Acute and Maintenance Treatment of Bipolar Depression

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Teaching Points

- Mood stabilizers are foundational agents and should be considered first line treatments, with the strongest evidence supporting the use of lithium and lamotrigine.
- Emerging data suggest atypical antipsychotics provide benefit in acute bipolar depression, with the strongest evidence supporting the use of quetiapine monotherapy and the olanzapine plus fluoxetine combination.
- The utility of adjunctive antidepressants in bipolar depression is controversial, as these agents can yield switching into mania or hypomania in some patients.

Pre-Lecture Exam
Question 1

1. The most pervasive symptoms in bipolar disorder are those of: (choose one)

A. Mania, hypomania

B. Hypomania

C. Depression

D. Mixed States

E. None of the above

Question 2

2. Which of the treatments below is the LEAST appropriate strategy in bipolar depression: (choose one)

A. Mood stabilizer without antidepressant

B. Mood stabilizer with antidepressant

C. Atypical antipsychotic with antidepressant

D. Antidepressant with neither mood stabilizer nor atypical antipsychotic

Question 3

3. Which antidepressant option carries the greatest risk of hypomania/mania: (choose one)

A. Tricyclic antidepressants (TCAs)

B. Selective serotonin reuptake inhibitors (SSRIs)

C. Serotonin norepinephrine reuptake inhibitors (SNRIs)

D. Bupropion

Question 4

4. Which of the following treatments do NOT have controlled data suggesting utility in bipolar depression: (choose one)

A. Lithium

B. Lamotrigine

C. Olanzapine plus fluoxetine combination

D. Quetiapine

E. Citalopram

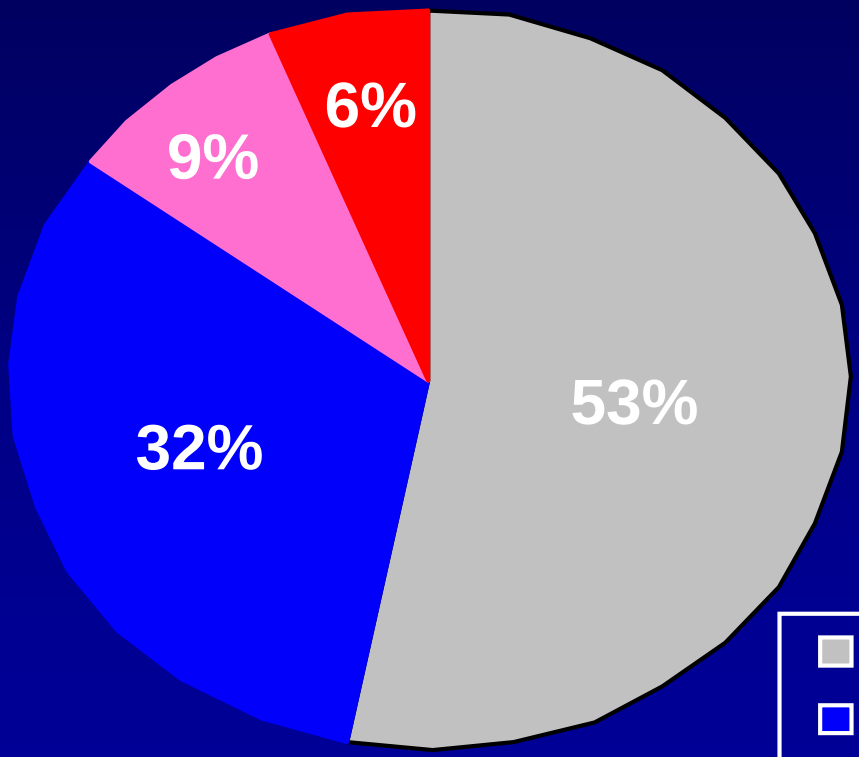
F. Pramipexole

Overview

- Treatment options
  - Mood stabilizers
  - Atypical antipsychotics
  - Adjunctive antidepressants
  - Alternative treatments
- Treatment of acute bipolar depression
- Prevention of bipolar depression

Bipolar disorders symptoms are chronic and predominantly depressive

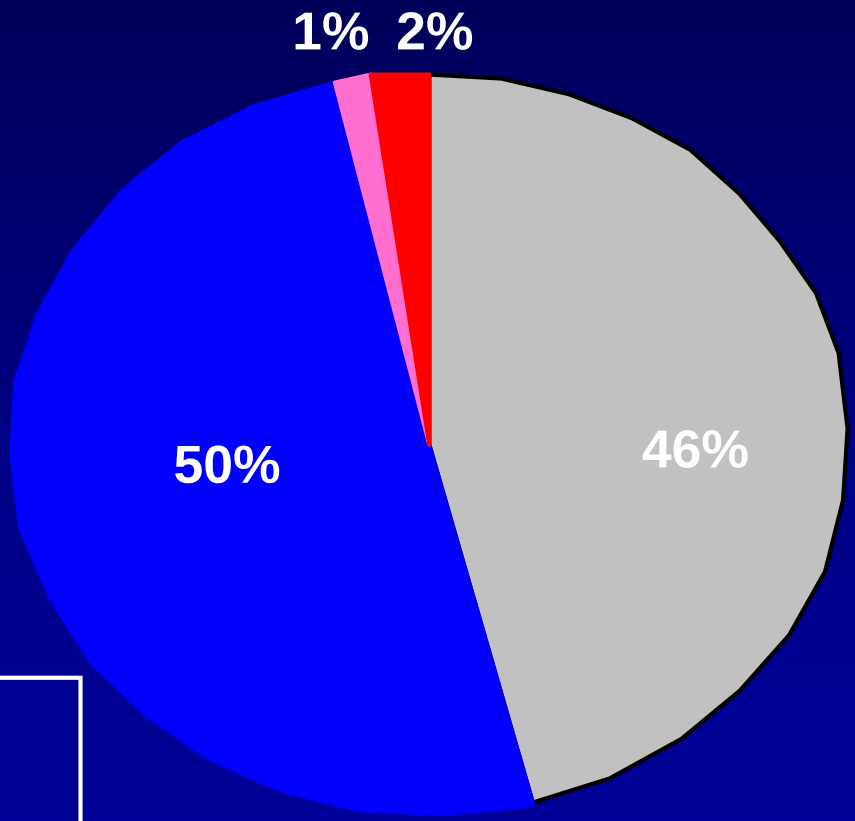
146 Bipolar I Patients
followed 12.8 yrs



Judd et al 2002

% of Weeks
- Asymptomatic
- Depressed
- Hypomanic
- Cycling / mixed

86 Bipolar II Patients
followed 13.4 yrs



Judd et al 2003

Treatment Options in Bipolar Depression

Mood Stabilizers

- Lithium
- Lamotrigine
- Carbamazepine
- Divalproex
- ECT

Atypical Antipsychotics

- Quetiapine
- Olanzapine

Adjunctive Antidepressants

- Fluoxetine + Olanzapine
- Bupropion
- SSRIs
- Venlafaxine
- Nefazodone
- Mirtazapine
- MAOIs
- TCAs

Alternative Treatments

- Pramipexole
- Gabapentin
- Omega-3 fatty acids
- Phototherapy
- Psychotherapy
- Sleep deprivation
- Thyroid hormones

Jefferson JW, Greist JH. Textbook of Psychiatry, Washington, DC, American Psychiatric Press, 1994; Post RM, et al. *Neuropsychopharmacology* 1998; Worthington JJ III, Pollack MH. *Am J Psychiatry* 1996; Amsterdam J. *J Clin Psychopharmacol* 1998; Barbini B, et al. *Psychiatry Res* 1998; Wirz-Justice A, et al. *Biol Psychiatry* 1999; Stoll AL, et al. *Arch Gen Psychiatry* 1999; Bowden CL. *J Clin Psychiatry* 1998; Tohen M, et al. Arch Gen Psychiatry 2003;60:1079-88; Calabrese JR, et al. J Clin Psychiatry 1999;60:79-88; Goldberg JF, et al. Am J Psychiatry 2004;161:564-6.

Acute Treatment of Bipolar Depression

Lithium in Acute Bipolar Depression

- Li > placebo in 5/7 studies (N=158)[1]
  - Pooled data
    - 19% little or no antidepressant effect
    - 81% significant antidepressant effect
- Li versus TCA studies[1,2]
  - Some included unipolars
  - TCA ≥ Li in 3 studies (N=98)[1,2]

Mendels J. Am J Psychiatry 1976;133:373-8[1] Watanabe S, et al. Arch Gen Psychiatry 1975;32:659-668[2]

Lithium and Suicide Risk in Major Affective Disorder

28 Reports* (16,800 Patients)

	No. of reports	Annual risk of suicide
With lithium	22	0.26 ± 0.4
Without lithium	10	1.68 ± 1.5

} 7 to 8-fold difference $p<0.0001$

*19 of 28 reports (16,000 patients) recorded only actual suicides.
Tondo, et al. 1997.

Suicide and Suicide Attempts with Randomized Lithium or Carbamazepine

30-month prospective study
in 285 recently hospitalized patients
(175 bipolar, 110 schizoaffective)

	Suicide	Suicide Attempts	Total Suicidal Behavior
Lithium	0	0	0
Carbamazepine	5	4	9

Thies-Flechtner et al. Pharmacopsychiatry 1994;29:103-7.

Mood Stabilizer Choice and Suicide Events in Bipolar Disorder Patients in Two Large HMOs

Events per 1,000 pt-years

Medication	# of PtÕs	Outpatient Attempts	Inpatient Attempts	Completed Suicides
Lithium	11,308	9.5	4.3	0.7
Divalproex	12,358	26.8*	10.65*	1.75*
Lithium + Divalproex[a]	3067	25.8*	11.8*	1.60

[a]Treatment-resistant patients; *Sig. Diff from Lithium alone (p<.05)

Goodwin et al. JAMA 2003;290:1467-73

Mood Stabilizer Choice and Suicide Events in Bipolar Disorder Patients in Two Large HMOs

Risk ratios of events relative to patients on lithium

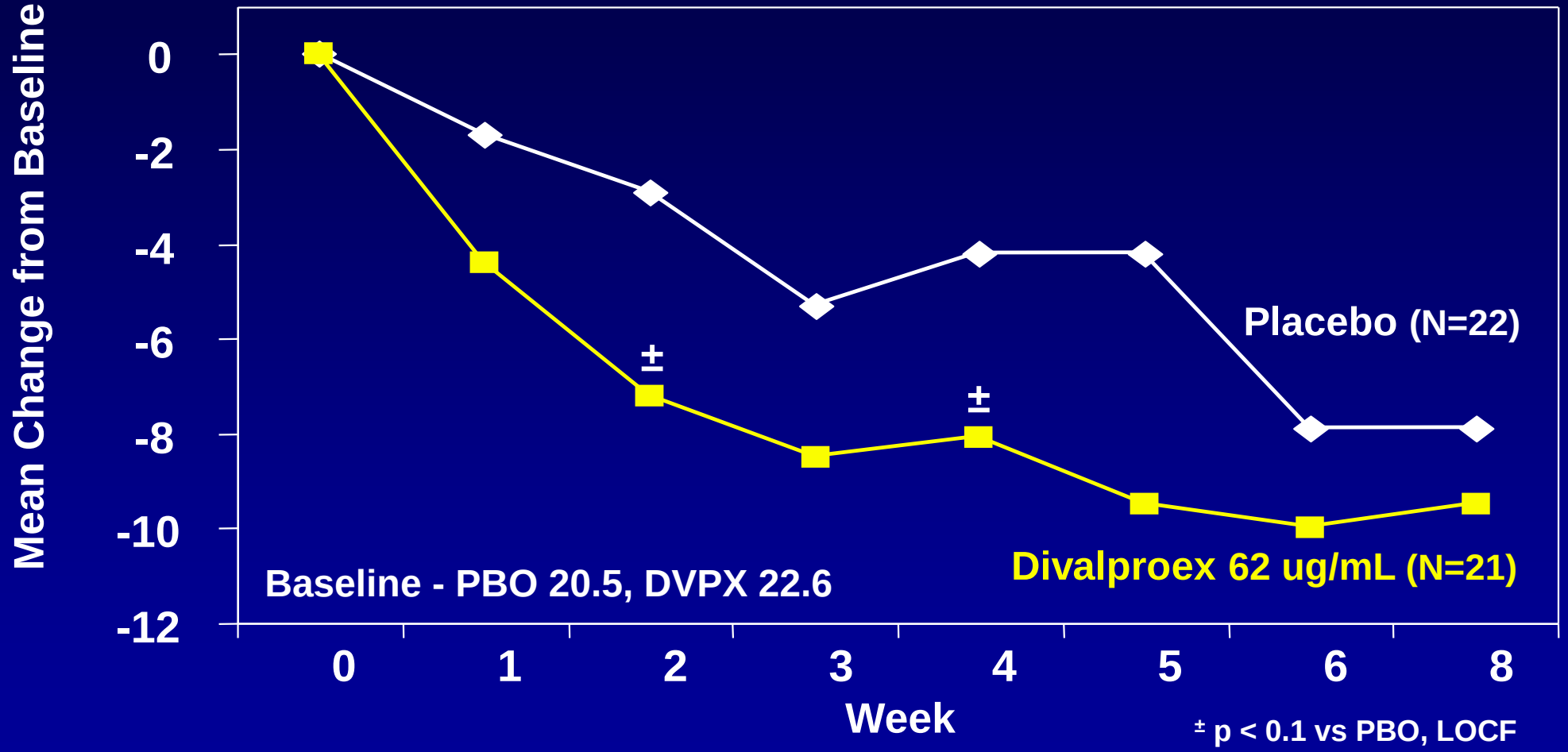
(Adjusted for age, sex, year of treatment, comedications, comorbidity)

Medication	Outpatient attempts	Inpatient attempts	Completed Suicides
Lithium	1.0	1.0	1.0
Divalproex	1.7*	1.6*	2.6**
Divalproex + Lithium[a]	2.1*	2.1*	2.6

[a]Treatment-resistant patients; Sig. Diff from Lithium alone (*p<.001; **p<.004)

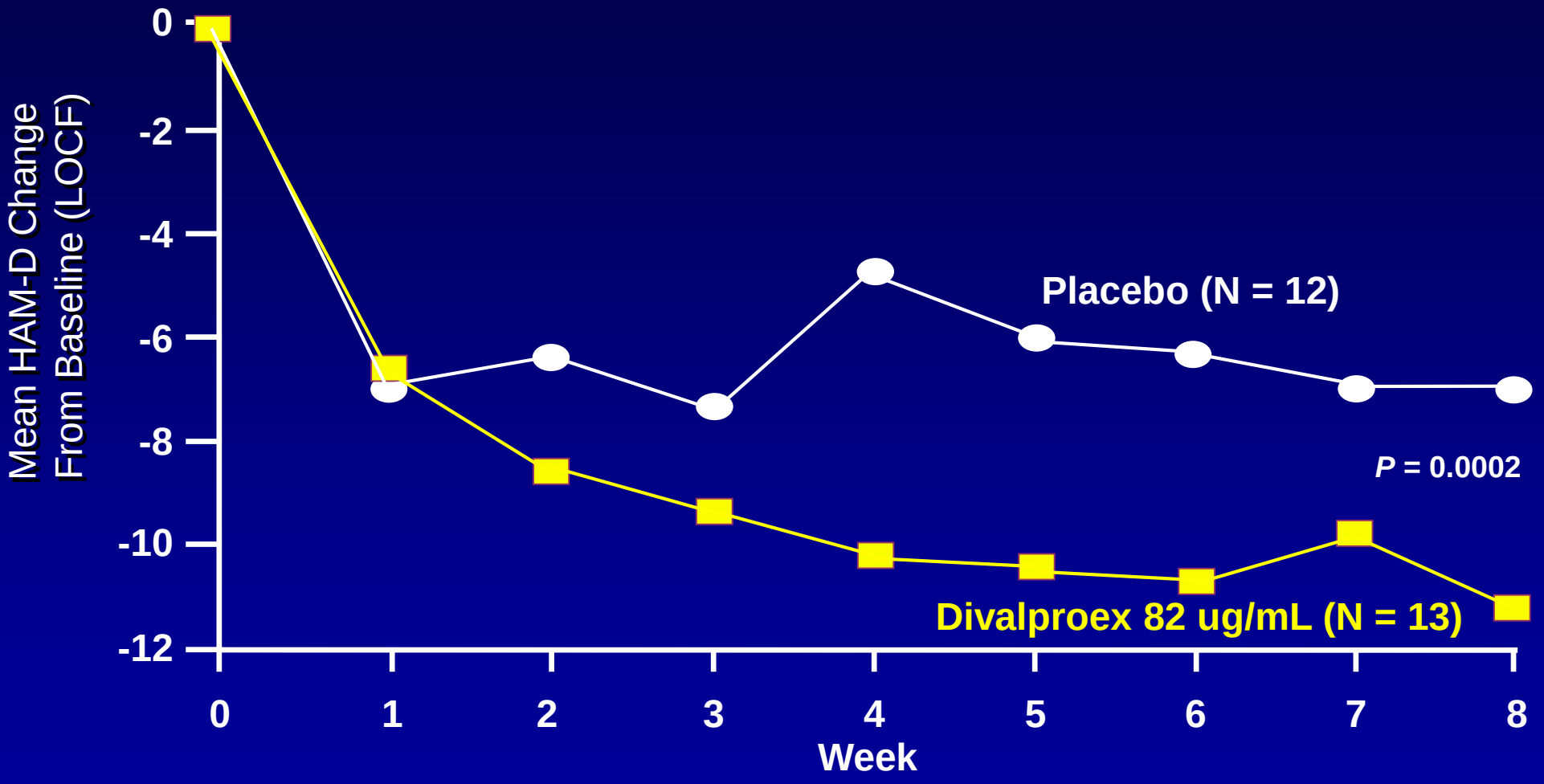
Goodwin et al. JAMA 2003;290:1467-73

8-Week Randomized Double-Blind Divalproex Monotherapy in Acute Bipolar Depression



Sachs G, et al. 40th Ann ACNP Mtg, December 9-13, 2001, Waikaloa, HI.

