Medicine for Bipolar Disorder

Theo Manschreck MD MPH
Harvard Medical School
James Jefferson, MD
University of Wisconsin

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Pre-Post Lecture Exam

1. **The most common misdiagnosis of bipolar depression is:**

   a) anxiety disorder

   b) substance abuse

   c) borderline personality disorder

   d) unipolar depression

   e) schizophrenia

2. Treatment of bipolar depression with antidepressants may lead to:

a) anxiety

b) greater mood instability

c) mania induction

d) psychosis

e) b and c

f) all of the above

3. In the treatment of moderate or severe mania, most guidelines recommend combination treatments, such as lithium or divalproex and atypical antipsychotics.

a) true

b) false

4. Which of the following is incorrect? Lithium therapy is known to:

a) induce tremor

b) cause urinary frequency

c) be associated with thirst

d) increase suicide risk

e) induce nausea, vomiting, and diarrhea

5. Kidney stones are associated with:

a) olanzapine

b) bipolar disorder complicated by substance abuse

c) lithium

d) divalproex

e) topiramate

* Lecture Topics

- **Overview: Bipolar disorder-- prevalence, misdiagnosis, phases, value of medication and other approaches**
- **Treatment: Acute mania, bipolar depression, maintenance, rapid cycling**
- **Specific agents: Indications, efficacy, side effects, interactions, other therapeutic issues**
- **Pregnancy**

Overview: Teaching Points

- Challenges to recognize
- Many medicines to consider
- Treatment goals to specify
- Treatment selections to make

Bipolar Disorder Challenges

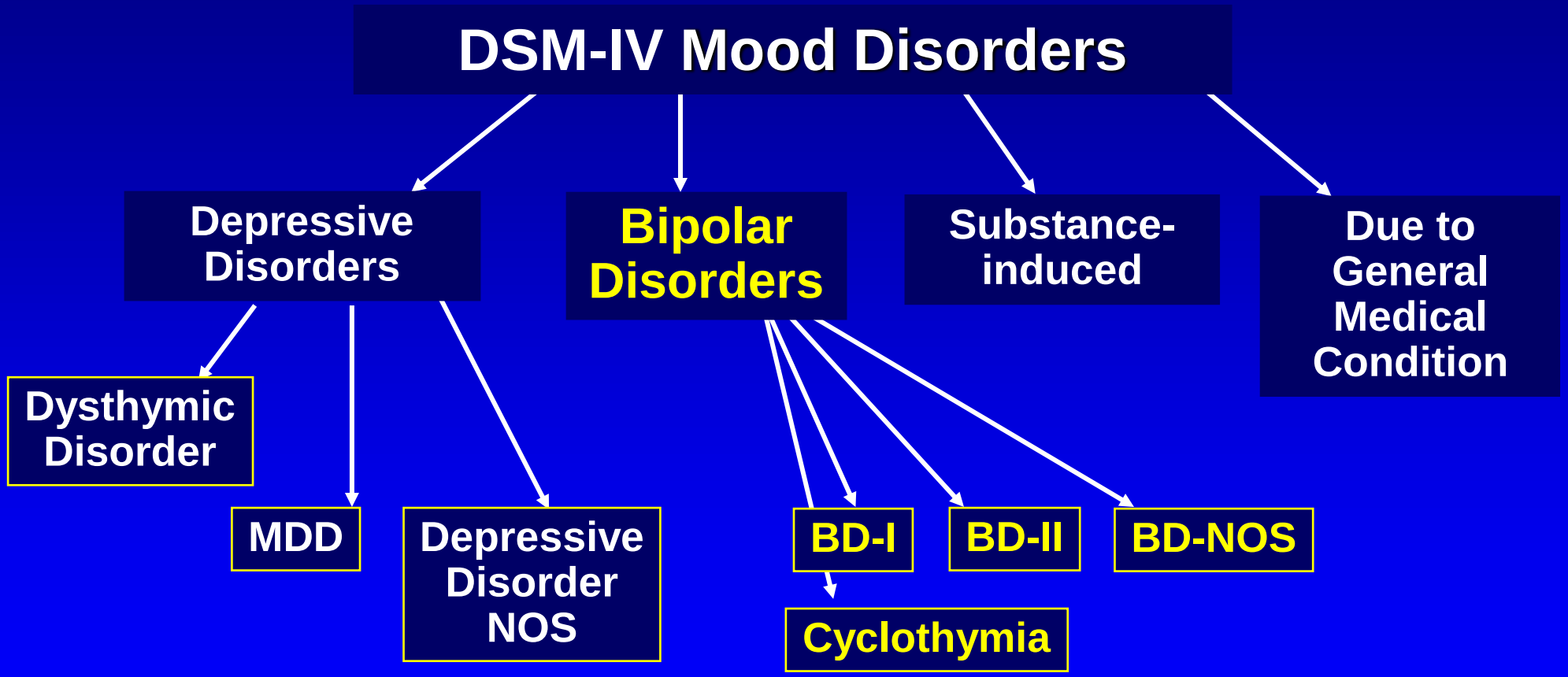
- **Prevalence: 1-4% or higher (narrow vs spectrum)**
- **Onset in young adulthood (for cases >60 years: medical disorders should be first thought)**
- **Chronic episodic course**
- **Morbidity (disability, hospitalization, maladjustment, substance problems, psychiatric disorder, medical problems)**
- **Mortality (suicide, accidents, and medical co-morbidities)**

Bipolar Disorder Challenges

- Onset to proper diagnosis: 3-10 year lag (35% wait >10 years for correct diagnosis)
- Misdiagnoses: unipolar depression (60%); anxiety disorders (26%); schizophrenia (18%); personality disorder (17%); alcohol/substance abuse (14%).
- Significant co-morbidities (e.g., 60% lifetime prevalence of alcohol and drug use disorders)
- Significant complications: cognitive, personal and occupational functioning

Regier et al, 1990; Hirschfeld et al, 2003; Klassen et al, 2009; Wingo & Ghaemi, 2007

Mood Disorders: DSM-IV Classification



APA (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: APA

Bipolar Spectrum Disorders

- Bipolar I disorder: history of mania*
- Bipolar II disorder: history of hypomania and major depressive episodes*
- Cyclothymia*
- Hyperthymic temperament
- Secondary mania (to other illnesses or drugs)
- Antidepressant-induced mania and hypomania

*DSM-IV categories; American Psychiatric Association (1994), Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, D.C.: American Psychiatric Publishing, Inc.

Phases of Bipolar Disorder

- Acute mania
- Bipolar depression
- Maintenance

* Treatment: Challenges of Bipolar Disorder

- **Complexity of the clinical presentation (heterogeneous symptom picture, co-morbid psychiatric disorders, and medical disorders)**
- **Recognition of bipolar depression**
- **Lack of adherence to treatment & education about the illness***
- **Necessity of <u>phase</u> relevant treatments & life long strategies.**

Foster et al, Cur Psychiatry, 2011; 10: 45-53

* Many Medicines

- Antipsychotics
- Mood stabilizers
- Combinations
- ? Antidepressants

* Treatment Goals

- **Acute mania**

  Rapid onset of action, relief of symptoms, no depression induction
- **Bipolar depression**

  Relief of symptoms, no mania induction
- **Maintenance**

  Prevention of relapse into depression or mania; reduction of co-morbid anxiety

*Selecting Medication(s)

- Phase specific considerations
- Prior response and tolerability
- Medical and psychiatric co-morbidities
- Side effects
- Drug interactions
- Patient preferences

Acute Mania

Acute Mania: FDA Approved

- 1970 Lithium*
- 1973 Chlorpromazine
- 1995 Divalproex
- 2004 Carbamazepine ER
- 2005 Divalproex ER

*Pediatric mania (12-17 yoa)

FDA Approved Atypical Antipsychotics for Mania

- Olanzapine (Zyprexa) 2000*
- Risperidone (Risperdal) 2003**
- Aripiprazole (Abilify) 2004**
- Quetiapine (Seroquel) 2004**
- Ziprasidone (Geodon) 2004
- Asenapine (Saphris) 2009

*Adolescent mania (13-17) 2009/**Pediatric mania (10-17): RIS 2007/ARI 2008/QTP 2009

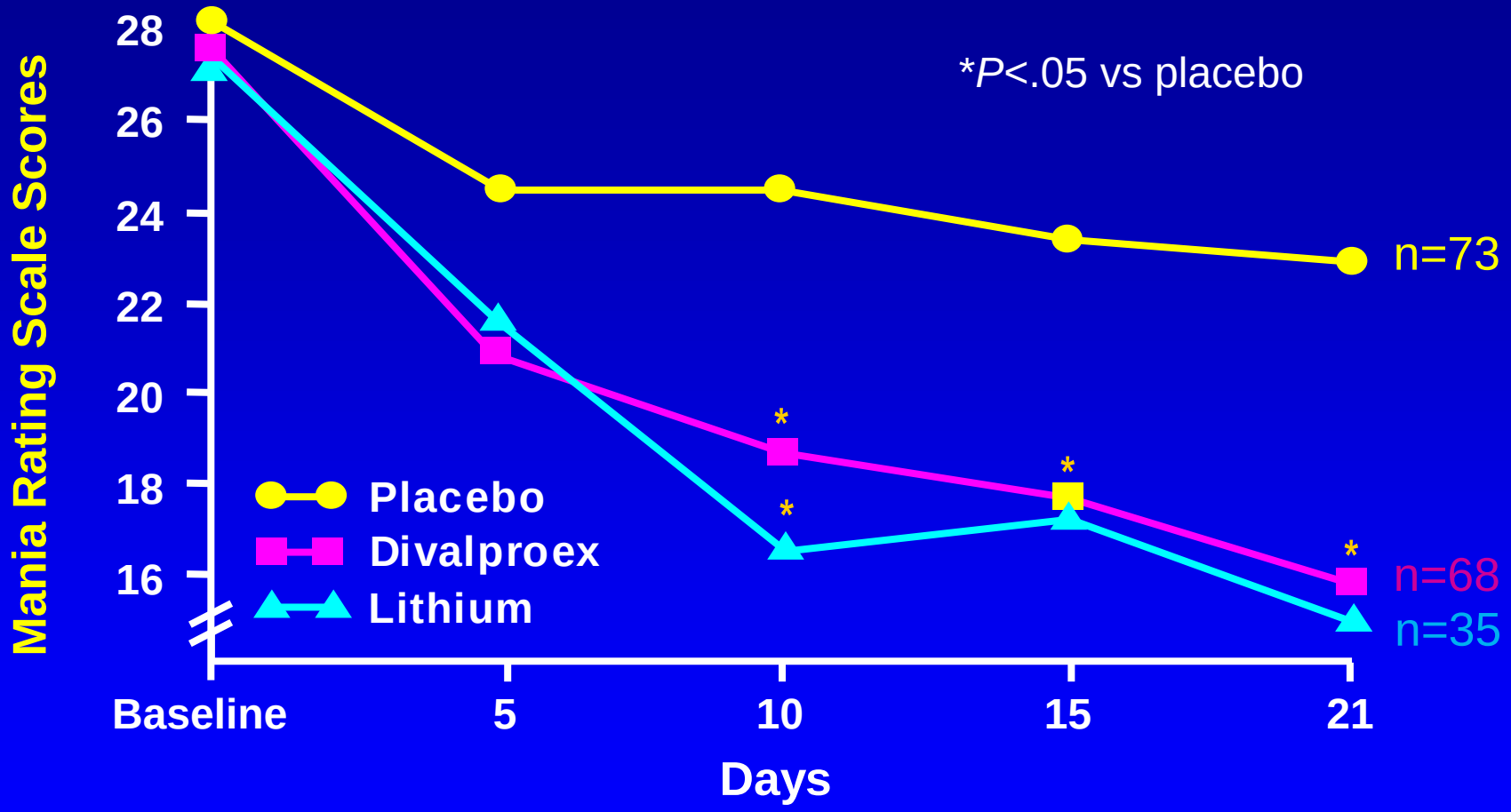
* Acute Mania: First-Line

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

APA Bipolar Guidelines, Revised 2002
APA Bipolar Guidelines Watch 2005
CANMAT & ISBN Guidelines 2009
***Weisler et al, J Clin Psych, 2005**

