

Bipolar Disorders: Therapeutic Options

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Part 3: Treatment of Rapid Cycling and Bipolar Maintenance

Teaching Points

- 1. APA revised guidelines (2002) recommend lithium or valproate, with lamotrigine as an alternative.**
- 2. A prospective, double-blind study of relatively small sample size found no difference between lithium and divalproex for treating rapid cycling (trends favored divalproex).**
- 3. Lamotrigine's benefit in rapid cycling may be restricted to bipolar II.**
- 4. TIMA bipolar I maintenance algorithm lists lithium, divalproex, and lamotrigine at level I if most recent episode was manic, mixed, or hypomanic.**
- 5. Lithium has most convincing data for reducing suicidal behavior.**

Outline

- I. Rapid Cycling**
 - A. APA Revised Guidelines (2002) for Rapid Cycling**
 - B. Prospective Lithium vs. Divalproex Study**
 - C. Lamotrigine Data**
- II. Bipolar Maintenance**
 - A. TIMA Recommendations**
 - 1. Why Divalproex is Level I**
 - 2. Why Olanzapine is an Alternative**
 - B. Lithium Maintenance**
 - 1. Efficacy**
 - 2. Effect on Suicidal Behavior**
 - C. Divalproex Maintenance – Data vs. Expert Opinion**
 - D. Lithium vs. Divalproex in Pediatric Bipolar Maintenance**
 - E. Lamotrigine Maintenance**
 - F. Olanzapine Maintenance**
 - G. Aripiprazole Maintenance**

Pre-Lecture Exam

Question 1

- 1. A 20-month double-blind comparison of lithium and divalproex for rapid cycling found:**
 - a. Divalproex more effective**
 - b. Lithium more effective**
 - c. No statistically significant difference**

Question 2

2. Which of the following medications is not FDA-approved for bipolar maintenance?
- a. Lithium
 - b. Divalproex
 - c. Olanzapine
 - d. Lamotrigine
 - e. Aripiprazole

Question 3

- 3. Which of the following medications has the most convincing evidence for reducing suicidal behavior in bipolar patients?**
- a. Clozapine**
 - b. Lamotrigine**
 - c. Olanzapine**
 - d. Divalproex**
 - e. Lithium**

Question 4

4. The most robust effect of lamotrigine in its bipolar I maintenance studies was in delaying time to which of the following?
- a. Depression
 - b. Mania
 - c. Mixed episodes
 - d. Hypomania
 - e. Cyclothymia

Question 5

5. An 18-month study comparing lithium and divalproex in pediatric bipolar maintenance found which of the following outcomes?
- a. Lithium more effective, less well tolerated
 - b. Divalproex more effective, better tolerated
 - c. No difference in effectiveness or tolerability
 - d. Divalproex more effective, no difference in tolerability
 - e. Lithium more effective, better tolerated

Rapid Cycling (4 or more episodes/year)

- **Stop antidepressants**
- **Use lithium or valproate**
- **Alternative – lamotrigine**
- **Combinations**
 - **add antipsychotic**
 - **add mood stabilizer**

Rapid Cycling: Is Valproate Better Than Lithium?

- **That's what everyone says**
- **But where are the data?**

Rapid Cycling: Lithium vs. Valproate

(20-month, double-blind, n=60)

- **Open-label Li + VPA (n=254)**
- **Stabilized, randomized**
 - **Li (n=32), VPA (n=28)**
 - **2/3 female, 2/3 bipolar II**

Rapid Cycling: Lithium vs. Valproate

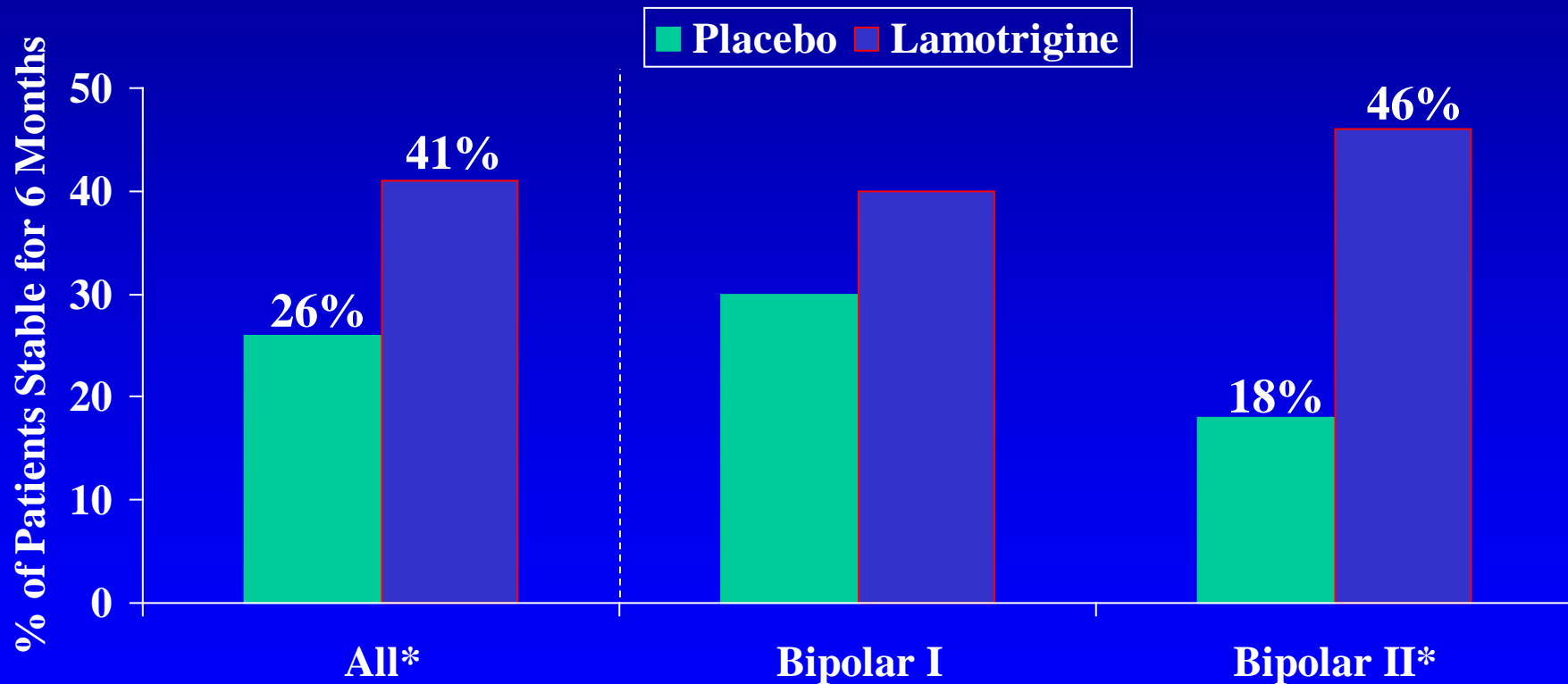
(20-month, double-blind, n=60)

