

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
- Treatment: Acute mania, bipolar depression, maintenance, rapid cycling
- Specific agents: Indications, efficacy, side effects, interactions, other therapeutic issues
- Pregnancy

Main Teaching Points

- **Challenges to recognize**
- **Many medicines to consider**
- **Treatment goals to specify**
- **Treatment selection to organize**

Bipolar Disorder Overview I

- **Prevalence: 1-4% or higher (narrow vs spectrum)**
- **Onset in young adulthood (>60 years: medical disorders should be first consideration)**
- **Chronic episodic course**
- **Morbidity (disability, hospitalization, adjustment, substance problems, psychiatric disorder, medical issues)**
- **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%). ADHD (controversial)
- Significant co-morbidities (e.g., 60% lifetime prevalence of alcohol and drug use disorders)
- Significant complications: cognitive, personal and occupational functioning

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**
- **2004** **Carbamazepine ER**
- **2005** **Divalproex ER**
- **2000 on** **SGAs**

Atypical Antipsychotics for Mania

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

*** Acute Mania: First-Line**

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

APA Bipolar Guidelines, Revised 2002

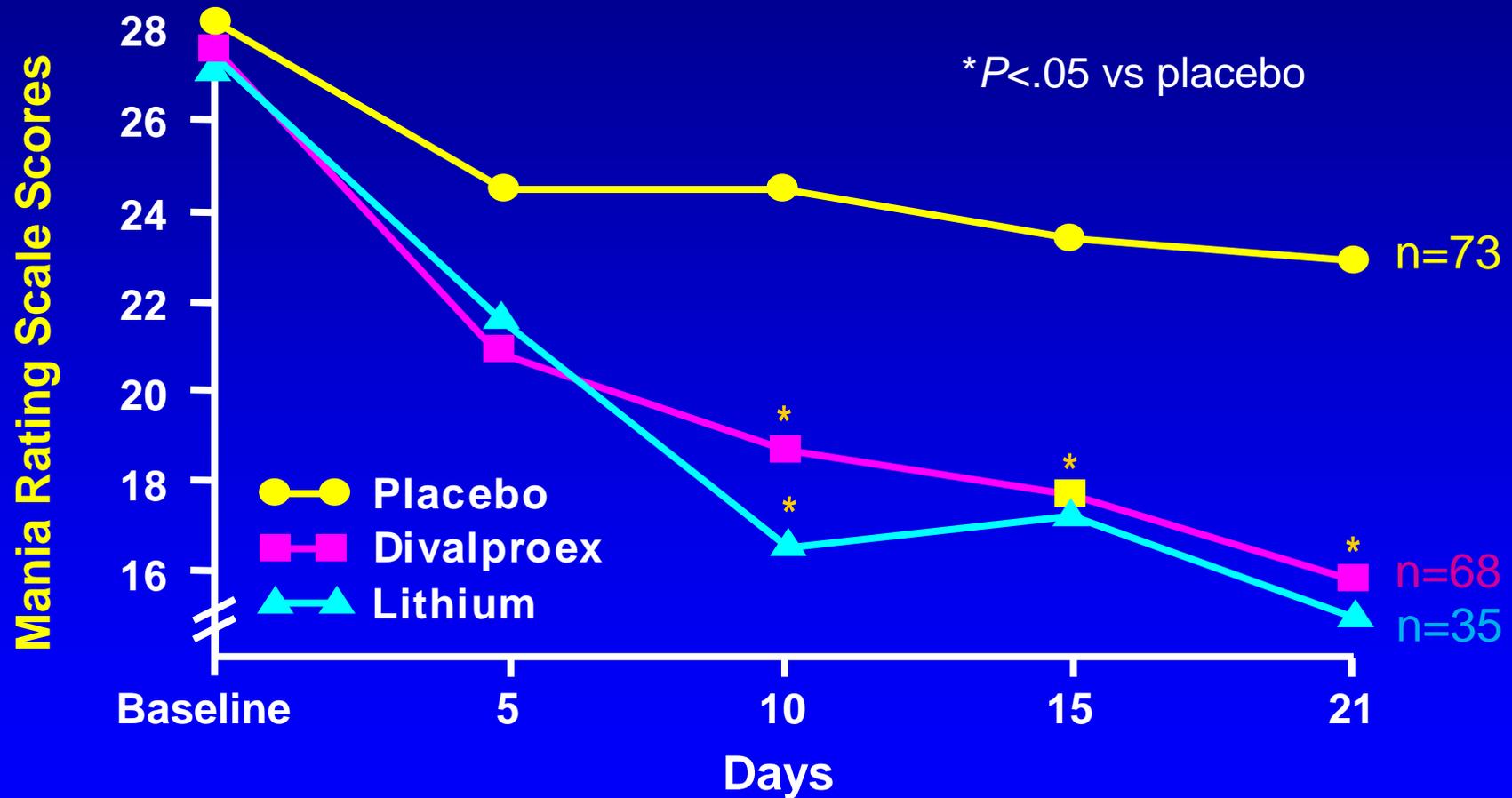
APA Bipolar Guidelines Watch 2005

CANMAT & ISBN Guidelines 2009

***Weisler et al, J Clin Psych, 2005**

* Double-Blind Controlled Study

Divalproex vs Lithium vs Placebo



*** Divalproex vs Valproic Acid**

- **Divalproex (Depakote) now generic; previously higher cost is declining**
- **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**
- **Recommend: Initiate new patients on single dose divalproex ER (advantages despite cost)**

