Acute and Maintenance Treatment of Bipolar Depression

Terence A. Ketter, M.D.

Overview

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

Teaching Points

Some atypical antipsychotics provide benefit in acute bipolar depression, with strongest evidence supporting lurasidone (monotherapy or adjunctive to lithium or valproate), quetiapine monotherapy, and olanzapine combined with fluoxetine.

Mood stabilizers are foundational bipolar disorder treatment agents, historically considered first line for acute bipolar depression, with strongest evidence supporting lithium and lamotrigine.

Utility of adjunctive antidepressants in bipolar depression remains controversial, as these can yield inefficacy or switching into hypo/mania 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. Lurasidone

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.

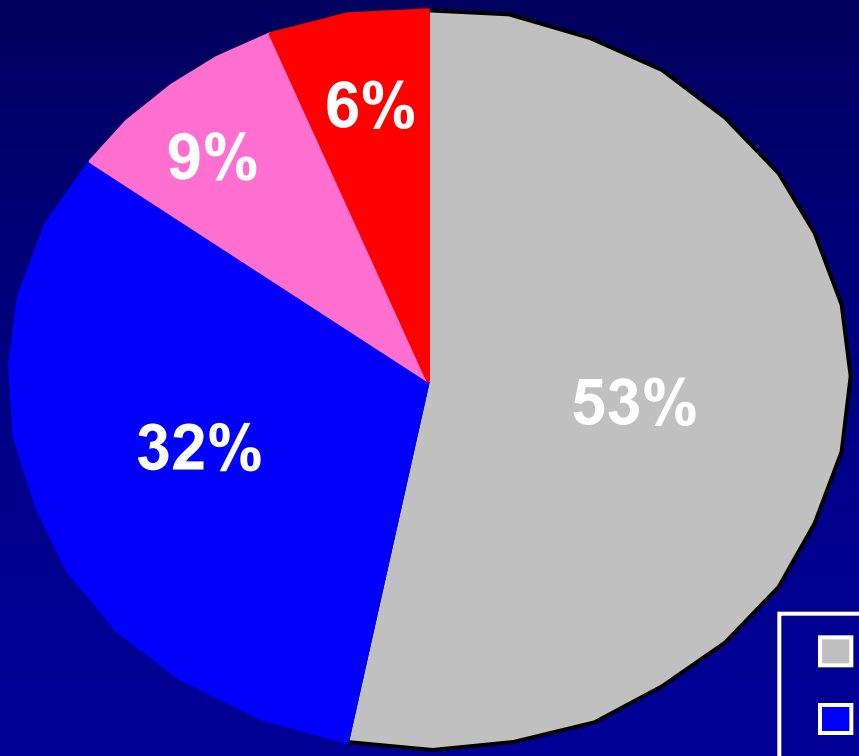
B. Long-term adjunctive antidepressants are never beneficial.

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

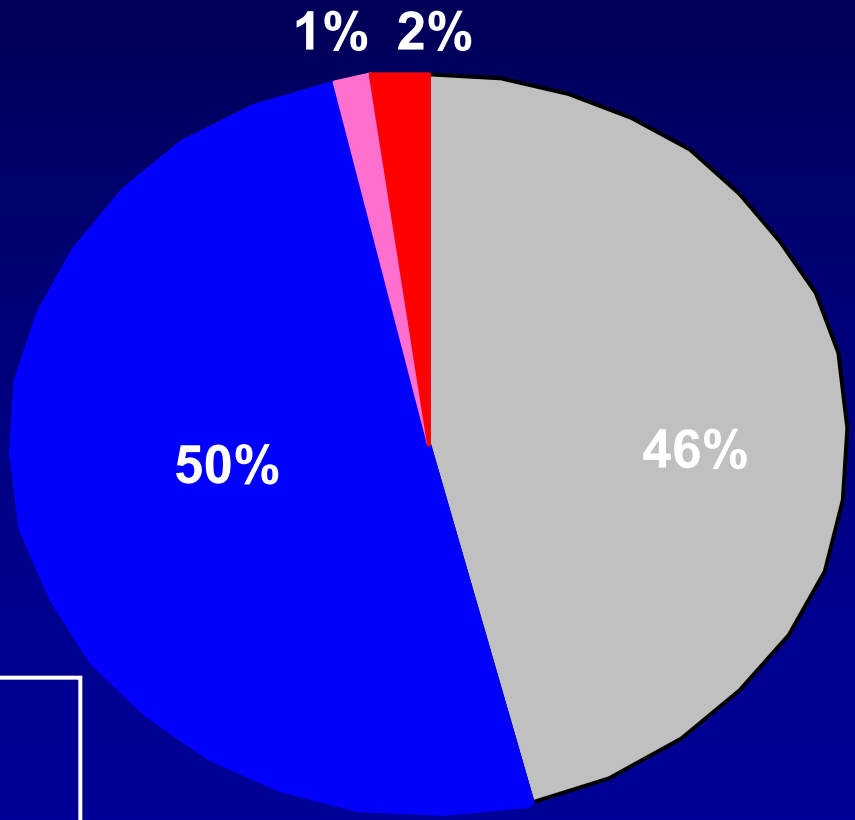


Judd et al 2002

% of Weeks

- Asymptomatic
- Depressed
- Hypomanic
- Cycling / mixed

86 Bipolar II Patients
followed 13.4 yrs



Judd et al 2003

Treatment Options in Bipolar Depression

Atypical Antipsychotics

- Lurasidone
- Quetiapine
- Olanzapine

Mood Stabilizers

- Lithium
- Lamotrigine
- Carbamazepine
- Divalproex
- ECT

Adjunctive Antidepressants

- Fluoxetine + Olanzapine
- Bupropion / SSRIs
- Mirtazapine
- SNRIs
- MAOIs
- TCAs

Adjunctive Psychotherapy

Alternative Treatments

- Armodafinil, modafinil
- Pramipexole
- Gabapentin
- Omega-3 fatty acids
- Phototherapy
- 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

FDA-Approved Agents for Bipolar Disorder

Acute Mania		Acute Depression		Longer-Term	
Year	Drug	Year	Drug	Year	Drug
1970	Lithium	2003	Olanzapine+fluoxetine combination	1974	Lithium
1973	Chlorpromazine	2006	Quetiapine, XR (2008)	2003	Lamotrigine
1994	Divalproex, ER (2005)	2013	Lurasidone*	2004	Olanzapine
2000	Olanzapine*			2005	Aripiprazole*
2003	Risperidone*			2008	Quetiapine, XR (adjunct)
2004	Quetiapine, XR (2008)*			2009	Risperidone LAI*
2004	Ziprasidone			2009	Ziprasidone (adjunct)
2004	Aripiprazole*				
2004	Carbamazepine ERC				
2009	Asenapine*				

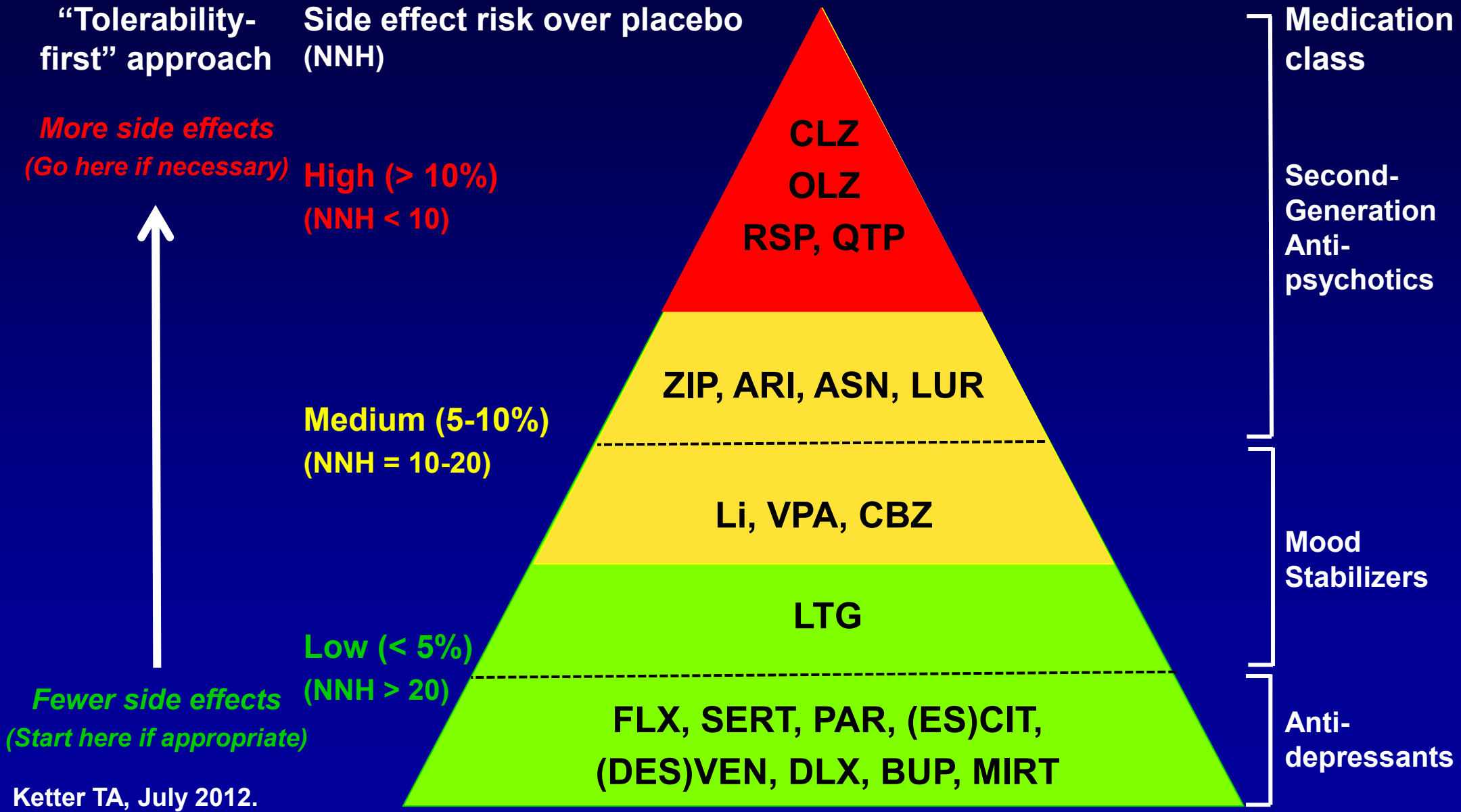
Unmet Need

Unmet Need

*Adjunctive and monotherapy; LAI = Long-Acting Injectable

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

Psychotropic Medication Side Effect Schematic



Ketter TA, July 2012.

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Unmet Need

Unmet Need

*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)

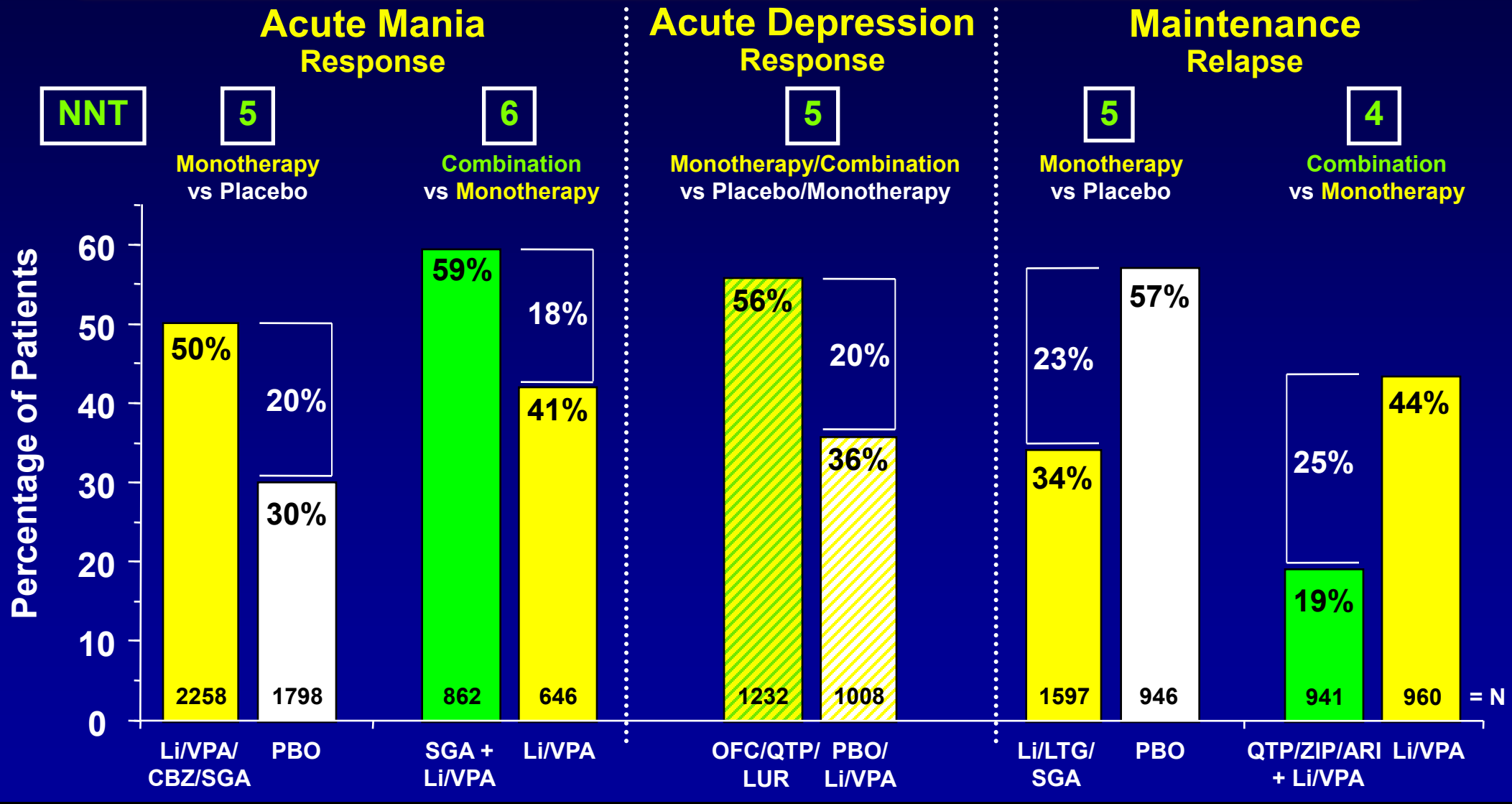
Medication	Oral Tab/Cap	Oral Fluid	Rapid Acting Injectable	Long Acting Injectable
Asenapine	SL			
Aripiprazole	+, ODT	+	IM	IM
Carbamazepine	+, ER	+		
Chlorpromazine	+	+	IM, IV	
Divalproex	+, ER	+	IV	
Lamotrigine	+, ER, ODT			
Lithium	+, ER	+		
Lurasidone	+			
Olanzapine	+, ODT		IM	IM
Olanzapine+fluoxetine	+			
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, 2010.

Overview of Bipolar Disorder Registration Studies

Numbers Needed to Treat for Response and Relapse Prevention, Rates



In aggregate, FDA-approved bipolar disorder treatments increase good outcomes by 18%-25%.

Acute Treatment of Bipolar Depression

FDA-Approved Agents for Bipolar Disorder

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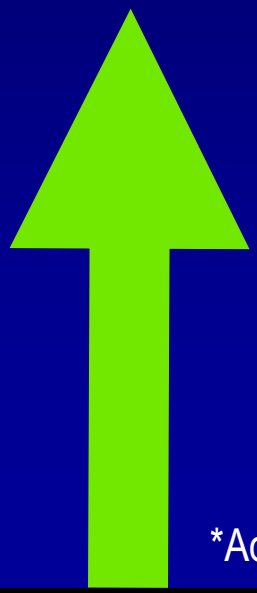
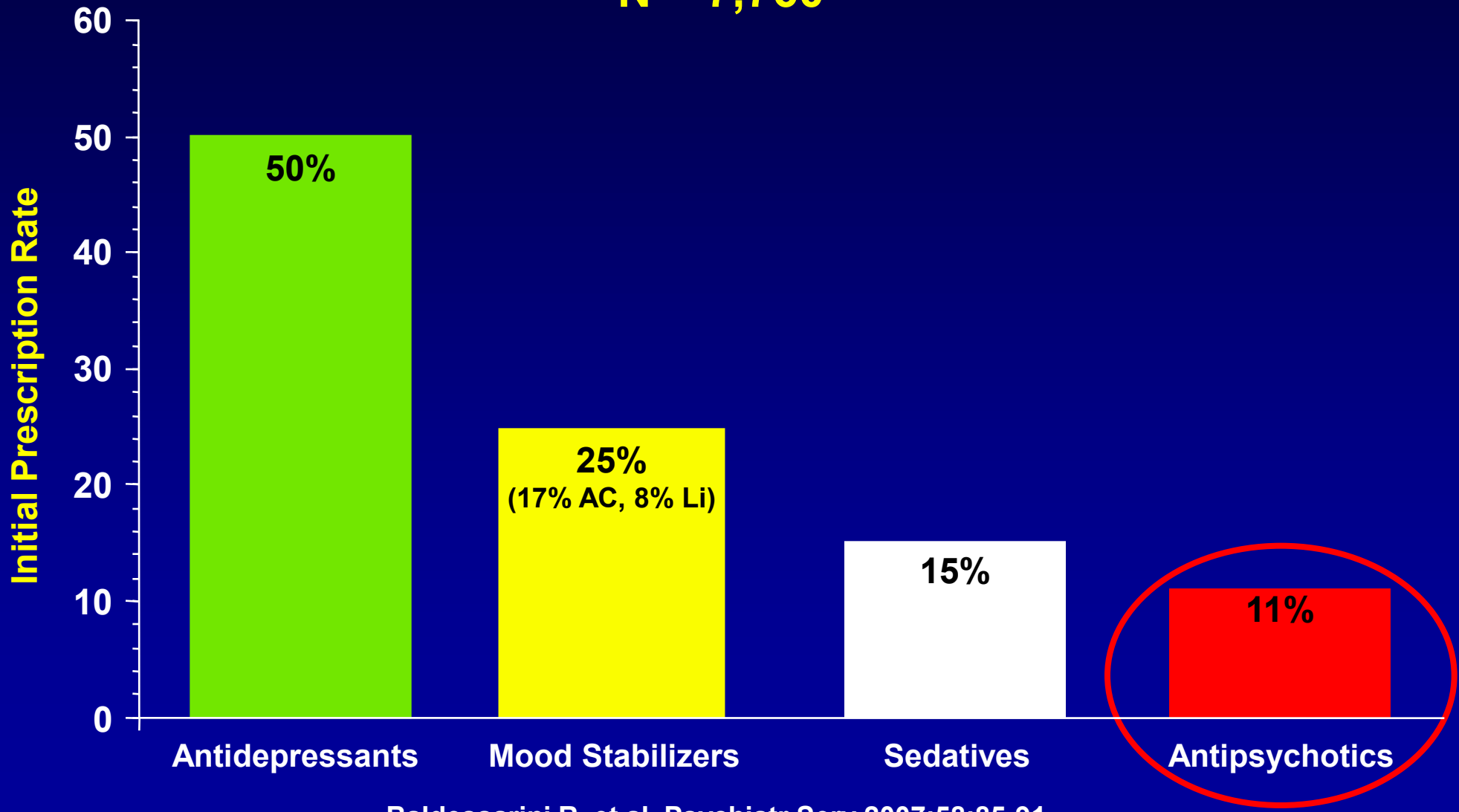


*Adjunctive and monotherapy; LAI = Long-Acting Injectable

All FDA-approved acute bipolar depression treatments involve Second Generation

Antipsychotics Fourth Most Common Initial Treatment for Bipolar Disorder Patients in United States in 2002-2003

N = 7,760



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

FDA Class Warnings/Precautions for Second Generation Antipsychotics

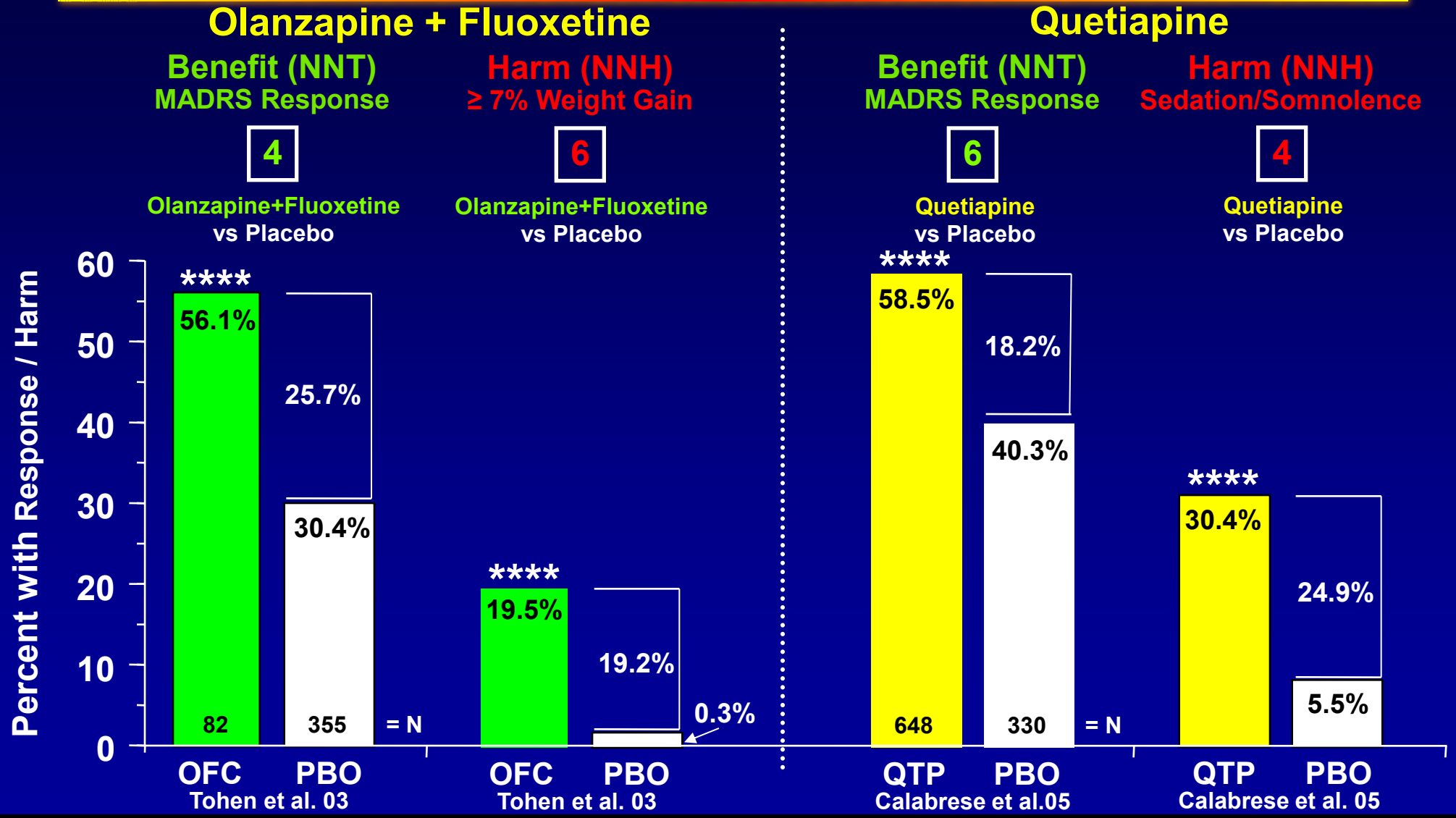
1. Increased Mortality in Elderly with Dementia-Related Psychosis (boxed)
2. Neuroleptic Malignant Syndrome
3. Tardive Dyskinesia
4. Hyperglycemia and Diabetes Mellitus
5. Orthostatic Hypotension ± Syncope
6. Leukopenia, Neutropenia, and Agranulocytosis
7. Seizures
8. Potential for Cognitive and Motor Impairment
9. Body Temperature Regulation (pyrexia, feeling hot)
10. Suicide (illness related)
11. Dysphagia
12. Use in Patients with Concomitant Medical Illness

