Bipolar Disorders: Therapeutic Options

James W. Jefferson, M.D.

Clinical Professor of Psychiatry
University of Wisconsin School
Of Medicine and Public Health
Distinguished Senior Scientist
Madison Institute of Medicine

Revised November 2009

Part 4: Specific Medications for Bipolar Disorder (Lithium and Antiepileptic Drugs)

Revised November 2009

Teaching Points

1. Lithium requires blood level monitoring, has a wide range of side effects and drug interactions.
2. Divalproex requires blood level monitoring, has three black box warnings, but only a few drug interactions of concern.
3. Carbamazepine, divalproex, and lamotrigine have established roles for treating bipolar disorders. The other antiepileptic drugs do not.

Outline

I. Lithium
   - A. Pharmacology
   - B. Side Effects
   - C. Interactions

II. Divalproex
   - A. Mechanism of Action
   - B. Pharmacology
   - C. Side Effects
   - D. Interactions

III. Carbamazepine
   - A. Mechanism of Action
   - B. Pharmacology
   - C. Side Effects
   - D. Interactions

IV. Lamotrigine
   - A. Mechanism of Action
   - B. Pharmacology
   - C. Side Effects
   - D. Interactions

V. Gabapentin

VI. Oxcarbasepine

VII. Topiramate

VIII. Tiagabine

IX. Other
   - A. Zonisamide
   - B. Levetiracetam
   - C. Omega-3 Fatty Acids

X. Pregnancy and Breastfeeing

XI. Depression and Bipolar Support Alliance (DBSA)

Pre-Lecture Exam Question 1

1. Which of the following is not a well-established side effect of lithium?
   a. Nephrotoxicity
   b. Tremor
   c. Hepatotoxicity
   d. Weight Gain
   e. Hypothyroidism

Question 2

2. Which of the following medications has been most closely associated with polycystic ovarian syndrome?
   a. Oxcarbazepine
   b. Divalproex
   c. Lithium
   d. Lamotrigine
   e. Gabapentin

Question 3

3. Which of the following medications is mostly likely to cause hyponatremia?
   a. Lithium
   b. Carbamazepine
   c. Topiramate
   d. Oxcarbazepine
   e. Zonisamide

Question 4

4. **Oral contraceptives cause substantial reductions in blood levels of which of the following medications?**
   a. Lamotrigine
   b. Divalproex
   c. Carbamazepine
   d. Gabapentin
   e. Lithium

Question 5

5. **Which of the following medications can double the blood level of lamotrigine?**
   - a. **Carbamazepine**
   - b. **Divalproex**
   - c. **Oxcarbazepine**
   - d. **Lithium**
   - e. **Topiramate**

Lithium

Lithium

- Half-life: 24 hours (varies with age)
- Not metabolized
  - Renal excretion
- Not protein bound
- Dosing based on blood levels

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
- Teratogenicity
- Toxicity

Lithium and the Thyroid

- **Main concerns: Clinical and subclinical hypothyroidism**
- **Thyroid function monitoring: Baseline and periodic (scheduled or as needed)**
- **Which tests: TSH, others as indicated**

Lithium and the Kidney

- Impaired concentration
- Polyuria (nephrogenic diabetes insipidus)
- Morphologic abnormalities
- Reduced GFR

Lithium and Monitoring Renal Function

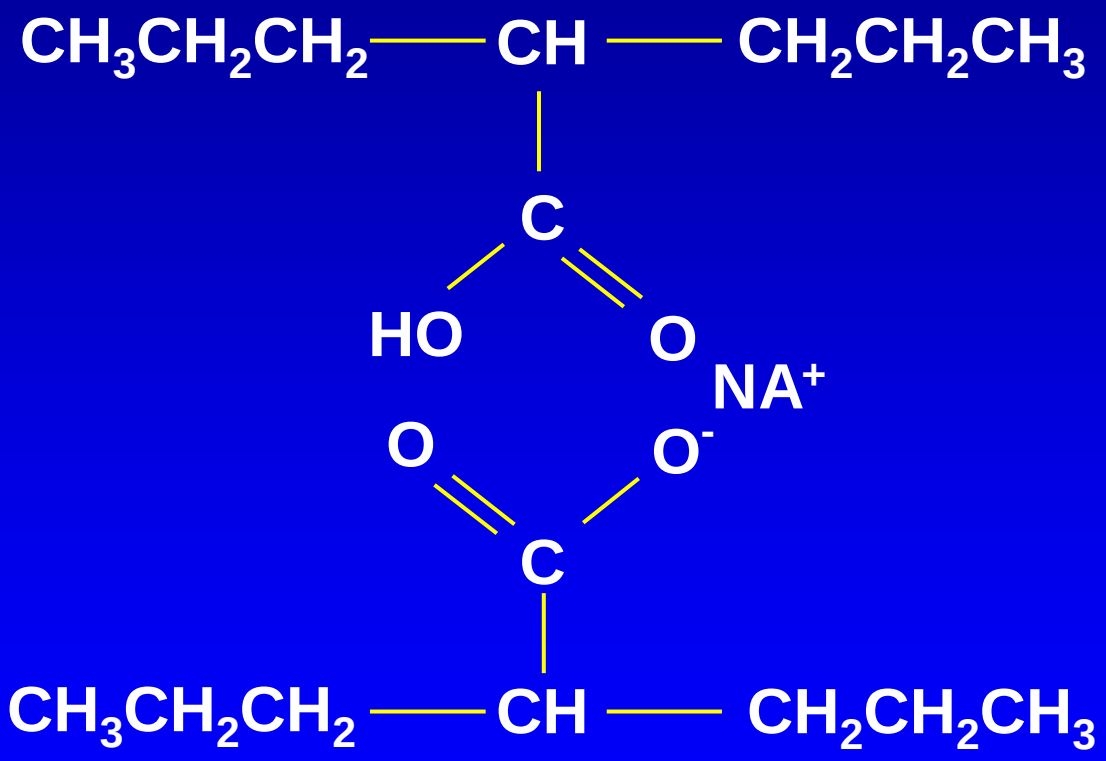
- Serum creatinine – yes! (1 to 3 times yearly)
- Urinalysis – easy to do
- Polyuria – by history
- Creatinine clearance – when indicated
  (volume and protein)
- Estimating equations for GFR
  - Cockcroft-Gault
  - MDRD (Modification of Diet in Renal Disease)

