Acute and Maintenance Treatment of Bipolar Depression

Terence A. Ketter, M.D.

Overview

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

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

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

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

A. Tricyclic antidepressants (TCAs)

B. Selective serotonin reuptake inhibitors (SSRIs)

C. Mirtazapine

D. Bupropion

Question 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

Question 5

Which of the following statements best describes the role of maintenance adjunctive antidepressants in patients with bipolar disorder: (choose one)

A. Long-term adjunctive antidepressants are always beneficial.

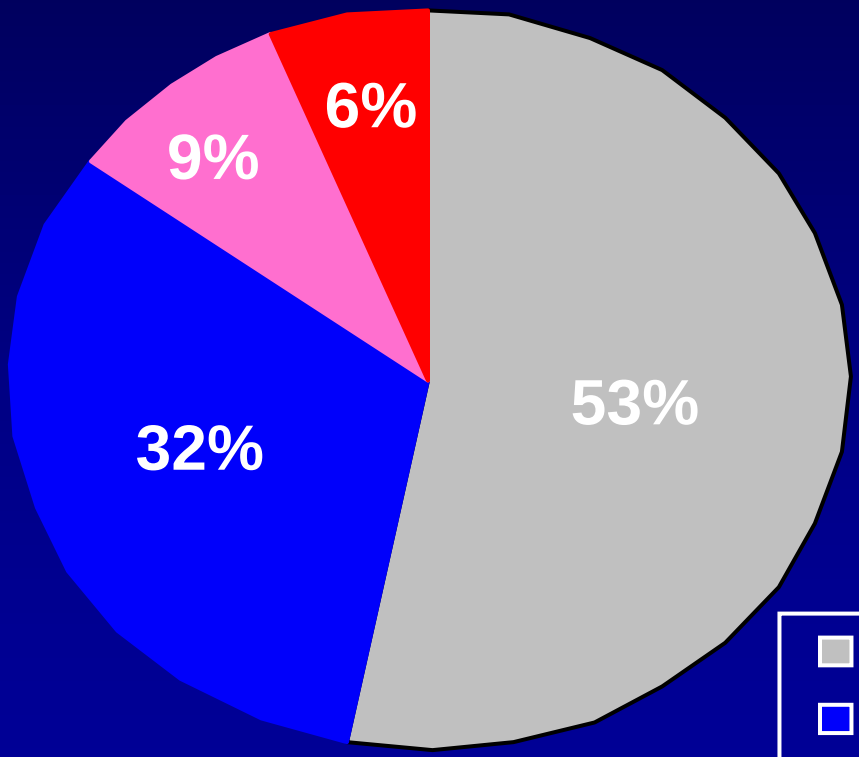
B. Long-term adjunctive antidepressants are never beneficial.

C. Long-term adjunctive antidepressants are beneficial in most patients.

D. Long-term adjunctive antidepressants may be beneficial in some patients.

Bipolar disorders symptoms are chronic and predominantly depressive

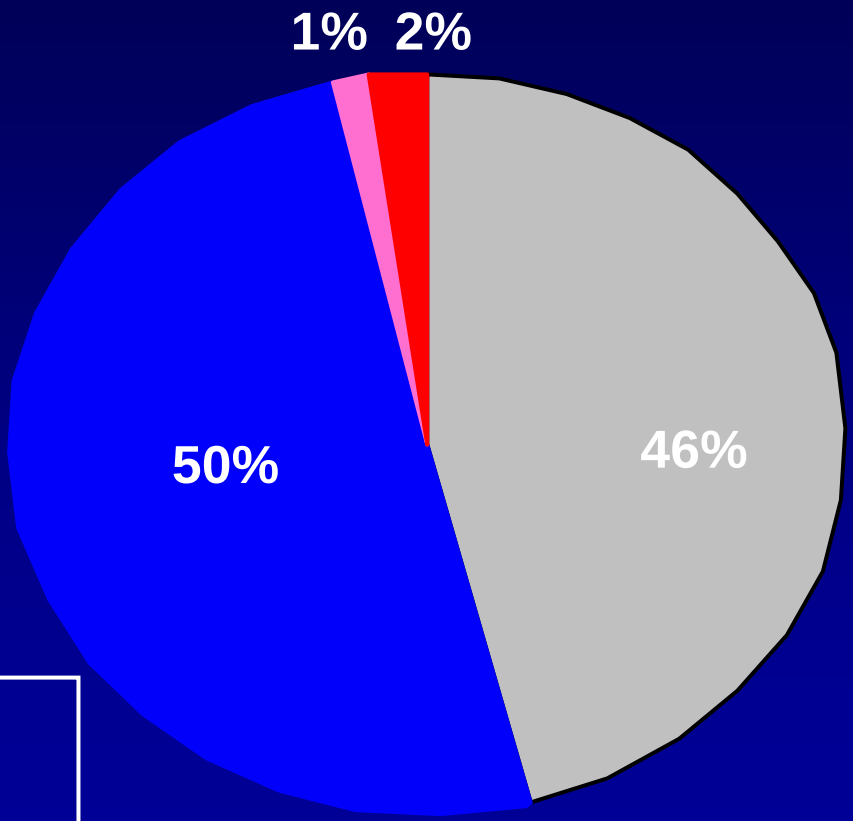
146 Bipolar I Patients
followed 12.8 yrs



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

Adjunctive Psychotherapy

Alternative Treatments

- Pramipexole
- Modafinil, Armodafinil
- 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; Frye M, et al. Am J Psychiatry 2007;164:1242-9

Approved Agents for Bipolar Disorder

Acute Mania

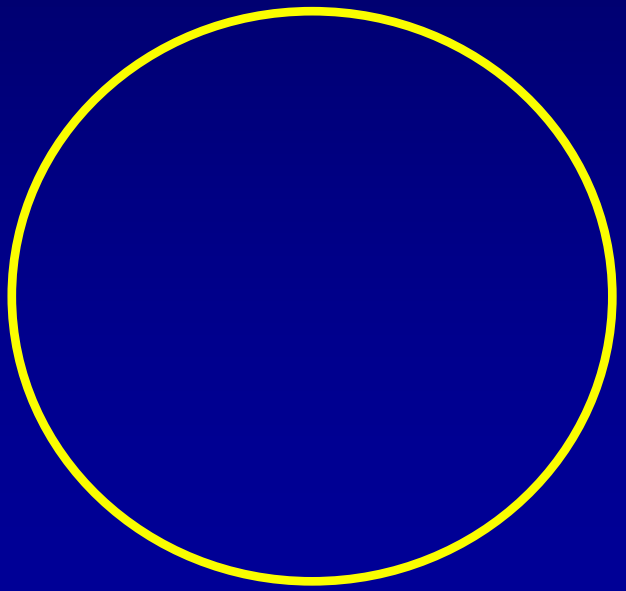
Year	Drug
1970	Lithium
1973	Chlorpromazine
1994	Divalproex, ER (2005)
2000	Olanzapine*
2003	Risperidone*
2004	Quetiapine, XR (2008)*
2004	Ziprasidone
2004	Aripiprazole*
2004	Carbamazepine ERC
2009	Asenapine

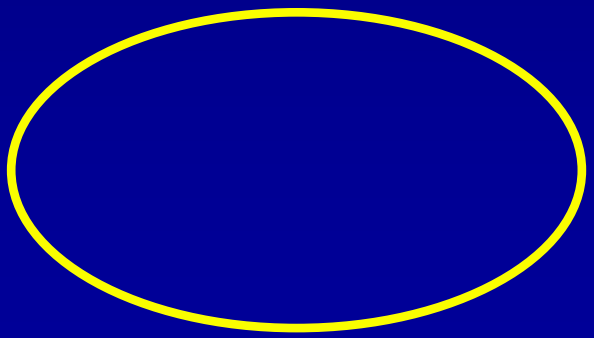
Acute Depression

Year	Drug
2003	Olanzapine+fluoxetine combination
2006	Quetiapine, XR (2008)

Longer-Term

Year	Drug
1974	Lithium
2003	Lamotrigine
2004	Olanzapine
2005	Aripiprazole
2008	Quetiapine, XR (adjunct)
2009	Risperidone LAI*
2009	Ziprasidone (adjunct)





*Adjunctive and monotherapy LAI = Long-Acting Injectable

Important unmet needs - well-tolerated treatments for acute depression and maintenance.

Formulations of Agents for Bipolar Disorder (Not all formulations have bipolar indications)

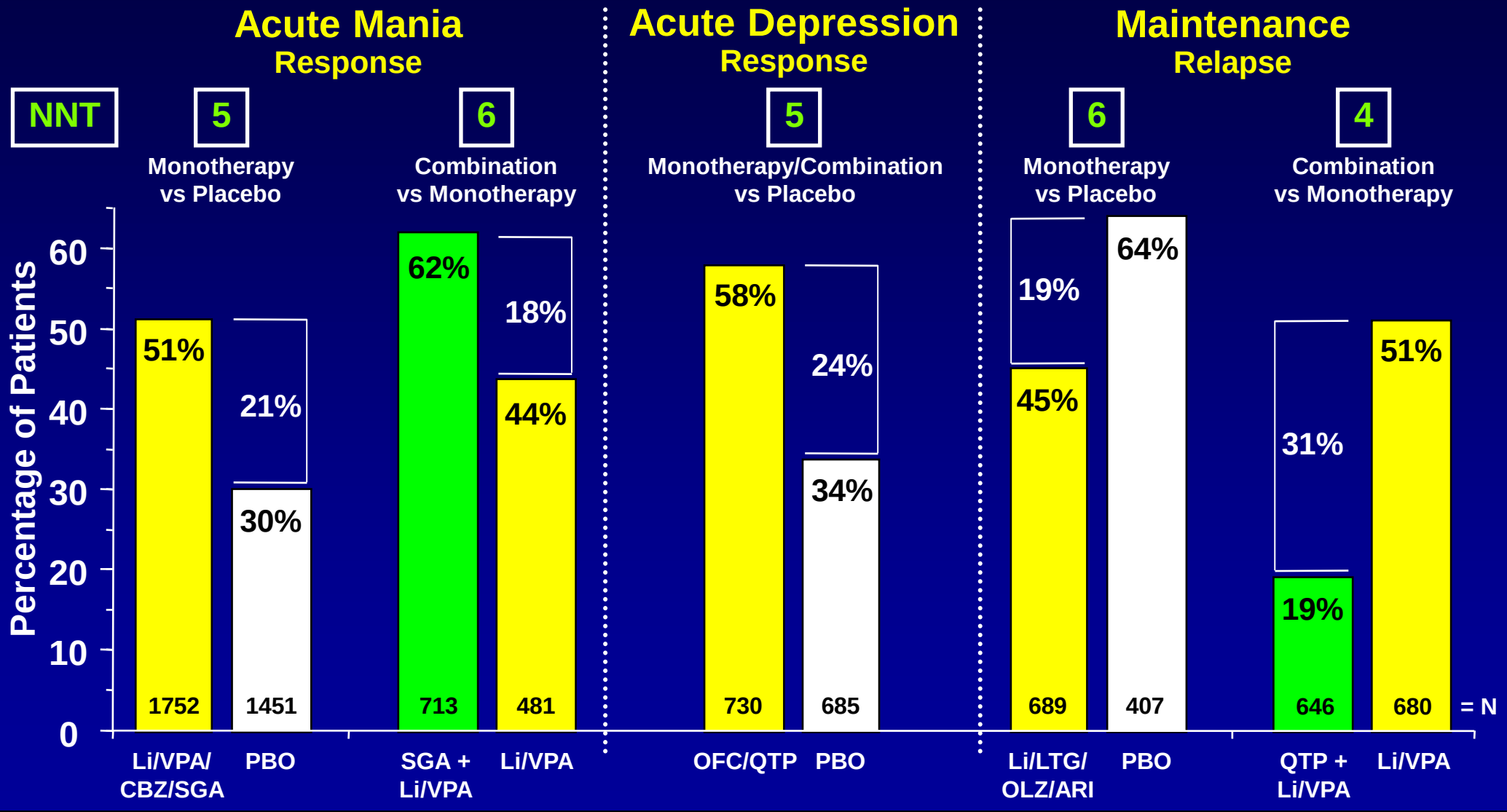
Medication	Oral Tab/Cap	Oral Fluid	Rapid Acting Injectable	Long Acting Injectable
Asenapine	SL			
Aripiprazole	+, ODT	+	IM	
Carbamazepine	+, ER	+		
Chlorpromazine	+	+	IM, IV	
Divalproex	+, ER	+	IV	
Lamotrigine	+, ER, ODT			
Lithium	+, ER	+		
Olanzapine	+, ODT		IM	IM
Olanzapine+fluoxetine	+			
Quetiapine	+, ER			
Risperidone	+, ODT	+		IM
Ziprasidone	+		IM	

ER = Extended Release; ODT = Orally Disintegrating Tab; IM = Intramuscular; IV = Intravenous; SL = Sublingual.

Ketter TA (ed). Handbook of Diagnosis and Treatment of Bipolar Disorder, Am Psych Pub, Inc., Washington, DC, 2009.

Overview of Bipolar Disorder Regaistration Studies

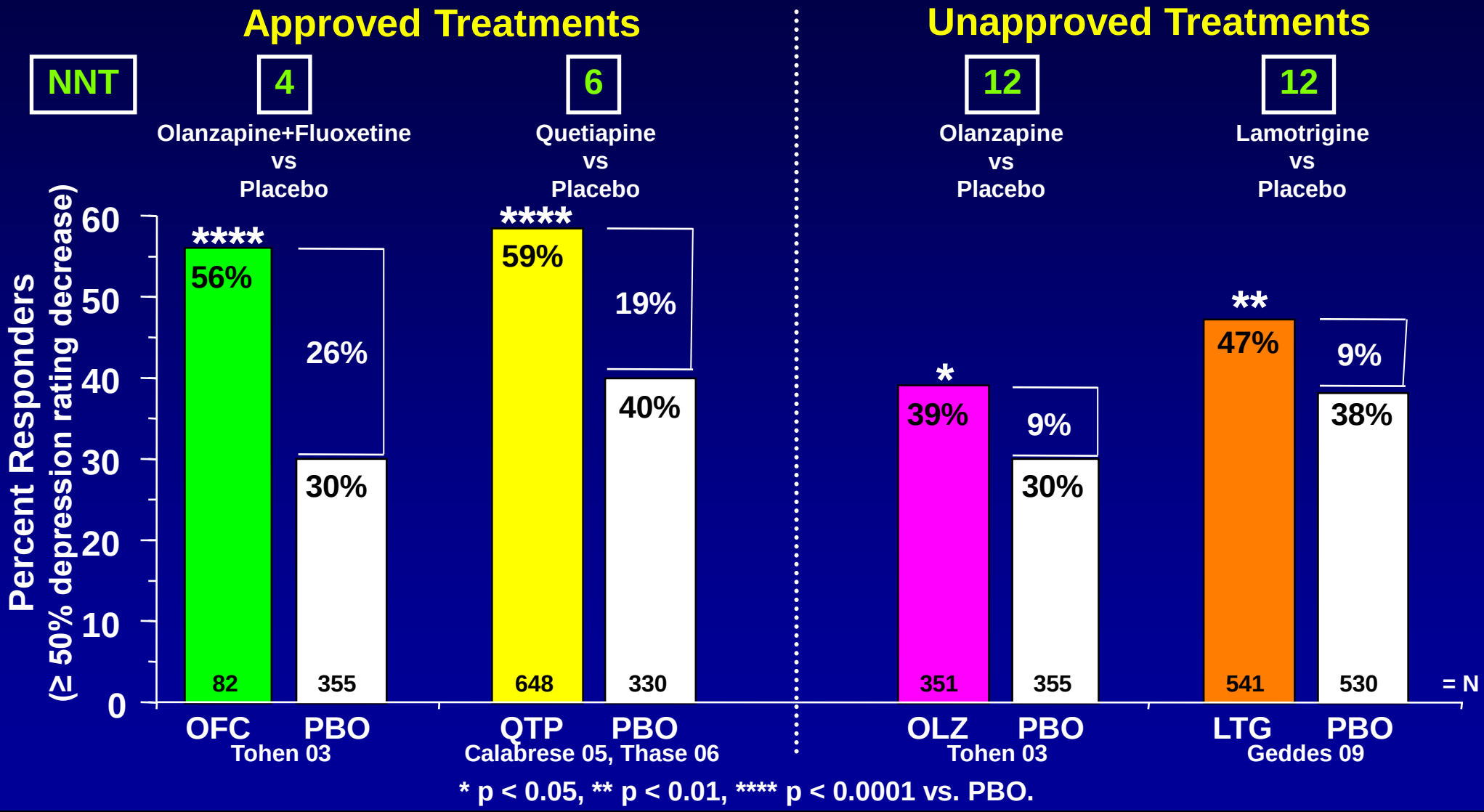
Numbers Needed to Treat for Response and Relapse Prevention, Rates



Approved treatments increase good outcomes by approximately 20%-30%.

Overview of Acute Bipolar Depression Studies

Numbers Needed to Treat for Response, Rates

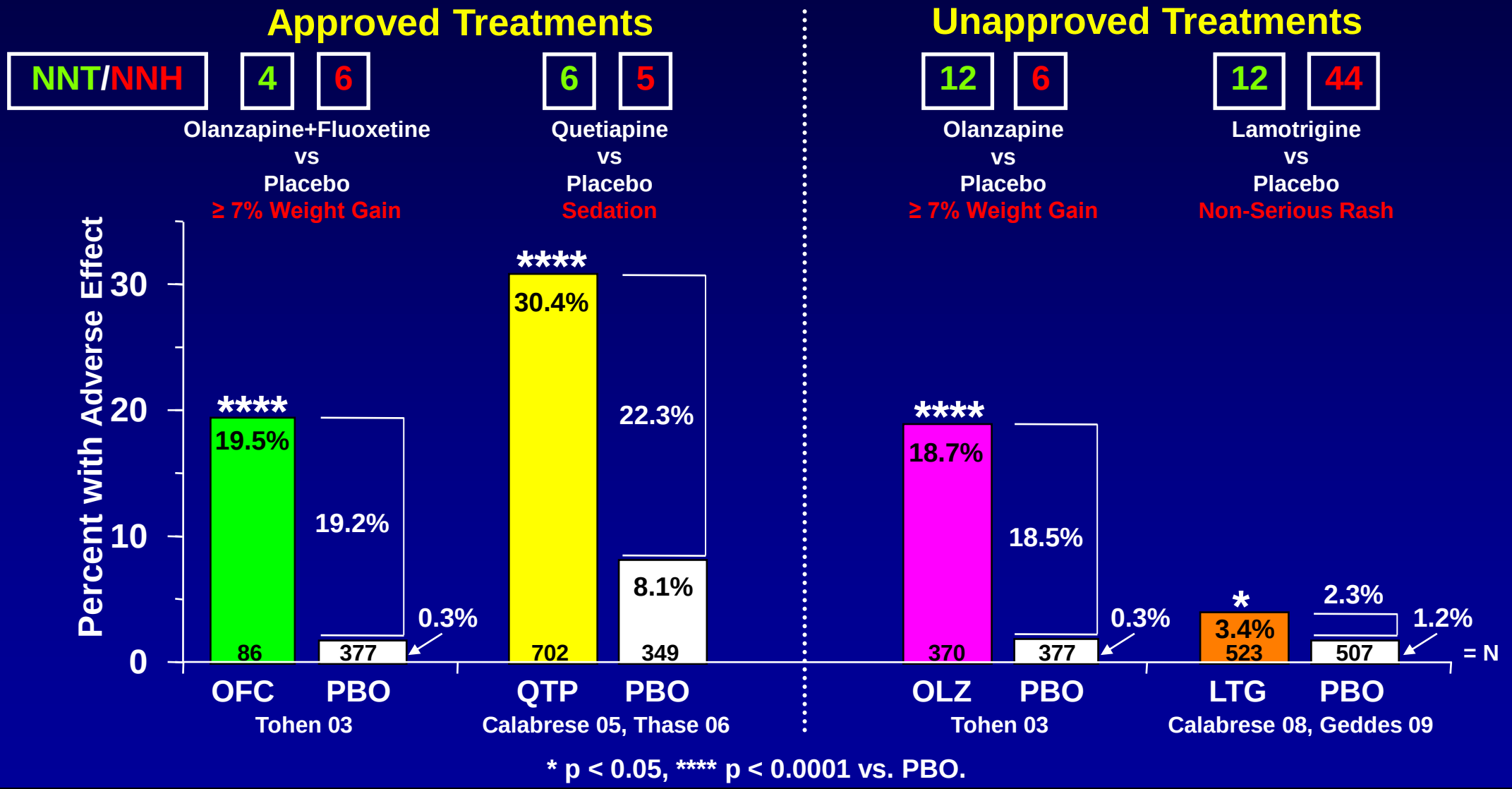


* p < 0.05, ** p < 0.01, **** p < 0.0001 vs. PBO.

Lamotrigine an unapproved alternative with limited efficacy (NNT = 12).

Overview of Acute Bipolar Depression Studies

Numbers Needed to Treat and Harm, Adverse Effect Rates



* p < 0.05, **** p < 0.0001 vs. PBO.

Lamotrigine has limited efficacy (NNT = 12), but good tolerability (NNH = 44).

Acute Treatment of Bipolar Depression

Lithium versus Placebo in Acute Bipolar Depression

- Li > placebo in 8/9 small crossover studies (N=163)[1]
  - In subset of 5 studies
    - 79% (63/80) Li response rate
    - 36% (29/80) unequivocal* Li response rate
- Li = placebo in 1 large parallel study (N=265)[2]
  - Li 600 mg/d = placebo (N = 136, 129)
  - Quetiapine 300 or 600 mg/d > placebo (N = 255, 263, 129)

*moderate to good Li response with subsequent relapse with switch to placebo.

[1]Zornberg GL, Pope HG. J Clin Psychopharmacol 13:397-48; [2]Young AH, et al. 55th Ann Mtg Soc Biol Psychiatry, Washington, May 1-3, 2008. Abstract 610. Biol Psychiatry 2008;63(7S):194S.

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

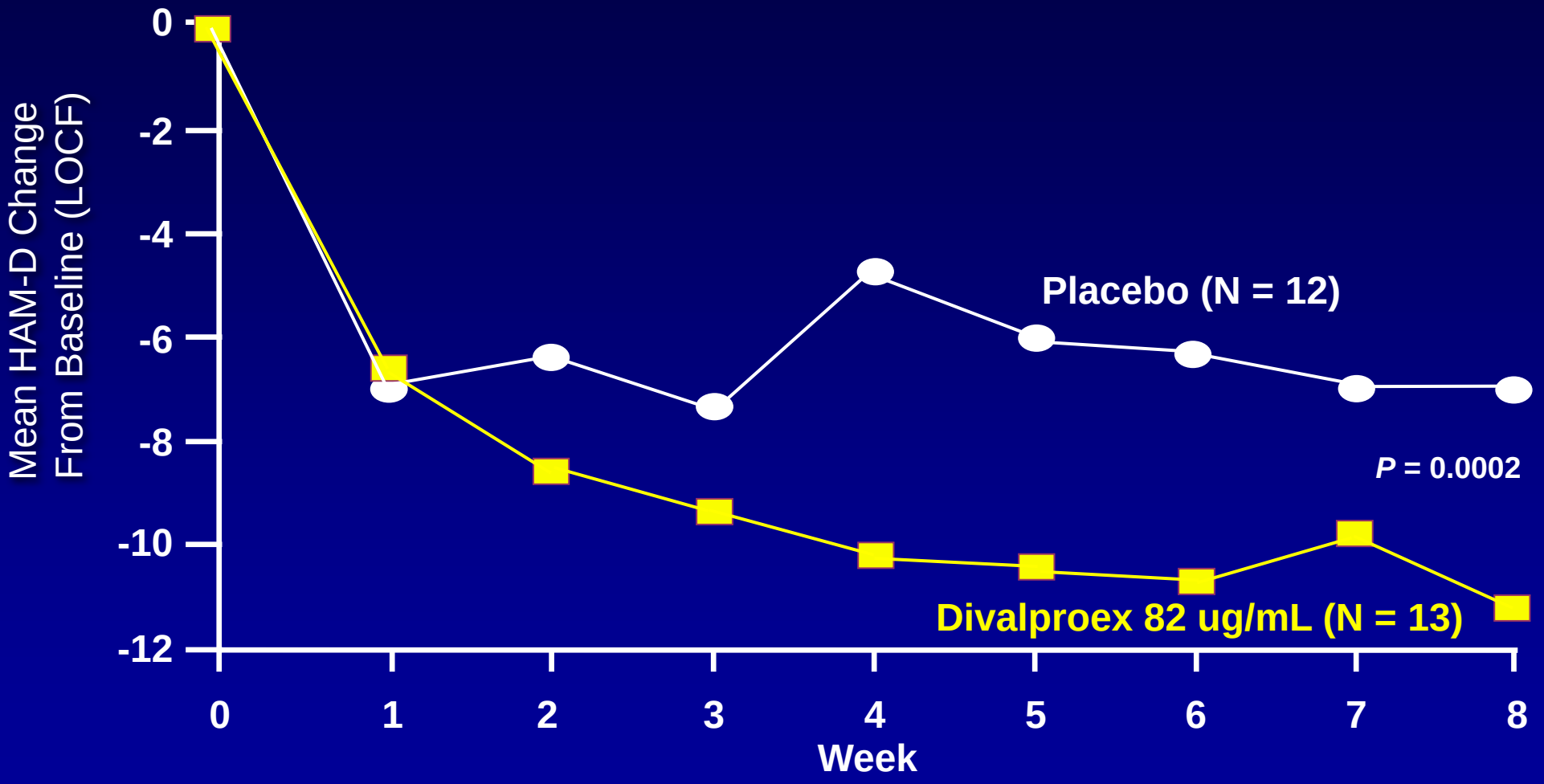
(Adjusted for age, sex, year of treatment, comedications, comorbidity)

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



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

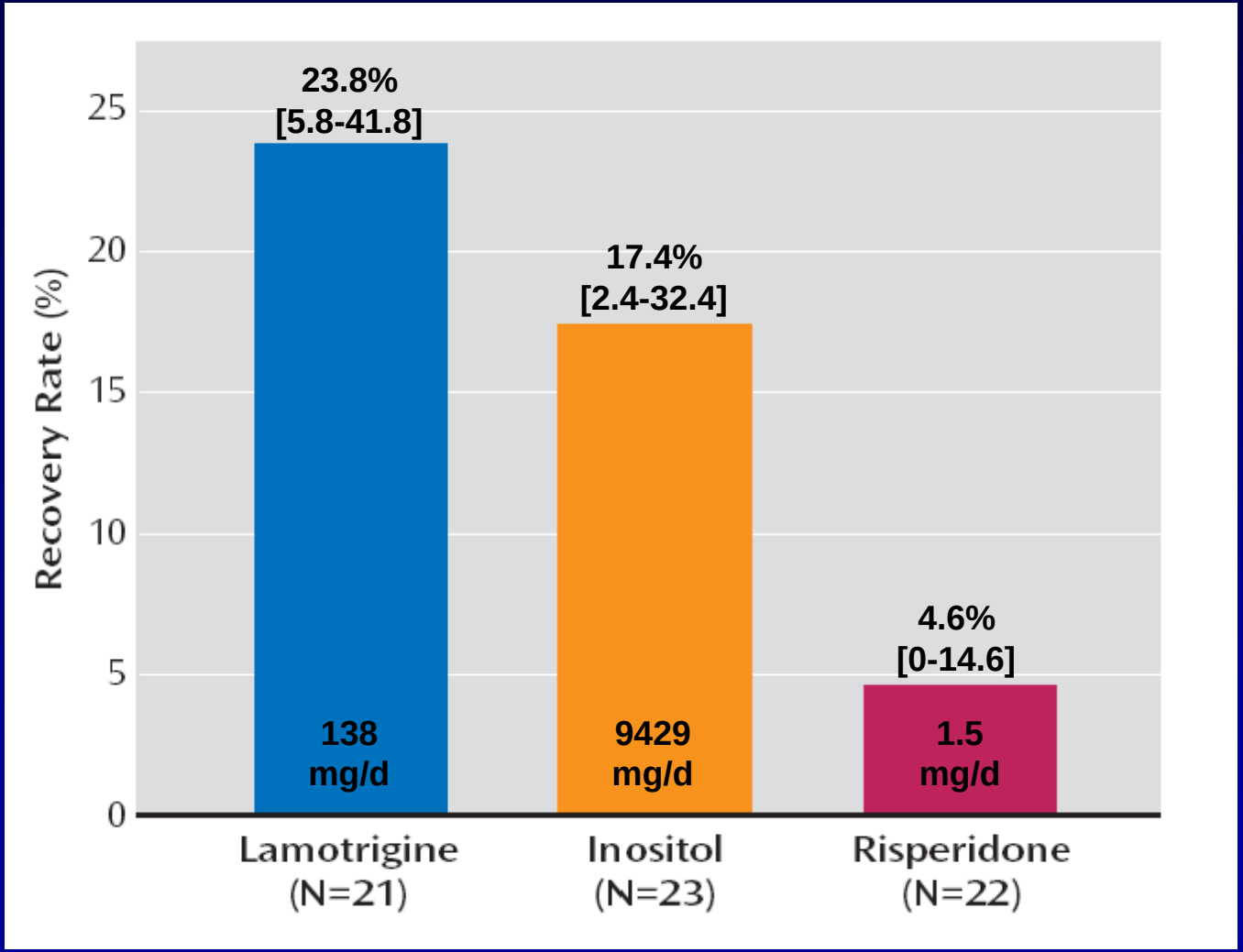
Davis LL, et al. J Affective Disord 2005;85:259-66.