- **Outcome: No significant differences**
- **All trends favored valproate**
 - **Relapse rate** **51% vs. 56%**
 - **Time to treatment** **45 vs. 18 weeks**
 - **Survival time** **26 vs. 14 weeks**
 - **A.E. dropouts** **4% vs. 16%**

Lamotrigine for Rapid-Cycling (open label [n=326] to double-blind [n=177])

- Time to additional pharmacotherapy
n.s., (p=0.177)
- Stable without relapse at 6 months (n=60)
 - Lamotrigine 41% (p=0.03)
 - Placebo 26%

Lamotrigine in Rapid Cycling 6 Months Without Relapse (n=60)



*p<.05

Calabrese et al. J Clin Psychiatry 2000;61:841-850



Bipolar Maintenance

Bipolar Maintenance

- **Polarity of index episode**
- **Outcome criteria**
 - **Time to episode or intervention**
 - **Fewer, shorter, less severe episodes**
- **Low completion rates**



Bipolar Maintenance

FDA-Approved

Lithium-1974

Lamotrigine-2003

Olanzapine-2004

Aripiprazole-2005

Bipolar Maintenance – Most Recently Manic/Mixed/Hypomanic (TIMA)

- **Level I Lithium*, Divalproex, Lamotrigine***
alternative: Olanzapine*
- **Level II Aripiprazole***
- **Level III Carbamazepine or Clozapine**
- **Level IV Quetiapine, Risperidone, Ziprasidone**
- **Level V Typicals, Oxcarbazepine, ECT**

***FDA-approved**

Bipolar Maintenance (TIMA)

- **Why is valproate Level I?
(Expert opinion and limited data)**
- **Why is olanzapine* an alternative?
(Long-term safety concerns)**
- **Why is aripiprazole* Level II?
(Single 6-month study)**

***FDA-approved for bipolar maintenance**

Bipolar Maintenance – Most Recently Depressed (TIMA)

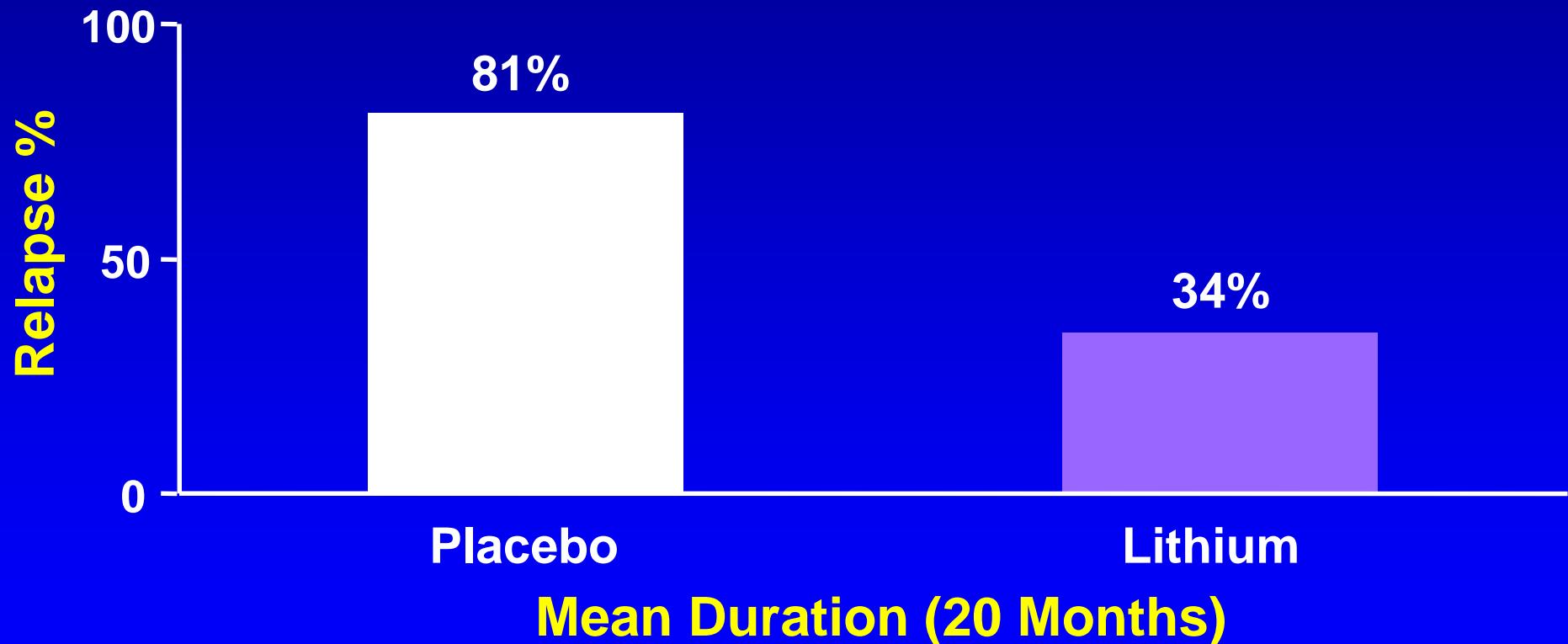
- **Level I** **Lamotrigine***
- **Level II** **Lithium***
- **Level III** **Antimanic+antidepressant effective in the past (including OFC)**
- **Level IV** **Divalproex, carbamazepine, atypical antipsychotic**
- **Level V** **Typicals, Oxcarbazepine, ECT**

