Bipolar Disorders: Therapeutic Options

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Revised October 2011

Part 3: Treatment of Rapid Cycling and Bipolar Maintenance

Revised October 2011

Teaching Points

- Rapid-Cycling:
  a. Understudied, no clear advantage to any treatment
  b. Small study found Li = DVPX (trends favored DVPX)
  c. Lamotrigine benefit, if any, restricted to bipolar II

Teaching Points

- **Maintenance:**
  a. Issues include polarity, enrichment, relapse vs recurrence, outcome criteria, low completion rates, comorbidity
  b. 7 FDA-approved maintenance treatments
  c. BALANCE study favors lithium over valproate
  d. Lamotrigine best for depression prevention
  e. Need to weigh benefit and risk

Outline

I. Rapid Cycling
   A. Lower response overall
   B. Lithium vs. Divalproex Study
   C. Lamotrigine
II. Bipolar Maintenance
   A. Lithium
   B. Divalproex
   C. Lamotrigine
   D. Olanzapine
   E. Quetiapine
   F. Aripiprazole
   G. Risperidone
   H. Ziprasidone

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 <u>not</u> 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**

Tondo et al., Acta Psychiatr Scand 2003;108:4-14

Rapid Cycling (4 or more episodes/year)

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

APA Bipolar Guidelines, Revised 2002

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")

Schneck et al., Am J Psychiatry 2008;165:370-377

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

- **Time to additional pharmacotherapy***

  n.s. (p=0.177)

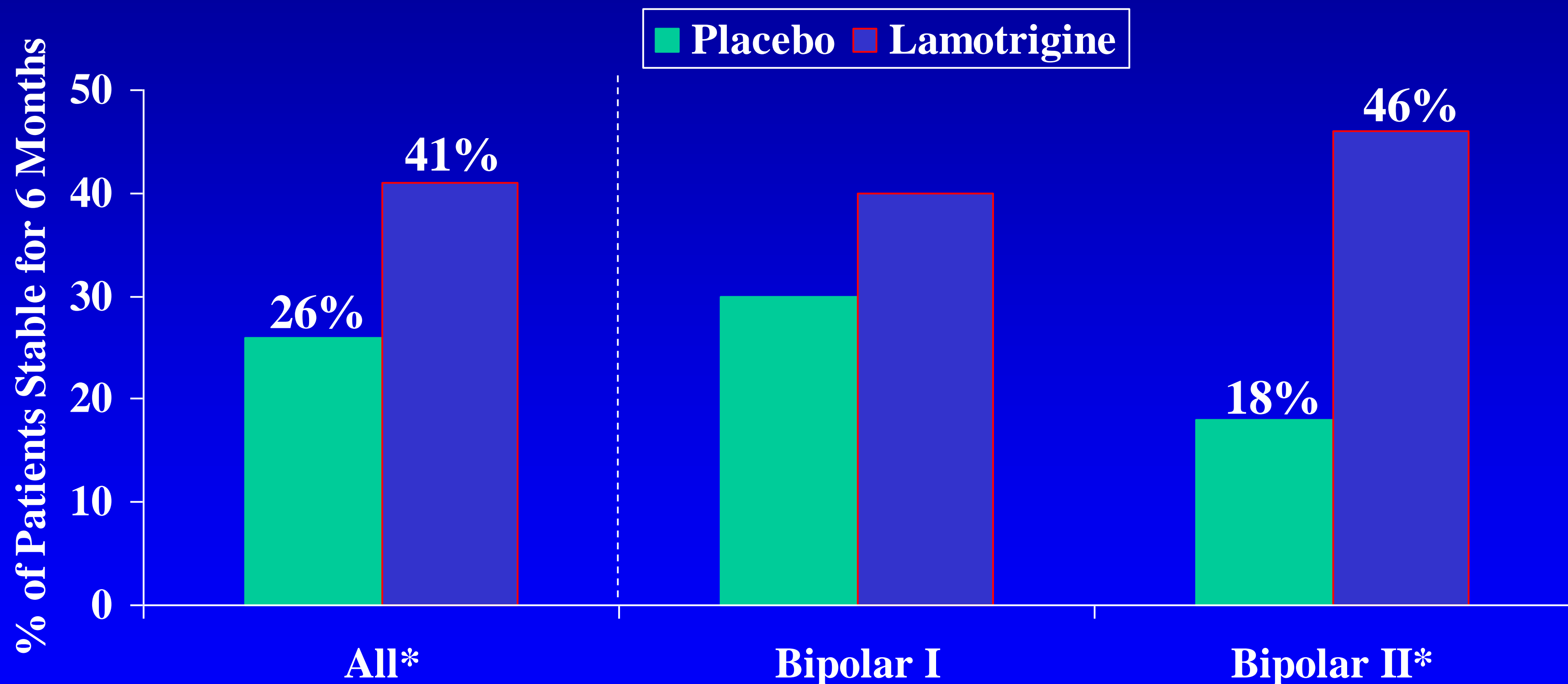
- **Stable without relapse at 6 months (n=60)**

- Lamotrigine	41%	(p=0.03)
- Placebo	26%	

***Primary efficacy measure**

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

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



*p<.05

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

Lamotrigine Adjunctive to Li + DVPX in Depressed Rapid Cyclers with Recent Substance Use Disorder

- Non-responders to Li + DVPX alone
- 12-week double-blind addition of LTG (n=18) or PBO (n=18)
- No significant differences in MADRS, YMRS, response, or remission
- LTG well tolerated

Wang et al. Psychopharmacol Bull 2010;43:5-21

Lamotrigine for Rapid-Cycling: Monotherapy or Add-On (n=137) (Unpublished)

- **Double-blind, placebo-controlled**
- **Time to additional pharmacotherapy***
  no significant difference (p=0.0734)

