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Lamictal

- **Lamictal (lamotrigine; since 1991)**
  - FDA-approval
    - Prevention of manic, depressed, or mixed episodes in bipolar disorder 2003.
    - Seizures in adults and Lennox-Gastaut syndrome in children and adults
  - 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 efficacy
    - Evidence in adults
      - Unipolar depression
        - Augmenting antidepressants in depression
          - Celexa plus Lamictal vs Celexa plus placebo—safe and effective
          - RCT, double blind study of folks with major depression who were resistant to at least one prior antidepressant: Prozac plus Lamictal 100 mg vs Prozac vs placebo; 85% response rate with Lamictal vs. 30% with placebo
          - Barbee and Jamhour, retrospective chart review of Lamictal augmentation, average 41.8 weeks, average dose 112.90 mg:
            - 62.1% improved (breakdown: 40.5% much improved; 21.6% mildly improved
            - 37.8% not improved
          - Erfuth, 1998
          - Barbee et al, 2011: multicenter trial, failed at least one trial, on Paxil up to 50-62.5 mg/day, with add-on Lamictal (up to 400 mg) vs. placebo for 10 weeks
            - not statistically superior
            - secondary measures showed improvement
            - those with more severe depression showed more improvement
          - Obrocea et al: Lamictal monotherapy effective (especially if bipolar)
          - Barbosa et al: Lamictal plus Prozac (included some folks with bipolar II): positive
          - Other studies: Lamictal as add-on; conflicting results
            - Non-refractory
              - 3 pharmacy-funded trials with Lamictal as monotherapy failed
              - Normann et al: Lamictal plus Paxil failed, though some secondary measures were positive (primarily sped up benefit from Paxil)
      - Bipolar depression—most robust effects
        - Summary of response rates across 6 Lamictal multicenter acute bipolar depression studies (Calabrese, 1999; Geddes, 2006; Van der Loos, 2009)
          - Response rates for Lamictal: 45-55%
          - Response rates for placebo: ~27-~48%
          - In each study, Lamictal had higher responses rates than placebo
        - Jae Seung Chang, 2011: positive in open-label, naturalistic study of bipolar II depression
        - Lamictal added to lithium (vs. placebo added to lithium) (Van der Loos, 2009)
          - Response rate for Lamictal 65.6%
          - Response rate for placebo 49.2%
        - Calabrese et al and Barbosa et al did **not** demonstrate significant benefit, but post-hoc analysis demonstrated

        - Lamictal, compared to placebo, had significantly higher likelihood of a >75% improvement in the Montgomery-Asberg Depression scale after 7 weeks
        - Significantly higher likelihood of >50% improvement in the same scale at weeks 5, 6 and 7
    - Nierenberg, 2006 (STEP-BD): treatment-resistant bipolar depression—patients on combination of adequate doses of established mood stabilizers plus at least one antidepressant; open label augmentation (additional) treatment of either Lamictal, Inositol or Risperdal:
        - Lamictal 23.8% recovery rate
        - Inositol 17.4% recovery rate
        - Risperdal 4.6% recovery rate
    - RCT, 7 weeks, bipolar depression; safe and effective (Calabrese et al, 1999)
    - RCT, 6 week, cross-over study of treatment-resistant, rapid cycling or unipolar depression; safe and effective (Frye et al, 2000)
    - **Two unpublished studies were negative**
- Hypomania
- Mania—least robust effects; definitely not to be used for acute mania
- Rapid cycling in bipolar disorder
    - Calabrese, 2000: multicenter, double-blind, placebo-controlled study of Lamictal in rapid cycling
        - 56% patients responded to open-label treatment
        - In the double-blind 6-month stage
            - Lamictal: 41% stable for 6 months (significantly better only for bipolar II)
            - Placebo: 26% stable for 6 months
    - Walden, 2000: 14 patients with rapid cycling were treated with either lithium or Lamictal
        - 57% of those on lithium continued with rapid cycling course
        - 14% of those on Lamictal continued with rapid cycling course
        - 43% of those on Lamictal experienced no further mood episodes in the year following.
    - Bowden, 199; Calabrese, 1999: 48-week, open-label, add-on or monotherapy in 41 rapid cyclers and 34 non-rapid cyclers; patients with more severe symptoms of mania did not improve; rapid-cycling patients with both depressive and hypomanic symptoms did improve.
    - Rapid cycling bipolar I and II disorders—open label Lamictal therapy; efficacy was evaluated in those who responded to open Lamictal via a 6-month, placebo-controlled discontinuation design.
        - Primary measure did not demonstrate efficacy
        - Secondary measures demonstrated efficacy on a number of measures
            - proportion that did not relapse during the double-blind phase: Lamictal 59% and placebo 74%
            - especially effective in rapid cycling bipolar II
- Frye, 2000: double-blind, placebo-controlled study of patients with refractory mood disorders, including those with rapid cycling, that used a crossover series of three 6-week monotherapy evaluations of Lamictal, Neurontin, and placebo
    - Lamictal
        - 52% overall response rate; 50% over the whole trial
        - 45% response rate for depression
        - 44% response rate for mania
    - Neurontin
        - 26% overall response rate; 33% over the whole trial

