

Medicine for Bipolar Disorder

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Acknowledgement: I wish to thank David Osser MD
for his review and encouragement.

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) cycle acceleration**
- 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**

5. Kidney stones are associated with:

a) olanzapine

**b) bipolar disorder complicated by
substance abuse**

c) lithium

d) divalproex

e) topiramate

*** Lecture Outline**

- **Basic Points: Prevalence, misdiagnosis, phases, treatment goals**
- **Treatment: Acute mania, bipolar depression, maintenance**
- **Specific agents: Indications, efficacy, side effects, other therapeutic issues**
- **Pregnancy**

*** Many Medicines**

- **Antipsychotics**
- **Mood stabilizers**
- **Combinations**
- **? Antidepressants**

Basic Points

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

Basic Points

- **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**
- **Significant complications (cognitive, personal and occupational functioning)**

* 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**

Phases of Bipolar Disorder

- **Acute mania**
- **Bipolar depression**
- **Maintenance**

* 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**

Atypical Antipsychotics for Mania

FDA-Approved Since 2000 *

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

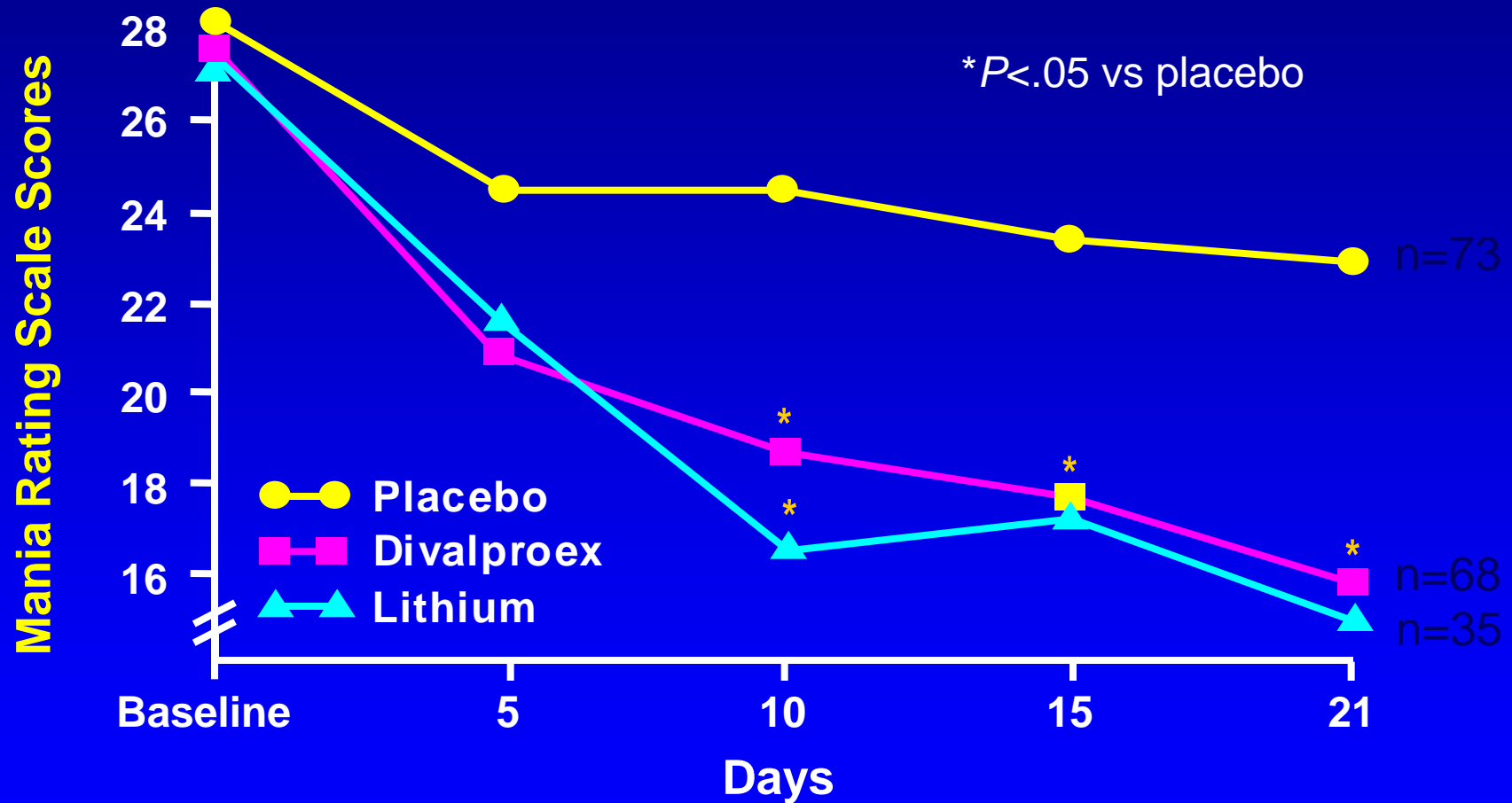
* **Acute Mania: First-Line**

- **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



*** Divalproex vs Valproate**

- **Divalproex (Depakote) is up to 5 times the cost of valproic acid (Depakene)**
- **Evidence-base is mostly with divalproex**
- **Valproate is available in liquid form**
- **Nausea is more frequent with valproate**
- **Recommend: Initiate new patients on VPA**