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		

Divalproex

Divalproex Sodium



Valproate: Mechanism of Action

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

Valproate

- FDA-approved indications
  - Epilepsy
  - Acute mania
  - Migraine prophylaxis
- Role
  - Acute and prophylactic treatment of bipolar disorder

Valproate

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

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

  Maintenance: serum conc=85-125 μg/ml

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 ovarian syndrome (?)

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
- PCOs: 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**

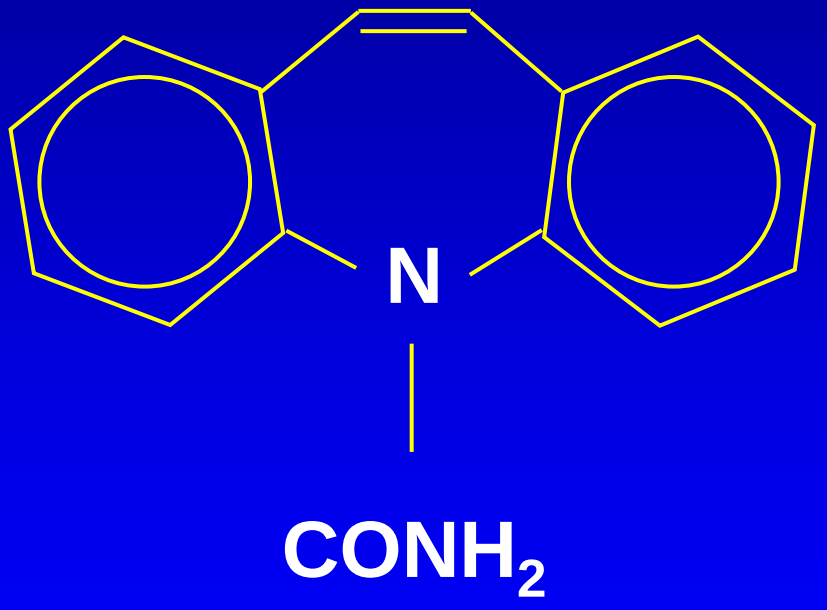
  ↓ VPA, CBZ-epoxide

- **Lamotrigine**

  lamotrigine

Carbamazepine

Carbamazepine



Carbamazepine: Mechanism of Action

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

Carbamazepine

- **Indications**
  - **Trigeminal neuralgia**
  - **Epilepsy**
  - **Acute manic and mixed episodes (ER formulation)**
- **Role**
  - **Acute and prophylactic treatment of bipolar disorder**
  - **Adjunctive treatment with other mood stabilizers**

