Medicine for Bipolar Disorder

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Pre-Post Lecture Exam

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

   a) anxiety disorder

   b) substance abuse

   c) borderline personality disorder

   d) unipolar depression

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 Outline

- **Overview: Bipolar Disorder-- Prevalence, misdiagnosis, phases**

  Main Teaching Points: Challenges, many medicines, treatment goals and selection
- **Treatment: Acute mania, bipolar depression, maintenance, rapid cycling**
- **Specific agents: Indications, efficacy, side effects, other therapeutic issues**
- **Pregnancy**

Bipolar Disorder Overview I

- Prevalence: 1-4% (narrow vs spectrum)
- Onset in young adulthood (>60 years: medical disorders should be first consideration)
- Chronic episodic course
- Significant morbidity (disability, hospitalization, adjustment, substance problems, psychiatric disorder, medical issues)
- Significant mortality (suicide, accidents, and medical co-morbidities)

Bipolar Disorder Overview II

- **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

Phases of Bipolar Disorder

- Acute mania
- Bipolar depression
- Maintenance

* 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**
- **Necessity of a phase relevant treatment strategy**

* 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 comorbidities
- Side effects
- Drug interactions
- Patient preferences

Acute Mania

Acute Mania

FDA-Approved

- 1970 Lithium
- 1973 Chlorpromazine
- 1995 Divalproex
- 2005 Divalproex ER
- 2000 on SGAs

Atypical Antipsychotics for Mania

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

*FDA approved since 2000

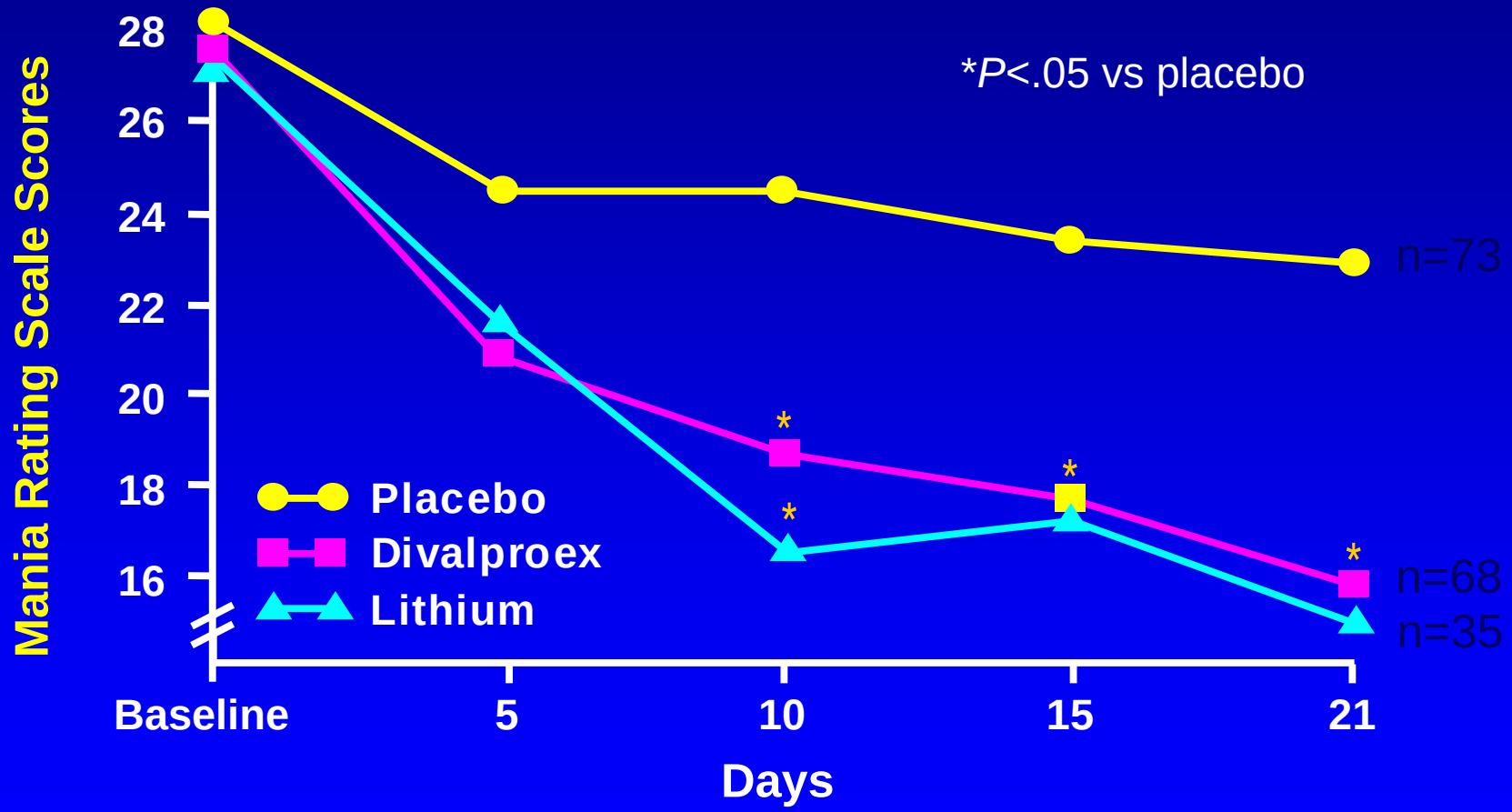
* Acute Mania: First-Line

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

APA Bipolar Guidelines, Revised 2002

* Double-Blind Controlled Study

Divalproex vs Lithium vs Placebo



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

* Divalproex vs Valproic Acid

- **Divalproex (Depakote) is up to 5 times the cost of valproic acid (Depakene)**
- **Evidence-base is mostly with divalproex**
- **Valproic acid is available in liquid form**
- **Nausea is more frequent with valproic acid**
- **Extended release offers single daily dose advantage**
- **Recommend: Initiate new patients on single dose divalproex ER (advantages despite cost)**