* Double-Blind Controlled Study

Divalproex vs Lithium vs Placebo



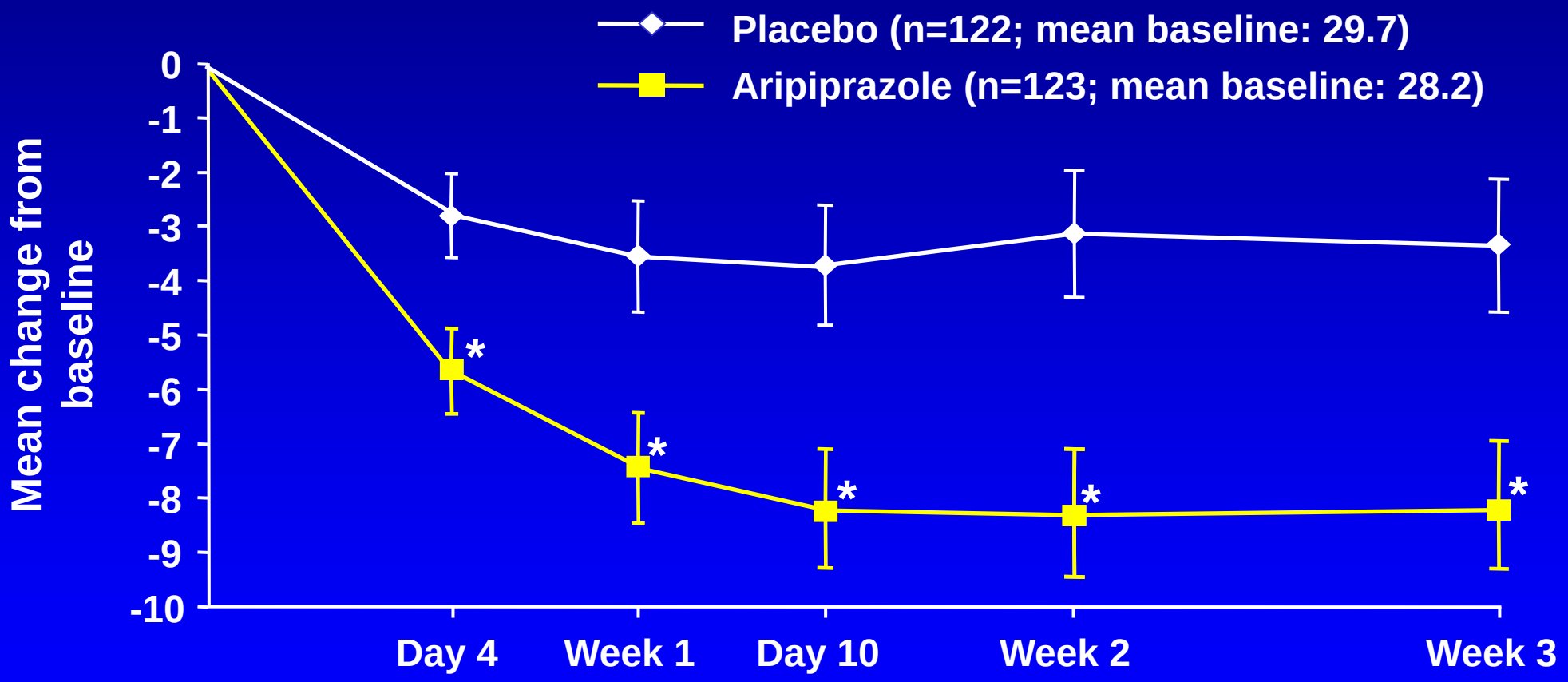
Reproduced with permission from Bowden CL, et al. *JAMA*. 1994;271:918-924.

*Second Generation Antipsychotics in Mania

- **All apparently effective**
- **Generally no worsening of depression (unlike conventional antipsychotics)**
- **Antidepressant effects (e.g., as seen with quetiapine) & some adjunctive mood stabilization effects**
- **Less EPS but be wary of metabolic risks, especially weight gain (except possibly for aripiprazole & ziprasidone) and abnormalities in glucose, lipids, or prolactin**

See also: Cipriani et al, Lancet 2011; 378: 1306-15

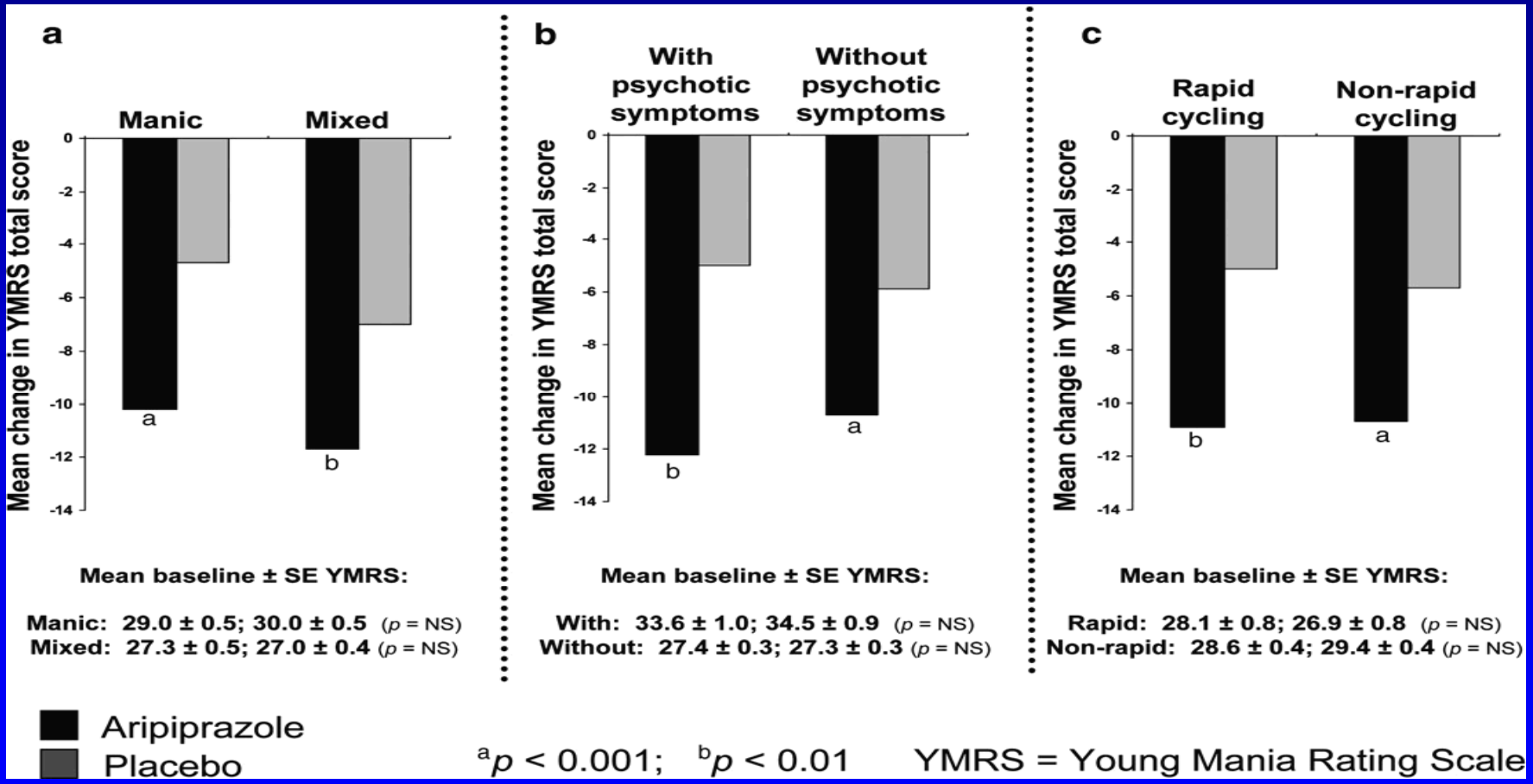
*Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS



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

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

*Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS

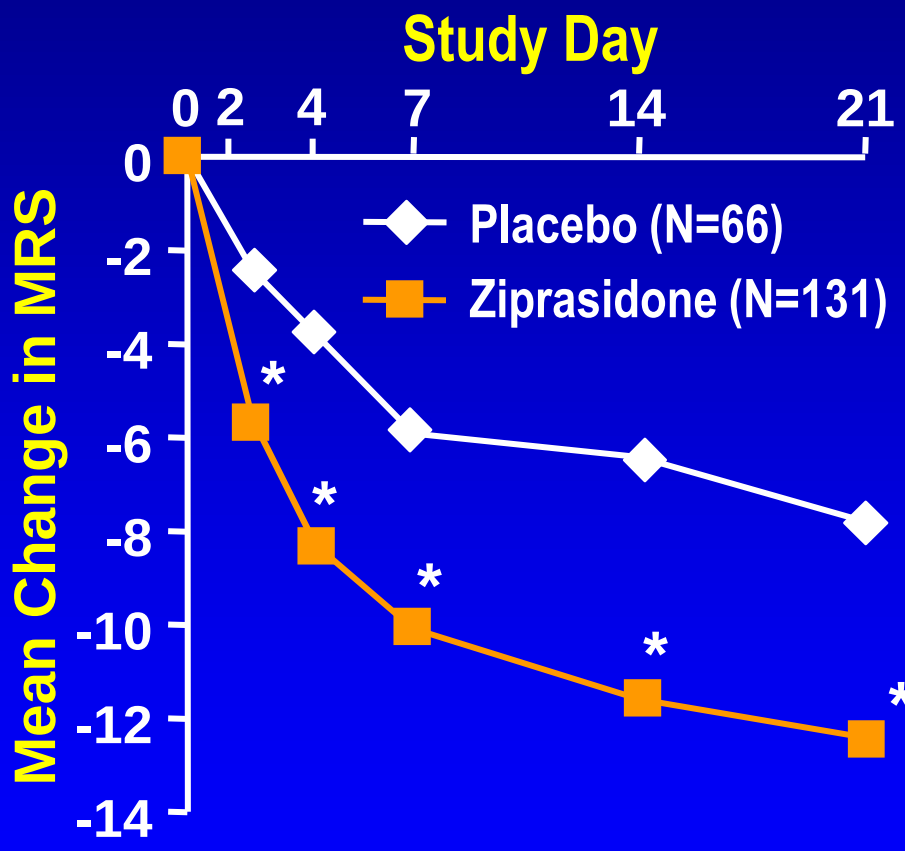


Mean change in YMRS total scores from baseline to trial end point(21 days)

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

Ziprasidone: Efficacy in Acute Mania

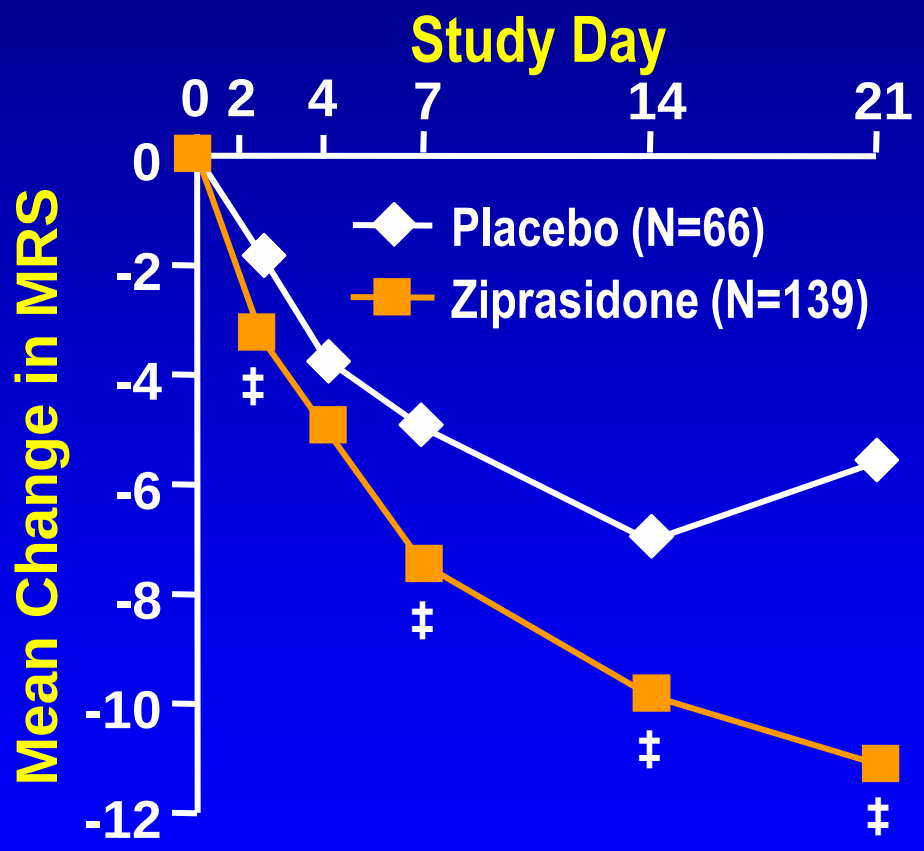
Mean Change From Baseline (LOCF)



*p<0.01;

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

Mean Change From Baseline† (LOCF)



†ziprasidone = 26.19; placebo = 26.49; ‡p<0.05;

Potkin et al.,J Clin Psychopharmacol 2005;25:301-310

Asenapine for Acute Mania

Despite clinical trial evidence*, clinical experience is limited; therefore, asenapine alone or in combination with lithium or divalproex is recommended as a second-line option.

