

# **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: Prospective Course from STEP-BD**

- **At study entry: 32% rapid-cycling in year prior. After 12 months, only 5% still rapid cyclers (treatment and/or natural history?)**
- **Antidepressants during follow-up: 3.8 times more likely to rapid cycle (but, “we cannot conclude that antidepressants bore a direct causal relationship to increased cycling”)**

# **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)**

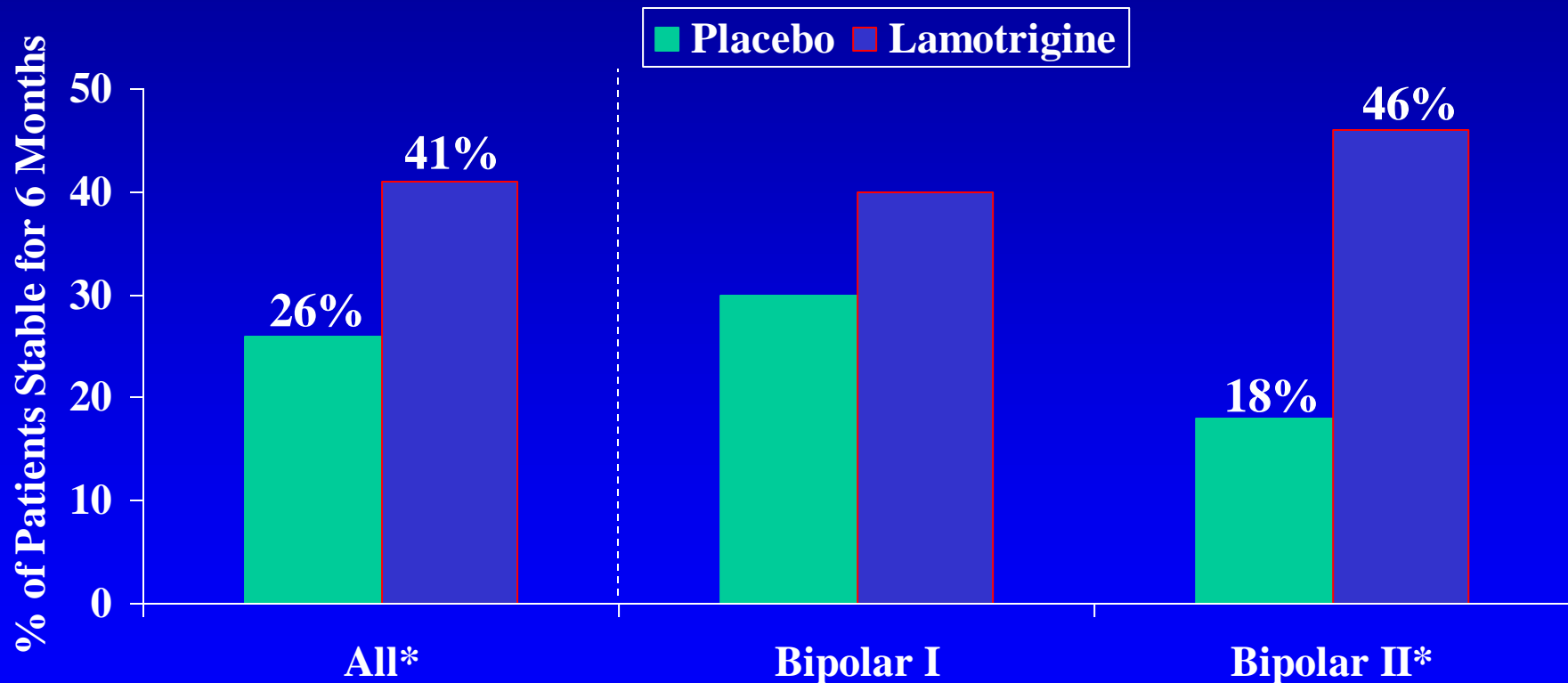
- **Outcome: No significant differences**
- **All trends favored valproate**
  - **Relapse rate**                      **51% vs. 56%**
  - **Time to treatment**                **45 vs. 18 weeks**
  - **Survival time**                      **26 vs. 14 weeks**
  - **A.E. dropouts**                    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

