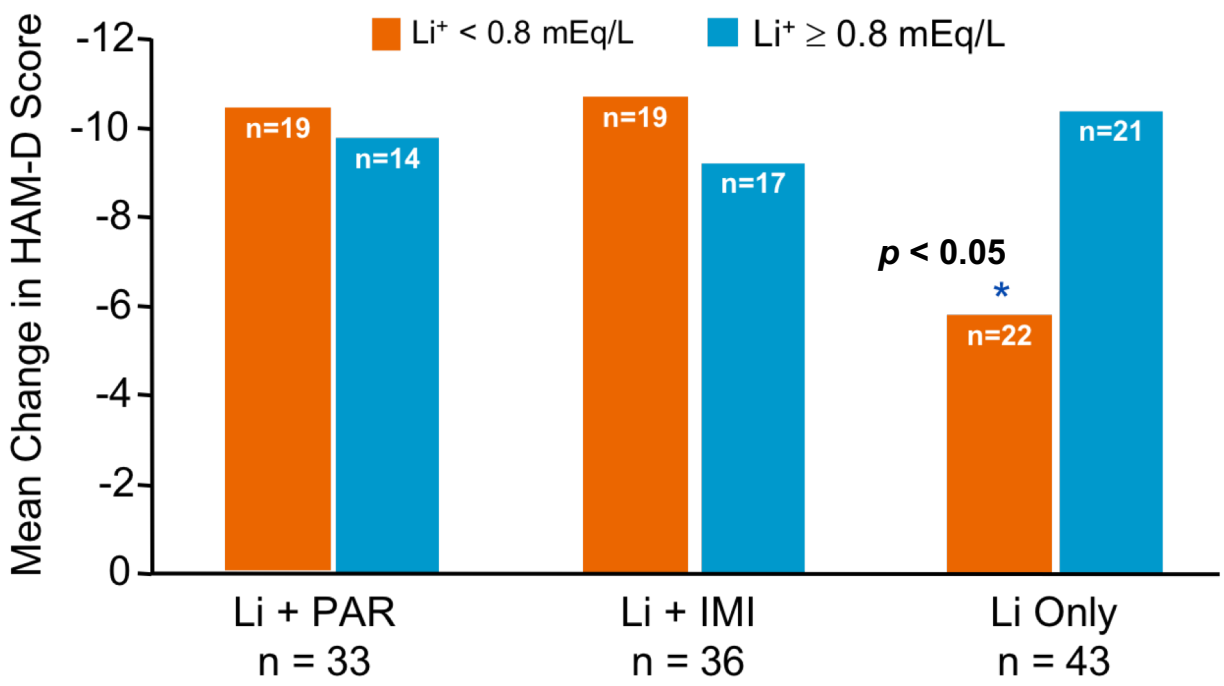
Meta-Analysis Divalproex in Acute BP Depression



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 Lithium & BP Depression



*Not FDA approved for bipolar depression.

Li = lithium, IMI = imipramine, PAR = paroxetine

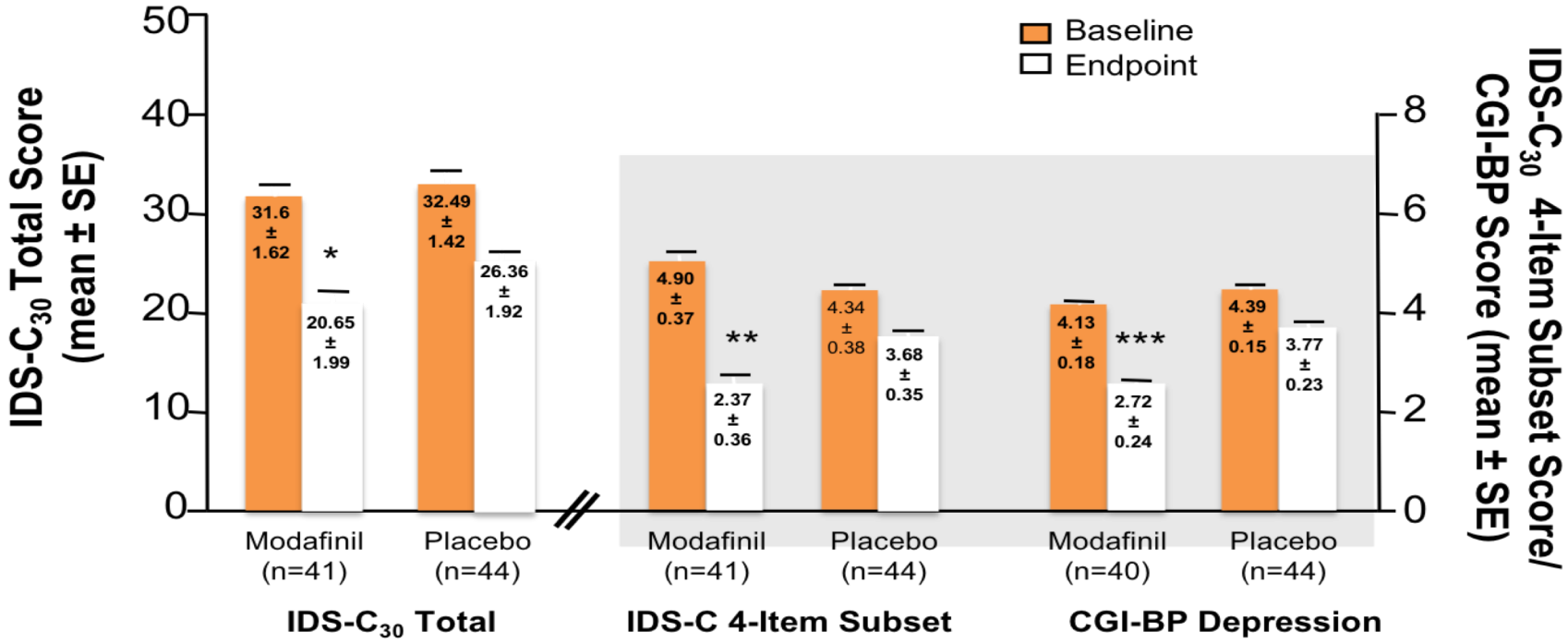
Nemeroff CB, et al. *Am J Psychiatry*. 2001;158(6):906-912.