CANMAT and ISBN, Guidelines Update 2009

*McIntyre et al, J Aff Disord, 2008; Bipolar Dis 2009; 11: 673-686.

* Use of Antipsychotics in Mania

- **Fairly rapid titration (e.g., 1-3 days), Example: ziprasidone start 40 mg bid and titrate dose.**
- **Often used adjunctively**
- **May discontinue antipsychotic at some point.**

Tohen et al AJP 2002; 159:1011-1017; Zajecka et al J Clin Psych 2002; 63:1148-1155

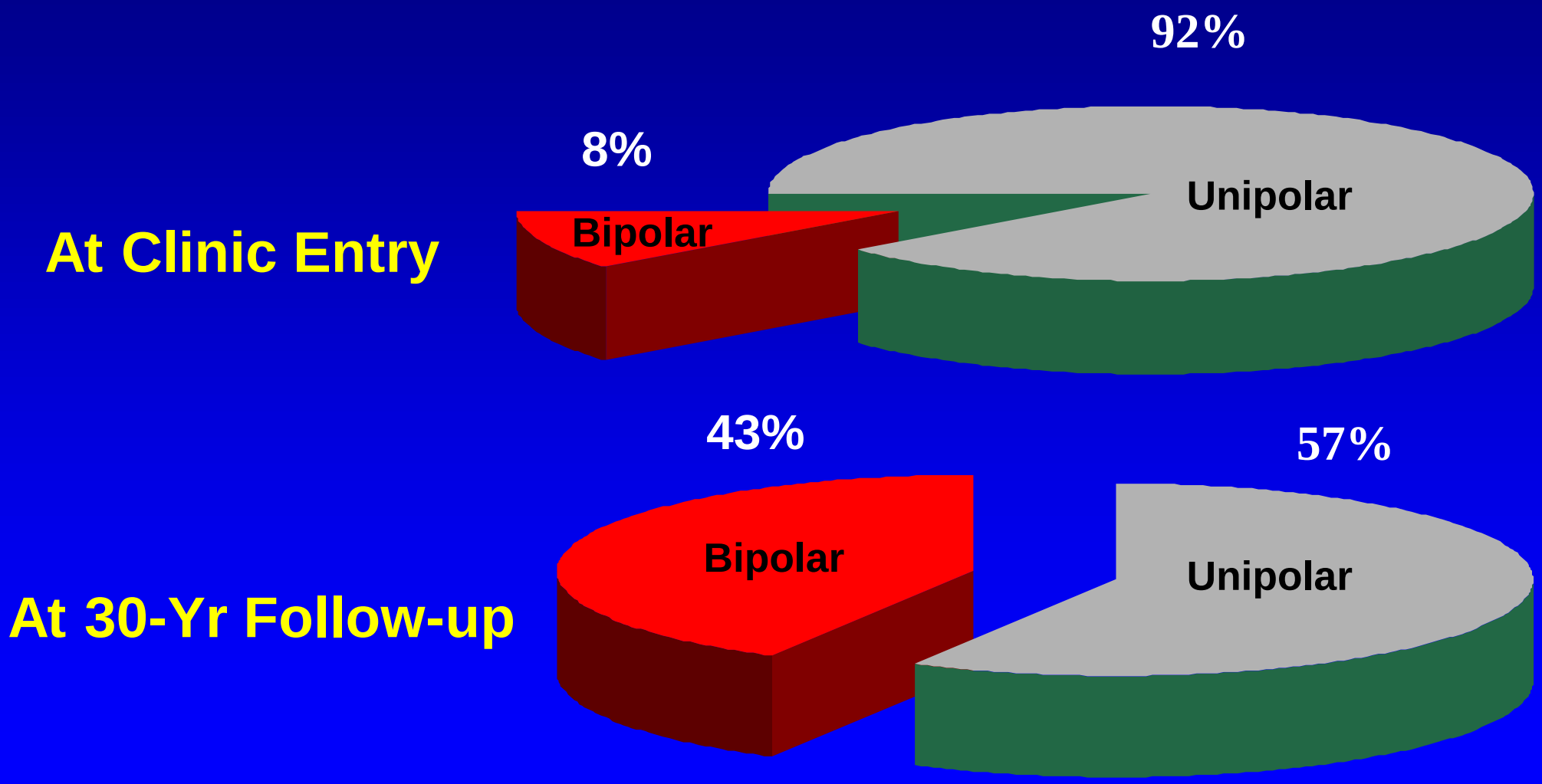
* Clozapine for Bipolar Disorder

- Open label reports of benefit for mania, maintenance, and possibly depression
- No double-blind studies

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

Bipolar Depression

Unipolar or Bipolar Disorder



Angst J, Sellaro R. Biol *Psychiatry* 2000;48:445-457.

Detecting Bipolar Patients Presenting With Depression

- Ask about history of mania and hypomania
- Ask about family history of bipolar disorder
- Consult family members or significant others
- Administer a bipolar screening instrument, such as the Mood Disorder Questionnaire (MDQ)

Hirschfeld RM, Vornik LA, J Clin Psychiatry 2004; 65(suppl 15):5-9

* Bipolar Depression (BPD)

- **First-line – lithium, quetiapine, lamotrigine,* OFC (olanzapine/fluoxetine combination)**
- **Antidepressant monotherapy not advised**
- **Moderate increase in risk (mania) with antidepressant therapy in BPD** but this matter remains controversial**
- **ECT: consider for serious cases *****

*4 of 5 RCTs show no advantage over placebo for LTG
Calabrese et al, Bipolar Disorder, 2008

**Tondo et al, Acta Psychiat Scand, 2009

***Ansari & Osser, Harvard Rev Psych, 2010

* Bipolar I Depression: Olanzapine and Olanzapine-Fluoxetine Combination (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**