Additional FDA Warnings/Precautions for Most Second Generation Antipsychotics (with exceptions)

1. Weight Gain (ziprasidone excepted)
2. Hyperprolactinemia (aripiprazole excepted)
3. Hyperlipidemia/Dyslipidemia (ziprasidone, asenapine excepted)
4. Cerebrovascular Accidents in Elderly with Dementia-Related Psychosis (quetiapine, ziprasidone excepted)

Older Approved Bipolar Depression Rx Benefits & Harms

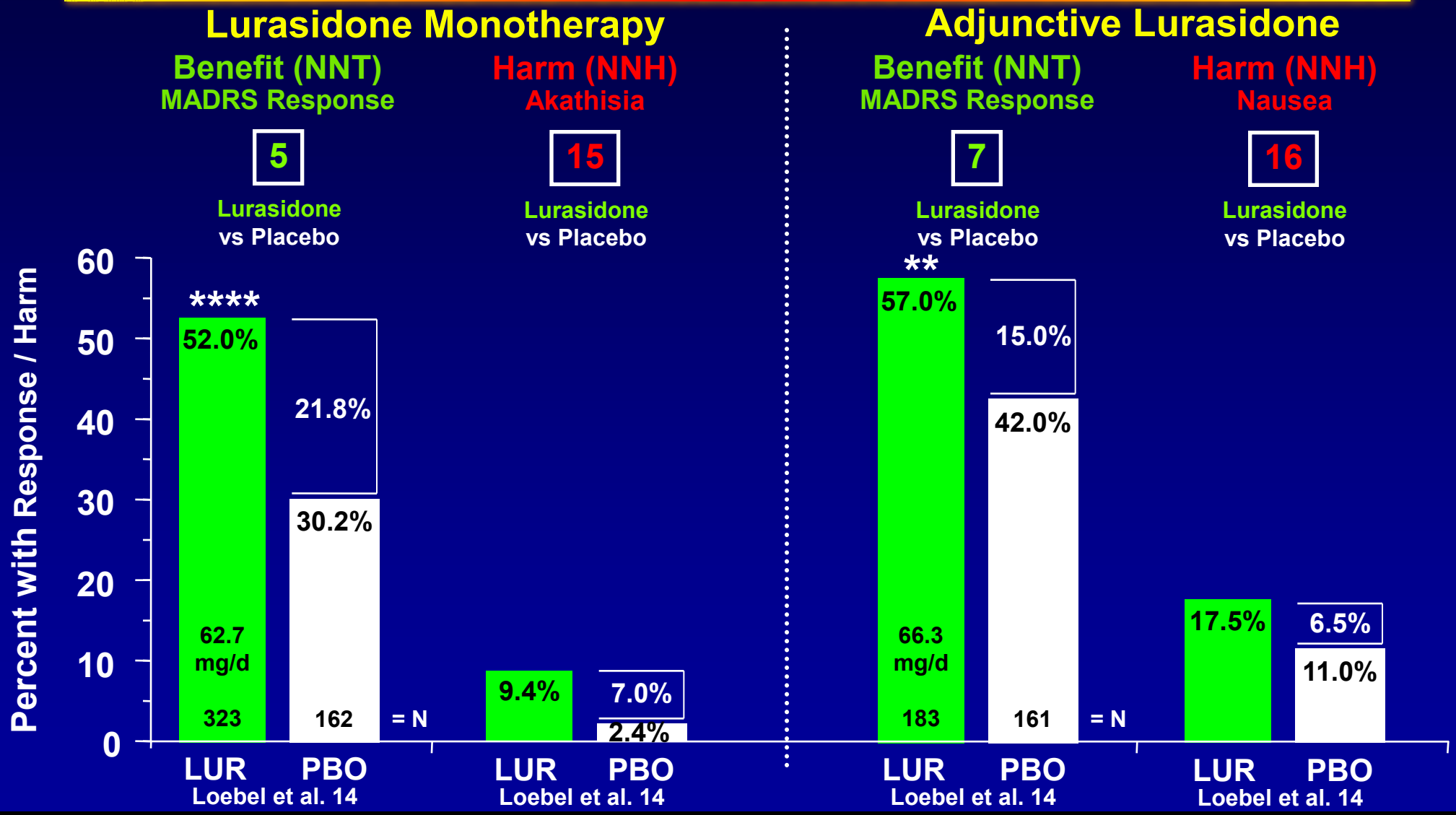
Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Approved treatments similarly likely to yield benefit and harm.

Newer Approved Bipolar Depression Rx Benefits & Harms

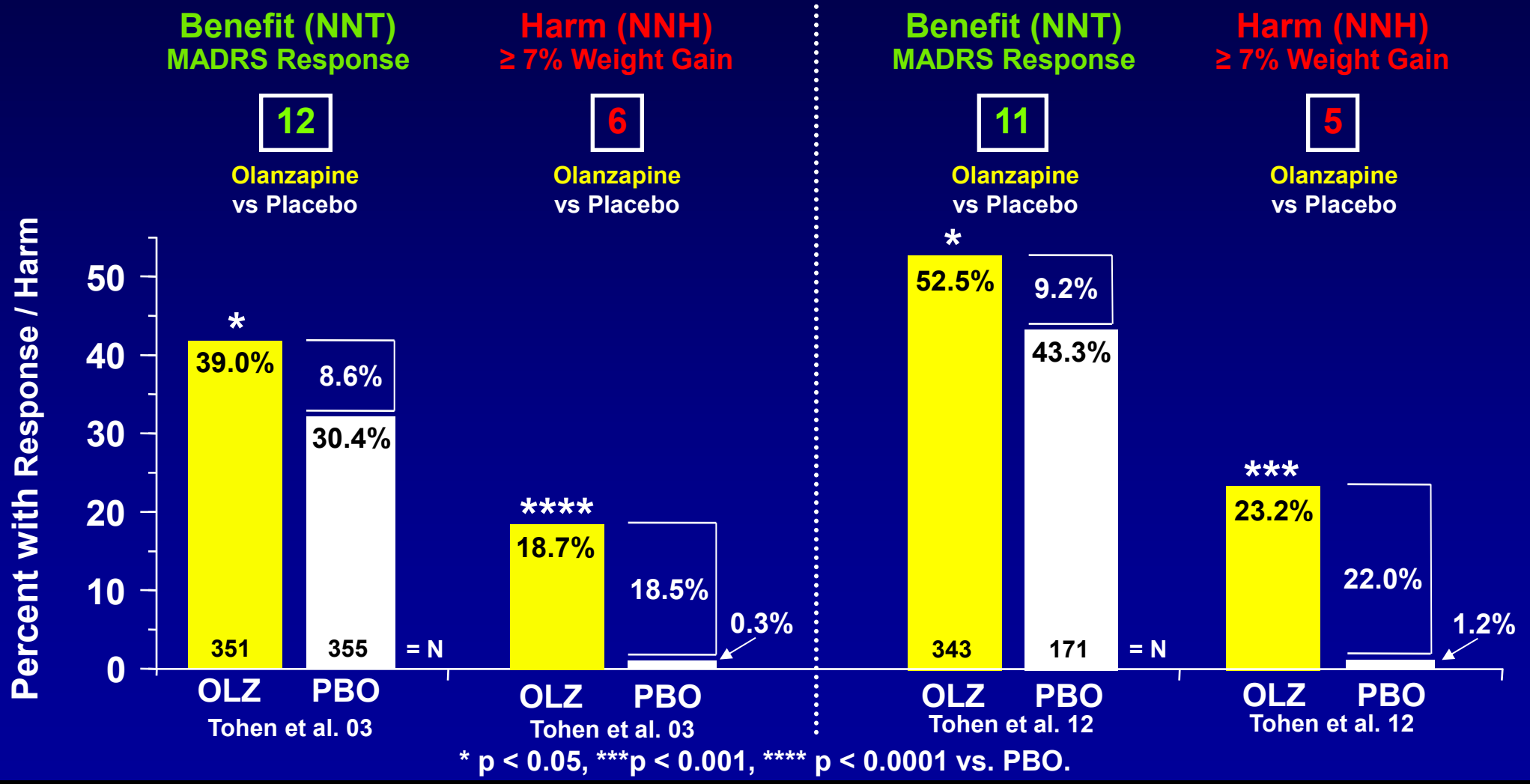
Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Lurasidone more than twice as likely to yield benefit as harm.

Unapproved Bipolar Depression Rx Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Olanzapine monotherapy more than twice as likely to yield harm as benefit.

Second Generation Antipsychotics in Bipolar Depression

- Fourth most common initial bipolar disorder treatment
  - Class somatic tolerability: < antidepressants; ≤ mood stabilizers
  - Class putative efficacy: acute mania & mania prevention
- FDA-approved for acute bipolar depression
  - Olanzapine (combined with fluoxetine)
  - Quetiapine (monotherapy)
  - Lurasidone (monotherapy and adjunctive therapy)
- Not FDA-approved for acute bipolar depression
  - Olanzapine (monotherapy)
  - Risperidone, ziprasidone, aripiprazole, asenapine
  - Clozapine, iloperidone, cariprazine
- Intolerability commonly limits utility

FDA-Approved Agents for Bipolar Disorder

Acute Mania		Acute Depression		Longer-Term	
Year	Drug	Year	Drug	Year	Drug
1970	Lithium	2003	Olanzapine+fluoxetine combination	1974	Lithium
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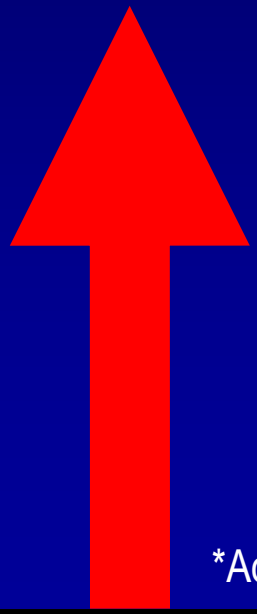
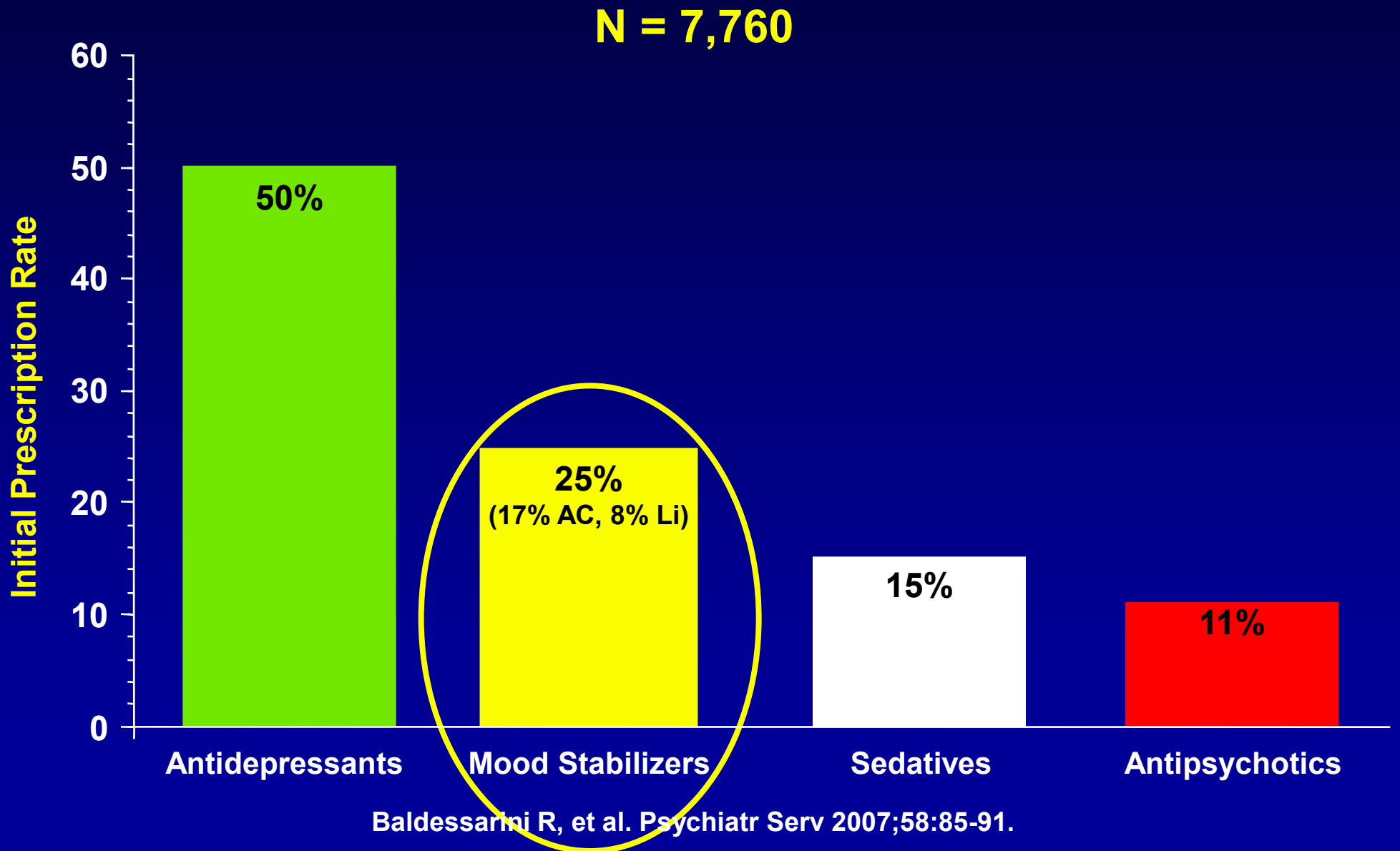
2004	Carbamazepine ERC				
2009	Asenapine*				



*Adjunctive and monotherapy; LAI = Long-Acting Injectable

No Mood Stabilizer has FDA approval for acute bipolar depression.

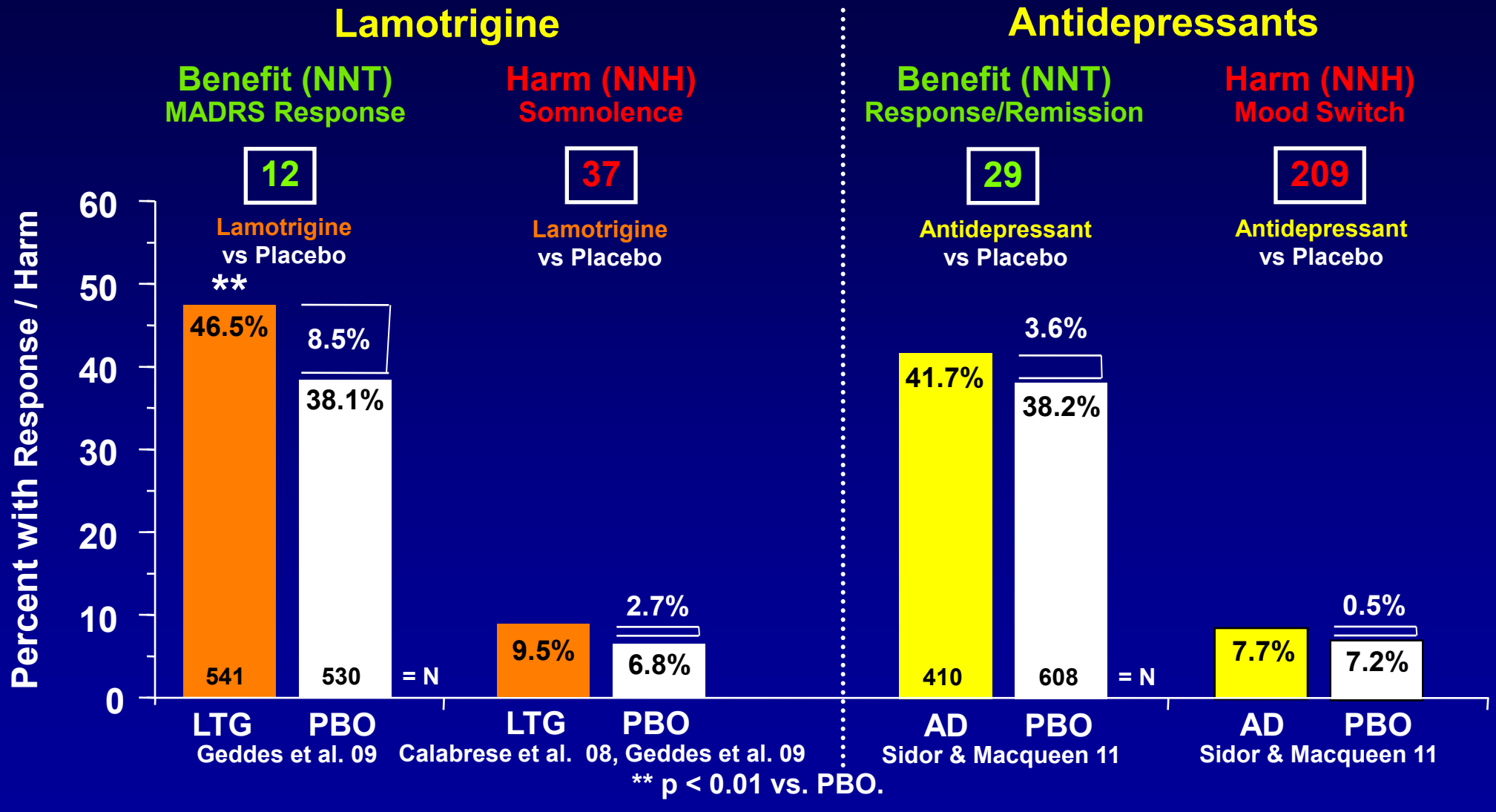
Mood Stabilizers Second Most Common Initial Treatment for Bipolar Disorder Patients in US in 2002-2003



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

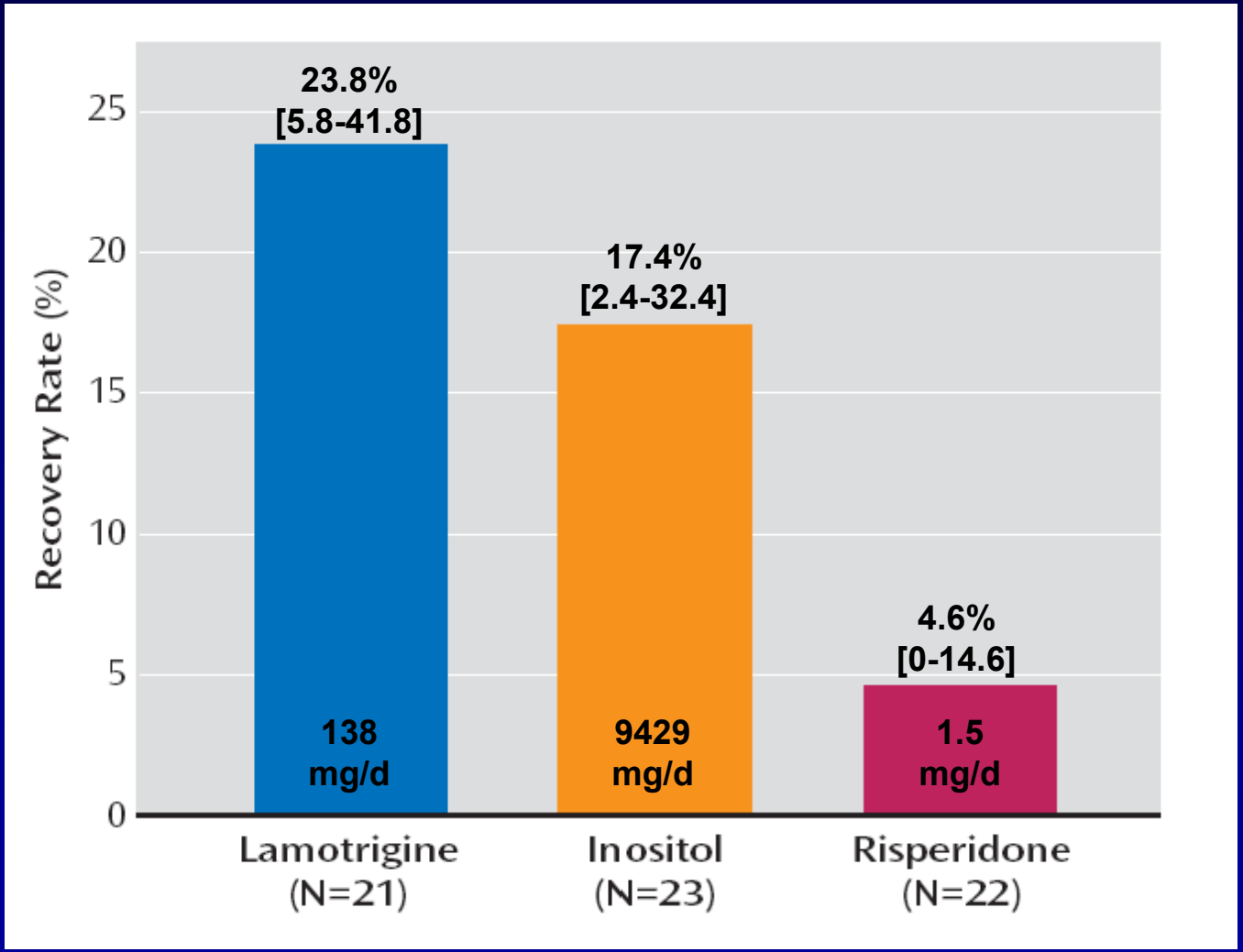
Unapproved Bipolar Depression Rx Benefits & Harms

Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



Lamotrigine & antidepressants more than twice as likely to yield benefit as harm.