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

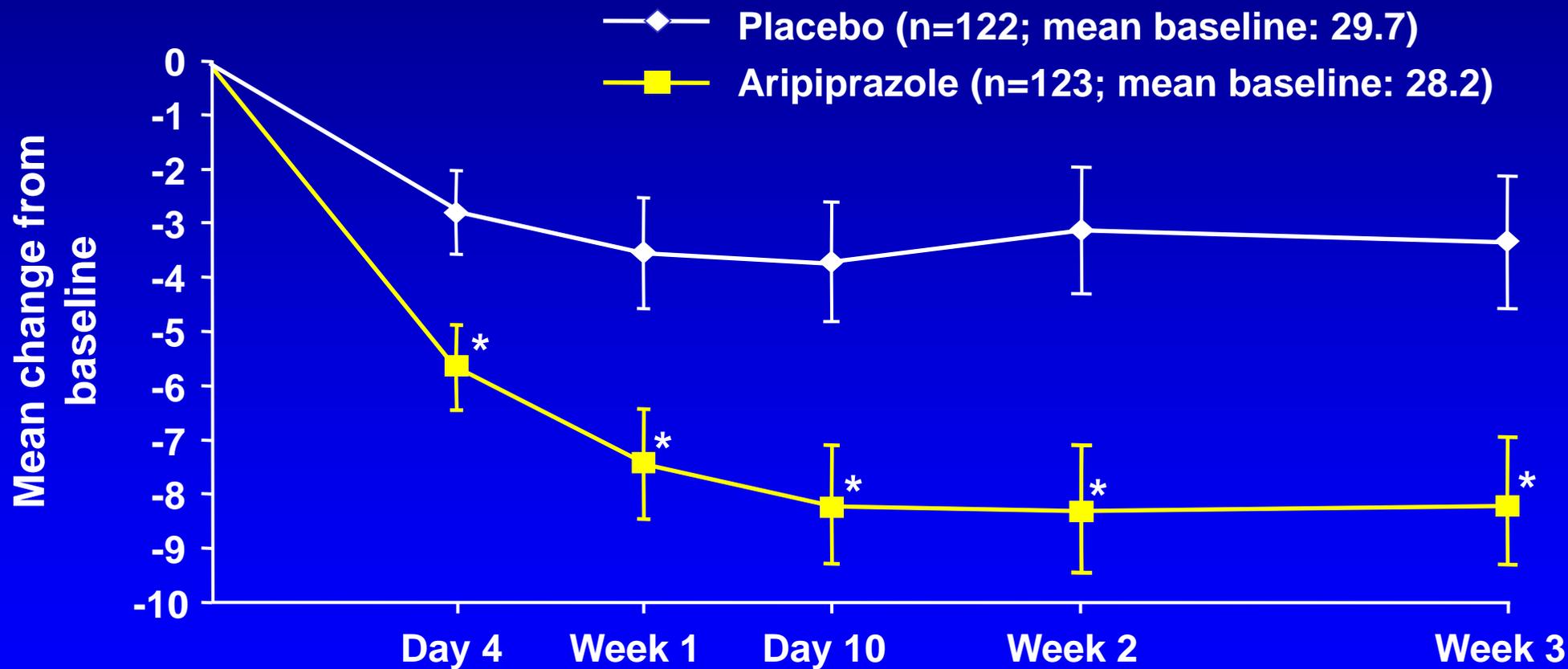
*** Atypical (Second Generation) Antipsychotics in Mania**

