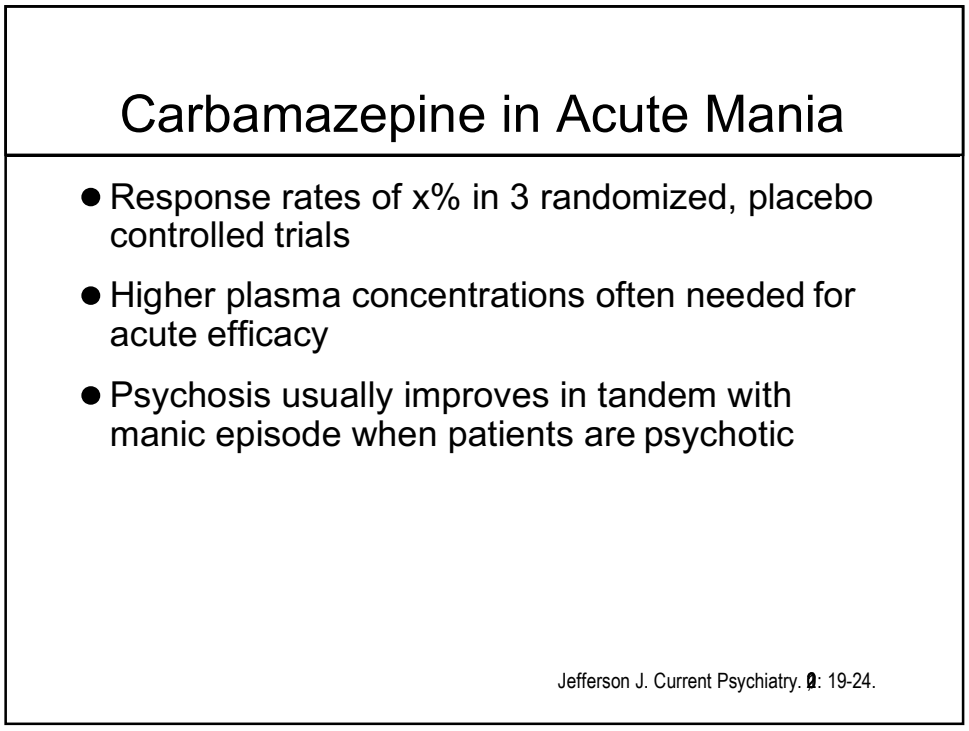
Mark W. Wilson, MD
330 West 58th Street, Suite 313
New York, New York 10019

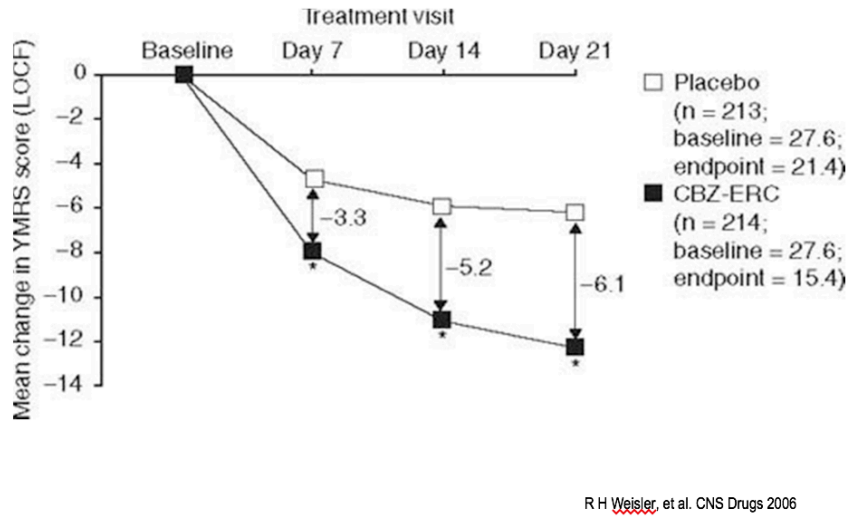
Mood Instability and Bipolar Spectrum Disorders
Mood Stabilizers: Carbamazepine