8-Week Randomized Double-Blind Divalproex Monotherapy in Acute Bipolar Depression

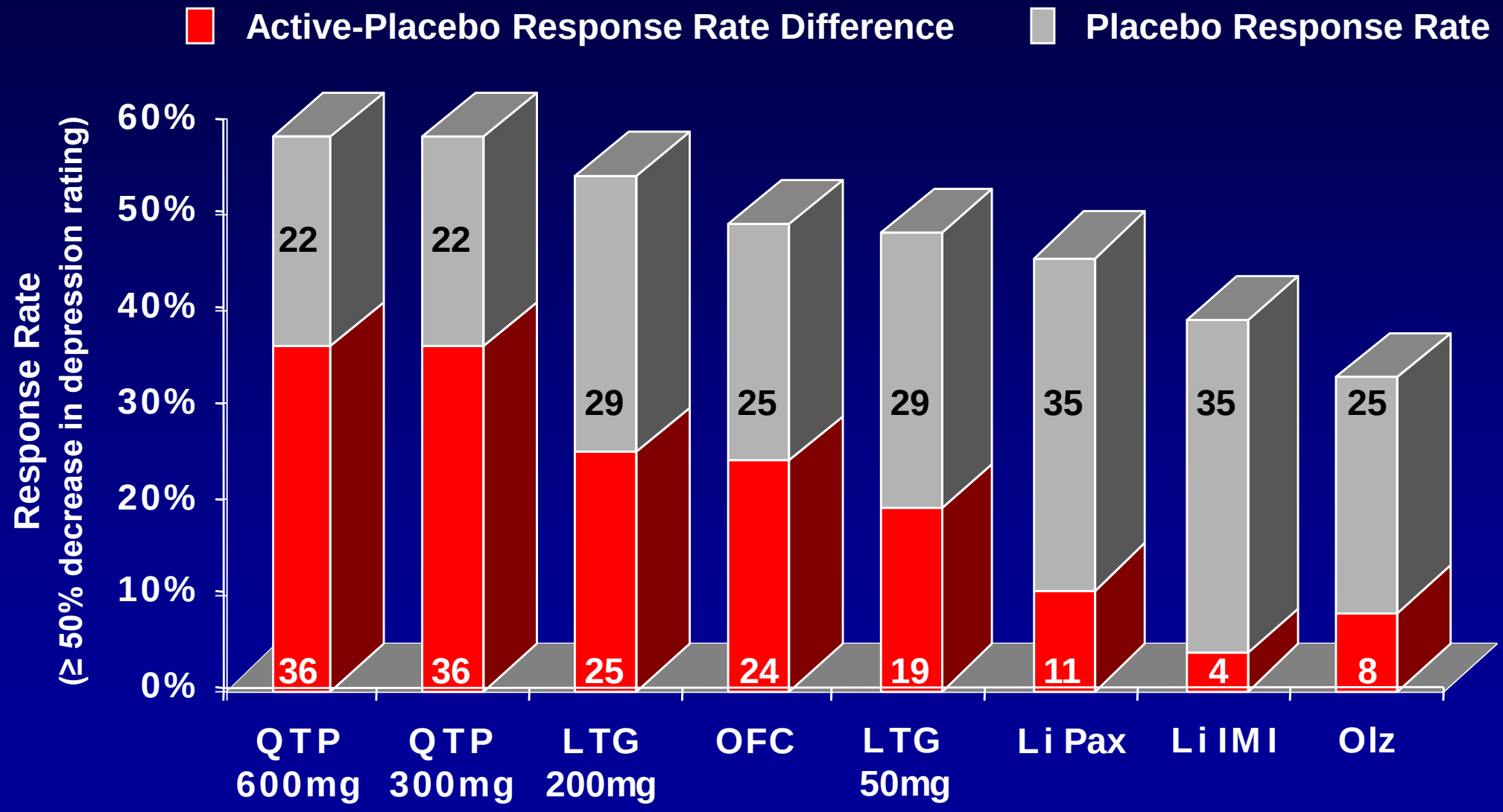


Baseline HAM-D: Placebo, 19.9; Divalproex 22.0. Last observation carried forward.

Davis LL, et al. J Affective Disord 2005;85:259-66.

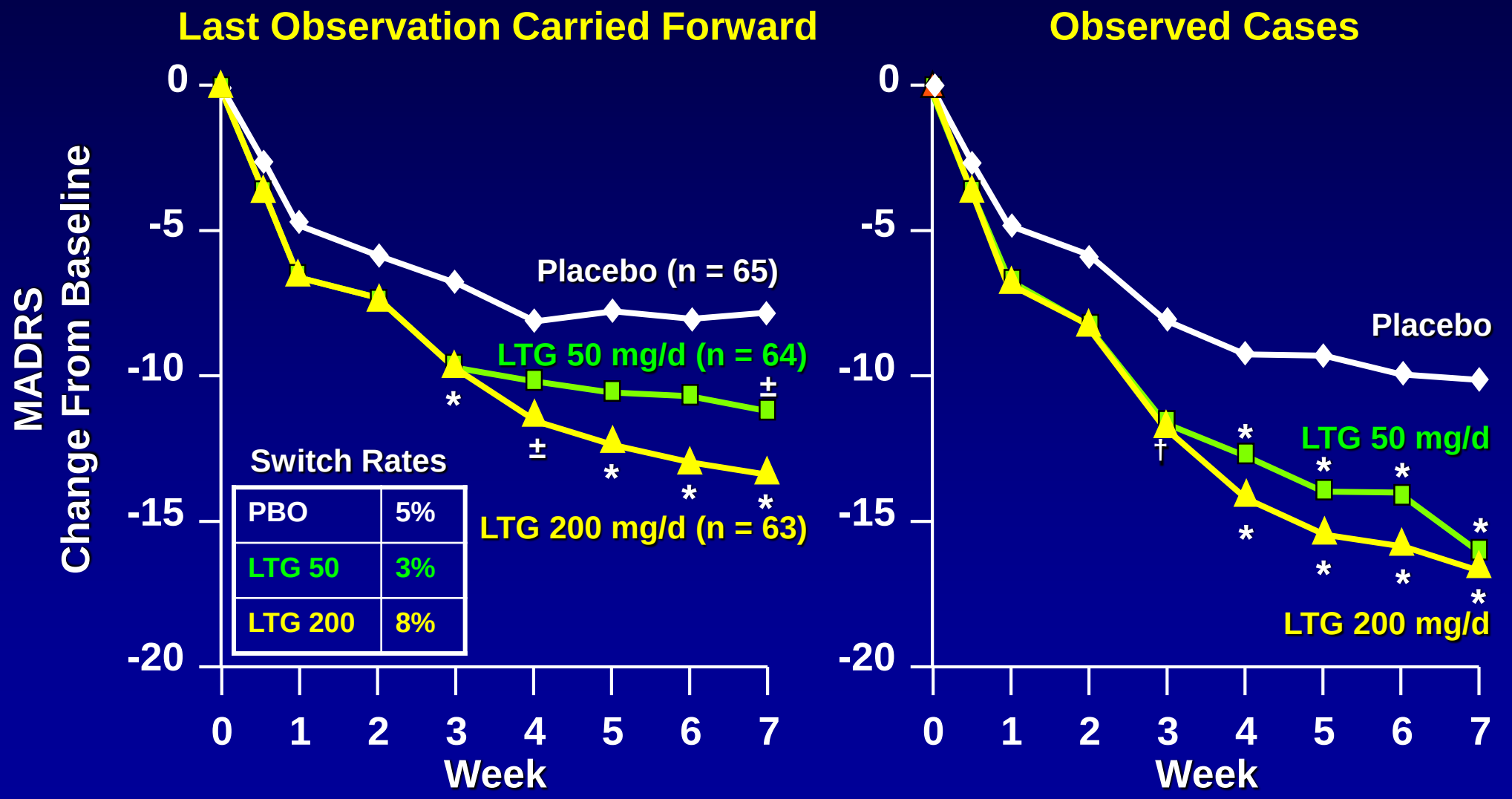
Summary of 4 Acute Bipolar Depression Studies

Response Rates



Sachs GS. In Ketter TA (ed). Advances in the Treatment of Bipolar Disorders. Am Psychiatric Press, Inc. 2005.

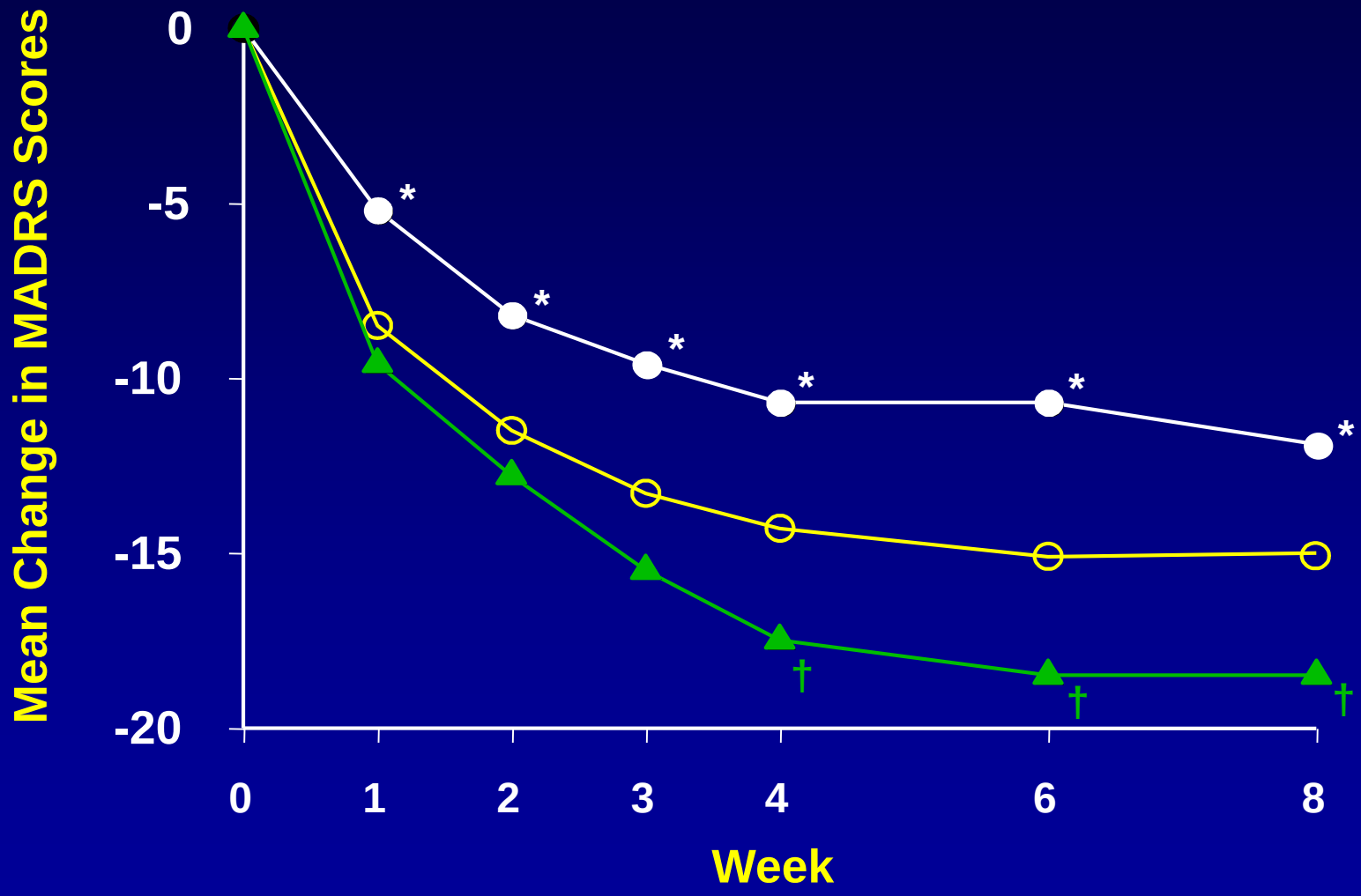
7-Week Randomized Double-Blind Lamotrigine Monotherapy in Acute Bipolar I Depression



± P<0.1; † * P<0.05.

Calabrese et al. J Clin Psychiatry. 1999;60:79-88.

8-Week Randomized Double-Blind Olanzapine ± Fluoxetine in Acute Bipolar I Depression



Switch Rates

PBO	7%
OLZ	6%
OFC	6%

PBO (N = 355)

OLZ 9.7 mg (N = 351)

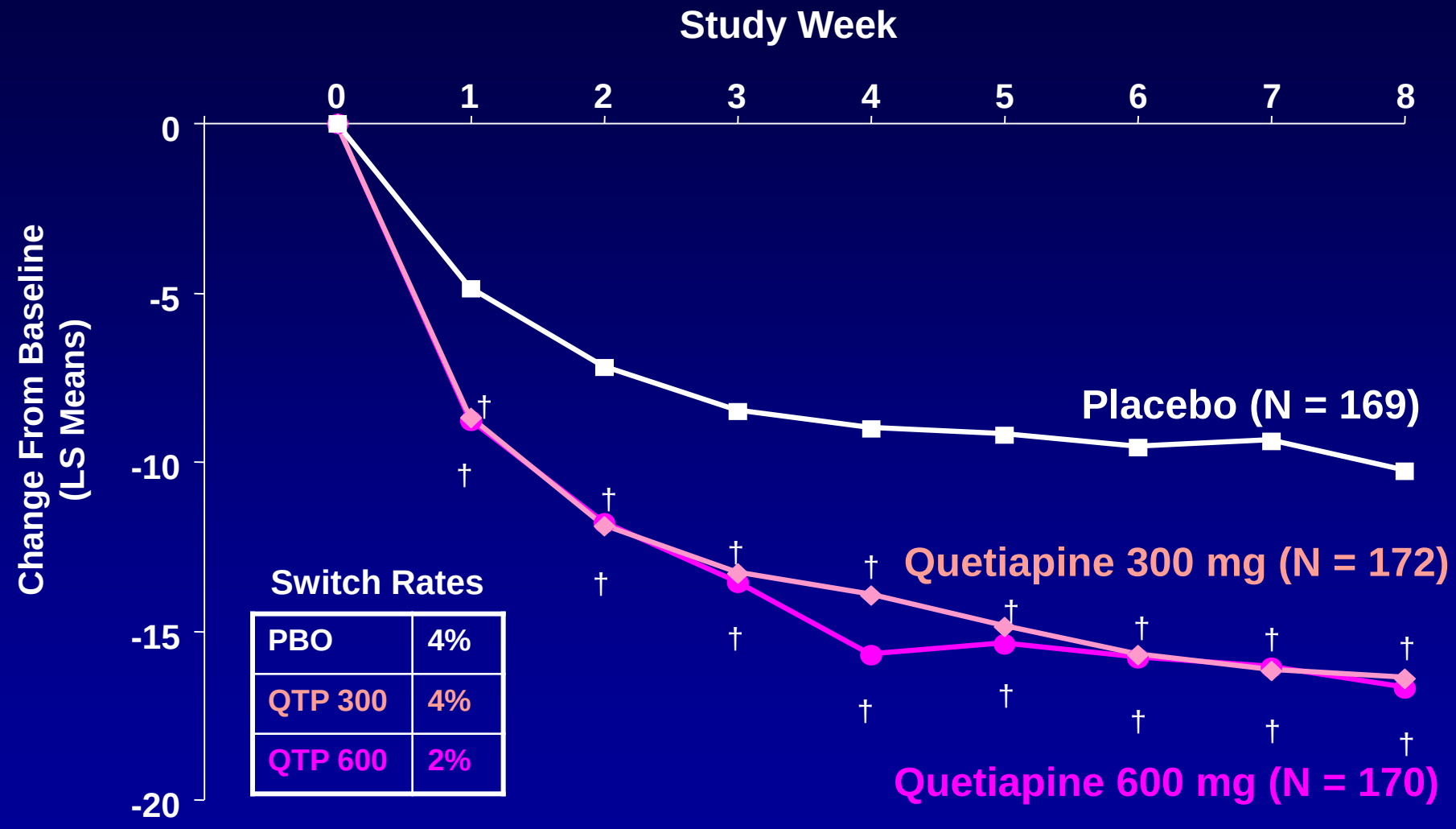
OLZ 7.4 mg + FLX 39.3 mg (N = 82)

Baseline MADRS 31.3 PBO, 32.6 OLZ, 30.8 OLZ+FLX.

* *P* < 0.05 vs OLN, OLN+FLX. † *P* < 0.05 vs OLN.

Tohen M, et al. Arch Gen Psychiatry 2003;60:1079-88.