Divalproex versus Placebo in Acute Bipolar Depression

- DVPX > placebo in 3 small parallel studies[1-3]
  - DVPX (81 ug/mL) > placebo (N = 13, 12)[1]
  - DVPX (70 ug/mL) > placebo (N = 9, 9)[2]
  - DVPX (82 ug/mL) > placebo (N = 26, 28)[3]
- DVPX = placebo in 1 small parallel study[4]
  - DVPX (62 ug/mL) > placebo (N = 21, 22)[4]
- Pooled response[2-4]/remission[1] rate (N=138)[1-4]
  - DVPX 40.6%, placebo 18.8% (p = 0.009)

[1]Davis LL, et al. J Affect Disord 2005;85:259-66; [2]Ghaemi SN, et al. J Clin Psychiatry 2007;68:1840-4;
[3]Muzina DJ, et al. APA 161st Ann APA Mtg, Washington, DC, May 3-8, 2008;
[4]Sachs G, et al. 40th ACNP Ann Mtg, Waikaloa, Hawaii, December 9-13, 2001.

16-Week Randomized Open Adjunctive Therapy of Treatment Resistant Bipolar Depression [a]



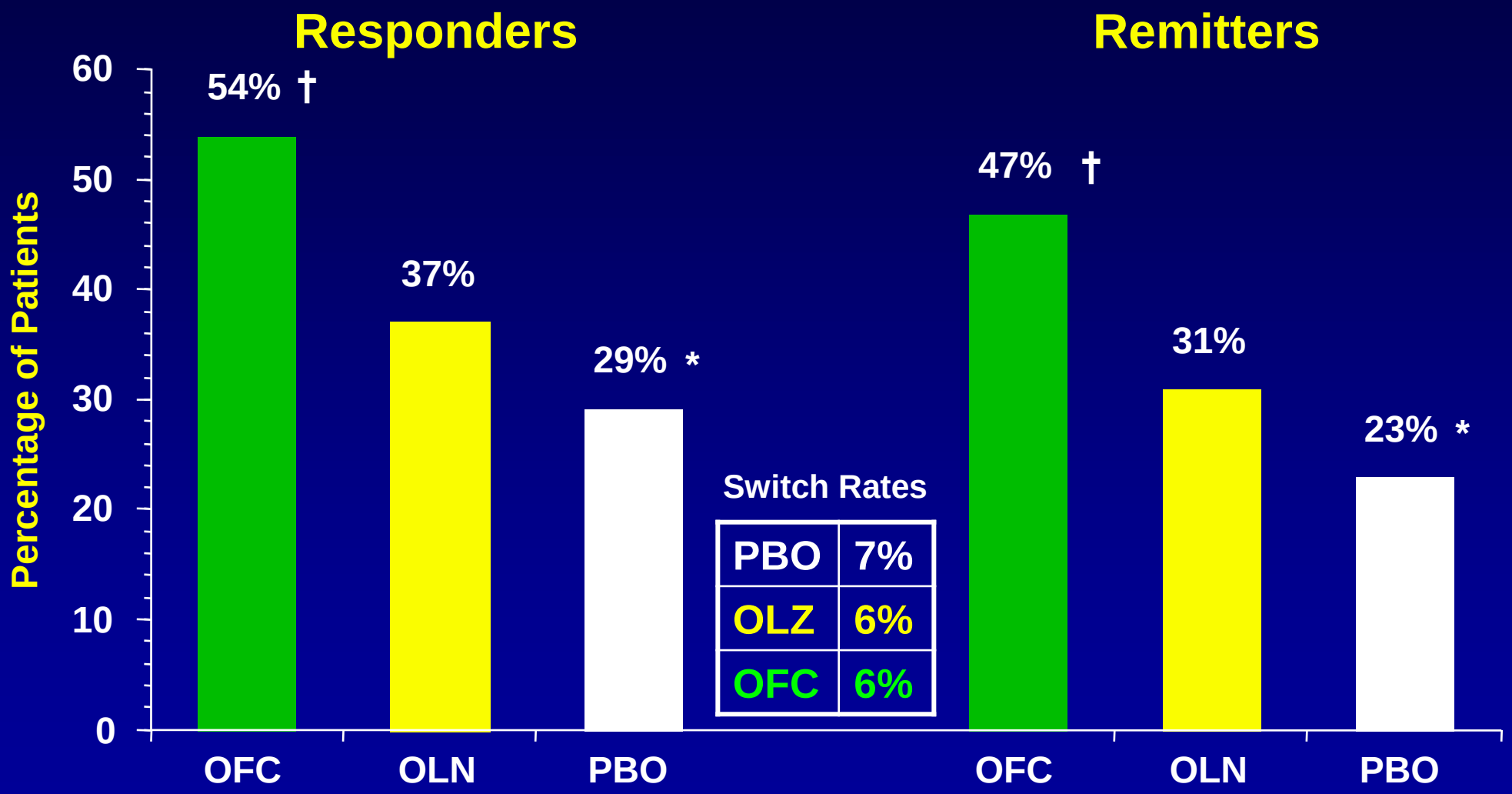
Switch Rates

Lamotrigine	19%
Inositol	13%
Risperidone	13%

Nierenberg AA, et al. Am J Psychiatry 2006;163;210-6.

[a] 54% BPI, 46% BPII.

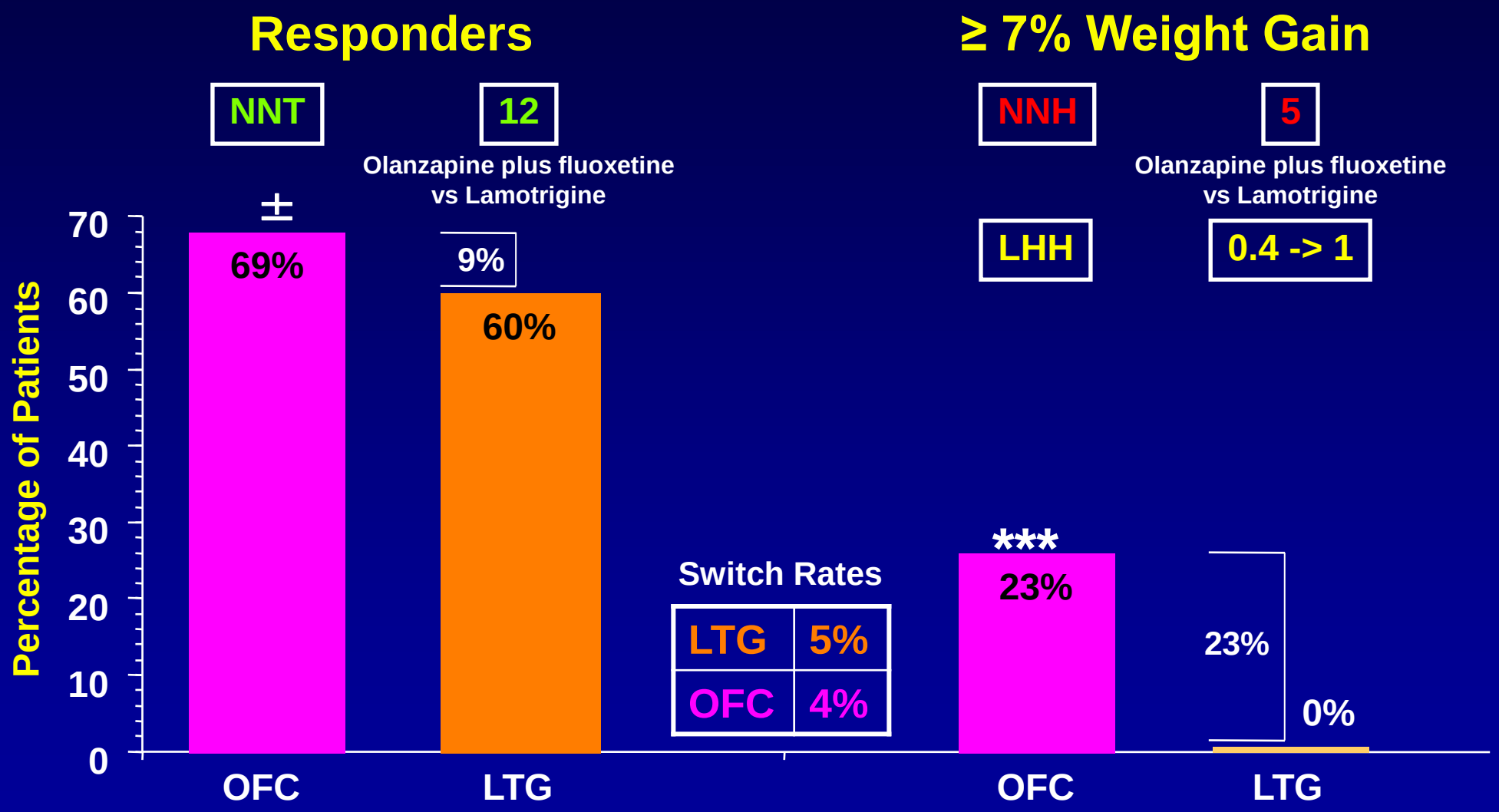
8-Week Randomized Double-Blind Olanzapine ± Fluoxetine in Acute Bipolar I Depression



* *P* < 0.05 vs OLN, OLN+FLX. † *P* < 0.05 vs OLN. ITT-LOCF

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

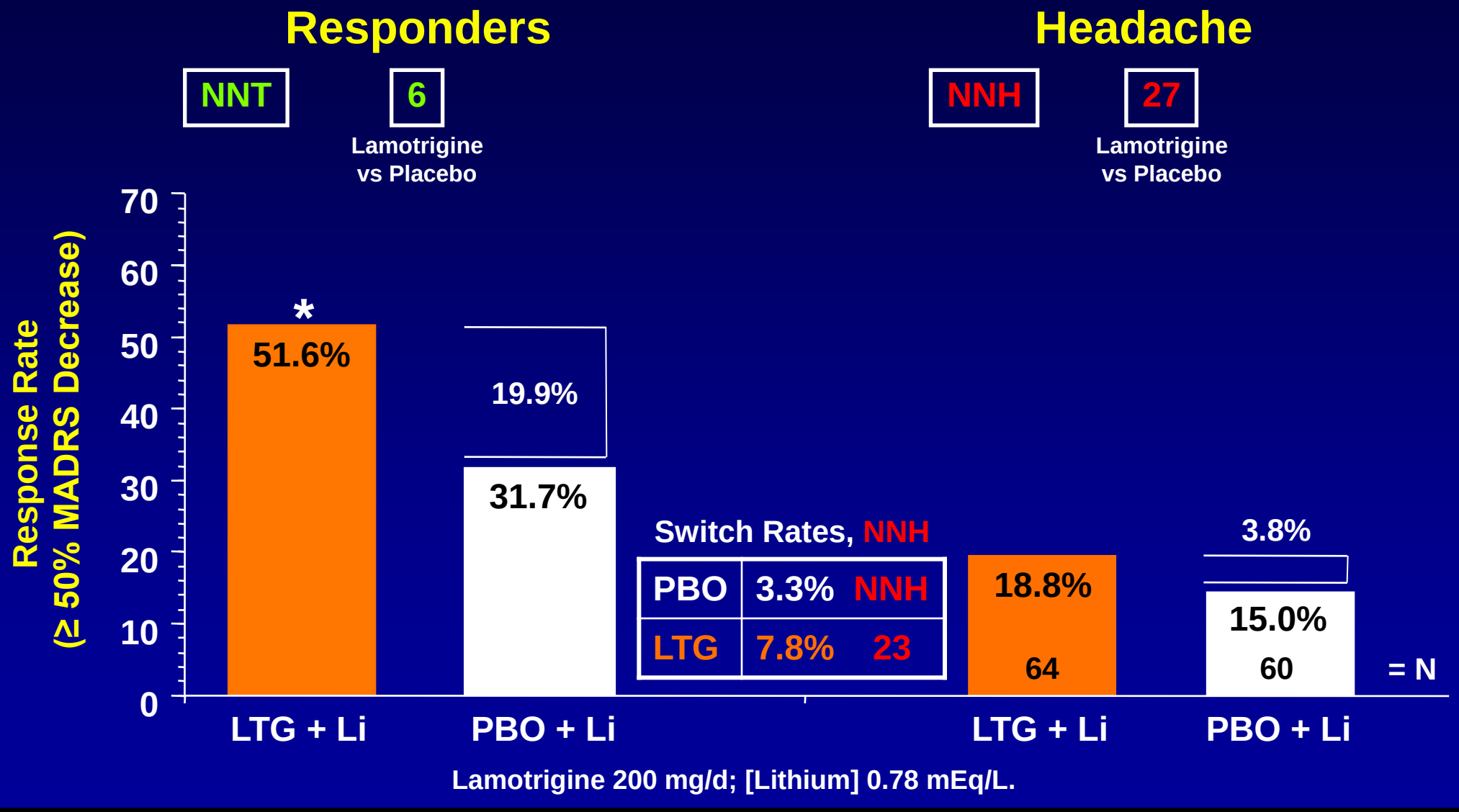
7-Week Randomized Double-Blind Lamotrigine vs Olanzapine + Fluoxetine in Acute Bipolar I Depression



± P < 0.08, *** P < 0.001 OFC vs LTG. Trade-off: 9% response vs 23% weight gain.

Olanzapine + fluoxetine vs. lamotrigine somewhat better efficacy, but more weight gain, LHH = 1.

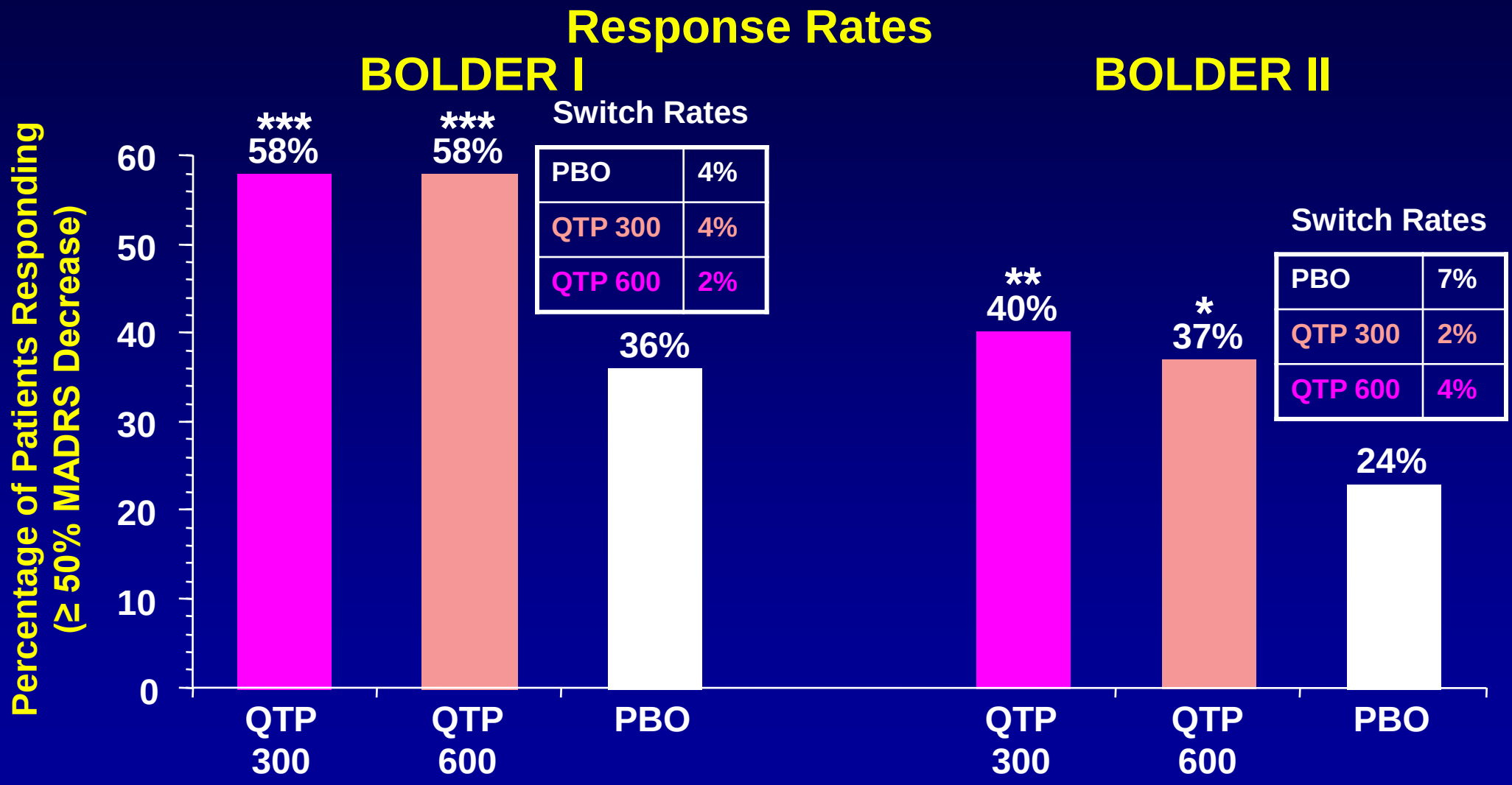
8-Week Randomized Double-Blind Adjunctive Lamotrigine vs Placebo in Acute Bipolar Depression



Lamotrigine 200 mg/d; [Lithium] 0.78 mEq/L.

Adjunctive (added to lithium) lamotrigine superior to placebo (NNT = 6), well tolerated.

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

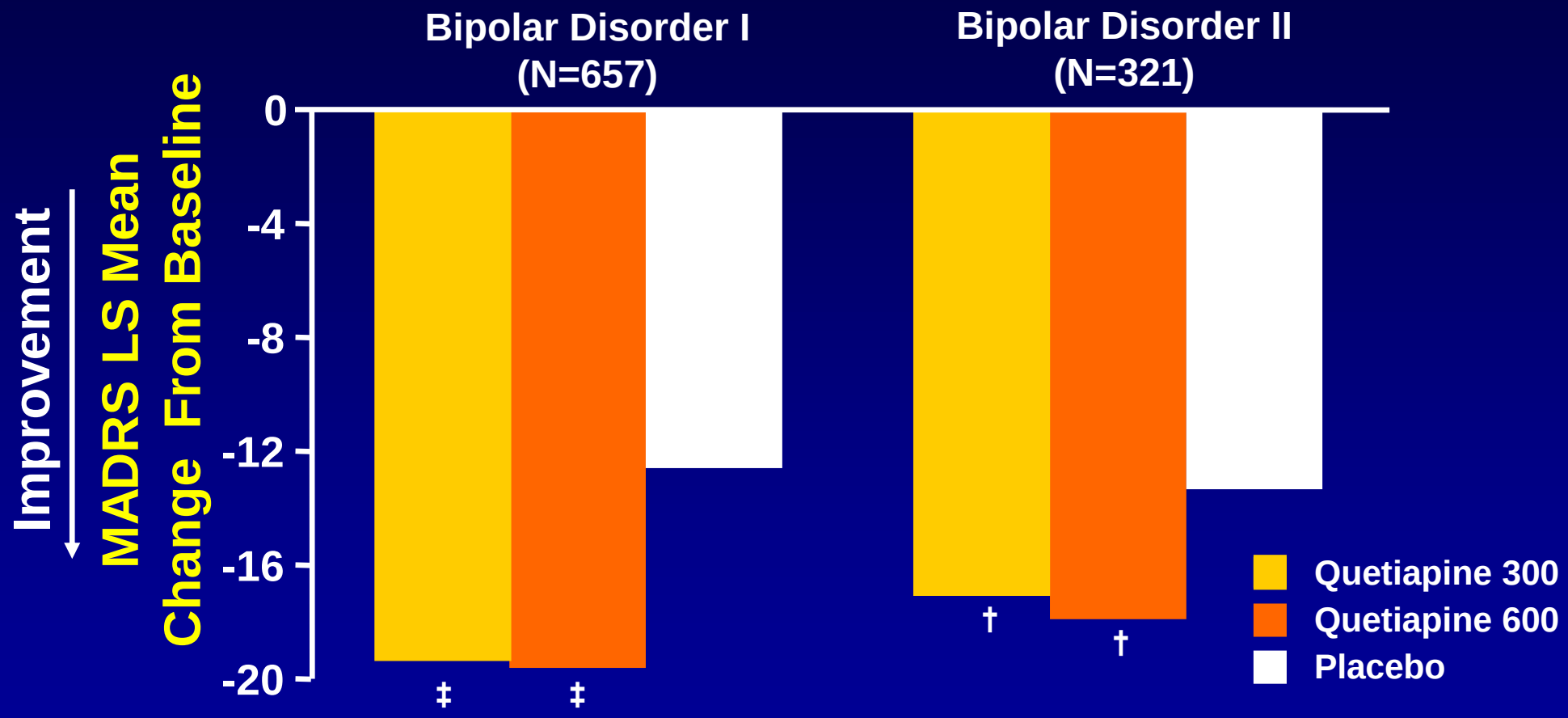


Calabrese JR, et al. Am J Psychiatry 2005;162:1351-60.

Thase ME, et al. J Clin Psychopharmacol 2006;26:600-9.

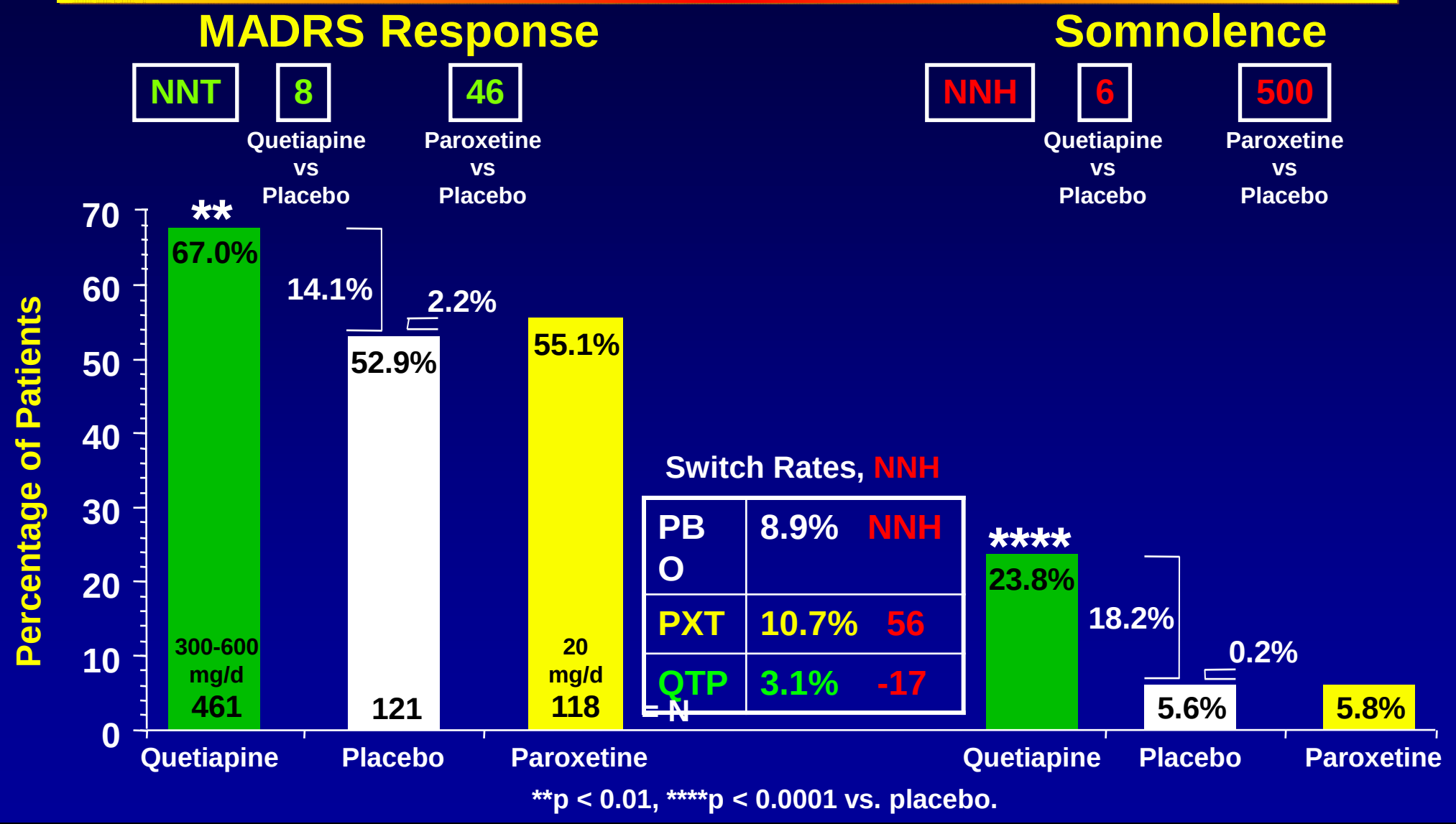
*p < 0.05, **p< 0.01, *** p < 0.001 vs placebo.