- **All 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**

*** Use of Antipsychotics II**

- **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.**

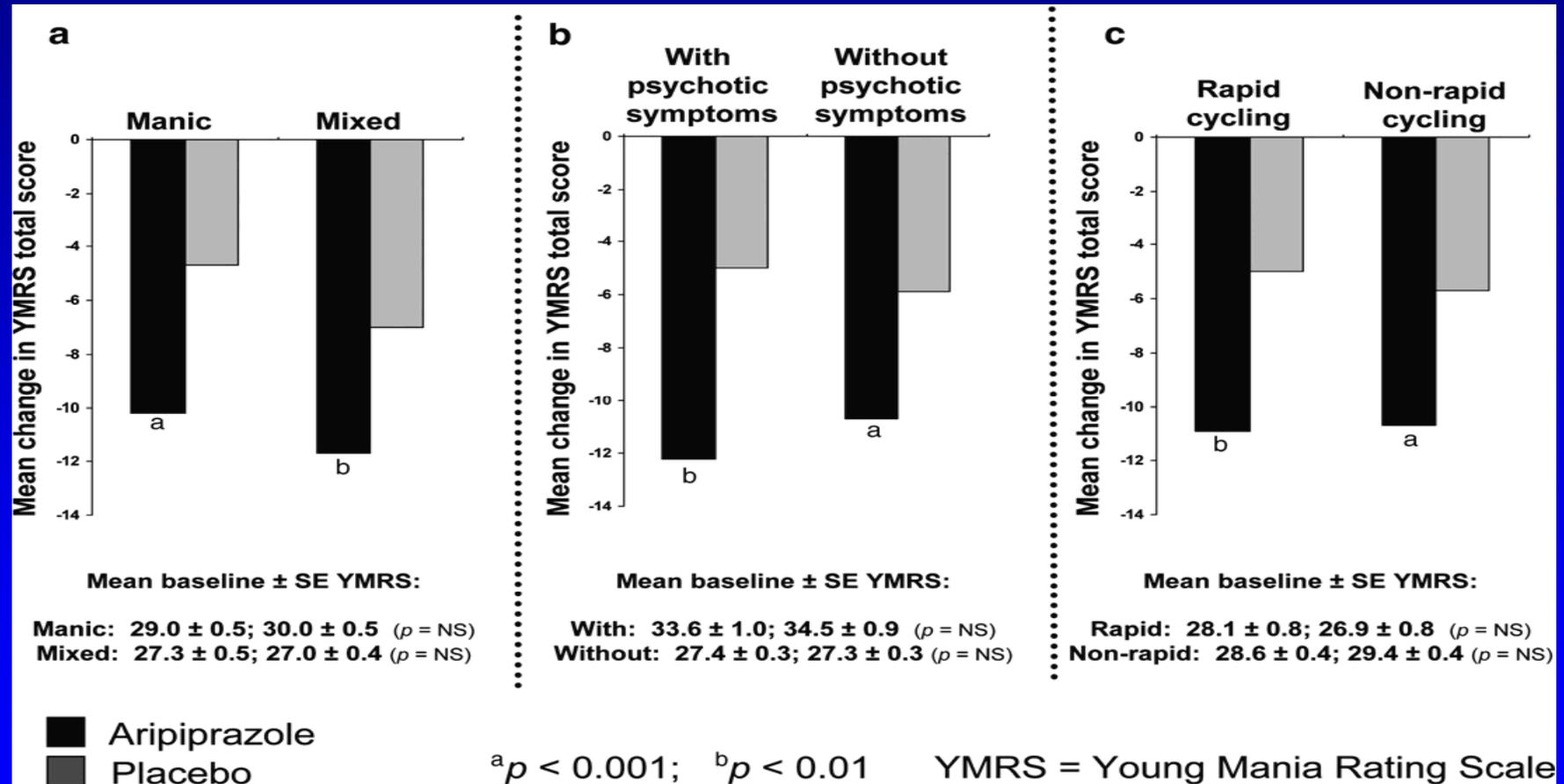
* Example: Aripiprazole in Acute Mania: Mean Change From Baseline in YMRS



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

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

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



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

Asenapine for Acute Mania

Despite clinical trial evidence*, clinical experience is lacking; 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**