- **Tegretol (carbamazepine; since 1962)/Equetro (carbamazepine ER)**
  - General and History
    - Synthesized in 1957
    - First used in the 1960's in the treatment of epilepsy (especially involving temporal lobes) and trigeminal neuralgia,
    - Clinical efficacy for reducing aggressivity in clients with epilepsy noted early.
    - First antiepileptic medication shown to have efficacy in the treatment of bipolar disorder.
    - Much of the early work on the treatment of bipolar disorder done in Japan in 1971
    - In 1980, study in the American Journal of Psychiatry demonstrated efficacy in bipolar disorder
    - In 1983, study from Kishimoto
    - Cowdry and Gardner, 1988: helpful in treating impulsivity in borderline personality disorder
    - Okuma, 1993: more efficacy with non-rapid cycling vs. rapid cycling disorder
    - Greil et al, 1998: more effective than lithium in treating mixed episodes or rapid cycling
    - Equetro (extended release form) finally obtained FDA-approval in 2005 for the treatment of acute mania (data includes Owen, 2006 and Weisler et al, 2006)



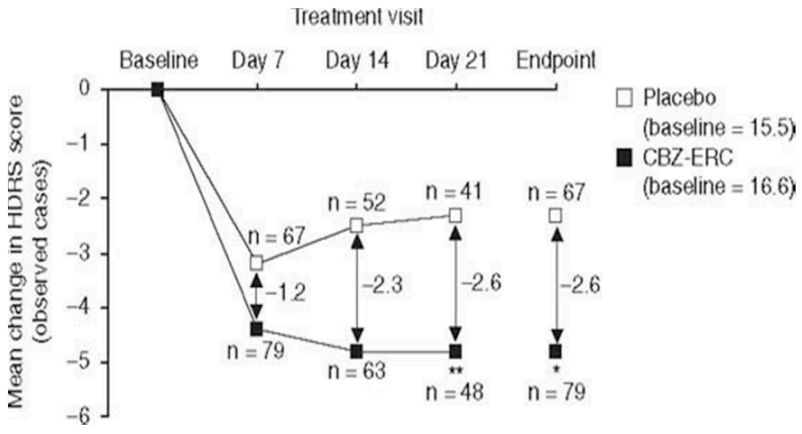
  - FDA-approval
    - Mania in 2004-2005
    - Epilepsy since 1974; treats complex partial seizures of the temporal lobe
  - Risk of suicidality in antiepileptic drugs (AEDs) (Arana, 2010; Gibbons, 2009)
    - There is no increase in the risk of suicidality in patients with bipolar disorder or epilepsy
    - There is a 1.7 fold increased risk when used in major depression
    - There is a 2.6-fold increased risk in NON-depressed, NON-bipolar, NON-epileptic patients
  - Evidence of safety and efficacy in adults with psychiatric disorders
    - Adults
      - Mania

CBZ-ERC vs PBO in Acute Mania: 2 Pooled Randomized Controlled Trials



R H Weisler, et al. CNS Drugs 2006

Mean Change in HDRS scores for CBZ-ERC vs PBO in Acute Mixed Mania: Pooled Results from 2 RCTs



R H Weisler, et al. CNS Drugs 2006

- 2004-2005: large multicenter trials demonstrated benefit of carbamazepine extended release (Equetro) in acute mania and mixed episodes; two 3 week placebo-controlled, RCT for adults with mania:
  - Equetro with 42-61% response rate
  - Placebo 22-29% response rate.
- 15 controlled studies in acute mania including Ballenger and Post in 1980; Weisler; Okuma; Lerer; Luznat; Brown; Okuma; Small
- Japanese researchers, 1971: efficacy for treating mania in adults first noted

- Depression
  - In one summary: overall response rate for bipolar depression thought to be around 33%.
  - One study, 35 patients:
    - 57% response with at least mild improvement vs. 34% on placebo
  - Another study, 12-week, 124 patients with bipolar depression and 111 patients with bipolar mania
    - 63.8% of depressed patients responded vs 34.8% placebo