Dopamine Compounds Reduce Symptoms of Bipolar Depression

- Pramipexole
  - A partial D3/D2 dopamine agonist
  - FDA approved for Parkinson's disease
- Modafinil/armodafinil
  - Dopamine reuptake inhibitor
  - FDA approved for daytime somnolence and fatigue associated with shift work disorder
- Lisdexamfetamine
  - Dopamine reuptake inhibitor also facilitating terminal release of dopamine and norepinephrine
  - FDA approved for children with attention deficit hyperactivity disorder

Goldberg JF, et al. *Am J Psychiatry.* 2004;161(3):564-566.; Zarate C, et al. *Biol Psychiatry* 2004;56(1):54-60.; McElroy S, et al. *J Clin Psychiatry* 2014;75(10):e26.; Frye MA, et al. *Am J Psychiatry* 2007;164(8):1242-1249.

Adjunctive Modafinil Improves Bipolar Depression



Response and remission rates were significantly higher in the modafinil group than in the placebo group ($P \leq 0.05$)

*ANCOVA: F=4.26, DF=1,82 p=.04, **F=6.72, DF=1,82 p=0.01, ***F=8.35, DF=1,82 p=0.005
CGI-BP=Clinical Global Impression for Bipolar Disorder; IDS=Inventory of Depressive Symptoms.
Frye MA, et al. *Am J Psychiatry* 2007;164(8):1242-1249.

From: **Effects of Modafinil on Dopamine and Dopamine Transporters in the Male Human Brain Clinical Implications**