8-Week Randomized Double-Blind Quetiapine Monotherapy in Acute Bipolar Depression

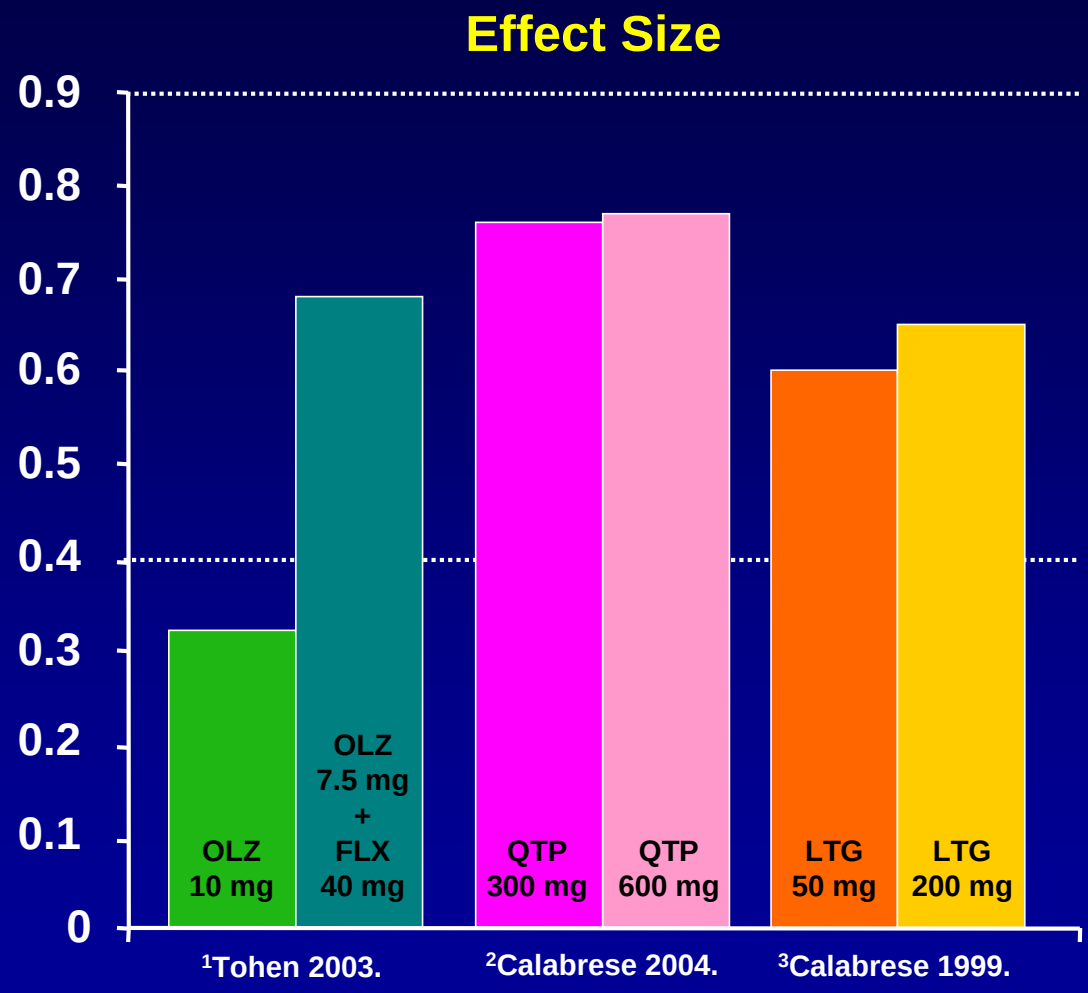


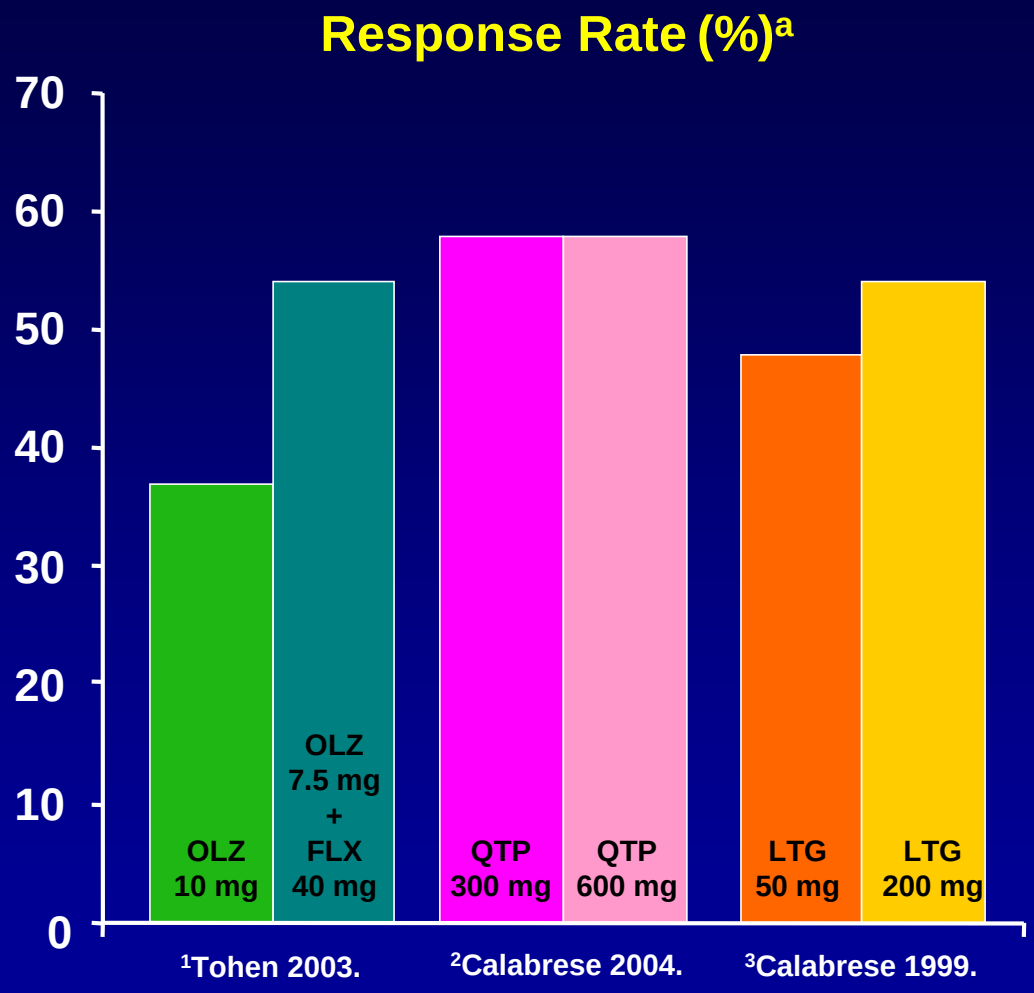
Baseline MADRS 30.3 PBO, 30.4 QTP 300, 30.6 QTP 600.
†$P<0.001$ (quetiapine vs placebo)

ITT, LOCF

Calabrese JR, et al. Am J Psychiatry 2005;162:1351-60.

Magnitudes of Effects in Controlled Trials in Acute Bipolar I Depression

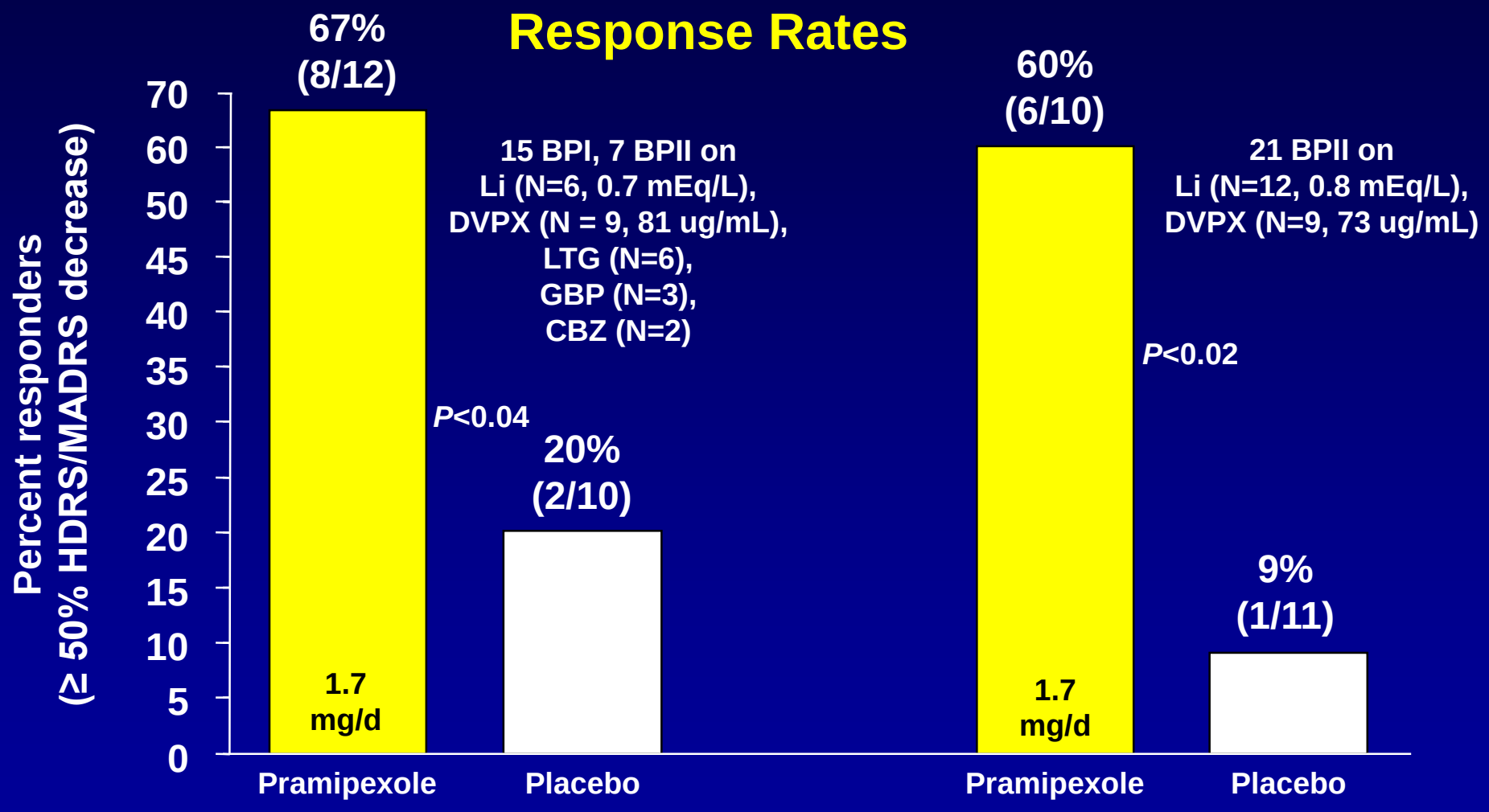




Effect Size (ES) = (improvement over PBO) / (pooled SD)(small ≤0.4; mod 0.5-0.9; large >1.0). [a] >50% MADRS decrease

[1]Tohen M, et al. *Arch Gen Psychiatry* 2003;60:1079-1088; [2]Calabrese JR, et al. 157th APA Annual Meeting, May 1-6, 2004, New York, NY. Abstract NR756. Page 284; [3]Calabrese JR, et al. *J Clin Psychiatry* 1999;60:79-88.

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

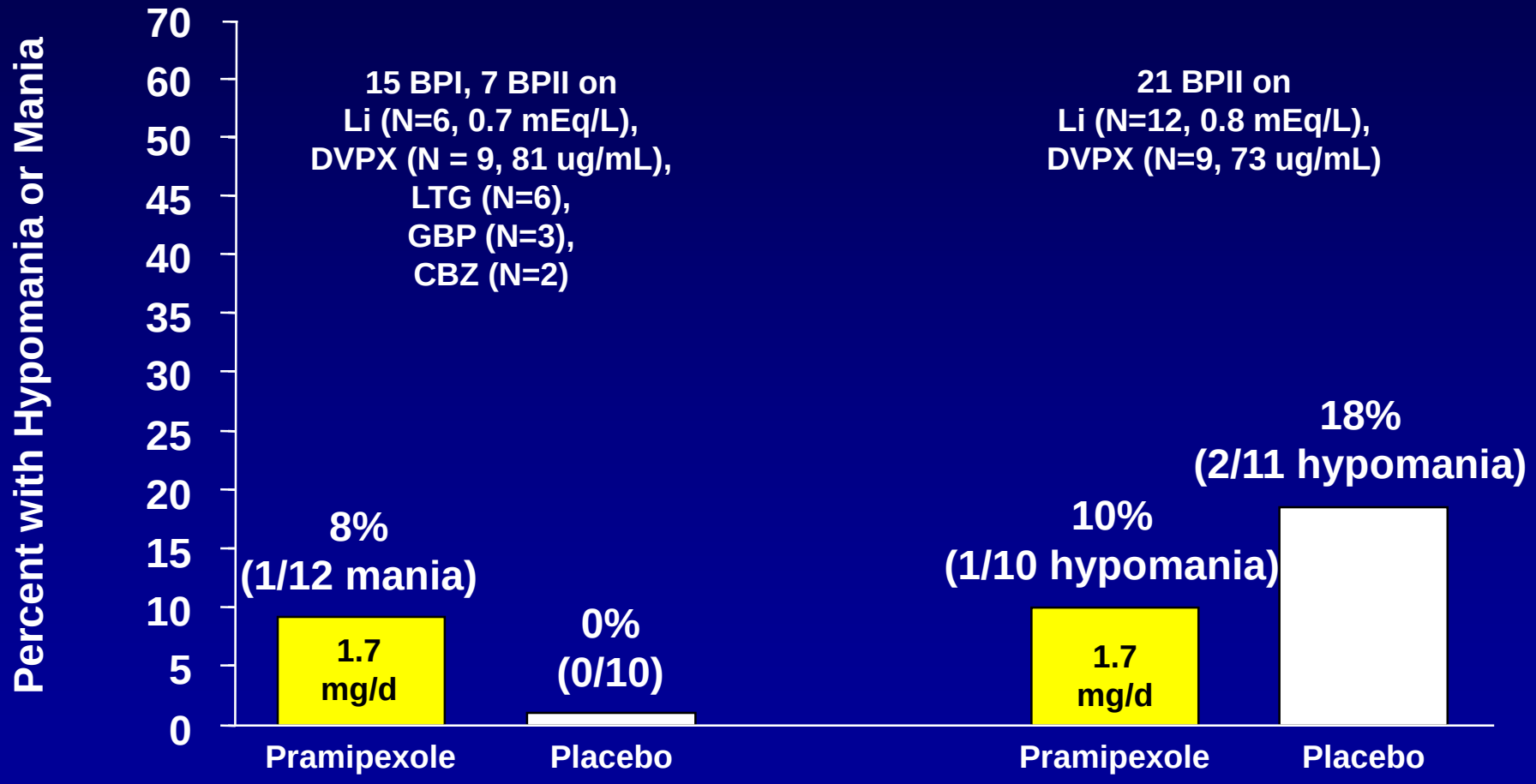


Goldberg JF, et al.
Am J Psychiatry 2004; 161:564-6

Zarate CA, et al.
Biol Psychiatry 2004; 56:54-60.

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

Switch Rates

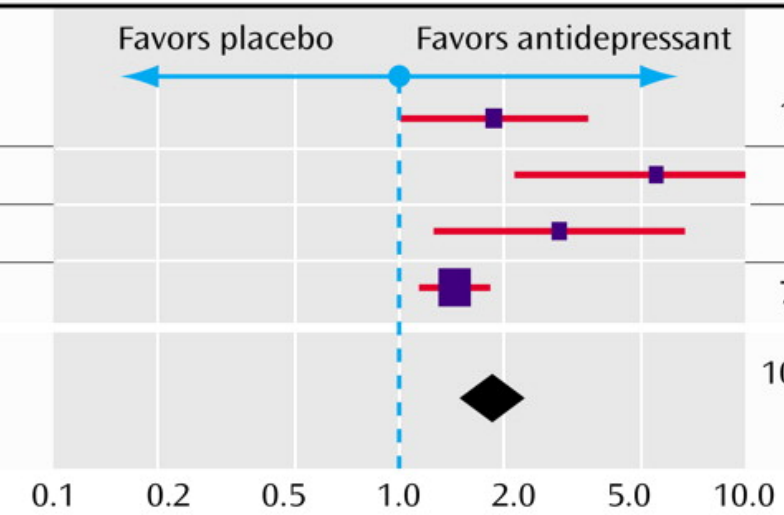


Goldberg JF, et al.
Am J Psychiatry 2004; 161:564-6

Zarate CA, et al.
Biol Psychiatry 2004; 56:54-60.

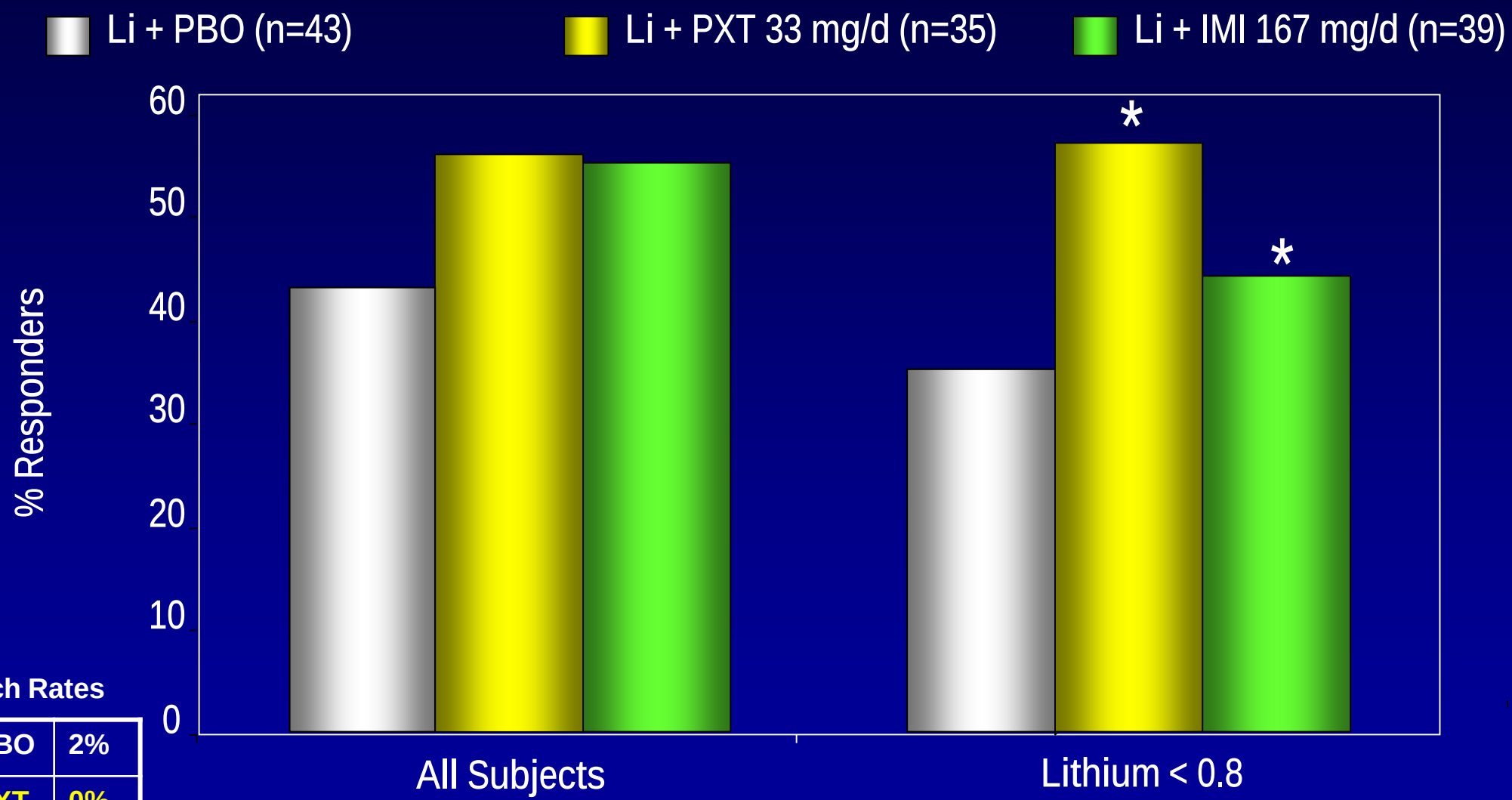
Response in Randomized Controlled Trials of Antidepressants vs. Placebo in Bipolar Depression

Study/ Subcategory	Antidepressant N of Subgroup/ Total N	Placebo N of Subgroup/ Total N	Weight (%)	Risk Ratio (fixed)	95% CI
Mendlewicz et al. 1980 (33)	27/39	7/19	13.14	1.88	1.01–3.51
Himmelhoch et al. 1982 (32)	20/28	4/31	5.30	5.54	2.15–14.23
Cohn et al. 1989 (31)	30/60	5/29	9.41	2.90	1.26–6.69
Tohen et al. 2004 (29)	46/86	137/370	72.14	1.44	1.14–1.83
Total (95% CI)[a]	213	449	100.00	1.86	1.49–2.30
Total events	123	153			



Gijsman et al, *American Journal of Psychiatry*. 2004;161:1537-1547.