(Wassef AA et al. AJP 2005;162:330-339)

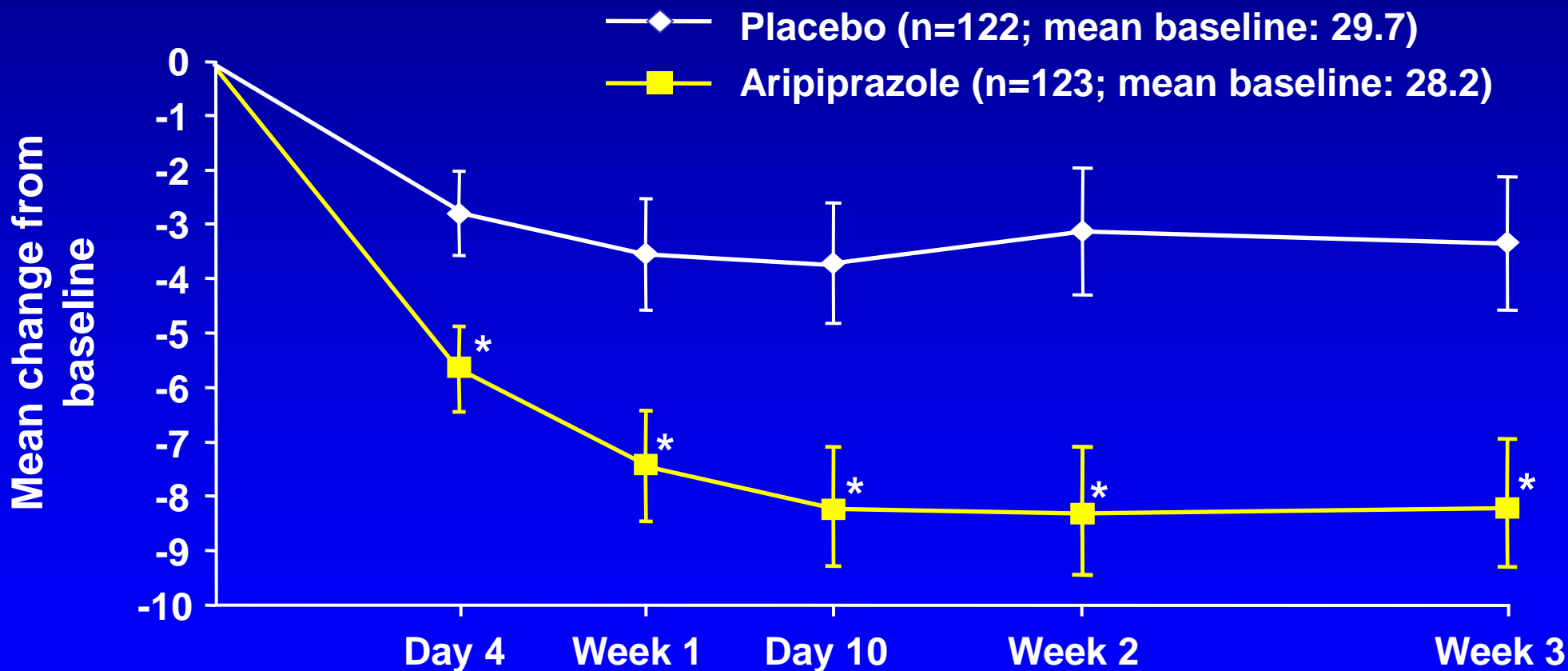
*** Atypical (Second Generation) Antipsychotics in Mania**

- **All such agents apparently effective**
- **Generally no worsening of depression (unlike conventional antipsychotics)**
- **Limited antidepressant effects, some adjunctive mood stabilization effects**
- **Less EPS but must be wary of metabolic risks, especially weight gain (except possibly for aripiprazole & ziprasidone) and deviances in glucose, lipids, or prolactin**

*** Use of Antipsychotics II**

- **Fairly rapid titration (e.g., 1-3 days), e.g. ziprasidone start 40 mg bid.**
- **Often will be used adjunctively**
- **Maybe 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**