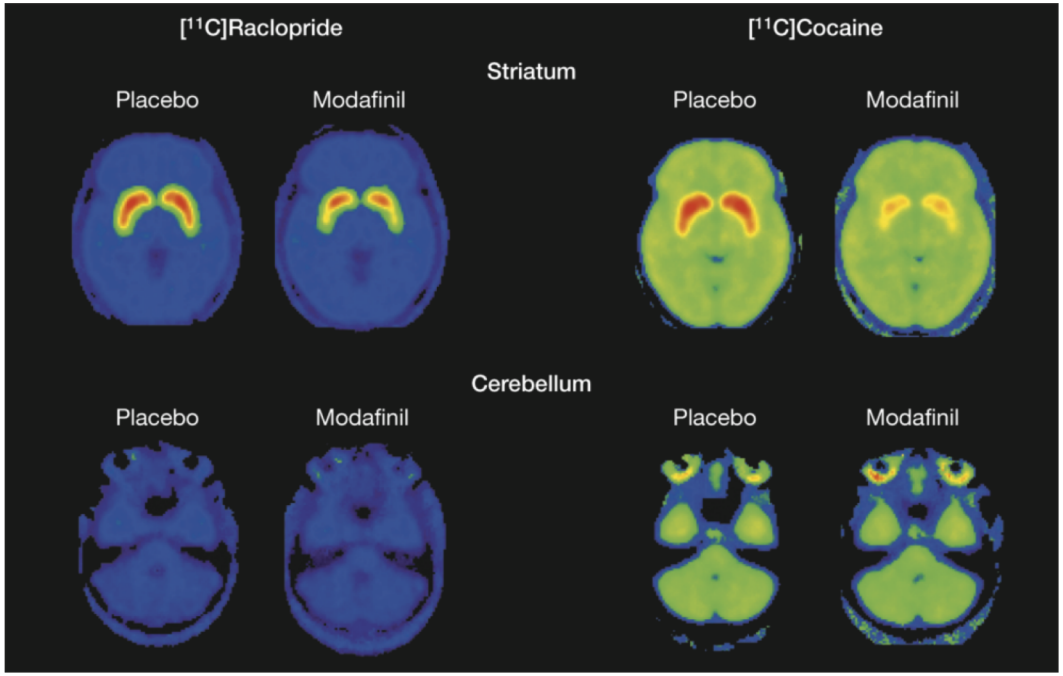


Figure Legend: Averaged [^{11}C]raclopride and [^{11}C]cocaine binding potential (BP_{ND}) images at the level of the striatum (top row) and cerebellum (bottom row) after placebo and after modafinil. The color scale is a rainbow scale with red representing the highest value, which corresponds to a BP_{ND} of 4.4 in the [^{11}C]raclopride images and a BP_{ND} of 1.1 in the [^{11}C]cocaine images.

Volkow ND, et al. *JAMA*. 2009;301(11):1148-1154.

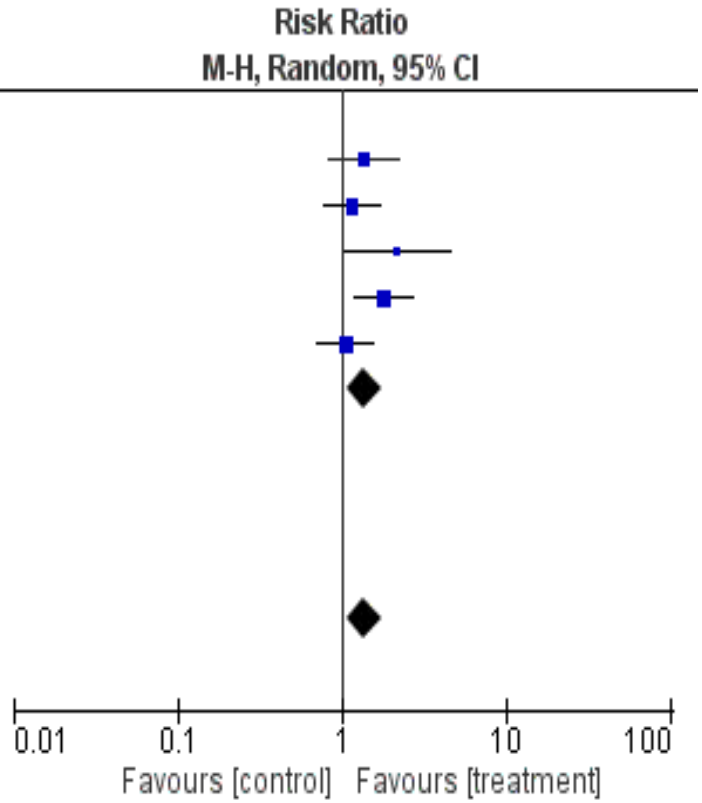
Armodafinil as Adjunctive Therapy in Bipolar Depression: Results from Studies 3071, 3072, 3073

	ARM Response	PLC Response	ARM Remission	PLC Remission
Calabrese 2014 (ARM=201, PLC=199)	**46%**	**34%**	21%	17%
Ketter 2015 (ARM=232, PLC=230)	40%	39%	18%	17%
Frye 2015 (ARM=197, PLC=196)	40%	39%	18%	17%

Calabrese JR, et al. *J Clin Psychiatry*. 2014;75(10):1054-61; Ketter TA, et al. *J Affect Disord.* 2015;181():87-91; Frye MA, et al. *Int J Bipolar Disord.* 2015;3:18.

