Bipolar Disorders: Therapeutic Opportunities

James Jefferson, M.D.

Pre-Lecture Exam
Question 1

1. **A patient with recurrent hypomanic episodes and major depressive episodes would be classified in DSM-IV with which diagnosis?**

A. Cyclothymic Disorder
B. Bipolar Disorder Not Otherwise Specified
C. Bipolar I Disorder
D. Bipolar II Disorder

Question 2

2. Features of rapid cycling bipolar disorder include all of the following <u>except</u>:

A. At least 4 episodes/year
B. More common in men
C. May be induced by antidepressants
D. May not persist

Question 3

3. Which one of the following predicts a good treatment response to lithium?

A. Mixed episodes
B. Depression-mania-euthymia course
C. Euphoric mania
D. Rapid cycling

Question 4

4. All of the following are FDA-approved for treating acute mania except:

A. Chlorpromazine
B. Carbamazepine
C. Olanzapine
D. Divalproex

Question 5

5. Which one of the following is likely to lower serum lithium levels?

A. Hydrochlorothiazide
B. Ketoprofen
C. Captopril
D. Theophylline

Question 6

6. Valproate shares all of the following side effects within lithium except for:

A. Tremor
B. Hepatic dysfunction
C. Weight gain
D. GI disturbance

Question 7

7. Which one of the following is characterized by no protein binding, no metabolism, and no important drug interactions?

A. Gabapentin
B. Lamotrigine
C. Topiramate
D. Tiagabine

Question 8

8. Which one of the following has been shown to be more effective than placebo as monotherapy for Bipolar I depression?

A. Gabapentin
B. Lamotrigine
C. Topiramate
D. Valproate

Question 9

9. Blood levels of lamotrigine are doubled by which one of the following?

A. Carbamazepine
B. Gabapentin
C. Lithium
D. Valproate

Question 10

10. Kidney stones can be a side effect of which one of the following?

A. Valproate
B. Lithium
C. Lamotrigine
D. Topiramate

Bipolar Disorders

DSM-IV

- **Bipolar I disorder**
  - **Hypomanic, manic, mixed, depressed, unspecified**
- **Bipolar II disorder**
- **Cyclothymic disorder**
- **Bipolar disorder NOS**

Mixed Bipolar Episode

DSM-IV

- **Criteria for** both **a major depressive episode and a manic episode**
- **For at least 1 week**

Bipolar II Disorder
DSM-IV

- **At least**
  - **1 hypomanic episode**
  - **1 major depressive episode**
- Never **manic or mixed**
- **Distress or impairment**

Cyclothymic Disorder

DSM-IV

- Many hypomanic and depressive periods
- At least 2 years (1 in children)
- No major depressive, manic or mixed episodes (first 2 years)

Mania Due to a General Medical Condition

- Central nervous system
  - Head trauma
  - Tumor
  - Epilepsy
  - Multiple sclerosis
- Infection (AIDS and other)
- Endocrine (hyperthyroidism)
- And many more

Substance-Induced Mania

- Steroids
- Stimulants
- Sympathomimetics
- Dopamine agonists
- And many more

Rapid-Cycling Bipolar Disorder

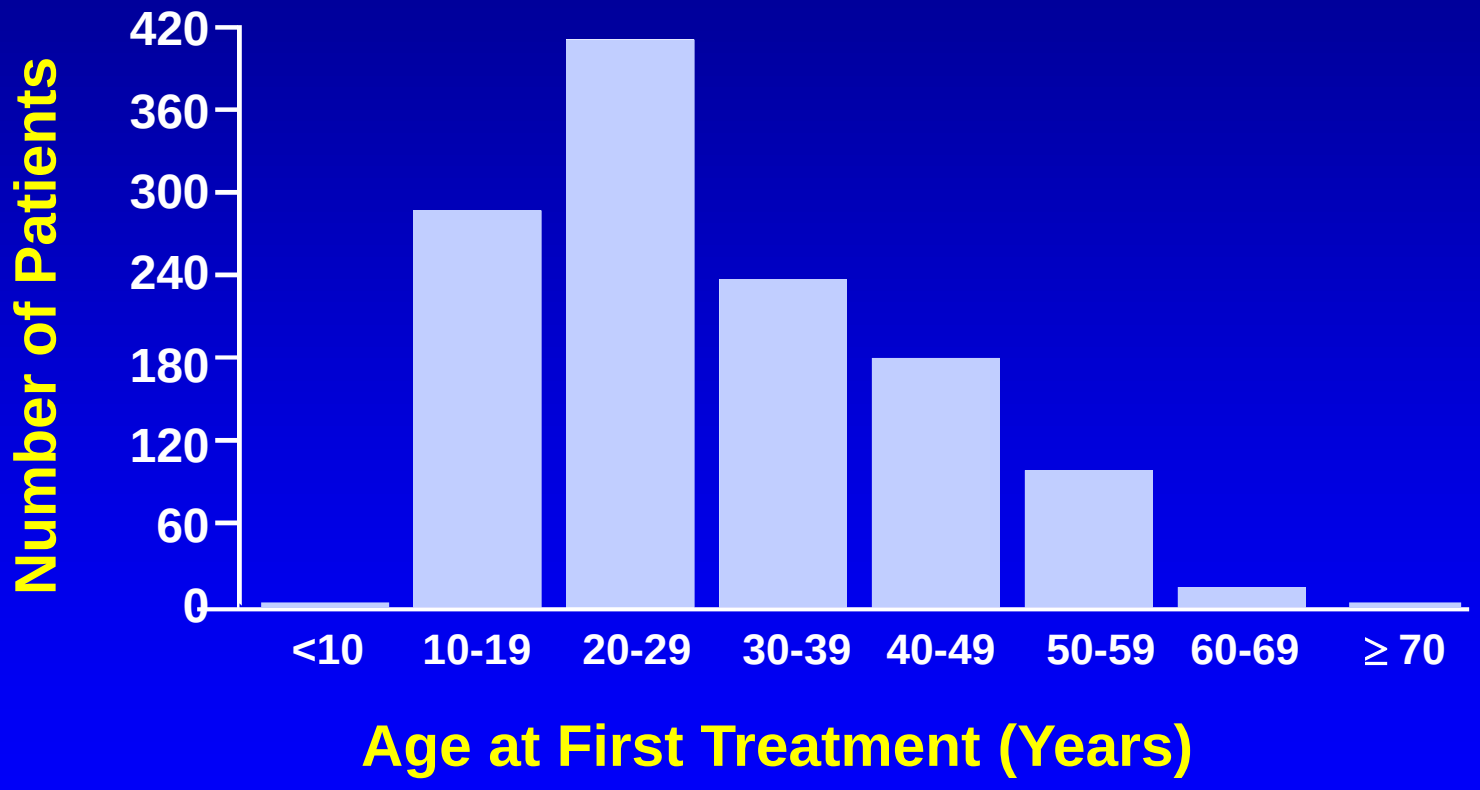
- At least 4 episodes per year
- Initial onset or later onset
- More common in women
- More thyroid abnormalities
- Role of antidepressants
- May not persist

Bipolar Epidemiology

- **Lifetime prevalence (adults)**
  - **Bipolar I** **0.8-1.6%**
  - **Bipolar II** **0.5-5.5%**
  - **(Both may be underestimates)**
- **Age of onset**
  - **Mean age** **21 years**
  - **Peak age** **15-19 years**
- **Gender**
  - **Bipolar I** **male = female**
  - **Bipolar II** **female > male**

Age at First Treatment (Pooled Data)

N=1,304



Modified from: Goodwin FK, Jamison KR. Manic-Depressive Illness, New York: Oxford University Press; 1990, p.132

Child and Adolescent Bipolar Disorder

- Onset before age 12 — Uncommon
- Diagnostic criteria — Same as in adults
- Atypical features — Common
- Comorbidity — Common
  - ADHD
  - Conduct disorder
  - Substance abuse

Bipolar Disorder Have Serious Consequences

- Impaired functioning
- Disrupted relationships
- Increased mortality (2-2.5 times)
- High suicide rate (19%)
- Financial disasters
- Alcohol and other substance abuse

Lifetime Prevalence of Substance Dependence/Abuse

ECA Study

- **Bipolar I** **61%**
- **Bipolar II** **48%**
- **Major depression** **27%**

JAMA. 1990 (Nov. 21)

Bipolar Disorder and Substance Use

Course of Illness

- More mixed episodes[1]
- Earlier onset[2]
- More frequent episodes[3]
- More comorbidity[4]
- Slower symptom remission[5]

[1]Sonne et al, 1994; Keller et al, 1986; Goldberg et al, 1997; Himmelhoch et al, 1976
[2]Sonne et al, 1994; Dunner & Feiner, 1996; Sokolski et al, 1994
[3]Sonne et al, 1994; Haywood et al, 1995
[4]Sonne et al, 1994; Dunner & Feiner, 1996
[5]Goldberg et al, 1997; Keller et al, 1986

Long-Term Prophylaxis in Bipolar I Disorder

- After 2 manic episodes — Always
- After 1 manic episode if: — Usually
  - Very severe or
  - Strong family history
- After 1 manic episode — Sometimes

Expert Consensus Guideline. J Clin Psychiatry. 1996;57(suppl 12A)

General Treatment Principles

- Confirm diagnosis
- Obtain longitudinal history
- Assess risk (e.g., suicide)
- Manage comorbidity
- Involve significant others

General Treatment Principles

- Psychosocial interventions
- Pharmacologic interventions
- Promote education
- Enhance compliance

Choice of Medication(s)

- Phase of illness
- Prior response and tolerability (including family
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient preferences

Polypharmacy is Not a Bad Word

- Monotherapy is the exception
- Combination therapy is effective
- Increased risk of side effects and drug interactions

“Many mad people, who have attempted to destroy themselves by cutting their throats... have been cured by the profuse haemorrhages.”

Benjamin Rush, Remedies for mania, 1812

Blood-letting for Mania

- It should be copious on the first attack
  – 20 to 40 ounces
- The effects are wonderful in calming mad people
- The quantity drawn should be greater than for any other organic disease

Benjamin Rush, 1812

Acute Mania

FDA-Approved

- 1970 Lithium
- 1973 Chlorpromazine
- 1995 Divalproex
- 2000 Olanzapine

First Manic Episode
Preferred Initial Strategies

- **Psychotic mania**
  - **Mood stabilizer + antipsychotic**
- **Euphoric, dysphoric or mixed mania**
  - **Mood stabilizer**
- **Hypomanic**
  - **Mood stabilizer**

Expert Consensus Guidelines. Post Grad Med 4/00

Acute Mania: First-Line

- **Severe**
  - **Li or DVPX + antipsychotic**
- **Less severe**
  - **Li or DVPX or antipsychotic**

APA Bipolar Guidelines, Revised 2002

“Some evidence suggests a greater efficacy of valproate compared with lithium in the treatment of mixed states.”

APA Bipolar Guidelines, Revised 2002

Atypical Antipsychotics for Mania

- Olanzapine (Zyprexa)*
- Aripiprazole (Abilify)
- Clozapine (Clozaril)
- Quetiapine (Seroquel)
- Risperidone (Risperdal)
- Ziprasidone (Geodon)

*FDA approved

All Antipsychotic Drugs Are Antimanic

Name one that isn't!

Divalproex vs. Olanzapine for Acute Mania

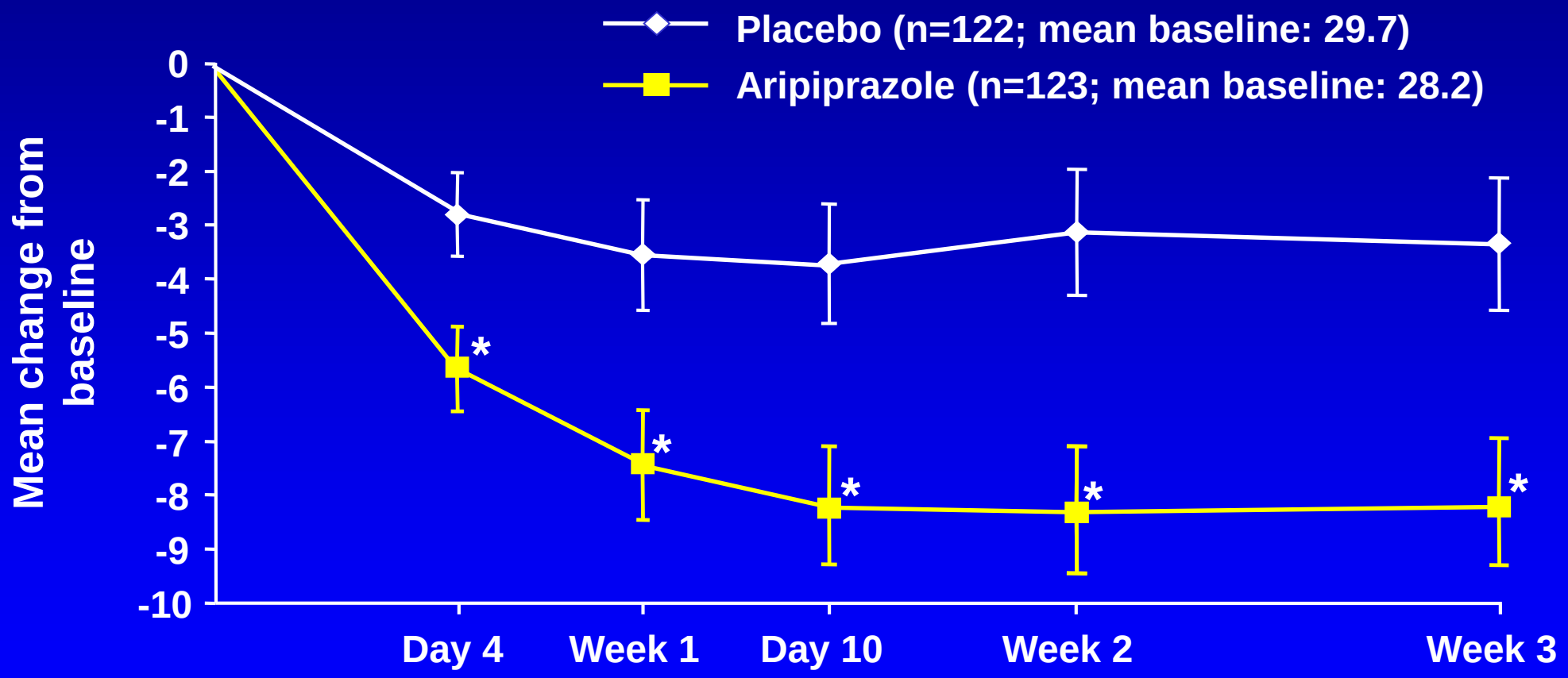
	Tohen et al., 2000		Zajecka et al., 2000	
Start	OLZ 15 mg DVPX 750 mg		OLZ 10 mg DVPX 20mg/kg/day	
MRS	OLZ DVPX	-13.4 -10.4 (p=.028)	OLZ DVPX	-17.2 -14.8 (n.s.)
↑ Weight	OLZ > DVPX		OLZ > DVPX	

Olanzapine for Acute Mania
(pooled analysis – 2 studies)

- **Response (≥ 50% ↓ YMRS)** **55% (29.5%)**
- **Euthymia (YMRS ≤ 12)** **50% (27%)**
- **Remission (YMRS ≤ 7, etc.)** **18% (7%)**

Chengappa et al. Bipolar Disord 5:1-5, 2003

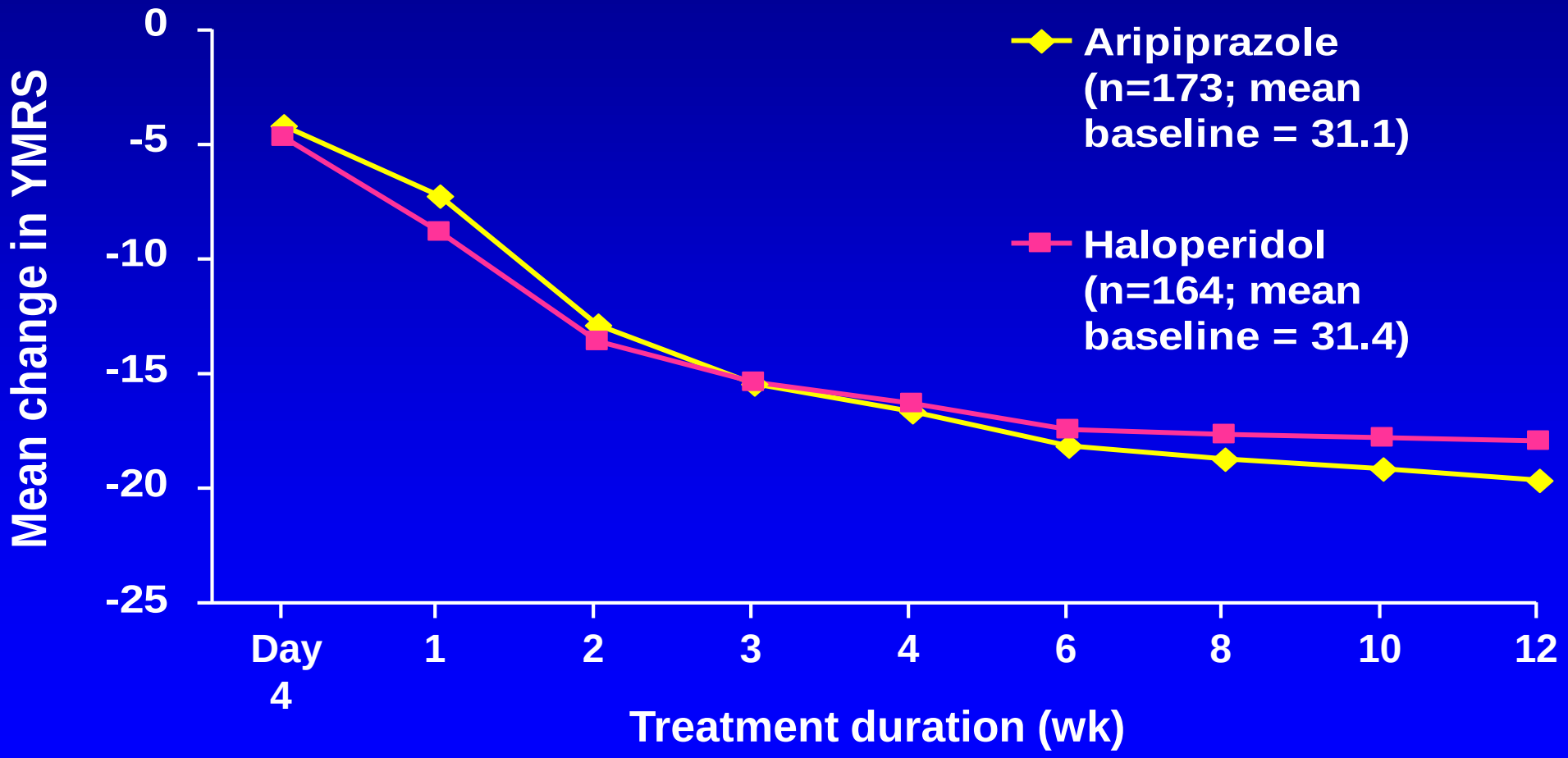
Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS



*P<0.01 vs placebo, last observation carried forward (LOCF) analysis.

Jody et al. *Int J Neuropsychopharmacol*. 2002;5(suppl 1):S57.

Aripiprazole (21.6mg) vs Haloperidol (11.1mg) Acute Mania Trial: Efficacy (LOCF)



Data on file.

Adjunctive Quetiapine for Adolescent Mania (6-week, double-blind, n=30)

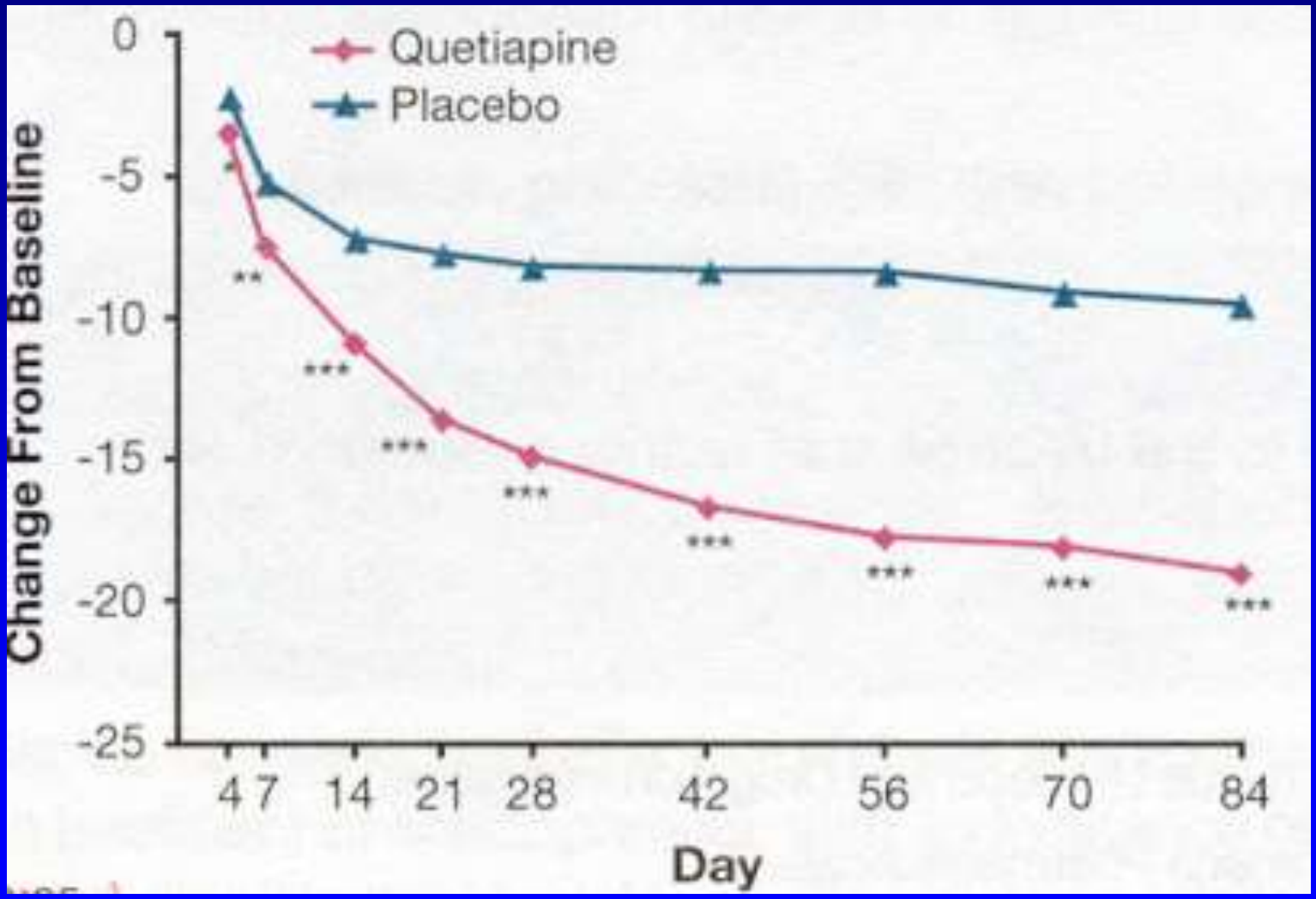
- **DVPX + quetiapine more effective than DVPX alone**
- **At least 50% ↓ in YMRS**

  quetiapine 87% $p = 0.05$

  placebo 53%

DelBello et al. J Am Acad Child Adolesc Psychiatry, Oct. 2002

Quetiapine vs. Placebo for Acute Mania (n = 403)



Jones et al., APA 5/03

Risperidone vs Placebo as Adjunct to Mood Stabilizer (Li, DVPX, CBZ) in Acute Mania