Bipolar Depression

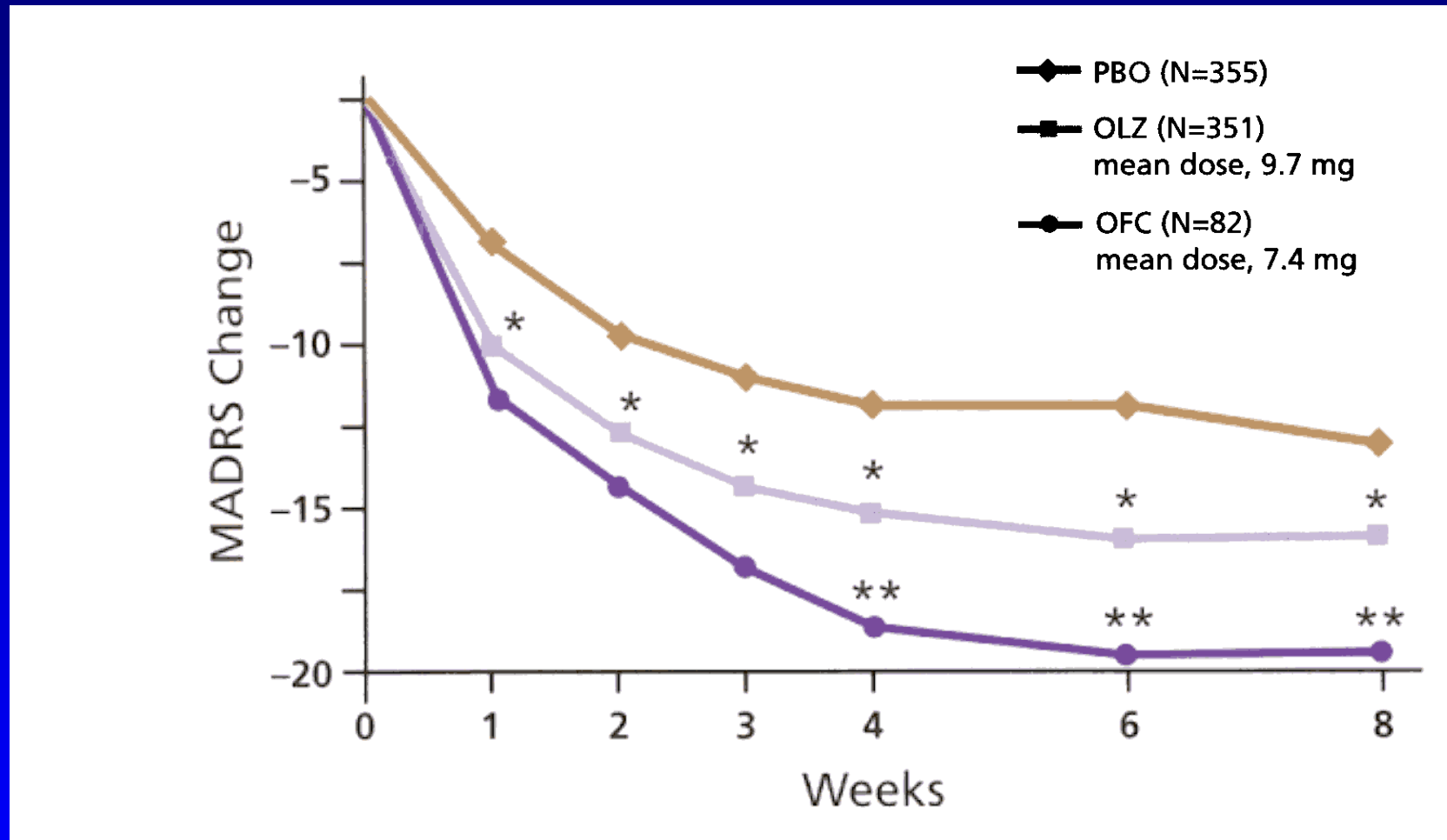
* **Bipolar Depression**

- **First-line - lithium or lamotrigine**
- **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**

* **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%

* Olanzapine/OFC for Bipolar Depression

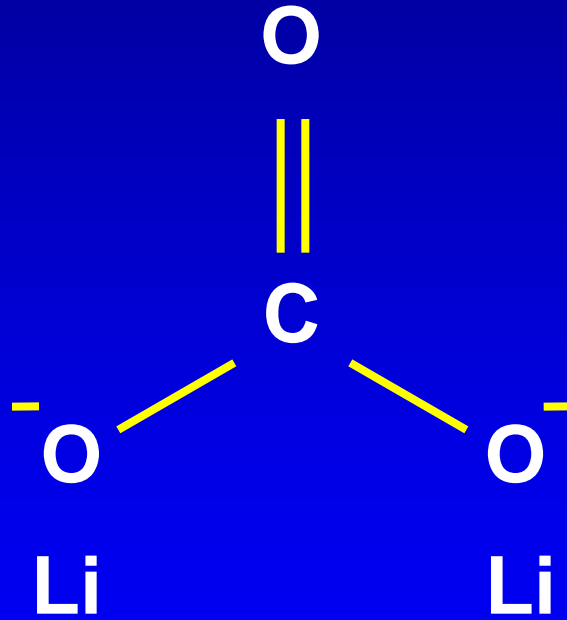


MMRM=Mixed Modal Repeated Measures,
OFC=Olanzapine-Fluoxetine Combination

* **Quetiapine 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 unexpected result needs replication.**