Carbamazepine

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

Carbamazepine

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

Carbamazepine

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

Carbamazepine Side Effects

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

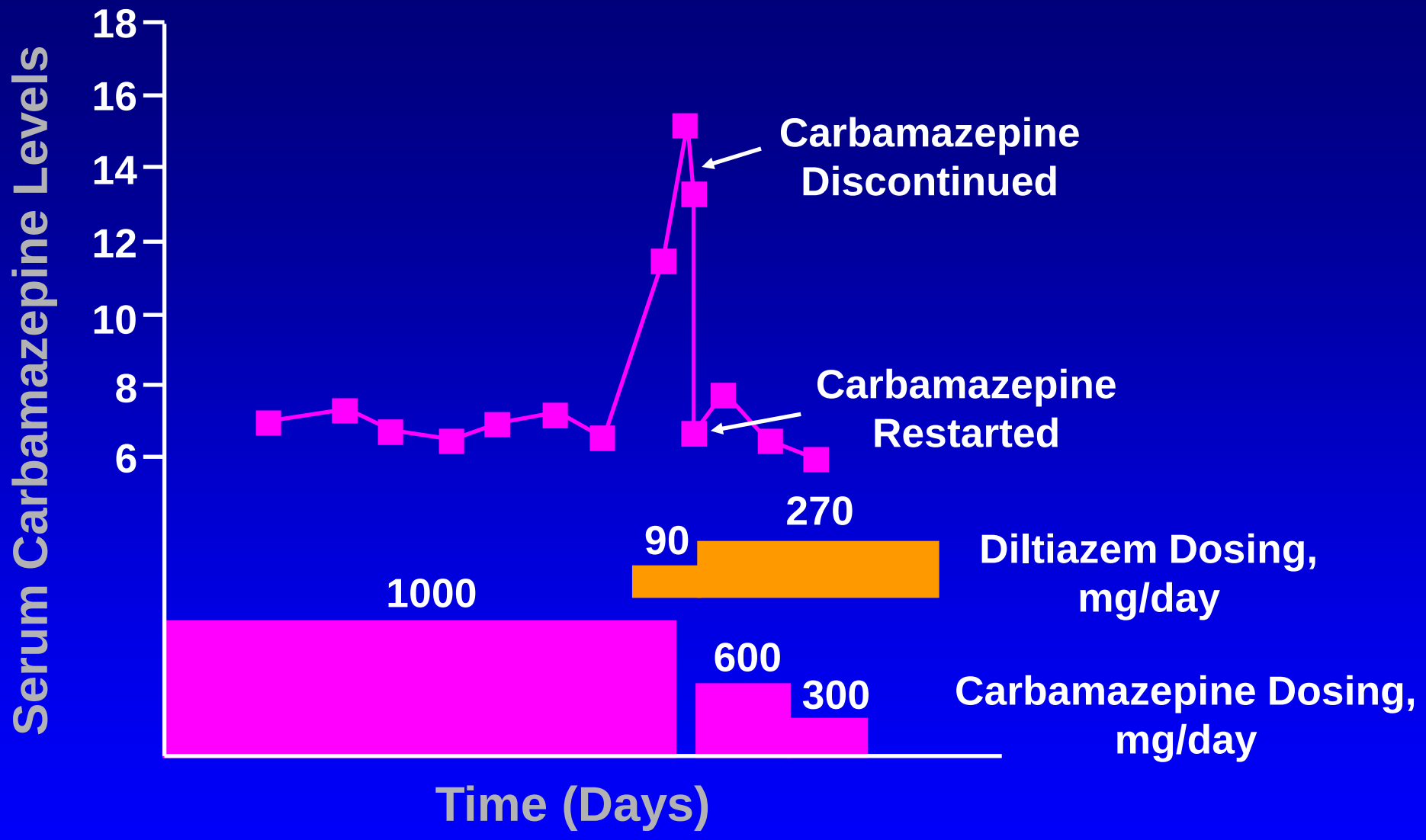
Carbamazepine: FDA Alert 12/12/07

- Dangerous or fatal skin reactions more common with HLA allele, HLA-B*1502
- Carried “almost exclusively in patients with ancestry across broad bands on Asia”
- Genetic screening advised, if + don’t start CBZ

Carbamazepine Interactions

An Incomplete Listing

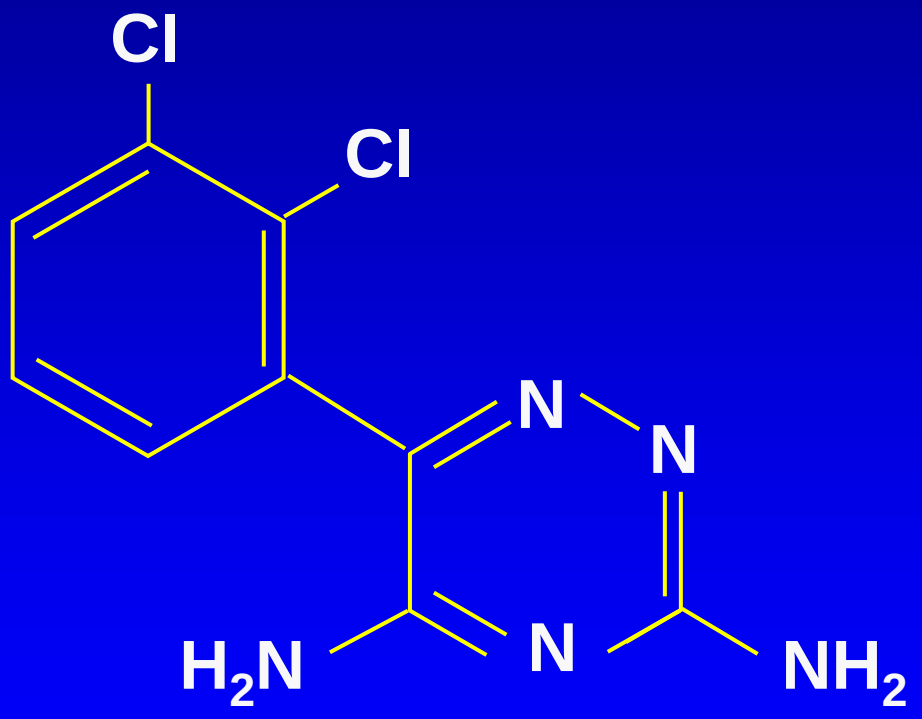
- **CBZ decreases levels of:**
  - **Clonazepam, clozapine, olanzapine, haloperidol, alprazolam, bupropion, oral contraceptives**
- **CBZ levels increased by:**
  - **Cimetidine, macrolides, fluoxetine, valproate, isoniazid, verapamil, ketoconazole**