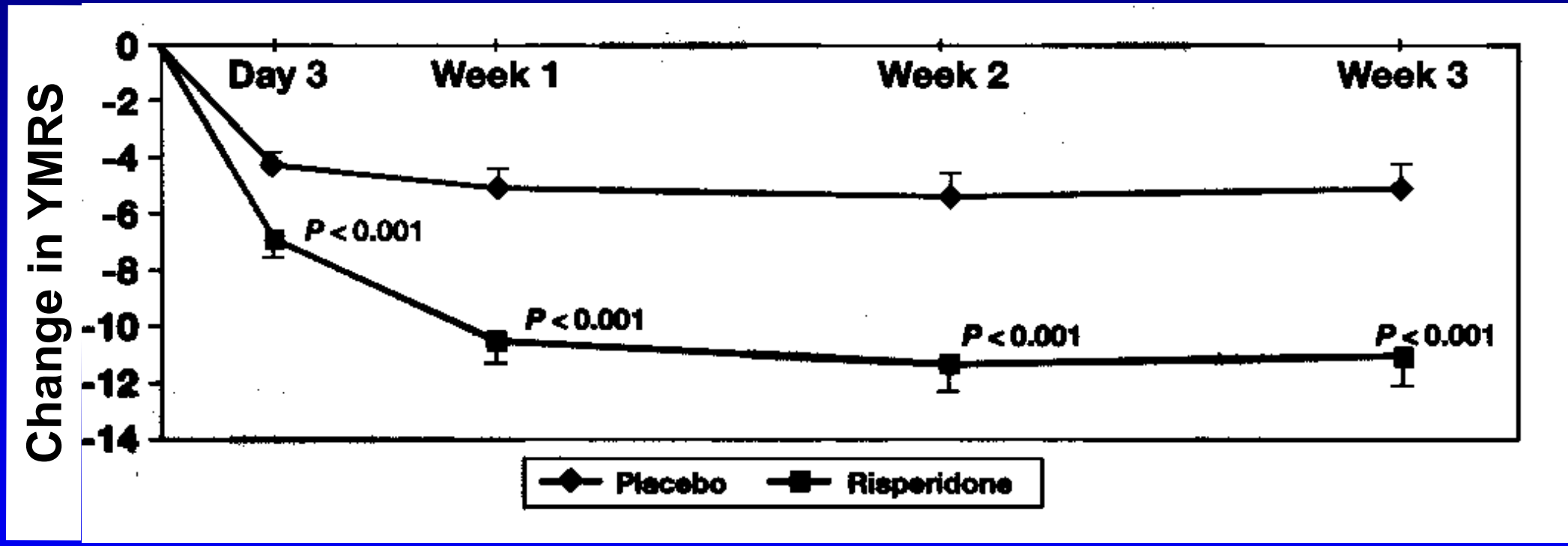
- **Response (≥ 50% ↓ YMRS)**

Risperidone	**59%**
Placebo	**41%**

- **Faster onset, too**
- **Mean modal dose 4 mg/day**

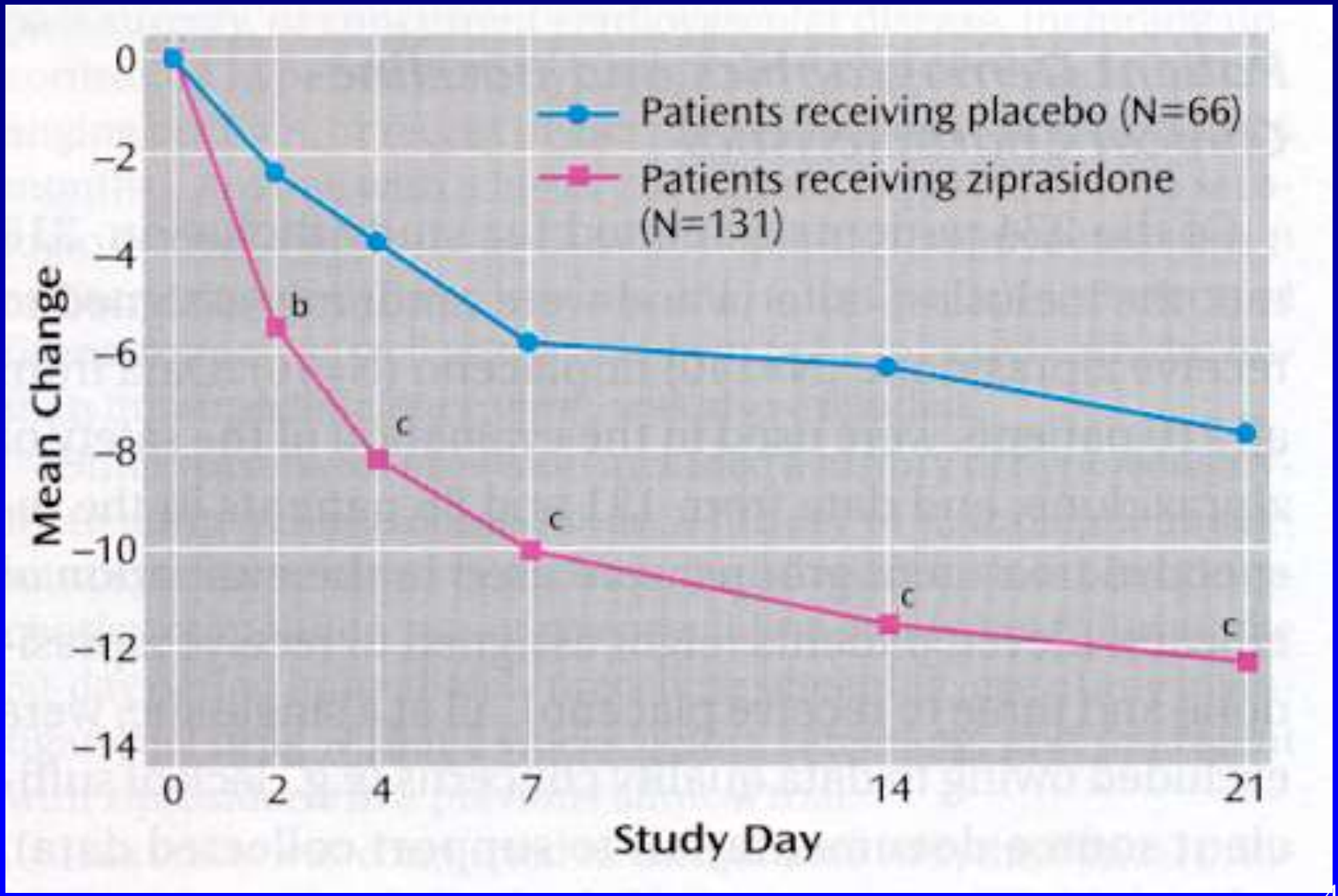
Yatham et al. Br J Psychiatry 182:141-147, 2003

Risperidone vs. Placebo For Acute Mania (n = 259)



Hirschfeld et al., APA 5/03

Ziprasidone for Acute Mania



Keck et al. Am J Psychiatry 160:741-748, April 2003

Mania Rating Scale

- For entry ≥ 14
- Endpoint reduction
  - Ziprasidone 12.4
  - Placebo 7.8

  $p < 0.005$
- Endpoint Score
  - Ziprasidone 14.6
  - Placebo 18.9

Keck et al. Am J Psychiatry 160:741-748, April 2003

Clozapine for Bipolar Disorder

- The ace in the hole
- Open label reports of benefit for mania, maintenance, and possibly depression
- No double-blind studies

Alphs and Campbell. Psychiatric Annals 32:722-729, Dec. 2002

Bipolar Major Depression

First Episode Bipolar Major Depression Without Psychosis – Preferred Initial Strategies

- **Mood stabilizer alone** - **Lithium*
Divalproex
Lamotrigine**
- **With antidepressant** - **Lithium*
Divalproex**
- **Preferred antidepressant** - **Bupropion
SSRI
Venlafaxine**

***Top choice**

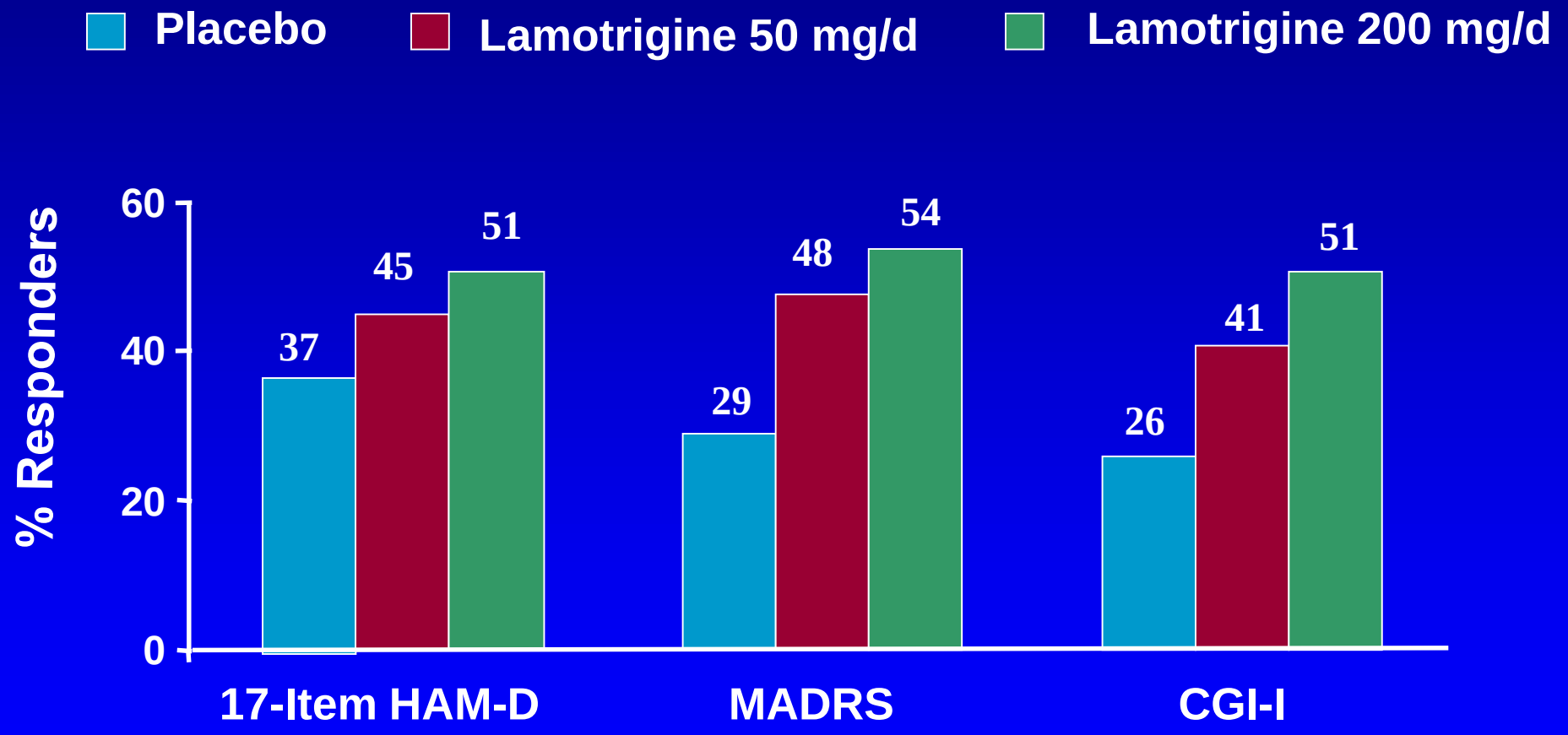
Expert Consensus Guidelines. Post Grad Med 4/00

Bipolar Depression

- First-line
  - Lithium or Lamotrigine
- Antidepressants
  - Monotherapy not advised
  - Use with mood stabilizer
  - Bupropion, paroxetine, others
- ECT, psychotherapy

APA Bipolar Guidelines, Revised 2002

Lamotrigine Monotherapy for Bipolar I Depression



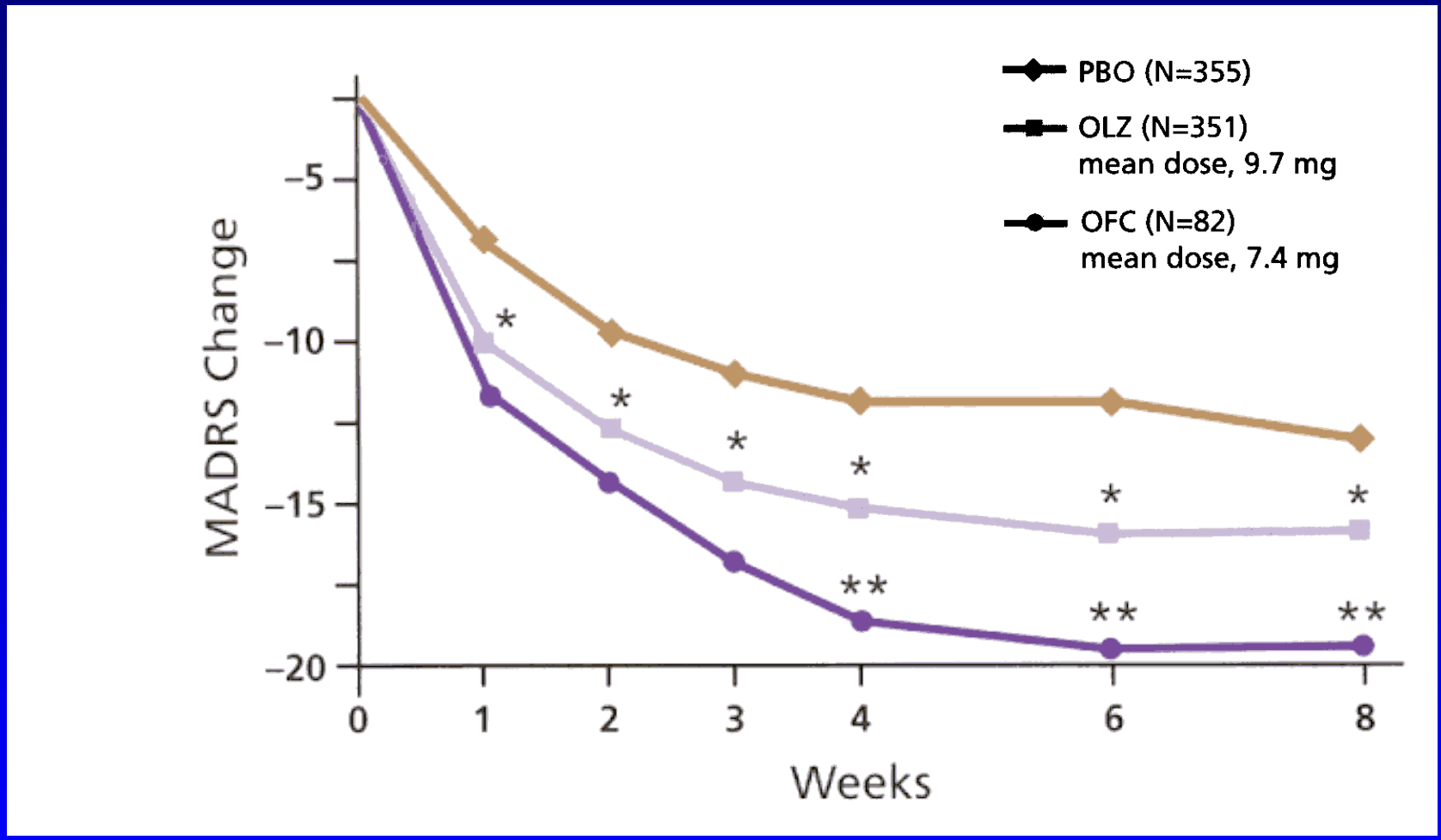
Calabrese et al. J Clin Psychiatry 2/99

Bipolar Depression: Olanzapine and OFC (8-week, double-blind, n=833)

- Olanzapine (n=370): 9.7 mg (mean)
  Dropouts 51.6%
- OFC (n=82):
  - Olanzapine 7.4 mg (mean)
  - Fluoxetine 25 mg
    Dropouts 36%
- Placebo (n=355)
  Dropouts 51.6%

Tohen et al. APA 5/02

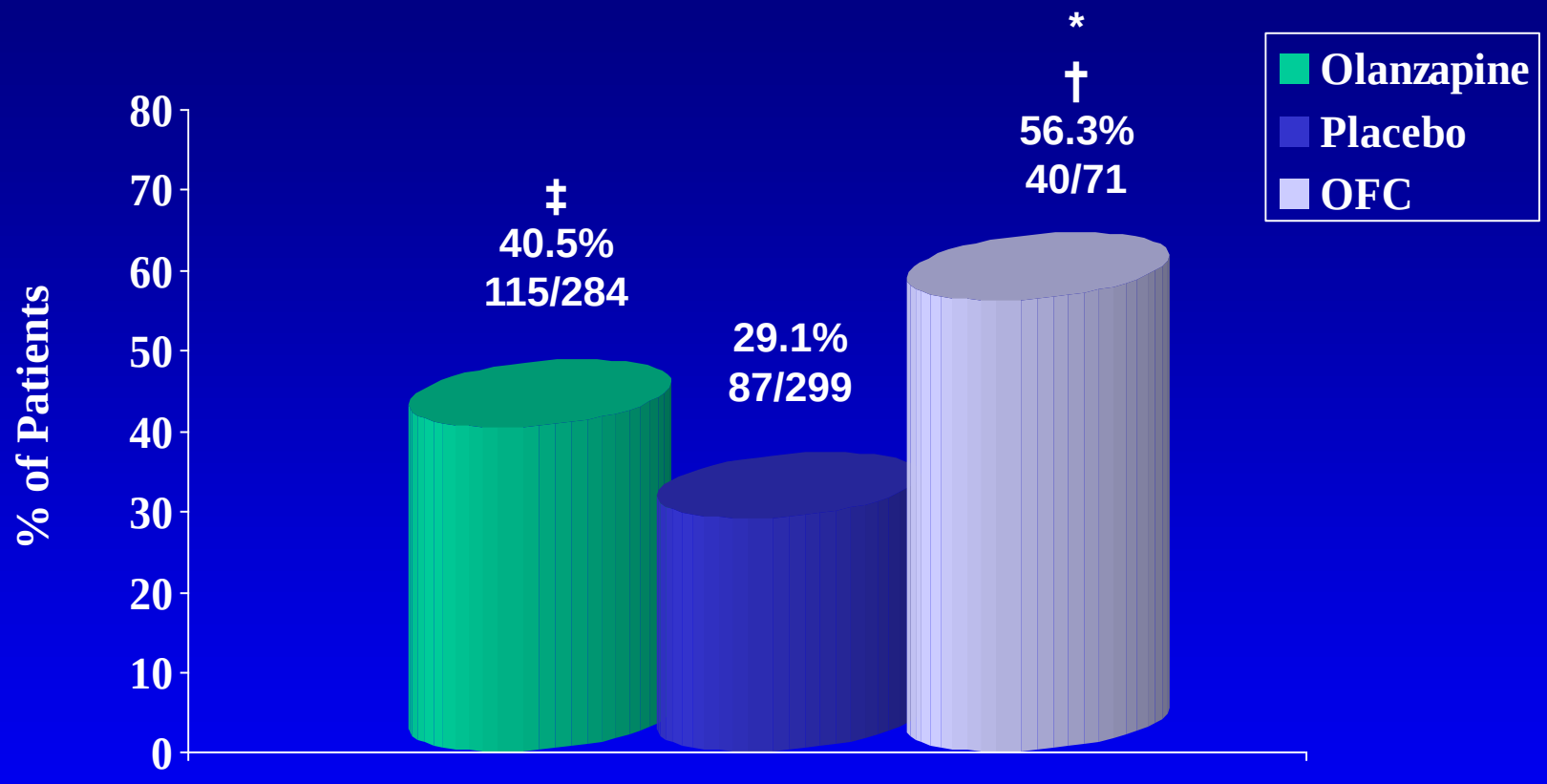
Olanzapine/OFC for Bipolar Depression



MMRM=Mixed Modal Repeated Measures,
OFC=Olanazapine-Fluoxetine Combination

Tohen et al. APA 5/02

Bipolar Depression: Remission

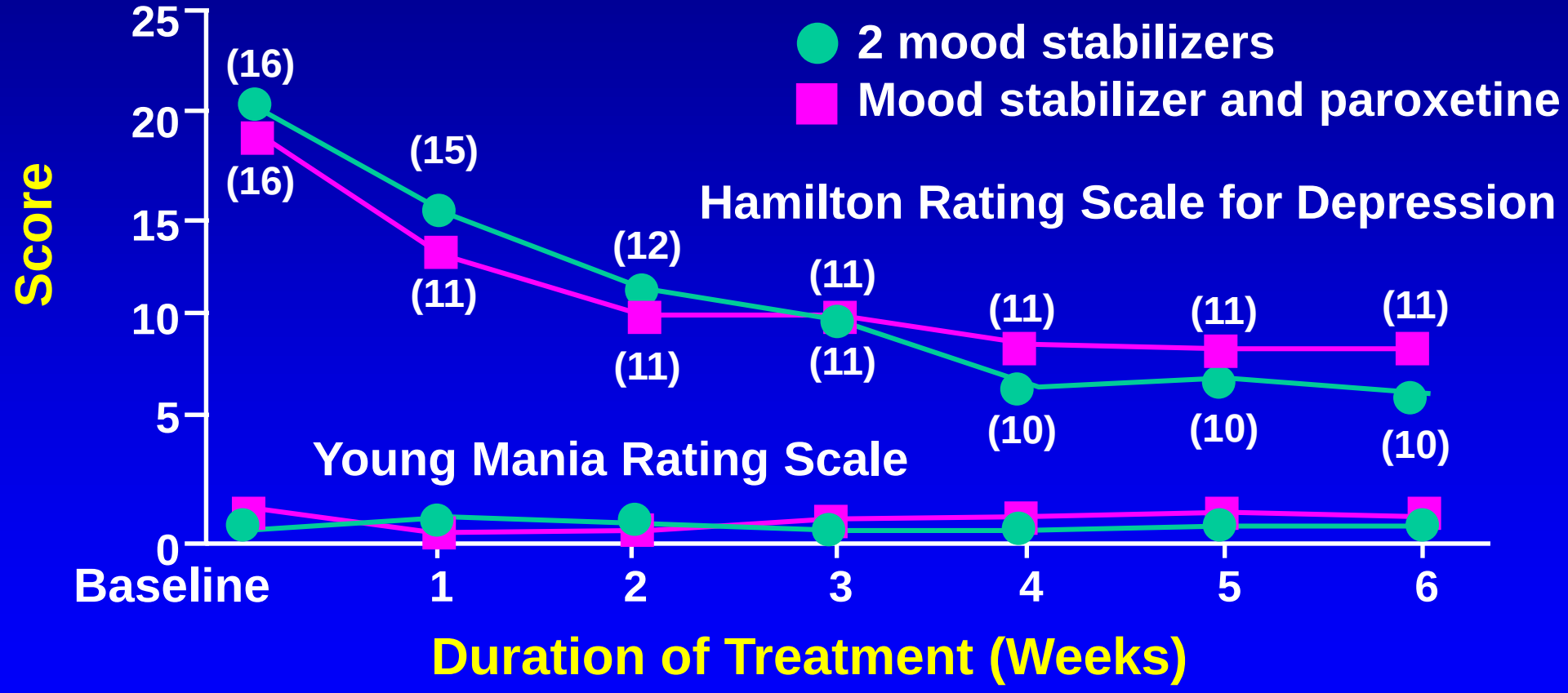


*ρ=.001: OFC vs placebo
†ρ=.012: OFC vs olanzapine
‡ρ=.027: olanzapine vs placebo