Meta-Analysis of Modafinil/Armodafinil in Bipolar Depression

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Remission BD						
Calabrese2010	30	124	22	123	18.2%	1.35 [0.83, 2.21]
Calabrese2014	46	234	34	199	24.2%	1.15 [0.77, 1.72]
Frye2007	16	41	8	44	9.4%	2.15 [1.03, 4.47]
Frye2015	52	197	29	196	23.6%	1.78 [1.19, 2.69]
Ketter2015	42	230	39	224	24.7%	1.05 [0.71, 1.56]
Subtotal (95% CI)		**826**		**786**	**100.0%**	**1.36 [1.07, 1.73]**
Total events	186		132			
Heterogeneity: Tau² = 0.02; Chi² = 5.49, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Total (95% CI)		**826**		**786**	**100.0%**	**1.36 [1.07, 1.73]**
Total events	186		132			
Heterogeneity: Tau² = 0.02; Chi² = 5.49, df = 4 (P = 0.24); I² = 27%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Not applicable						



Nunez, et al. Accepted for Presentation 2019 New Research American Society of Clinical Pharmacology (ASCP)

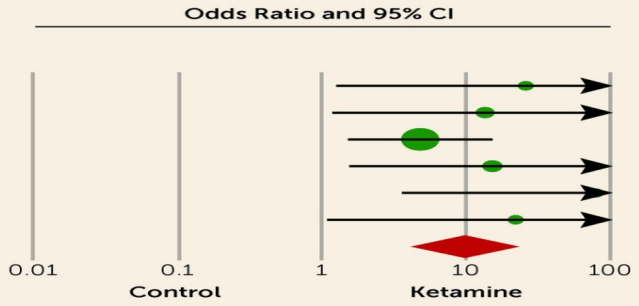
THE AMERICAN JOURNAL OF PSYCHIATRY

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

American Journal of Psychiatry

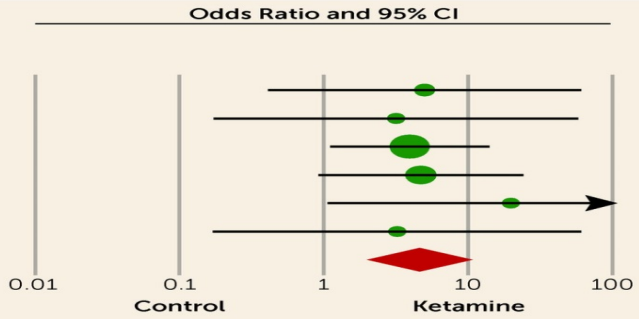
A

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

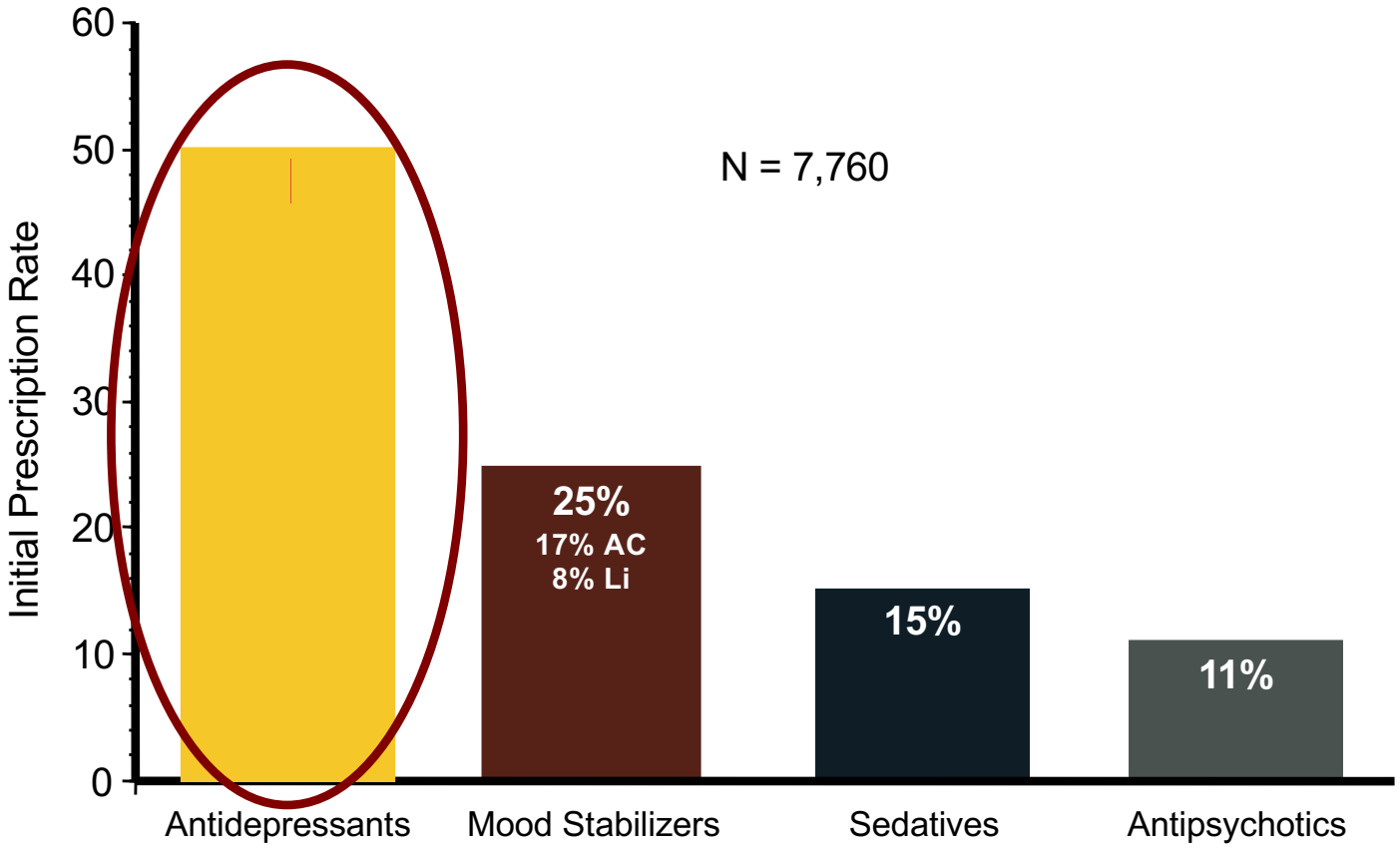
Study	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Diazgranados et al. (85)	5.000	0.426	58.636	1.281	0.200
Lapidus et al. (84)	3.171	0.179	56.222	0.787	0.431
Murrough et al. (87)	3.937	1.149	13.492	2.181	0.029
Sos et al. (91)	4.706	0.950	23.302	1.898	0.058
Zarate et al. (88)	19.783	1.060	369.109	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.