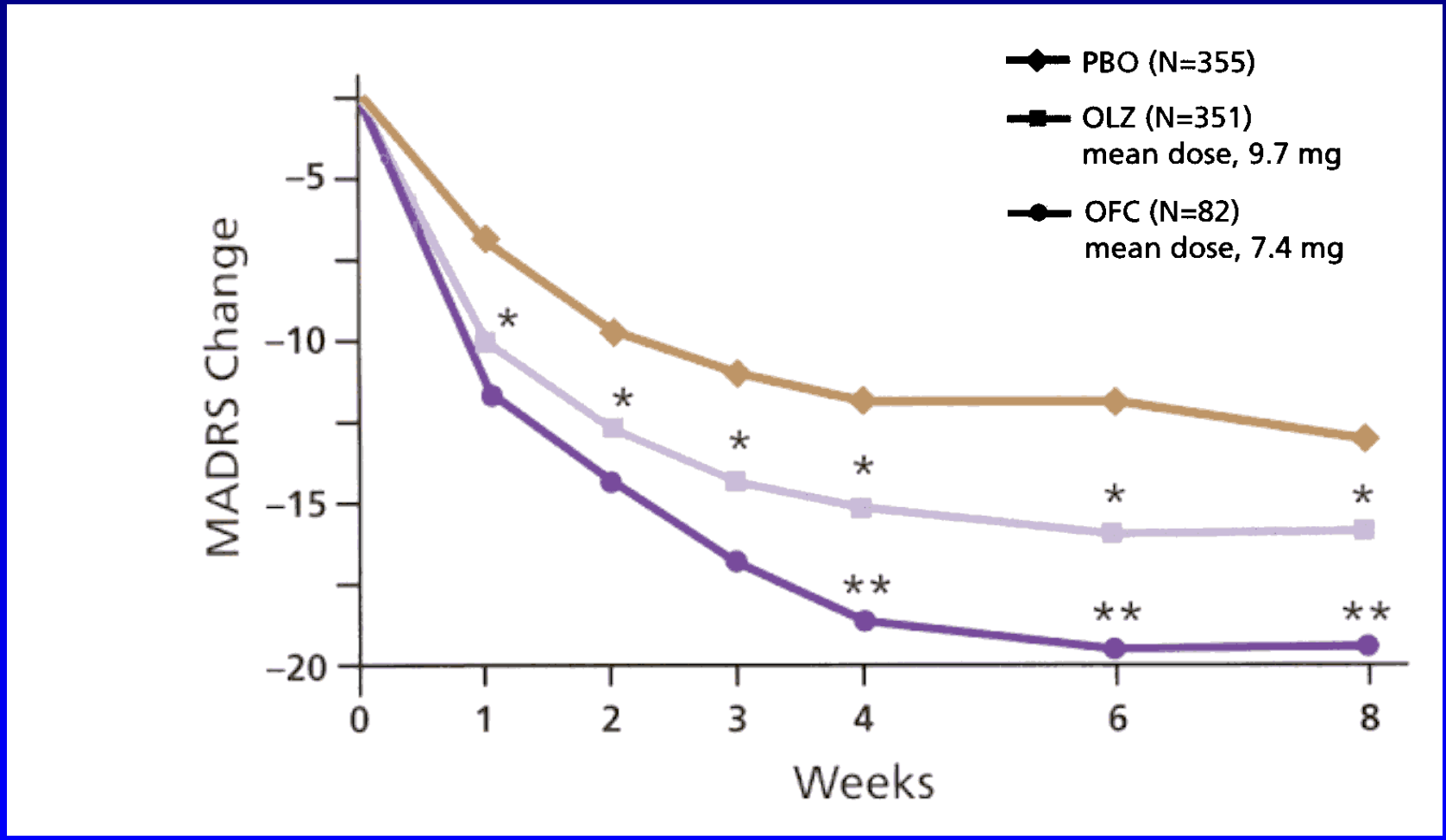
    Dropouts 36%

- **Placebo (n=355)**

  Dropouts 51.6%

Tohen et al. AGP, 2003; 60:1079-1088

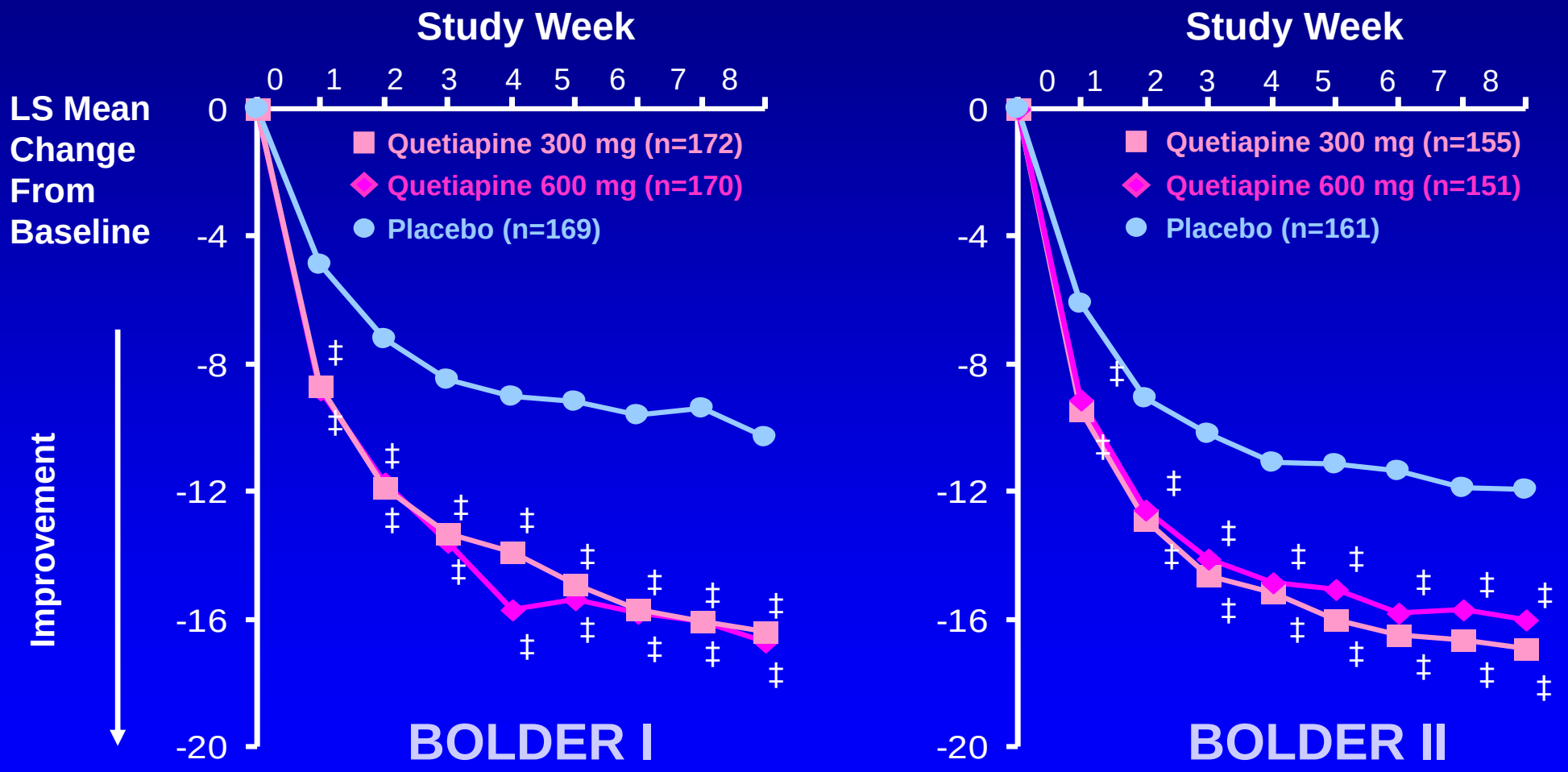
* Olanzapine/OFC for Bipolar I Depression (FDA -Approved)



MMRM=Mixed Modal Repeated Measures,

Tohen et al. AGP, 2003; 60: 1079-1088

Quetiapine for Bipolar I and II Depression
MADRS Total Score



‡p<0.001 vs placebo

Calabrese et al. Am J Psychiatry 2005;162:1351-1360
Thase et al. J Clin Psychopharmacol 2006;26:600-609

ITT, LOCF

* Quetiapine in Bipolar Depression

- 8 weeks of monotherapy with 300 or 600 mg/day vs. placebo (post hoc analysis of 2 RCTs)
- Remission in 53% of quetiapine patients vs. 28% on placebo
- Core symptoms of depression improved on quetiapine.
- Treatment-emergent mania in 3.2% vs 3.9%
- This result has been replicated
- FDA-approved for bipolar (I & II) depression.

Weisler RH et al, J Clin Psychiatry. 2008

Lamotrigine for Bipolar Depression (5 multicenter, placebo-controlled studies)

- Lamotrigine did **not** separate from placebo on the primary endpoint in any of the 5 studies
- But a meta-analysis found "consistent evidence of a mild to modest, but clinically worthwhile benefit for lamotrigine that is unlikely to be due to chance."*
- Benefit greater in more severely depressed**

*Geddes et al., NCDEU Annual Meeting poster I-64, June 2007
**Geddes et al. Br J Psychiatry 2009;194:4-9
Calabrese et al. Bipolar Disorders 2008;10:323-333

Acute Bipolar I Depression: CANMAT

- **First Line:** Lithium, LTG, QTP, QTP XR, Li or DVPX + SSRI, Li + DVPX, Li or DVPX + bupropion
- **Second Line:** QTP + SSRI, DVPX, Li or DVPX + LTG, adjunctive modafinil
- **Third Line:** Many combinations
- **Not Recommended:** Gabapentin monotherapy, aripiprazole monotherapy

Yatham et al. Bipolar Disorders 2009;11:225-255

Acute Bipolar II Depression: Current Evidence

- **Quetiapine: Compelling evidence**
- **Lithium, antidepressants, pramipexole: Preliminary support for efficacy**
- **Lamotrigine: Mixed support**

Swartz HA, Thase ME. J Clin Psychiatry 2011;72:356-366

Bipolar Maintenance

* Bipolar Maintenance

- **Best evidence: Lithium, olanzapine, or aripiprazole (FDA has approved adjunctive quetiapine 2008; risperidone microspheres 2009; ziprasidone 2009)**
- **Alternatives: LTG, CBZ, OXC, DVX**
- **Combinations may be necessary**
  - **Antipsychotic**
  - **Antidepressant**
  - **Psychosocial**

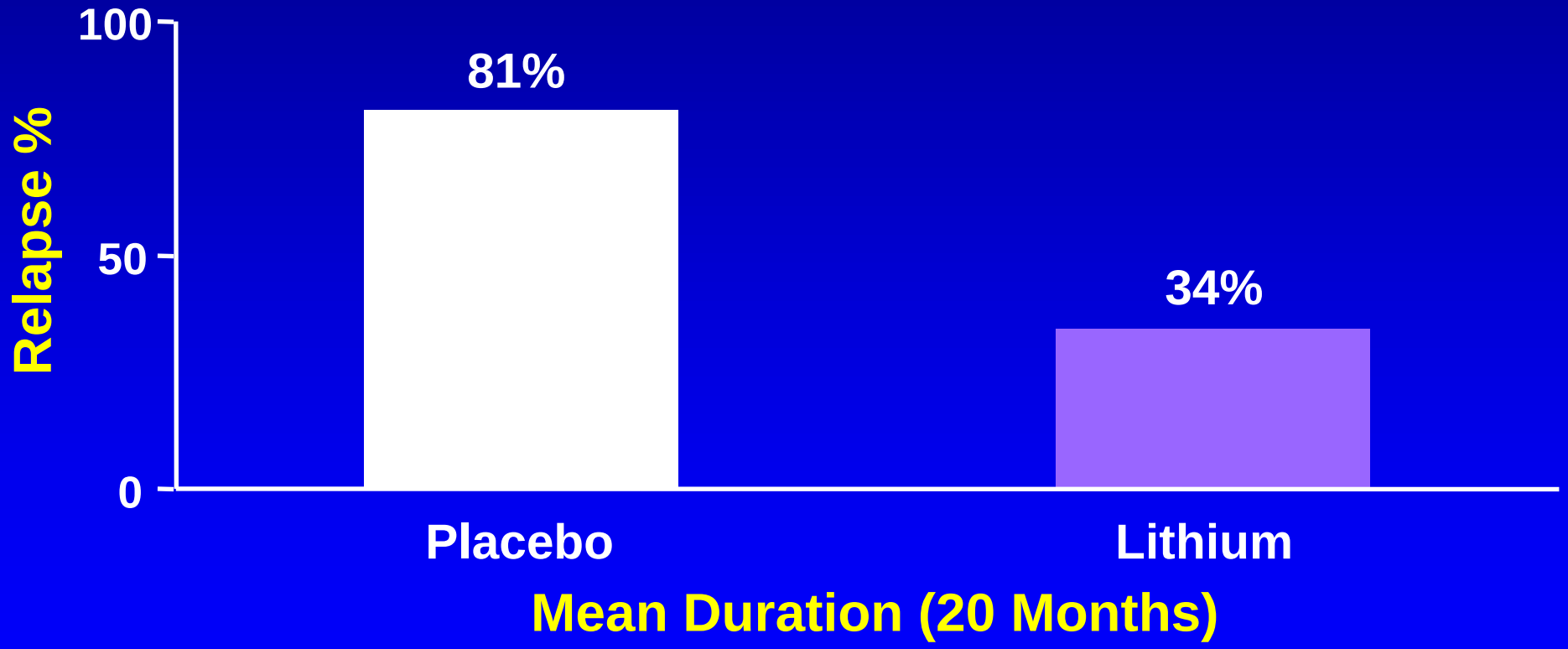
Bipolar Maintenance: FDA-Approved

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 Maintenance

10 Placebo-Controlled Studies (Prior to 1990)



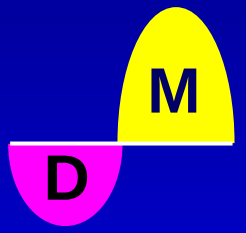
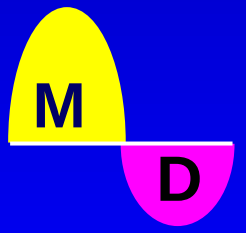
Goodwin FK, Jamison KR, Manic-Depressive Illness. New York: Oxford University Press; 1990

Long-Term Lithium Maintenance 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

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

* 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	

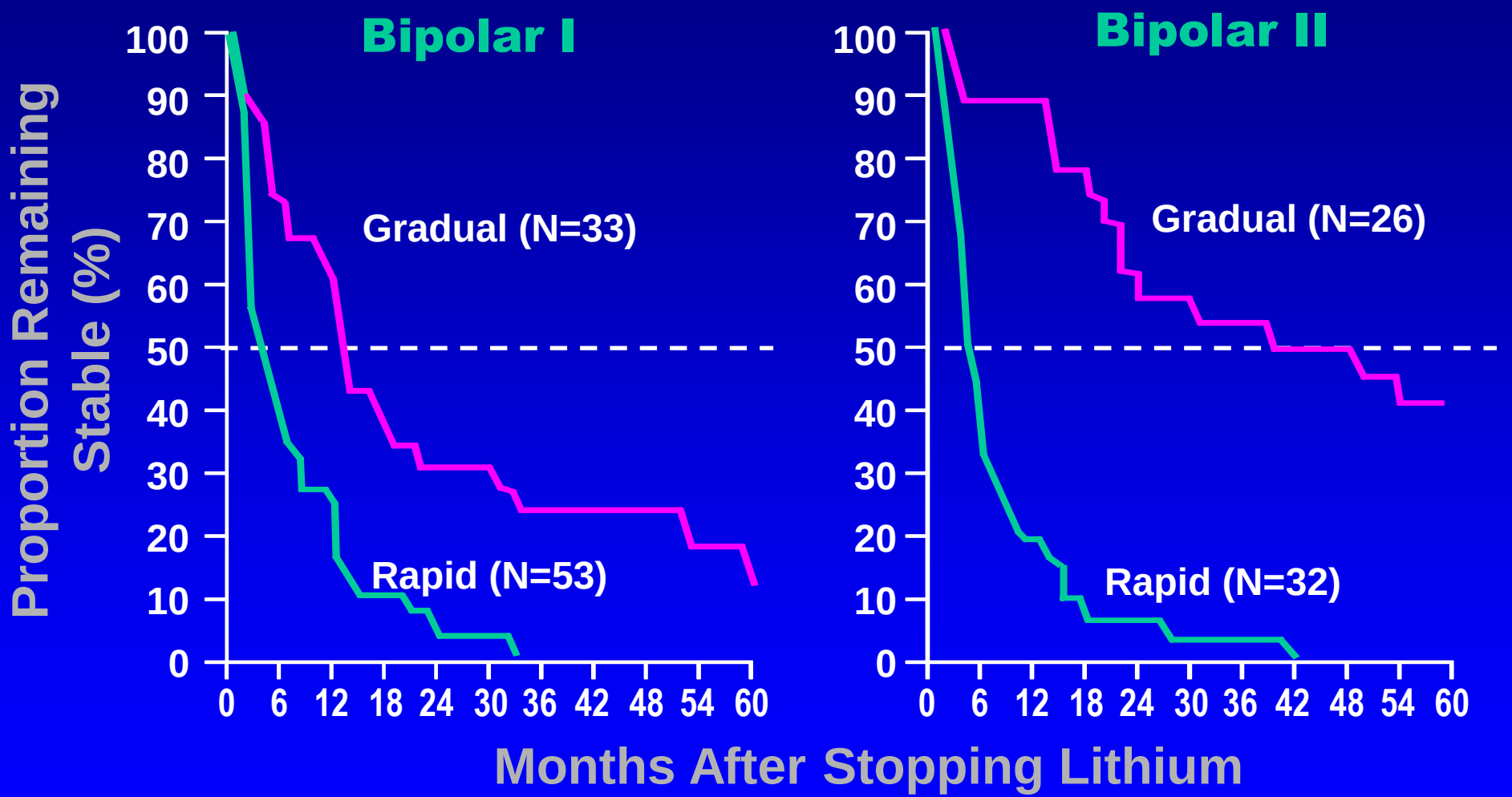
* Long-Term Lithium Maintenance

(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

Continuation v Discontinuation of Lithium in Recurrent Bipolar Illness: A Naturalistic Study