- **Wassief AA et al. AJP 2005;162:330-339**

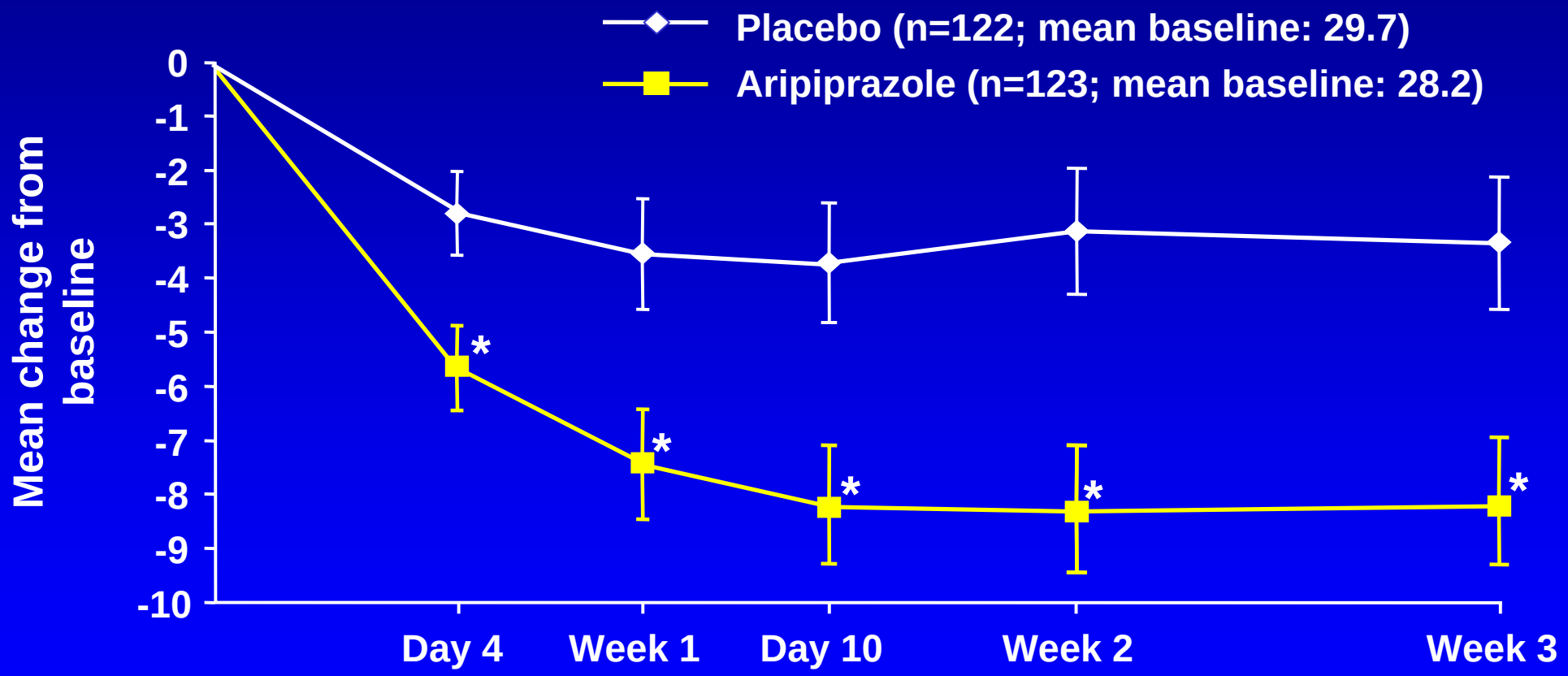
* Atypical (Second Generation) Antipsychotics in Mania

- All such agents apparently effective
- Generally no worsening of depression (unlike conventional antipsychotics)
- Antidepressant effects (i.e., 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

* Use of Antipsychotics II

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

* Example: 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.