Paroxetine, Imipramine, Placebo Added to Lithium in Bipolar Depression



Switch Rates

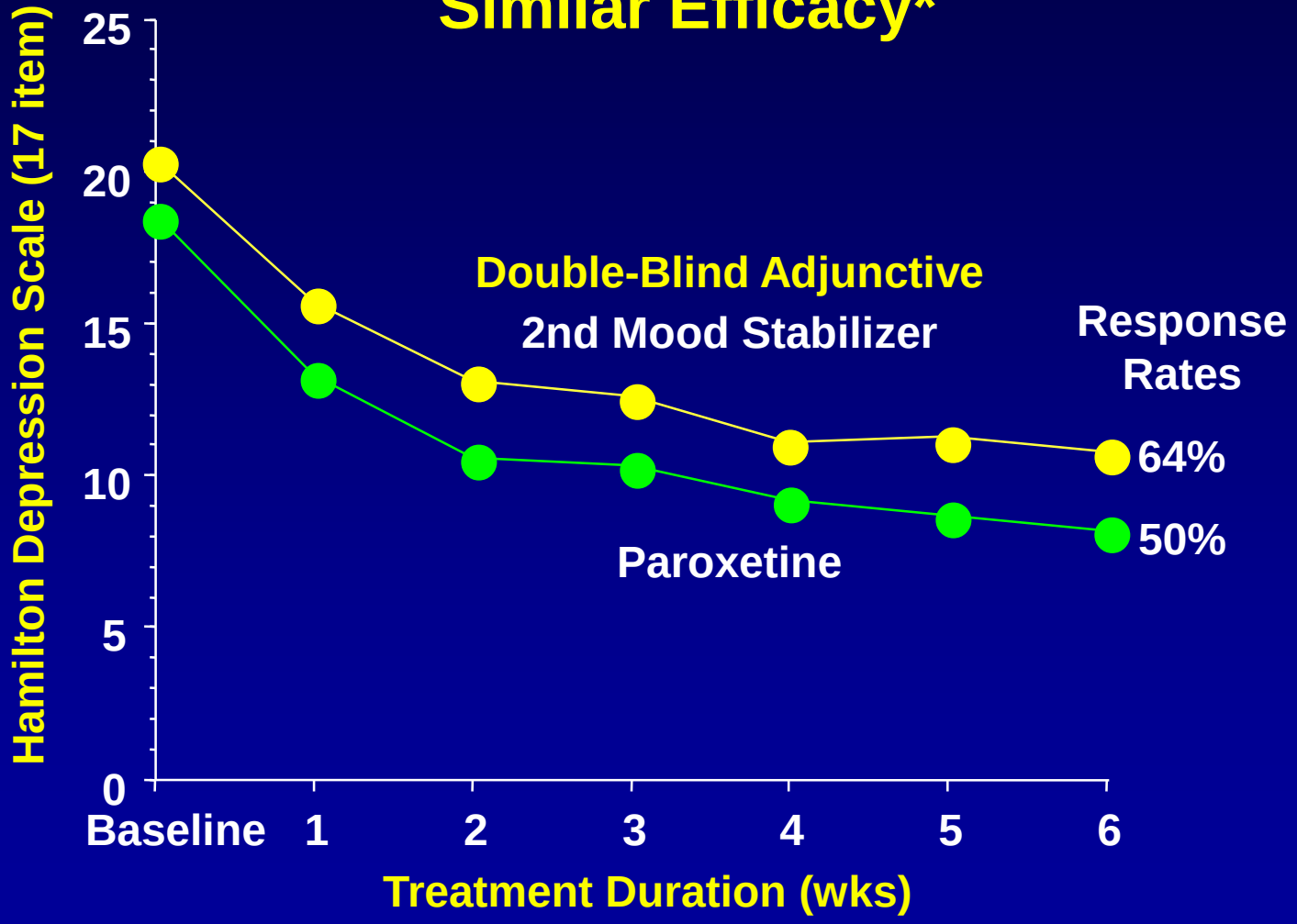
Li + PBO	2%
Li + PXT	0%
Li + IMI	8%

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

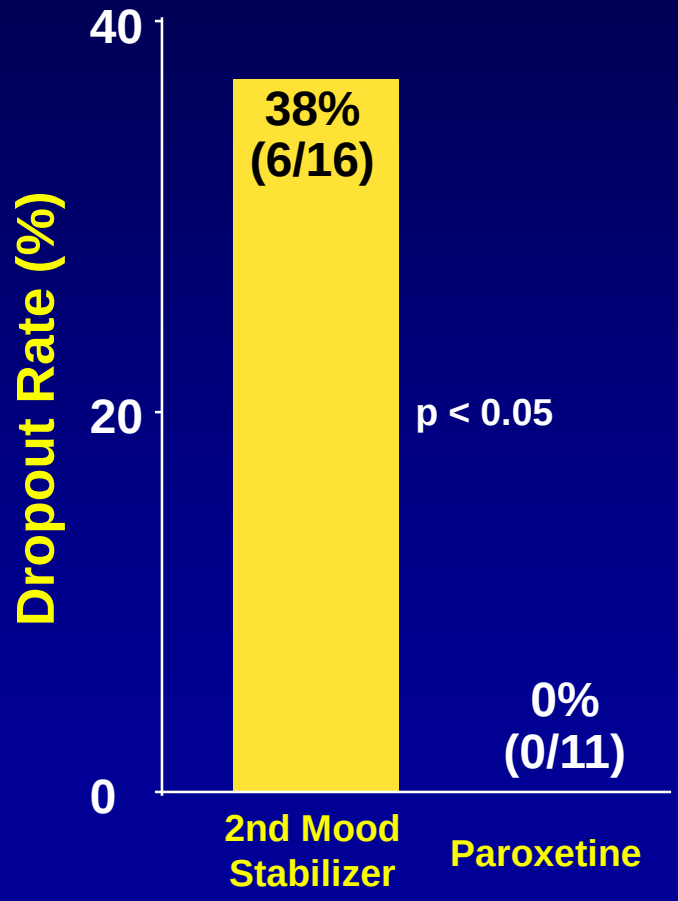
*p < 0.05

Adjunctive Paroxetine vs Second Mood Stabilizer in Bipolar Depression

Similar Efficacy*



Better Tolerability



*Last Observation Carried Forward Analysis

Young, et al. Am J Psychiatry 2000;157:124-6.

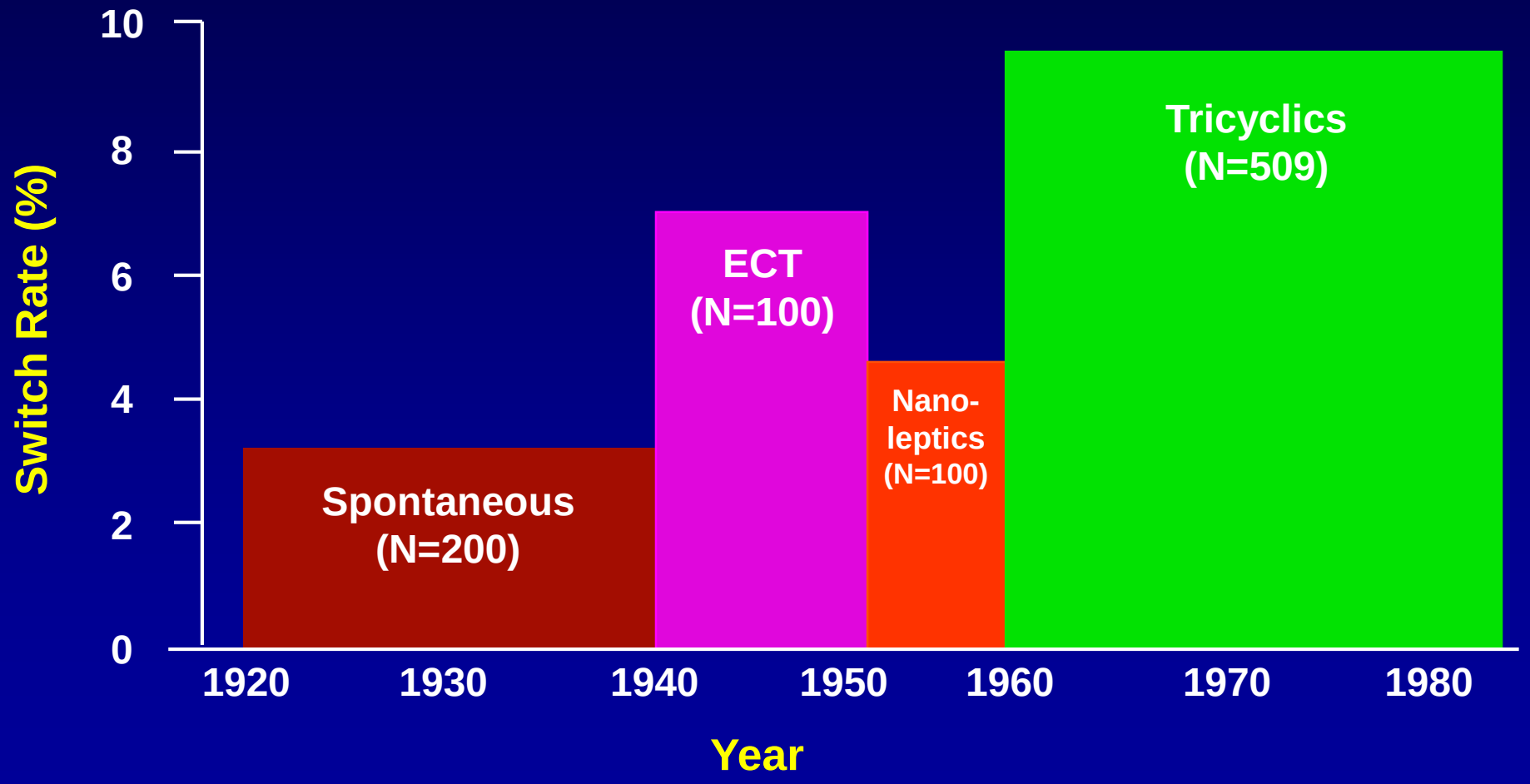
Do Antidepressants Induce Mania?

- 41% Natural switch rate depression to mania (on no antidepressants) [1]
- Switch rate on medications [2]
  - 53% Imipramine
  - 28% Lithium plus imipramine
  - 26% Lithium

Lewis JL, Winokur G. Arch Gen Psychiatry 1982[1]; Prien RF, et al. Arch Gen Psychiatry 1984.

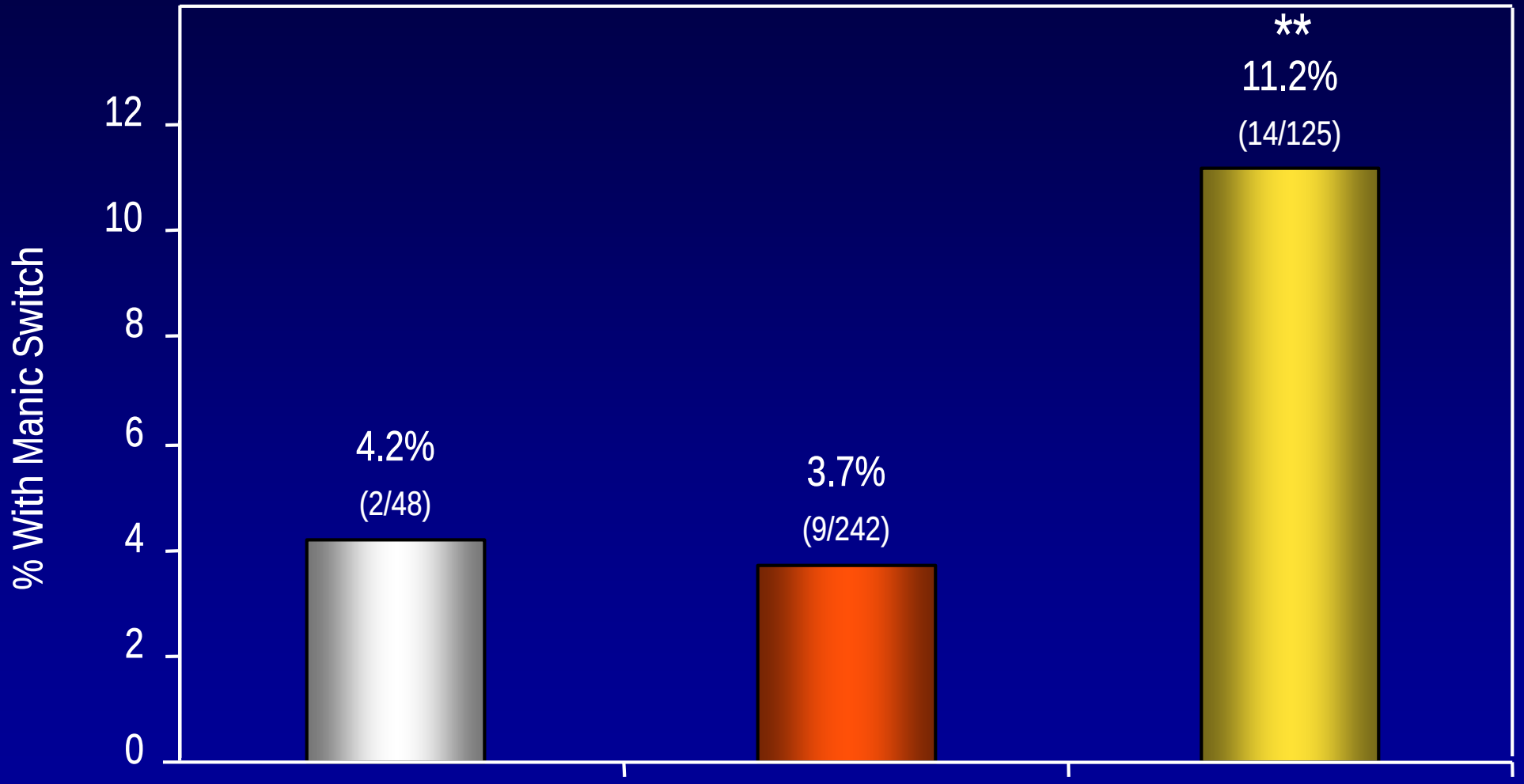
Switch Rate From Index Depression Into Mania

By Era and Prevailing Treatment



Angst J. Psychopathology 1985.