BOLDER I and II: MADRS Total Score
Bipolar I vs. II Disorder



†p<0.01; ‡p<0.001 vs. placebo (N at baseline); ITT = intent to treat; AstraZeneca (data on file); Thase ME (2006), Presented at the 159th Annual Meeting of the APA. Toronto, Canada; May 20-25; Calabrese JE et al. (2005), Am J Psychiatry 162(7):1351-1360

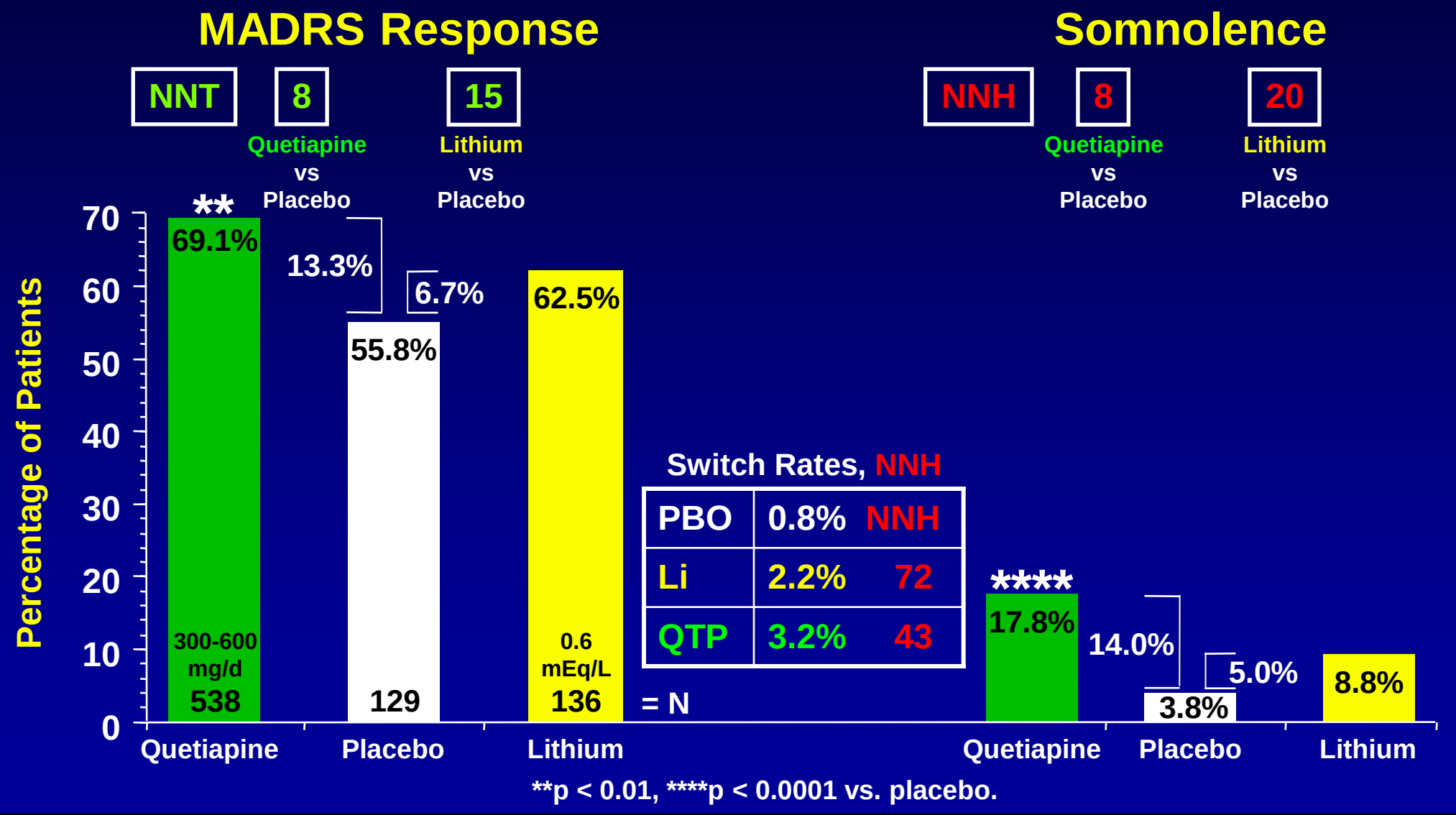
8-Week Randomized Double-Blind Quetiapine, Paroxetine, and Placebo in Acute Bipolar Depression



**p < 0.01, ****p < 0.0001 vs. placebo.

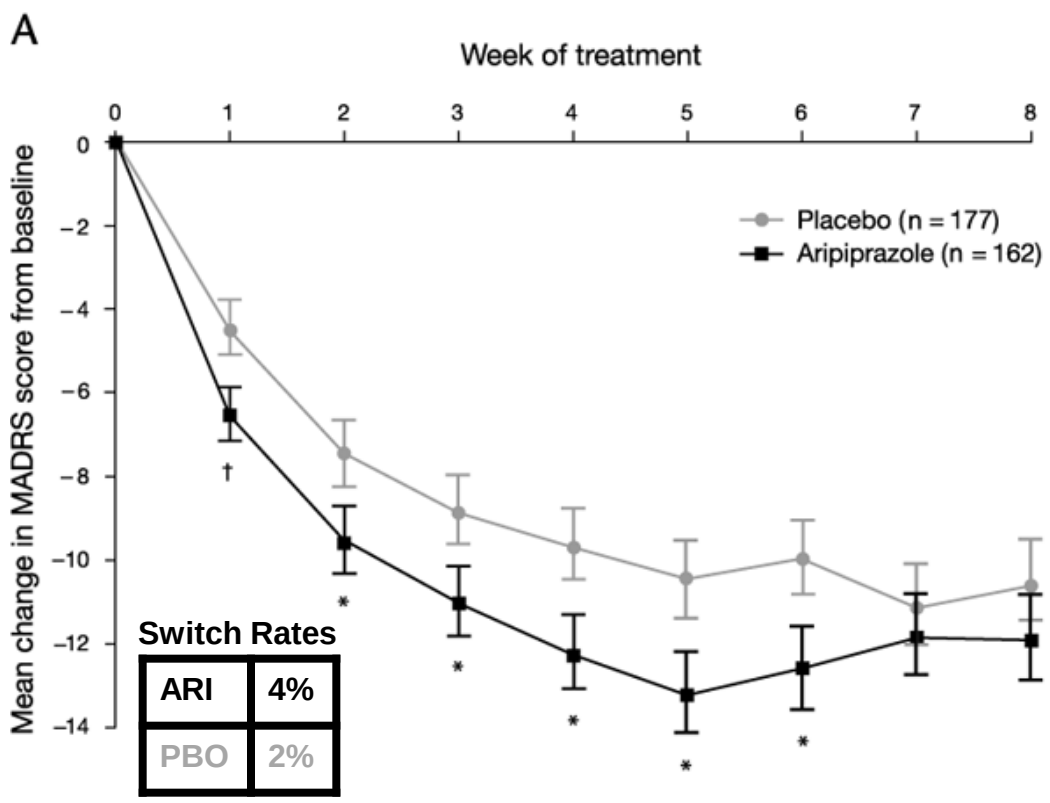
Quetiapine (but not paroxetine) monotherapy superior to placebo.

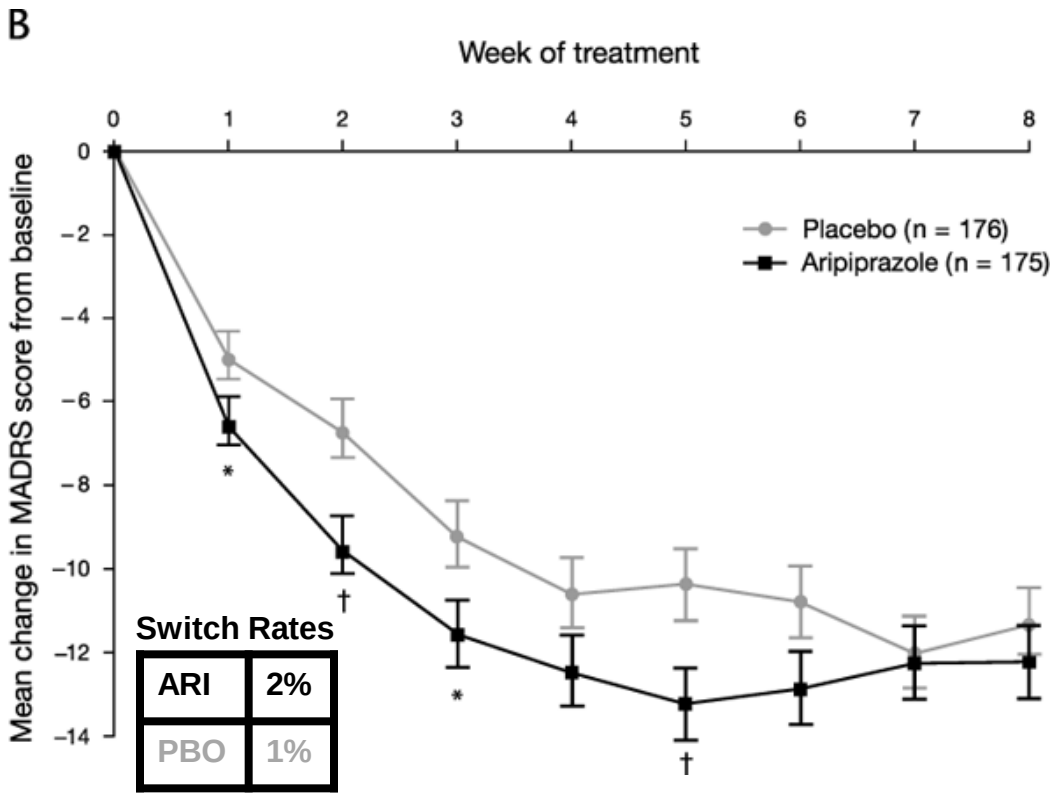
8-Week Randomized Double-Blind Quetiapine, Lithium, and Placebo in Acute Bipolar Depression



Quetiapine (but not lithium) monotherapy superior to placebo.

8-Week Randomized Double-Blind Aripiprazole Monotherapy in Acute Bipolar I Depression





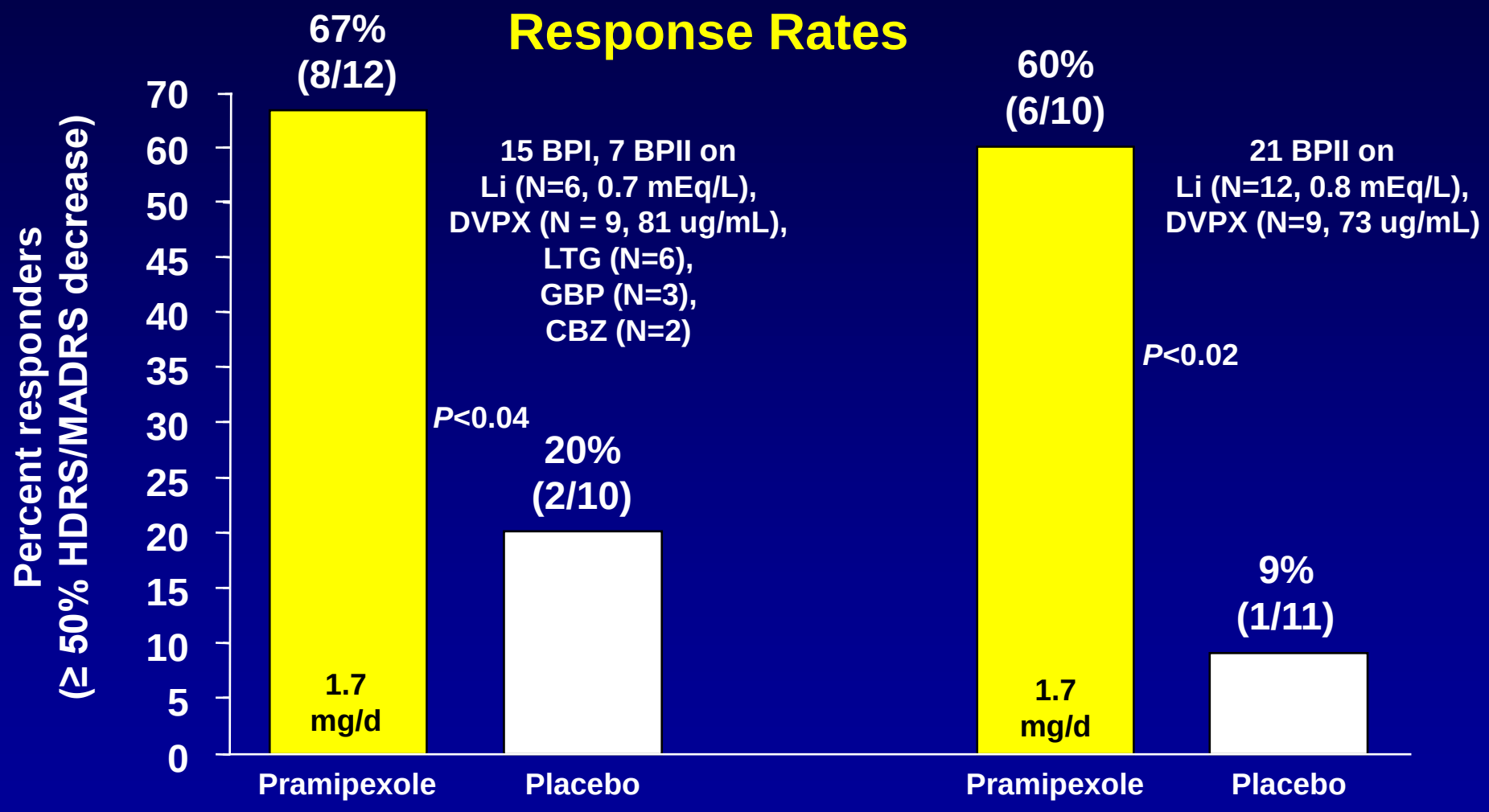
A. Study 1: Baseline MADRS 28.5 PBO, 29.1 ARI 17.6 mg/d;

B. Study 2: Baseline MADRS 29.4 PBO, 29.6 ARI 15.5 mg/d.

*P<0.05, †P<0.01 (aripiprazole vs placebo).

Thase ME, et al. J Clin Psychopharmacol 2008;28:13-20.

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

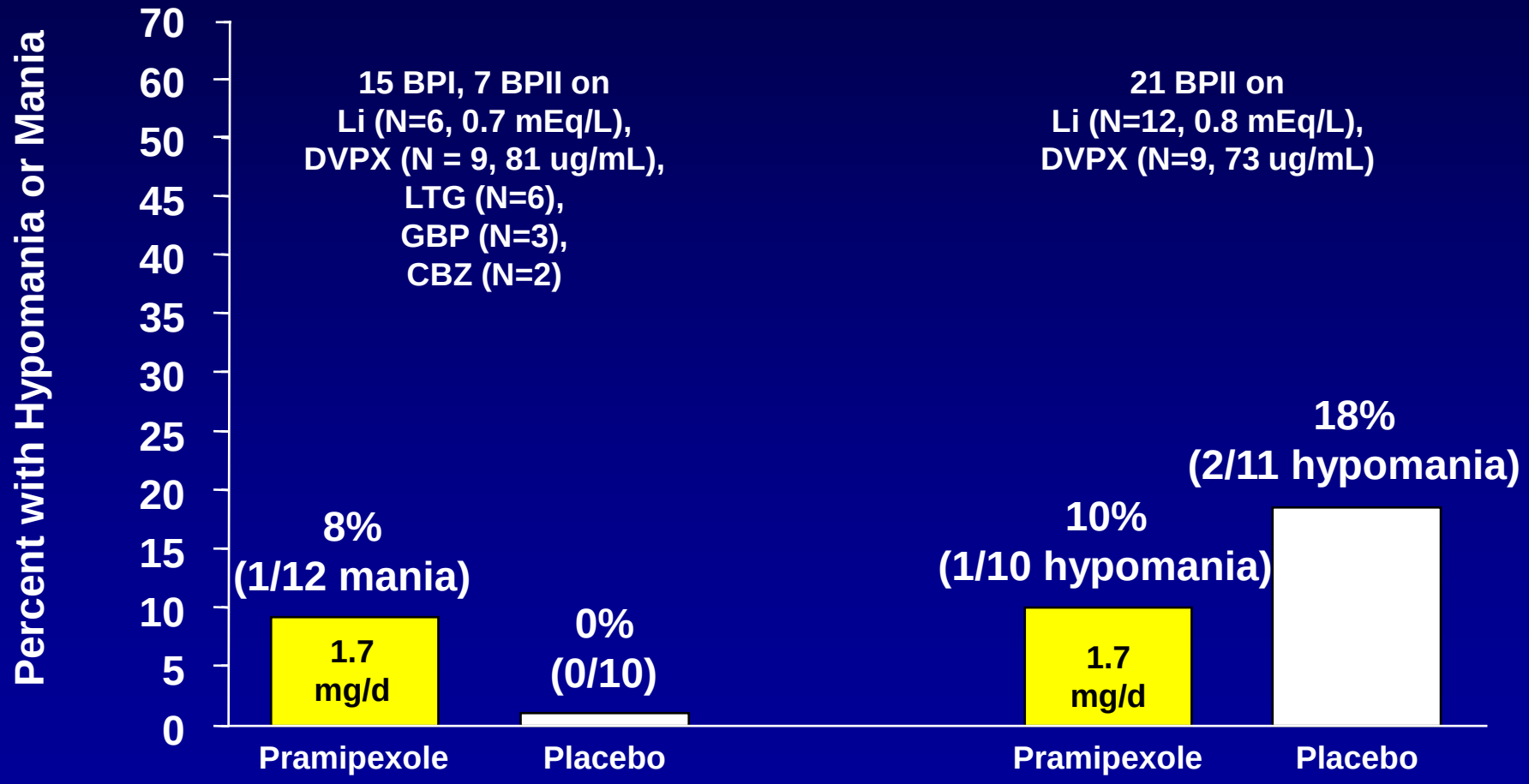


Goldberg JF, et al.
Am J Psychiatry 2004; 161:564-6

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

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

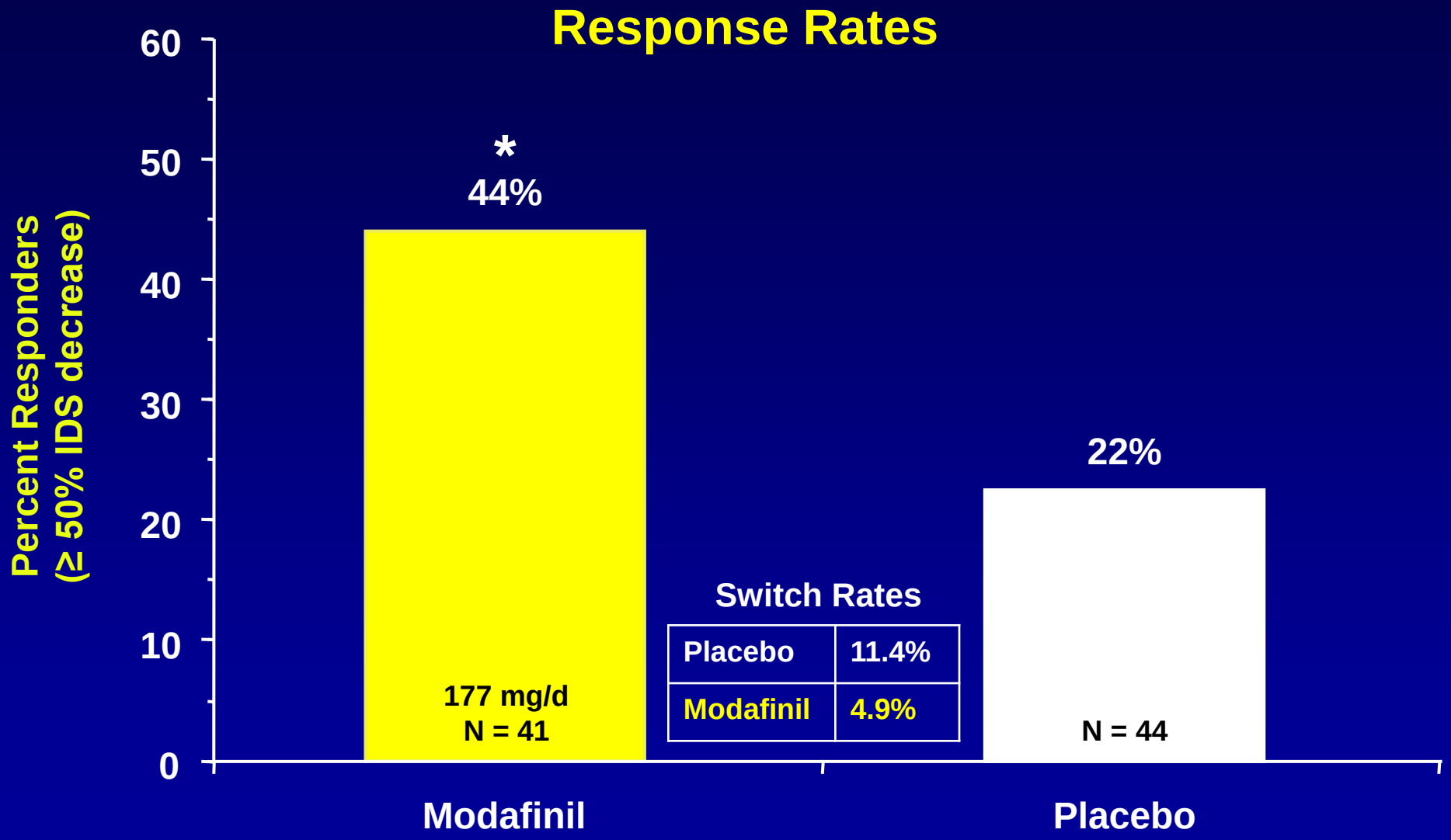
Switch Rates



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

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

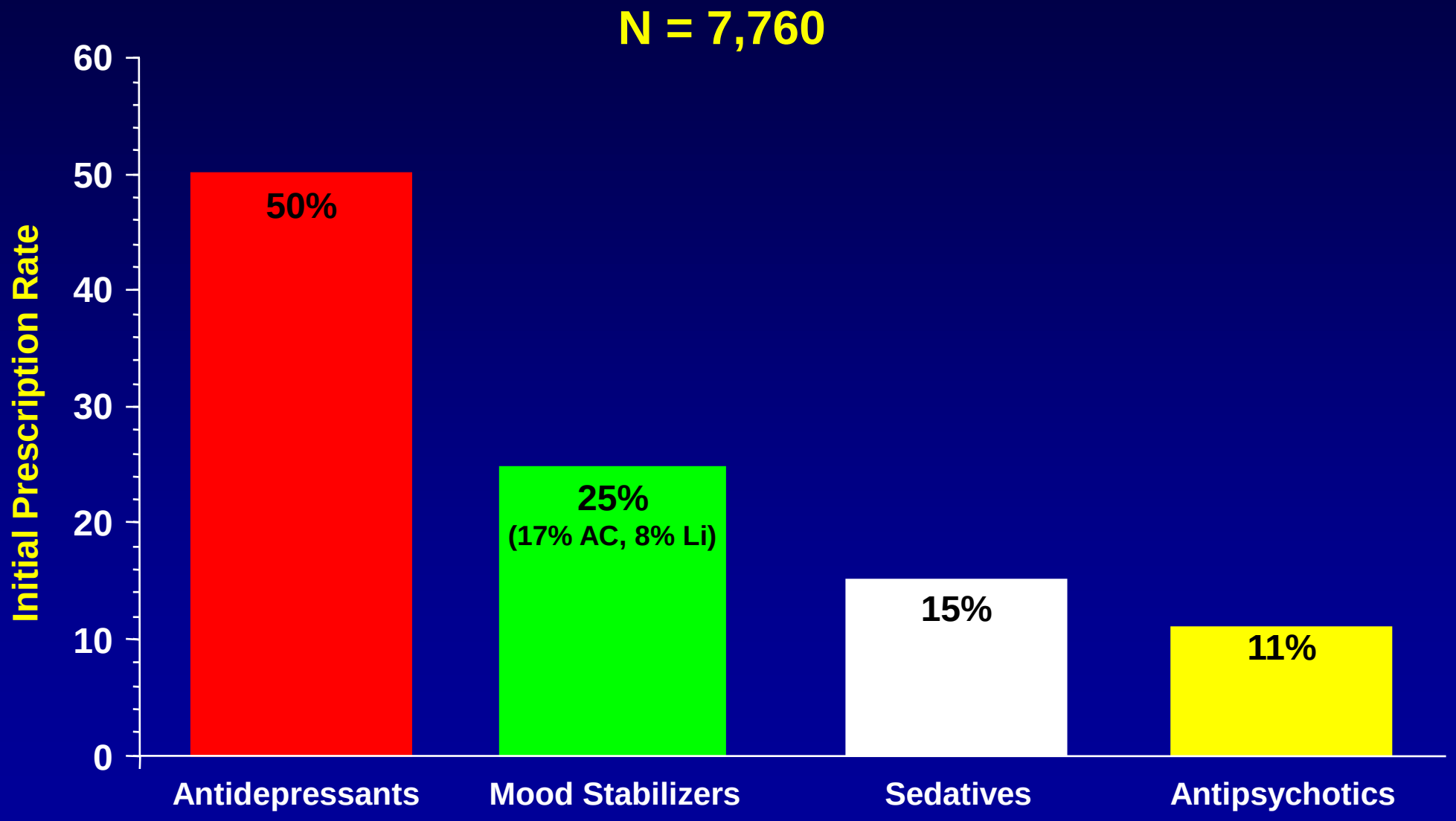
6-week Randomized Double-Blind Adjunctive Modafinil in Acute Bipolar Depression



*p < 0.05 vs placebo.

Frye M, et al. Am J Psychiatry 2007;164:1242-9.

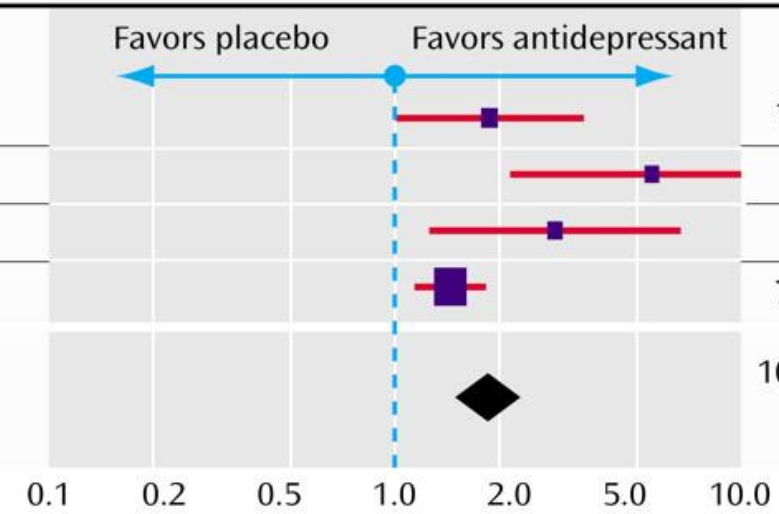
Antidepressants Most Common Initial Treatments for Bipolar Disorder Patients in US in 2002-2003



Baldessarini R, et al. Psychiatr Serv 2007;58:85-91.