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



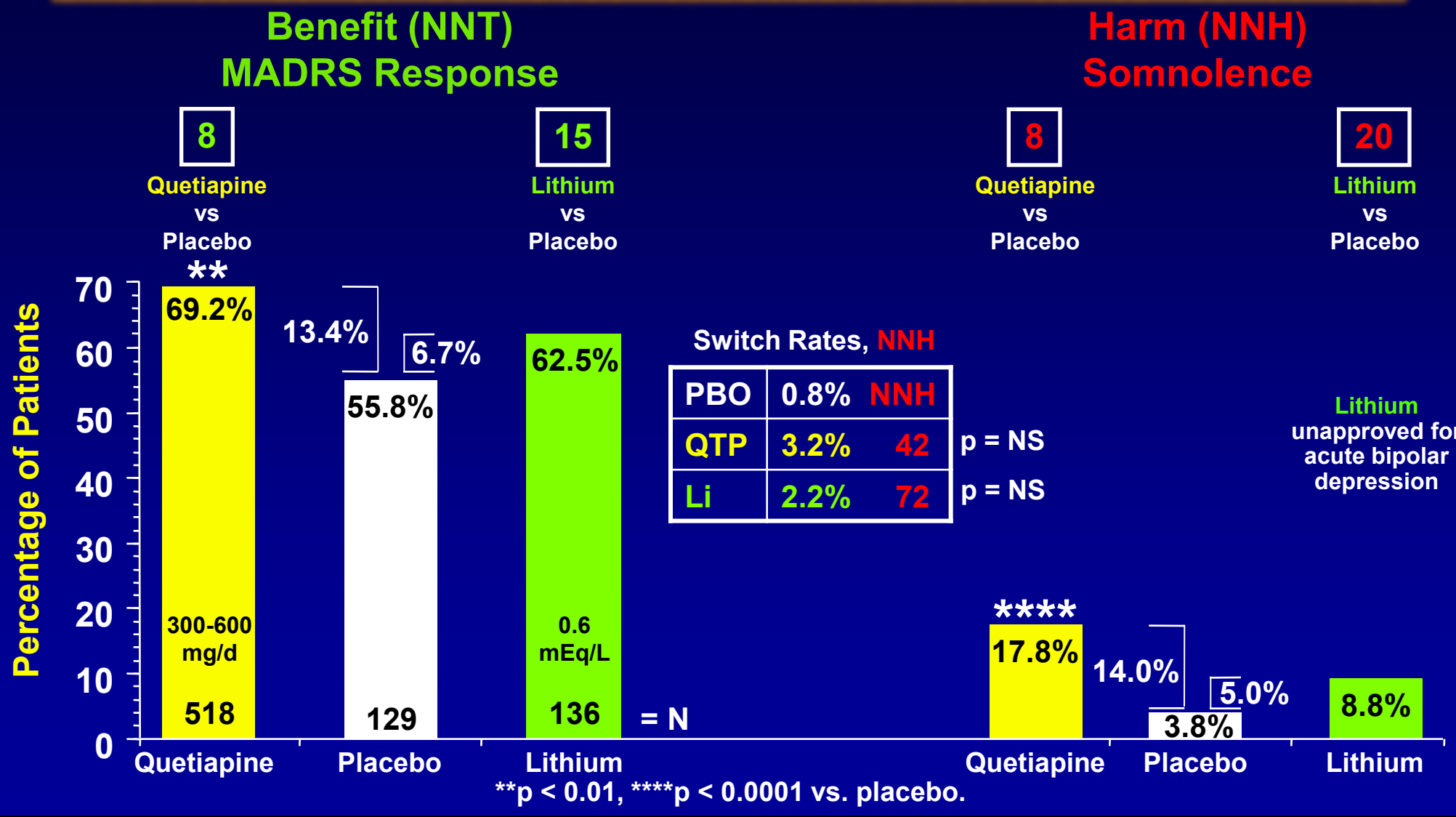
Switch Rates

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 Quetiapine, Lithium, and Placebo in Acute Bipolar Depression (EMBOLDEN I)



Quetiapine and lithium similarly likely to yield benefit and harm.

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 Pt's	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

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.

Mood Stabilizers in Acute Bipolar Depression

- Second most common initial bipolar disorder treatment
  - Class somatic tolerability: ≥ antipsychotics; ≤ antidepressants
  - Class established efficacy: acute mania and/or bipolar maintenance
- FDA-approved for acute bipolar depression
  - None!
- Not FDA-approved for acute bipolar depression (all!)
  - Lamotrigine (approved for maintenance - esp. depression prevention)
  - Lithium (approved for acute mania & maintenance - esp. mania prevention)
  - Divalproex (approved for acute mania; depression prevention efficacy?)
  - Carbamazepine (approved for acute mania)
- Inefficacy and/or intolerability can limit utility

FDA-Approved Agents for Bipolar Disorder

Acute Mania		Acute Depression		Longer-Term	
Year	Drug	Year	Drug	Year	Drug
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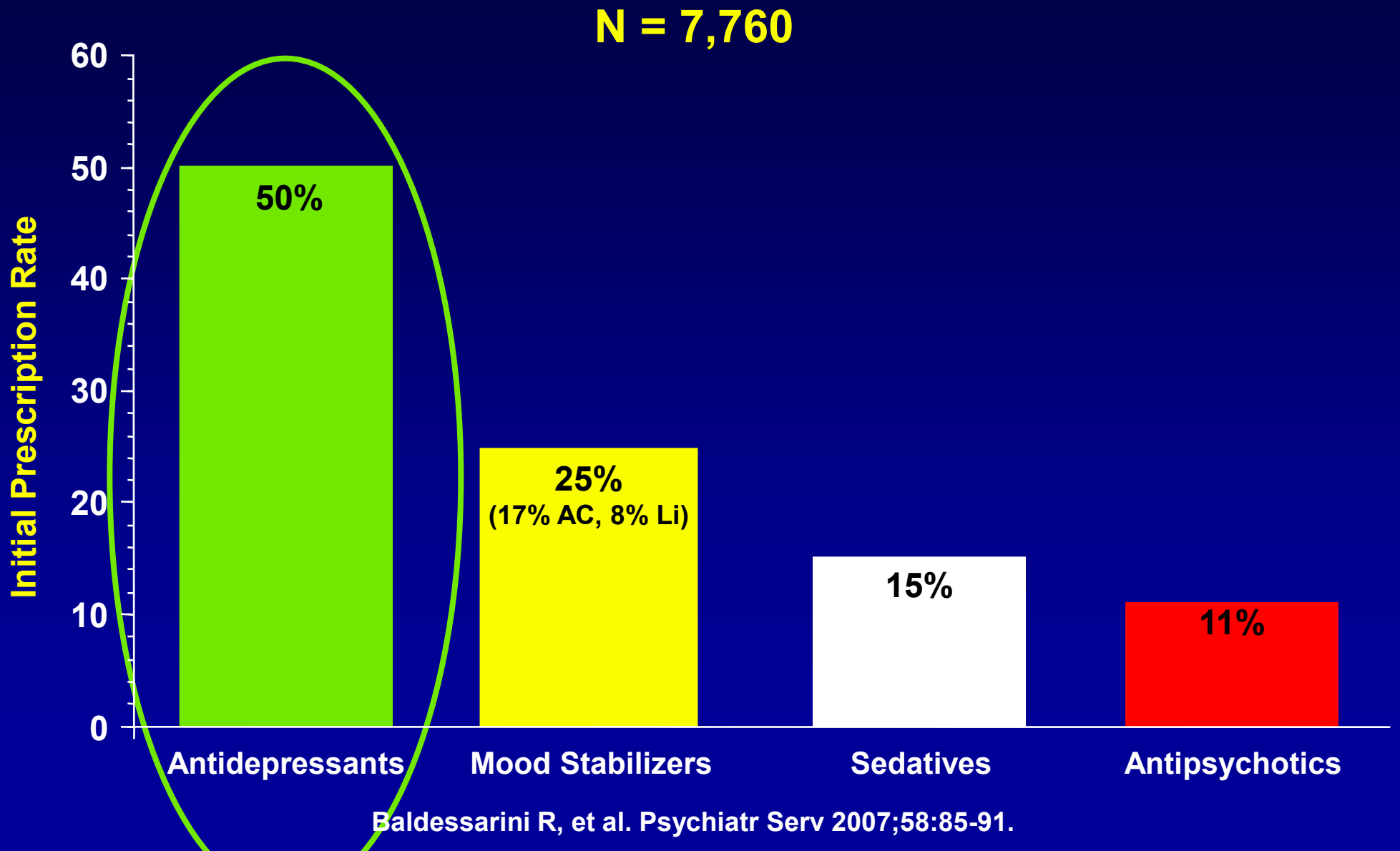
2004	Carbamazepine ERC				
2009	Asenapine*				

*Adjunctive and monotherapy; LAI = Long-Acting Injectable

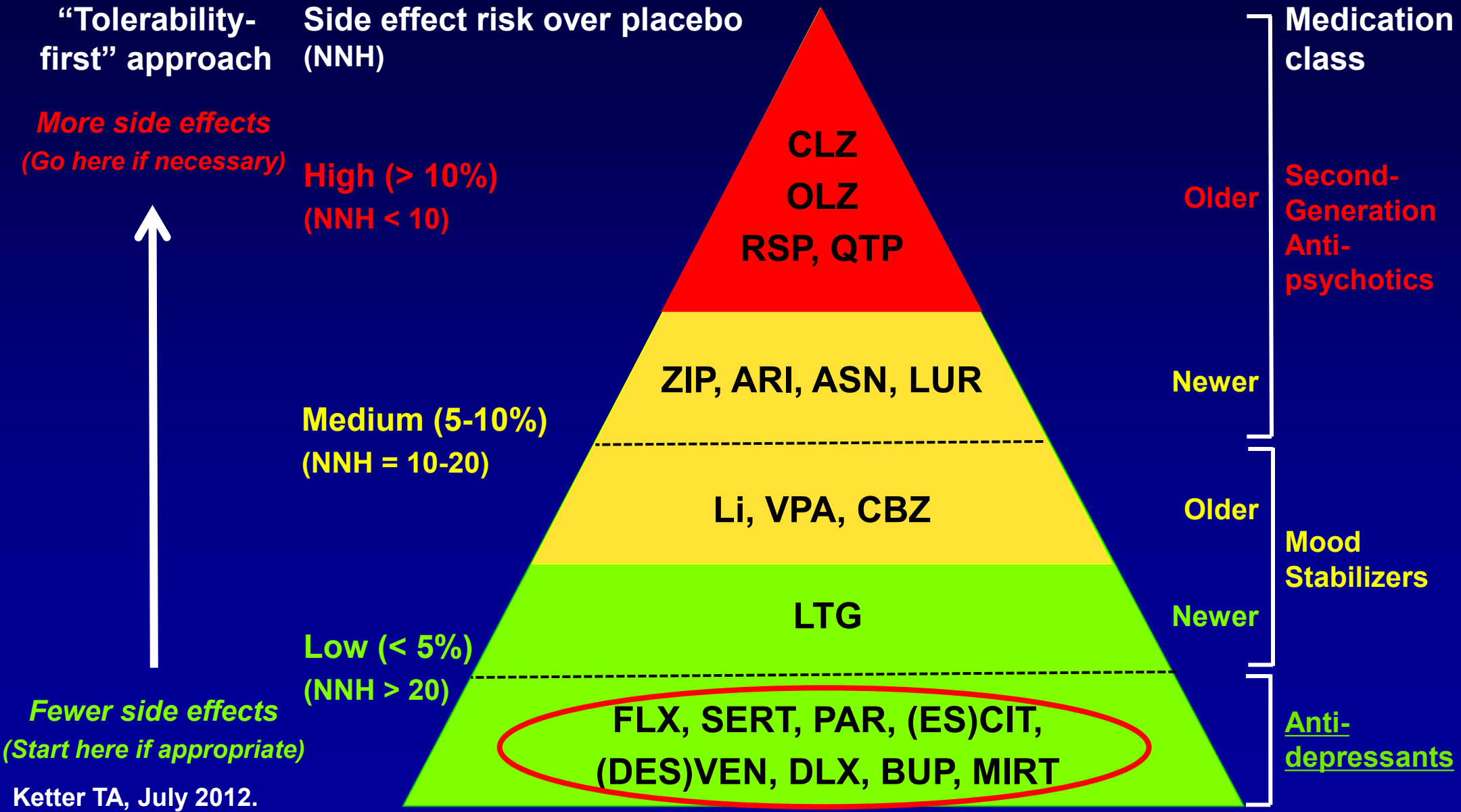
Fluoxetine (only with olanzapine) is sole antidepressant with FDA approval for bipolar depression.

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



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

Antidepressants Have Fewer Side Effects Compared to Other Agents



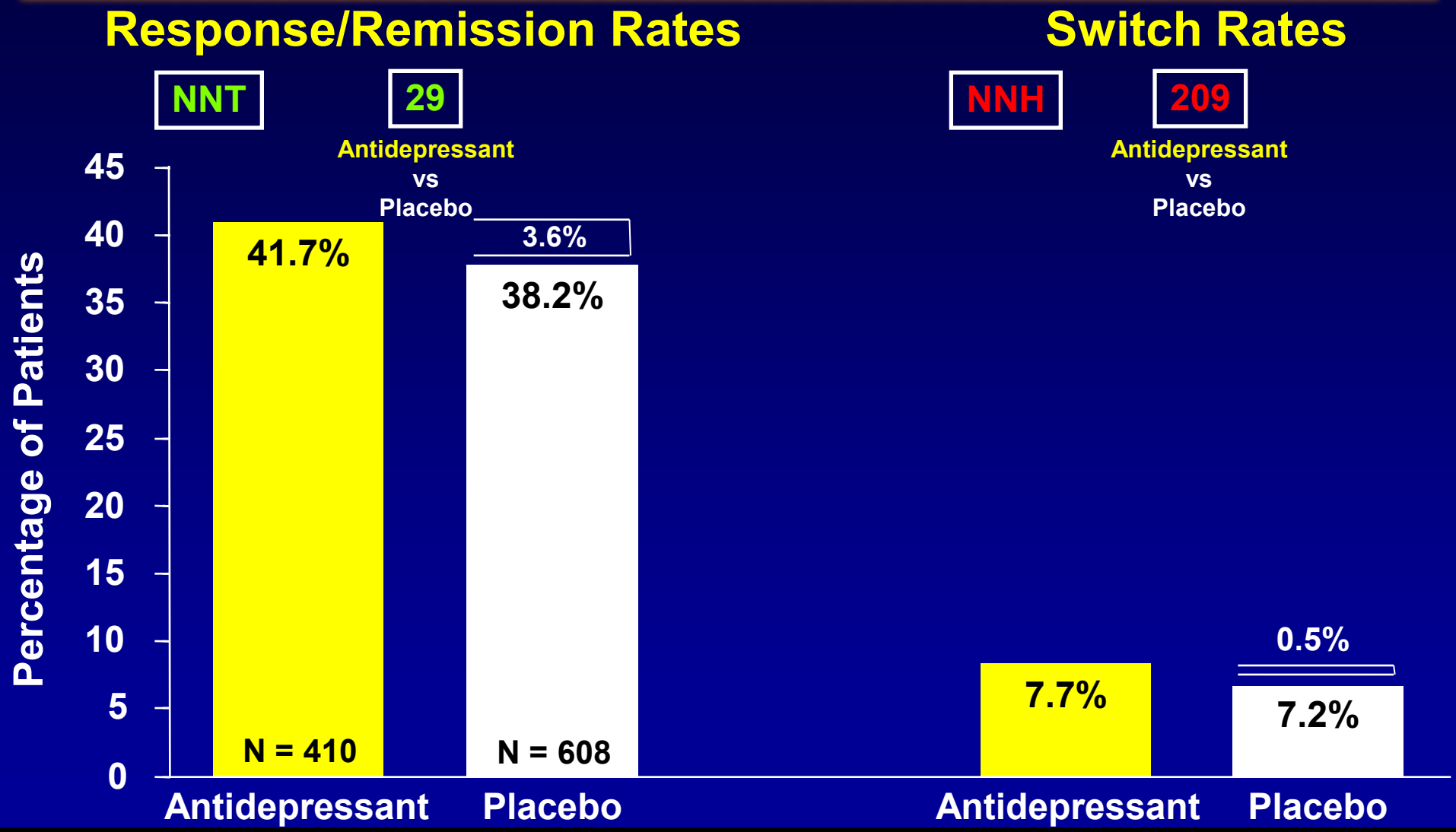
Ketter TA, July 2012.

Antidepressant Class Suicidality Label Changes (2005-7)

- Increased suicidality (suicidal behavior/ideation)
- Data from diverse antidepressants
- Children, adolescents, young adults (age ≤ 24)
- Screen depressed patients for risk of bipolar
- Suicidality risk increase
  - Children & adolescents (age < 18) – 14/1,000 (NNH = 72)
  - Young adults (age 18-24) – 5/1,000 (NNH = 200)

Antidepressant class warning – boxed, age ≤ 24, NNH 72-200.

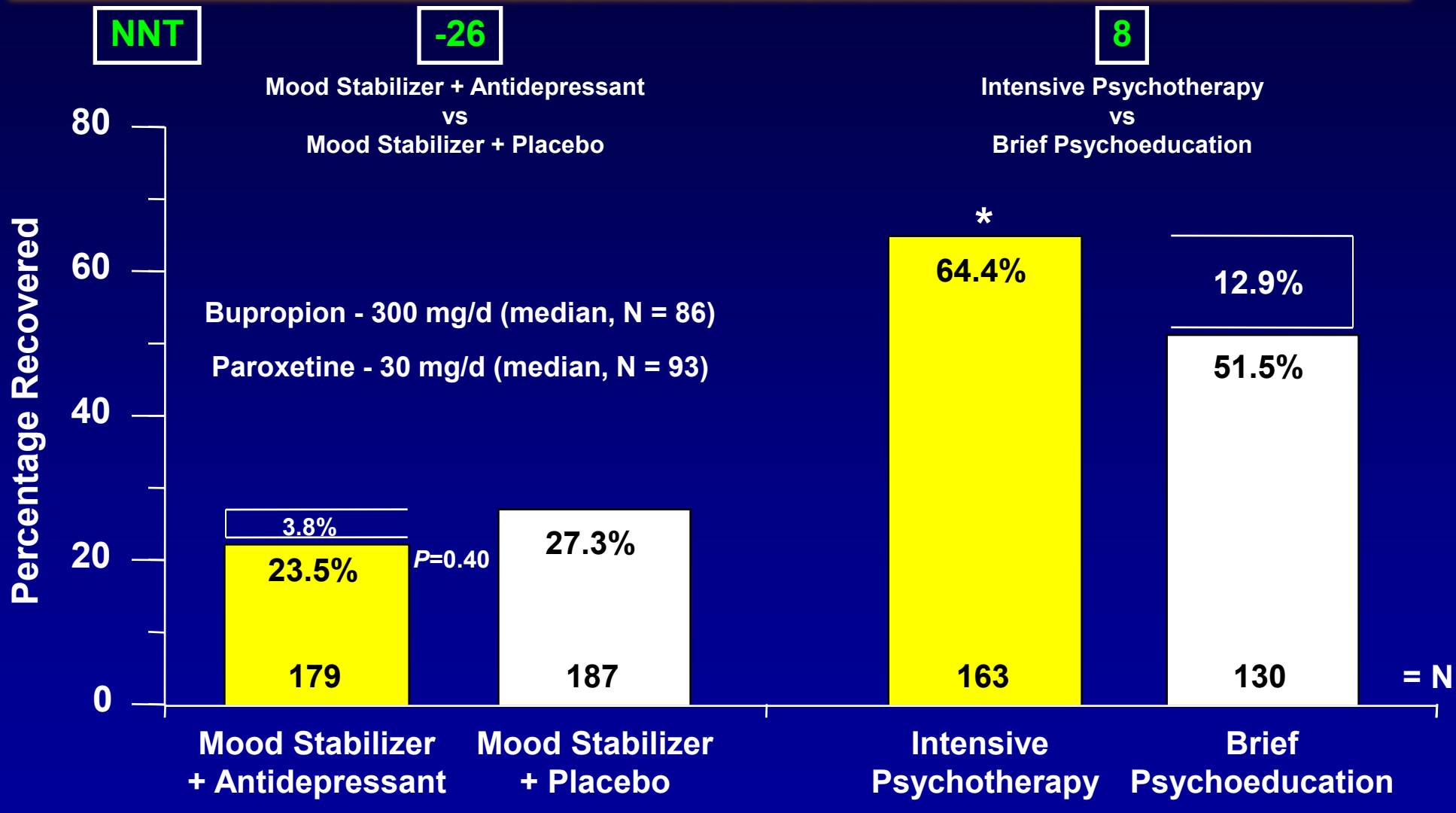
Meta-Analysis of Antidepressants in Acute Bipolar Depression



Inefficacy may be most substantive problem with antidepressants in bipolar depression.

