

Mood Stabilizers

James W. Jefferson, M.D.
Distinguished Senior Scientist
Madison Institute of Medicine
Clinical Professor of Psychiatry
University of Wisconsin Medical School

Image removed due to possible copyright infringements.

Bipolar Disorders: DSM-IV (1994)

- Bipolar I Disorder
- Bipolar II Disorder
- Cyclothymic Disorder
- Bipolar Disorder NOS
(Not Otherwise Specified)

Early, Accurate Diagnosis Impacts Outcomes

- Missed diagnosis can lead to inappropriate treatment, aggravated course and future treatment resistance¹⁻³
- Delaying correct diagnosis increases risk of suicide attempts⁴
- Inappropriate antidepressant use may induce mania or rapid cycling³

¹Angst J (1985). Psychopathology 18(2-3):140-154. ²Goldberg JF et al. (2001). Am J Psychiatry 158(8):1265-1270. ³Goodwin AK, Jamison KR (1990). Manic-Depressive Illness, New York, N.Y.: Oxford University Press. ⁴Dunner DL et al. (1976). Am J Psychiatry 133(8):905-908

Image removed due to possible copyright infringements.

Why Is Bipolar Disorder Underdiagnosed?

How Patients With BD Present to Healthcare Providers

- Depressed
- Anxious
- Mood swings
- Insomnia
- Irritability
- Low energy/fatigue
- Unable to focus
- Drinking too much
- Abusing drugs
- Trouble with the law
- Relationship problems
- Impulse control problems
- No complaints

Improving Bipolar Diagnosis

- Explain symptoms
- Explain illness features
- Ask patient about hypomania
- Interview family, significant others
- Complete Mood Disorder Questionnaire

Hirschfeld et al. *Am J Psychiatry*. 2000;157:1873-1875; Hirschfeld et al. *Am J Psychiatry*. 2003;160:178-180.

Image removed due to possible copyright infringements.

Choice of Medication(s)

- Phase of illness
- Prior response and tolerability
- Medical and psychiatric comorbidities
- Side effects
- Drug interactions
- Patient preferences

Polypharmacy is Not a Bad Word

- Monotherapy is the exception
- Combination therapy is effective, and usually necessary
- Increased risk of side effects and drug interactions

Mania



Acute Mania: FDA-Approved

- 1970 Lithium
- 1973 Chlorpromazine (Thorazine)
- 1995 Divalproex (Depakote)
- 2000 Olanzapine (Zyprexa)
- 2003 Risperidone* (Risperdal)
- 2004 Quetiapine (Seroquel)
- 2004 Ziprasidone (Geodon)
- 2004 Aripiprazole* (Abilify)
- 2004 Carbamazepine ER (Equetro)
- 2005 Divalproex ER (Depakote ER)

*Also pediatric (10-17) mania (RIS 2007, ARI 2008)

Atypical Antipsychotic + Mood Stabilizer (Lithium or Divalproex) for Acute Mania

- Effective vs. placebo (FDA-approved)
 - Olanzapine (Zyprexa)
 - Quetiapine (Seroquel)
 - Risperidone (Risperdal)
- Probably effective (pending studies)
 - Others

Tohen M, Chengappa KN, Suppes T, et al. Arch Gen Psychiatry. 2002(Jan);59(1):62-69; Sachs GS, Grossman F, Ghaemi SN, et al. Am J Psychiatry. 2002(July);159(7):1146-1154; Mullen JA et al. APA, May 2003

Image removed due to possible copyright infringements.

Bipolar Depression: FDA Approved

- Olanzapine/fluoxetine combination (Symbyax)
 - 2003 for bipolar I depression
- Quetiapine (Seroquel)
 - 2006 for bipolar I and II depression (XR in 2008)

Image removed due to possible copyright infringements.

Antidepressants in Bipolar Disorder

- Disadvantages
 - Poor response
 - Manic switches
 - Cycle acceleration
 - Late response loss

(Ghaemi et al., Am J Psychiatry 161:163-165, 2004)

- Advantages
 - An exceptional subgroup

(Altshuler et al., Am J Psychiatry 160:1252-1262, 2003)

The Role of Antidepressants in Bipolar Disorder
Continues to Be Debated

But don't use antidepressants alone for Bipolar I
depression

Image removed due to possible copyright infringements.

Bipolar Maintenance: FDA-Approved

Lithium-1974
Lamotrigine (Lamictal)-2003
Olanzapine (Zyprexa)-2004
Aripiprazole (Abilify)-2005
Quetiapine (Seroquel)-2008*

***Approved only as adjunct to lithium or valproate**

What About Divalproex (Depakote) for Bipolar Maintenance?

- Not FDA-approved, but widely used
- Limited positive research evidence
- Much positive expert opinion
- Much positive clinical experience

Mood Stabilizer Noncompliance

- Mood control by meds
- Missed highs
- A hassle
- Reminder of illness
- Felt well
- Less creative
- Less attractive
- Side effects
- Cost

Group Psychoeducation for Stabilized Bipolar Disorders: 5-Year Outcome

- Improved medication adherence
- Reduced recurrences
- Improved psychosocial functioning
- Improved occupational functioning
- Improved quality of life

Colom et al. Br J Psychiatry 2009;194:260-265

In the beginning there was ...

