

# **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

# Rapid Cycling Bipolar Disorder

## Long-Term Treatment Review

- 4 or more episodes/year
- DSM-IV course specifier
- Lower treatment effectiveness for ALL treatments evaluated
- No clear advantage for any treatment
- Available evidence does not provide clear guidance for treatment selection

# **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)**

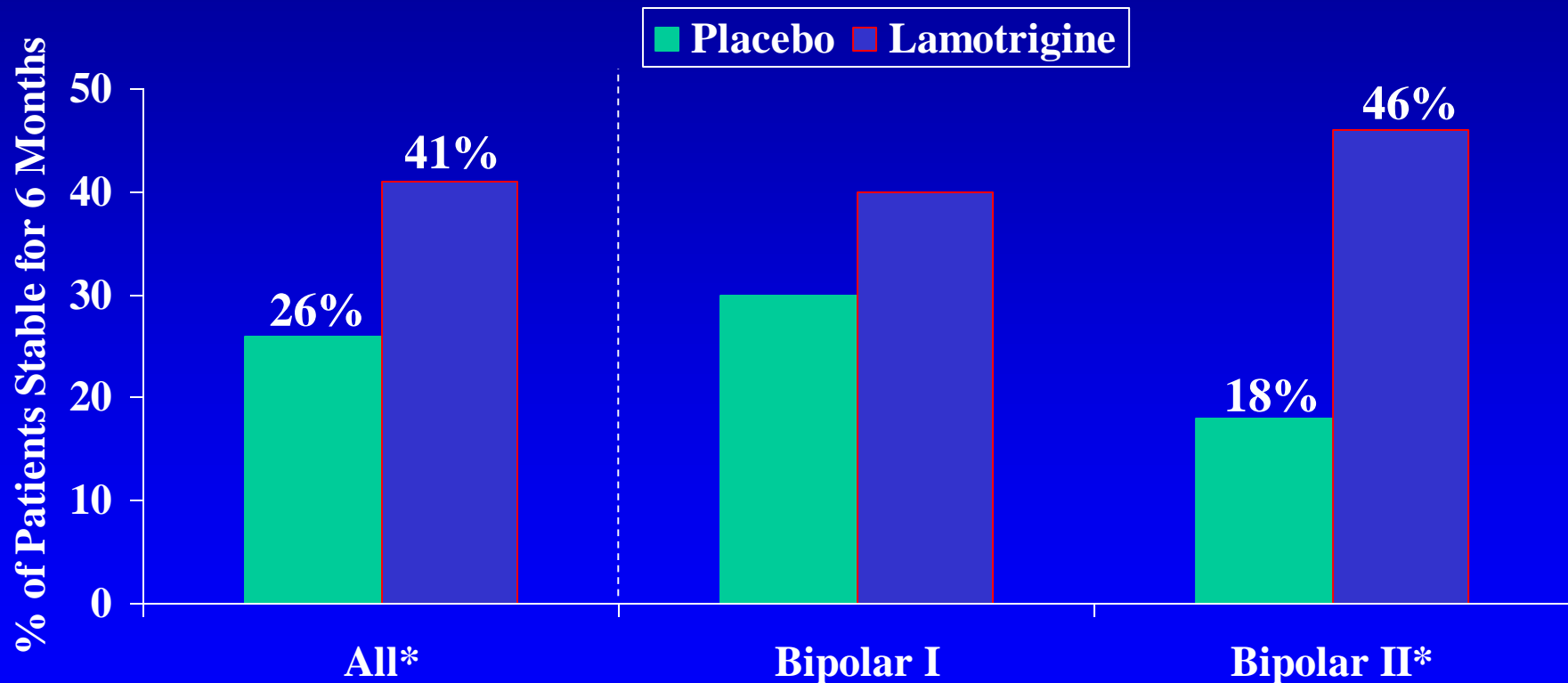
- **Outcome: No significant differences**
- **All trends favored valproate**
  - **Relapse rate**                      **51% vs. 56%**
  - **Time to treatment**              **45 vs. 18 weeks**
  - **Survival time**                      **26 vs. 14 weeks**
  - **A.E. dropouts**                      **4%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

# Rapid Cycling Bipolar Disorder

- **Controversy about whether antidepressants precipitate rapid cycling**
- **More support for lithium and lamotrigine**
- **Consider lithium plus lamotrigine, carbamazepine or valproate**
- **More research needed**

# Bipolar Maintenance

# **Bipolar Maintenance Issues**

- **Polarity of index episode may influence outcome**
- **Enriched study design may influence outcome**
- **Outcome criteria may vary**
  - **Time to episode or intervention**
  - **Fewer, shorter, less severe episodes**
- **Low completion rates are problematic**
- **Comorbidity is common**