Tohen et al. APA 5/02

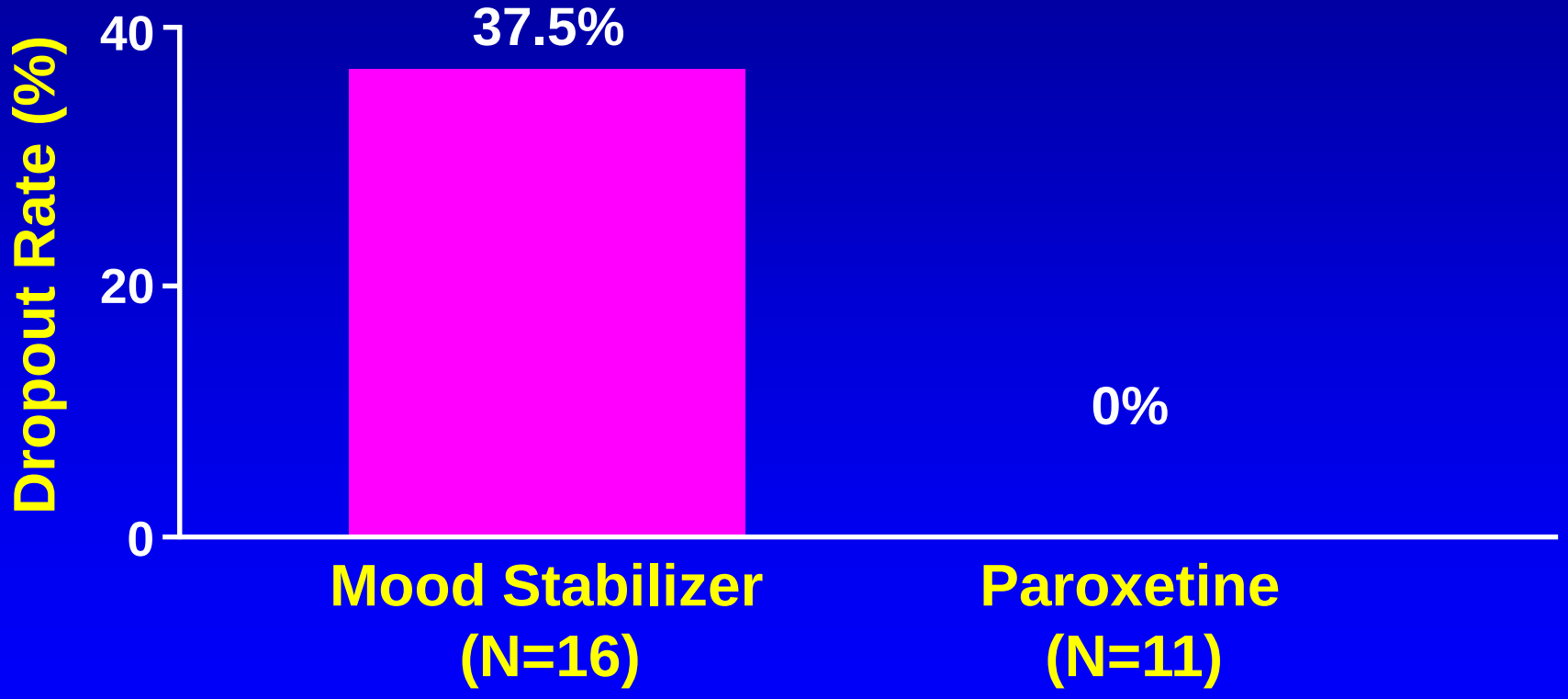
Breakthrough Bipolar Depression

Double-Blind



Young LT, Joffee RT, Robb JC, et al. Am J Psychiatry. 2000;157:124-126

Breakthrough Bipolar Depression on Lithium or Valproate (N=27)



Young LT, Joffee RT, Robb JC, et al. Am J Psychiatry. 2000;157:124-126

Bipolar Depression – Adding Bupropion SR or Topiramate (8 week, single-blind, n=36)

- Equal efficacy, no mood switch
- Mean daily dose
  - Bupropion SR 250 mg
  - Topiramate 176 mg

McIntyre, et al. ACNP poster 107;12/00

Bipolar Depression – Adding Bupropion SR or Topiramate

- **Adverse event dropouts**
  - **Bupropion SR 22%**
  - **Topiramate 33%**
- **Weight loss after 8 weeks**
  - **Bupropion SR 1.2 kg**
  - **Topiramate 5.8 kg**

McIntyre, et al. ACNP poster 107;12/00

Rapid Cycling

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

APA Bipolar Guidelines, Revised 2002

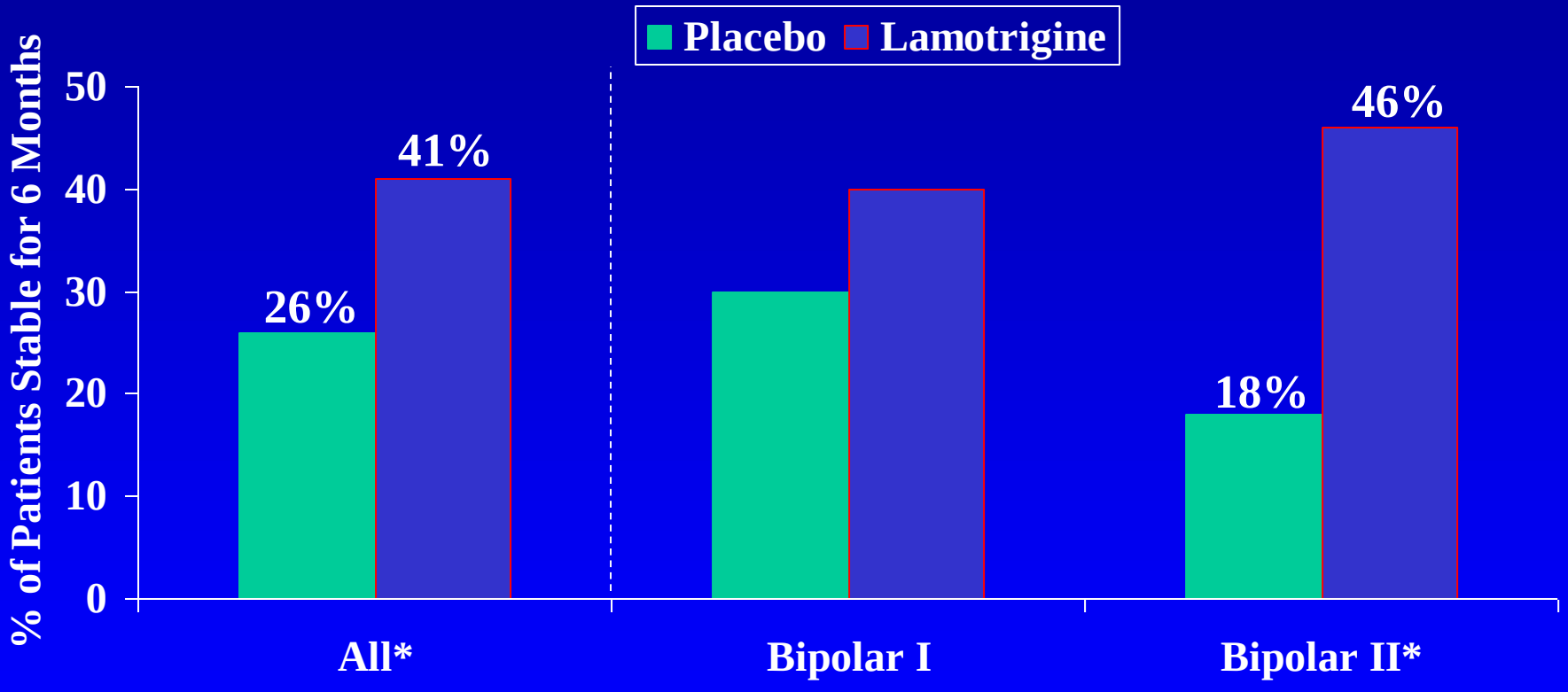
Lamotrigine for Rapid-Cycling
(open label [n=326] to double-blind [n=177])

- **Time to additional pharmacotherapy**
  n.s., (p=0.177)

- **Stable without relapse at 6 months**
  - **Lamotrigine 41%** (p=0.03)
  - **Placebo 26%**

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

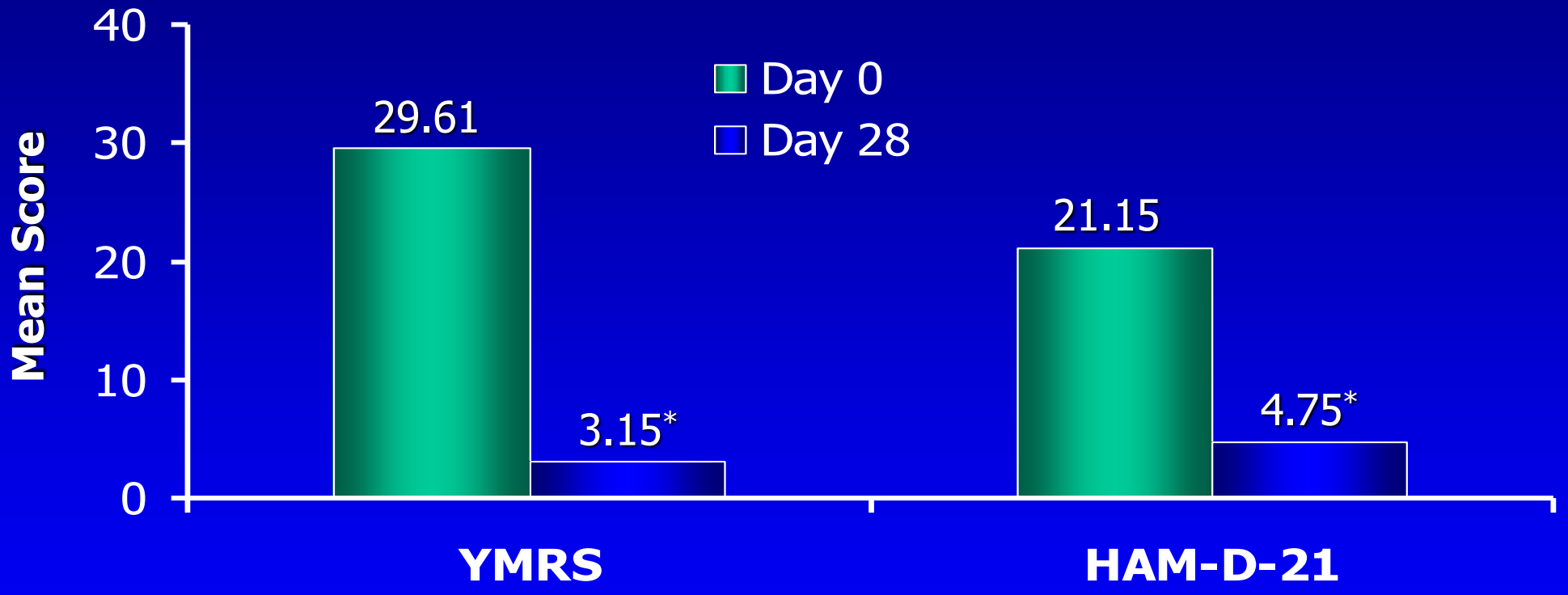
Lamotrigine in Rapid Cycling
6 Months Without Relapse



*p<.05

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

Olanzapine Added to Mood Stabilizer in Rapid Cycling Bipolar I Patients



Day 0: Patients had been treated for at least 1 year with divalproex (n=9), divalproex and lithium (n=3), or lithium and carbamazepine (n=1) when olanzapine was added.

Day 28: Results after 28 days of treatment with olanzapine plus initial mood stabilizer regimen.

***P<0.001 compared with day 0.**

Gonzalez-Pinto et al. *J Clin Psychopharmacol*. 2002;22:450-454.

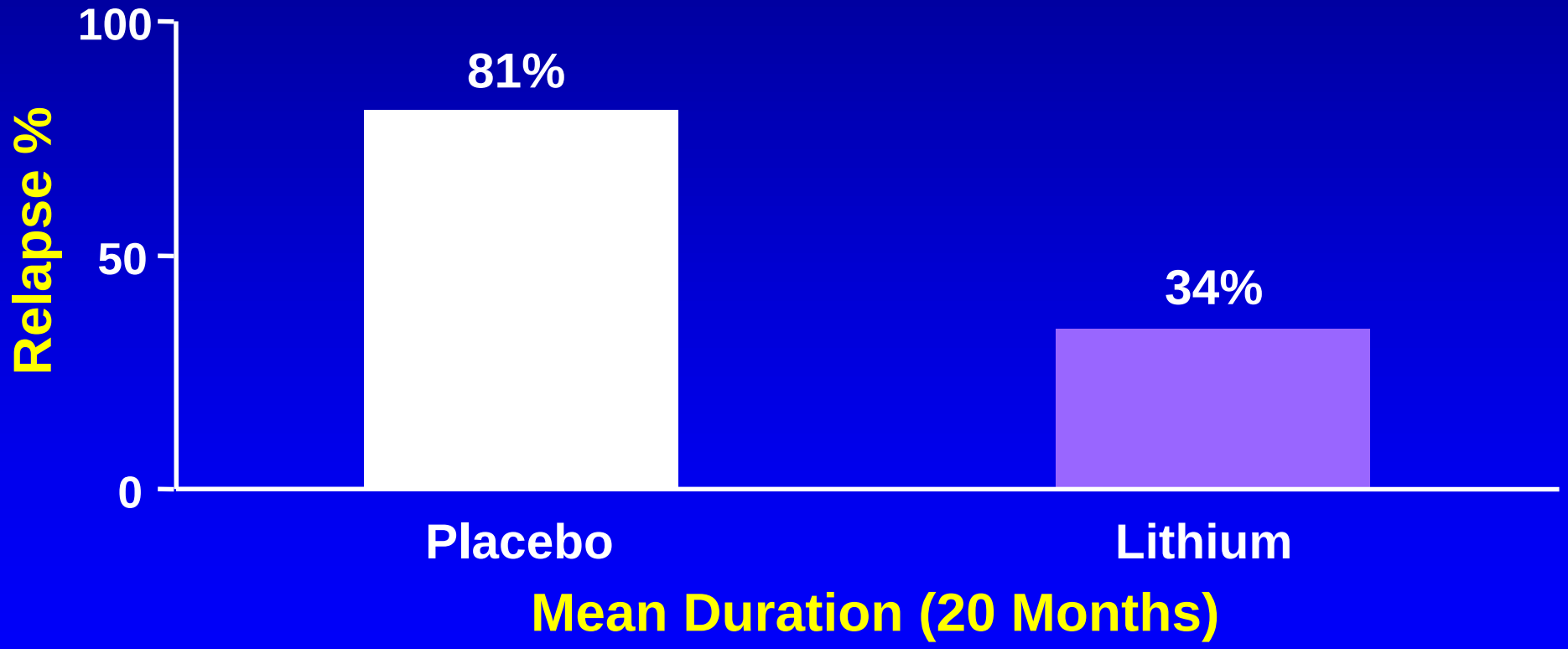
Bipolar Maintenance

- **Best evidence: Lithium or valproate**
- **Alternatives: LTG, CBZ, OXC**
- **Combinations may be necessary**
  - **Antipsychotic**
  - **Antidepressant**
  - **Psychosocial**

APA Bipolar Guidelines, Revised 2002

Lithium Maintenance

10 Placebo-Controlled Studies

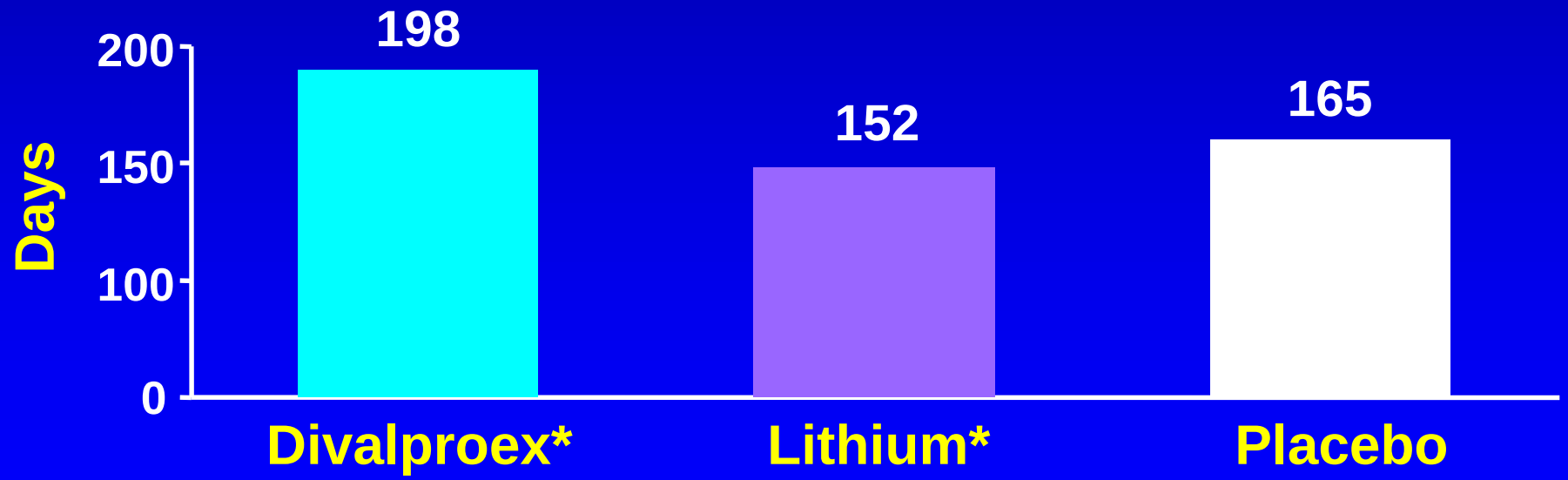


Goodwin FK, Jamison KR, Manic-Depressive Illness. New York: Oxford University Press; 1990

12-Month Maintenance: Bipolar I

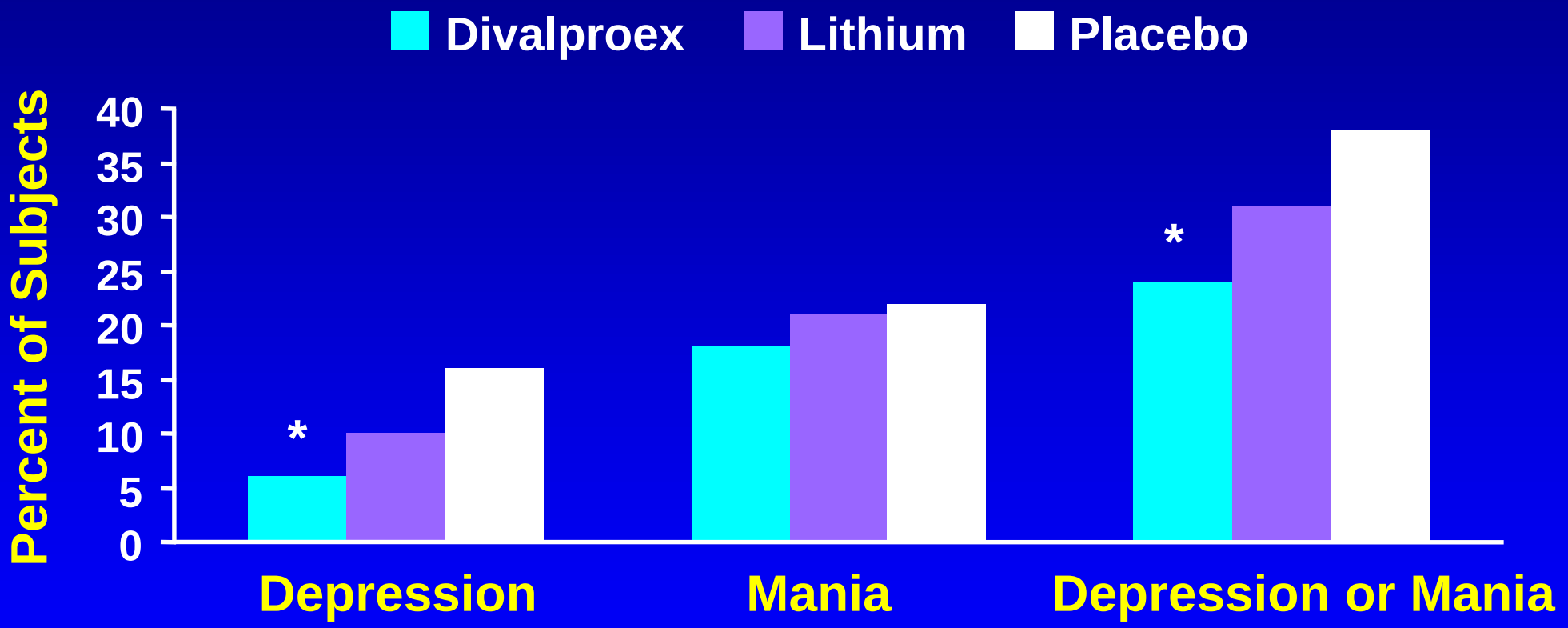
Entry After Index Manic Episode

- Primary outcome measure: time to any mood episode
  - DVPX = Li = Pbo
- Mean duration of continued treatment (days)



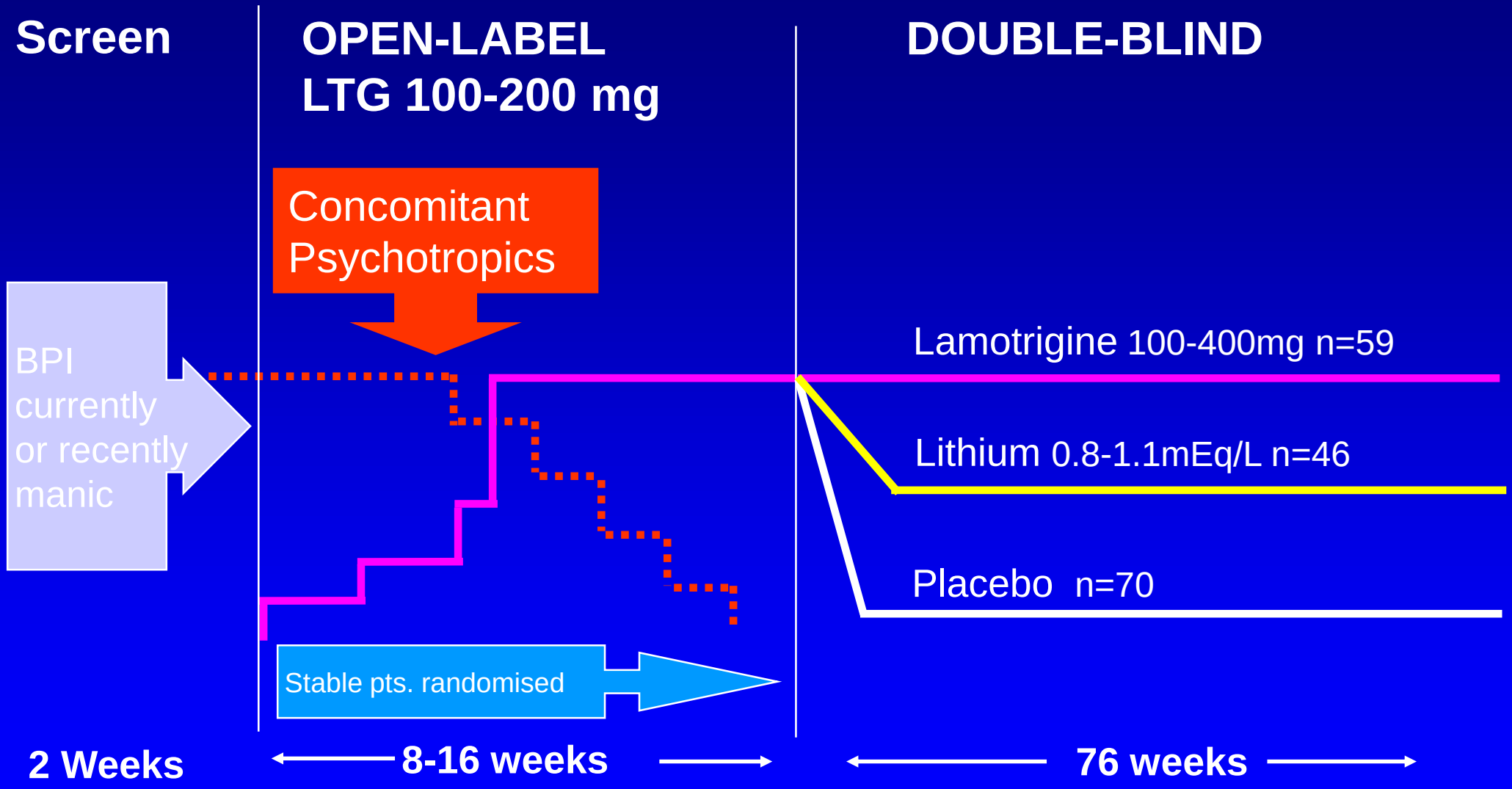
*p=0.02; Bowden CL, Calabrese JR, McElroy SL, et al. Arch Gen Psychiatry. 2000(Mar);57(5):481-489