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

Lamotrigine

Lamotrigine



Lamotrigine
Mechanism of Action

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

Xie and Hagan. Neuropsychobiology 1998;38:119-130

Lamotrigine

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

Lamotrigine and Pregnancy

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

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

Side Effects of Lamotrigine

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

Lamotrigine and Serious Rash in Mood Disorders Trials

- **Monotherapy (1/1233) 0.08%**
- **Adjunctive (2/1538) 0.13%**

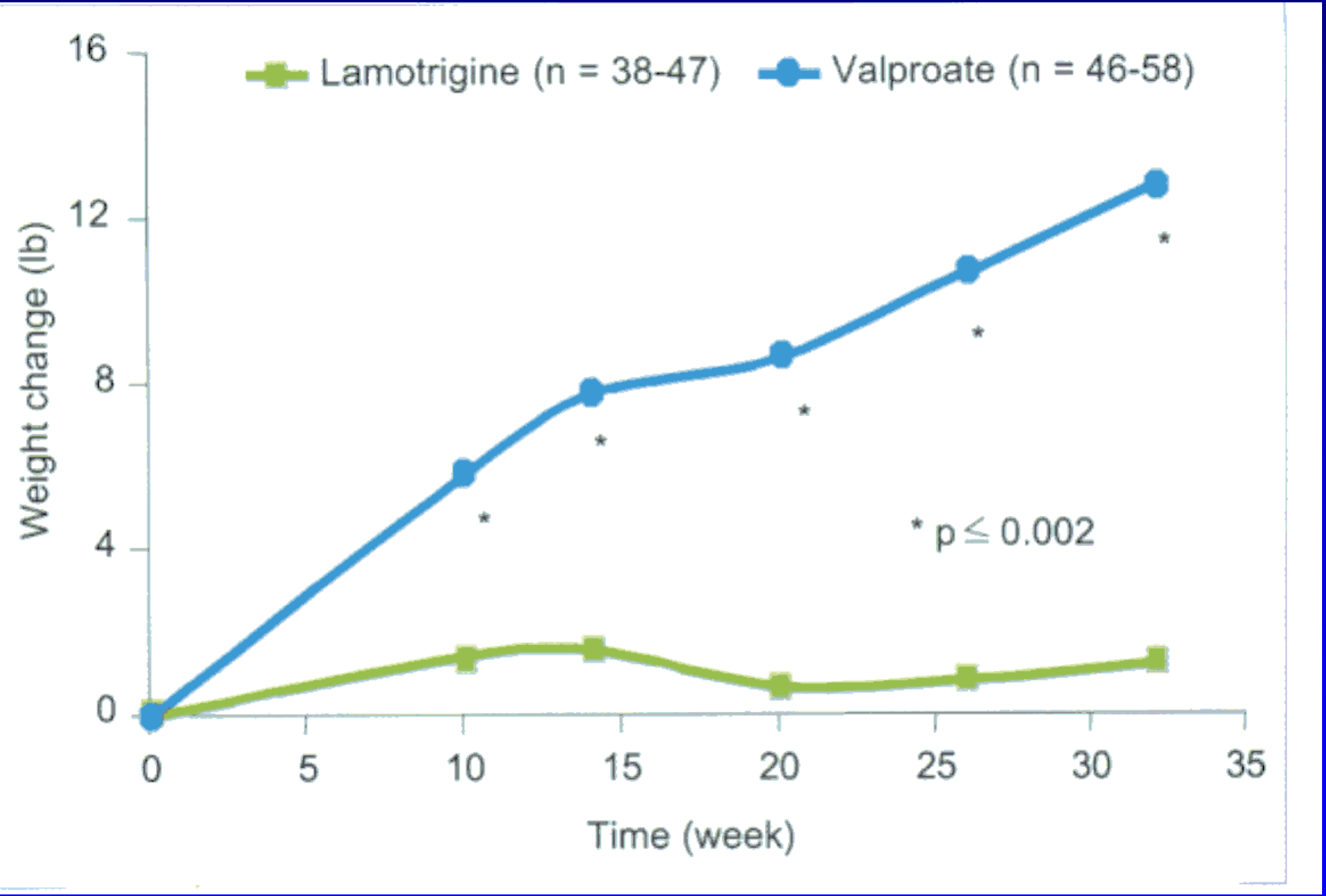
Package Insert, June 2003

Lamotrigine and Rash: Management

- **According to its package insert, the drug "should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring."**

Package Insert, Lamictal, 2009

Lamotrigine vs. Valproate: Weight Change



Edwards et al., APA 5/02

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 (LTG) Interactions

- Valproate doubles LTG levels
- LTG ↓ valproate levels 25%
- CBZ ↓ LTG levels 40% (OXC-ok)
- Oral contraceptives ↓ LTG levels 50%
- Pregnancy ↑ LTG clearance >90%
- Valproate markedly reduces induction by oral contraceptives and pregnancy