# **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**

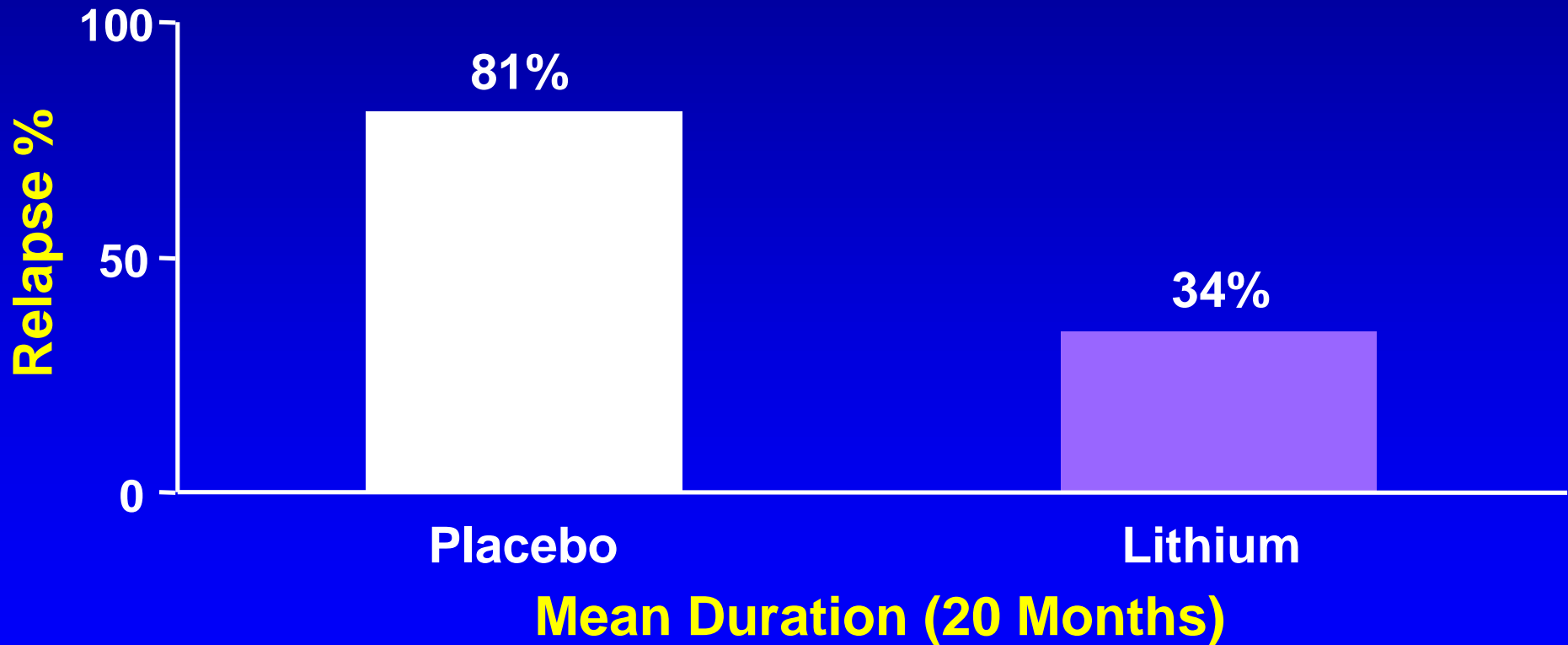
**\*FDA-approved**

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



# Lithium Maintenance

10 Placebo-Controlled Studies (Prior to 1990)



# **Long-Term Lithium Maintenance**

## **A 2004 Meta-analysis of Clinical Trials**

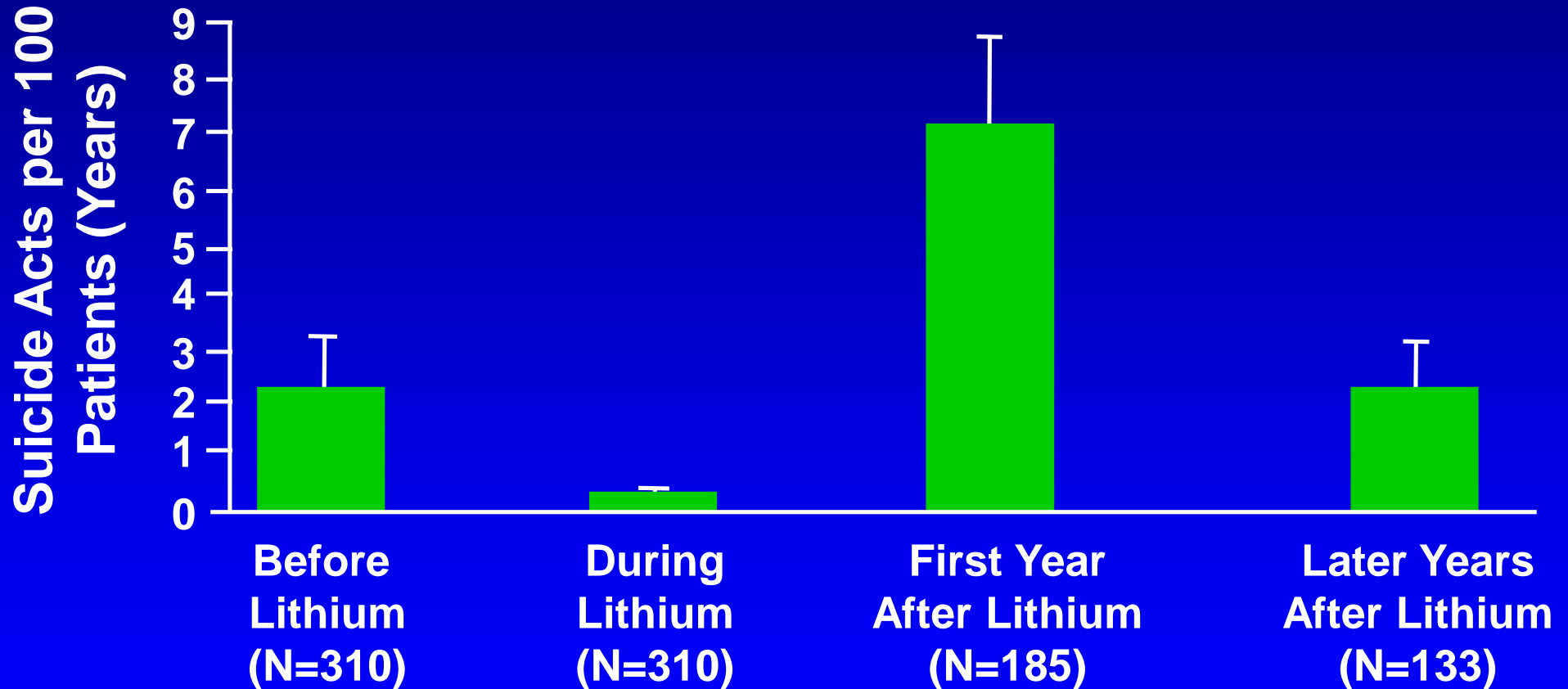
- **Over 70% of the total high-quality studies published or reported since 2000**
- **5 trials, n=770 included**
- **Relapse rate: Lithium 40%, placebo 60%**
- **Manic relapse: Lithium 14%, placebo 24%**
- **Depressive relapse: Lithium 25%, placebo 32%**
- **Preventive effect best for mania**