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

Sidor MM, Macqueen GM. *J Clin Psychiatry.* 2011;72(2):156-67.; Sidor MM, Macqueen GM. *Curr Psychiatry Rep.* 2012;14(6):696-704.

Switching and Response Outcomes by Treatment Group

	Lithium (n = 49)	Sertraline (n = 45)	Combination (n = 48)	*p*
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 Li alone or sertraline alone

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

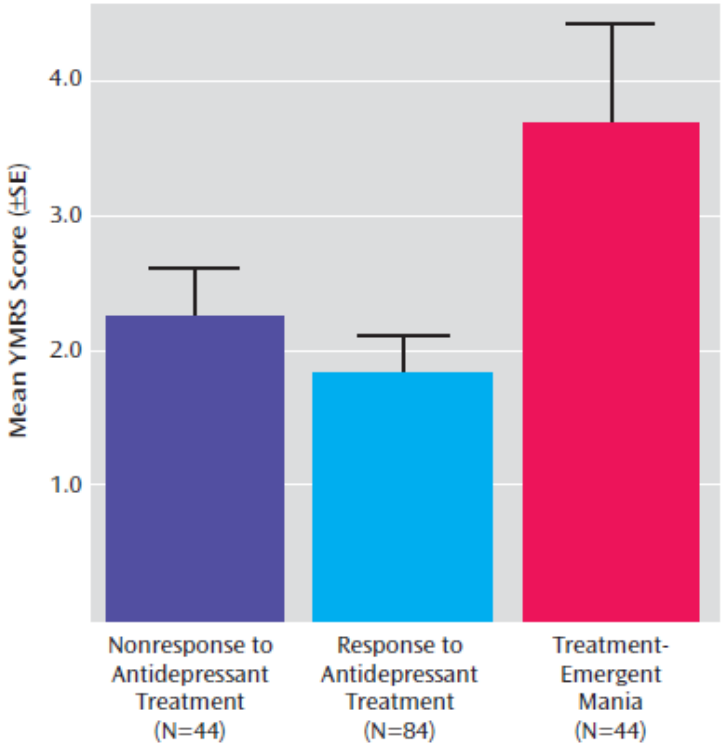
Proposed Risk Factors for AIM Switch

- Tricyclic antidepressant (TCA)
- Antidepressant monotherapy
- Mixed depression
- Hyperthymic temperament
- Comorbid alcoholism
- Comorbid anxiety disorder
- Female gender
- Age (children / adolescents > adults)
- BP I (> BP II)
- **Genetic variants in SLC6A4**

Frye MA, et al. *Am J Psychiatry.* 2009;166(2):164-172; Frye MA, et al. *J Clin Psychiatry.* 2015;76(2):174-180.