12-Month Maintenance: Relapse Rates



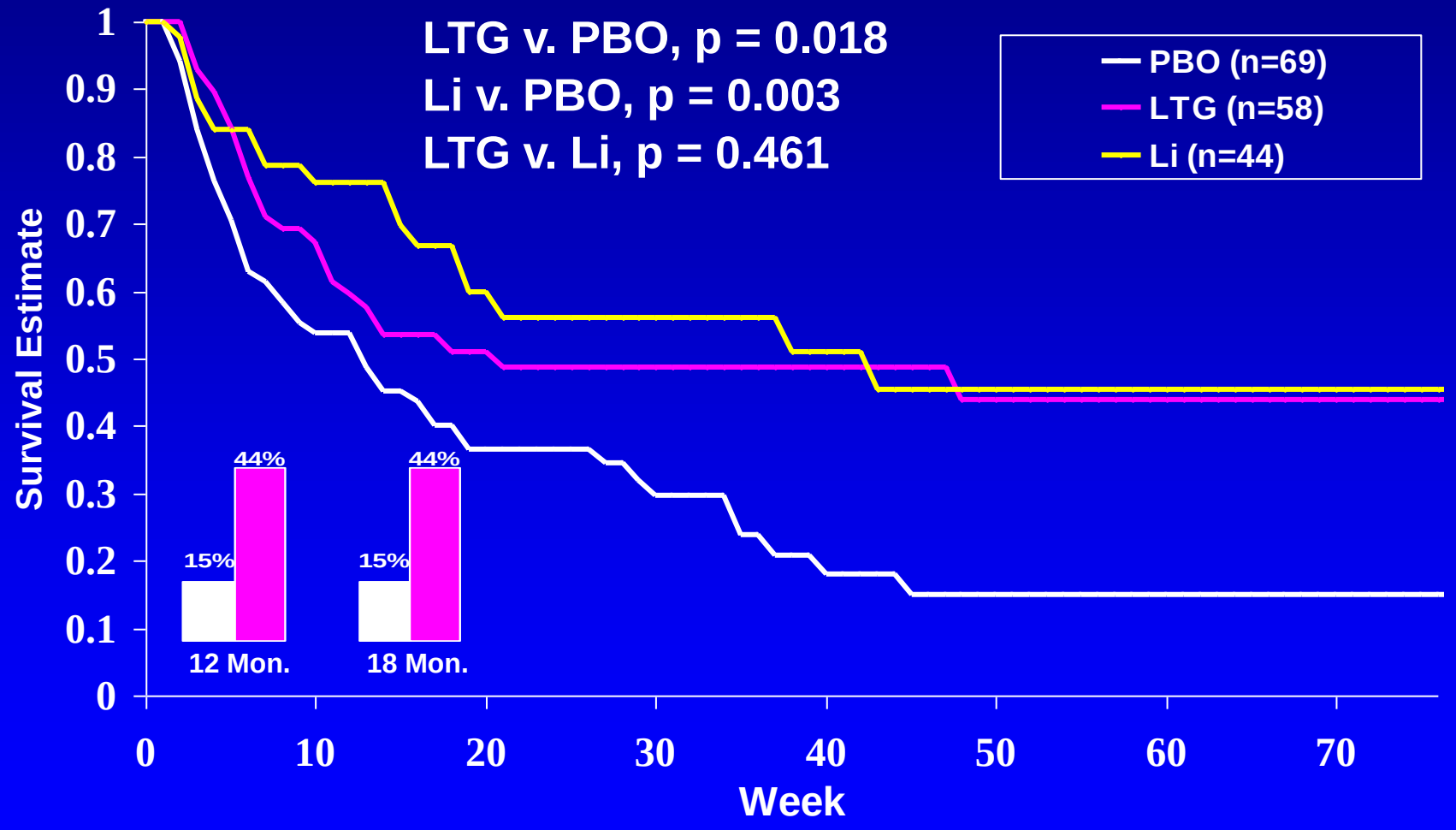
*p<0.05 vs. placebo; Bowden CL, Calabrese JR, McElroy SL, et al. Arch Gen Psychiatry. 2000(Mar);57(5):481-489