# 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



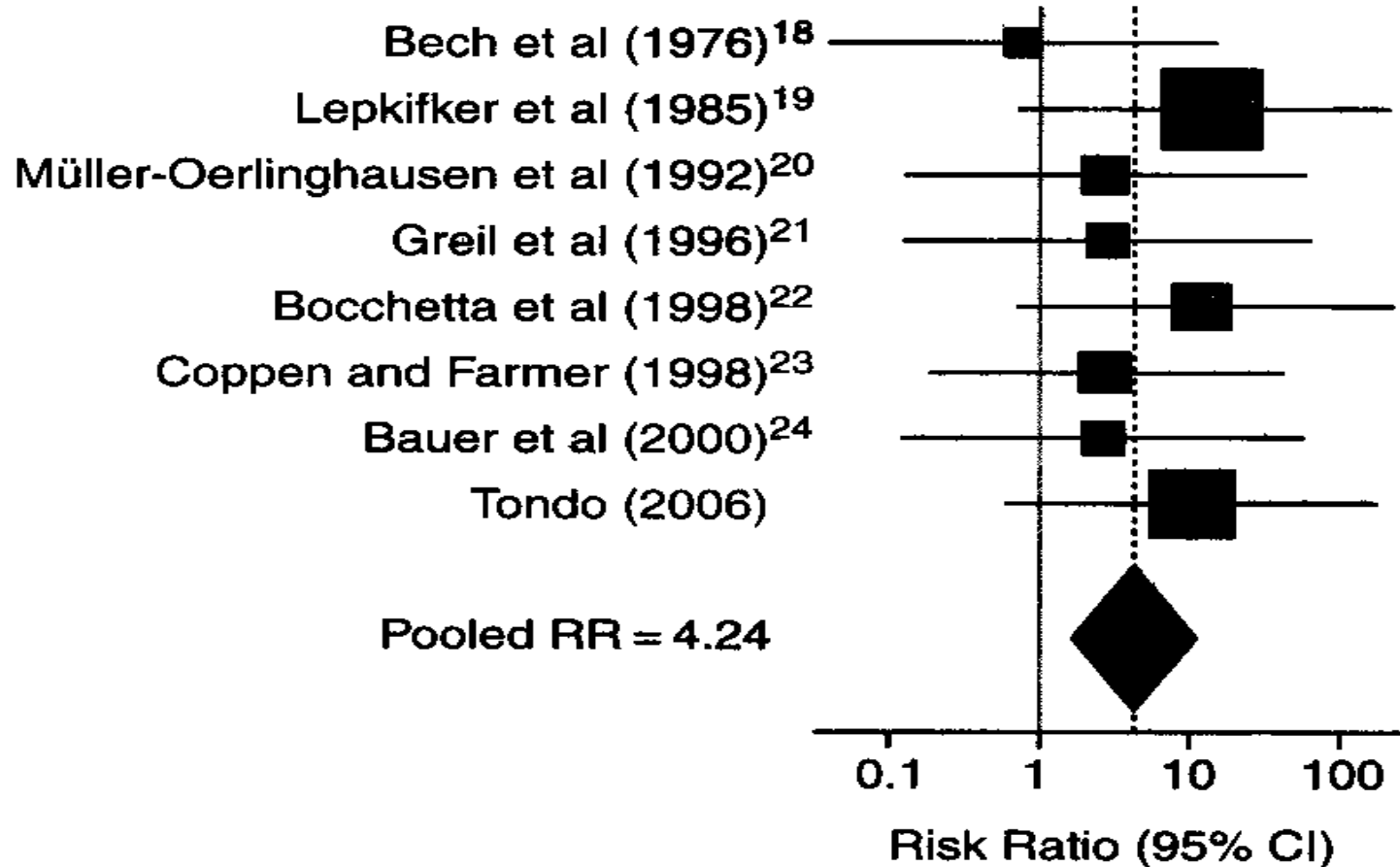
# **Lithium Effective in Preventing Suicide, Deliberate Self-Harm, and Death from All Causes in Mood Disorder Patients**