STEP-BD Randomized Bipolar Depression Studies

Numbers Needed to Treat for Recovery, Rates



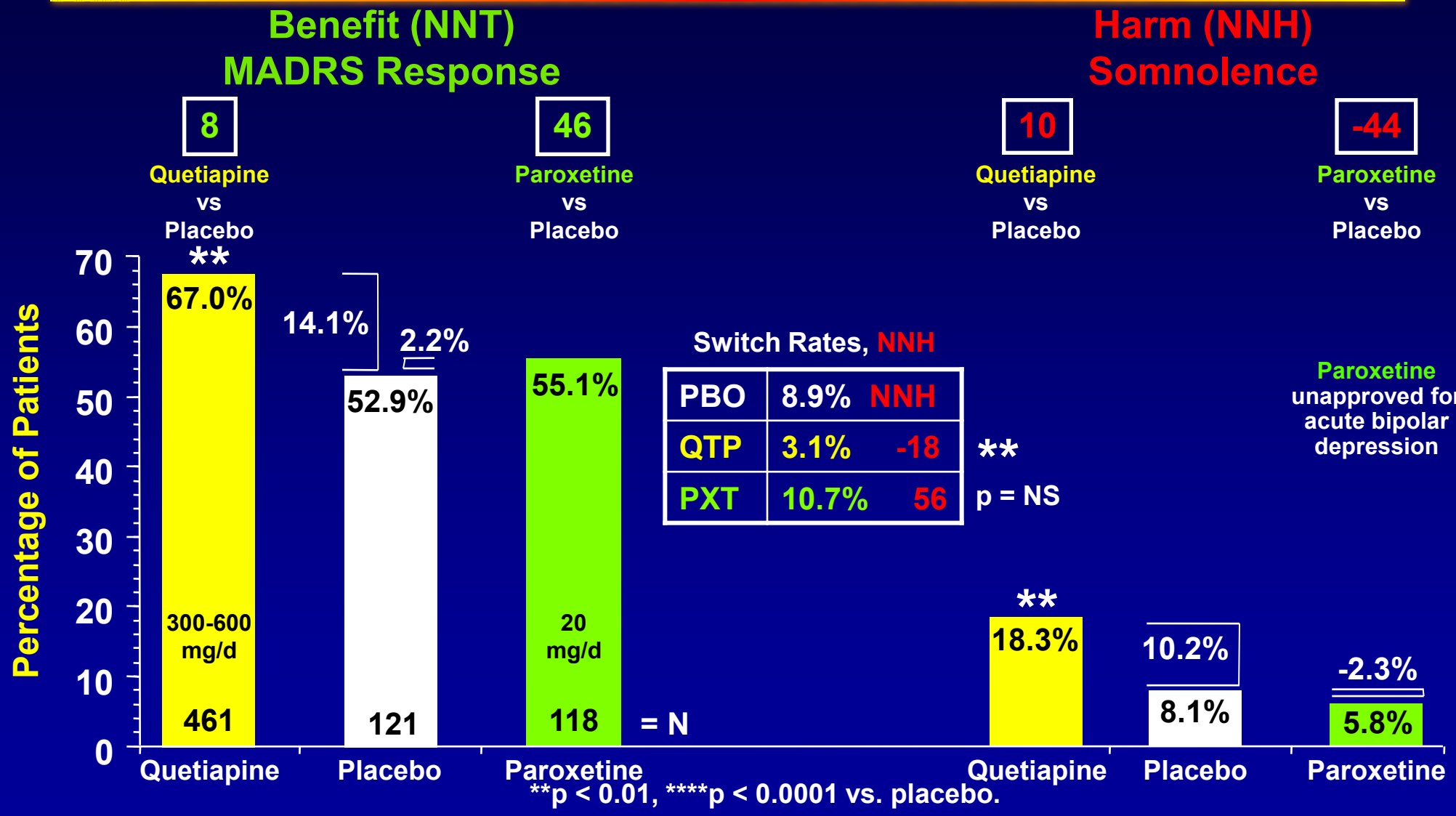
*p < 0.05 vs. Cntl.

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.

8-Week Randomized Double-Blind Quetiapine, Paroxetine, and Placebo in Acute Bipolar Depression (EMBOLDEN II)



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

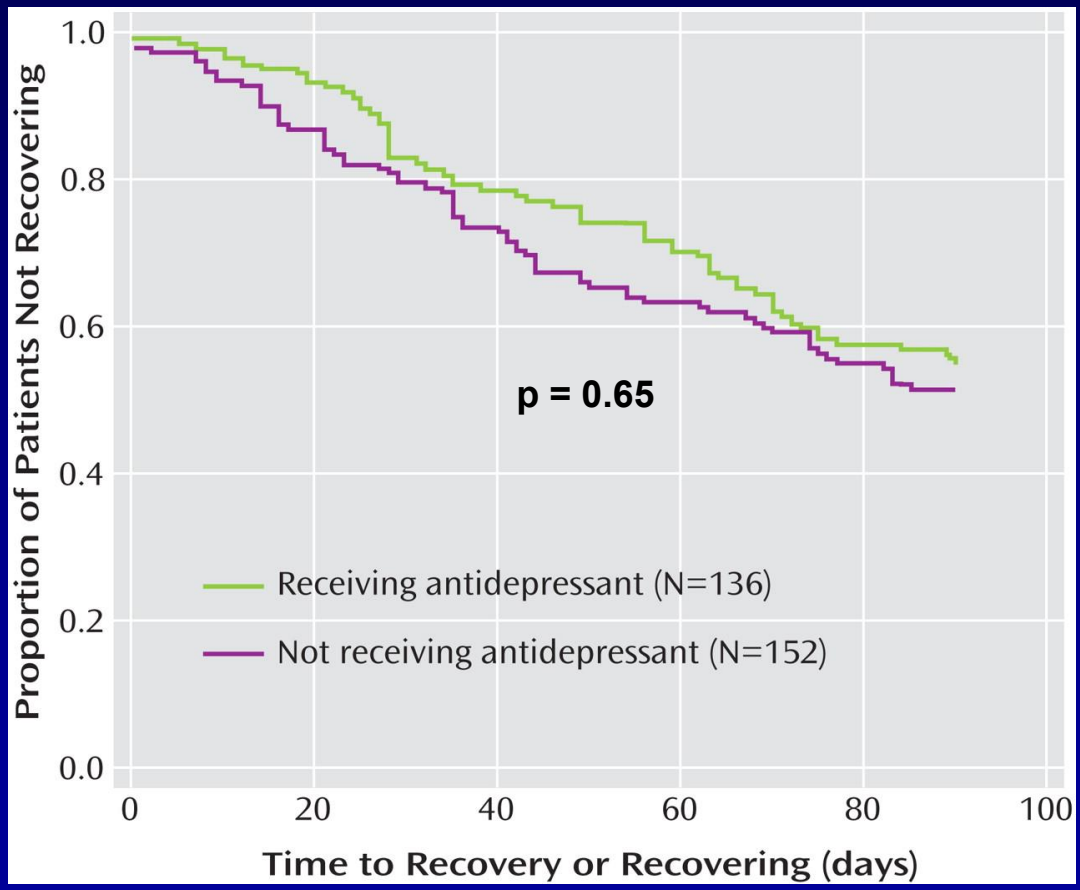
Quetiapine similarly and paroxetine more likely to yield benefit as harm.

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.

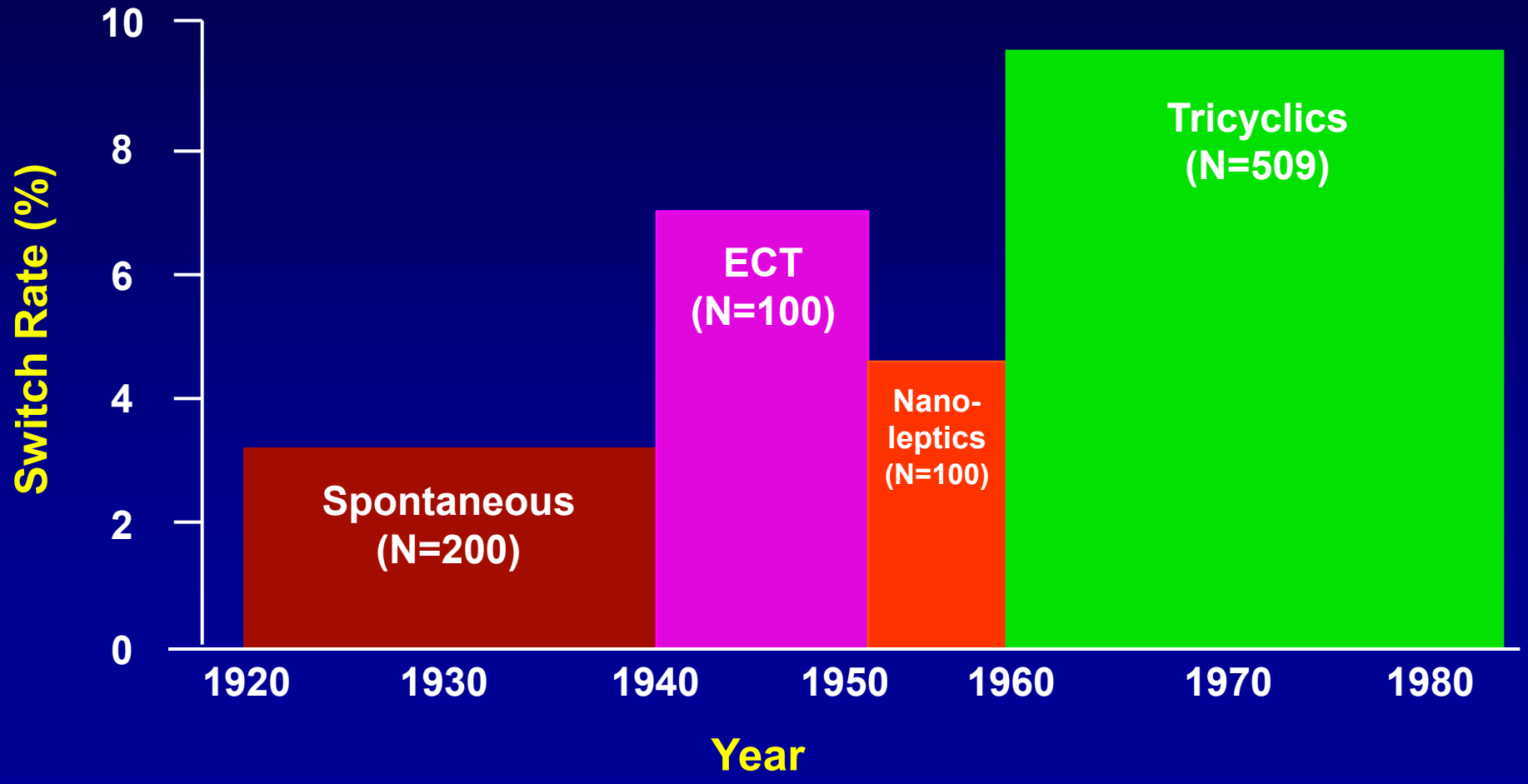
Do Antidepressants Induce Mania?

- 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.

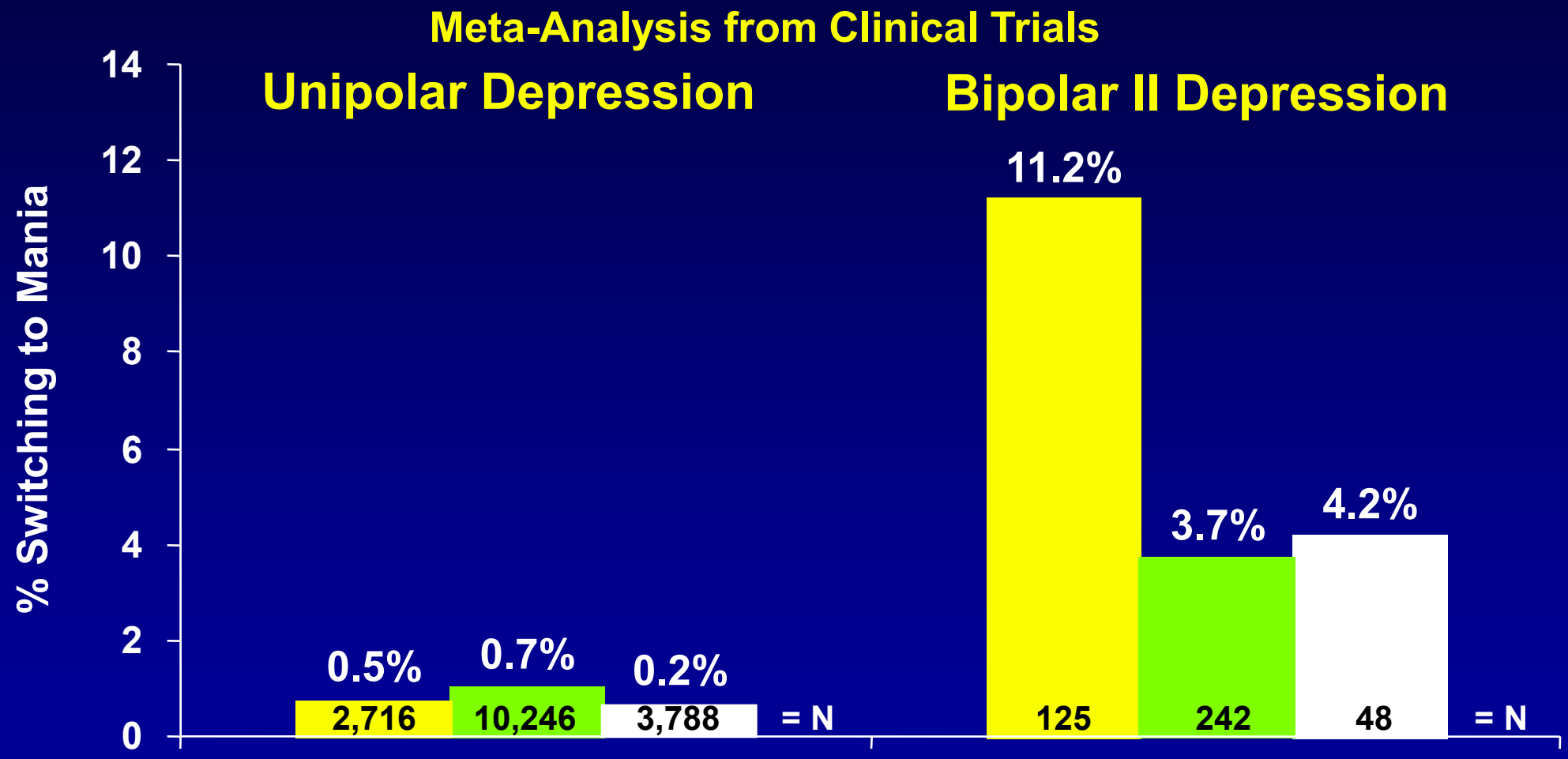
Switch Rate From Index Depression Into Mania

By Era and Prevailing Treatment



Angst J. Psychopathology 1985.

Antidepressant-Induced Mania More Common in Bipolar II Compared to Unipolar Depression

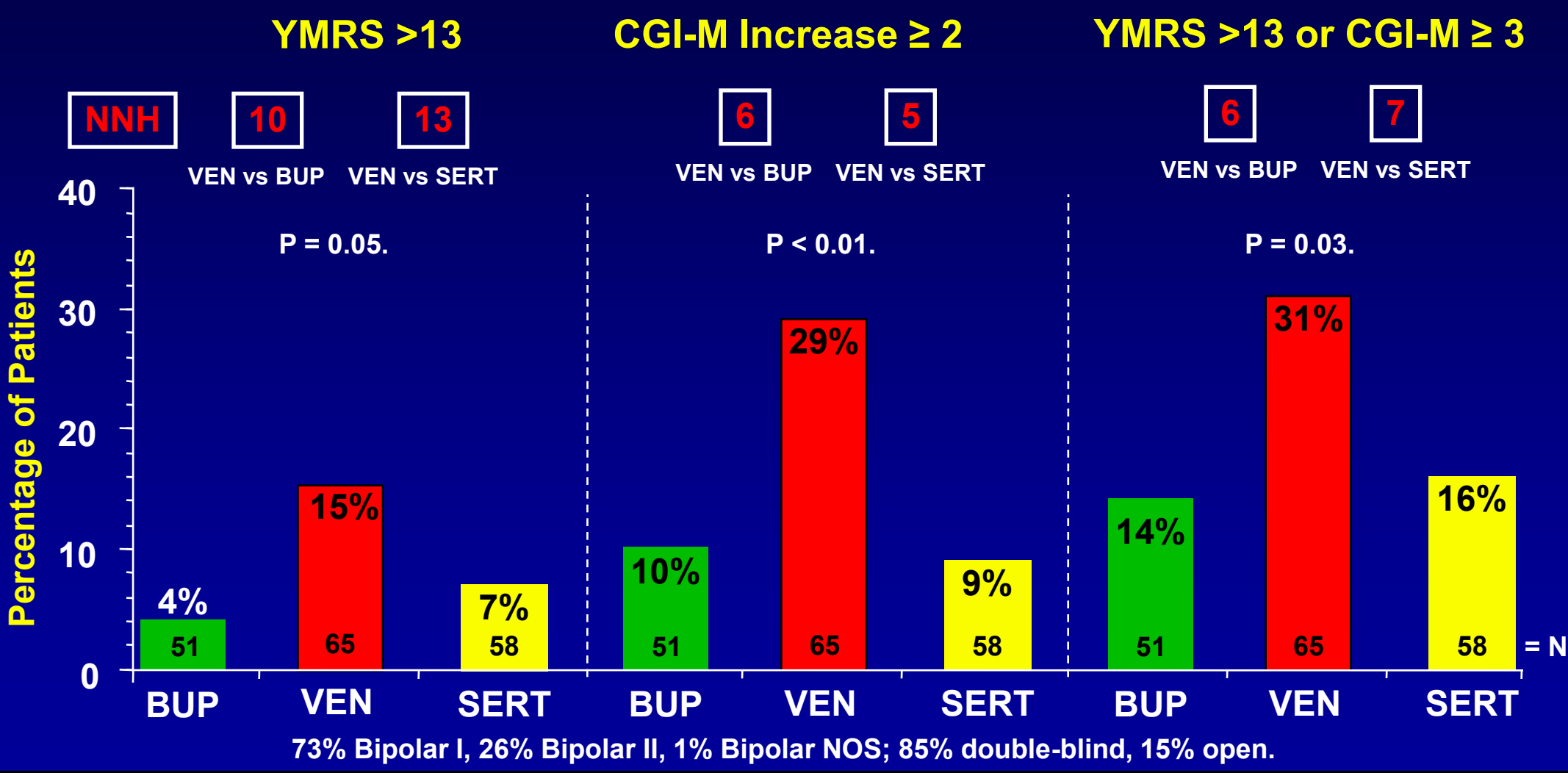


SSRI = fluoxetine, fluvoxamine, paroxetine,or sertraline

Switch Risk: Bipolar II > Unipolar; TCA ≥ SSRI ≥ Placebo.

Increased Switching with Adjunctive Venlafaxine Compared to Bupropion and Sertraline in Acute Bipolar Depression

Switch Rates



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

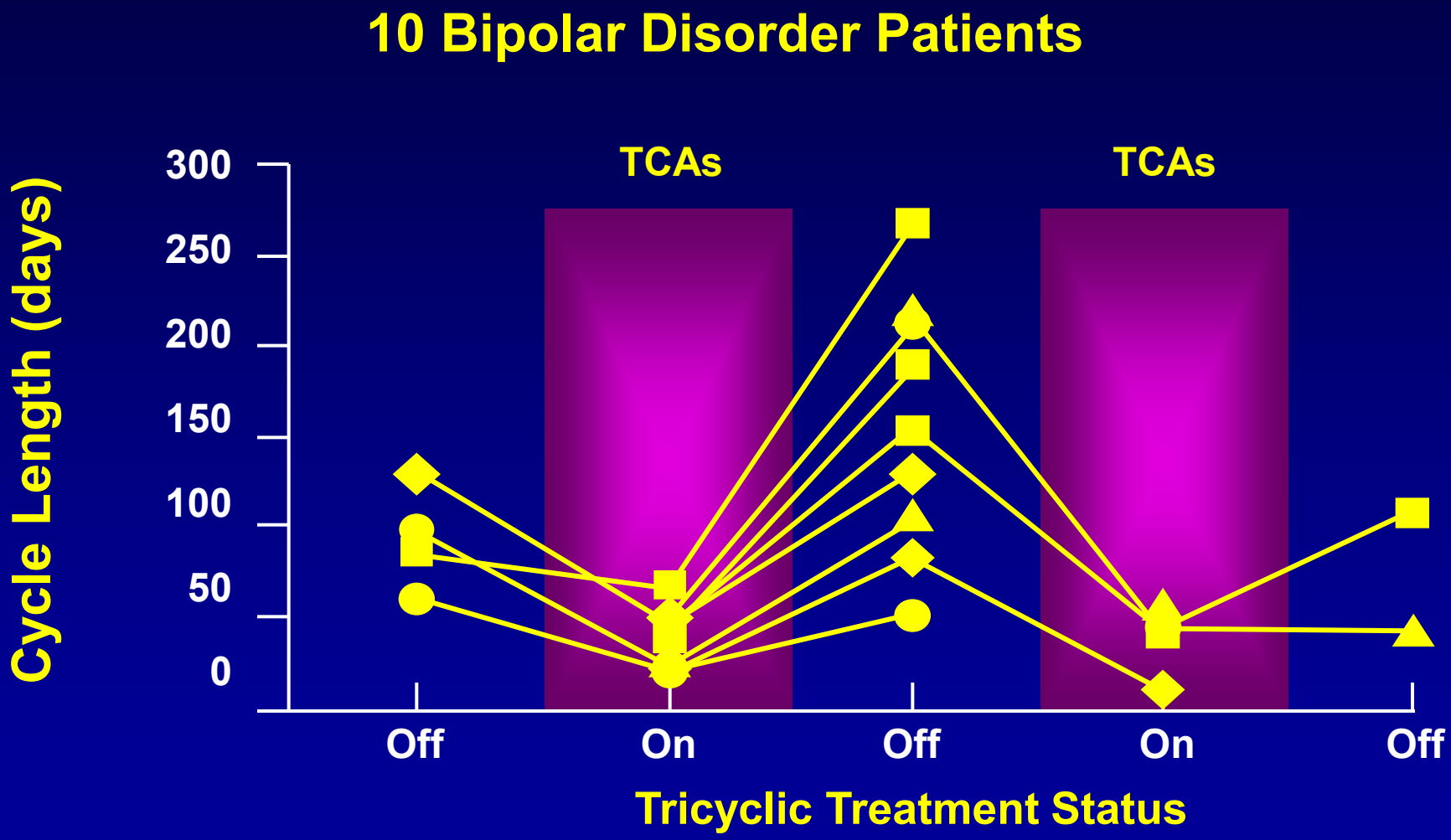
Adjunctive venlafaxine (compared to sertraline, bupropion) yielded more switching.