Lithium Carbonate



FDA Approved Lithium Indications

- **Acute mania**
- **Maintenance in bipolar disorder**

* Lithium Response Rates

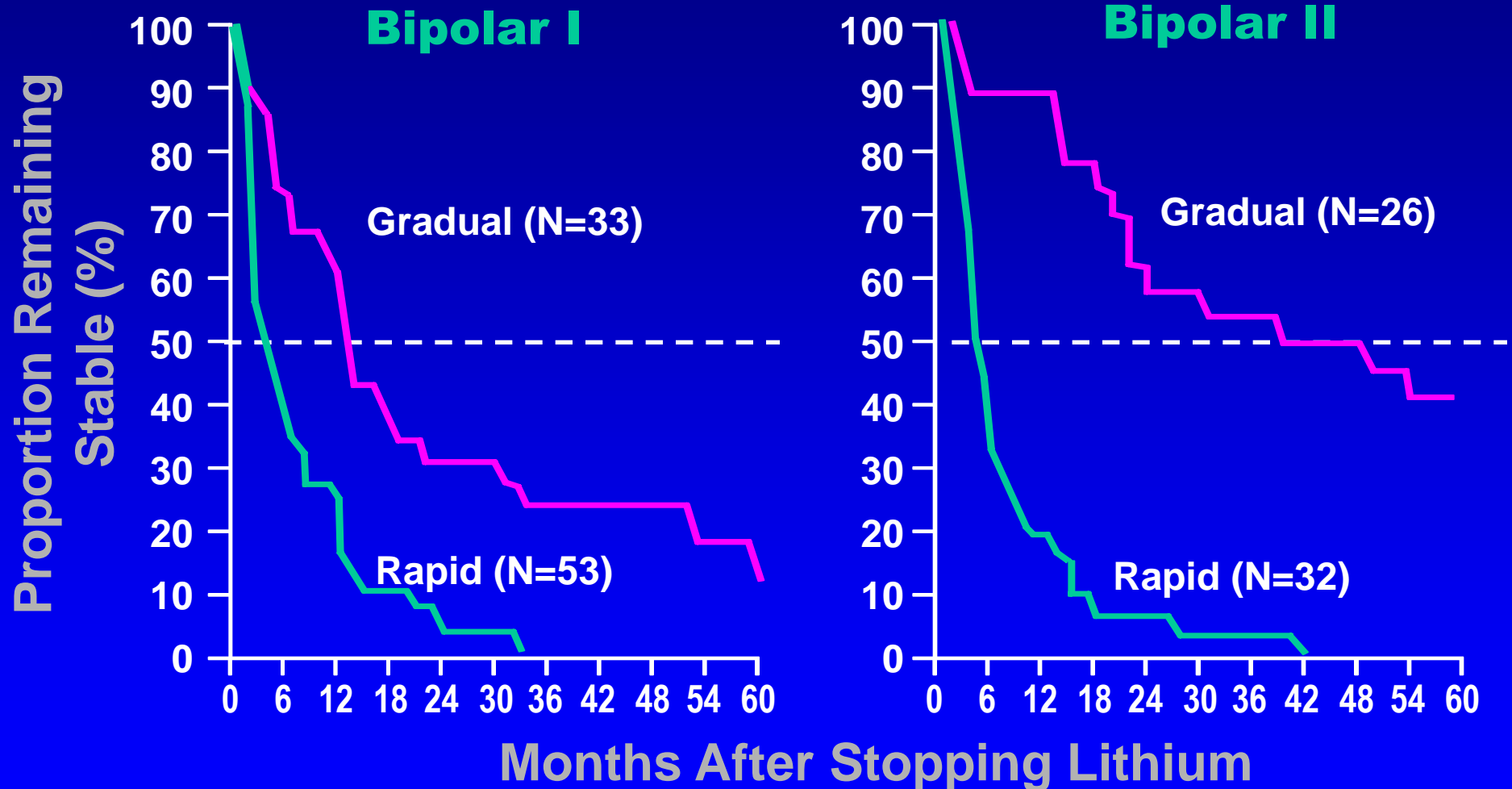
30%	Rapid cycling	Dysphoric mania	History of substance abuse	(-) Family history	>3 episodes	
70%	Nonrapid cycling	Euphoric mania	No substance abuse	(+) Family history	Few lifetime episodes	

* 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

* Gradual vs. Rapid Lithium Discontinuation



* Antisuiicidal Effect of Lithium

Clinical Response

No Attempts

- | | |
|---------------------------|--------------|
| • Excellent (n=45) | 93.3% |
| • Moderate (n=81) | 82.7% |
| • Poor (n=41) | 48.8% |

* 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

Thiazides

NSAIDs

ACE inhibitors

Low sodium diet

Dehydration

Elderly

Renal disease

Not Changed

Amiloride (?)