**(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**

Odds ratio <1 favors lithium vs placebo or other agents

# Long-term Lithium Reduces Suicide and Suicide Attempt Risk in Major Depressive Disorder

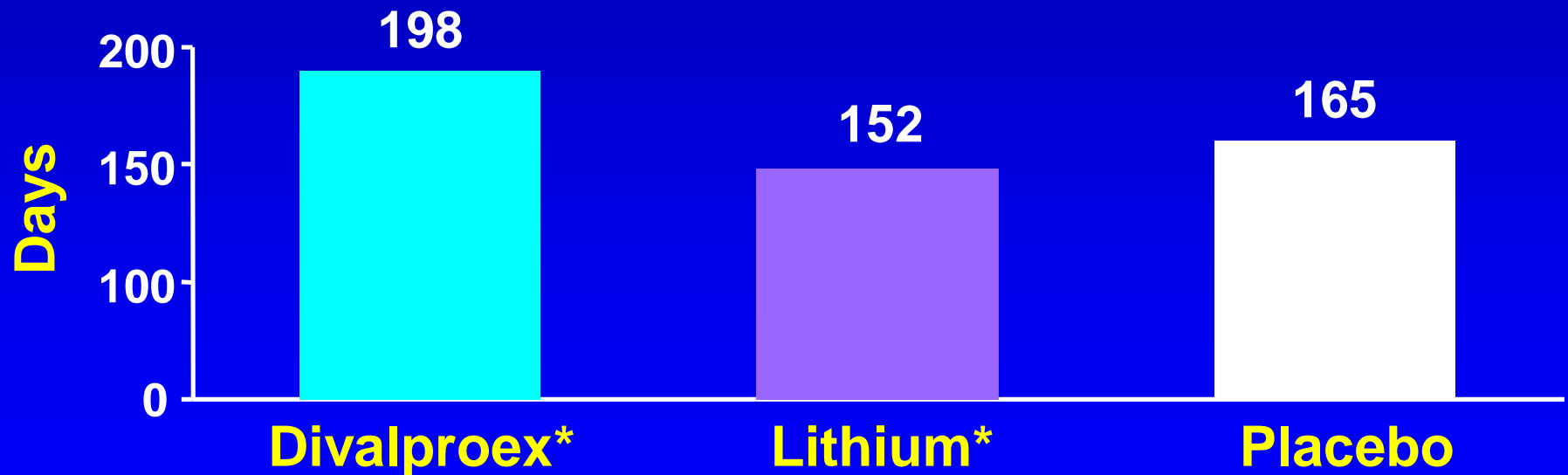


**88.5% risk reduction with  
vs. without lithium**

# Divalproex: 12-Month BP I Maintenance

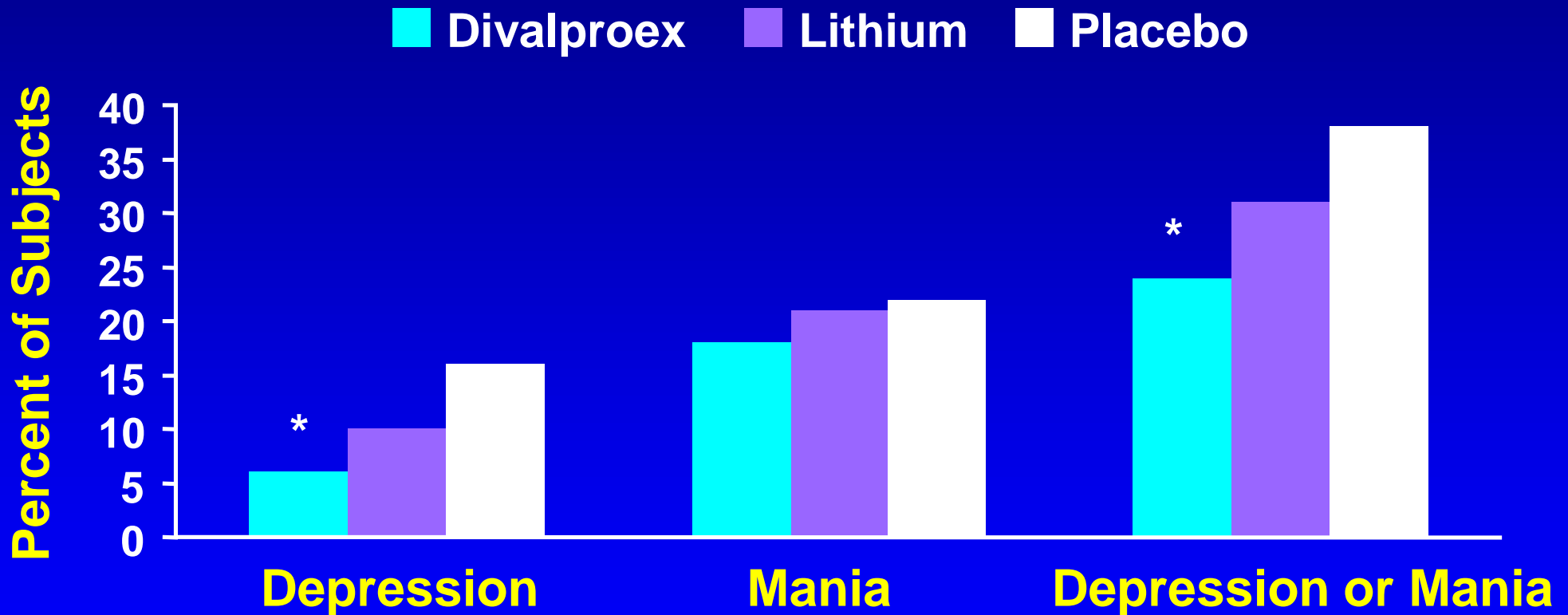
