“There are two things to aim at in life; first to get what you want, and after that to enjoy it. Only the wisest of mankind achieve the second.”

Logan Pearsall Smith, essayist (1865-1946)
Anticonvulsants

Learning Objectives
1. Provide a broad understanding of the use of valproate, carbamazepine, oxcarbazepine and lamotrigine in child psychiatry. Their respective pharmacological properties, potential side and adverse effects and the literature to support their efficacy will be reviewed.
2. Highlight and briefly describe the association between anticonvulsants and suicidality.
3. Discuss the etiology and ways to minimize the risk of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) as a severe adverse reaction to a number of anticonvulsants.

Outline
• Medications to be covered:
  – Valproate (VPA)
  – Carbamazepine (CBZ)
  – Oxcarbazepine (OXC)
  – Lamotrigine (LTG)

Outline (cont.)
• Topics to be covered for each medication:
  – Indications & clinical use
  – Pharmacodynamics & pharmacokinetics
  – Efficacy
  – Adverse effects
  – Contraindications & drug interactions
  – Monitoring
  – Dosing

But first…Anticonvulsants and Suicidality
• In December 2008, the FDA ordered new warnings and issued a public-health advisory about ↑ risk of suicidal behaviour or ideation associated with antiepileptic drugs (AEDs) as a class and manufacturers were required to change their labelling/add warnings
• These actions were based on an analysis of suicide-related events (SREs) in 199 PBO-controlled trials of 11 anticonvulsants (valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin, felbamate, levetiracetam, pregabalin, tiagabine, and zonisamide)
• N=43,892 with epilepsy, psychiatric disorders and ‘other conditions’ (20, e.g. neuropathic pain)

Acknowledgments
We would like to thank Dr. Kate Cochrane-Brink, who contributed to this presentation.
Suicidality (cont.)

- Patients receiving AEDs had approximately twice the risk of SREs (0.43%) compared with patients receiving PBO (0.22%).
- The ↑ risk of SREs was observed as early as 1 week after starting the AED and continued through 24 weeks.
- The relative risk of SREs was higher in patients with epilepsy compared with patients treated for psychiatric or other conditions (e.g. pain).

Subsequent studies attempted to address:

- The risk associated with individual AEDs: Pantorno et al., 2010, Andersohn et al., 2010.
- Whether AEDs as a class increase the risk of suicide attempts in bipolar patients: Leon et al., 2012, Gibbons et al., 2009.

Consensus is lacking and the FDA position is unchanged with obvious implications for prescribers to address issues of informed consent and monitoring.

Also keep in mind... SJS/TEN

- Rare but life-threatening cutaneous hypersensitivity reactions.
- Almost exclusively due to drugs – sulphonamides, AEDs > penicillins, NSAIDs > acetyaminophen.
- Studies in children show the AEDs most often suspected of causing SJS/TENS:
  - Carbamazepine, lamotrigine, phenobarbital – highest risk.
  - Valproate.
  - Oxcarbazepine.

SJS/TEN (cont.)

- Certain Human Leukocyte Antigens (HLA) alleles are associated with CBZ-induced SJS/TEN.
- The strongest association is for the HLA-B*1502 allele which is exclusive to peoples of Asian ancestry (esp. Han Chinese).
- Genotyping is recommended for all ethnically Asian patients prior to starting CBZ and other anticonvulsants associated with SJS/TENS.
- See also slides in CBZ and LTG sections.

Indications

- Valproate (VPA) is approved by HC and the FDA for the treatment of seizures in adults and children (extreme caution recommended for children ≤2 years old).
- VPA is approved by the FDA (but not HC) for prophylaxis of migraine headaches in adults (≥16 years).
- VPA is approved by HC and the FDA for the treatment of acute mania in adults (≥18 years) with bipolar disorder.
- VPA is not approved by HC or the FDA for any psychiatric indication in children or adolescents.
Psychiatric Uses
• Clinically, valproate has been used in children, adolescents, and adults to treat:
  – Bipolar disorder
  – Aggression & conduct disorder
  – Behavioural dyscontrol in individuals with developmental disorders or MR

Compounds
• Valproic acid was first synthesized in 1880s and used as an inert solvent
• Used to treat epilepsy starting in the 1960s
• Abbott synthesized valproate sodium much later (1980s or 90s)
• Then divalproex sodium (DVP) synthesized by combining valproic acid and valproate sodium in a 1:1 molar ratio
• All 3 compounds convert to the valproate ion (VPA)

Compounds and Preparations
• Depakene = valproic acid
• Epival = divalproex sodium (DVP)
• Depacon = valproate sodium (US)
• DVP is available in Canada as an enteric-coated tablet (Epival)
• Valproic acid available as Depakene gel capsules and syrup

Pharmacodynamics
• The mechanism of action of valproate remains uncertain, but it has multiple effects that have been implicated:
  1. Potentiation of CNS GABA function:
     a) Inhibition of the catabolism of GABA
     b) ↑ in the release of GABA
     c) ↑ in GABA_B receptor density
     d) Possible enhancement of neuronal responsiveness to GABA
  2. Direct neuronal effects
    a) ↓ sodium influx
    b) ↑ potassium efflux
  3. Interactions with gamma hydroxybutyrate (GHB)
  4. ↓ dopamine turnover
  5. Alteration of serotonin function
  6. ↓ in N-methyl-D-aspartate (NMDA)-mediated currents

Pharmacodynamics (cont.)
  7. ↓ aspartate release
  8. ↓ in CSF somatostatin concentrations
  9. Regulation of calcium-calmodulin-dependent protein kinase, which in turn regulates various cytoskeletal processes
  10. Regulation of the expression of genes through its effects on intranuclear transcription factors
Pharmacokinetics

• Valproate ion absorbed in the GI tract
• Rate of absorption depends on compound, preparation and GI tract (e.g. fasting or full)
• Side effects, effects and metabolism may vary with above as well
• Epival
  – $T_{\text{max}}=3-4$ hrs (absorption slightly delayed when taken with food)
• Epival ER
  – Absorbed over 18-24 hrs
  – $T_{\text{max}}=16$ hrs
  > N.B. VPA level 12 hrs after last dose of Epival ER will be close to a peak level. To obtain a trough level, blood should be drawn 24 hours after last dose.

Pharmacokinetics (cont.)

• The bioavailability of both Epival and Epival ER is about 90%
• VPA $T_{1/2}=6-16$ hours
• In adults, Epival ER given QD produced steady-state plasma concentrations (AUC) equivalent to those of Epival tablets given BID, with a lower degree of fluctuation

Pharmacokinetics (cont.)

• VPA is strongly bound to plasma proteins (90%), but ↑ in dose may result in ↓ in the extent of protein binding as well as variable changes in elimination
• VPA may displace other drugs from protein-binding sites
• Because the protein binding is saturable, the relationship between dose and total VPA concentration is nonlinear; concentration does not ↑ proportionally with the dose, but rather ↑ to a lesser extent
• However, the kinetics of unbound VPA are linear

Pharmacokinetics (cont.)