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

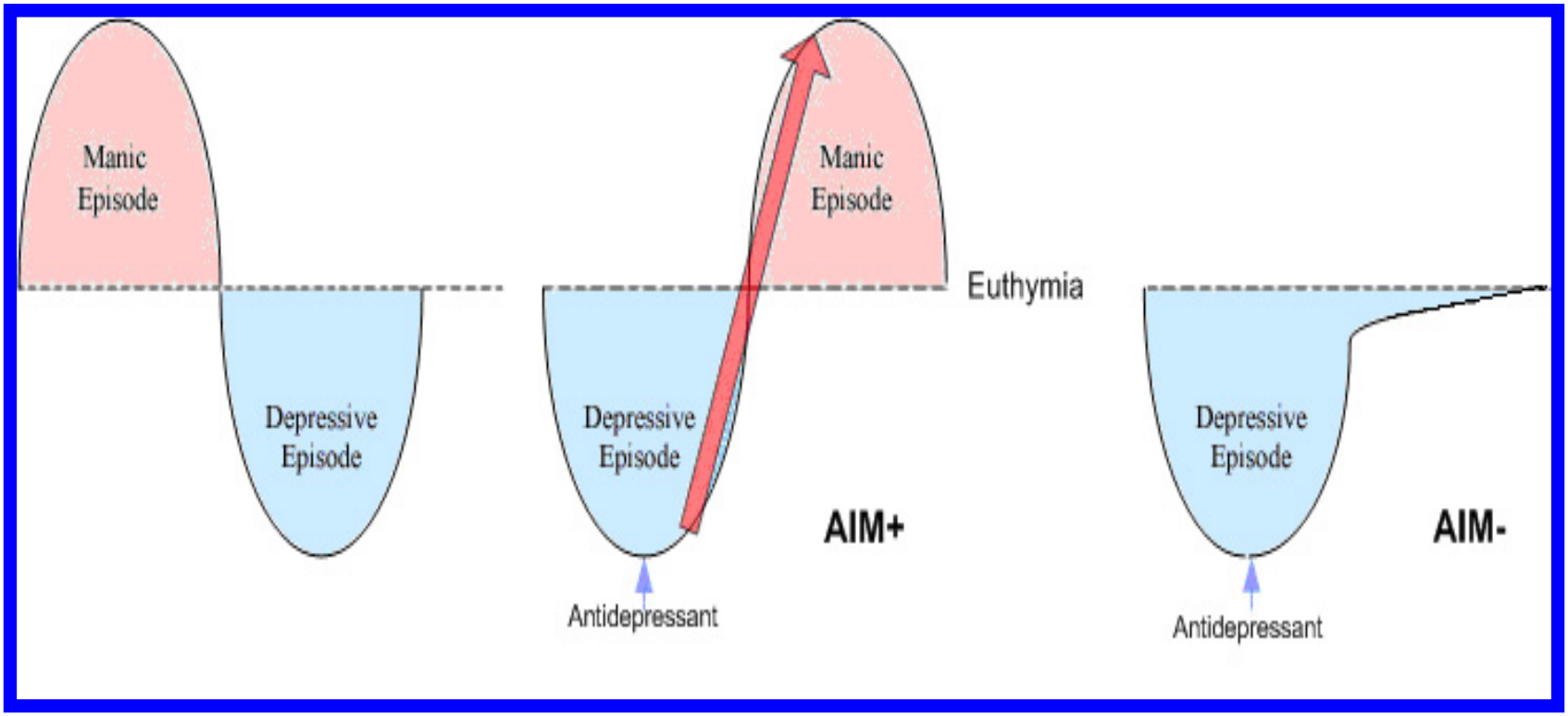


Baseline Manic Symptom Severity Prior to Antidepressant Treatment

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

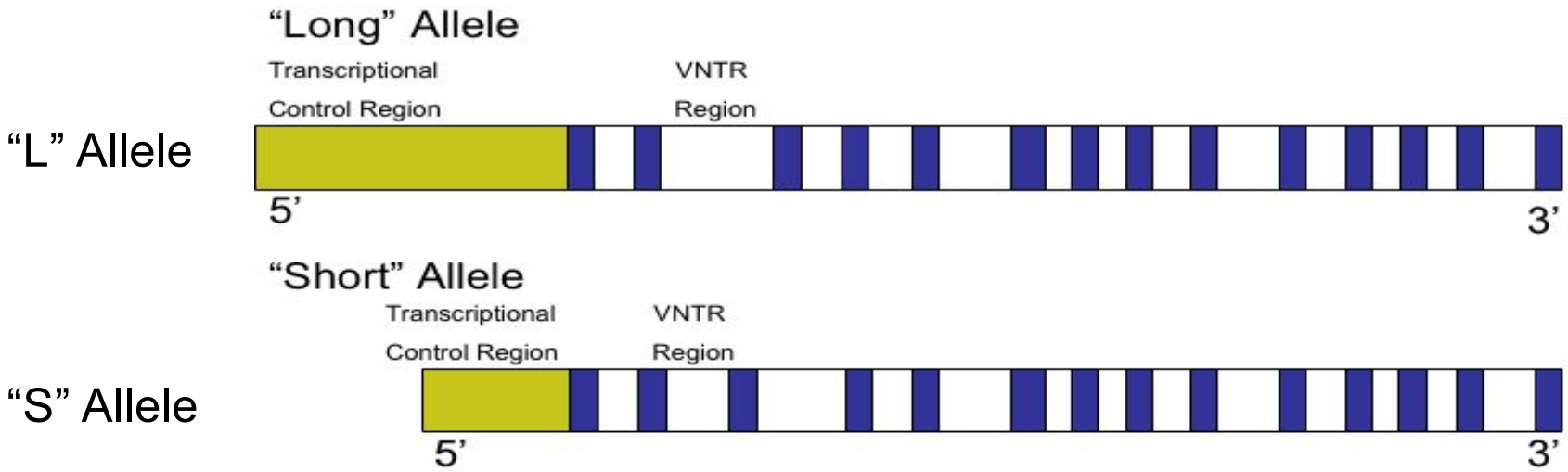
Mayo Clinic Individualized Medicine Biobank for Bipolar Disorder (BP)