## Entry After Index Manic Episode

- 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)**

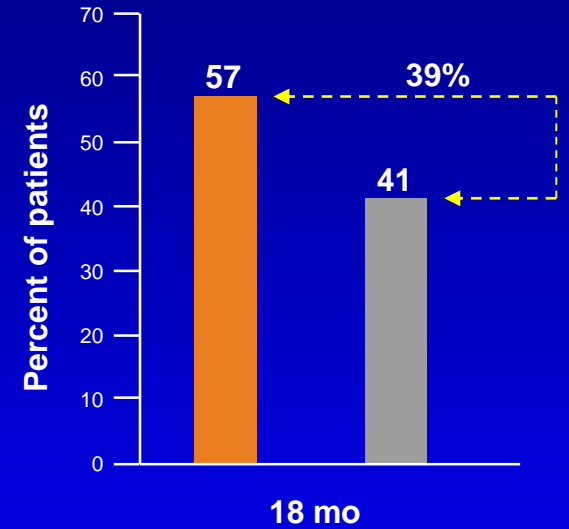
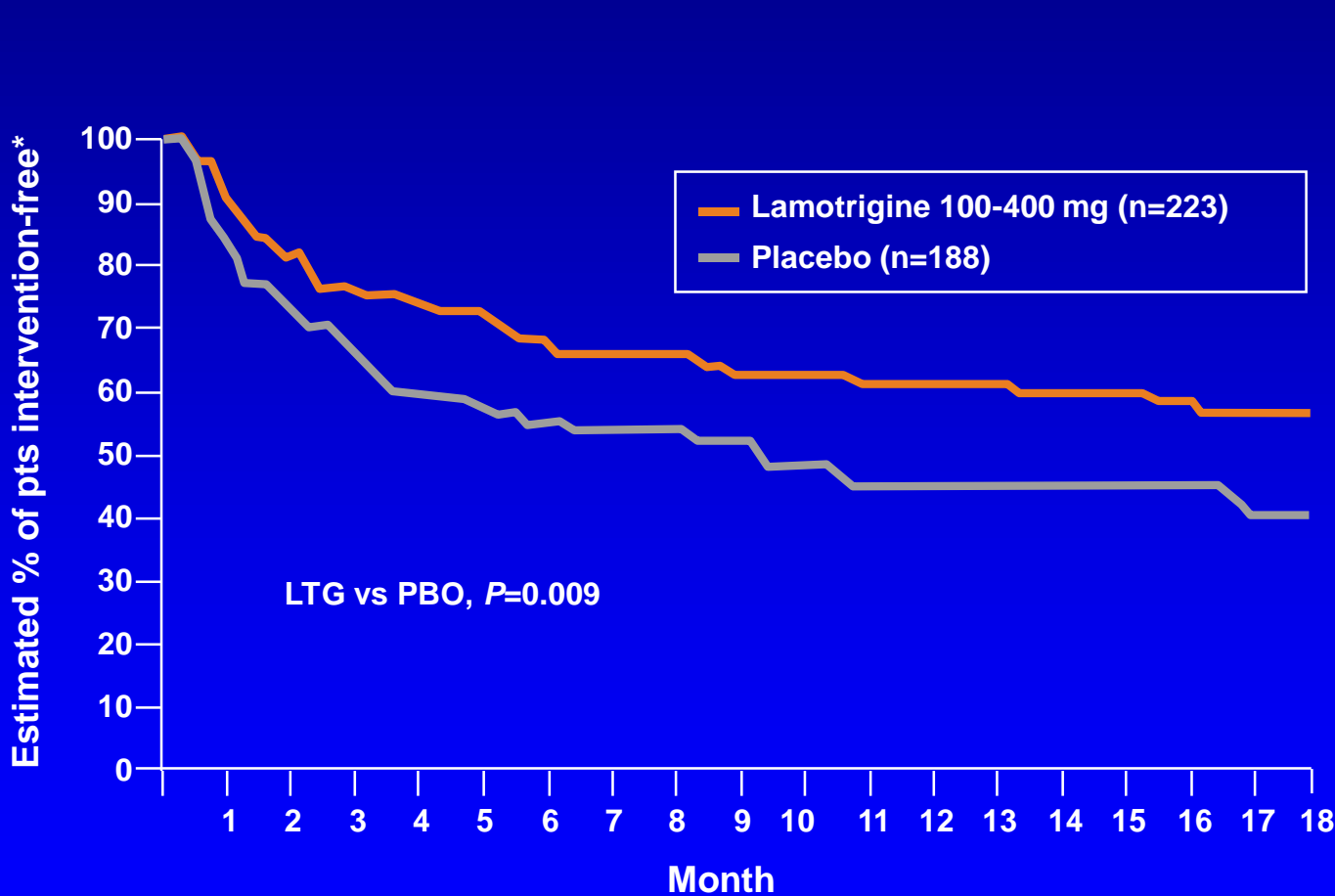
- **Open stabilization: Li + DVPX**  
(n=139, mean age 10.8 years)
- **Double-blind randomization (n=60)**
- **Completed study**