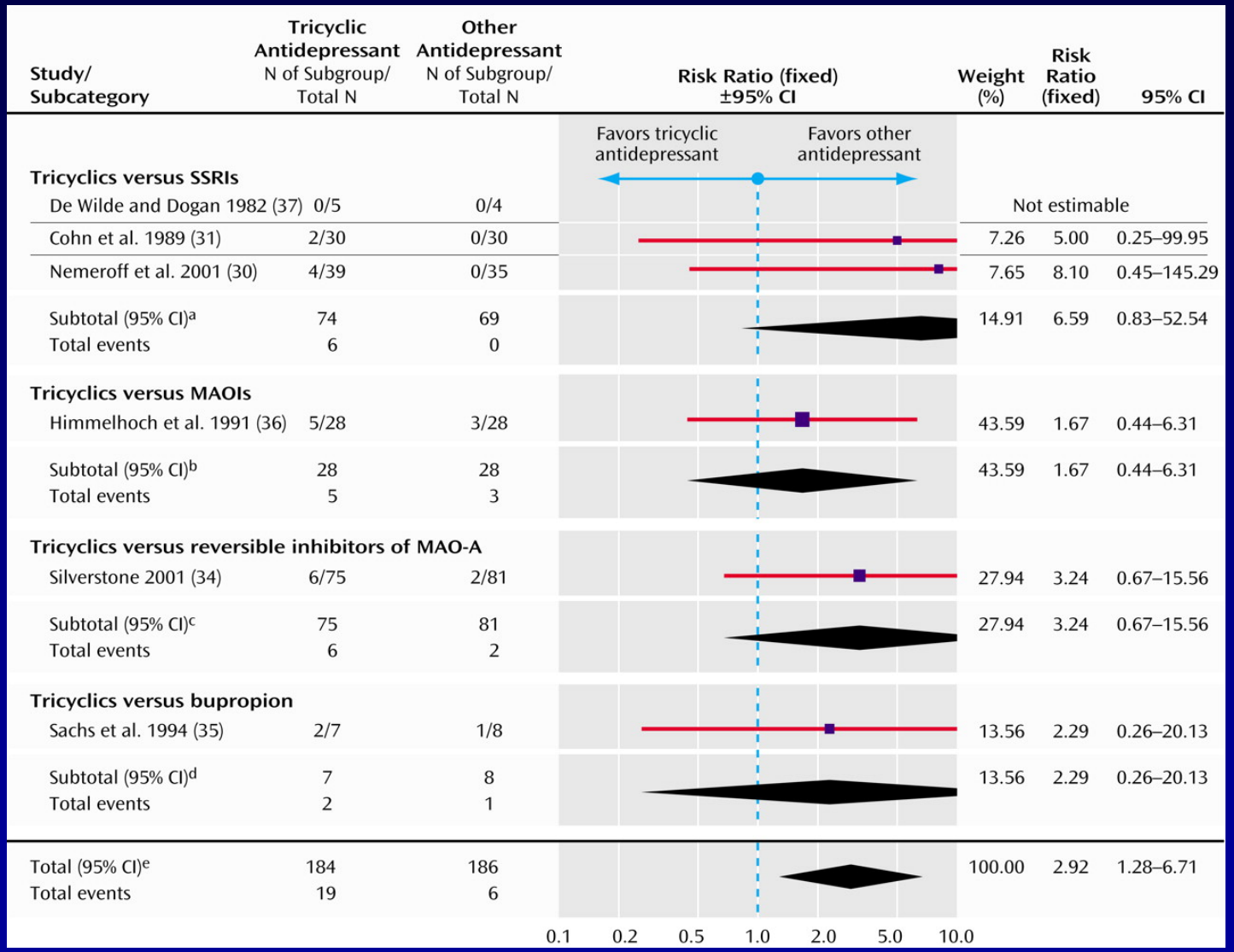
Increased Mania Switch Rates with Tricyclics



** p < 0.01 vs PBO

Peet M. Br J Psychiatry. 1994;164:549-550.

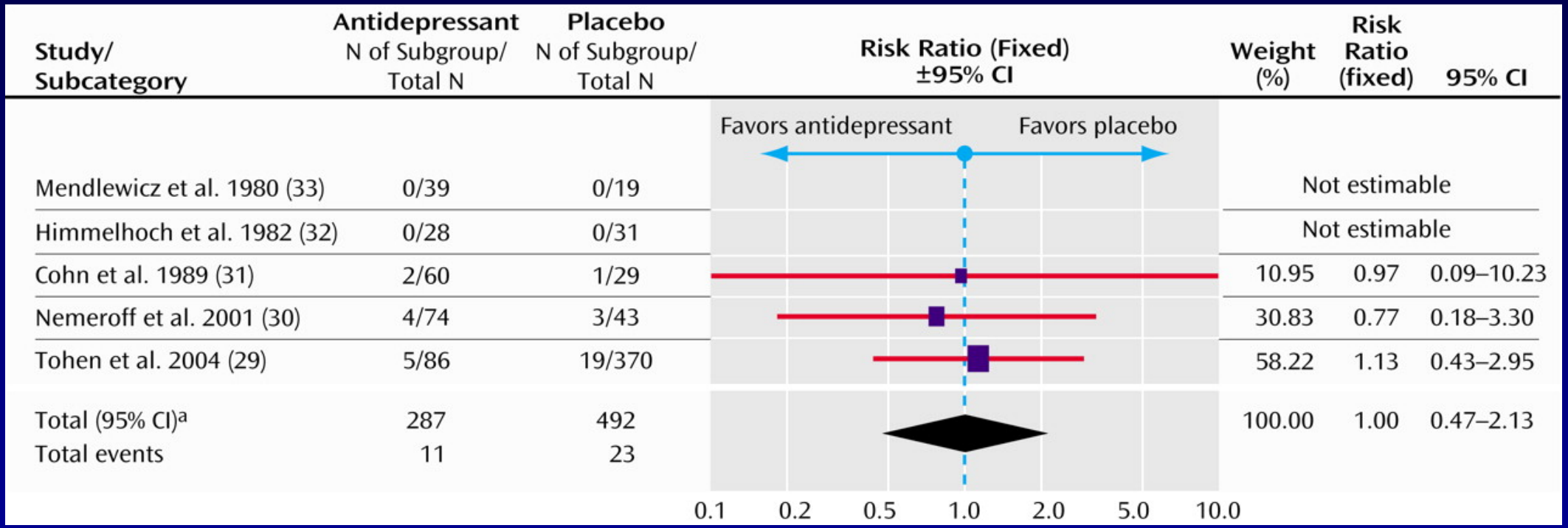
Switch Rates With Tricyclic vs. Other Antidepressants



Study/ Subcategory	Tricyclic Antidepressant N of Subgroup/ Total N	Other Antidepressant N of Subgroup/ Total N	Weight (%)	Risk Ratio (fixed)	95% CI
Tricyclics versus SSRIs					
De Wilde and Dogan 1982 (37)	0/5	0/4	Not estimable		
Cohn et al. 1989 (31)	2/30	0/30	7.26	5.00	0.25–99.95
Nemeroff et al. 2001 (30)	4/39	0/35	7.65	8.10	0.45–145.29
Subtotal (95% CI)[a]	74	69	14.91	6.59	0.83–52.54
Total events	6	0			
Tricyclics versus MAOIs					
Himmelhoch et al. 1991 (36)	5/28	3/28	43.59	1.67	0.44–6.31
Subtotal (95% CI)[b]	28	28	43.59	1.67	0.44–6.31
Total events	5	3			
Tricyclics versus reversible inhibitors of MAO-A					
Silverstone 2001 (34)	6/75	2/81	27.94	3.24	0.67–15.56
Subtotal (95% CI)[c]	75	81	27.94	3.24	0.67–15.56
Total events	6	2			
Tricyclics versus bupropion					
Sachs et al. 1994 (35)	2/7	1/8	13.56	2.29	0.26–20.13
Subtotal (95% CI)[d]	7	8	13.56	2.29	0.26–20.13
Total events	2	1			
Total (95% CI)[e]	184	186	100.00	2.92	1.28–6.71
Total events	19	6			

Gijsman et al, *American Journal of Psychiatry*. 2004; 161: 1537-1547

Manic Switch Rates in Randomized Controlled Trials of Antidepressants vs. Placebo



Gijsman et al, *American Journal of Psychiatry*. 2004;161:1537-1547

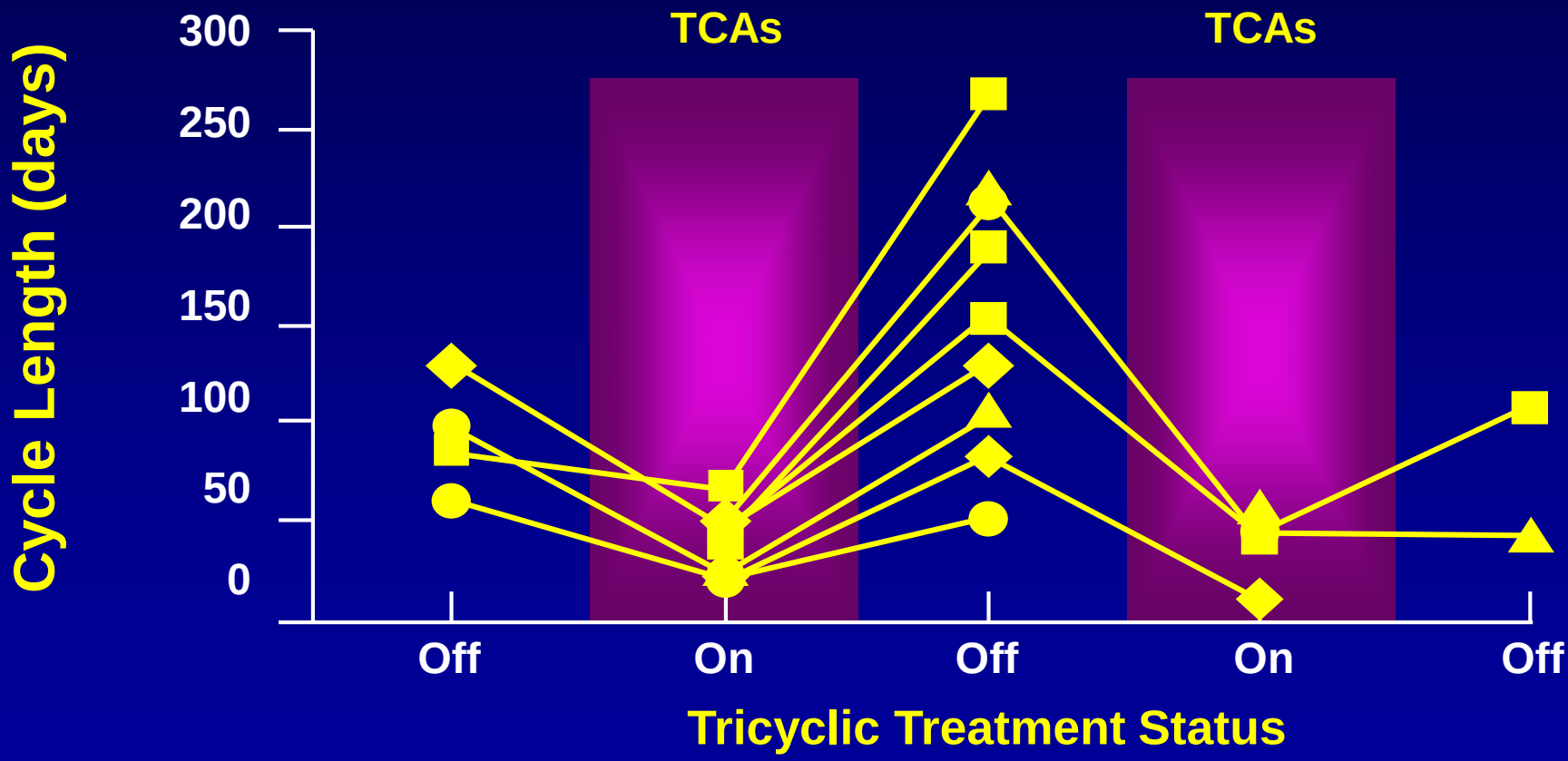
Do Antidepressants Induce Rapid Cycling?

- Increased rapid cycling since TCAs introduced [1]
- Mania rates over 2 years [2]
  - 67% Imipramine
  - 33% Placebo
  - 18% Lithium
- Antidepressants induce reversible rapid cycling in double-blind placebo-controlled studies.[3]

Angst J. Psychopathology 1985[1]; Prien RF, et al. Arch Gen Psychiatry 1973[2];
Wehr TA, Goodwin FK. Psychopharmacol Bull 1987[3]

Tricyclics Shorten Cycle Length

10 Bipolar Disorder Patients



Wehr TA, Goodwin FK. Am J Psychiatry 1987.

Acute Bipolar I Depression Algorithm

- **Stage 2: If Stage 1 ineffective or not tolerated***
  - **QTP monotherapy or OFC**
    - **Although onset of action faster than LTG, overall efficacy and long-term tolerability evidence favors LTG (at Stage 1)**
- **Stage 3: If Stages 1 and 2 ineffective or not tolerated***
  - **Combination of two agents already introduced in algorithm**
    - **Li, LTG, QTP, and OFC combination**
    - **OFC a two-drug combination, so adding another agent yields three-drug combination**

Number of iterations at each level and adjunctive treatment(s) to be determined by clinician judgment

Suppes T, et al. J Clin Psychiatry 2005;66:870-86.

Acute Bipolar I Depression Algorithm

- **Stage 4: If Stages 1, 2, and 3 ineffective or not tolerated***
  - **ECT and combination therapy (Li, LTG, QTP, OFC combination, VPA or CBZ in combined with SSRI, bupropion, or venlafaxine)**
  - **Minority opinion that Stage 4 should precede Stages 2 and 3**
- **Stage 5: If Stages 1, 2, 3, and 4 ineffective or not tolerated***
  - **MAO-I, other atypical antipsychotics not included, pramipexole, new combinations of drugs included in the algorithm, inositol, stimulants, and thyroid supplementation**

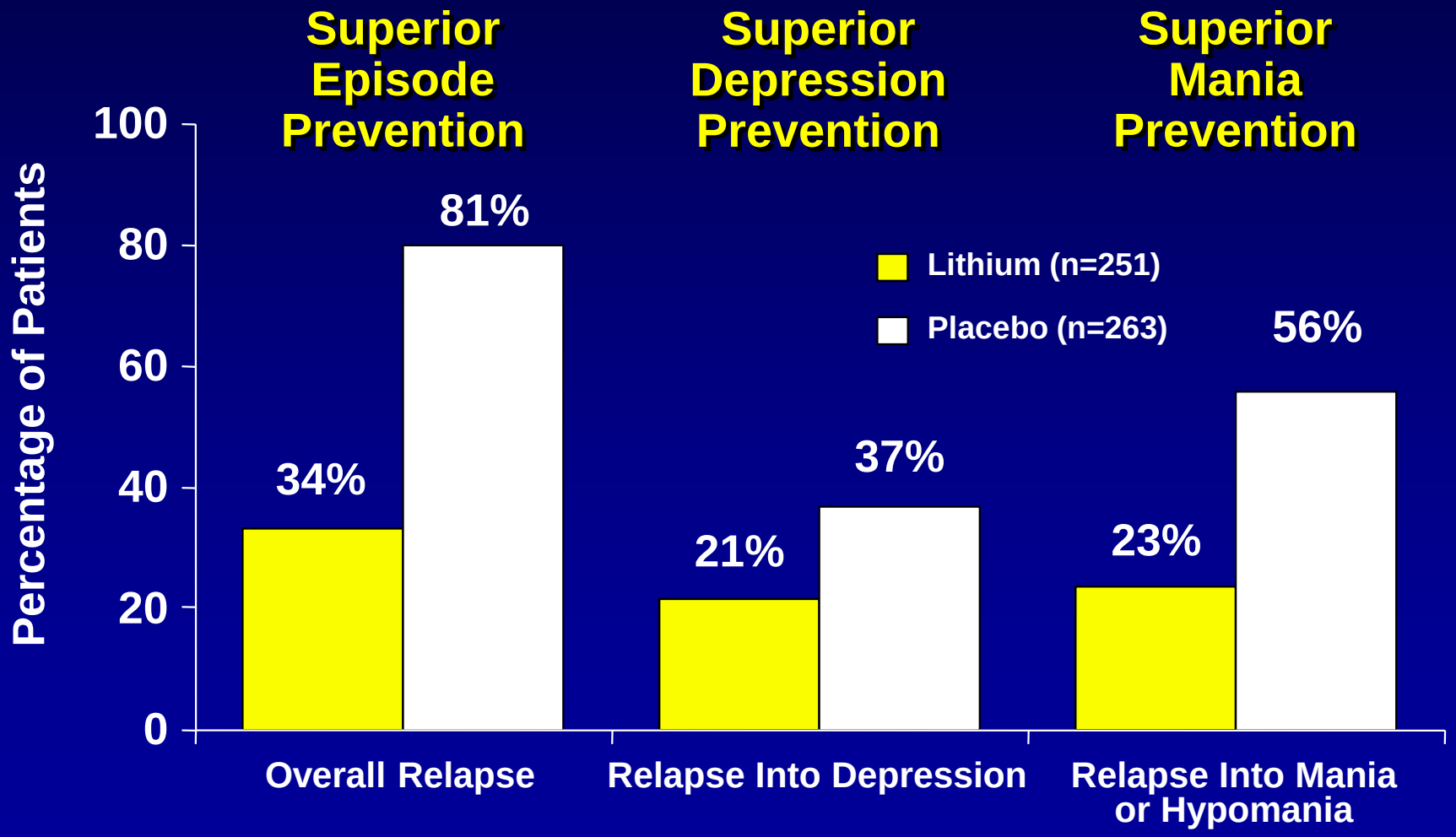
Number of iterations at each level and adjunctive treatment(s) to be determined by clinician judgment

Suppes T, et al. J Clin Psychiatry 2005;66:870-86.