Furosemide

Aspirin

Sulindac

Decreased

Acetazolamide

Mannitol

Aminophylline

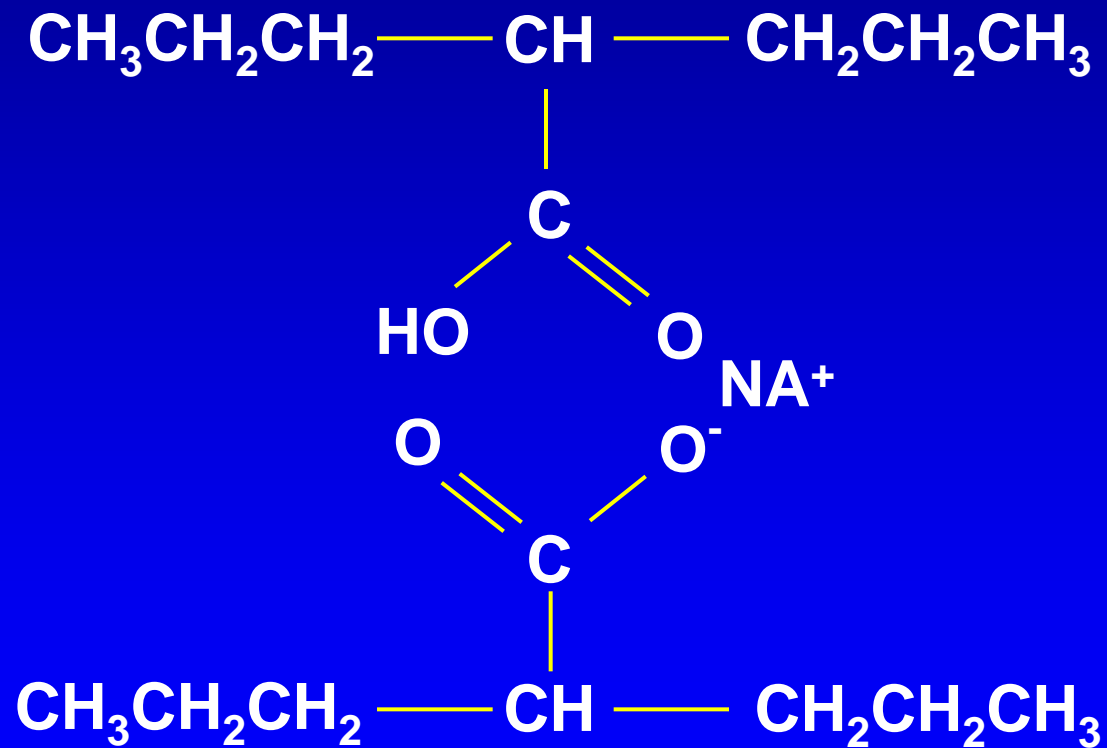
Theophylline

Caffeine

Mania

Pregnancy

Divalproex Sodium



* Valproate

- **Indications**
 - Epilepsy
 - Acute mania
 - Migraine prophylaxis
- **Role**
 - Acute and prophylactic treatment of bipolar disorder
 - Good therapeutic index
 - Superior to lithium for acute mixed episode
 - More rapid response than lithium

* 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**
- **Daily formulation available**