<b>Li</b>	<b>n=10</b>
<b>DVPX</b>	<b>n=10</b>

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

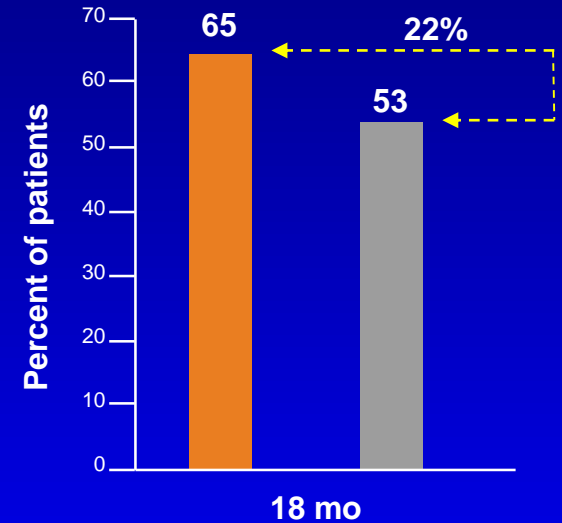
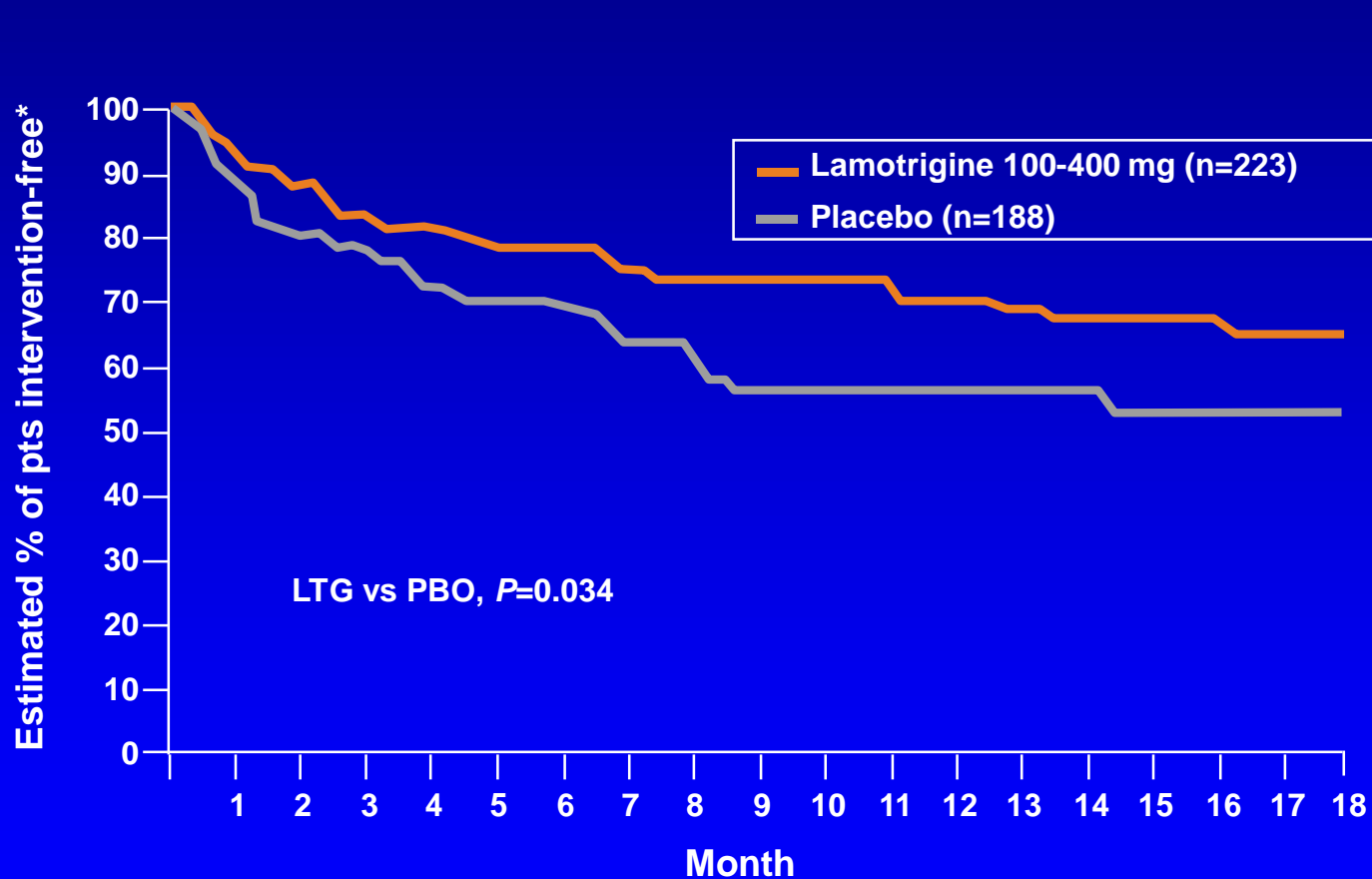
- **Time to mood relapse**  
**The same**
- **Time to study discontinuation**  
**The same**
- **Adverse Event Dropouts**  
**The same (Li 6.7%, DVPX 10%)**

# 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

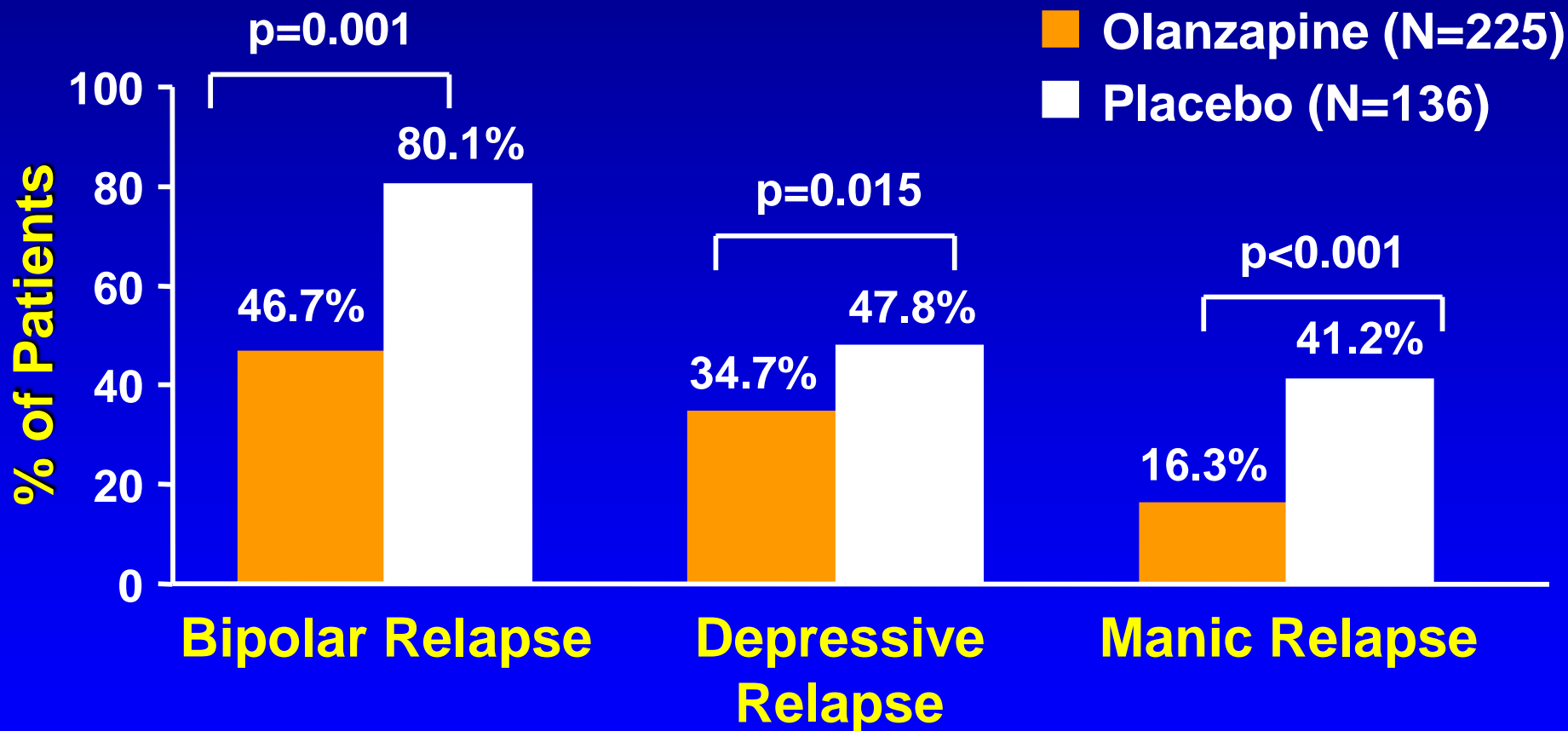
“...a combined analysis of the 2 studies revealed a statistically significant benefit ... over placebo in delaying time to occurrence of both depression and mania, although **the finding was more robust for depression.**”