LITHIUM

FDA Approved Lithium Indications

- Acute Mania- 1970
- Bipolar Maintenance- 1974

Image removed due to possible copyright infringements.

Lithium

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

The Twelve Hour Standardized Serum Lithium Level

(Amdisen A)

Lithium Side Effects

- Cognitive
- Tremor
- Gastrointestinal
- Endocrine
 - Thyroid
 - Parathyroid
- Weight gain
- Skin
- Renal
- Toxicity



Lithium and the Kidney

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

The Case of the Malevolent Micturater

Lithium Intoxication: Causes

- Excessive intake
- Dehydration
- Kidney Disease
- Low-salt diet
- Drug interactions

Lithium-Drug Interactions

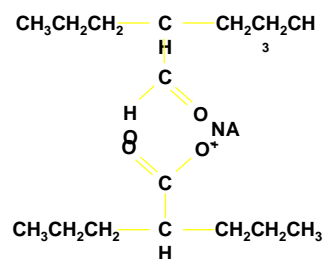
•Levels Increased by:

Thiazides (also some other diuretics)
NSAIDs (including COX-2 inhibitors)
ACE inhibitors
Angiotensin II receptor antagonists
Metronidazole

•Levels Decreased by:

Acetazolamide
Xanthines (including caffeine)
Mannitol
Sodium bicarbonate

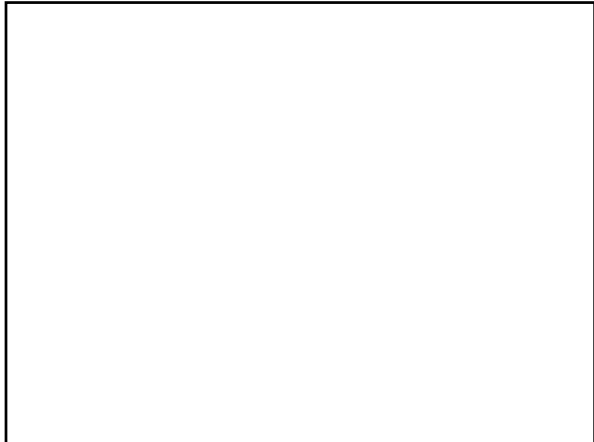
Divalproex (Depakote)



Divalproex Blood Levels

- Sample timing does matter
- Immediate release: 12 hours after last dose
- Extended-release (ER): at least 18 hours after last dose

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



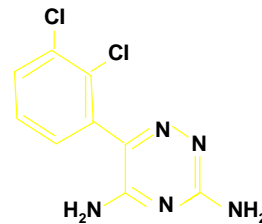
Valproate Side Effects

- Cognitive (uncommon)
- Tremor
- Gastrointestinal
- Weight gain
- Hair loss
- Hepatotoxicity
- Pancreatitis
- Teratogenicity
- Polycystic ovarian syndrome

Valproate Interactions (An Incomplete Listing)

- Aspirin (avoid)
 ↑ free VPA, ↓ platelet function
- Carbamazepine
 ↓ VPA, ↑ CBZ-epoxide
- Lamotrigine
 ↑ lamotrigine

Lamotrigine (Lamictal)



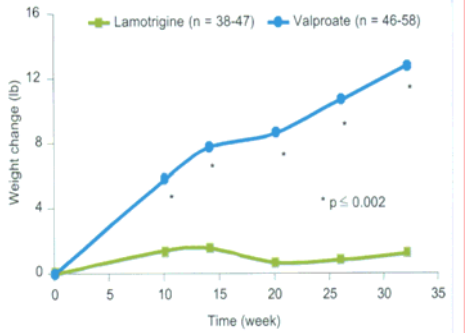
Lamotrigine Dosing

- Monotherapy
 - Weeks 1 and 2: 25 mg/day
 - Weeks 3 and 4: 50 mg/day
 - Week 5: 100 mg/day
 - Week 6: 200 mg/day
- With valproate: ↓ dose by 50%
- Maintenance: target 200 mg/day

Stevens-Johnson Syndrome



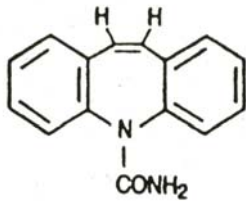
Lamotrigine vs. Valproate: Weight Change



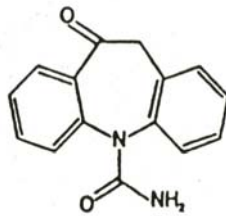
Edwards et al., APA 5/02

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

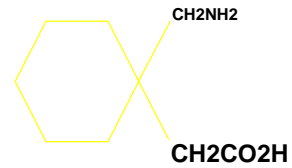


Carbamazepine



Oxcarbazepine

Gabapentin (Neurontin)



Topiramate (Topamax)

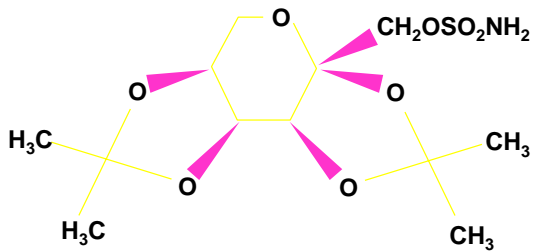


Image removed due to possible copyright infringements.

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