Maintenance Treatment of Bipolar Depression

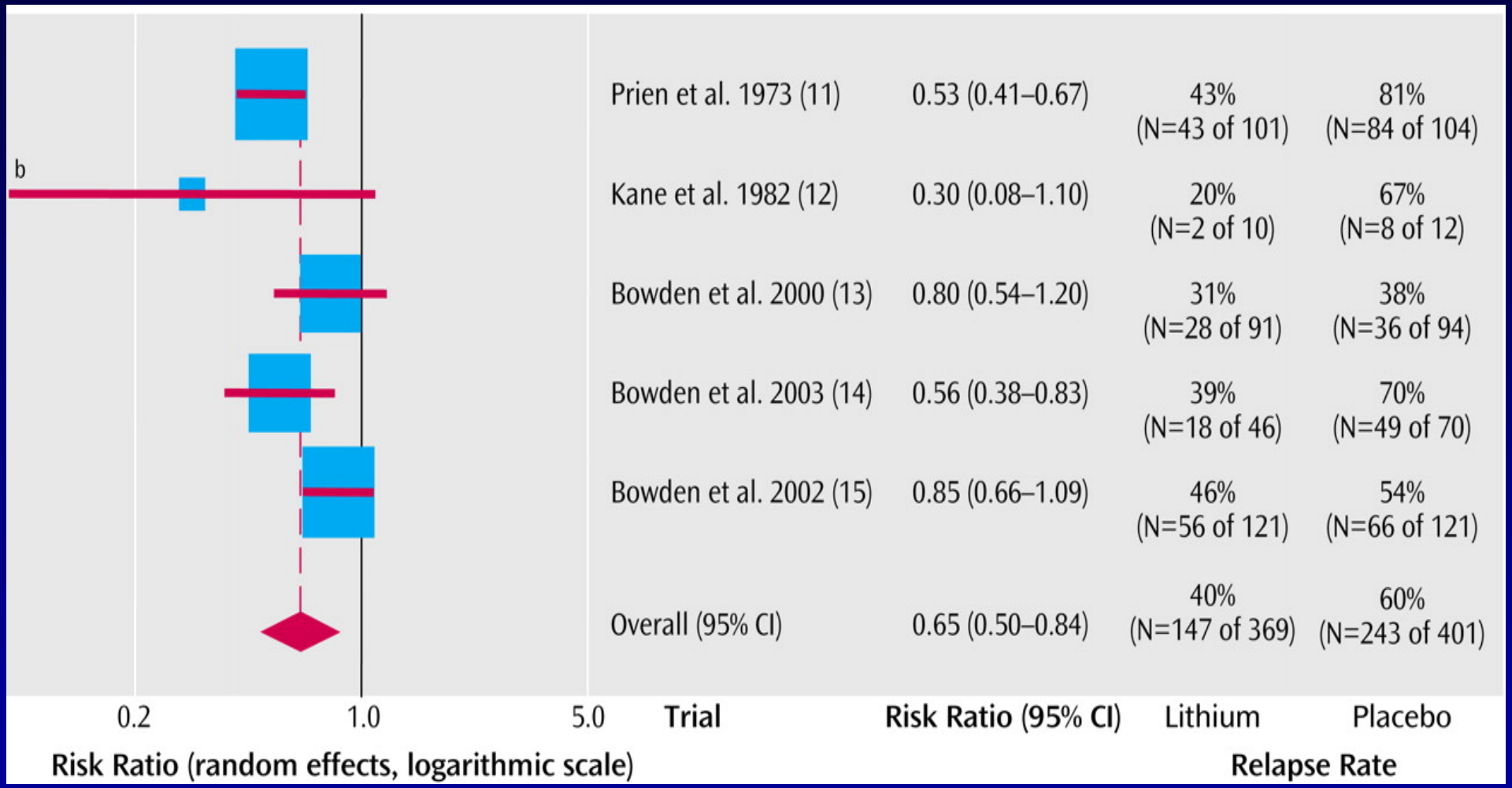
Summary of Double-Blind Lithium Monotherapy vs Placebo Maintenance Trials in 1970s

Lithium Compared to Placebo, Primarily After Manic/Mixed Episodes



Goodwin FK, Jamison KR: Manic-Depressive Illness, Oxford University Press, New York 1990:688-9.

Lithium Prevention of Any Relapse in Bipolar Disorder

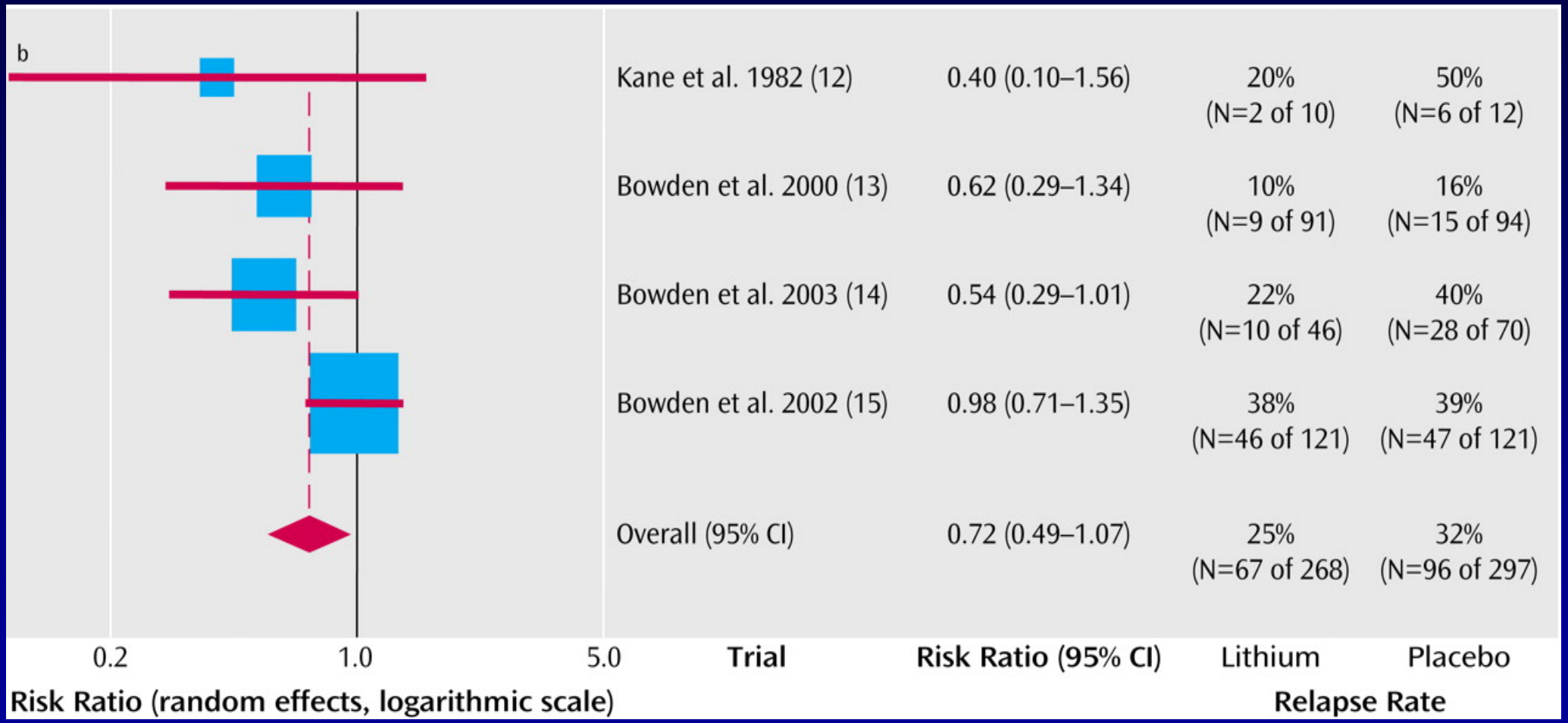


Areas of blue boxes reflect weights of studies in meta-analysis.

[b]Lower confidence interval extends beyond graph (0.08).

Geddes JR et al. *Am J Psychiatry* 2004;161:217-222.

Lithium Prevention of Depressive Relapse in Bipolar Disorder

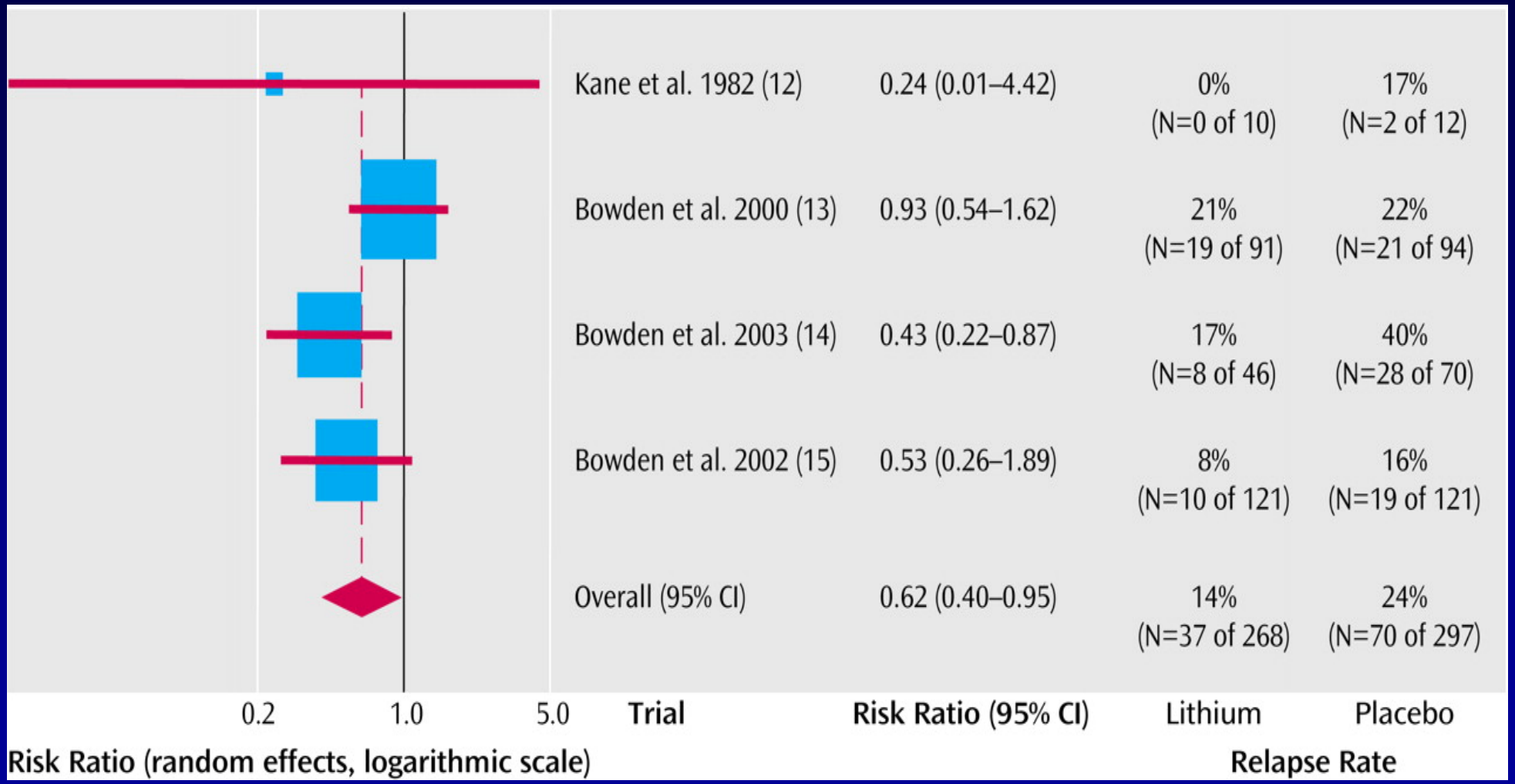


Areas of blue boxes reflect weights of studies in meta-analysis.

[b]Lower confidence interval extends beyond graph (0.10).

Geddes JR et al. *Am J Psychiatry* 2004;161:217-222.

Lithium Prevention of Manic Relapse in Bipolar Disorder



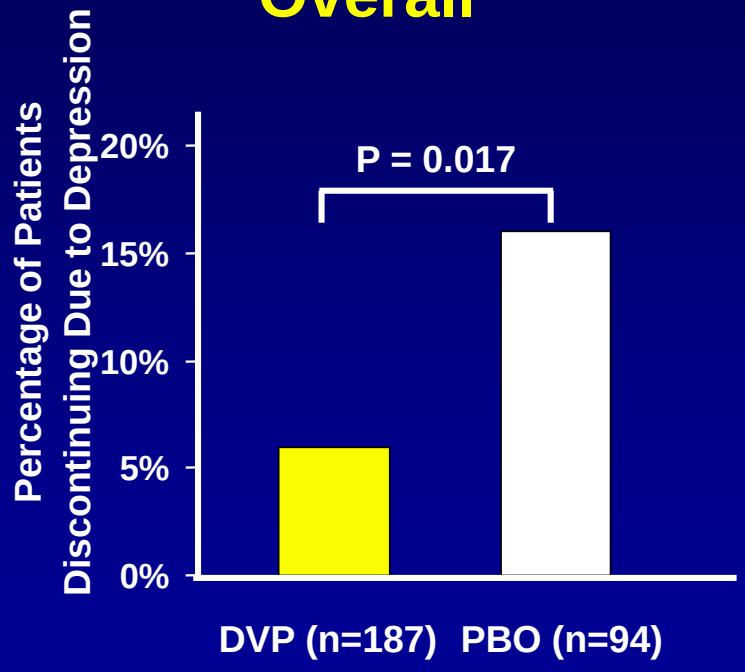
Areas of blue boxes reflect weights of studies in meta-analysis.

Geddes JR et al. *Am J Psychiatry* 2004;161:217-222.

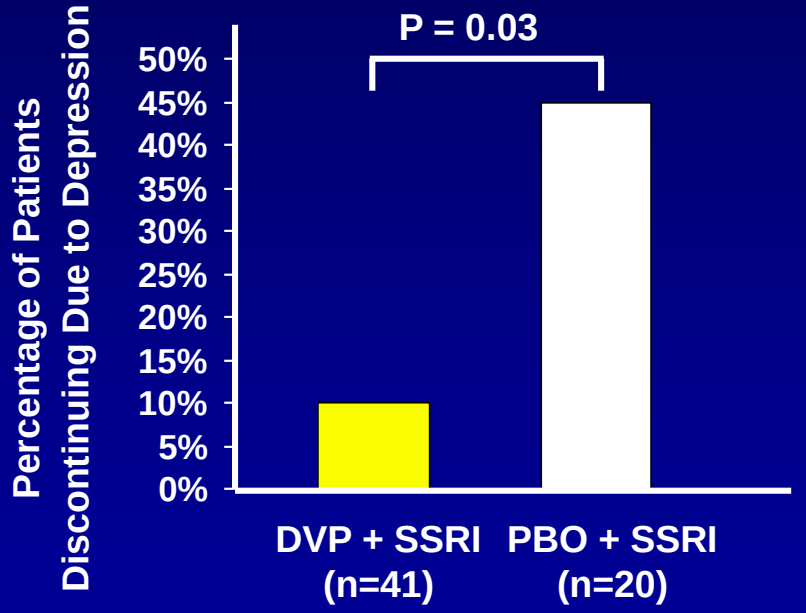
12-Month Double-Blind Divalproex, Lithium Monotherapy vs Placebo Maintenance

Fewer Dropouts Due to Depression with Divalproex vs Placebo After Manic/Mixed Episodes

Overall



Patients Receiving SSRI Rescue



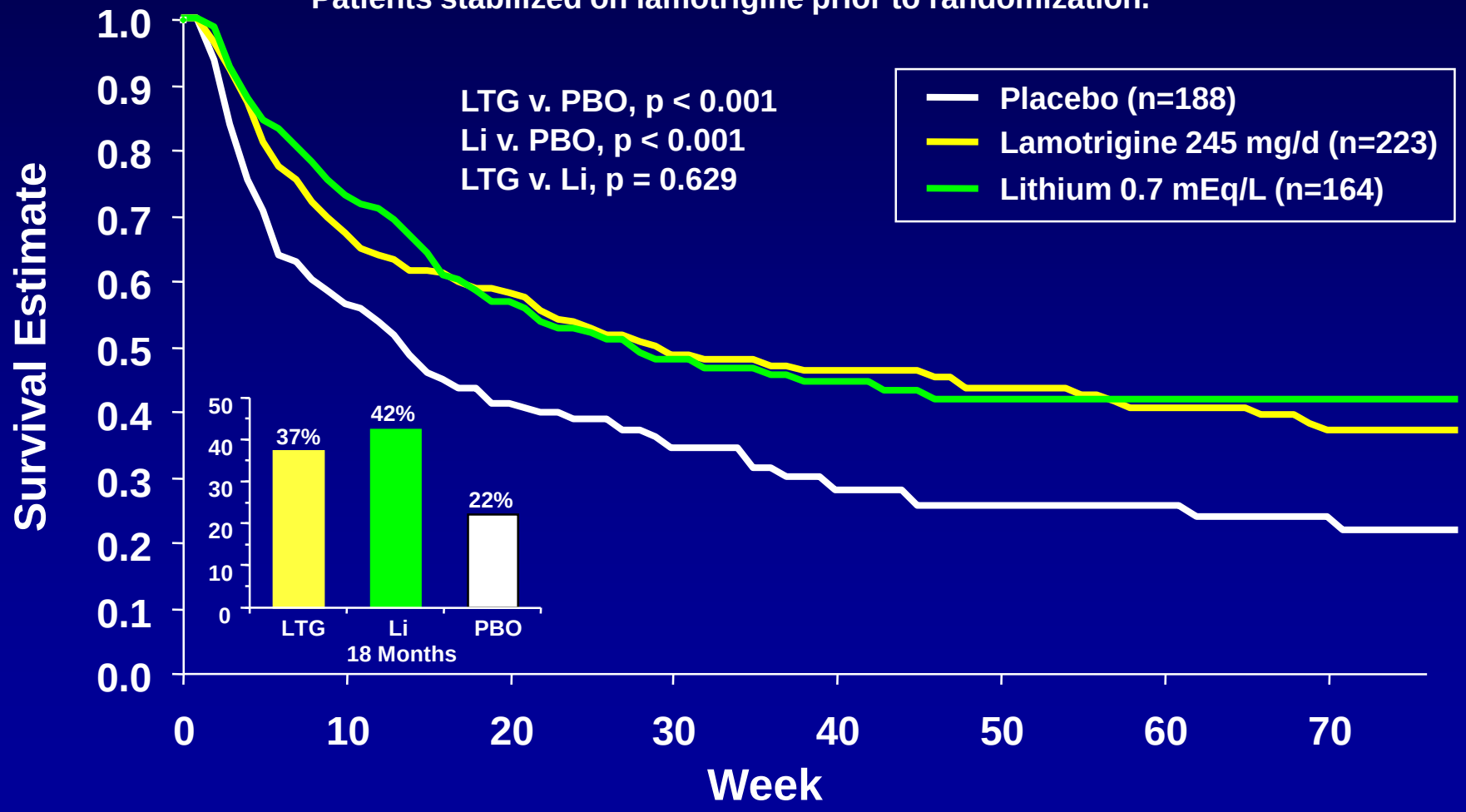
DVP = divalproex PBO = placebo LI = lithium
SSRI = selective serotonin reuptake inhibitor

Gyulai et al. Neuropsychopharmacol 2003;28:1374-82.

