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Valproic Acid (Depakote, Depakote ER), Valnoctamide

Valproic Acid

- General and History
  - Similar to fatty acids
  - First synthesized in 1882
  - Used as organic solvent for bismuth salts, which were used to treat stomach and skin disorders
  - In early 1960's neurologists used valproic acid as a solvent for various compounds they were investigating for the treatment of seizures. Valproic acid was the common solvent in many compounds that appeared to be effective in treating seizures; it was eventually realized that valproic acid itself was the therapeutic compound.
  - In the 1960's and 70's valproic acid was found to improve mood; Lambert published a series of reports about it's use in bipolar disorder
  - FDA-approval:
    - Depakote ER is FDA-approved for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features
    - Depakote is FDA-approved for mania in adults since 1995
    - FDA-approved for treating epilepsy in 1978
    - Migraine prevention
  - 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:
  - May be less helpful than lithium in treating or preventing bipolar depression
  - Adults
    - General
      - Proven efficacy in patients with a family history of affective disorder, no prior lithium therapy, and bipolar II or mixed states.
      - Ichikawa et al, 2006: Depakote potentiates antipsychotic dopamine release in the prefrontal cortex
      - Patients with more frequent or severe mania or borderline personality disorder usually do not respond as well (though 2005 evidence of efficacy in the latter).
      - May also be useful in anxiety, migraines, psychotic disorders, borderline personality disorder; some evidence of safety and efficacy in adolescent boys with explosive anger problems as well as adolescent boys with explosive anger and marijuana abuse.
      - Emerging evidence of safety and efficacy in augmenting antipsychotic medication in schizophrenia.
      - Frankenburg, 2002: double-blind, placebo-controlled trial in women with borderline personality disorder AND bipolar II disorder; safe and effective; reduced interpersonal sensitivity, anger/hostility, overall aggression.
      - May lower cholesterol when added to antipsychotic medications in schizophrenia.

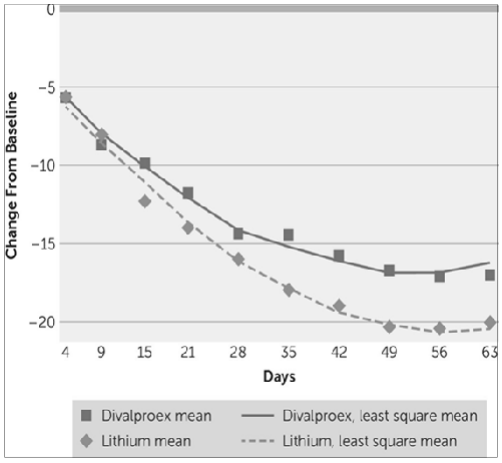
- Mania

Valproate in Acute Mania

- Response rates of 48-53% in x randomized, placebo controlled trials
- Both IR and ER efficacious
- Higher plasma concentrations (>80 units) often needed for acute efficacy
- Depressive symptoms improve in patients with mixed features
- Psychosis usually improves in tandem with manic symptoms when patients are psychotic

Pope HG Jr et al. Arch Gen Psychiatry, 1991; Bowden CL et al. JAMA, 1994; Bowden CL et al. J Clin Psych, 2006

Li vs Valproate in Older Persons with Bipolar I Mania



224 in- and out-patients ≥60 years of age with hypo/mania (YMRS ≥18)