Lamotrigine (LTG) Interactions

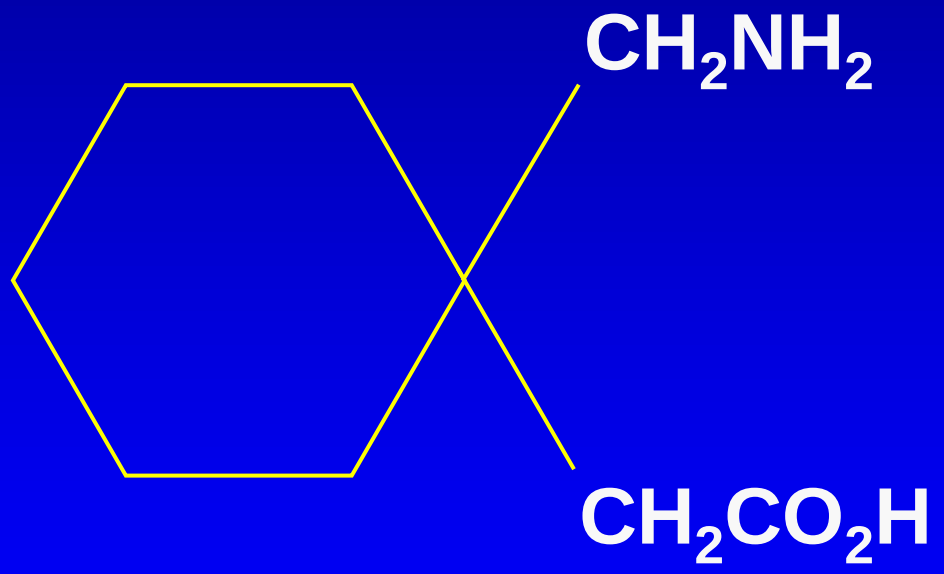
- Lopinavir/ritonavir ↓ LTG levels 50% (n=18)
- Sertraline ↑ LTG levels 2-fold (n=2)
- LTG ↑ clozapine levels 3-fold (n=1)

Not all Anticonvulsants Are Antimanic

- **For example –**
  - **Gabapentin**
  - **Lamotrigine**
  - **Tiagabine**
  - **Topiramate**
  - **etc.**

Gabapentin

Gabapentin



Limitations of Gabapentin In Bipolar Disorders

- Not effective as monotherapy in treatment-resistant rapid cycling
- Not effective as primary add-on antimanic agent
- Possible use for associated anxiety/insomnia

Gabapentin

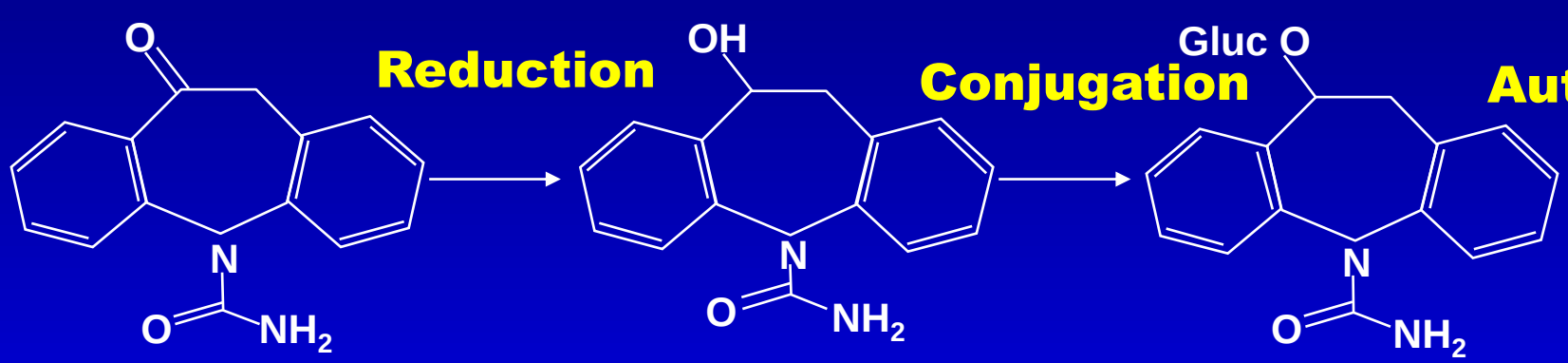
- **Half-life: 5-7 hours**
- **Bioavailability decreases with dose**
- **Not protein bound**
- **Not metabolized**
- **No important drug interactions (except ↑ felbamate)**

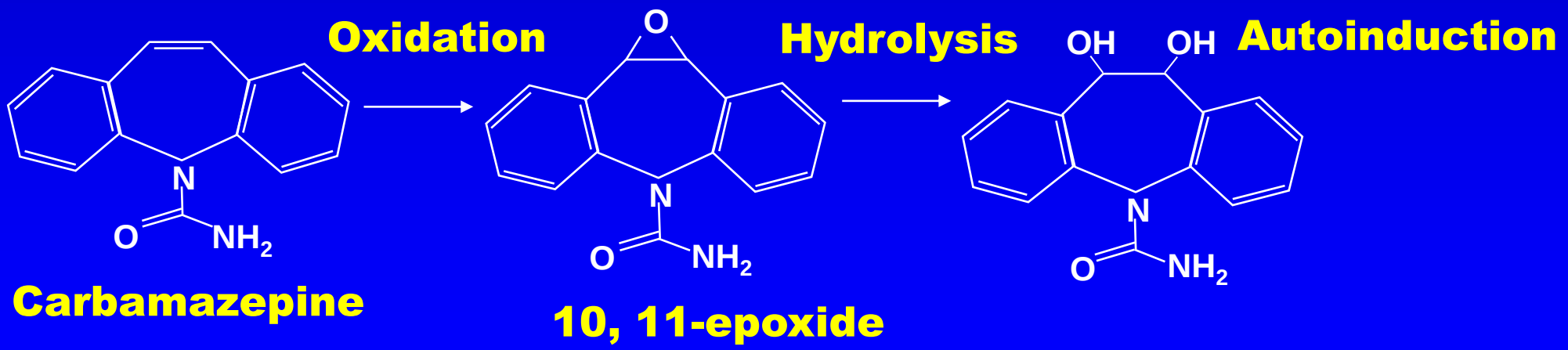
Gabapentin Side Effects

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

Oxcarbazepine

Oxcarbazepine and Carbamazepine Metabolic Differences





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

Oxcarbazepine

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

Oxcarbazepine for Acute Mania (Double-Blind Studies)