* Valproate

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

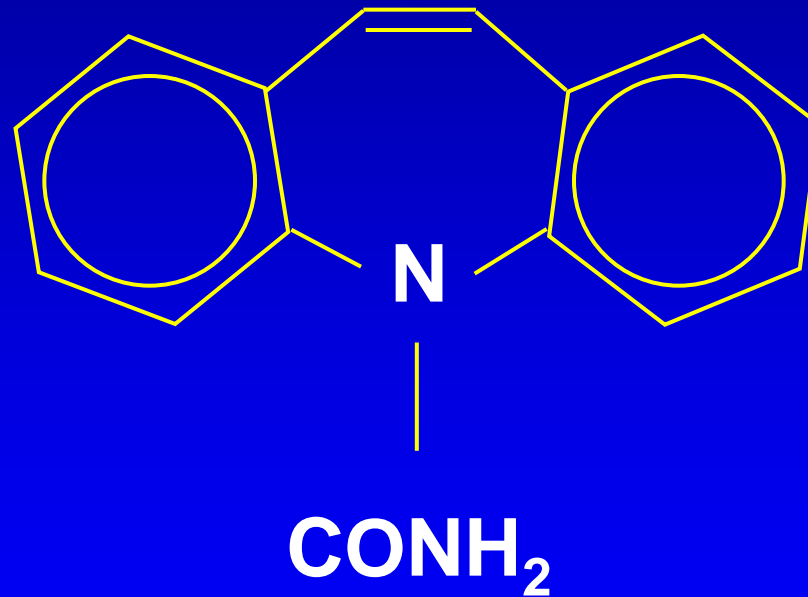
* Valproate Side Effects

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

* 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

- **Immediate and extended release**
- **Dosing**
 - **Initial: 200-400 mg/day (divided)**
 - **Maintenance: serum conc = 4-12 $\mu\text{g/ml}$**

* Carbamazepine

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

* Carbamazepine Side Effects

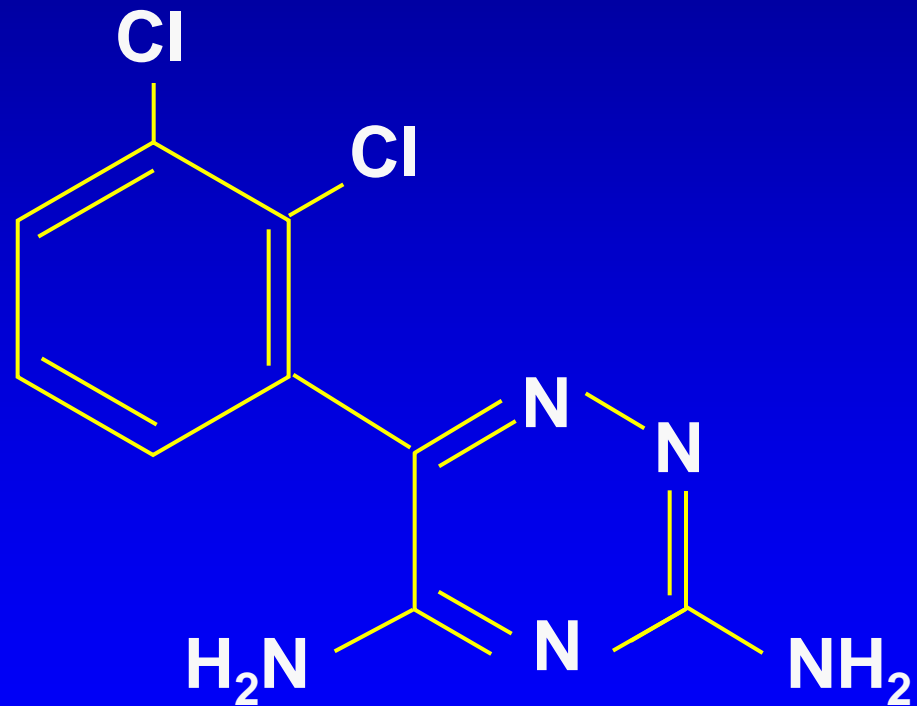
- Sedation
- Dizziness
- Ataxia
- Double/blurred vision
- GI distress
- Hematopoietic suppression
- Hepatotoxicity (rare)
- Dermatologic
- Teratogenicity
- Hyponatremia

* 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

Dizziness

Diplopia

Ataxia

Blurred vision

Nausea and vomiting

Insomnia

Not Dose Related

Headache

Dermatologic

10% benign rash

3/1,000 adults—severe rash

Do not rapidly escalate dose

Warn patients about rash

Malformations: 2.7%(Messenheimer JA, 2006)

*



* **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**

* 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**

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%

¹Requiring hospitalisation and drug discontinuation

* 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

- 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%)**
- **Rare: Stevens-Johnson syndrome and toxic epidermal necrolysis**