Divalproex (started at 500 mg/kg/d) or Li (started at 300 mg/d) for 9 weeks

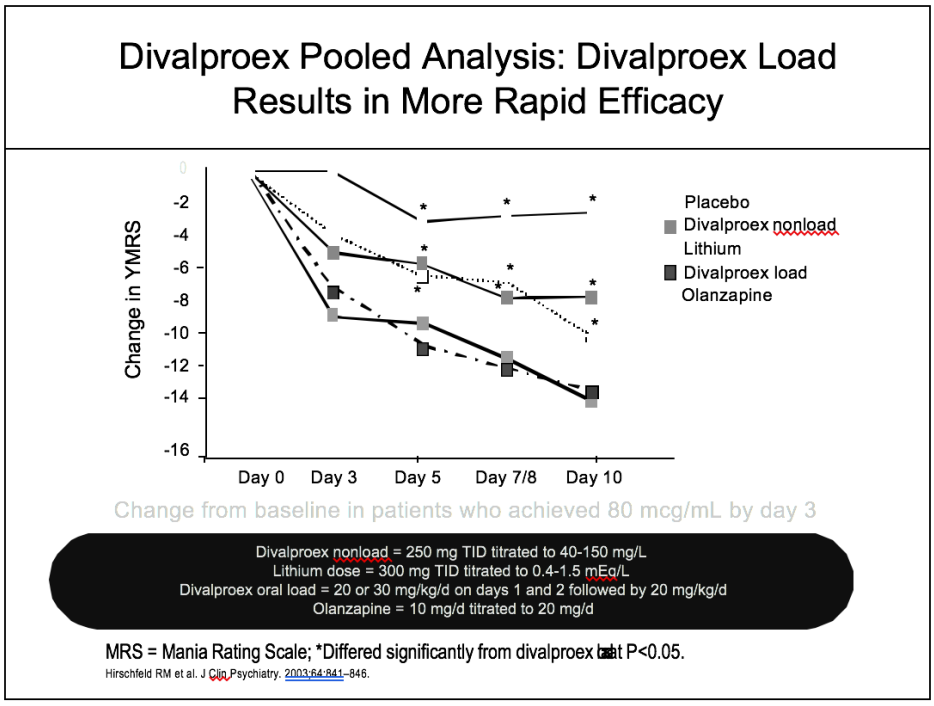
Primary outcome: Change in YMRS

Treatments comparable, though Li a little better

Similar discontinuation rates, including for side effects

Young R C et al. Am J Psychiatry. 1974:1086-93

- Acute loading at 20 mg/kg/day (in inpatient settings) is most rapidly effective

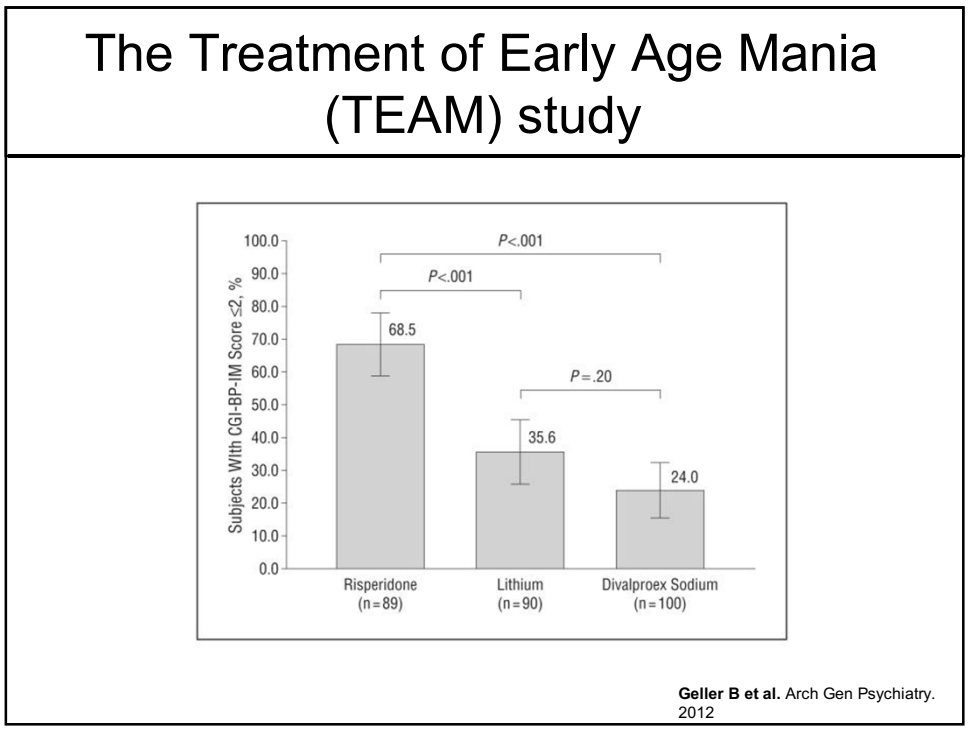


- Bowden et al, 2006: RCT, placebo-controlled, multicenter study of Depakote ER in the treatment of acute mania in adults, 377 patients, 21 days, Depakote ER dosed at 25 mg/kg then increased by 500 mg on day 3 then adjusted to adequate blood level:
  - Safe and effective
  - Percentage of those whose symptoms improved by 50% or more:
    - 48% on Depakote ER
    - 34% on placebo
- Allen, 2006: valproic acid levels in the lowest range are 60% more effective than placebo; levels in the highest range (above 94 and up to 110) are 120% more effective than placebo.
- Pope; Bowden; Emrich; Freeman; Vasudev; Tohen; Zajecka
- Early work in the late 1960's by Lambert identified valproate as effective in mania and schizoaffective disorder.