*** Clozapine for Bipolar Disorder**

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

Bipolar Depression

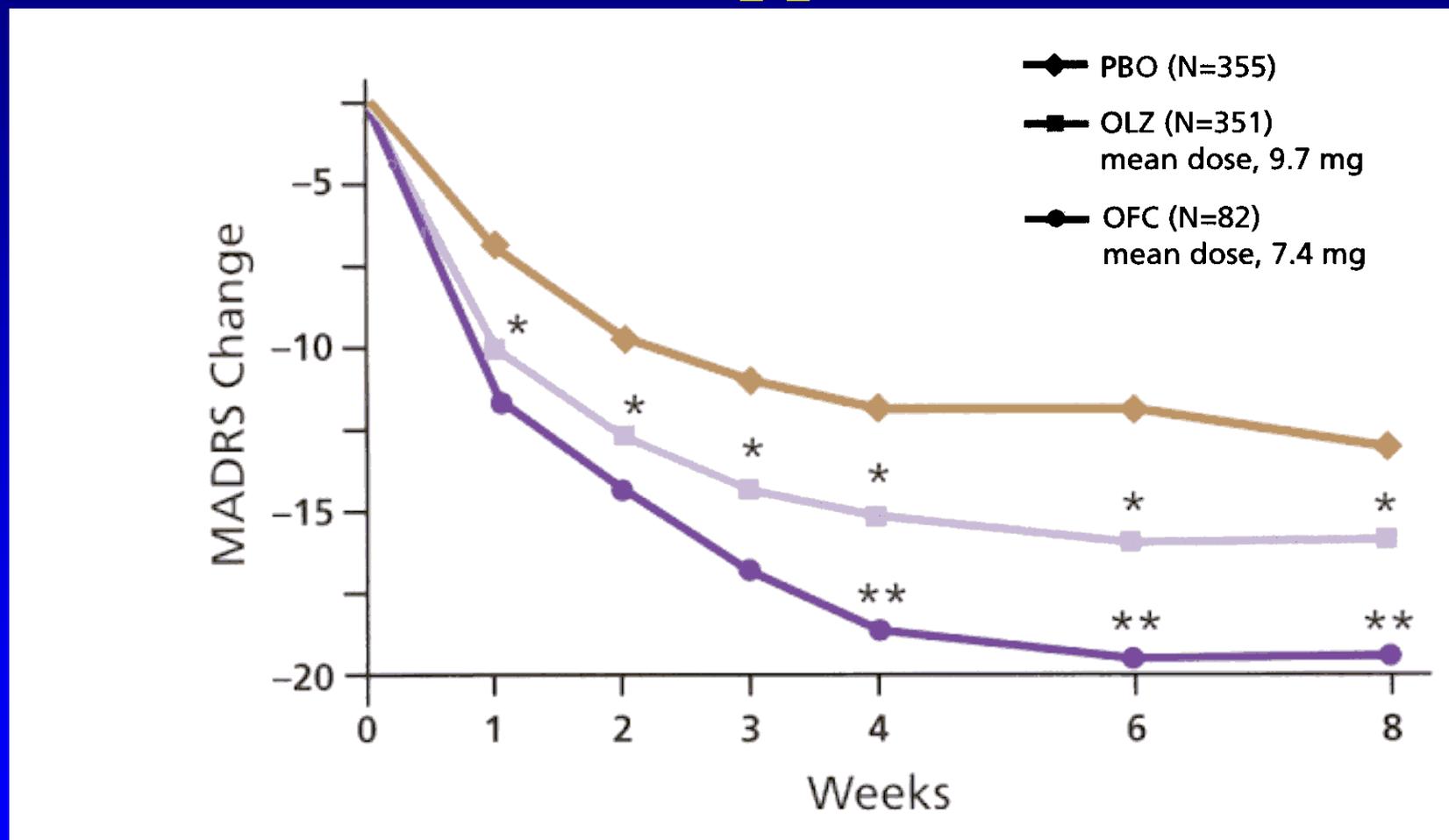
* **Bipolar Depression**

- **First-line – lithium, quetiapine, lamotrigine,* OFC (olanzapine/fluoxetine combination)**
- **Antidepressant monotherapy not advised**
- **Moderate increase in risk with AD in BPD****
Bupropion, SSRIs, venlafaxine may be added to mood stabilizer but rate of response (without stimulating mania) is 16%-- but no placebo group to know spontaneous switch rate (Leverich et al, AJP, 2006;23)
- **ECT, psychotherapy**
***4 out of 5 RCTs show no advantage over placebo for LTG Calabrese et al, Bipolar Disorder, 2008**
****Tondo et al, Acta Psychiat Scand, 2009**

*** 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%

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

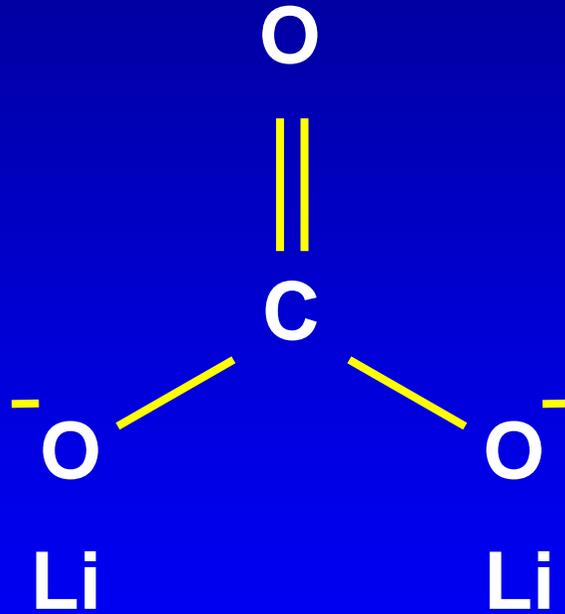


MMRM=Mixed Modal Repeated Measures,

* **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.**

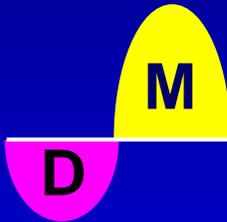
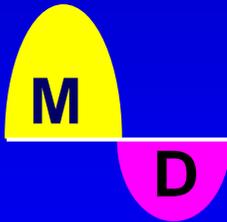
Lithium Carbonate