***Primary efficacy measure**

www.gsk-clinicalstudy register.com

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

Calabrese et al., Am J Psychiatry 2005;162:2152-2161

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%

Calabrese et al., Am J Psychiatry 2005;162:2152-2161

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

Coryell W. CNS Drugs 2005;19:557-569

Bipolar Maintenance

Bipolar Maintenance Issues

- Polarity of index episode may influence outcome
- Enriched study design may influence outcome
- Is it relapse or is it recurrence
- 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

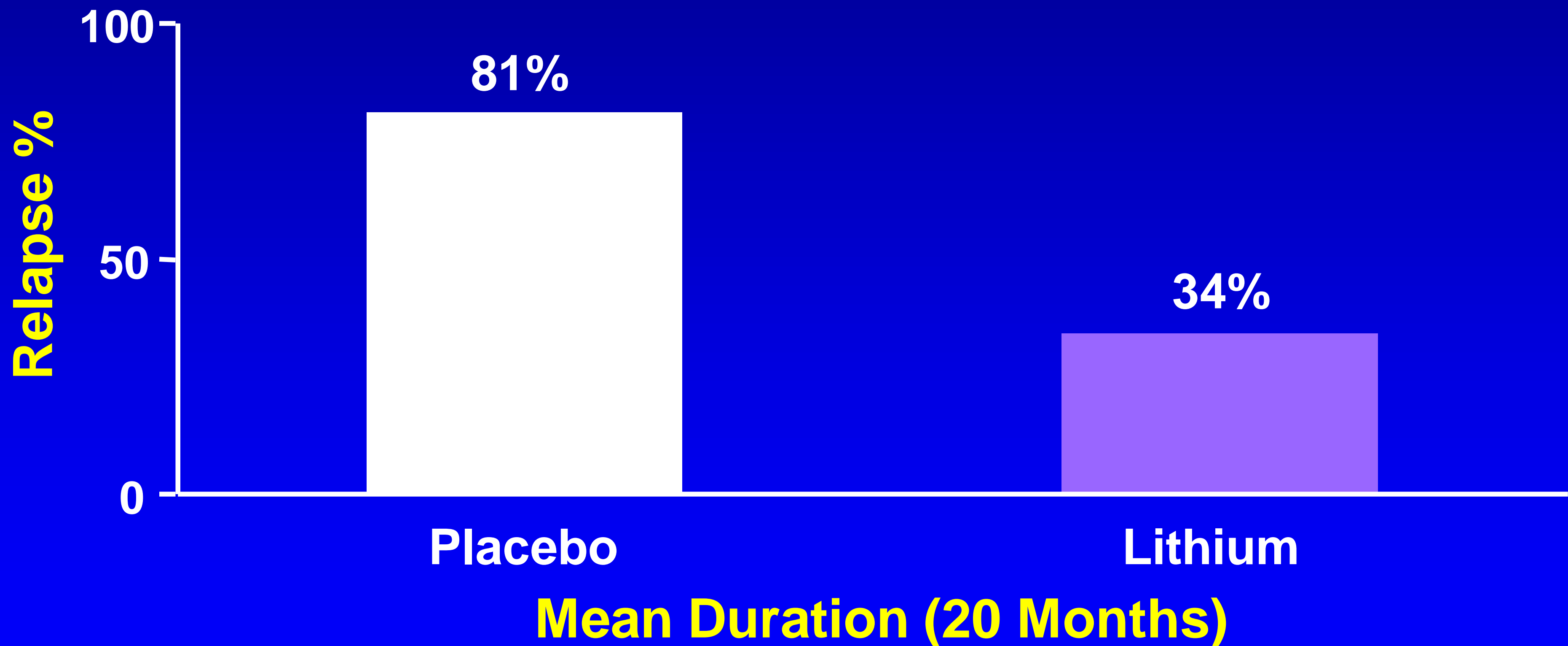
Lithium-1974
Lamotrigine-2003
Olanzapine-2004**
Aripiprazole-2005
Quetiapine-2008*
Risperidone L-A injection-2009**
Ziprasidone-2009*

**Approved for monotherapy and adjunctive to lithium and valproate
*Approved only as adjunct to lithium or valproate

Lithium

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

Tondo et al. BJP 2001;178(suppl 41):184-190

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

Gedddes et al. Am J Psychiatry 2004;161:217-222

Lithium + Valproate Combo vs. Monotherapy for Bipolar I Maintenance (BALANCE*)

- 41 sites (UK, France, Italy, USA)
- 4-8 week run-in on Li+VPA, then open-label randomized to Li (n=110), VPA (n=110) or combo (n=110)
- Follow-up: Up to 2 years
- Primary outcome: New intervention for mood episode

Lancet. 2010;375:385-395

*BALANCE= Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation

Lithium + Valproate Combo vs. Monotherapy for Bipolar I Maintenance (BALANCE*)

- Primary outcome event: Li+VPA 54%
  Li 59%
  VPA 69%
- Li+VPA > VPA (NNT=7, p=0.0014)
- Li+VPA = Li (NNT=19, p=0.23)
- Li > VPA (NNT=10, p=0.0472)

*BALANCE= Bipolar Affective disorder: Lithium/ANtiConvulsant Evaluation

Lancet. 2010;375:385-395

Lithium + Valproate Combo vs. Monotherapy for Bipolar I Maintenance (BALANCE*)