- Bipolar depression
  - Overall response rate in bipolar depression thought to be about 30%.
- Rapid cycling
  - Perhaps more effective than lithium
  - More effective in combination therapy
- Maintenance
  - Two recent large, placebo-controlled, randomized, parallel-group, double-blind studies provide good evidence for effectiveness of Depakote in prophylaxis. Depakote extended time to relapse of mania in 25% of the patients by 93% over placebo. Depakote extended time to relapse of depression in 25% of the patients by 25% more than placebo.
  - Patients in the best maintenance study of Depakote had valproic acid levels of 85 mcg/ml.
- Borderline personality disorder
  - Hollander et al, 2001
  - Frankenburg et al, 2002

- Children and adolescents
  - General
    - Blader et al, 2010: adjunctive Depakote ER to stimulant refractory aggression in children with ADHD
      - Depakote ER > placebo
    - Saxena et al, 2006 and Chang et al, 2006: retrospective analysis of Depakote for aggression in youth at high risk for bipolar disorder, 12-week, open-label trial, 24 youth aged 6-18 yo, children of parent(s) with bipolar disorder; youth had mixed diagnoses including depression, cyclothymia, ADHD, and oppositional defiant disorder; safe and effective. 71-80% response (in 24 youth)
      - State et al, 2004
      - Davanzo et al, 2003
      - Lee Cohen and Kim Ching performed a meta-analysis of published literature addressing the use of valproate in children and adolescents without co-morbid epilepsy; nine studies, looking at 128 youths under age 18 years, were included; some evidence of efficacy was demonstrated.

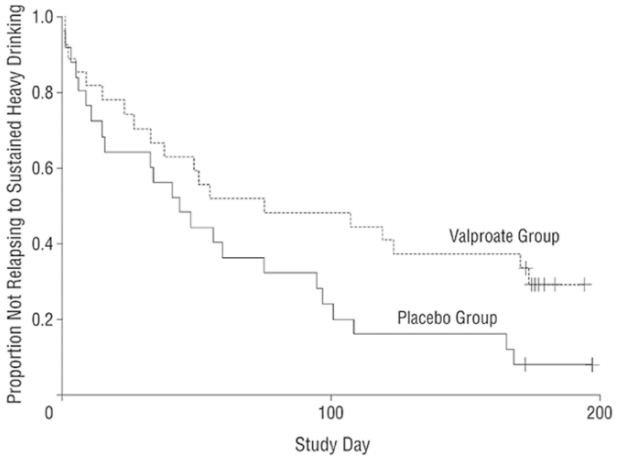
- Mania
  - Risperdal>Depakote and lithium



  - Seroquel>Depakote
  - Geller et al, 2012/Vitello et al, 2012; Team study: Risperdal vs lithium vs Depakote in bipolar I mania/mixed episodes
    - Risperdal > lithium > Depakote
  - West et al, 2011
  - Pavuluri et al, 2010: Risperdal vs. Depakote in 6-17 yo youth with mania
    - Risperdal 65-78% response rate and 65% remission rate
    - Depakote 42-45% response rate and 33% remission rate
  - Kowatch et al, 2009
  - Wagner et al, 2009
    - Depakote ER > placebo
  - Wozniak, 2007: open-label trial, Depakote ER, 8 weeks, ~9 yo: 22% (of 18 youths) response rate
  - Mick et al, 2006: open-label trial of Depakote ER for pediatric bipolar disorder, youth aged 7-10, 8-week trial, only 7 of 18 subjects completed the study
    - 67% with significant response
    - 33% with worsened response (?due to failure of medication to help?)
    - Depakote ER in the treatment of bipolar I disorder, manic or mixed; 150 youth aged 10-17, 20 sites: negative
  - Barzman et al, 2006
  - DelBello et al, 2006
  - Calabrese: open-label, prospective study: effective in mania for 72%, 94% for mixed states
  - Pavuluri, 2005: 6-month open trial for mania/mixed mania, 34 children average age 12 (range 5-18 yo); Ritalin used in 38.2% and Risperdal at some point in 50%; 73.5% response rate; 52.9% remission.
  - Findling et al, 2005
  - Scheffer et al, 2005: 40 youth, bipolar I and II, average age 9.4 yo, 80% response rate
  - Scheffer et al, 2004: Depakote, open-label, in 26 manic preschool children aged 2-5; effective even long-term
  - DelBello et al 2004: 15 hospitalized adolescents with bipolar I, predominantly mixed, with aggression; average blood level 102; 60-80% reduction in key symptoms
  - Henry, 2003: chart review of 15 youth aged 4-18 yo (average 13.3 yo) with open-label Depakote dosed 500-1500 mg/day, blood level ~80, followed ~0.1-3 years; 53% response rate but 40% discontinued due to side effects
  - Davanzo, 2003, naturalistic study, 44 hospitalized youth aged 5-12 years: effective and, by week 2, Depakote equivalent to lithium and more effective than carbamazepine