***FDA-approved**

Suppes et al., J Clin Psychiatry 2005;66:870-86 (July)

Lithium Maintenance

10 Placebo-Controlled Studies (Prior to 1990)



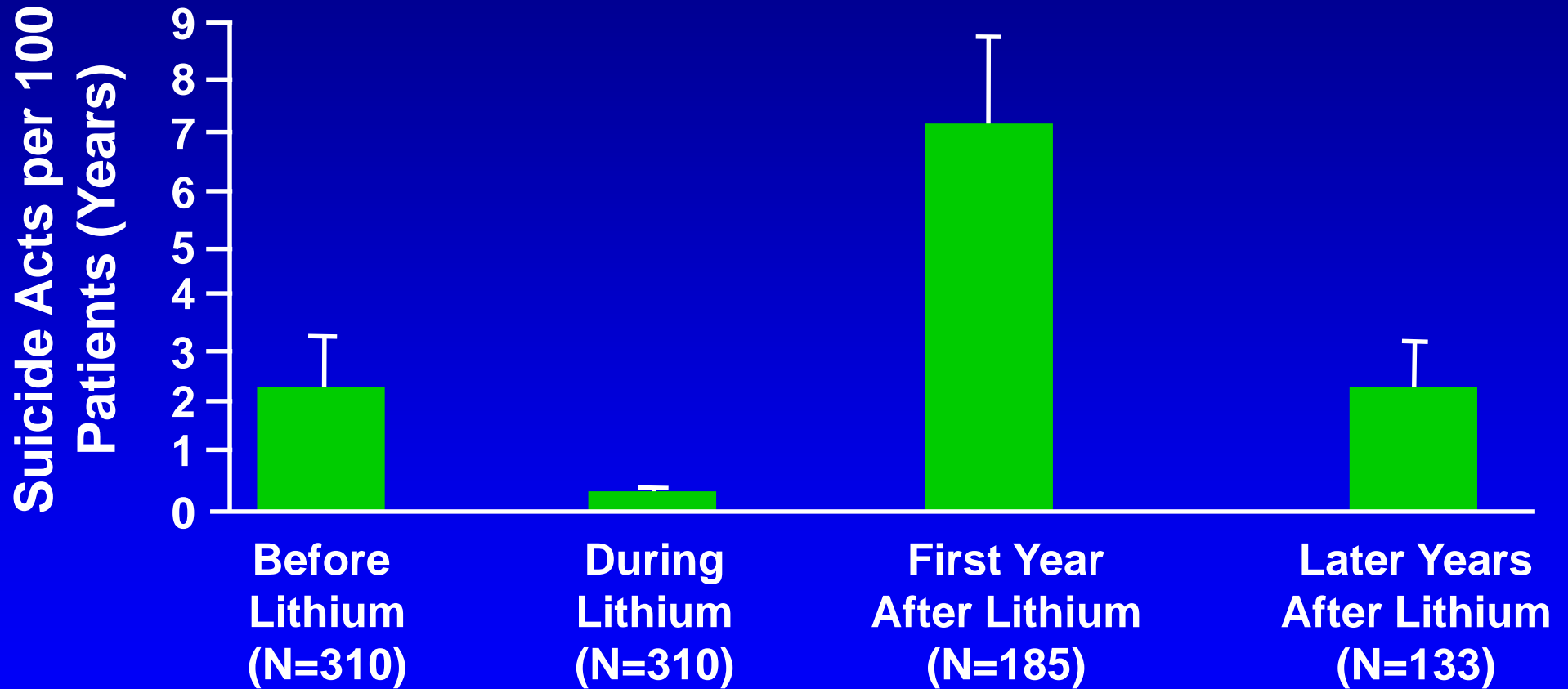
Goodwin FK, Jamison KR, Manic-Depressive Illness. New York: Oxford University Press; 1990

Long-Term Lithium Maintenance

(n=360, average duration 6 years)

- Complete remission 29%
- 50-90% improved 36%
- Poor outcome not related to psychotic, mixed, rapid cycling, or episode sequence

Lithium and Suicidal Behavior



Lithium Effective in Preventing Suicide, Deliberate Self-Harm, and Death from All Causes in Mood Disorder Patients