FDA Approved Lithium Indications

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

* Lithium Response Rates

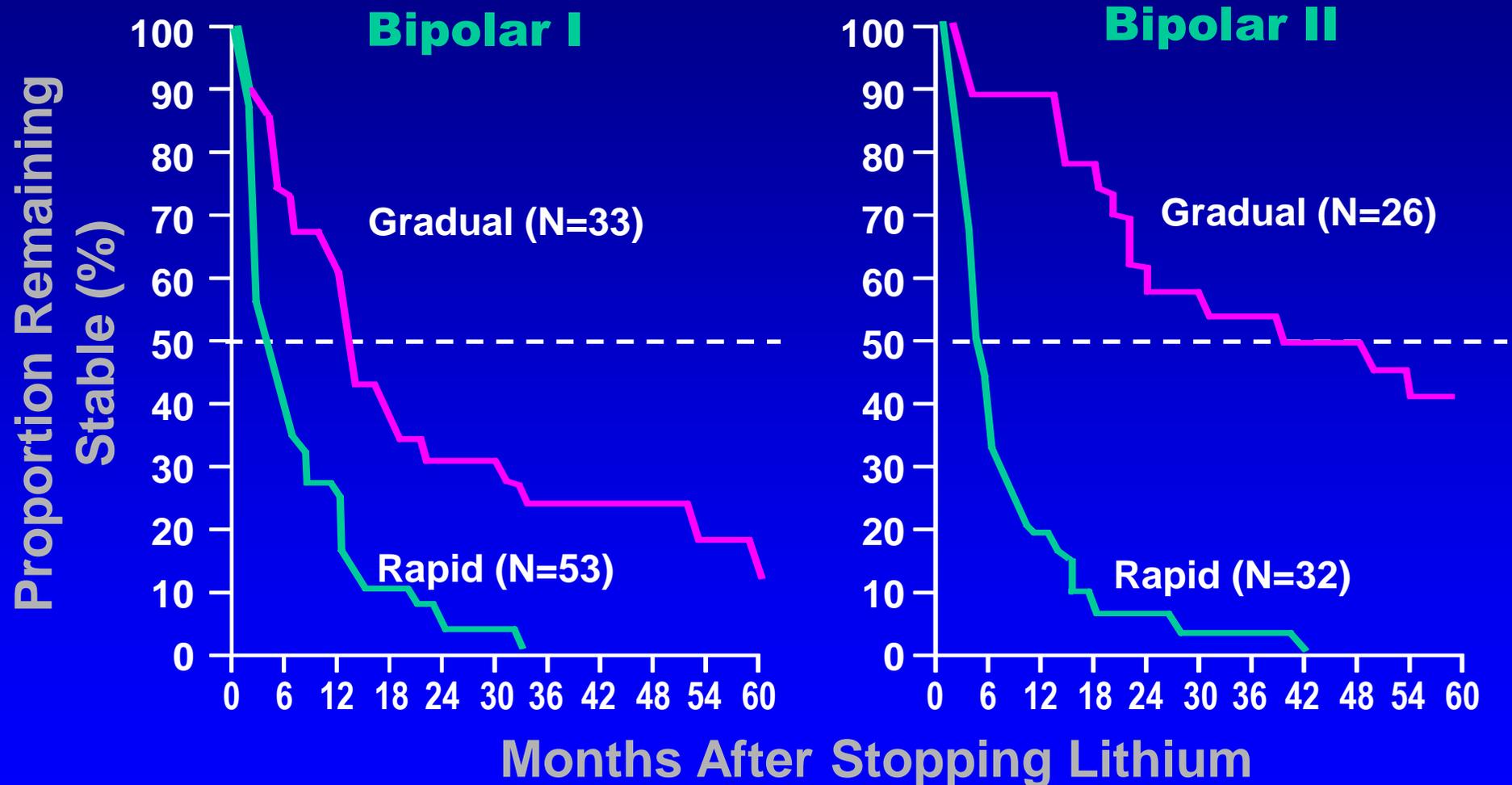
30%	Rapid cycling	Dysphoric mania	History of substance abuse	(-) Family history	>3 episodes	
70%	Nonrapid cycling	Euphoric mania	No substance abuse	(+) Family history	Few lifetime episodes	

*** 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



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

- 213 bipolar pts stable on lithium monotherapy 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

* Antisuiicidal Effect of Lithium

Clinical Response

No Attempts

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

* **Antisuiicidal 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.