Study Design



Bowden et al., Arch. Gen. Psych. 2003

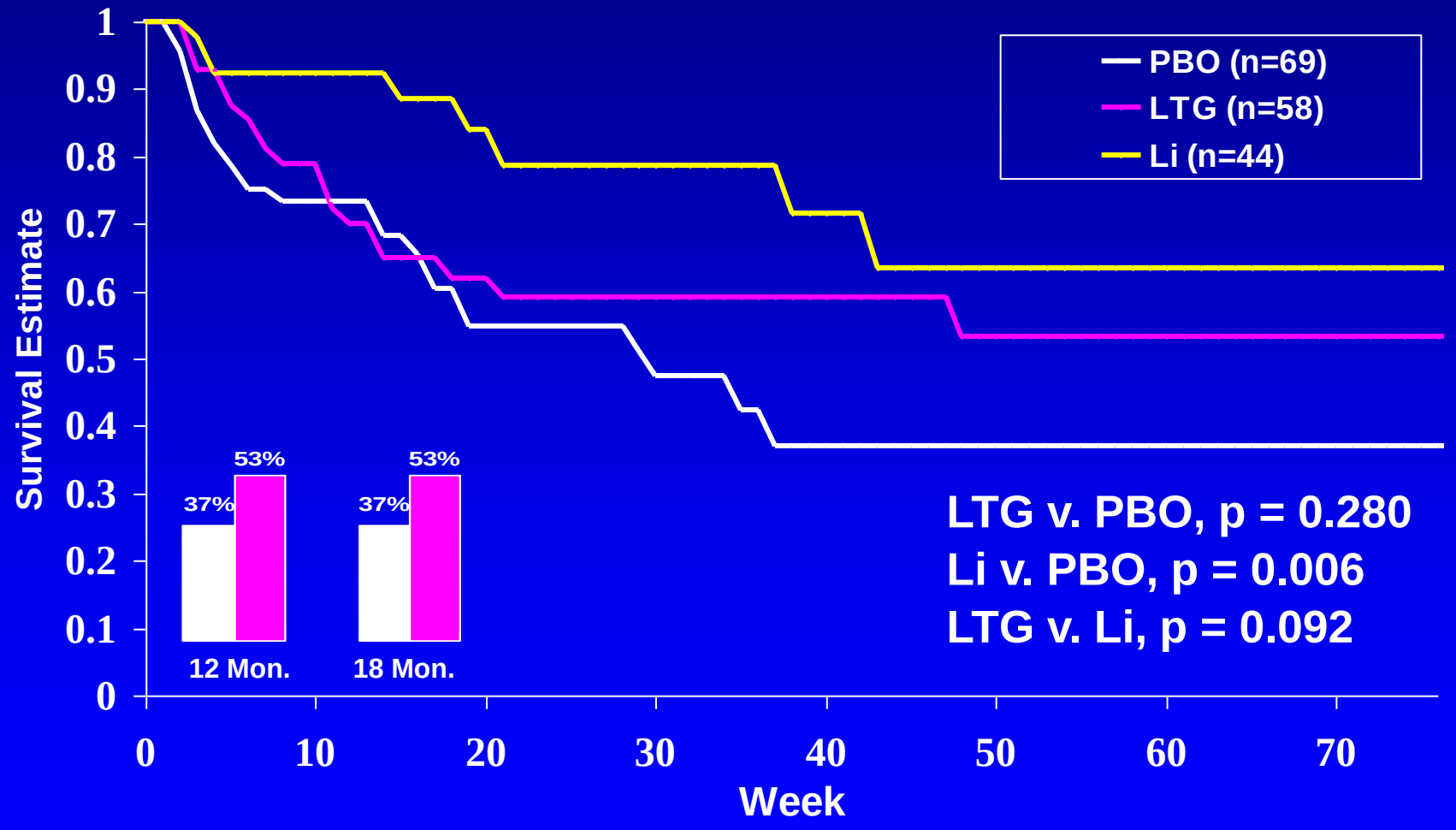
Time to Intervention for a Mood Episode



Index Mania

Bowden et al., Arch. Gen. Psych. 2003

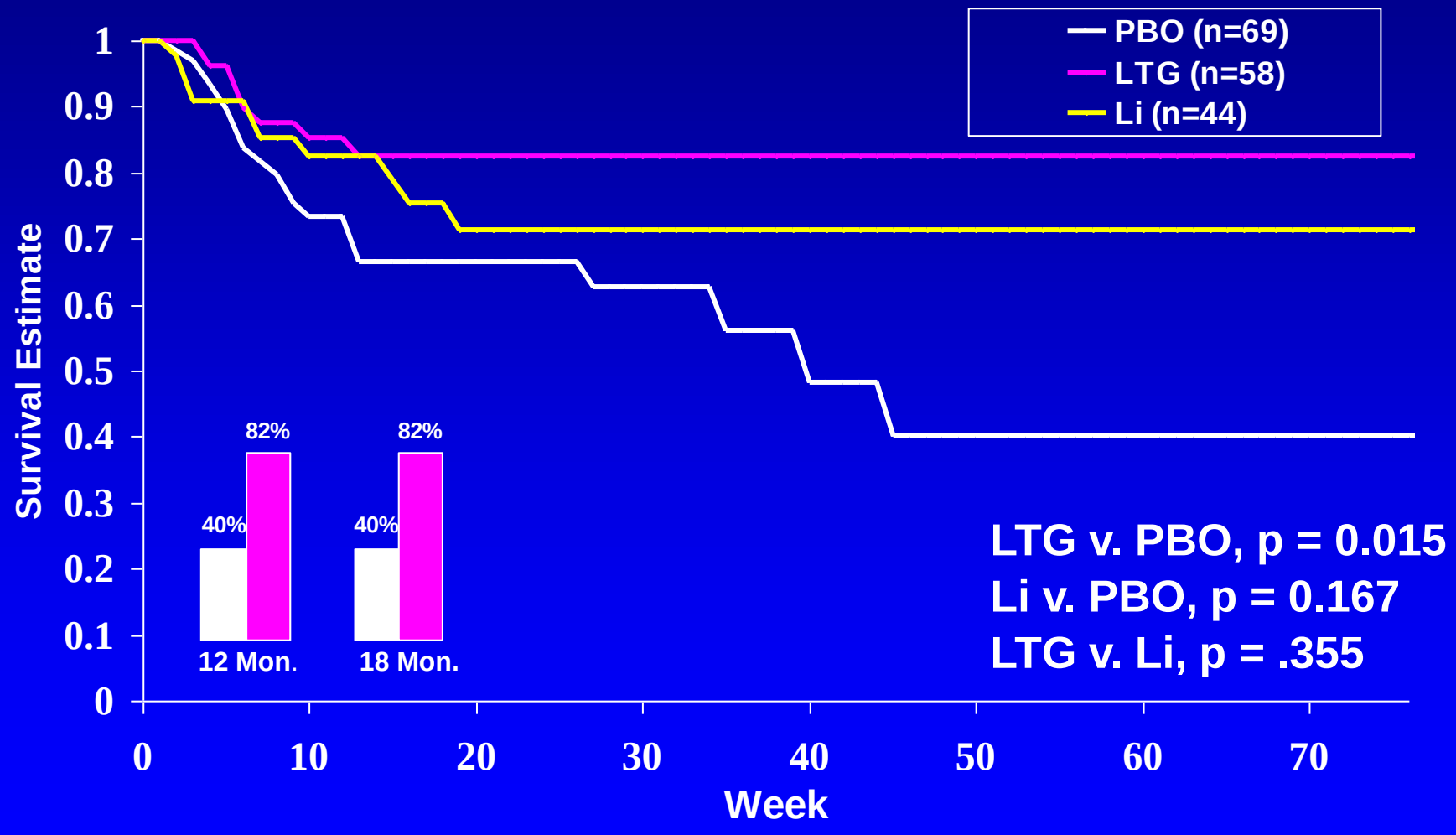
Time to Intervention for Mania



Index Mania

Bowden et al., Arch. Gen. Psych. 2003

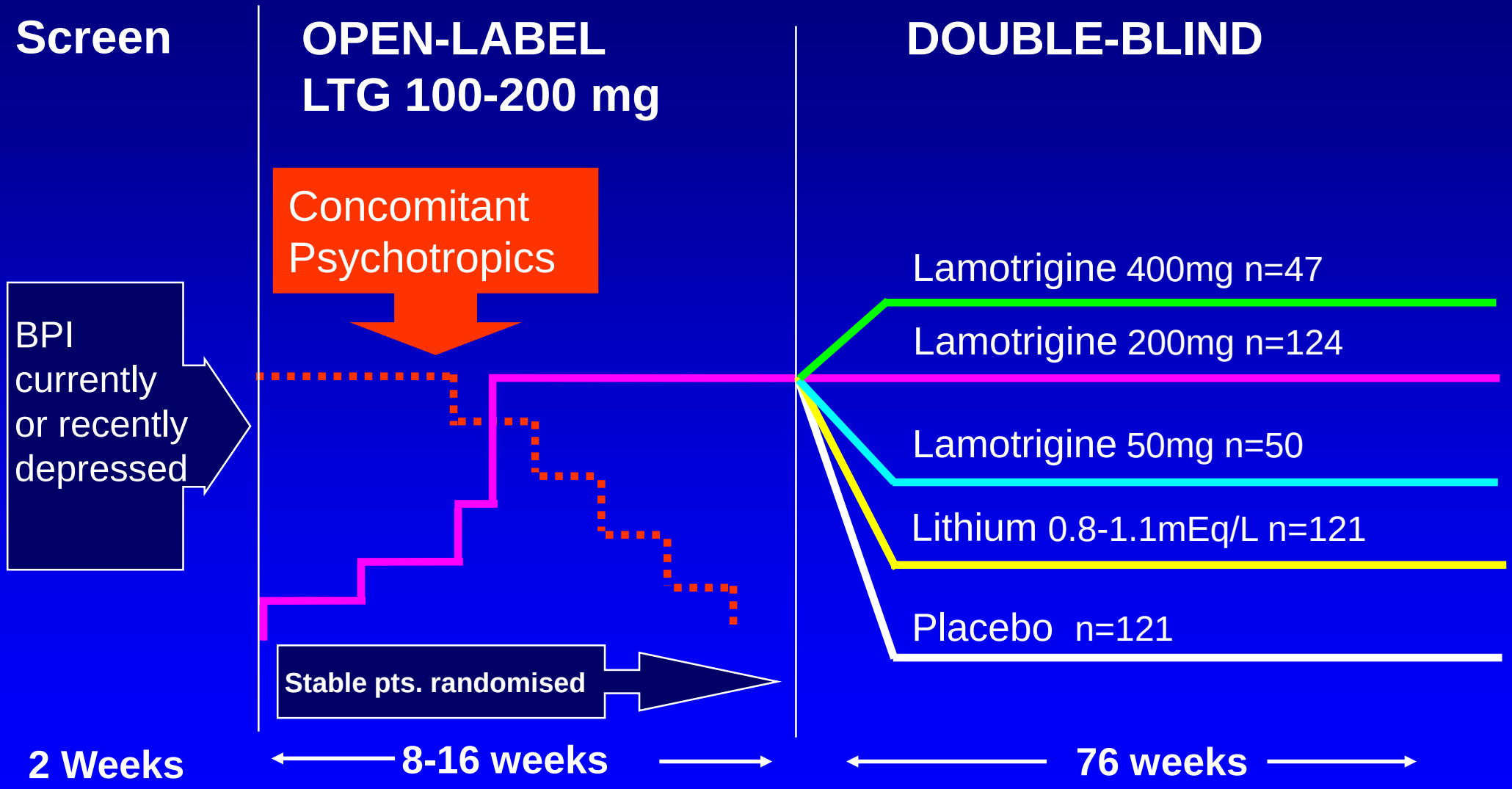
Time to Intervention for Depression



Index Mania

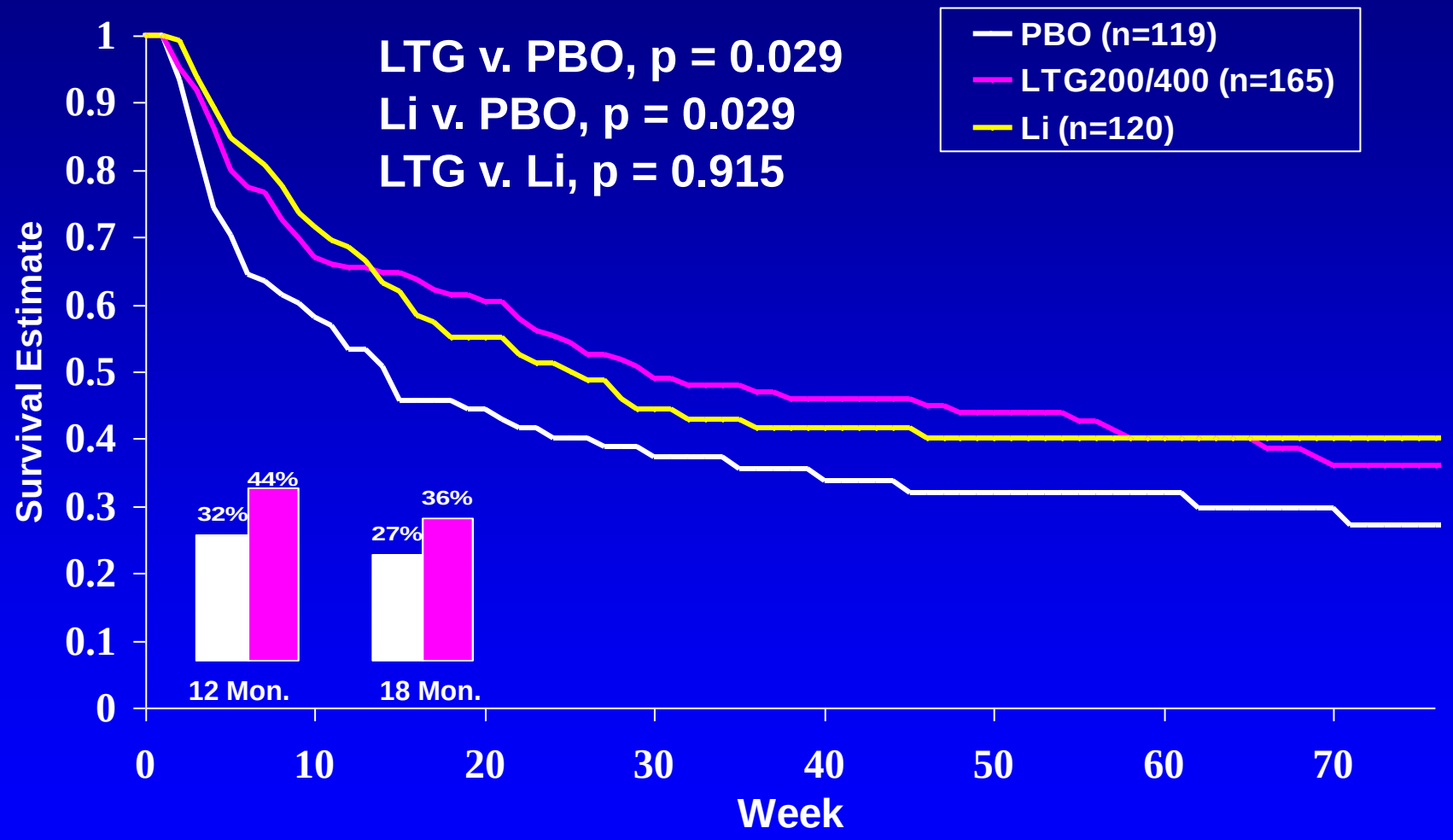
Bowden et al., Arch. Gen. Psych. 2003

Study Design



Calabrese et al., 2003 submitted

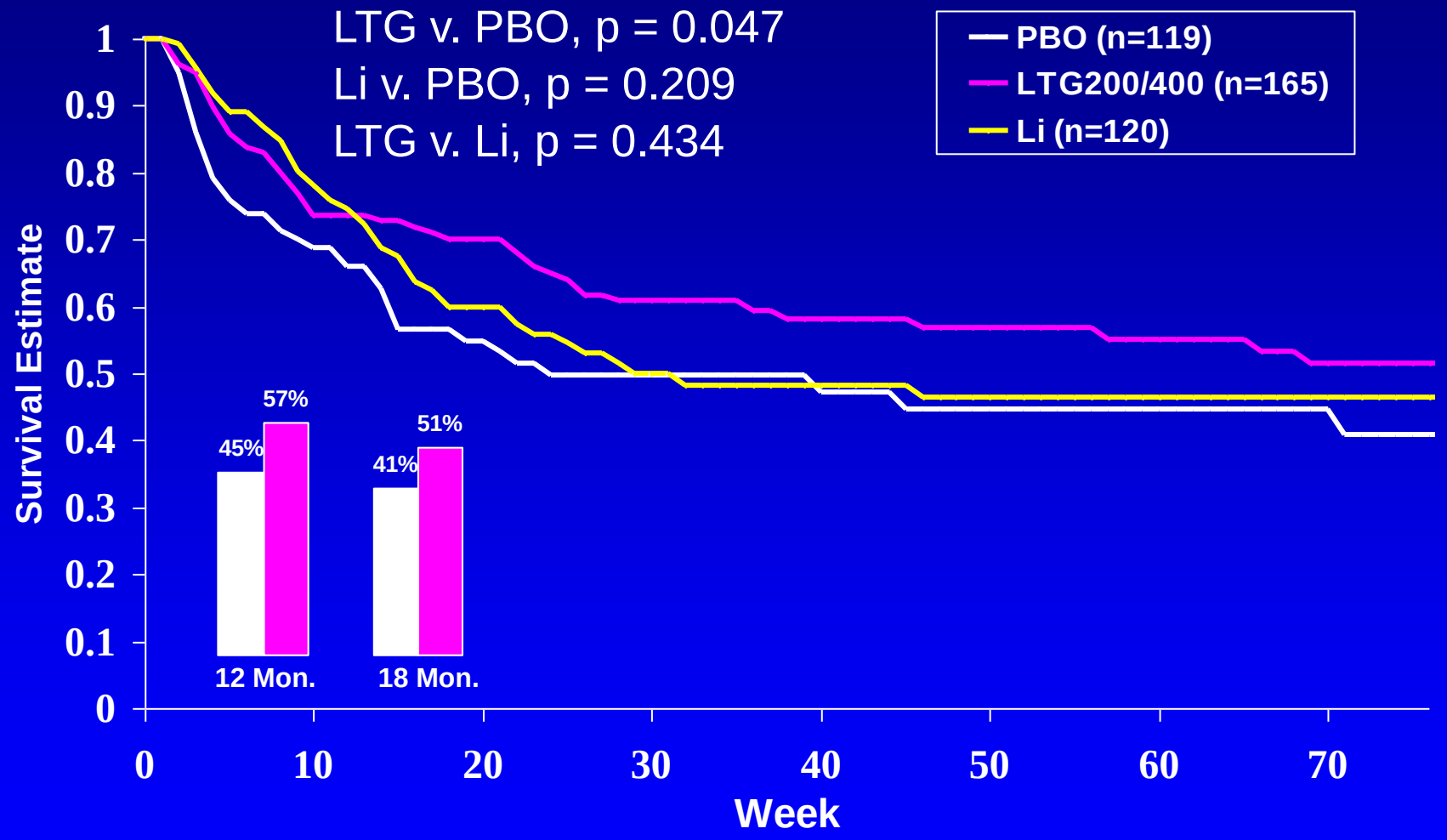
Time to Intervention for a Mood Episode



Index Depressed

Calabrese et al., 2003 submitted

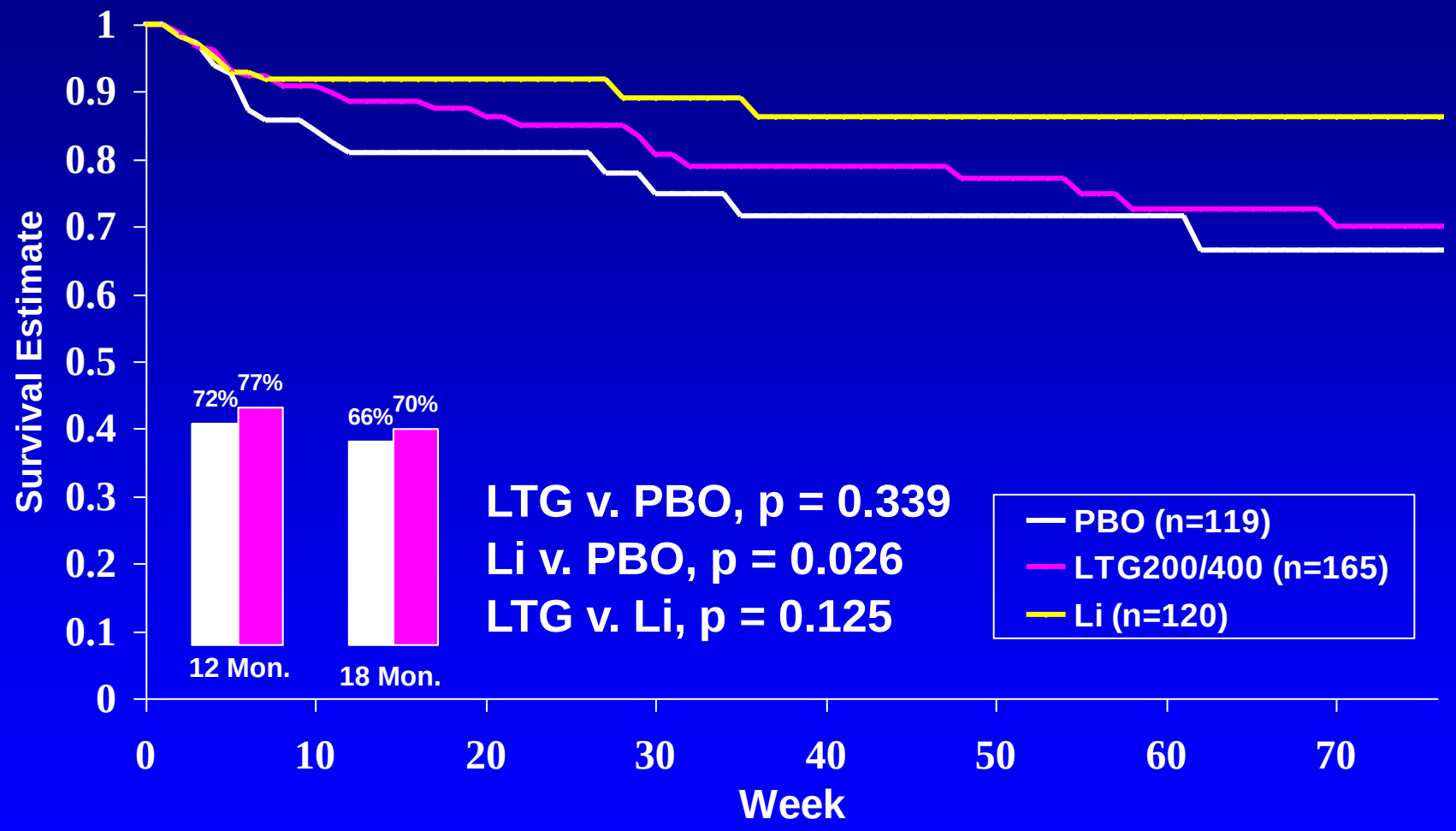
Time to Intervention for Depression



Index Depressed

Calabrese et al., 2003 submitted

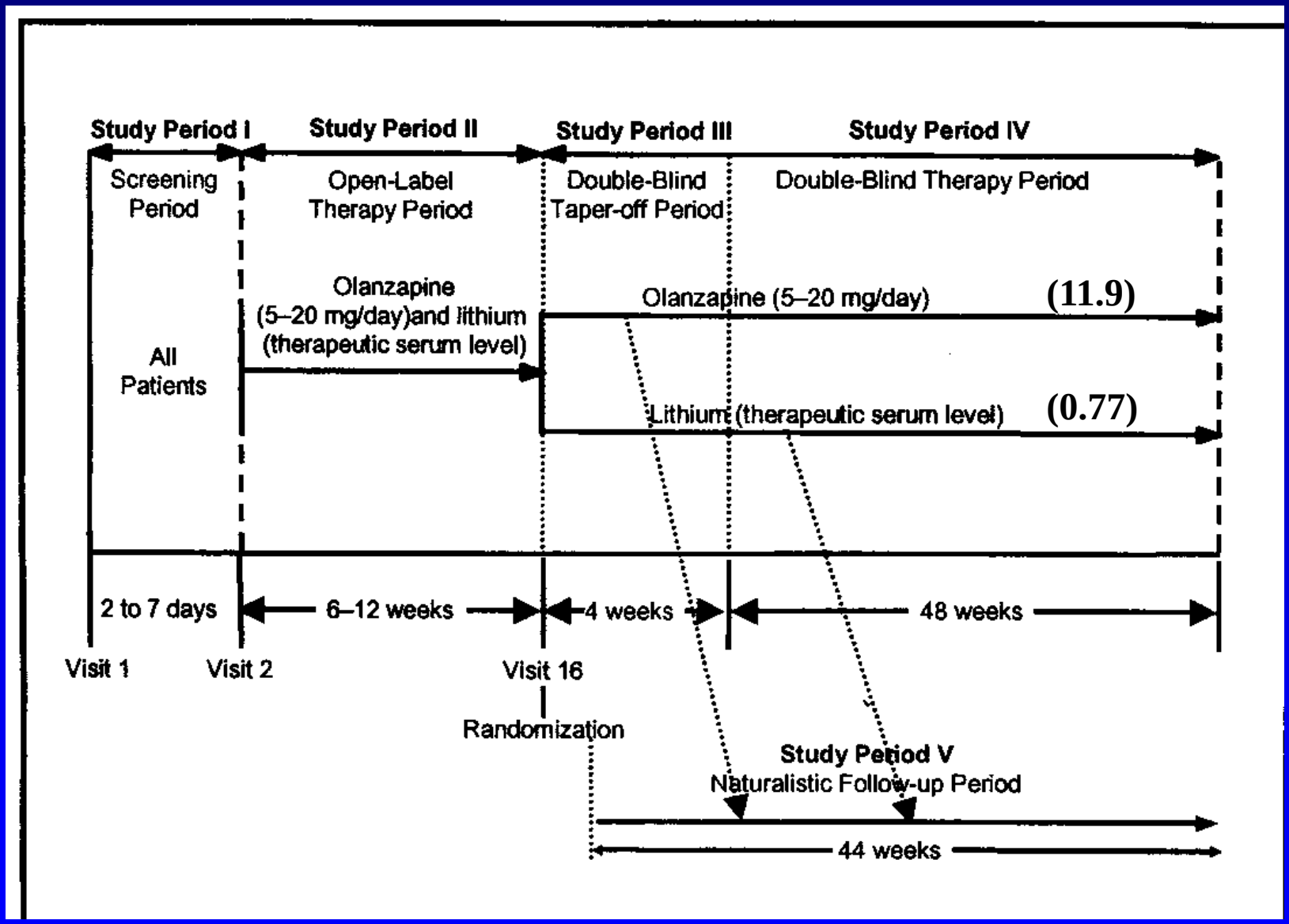
Time to Intervention for Mania



Index Depressed

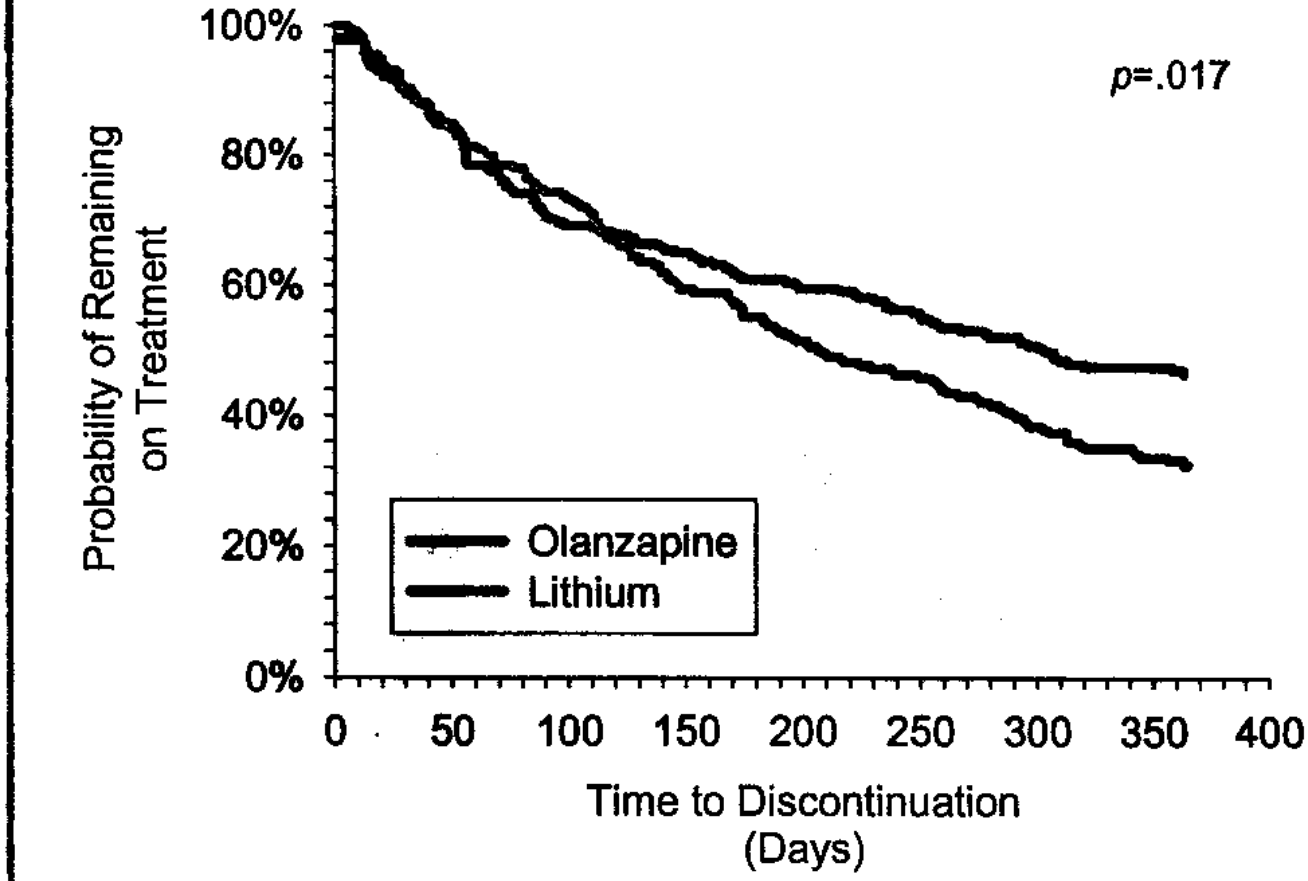
Calabrese et al., 2003 submitted

Bipolar Maintenance: Olanzapine vs. Lithium



Tohen et al. ACNP 12/02

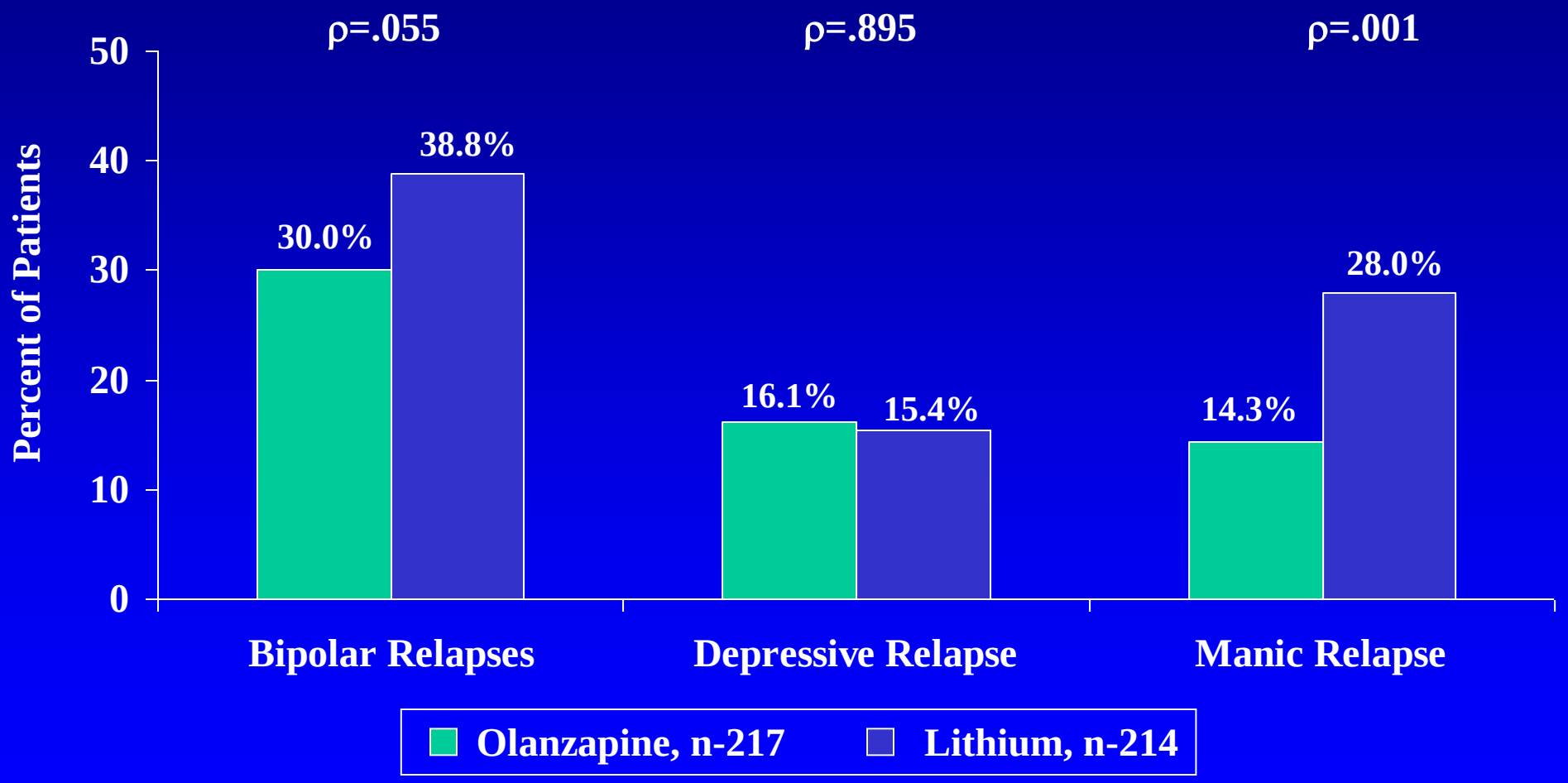
Bipolar Maintenance



The median time to discontinuation was 303 days for olanzapine and 207 days for lithium.

Tohen et al. ACNP 12/02

Bipolar Symptomatic Relapse



Tohen et al. ACNP 12/02

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

- **Time to relapse**
  - Olanzapine 174 days
  - Placebo 22 days
- **Mania relapse**
  - Olanzapine 16%
  - Placebo 14%
- **Depression relapse**
  - Olanzapine 35%
  - Placebo 49%

APA 5/03

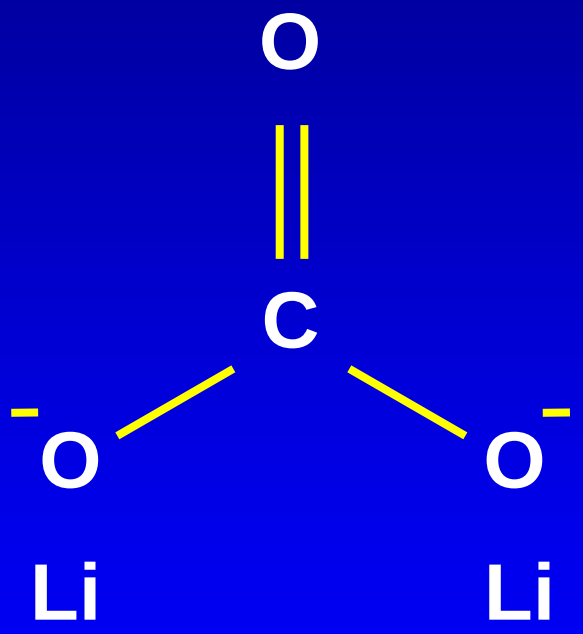
Bipolar Maintenance: Olanzapine vs. Placebo (1 year, n = 361)

- **Completed one year**

Olanzapine	**24%**
Placebo	**10%**

… a little wizened man of 51 who had been in a state of manic excitement for 5 years

Lithium Carbonate



Lithium: Mechanism of Action

- Electrolyte substitution
- Second messenger effects
- Neurotropic factor effects
- Modulates glutamatergic neurotransmission
- Increases brain GABA levels

FDA Approved Lithium Indications

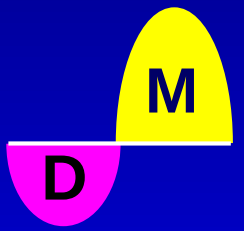
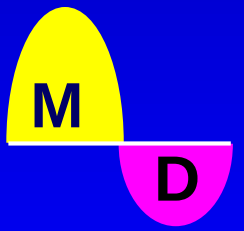
- **Acute Mania**
- **Maintenance in bipolar disorder**

Lithium Succinate Cream for Anogenital Warts
(placebo-controlled, 4 w, n=101)

- **Lesion reduction from lithium**
  - **Overall 42% (p=0.013)**
  - **Male 65% (p=0.002)**
  - **Female 11% (n.s.)**
- **Human papillomavirus (DNA)**

Ward et al., Int J STD & AIDS 8:515-517, 1997

Lithium Response Rates

30%	Rapid cycling	Dysphoric mania	History of substance abuse	(-) Family history	>3 episodes	
70%	Nonrapid cycling	Euphoric mania	No substance abuse	(+) Family history	Few lifetime episodes	

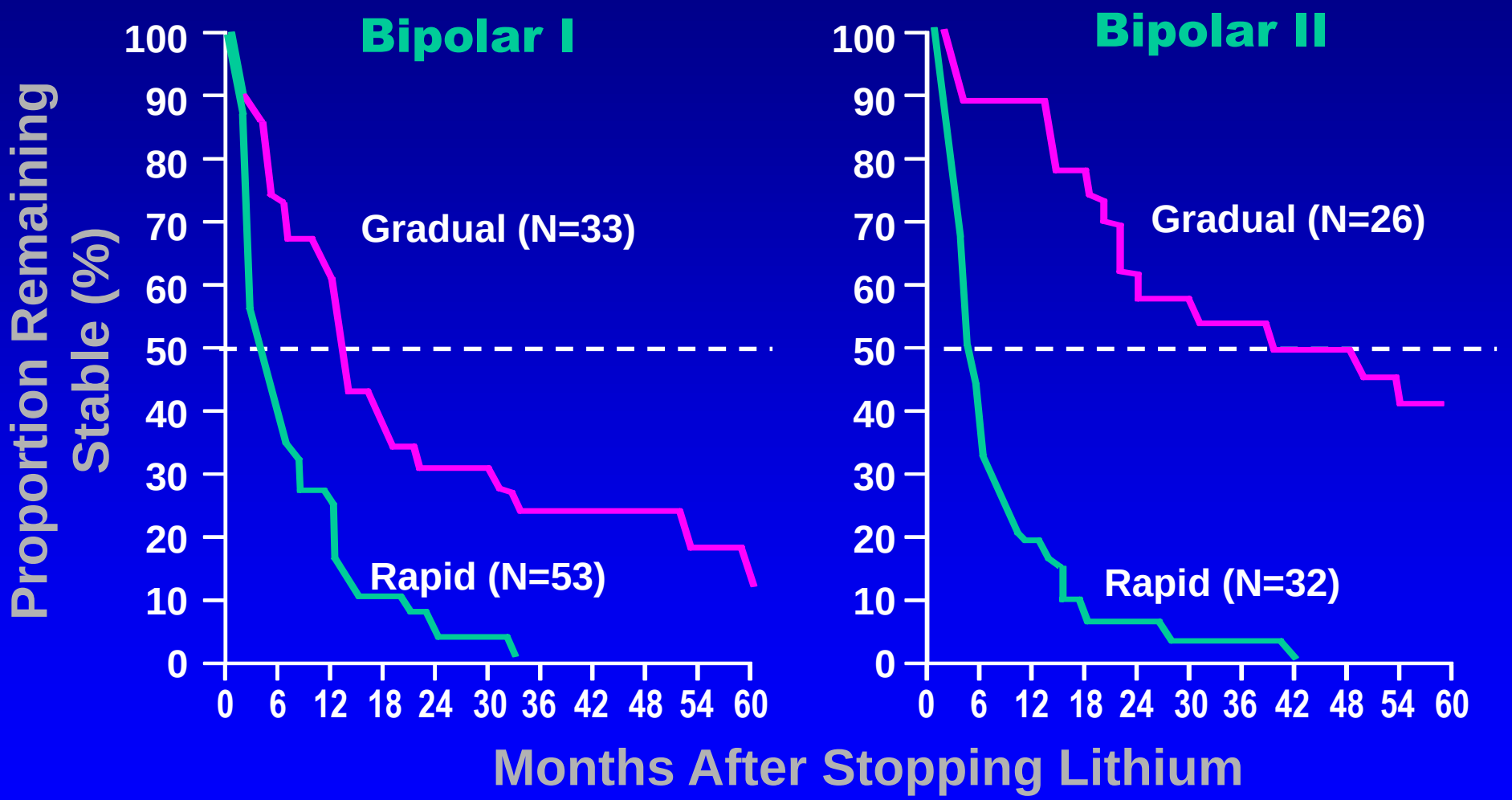
Long-Term Lithium Maintenance

(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

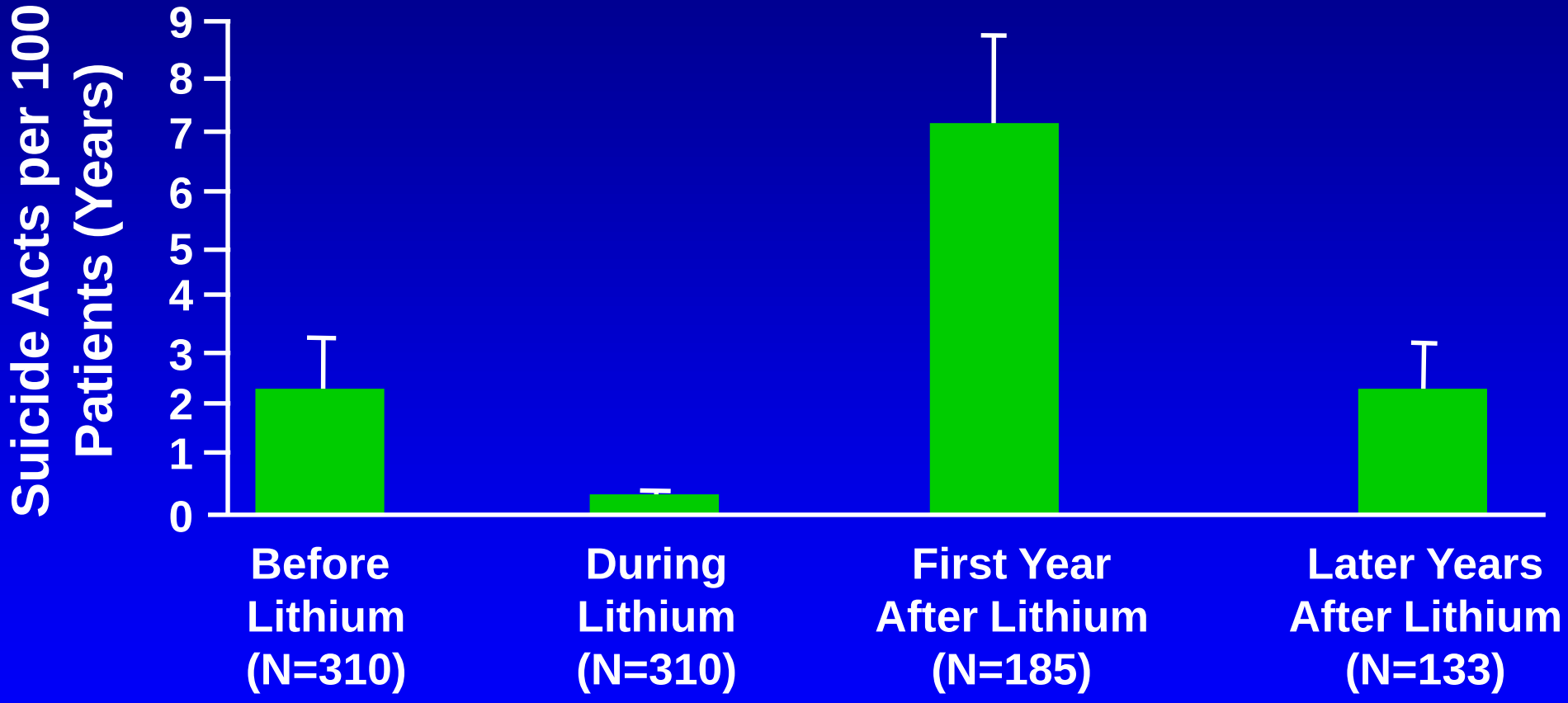
Tondo et al. BJP 2001;178(suppl 41):184-190