* 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, Dec. 2002

Bipolar Depression

* Bipolar Depression

- **First-line – lithium, quetiapine, lamotrigine,* OFC (olanzapine/fluoxetine combination)**
- **Antidepressants**
  - **Monotherapy not advised**
  - **Bupropion, SSRIs, venlafaxine may be added to mood stabilizer but rate of response (without stimulating mania) is 16%. (Leverich GS et al, Am J Psychiatry 2006;232-9)**
- **ECT, psychotherapy**

* Yet several studies show no advantage over placebo for LTG

* Bipolar 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**

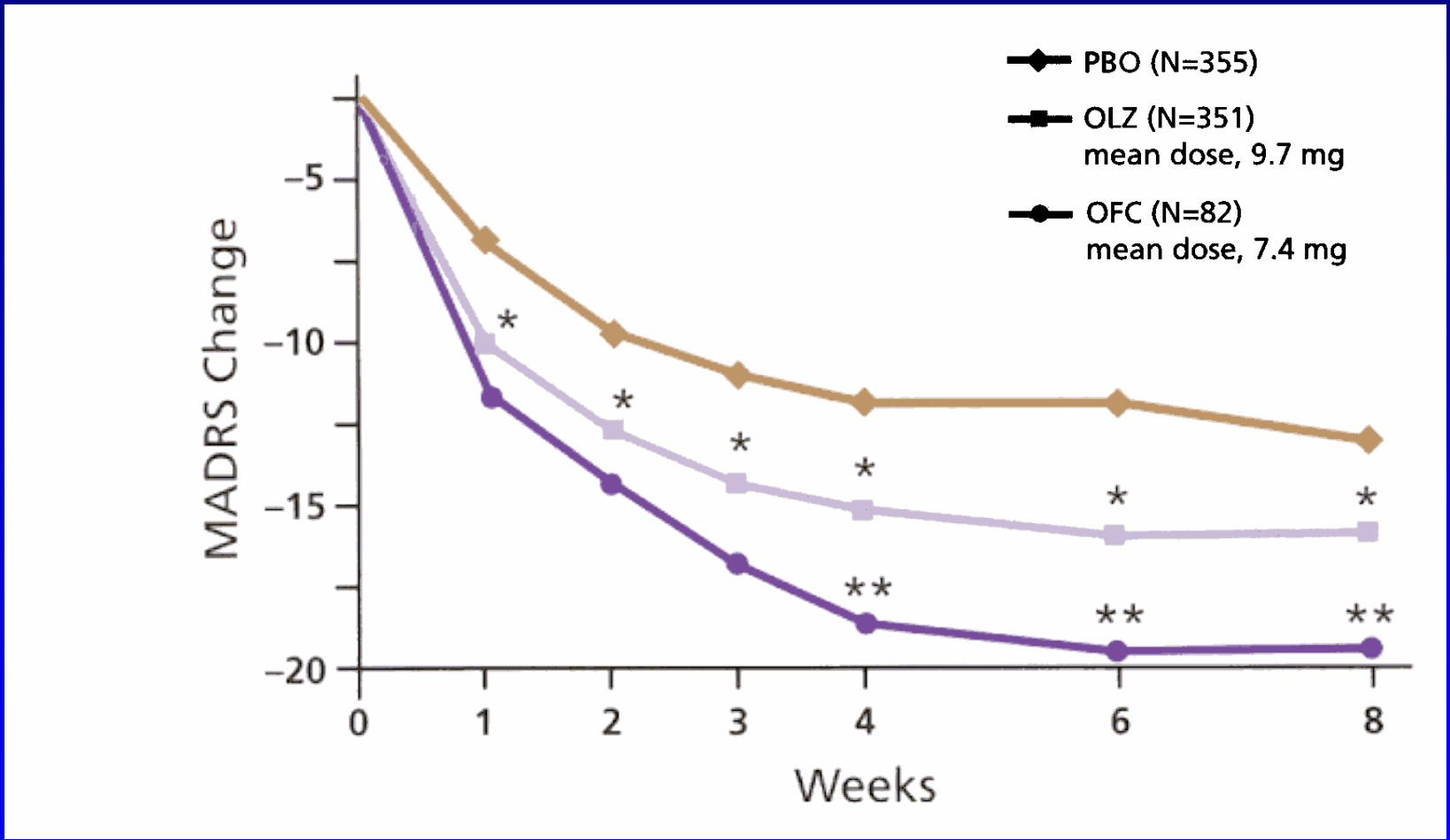
    Dropouts 36%

- **Placebo (n=355)**

  Dropouts 51.6%

Tohen et al. AGP, 2003

* Olanzapine/OFC for Bipolar Depression (FDA Approved)



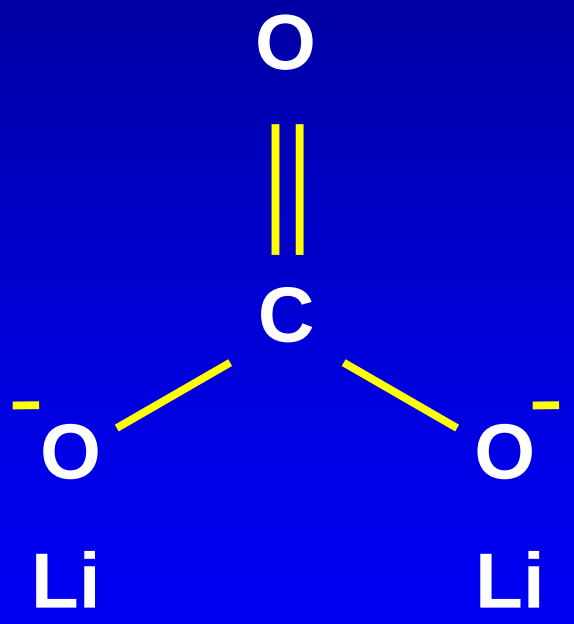
MMRM=Mixed Modal Repeated Measures,

Tohen et al. AGP, 2003

* Quetiapine (QTP) in Bipolar Depression

- **8 weeks of monotherapy with 300 or 600 mg/day vs. placebo (Calabrese JR et al. AJP 2005;162:1351-1360)**
- ***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**
- **QTP: FDA-approved for bipolar depression.**