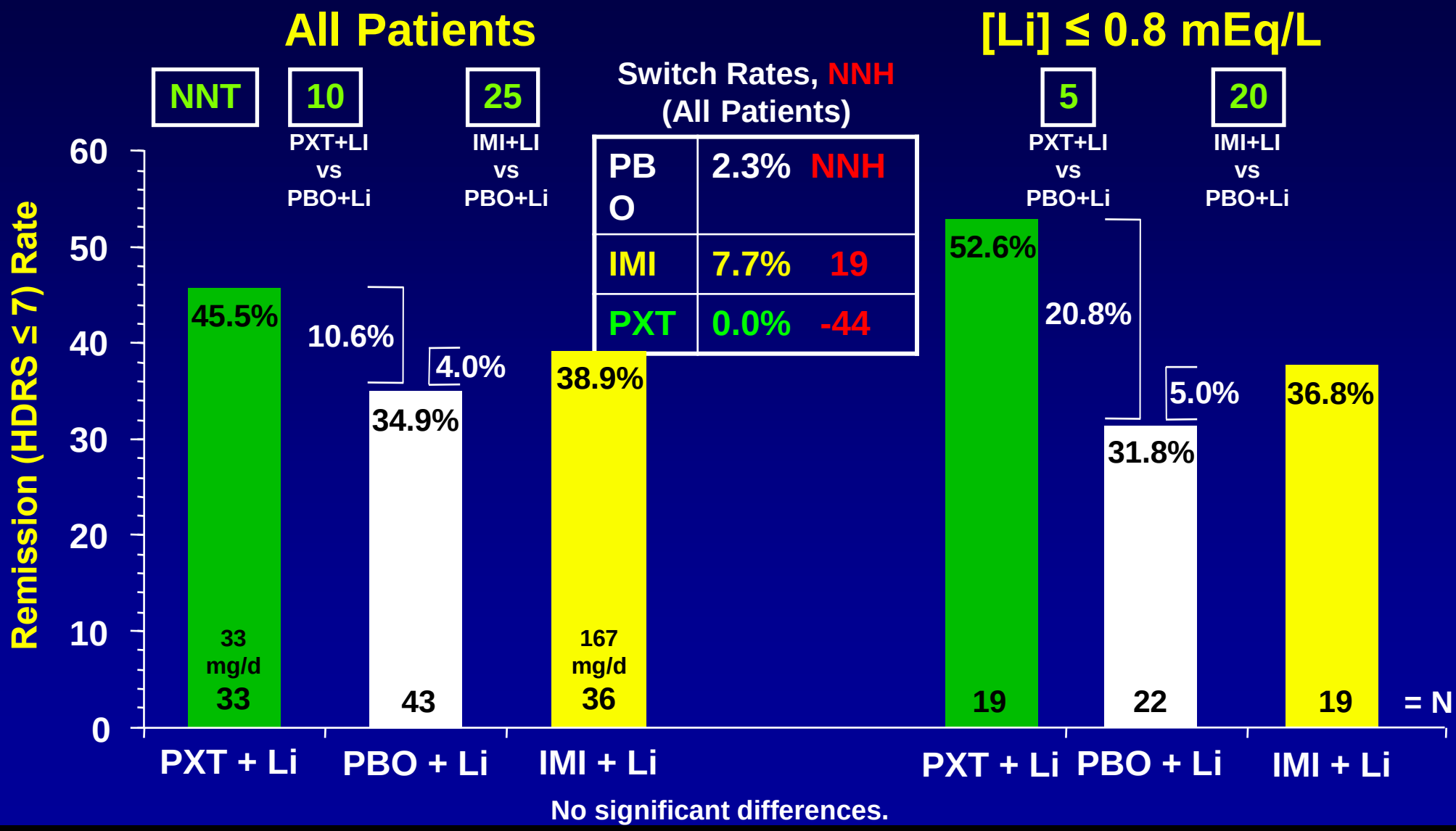
Response in Randomized Controlled Trials of Antidepressants vs. Placebo in Bipolar Depression

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.

10-Week Randomized Double-Blind Adjunctive Paroxetine, Imipramine in Acute Bipolar I Depression



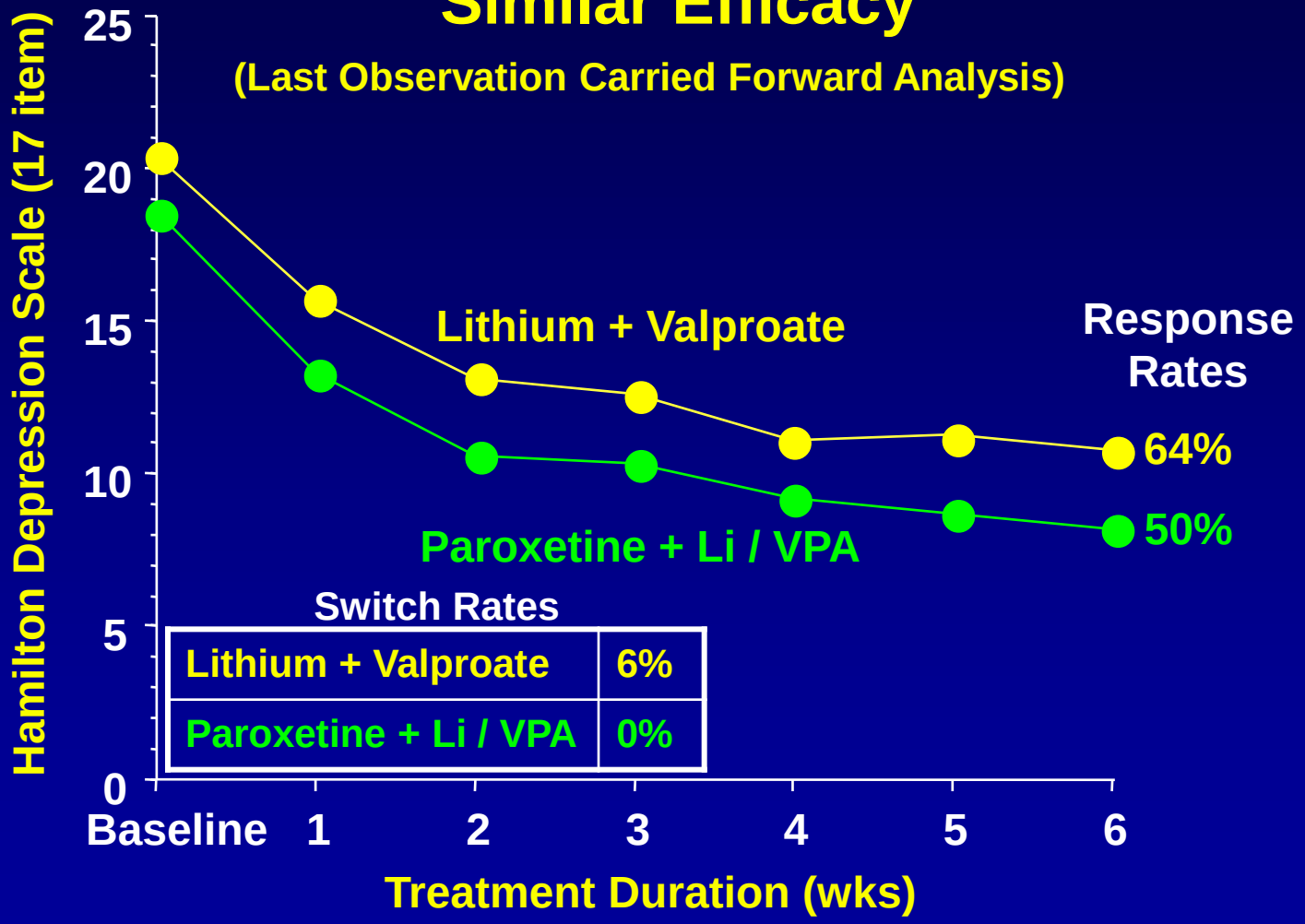
No significant differences.

Adding paroxetine or imipramine to lithium no better or worse than adding placebo .

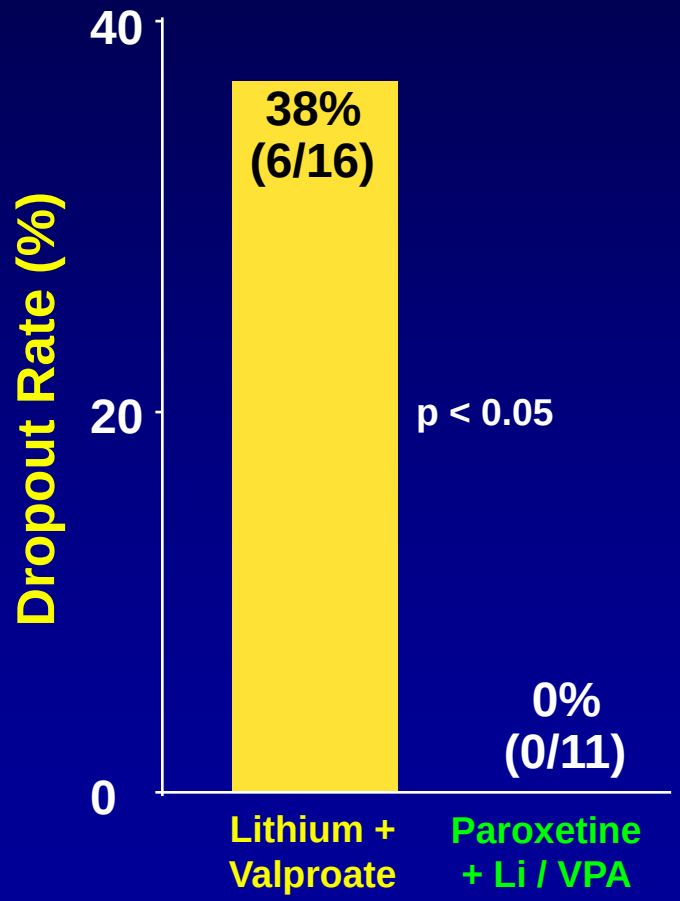
6-Week Randomized Double-Blind Adjunctive Paroxetine versus Second Mood Stabilizer in Bipolar Depression [a]

Similar Efficacy

(Last Observation Carried Forward Analysis)



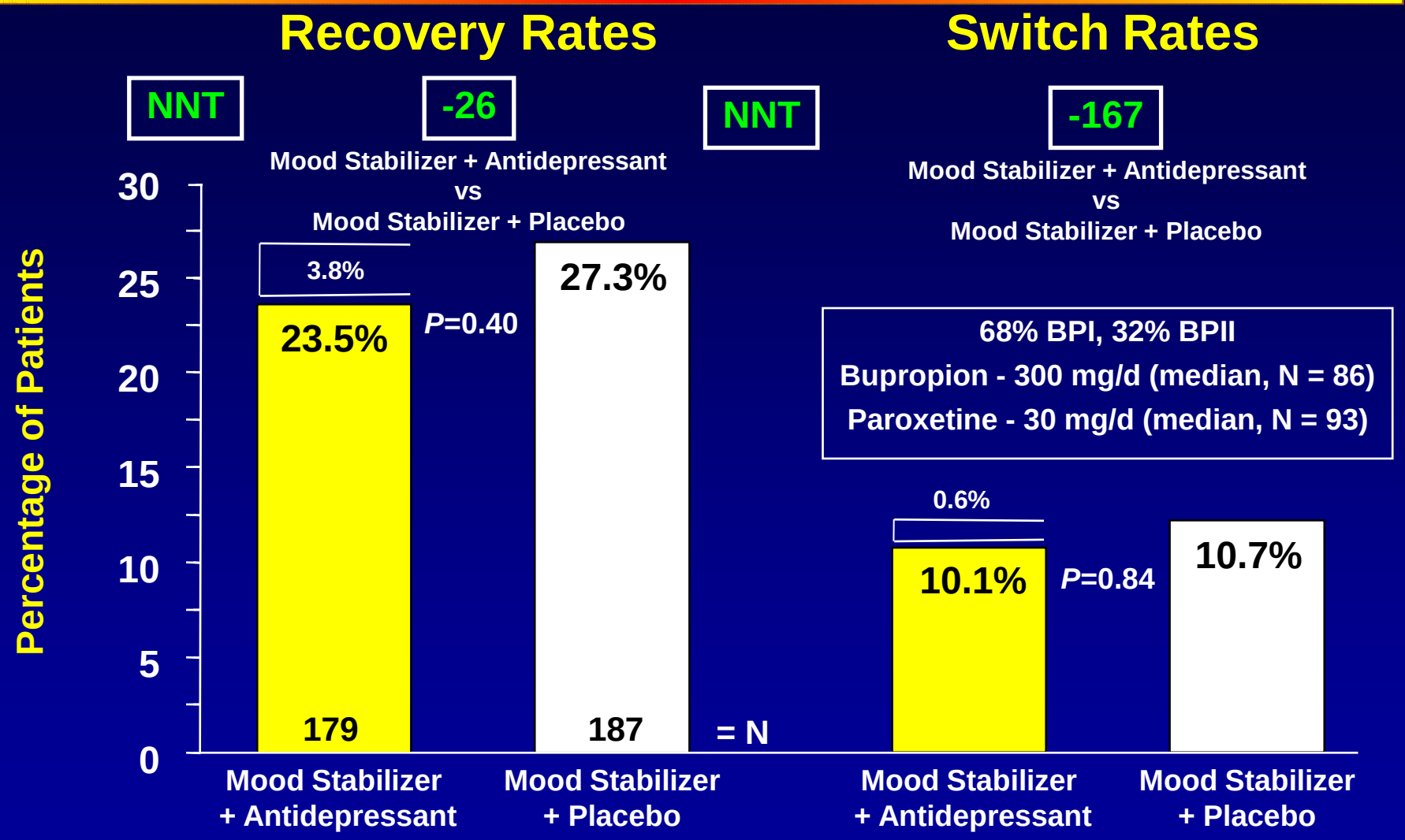
Better Tolerability



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

[a] 41% BPI, 59% BPII

26-Week Double-Blind Adjunctive Antidepressant vs Placebo in Acute Bipolar Depression

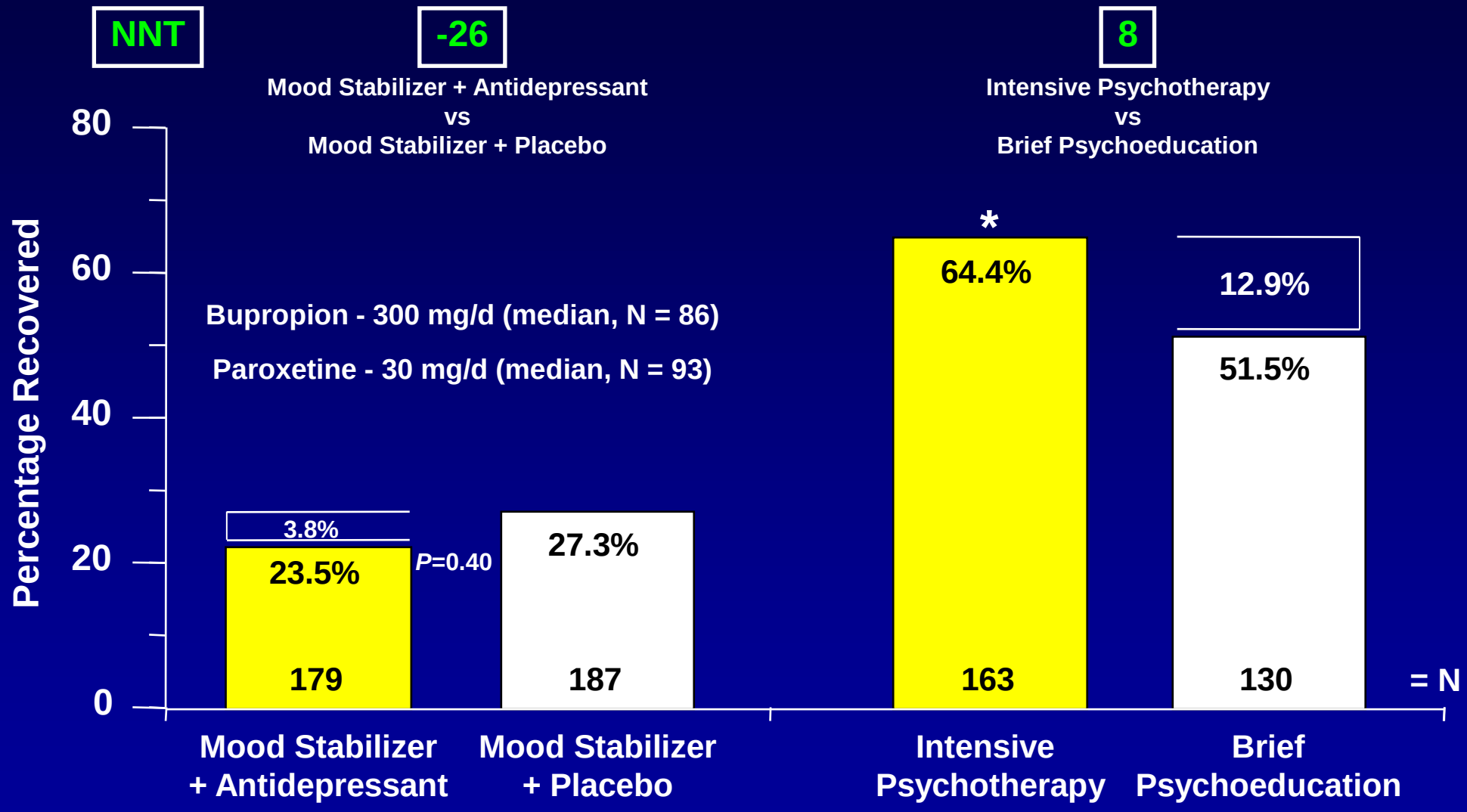


Sachs GS, et al. N Engl J Med 2007;356:1711-22.

Adding antidepressant to mood stabilizer(s) no better or worse than adding placebo.

STEP-BD Randomized Bipolar Depression Studies

Numbers Needed to Treat for Recovery, Rates



*p < 0.05 vs. Cntl.

Sachs GS, et al. N Engl J Med 2007;356:1711-22.

Miklowitz DJ, et al. Arch Gen Psychiatry 2007;64:419-27.

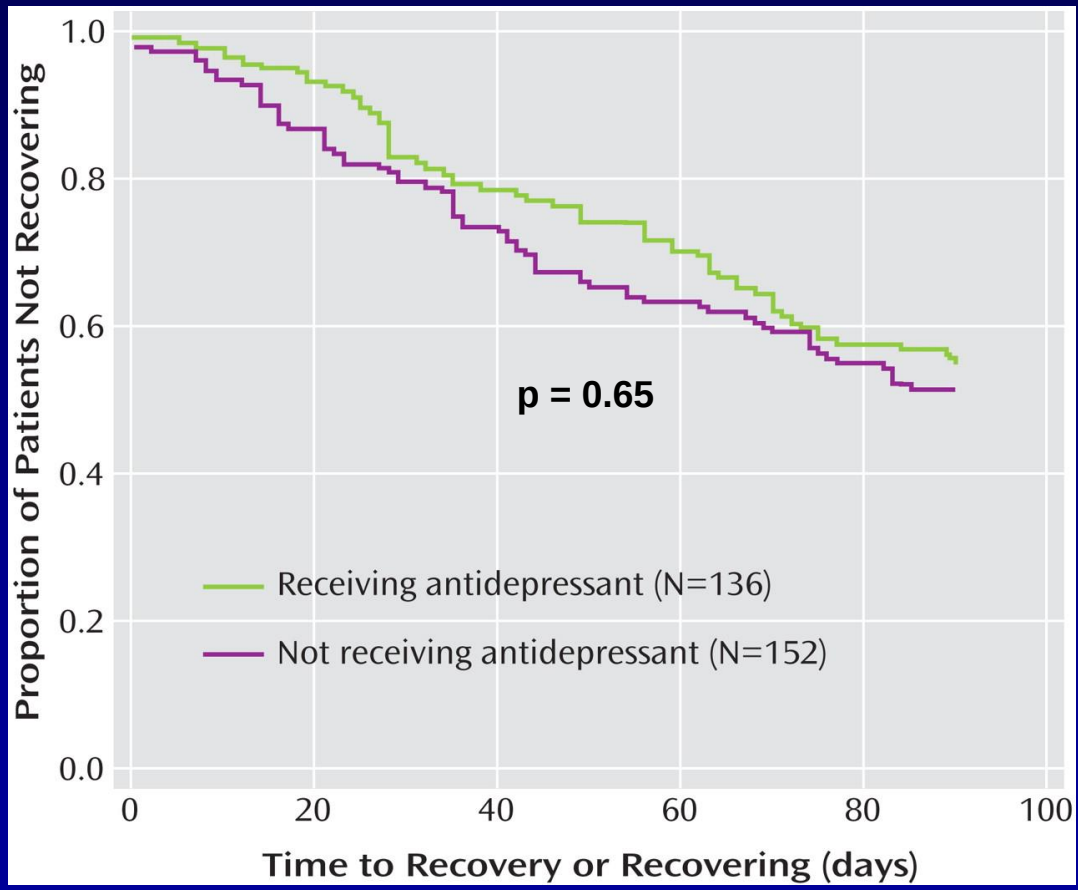
Adjunctive psychotherapy (but not adjunctive antidepressants) increased recovery rate.

Adjunctive Antidepressants in Bipolar Depression with ≥ 2 Concurrent Manic Symptoms

STEP-BD Patients
Taking Mood Stabilizer or Atypical Antipsychotic

Adjunctive Antidepressants vs. None

- Recovery - neither hastened nor delayed
- Mania symptom severity - greater at 3 months



Goldberg JF, et al. Am J Psychiatry 2007;164:1348-55.

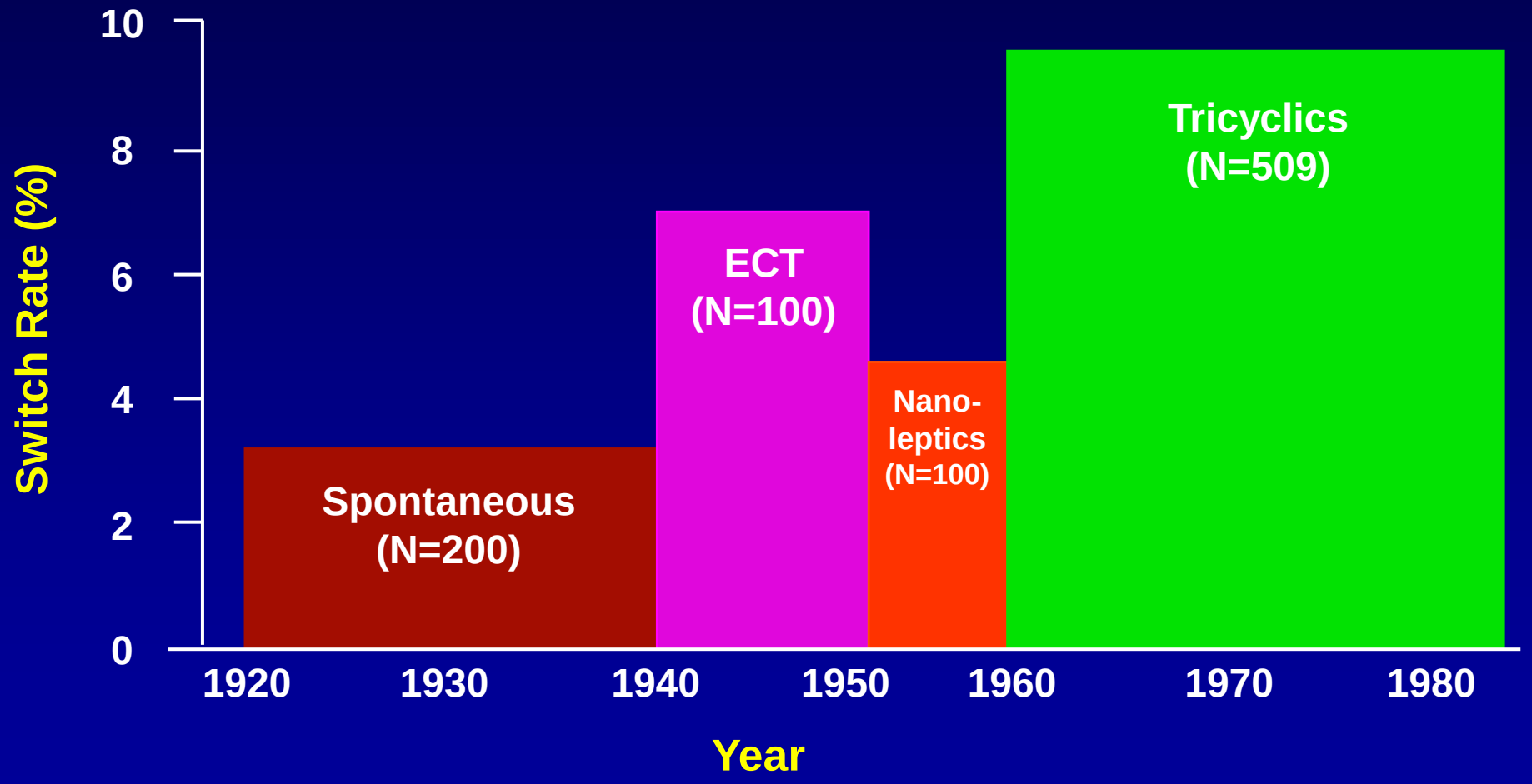
Do Antidepressants Induce Mania?

- 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.

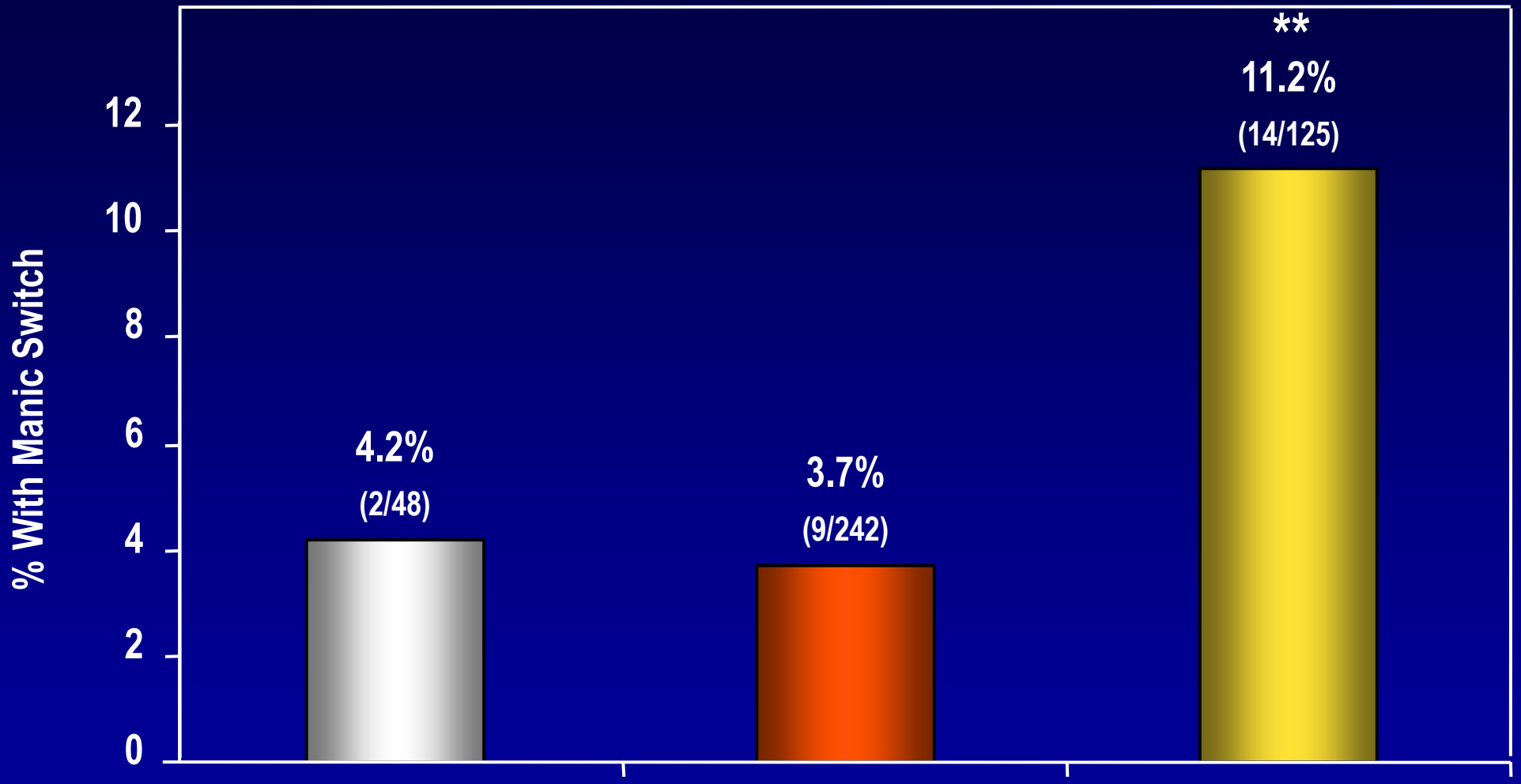
Switch Rate From Index Depression Into Mania

By Era and Prevailing Treatment



Angst J. Psychopathology 1985.