        - 26% response rate for depression
        - 20% response rate for mania
    - Placebo
        - 23% overall response rate; 18% over the whole trial
        - 19% response rate for depression
        - 32% response rate for mania
- Maintenance in bipolar disorder
    - Preventive Effects of Lamotrigine in Bipolar II Versus Bipolar I Disorder
      Takeshi Terao, Atsuko Ishida, Toshifumi Kimura, Masao Yarita, Terufumi Hara
      Journal of Clinical Psychiatry 2017 August 15
      OBJECTIVE: The preventive effects of mood stabilizers on recurrence/relapse in bipolar disorders have been investigated mostly in bipolar I disorder (BPI) patients, with limited reports on bipolar II disorder (BPII) patients. Here, we conducted an explorative data analysis to investigate whether the preventive effect of lamotrigine on recurrence /relapse in BPII is better than in BPI.
      METHODS: Data from Japanese patients with a diagnosis of BPI or BPII according to DSM-IV-TR were analyzed in an open-label, noninterventional, naturalistic, prospective postmarketing surveillance study of lamotrigine. This study was carried out from October 2011 to November 2014, and each patient was observed for 1 year. The time to recurrence/relapse of mood episodes after commencement of lamotrigine treatment was evaluated as a primary endpoint. Kaplan-Meier curves were generated to compare the time to recurrence/relapse of mood episodes in BPI with in BPII using a log-rank test.
      RESULTS: Lamotrigine was associated with a significantly longer time to recurrence/relapse of mood episodes in BPII than in BPI (log-rank test, P = .0103). Lamotrigine also prolonged time to recurrence/relapse of mania-related episodes, including hypomanic episodes, more in BPII than in BPI (P = .0110).
      CONCLUSIONS: Although the preventive effect of lamotrigine on recurrence/relapse of mood episodes in BPI has been established in a variety of clinical studies, the present study suggests that lamotrigine may be more suitable for maintenance treatment in BPII than in BPI.
    - Two 18-month RCT's; safe and effective (Bowden et al, 2003)
    - Mild preventative effects against mania; robust preventative effects against bipolar depression
- Other
    - Borderline personality disorder
        - Weinstein and Jamison, 2007, chart review: safe and effective
        - Tritt et al, 2005
        - Preston, 2004
        - Pinto and Akiskal 1998
    - Cyclothymia
    - Schizoaffective disorder
    - Augmentation/adjunct in schizophrenia
        - Tiihonen et al, 2009 demonstrated efficacy alongside Clozaril
        - But Goff et al, 2007 (two large trials) showed no benefit
    - Chronic pain
    - Anxiety
        - OCD
            - 16 wk, randomized, DB, placebo-controlled, add-on study, 100 mg vs. placebo in Bruno et al, 2012
            - Safe and effective
        - PTSD