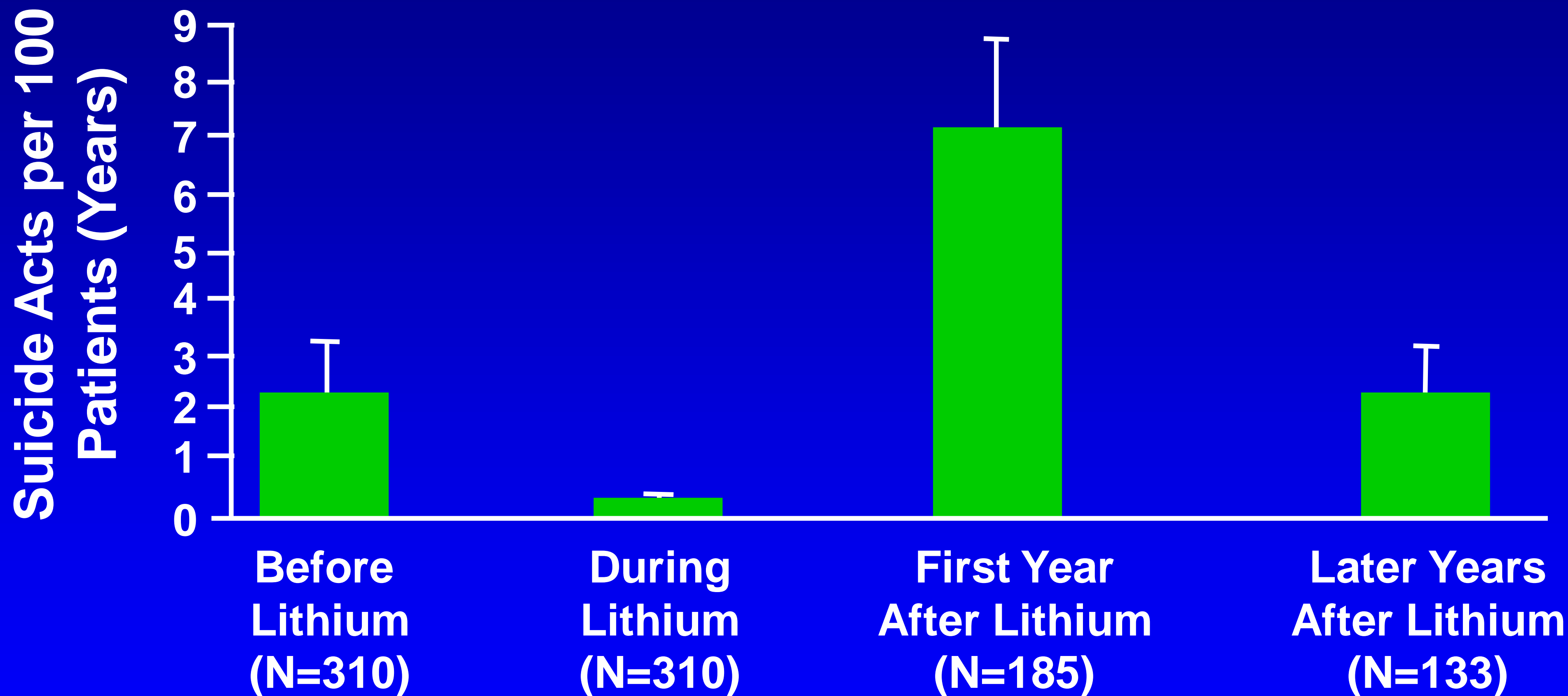
- New Rx for mania: Li+VPA 27%
  Li 36%
  VPA 45%
- New Rx for depression: : Li+VPA 35%
  Li 32%
  VPA 45%
- Results suggest Li+VPA or Li preferred over VPA

Lancet. 2010;375:385-395

The BALANCE bottom line:

Both lithium alone and lithium plus valproate more likely to prevent Bipolar I relapse than valproate alone

Lithium and Suicidal Behavior



Tondo et al. JCP 8/98

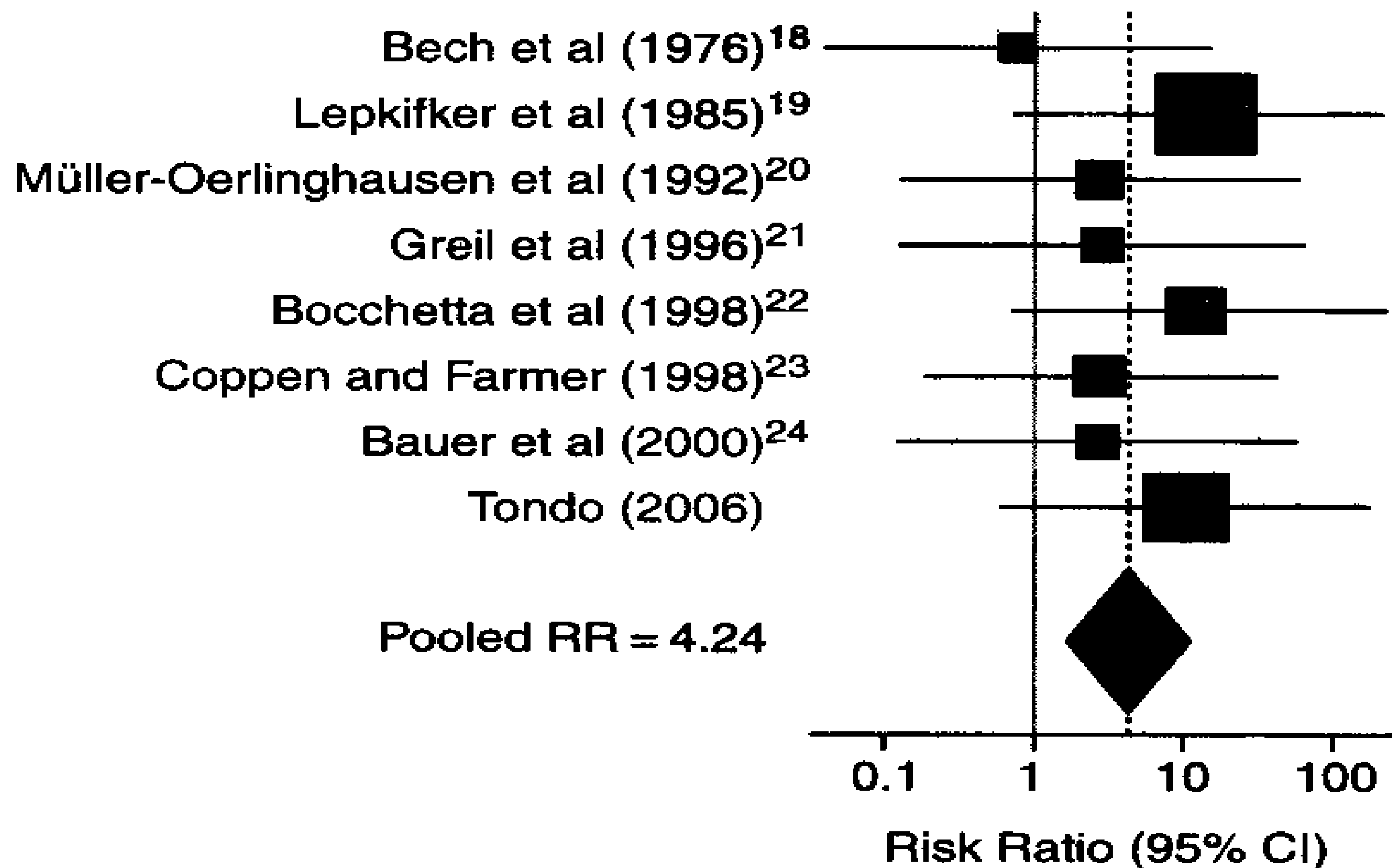
Lithium Effective in Preventing Suicide, Deliberate Self-Harm, and Death from All Causes in Mood Disorder Patients (systematic review of randomized trials)