- Better than placebo (N=6)
  - Emrich et al, 1983
- Equal to haloperidol (N=20)
  - Muller and Stoll, 1984
- Equal to haloperidol (N=38)
  - Emrich, 1990
- Equal to lithium (N=52)
  - Emrich, 1990

Emrich HM, et al. Pharmacol Biochem Behav.1983;19:369-372
Emrich HT. Int Clin Psychopharmacol.1990;5(suppl 1):83-89

Oxcarbazepine for Manic or Mixed Episodes in Children and Adolescents (7-week, double-blind, n=116)

- **No statistically significant difference in efficacy between OXC and placebo**

Wagner et al. Am J Psychiatry 2006;163:1179-1186

Oxcarbazepine vs. Carbamazepine for Residual Symptoms in Bipolar I/II Patients on Maintenance Lithium

(8-week, double-blind, n=52)

- OXC and CBZ both ↓ residual symptoms
- OXC > CBZ on mania/hypomania and depressive symptoms
- Mean final dose: OXC 637.7 mg/day
  CBZ 673.5 mg/day

Juruena et al. Prog Neuropsychophamacol Biol Psychiatry 2009;33:94-99

Oxcarbazepine Side Effects (Epilepsy Studies)

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

Package insert July 2005

Oxcarbazepine and Hyponatremia

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

CBZ and OXC Hyponatremia

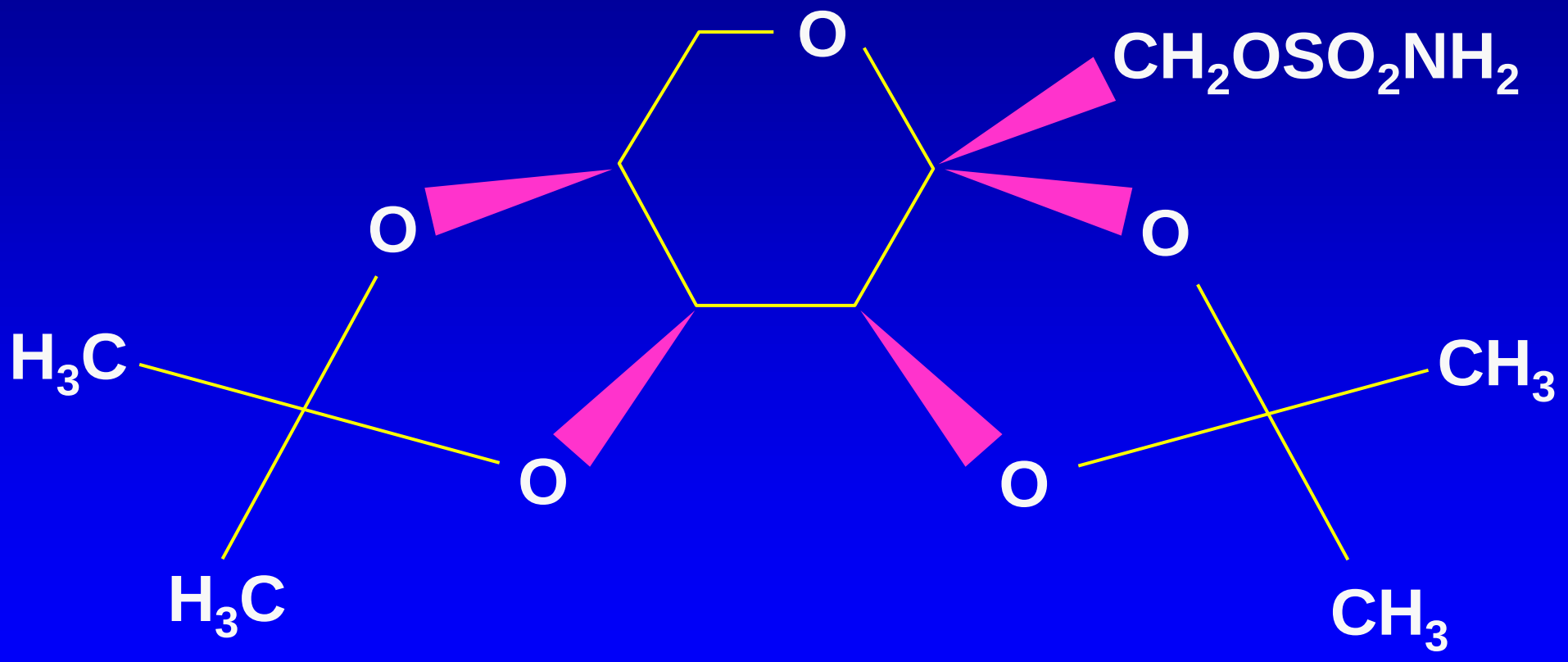
- ↑ renal sensitivity to ADH
- Direct ADH-like activity
- ↑ central release of ADH
- ↓ vasopressinase activity