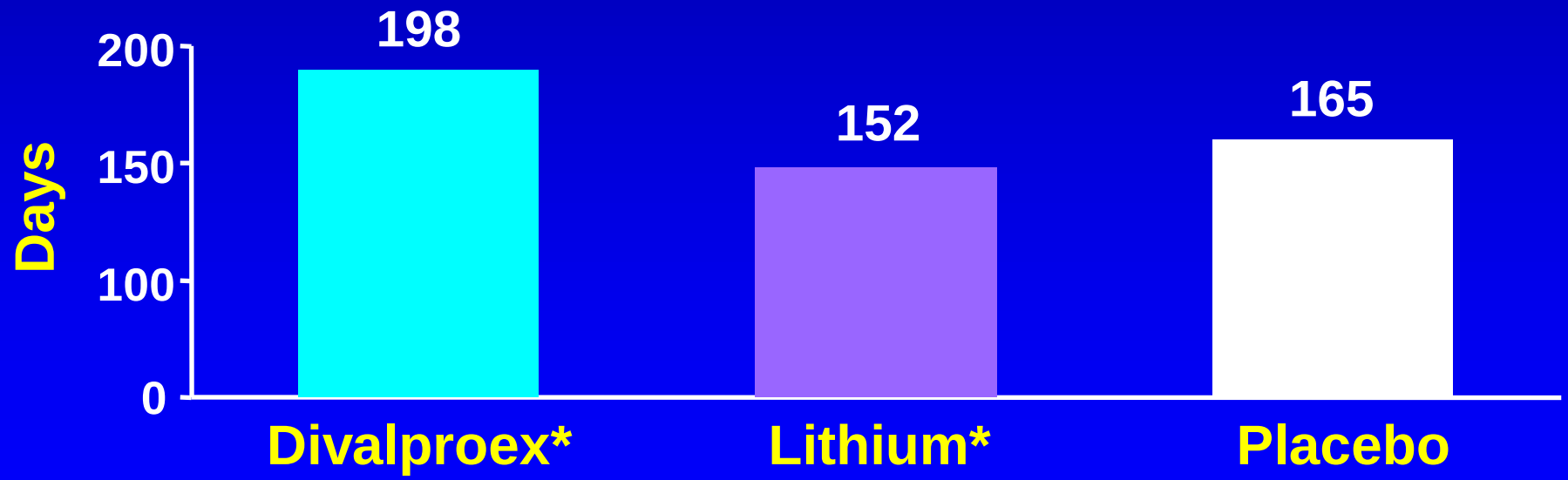
- 213 bipolar patients stable on lithium for 2 years
- Open label, clinical practice setting
- Continuation (N=159) vs (Slow) Discontinuation (N=54)
- **Risk of recurrence during the first year and follow-up period of treatment for continuation group: roughly one third that of discontinuation group**
- Median time to recurrence: 7.33 yrs vs 1.33 yrs

Biel et al, Bipolar Dis. 2007

Divalproex: 12-Month BP I Maintenance

Entry After Index Manic Episode

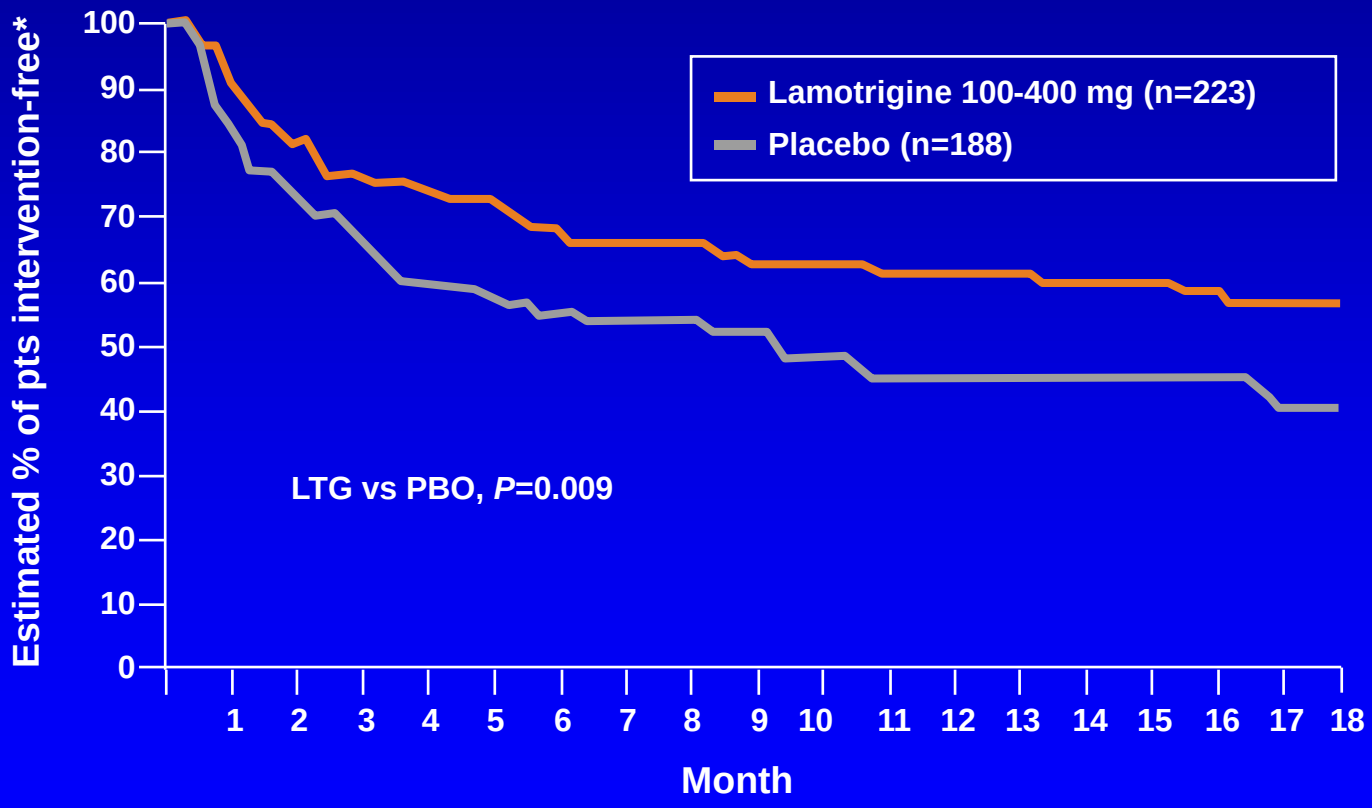
- Primary outcome measure: time to any mood episode
  - DVPX = Li = PBO (a failed trial)
- Mean duration of continued treatment (days)

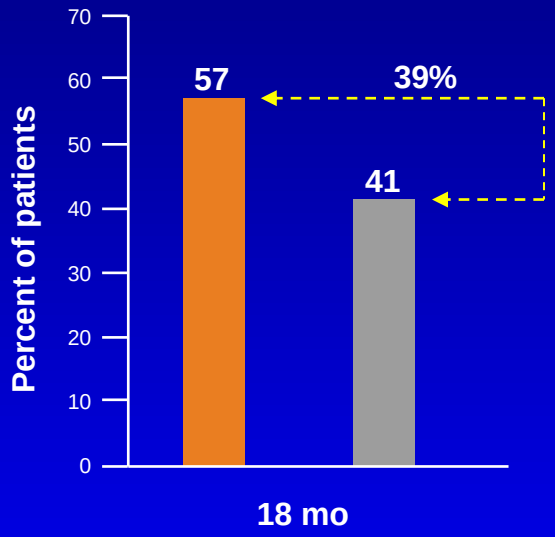


*p=0.02; Bowden CL, Calabrese JR, McElroy SL, et al. Arch Gen Psychiatry. 2000(Mar);57(5):481-489

See also: Kessing et al, BJP 2011; 199: 57-63

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.

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

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

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

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 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

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

Rapid Cycling Bipolar Disorder

* Rapid-Cycling Bipolar Disorder

- At least 4 episodes/year
- Initial onset or later onset
- More common in women
- Thyroid abnormality seen
- Role of antidepressants
- May not persist
- No clear therapy guidance

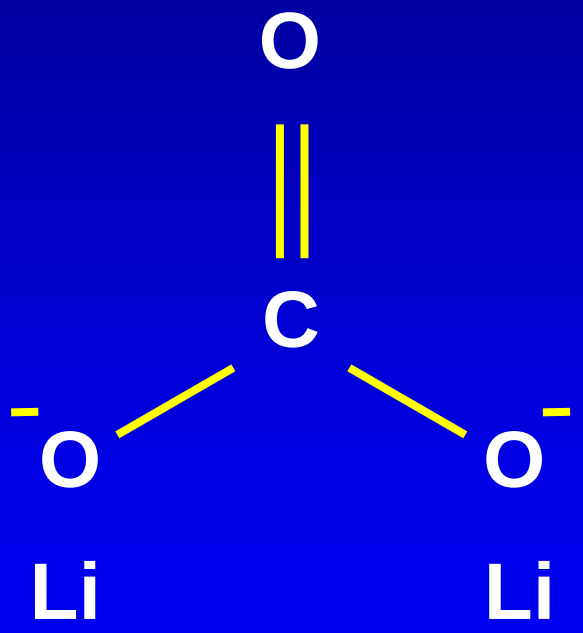
* Rapid Cycling

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

APA Bipolar Guidelines, Revised 2002

Specific Agents

Lithium Carbonate



FDA Approved Lithium Indications

- Acute mania
- Maintenance in bipolar disorder

* 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 Baseline Tests

- BUN, creatinine
- Thyroid
- CBC
- Urinalysis
- EKG (if indicated)
- Pregnancy (if indicated)

*Lithium and the Thyroid

- Main concerns: clinical and subclinical hypothyroidism
- Thyroid function monitoring: baseline and periodic
- Which tests: TSH, others as indicated

*Lithium and Monitoring Renal Function

- Serum creatinine – yes! (1 to 3 times yearly)
- Urinalysis – easy to do
- Polyuria – by history
- Creatinine clearance – when indicated
  (volume and protein)
- Estimating equations for GFR
  Cockcroft-Gault
  MDRD (Modification of Diet in Renal Disease)

Jefferson JW. J Clin Psychiatry 2010;71:1153-1157

* 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 (incomplete list)