- **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

Cipriani et al. Am J Psychiatry 2005;162:1805-1819 (Oct)

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



88.5% risk reduction with vs. without lithium

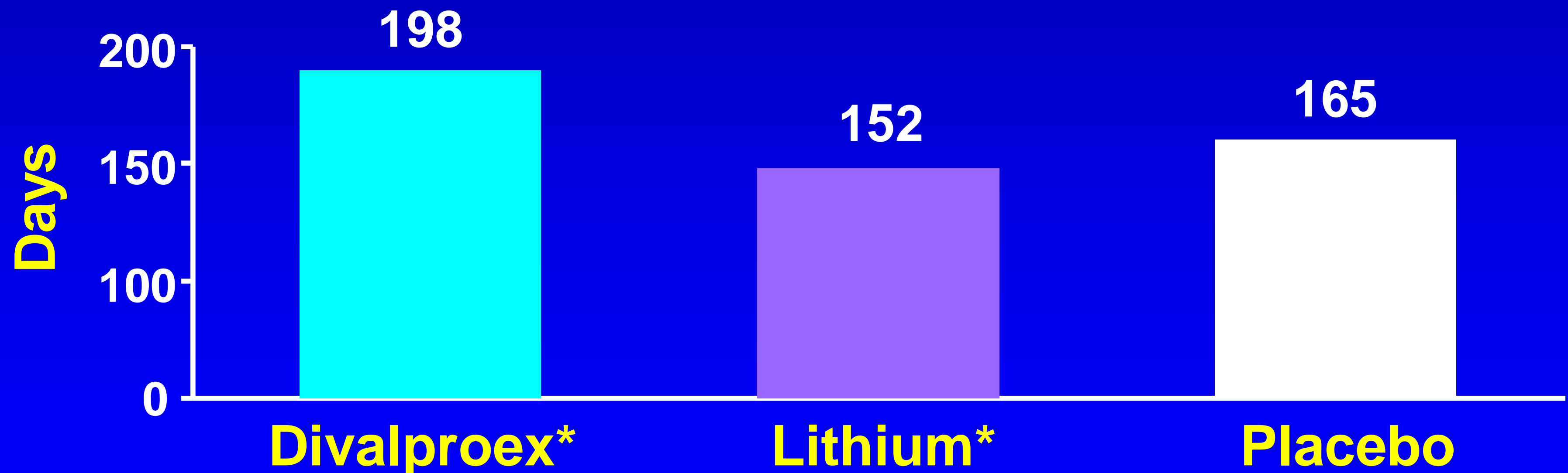
Guzzetta, et al.: J Clin Psychiatry 2007;68:380-383