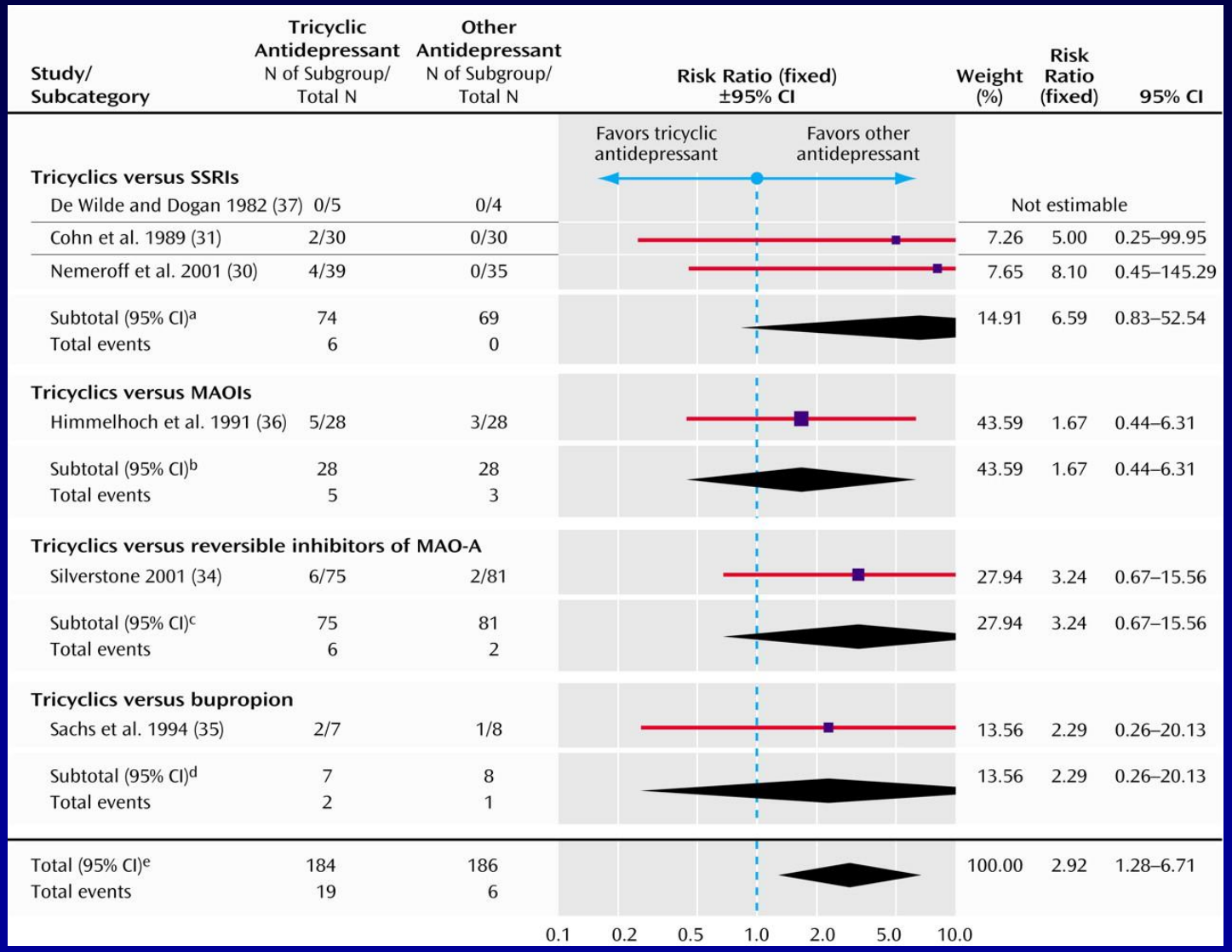
Increased Mania Switch Rates with Tricyclics



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

** p < 0.01 vs PBO

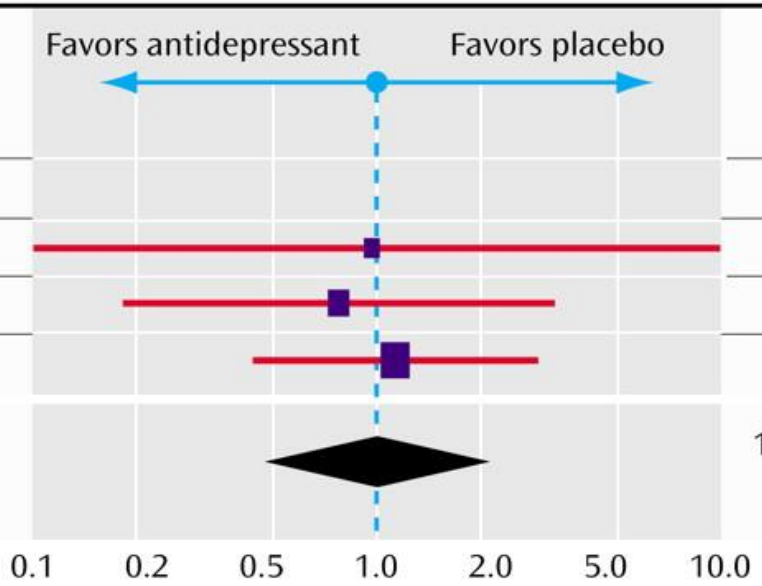
Switch Rates With Tricyclic vs. Other Antidepressants



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

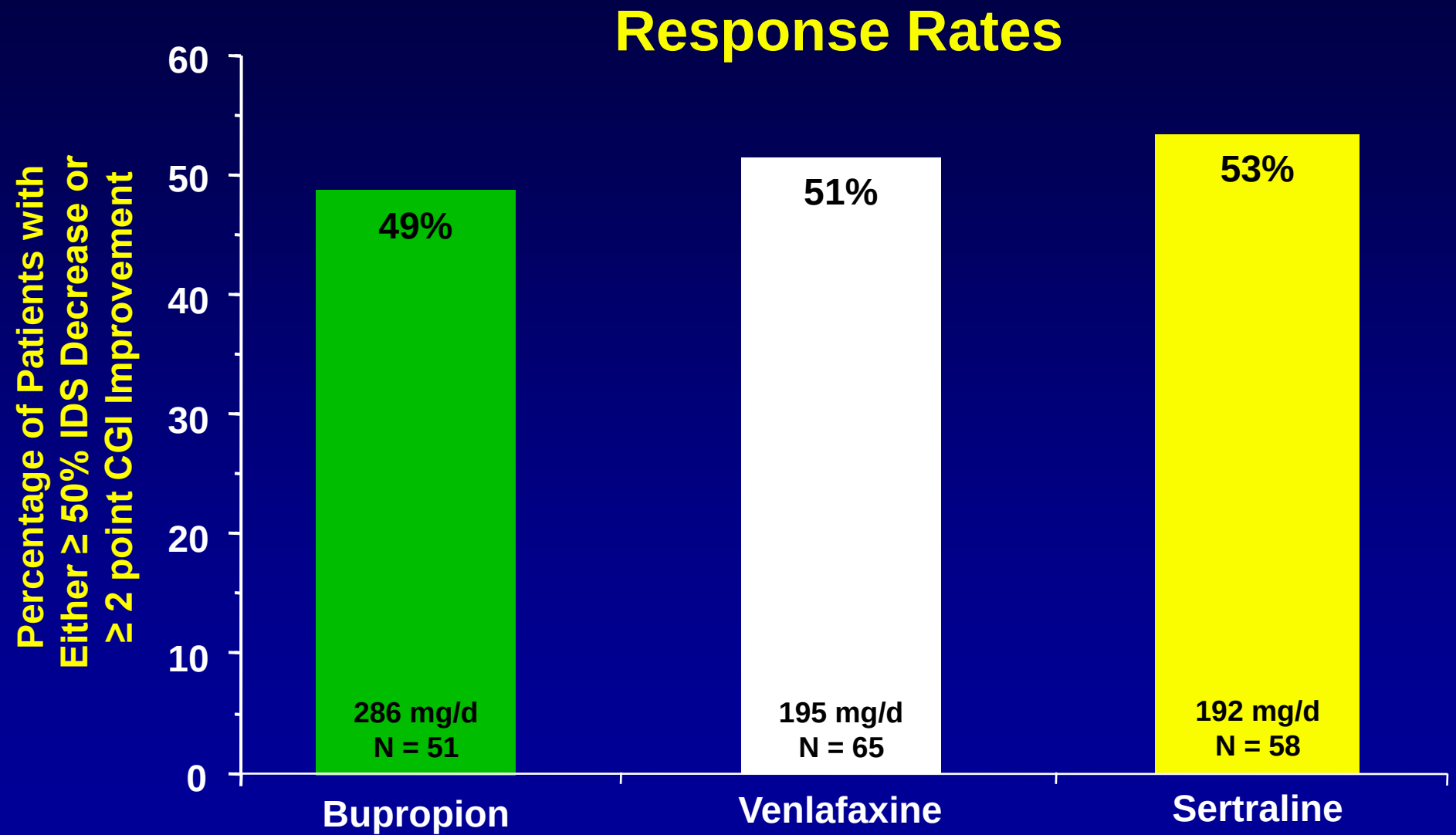
Manic Switch Rates in Randomized Controlled Trials of Antidepressants vs. Placebo

Study/ Subcategory	Antidepressant N of Subgroup/ Total N	Placebo N of Subgroup/ Total N	Risk Ratio (Fixed) ±95% CI	Weight (%)	Risk Ratio (fixed)	95% CI
			Favors antidepressant / Favors placebo			
Mendlewicz et al. 1980 (33)	0/39	0/19		Not estimable		
Himmelhoch et al. 1982 (32)	0/28	0/31		Not estimable		
Cohn et al. 1989 (31)	2/60	1/29		10.95	0.97	0.09–10.23
Nemeroff et al. 2001 (30)	4/74	3/43		30.83	0.77	0.18–3.30
Tohen et al. 2004 (29)	5/86	19/370		58.22	1.13	0.43–2.95
Total (95% CI)[a]	287	492		100.00	1.00	0.47–2.13
Total events	11	23				



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

10-Week Randomized Adjunctive Antidepressants in Acute Bipolar Depression

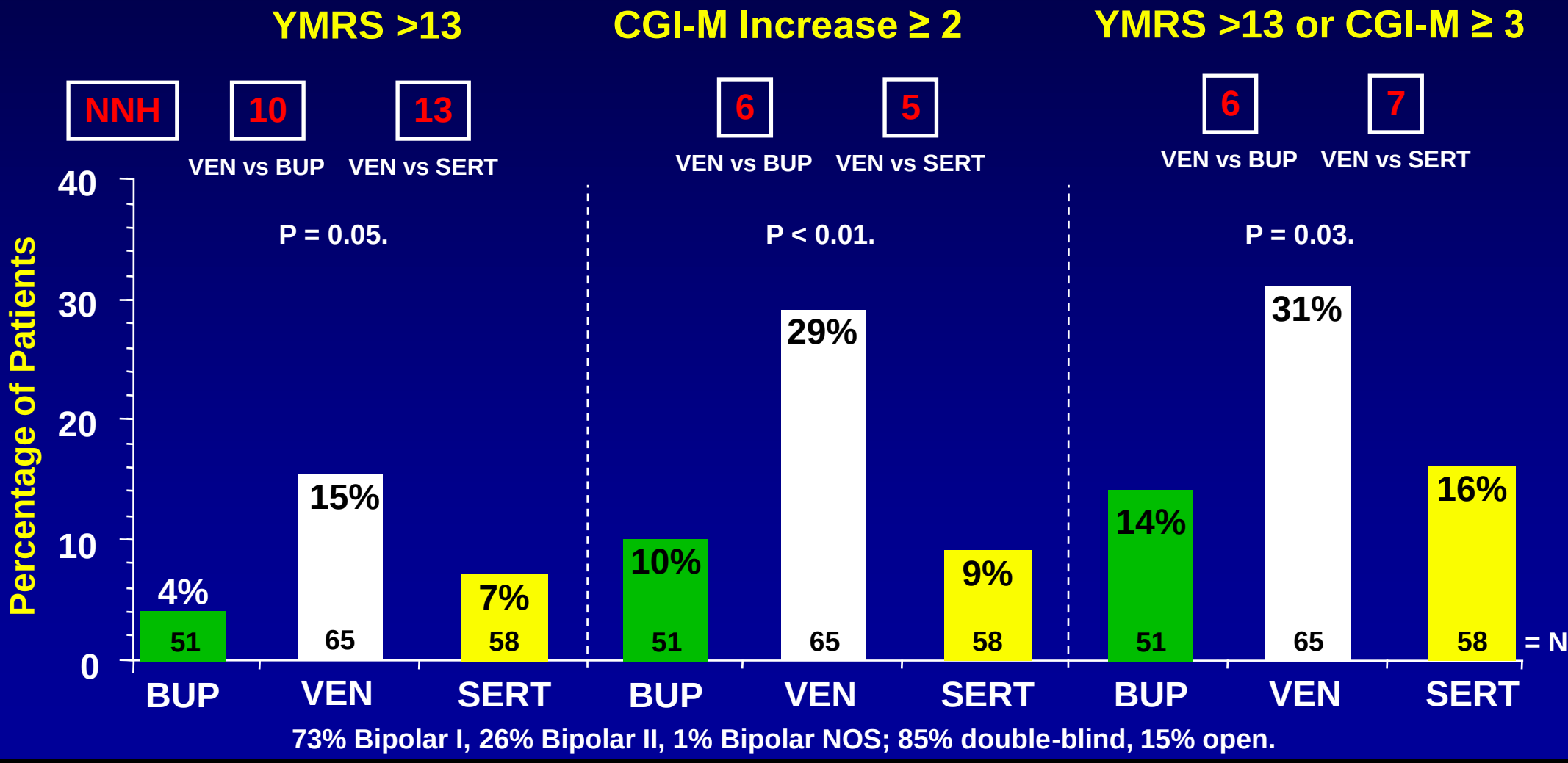


73% Bipolar I, 26% Bipolar II, 1% Bipolar NOS; 85% double-blind, 15% open.

Absence of placebo group makes efficacy assessment challenging.

10-Week Randomized Adjunctive Antidepressants in Acute Bipolar Depression

Switch Rates



73% Bipolar I, 26% Bipolar II, 1% Bipolar NOS; 85% double-blind, 15% open.

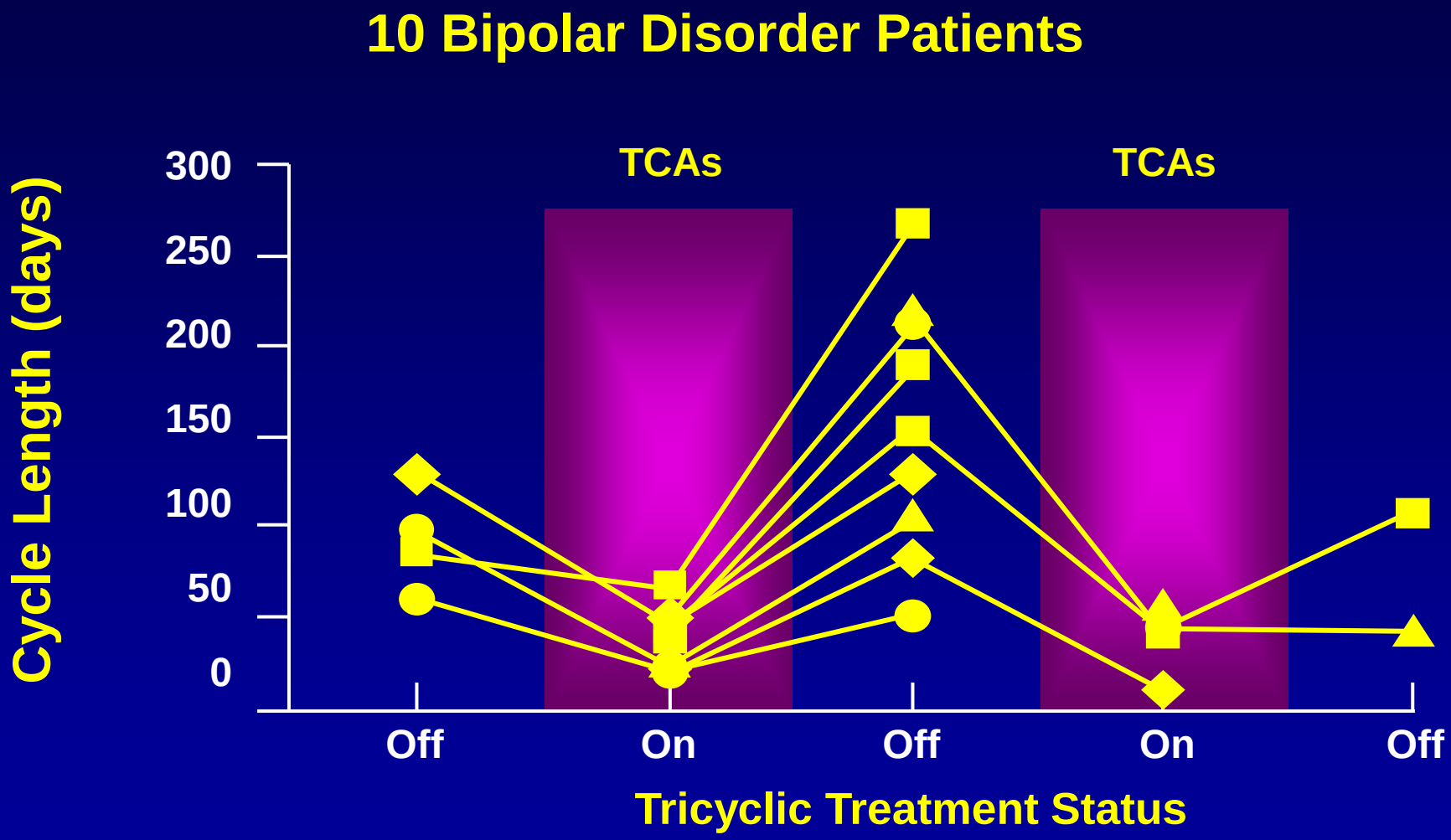
Adjunctive venlafaxine (compared to sertraline, bupropion) yielded more switching.

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



Wehr TA, Goodwin FK. Am J Psychiatry 1987.

Acute Bipolar I Depression Algorithm

- Optimize current mood stabilizer (if applicable) before initiating additional treatment for depression
  - Patients on Li - optimize (serum Li level ≥ 0.8 mEq/L) to determine whether adjunctive intervention necessary
  - Patients with recent and/or severe history of mania - receive or add an effective antimanic agent
- Stage 1
  - Adjunctive LTG if depression persists after mood stabilizer optimization

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 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

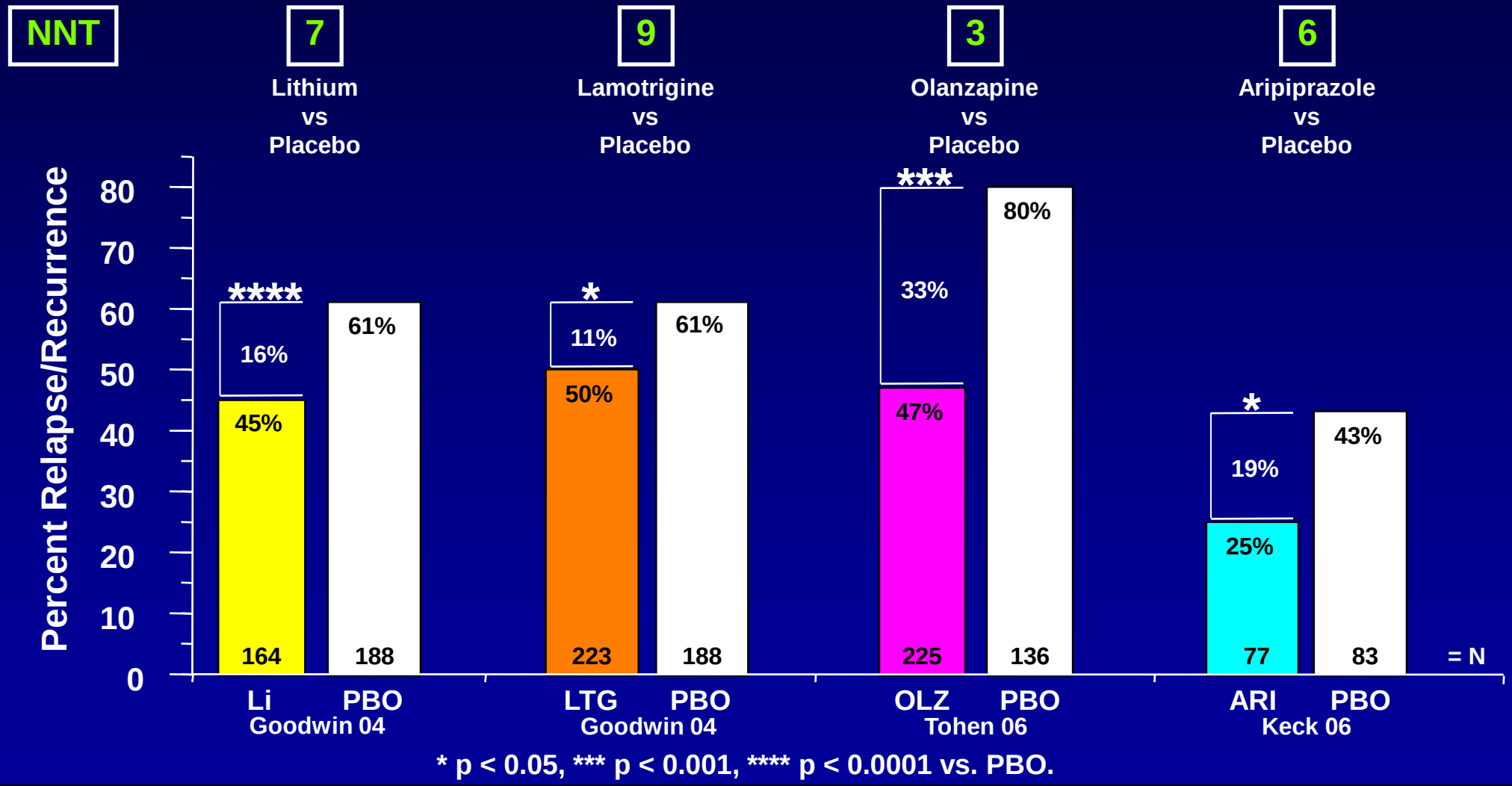
Suppes T, et al. J Clin Psychiatry 2005;66:870-86.

Maintenance Treatment of Bipolar Depression

Overview of Bipolar Monotherapy Maintenance Studies

Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

Contemporary Registration Studies



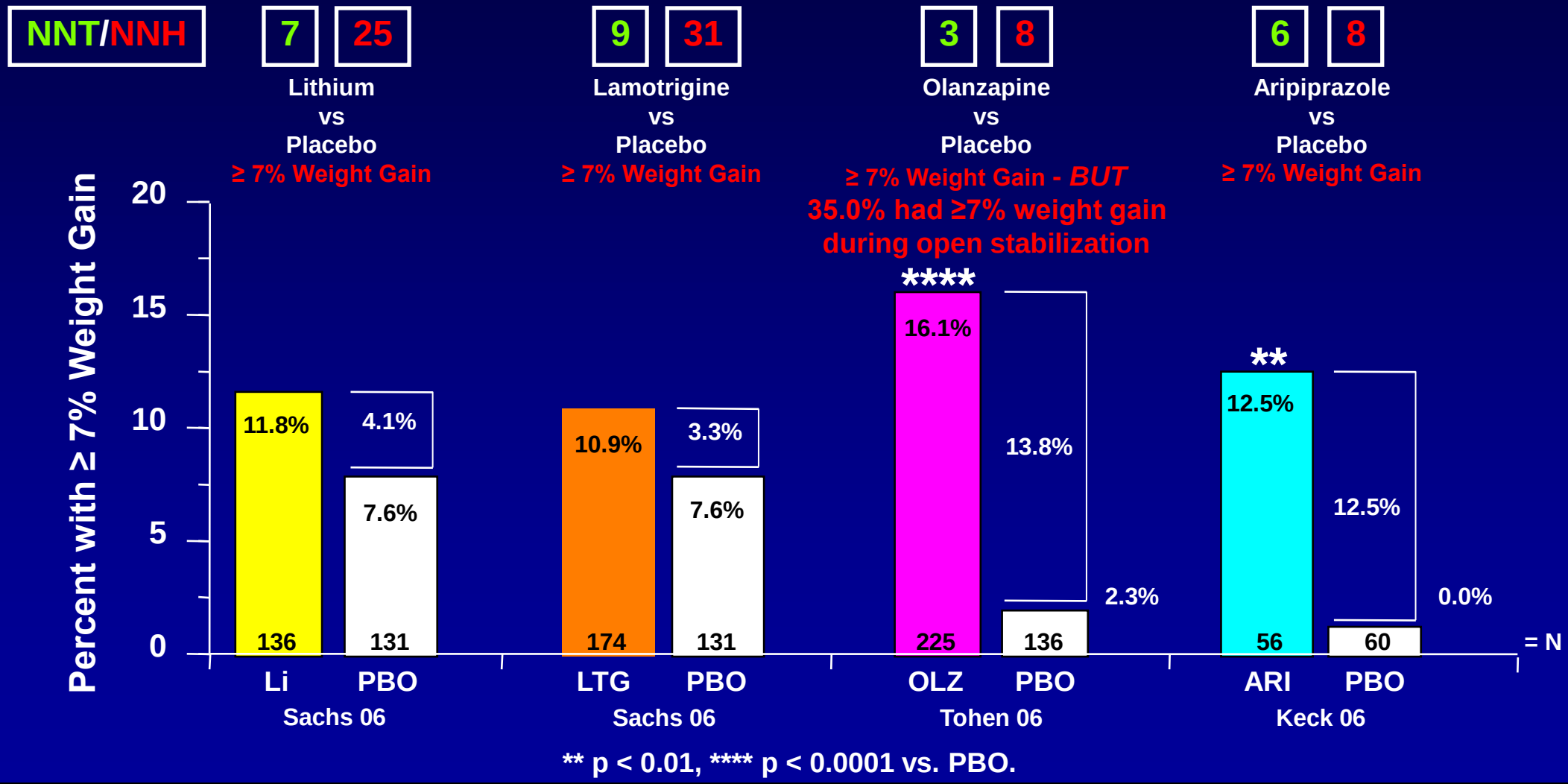
* p < 0.05, *** p < 0.001, **** p < 0.0001 vs. PBO.

Approved maintenance treatments have single-digit NNTs.

Overview of Bipolar Monotherapy Maintenance Studies

Numbers Needed to Treat and Harm, ≥ 7% Weight Gain Rates

Contemporary Registration Studies



** p < 0.01, **** p < 0.0001 vs. PBO.

Mood stabilizers compared to antipsychotics - slightly less efficacy, but better tolerability.

Numbers Needed to Treat in Bipolar Maintenance

	Episode Prevention	Mania Prevention	Depression Prevention
Mood Stabilizers			
Lithium[1]	**7**	**8**	49
Divalproex[2]	**8**	22	11
Lamotrigine[1]	**9**	23	15
Atypical Antipsychotics			
Olanzapine[3]	**3**	**5**	12
Aripiprazole[4]	**6**	**6**	64
Quetiapine + Lithium/Divalproex[5-6] *	**4**	**8**	**6**

Boldface indicates approved treatments. Yellow boldface indicates noteworthy (single-digit) NNTs.*Compared to Li/VPA Monotherapy.