Oxcarbazepine Interactions

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

Topiramate

Topiramate



Topiramate

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

Topiramate for Bipolar Disorder

- Manic or mixed episodes: 4 double-blind, placebo-controlled monotherapy trials*
  Not effective
- Adjunctive to mood stabilizer: placebo-controlled, n=287**
  Not effective
- Possible use for comorbid alcohol use disorders(off label)

*Kushner et al., Bipolar Disorders 2006;8:15-27
**Chengappa et al., J Clin Psychiatry 2006;67:1698-1706

Adjunctive Topiramate for Bipolar Manic or Mixed Episodes
(12-week, double-blind, n=287)

- Added to lithium or valproate
- Mean daily dose 255 mg
- Efficacy equal to placebo
- AE dropouts: TOP 14%, PBO 7%
- More weight loss on topiramate

Chengappa et al., J Clin Psychiatry 2006;67:1698-1706 (November)

Topiramate

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

Topiramate and Kidney Stones

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

Topiramate Adverse Events
(drug minus placebo, epilepsy trials)

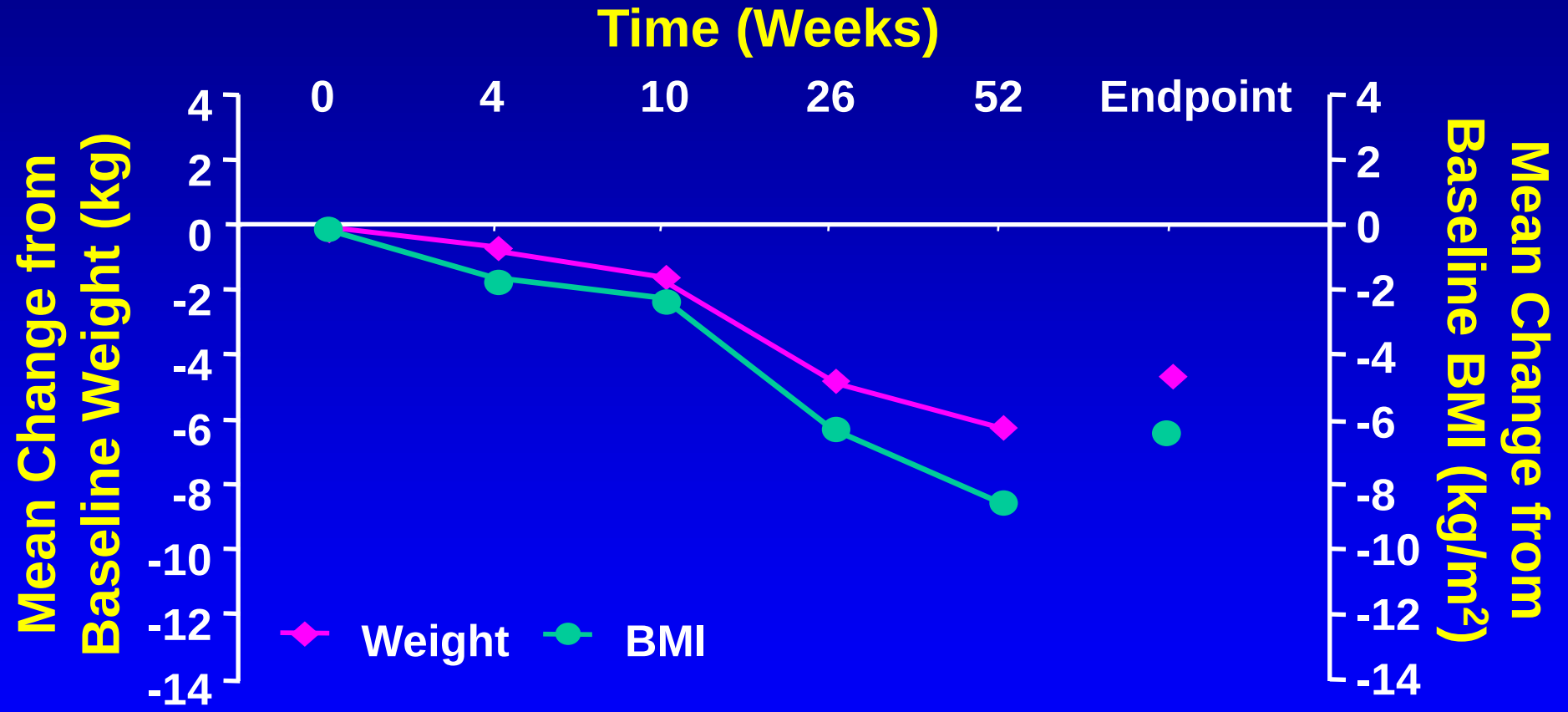
	200 mg	400 mg	600-1000 mg
• Nervousness	5.8%	10.1%	13.1%
• Depression	2.6%	1.1%	7.1%
• Mood problems	0	4.2%	8.4%

Package insert

Topiramate Warnings

- Metabolic acidosis
  - Hyperchloremic, non-anion gap acidosis
  - Low serum bicarbonate
  - Baseline and periodic bicarbonate levels
- Acute myopia and secondary angle closure glaucoma
- Oligohidrosis and hyperthermia

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



*Last observation carried forward; p<0.05; compared with baseline

McElroy SL et al. Biol Psychiatry. 2000;47:1025-1033

Tiagabine

Tiagabine

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

Tiagabine – A Mood Stabilizer?