Divalproex

Divalproex: 12-Month BP I Maintenance

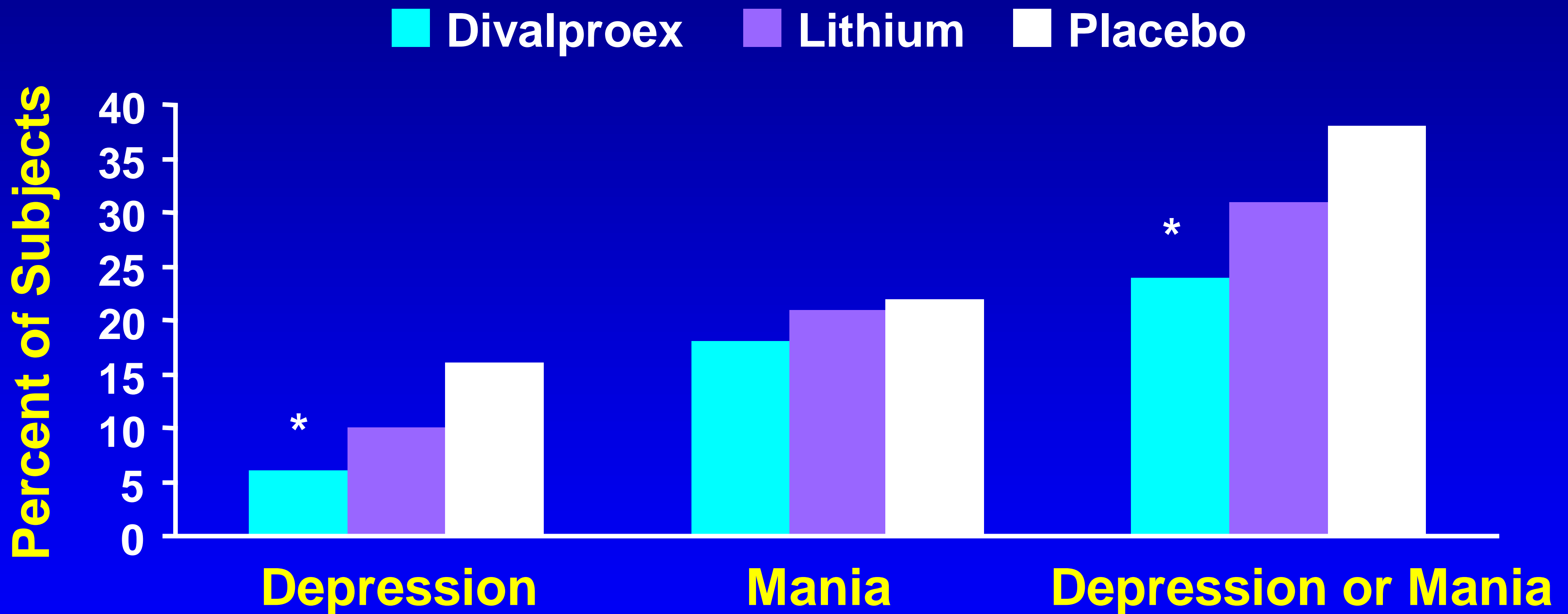
Entry After Index Manic Episode

- 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
  - Li n=10
  - DVPX n=10

Findling et al., J Am Acad Child Adolesc Psychiatry 2005;44:409-417

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%)

Findling et al., J Am Acad Child Adolesc Psychiatry 2005;44:409-417

Lamotrigine

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

Estimated % of pts intervention-free*

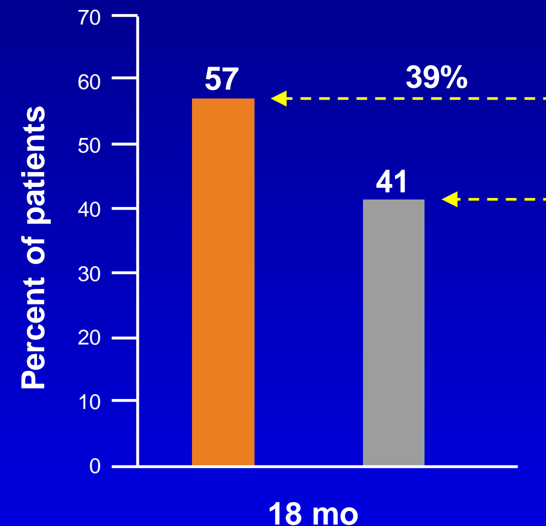
100
90
80
70
60
50
40
30
20
10
0

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18

Month

Lamotrigine 100-400 mg (n=223)
Placebo (n=188)

LTG vs PBO, *P*=0.009

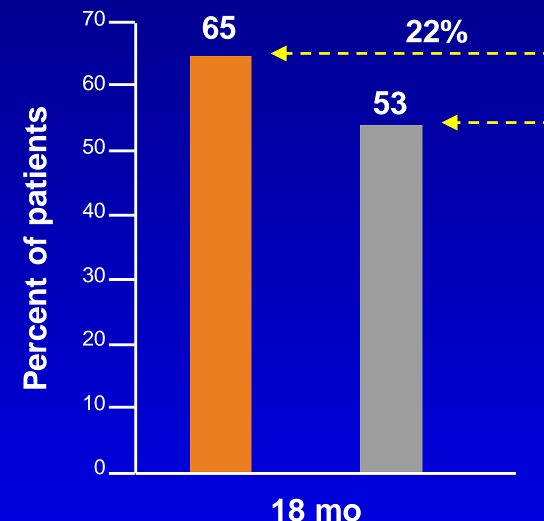


* Some patients considered intervention-free for depressive episodes could have had intervention for manic episodes.

Data on file, GlaxoSmithKline.; Goodwin et al., J Clin Psychiatry 65:432-441, 2004

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

Estimated % of pts intervention-free*
100
90
80
70
60
50
40
30
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
Month
Lamotrigine 100-400 mg (n=223)
Placebo (n=188)
LTG vs PBO, *P*=0.034



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

Data on file, GlaxoSmithKline.; Goodwin et al., J Clin Psychiatry 65:432-441, 2004

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

Lamotrigine for Bipolar Maintenance 18-Month Completion Rates

• **Lamotrigine**	**14.6%**
• **Lithium**	**12.6%**
• **Placebo**	**6.3%**

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

Lamotrigine vs. Lithium for Bipolar I Maintenance (randomized, open-label, DUAG*-6 Trial, n=155)