- 12 wk, randomized, DB, placebo-controlled, combat veterans, n=15, titrated up to 500 mg/day over 8 weeks (Hertzberg et al, 1999); safe and effective (50% response rate vs. 25% on placebo)
- Unipolar depression
  - Refractory depression
    - Barbee et al, 2011: multicenter trial, failed at least one trial, on Paxil up to 50-62.5 mg/day, with add-on Lamictal (up to 400 mg) vs. placebo for 10 weeks
      - not statistically superior
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    - 3 pharmacy-funded trials with Lamictal as monotherapy failed
    - Normann et al: Lamictal plus Paxil failed, though some secondary measures were positive (primarily sped up benefit from Paxil)
    - Lamictal augmentation with doses up to 400 mg/day failed in Barbee et al, 2011
- Youth with bipolar disorder
  - Findling, et al, 2015
    - No randomized placebo controlled studies in acute mania or bipolar depression
    - 2 positive open trials in youth
    - Studied for relapse prevention (add on to mood stabilizers)
      - Significantly prolonged time to mania in teens
      - Significantly prolonged time to depression relapse in teens
  - Pediatric add-on trial for manic, mixed, or depressed episodes completed, results pending
  - Chang, 2013
    - Overall rate of response 59.6%
      - 58% rate with mania
      - 60% rate with mixed episodes
      - 62% with depression
  - Biederman et al, 2010
  - Pavluri et al, 2009
  - Soutullo et al, 2006: adjunctive Lamictal treatment for adolescents with bipolar disorder, 1 male, 4 females; 1 with bipolar I, 1 with bipolar II, 3 with bipolar disorder not otherwise specified. Mean dose 100 mg (15-180 mg), mean duration of treatment 28 weeks (0-56 weeks)—safe and effective
  - Chang, 2006: 20 adolescents with bipolar I, II, NOS in depressive episode; 8-week, monotherapy or adjunctive, 84% improved; no serious rashes.
  - Swope, 2004: 23 adolescents with bipolar I depression or mixed mania, 12-week, open-label; effective; no rash.
  - Saxena, 2004: 18 patients, 12-17 yo, with bipolar disorder; open trial of Lamictal monotherapy or add-on to other mood stabilizer; 8 week study; 65-90% response rate
  - Carandang, 2003 reported improvement of refractory mood symptoms in 8 of 9 adolescents with treatment-refractory mood disorders (of which 6 were bipolar)
  - Kusumaker and Yatham, 1997: case studies
- Side effects
  - **Common**
    - *24% double vision/blurred vision

- *15-18% headache
- 14-18% nausea
- 11% vomiting
- 11% blurred vision
- *10% balance/coordination/gait problems
- 10% insomnia (though not seen in my experience)
- *9-10% sedation (though, in my opinion, extremely rare at doses of 250 mg or below)
- 7% diarrhea
- *6-31% dizziness (more frequent at 400 mg or more)
- 4% tremor
- rare activation
- hypomania (risk is less than that of placebo so this may be simply Lamictal failing to prevent or treat hypomania)
- decreased libido, delayed orgasms (due to serotonergic properties)
- likely weight neutral at doses of 50-250 mg/day; Meredith, 2006: may cause weight loss in overweight clients
- hair loss (very rare)
- little to no cognitive impairment except at higher doses
    - associated with improved alertness, longer attention span
    - in pediatric bipolar disorder (Ajshar et al, 2006)
        - clinical improvement in neurocognition
        - clinical improvement in social cognition
- a number of other side effects and risks in multiple organ systems

- **Risk of rash/allergic reaction:**
    - risk is greatest in first eight weeks
    - risk of **non-serious rash**
        - **If mild: similar to mild sunburn**
        - **If total body rash: resembles severe case of poison ivy; see below—this is more serious**
        - **3.1-14% risk; elsewhere listed as 2-5% and within the first two weeks**
        - **3.1% in a 2005 study of 100 patients with bipolar disorder**
        - **In controlled settings: 8.3% vs. 6.4% in placebo with no cases of serious rash**
        - **In multicenter, double-blind, placebo-controlled bipolar trials (Calabrese, 2001)**
            - **Lamictal**
                - **9% of 1198 patients with benign rash**
                - **0.06% of 3,153 patients with severe rash**
            - **Placebo**
                - **8% of 1056 patients with benign rash**
                - **0.09% of 1053 with severe rash**
            - **No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis**
        - **Calabrese, 1999: 11-14% rash in patients on Lamictal AND in patients on placebo; discontinuation due to rash was 3-6% in both groups as well.**
    - Severe allergic reactions, including Stevens-Johnson syndrome (SJS)
        - Hallmarks
            - Abrupt onset of rash/large connected areas of redness
            - Fever
            - Complete exhaustion
            - Facial swelling, swelling of eyelids
            - Skin pain
            - Blisters around the mouth