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.

Antidepressant (AD) use in Bipolar Disorder: The ISBD Task Force Consensus Report

1. Adjunctive ADs for acute bipolar depression
   - Permissible if history of positive AD response
   - Avoid if ≥ 2 manic symptoms, psychomotor agitation, or rapid cycling
2. Adjunctive ADs for bipolar maintenance
   - Permissible if depressive relapse after stopping AD
3. AD monotherapy for acute bipolar depression
   - Avoid in bipolar I disorder
   - Avoid in bipolar I & II depression if ≥ 2 manic symptoms

Pacchiarotti I, et al. (65 bipolar experts). Am J Psychiatry 2014;170:1249-62.

Antidepressant (AD) use in Bipolar Disorder: The ISBD Task Force Consensus Report

4. **AD Switching to Hypo/mania, Mixed Features, Rapid Cycling**
   - **Discontinue** if AD-emergent hypo/mania or psychomotor agitation
   - **Discourage** if prior AD-emergent hypo/mania or mixed features
   - **Avoid** if high number of episodes or rapid cycling
5. **AD Use in Mixed States**
   - **Avoid** in manic/depressive episodes with mixed features
   - **Avoid** in patients with predominantly mixed states
   - **Discontinue** if mixed state emerges
6. **ADs with Increased Switch Risk (SNRIs & TCAs)**
   - **Permissible** only if other ADs already tried & patient closely monitored

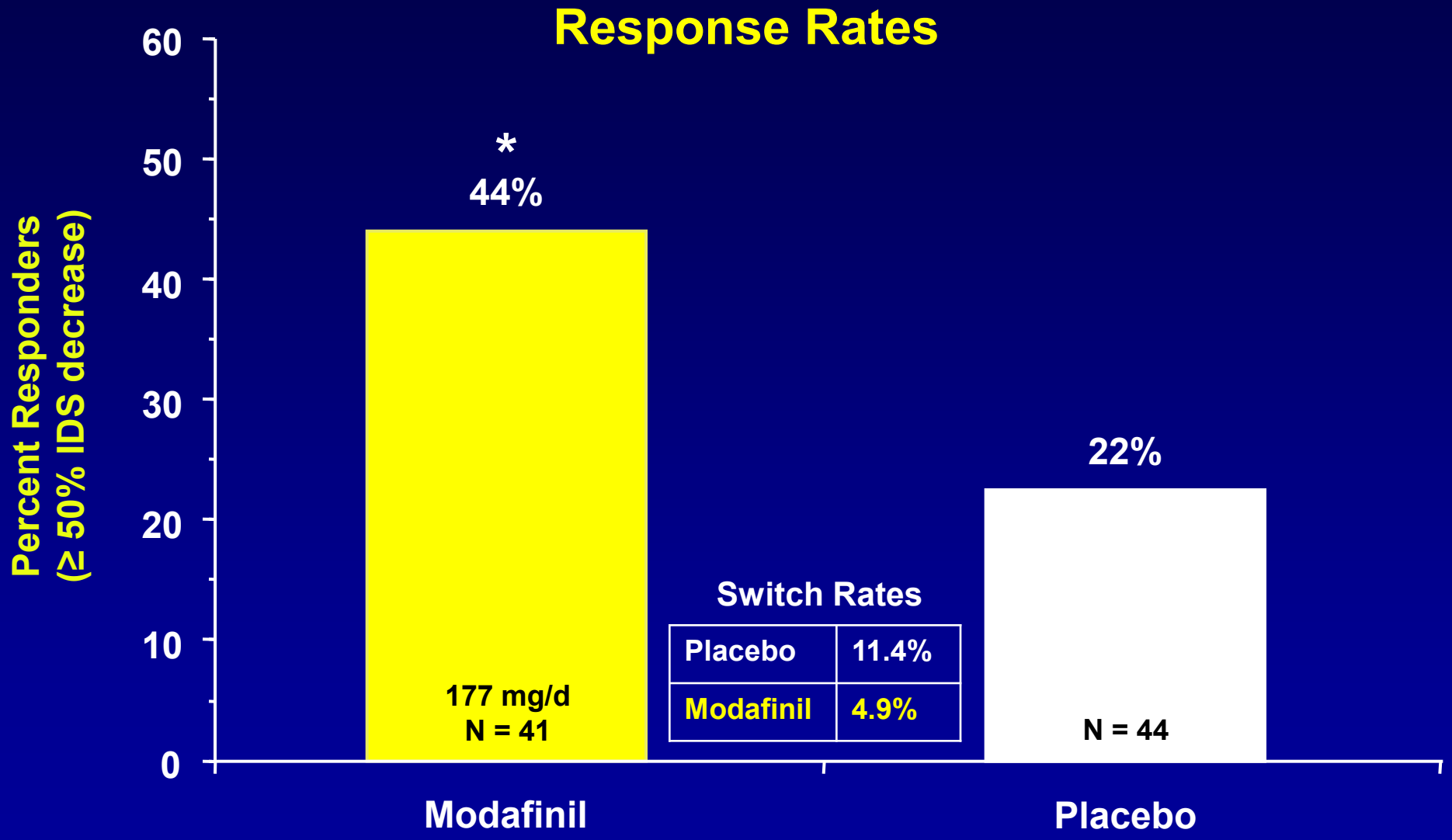
3/12 Permissible; 9/12 Avoid, Discontinue, Discourage.

Pacchiarotti I, et al. (65 bipolar experts). Am J Psychiatry 2014;170:1249-62.

Antidepressants in Acute Bipolar Depression

- Most common initial bipolar disorder treatment
  - Class somatic tolerability: > antipsychotics; ≥ mood stabilizers
  - Class established efficacy: unipolar (but not bipolar) depression
- FDA-approved for acute bipolar depression
  - Fluoxetine (only combined with olanzapine)
- Not FDA-approved for acute bipolar depression
  - Fluoxetine with other antimanic agents
  - All other antidepressants with antimanic agents
  - All antidepressants as monotherapy
- Inefficacy perhaps more than switching may limit utility

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

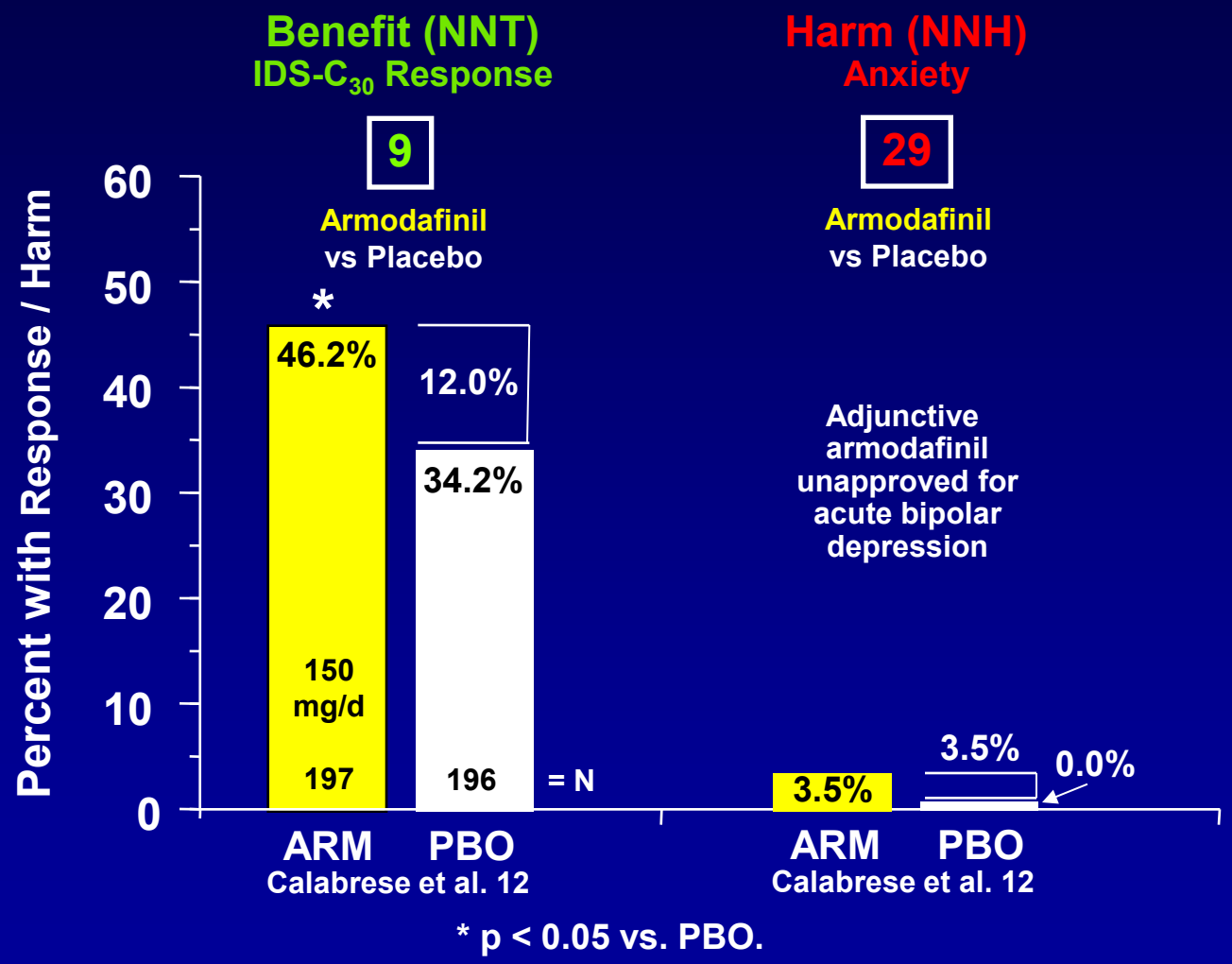


*p < 0.05 vs placebo.

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

Adjunctive Armodafinil in Bipolar Depression Benefits & Harms

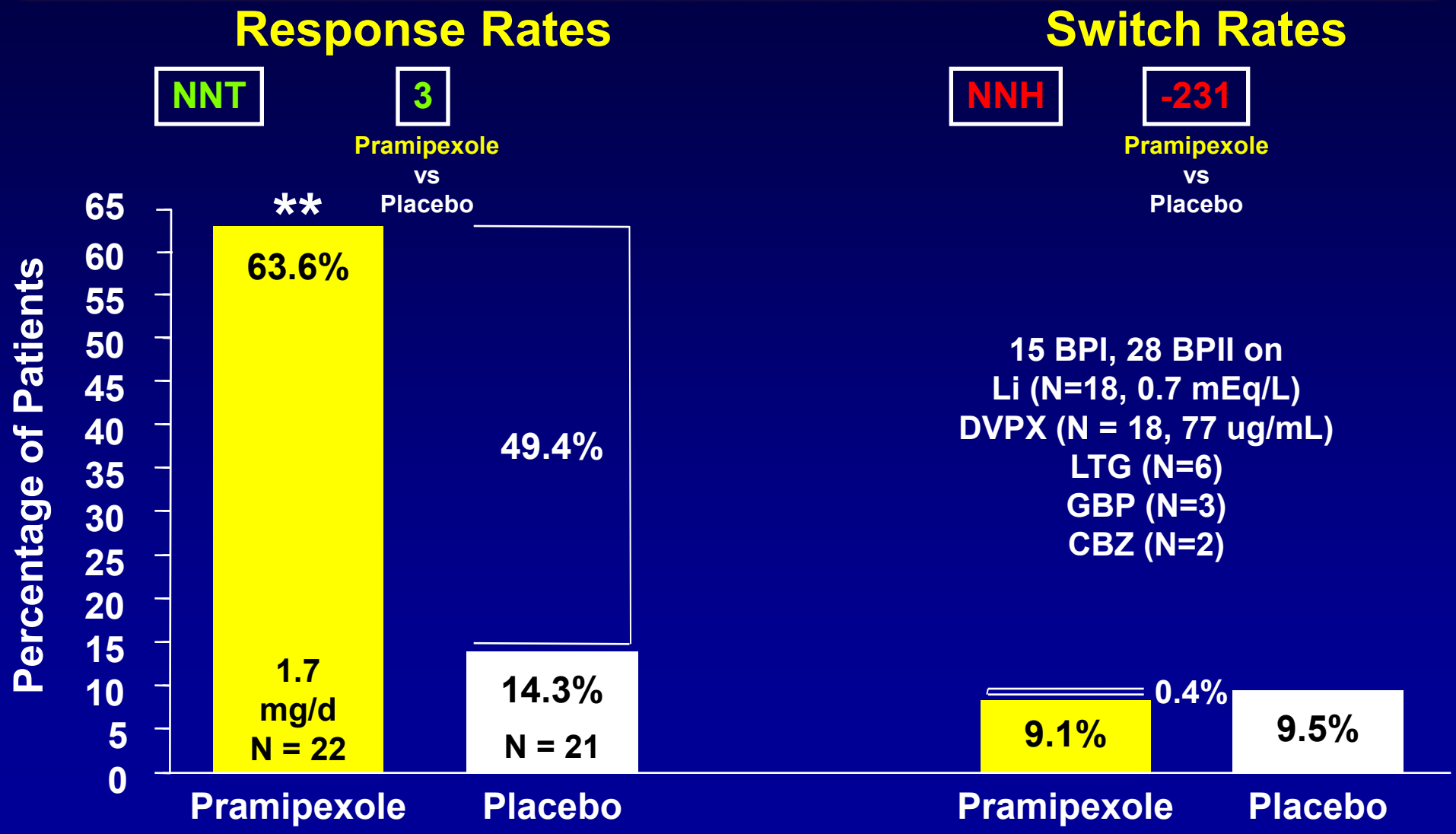
Numbers Needed to Treat & Harm, Response & Adverse Effect Rates



* $p < 0.05$ vs. PBO.

2 subsequent studies were negative.

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



**p = 0.0016 vs. PBO

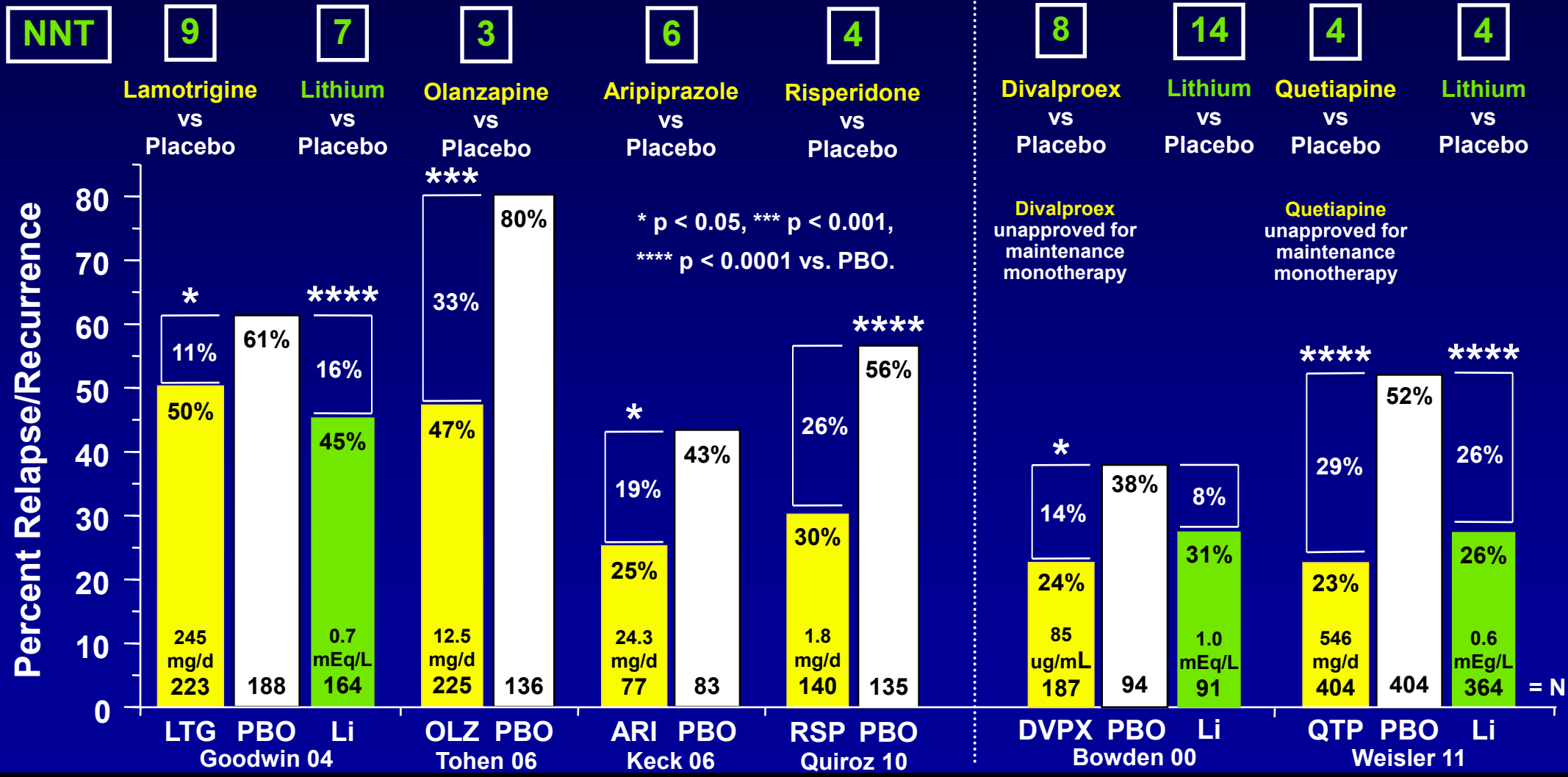
Response: ≥ 50% HDRS/MADRS decrease

Goldberg JF, et al. Am J Psychiatry 2004;161:564-6; Zarate CA, et al. Biol Psychiatry 2004;56:54-60.

Maintenance Treatment of Bipolar Depression

Overview of Monotherapy Bipolar Preventive Studies

Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

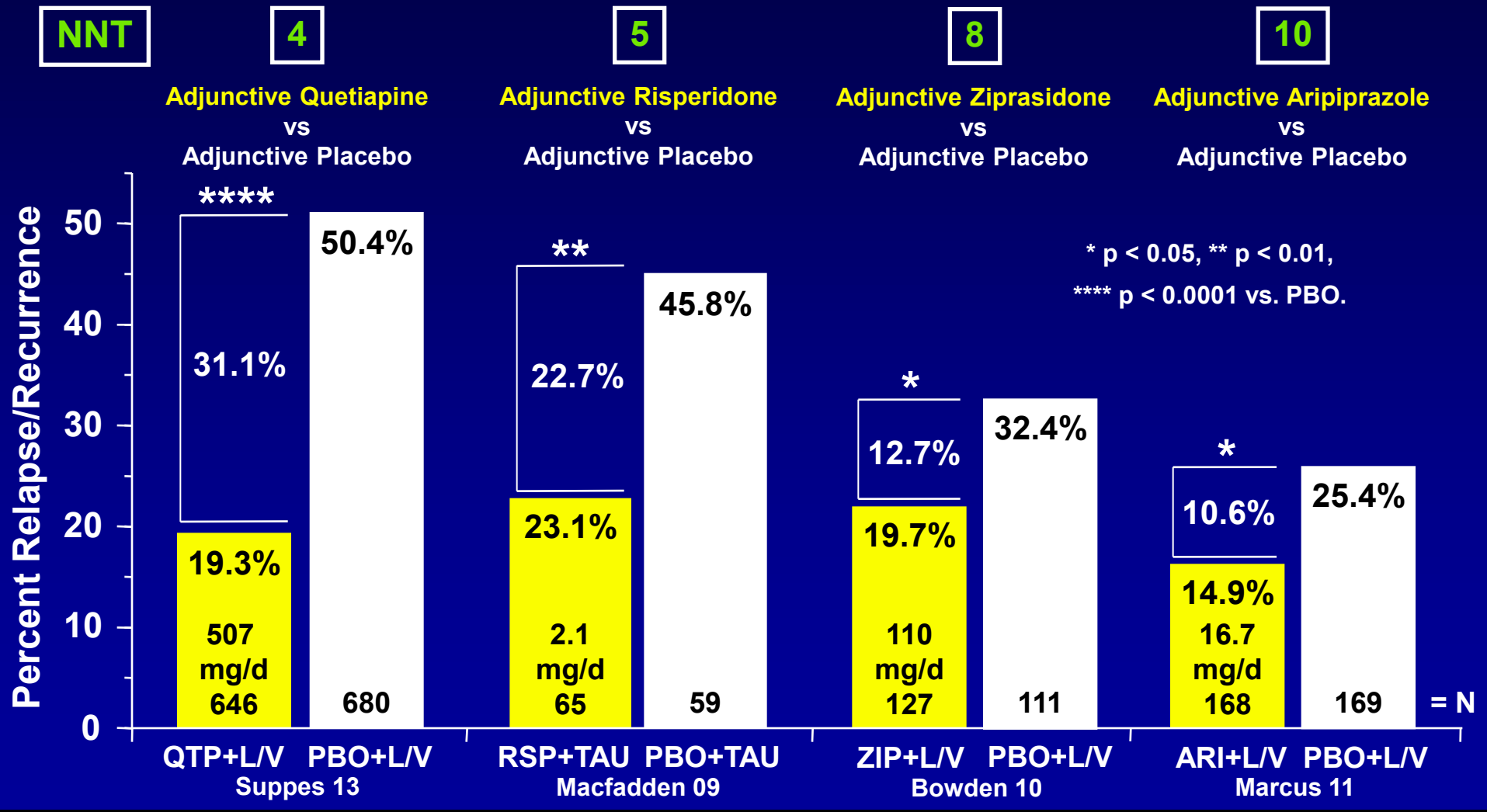


Approved maintenance treatments generally have single-digit NNTs.