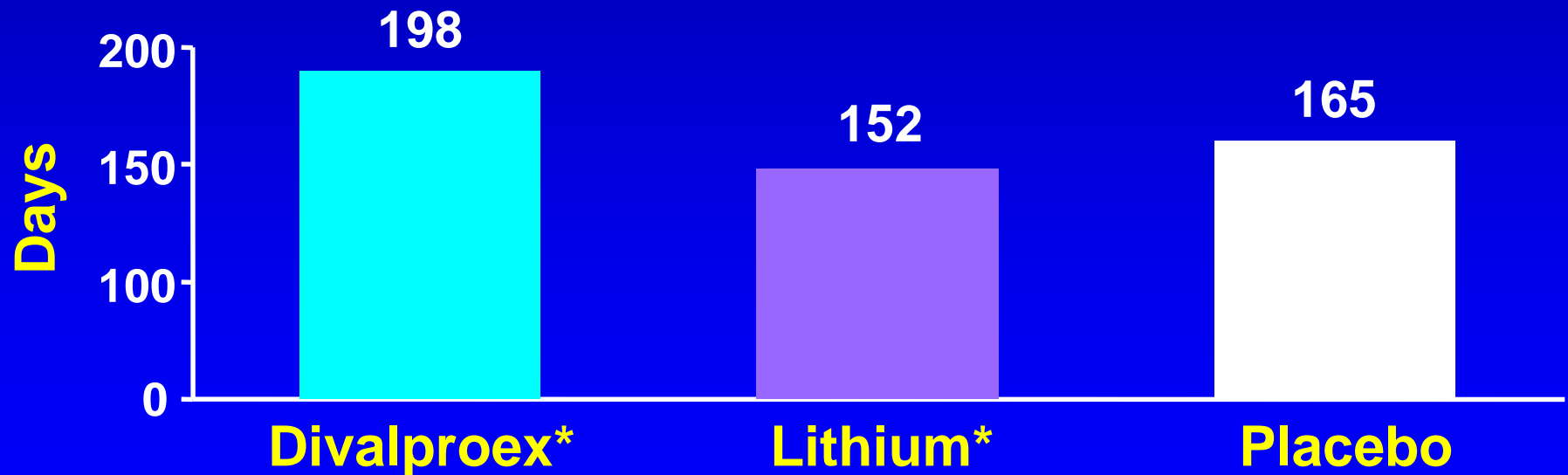
(systematic review of randomized trials)

- **Suicide: odds ratio=0.26**
- **Suicide plus deliberate self-harm:
odds ratio=0.21**
- **All cause deaths: odds ratio=0.42**

Divalproex: 12-Month BP I Maintenance

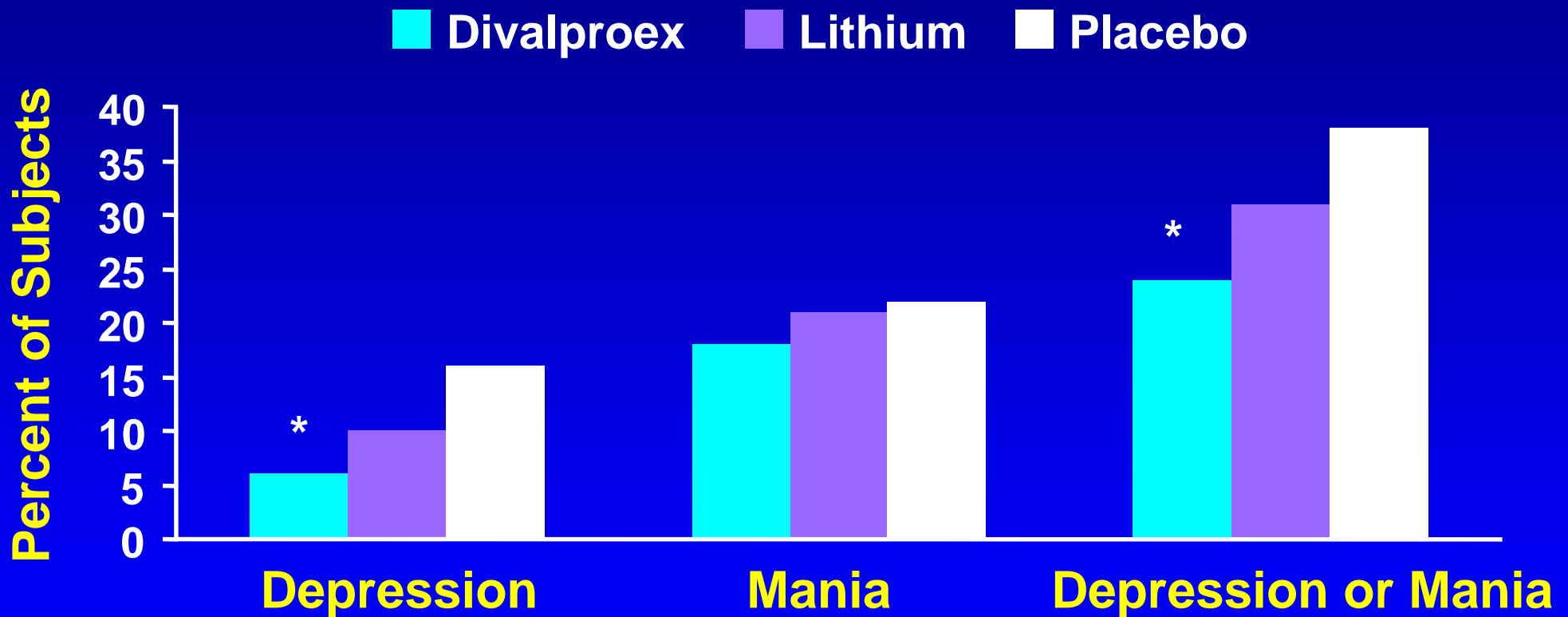
Entry After Index Manic Episode

- Primary outcome measure: time to any mood episode
 - **DVPX = Li = PBO** (a failed trial)
- Mean duration of continued treatment (days)



*p=0.02; Bowden CL, Calabrese JR, McElroy SL, et al. Arch Gen Psychiatry. 2000(Mar);57(5):481-489

12-Month Relapse/Recurrence Rates



*p<0.05 vs. placebo; Bowden CL, Calabrese JR, McElroy SL, et al. Arch Gen Psychiatry. 2000(Mar);57(5):481-489

Pediatric Bipolar Maintenance Lithium vs. Divalproex (18-month)