• VPA is primarily metabolized in the liver by glucuronidation and oxidation, and its metabolites (several of which are active) are excreted mainly in the urine
• Inhibition or induction of CYP450 enzymes by other drugs has little effect on VPA clearance because CYP450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared with glucuronidation and mitochondrial β-oxidation
• By contrast, drugs that affect glucuronyl transferases may have a considerable influence on VPA clearance

Efficacy: Bipolar Disorder

• A number of open trials support the use of valproate for pediatric bipolar disorder:
  – Papatheodorou & Kutcher, 1993
  – West et al., 1994
  – West et al., 1995
  – Papatheodorou et al., 1995
  – Wagner et al., 2002
  – Pavuluri et al., 2005

Efficacy: Bipolar Disorder (cont.)

• 6 prospective comparator trials of DVP for PBD have been published:
  – Kowatch et al., 2000: DVP vs. Li vs. CBZ (open)
  – Findling et al., 2005: DVP vs. Li (dbl-blind, maintenance treatment)
  – DelBello et al., 2006: DVP vs. QUE (dbl-blind)
  – Barzman et al., 2006: DVP vs. QUE (dbl-blind)
  – Pavuluri et al., 2010: DVP vs. RISP (dbl-blind)
  – Geller et al., 2012: DVP vs. Li vs. RISP (dbl-blind)
Li vs. DVP vs. CBZ for PBD

- Kowatch et al., 2000:
  - Randomized, open study comparing Li, DVP, and CBZ for pediatric bipolar disorder
  - 42 outpatient children and adolescents:
    - 20 with bipolar I disorder, 22 with bipolar II disorder
    - Mixed or manic episode
  - Primary outcome measures: YMRS and CGI-I
  - Response rates:
    - Li=38%, DVP=53%, CBZ=38% (p=0.6)
  - Effect sizes (using YMRS change from baseline)
    - Li=1.1, DVP=1.6, CBZ=1.0

Li+DVP for PBD – Findling et al., 2003, 2005 & 2006

- 2003: Open, prospective study of Li+DVP in children and adolescents (5-17 yrs) with bipolar I or II disorder: Remission rate: 47%
- 2005: Randomized, double-blind trial of Li vs. DVP maintenance treatment for up to 76 weeks. Either Li or DVP was discontinued: Median time to relapse: Li=114 days, DVP=112 days (p=0.6)
- 2006: Open, prospective study of Li+DVP - whichever drug had been stopped was now added back: 90% restabilized with resumption of Li+DVP

Delbello et al., 2006

- Double-blind RCT of QUE vs. DVP for 4 weeks in 50 adolescents with bipolar disorder (manic or mixed episode)
- Note that 11/25 (44%) in the QUE group and 12/25 (48%) in the DVP group had psychotic features
- Primary outcome measure:
  - Change in YMRS score

Delbello et al., 2006 (cont.)

- Results:
  - Both groups improved from baseline (p<0.0001)
  - QUE = DVP on the YMRS
  - Improvement in YMRS scores occurred more rapidly in the QUE group (p=0.03)
  - Response rate: QUE (72%) > DVP (40%) (p=0.02)
  - Remission rate: QUE (60%) > DVP (28%) (p=0.02)
  - [Response = CGI-BP-I ≤ 2 & Remission = YMRS≤12]
  - Rates of adverse events did not differ significantly between groups* and both QUE and DVP were considered to be well tolerated

  * Average wt gain: QUE = 4.4 kg, DVP = 3.6 kg

Pavuluri et al., 2010

- Double-blind randomized outpatient trial with n=66 (8-18 yrs) with mania
- Assigned to either risperidone or DVP for a 6 week period, no placebo arm
- Primary outcome measures:
  - YMRS (2° - CDRS-R)
  - Psychotic Sx: RISP arm – 7, DVP - 6
- Mean doses: RISP = 1.4 mg
  - DVP = 856 mg (96*µg/mL=666µmol/L)

  *Therapeutic serum range for adults with acute mania 50-125 µg/mL (350-865 µmol/L)(Connor & Meltzer, 2006)

Pavuluri et al., 2010 – cont.

- Results:
  - Response rate on YMRS: RISP (78%) > DVP (46%) (p<0.01)
  - Remission rate: RISP (63%) > DVP (33%) (p<0.05)
  - Improvement was more rapid for risperidone
  - Parent report (CMRS-P): RISP=DVP
  - Dropout rate: DVP – 48%, RISP – 24%
  - Adverse effects – increased irritability with DVP, 3 fold increase in prolactin and 2 subjects with EPS with RISP

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West et al., 2011
(Secondary analysis of Pavuluri et al., 2010)
• Presence of disruptive behaviour disorders (DBDs) and aggression predicted response to risperidone vs. divalproex
• DBD group: greater reduction in manic symptoms with risperidone vs. divalproex
• Non-DBD group: risperidone=divalproex
• DBD group improved less over time and had worse global functioning (6 week trial)

Geller et al., 2012 – TEAM* Study
– 8 week, randomized, comparator trial with medication naïve 6-15 yr olds (n=279) in manic or mixed phase, outpatients
– Primary outcome measures: CGI-BP-IM & Modified Side Effects Form for Child/Adoles
– Response rate: RISP>Li=DVP
– Discontinuation rate: Li=DVP>RISP
– Wt, BMI, prolactin increases: RISP>Li=DVP
– TSH increased in Li group
*Treatment of Early Age Mania

DBPC Trials of DVP for Pediatric Bipolar Disorder
• Wagner et al., 2009:
  ~ Negative result
• Kowatch et al., 2007:
  ~ Presented but not published (as of March 2009)
  ~ Positive result (for DVP, though not for Li)

Wagner et al., 2009
• DBPC trial of extended-release DVP in 150 outpatient youth (10-17 years old) who had bipolar I disorder and were experiencing a manic or mixed episode
• DVP vs. PBO for 4 weeks, then open-label DVP (N=66) for 6 months
• DVP was titrated to clinical response or VPA level of 80-125 μg/mL (555-867 µmol/L)
• Primary outcome measure: YMRS

Wagner et al., 2009 (cont.)
• Efficacy Results:
  ~ DVP = PBO on the YMRS
    • DVP =-8.8, PBO =-7.9
  ~ DVP = PBO on secondary outcome measures
  ~ Long-term open-label treatment with DVP resulted in a small ↓ in mean YMRS score (-2.2 from open-label baseline)

Wagner et al., 2009 (cont.)
• Adverse event results:
  ~ No significant group differences in the overall incidence of AEs (DVP=67%, PBO=59%) or in the incidence of any individual AE
  ~ Patients who discontinued the study because of AEs:
    • DVP=4 (including 1 case of ↑NH3 resulting in disorientation and hospitalization, and 1 case of intentional OD resulting in hospitalization)
    • PBO=3 (including 1 case of SI requiring hospitalization)
  ~ Weight gain: DVP (+1.0 kg) > PBO (+0.3 kg) (p<0.01)
  ~ In the long-term, open-label study, the most common adverse events were headache (17%) & vomiting (9%)
Wagner et al., 2009 (cont.)