                - the addition of a Chinese herbal medication (Free and Easy Wanderer Plus) to carbamazepine further increased the likelihood of response to 84.8%
        - Maintenance
            - 10 controlled studies in maintenance treatment (including Kishimoto), with response rates up to 60%.
            - Kishimoto, 1983: safe and effective as maintenance therapy
            - Seems more effective in combination with lithium or Depakote
        - Rapid cycling
            - In monotherapy, not very effective
            - In combination with lithium, more effective
- Youth
    - Mania
        - Joshi et al, 2010
            - 27 youth (~age 9 yo)
            - 67% mixed episode, 22% manic, 11% hypomanic
            - 16 subjects completed
            - 788 mg/day average, 6.6 meq/l level
            - 44% response rates
            - 43% improved depression
            - 62% improved ADHD symptoms
        - Ginsberg, 2006
        - Davanzo, 2003, naturalistic study, 44 hospitalized youth aged 5-12 years: effective by, by week 2, lithium and Depakote more effective
        - Kowatch, 2000: pediatric mania, open-label monotherapy; 38% response rate
        - Woolston, 1999: adolescents with bipolar, Tegretol monotherapy (case reports)
        - Hsu, 1999: adolescents with bipolar, adjunctive with lithium (case reports)
        - Hsu, 1986
    - Maintenance
        - Woolston, 1999: two bipolar adolescents successfully treated with 200-300 mg/day (levels of 7-8)
        - Bovard et al, 1993: open-label, 11 adolescents (10-17 yo), 1 year or more, 82% with moderate to marked response

- Side effects/risks
    - Common
        - nausea/vomiting 54%
        - headache 46%
        - double vision 38%
        - dizziness 35-54%
        - sedation/lethargy/fatigue 29-46%
        - stomachache 23%
        - balance problems 23%
        - blurred vision 23%
        - weight gain 15-25%
            - 8% with weight gain of 12 pounds or more, but 3% at one year
            - other research and clinical experience suggests Tegretol (and Trileptal) are more or less weight neutral.
        - speech articulation disorder 8%
        - irritability 8%
        - decreased appetite 8%
        - benign leukopenia (reduced white blood cells) 12-46%
            - 7-13% of adults; usually non-progressive and usually does not require drug discontinuation
            - 12% of children
            - drops in white blood count to the low 3,500s are not uncommon
                - blood disorders
                    - agranulocytosis 1-50/million, depending on study
                    - aplastic anemia 5-16/million (27 cases in 12 years)
                        - Watch for easy bruising
                        - Watch for chronic infections
                        - Photosensitivity (sensitivity in sun)
                        - Fever
                        - Sore throat
                        - Purple spots on the skin
                    - other data: 1/10,000 to 1/125,000 risk of either
                    - overt symptoms: fever, bruising, bleeding, sore throat, tiny red dots in skin or eye
                    - 12% in adults and 7% in children--low white cells
                    - low red cells
                    - increased number blood cells