* 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

- **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

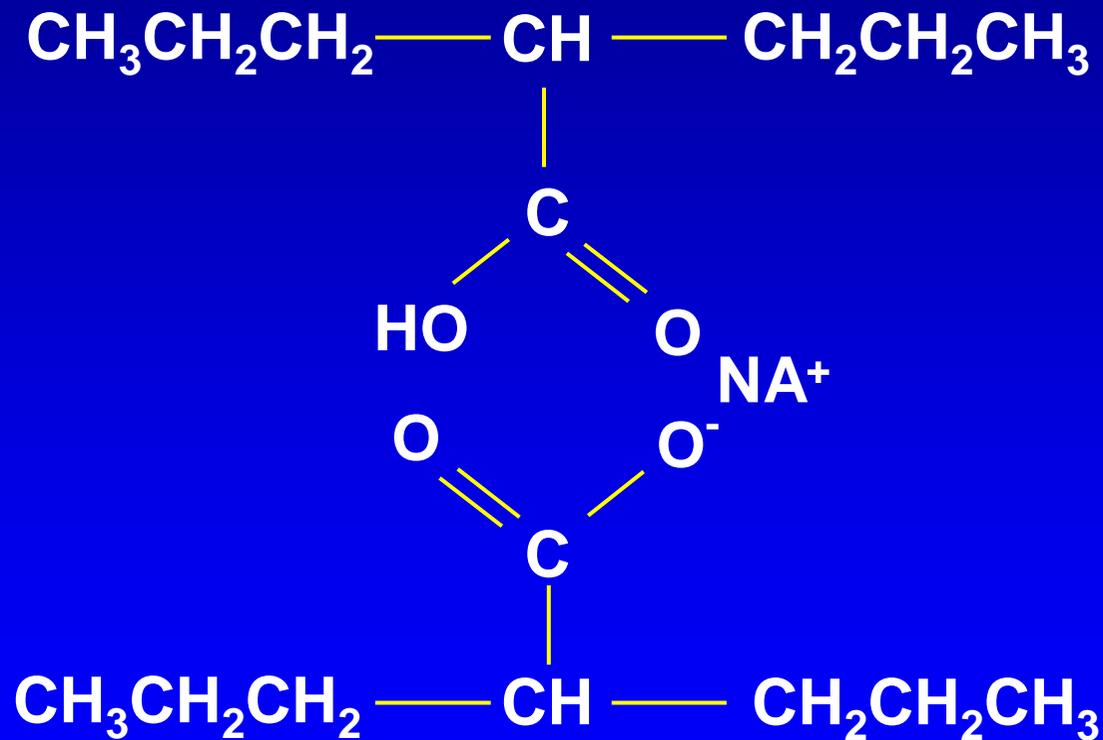
Theophylline

Caffeine

Mania

Pregnancy

Divalproex Sodium/Valproate



* 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%**
- **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

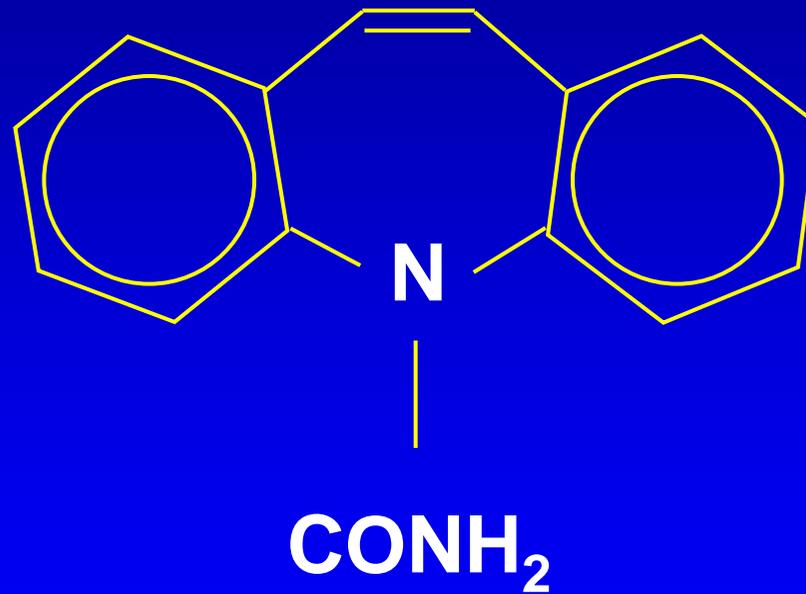
- **Carbamazepine**

↓ 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 $\mu\text{g/ml}$**

* Carbamazepine

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

* Carbamazepine Side Effects

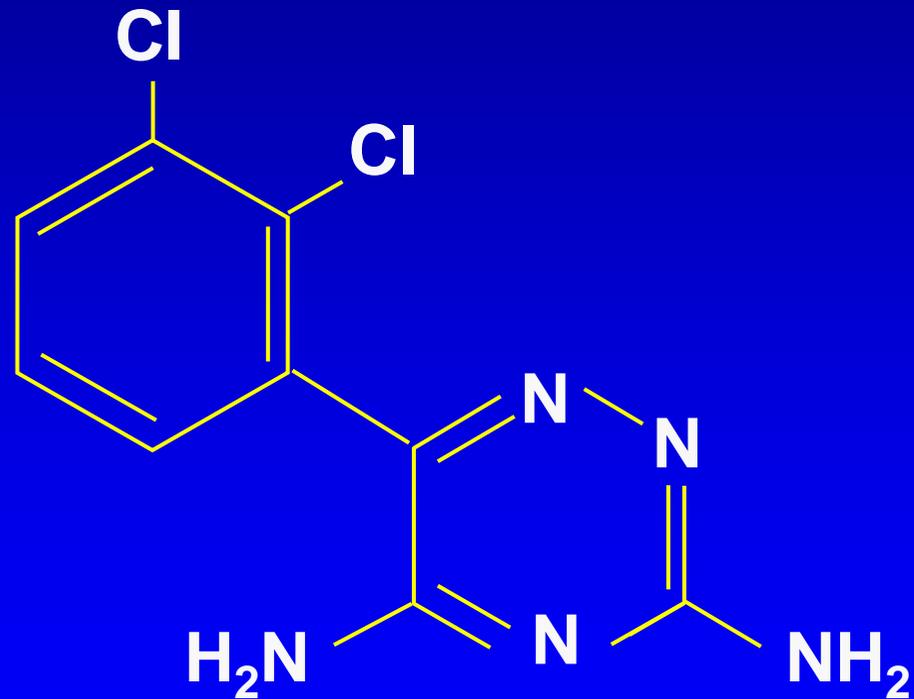
- Sedation
- Dizziness
- Ataxia
- Double/blurred vision
- GI distress
- Hematopoietic suppression
- Hepatotoxicity (rare)
- Dermatologic
- Teratogenicity
- Hyponatremia