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.

# **Bipolar I Maintenance: Olanzapine vs. Placebo (1 year, n = 361)**

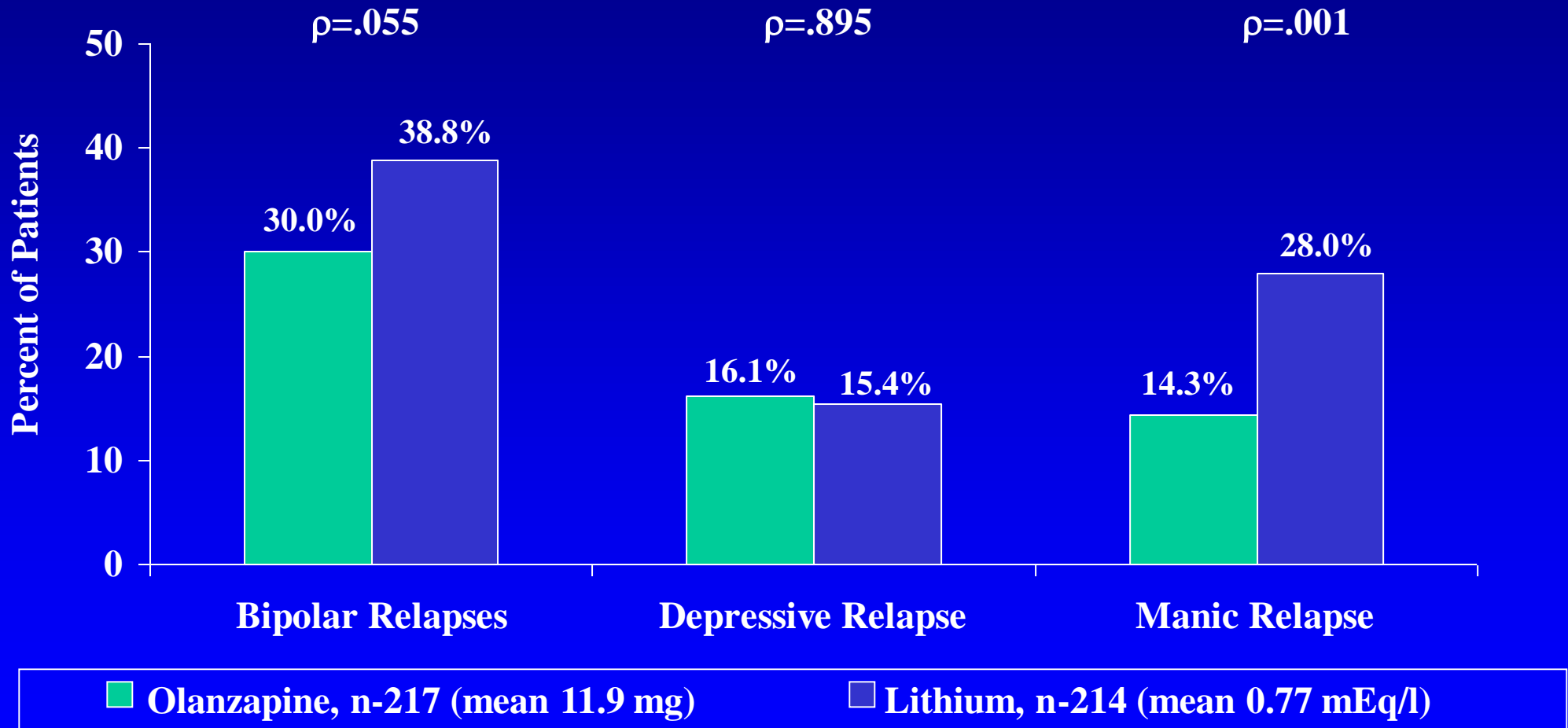
- **Completed one year**

<b>Olanzapine</b>	<b>21.3%</b>
<b>Placebo</b>	<b>6.6%</b>
- **Weight gain  $\geq 7\%$** 