Long-term study:
• Mean changes from open-label baseline to final value for each lab parameter were generally small, except for ↓ platelets and ↑ NH₃.
• 7/66 (11%) subjects had platelet counts below normal.
• 11/66 (17%) subjects had clinically significant elevations in NH₃.

Kowatch et al., 2007 (Presented but Not Published)

• Federally funded DBPC trial in 154 outpatient youth (7-17 years old) who had bipolar I disorder and were experiencing a manic or mixed episode.
• Randomized to Li, DVP, or PBO in a 2:2:1 ratio for 8 weeks.
• Primary outcome measures:
  – YMRS
  – CGI-Improvement.

Kowatch et al., 2007 (cont.)

• Efficacy results (change in YMRS score):
  – DVP > PBO
  – Li = PBO (but trend favouring Li)
  – DVP = Li
• Percentage with >50% ↓ in YMRS score:
  – DVP = 56%
  – Li = 41%
  – PBO = 30%

Efficacy: “High Risk” for Bipolar Disorder

• Findling et al., 2007:
  – DBPC trial of DVP for up to 5 years in 56 youths (5-17 years old) with bipolar disorder NOS or cyclothymia who also had ≥1 parent with bipolar disorder.
  – Primary outcome measure: time to study discontinuation for any reason.
  – Both groups showed significant improvements in mood symptoms and psychosocial functioning.
  – Primary outcome measure:
    • DVP (164 days) = PBO (187 days)
  – On all secondary outcome measures:
    • DVP = PBO.

Efficacy: Aggression

• Saxena et al., 2006:
  – 12-week, open-label trial of DVP in 24 bipolar offspring, ages 6-18 years (mean 11.3).
  – Subjects had mixed diagnoses of MDD, cyclothymia, ADHD, and ODD.
  – Primary outcome measure: Overt Aggression Scale.
  – Results:
    • Response rate: 71% of evaluable subjects.
    • Serum VPA level did not correlate with treatment response.

Efficacy: Aggression (cont.)

• Donovan et al., 2000:
  – 20 outpatient youth, 10-18 years old, with (a) ODD or CD, and (b) explosive temper & mood lability.
  – 2-phase DBPC crossover: randomization to DVP x 6 weeks (phase 1) and then PBO x 6 weeks (phase 2), or vice versa.
  – Outcome measures: Modified Overt Aggression Scale and 6 anger-hostility items from the SCL-90.
  – Results:
    • End of phase 1: response rate was 8/10 for DVP, 0/10 for PBO (p<0.001).
    • End of phase 2: 12/15 had superior response to DVP than PBO (p=0.003).
Efficacy: Aggression (cont.)
- Steiner et al., 2003:
  - 71 adolescent males with CD and at least one crime conviction were randomized for 7 weeks to high-dose DVP vs. low-dose DVP
  - Results:
    - High-dose DVP > Low-dose DVP:
      - CGI-Seriously of illness (p<0.02)
      - CGI-Improvement (p=0.008)
      - Self-reported impulse control (p<0.05)
      - Self-restraint (p<0.06)
    - Analyses comparing outcome by blood VPA level strengthened the results

VPA for Aggression:
- Canadian Guidelines on Pharmacotherapy for Disruptive and Aggressive Behaviour in Children and Adolescents With ADHD, ODD, or CD (Gorman et al., 2015)
- VPA for Aggression in Children and Adolescents With ODD or CD, With or Without ADHD
  - Quality of evidence: low
  - Magnitude of benefit: large
  - Side effect burden: major
  - Strength of recommendation: conditional, in favour(†?)

Adverse Effects: Minor

Efficacy: Aggression in PDD
- Hellings et al., 2005:
  - 8-week DBPC trial of DVP for aggression in 30 children and adolescents with PDD
  - DVP = PBO on the primary and secondary outcome measures, although there was a large PBO response

Adverse Effects: Serious

Adverse Effects: Minor

Table 31.8-5 Non-Life-Threatening Side Effects Associated with Valproate

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management Considerations</th>
</tr>
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<tbody>
<tr>
<td>Tremor</td>
<td>• Head dose related: Decrease dose, change to formulation with less serum acetate (Depakote ER or Depakote Sprinkle)</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive (β-blocker or benzodiazepine)</td>
</tr>
<tr>
<td>GI upset</td>
<td>• Give with food or dose at bedtime, or both</td>
</tr>
<tr>
<td></td>
<td>• Depakote or Depakote ER has less GI upset than valproate</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive histamine 2 antagonist</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>• Transient (new full-blown alopecia)</td>
</tr>
<tr>
<td></td>
<td>• Amebicidal evidence of zinc and selenium supplements</td>
</tr>
<tr>
<td>Weight gain and increased appetite</td>
<td>• Some suggestion of dose relationship</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive pharmacotherapy (i.e., ropinirole [Requip], rasagiline [Reparil], selegiline [Eldepryl], levodopa)</td>
</tr>
<tr>
<td>Hepatic enzyme elevation</td>
<td>• Monitor for waxing and waning vs. continual persistent increase</td>
</tr>
<tr>
<td>(less than three times normal)</td>
<td>• Enquire about symptoms (right upper quadrant pain, malaise, urticaria color change)</td>
</tr>
<tr>
<td></td>
<td>• Close decrease recommend for elevation or side effects</td>
</tr>
</tbody>
</table>

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)
Hepatotoxicity

- Two types:
  - **Type I**: Common (5-40%), nonprogressive, dose-related ↑ in LFTs that often resolves with discontinuation of DVP, dose ↓, or even continuation at the same or higher dose
  - **Type II**: Rare, idiosyncratic, severe, often fatal hepatotoxicity that appears to be unrelated to dose, but has usually occurred during the first 6 months of DVP treatment

Severe Hepatotoxicity

- Besides young age, other reported risk factors include treatment with multiple anticonvulsants, congenital metabolic disorders, mental retardation, developmental delay, and organic brain disease
- No cases of severe hepatotoxicity have been reported in medically well children >2 years old receiving DVP monotherapy (Connor & Meltzer, 2006)

Risk Underestimated?: Severe Hepatotoxicity

- Risk reported to be 1:40,000 adults and 1:5,000 children (Dreifuss et al., 1987), but these estimates may be too low, as 31 cases of DVP-induced hepatotoxicity (22 reversible, 9 fatal) were identified in Germany from 1994 to 2003 (Koenig et al., 2006)
- 80-90% of cases have been in individuals ≤25 years, including 50-70% in children ≤10 years (Koenig et al., 2006)

Risk Underestimated?: Pancreatitis

- Gerstner et al., 2007:
  - 16 cases of DVP-induced pancreatitis were identified in Germany from 1994 to 2003 (none had been published previously)
- Cofini et al., 2015
  - DVP-induced pancreatitis does not depend on VPA serum levels or length of treatment
  - Re-challenge should be avoided
  - Likely underestimated – report 4 cases in children 2008 to 2012

Risk Underestimated?: Encephalopathy

- Gerstner et al., 2006
  - 19 cases of DVP-associated encephalopathy were identified in Germany from 1994 to 2003
  - Typical signs: Impaired consciousness, confusion, marked EEG background slowing (sometimes), ↑ seizure frequency, hyperammonemia may be present or absent
- Risk factors (in cases with hyperammonemia) include polypharmacy, carnitine deficiency, MR and urea cycle disorders (Chopra et al., 2012)

Other Adverse Effects

- Suicidality (see slides 5-7)
- Likely ↑ risk of SJS or TEN (Levi et al., 2009)
- Coagulopathies in almost 4% of children (Gerstner et al., 2006):
  - Especially thrombocytopenia, Von Willebrand disease, and ↓ factor XIII
- Possible lipid abnormalities, but the evidence is mixed (Sözüer et al., 1997; Verrotti et al., 1998; Voudris et al., 2006; Sonmez et al., 2006; Karikas et al., 2006; Castro-Gago et al., 2006):
Other Adverse Effects (cont.)