**Quetiapine-2008\***

**Risperidone L-A injection-2009\*\***

**\*\*Approved for monotherapy and adjunctive to lithium and valproate**

**\*Approved only as adjunct to lithium or valproate**

# **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**

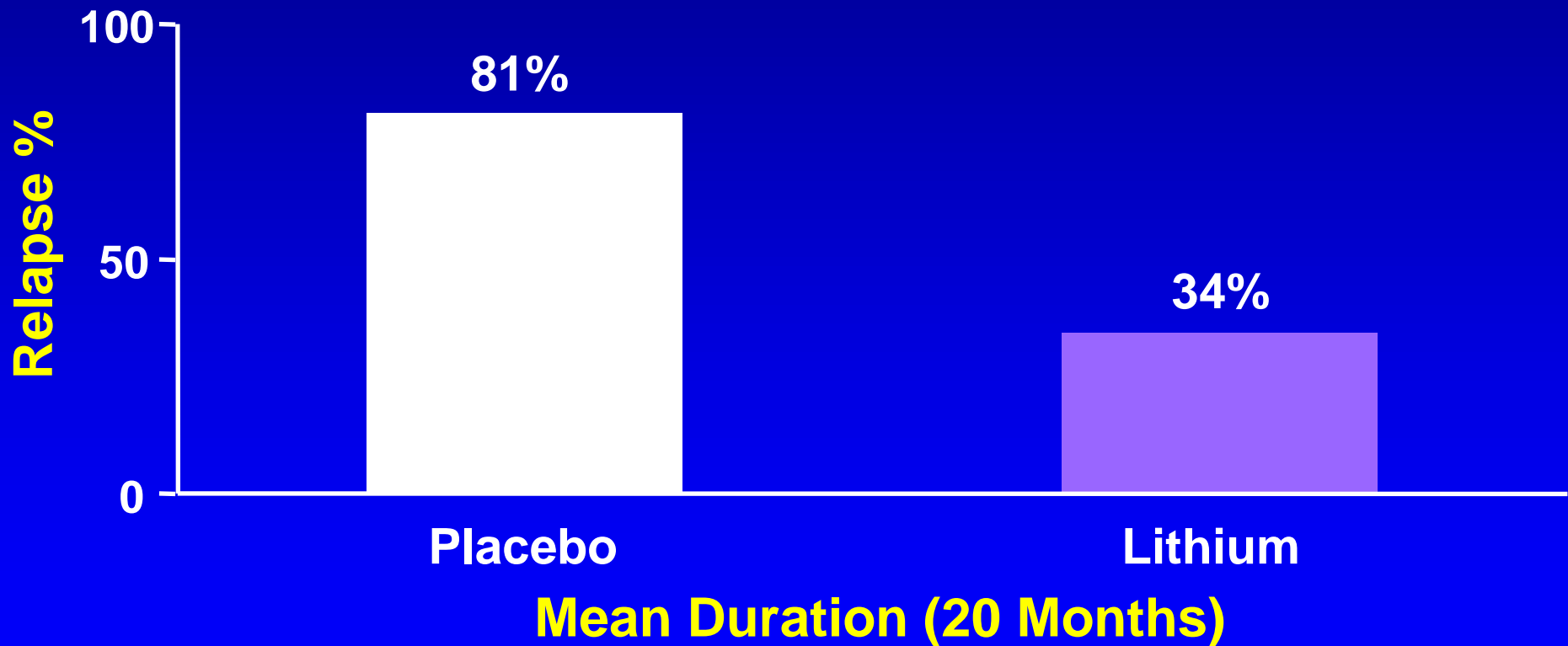
**\*FDA-approved**

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

# Lithium

# Lithium Maintenance

10 Placebo-Controlled Studies (Prior to 1990)



# **Long-Term Lithium Maintenance**

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

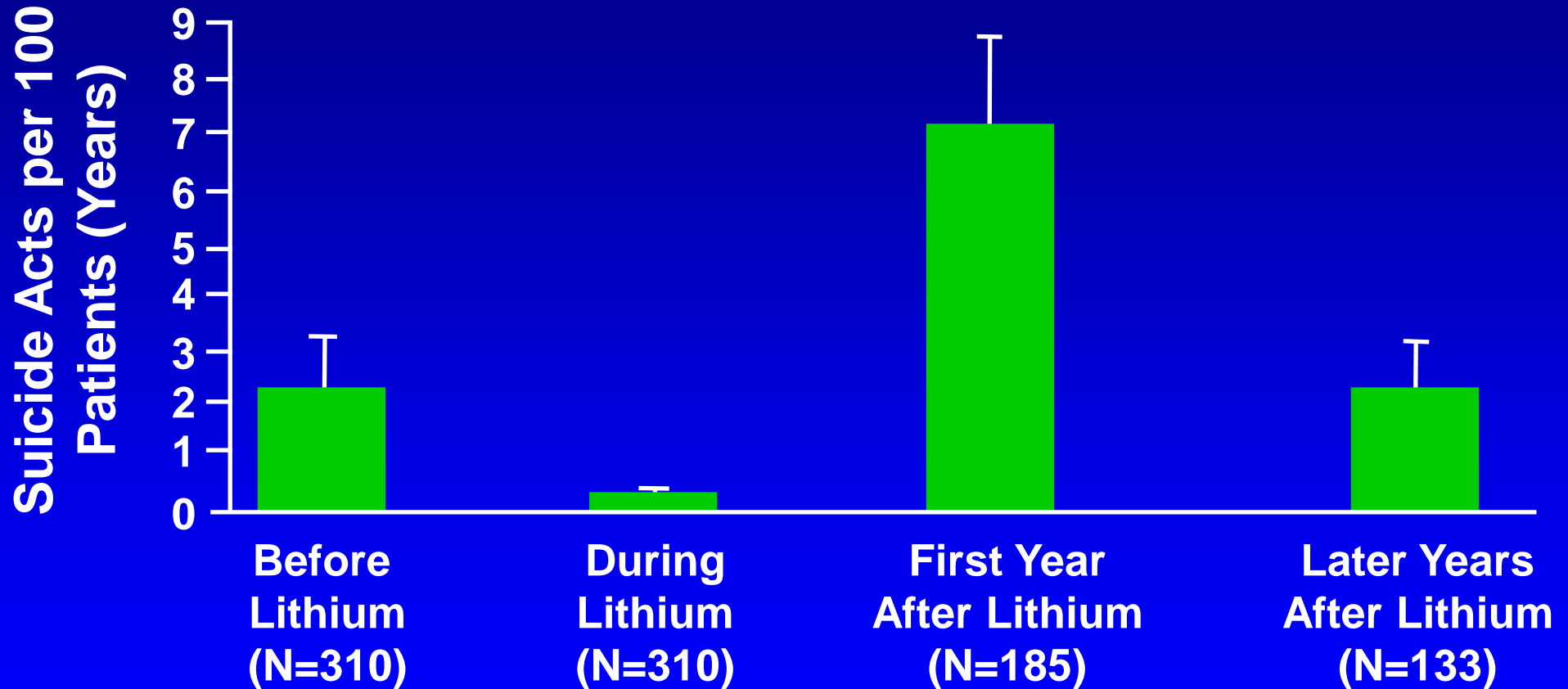
- **Over 70% of the total high-quality studies published or reported since 2000**
- **5 trials, n=770 included**
- **Relapse rate: Lithium 40%, placebo 60%**
- **Manic relapse: Lithium 14%, placebo 24%**
- **Depressive relapse: Lithium 25%, placebo 32%**
- **Preventive effect best for mania**