Lamotrigine and Lithium Effective in Bipolar I Prophylaxis

Time to Intervention for Any Episode (pooled recently manic/dep pts)

Patients stabilized on lamotrigine prior to randomization.

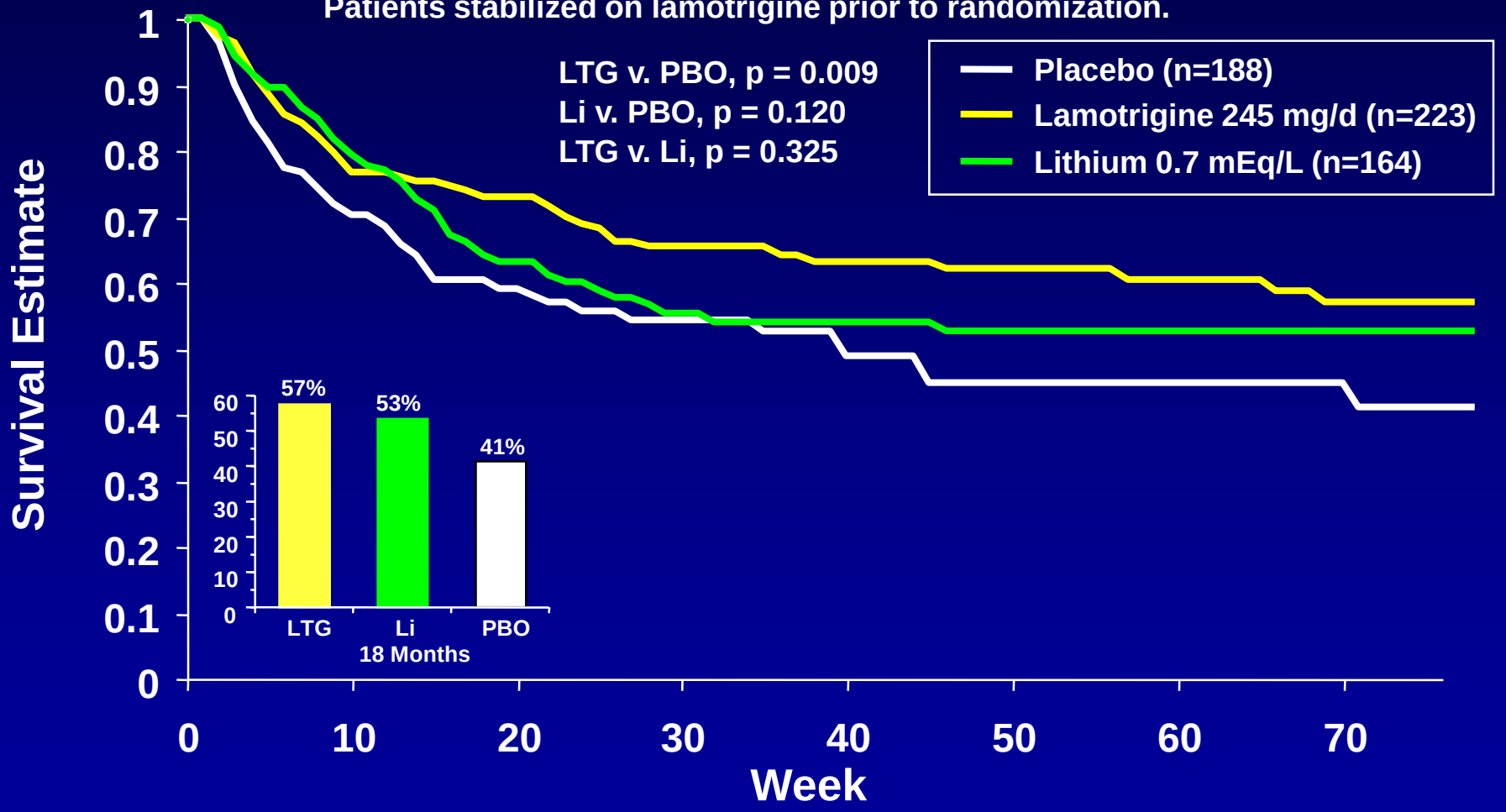


Goodwin GM, et al. J Clin Psychiatry 2004;65:432-41.

Lamotrigine Effective in Bipolar I Depression Prophylaxis

Time to Intervention for Depression (pooled recently manic/dep pts)

Patients stabilized on lamotrigine prior to randomization.

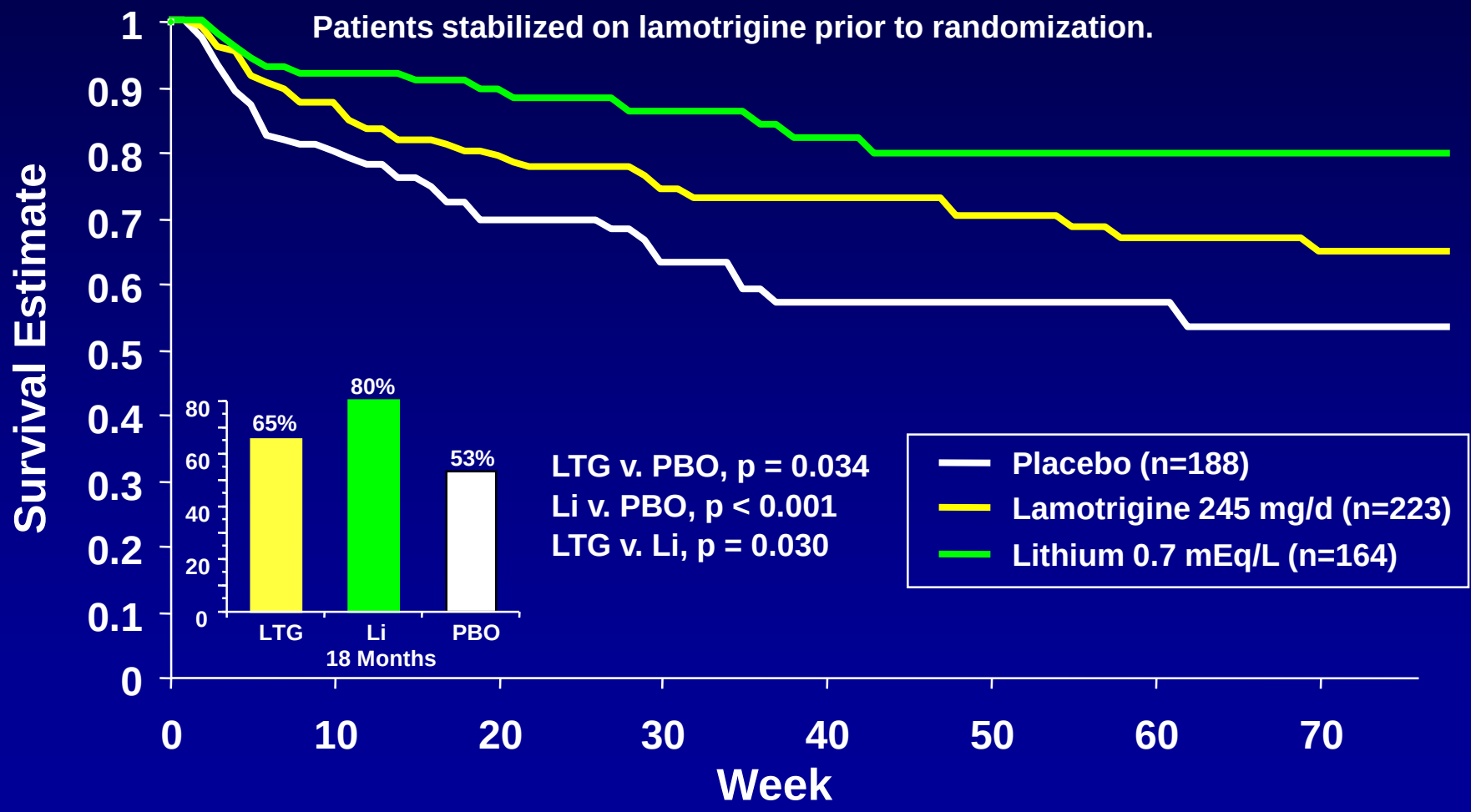


Some patients considered intervention-free for depression could have had intervention for mania.

Goodwin GM, et al. J Clin Psychiatry 2004;65:432-41.

Lamotrigine and Lithium Effective in Bipolar I Mania Prophylaxis

Time to Intervention for Mania (pooled recently manic/dep pts)



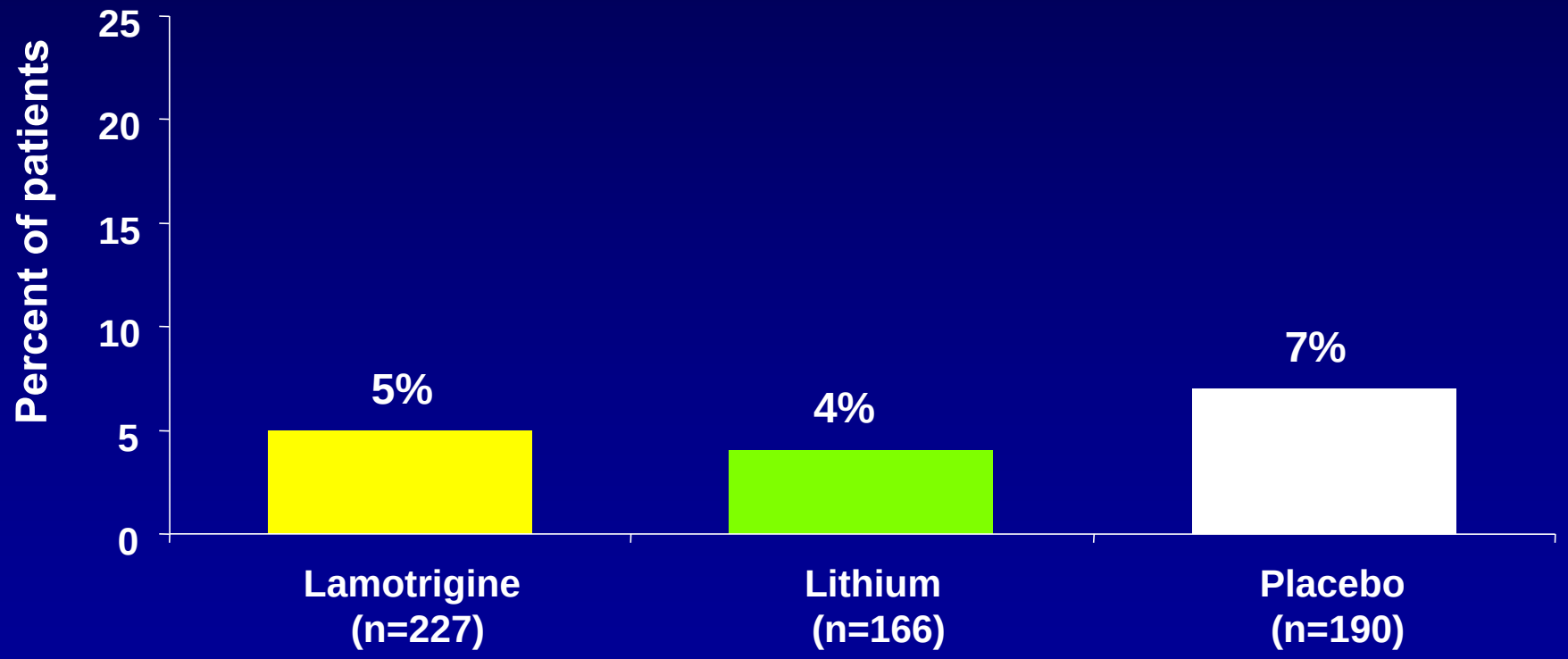
Some patients considered intervention-free for mania could have had intervention for depression.

Goodwin GM, et al. J Clin Psychiatry 2004;65:432-41.

Incidence of Mania/Hypomania/Mixed Episodes Reported as Adverse Events

Combined Analysis

Patients stabilized on lamotrigine prior to randomization.

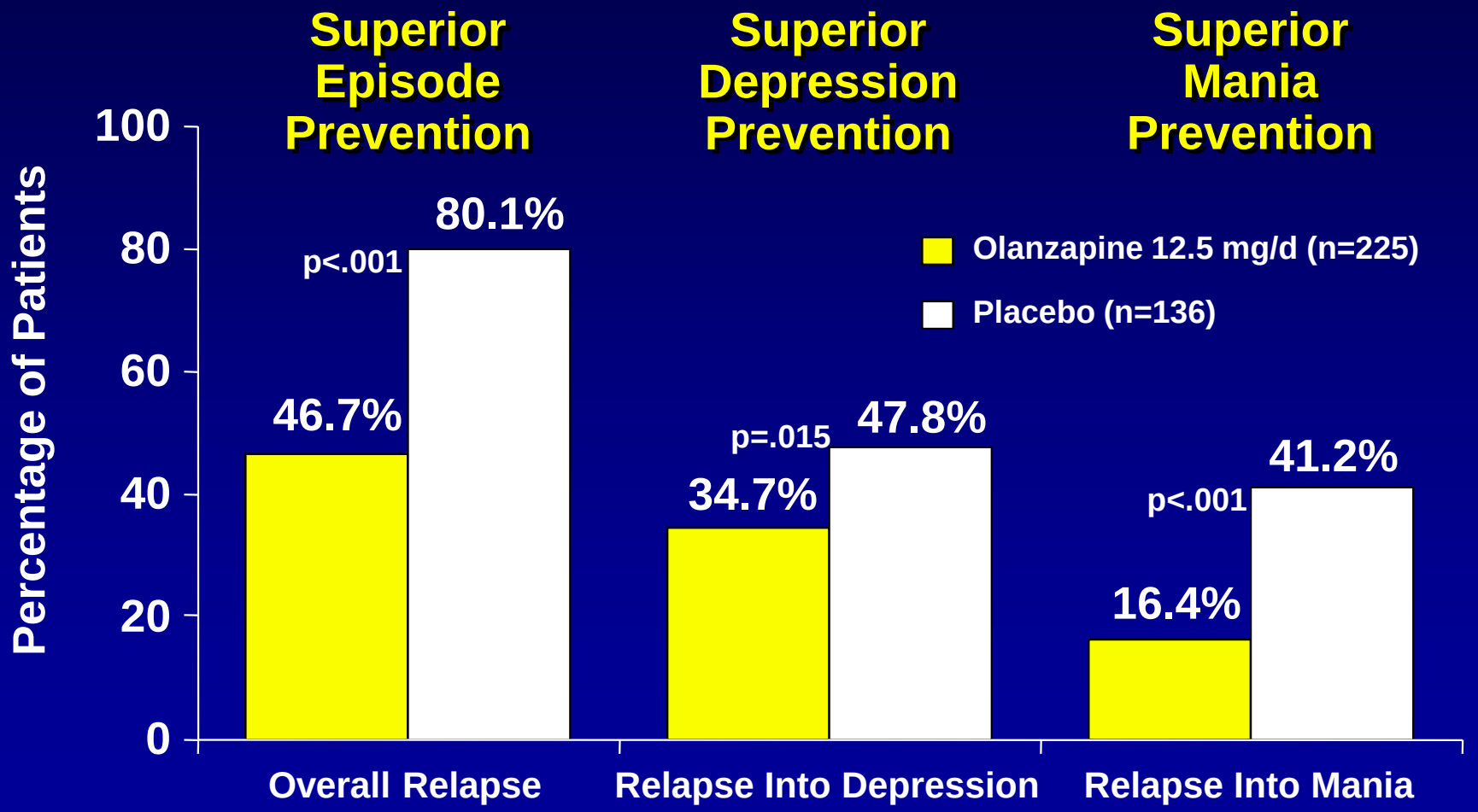


In all bipolar controlled trials, adverse events of mania were reported as 5% lamotrigine, 3% lithium, and 4% placebo.

Goodwin GM, et al. J Clin Psychiatry 2004;65:432-41.