* 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%

*



* **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)
- 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**

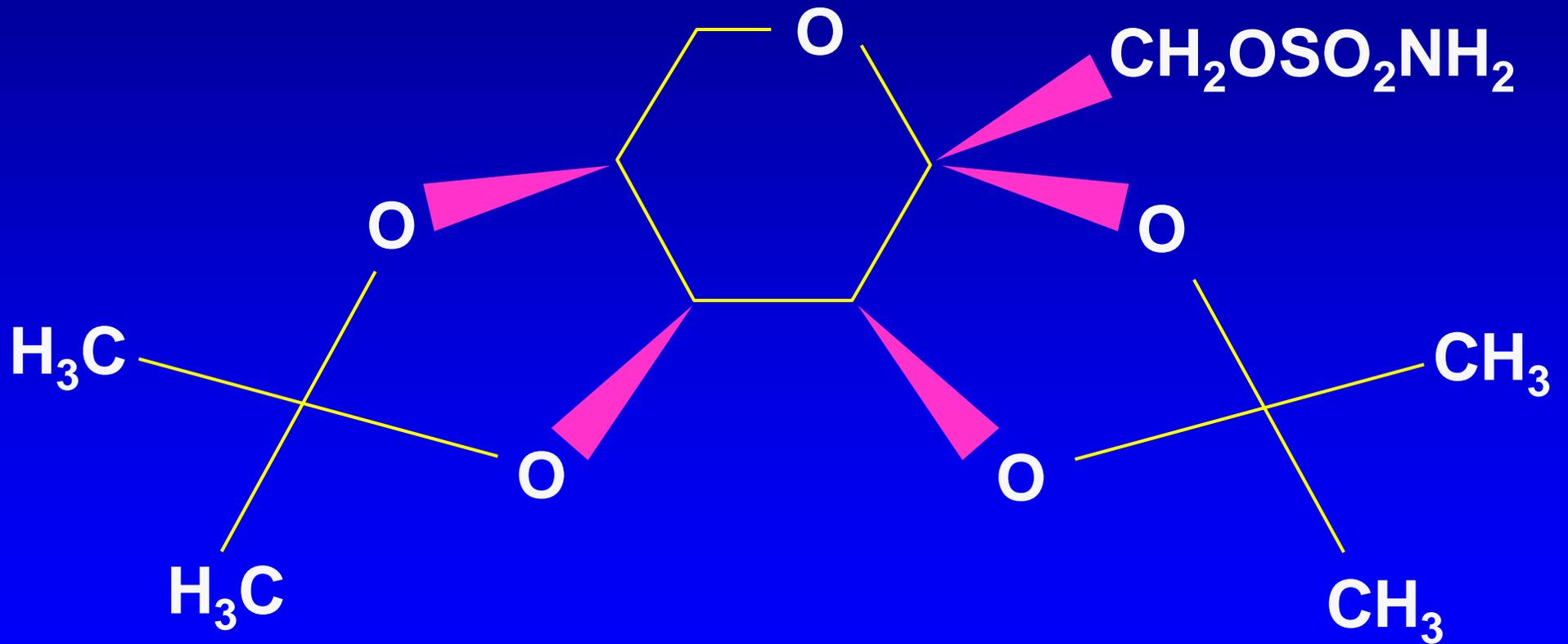
* Oxcarbazepine and Hyponatremia

- 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

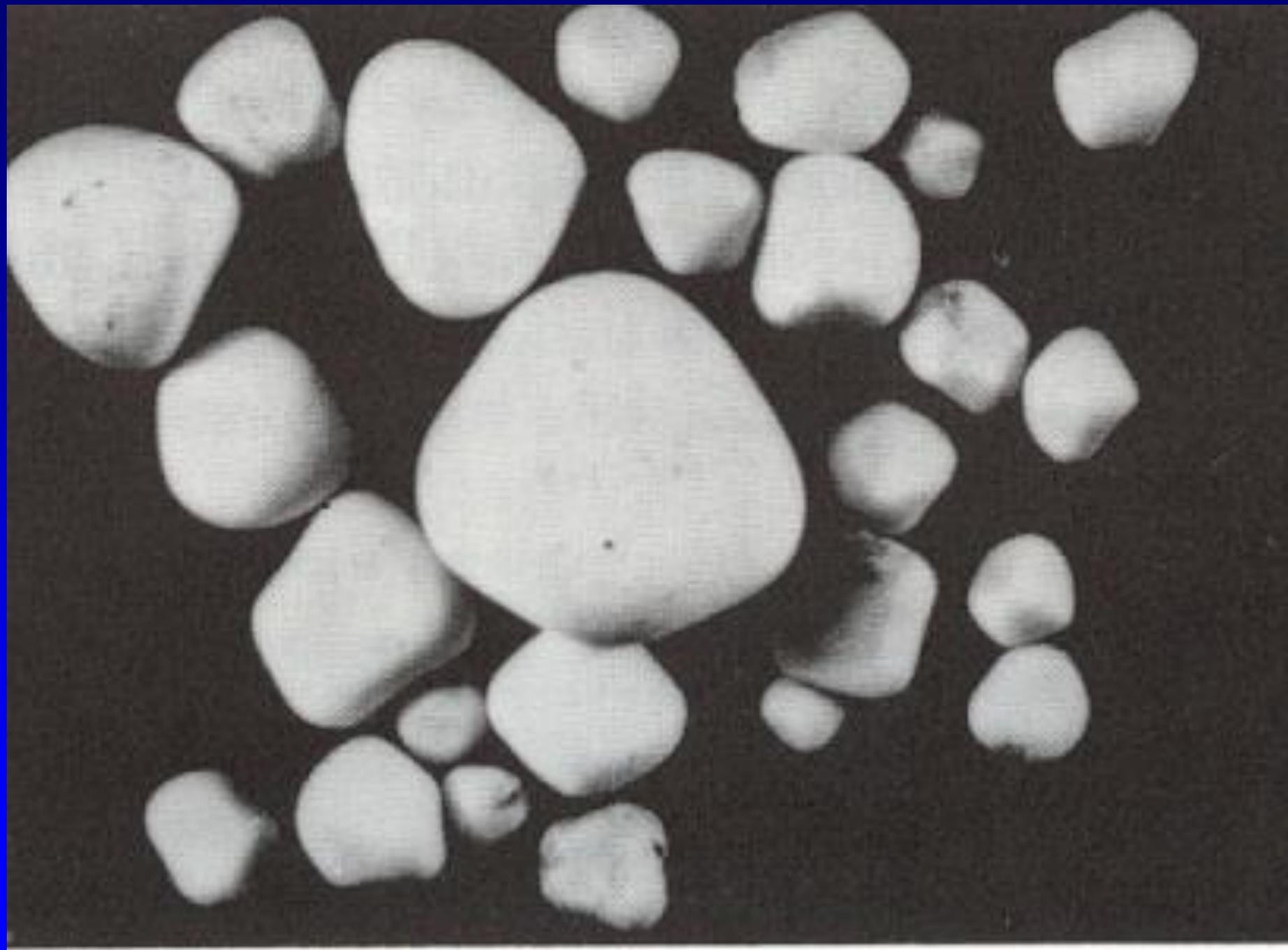


Topiramate (Topamax)

- **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**



*** Topiramate**

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

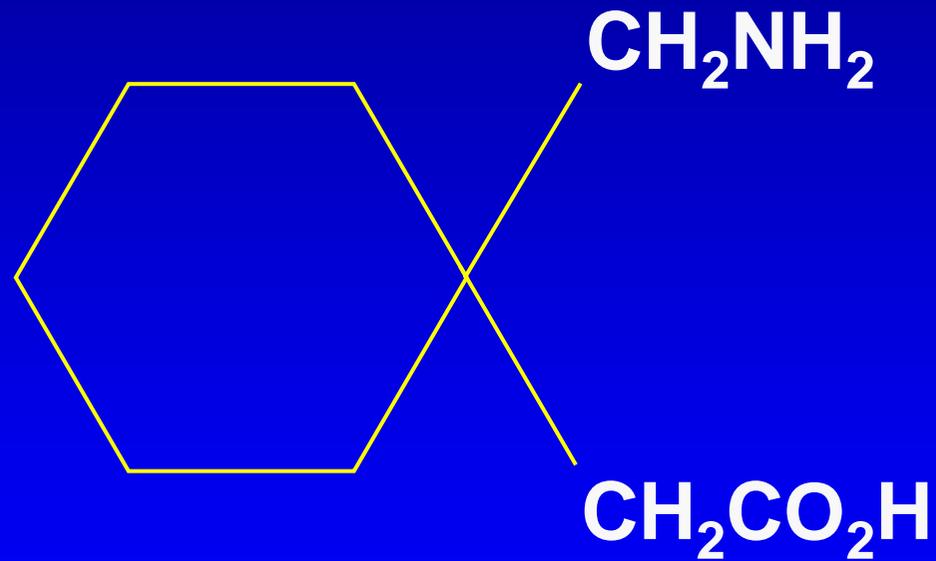
* Topiramate and Kidney Stones

- 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

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 symptom but not manic symptoms in bipolar disorder. There is an acute need for well-designed and executed randomised controlled trials in this field.

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

* **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, 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**

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