        - Wagner, 2002: 5-site study, 40 youth aged 7-19 (average 12 yo) with bipolar disorder; open-label, 2-8 weeks; dose range 500-1200 mg/day; 61% response, though many also on haloperidol.
        - DelBello, 2002, small study of adolescents with mania—the efficacy of Depakote in the treatment of mania was improved with Seroquel.
        - Mota-Castillo, 2001: case series in nine young children (aged 2-7) with symptoms suggestive of mania; effective
        - Kowatch, 2000: 42 youth, bipolar I and II, ~11 yo; 53% effective in mania
        - Deltito et al, 1998: effective in 36 adolescents hospitalized for mood disorders
        - Papatheodorou, 1993, 1995; 80% with moderate to marked improvement
        - West, 1994 with overall response rates of 65%
    - Bipolar depression
        - Calabrese: open-label, prospective study: effective in 33% for depression.
    - Maintenance
        - Findling et al, 2007: RCT, DB trial of Depakote in the treatment of youth aged 5-17 with bipolar disorder not otherwise specified or cyclothymia AND who have a parent with a diagnosis of bipolar disorder, 56 youths (average age 10.7) randomly assigned to Depakote (n=29) or placebo (n=27); study was up to 5 years; studied discontinuation (due to need for further treatment interventions, side effects or non-compliance) was examined
            - No differences in time to discontinuation from study for any reason
            - No differences in time to discontinuation from study due to mood event
            - Changes in mood symptom ratings and psychosocial functioning from baseline to study discontinuation did not differ between Depakote and placebo
            - Both groups showed improvements in mood symptoms and psychosocial functioning over time
        - Scheffer et al, 2006: pilot study of the safety and effectiveness of changing Depakote to Depakote ER in pediatric bipolar disorder, ages 7-17 with bipolar I or II with or without ADHD who were stable on Depakote: greater effectiveness noted, reduced side effects noted
        - Findling, 2005: double-blind, 18-month trial of lithium versus Depakote in pediatric bipolar disorder; both medications were equally effective.
        - Findling, 2003 demonstrated safety and efficacy of the combination of Depakote and lithium in the treatment of bipolar disorder in children; response rates were 47%
        - Henry, 2003, chart review of 15 children and adolescents with bipolar disorder suggested long-term safety and efficacy of Depakote.
    - PTSD in youth with severe conduct disorder
        - Steiner et al, 2007: 12 youth's had PTSD out of 71 with severe conduct disorder; 5 of the 6 who were treated with high dose Depakote had improvement
    - Conduct disorder
        - Some evidence of efficacy
    - Other

Adjunctive Valproate Maintenance in Patients with BP and Alcoholism



KM survivals curve for time to relapse to heavy drinking, by treatment group (log-rank test, P=.048)

Salloum et al. Arch Gen Psychiatry 2005

- Some of the side effects/risks include
  - Side effects are usually mild and transient (after 2-3 weeks)
  - Common
    - Lethargy
      - 33-55% in adults (ER formulation) vs. 14% placebo; mostly mild
      - 34.5-36% in youth vs. 14.8% placebo
    - Gastrointestinal—33% overall, but 2% at 12 month follow-up
      - Nausea or vomiting:
        - 35-46% in adults (ER formulation) vs. 21% placebo; mostly mild
        - 48.3% in youth vs. 29.6% placebo
        - Elsewhere: indigestion, heartburn, and nausea noted at 13.8%
        - Elsewhere: vomiting noted at 19.2%
      - Stomach upset/heartburN
        - 20-26% in adults (ER formulation) vs. 10% placebo
        - 28% in youth patients
      - Diarrhea
        - 1.7-35% in adults (ER formulation) vs. 10% placebo; mostly mild
        - 20.7% in youth vs. 11.1% placebo
        - Abdominal pain
          - 10% in adults (ER formulation) vs. 4% placebo
          - 20.7% in youth vs. 22.2% placebo
    - Headache
      - 20% in one study (10% mild; 10% moderate)
      - 27.6% in youth vs. 29.6% placebo
    - Decreased neutrophil white blood cells
      - 27%
    - Dizziness
      - 19% in adults (ER formulation) vs. 8% placebo
      - 10.3-36% in youth vs. 0 placebo
    - Low platelets
      - 13-54% with low platelets
      - easy bruising, heavy menstrual periods, more frequent bloody noses
    - Appetite/weight:
      - Appetite increase
        - 12-20.7% in youth vs. 3.7% placebo
        - Due to a direct effect on the hypothalamic centers that regulate hunger
      - Appetite decrease
        - 10.3-11.6% vs. 3.7% placebo (in youth)