# 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



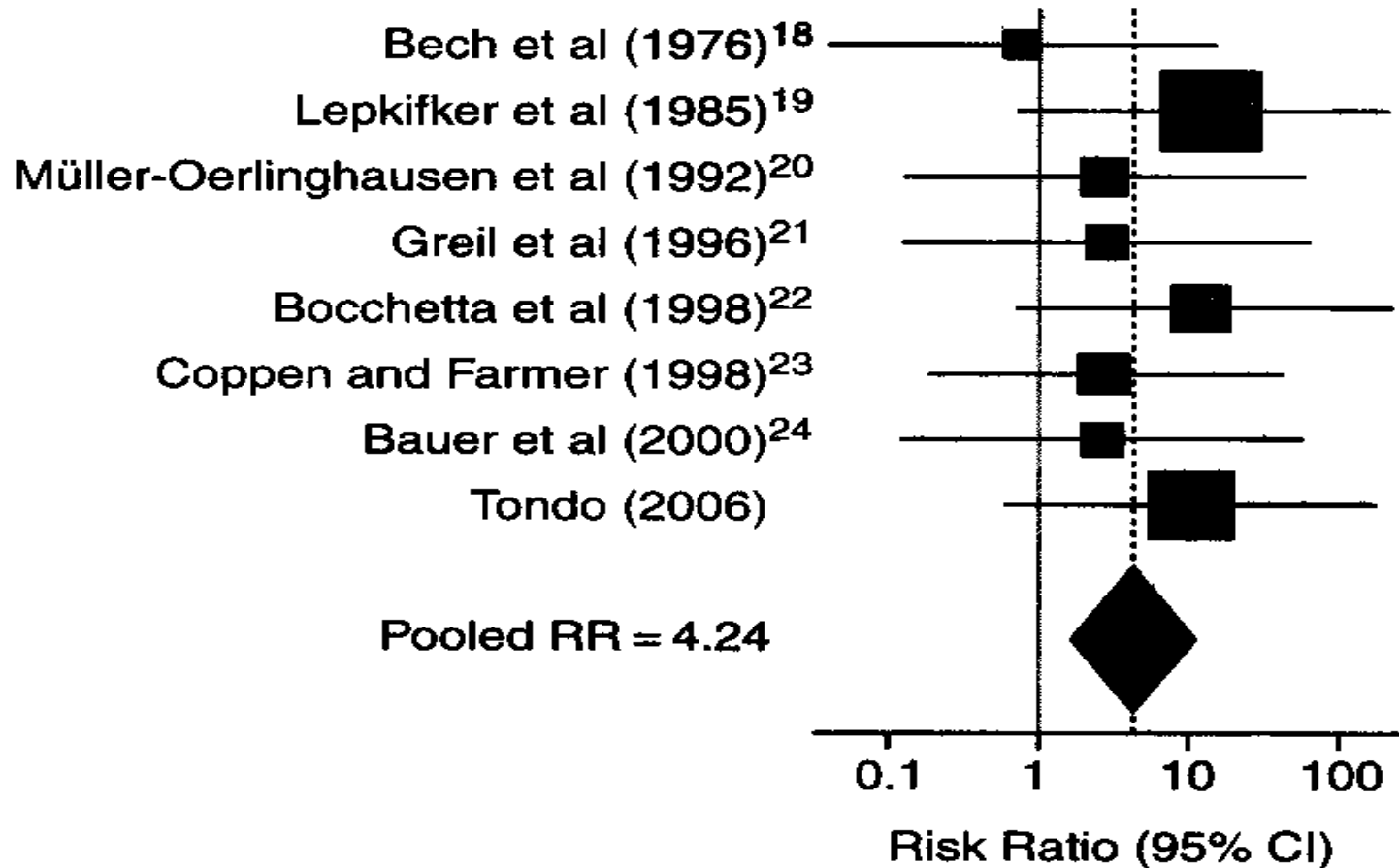
# **Lithium Effective in Preventing Suicide, Deliberate Self-Harm, and Death from All Causes in Mood Disorder Patients**