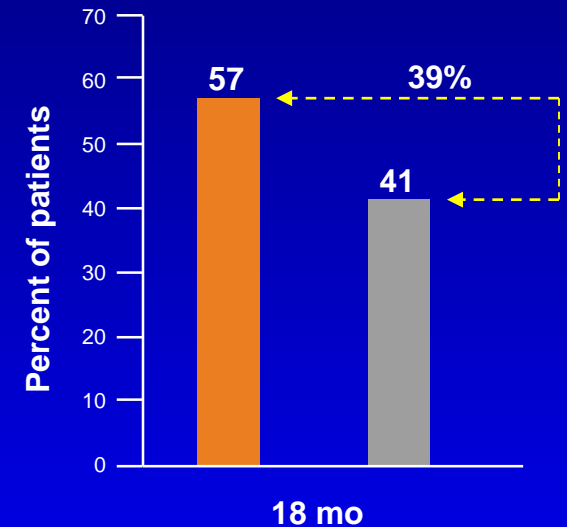
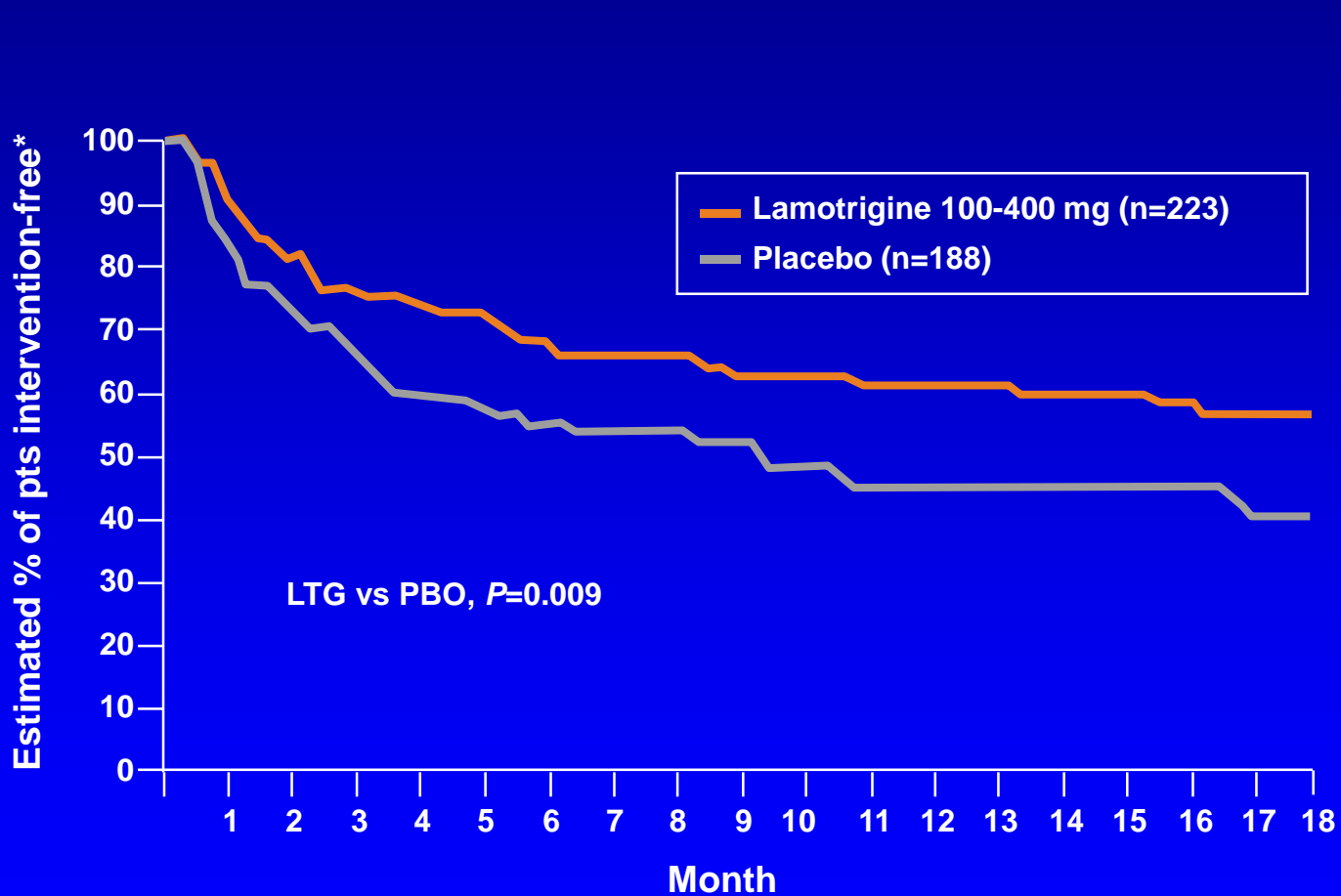
- **Open stabilization: Li + DVPX**
(n=139, mean age 10.8 years)
- **Double-blind randomization (n=60)**
- **Completed study**

Li	n=10
DVPX	n=10

Pediatric Bipolar Maintenance Lithium vs. Divalproex (18-month)