12-Month Double-Blind Olanzapine Monotherapy vs Placebo Maintenance

Olanzapine Compared to Placebo After Manic/Mixed Episodes

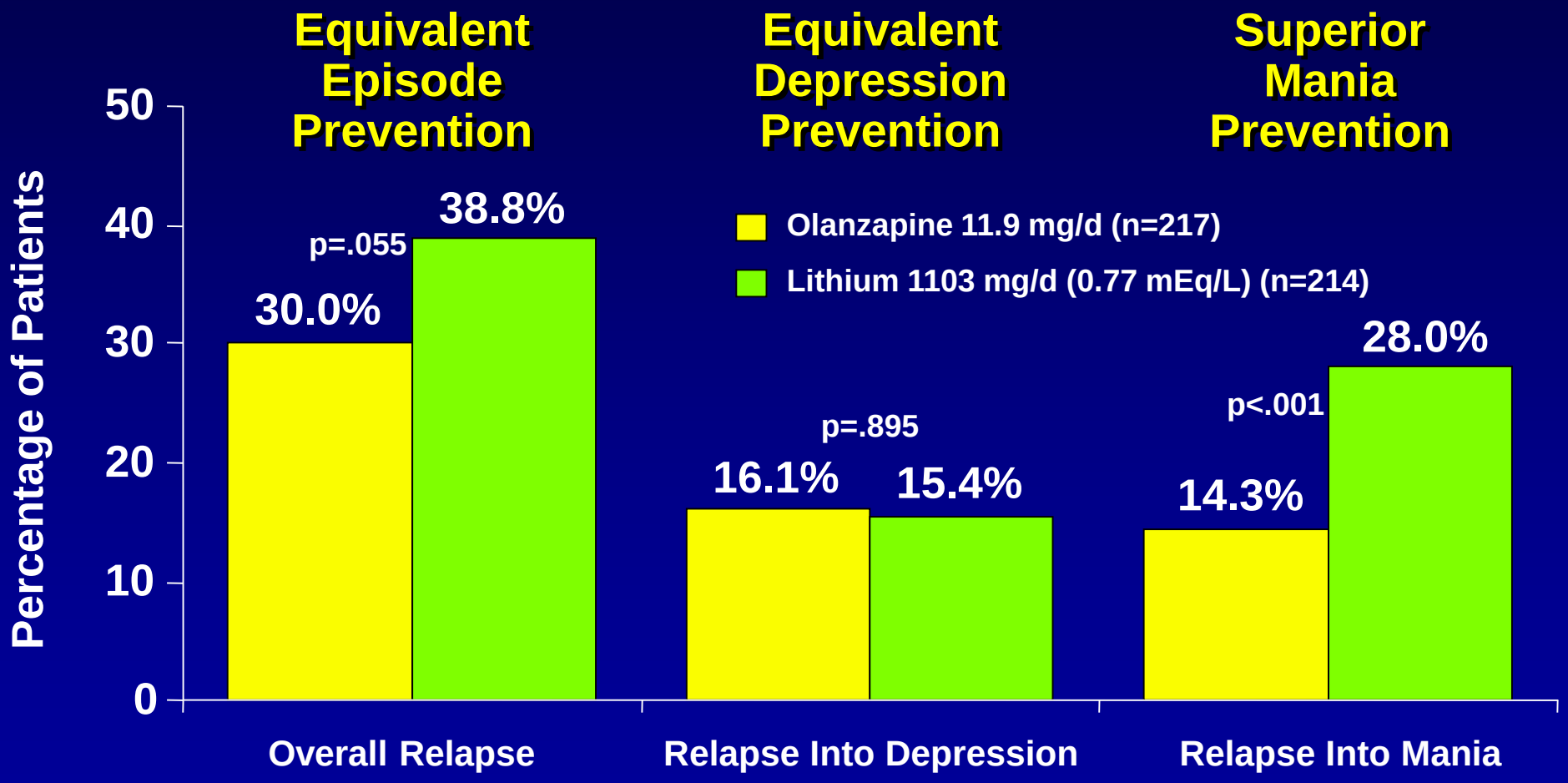


Stabilized on OLZ before randomization. Relapse criteria - hospitalized or YMRS or HAMD-21 >= 15.

Tohen MF, et al. Am J Psychiatry 2006;163:247-56.

12-Month Double-Blind Olanzapine vs Lithium Maintenance Monotherapy

Olanzapine Compared to Lithium After Manic/Mixed Episodes

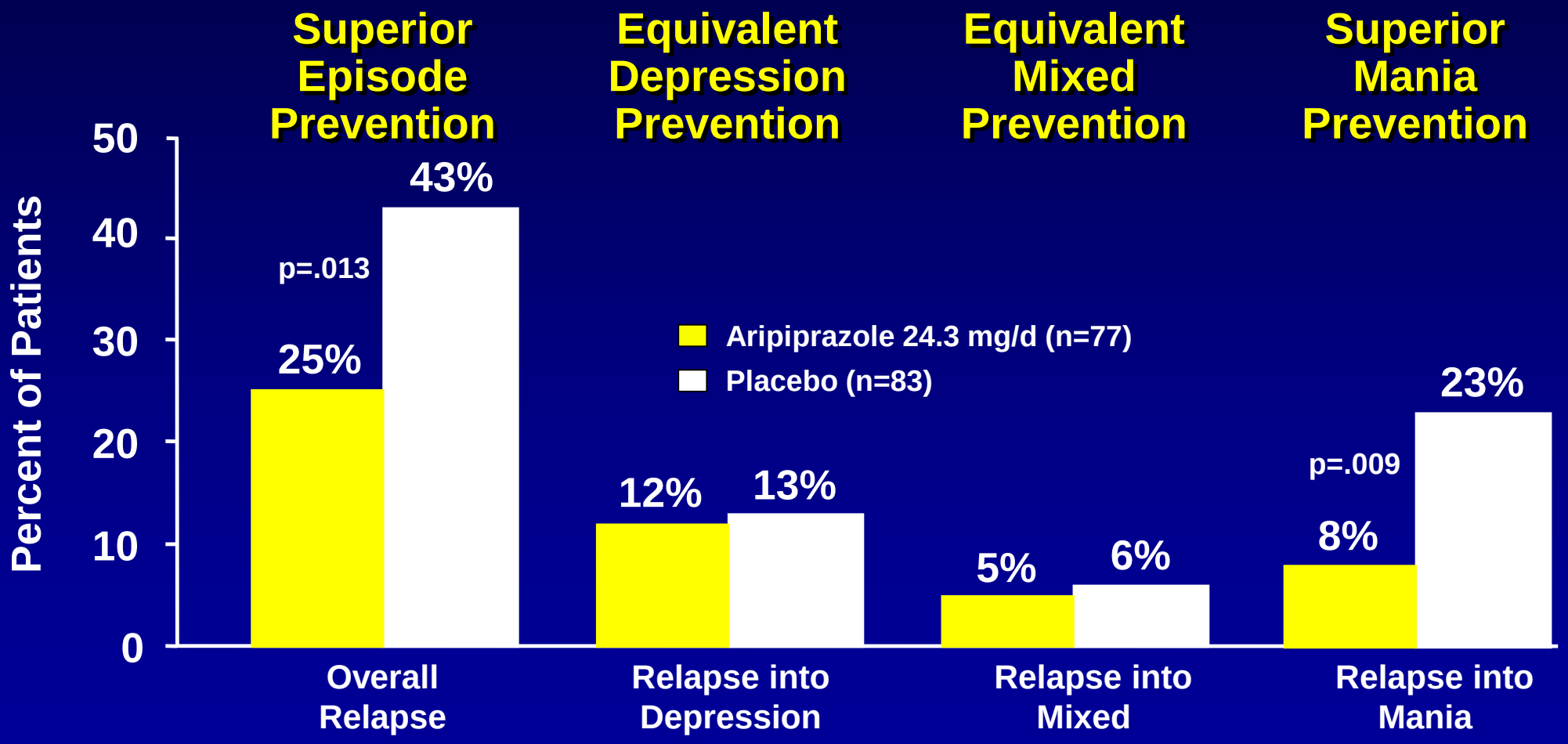


Stabilized on OLZ+Li before randomization. Relapse criteria - YMRS or HAMD-21 >= 15.

Tohen MF, et al. Am J Psychiatry 2005;162:1281-90.

26-Week Double-Blind Aripiprazole vs Placebo Continuation/Maintenance Monotherapy

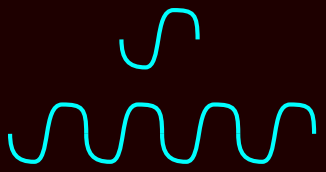
Aripiprazole Compared to Placebo After Manic/Mixed Episodes



Stabilized on ARI before randomization.

Keck PE, et al. 157th APA Annual Meeting; May 1-6, 2004; New York, NY. Abstract NR746.

Antidepressants After Depression Resolution

Disorder / Episode Pattern	Begin Taper	Comments
Unipolar 	6–12 months	Maintenance if ≥ 3 episodes
Bipolar Monophasic Biphasic - MDE 	6–12 weeks	Repeat if relapse Maintenance if repeated relapses
Bipolar Biphasic - DME Polyphasic Hx rapid cycling Hx iatrogenic mania 	6–12 days	Start taper after first euthymic visit

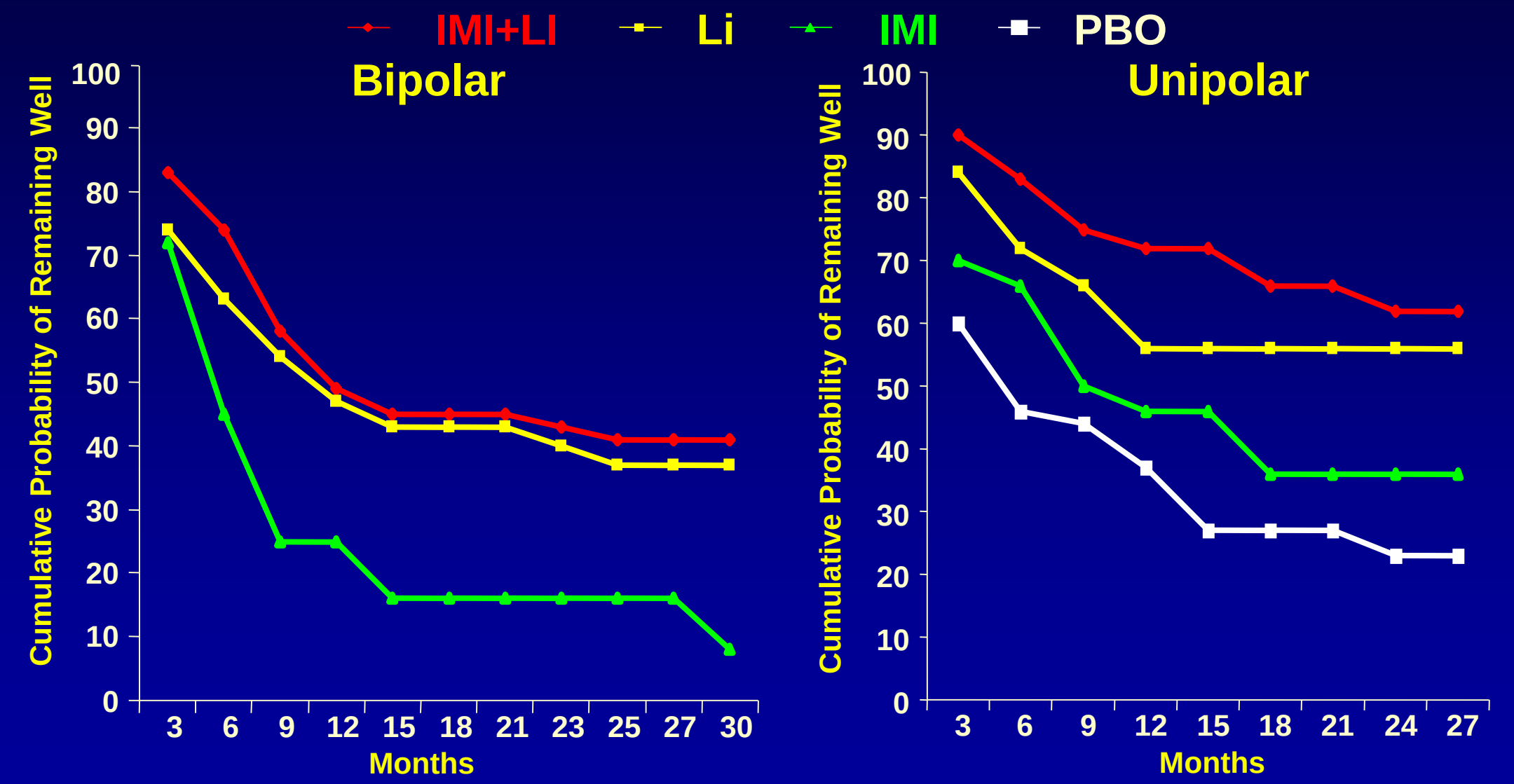
Sachs G, 2000. Personal communication.

Controlled Maintenance Studies of Antidepressants for Bipolar Depression

Study	N, Duration	Efficacy	Switch
Prien et al ’73	N=44, 24 mo	Li > IMI = PBO	
Wehr & Goodwin ‘79	N=5, 27 mo	Li = Li + DMI	Li + DMI >> Li
Quitkin et al ‘81	N=75, 19 mo	Li = Li + IMI	Li + IMI > Li
Kane et al ‘82	N=22, 11 mo	Li > PBO = IMI	
Prien et al ‘84	N=117, 30 mo	Li = Li + IMI> IMI	IMI > Li + IMI = Li
Sachs et al ‘94	N=15, 12 mo	Li + BUP= Li + DMI	Li + DMI > Li + BUP

Kane et al Arch Gen Psychiatry 1982;39:1065-9; Prien et al Arch Gen Psychiatry 1984;41:1096-1104; Prien et al Arch Gen Psychiatry 1973;29:420-5; Quitkin et al Arch Gen Psychiatry 1981;38:902-7; Sachs et al J Clin Psychiatry 1994;55:391-3; Wehr & Goodwin Arch Gen Psychiatry 1979;36:555-9.

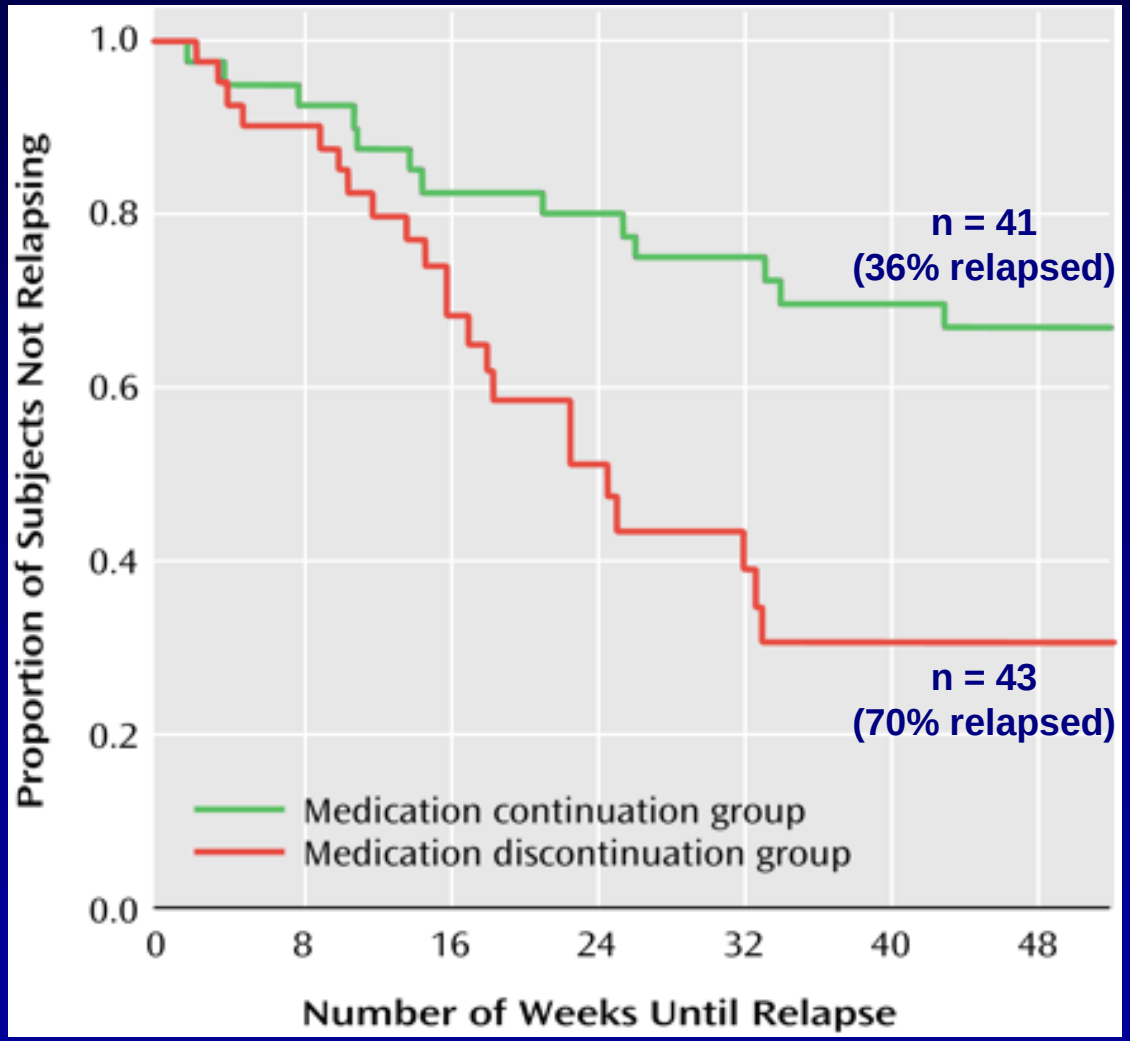
Bipolar Versus Unipolar Maintenance Treatment Dissociation



Li 0.8 mEq/L; IMI 125 mg/d

Adapted from Prien et al Arch Gen Psychiatry 1984;41:1096:1104.

Antidepressant Continuation Beneficial in Some (15%?) Patients



Prospective 1-year follow-up
Remission of MDE with AD added to mood stabilizer

Tolerated AD ≥ 2 months

Continuation: AD > 6 months
Discontinuation: AD < 6 months

Altshuler et al. Am J Psychiatry. 2003;160:1252-62.

Treatment of Bipolar Depression

- Acute treatment
  - Lithium, lamotrigine
  - Olanzapine plus fluoxetine, quetiapine
  - Adjunctive antidepressants
  - Alternative treatments
- Maintenance treatment
  - Lithium, lamotrigine
  - Divalproex
  - Adjunctive antidepressants (controversial)
  - Alternative treatments
- New treatment options emerging

Post-Lecture Exam Question 1

1. The most pervasive symptoms in bipolar disorder are those of: (choose one)

A. Mania, hypomania

B. Hypomania

C. Depression

D. Mixed States

E. None of the above

Question 2

2. Which of the treatments below is the LEAST appropriate strategy in bipolar depression: (choose one)

A. Mood stabilizer without antidepressant

B. Mood stabilizer with antidepressant

C. Atypical antipsychotic with antidepressant

D. Antidepressant with neither mood stabilizer nor atypical antipsychotic

Question 3

3. Which antidepressant option carries the greatest risk of hypomania/mania: (choose one)

A. Tricyclic antidepressants (TCAs)

B. Selective serotonin reuptake inhibitors (SSRIs)

C. Serotonin norepinephrine reuptake inhibitors (SNRIs)

D. Bupropion

Question 4

4. Which of the following treatments do NOT have controlled data suggesting utility in bipolar depression: (choose one)

A. Lithium

B. Lamotrigine

C. Olanzapine plus fluoxetine combination

D. Quetiapine

E. Citalopram

F. Pramipexole

Answers to Pre & Post Competency Exam

1. C
2. D
3. A
4. E