Increased	Not Changed	Decreased
Thiazides	Amiloride (?)	Acetazolamide
NSAIDs	Furosemide	Mannitol
ACE inhibitors	Aspirin	Theophylline
Angiotensin II receptor (type AT_1) antagonists	Sulindac (?)	Caffeine
Metronidazole		Mania
Low sodium diet		Pregnancy
Dehydration		
Elderly		
Renal disease		

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

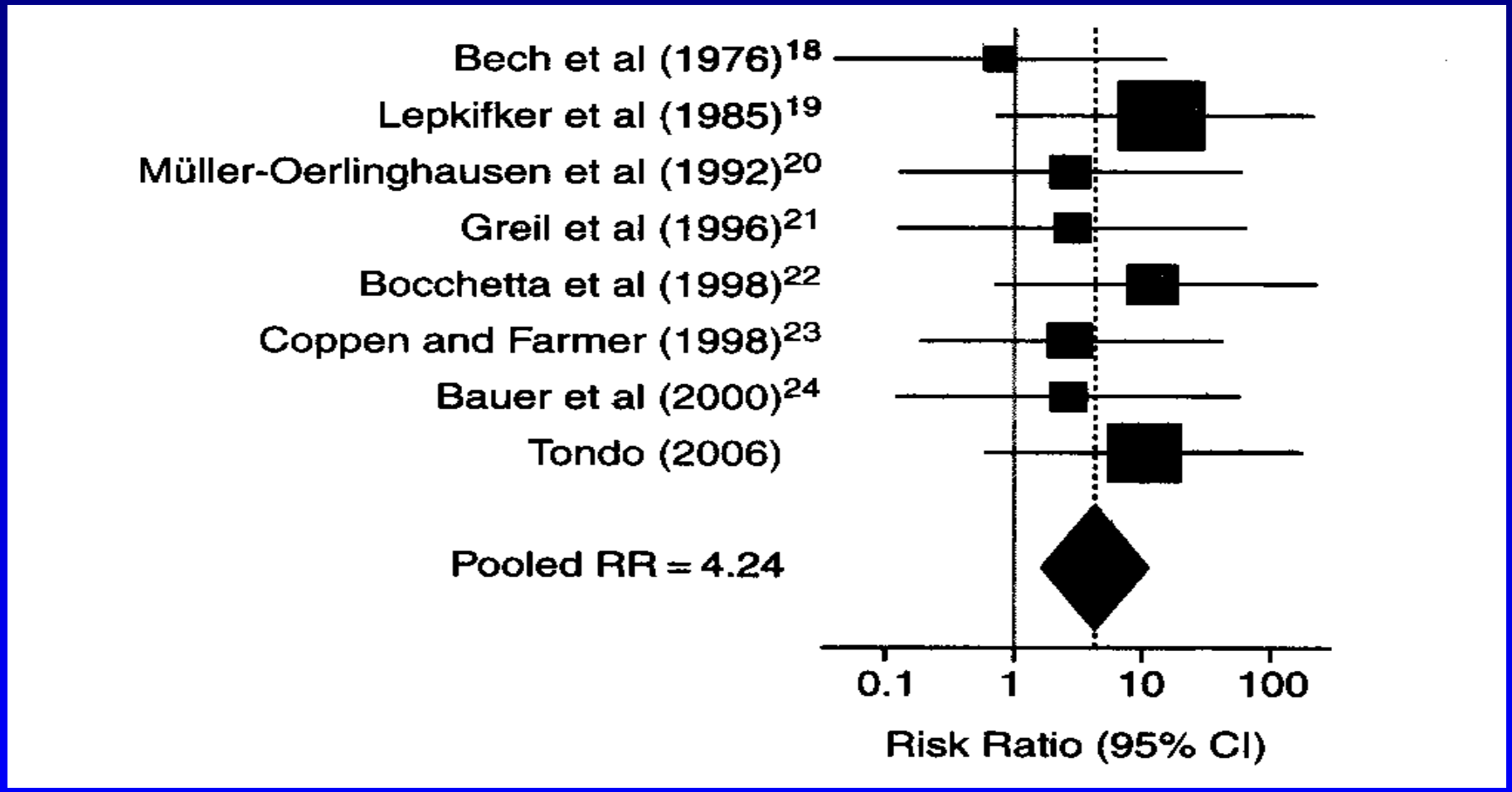
(review of randomized trials)

- **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

* Antisuicidal Effect of Lithium

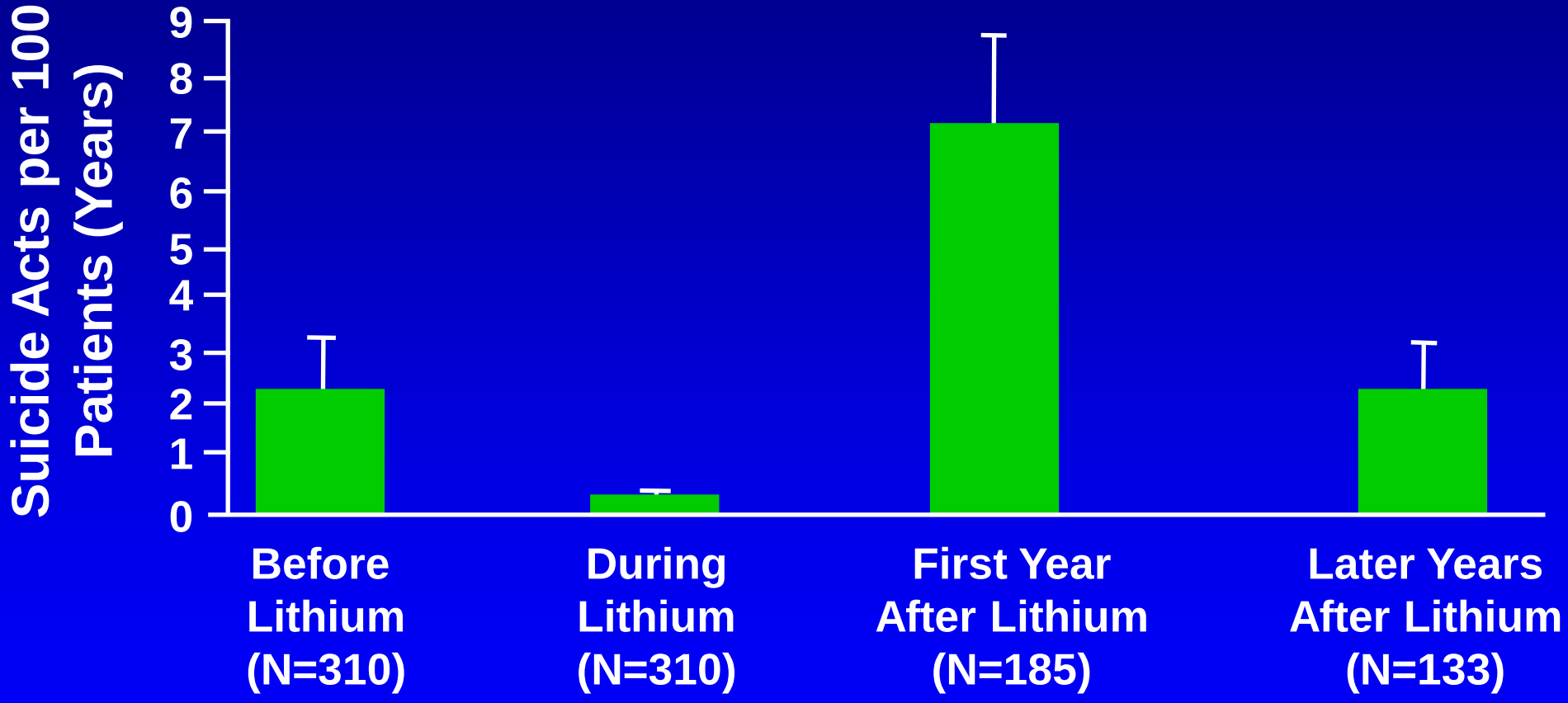
72 BP I patients followed prospectively for up to 10 years.

Observed rates of suicide were 0.143; attempts 2.01%/year.

There was a 5.2-fold greater risk among patients rated poorly versus highly adherent to lithium prophylaxis.

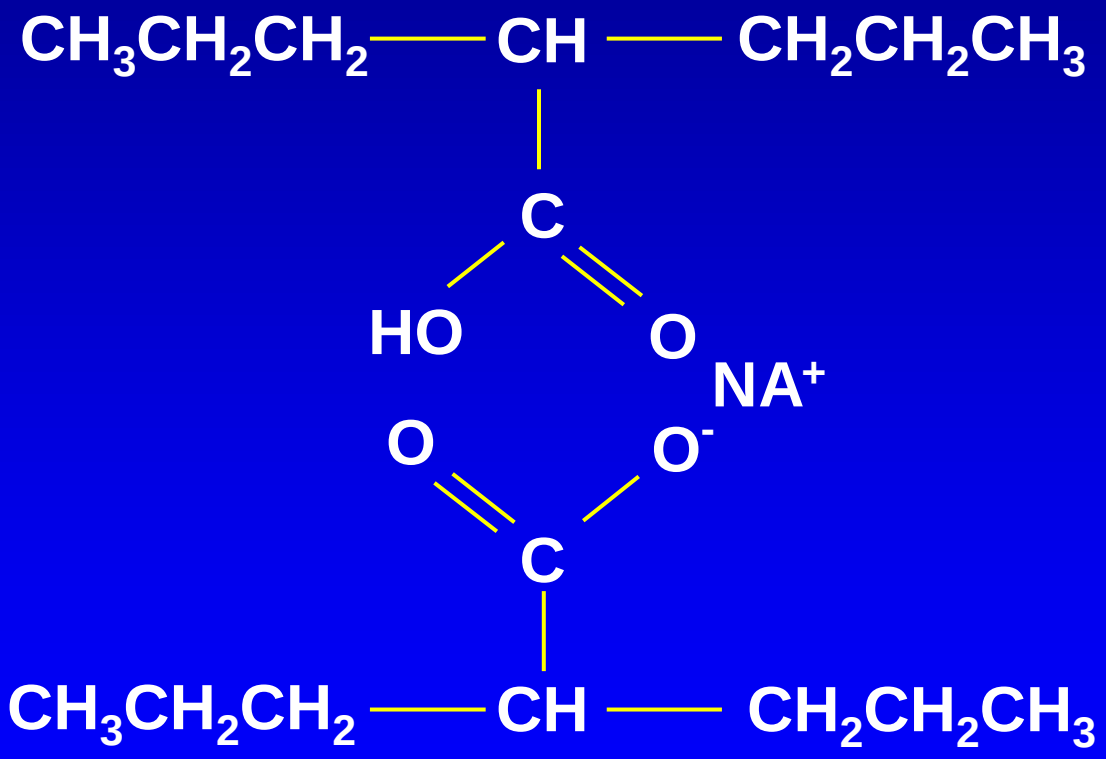
Gonzalez-Pinto et al, Bipolar Dis. 2006

Lithium and Suicidal Behavior



Tondo et al. JCP 8/98

Divalproex Sodium/Valproate



* Valproate

- **Indications**
  - **Epilepsy**
  - **Acute mania (FDA: 1995)**
  - **Migraine prophylaxis**
  - **Manic and mixed episodes--divalproex ER (FDA: 2005)**
- **Role**
  - **Acute and prophylactic treatment of bipolar disorder**
  - **-- Good therapeutic index**
  - **-- Superior to lithium for acute mixed episode**

* Valproate Baseline Tests

- CBC
- LFTs
- If applicable, pregnancy

Valproate

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

  Initial: 25mg/kg/day (single daily dose)

  Maintenance: serum conc=85-125 μg/ml

* Divalproex vs Valproic Acid

- Divalproex (Depakote) now generic
- Evidence base is mostly with divalproex
- Valproic acid (Depakene) is available in liquid form
- Nausea is more frequent with valproic acid
- Extended release offers single daily dose advantage
- Recommended: initiate new patients on single dose divalproex ER