**(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**

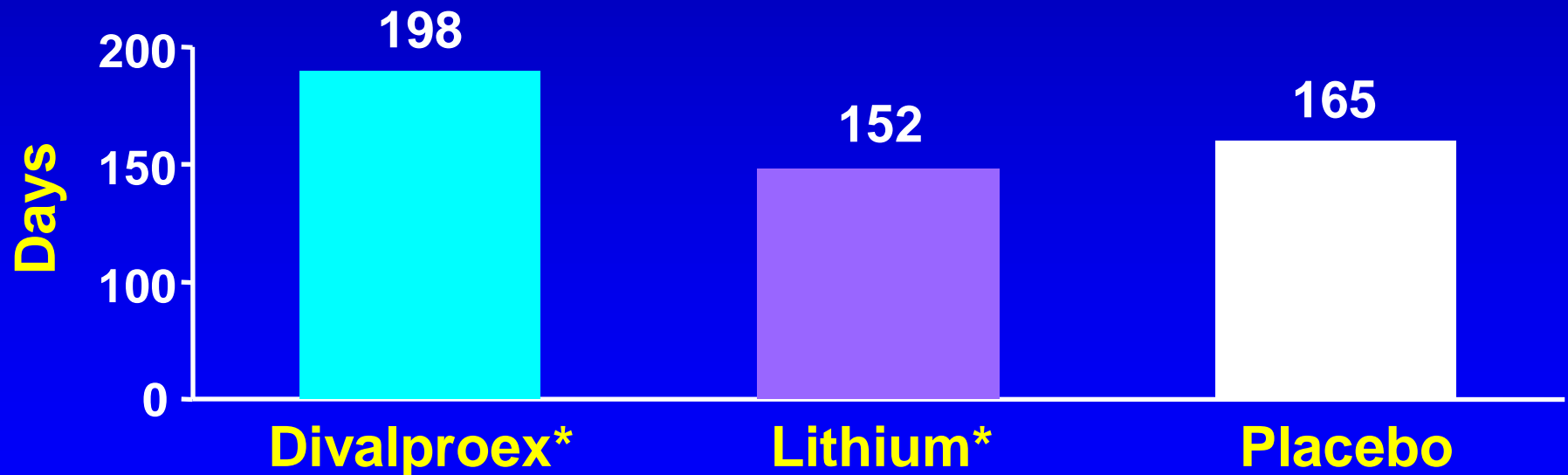


# Divalproex

# Divalproex: 12-Month BP I Maintenance

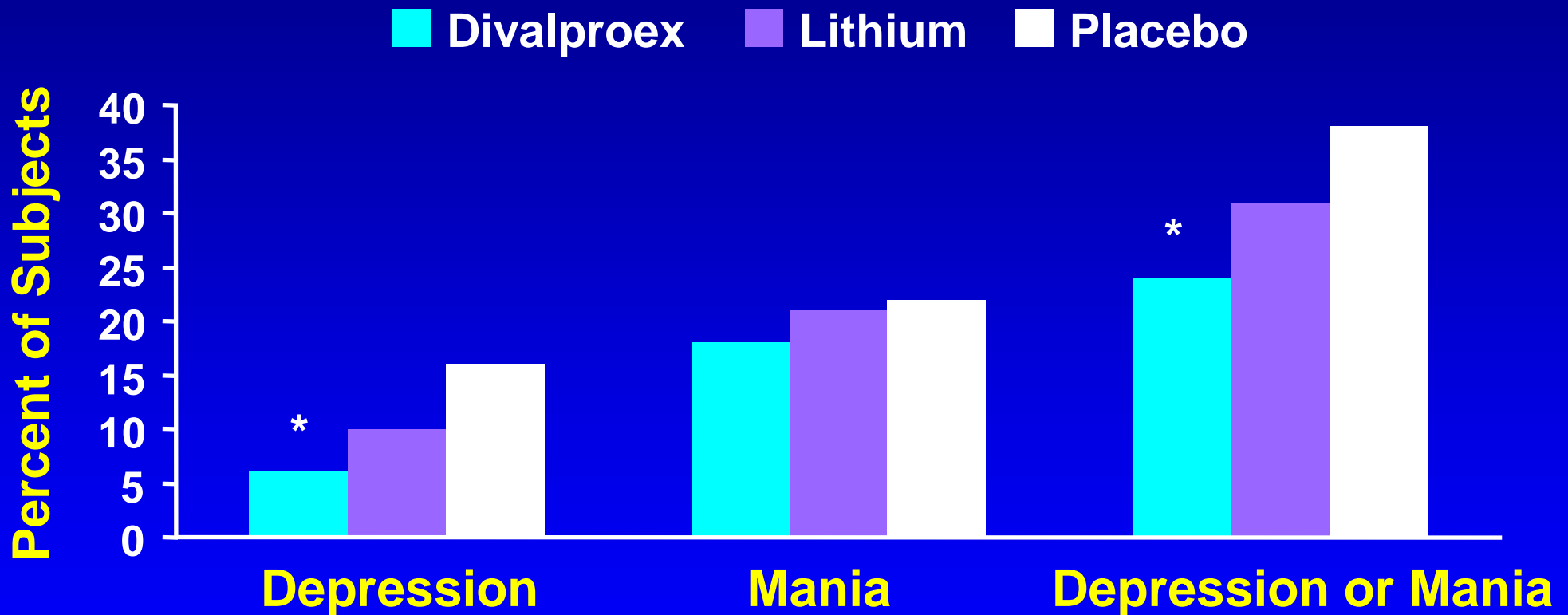
## Entry After Index Manic Episode

- 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**

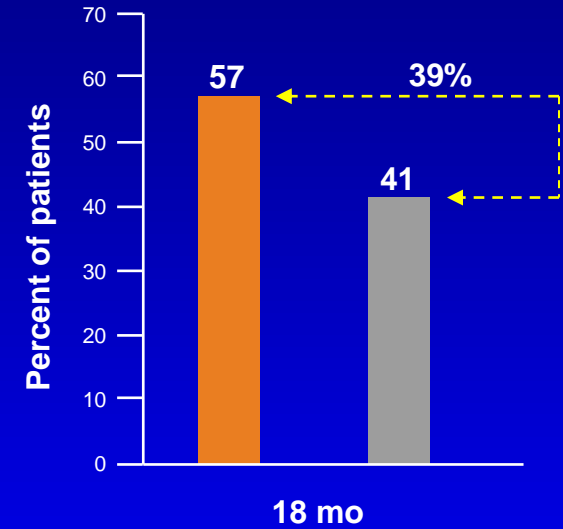
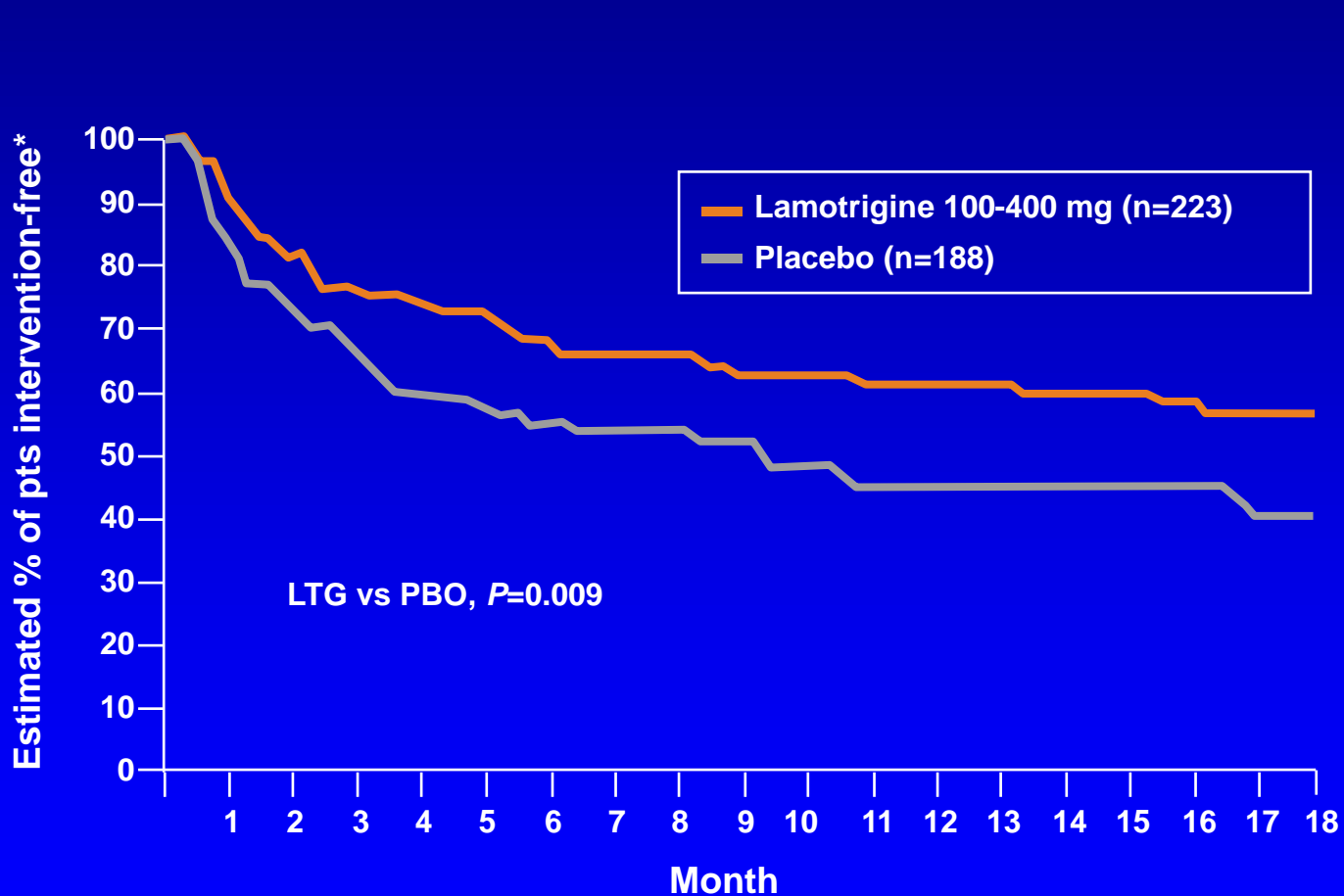
<b>Li</b>	<b>n=10</b>
<b>DVPX</b>	<b>n=10</b>