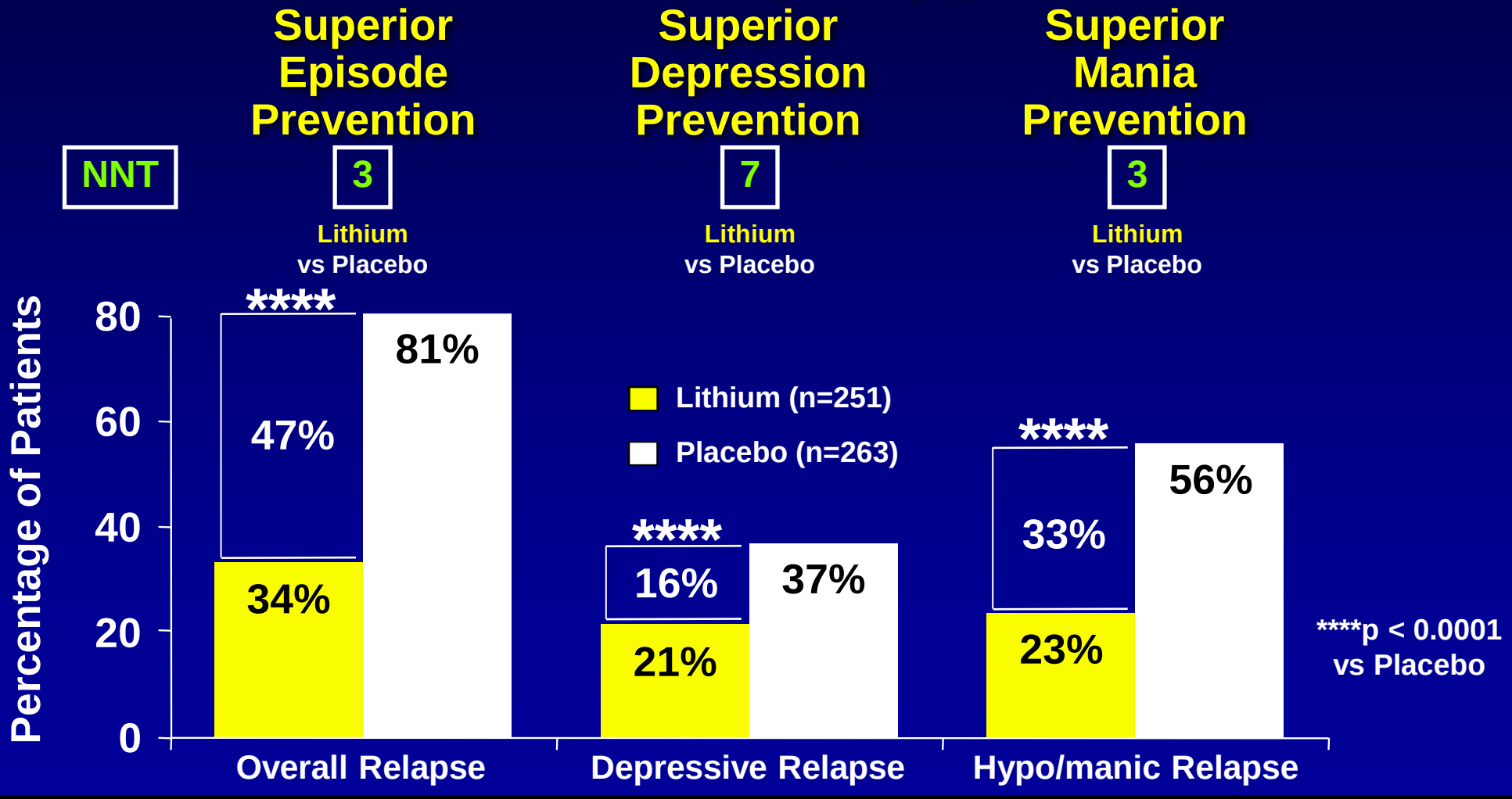
Ketter TA (ed). Handbook of Diagnosis and Treatment of Bipolar Disorder, Am Psychiat Pub, Inc., Washington, DC, 2009.
Data from: [1] Goodwin et al. J Clin Psychiatry 2004;65:432-41; [2]Bowden CL, et al. Arch Gen Psychiatry 2000;57:481-9;
[3]Tohen MF, et al. Am J Psychiatry 2006;163:247-56; [4]Keck PE, et al. J Clin Psychiatry 2006;67:626-37;
[5]Vieta E, et al. J Affect Disord 2008;109:251-63; [6]Suppes T, at al. Am J Psychiatry 2009;166:476-88.

FDA approved Bipolar Disorder maintenance treatments have single-digit overall NNTs.

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

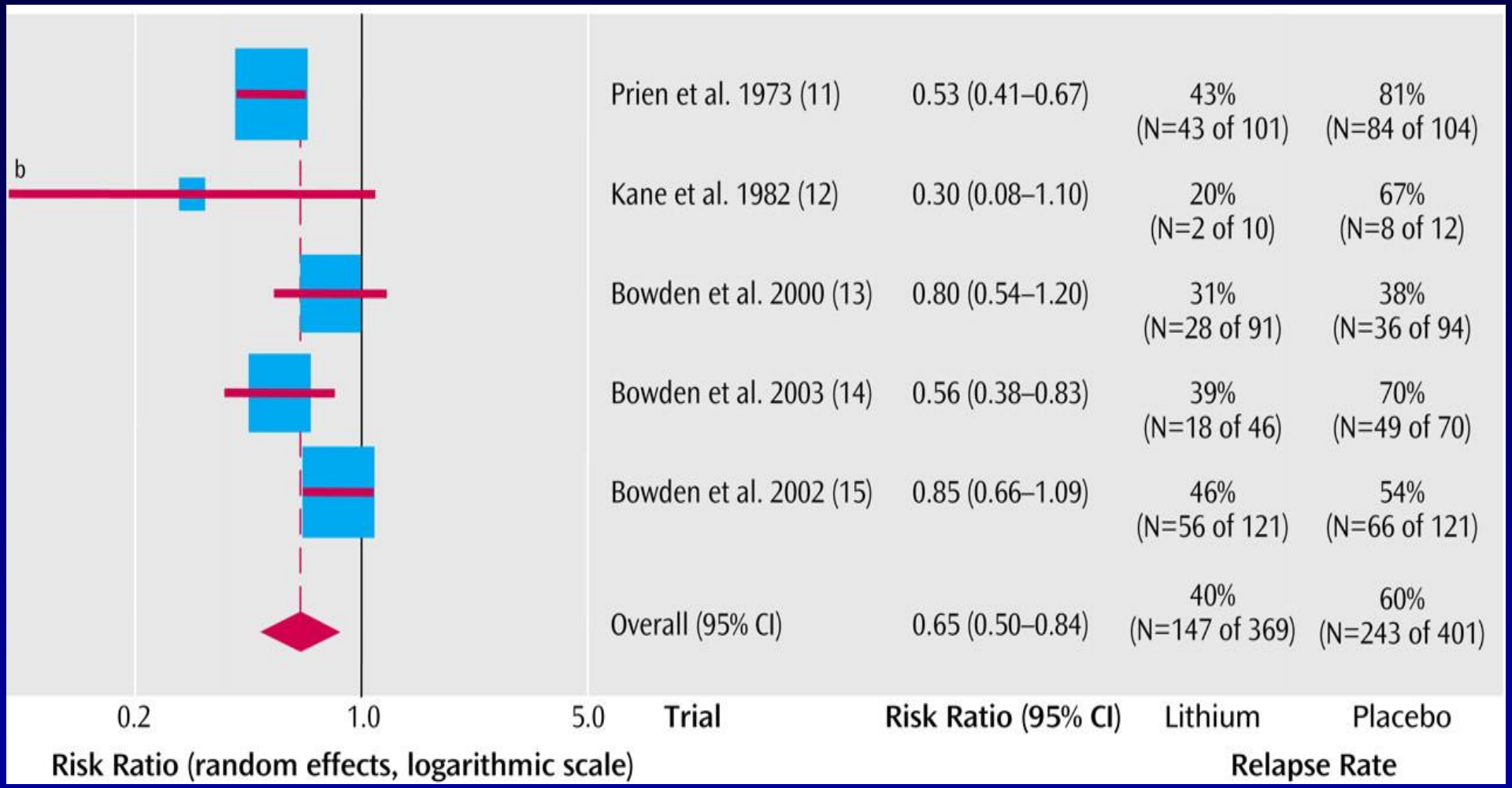
Lithium Compared to Placebo, Primarily After Manic/Mixed Episodes

9/10 Placebo-Controlled Studies (499/514 pts) Positive



Rapid discontinuation can yield rebound episodes.

Lithium Prevention of Any Relapse in Bipolar Disorder

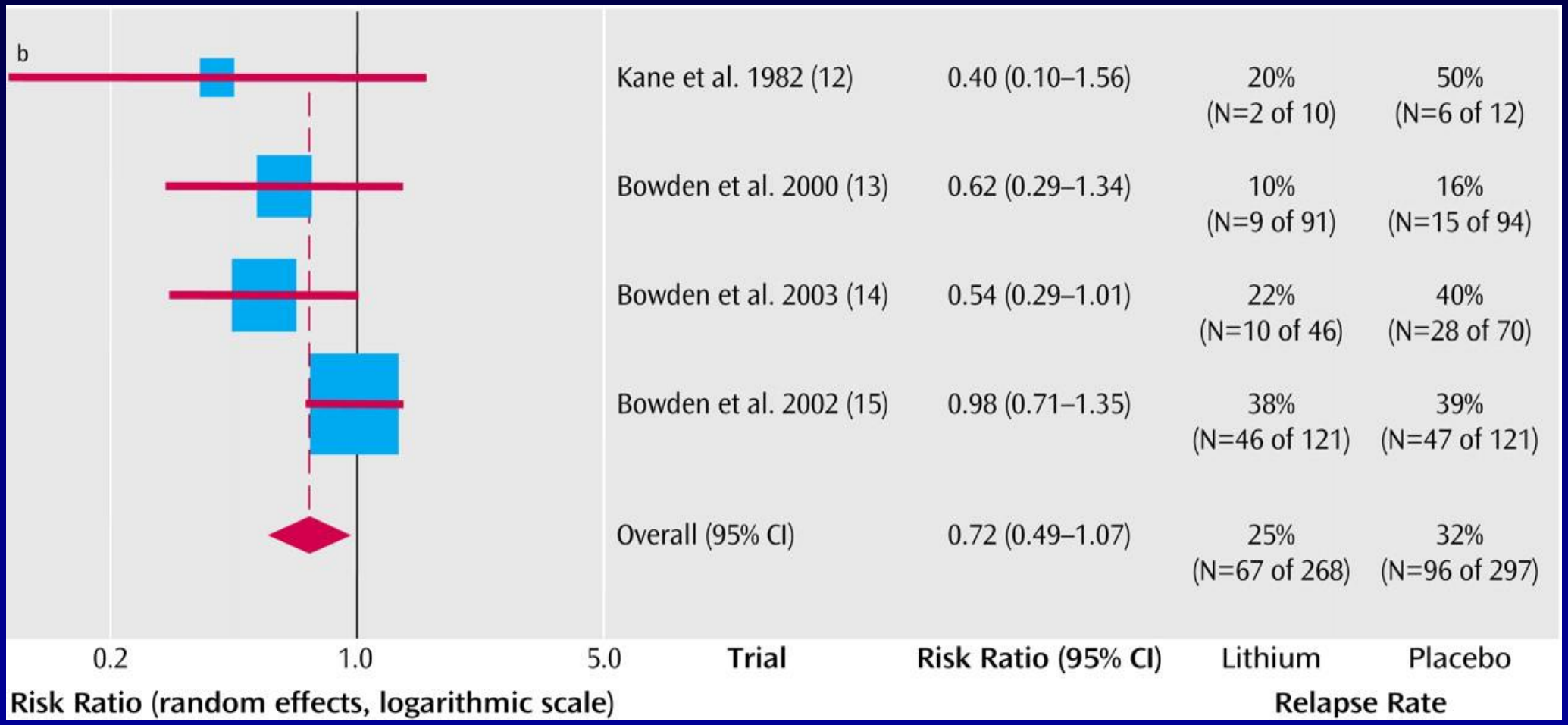


Areas of blue boxes reflect weights of studies in meta-analysis.

[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

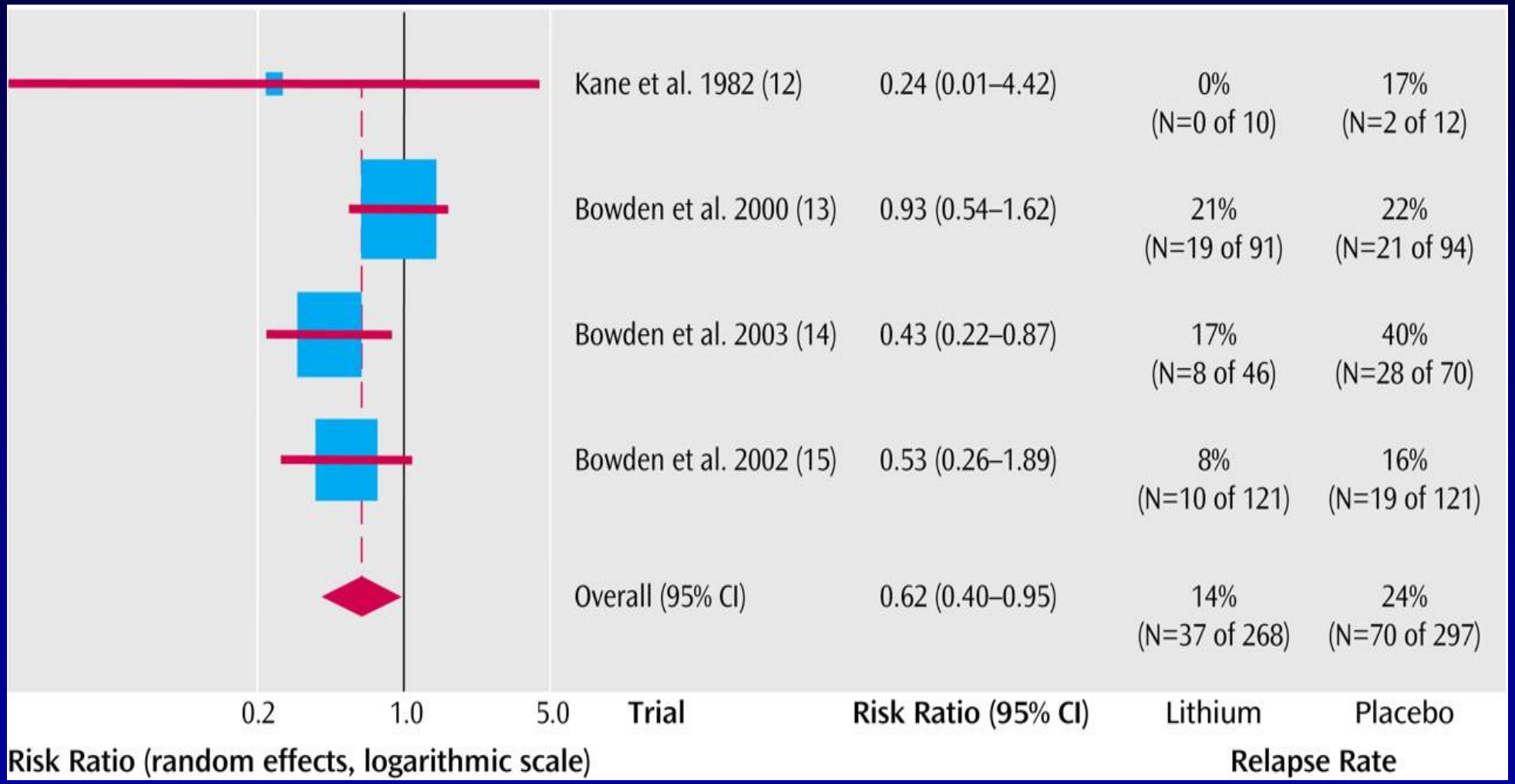


Areas of blue boxes reflect weights of studies in meta-analysis.

[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

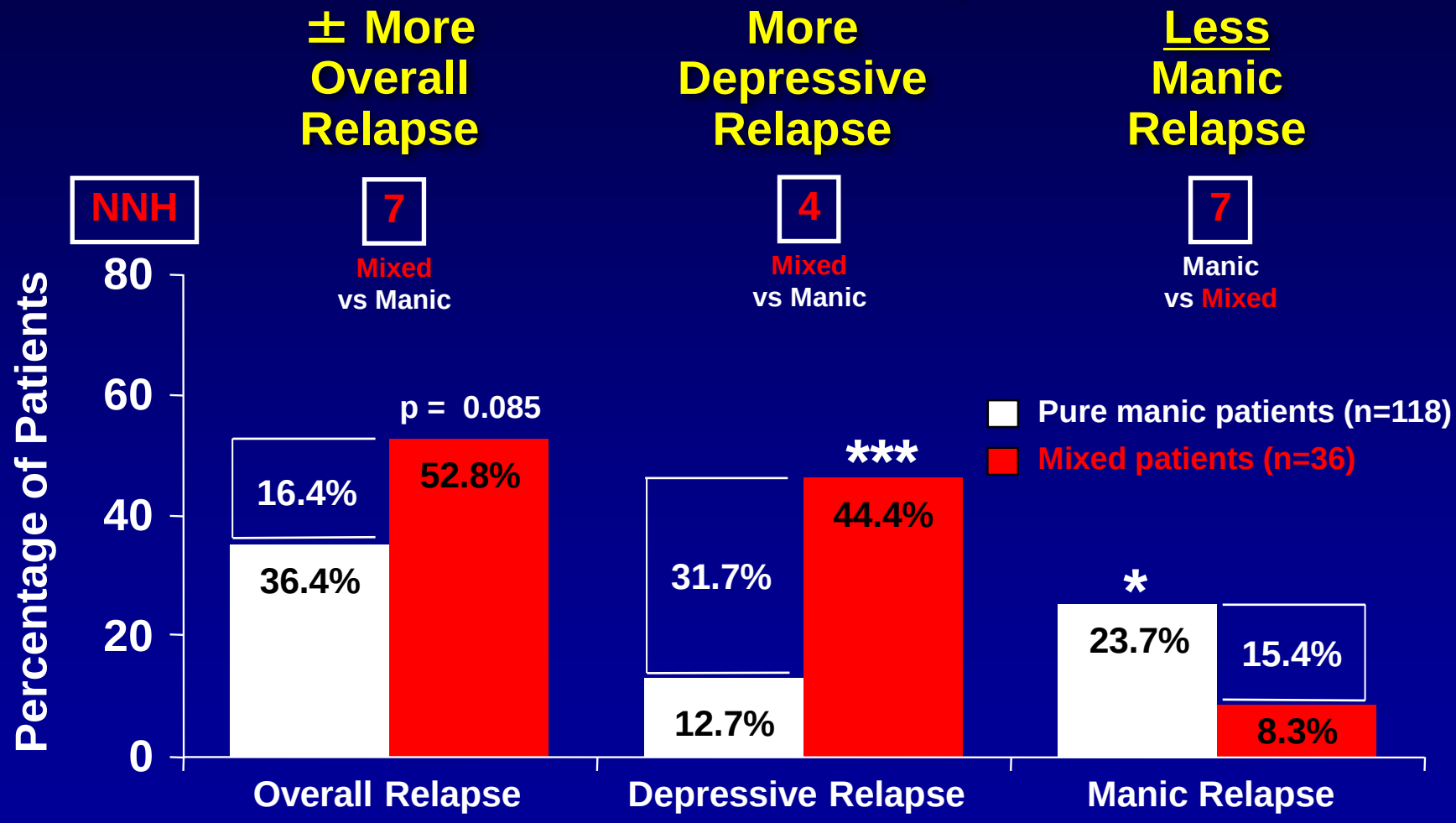


Areas of blue boxes reflect weights of studies in meta-analysis.

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

Differential Recurrence Risks with Mixed Compared to Pure Manic Index Episodes

24-Month Naturalistic Maintenance in Mixed Compared to Pure Manic Patients



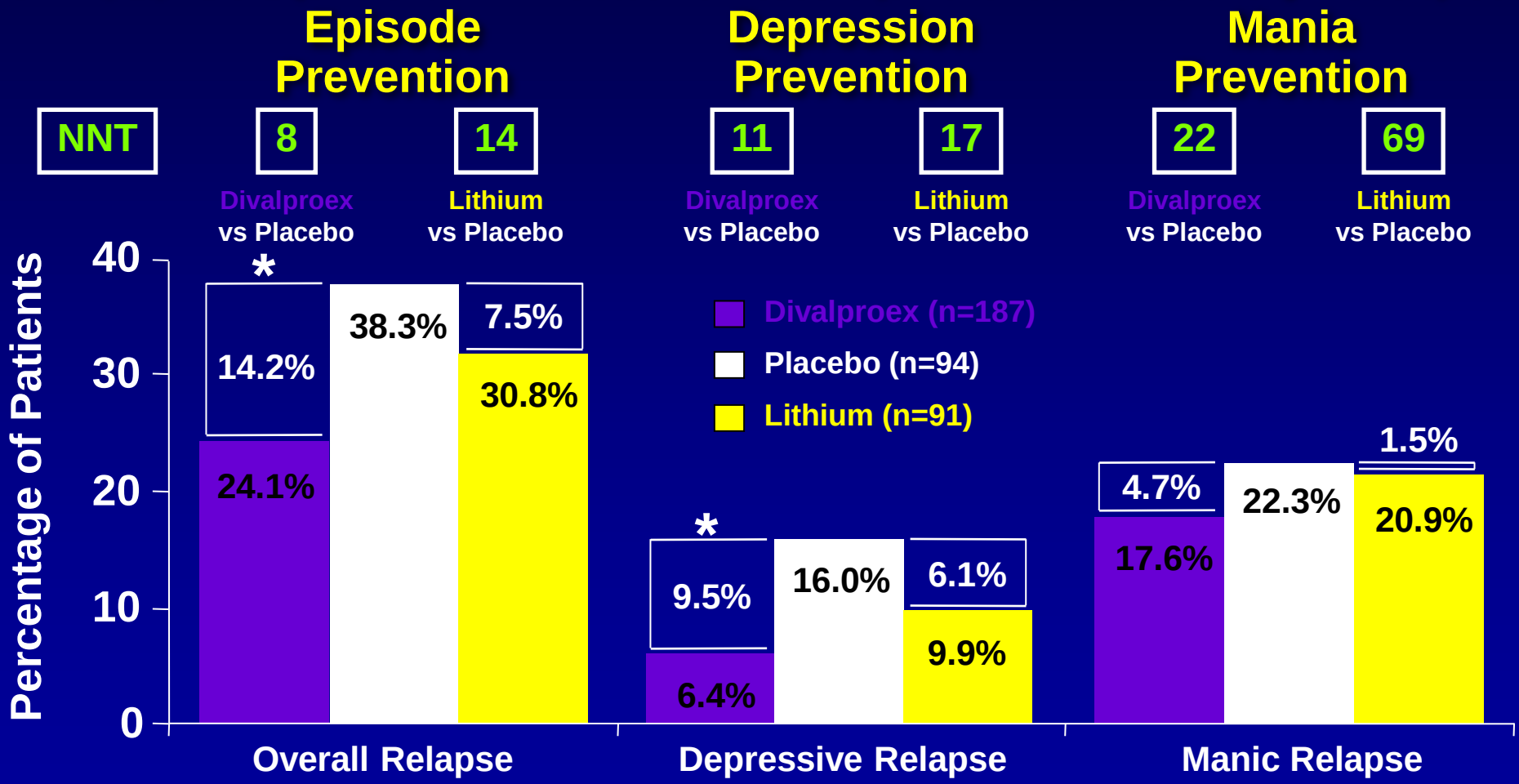
Tohen M, et al. Am J Psychiatry 2003;160:2099–2107. *p < 0.05, ***p < 0.001.

Mixed episodes increased depression recurrence, pure manic episodes increased mania recurrence.

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

Divalproex Compared to Lithium/Placebo After Manic/Mixed Episodes

DVPX, Li, PBO Equivalent on 1° Outcome Measure (time to recurrence of any mood episode)



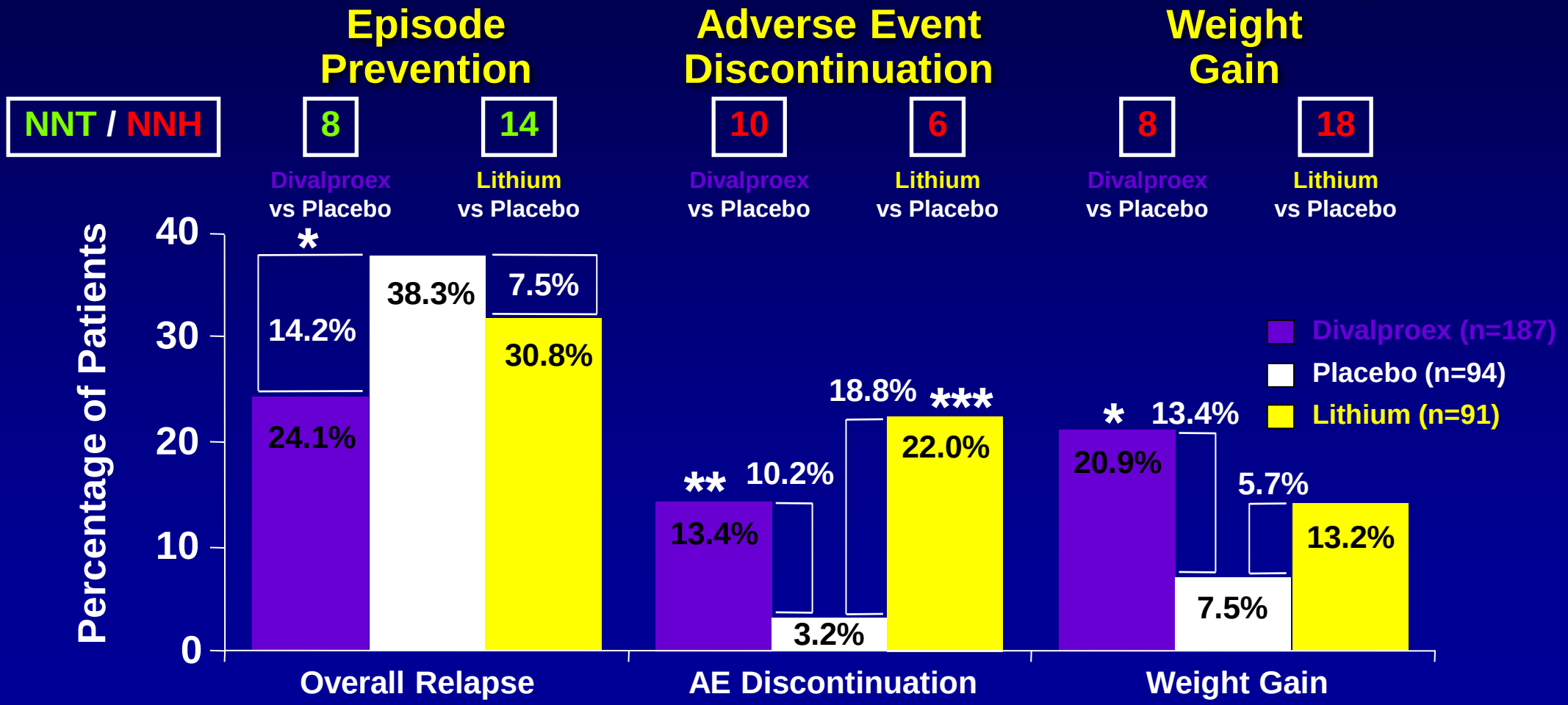
Stabilized on open treatment for 2 consecutive visits at least 6 days apart. *p < 0.02 vs PBO.

Divalproex (but not lithium) compared to placebo yielded less overall and depressive relapse/recurrence.

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

Divalproex Compared to Lithium/Placebo After Manic/Mixed Episodes

DVPX, Li, PBO Equivalent on 1° Outcome Measure (time to recurrence of any mood episode)



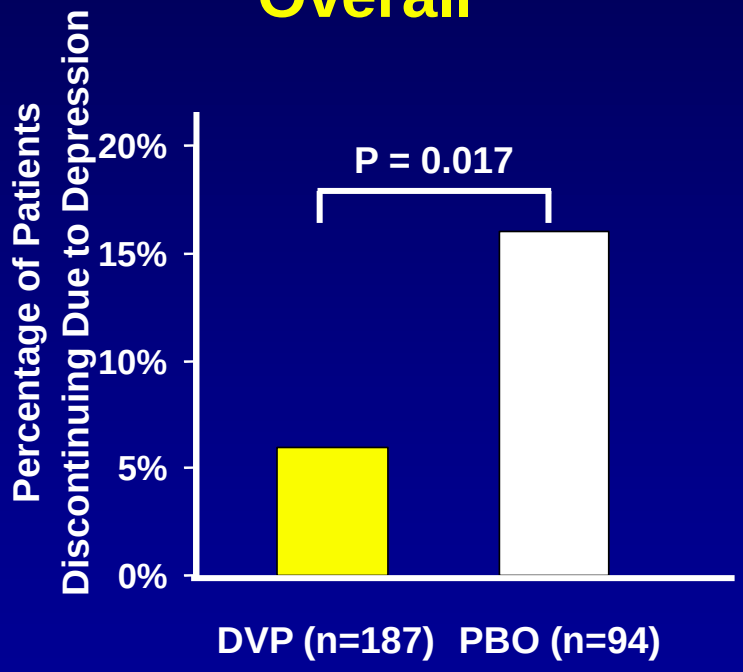
Stabilized on open treatment for 2 consecutive visits at least 6 days apart. *p < 0.05, **p < 0.01, ***p < 0.001 vs PBO.