• Possible alteration in TFTs (although it has been suggested that DVP can cause falsely abnormal TFT results):
  – Cansu et al., 2006: ↑ TSH without a change in T4, T4, T3, or T3
  – Verotti et al., 2009: no alteration in thyroid hormones

• Possible ↓ in 25-hydroxyvitamin D and serum parathyroid hormone (Nicolaidou et al., 2006)

Other Adverse Effects: Cognitive

• Henin et al., 2009:
  - 173 children and adolescents (6-17 years) with ‘DSM IV’ bipolar d/o given neuropsychological assessment as part of entry into clinical trial
  - 66 receiving naturalistic treatment with 4 classes of meds (MSs, SGAs, stimulants, ADs)
  - those treated with MSs (lithium & AEDs, n=21) showed impairments in processing speed and working memory relative to unmedicated bipolar d/o patients

VPA & Carnitine

• Carnitine (CAR) is a nutrient supplied mainly by meat and dairy products, and it is also synthesized de novo in the liver

• The main function of CAR is to transport fatty acids from the cytosol to the inner compartment of the mitochondria where fatty acids are used for energy production by β-oxidation

Carnitine: DeVivo, 2002 [Letter]

• L-carnitine stores are depleted during chronic valproate (VPA) treatment

• L-carnitine mitigates VPA-induced hyperammonemia

• Serum L-carnitine concentrations do not necessarily reflect tissue L-carnitine concentrations

• IV L-carnitine given within 5 days of symptoms rescues 100% of patients with VPA-induced hepatotoxicity (Bohan et al., 2001)

DeVivo, 2002 (cont.)

• “Patients receiving chronic valproate treatment for epilepsy, migraine, or psychiatric illness should receive L-carnitine supplementation (100 mg/kg/day or 2 g/day, whichever is less) concomitantly. An ounce of prevention is worth a pound of cure.”

Carnitine Supplementation

• Levocarnitine (Carnitor) 330 mg tablets

• In children, start with 50 mg/kg/day and titrate up to the lesser of 100 mg/kg/day or 2 g/day dosed BID-TID

• CPS: “Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition”

• Adverse effects: GI symptoms (nausea, vomiting, abdominal cramps, diarrhea), body odour (fishy), seizures (in patients with or without prior seizures)
VPA & PCOS

- Polycystic ovarian syndrome (PCOS):
  - Chronic endocrine disorder characterized by:
    - Menstrual cycle irregularities (≤9 menstrual cycles/year)
    - Hyperandrogenism (≥1 feature of hirsutism, acne, male-pattern alopecia, or elevated serum androgens)
  - The majority of women with PCOS also have obesity, insulin resistance, and polycystic ovarian morphology, but these characteristics are not required for diagnosis

VPA & PCOS (cont.)

- Isojarvi et al., *NEJM*, 1993:
  - 238 women taking anticonvulsants for epilepsy
  - VPA was associated with a high rate of hyperandrogenism and PCO (polycystic ovaries), whereas the CBZ group was not significantly different from controls
  - 43% of women receiving VPA had PCO on US, while an additional 17% had elevated testosterone without PCO
  - 80% of young women who started taking VPA during adolescence had either PCO or hyperandrogenism

VPA & PCOS (cont.)

- Other studies describing high rates of PCOS in women with epilepsy treated with VPA:
  - Murialdo et al., 1997
  - Murialdo et al., 1998
  - Isojarvi et al., 1998
- 3 pilot studies have investigated PCOS in women with bipolar disorder treated with VPA:
  - 2 found an association between VPA and PCOS (O’Donovan et al., 2002) or hyperandrogenism (McIntyre et al., 2003)
  - 1 found no association (Rasgon et al., 2000)

VPA & PCOS: Caveats

- Two earlier studies document an association between epilepsy (treated and untreated) and reproductive endocrine disorders, including PCOS (Bilo et al., 1988; Herzog et al., 1986)
- PCOS is a relatively common condition in the general population of women, with an estimated prevalence of 2-22% (Chappell et al., 1999)

VPA & PCOS: Debate

- Geller (1997 [Letter]) argues that because of the risk of PCOS, DVP is not a useful agent in young females with bipolar disorder
  
  *On the other hand…*
  
  - Kowatch et al., 2005:
    - Treatment guidelines include VPA as a first-line treatment for PBD, without reference to the sex of the child or adolescent
    - “In short, until more rigorous data are available, no definitive conclusions can be drawn about DVP and PCOS in the treatment of [bipolar disorder].”

VPA & PCOS: More Rigorous Data

- Joffe et al., 2006a:
  - Cohort study of 230 women (18-45 years old) with bipolar disorder who participated in STEP-BD
  - Compared the incidence of hyperandrogenism with oligoamenorrhea (O+H) that developed while taking valproate vs. other anticonvulsants or lithium

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Joffe et al., 2006a (cont.)

• Results:
  – Incidence of O+H:
    • VPA (10.5%) > other mood stabilizers (1.4%) (p=0.002)
  – Oligomenorrhea always began within 12 months of VPA use
  – compared with VPA users who did not develop O+H, those who did develop O+H were:
    • Younger (mean 25 vs. 31 years, p=0.02)
    • Taking more psychotropic medications (p=0.03)

Follow-Up to Joffe et al., 2006a

• Joffe et al., 2006b:
  – Follow-up assessments (mean 17 months) were completed in 14 women treated with VPA:
    • 5 with treatment-emergent PCOS
    • 9 on VPA ≤ 6 months
  – Of 7 women who developed VPA-associated PCOS, reproductive features of PCOS…
    • Remitted in 3/4 discontinuing VPA
    • Persisted in all 3 continuing VPA

VPA & PCOS: What to Do

• Female patients taking VPA should be carefully monitored for early signs of PCOS, including:
  – Menstrual irregularities, hirsutism, acne, alopecia, and changes in BMI
  – If these signs are present, consider pelvic US and GYN consultation
  – Pelvic US has not been recommended for routine monitoring of female patients taking VPA, especially because ovarian cysts may occur in healthy females without PCOS as a normal variant (Piontek & Wisner, 2000)

Contraindications

• Hypersensitivity to the drug
• Hepatic disease or significant hepatic dysfunction
• Urea cycle disorders
  – Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate in patients with UCDs
• Presence of the HLA-B*1502 allele (see seminar on “Carbamazepine and Other Anticonvulsants” for further details)
• Pregnancy (relative contraindication) – IQ lowering, birth defects