SLC6A4 polymorphism & Antidepressant Induced Mania



Serotonin Transporter Gene (SLC6A4) on 17q11.2

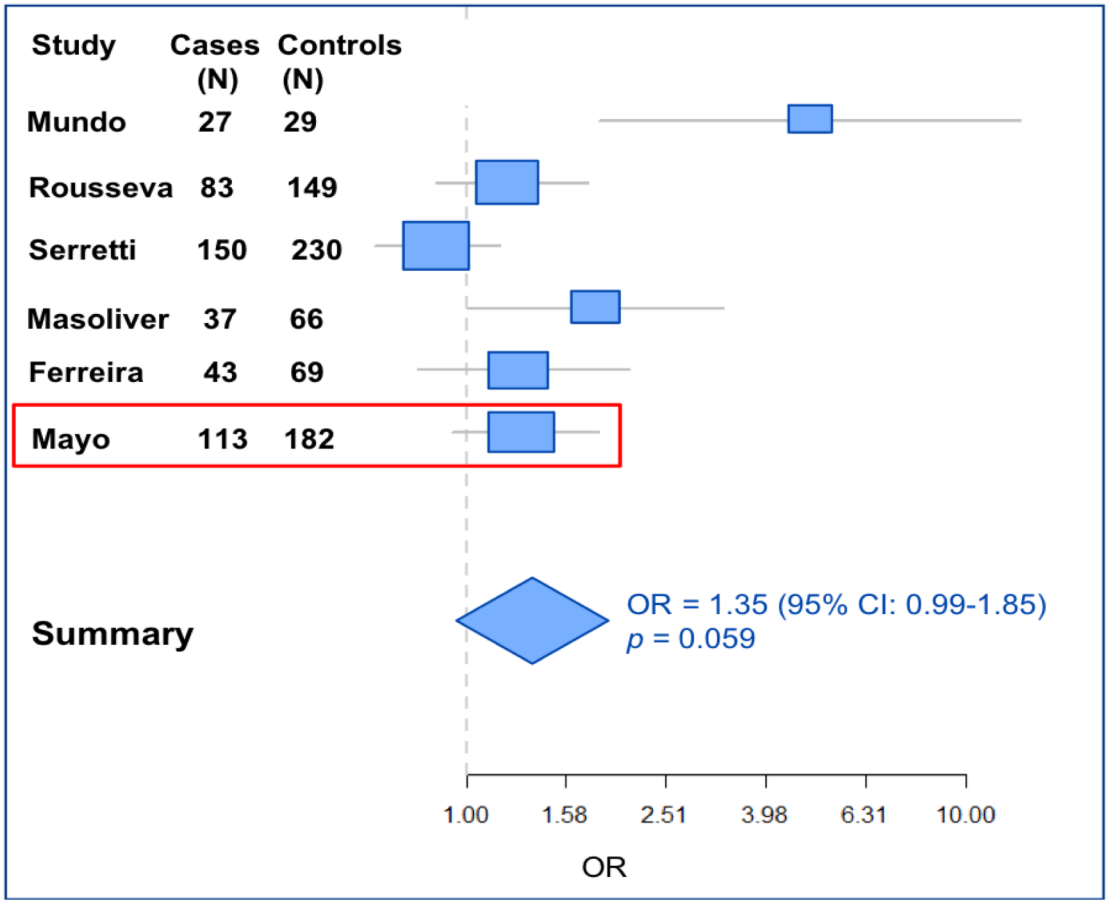
- 5HTT-LPR
  - (44 bp insertion/deletion polymorphism in the Promoter Region)



- Long/long almost doubles 5HT-T expression (Lesch et al. 1996 Science)

Courtesy of Dr. Gen Shinozaki
Lesch KP, et al. *Science*. 1996;27(5292):1527-1531.