Gradual vs. Rapid Lithium Discontinuation



Baldessarini RJ, Tondo L, Faedda GL, et al. J Clin Psychiatry. 1996(Oct);57(10):441-448

Lithium and Suicidal Behavior



Tondo et al. JCP 8/98

Antisuicidal Effect of Lithium

Clinical Response	No Attempts
• Excellent (n=45)	93.3%
• Moderate (n=81)	82.7%
• Poor (n=41)	48.8%

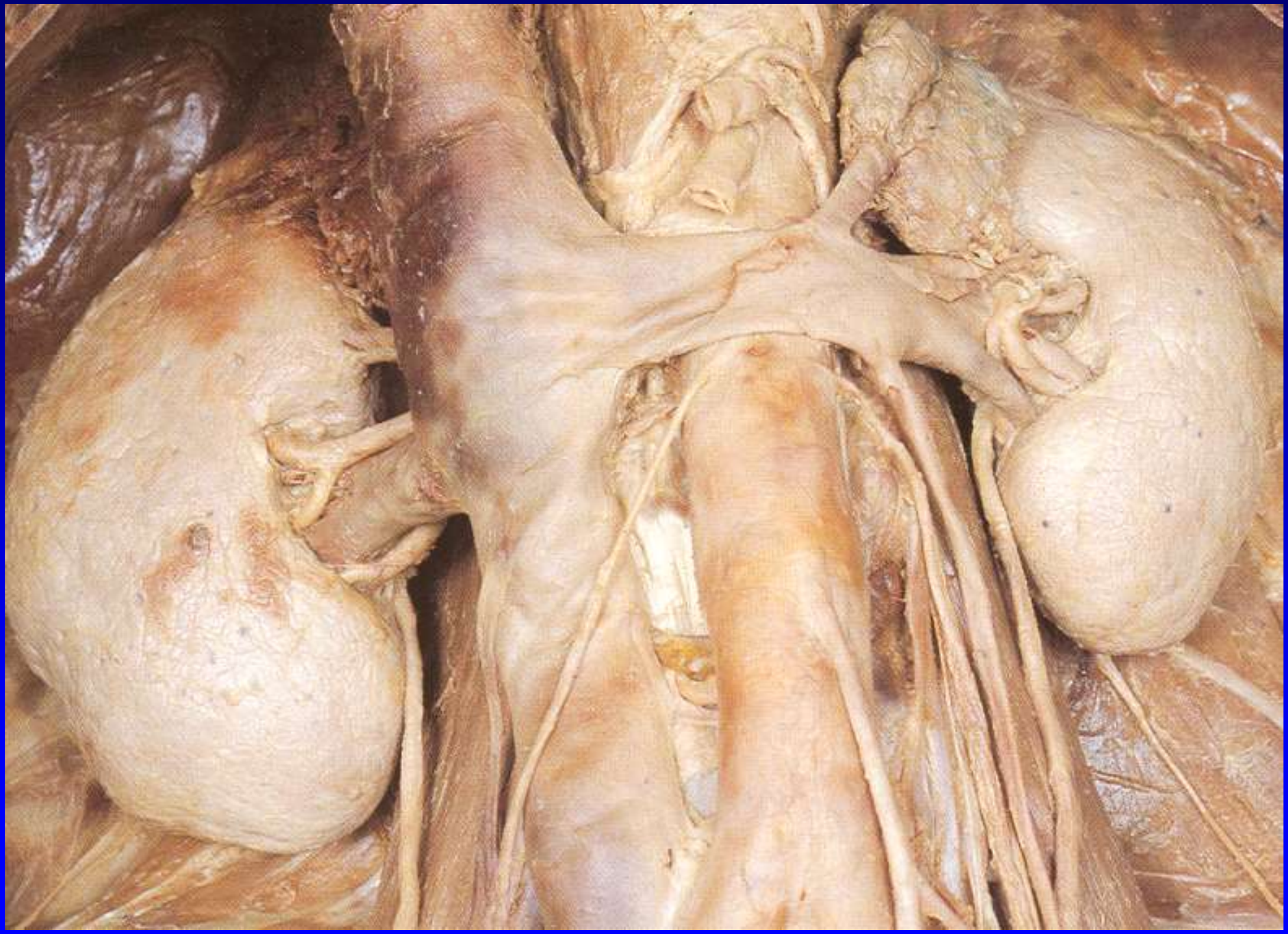
Ahrens and Müller-Oerlinghausen. Pharmacopsychiatry 2001;34:132-136

Lithium

- **Half-life: 24 hours**
- **Not metabolized**
  - **Renal excretion**
- **Not protein bound**
- **Dosing**
  - **Initial**
    - 600-900 mg/day (divided or single dose)
  - **Maintenance**
    - Serum levels: 0.6-1.2 mmol/l

Lithium

- **Black box warning**
  - **Toxicity**
- **Monitoring**
  - **Serum levels**
  - **Kidney and thyroid function**
  - **Serum calcium (?)**

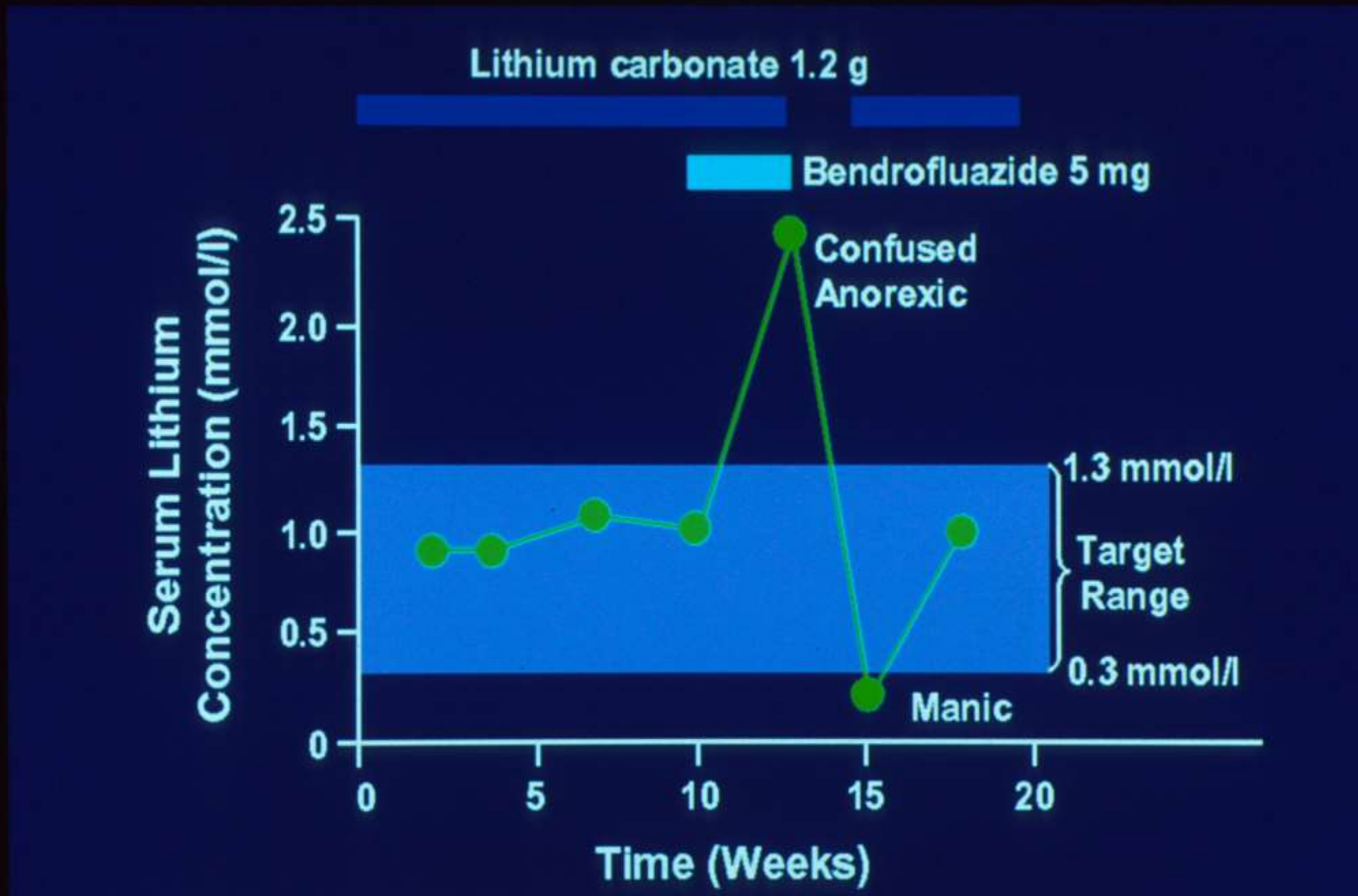


Lithium Side Effects

- Cognitive
- Tremor
- Gastrointestinal
- Endocrine
  - Thyroid
  - Parathyroid
- Weight gain
- Skin
- Renal
- Toxicity

Serum Lithium Levels

Increased	Not Changed	Decreased
Thiazides	Amiloride (?)	Acetazolamide
NSAIDs	Furosemide	Mannitol
ACE inhibitors	Aspirin	Aminophylline
Low sodium diet	Sulindac	Theophylline
Dehydration		Caffeine
Elderly		Mania
Renal disease		Pregnancy

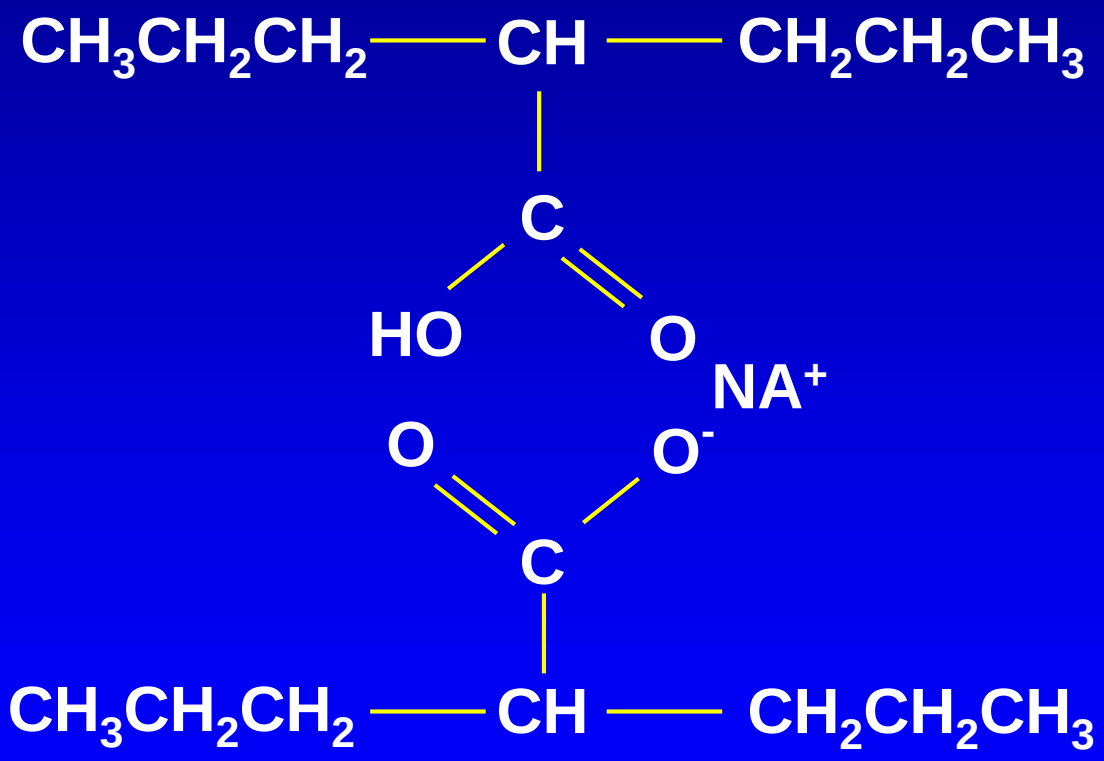


Aronson JK, Reynolds DJM. Br Med J. 1992;305:1273-1276

Angiotensin II Receptor (Type AT_1) Antagonists

- Case reports of lithium toxicity
  - candesartan (Atacand)
  - losartan (Cozaar)
  - valsartan (Diovan)
- Not mentioned in 2002 PDR

Divalproex Sodium



Valproate: Mechanism of Action

- Increases brain GABA levels
- Inhibits GABA catabolism
- Potentiates postsynaptic GABA responses
- Blocks voltage-dependent sodium channels
- Modulates glutamatergic neurotransmission

Valproate

- **Indications**
  - **Epilepsy**
  - **Acute mania**
  - **Migraine prophylaxis**
- **Role**
  - **Acute and prophylactic treatment of bipolar disorder**

Valproate

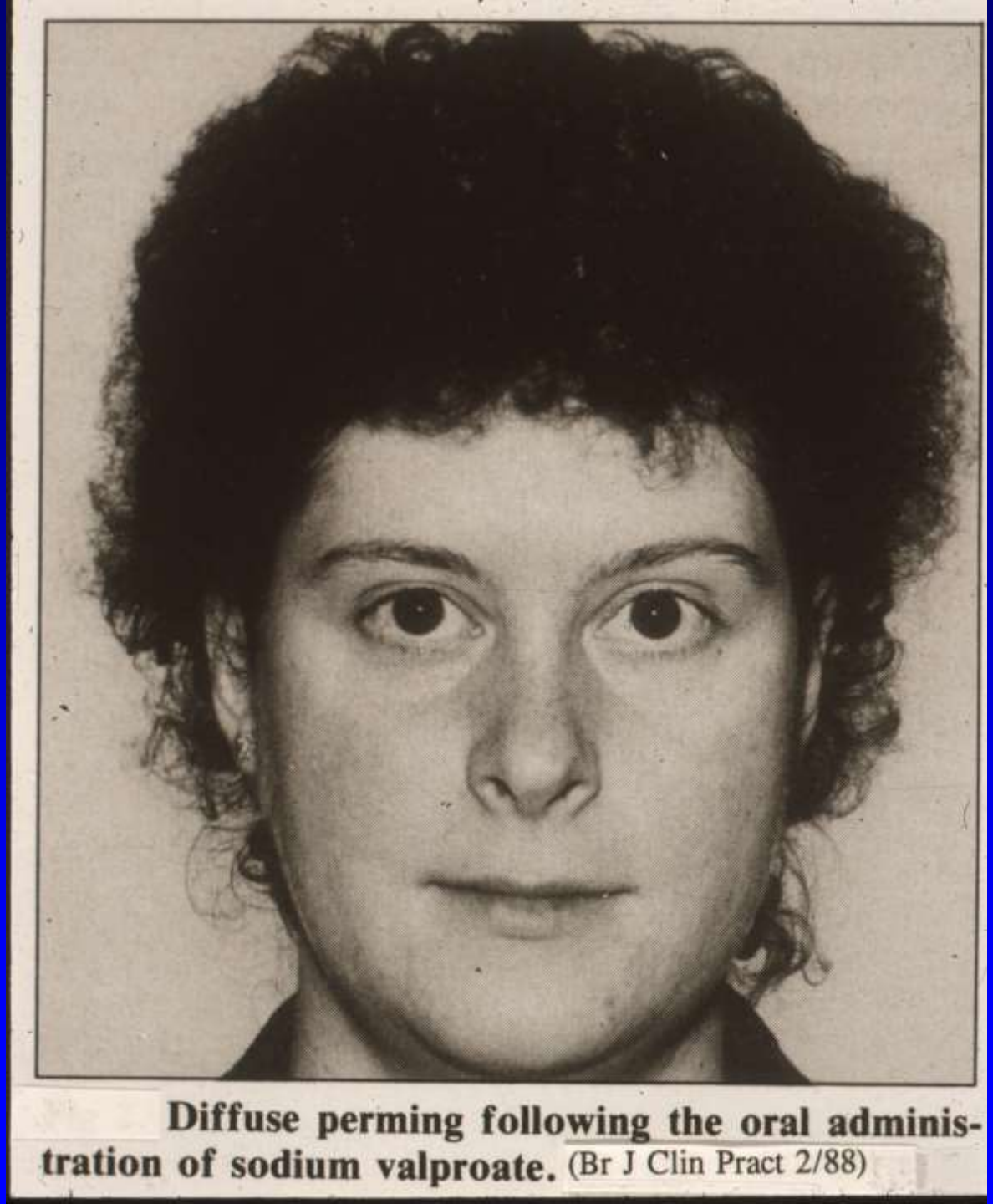
- Half-life: 6-16 hours
- Protein binding: >90%
- Dosing in mania
  - Initial: 250 mg tid or oral loading (20-30 mg/kg)
  - Maintenance: serum conc = 50-125 μg/ml
- qd formulation available

Valproate

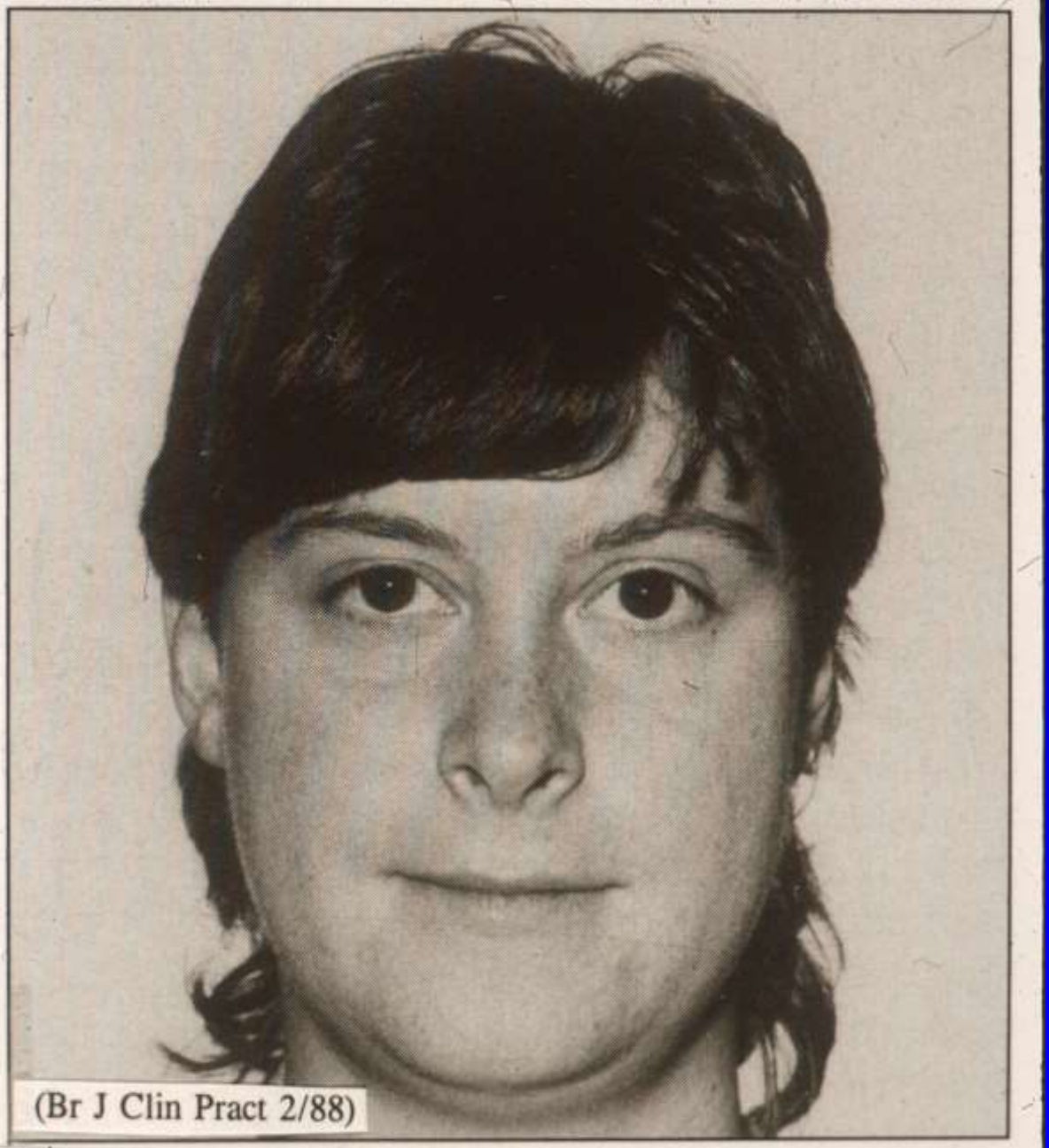
- **Black box warnings**
  - **Hepatotoxicity**
  - **Teratogenicity**
  - **Pancreatitis**
- **Monitoring**
  - **Blood levels**
  - **CBC, platelets, LFTs**

Valproate Side Effects

- Cognitive (uncommon)
- Tremor
- Gastrointestinal
- Weight gain
- Hair loss
- Hepatotoxicity
- Pancreatitis
- Teratogenicity
- Polycystic ovaries (?)



Diffuse perming following the oral administration of sodium valproate. (Br J Clin Pract 2/88)



Normal hair appearance approximately 19 months after valproic acid withdrawal.