Wassief AA et al. AJP 2005;162:330-339/Bowden et al, JClinPsy 2006;67:1501-1510

Divalproex ER Blood Levels

- Sample timing does matter
- At 12 to 15 hrs post-dose: 18% to 25% higher than trough
- At 18 to 21 hrs post-dose: 3% to 13 % higher than trough
- Therefore, dose ER once daily, draw blood at least 18 hrs later

Reed and Dutta. Ther Drug Monit 2006;28:413-418

* 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 (?)
- Bleeding tendencies

Valproate and Polycystic Ovarian Syndrome

- 230 women, ages 18-45, in STEP-BD study
- Oligomenorrhea and hyperandosteronism

  Valproate: **10.5%** (9/86)

  non-Valproate: **1.4%** (2/144)

  (P=.002)
- All oligomenorrhea in first 12 months
- Polycystic ovaries: no significant difference

Joffe H et al. Biol Psychiatry 2006:59:1078-1086

* Valproate Interactions (An Incomplete Listing)

- **Aspirin (avoid)**

  free VPA, ↓ platelet function

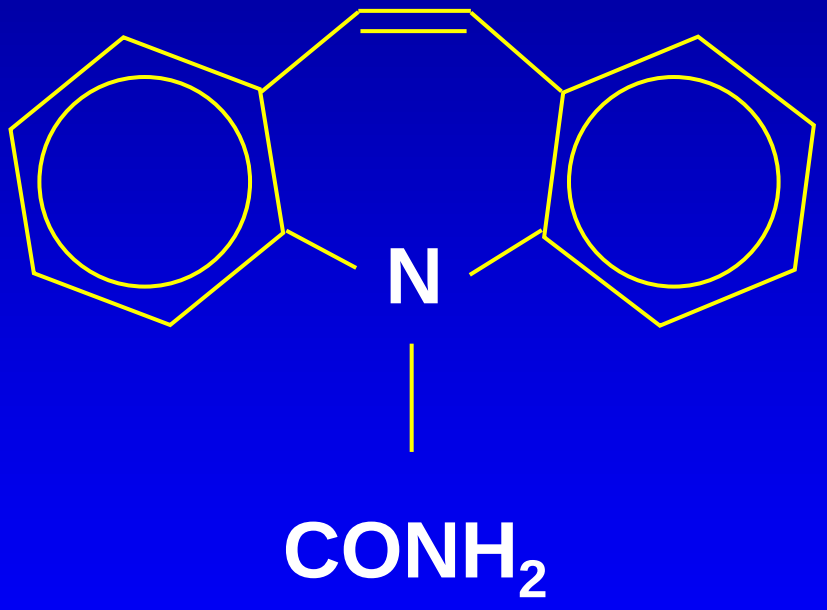
- **Carbamazepine**

  ↓ VPA, CBZ-epoxide

- **Lamotrigine**

  lamotrigine

Carbamazepine



* Carbamazepine

- **Indications**
  - **Trigeminal neuralgia**
  - **Epilepsy**
  - **-- Acute mania (extended release)**
- **Role**
  - **Acute and prophylactic treatment of bipolar disorder**
  - **Adjunctive treatment with other mood stabilizers**
  - **Favored in Japan and Europe over VPA, though lithium #1.**

* Carbamazepine

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

* Carbamazepine Baseline Tests

- CBC with platelets
- LFTs
- If applicable, pregnancy testing

* 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

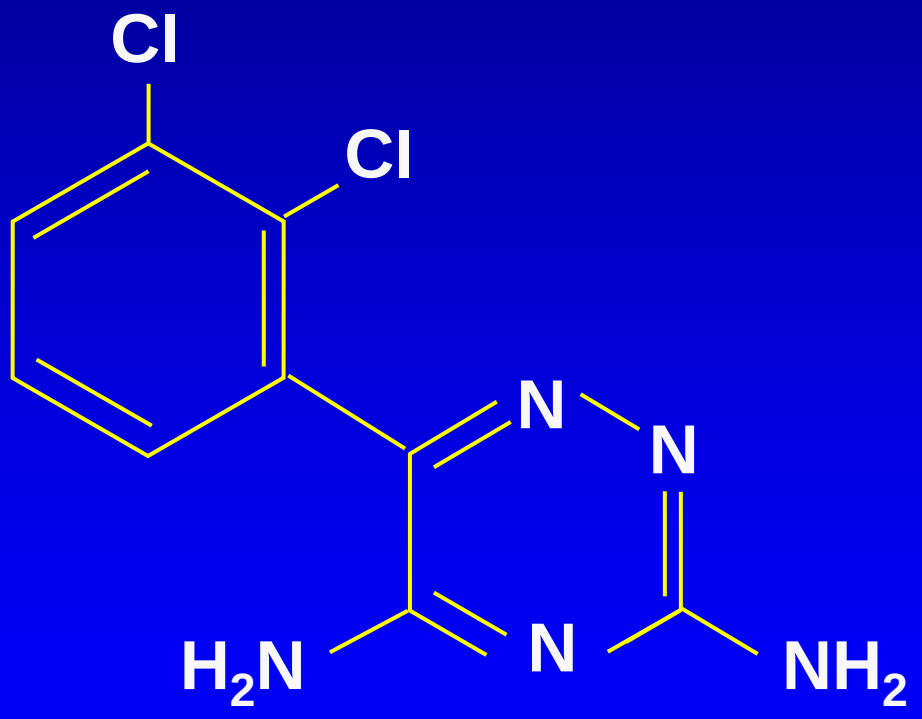
- Sedation
- Dizziness
- Ataxia
- Double/blurred vision
- GI distress
- Hematopoietic suppression
- Hepatotoxicity (rare)
- Dermatologic
- Teratogenicity
- Hyponatremia

* 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**

Lamotrigine



* 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**

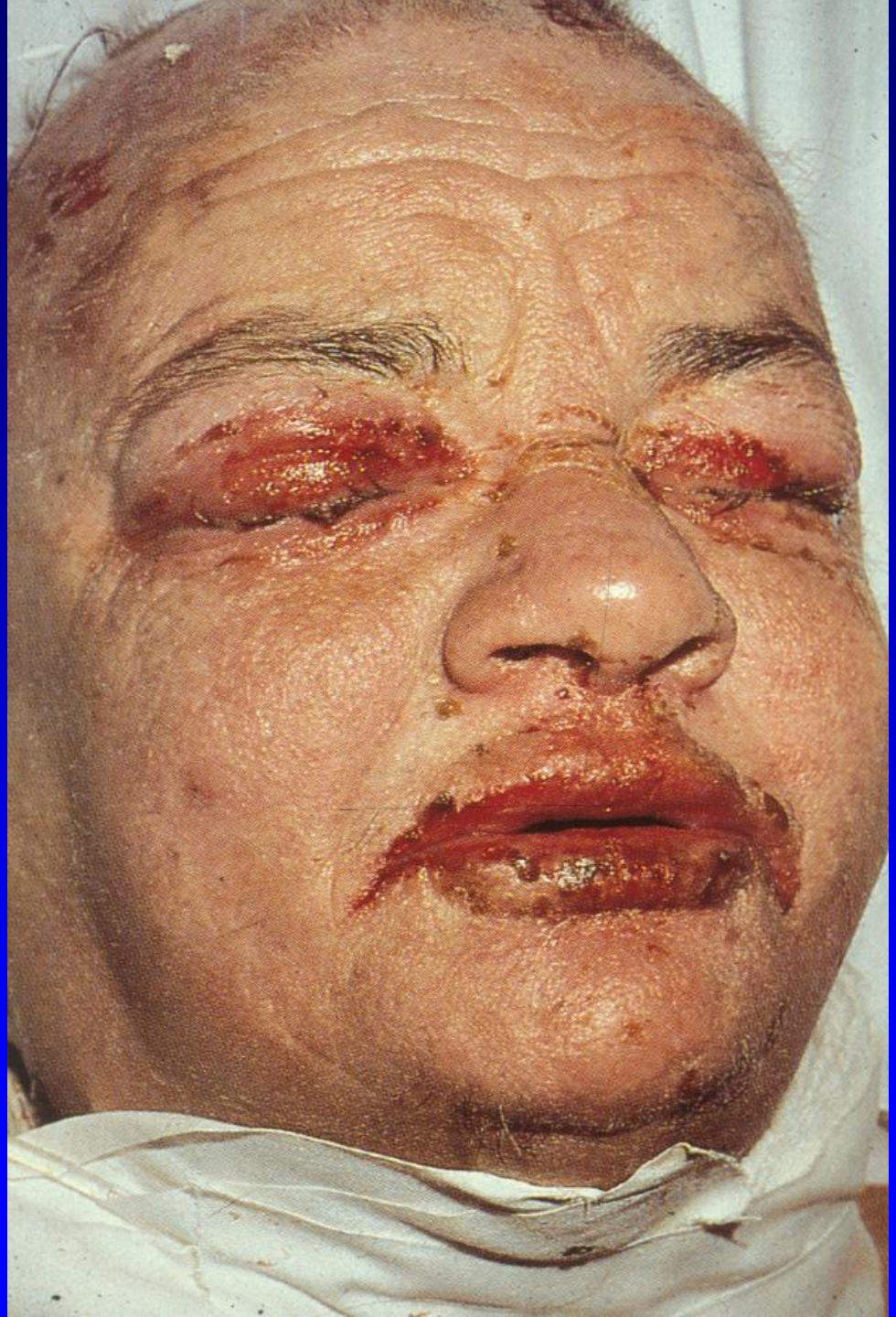
* Side Effects of Lamotrigine

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
	Malformations: 2.7%

Carbamazepine: FDA Alert 12/12/07

- Dangerous or fatal skin reactions more common with HLA allele, **HLA-B*1502**
- Carried "almost exclusively in patients with ancestry across broad bands of Asia"
- High risk (10-15%): Chinese, Thai, Malaysian, Philippine, Taiwanese ancestry
- Low risk (<1%): Japanese or Korean ancestry
- Genetic screening advised, if + don't start CBZ

*



* Rash with Lamotrigine Use

- Black box warning
- Overall rash prevalence: 10%
  - 0.3% severe in adults
  - 1% severe in children (not for those <15yoa)
- 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 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, 2001

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 hospitalization and drug discontinuation

Bowden et al., 2003

* 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)
- Pregnancy ↑ LTG clearance >50%

* Oxcarbazepine

- 10-keto analogue of CBZ
- Prodrug ⟶ MHD
  (10-hydroxycarbazepine)
- Half-life OXC 2 hours
  MHD 9 hours
- Protein binding 40%
- Initial 150 mg bid/target 800-1800 mg/day

* 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)
  Emrich, 1990
- No better than placebo in children and adolescents (n=116)
  - Wagner et al, 2006

* Oxcarbazepine Side Effects

- AE dropouts 23%
  - monotherapy 9%
  - pediatrics 11%
- Common – nausea, vomiting, dizziness, somnolence, ataxia
- Uncommon – hyponatremia (< 125 mEq/L 2.5%)
- Rare: Stevens-Johnson syndrome and toxic epidermal necrolysis