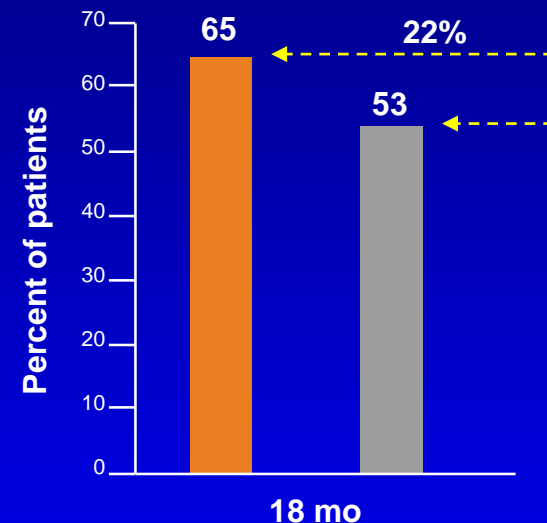
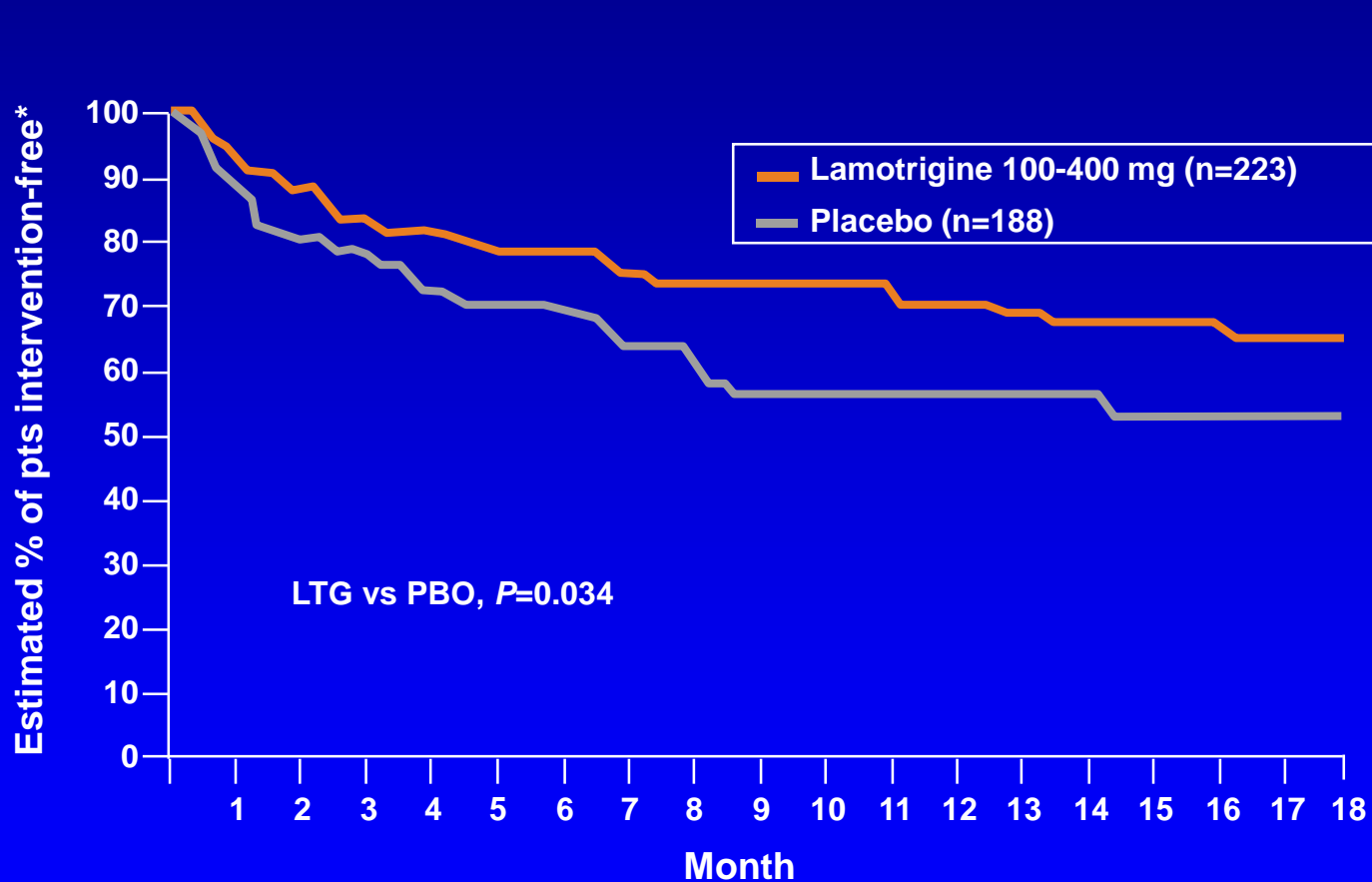
- **Time to mood relapse**
The same
- **Time to study discontinuation**
The same
- **Adverse Event Dropouts**
The same (Li 6.7%, DVPX 10%)

Lamotrigine: Time to Intervention for a Depressive Episode (Combined Analysis)



* Some patients considered intervention-free for depressive episodes could have had intervention for manic episodes.

Lamotrigine: Time to Intervention for a Manic Episode (Combined Analysis)



* Some patients considered intervention-free for manic episodes could have had intervention for depressive episodes.

Lamotrigine for Bipolar Maintenance

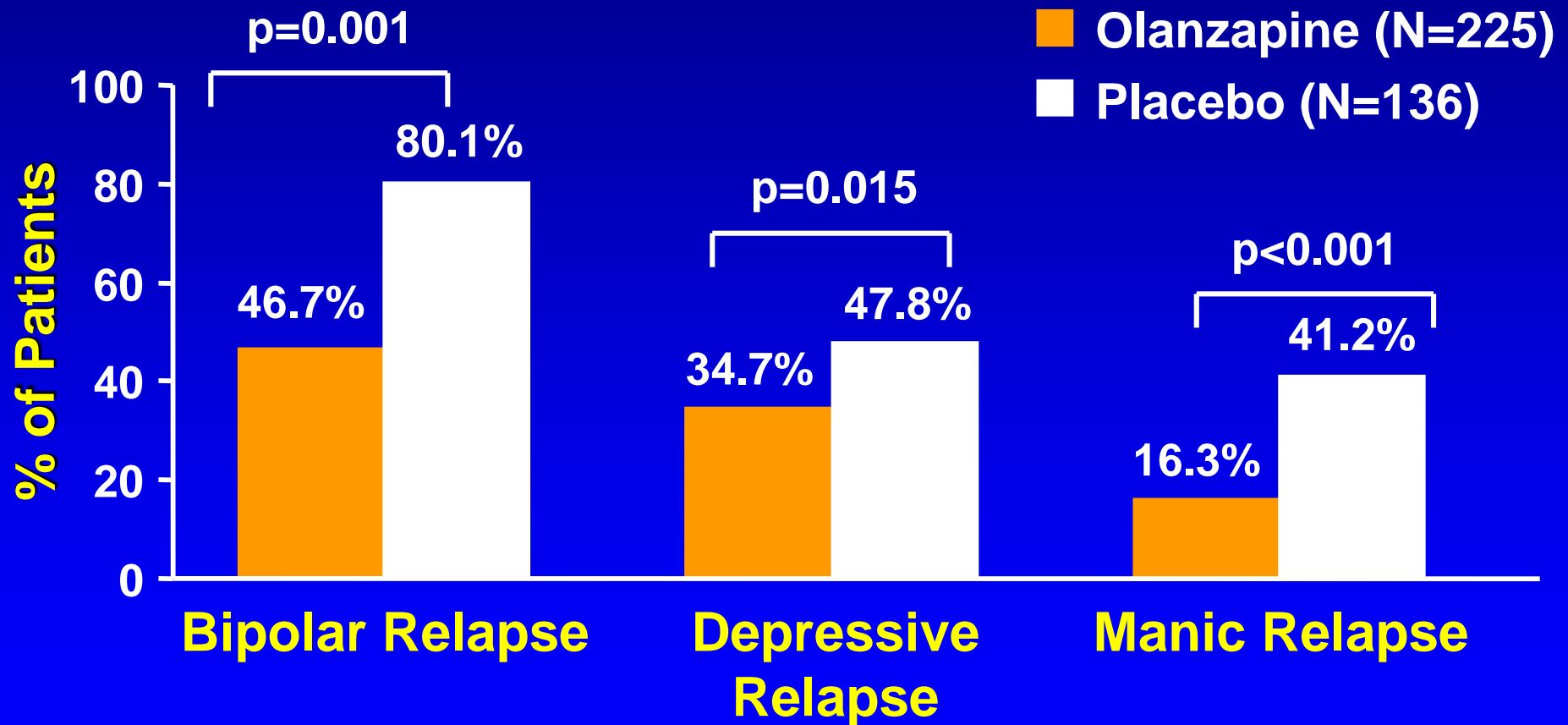
“...a combined analysis of the 2 studies revealed a statistically significant benefit ... over placebo in delaying time to occurrence of both depression and mania, although **the finding was more robust for depression.**”