Drug Interactions: General Considerations

• Drugs that ↑ the expression of hepatic enzymes, particularly those that elevate levels of glucuronid transferases, may ↓ VPA levels:
  – Examples: phenytoin, carbamazepine, phenobarbital

• Combining VPA with drugs that exhibit extensive protein binding may result in altered serum drug levels:
  – Examples: ASA, carbamazepine, warfarin, phenytoin, diazepam

Drug Interactions: Carbamazepine

• The combination of CBZ and valproate (VPA) usually requires:
  – ↓ in the dose of CBZ, because VPA…
    a) displaces CBZ from its protein binding sites
    b) ↑ levels of the active CBZ-10,11 epoxide (not measured by routine serum CBZ assay) by inhibiting the epoxide hydroxylase
  – ↑ in the dose of VPA, because CBZ induces its metabolism
Drug Interactions: Other Anticonvulsants

- Effect of VPA on the levels of other anticonvulsants:
  - ↑ lamotrigine levels
  - When LTG and DVP are combined, the dose of LTG should be half the usual dose, irrespective of the dose of DVP (Kanner & Frey, 2000)
  - ↓ phenytoin levels
  - ↑ phenobarbital levels

Drug Interactions: Other Psychotropics

- Antipsychotics, MAOIs, TCAs, alcohol:
  - Worsening of CNS depression when used with VPA
- SSRIs:
  - Some evidence suggests that SSRIs inhibit the metabolism of VPA
- Benzodiazepines:
  - VPA may ↓ oxidative metabolism of some benzodiazepines, resulting in ↑ levels
  - VPA not only inhibits the metabolism of diazepam, but it also displaces diazepam from its plasma albumin-binding sites, increasing the free fraction of diazepam by 90%

Drug Interactions: Other Drugs

- ASA:
  - ↓ in protein binding of valproate (VPA)
  - Inhibition of metabolism of VPA
  - Both drugs affect coagulation
- Cimetidine:
  - Inhibition of metabolism of VPA

No Drug Interactions

- Valproate does NOT interact significantly with the following commonly used drugs:
  - Acetaminophen
  - Clozapine
  - Lithium
  - Lorazepam
  - Oral contraceptives

Pre-treatment Work-up

- Medical history & physical exam
- Labs:
  - CBC, LFTs, and (?) serum amylase
  - Serum ammonia (suggested)
  - Fasting lipid profile (suggested)
  - (?) TFTs
  - Given the possible ↑ risk of SJS/TEN, consider HLA-B*1502 genotyping in individuals of Asian ancestry
  - Pregnancy test for menstruating females

Monitoring

- VPA levels as necessary for dose titration:
  - Epival: measure trough VPA level 8-12 hours after last dose
  - Epival ER: measure trough VPA level about 24 hours after last dose
  - Check VPA level 4-5 days after starting medication or adjusting dose, so that it’s at steady state
- VPA level, CBC, LFTs, and (?) serum amylase:
  - Monthly for the first 3 months, at 6 months, and every 3-6 months thereafter
Monitoring (cont.)

- Coagulation profile before surgical procedures or if ⬆ bleeding tendency is observed (Gerstner et al., 2006):
  - Platelet count, thrombelastography, PT, aPTT, TT, fibrinogen, von Willebrand factor, factor XIII

- Fasting lipid profile (suggested):
  - At 3 months and every 6 months thereafter

- (?) TFTs

Monitoring (cont.)

- Serum ammonia:
  - If patient develops vomiting, lethargy, or changes in mental status, check serum NH₃ to assess for hyperammonemic encephalopathy
  - The CPS does not explicitly recommend routine monitoring of serum NH₃, but it indicates that if asymptomatic elevation of serum NH₃ persists, discontinuation of DVP should be considered; this implies that serum NH₃ should be checked periodically in asymptomatic patients
  - Therefore, suggest routine monitoring of NH₃ at 3 months and every 6 months thereafter

Monitoring (cont.)

- Evidence of suicidality or depression (as with all anticonvulsants in all age groups)

- Weight and height

- In females, monitor clinically for early signs and symptoms of PCOS

Dosing

- Desired serum level:
  - Based on adult studies, the therapeutic range for mania is 50-125 µg/mL or ~350-865 µmol/L (1 µg/mL = 6.934 µmol/L)

- Therapeutic doses generally range from 375 to 2000 mg/day:
  - In the negative DBPC trial by Wagner et al., 2009, the mean modal daily dose of DVP ER was 24.3 mg/kg (1,286 mg)

Dosing (cont.)

- To achieve equivalent serum levels, Epival ER needs to be given at doses 8-20% higher than the total daily dose of Epival

- Epival may be given in 2 or 3 divided doses

- Epival ER should be given once daily (usually at bedtime)

Dosing (cont.)

- Gradual titration (e.g., for outpatients):
  - Start 125-250 mg po qhs
  - ⬆ by 125-250 mg/day every 3-4 days to achieve desired serum VPA levels

- Loading (consider for inpatients):
  - Start with 15 mg/kg/day
  - In adolescents, this is likely to produce a serum level of 350-830 µmol/L by day 5
  - However, because children ≤10 years clear VPA 50% faster than patients ≥10 years, the same loading strategy may produce lower serum levels in younger children

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Carbamazepine

Indications
- HC has approved CBZ for epilepsy, trigeminal neuralgia, acute mania, and prophylactic treatment in bipolar disorder
- The FDA has approved CBZ for epilepsy and trigeminal neuralgia, but not mania or bipolar disorder
- For treating epilepsy, the CPS (Canada) provides dosage recommendations down to age 6 years, whereas the PDR (USA) provides dosage recommendations for <6 years (no minimum age indicated)
- For treating bipolar disorder, the CPS makes no reference to children or adolescents

Psychiatric Uses
- Clinically, CBZ has been used in children, adolescents, and adults to treat:
  - Bipolar disorder
  - Aggression
  - Conduct disorder

Pharmacodynamics
- CBZ possesses some structural similarity to the TCA imipramine (in fact, CBZ was first synthesized as a potential antidepressant)
- Mechanisms for CBZ’s anticonvulsant and mood-stabilizing properties remain unclear

Pharmacodynamics (cont.)
- Nonetheless, CBZ has multiple effects that may be involved in its mechanisms of action:
  - CBZ has been described to have “antikindling” activity, probably via potentiation of GABA<sub>B</sub> receptor agonists
  - CBZ may act as an antagonist of A1 adenosine receptors
  - CBZ may inhibit α<sub>2</sub>-adrenergic receptors, thereby ↑ the release of NE into the synaptic cleft
  - CBZ ↓ calcium influx into glial cells and neurons through the NMDA receptor
  - CBZ blocks sodium channels in many brain regions

Pharmacokinetics
- PK parameters of CBZ are generally similar in children compared with adults
- However, in children…
  - CBZ dosage correlates poorly with plasma concentration
  - CBZ elimination may be slightly faster; therefore, children may require higher weight-adjusted doses compared with adults

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Pharmacokinetics (cont.)