Overview of Adjunctive Therapy Bipolar Preventive Studies

Numbers Needed to Treat for Relapse/Recurrence Prevention, Rates

Contemporary Registration Studies



Approved maintenance treatments generally have single-digit NNTs.

Numbers Needed to Treat in Bipolar Maintenance

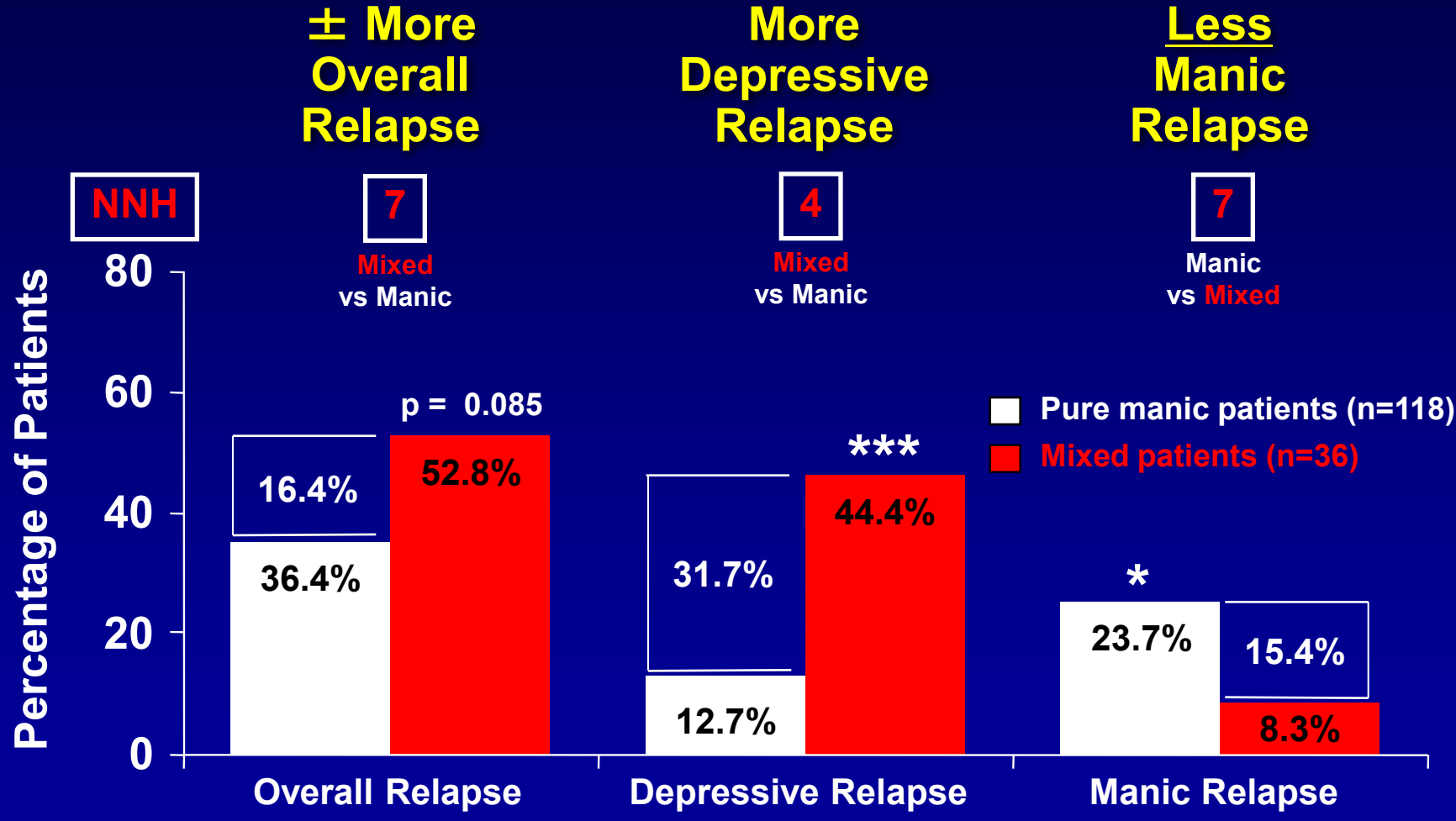
	Episode Prevention	Mania Prevention	Depression Prevention
Mood Stabilizers			
Lithium[1]	**5**	**7**	17
Divalproex[2]	**8 (unapproved)**	22 (unapproved)	11 (unapproved)
Lamotrigine[1]	**9**	23	15
Atypical Antipsychotics			
Olanzapine[3]	**3**	**5**	12
Aripiprazole[4]	**6**	**6**	64
Risperidone LAI[5]	**4**	**4**	-26
Quetiapine[6]	**4 (unapproved)**	**6 (unapproved)**	**9 (unapproved)**
Paliperidone[7]	13 (unapproved)	**8 (unapproved)**	-17 (unapproved)
Aripiprazole + Lithium/Divalproex[8] *	**10**	**13**	42
Quetiapine + Lithium/Divalproex[9]*	**4**	**6**	**9**
Ziprasidone + Lithium/Divalproex[10] *	**8**	**10**	56
Risperidone LAI + Lithium/Divalproex[11] *	**5**	**7**	16

White boldface indicates approved treatments. **Yellow boldface** indicates noteworthy NNTs. *vs. lithium/divalproex monotherapy.

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

Differential Recurrence Risks with Mixed Compared to Pure Manic Index Episodes

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

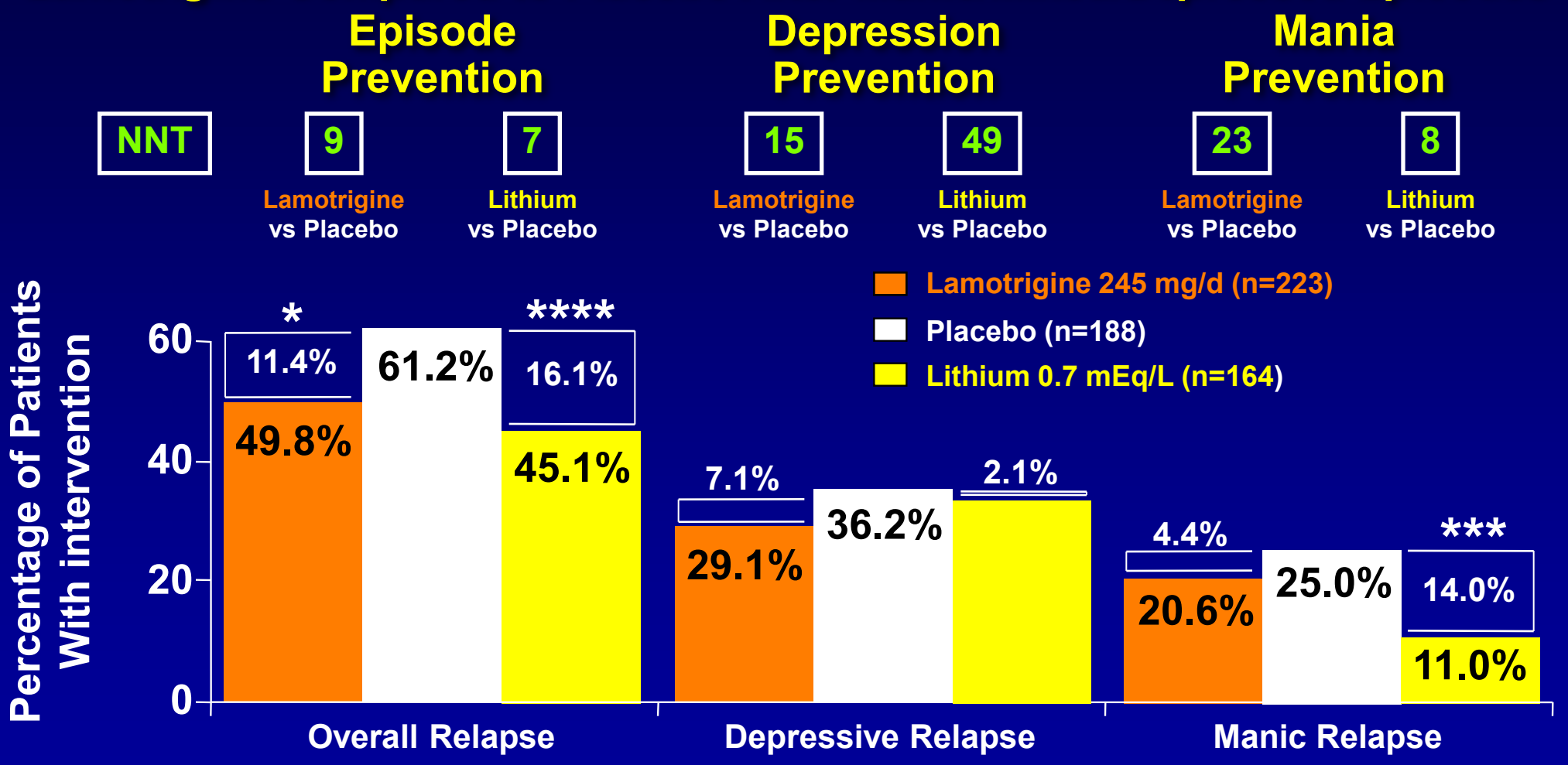


Tohen M, et al. Am J Psychiatry 2003;160:2099–2107. *p < 0.05, ***p < 0.001.

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

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

Lamotrigine Compared to Placebo After Manic/Mixed/Depressed Episodes



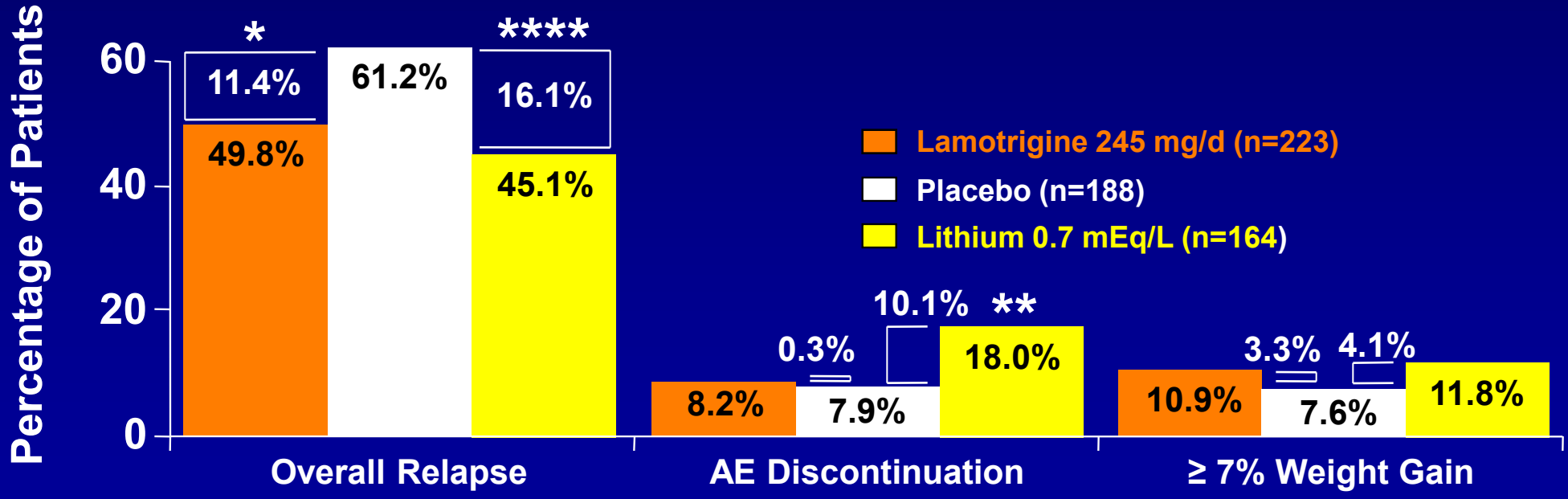
Goodwin et al. J Clin Psychiatry 2004;65:432-41. *p<.05, ***p < 0.001, ****p < 0.0001 vs PBO.

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



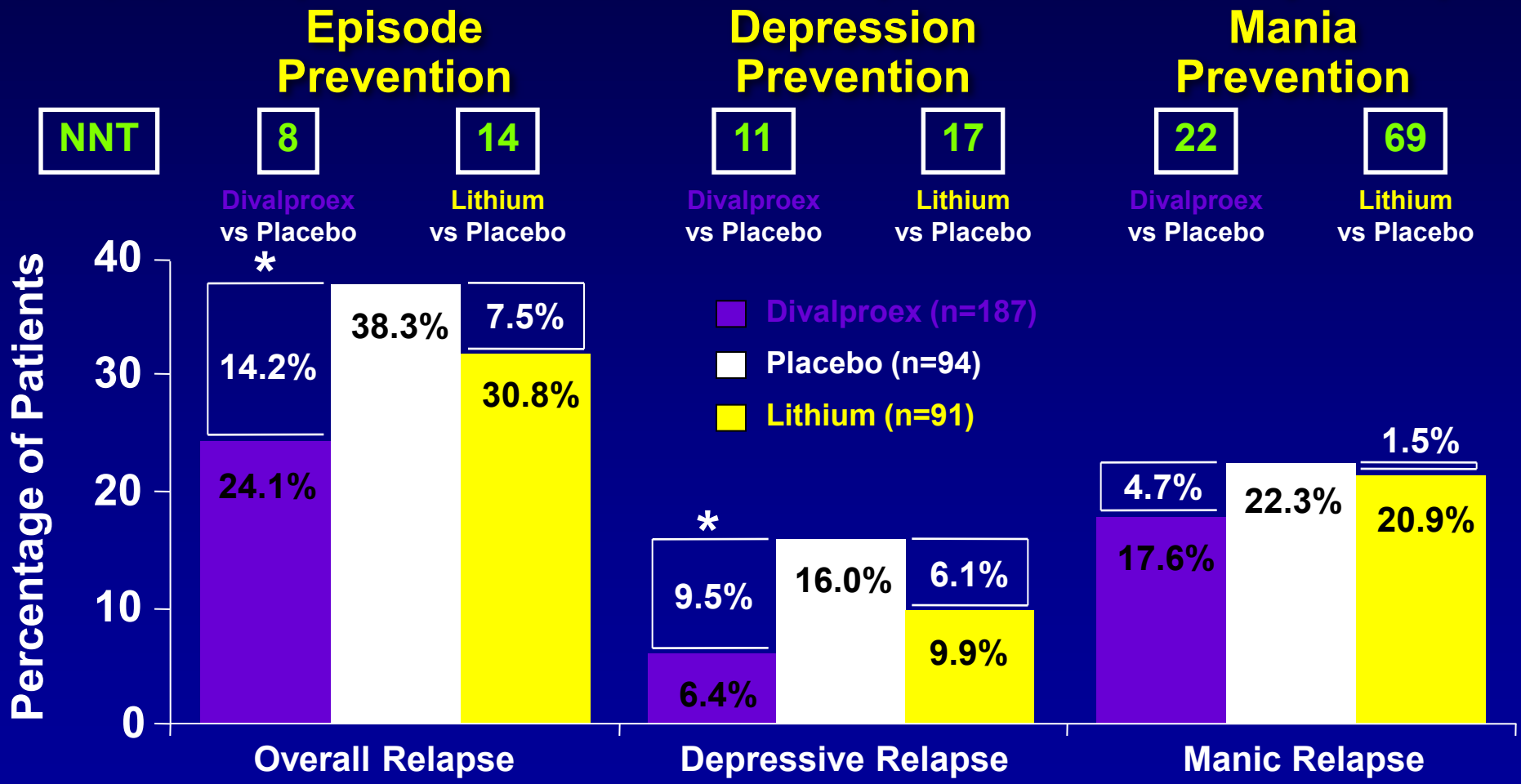
Goodwin et al. J Clin Psychiatry 2004;65:432-41. *p<.05, **p < 0.01, ****p < 0.0001 vs PBO.

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

12-Month Double-Blind 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)



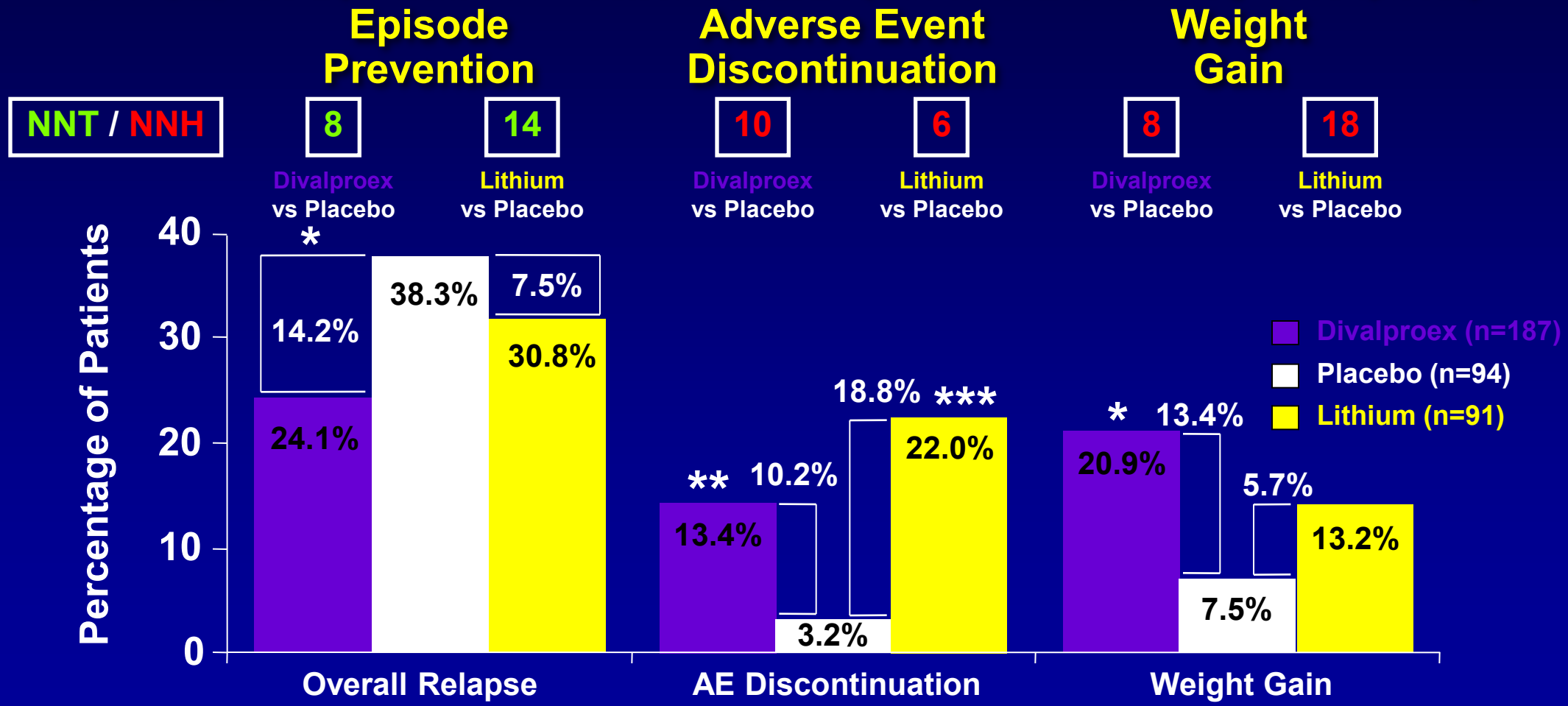
Stabilized on open treatment for 2 consecutive visits at least 6 days apart. *p < 0.02 vs PBO.