# **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%)**

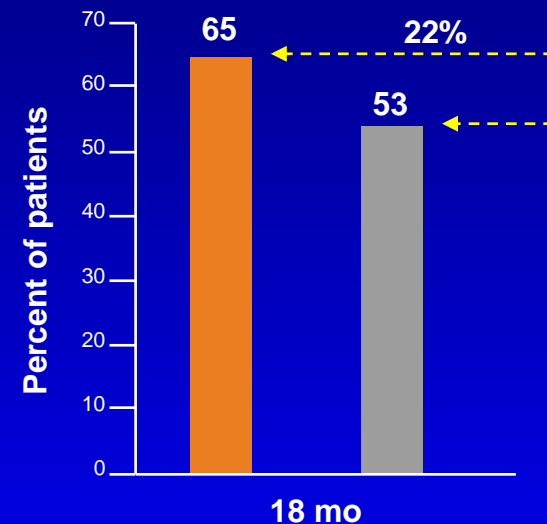
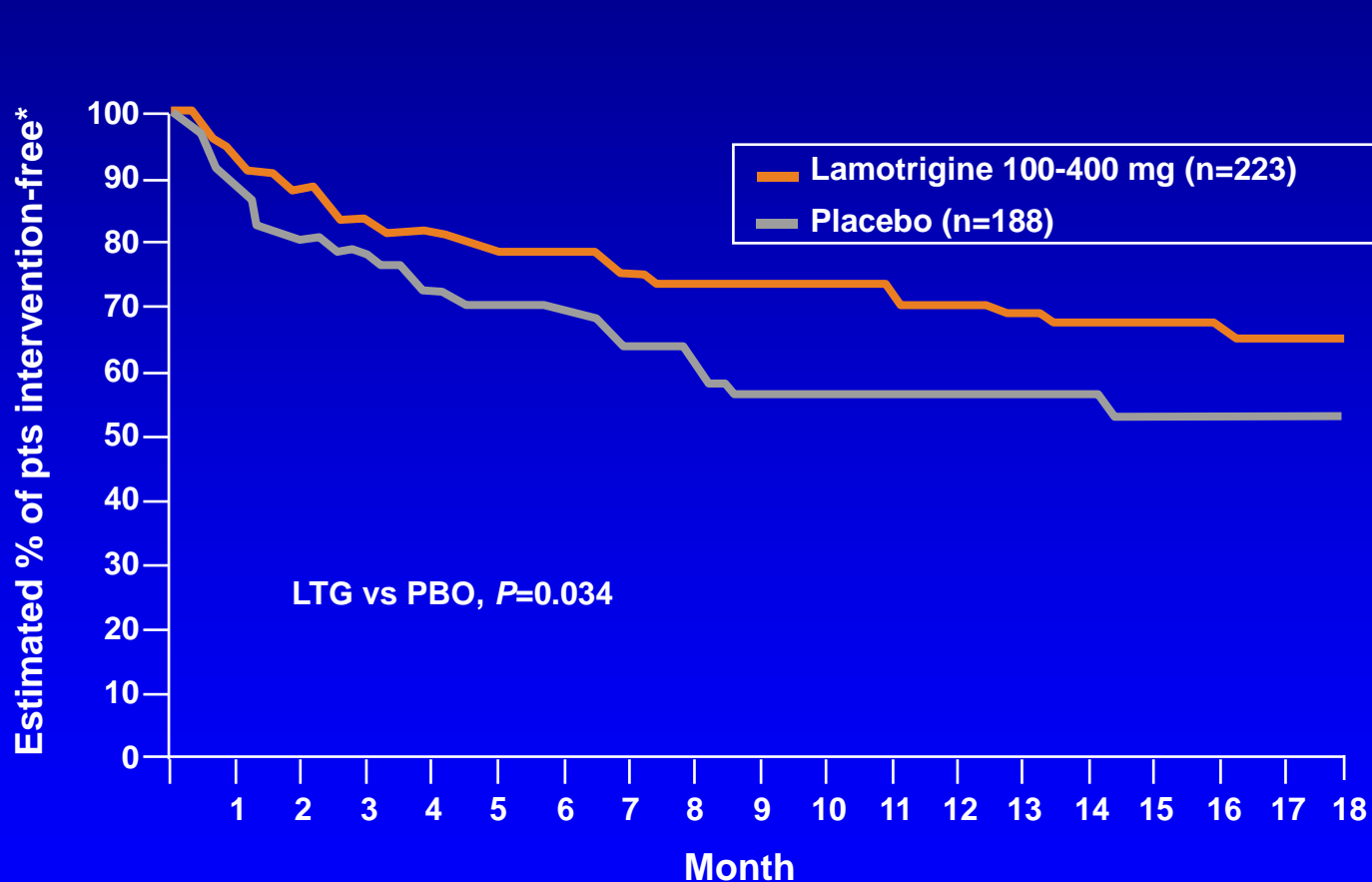
# Lamotrigine