- CBZ is available in Canada as a conventional tablet, a chewtab (cherry-mint flavour), a suspension (citrus-vanilla flavour), and a controlled-release tablet (Tegretol CR)
- $T_{\text{max}}$ (with chronic administration):
  - Conventional and chewable tablets: 4-5 hrs
  - Suspension: 1.5 hrs
  - Controlled release tablet: 3-12 hrs
- The absorption of CBZ from the GI tract is not influenced by the ingestion of food
- Protein-binding: 70-80%

Pharmacokinetics (cont.)

- A major metabolic pathway is oxidation of CBZ by CYP3A4 to its primary metabolite, the pharmacologically active CBZ-10,11-epoxide
- CBZ induces CYP3A4 and CYP2C19

Pharmacokinetics (cont.)

- Repeated administration leads to autoinduction of hepatic enzymes, which is usually complete after 3-5 weeks. Consequently...
  - $T_{1/2} = 25-65$ hrs after a single dose
  - $T_{1/2} = 12-17$ hrs during chronic treatment
- About 70% is excreted in the feces and 30% in the urine, with only 2-3% excreted unchanged in the urine

Efficacy: Bipolar Disorder

- No randomized, placebo-controlled trial of CBZ for the treatment of pediatric bipolar disorder has been published

Efficacy: Bipolar Disorder (cont.)

- A few case reports suggest that CBZ may be beneficial in pediatric bipolar disorder:
  - Tuzun et al., 2002
  - Craven & Murphy, 2000
  - Woolston, 1999
- However, other case reports suggest that CBZ may precipitate mania in children (recall that CBZ is structurally similar to imipramine):
  - Myers & Carrera, 1989
  - Pleak et al., 1988
  - Reiss & O’Donnell, 1984

Efficacy: Bipolar Disorder (cont.)

- Bouvard et al., 1993:
  - 11 youth (10-17 years old) with bipolar disorder
  - Open treatment with CBZ for >1 year
  - 7 “positive” responders, 2 “moderate” responders, and 2 who did not respond
  - CBZ was well tolerated and did not have to be discontinued in any patient
Efficacy: Bipolar Disorder (cont.)

• Ginsberg, 2006:
  – Retrospective chart review of extended-release CBZ in 300 outpatient youth (4-17 years old) with bipolar disorder (type I, type II, or NOS)
  – Outcome measure: CGI-Improvement
  – Results:
    • Response rate: 76%
    • Most common adverse events: somnolence (10%), nausea (6%), dizziness (5%), and rash (4%)
    • 1 patient nearly developed SJS
    • 8 patients attempted suicide, including 1 completed suicide

• Joshi et al., 2010:
  – Prospective open 8-week study of carbamazepine ER monotherapy for pediatric bipolar disorder with mania
  – 27 outpatient children 6-12 years (70% male) with bipolar I (82%). bipolar II or bipolar disorder NOS
  – High co-morbidity: depression (67%), ADHD (82%)
  – 1st outcome measures: YMRS, CGI-I, CDLS & BPRS
  – "Modest" anti-manic effects, "stronger" improvements for depression, ADHD & psychosis
  – Reported as efficacious and well tolerated, but 11 (41%) children dropped out due to adverse effects (rash, GI, neurological) or lack of response (or worsening of mania)
  – No lab abnormalities or weight gain

• Findling & Ginsberg, 2014:
  – Open trial of extended-release CBZ in 157 youth aged 10-17 years with an acute manic or mixed episode
  – 5 week titration then 21 week treatment
  – Outcome measure: YMRS
  – Results:
    • 66 (42%) completed the entire study
    • 26 subjects discontinued due to adverse effects including rash, decreased WBC, nausea, vomiting
    • Most common AEs were headache (n=41) and somnolence (n=30)
    • YMRS decreased from 28.6 (SD 6.2) at baseline to 13.8 (SD 9.4) (P<0.0001) at endpoint

Efficacy: CD & Aggression

• Kafantaris et al., 1992:
  – Open pilot study of CBZ in 10 hospitalized children (5-10 years old; 9 boys, 1 girl) with a diagnosis of CD who were aggressive and explosive
  – CBZ treatment was associated with clinically and statistically significant ↓ in the target symptoms of aggressiveness and explosiveness
  – Optimal daily doses of CBZ ranged from 600 to 800 mg/day
  – Plasma levels at post-treatment rating ranged from 4.8 to 10.4 µg/mL (20.3 to 44.0 µmol/L)

• Cueva et al., 1996:
  – DBPC trial of CBZ in 22 children (5-11 years old) with a diagnosis of CD who were hospitalized for treatment-resistant aggressiveness and explosiveness
  – CBZ dose range: 400-800 mg/day (serum levels: 5.0-9.1 µg/mL [21.2-38.5 µmol/L])
  – CBZ vs. PBO on all efficacy outcome measures
  – CBZ was associated with considerable adverse effects; the most common were transient moderate & marked leukopenia, rash, dizziness, and diplopia

Li vs. DVP vs. CBZ for PBD

• Kowatch et al., 2000:
  – Randomized, open study comparing Li, DVP, and CBZ for pediatric bipolar disorder
  – 42 outpatient children and adolescents:
    • 20 with bipolar I disorder, 22 with bipolar II disorder
    • Mixed or manic episode
  – Primary outcome measures: YMRS and CGI-I
  – Response rates:
    • Li=38%, DVP=53%, CBZ=38% (p=0.6)
  – Effect sizes (using YMRS change from baseline)
    • Li=1.1, DVP=1.6, CBZ=1.0

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CBZ for Aggression:
- Canadian Guidelines on Pharmacotherapy for Disruptive and Aggressive Behaviour in Children and Adolescents With ADHD, ODD, or CD (Gorman et al., 2015)
- CBZ for Aggression in Children and Adolescents With CD
  - Quality of evidence: very low
  - Magnitude of benefit: none
  - Side effect burden: major
  - Strength of recommendation: strong, against ↓↓

Adverse Effects: General Comments
- Suicidality as for all AEDs (see slides 5-7)
- CBZ has been found to be better tolerated than DVP as long-term monotherapy in children with epilepsy or febrile convulsions (Herranz et al., 1988)
- However, in the study by Kowatch et al. (2000) involving children and adolescents with bipolar disorder randomized to Li, DVP, or CBZ:
  - Combined rates of nausea and sedation were highest for CBZ

Adverse Effects: Neurological
- Diploplia (often remits spontaneously or after dose reduction)
- Glare sensitivity
- Exacerbation of seizures or worsening of the EEG (mechanism unclear)
- Vertigo
- Nystagmus
- Drowsiness

Adverse Effects: Cognitive
- Henin et al., 2009:
  - 173 children and adolescents (6-17 years) with ‘DSM IV’ bipolar d/o given neuropsychological assessment as part of entry into clinical trial
  - 66 receiving naturalistic treatment with 4 classes of meds (MSs, SGAs, stimulants, ADs)
  - those treated with MSs (lithium & AEDs, n=21) showed impairments in processing speed and working memory relative to unmedicated bipolar d/o patients

Adverse Effects: Hematological
- Common, benign, nonprogressive, dose-related leukopenia:
  - 1-2% of adults
  - 13% of a sample of 220 children <16 years, with spontaneous reversal occurring in three-quarters (Pellock, 1987)
- Dose-related and often transient thrombocytopenia that may not require dose reduction or discontinuation

Adverse Effects: Hematological (cont.)
- Rare, idiosyncratic, dose-unrelated leukopenia that progresses to agranulocytosis or aplastic anemia
  - 1:125,000 overall (not just children)
  - Fatal in 1:500,000 overall (Trimble, 1990)
  - Medical emergency; discontinue CBZ immediately

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Adverse Effects: Dermatological

- Benign rashes are common with CBZ treatment (5-15% of individuals), especially in the first 1-3 weeks of treatment
- However, in rare instances the rash may progress to exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis (Levi et al., 2009)
- >90% of patients treated with CBZ who develop SJS/TEN do so within the first few months of treatment

Adverse Effects: Dermatological (cont.)