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)

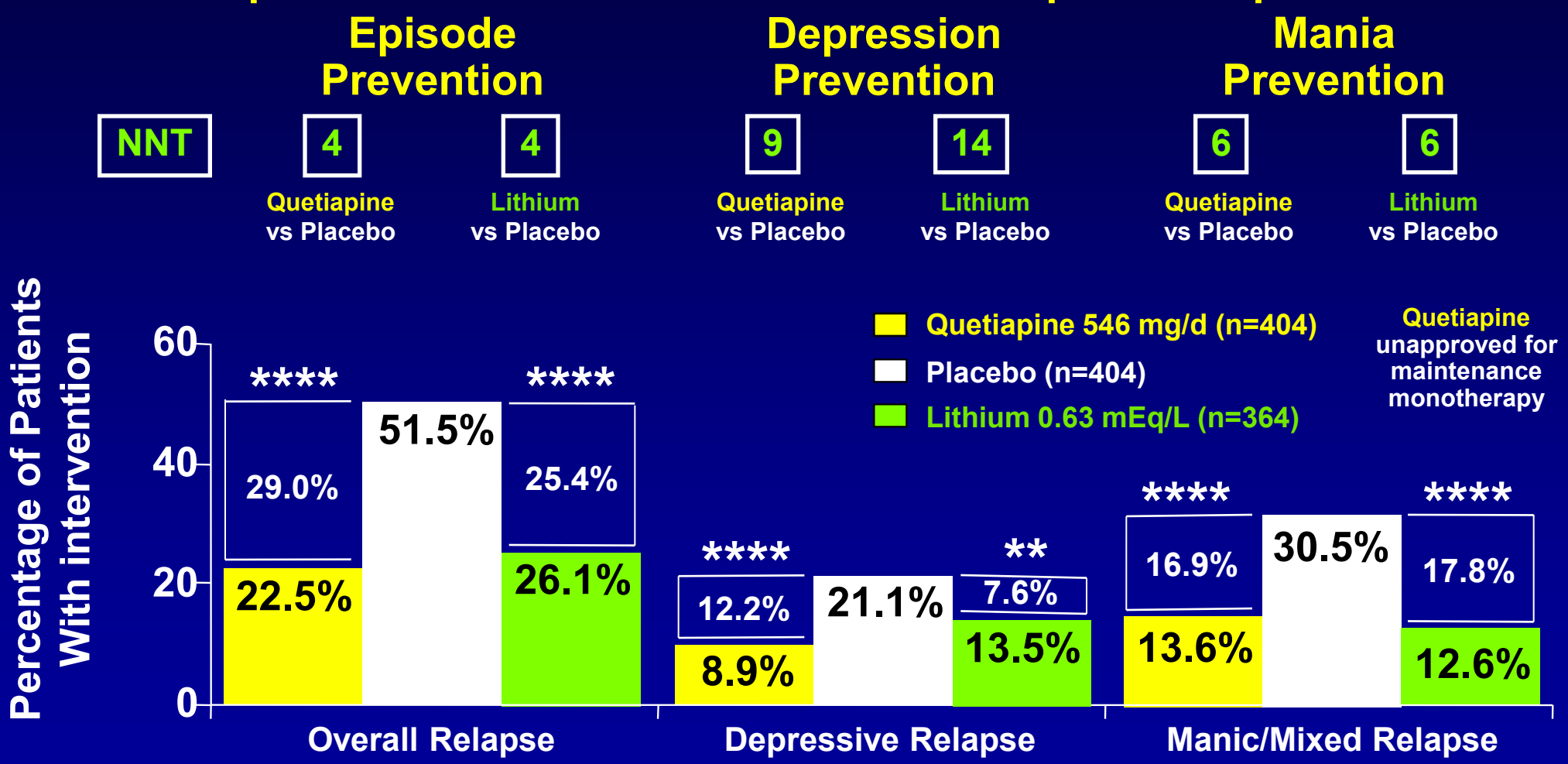


Stabilized on open treatment for 2 consecutive visits at least 6 days apart. *p < 0.05, **p < 0.01, ***p < 0.001 vs PBO.

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

24-Month Double-Blind Quetiapine Monotherapy vs Lithium Monotherapy vs Placebo Maintenance

Compared to Placebo After Manic/Mixed/Depressed Episodes

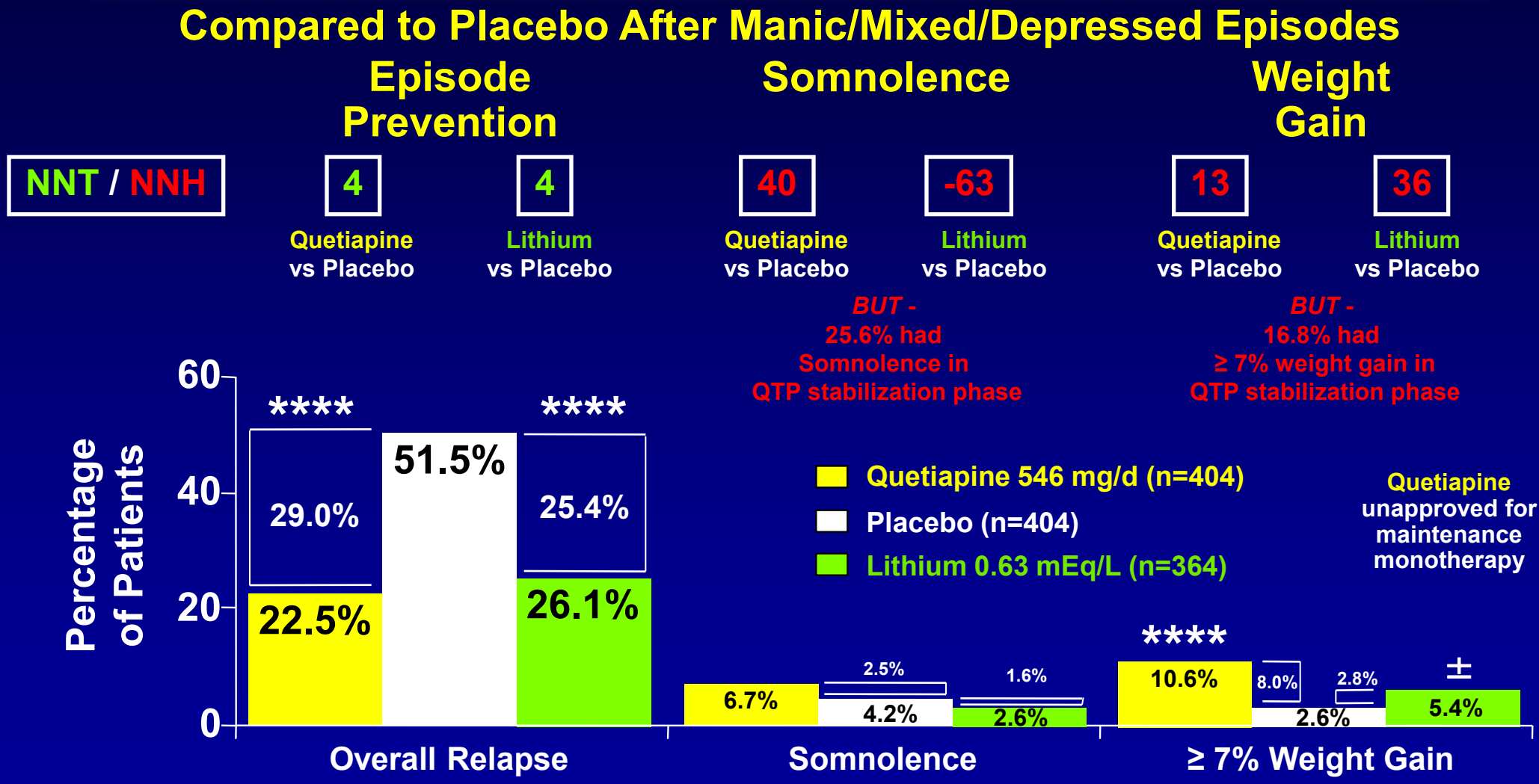


Weisler RH, et al. J Clin Psychiatry 2011;72:1452-64. **p < 0.01, ****p < 0.0001 vs PBO.

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

24-Month Double-Blind Quetiapine Monotherapy vs Lithium Monotherapy vs Placebo Maintenance

Compared to Placebo After Manic/Mixed/Depressed Episodes

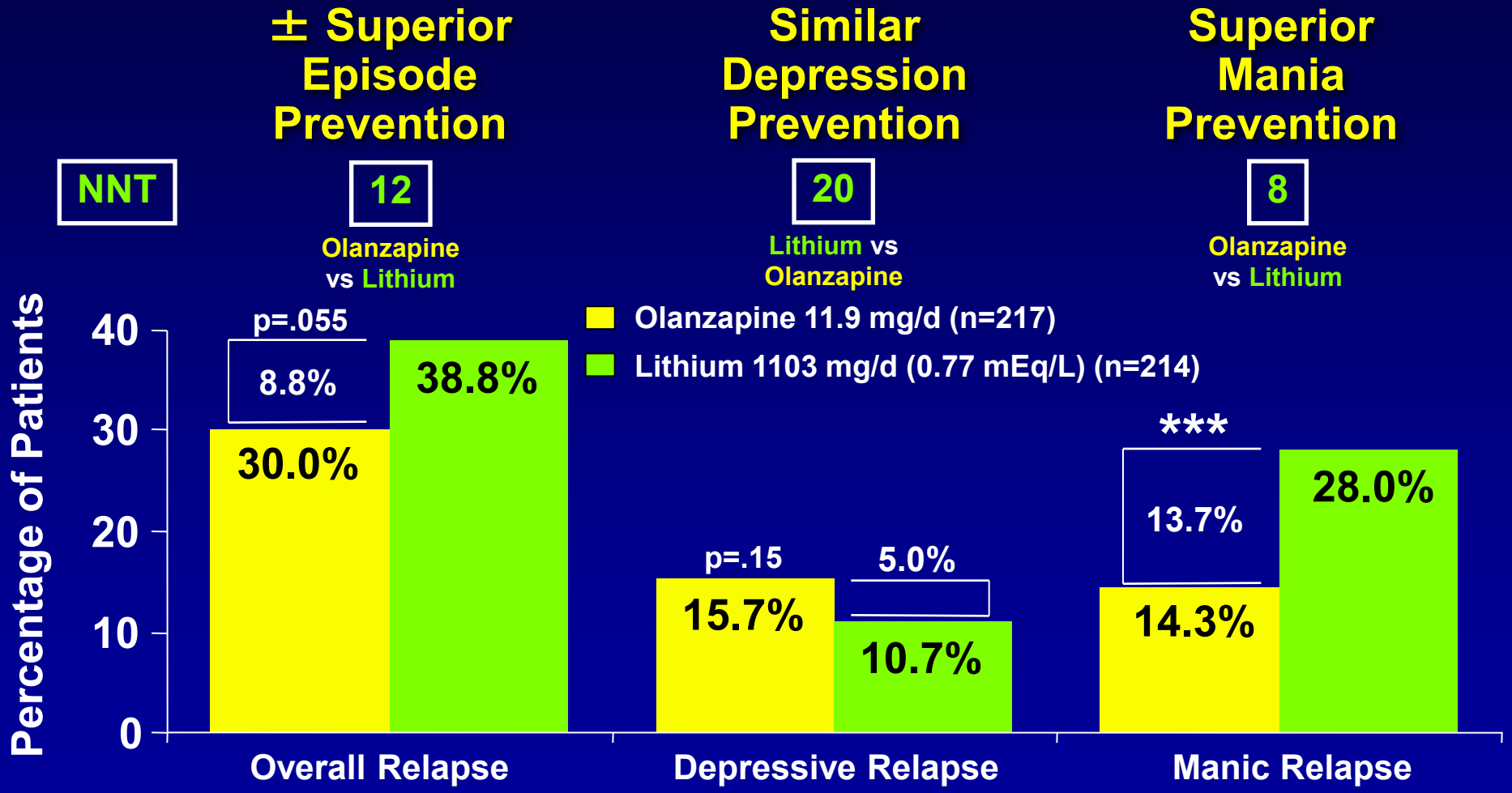


Weisler RH, et al. J Clin Psychiatry 2011;72:1452-64. $^{\pm}p < 0.10$, $^{*}p < 0.05$, $^{****}p < 0.0001$ vs PBO.

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

12-Month Double-Blind Olanzapine vs Lithium Maintenance Monotherapy

Olanzapine Compared to Lithium After Manic/Mixed Episodes

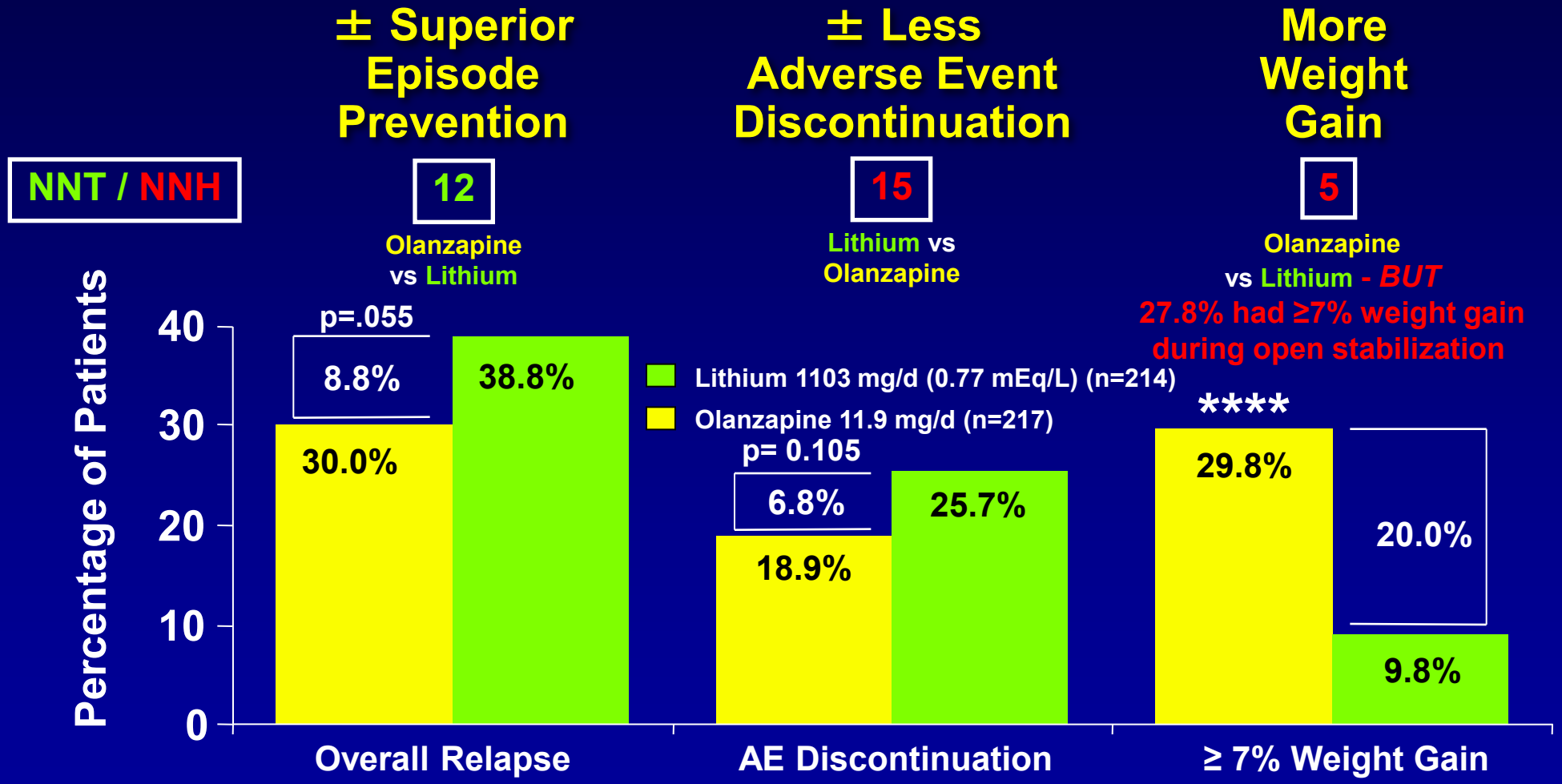


Stabilized on open OLZ+Li before randomization (mean 20.2 days). Relapse criteria - YMRS or HAMD-21 >= 15.

Olanzapine compared to lithium yielded less manic relapse/recurrence.

12-Month Double-Blind Olanzapine vs Lithium Maintenance Monotherapy

Olanzapine Compared to Lithium After Manic/Mixed Episodes

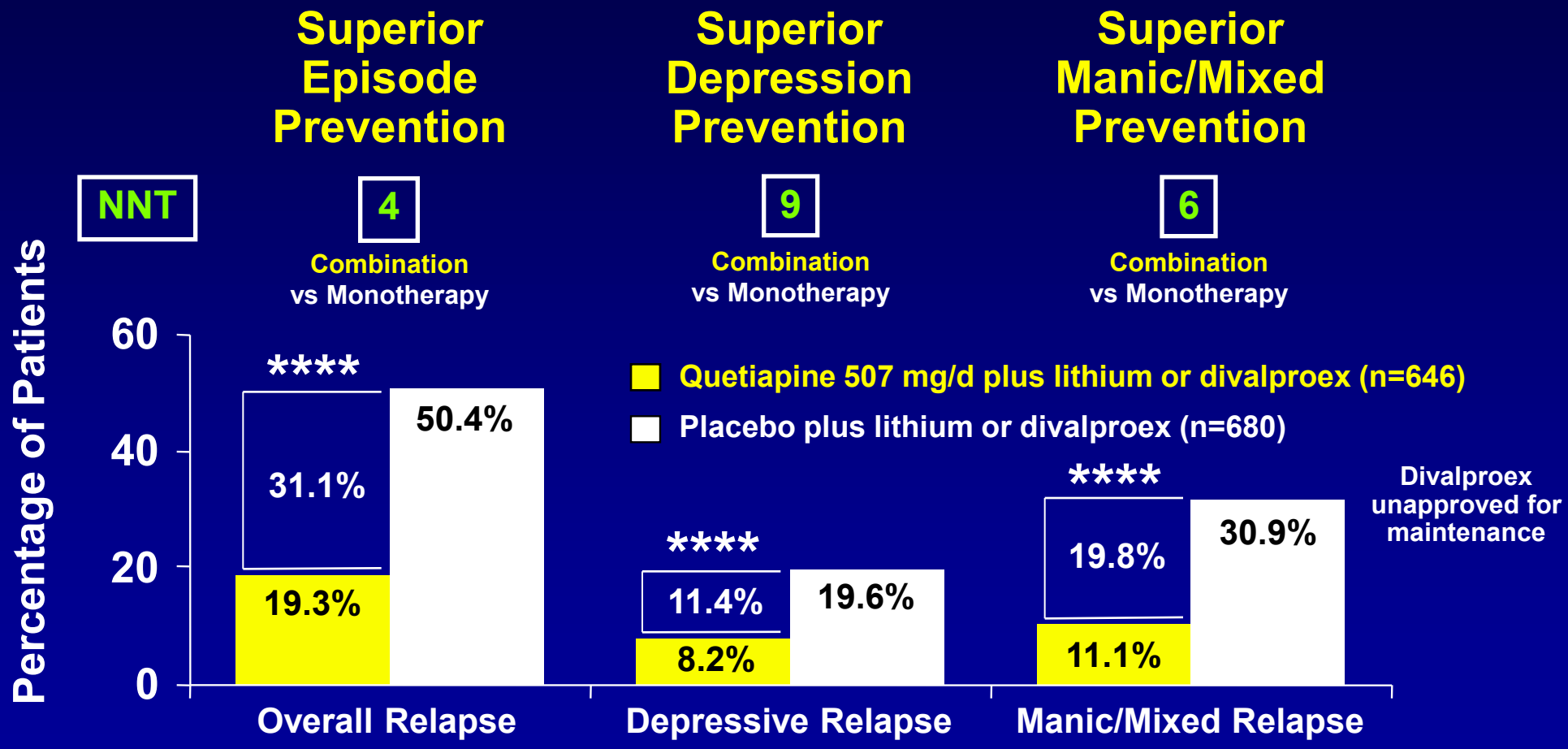


Stabilized on open OLZ+Li before randomization (mean 20.2 days). Relapse criteria - YMRS or HAMD-21 >= 15.

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

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

After Manic, Mixed, or Depressed Episodes



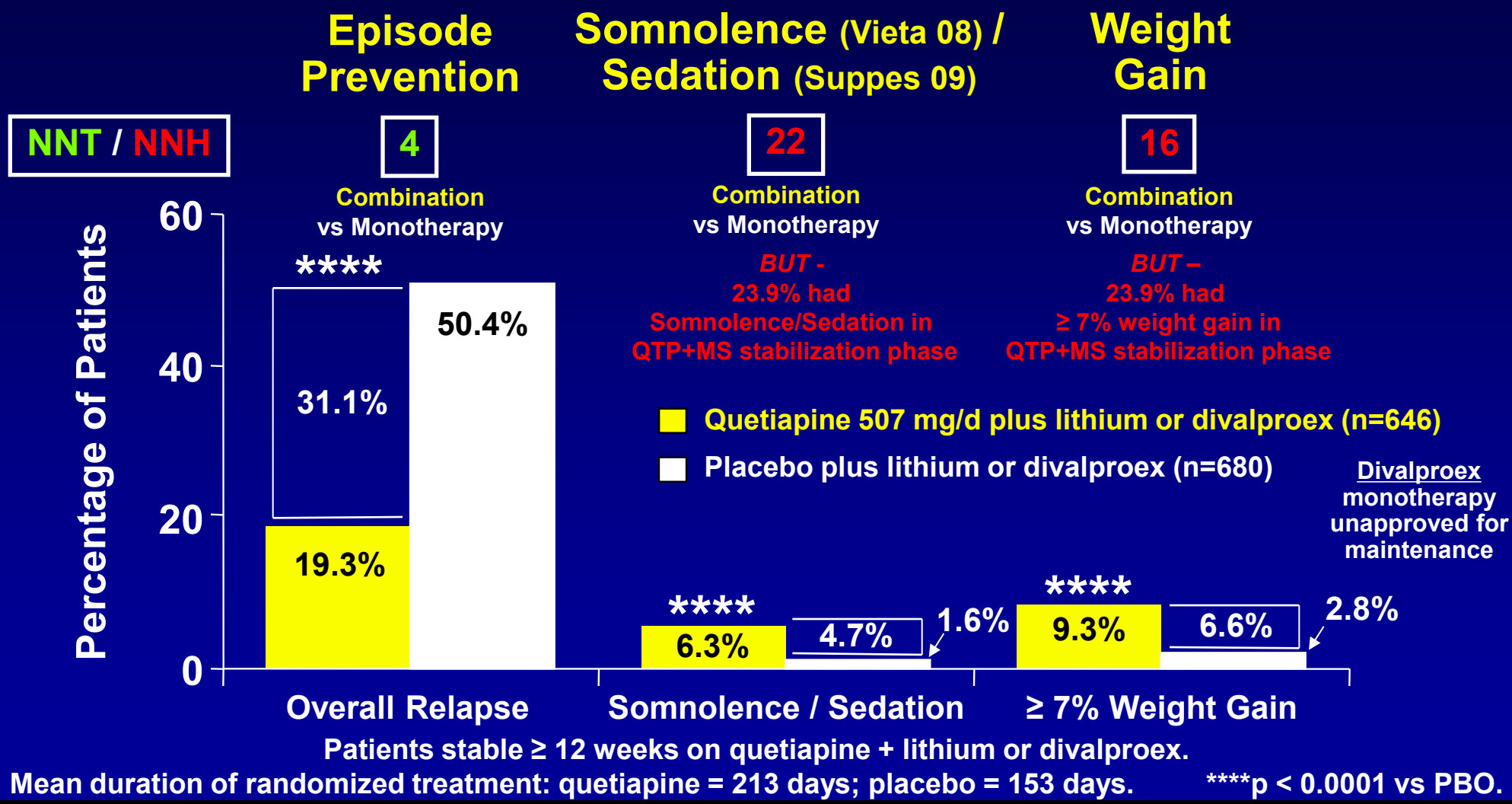
Patients stable ≥ 12 weeks on quetiapine + lithium or divalproex.