# 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.



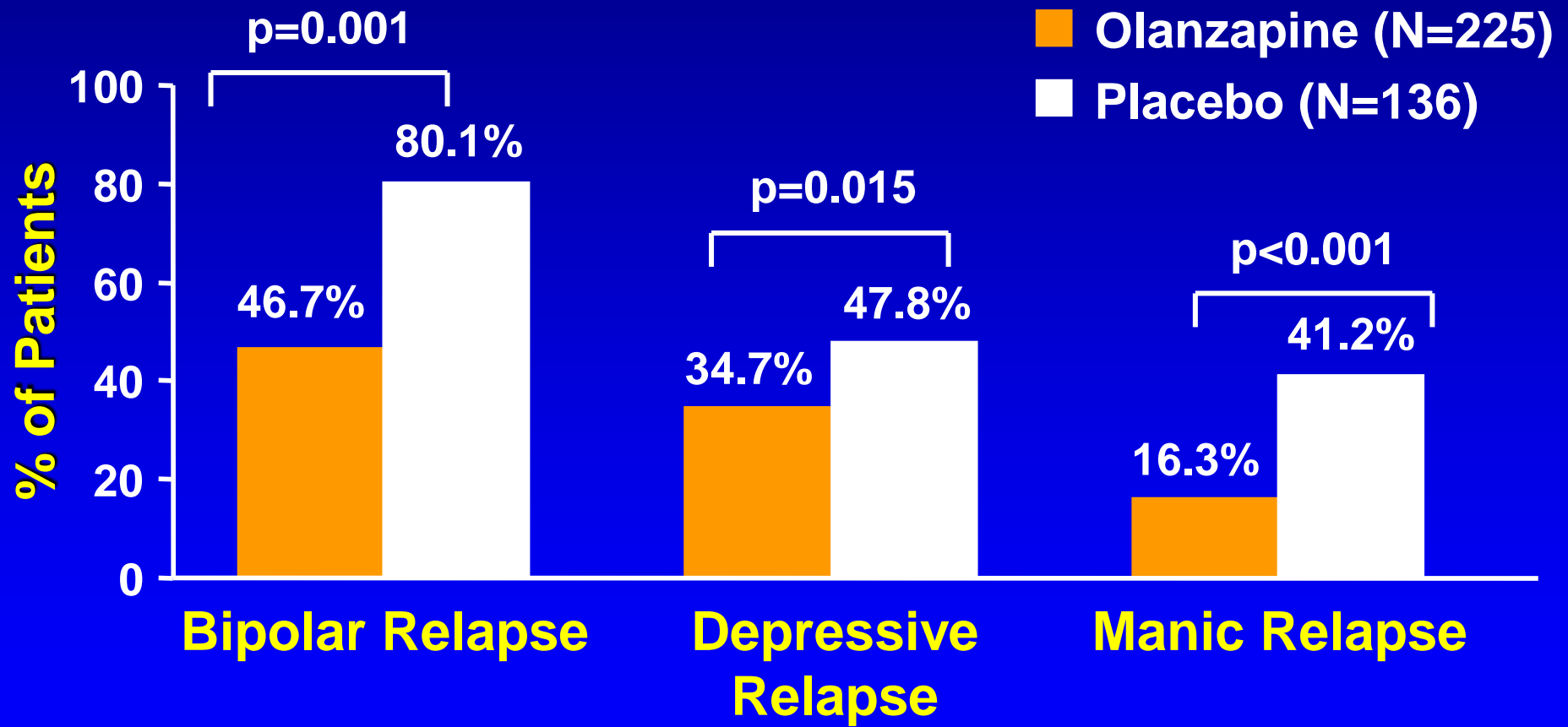
# Lamotrigine for Bipolar Maintenance

“...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

# Olanzapine

# 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.

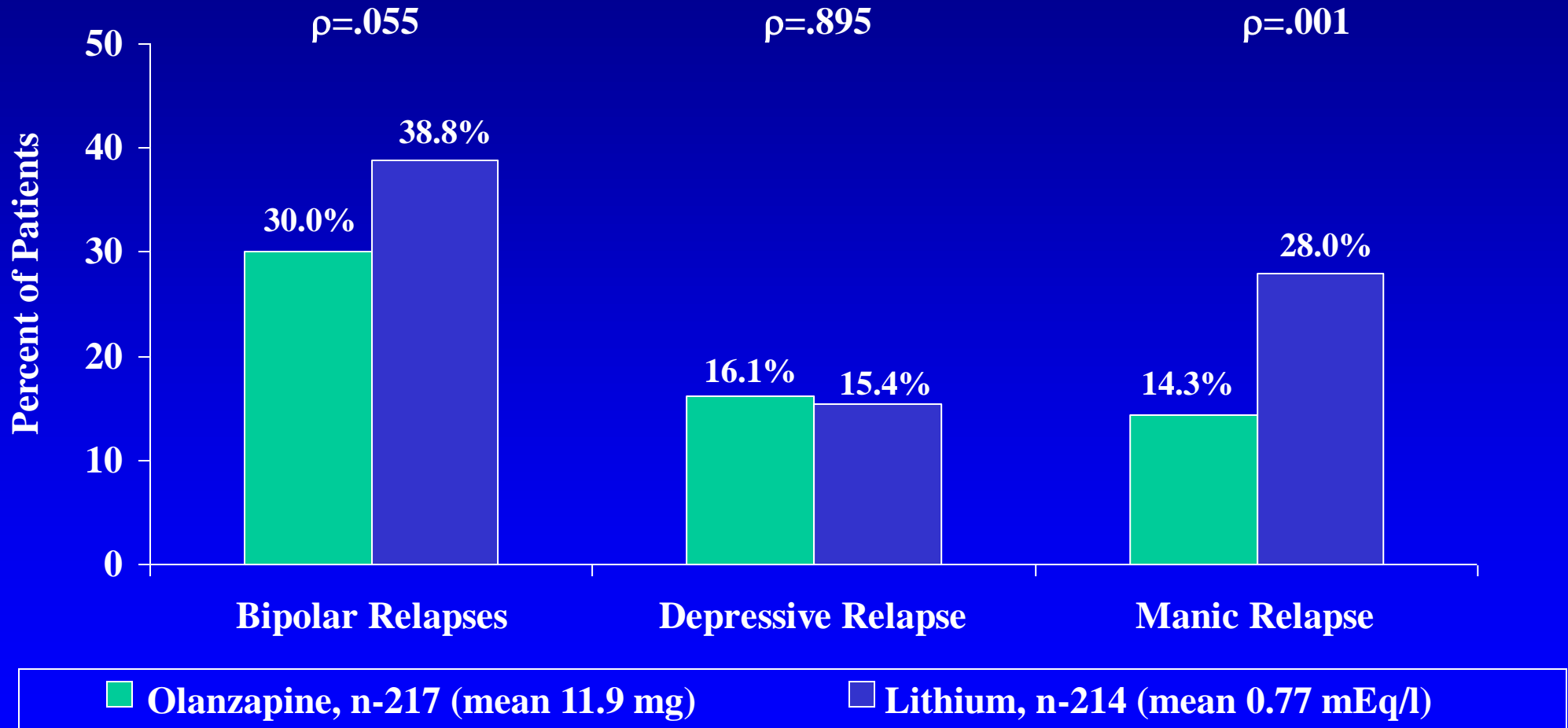
# **Bipolar I Maintenance: Olanzapine vs. Placebo (1 year, n = 361)**