        - or skin layers detaching from each other
        - Conjunctivitis
        - Erosions in mucous membranes (e.g., mouth, eye)
        - Enlarged lymph nodes
        - Joint paint
        - Shortness of breath, wheezing, laryngeal edema
        - High eosinophil counts
        - Abnormal liver function tests
    - Risk is 0.3% (0.1-0.5%) in adults and 0.8% (0.5-1%) in children
    - Risk of toxic epidermal necrolysis 1/5000 adults and 1/2500 children
        - Resembles extensive burn with severe lesions
    - Other estimates
        - German rash registry (2005) states risk with proper titration is **1/10,000 (which is similar to Depakote and similar or better than 13 other medications that can cause SJS, including sulfonamide antibiotics**
        - **Bowden, 2003, incidence of rash in controlled bipolar disorder studies: 0/827 on Lamictal and 0/280 on lithium and 1/685 on placebo with dangerous rash.**
        - **in one study, 3 cases of 1198 developed the syndrome**
        - **Calabrese, 1999: no serious rash**
        - **PDR, 1999: 0.017% risk SJS**
        - **PDR, 1993: 0.112% risk SJS**
- usually within the first two months
- in the first 3 months of use
    - avoid new food, deodorants, detergents, cosmetics, fabric softeners
    - avoid excessive sun exposure or tanning
- risk is increased with concomitant use of valproic acid or if dose is raised quickly; in some studies
- if rash is accompanied by fever, malaise, discomfort in mouth, eye, or bladder→ go to ER.

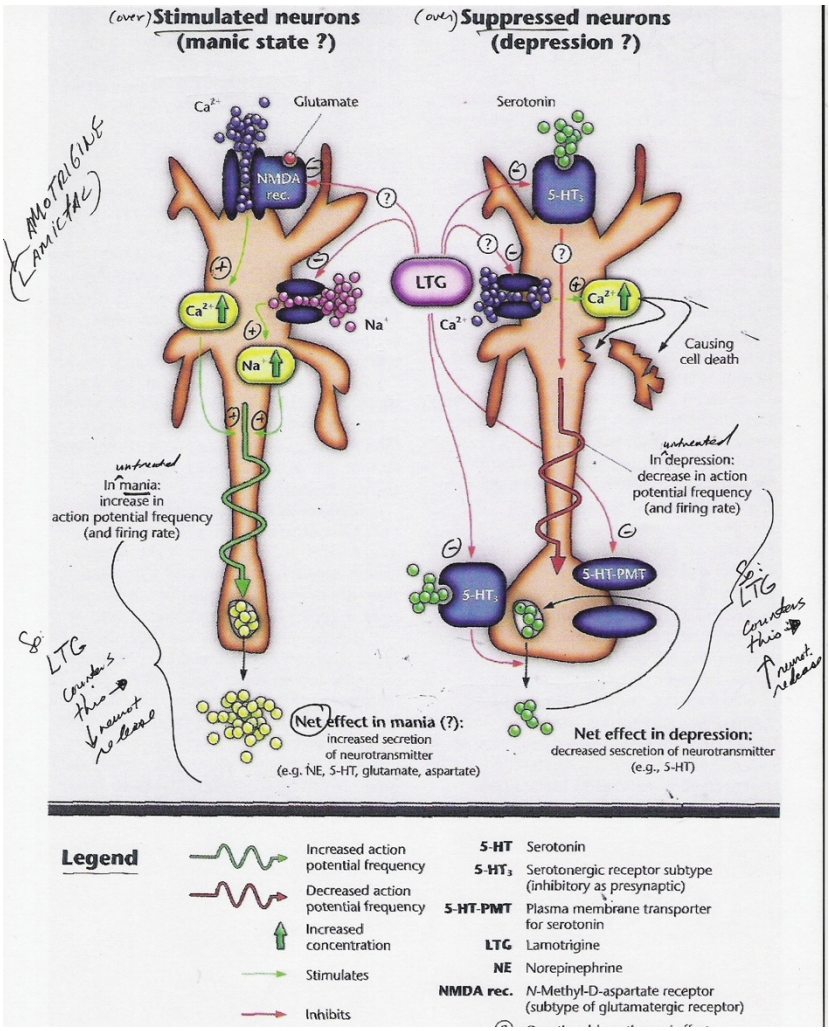
- **Serious Immune System Reaction [Posted 04/25/2018]**
    - **ISSUE:** The FDA is warning that the medicine Lamictal (lamotrigine) for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, we are requiring a new warning about this risk be added to the prescribing information in the lamotrigine drug labels.
    - **BACKGROUND:** The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, usually greater than 101°F, and it can lead to severe problems with blood cells and organs throughout the body such as the liver, kidneys, and lungs.
    - Lamotrigine is used alone or with other medicines to treat seizures in patients two years and older. It may also be used as maintenance treatment in patients with bipolar disorder to help delay the occurrence of mood episodes such as depression, mania, or hypomania. Stopping lamotrigine without first talking to a prescriber can lead to uncontrolled seizures, or new or worsening mental health problems. Lamotrigine has been approved and on the market for 24 years, and is available under the brand name Lamictal and as generics.
    - **RECOMMENDATION:** Healthcare professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms