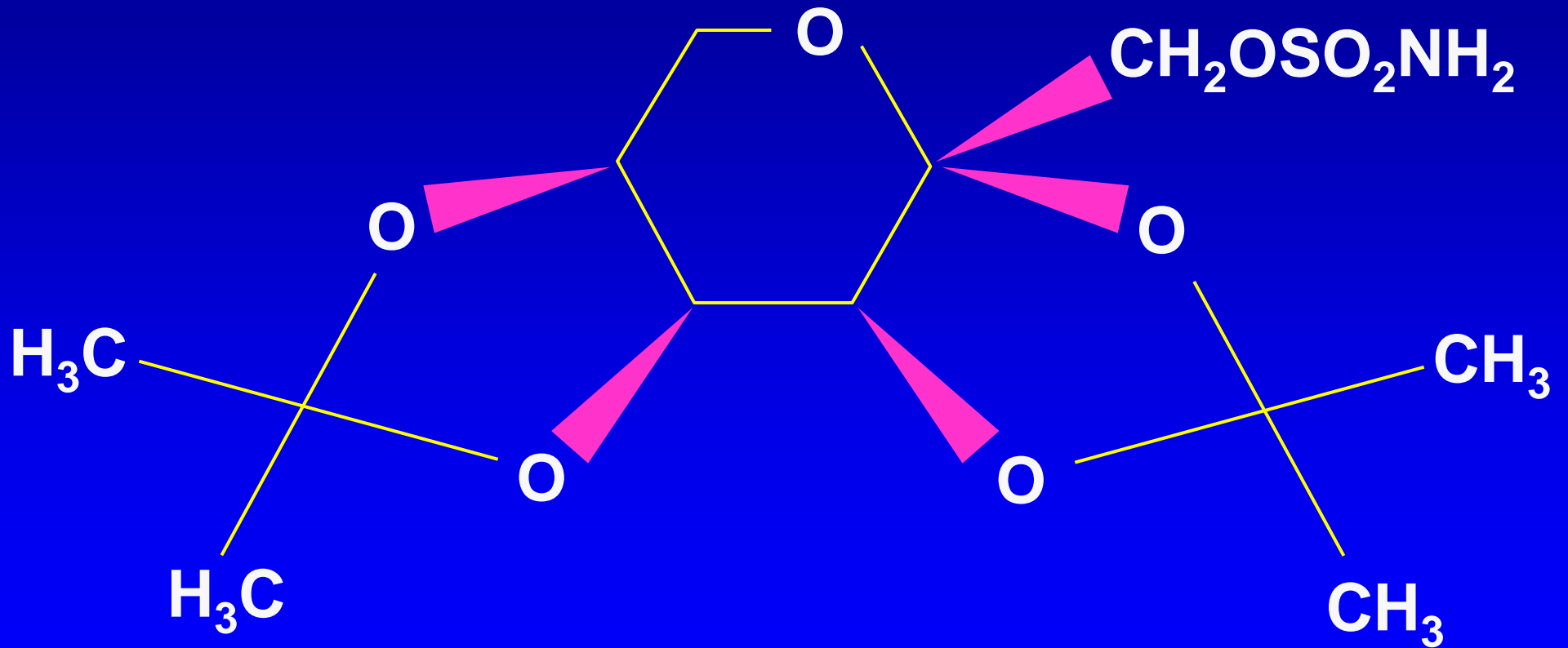
* Oxcarbazepine and Hyponatremia

- 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



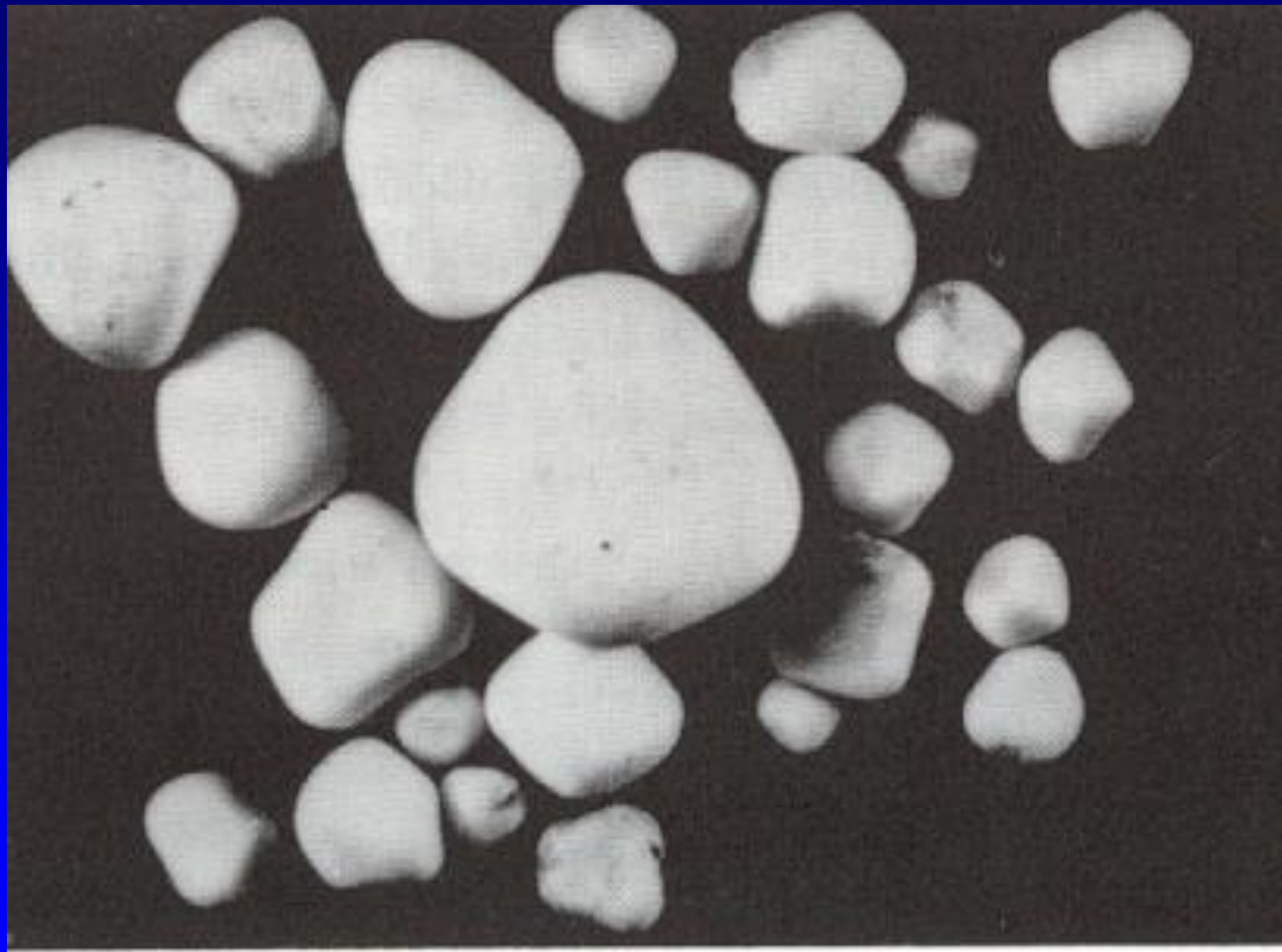
Topiramate (Topamax)