- Weight gain
  - 5% in adults (~4 pounds with ER formulation vs. 1 pound with placebo)
  - Elsewhere:
    - 15% in an open-label study in borderline personality disorder
      - Mild in 5%
      - Moderate in 10%
      - Severe in none
    - 20% with weight gain greater than 12 pounds, but 13% at one year
    - 12% in youth
    - Significant in 50% of those who gain weight on it
- Coughing
  - 10.3% in youth vs. 7.4% placebo
- Insomnia
  - 20% in one study (10% mild and 10% moderate)
  - 10.3% in youth vs. 0 placebo
- Sexual side effects
  - 10%, but 1% at one year
- Hair loss
  - 0-12% in adults, but 4% at one year
  - usually temporary
  - quickly resolved with zinc, copper, and selenium supplementation
- Tremor
  - 5-6% in adults
  - 10.3% in youth vs. 3.7% placebo
- Muscle aches
  - 5% in one study
- Muscle weakness
  - 5% in one study
- Sedation (sleepiness)
  - 4%
- Hepatitis/liver dysfunction
  - 3%, but 0% at 12 month follow-up
  - 20% (3-44%) with liver enzyme elevations even up to three times normal does not necessarily demand cessation of Depakote
  - Highest risk is with youth less than 2 years of age, and the risk decreases with age
  - Liver toxicity may be due to the 4-ene-valproic acid metabolite
  - Severe hepatitis
    - Nausea/vomiting
    - Poor appetite
    - Fatigue/weakness/lethargy
    - Swelling in the ankles
    - Jaundice (yellowing of the eyes or skin
    - Easy bruising
- Cognitive dysfunction; associated with modest psychomotor slowing and decreased attention and memory.
- Difficulty with balance
- Double or blurred vision
- Rash
  - 1%, but 0% at 12 month follow-up
  - early symptoms: less appetite, yellowy skin, nausea, lethargy
  - liver function tests every 6-12 months recommended
  - highest risk is in children under 2 years of age where can be fatal
  - fatal in 1/49,000
  - almost entirely in children under 2 with epilepsy; most of whom had other medical problems and were on multiple anticonvulsants
  - no fatalities ever reported (through 2006) in patients over the age of ten taking only valproic acid
- Pancreatitis
  - Abdominal pain
  - Nausea/vomiting
  - Decreased appetite
  - Can be dangerous
- Increased ammonia
  - Rates 5.6-53% vs. 0-21.7% in controls
  - 5.6-16.2% rate in one study

- 51.2% with asymptomatic hyperammonemia in another study vs. 21.7% in controls (not taking Depakote)
- 53% in another study vs. 0% in controls
- no evidence of liver injury
- levels of ammonia correlate with valproic acid levels (which means reducing Depakote reduces ammonia)
- symptomatic hyperammonia is very rare; when ammonia levels cause symptoms, they include:
    - confusion
    - impaired consciousness
    - lethargy
    - vomiting
    - balance problems
    - aggression
    - neurologic signs
- 11 case reports of ammonia-related encephalopathy in 14 patients with various psychiatric disorders, one of which also had epilepsy
    - the reports have been complicated by unrelated (to Depakote) risk factors and poor details
    - in one case, vegetarianism may have led to low carnitine (which raises ammonia levels)
    - some were on multiple medications
    - in four cases, medical or psychiatric histories not documented; these four cases were four of the five cases of patients with encephalopathy who lapsed into coma
    - five of the 14 cases of encephalopathy lapsed into coma
    - two of the five were being treated on an inpatient unit
    - all resolved
    - can use carnitine 250-330 mg twice-a-day to treat high ammonia levels
        - side effects of carnitine: upset stomach, nausea; comes as an elixir.