<b>Open-label acute</b>	<b>35%</b>
<b>Double-blind maintenance</b>	
<b>-Olanzapine</b>	<b>17.7%</b>
<b>-Placebo</b>	<b>2.2%</b>



# 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
  - Mono 40.5 days (n.s.)
- Symptomatic relapse
  - Combo 163 days
  - Mono 42 days (p<0.023)

(only significant in women)

# Quetiapine or Placebo with Lithium or Divalproex for Bipolar I Maintenance

- **Open-label QTP + Li or DVPX until 12 weeks of stability (n=1461)**
- **Double-blind QTP\* or placebo with Li or DVPX (up to 104 weeks, n=703)**
- **Time to any mood event: QTP > placebo**
- **Discontinue due to mood event:**

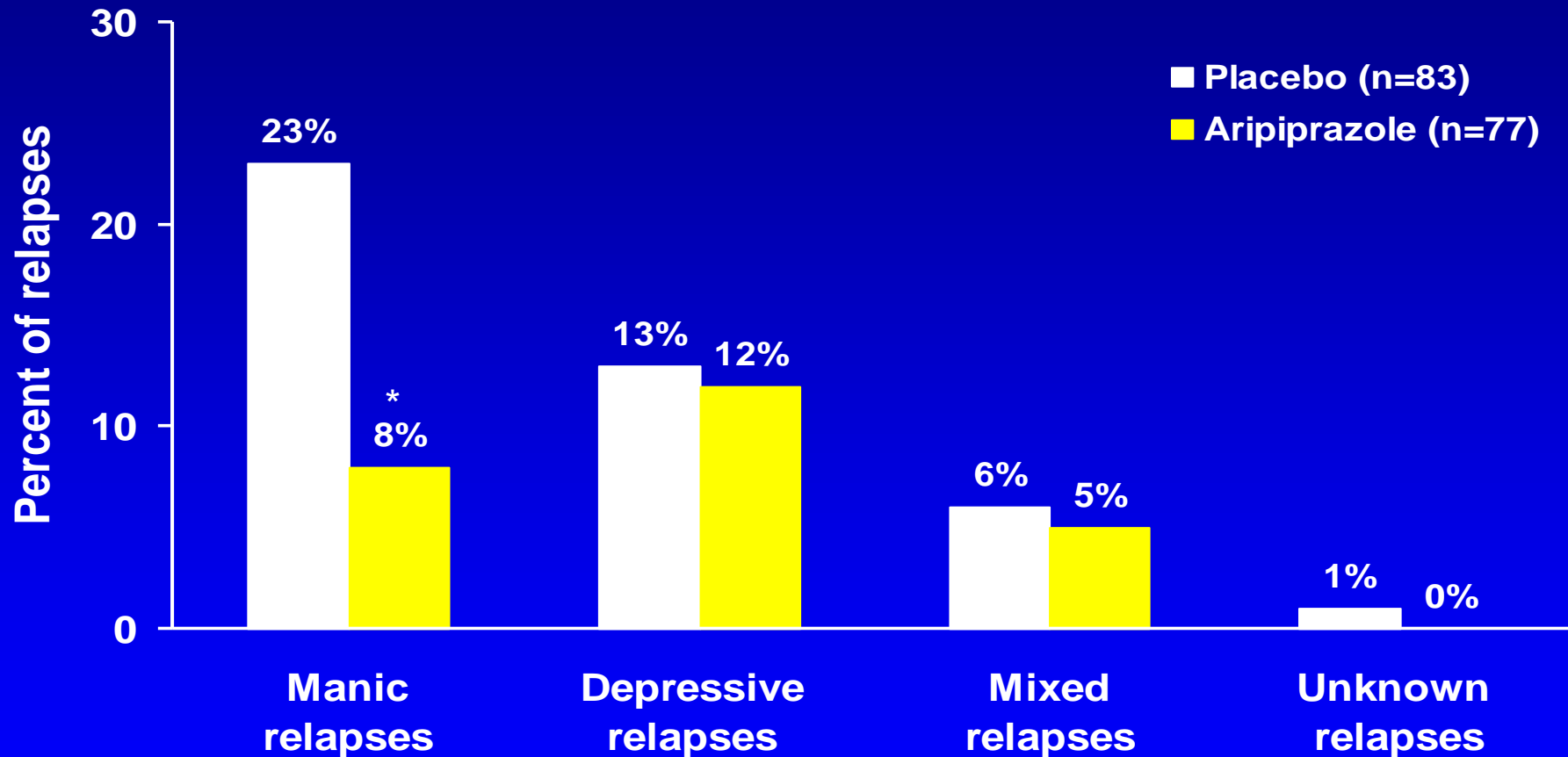
<b>QTP</b>	<b>18.5%</b>
<b>placebo</b>	<b>49%</b>

\*mean median daily dose 497 mg

# **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%)<sup>1</sup>**
- **47-week: OLZ (15.2%), VPA (15.9%)<sup>2</sup>**
- **1-year: OLZ (46.5%), Li (32.7%)<sup>3</sup>**
- **1-year: OLZ (24%), PBO (10%)<sup>4</sup>**
- **18-month: LTG (14.6%), Li (12.6%), PBO (6.3%)<sup>5</sup>**

<sup>1</sup>Marcus et al., ACNP, Dec 2003

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

<sup>3</sup>Tohen et al., APA, May 2003

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

<sup>5</sup>Goodwin 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**

## **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**

# Answers to Pre & Post Lecture Exams

1. c

2. b

3. e

4. a

5. c