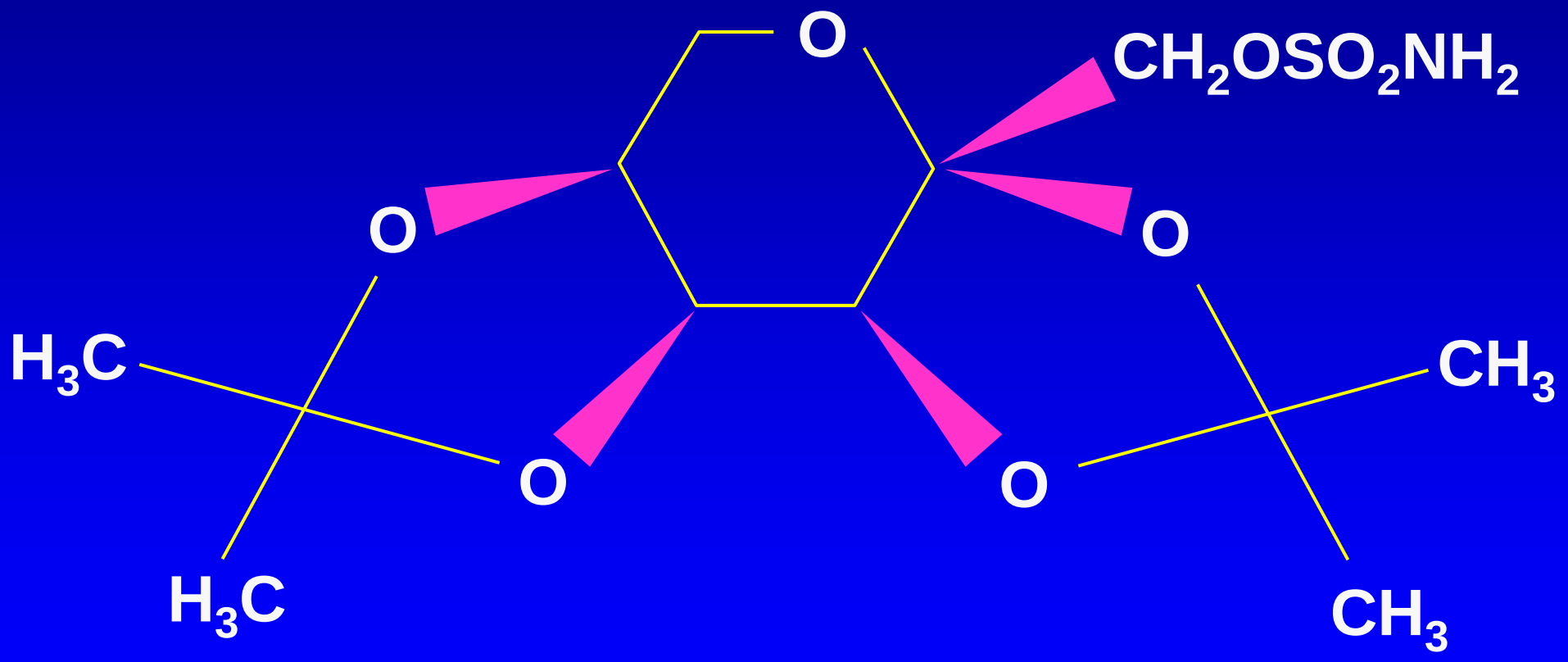
* Oxcarbazepine and Hyponatremia

- 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

* Oxcarbazepine Interactions

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

Topiramate



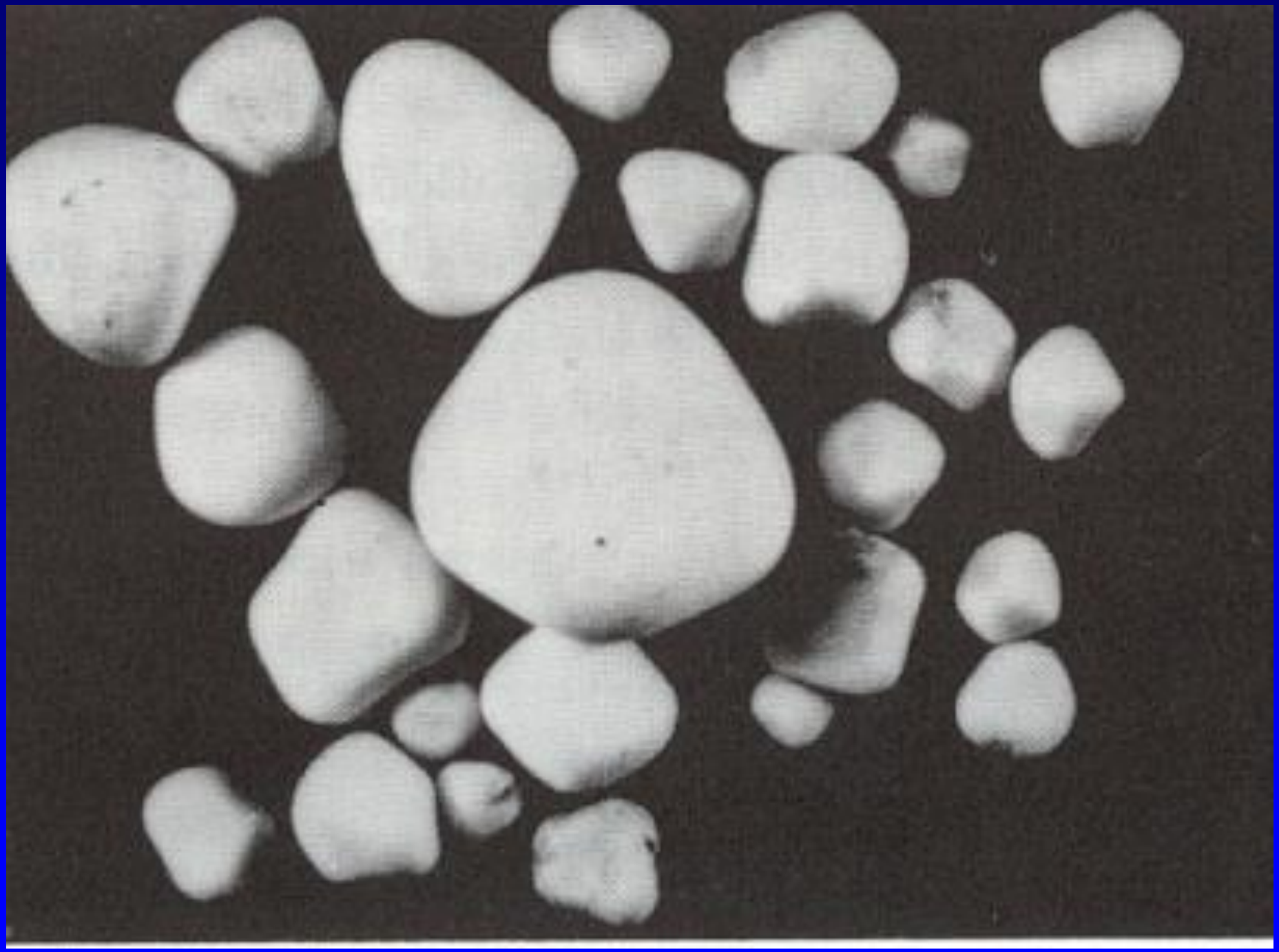
Topiramate (Topamax)

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

* Topiramate for Bipolar Disorders

- Four double-blind controlled efficacy studies in bipolar disorder: no better than placebo
- Dose range: to 600 mg/day

Kushner et al, Bipolar Dis, 2006



* 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

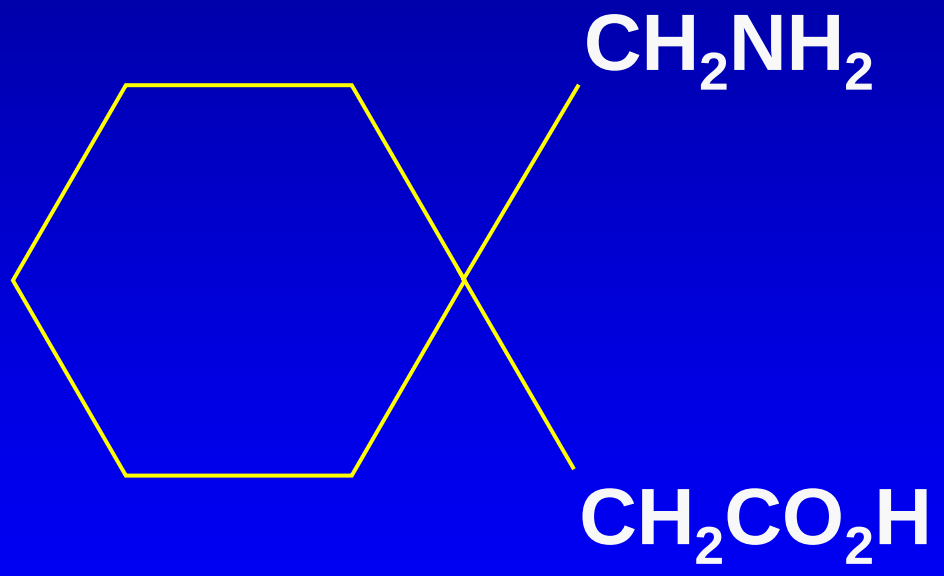
- Occurred in 1.5% (32/2086)
- 2 to 4 times ↑ risk
- Men > women
- Reported in kids
- One bipolar II woman
- Carbonic anhydrase inhibition

* Adding Topiramate vs. Bupropion SR for Bipolar Depression

- 8 weeks, single blind, n=36, added to Li+ or VPA
- Topiramate 176 mg/day, bupropion 250 mg/day
- >50% drop in HDRS: 56% with topiramate, 59% with bupropion
- No mood switches
- Six dropouts due to side effects in topiramate group, four in bupropion group.
- Weight loss: 5.8 kg on topiramate, 1.2 on bup.

(Mcintyre RS et al. Bipolar Disorders 2002;4:207-213)

Gabapentin



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

* Gabapentin: Limitations in Bipolar Disorders

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

Other Mania Treatments

Protein Kinase C Inhibitor-Tamoxifen

Omega-3 Fatty Acids ?

Stoll A et al, Arch Gen Psych 56: 407-412, 1999
Zarate et al, Bipolar Disorder 9: 561-570, 2007
Yildiz et al, Arch Gen Psych, 65: 255-263, 2008

Tamoxifen for Acute Mania
3-week, double-blind, placebo-controlled, n=16

- Relatively selective protein kinase C inhibitor
- Dose: Start 20 mg/day, range 20 to 140 mg/day
- Tamoxifen > placebo on ↓ YMRS from day 5 on.
- Response: Tamoxifen 63%
  Placebo 13%

Zarate et al., Bipolar Disorders 2007;9:561-570

Tamoxifen for Acute Mania

3-week, double-blind, placebo-controlled, n=66

- Relatively selective protein kinase C inhibitor and selective estrogen receptor modulator
- Dose: Start 40 mg/day, max 80 mg/day
- Tamoxifen > placebo on ↓ YMRS, response (44% vs. 5%), remission (28% vs. 0%)*

Response ≥ 50% ↓YMRS; Remission YMRS ≤12

*No patient achieved response or remission prior to day 21

Yildiz et al. Arch Gen Psychiatry 2008;65:255-263

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

- 4 month, double-blind, placebo-controlled study
- Recurrence: Omega-3 7%
  Placebo 47%
- Mechanism: Altered post-synaptic transduction

Stoll A et al., Arch Gen Psych 56: 407-412, 1999

Omega-3 fatty acids for bipolar disorder

Five studies met inclusion criteria for the review, however, methodological quality was highly variable. Only one study, involving 75 participants, provided data for analysis, and showed a benefit of active treatment over control for depression symptoms but not manic symptoms in bipolar disorder. There is an acute need for well-designed and executed randomised controlled trials in this field.

Montgomery P et al, Cochrane Database Syst Rev. 2008

Pregnancy

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**

New Anticonvulsants and Pregnancy FDA Risk Categories*

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

*See elsewhere in Model Psychopharmacology Curriculum risk estimates for antipsychotics

Pre-Post Lecture Exam

- 1. The most common misdiagnosis of bipolar depression is:

  a) anxiety disorder

  b) substance abuse

  c) borderline personality disorder

  d) unipolar depression

  e) schizophrenia

2. Treatment of bipolar depression with antidepressants may lead to:

a) anxiety

b) greater mood instability

c) mania induction

d) psychosis

e) b and c

f) all of the above

3. In the treatment of moderate or severe mania, most guidelines recommend combination treatments, such as lithium or divalproex and atypical antipsychotics.

a) true

b) false

4. Which of the following is incorrect? Lithium therapy is known to:

a) induce tremor

b) cause urinary frequency

c) be associated with thirst

d) increase suicide risk

e) induce nausea, vomiting, and diarrhea

5. Kidney stones are associated with:

a) olanzapine

b) bipolar disorder complicated by substance abuse

c) lithium

d) divalproex

e) topiramate

Answers to Quiz

- 1) d
- 2) f
- 3) a
- 4) d
- 5) e