Valproate Interactions
(An Incomplete Listing)

- **Aspirin (avoid)**

  free VPA, ↓ platelet function

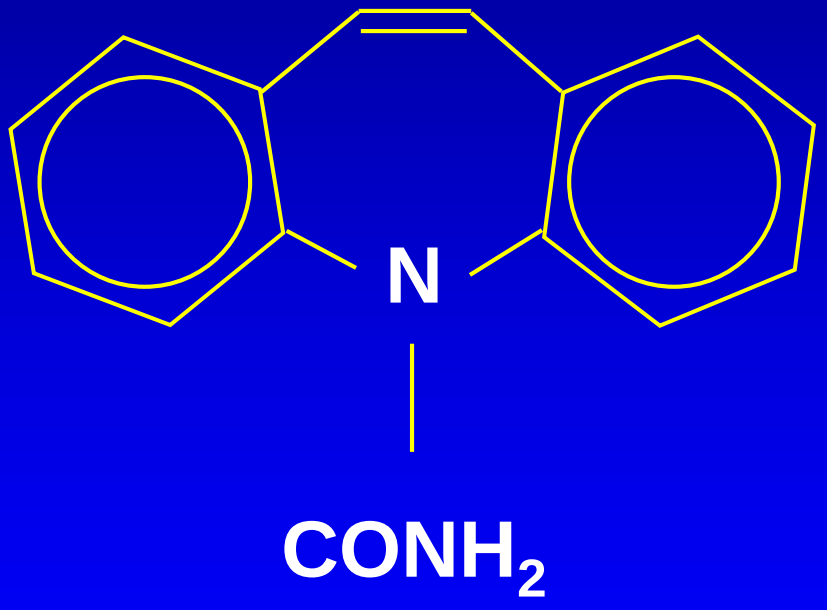
- **Carbamazepine**

  ↓ VPA, CBZ-epoxide

- **Lamotrigine**

  lamotrigine

Carbamazepine



Carbamazepine: Mechanism of Action

- Blocks voltage-dependent sodium channels
- Inhibits glutamatergic neurotransmission
- Modifies adenosine receptors
- Increases extracellular serotonin

Carbamazepine

- **Indications**
  - **Trigeminal neuralgia**
  - **Epilepsy**
- **Role**
  - **Acute and prophylactic treatment of bipolar disorder**
  - **Adjunctive treatment with other mood stabilizers**

Carbamazepine

- **Half-life**
  - **Initial: 25-65 hours**
  - **Induced: 12-17 hours**
- **Protein binding: 76%**
- **Metabolism**
  - **CYP3A4**
  - **Hepatic autoinduction**
  - **10, 11-epoxide**

Carbamazepine

- **Immediate and extended release**
- **Dosing**
  - **Initial: 200-400 mg/day (divided)**
  - **Maintenance: serum conc = 4-12 μg/ml**

Carbamazepine

- **Black box warnings**
  - **Aplastic anemia (1/100,000)**
  - **Agranulocytosis (1/100,000)**
- **Monitoring**
  - **Blood levels**
  - **CBC, platelets, LFTs**

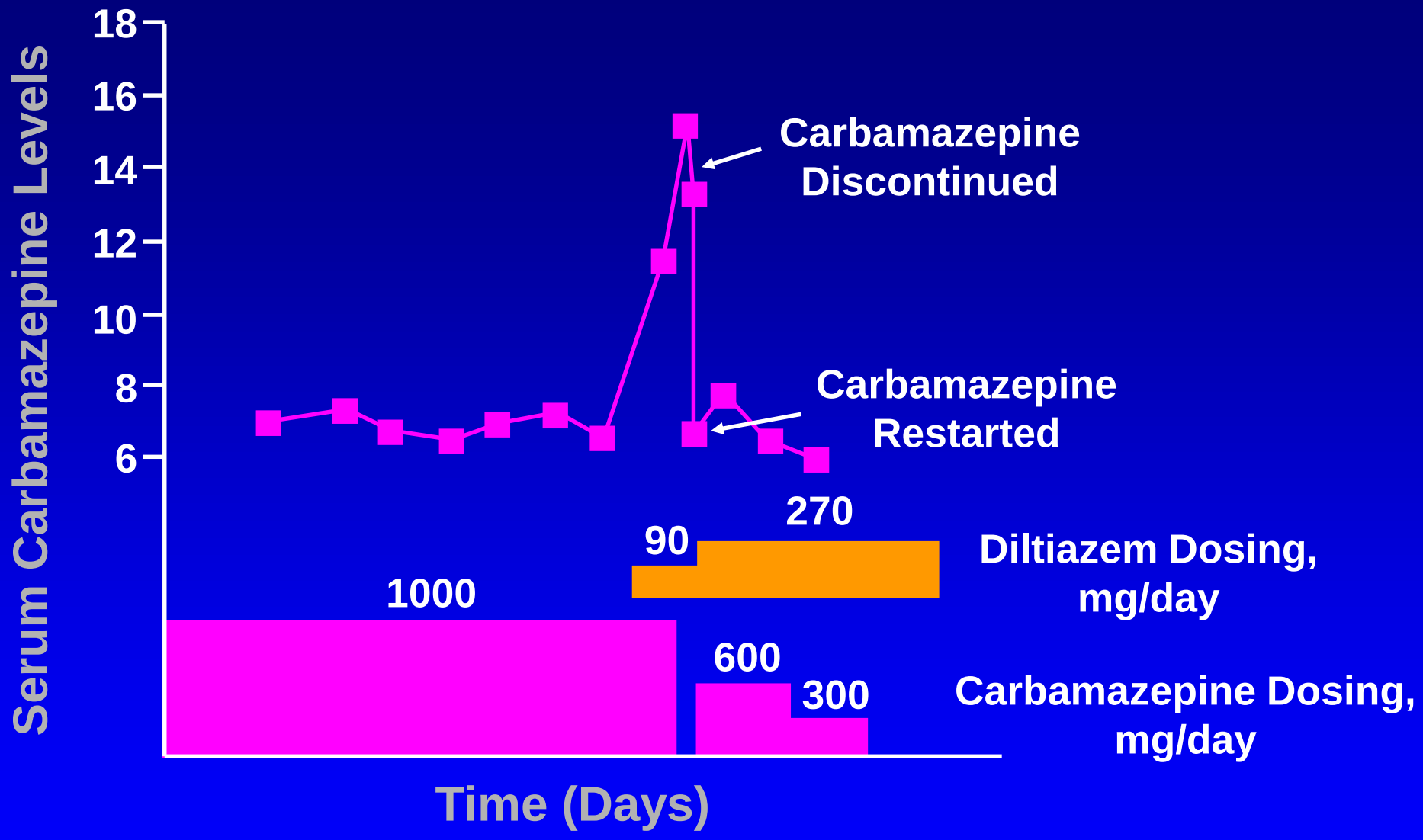
Carbamazepine Side Effects

- Sedation
- Dizziness
- Ataxia
- Double/blurred vision
- GI distress
- Hematopoietic suppression
- Hepatotoxicity (rare)
- Dermatologic
- Teratogenicity
- Hyponatremia

Carbamazepine Interactions

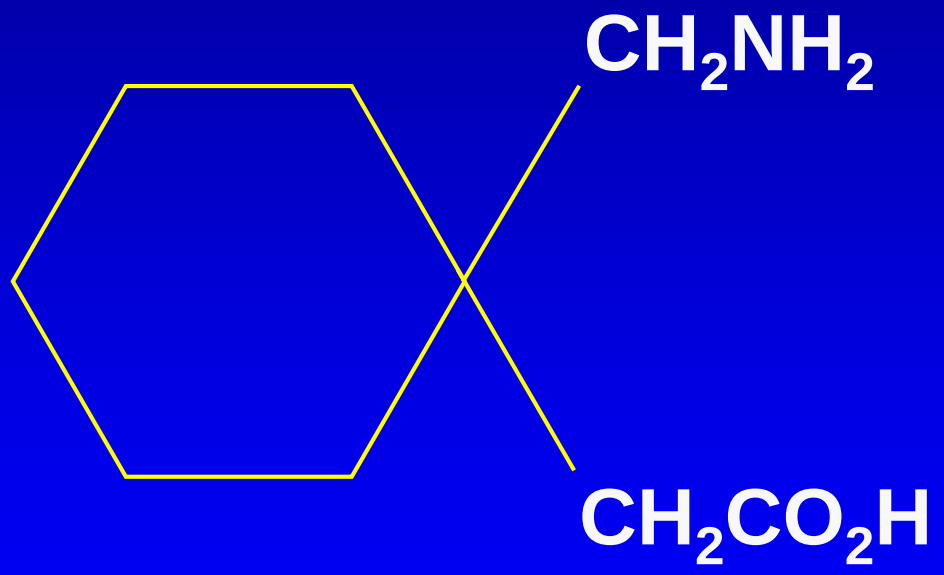
An Incomplete Listing

- **CBZ decreases levels of:**
  - **Clonazepam, clozapine, olanzapine, haloperidol, alprazolam, bupropion, oral contraceptives**
- **CBZ levels increased by:**
  - **Cimetidine, macrolides, fluoxetine, valproate, isoniazid, verapamil, ketoconazole**



Shaughnessy AF, Mosley MR. Neurology. 1992(Apr);42(4):937-938

Gabapentin



Limitations of Gabapentin In Bipolar Disorders

- Not effective as monotherapy in treatment-resistant rapid cycling
- Not effective as primary add-on antimanic agent

Adjunctive Gabapentin for Bipolar Disorders

- Positive response[1] 18/28 (65%)
- Marked improvement[2] 3/5 (60%)
- Cycling stopped[3] 67/73 (92%)
- Improved[4] 8/9 89%)
- Majority improved[5] (N=47)

[1]Schaffer & Schaffeer, 1997; [2]Bennett et al, 1997; [3]Ryback et al, 1997; [4]McElroy et al, 1997; [5]Marvott et al, 1997

Gabapentin

- **Half-life: 5-7 hours**
- **Bioavailability decreases with dose**
- **Not protein bound**
- **Not metabolized**
- **No important drug interactions (except ↑ felbamate)**

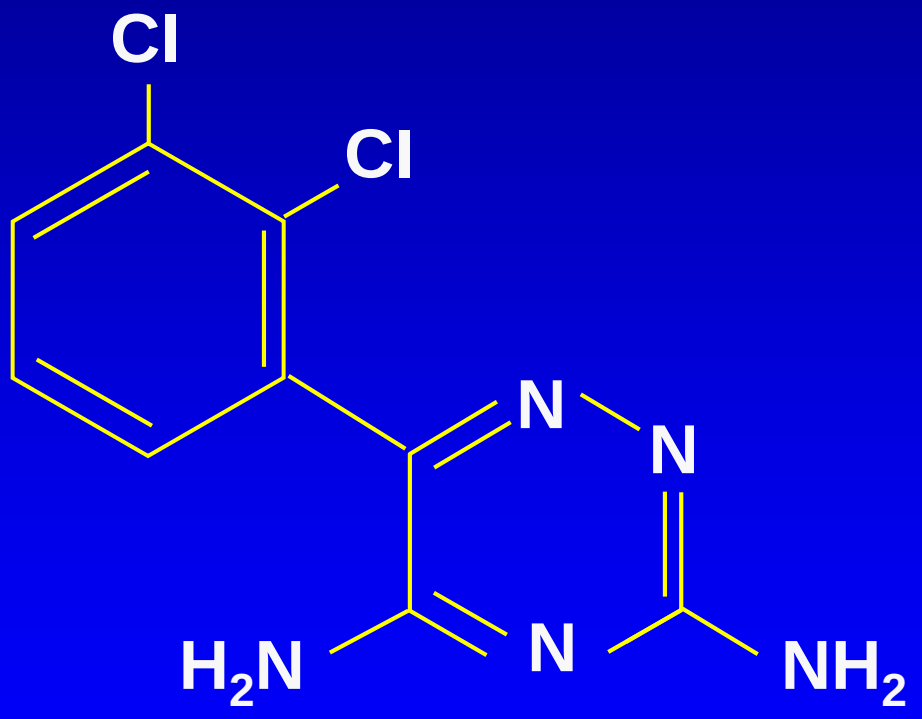
Gabapentin Side Effects

- AE dropouts (epilepsy trials): 7%
- Most common—somnolence, fatigue, ataxia, dizziness
- Uncommon—weight gain, edema, incontinence, hypomania

Pregabalin

- GABA analogue
- Similar to, but more potent than gabapentin
- Under investigation for
  - epilepsy
  - pain disorders
  - mood disorders
  - anxiety disorders

Lamotrigine



Lamotrigine
Mechanism of Action

- Inhibits use-dependent voltage-sensitive sodium channels
- Stabilizes neuronal membranes
- Modulates presynaptic release of excitatory amino acid neurotransmitters such as glutamate
- Reduces repetitive neuronal after-discharge

Xie et al., 1998

Lamotrigine

- Metabolized by conjugation
- Autoinduction
  - Half-life: 25% ↓
  - Clearance: 37% ↑
- Inhibits dihydrofolate reductase
- Melanin binding
  (52 weeks after single dose)

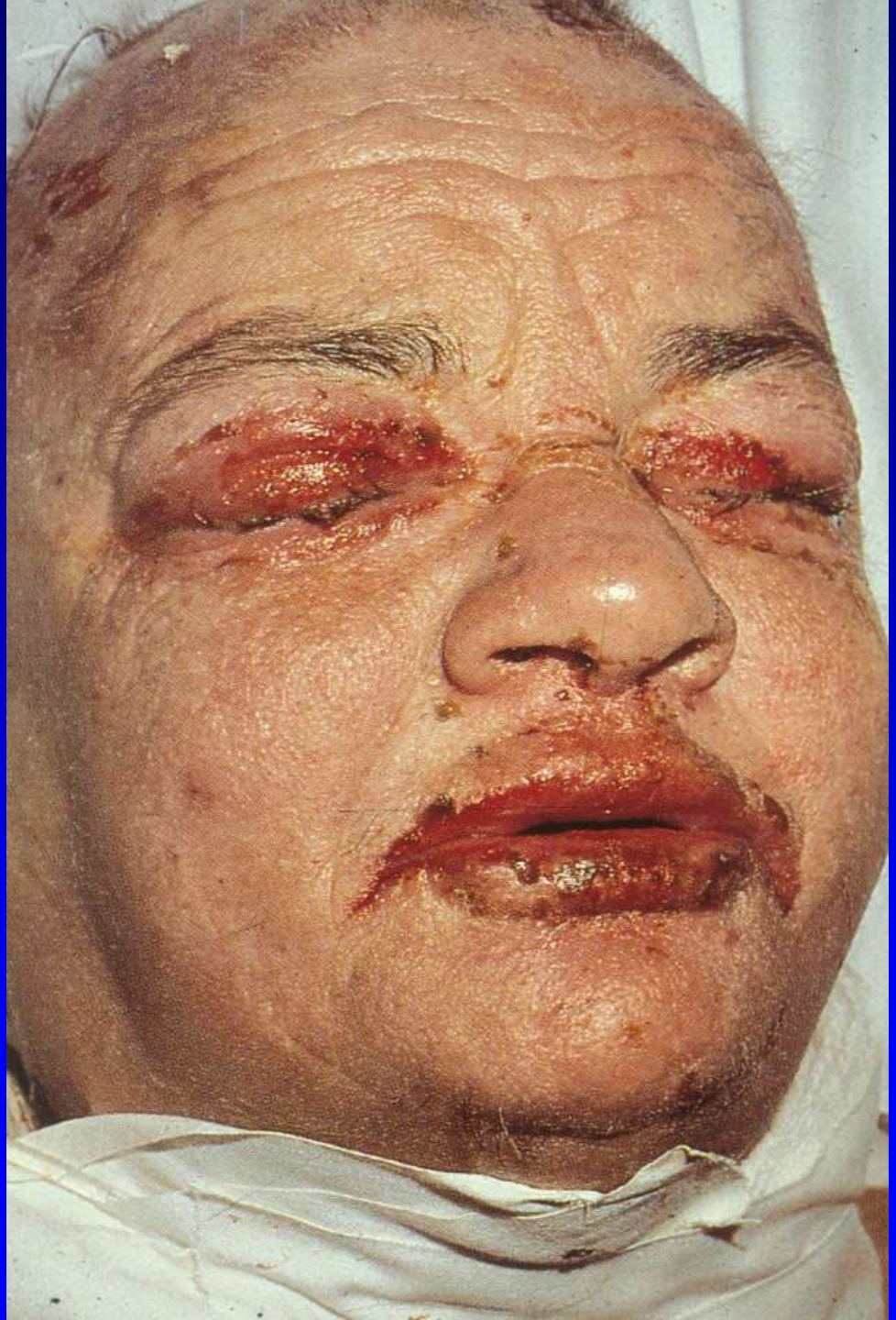
Lamotrigine and Pregnancy

- Clearance increased > 50% early in pregnancy
- Clearance normalized rapidly postpartum
- Be alert for ↓ efficacy during and ↑ side effects after

Tran et. al. Neurology 59:251-255, 2002

Side Effects of Lamotrigine

Dose Related	Not Dose Related
Dizziness	Headache
Diplopia	Dermatologic
Ataxia	10% benign rash
Blurred vision	3/1,000 adults—severe rash
Nausea and vomiting	Do not rapidly escalate dose
Insomnia	Warn patients about rash



Rash with Lamotrigine Use

- Black box warning
- Overall rash prevalence: 10%
  - 0.3% severe in adults
  - 1% severe in children
- Predictors of rash: starting dose, titration, concurrent divalproex, use in children, history of prior rash
- Stevens-Johnson syndrome with lamotrigine
  - 1993: 5/4,450
  - 1999: 3/17,648

Messenheimer et al. Drug Safety. 1998;18:281-96; Physicians' Desk Reference. 55th ed. 2001

Lamotrigine Dosing

- **Monotherapy**
  - **Weeks 1 and 2: 12.5-25 mg/day**
  - **Weeks 3 and 4: 25-50 mg/day**
- **With valproate: ↓ dose by 50%**
- **Maintenance: 50-400 mg/day**

Lamotrigine and Rash
Mood Disorder Clinical Trials

- **Rash (all types)**
  - **LTG (92/979) 9.4%**
  - **Placebo (77/935) 8.2%**
  - **Other (21/307) 7.0%**
- **Serious rash**
  - **LTG (1/979) 0.1%**
  - **Placebo (1/935) 0.1%**
- **No cases of SJS, TEN**

Calabrese et al. ACNP 12/01

Incidence of Rash in Controlled Bipolar Disorder Studies

	Non-serious Rash	Serious Rash[1]
Lamotrigine (n=827)	8.8%	0.0%
Lithium (n=280)	4.3%	0.0%
Placebo (n=685)	7.7%	0.1%

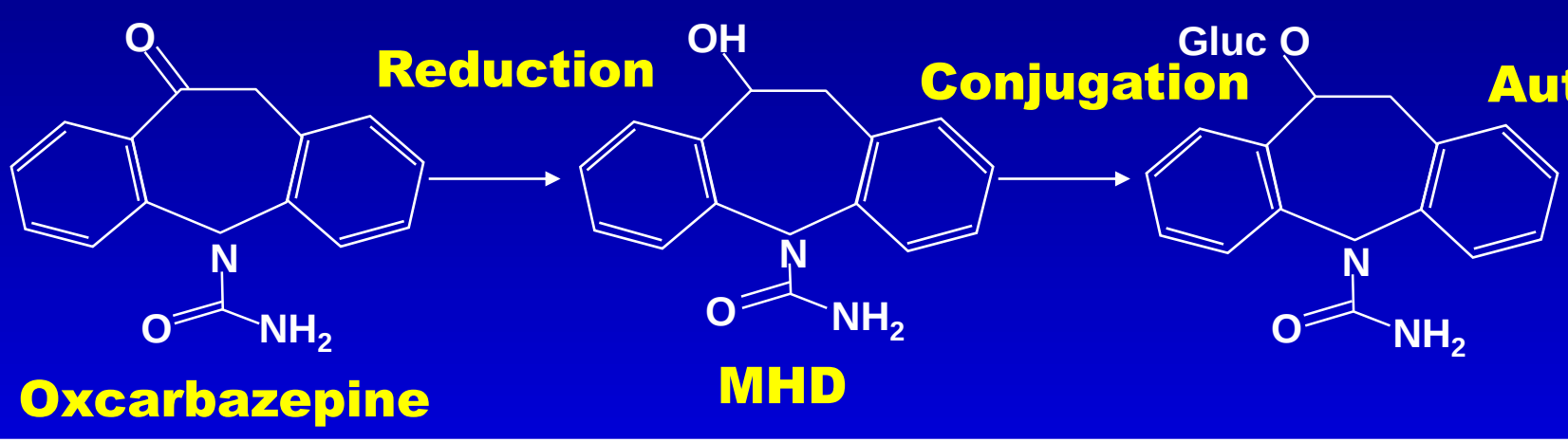
[1]Requiring hospitalisation and drug discontinuation

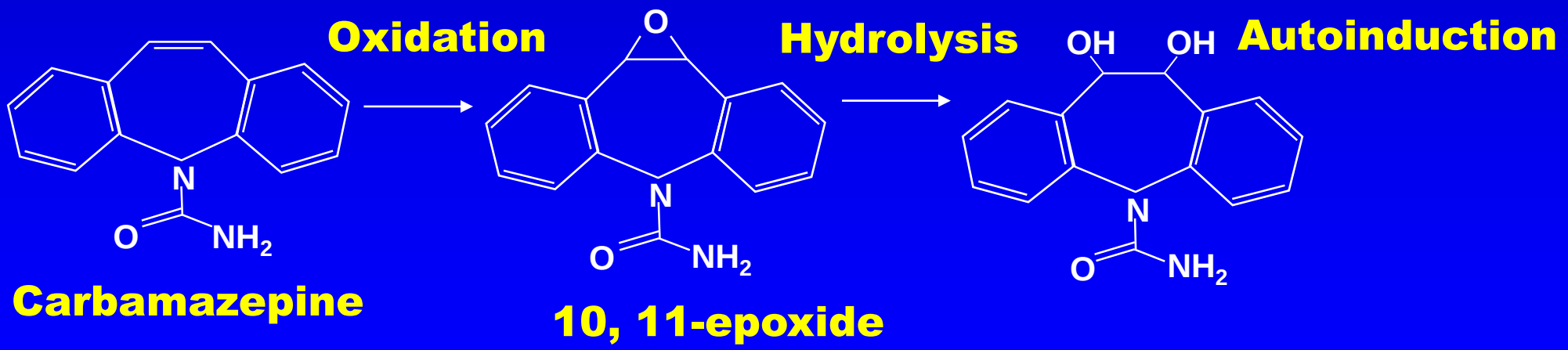
Bowden et al., 2003 submitted

Lamotrigine (LTG) Interactions

- Valproate doubles LTG levels
- LTG ↓ valproate levels 25%
- CBZ ↓ LTG levels 40%
- Oral contraceptives ↓ LTG levels 49% (n=7)
- Sertraline ↑ LTG levels 2-fold (n=2)
- LTG ↑ clozapine levels 3-fold (n=1)

Oxcarbazepine and Carbamazepine Metabolic Differences





Schacter S. *Exp Opin Invest Drugs.* 1999;8(7):1-10

Oxcarbazepine

- 10-keto analogue of CBZ
- Prodrug → MHD
  (10-hydroxycarbazepine)
- Half-life OXC 2 hours
  MHD 9 hours
- Protein binding 40%

Oxcarbazepine for Acute Mania

- **Better than placebo (n=6)**

  Emrich et al., 1983

- **Equal to haloperidol (n=38)**

  Emrich, 1990

- **Equal to lithium (n=52)**

  Emerich, 1990

Oxcarbazepine Side Effects

- AE dropouts 23%
  - monotherapy 9%
  - pediatrics 11%
- Common – nausea, vomiting, dizziness, somnolence, ataxia
- Uncommon – hyponatremia (< 125 mEq/L 2.5%)

Oxcarbazepine and Hyponatremia

- Sodium < 125 mmol/l in 2.5%
- Symptomatic hyponatremia – uncommon
- CBZ → OXC: Sodium levels may ↓
- Monitor at risk patients
- Treat - ↓ or stop drug, restrict fluids

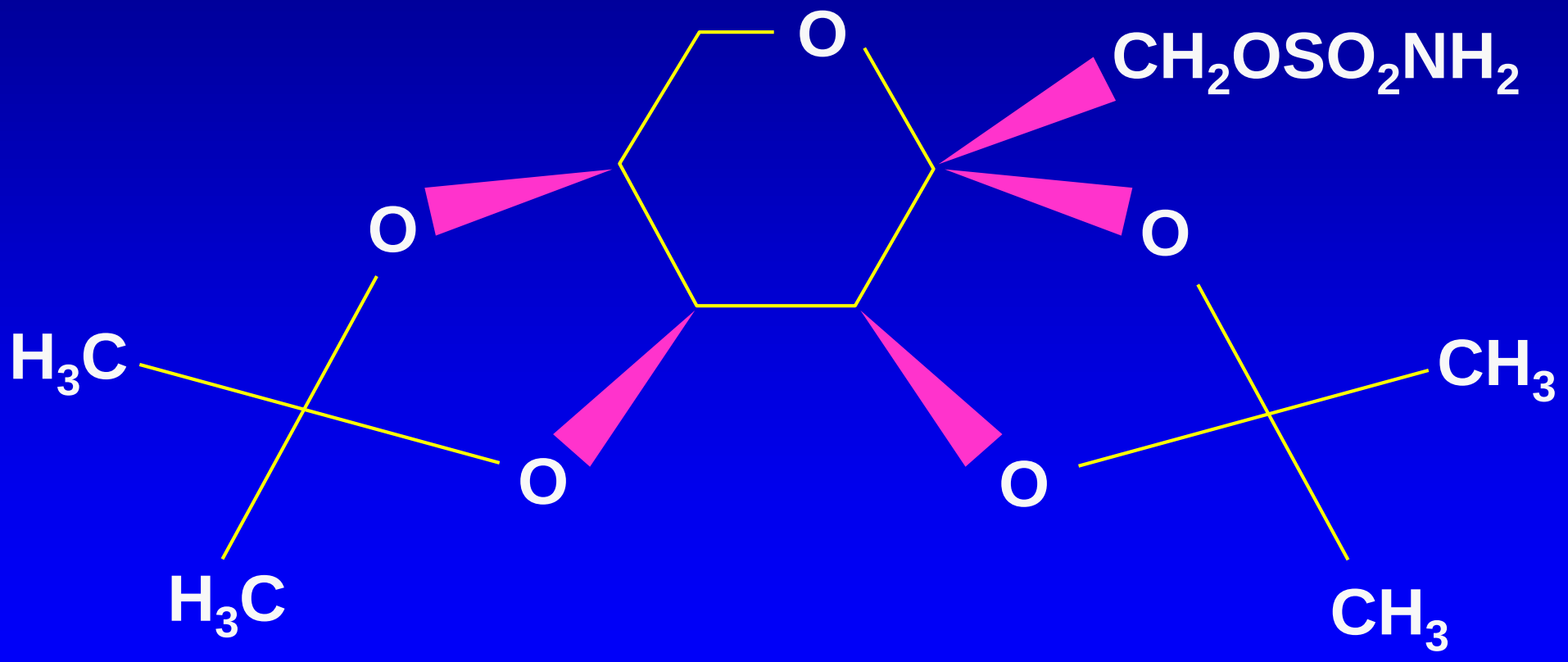
CBZ and OXC Hyponatremia

- ↑ renal sensitivity to ADH
- Direct ADH-like activity
- ↑ central release of ADH
- ↓ vasopressinase activity

Oxcarbazepine Interactions

- No autoinduction
- Inhibits 2C19 (e.g., ↑ phenytoin)
- Induces 3A4 (e.g., ↓ ethinylestradiol
- Fewer interactions than CBZ