- Polycystic ovary syndrome (PCOS)

PCOS in Bipolar Women (STEP-BD)

- Naturalistic follow-up of women with Bipolar Disorder
- Treatment-emergent PCOS
    - VPA Users – 10.5% (9 out of 86)
    - Non VPA Users – 1.4% (2 out of 144)
- Did not control for confounding variables such as obesity, age, diabetes

PCOS = polycystic ovary syndrome; STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder; VPA = valproate.

Joffe H, et al. Biol Psychiatry 2006;60:1378-81

- ***In healthy control subjects NOT on Depakote, the rate of PCOS is 4-7% (range 1.4-14%) (Joffe and Cohen)***
- ***In folks on Depakote, the rate is 10.5%(Joffe's 2006 study)***
- Associated with
    - Increase in male hormones (androgens) which may impact carbohydrate metabolism.
    - Clinical signs: hirsutism, acne, infertility, menstrual abnormalities
    - Endocrine signs: chronically elevated plasma free and total testosterone, increased LH, low or normal FSH, hyperinsulinemia and insulin resistance, obesity, type 2 diabetes, cardiovascular disease related to type 2 diabetes
- Risk

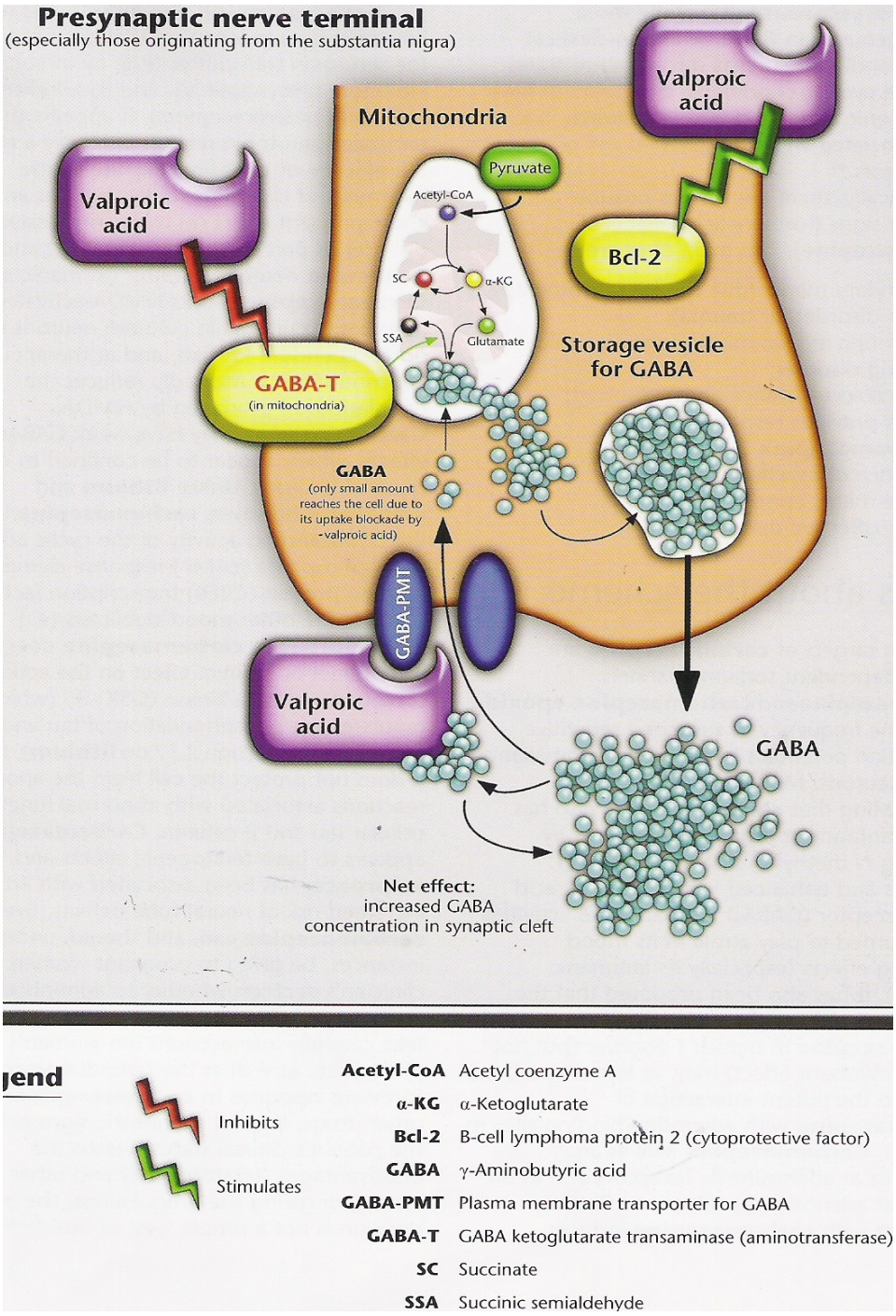
- Joffe et al, 2006: 300 women aged 18-45 yo with bipolar disorder evaluated at 16 sites in the STEP-BD trial; a comparison was made between the incidence of indicators of possible PCOS between Depakote and other non-Depakote anticonvulsants: the incidence of signs of increased male hormones and abnormally light menstrual periods was 10.5% for those on Depakote and 1.4% for those who were not.
- Klipstein et al, 2006, pilot study, women with PCOS (78 such women in this study): 19 of 78 had bipolar disorder, 6 of 78 had a past diagnosis of such; a total of 27% screened positive for bipolar disorder or had a diagnosis of such; 0 were currently using Depakote, 3 had a past exposure of Depakote, 2 of the 3 of which took Depakote prior to being diagnosed with PCOS
    - 30% in clients with epilepsy taking Depakote
    - 80% in overweight women with epilepsy who took valproic acid since before 20 years of age and for a long duration
- 10.5% (9 of 86 women) taking Depakote developed polycystic ovary syndrome (PCOS) in Systematic Treatment Enhancement Program (STEP) for Bipolar Disorder (2005), prelim data
- 6% in 72 women with bipolar disorder on mood stabilizers (Altshuler, 2004)
    - LH, FSH, and prolactin were increased
    - Estrogen was decreased
    - 3 women receiving Depakote (6%) had PCOS; similar rate to women not on Depakote and similar to women in the general population.
- 8% in women with bipolar disorder and on Depakote (Joffe, 2004)
- Rasgon, 2000: women with bipolar on Depakote: no increased risk PCOS
- Matsunaga, 1993: cases of 12 women with bipolar or psychotic symptoms that fluctuated with menstrual cycles. Polycystic ovaries in 8 of the 12.
- Ghazuidin, 1989; Petho, 1982: cases of polycystic ovary syndrome (PCOS)-like changes in women with psychiatric illnesses