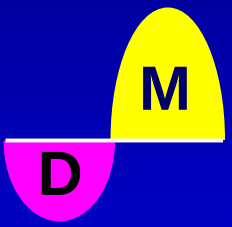
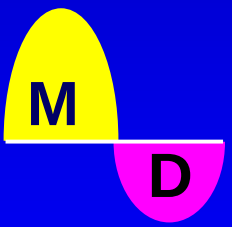
Lithium Carbonate



FDA Approved Lithium Indications

- Acute mania
- Maintenance in bipolar disorder

* 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	

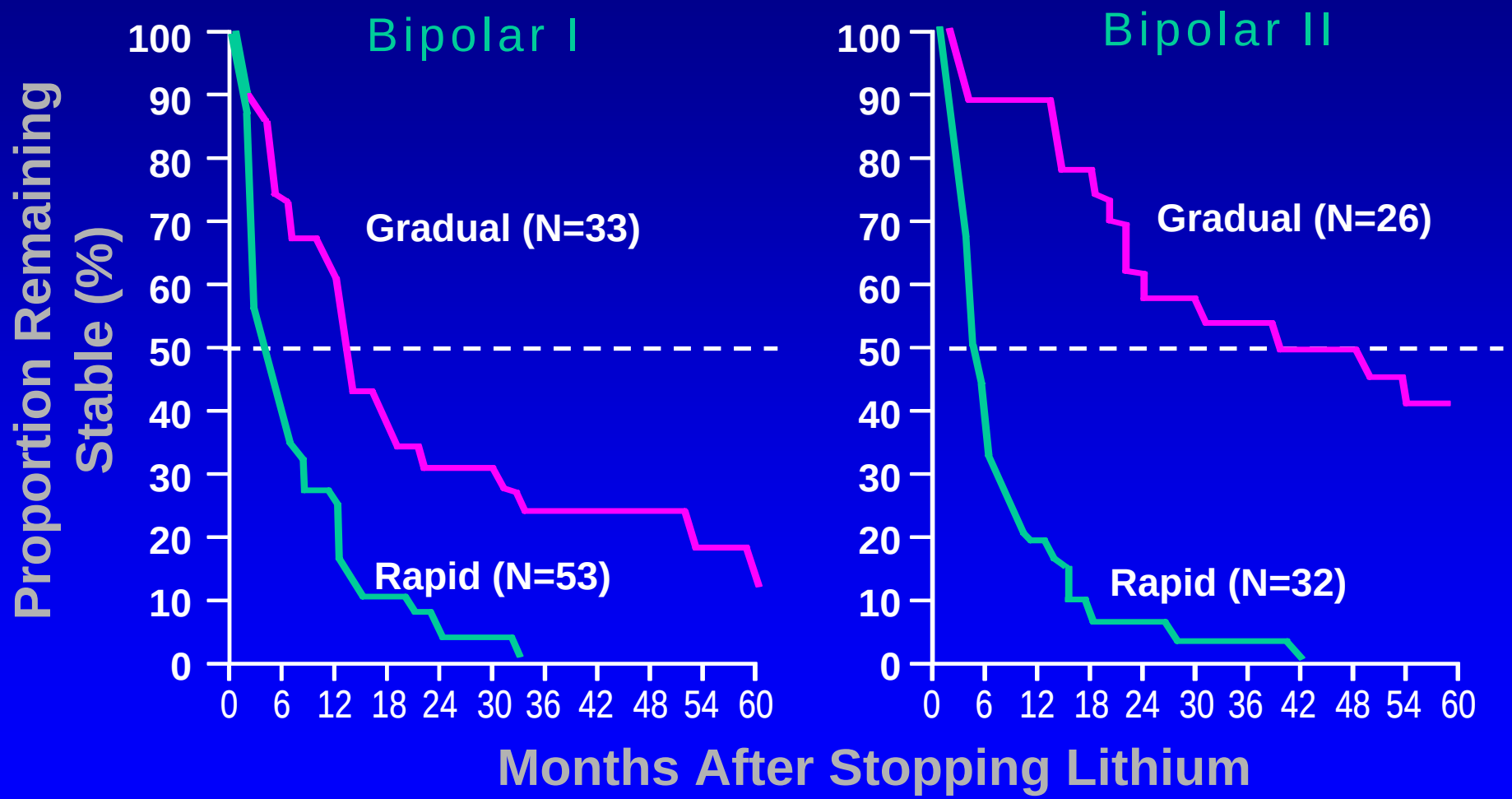
* Long-Term Lithium Maintenance

(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

* 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 Baseline Tests

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

* Lithium

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

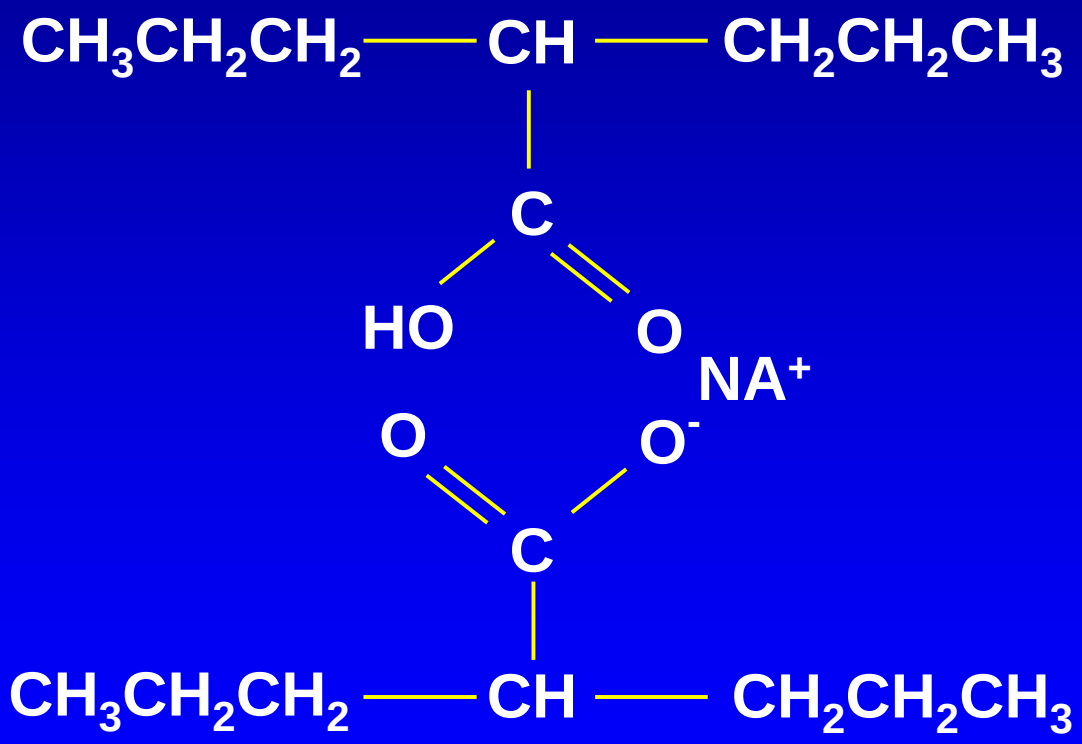
* Lithium Side Effects

- 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

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
- Amylase
- If applicable, pregnancy

* Valproate

- **Half-life: 6-16 hours**
- **Protein binding: >90%**
- **Daily formulation (divalproex ER) available**
- **Dosing in mania**
  - **Initial: 250 mg tid or oral loading (20-30 mg/kg)**
    (ER version bioequivalent to divalproex at ER dose 8 to 20% higher)
  - **Maintenance: serum concentration (trough) = 50-125 μg/ml (ER 85-125 μg/ml)**

* 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 Interactions
(An Incomplete Listing)