Divalproex and lithium yielded more AE discontinuation. Divalproex yielded more weight gain.

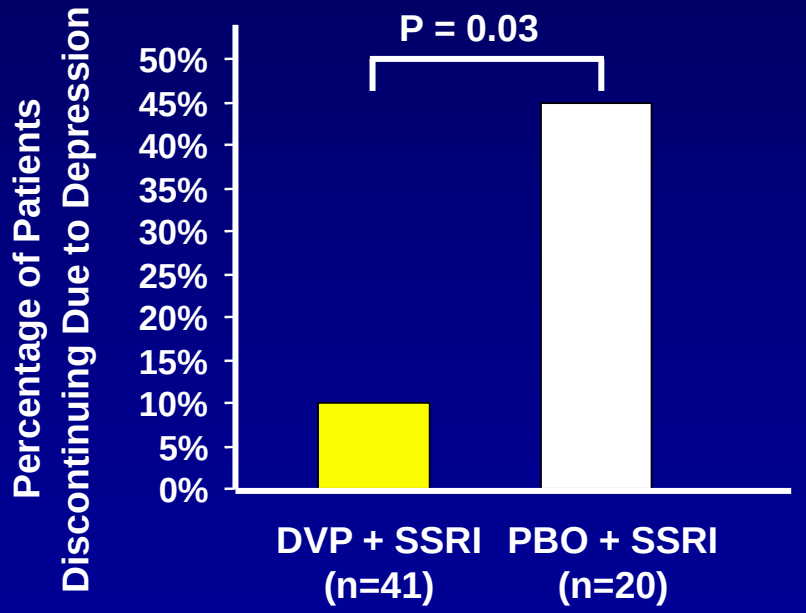
12-Month Double-Blind Divalproex, Lithium Monotherapy vs Placebo Maintenance

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

Overall



Patients Receiving SSRI Rescue

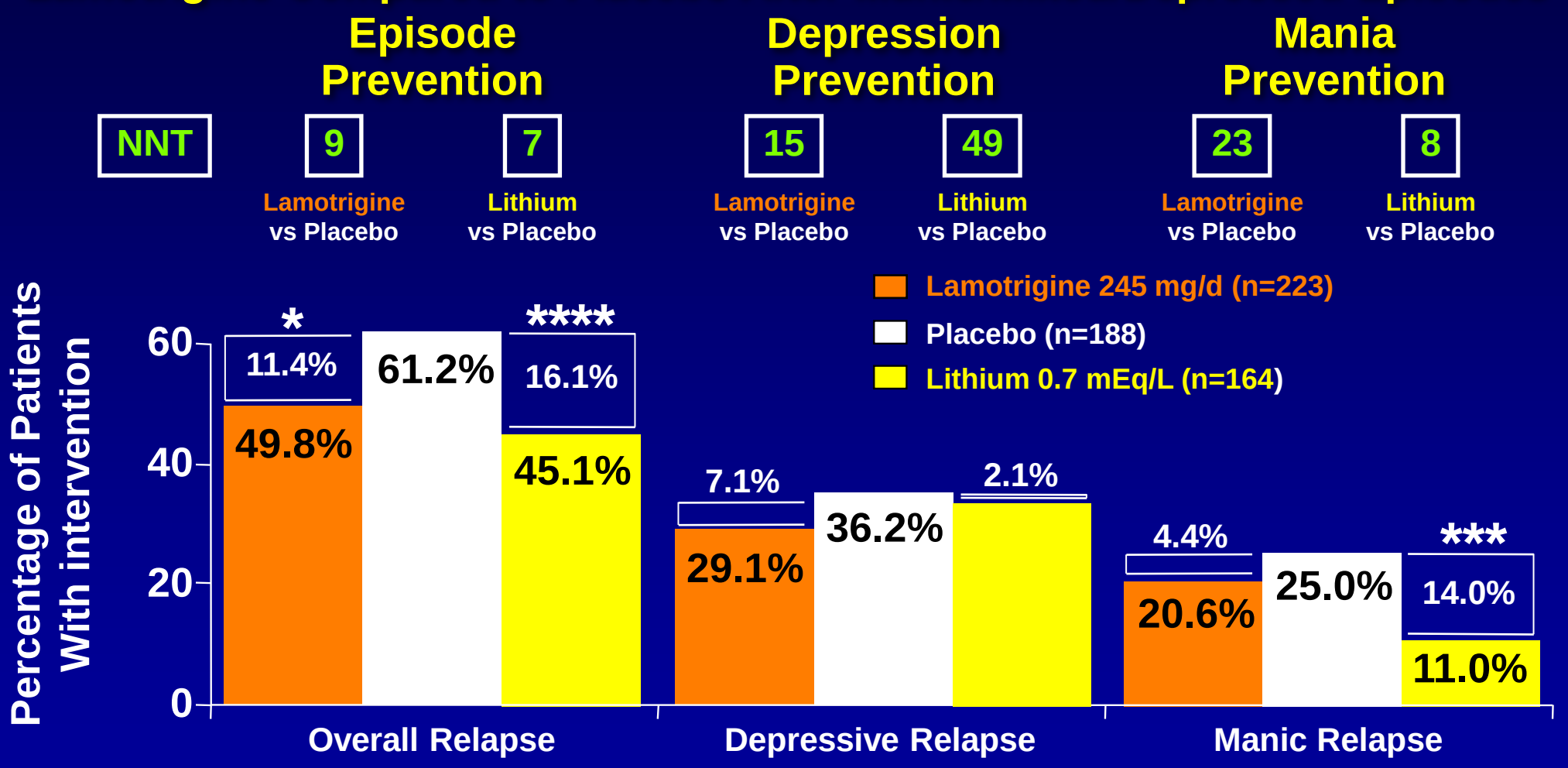


DVP = divalproex PBO = placebo LI = lithium
SSRI = selective serotonin reuptake inhibitor

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

18-Month Double-Blind Lamotrigine Monotherapy vs Lithium Monotherapy vs Placebo Maintenance

Lamotrigine Compared to Placebo After Manic/Mixed/Depressed Episodes



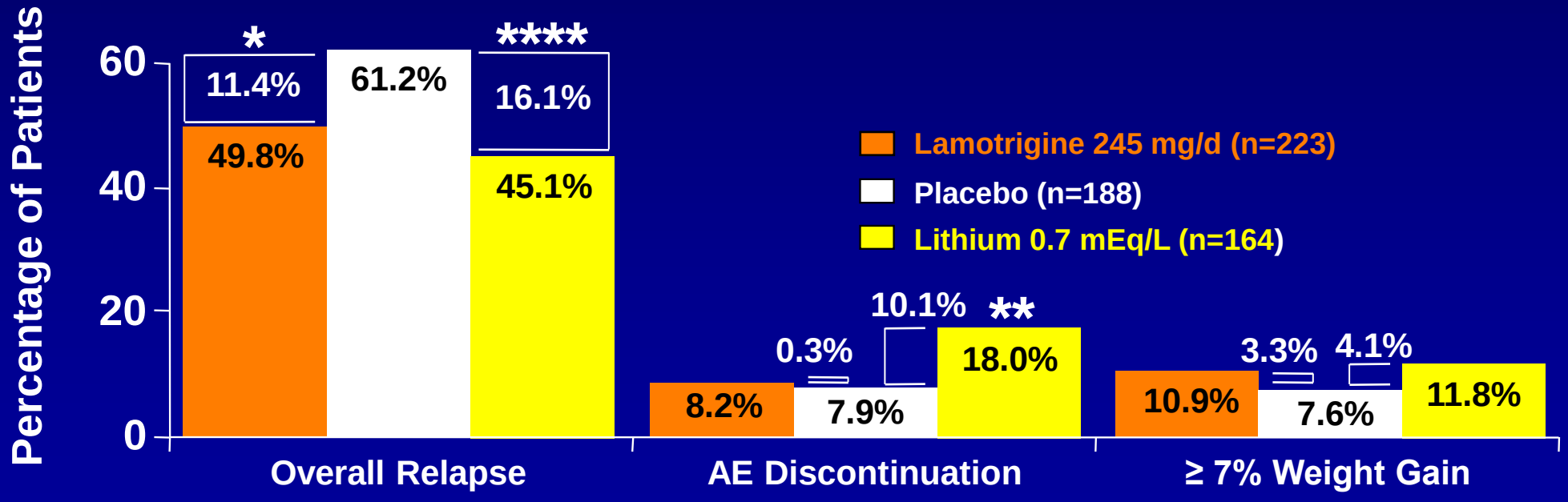
Goodwin et al. J Clin Psychiatry 2004;65:432-41. *p<.05, ***p < 0.001, ****p < 0.0001 vs PBO.

Lamotrigine and lithium compared to placebo yielded less relapse/recurrence.

18-Month Double-Blind Lamotrigine Monotherapy vs Lithium Monotherapy vs Placebo Maintenance

Lamotrigine Compared to Placebo After Manic/Mixed/Depressed Episodes

	Episode Prevention		Adverse Event Discontinuation		Weight Gain	
NNT / NNH	9	7	313	10	31	25
	Lamotrigine vs Placebo	Lithium vs Placebo	Lamotrigine vs Placebo	Lithium vs Placebo	Lamotrigine vs Placebo	Lithium vs Placebo

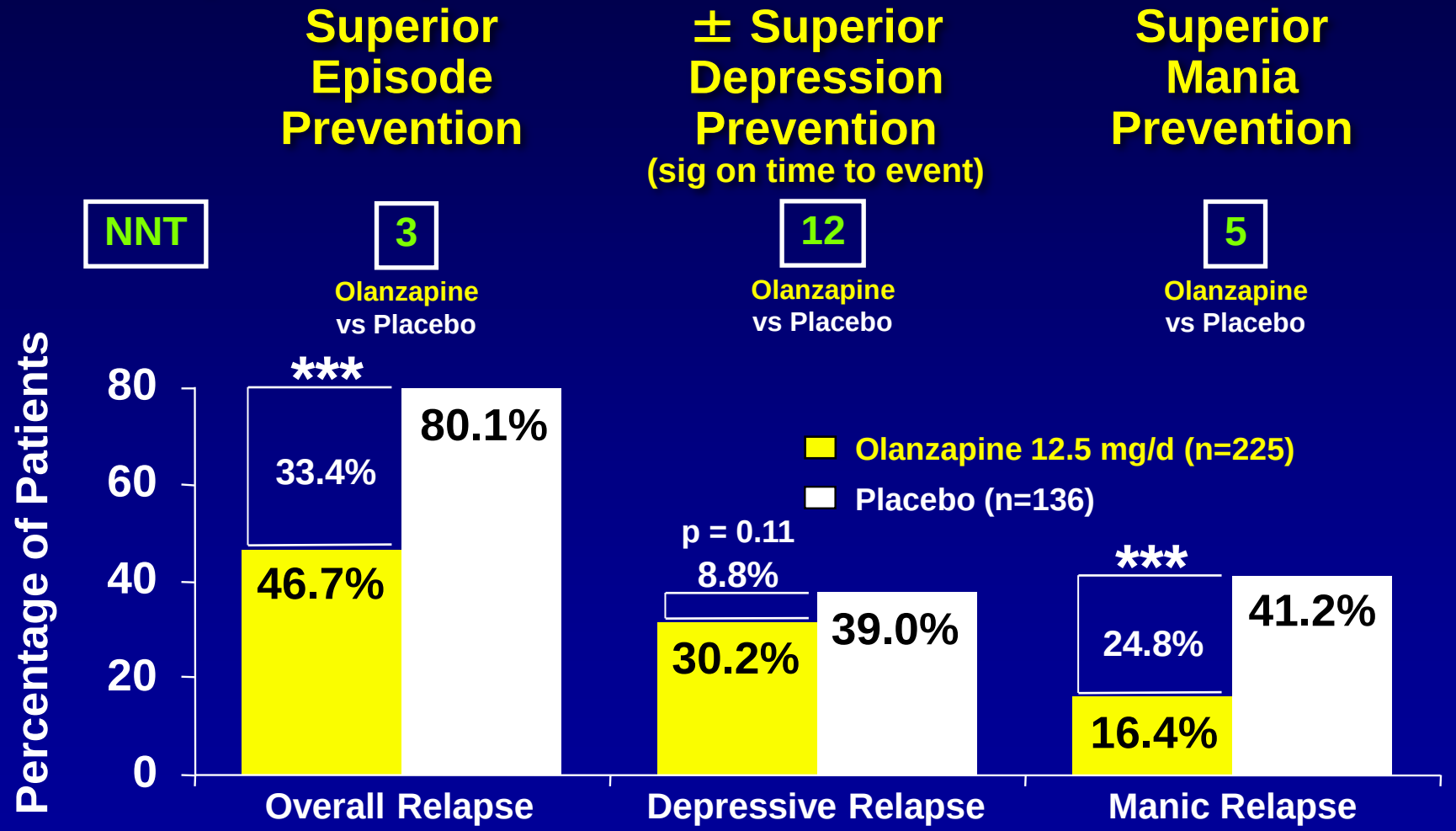


Goodwin et al. J Clin Psychiatry 2004;65:432-41. *p<.05, **p < 0.01, ****p < 0.0001 vs PBO.

Lithium (but not lamotrigine) compared to placebo yielded more AE discontinuation.

12-Month Double-Blind Olanzapine Monotherapy vs Placebo Maintenance

Olanzapine Compared to Placebo After Manic/Mixed Episodes

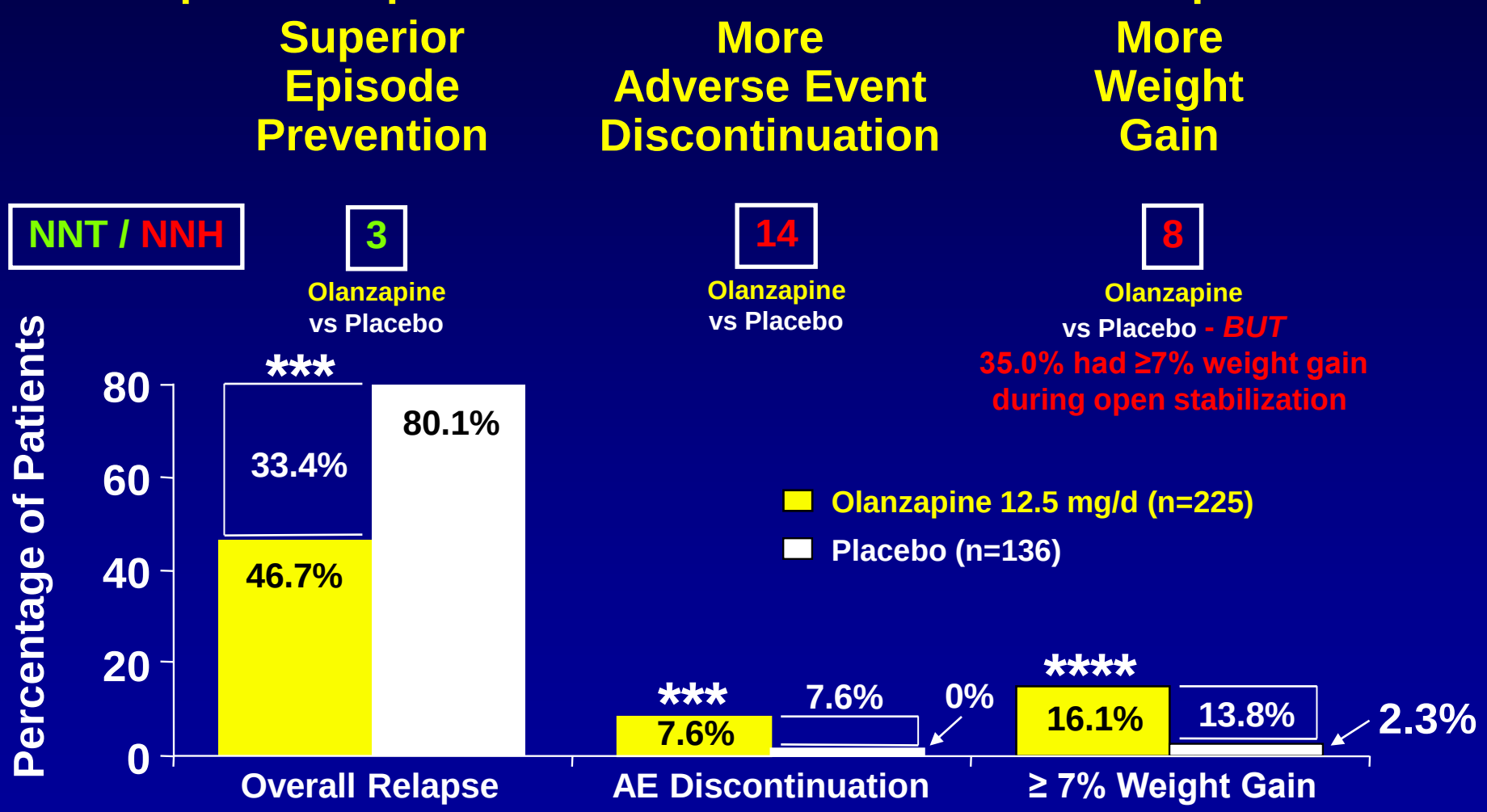


Stabilized on OLZ before randomization (mean 16.3 days). Relapse criteria - hospitalized or YMRS or HAMD-21 >= 15.

Olanzapine compared to placebo yielded less overall and manic relapse/recurrence.

12-Month Double-Blind Olanzapine Monotherapy vs Placebo Maintenance

Olanzapine Compared to Placebo After Manic/Mixed Episodes

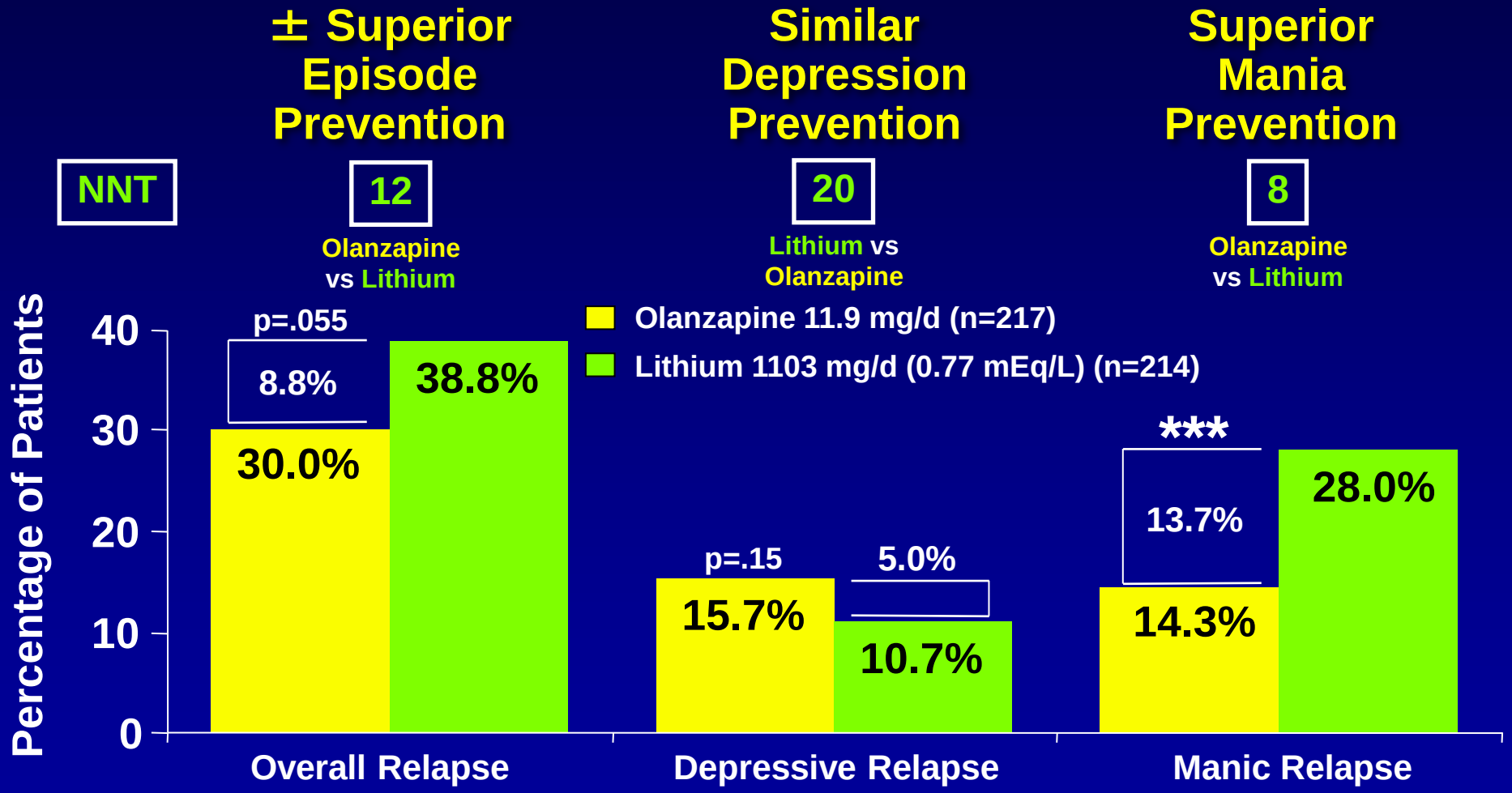


Stabilized on OLZ before randomization (mean 16.3 days). Relapse criteria - hospitalized or YMRS or HAMD-21 >= 15.

Olanzapine compared to placebo yielded more AE discontinuation and weight gain.

12-Month Double-Blind Olanzapine vs Lithium Maintenance Monotherapy

Olanzapine Compared to Lithium After Manic/Mixed Episodes

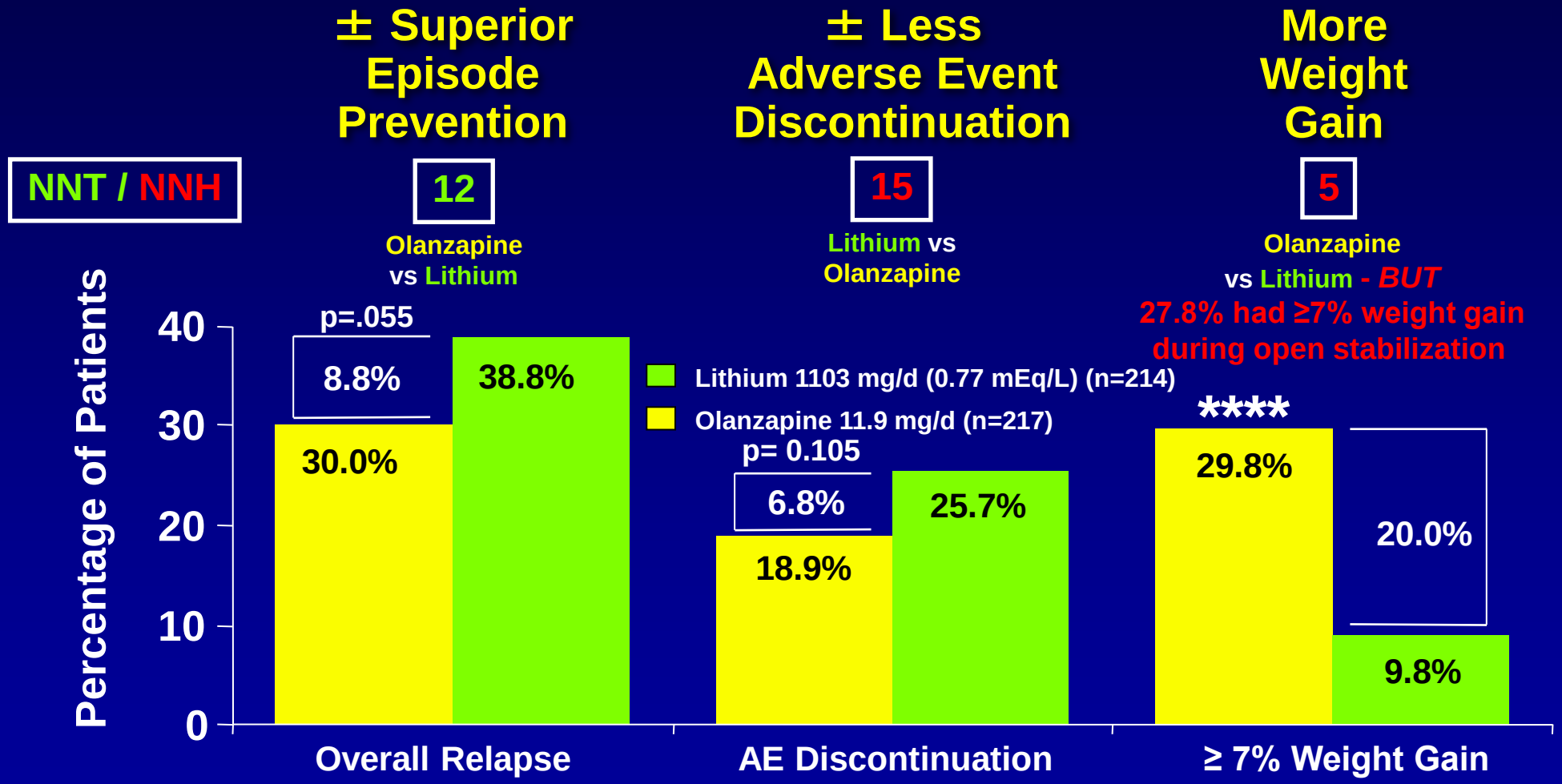


Stabilized on open OLZ+Li before randomization (mean 20.2 days). Relapse criteria - YMRS or HAMD-21 >= 15.

Olanzapine compared to lithium yielded less manic relapse/recurrence.