- Oral contraceptive use may help prevent PCOS

- Risk of birth defects if taken when pregnant
    - Background rates of birth defects 2-6%, depending on the study
        - 10.7% risk overall (range 6-20.3%) in children born to women exposed to 1000 mg Depakote monotherapy or more during pregnancy
    - Neural tube defect spina bifida
        - 9.3% of children exposed to Depakote in the first trimester
        - 12-17 fold increased risk (elsewhere: 50-fold more than baseline risk)
        - To minimize risk
            - folate 1 mg/day
            - ultrasound at 18-20 weeks
    - 2-7 fold increased risk for
        - atrial septal defect
        - hypospadias
        - cleft palate
        - polydactyly
        - craniosynostosis
    - Also, may see the following facial features in children exposed in utero to valproic acid:
        - tall forehead
        - medial eyebrow deficiency
        - flat nasal bridge
        - broad nasal root
        - shallow philtrum
        - long upper lip
        - thin vermillion border
        - Perinatal bleeding
    - In last 6 weeks, vitamin K to minimize bleeding
    - There is some evidence that in utero exposure to valproic acid is linked to
        - delayed development
        - higher risk of long term behavioral problems
        - possibly, to decrements in IQ in children
        - this data is very controversial, with many factors confounding results and conclusions.
- Concentrations in breast milk: 1-10% of maternal blood level
    - AAP considers it safe/compatible with breastfeeding
- Comparative neurocognitive effects of lithium and AED mood stabilizers (Gualtieri and Johnson, 2006): from least detrimental to most: Lamictal>Trileptal>lithium>topamax>Depakote>Tegretol.