- **Aspirin (avoid)**

  ↑ free VPA, ↓ platelet function

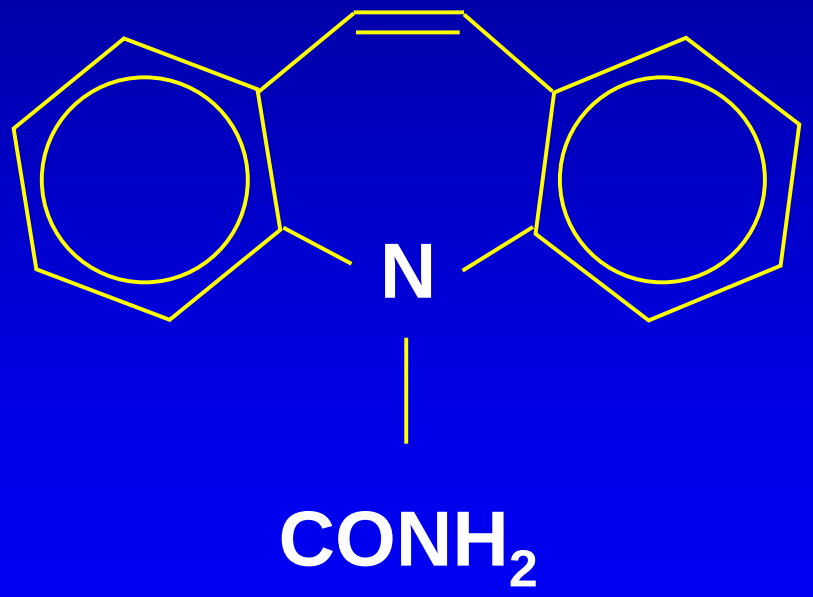
- **Carbamazepine**

  ↓ 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

* 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

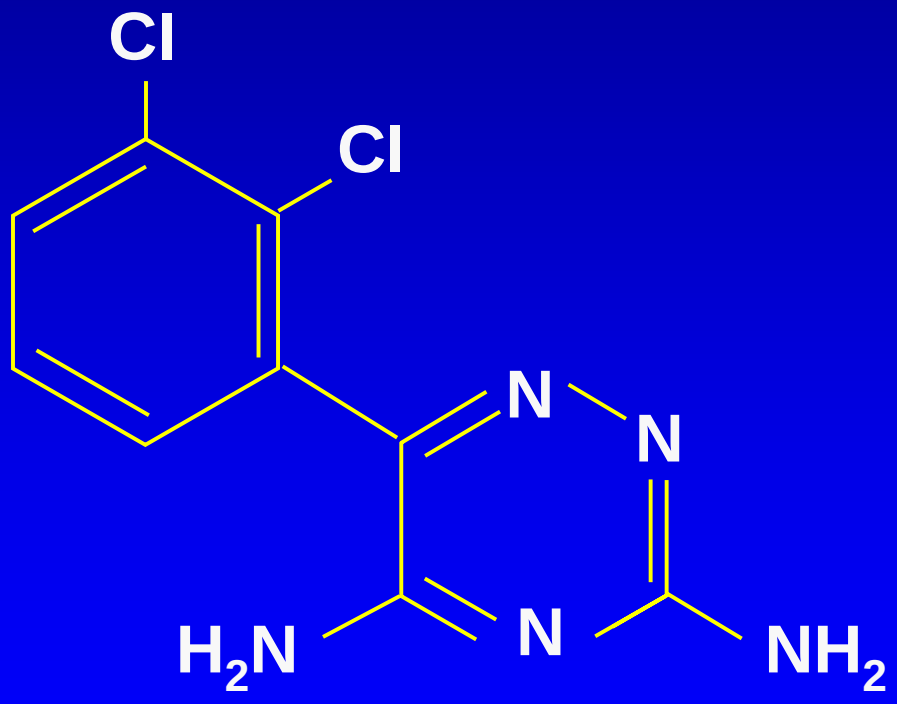
- Sedation
- Dizziness
- Ataxia
- Double/blurred vision
- GI distress
- Hematopoietic suppression
- Hepatotoxicity (rare)
- Dermatologic