- Because one cannot predict which rashes will be benign and which will progress to more serious ones, CBZ should be discontinued if even a benign-appearing CBZ-related rash develops
- Nonetheless, many patients who develop a CBZ-related rash and discontinue the medication will not have reemergence of the rash upon re-exposure to CBZ

HC Warning (March 2008) for CBZ: Serious Rashes & HLA-B*1502

- “The risk of SJS and TEN exists in all patients, but these reactions are generally very rare. However, in some Asian countries the risk is estimated be approximately 10 times higher than in Western countries.”
- “In studies that included small samples of patients of Han Chinese ancestry a strong association was found between the risk of developing SJS/TEN and the presence of HLA-B*1502”

HC Warning (cont.)

- “The HLA-B*1502 allele is found almost exclusively in individuals with ancestry across broad areas of Asia. Therefore, physicians should consider HLA-B*1502 genotyping as a screening tool in genetically at-risk patients.”
  - Note: the prevalence of HLA-B*1502 is ~5-10% in Han Chinese, and ranges from <1% to >15% in other Asian ethnic populations
- “Until further information is available, the use of Tegretol and other anti-epileptic drugs associated with SJS/TEN [emphasis added] should be avoided in patients who test positive for the HLA-B*1502 allele.”

Adverse Effects: Renal & Cardiac

- Renal:
  – Because CBZ has direct or indirect agonist-like effects at the vasopressin receptor, some individuals may develop hyponatremia (Dong et al., 2005: 13.5% with Na<134 mEq/L & 2.8% with Na<128 mEq/L)
- Cardiac:
  – Although CBZ’s cardiac effects generally are not prominent, CBZ does ↓ atrial ventricular conduction and is relatively contraindicated in patients with heart block
  – Bradycardias and syncopal episodes have been reported in rare instances

Adverse Effects: Hepatic & Metabolic

- Hepatic:
  – Hepatitis is extremely rare
  – Camfield & Camfield (1985) found that 9% of children on CBZ had mildly elevated AST
- Metabolic:
  – Long-term treatment with CBZ is associated with a small amount of weight gain
  – Possible lipid abnormalities, but the evidence is mixed (Szézier et al., 1997; Verottti et al., 1996; Voudris et al., 2006; Sonmez et al., 2006; Castro-Cago et al., 2006)
Adverse Effects: Endocrine

- Thyroid (Verotti et al., 2009):
  - ↓ T4 & ↓ fT4, but normal T3, fT3, and TSH
  - However, these thyroid hormone alterations are not generally associated with clinical hypothyroidism
- Calcium metabolism (Mintzer et al., 2006; Nicolaidou et al., 2006; Chou et al., 2007):
  - ↓ 25-hydroxyvitamin D, possibly ↑ serum parathyroid hormone, and ↓ bone density

Contraindications

- Hypersensitivity to CBZ or to any of the TCAs (since CBZ is structurally similar to imipramine)
- Presence of the HLA-B*1502 allele
- Hepatic disease
- History of bone marrow depression or other serious blood disorder
- History of acute intermittent porphyria
- AV block
- Concurrent MAOI
- Pregnancy (relative contraindication)

Drug Interactions

- Because CBZ induces and is metabolized by CYP3A4, it interacts with drugs that are CYP3A4 substrates, inhibitors, or inducers (see tables)
- Because CBZ induces CYP2C19, it lowers levels of drugs that are metabolized by this enzyme
- Because CBZ is structurally similar to imipramine, it should not be used with MAOIs
- Combined use of CBZ with Li, haloperidol, or metoclopramide may ↑ the risk of neurotoxic side effects (even in the presence of “therapeutic” plasma levels)

Drug Interactions: Carbamazepine

- The combination of CBZ and DVP usually requires:
  - ↓ in the dose of CBZ, because DVP...
    - a) displaces CBZ from its protein binding sites
    - b) ↑ levels of the active CBZ-10,11-epoxide (not measured by routine serum CBZ assay) by inhibiting the epoxide hydroxylase
  - ↑ in the dose of DVP, because CBZ induces its metabolism

Drug Interactions (cont.)

- Avoid combining CBZ with clozapine because of the additive risk of agranulocytosis
- Concurrent use of CBZ and isoniazid may increase the risk of isoniazid-induced hepatotoxicity
- Because CBZ may reduce tolerance to alcohol, the CPS advises abstaining from alcohol during CBZ treatment
Table 31.8a-2 Carbamazepine Decreases Serum Concentrations of Other Drugs Via Prominent Induction of CYP3A4 (continued)

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Antivirals</th>
<th>Immuno-suppressants</th>
<th>Muscle relaxants</th>
<th>Steroids</th>
<th>Stimulants</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>Delavirdine</td>
<td>Cyclosporine</td>
<td>Doxacurium</td>
<td>Mifepristone</td>
<td>Bepridil</td>
<td>Dihydropyridine calcium channel blockers</td>
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<td>Doxycycline</td>
<td>Protease inhibitors</td>
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Table 31.8a-5 Drugs That Increase Serum Concentrations of Carbamazepine

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Hypolipidemics</th>
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<tbody>
<tr>
<td>Fluoxetine</td>
<td>Gemfibrozil</td>
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<tr>
<td>Fluvoxamine</td>
<td>Nicotinamide</td>
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<tr>
<td>Nefazodone</td>
<td>Others</td>
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<td>(enlarged slide appended)</td>
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</table>

Pre-treatment Work-up

- Medical history & physical exam
- Labs:
  - HLA-B*1502 genotyping in individuals of Asian ancestry
  - CBC (with differential, platelet count, and possibly reticulocytes and serum iron)
  - LFTs
  - BUN & creatinine
  - Electrolytes
  - Fasting lipid profile (suggested)
  - (?TFTs
  - Pregnancy test for menstruating females
  - Urinalysis

Monitoring

- Monitor closely for rash, and if one develops, discontinue CBZ
- Evidence of suicidality or depression (as with all anticonvulsants in all age groups)
- CBZ levels:
  - As necessary during dose titration (mainly to minimize risk of toxicity)
  - Monthly for the first 3 months, at 6 months, and every 3-6 months thereafter
- CBC:
  - At 2 weeks, 1 month, 2 months, 3 months, and every 3-6 months thereafter

Monitoring (cont.)