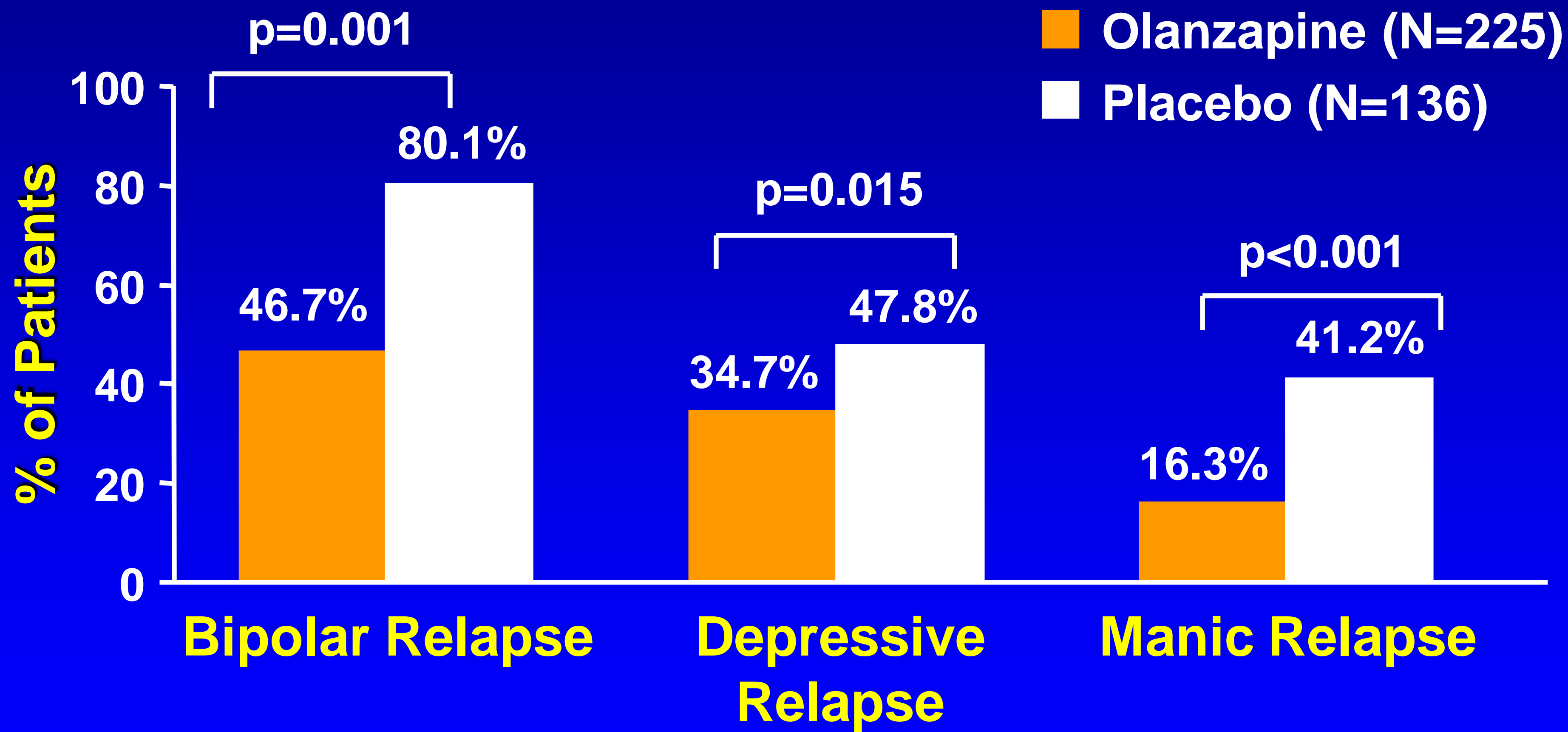
- Li, n=78, 0.5-1.0 mmol/l; LTG, n=77, 400 mg max
- No significant difference in effectiveness (trend favored Li for mania, LTG for depression)
- LTG better tolerated, but no effect on outcome
- Almost no patients maintained successfully on monotherapy with either drug!