- Teratogenicity
- Hyponatremia

* 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**

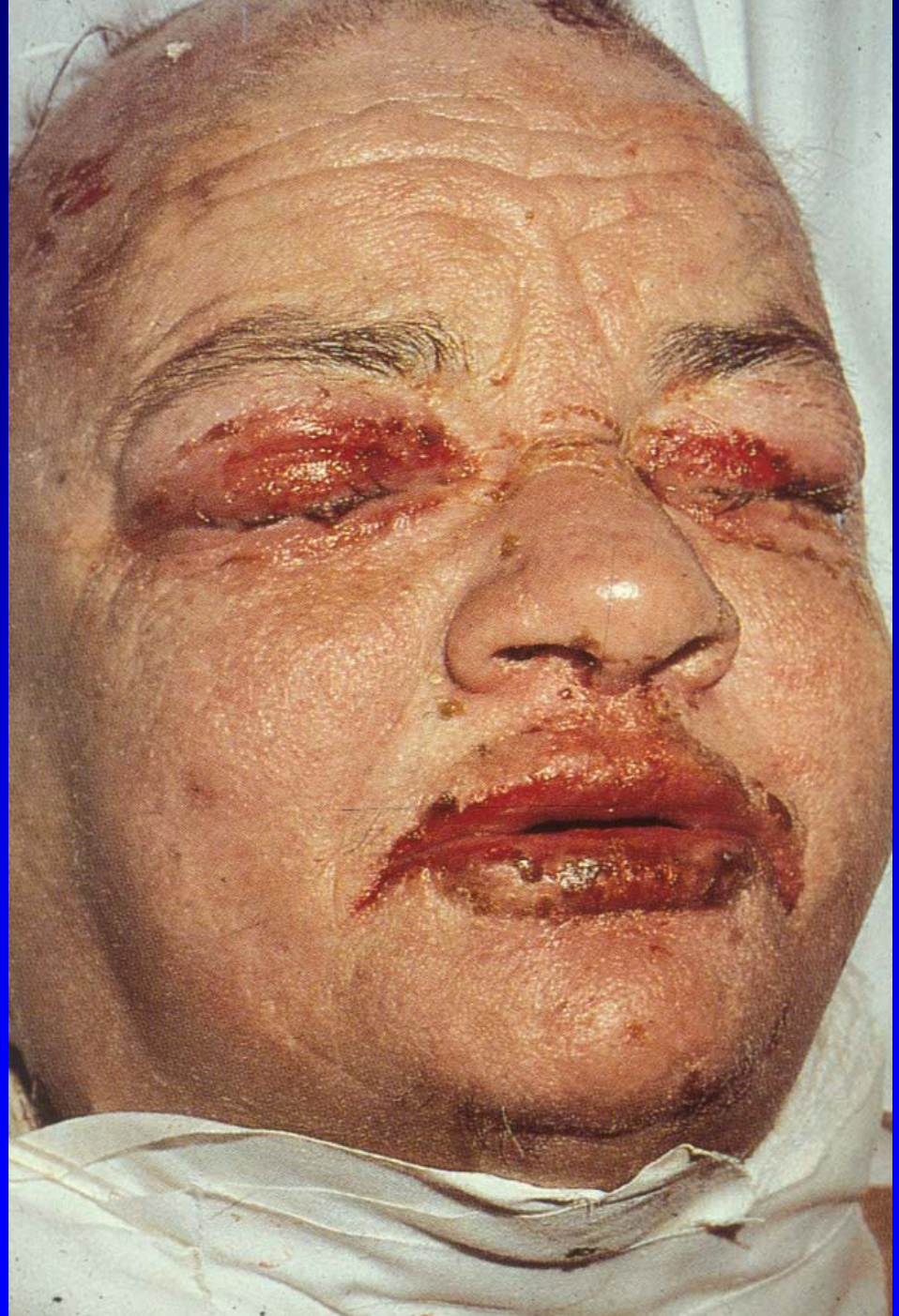
Lamotrigine



* Side Effects of Lamotrigine

Dose Related	Not Dose Related
Dizziness	Headache
Diplopia	Dermatologic 10% benign rash 3/1,000 adults—severe rash Do not rapidly escalate dose Warn patients about rash
Ataxia	
Blurred vision	
Nausea and vomiting	
Insomnia	Malformations: 2.7%