12-Month Double-Blind Olanzapine vs Lithium Maintenance Monotherapy

Olanzapine Compared to Lithium After Manic/Mixed Episodes

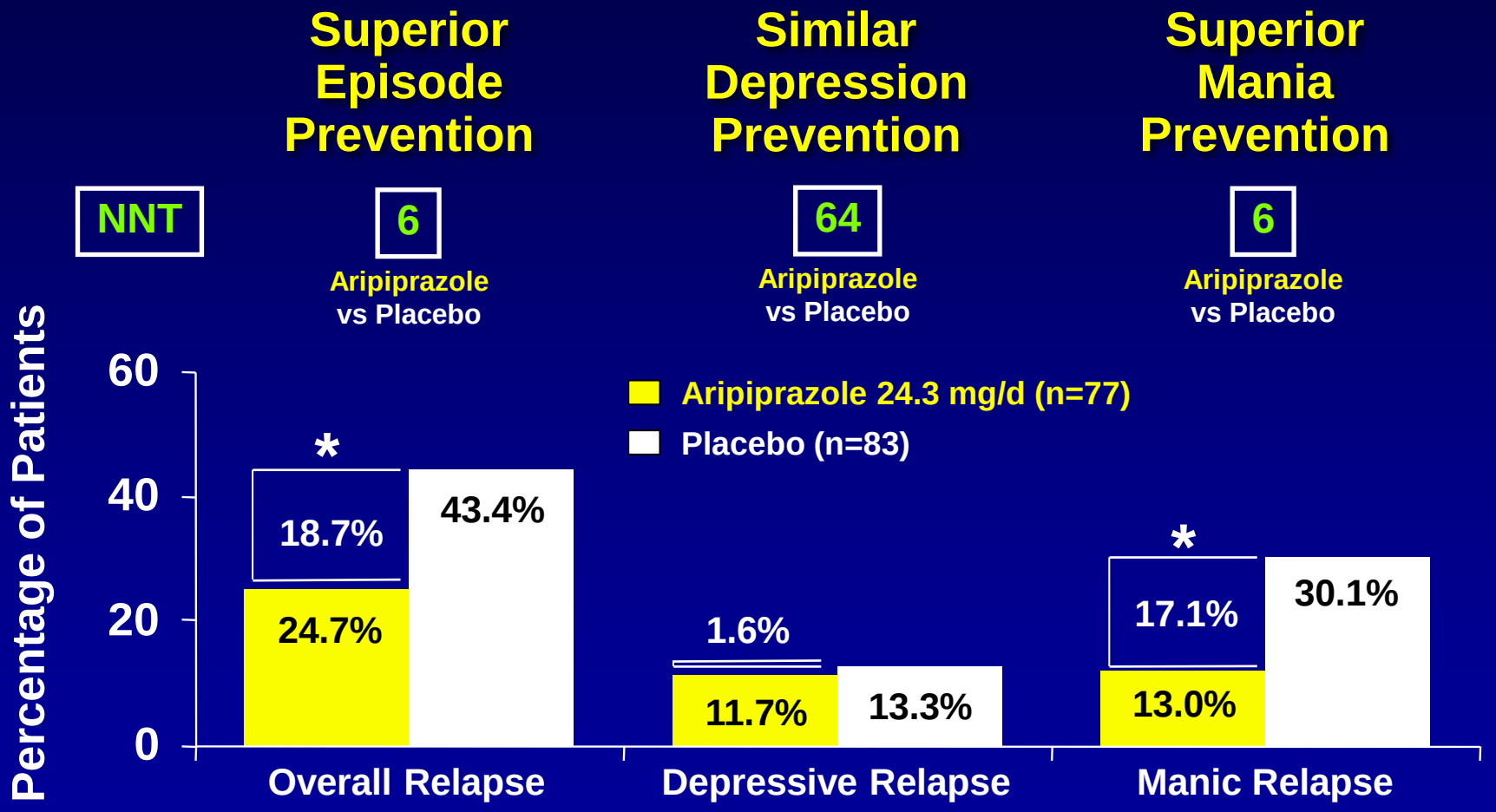


Stabilized on open OLZ+Li before randomization (mean 20.2 days). Relapse criteria - YMRS or HAMD-21 >= 15.

Olanzapine compared to lithium yielded ± less AE discontinuation, more weight gain.

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

Aripiprazole Compared to Placebo After Manic/Mixed Episodes



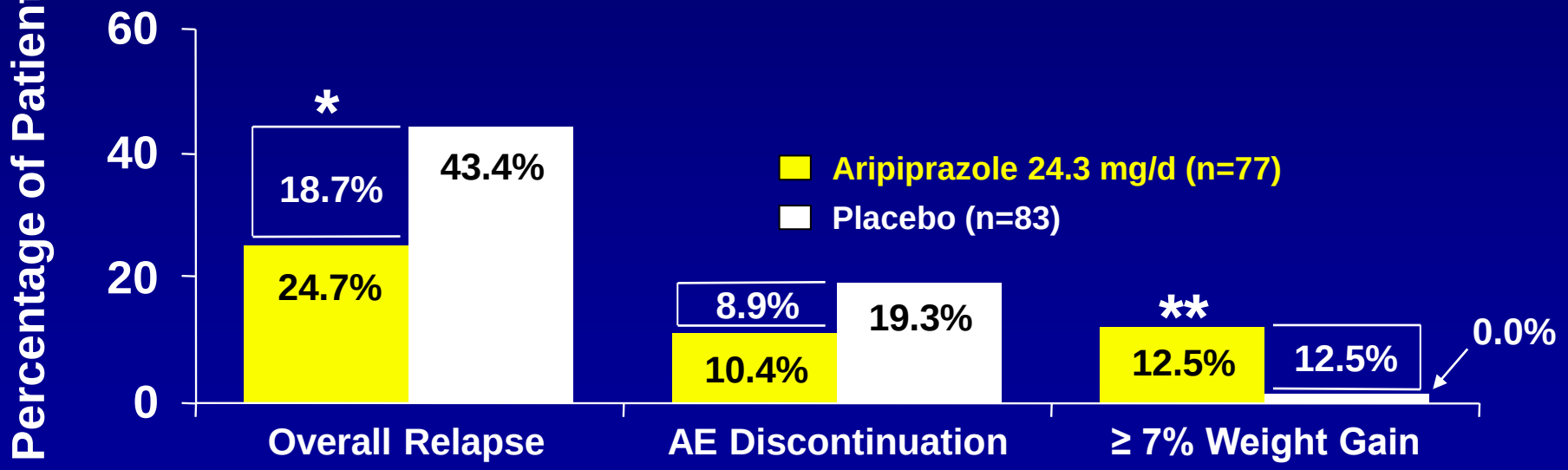
Stabilized on open ARI before randomization (mean 12.7 weeks). Relapse criteria - hospitalized or medication added.

Aripiprazole compared to placebo yielded less overall and manic relapse/recurrence.

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

Aripiprazole Compared to Placebo After Manic/Mixed Episodes

	Superior Episode Prevention	Similar Adverse Event Discontinuation	More Weight Gain
NNT / NNH	6	12	8
	Aripiprazole vs Placebo	Placebo vs Aripiprazole	Aripiprazole vs Placebo

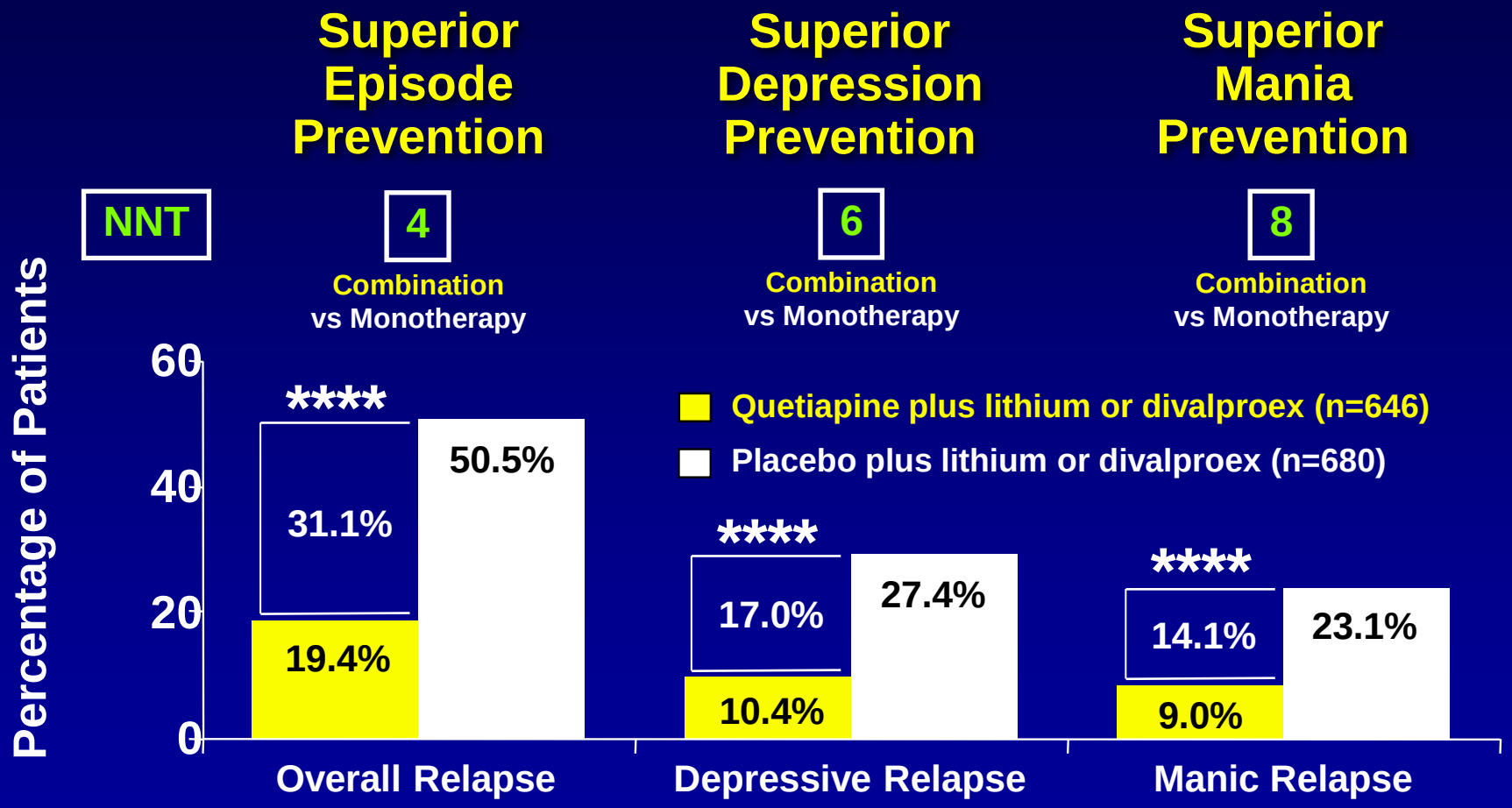


Stabilized on open ARI before randomization (mean 12.7 weeks). Relapse criteria - hospitalized or medication added.

Aripiprazole compared to placebo yielded more weight gain.

24-Month Quetiapine vs Placebo Added to Lithium or Divalproex Bipolar I Maintenance

After Manic, Mixed, or Depressed Episodes

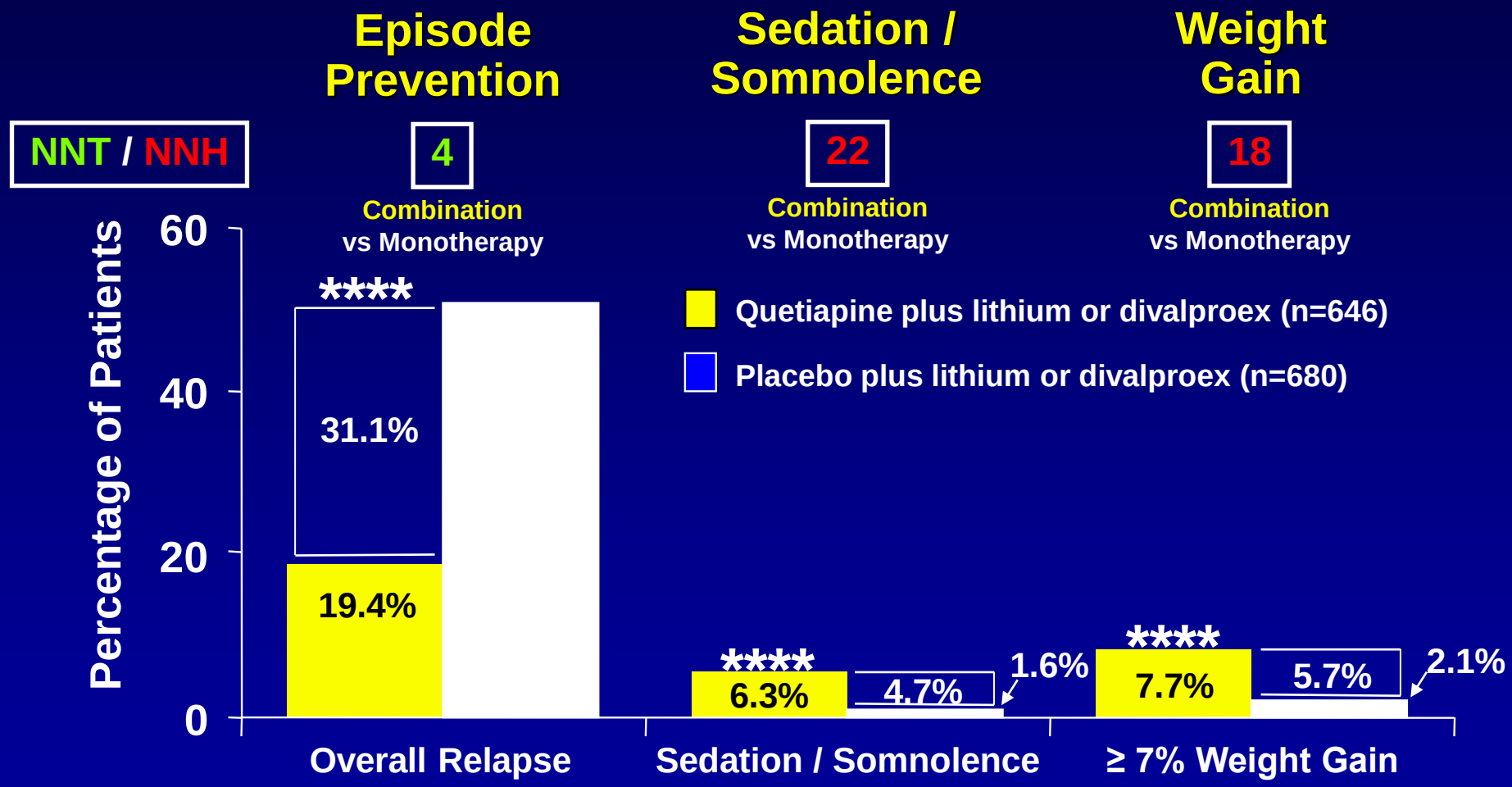


Patients stable on average 15 weeks on quetiapine + lithium or divalproex after manic, mixed, or depressed episodes.
Mean duration of randomized treatment: quetiapine = 213 days; placebo = 152 days. ****p < 0.0001 vs PBO.

Combination compared to monotherapy yielded less overall, depressive, and manic relapse.

24-Month Quetiapine vs Placebo Added to Lithium or Divalproex Bipolar I Maintenance

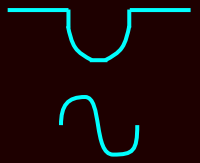
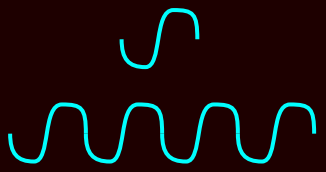
After Manic, Mixed, or Depressed Episodes



Patients stable on average 15 weeks on quetiapine + lithium or divalproex after manic, mixed, or depressed episodes.
Mean duration of randomized treatment: quetiapine = 213 days; placebo = 152 days. ****p < 0.0001 vs PBO.

Combination compared to monotherapy yielded less relapse, more sedation and weight gain.

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

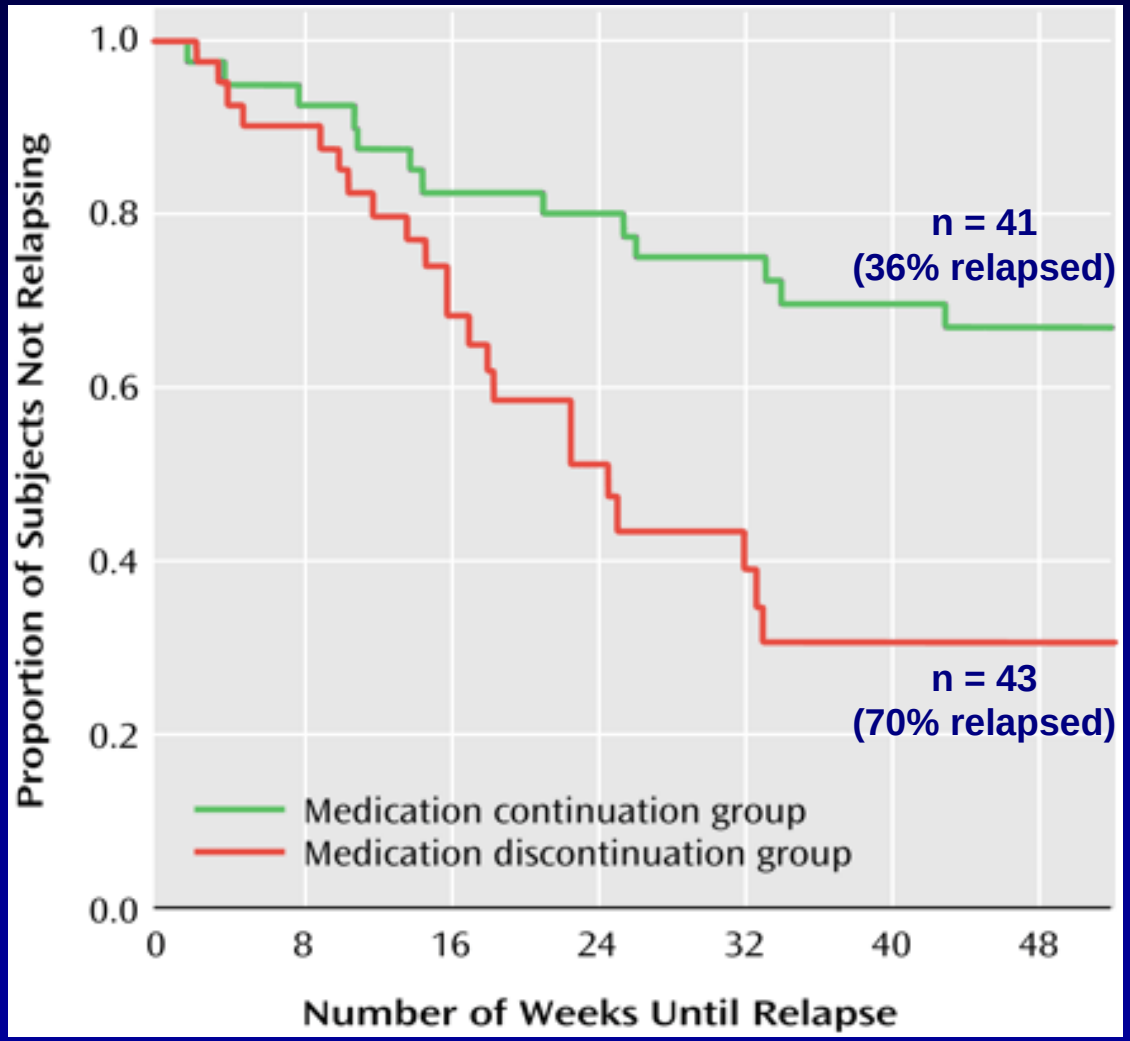
Sachs G, 2000. Personal communication.

Antidepressant Maintenance Ineffective in Controlled Studies of Bipolar Depression

Study	N	Duration	Efficacy	Switch
Prien, et al. 1973	44	24 mo	Li > IMI = PBO	
Wehr, Goodwin 1979	5	27 mo	Li = Li+DMI	Li << Li+DMI
Quitkin, et al. 1981	75	19 mo	Li = Li+IMI	Li < Li+IMI
Kane, et al. 1982	22	11 mo	Li > IMI = PBO	
Prien, et al. 1984	117	30 mo	Li = Li+IMI > IMI	Li = Li+IMI < IMI
Sachs, et al. 1994	15	12 mo	Li+BUP = Li+DMI	Li+BUP < Li+DMI

Adapted from Ghaemi SN, et al. J Clin Psychiarty 2001;62:565-9.
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.

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

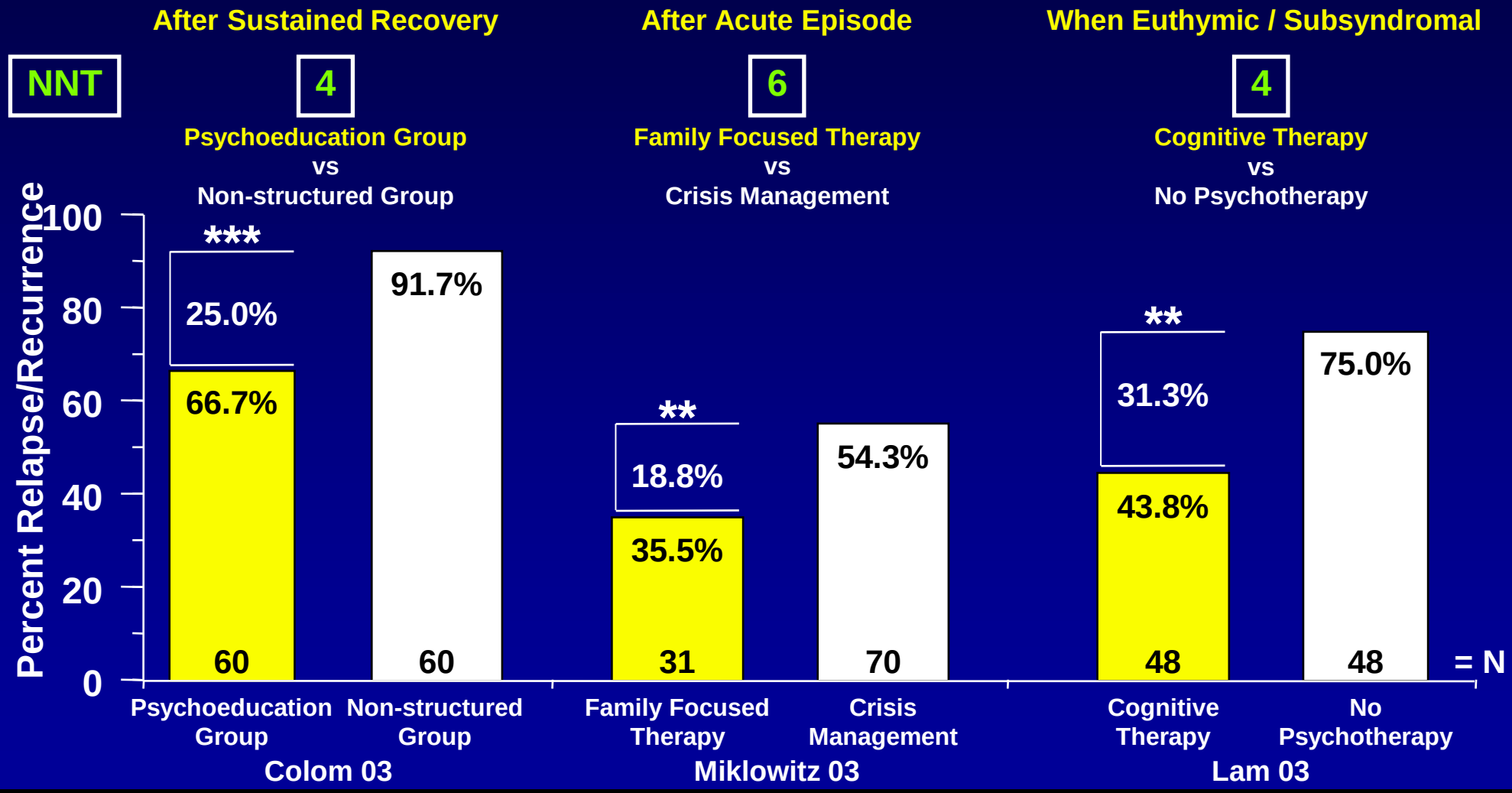
Continuation: AD > 6 months
Discontinuation: AD < 6 months

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

Overview of Adjunctive Psychosocial Maintenance Studies

Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

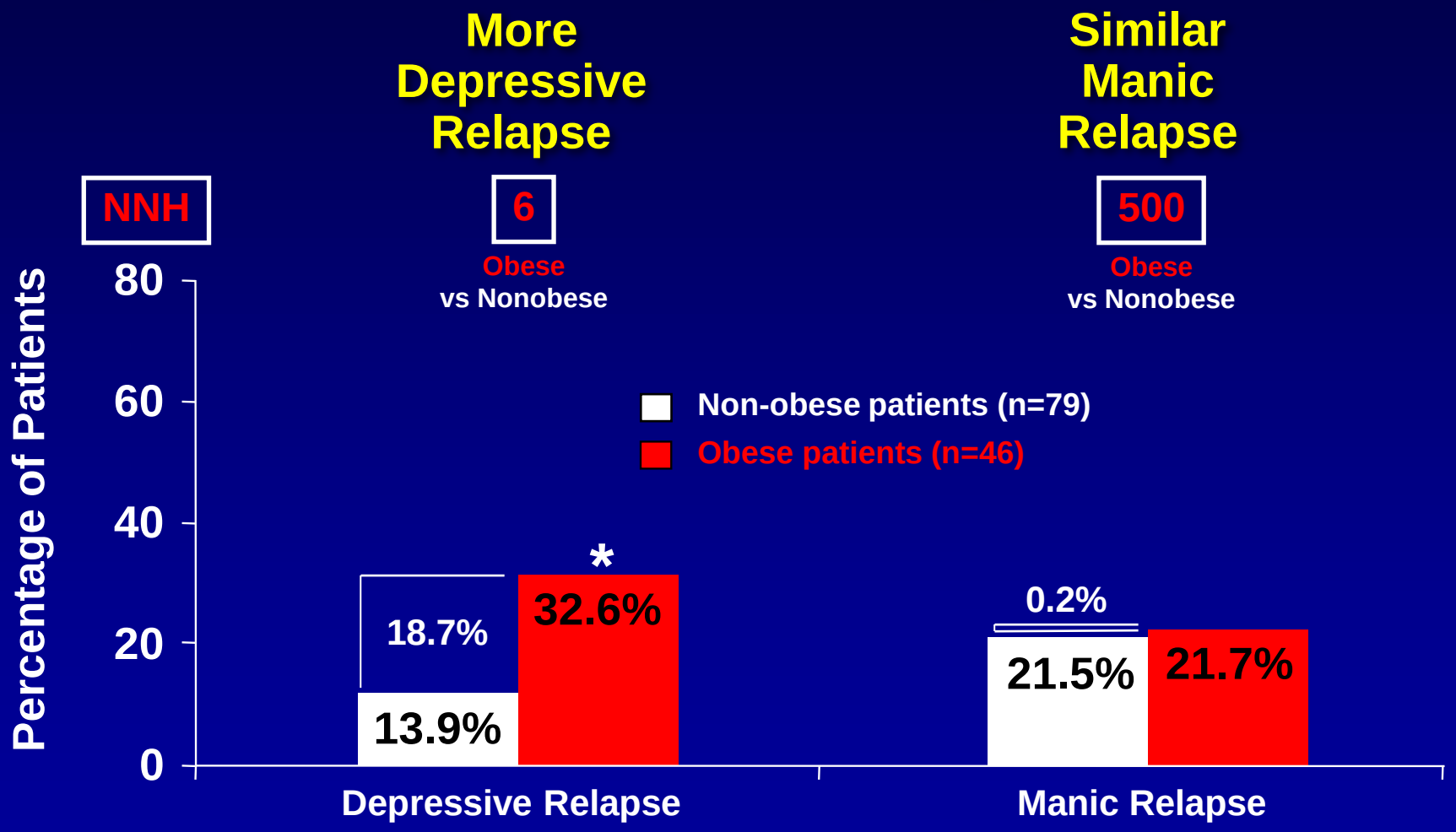
Contemporary Manualized Intensive Psychotherapy Studies



Psychosocial interventions had single-digit NNTs, comparable to approved pharmacotherapies.

Obesity Associated with More Frequent Depressive Relapse / Recurrence

24-Month Naturalistic Maintenance in Obese Compared to Non-obese Patients



Fagiolini A et al. Am J Psychiatry. 2003;160:112-7. *p < 0.05.

Obese compared to non-obese patients had more depressive relapse / recurrence (NNH = 6).

Treatment of Bipolar Depression

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

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

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

A. Tricyclic antidepressants (TCAs)

B. Selective serotonin reuptake inhibitors (SSRIs)

C. Mirtazapine

D. Bupropion

Question 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

Question 5

Which of the following statements best describes the role of maintenance adjunctive antidepressants in patients with bipolar disorder: (choose one)

A. Long-term adjunctive antidepressants are always beneficial.

B. Long-term adjunctive antidepressants are never beneficial.

C. Long-term adjunctive antidepressants are beneficial in most patients.

D. Long-term adjunctive antidepressants may be beneficial in some patients.

Answers to Pre & Post Competency Exam

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