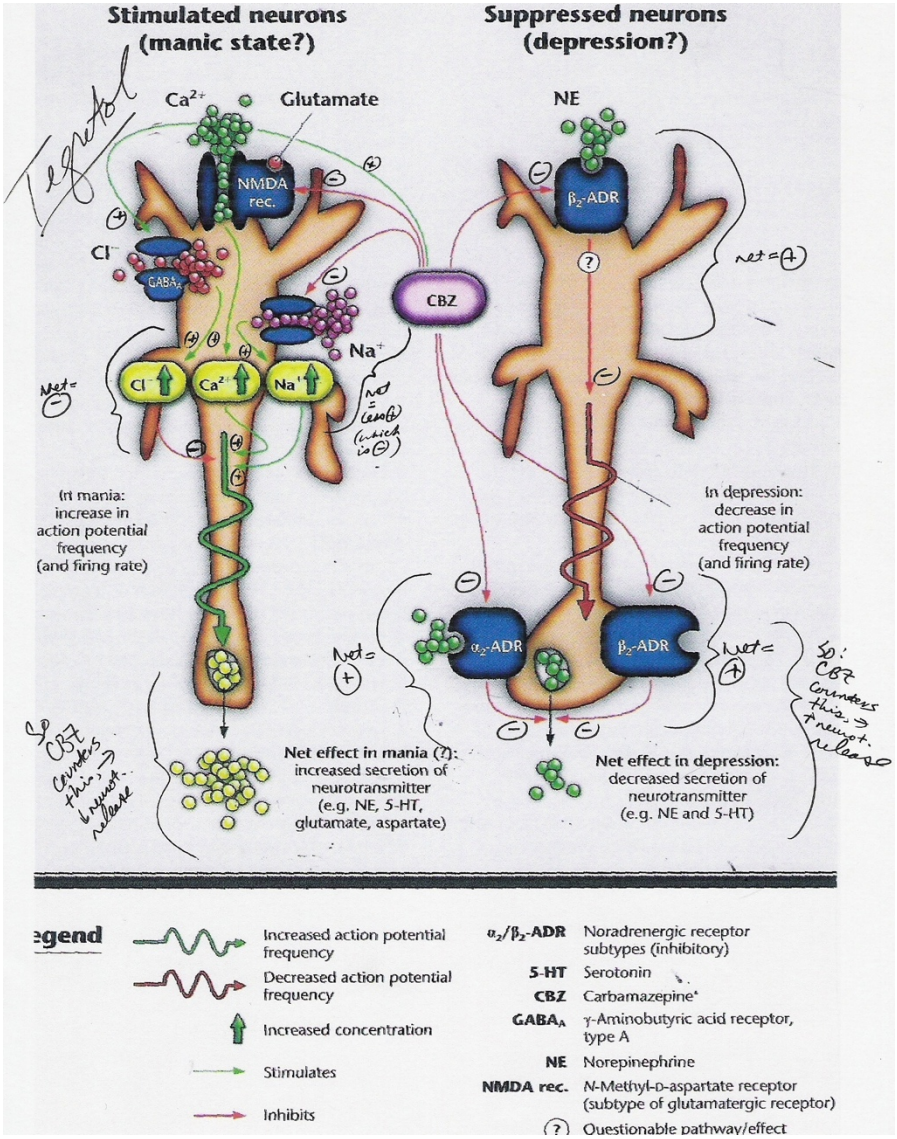
- **rash 5-46% rash, but 1% at one year**
  - **2-5% within the first 2 weeks, with recovery after discontinuation**
  - **May be associated with bone marrow suppression, so will need a CBC if rash occurs**
  - **Severe dermatologic problems**
    - **1-2% of prepubertal youth; less in postpubertal youth and adults**
    - **Include Stevens-Johnson syndrome/TEN**
      - **1.6/10,000 caucasians**
      - **5-30X more common in some Asian groups; HLA-B*1502 increases risk**
        - **Hong Kong >15%**
        - **Malaysia >15%**
        - **Parts of the Philippines >15%**
        - **Taiwan 10%**
        - **Thailand 8%**
        - **North China 4%**
        - **South Asia, including India: 2-4%+**
        - **Korea 2%**
        - **Japan <1%**
- hyponatremia/water intoxication 5%
  - Symptoms
    - Reduced appetite
    - Vomiting
    - Confusion
    - Ankle swelling
    - Headache
    - Tiredness
    - Reduction in urination
    - If very severe, seizures and coma
  - Sodium levels below 135 should be monitored closely
  - Treatment in youth: every 4th drink should be a sodium-containing one such as milk or Gatorade
- liver inflammation 4%
  - 12 cases of severe inflammation, two of which were fatal, reviewed in 1983, several more cases in 1988, 1991
  - Signs and symptoms: fever, yellow skin and eyes, rash, liver tenderness or enlargement, poor appetite, and nausea
  - Elevation of liver function tests in 5-15%
  - GGT increased up to 100%; not typically concerning unless 300% above normal
- sexual side effects 2-7%
- hair loss 1-6%
- numbness/tingling in extremities
- taste abnormalities
- dry mouth
- increased intraocular pressure due to anticholinergic side effects
- cognitive dysfunction; associated with modest psychomotor slowing and decreased attention and memory; also associated with EEG slowing in the alpha range—however, it's relatively minimal
- cardiovascular problems (including heart rhythm problems); can slow cardiac conduction
- bone loss (and increased risk of hip fracture); prophylactic calcium (1000 mg/day) and vitamin D (500 IU/day) may be helpful
- hypothyroidism
- muscle spasm
- delirium and hallucinations due to anticholinergic side effects

- Risk of birth defects
  - Overall: 2-6%, depending on the study
  - 0.5-1% risk of cardiac and craniofacial malformations in one study, but in others:
    - Neural tube defect spina bifida is estimated to be 0.5-3%
    - Craniofacial defects 11-26%
      - Fetal carbamazepine syndrome
        - Epicanthic folds
        - Facial dysmorphisms
        - Fingernail hypoplasia
        - Microcephaly
        - Developmental delay
  - Supplement with folic acid
  - Enters breast milk; infant levels may be as high as 15% of maternal serum level
    - AAP considers it safe/compatible with breastfeeding
- May decrease female and male hormones, causing sexual dysfunction.