*



* 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 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, 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 hospitalisation 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

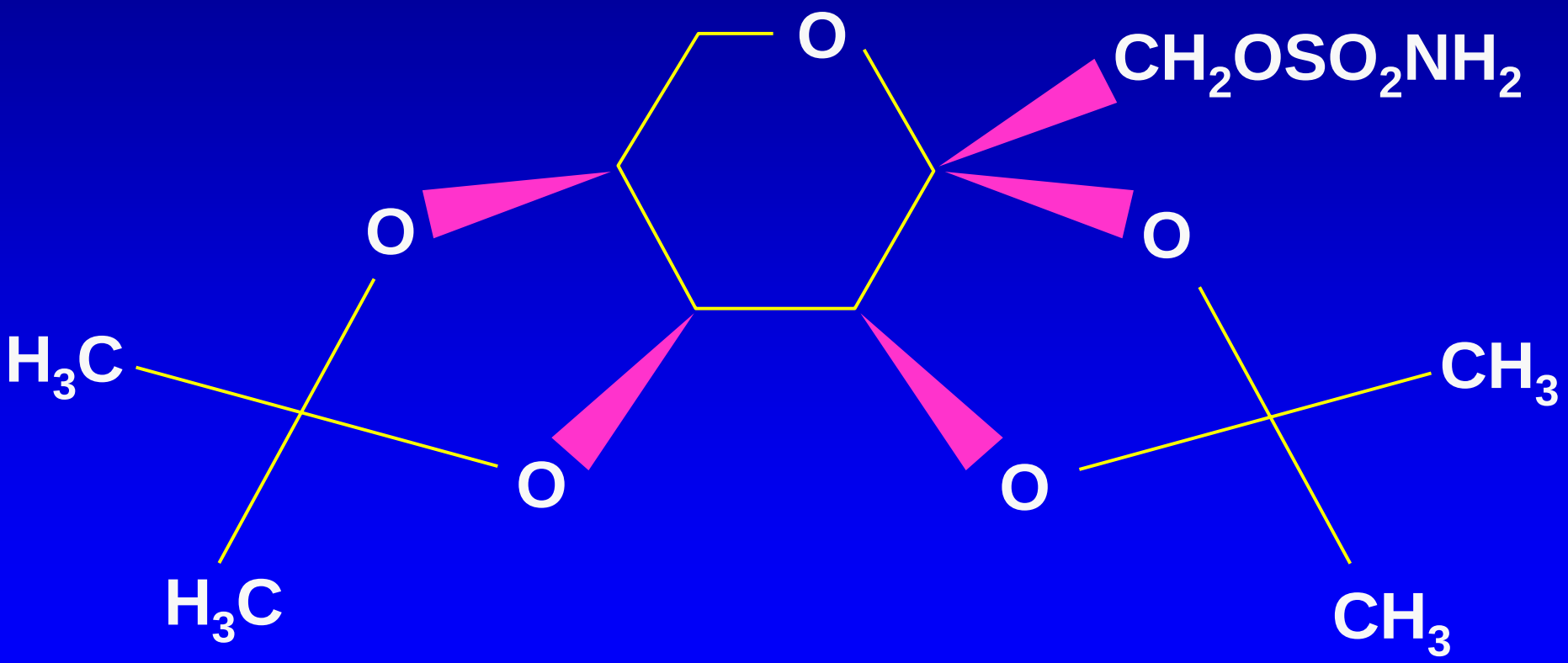
* Oxcarbazepine and Hyponatremia

- 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

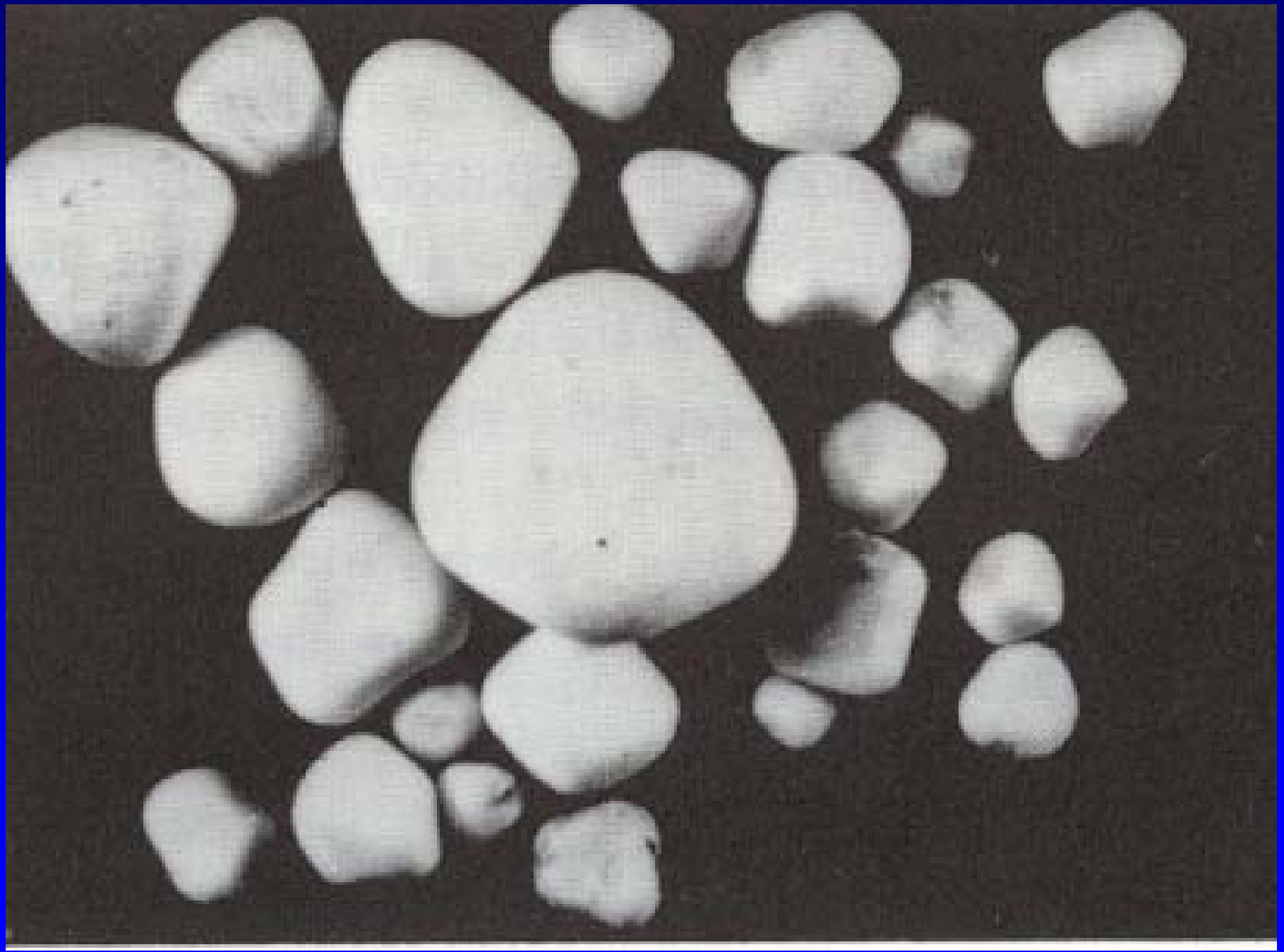
* Topiramate for Bipolar Disorders

- No double-blind controlled efficacy studies in bipolar
- Dose range: 25-400 mg/day
- Open-label results:

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

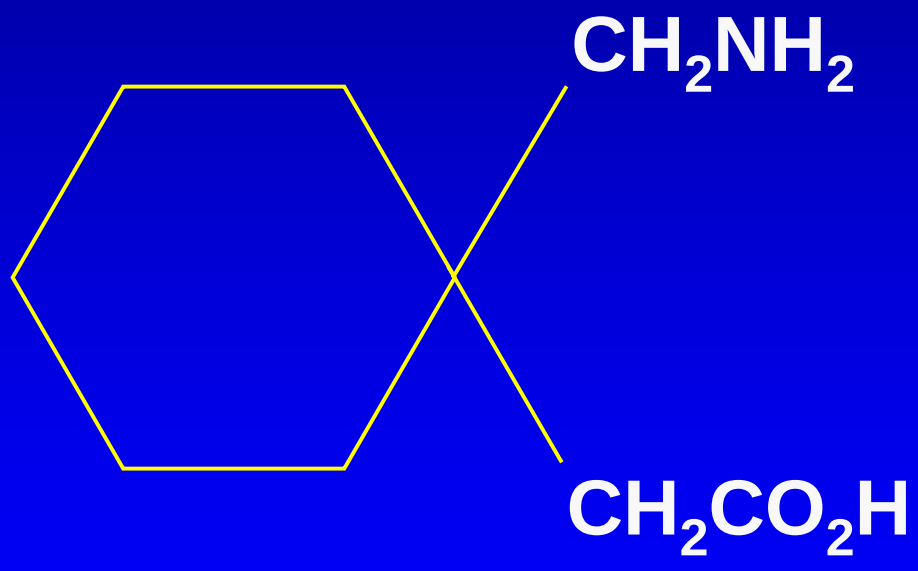
- Occurred in 1.5% (32/2086)
- 2 to 4 times ↑ risk
- Men > women
- Reported in kids
- One bipolar II woman
- Carbonic anhydrase inhibition

* 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

*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
- Note: 3 other blind studies, 2 negative and 1 positive

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

Other Promising 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

* 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

* Rapid Cycling

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

APA Bipolar Guidelines, Revised 2002

Bipolar Maintenance

* Bipolar Maintenance

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

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** **C**

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

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