*DUAG-Danish University Antidepressant Group

Licht et al. Bipolar Disorders 2010;12;483-483

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

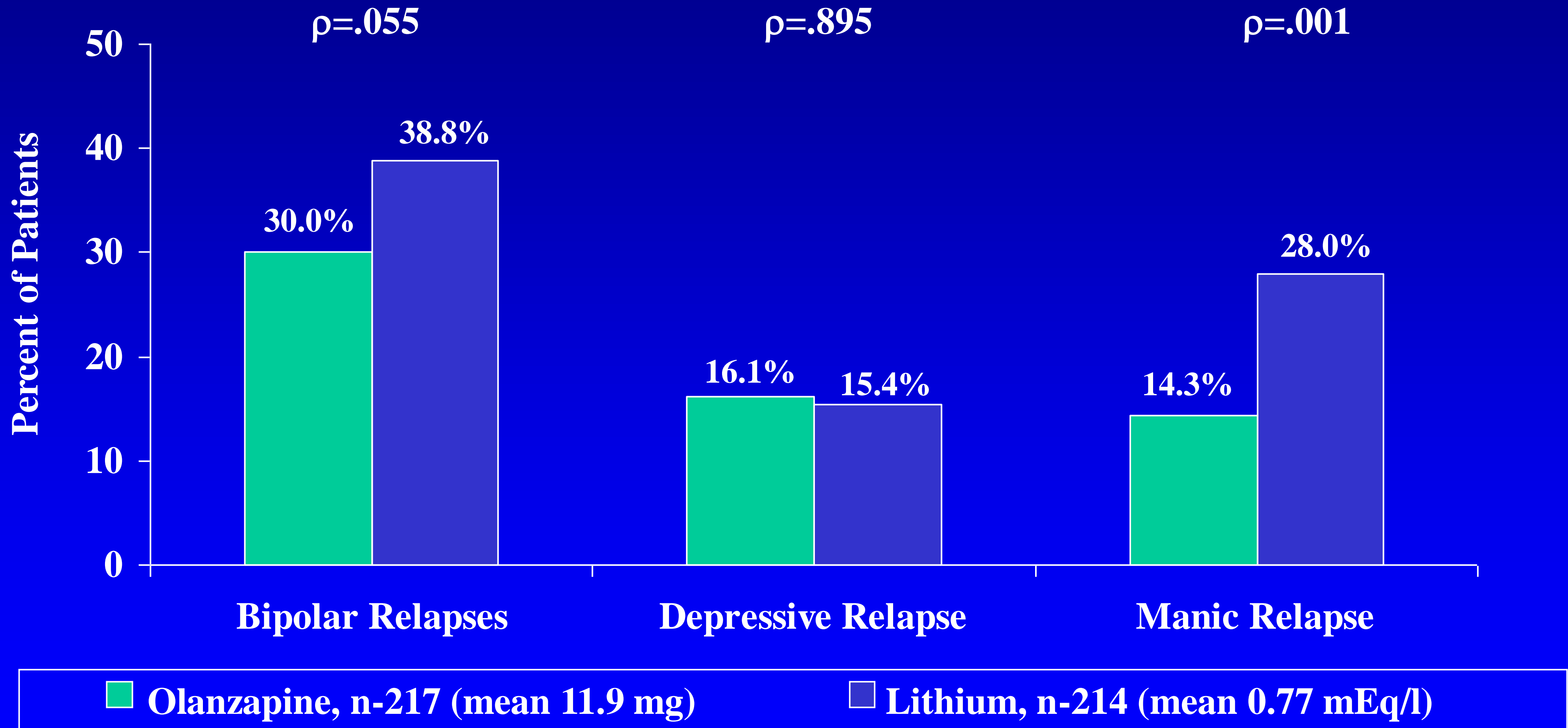
Olanzapine	21.3%
Placebo	6.6%

- Weight gain ≥7%

Open-label acute	35%
Double-blind maintenance	
-Olanzapine	17.7%
-Placebo	2.2%

Tohen et al., Am J Psychiatry 2006;163:247-256

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



Tohen et al. ACNP 12/02; Tohen et al., Am J Psychiatry 2005;162:1281-1290 (July)

Bipolar I Maintenance: One Year Olanzapine vs. Lithium

Weight gain ≥ 7%

- **Open-label: 6-12 weeks**

OLZ + Li	27.8%

- **Double-blind: 1 year**

OLZ	29.8%
Li	9.8%

Tohen et al,. Am J Psychiatry 2005;162:1281-1290 (July)

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	

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

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)

Tohen et al., Br J Psychiatry 184:337-345, 2004

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: QTP 20.3%**
  Placebo 52.1%

*mean median daily dose 519 mg

Suppes et al. Am J Psychiatry 2009;166:476-488

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: QTP 18.5%**
  Placebo 49.0%

*mean median daily dose 497 mg

Vieta et al. J Affective Disorders 2008;109:251-263

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 ≥ 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 ↓ risk of depressive events

Weisler et al. Poster 35. Psychiatric Services, Chicago 10/2-5/2008

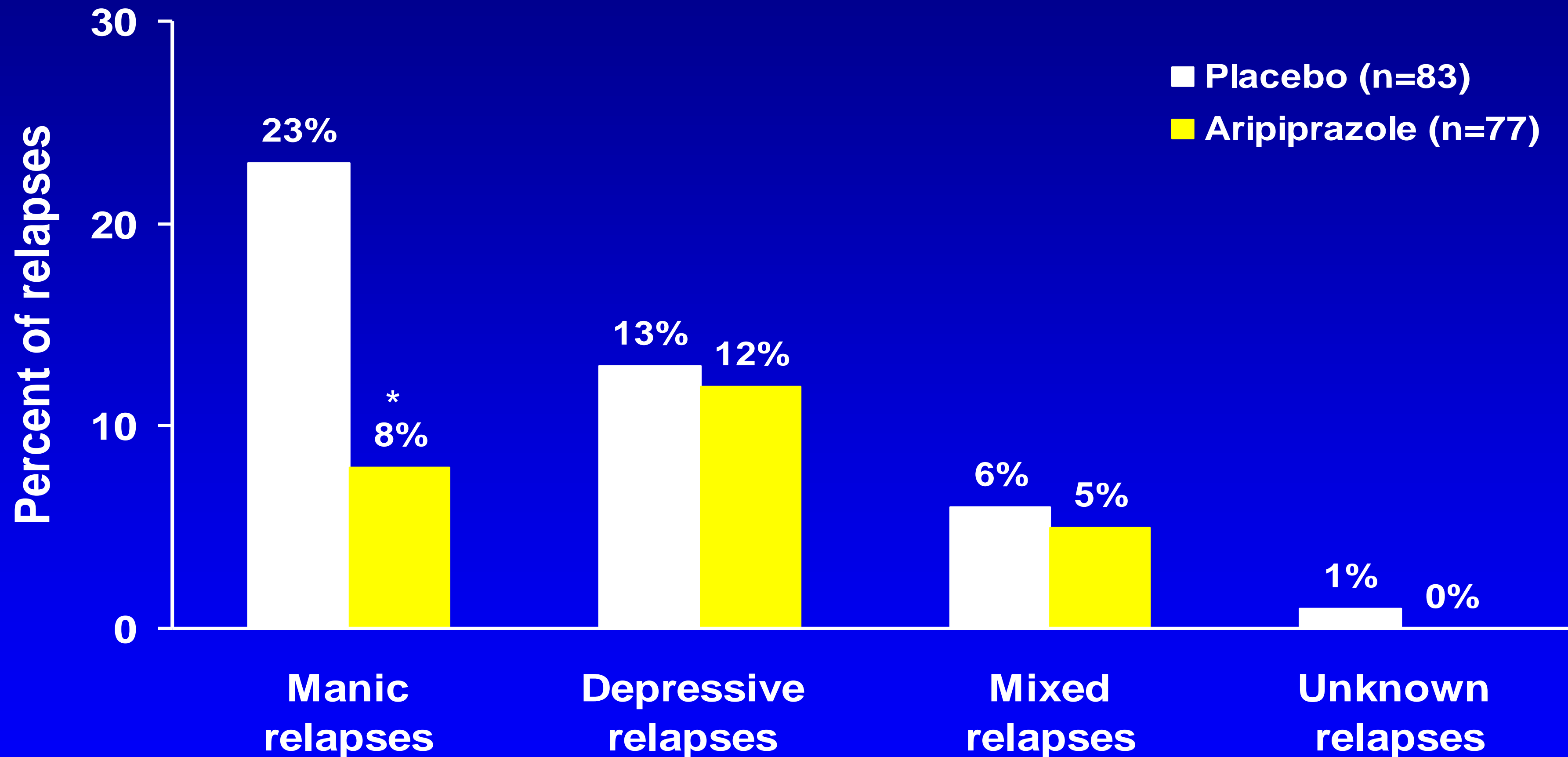
Aripiprazole

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

Package insert-March 2005

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

Keck et al., J Clin Psychiatry 2007;68:1480-1491

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

Package insert, May 2009

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

Quiroz et al. APA San Francisco, NR4-092 poster, 16-20 May 2009

Risperidone Long-Acting Injection for Bipolar I Maintenance: Adjunctive (≥4 episodes in past year)