such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

- Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established. Advise patients to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment. A diagnosis of HLH can be established if a patient has at least five of the following eight signs or symptoms:
    - fever and rash
    - enlarged spleen
    - cytopenias
    - elevated levels of triglycerides or low blood levels of fibrinogen
    - high levels of blood ferritin
    - hemophagocytosis identified through bone marrow, spleen, or lymph node biopsy
    - decreased or absent Natural Killer (NK) Cell activity
    - elevated blood levels of CD25 showing prolonged immune cell activation
- Patients or their caregivers should contact their health care professionals right away if they experience any symptom of HLH while taking lamotrigine. HLH can occur within days to weeks after starting treatment. A physical examination and specific laboratory blood tests and other evaluations are used to diagnose HLH. Signs and symptoms of HLH include but are not limited to:
    - fever
    - enlarged liver; symptoms may include pain, tenderness, or unusual swelling over the liver area in the upper right belly
    - swollen lymph nodes
    - skin rashes
    - yellow skin or eyes
    - unusual bleeding
    - nervous system problems, including seizures, trouble walking, difficulty seeing, or other visual disturbances

- 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:



  - May act on voltage-gated sodium channels to enhance GABA release and decrease NMDA glutamatergic activity and/or glutamate release
  - May also affect voltage-gated calcium channels.
  - Blocks sodium influx and enhances potassium efflux.
  - May block serotonin reuptake (leading to increased serotonin).
  - May block 5HT3 receptors
  - Appears to have neuroprotective effects
  - In youth with bipolar disorder, Lamictal led to increased neuronal density in the left dorsolateral prefrontal cortex and a related decrease in right amygdalar activation (in response to emotional stimuli)
- Pharmacodynamics
  - Drug-drug interactions, etc
    - Oral contraceptives reduce Lamictal plasma levels by 41-64% (with an average of 49%)
    - Pregancy reduces levels by >51%; normalizes quickly postpartum.
    - Zoloft increases Lamictal
    - Depakote doubles levels of Lamictal
    - Tegretol nearly halves Lamictal levels
  - Liver metabolism; no induction of liver enzymes; metabolized primarily by **UGT 1A4**
  - Half-life 25-33 hours (12-60 hours in some studies)
  - Steady state in 3-15 days
  - Target plasma range for seizures (not clear for psychiatric purposes): 3-14 mcg/ml
  - Dosing