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-10 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

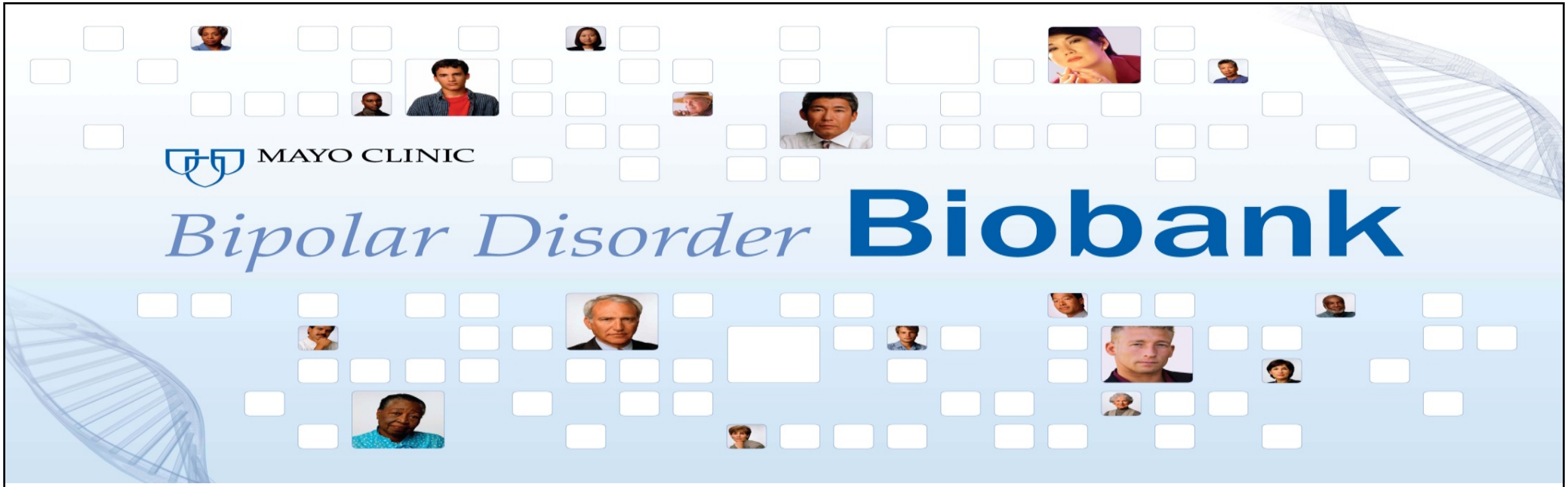
Haplotype analysis suggests an association between AIM and haplotypes composed of the 5HTTLPR, rs25531, and the intron 2 VNTR in the SLC6A4 gene, with the L-A-10 haplotype being associated with reduced risk of AIM

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

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Evaluate evidence-based options for bipolar depression
  - OFC, quetiapine, lamotrigine, lurasidone
- Maximize the mood stabilizer
- Apply the evidence base + comorbidity to treatment decisions
  - Psychotic depression or psychotic illness – AAP
  - Weight neutrality – ARI, LUR, ZIP, LTG
  - Migraine – valproate
  - Smoking cessation – bupropion (with MS)
  - Anti-suicidal or classic illness- lithium
- Evidence does not support monotherapy antidepressant use in BP depression
  - Switch rate is not 0%



Funding for the bipolar genomics work was provided
by the Marriott Foundation

Thank you to our bipolar patients and their families who have contributed to the development and richness of this resource

Mayo Clinic
Joanna M. Biernakca Ph.D., William V. Bobo M.D., Doo-Sup Choi Ph.D., Paul E. Croarkin D.O., Simon Kung M.D., Katherine M. Moore M.D., Teri Rummans M.D., Balwinder Singh M.D., Sue Tye Ph.D., Jennifer Vande Voort M.D., Marin Veldic M.D., Richard Weinshilboum M.D., Alfredo Cuellar Barboza M.D., Miguel Prieto M.D., Manuel Feuntes M.D.

UCLA
Lori L. Altshuler M.D., Michael Gitlin M.D.

NIMH
Robert M. Post M.D.

Stanley Foundation Bipolar Network
Susan L. McElroy M.D., Paul E. Keck M.D., Trisha Suppes M.D., Ph.D., Wilam Nolan M.D., Ralph Kupka M.D., Ph.D., Heinz Grunze M.D.

Questions & Answers

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