        - Prospective, observational study assessed development of preschool children aged 3-6 years old, 11 months after in-utero exposure to Lamictal or Depakote compared to those not exposed to an antiepileptic medication (Rihtman et al, 2013)
            - When combining those exposed to Lamictal or Depakote
                - Reduced non-verbal IQ scores
                - Lower scores on motor measures
                - Lower scores on sensory measures
                - Lower scores of parent-report executive function, behavioral and attentional measures
            - No differences when Lamictal-exposed group compared to Depakote-exposed group
            - This study does not delineate between the risk from exposure to these meds versus the neurologic and/or psychiatric condition that necessitated the use of such meds; in other words, it did not delineate the risk that comes from the condition from the risk of the medications
        - A number of other side effects and risks in multiple organ systems.
- Recommended supplements to take while on Depakote
    - Vitamins B12, B6, A, D, E, K
    - Folic acid
    - Carnitine
    - Zinc
    - Copper
    - Selenium
    - Biotin
    - Calcium

- Mechanisms of action:



- In adolescents with mood dysregulation who have a parent with bipolar disorder, Depakote is effective in stabilizing mood dysregulation and is associated with increased neuronal density in the dorsolateral prefrontal cortex and reduced activation of the amygdala in response to emotional stimuli
- Ion channels
  - Enhances potassium efflux
  - Inhibits voltage-gated type 2 sodium channel function (and thereby boost GABA inhibitory function and reduce NMDA glutaminergic excitatory function)
  - Inhibits voltage-gated t-type calcium channel function (and thereby boost GABA inhibitory function and reduce NMDA glutaminergic excitatory function)
- GABA
  - Increases GABA-B receptors in the hippocampus
  - Decreased GABA turnover
  - Decreased GABA breakdown
  - Increased GABA release
- May reduce cAMP production
- Reduce protein kinase C.

- Increase in the cytoprotective protein bcl-2 (via activation of ERK MAP kinase cascade). Bcl-2 is a major neuroprotective protein which protects the brain against many toxic insults and stresses. Bcl-2 also enhances regeneration of central nervous system neurons. Bcl-2 also enhances other trophic factors in the brain, including pERK 42, pERK 44, pRSK, pCREB, and pBAD. Carbamazepine, desipramine, and haloperidol do not have this effect, while clozapine appears to have this effect.
- Dopamine
  - Decrease dopamine turnover in the nucleus accumbens
  - Indirectly block dopaminergic tone
  - Decreases dopamine
- Blocks GSK-3B
- Decreases phospholipase A2 and AA.
- Increased AP-1 binding
- Decreased NMDA currents
- Decreased SRIF
- Decreased aspartate release
- Increased l-tryptophan
- Decreased MARCKS
- Pharmacodynamics
  - Onset of action in 7-14 days; full efficacy in 4-6 weeks.
  - Dosing
    - 750-3000 mg/D (max 60 mg/kg/day); common range 1000-1250 mg/day
    - Common initial dose in youth: 125 mg in kids, 250 mg in adolescents
    - Common initial doses in adults—5-10 mg/kg/day (250-750 mg/day)
    - In adults with mania, can load at 20 mg/kg/day which leads to benefit in 5 days
    - Common maintenance doses in adults: 15-60 mg/kg/day; 750-4000 mg/day
    - Common pediatric maintenance dose range 15-60 mg/kg/day
    - Effective plasma levels 50-150 (good target range is 70-100).
  - Comes in
    - Depakene caps are 250 mg caps
    - Depakene syrup (250 mg/5 ml)
    - Depakote 125 mg sprinkle caps, 250 mg caps
    - Depakote ER: 125, 250, 500 mg tabs
  - Metabolized by the liver
  - If taken with meals, absorption is delayed by 5-6 hours
  - Inhibits liver enzymes; Inhibits metabolism of Lamictal and the active metabolite of Tegretol
  - Metabolism of Depakote is induced by Tegretol.
  - Food delays absorption by 5-6 hours
  - Peak in 3-8 hours; with Depakote ER, peak in 4-17 hours
  - Half-life 6-20 hours and, in youth on polytherapy 5-13 hours

Valnoctamide

- General
  - Analogue of valproic acid
  - Does not undergobiotransformation to the corresponding free acid
  - It lacks key structural groups (e.g., free carboxylic groups) implicated in valproic acid's teratogenicity
  - Preclinical studies demonstrate safety in pregnancy
  - Anticonvulsant properties
  - Marketed as an anxiolytic and sedative in several European countries
- Evidence
  - 2012 double-blind, 5-week, add-on (with Risperdal up to 6 mg/d), controlled trial (32 subjects) in mania
    - 600 mg/d, increased to 1200 mg/d after 4 days
    - More effective than placebo beginning at week 3 through 5
    - Adverse events included abnormal liver function tests (less than 3 times normal) in 1 patient; test results normalized after the patient was switched back to Depakote