- **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%**

# 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**

# Bipolar I: 18-Month Relapse Prevention

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

<b>Combo</b>	<b>94 days</b>	<b>(n.s.)</b>
<b>Mono</b>	<b>40.5 days</b>	
- **Symptomatic relapse**

<b>Combo</b>	<b>163 days</b>	<b>(p&lt;0.023)</b>
<b>Mono</b>	<b>42 days</b>	

**(only significant in women)**



# Quetiapine

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

- **Open-label QTP + Li or DVPX until 12 weeks of stability (n=1953)**
- **Double-blind QTP\* or placebo with Li or DVPX (up to 104 weeks, n=628)**
- **Time to any mood event: QTP>placebo**
- **Discontinue due to mood event:**

<b>QTP</b>	<b>20.3%</b>
<b>placebo</b>	<b>52.1%</b>

\*mean median daily dose 519 mg

# 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

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

- Completed randomized phase:

Trial 126*-	QTP	63.4%
	PBO	36.5%
Trial 127**-	QTP	35.5%
	PBO	21.1%

\*Vieta et al. J Affective Disorders 2008;109:251-263 (Trial 126, US, Europe, Aust, S. Africa, 177 sites)

\*\*Suppes et al. Am J Psychiatry 2009;166:476-488 (trial 127, US, Canada 127 sites)

# Quetiapine vs. Lithium for Bipolar I Maintenance

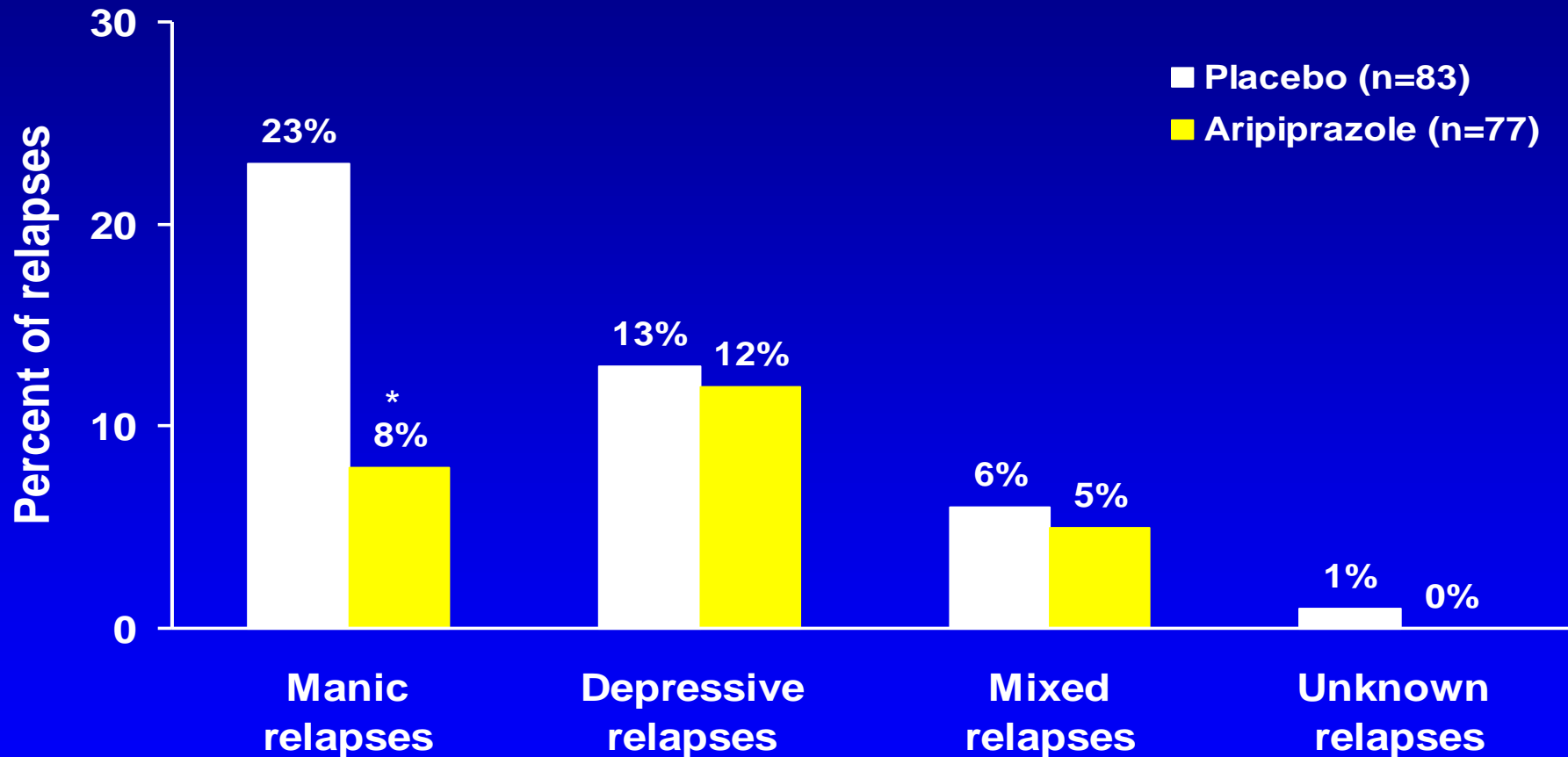
- Open-label QTP (300-800 mg) until stable  $\geq 4$  weeks. Then double-blind QTP (n=404), Lithium (n=364) or placebo (n=404) for up to 104 weeks
- Time to recurrence of any mood event:
  - QTP = Lithium > Placebo
  - QTP > Lithium at  $\downarrow$  risk of depressive events