Mean duration of randomized treatment: quetiapine = 213 days; placebo = 153 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



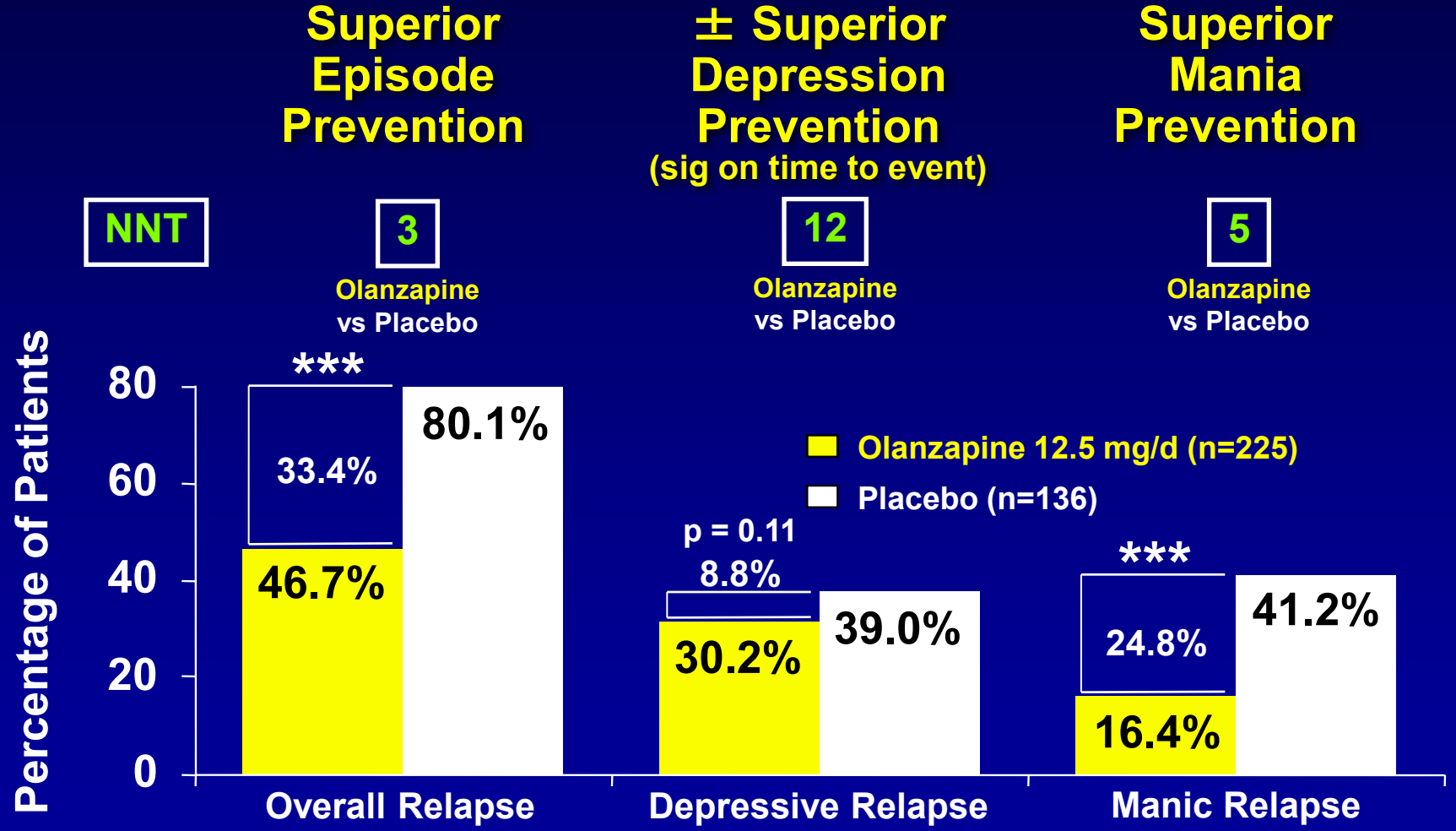
Patients stable ≥ 12 weeks on quetiapine + lithium or divalproex.

Mean duration of randomized treatment: quetiapine = 213 days; placebo = 153 days. ****p < 0.0001 vs PBO.

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

12-Month Double-Blind Olanzapine Monotherapy vs Placebo Maintenance

Olanzapine Compared to Placebo After Manic/Mixed Episodes

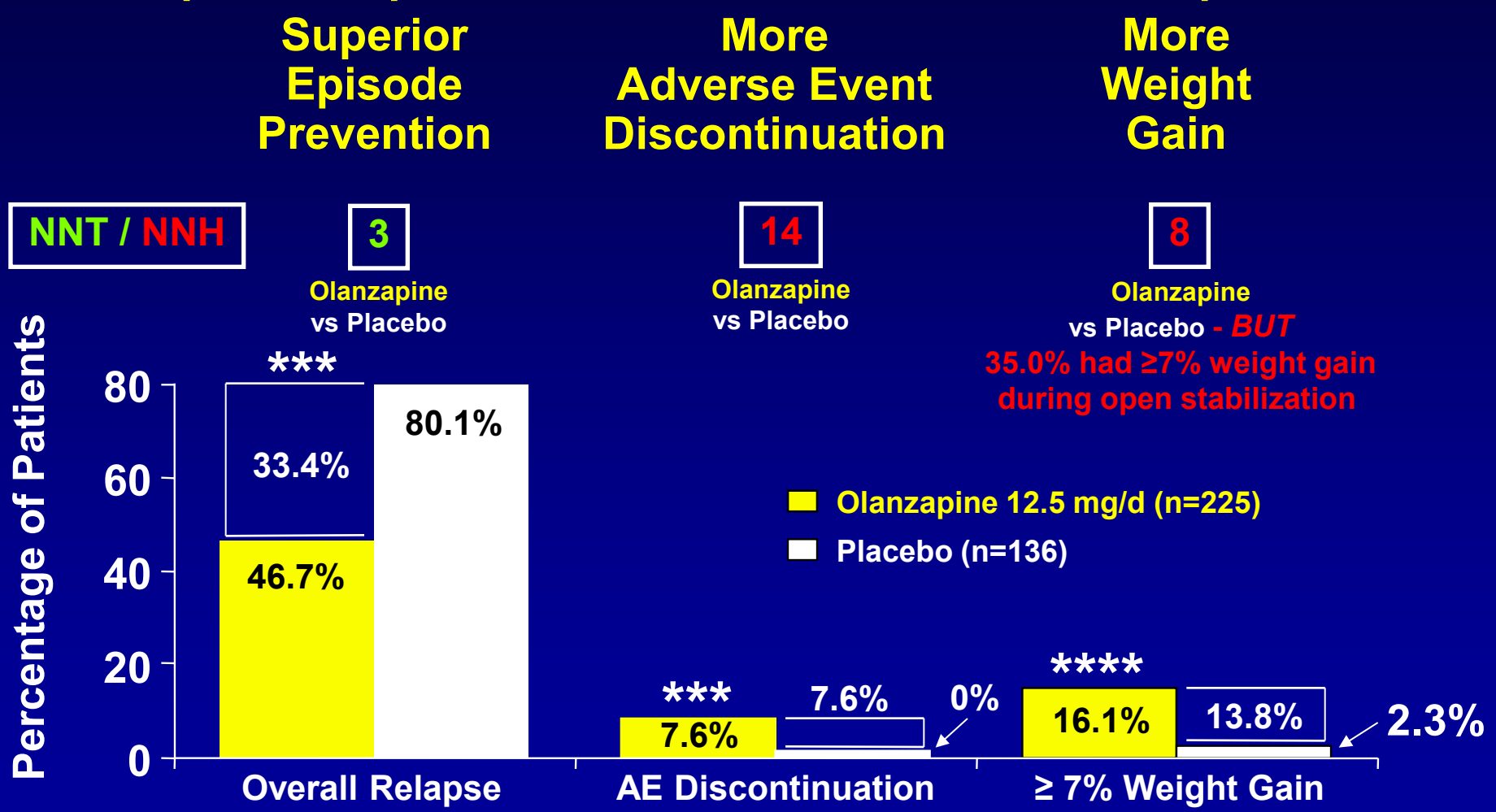


Stabilized on OLZ before randomization (mean 16.3 days). Relapse criteria - hospitalized or YMRS or HAMD-21 >= 15.

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

12-Month Double-Blind Olanzapine Monotherapy vs Placebo Maintenance

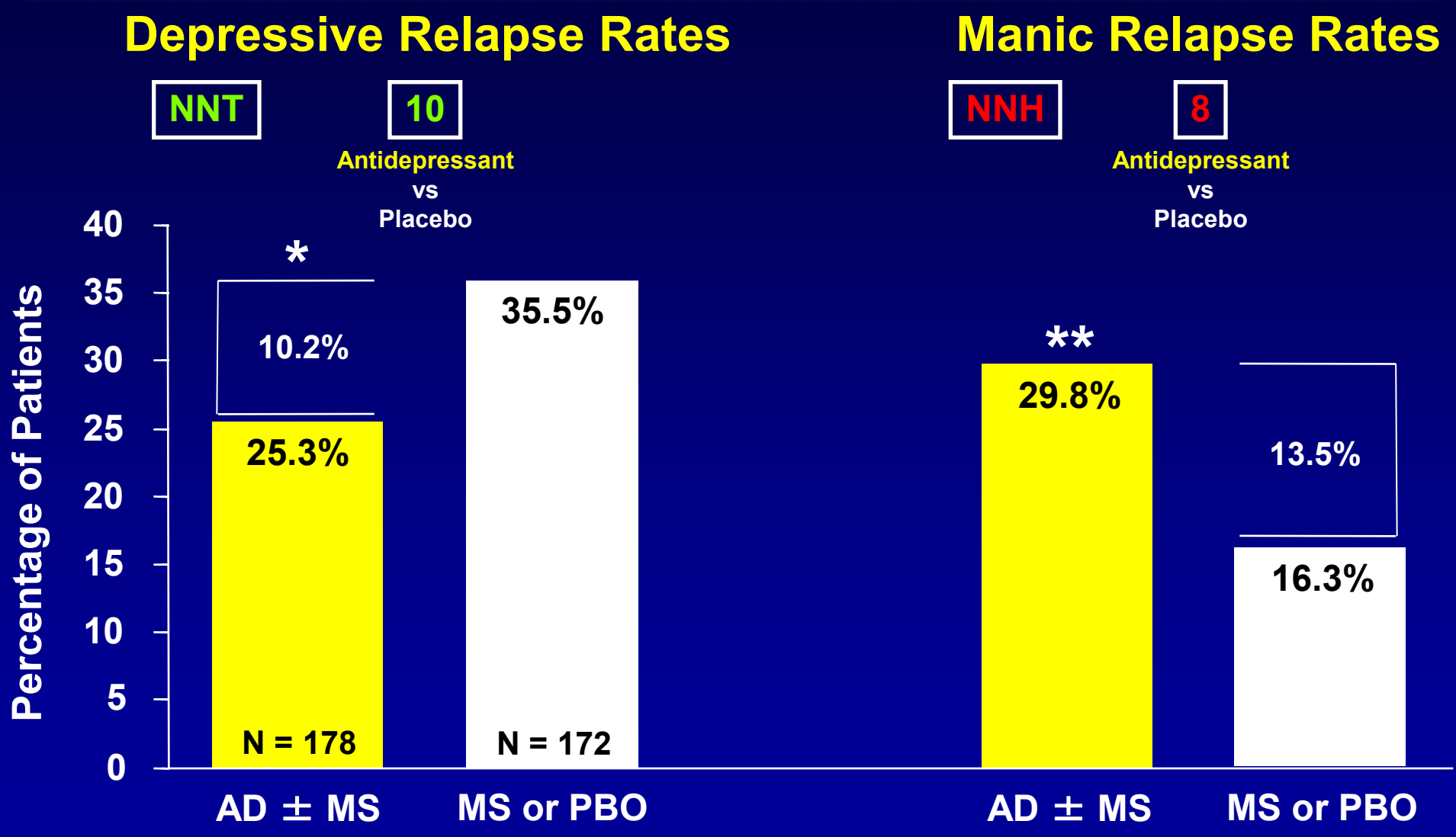
Olanzapine Compared to Placebo After Manic/Mixed Episodes



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.

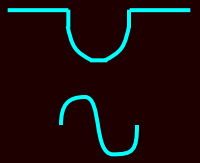
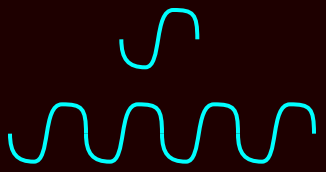
Meta-Analysis of Antidepressants in Bipolar Maintenance



Patients with BPI, BPII, or BPNOS. AD = Antidepressant; MS = Mood Stabilizer; PBO = Placebo.

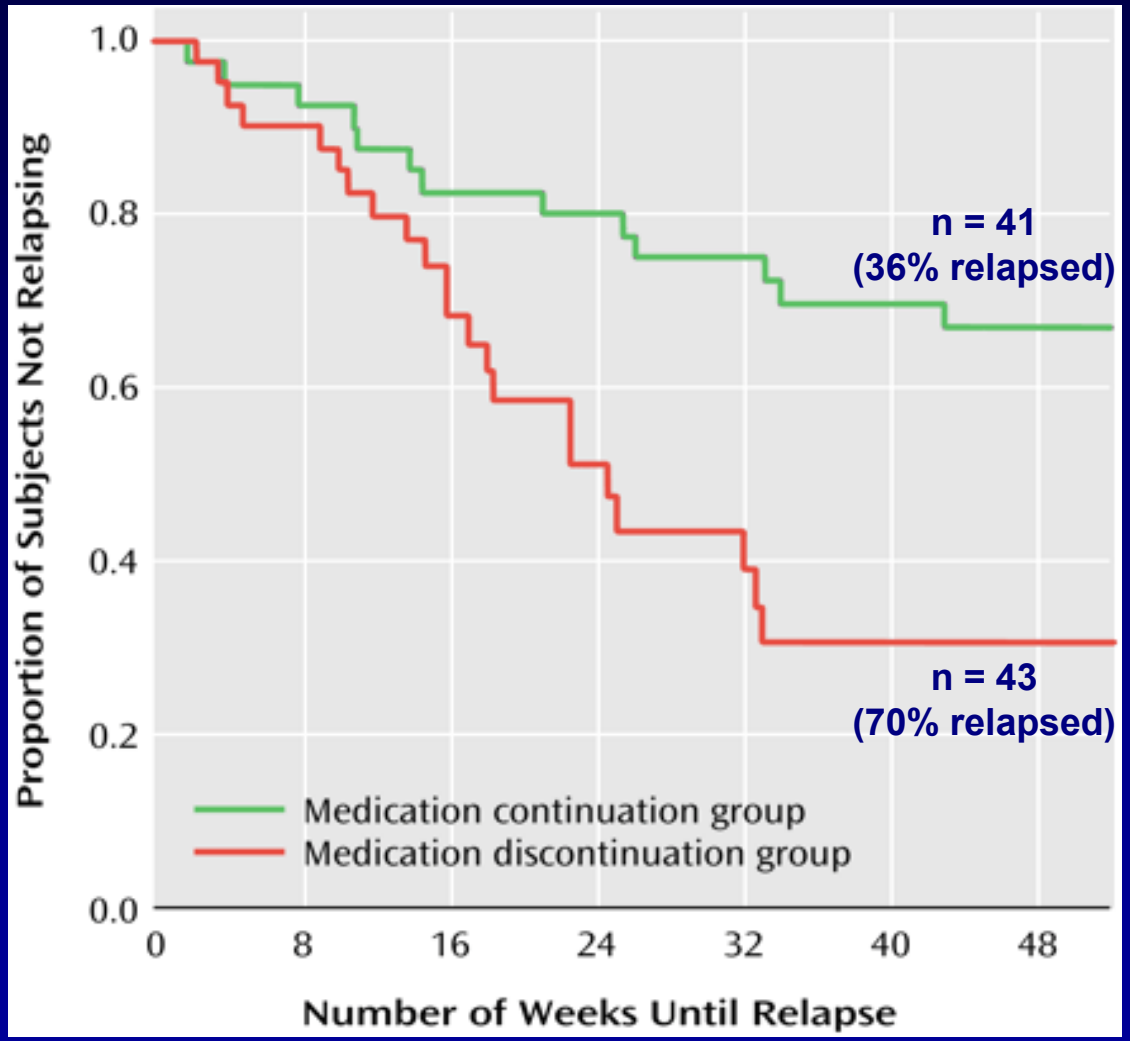
*p < 0.05, **p < 0.01 vs. PBO. Adapted from Ghaemi SN, et al. Acta Psychiatr Scand 2008;118(5):1-10.

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 Continuation Beneficial in Some (15%?) Patients



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

Tolerated AD ≥ 2 months

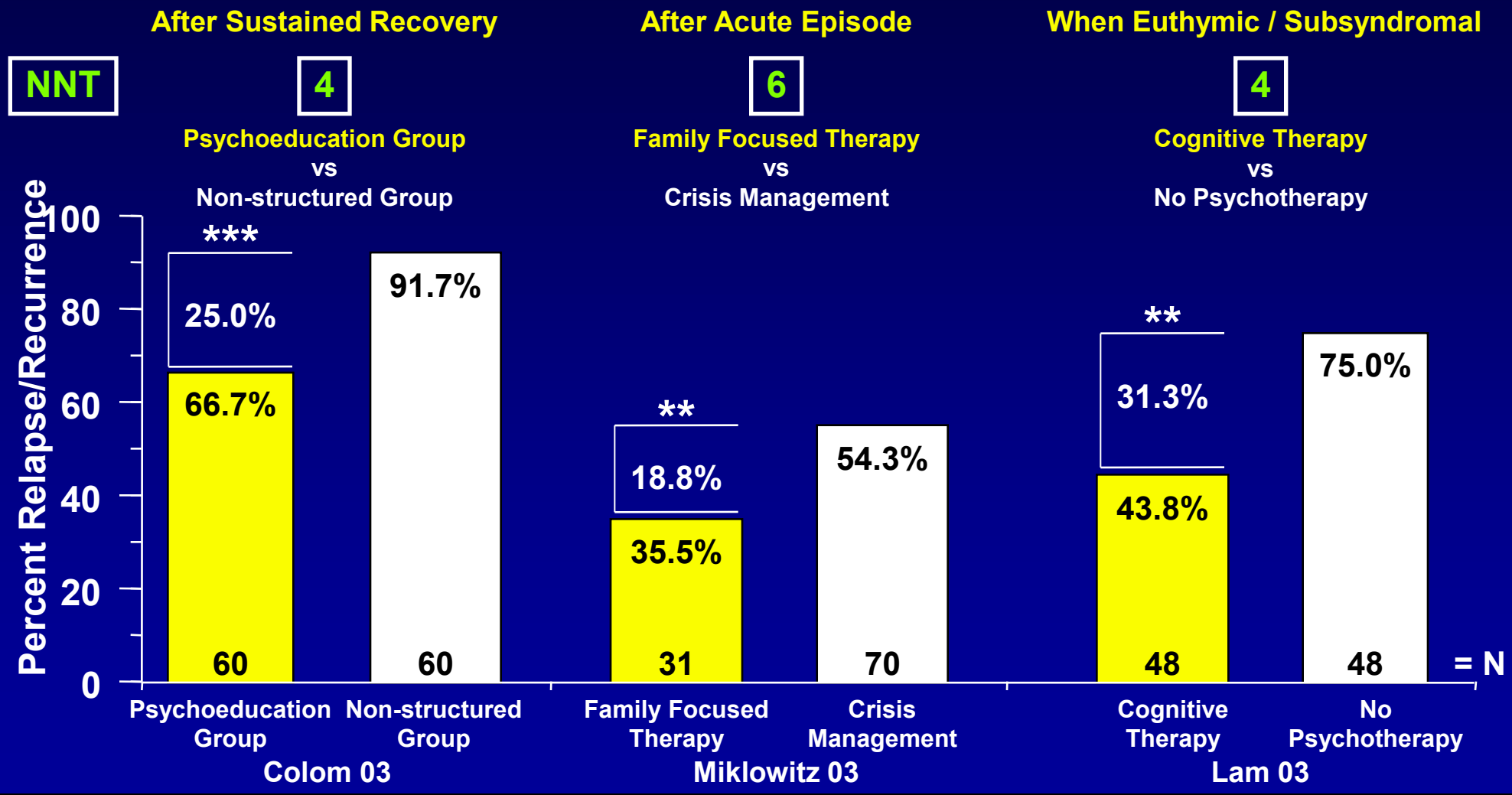
Continuation: AD > 6 months
Discontinuation: AD < 6 months

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.

Treatment of Bipolar Depression

- Acute treatment
  - Lurasidone, quetiapine, olanzapine plus fluoxetine
  - Lithium, lamotrigine
  - Adjunctive antidepressants
  - Alternative treatments
  - Adjunctive psychotherapy
- Maintenance treatment
  - Lithium, lamotrigine, divalproex
  - Atypical antipsychotics
  - Adjunctive antidepressants (controversial)
  - Adjunctive psychotherapy
- 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. Lurasidone

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