- Recommended supplements to take while on Depakote
    - Vitamins B12, B6, A, D, E, K
    - Folic acid
    - Carnitine
    - Zinc
    - Copper
    - Selenium
    - Biotin
    - Calcium

- Drug-drug intertactions; reduces levels of
    - ***birth control pills (and thus their effectiveness)***
    - Tegretol
        - chronic Tegretol use leads to increased metabolism of Tegretol and lower blood levels
        - the level at 6 weeks may be 30% less than the level at 3 weeks
    - Lamictal
    - benzodiazepines
    - doxycycline
    - fentanyl
    - glucocorticoids
    - haloperidol
    - methadone
    - phenothiazines
    - phenytoin
    - Zoloft
    - tricyclic antidepressants
    - theophylline

- Mechanism



- GABA
  - Decrease GABA turnover
  - Chronic (but not acute) administration of mood stabilizers increasing limbic (in hippocampus but not frontal, thalamic, or striatal) GABAb (but not GABAa) receptors
- Dopamine
  - Decrease dopamine turnover in the nucleus accumbens
  - Indirectly block dopaminergic tone
- NE
  - Mild NE reuptake inhibition
- Serotonin
  - May block serotonin reuptake (leading to increased serotonin).
  - Increased l-tryptophan
- Ion channels
  - Exerts use-dependent effects on overactive systems via
    - blocking voltage-gated sodium channels
    - blocking calcium influx through the NMDA receptor.
    - (does not block l-type calcium channels)
  - Blocks voltage-gated type 2 sodium channels in a frequency- and membrane-depolarization-dependent manner
  - Enhances potassium channels, enhancing GABA transmission
- Second messengers
  - Inhibits cAMP mediated signaling
  - Decreased cGMP
  - May inhibit adenylate cyclase
  - Inhibits protein kinase C.
  - Blocks and then upregulates adenosine receptors→ reduces inositol transport, regulates phosphoinositol system (also via NMDA receptor blockade)

        - Decreases phospholipase A2 and arachidonic acid (AA) cascade. Bazinet, 2005: decreases the rate of incorporation of AA-CoA and turnover of AA in brain phospholipids in animals.
    - Other
        - Blocks adenosine receptors
        - Blocks GSK-3B.
        - Decreased thyroxine (T4)
        - Increased Sub-P
        - Decreased SRIF
        - Decreased aspartate release
        - Augments cholinergic activity
- Pharmacodynamics
    - Metabolized by the liver; active metabolite which is not measured in blood tests
    - Onset of action 7-14 days
    - Half-life 18-55 hours (fuller range 12-60 hours) at first; 5-22 hours over time
    - Peak 3-6 hours after dose
    - Time to steady state: 3-5 weeks at initiation, 2-4 days after autoinduction (for each increase in dose, it takes 2-7 days for autoinduction to even out)
    - Dosing
        - Dose 300-1600 mg/D
        - In adults, starting dose is usually 100-200 mg/pm for 5-7d, then increase by 200 mg (split 2-4 times-a-day) every 5-7d
        - In adults, maintenance dose usually 800-1200 mg/day (8-20 mg/kg/d)
        - Optimal effective plasma levels 6-10 mcg/mL (but fuller effective range is 4-12 mcg/ml)
        - Maximum studied dose is 1600 mg/day
        - In children, maintenance dose usually 10-35 mg/kg/day
        - Comes in:
            - Tegretol: 100 mg chew tabs, 200 mg tabs, Suspension (100 mg/5 ml)
            - Tegretol XR: 100 mg tab, 100 mg capsule, 100 mg chew tab, 200 mg tab, 200 mg capsule, 300 mg capsule, 400 mg tab
            - Equetro: 100-, 200-, and 300-mg capsules
                - Cap contains 25% immediate release, 40% extended release, and 35% enteric release
        - Monitor blood levels weekly throughout the first 4-8 weeks then monthly then every 3 months
        - In adults:
            - start with 100 mg/pm day 1
            - if tolerated, 100 twice-a-day day 2
            - then, if tolerated, 200 twice-a-day there after
            - Equetro—once-a-day, check levels twice-a-week for the first 2 weeks
            - over time, move all or most to night to minimize oversedation
        - In children, start with 100-200 mg twice-a-day with max dose 1000-1200 mg/d

- ***Licarbazepine***
    - Active metabolite of carbamazepine
    - Under study
- Comparative neurocognitive effects of lithium and AED mood stabilizers (Gualtieri and Johnson, 2006): from least detrimental to most: Lamictal>Trileptal>lithium>topamax>Depakote>Tegretol.