        - Comes in
            - 25, 100, 150, and 200 mg tabs
            - 2, 5, and 25 mg chew tabs.
        - Approved in generic in 2007.
        - Dose 50-500 mg/D
        - If weigh less than 30 kg, may need to increase maintenance dose by 50%
        - If given during pregnancy, dose may need to be increased and then lowered after delivery
        - Current recommendation for lamotrigine monotherapy is as follows:
            - In adults: 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 1 week, then 200 mg/d thereafter. I will often go much slower as well.
            - In children: 25 mg every other day (or 12.5 mg/day) for 2 weeks then 25 mg/day for 2 weeks then increase by 25 mg each week to target dose between 100-200 mg/day
            - When on Depakote: 25 mg every other day (or 12.5 mg/day) for 2 weeks then 25 mg/day for 2 weeks then 50 mg/day for 1 week then 100 mg/d thereafter
            - When on carbamazepine: 25 mg twice-a-day for 2 weeks then 50 mg twice-a-day for 2 weeks then 100 mg twice-a-day for 1 week then 150 mg twice-a-day for 1 week then 200 mg twice-a-day thereafter
        - May need to increase dose in winter and decrease dose in spring
    - Drug-drug interactions
        - **Tegretol decreases levels by 25-50%**
        - **Zoloft can substantially increase Lamictal levels by 25% and lead to toxicity**
        - Birth control pills can lower levels by 50% or more
- Pregnancy:
    - NB: background population rate of birth defects/major congenital malformations unrelated to any medications is 2-6%, depending on the study
    - Overall, rate of total malformations in those on Lamictal comparable to general population (2-3%)
    - Orofacial clefts
        - Increased risk of 0.45% per the North American AED registry; not replicated by other registries/studies
    - Supplement with folic acid 4-5 mg/day
    - Messenheimer, 2006 (GlaxoSmithKline): of 2000 pregnancies (256 of which were using Lamictal with other anticonvulsants but NOT Depakote and 119 of which were using Lamictal and Depakote):
        - 20 major congenital malformations
            - 2—club feet
            - 2—anencephaly
            - 3—ventricular septal defects (of the heart)
            - Remaining—
                - midline deficits
                - urogenital defects
                - cortical (brain) dysplasia
                - hypoplastic left heart syndrome
                - hypoplasia of the left ventricle
                - diaphragmatic hernia with abdominal organ displacement
        - Lamictal monotherapy malformation rate 2.8%
            - Of 100 women who took Lamictal > 400 mg/day, rate was 4%
        - Lamictal with anticonvulsants other than Depakote—2.7%
        - Lamictal with Depakote—11.8%
    - Cunnington, 2004: rates of congenital malformations are similar to those encountered in the general population, and lower than those with Depakote.

- 1.8% of 165 live births from women taking Lamictal during the first trimester had birth defects; the rate was higher when Lamictal was taken with other antiepileptic medications
- In national registry, over 400 first-trimester exposures to Lamictal monotherapy with an overall risk of major malformations of 2.9%, which falls between the 2-4% baseline risk for major malformations in the general population.
    - 8.9/1000 exposures (vs. 0.37/1000 women in general population) with cleft lip/palate after first trimester use of Lamictal; relative risk thought to be 10.4, but this was not confirmed in a survey of 3.9 million births from 19 registries
    - 7.7% incidence of birth defects vs. 4.3% general rate in women with epilepsy who do not take an antiepileptic in the first trimester
    - Elsewhere: risk of major congenital malformations 2.2% (which is within the normal rate in the general population)
    - 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
- Lactation
    - High infant serum levels have been reported: 30% (18-50%) of maternal levels; no adverse events in infants
    - Adjust maternal dose postpartum to avoid toxicity
    - No reports of Steven's Johnson syndrome
    - Breastfed infant to be monitored closely

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Takeshi Terao, Atsuko Ishida, Toshifumi Kimura, Masao Yarita, Terufumi Hara
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RESULTS: Lamotrigine was associated with a significantly longer time to recurrence/relapse of mood episodes in BPII than in BPI (log-rank test, P = .0103). Lamotrigine also prolonged time to recurrence/relapse of mania-related episodes, including hypomanic episodes, more in BPII than in BPI (P = .0110).
CONCLUSIONS: Although the preventive effect of lamotrigine on recurrence/relapse of mood episodes in BPI has been established in a variety of clinical studies, the present study suggests that lamotrigine may be more suitable for maintenance treatment in BPII than in BPI.