- **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%**



* Topiramate

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

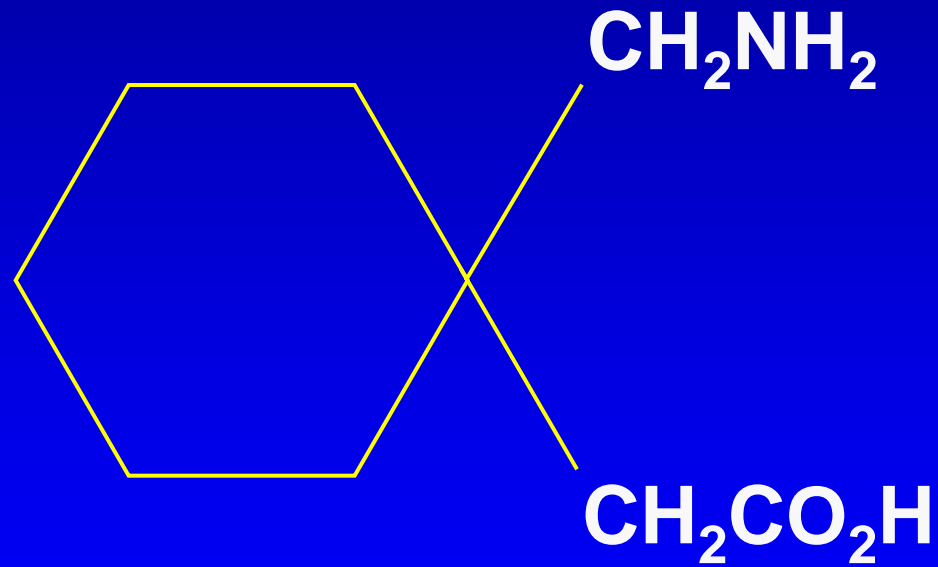
* **Topiramate and Kidney Stones**

- **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**

Adjunctive Gabapentin for Bipolar Disorders

- **Positive response¹** **18/28 (65%)**
- **Marked improvement²** **3/5 (60%)**
- **Cycling stopped³** **67/73 (92%)**
- **Improved⁴** **8/9 (89%)**
- **Majority improved⁵** **(N=47)**

¹Schaffer & Schaffeer, 1997; ²Bennett et al, 1997; ³Ryback et al, 1997;

⁴McElroy et al, 1997; ⁵Marvott et al, 1997

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

(Stoll A et al. Arch Gen Psychiatry 1999;56:407-412)

- 4 months, db, placebo-controlled**
- Recurrence:**

Omega-3	7%
Placebo	47%
- Mechanism: altered post-synaptic transduction**
- Needs replication before use should become widespread**

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**

* **Combination Therapy**

- **Monotherapy is the exception**
- **Combination therapy is effective**
- **But, this means increased risk of side effects and drug interactions**

* **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**

Bipolar Maintenance

*** Bipolar Maintenance**

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

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) cycle acceleration**
- 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**

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