- **Effective**
  Kaufman, 1998, n=3
  Schaffer and Schaffer, 1999, n=2
- **Ineffective**
  Grunze et al., 1999
- **Controlled studies: not effective**

Tiagabine

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

Zonisamide

Zonisamide

- Sulfonamide AED
- Half-life 63 hours
  (105 hours in RBCs)
- Carbonic anhydrase inhibitor (weak)
- Metabolized by CYP3A4 and acetylation
- Does not inhibit P450 enzymes

Zonisamide for Psychiatric Disorders

- Promising as add-on (n=24)*
  - Bipolar mania, n=15
  - Schizoaffective mania, n=6
  - Schizophrenic excitement, n=3
- But bipolar development stopped

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

Zonisamide

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

Levetiracetam

Levetiracetam

- Add-on for partial onset seizures in adults (FDA-approved 1999)
- Structural analog of piracetam
- Role in bipolar disorder unlikely despite some favorable case reports. **Bipolar indication not being pursued**

Muralidharan A, Bhagwagar Z. CNS Drugs 2006;20:969-979

Levetiracetam: A Synaptic Vesicle Protein Modulator

- High affinity binding to SV2A (synaptic vesicle protein 2A)
- SV2A knockout mice – seizures and death within 3 weeks
- But does this explain mechanism of action?

Stahl SM, J Clin Psychiatry 65:1162-63, Sep 2004

Omega-3 Fatty Acids

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

- 4 months, db, placebo-controlled
- Dose: EPA 6.2 gm, DHA 3.4 gm/day
- Completed study: Omega-3 78.6% (11/14)
  Placebo 37.5% (6/16)
- Many limitations

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

Eicosapentanoic Acid (EPA) for Bipolar Depression

- Two 4-month, placebo-controlled studies (6 gms/day)
- Study 1. – Acute BP I, II, NOS depression (n=59)
- Study 2. – Rapid cycling BP I, II, NOS depression (n=62)
- EPA = placebo in both

Keck et al. Bipolar Disord 5(suppl 1): 58, 2003
Keck et al. Biol Psychiatry 2006;60:1020-1022. Epub 2006 June 30

Eicosapentanoic Acid (EPA) for Bipolar Depression (12 week, double-blind)

- Ethyl-EPA 1 gm (n=24) or 2 gm (n=25)/day, placebo (n=26)
- 87% bipolar I, 85% adjunctive
- Entry HAM-D >9, baseline 15
- 1 gm=2gm=placebo
- 1gm+2gm >placebo

Frangou et al. Br J Psychiatry 2006;188:46-50

The role of omega-3 fatty acid therapy in bipolar disorder remains unresolved

Freeman et al., J Clin Psychiatry 2006;67:1954-1967

Mazza et al., Prog Neuro-Psychopharmacol Biol Psychiatry 2007;31:12-26

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**

***risk with lithium may be lower than with the other two**

Fetal Valproate Syndrome

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

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

New Anticonvulsants and Pregnancy FDA Risk Categories

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

Limited data in women for all

Lamotrigine and Pregnancy

- **International Registry (GSK)***
  - **Total exposures n=2399 (2/3 monotherapy)**
  - **Major malformation risk 2.9%**
  - **No signal for ↑ risk (sample size still small)**
- **North American AED Registry (n=564)****
  - **↑ risk of oral clefts (palate or lip)**

***Thompson et al, APA New Research 717, May 2007**

****Holmes et al., Abstract. Birth Defects Res A Clin Mol Teratol 2006;76:318**

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

Wisner,et al. Am J Psychiatry 1996;153:1132-1137

Atypical Antipsychotics

Please see elsewhere in the Model Psychopharmacology Curriculum for pharmacology, side effeccts, drug interactions

Depression and Bipolar Support Alliance (DBSA)

730 N. Franklin Street, Suite 501

Chicago, IL 60610

(800) 826-3632

www.dbsalliance.org

Formerly: National Depressive and Manic Depressive Association (NMDA)

New Options for Bipolar Disorders

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

Post-Lecture Exam Question 1

1. Which of the following is not a well-established side effect of lithium?
   a. Nephrotoxicity
   b. Tremor
   c. Hepatotoxicity
   d. Weight Gain
   e. Hypothyroidism

Question 2

2. Which of the following medications has been most closely associated with polycystic ovarian syndrome?
   a. Oxcarbazepine
   b. Divalproex
   c. Lithium
   d. Lamotrigine
   e. Gabapentin

Question 3

3. Which of the following medications is mostly likely to cause hyponatremia?
   a. Lithium
   b. Carbamazepine
   c. Topiramate
   d. Oxcarbazepine
   e. Zonisamide

Question 4

4. Oral contraceptives cause substantial reductions in blood levels of which of the following medications?
   a. Lamotrigine
   b. Divalproex
   c. Carbamazepine
   d. Gabapentin
   e. Lithium

Question 5

5. **Which of the following medications can double the blood level of lamotrigine?**

   a. **Carbamazepine**

   b. **Divalproex**

   c. **Oxcarbazepine**

   d. **Lithium**

   e. **Topiramate**

Answers to Pre and Post Lecture Exams

1. c
2. b
3. d
4. a
5. b

The end