Topiramate



Topiramate (Topamax)

- Half life 21 hours
- Minimal metabolism (< 30%)
- Inhibits CYP2C19
- ↓ estrogen in oral contraceptives

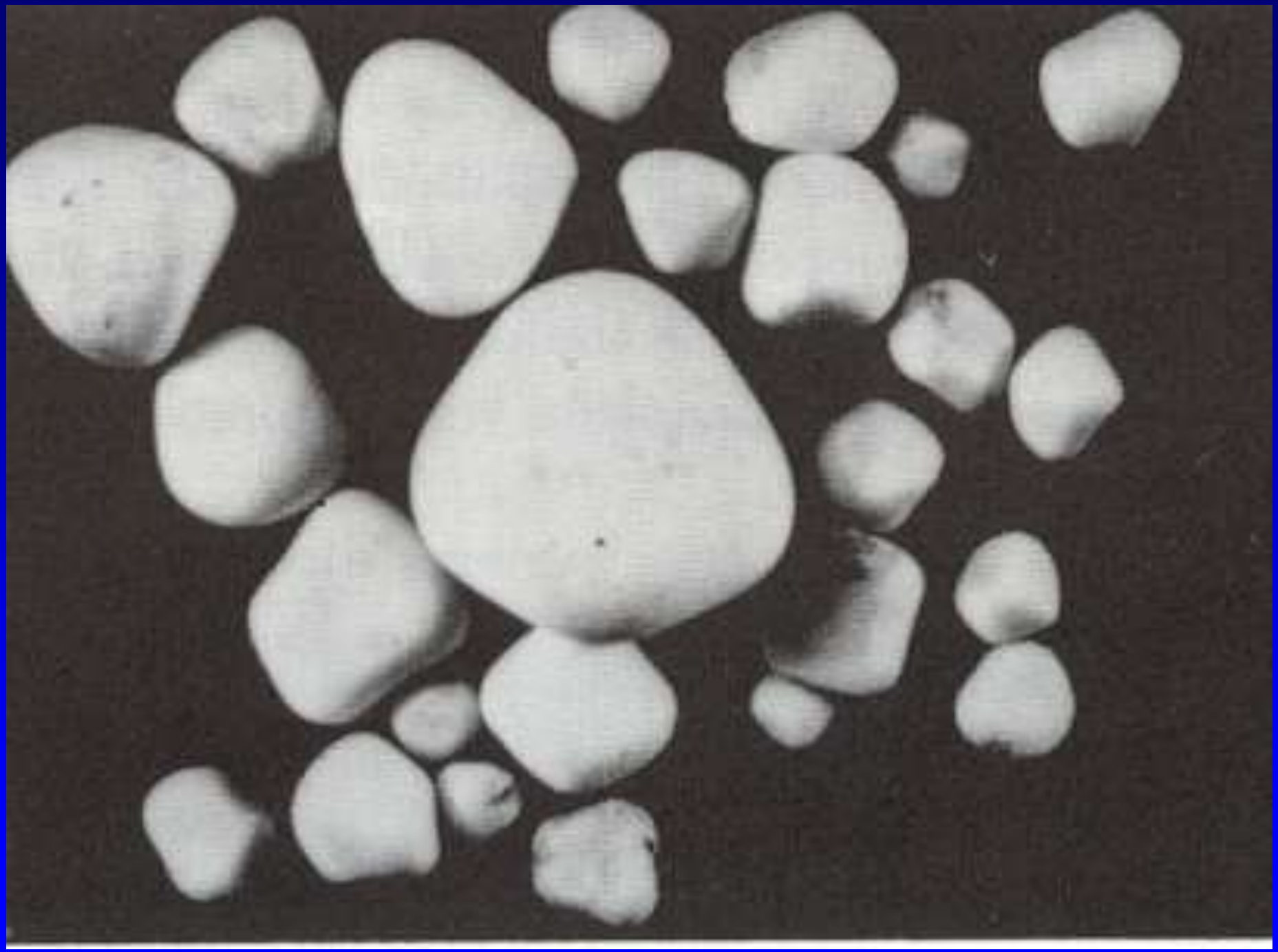
Topiramate for Bipolar Disorders

- **Dose range: 25-400 mg/day**
- **Efficacy**

moderate/marked improvement	52%
minimal/no improvement	36%
worse	11%

- **Adverse events dropouts (6/58) 10%**

Marcott D: J Affect Dis 1998;50:245-251



Topiramate

- **AE dropouts (epilepsy trials): 28%**
- **More common: somnolence, cognitive impairment, dizziness, ataxia, psychomotor slowing, paresthesias, weight loss**
- **Kidney stones: 1.5%**

Topiramate and Kidney Stones

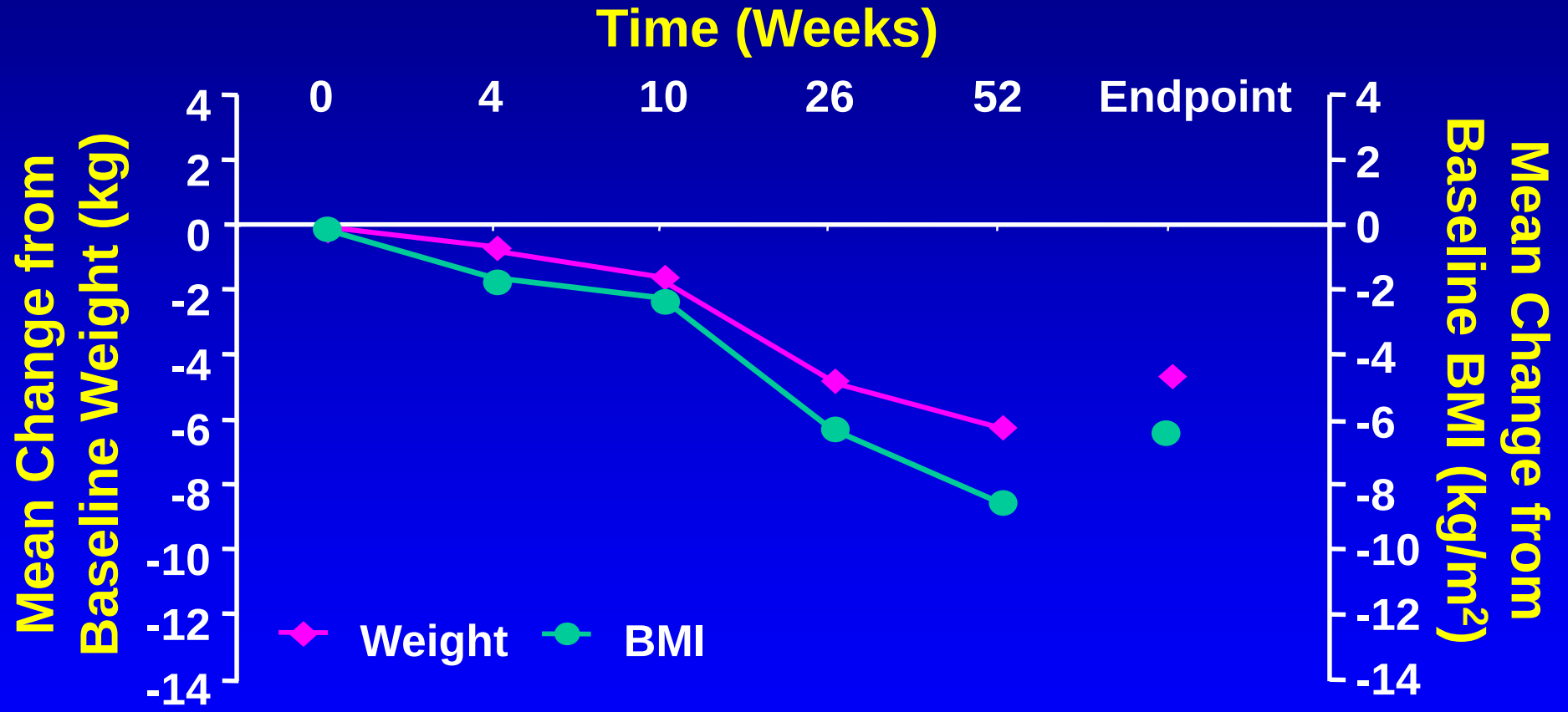
- Occurred in 1.5% (32/2086)
- 2 to 4 times ↑ risk
- Men > women
- Reported in kids
- One bipolar II woman
- Carbonic anhydrase inhibition

Topiramate Adverse Events
(drug minus placebo, epilepsy trials)

	200 mg	400 mg	600-1000 mg
• Nervousness	5.8%	10.1%	13.1%
• Depression	2.6%	1.1%	7.1%
• Mood problems	0	4.2%	8.4%

Package insert

Topiramate as Adjunct Therapy in Bipolar Disorder: Change in Weight and BMI*



*Last observation carried forward; p<0.05; compared with baseline; McElroy SL et al. Biol Psychiatry. 2000;47:1025-1033

Topiramate for Obesity
(12 w, max 100 mg/day)

	Wt. Loss	A.E. drops
• No diagnosis (n=25)	16.4 lbs	12%
• Bipolar, stable (n=25)	16.7 lbs	36%
• Bipolar, partial (n=25)	13.5 lbs	56%

Hussain et al. APA NR 709, May 2000

Tiagabine

- GABA uptake inhibitor
- Metabolized by CYP3A
- Half-life: 7 to 9 hours
- Protein binding: 96%

Tiagabine – A Mood Stabilizer?

- **Effective**
  Kaufman, 1998 n=3
  Schaffer and Schaffer, 1999 n=2

- **Ineffective**
  Grunze et al., 1999 n=8

Tiagabine

- Side effect dropout: 21%
- More common side effects
  - Dizziness, nervousness
  - Somnolence, fatigue
  - Difficulty concentrating
  - Tremor
  - Abdominal pain

Zonisamide for Psychiatric Disorders

- Promising as add-on (n=24)
  - Bipolar mania, n=15
  - Schizoaffective mania, n=6
  - Schizophrenic excitement, n=3
- No A.E. dropouts

Kanba S et al. Prog Neuropsychopharmacol Biol Psychiatry. 1994;18:707-715

Zonisamide

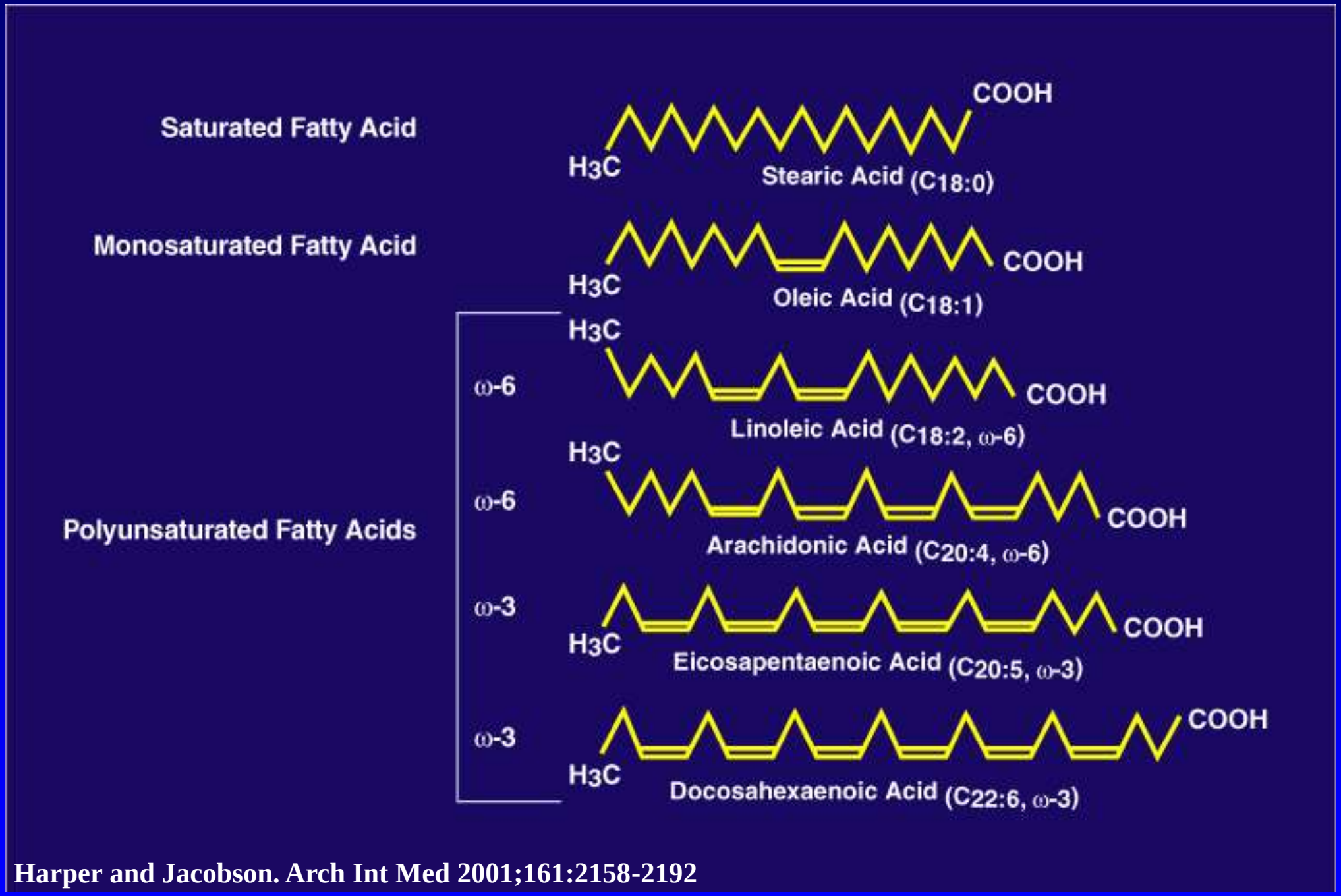
- **Kidney stones – 4% (40/991)**
- **Serum creatinine – 8% mean increase**
  - **Clinical significance?**
  - **Consider periodic monitoring**
- **Oligohidrosis and hyperthermia (especially in kids)**

Levetiracetam

- Add-on for partial onset seizures in adults (FDA Nov. 99)
- Structural analog of piracetam
- Unique mechanism of action

Levetiracetam

- Effective in animal anxiety models
- Effective in animal mania model
- Effective in one manic patient
  (Goldberg and Burdick. AJP 2002;159:148)
- Studies underway



Harper and Jacobson. Arch Int Med 2001;161:2158-2192

Omega-3 Fatty Acids for Unstable Bipolar Disorder (n=30)

- 4 months, db, placebo-controlled
- Recurrence: Omega-3 7%
  Placebo 47%
- Mechanism: altered post-synaptic transduction

Stoll et al. ACNP Poster 12/97

FDA Pregnancy Categories

A: Controlled Studies – No Risk

B: No Evidence of Risk in Women

C: Risk Cannot be Ruled Out

D: Positive Evidence of Risk

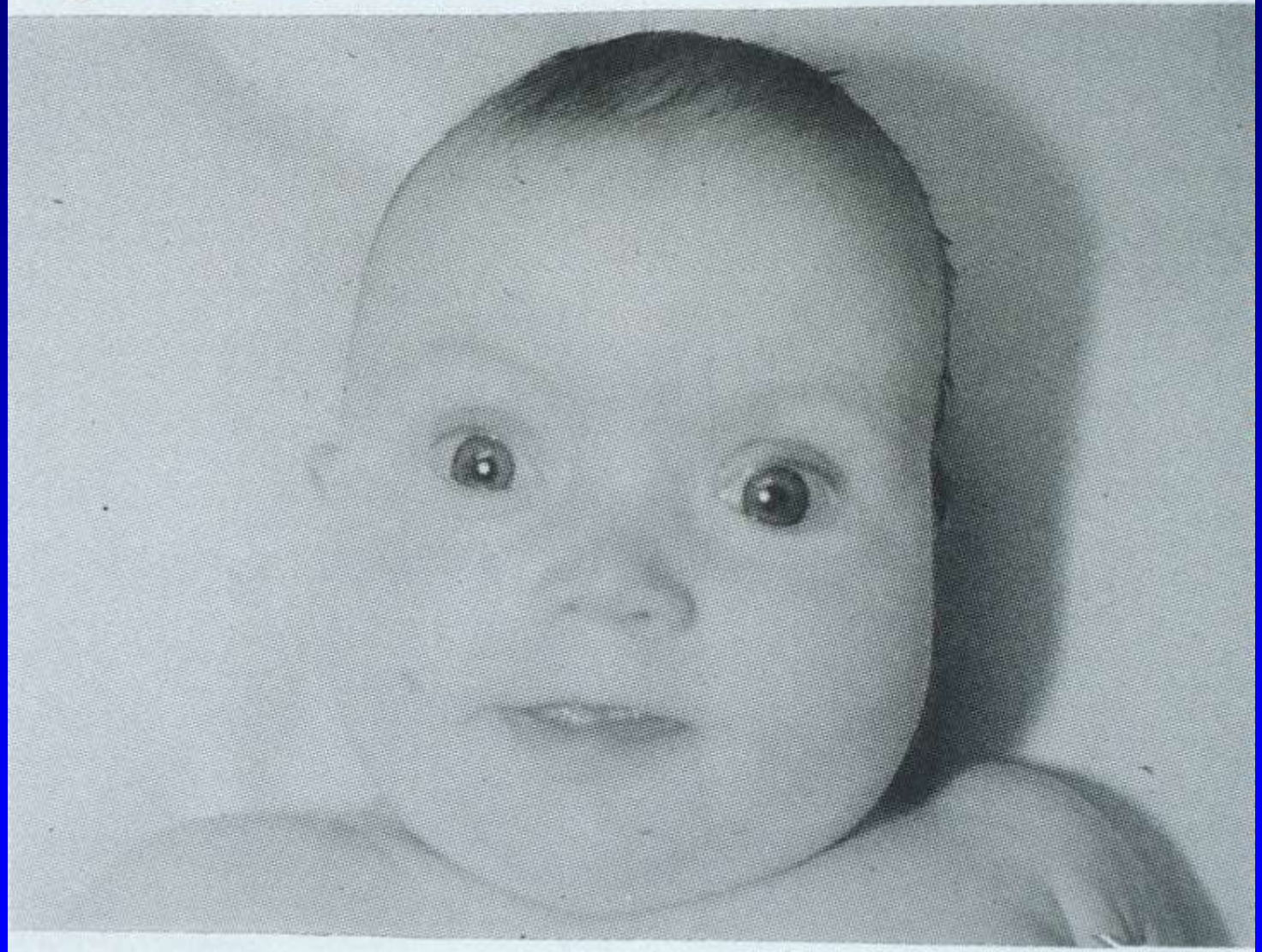
X: Contraindicated in Pregnancy

Mood Stabilizers and Pregnancy

FDA Risk Category

- **Lithium** **D**
- **Valproate** **D**
- **Carbamazepine** **D**

Typical facial features of FVS in an infant. Note trigonocephaly, epicanthic folds, and infraorbital grooves



Clayton-Smith J, Donnai D: J Med Genet 32:724, 1995

Fetal Valproate Syndrome

- Distinctive facial phenotype
- Nueral tube defects 10x
- Congenital heart defects 4x
- Oral clefts 5x

Clayton-Smith and Donnal, J Med Genet 32:727-727, 1995

New Anticonvulsants and Pregnancy FDA Risk Categories

- Gabapentin C
- Lamotrigine C
- Tiagabine C
- Topiramate C

Mood Stabilizers and Pregnancy

Teratogenicity

- Gabapentin ?
- Lamotrigine ?
- Topiramate ?
- Tiagabine ?

Briggs, Freeman, Haffe, eds. Drugs in Pregnancy and Lactation: a reference guide to Fetal and Neonatal Risk. 5th ed. Williams and Wilkins, 1998

Breast-feeding during maternal pharmacotherapy is acceptable if the risk-benefit analysis is carefully considered and the mother-baby pair is monitored

Wisner, et al. AJP 153:1132-1137, 1996 (Sept)

Summary

- Current mood stabilizers not always effective or well-tolerated
- Newer anticonvulsants show promise in bipolar disorder
- More research needed

Psychosocial and Other Non-pharmacologic Treatments

Psychoeducation Goals

- Improve medication adherence
- Reduce recurrences
- Improve psychosocial functioning
- Improve occupational functioning
- Improve quality of life

Mood Stabilizer Noncompliance

- Mood control by meds
- Missed highs
- A hassle
- Reminder of illness
- Felt well
- Less creative
- Less attractive
- Side effects
- Cost

Compliance is Crucial
Enhancing Compliance

- Education
- Availability
- Maximize benefit
- Minimize side effects
- Keep it simple

Bipolar Psychotherapies

- **Family Focused**
  - **Miklowicz and Gadstein**
- **Interpersonal and Social Rhythm**
  - **Frank, Kupfer, et al.**
- **Cognitive-Behavioral**
  - **Basco and Rush**
- **Life Goals Program**
  - **Bauer and McBride**

Psychosocial Bipolar Treatments

- Here and now focus
- Time limited
- Supportive of pharmacotherapy
- Educational
- Practical stressor coping techniques

Family-Focused Treatment for Bipolar Disorders (FFT)

- Initial assessment
- Education
- Communication enhancement training
- Problem-solving skills
- Crisis intervention

Miklowitz and Goldstein

Cognitive-Behavioral Therapy for Bipolar Disorder

Basco and Rush, 1996 (book)

Interpersonal and Social Rhythm Therapy for Bipolar Disorder (IP/SRT)

- Regulate social rhythms and sleep-awake cycle
- Develop symptom management plan
- Master interpersonal conflicts

Frank, Kupfer, et al.

Life Goals Program for Bipolar Disorder

- Structured, manual-based group psychotherapy program
- Part 1 - illness management (educational)
- Part 2 - improving functional status (goals)

Bauer and McBride, 1996 (book)

Nonpharmacologic Treatments

- Psychotherapies for depression
  - CBT, IPT, other
- Light therapy for depression (risk of mania/hypomania)
- ECT for mania and depression
- Investigational (sleep, manipulation, rTMS, VNS)

Education

Education

Education

Depression and Bipolar Support Alliance (DBSA)

730 N. Franklin Street, Suite 501

Chicago, IL 60610

(800) 826-3632

www.dbsalliance.org

Formerly: National Depressive and Manic Depressive Association (NMDA)

New Options for Bipolar Disorders

- The future looks bright
- Data-based treatment when possible
- Treatment need often exceeds data availability
- The skillful combination of art and science will prevail

Post Lecture Exam
Question 1

1. **A patient with recurrent hypomanic episodes and major depressive episodes would be classified in DSM-IV with which diagnosis?**

A. Cyclothymic Disorder
B. Bipolar Disorder Not Otherwise Specified
C. Bipolar I Disorder
D. Bipolar II Disorder

Question 2

2. Features of rapid cycling bipolar disorder include all of the following <u>except</u>:

A. At least 4 episodes/year
B. More common in men
C. May be induced by antidepressants
D. May not persist

Question 3

3. Which one of the following predicts a good treatment response to lithium?

A. Mixed episodes
B. Depression-mania-euthymia course
C. Euphoric mania
D. Rapid cycling

Question 4

4. All of the following are FDA-approved for treating acute mania except:

A. Chlorpromazine
B. Carbamazepine
C. Olanzapine
D. Divalproex

Question 5

5. Which one of the following is likely to lower serum lithium levels?

A. Hydrochlorothiazide
B. Ketoprofen
C. Captopril
D. Theophylline

Question 6

6. Valproate shares all of the following side effects within lithium except for:

A. Tremor
B. Hepatic dysfunction
C. Weight gain
D. GI disturbance

Question 7

7. Which one of the following is characterized by no protein binding, no metabolism, and no important drug interactions?

A. Gabapentin
B. Lamotrigine
C. Topiramate
D. Tiagabine

Question 8

8. Which one of the following has been shown to be more effective than placebo as monotherapy for Bipolar I depression?

A. Gabapentin
B. Lamotrigine
C. Topiramate
D. Valproate

Question 9

9. Blood levels of lamotrigine are doubled by which one of the following?

A. Carbamazepine
B. Gabapentin
C. Lithium
D. Valproate

Question 10

10. Kidney stones can be a side effect of which one of the following?

A. Valproate
B. Lithium
C. Lamotrigine
D. Topiramate

Answers to Pre & Post Competency Exams

1. D
2. B
3. C
4. B
5. D
6. B
7. A
8. B
9. D
10. D