Package Insert, June 2003

Acute Mania and Bipolar Maintenance Olanzapine vs. Divalproex (47 weeks)

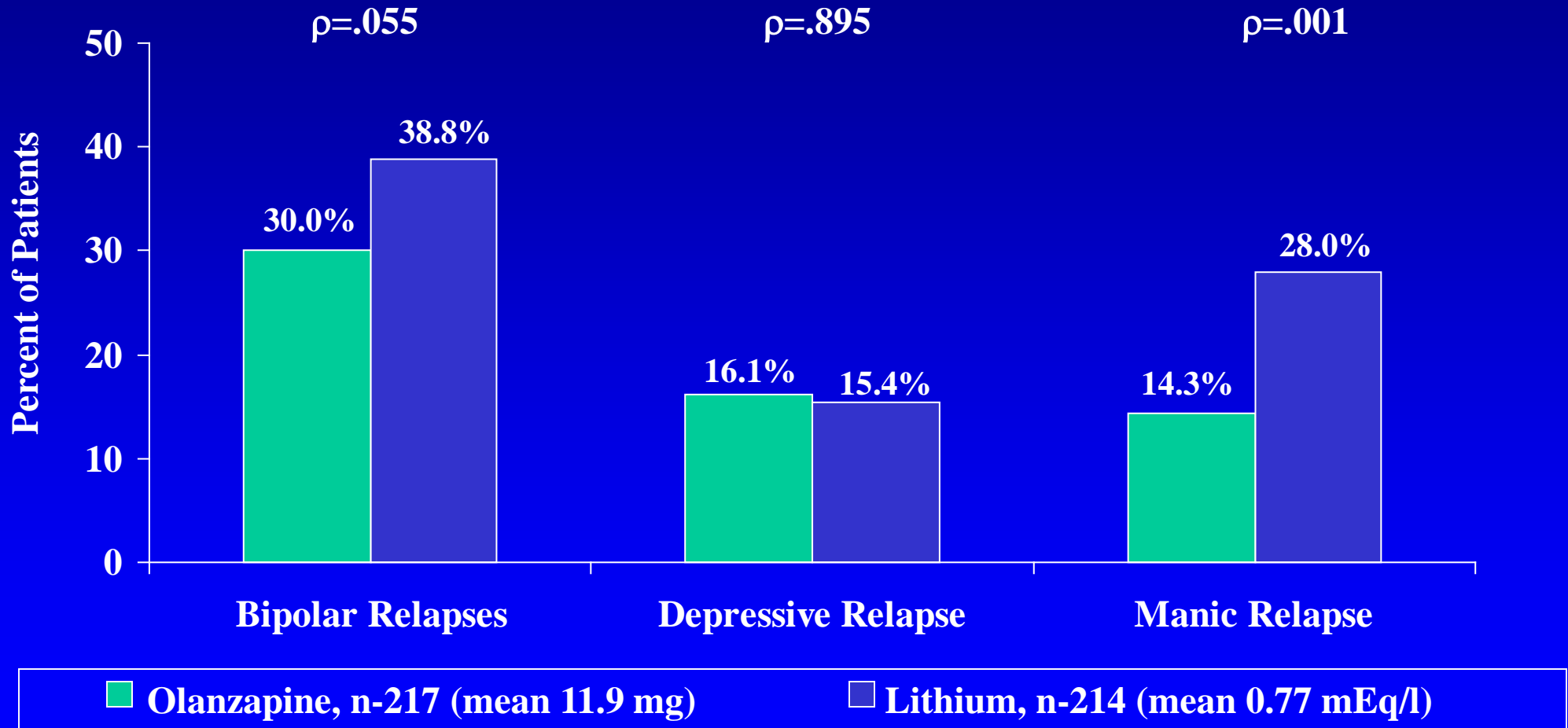
- **Dosing:** **OLZ 5-20 mg/day**
 DVPX 500-2500 mg/day
- **Completers:** **OLZ 15.2%**
 DVPX 15.9%
- **Relapse rates:** **No difference**

Olanzapine vs. Placebo: Bipolar I Maintenance (52 Weeks)—Relapse



Tohen et al. 156th Annual Meeting APA; San Francisco, Calif.; May 17-22, 2003. Manic or mixed responders to open-label olanzapine.