- 16-week, open-label stabilization, TAU+RIS-LA n=240
- 51.7% (n=124) stable at least 4-weeks randomized to double-blind for 52-weeks
- Time to relapse: RIS > PBO ($p=0.01$)
- Relapse rates: RIS 23.2%, PBO 45.8%
- Completion: RIS 60% (39/65), PBO 42.4% (25/59)

Macfadden et al. Bipolar Disorders 2009;11:827-839

Ziprasidone

Ziprasidone or Placebo with Lithium or Divalproex for Bipolar I Maintenance

- Open-label ZIP (80 to 160 mg/day) + Li or DVPX (n=584) until 8 weeks of stability (AE drops 24.8%)
- 6-month double-blind ZIP (n=127) or placebo (n=113) with Li or DVPX
- Time to any mood event: ZIP>placebo (p=.0104)
- Intervention for mood event: ZIP 19.7%
  PBO 32.4%

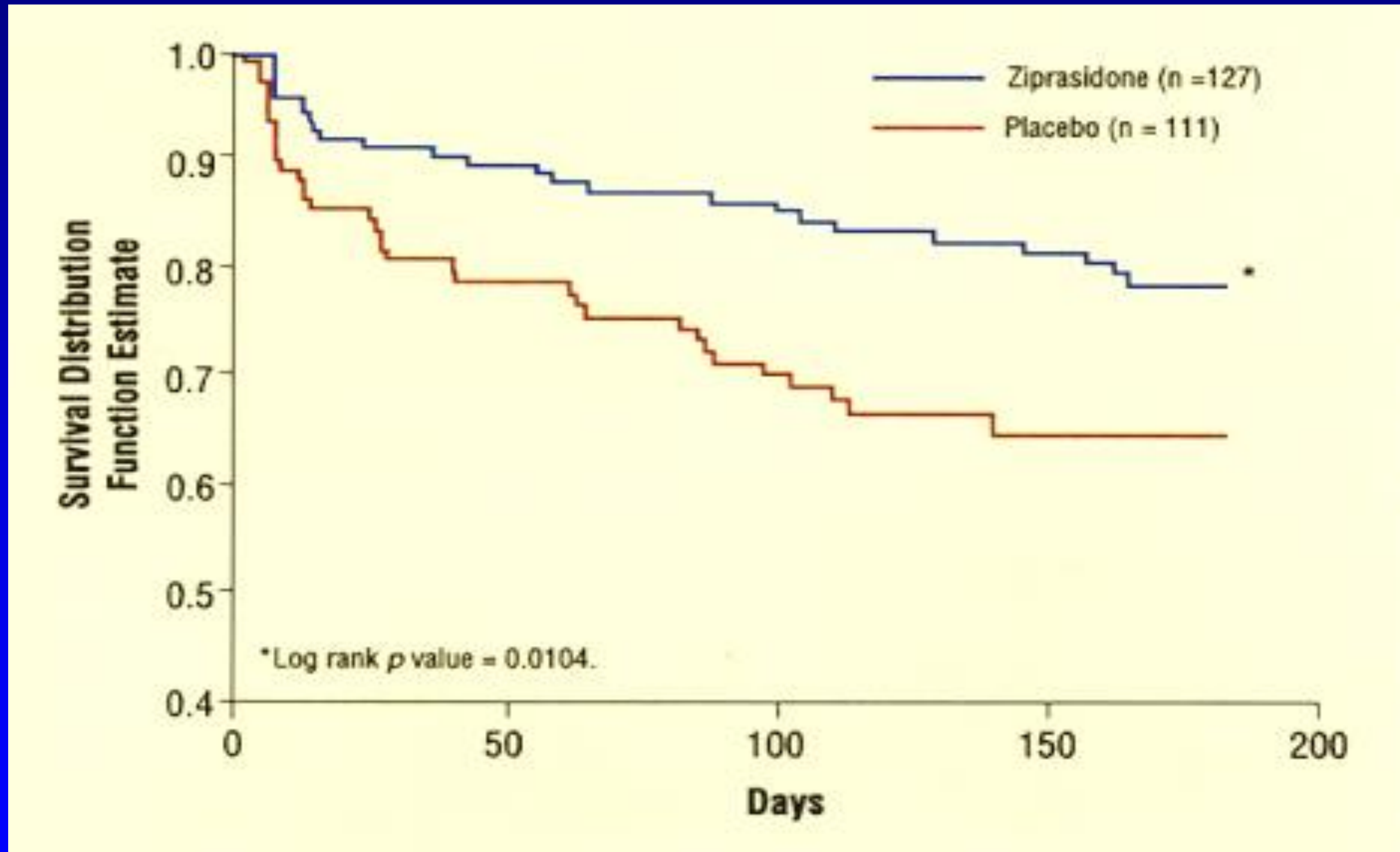
Bowden et al. J Clin Psychiatry 2010;71:130-137

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%

Vieta et al. Eur Psychiatry 2009;24(suppl 1):S594 (poster 17th EPS Congress 1/09)

Ziprasidone or Placebo with Lithium or Divalproex for Bipolar I Maintenance



Karayal, et al.: NCDEU Poster II-18. Hollywood FL 6/29-7/3/09

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]
- 24-month: RIS L-A inj. (46.8%), PBO (20.8%)[6]

[1]Marcus et al., ACNP, Dec 2003; [2]Tohen et al., Am J Psychiatry 2003;160:1263-1271;
[3]Tohen et al., APA, May 2003; [4]Tohen et al., Am J Psychiatry 2005;162:1281-1290
[5]Goodwin et al., J Clin Psychiatry 2004;65:432-441;
[6]Quiroz et al. APA San Francisco, NR4-092 poster, 16-20 May 2009

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 <u>not</u> 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