# Aripiprazole

# **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.



# **Aripiprazole: Bipolar I Maintenance 100-Week, Double-Blind vs. Placebo**

- 6-month study extended, double-blind for 74 more weeks**
- ARI: 39 entered, 7 completed; PBO: 27 entered, 5 completed**
- Time to any relapse: ARI>PBO (p=0.011)**
- Time to manic relapse: ARI>PBO (p=0.005)**
- Time to depressive relapse: No difference**

# Risperidone Long-Acting Injection

# **Risperidone Long-Acting Injection for Bipolar I Maintenance**

- **FDA-approved May 2009 for monotherapy and adjunctive therapy (with lithium or valproate)**
- **Dose: 25 mg i.m q 2 weeks, could ↑ to 37.5 or 50 mg or ↓ to 12.5 mg**
- **Primary efficacy measure: Time to relapse**

# **Risperidone Long-Acting Injection for Bipolar I Maintenance: Monotherapy**

- **26-Week, open-label stabilization, n=501**
- **60.5% who maintained response randomized to double-blind for up to 24-months**
- **Time to relapse: RIS > PBO (p<0.001)**
- **Relapse: RIS 30%, PBO 56%**
- **NNT for relapse prevention at 9-months: 3.3**

# **Risperidone Long-Acting Injection for Bipolar I Maintenance: Adjunctive**

- **16-Week, open-label stabilization, n=275\***
- **50.5% (n=139)\* stable at least 4-weeks randomized to double-blind for 52-weeks**
- **Time to relapse: RIS > PBO (p<0.004)**
- **Relapse rates: RIS 22.2%, PBO 47.8%**

**Alphs et al. APA San Francisco, NR3-066 poster, 16-20 May 2009**

**\*sample sizes different in package insert May 2009-n=240 and 124 (51.7%,)**

# 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>**
- **24-month: RIS L-A inj. (46.8%), PBO (20.8%)<sup>6</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;

<sup>6</sup>Quiroz et al. APA San Francisco, NR4-092 poster, 16-20 May 2009

# Ziprasidone

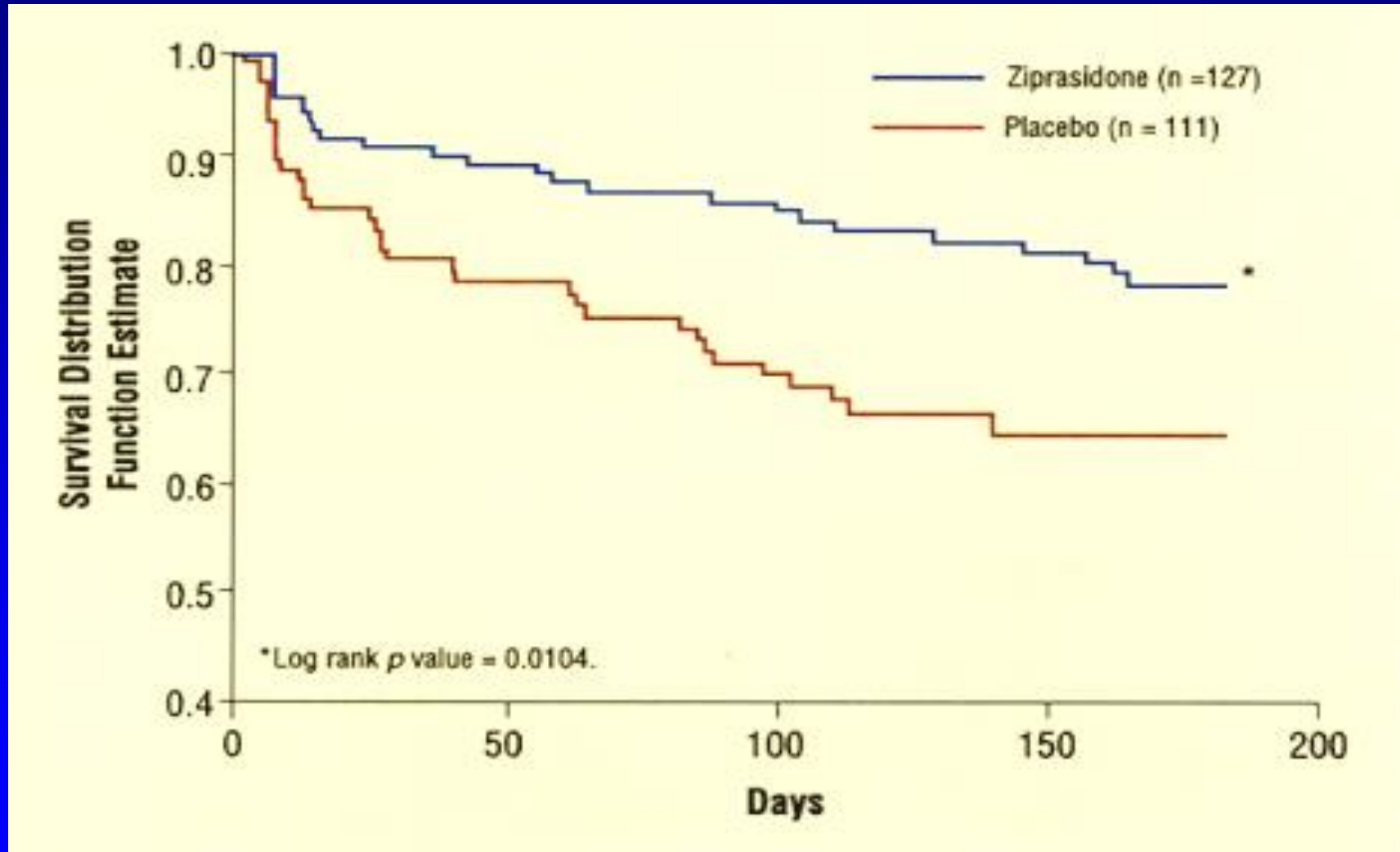
As of Nov 2009, not FDA-approved for adjunctive bipolar maintenance

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

- Open-label ZIP + Li or DVPX (n=586) until 8 weeks of stability
- 6-month double-blind ZIP (n=127) or placebo (n=112) with Li or DVPX
- Time to any mood event: ZIP > placebo (p=.0104)
- Intervention for mood event: ZIP 19.7%  
PBO 32.4%



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



# **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:**
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  - b. Lithium more effective**
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# 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