Olanzapine vs. Lithium: 1 year Bipolar Maintenance-Relapse Rates



Bipolar I Maintenance: One Year Olanzapine vs. Lithium

Weight gain $\geq 7\%$

- Open-label: 6-12 weeks

OLZ + Li 27.8%

- Double-blind: 1 year

OLZ 29.8%

Li 9.8%

Bipolar I: 18-Month Relapse Prevention

- **Lithium or valproate plus olanzapine or placebo (n=99)**
- **Syndromic relapse**

Combo	94 days	(n.s.)
Mono	40.5 days	
- **Symptomatic relapse**

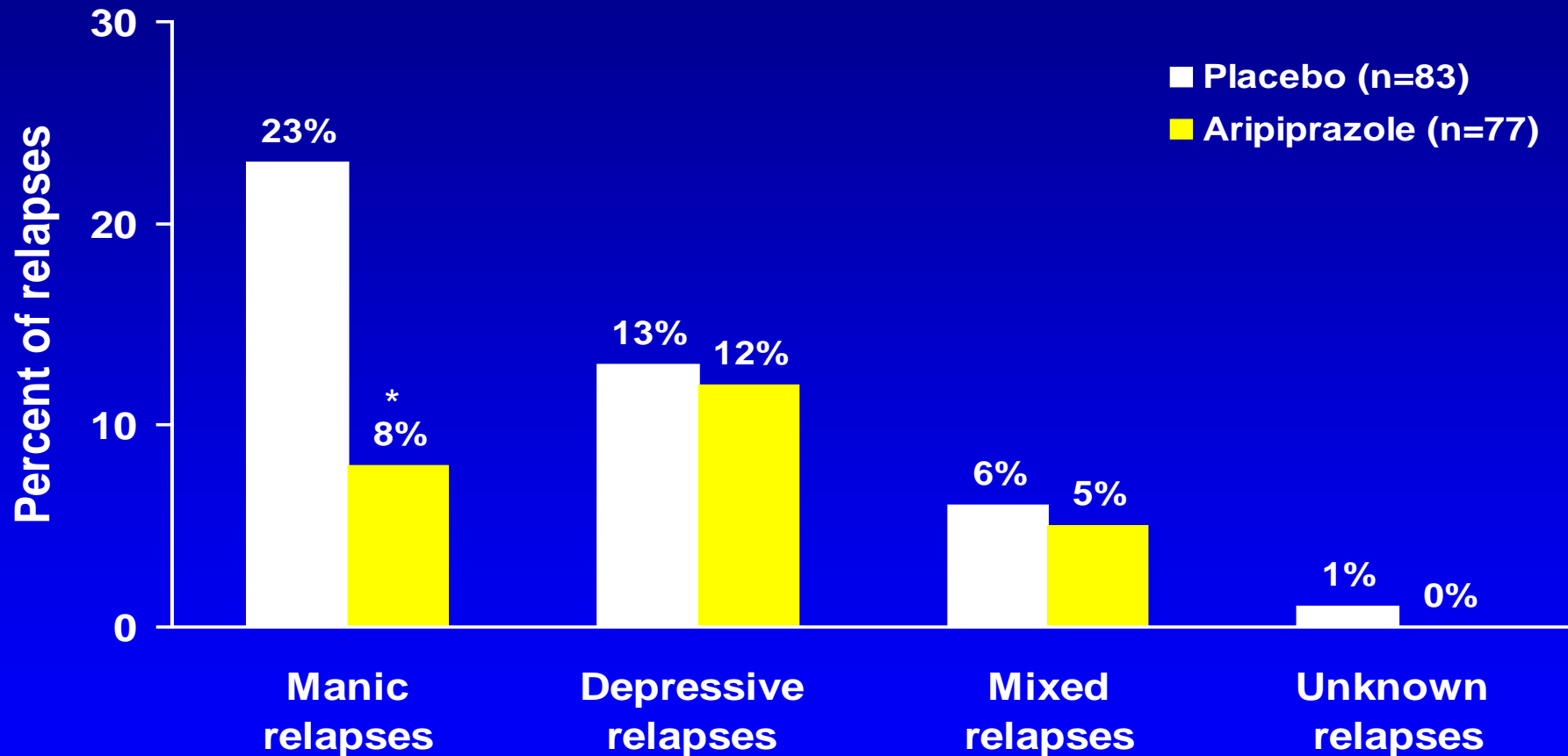
Combo	163 days	(p<0.023)
Mono	42 days	

(only significant in women)

Aripiprazole: Bipolar I Maintenance (6-Month)

- **Superior to placebo on time to number of combined affective relapses**
- **Majority of relapses were manic**
- **Insufficient data to know if effective in delaying time to occurrence of depression**

Aripiprazole Maintenance: 6-Month Relapse



* $P=0.009$.

Adapted from Marcus et al. ACNP, 2003.

Bipolar I Maintenance Completers

- **6-month: ARI (50%), PBO (34%)¹**
- **47-week: OLZ (15.2%), VPA (15.9%)²**
- **1-year: OLZ (46.5%), Li (32.7%)³**
- **1-year: OLZ (24%), PBO (10%)⁴**
- **18-month: LTG (14.6%), Li (12.6%), PBO (6.3%)⁵**

¹Marcus et al., ACNP, Dec 2003

²Tohen et al., Am J Psychiatry 2003;160:1263-1271

³Tohen et al., APA, May 2003

⁴Tohen et al., Am J Psychiatry 2005;162:1281-1290

⁵Goodwin et al., J Clin Psychiatry 2004;65:432-441

Don't Forget to Consider

- **Compliance**
- **Comorbidities**
- **Side Effects (acute and long-term)**
- **Drug Interactions**

Post-Lecture Exam

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Answers to Pre & Post Lecture Exams

1. C

2. B

3. E

4. A

5. C