- BUN & creatinine, electrolytes, and LFTs:
  - Monthly for the first 3 months, at 6 months, and every 3-6 months thereafter
- Fasting lipid profile (suggested):
  - At 3 months and every 6 months thereafter
- (?)TFTs
- "Periodic" urinalysis (per CPS)
- Be aware that treatment with CBZ may result in:
  - False-negative pregnancy tests if HCG is being assayed
  - False-positive ketones in urine

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)
Monitoring CBZ Levels

- Because of hepatic enzyme autoinduction, CBZ levels drawn during the first several weeks of treatment, or when the dose is changing, should be interpreted cautiously.
- Monitoring of the active CBZ-10,11-epoxide metabolite may also be required, as serum CBZ levels alone may not be adequate to detect toxicity in some patients.
- Total CBZ metabolite serum levels >9 µg/ml (38 µmol/L) are associated with greater side effects.

Monitoring for Leukopenia

- If WBC ↓ to <2,000/mm³, then gradual tapering and discontinuation of CBZ is recommended (Cueva et al., 1996).
- Because of the very low risk of agranulocytosis and aplastic anemia, monitor for:
  - Bruising or bleeding
  - Sore throat
  - Fever
  - Lethargy
  - Mouth ulcers

Dosing

- Take with food if possible to minimize nausea.
- Starting dose:
  - >12 yrs: 100-200 mg po QD-BID
  - 6-12 yrs: 50 mg po BID
  - <6 yrs: 25-50 mg po BID or 5 mg/kg/day
- For children ≥6 yrs, increase q5-7 days by 100 mg/day
- For children <6 yrs, increase q5-7 days by 50-100 mg/day or 5 mg/kg/day

Dosing (cont.)

- Maximum dose:
  - <12 yrs: 1000 mg/day
  - ≥12 yrs: 1200 mg/day
- Usual maintenance dose: 10-20 mg/kg/day administered BID or TID
- Conventional tablets, chewtabs, and suspension should be dosed BID-QID
- Tegretol CR is generally dosed BID, but sometimes TID may be necessary

Dosing (cont.)

- Target plasma level for seizure control:
  - 4-12 µg/mL or 17-51 µmol/L (1 µg/ml = 4.23 µmol/L)
- CPS indicates that “plasma levels are probably not helpful for guiding therapy in bipolar disorders”; however, they are still useful to minimize risk of toxicity.
- Time to reach steady state:
  - Up to 2 weeks after initially starting CBZ
  - With chronic treatment, 3-4 days after adjusting dose (recall that autoinduction results in shorter T½)
- Trough level is generally drawn in the morning, about 12 hours after last dose

Discontinuing CBZ

- Abrupt discontinuation of CBZ may result in symptoms of withdrawal, such as anxiety, muscle twitching, tremors, weakness, nausea, and vomiting.
- Gradual tapering of the drug is therefore recommended, e.g., ↓ dose by 10% each day (or even more gradually).
Oxcarbazepine

Indications & Clinical Use

• Approved Uses:
  – Treatment of partial seizures in adults and children (≥6 years per HC, ≥4 years per FDA) with epilepsy
  – Clinically, OXC has also been used to treat bipolar disorder in adults and children

Indications & Clinical Use (cont.)

• In most current treatment guidelines for PBD (Kowatch et al., 2005), OXC is included at Stage 5 of the pharmacologic algorithm (after combined treatment with 3 first-line agents, and just before ECT or clozapine)
• These guidelines were published before publication of a large DBPC trial of OXC for PBD that was negative (Wagner et al., 2006)

Pharmacodynamics

• OXC is a 10-keto analogue of CBZ
• Although OXC and CBZ have very different PK profiles, they have a similar clinical spectrum of efficacy in seizure, pain, and mood disorders
• The pharmacological activity of OXC is exerted primarily through the 10-monohydroxy metabolite (MHD)

Pharmacodynamics (cont.)

• The mechanisms of action of OXC and MHD remain unclear, but they have several effects that have been implicated:
  – Blockade of voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and ↓ propagation of synaptic impulses
  – ↑ potassium conductance
  – Modulation of high-voltage-activated calcium channels
• No significant interactions of OXC or MHD with brain neurotransmitter or modulator receptor sites have been demonstrated

Pharmacokinetics

• OXC is completely absorbed, and taking it with food has no effect on absorption
• OXC is extensively metabolized by cytosolic enzymes in the liver to MHD, which in turn is metabolized by glucuronidation
• Because only 60% of OXC and 40% of MHD is protein-bound, clinically significant interactions with other drugs through competition for protein binding sites are unlikely
Pharmacokinetics (cont.)

- Adults:
  - $T_{\text{max}}$: OXC=4.5 hrs, MHD=6 hrs
  - $T_{1/2}$: OXC=2 hrs, MHD=9 hrs

- Children:
  - After single-dose administration of OXC, AUC values of MHD are 30-40% lower in children <8 years than in children >8 years, whose clearance approaches that of adults.

- OXC has minimal or no autoinduction and far fewer CYP450 interactions compared with CBZ.
- Mild-to-moderate hepatic impairment does not affect the PK of OXC or MHD, and therefore no dose adjustment is required.
- 95% is excreted in the urine in the form of metabolites.
- Because ~50% is excreted in the urine as MHD, which is pharmacologically active, dose reduction is required in individuals with renal impairment.

Pharmacokinetics (cont.)

Efficacy: Adult Bipolar Disorder

- 5 small controlled studies, including 2 DBPC trials, suggest that for adult mania OXC is superior to PBO and has an efficacy comparable to that of VPA, Li, and haloperidol (Hirschfeld & Kasper, 2004): Emrich et al., 1983 (DBPC); Emrich et al., 1984 & 1985 (DBPC); Müller & Stoll, 1984; Emrich, 1990 (2 studies).

Efficacy: Pediatric Bipolar Disorder

- 3 case reports of youths with bipolar disorder described a positive response to OXC (Davanzo et al., 2004; Teitelbaum, 2001).
- 1 case report of an adolescent with various diagnoses (ADHD, ODD, IED, mood symptoms, cognitive deficits) indicated that aggression responded well to OXC (Gaudino et al., 2003).

Efficacy: PBD (cont.)

- MacMillan et al., 2006:
  - Review of medical records for youths with PBD and severe aggression treated with DVP (n=20) or OXC (n=11).
  - Outcome measure: CGI at 4 months.
  - Results:
    - DVP > OXC ($p=0.007$)
    - Patients on DVP improved significantly from baseline, but patients on OXC did not.
    - Rates of discontinuation due to adverse events were similar in the two groups, but more discontinuations due to worsening aggression occurred with OXC ($p=0.04$).
Efficacy: PBD (cont.)

- Wagner et al., 2006:
  - Multisite DBPC trial in 116 pediatric outpatients, 7-18 years old, with bipolar I disorder, manic or mixed episode
  - Randomized to 7 weeks of OXC or PBO
  - Primary efficacy measure: mean change from baseline to endpoint in the YMRS

Wagner et al., 2006: Efficacy Results

- No significant difference in YMRS improvement: OXC=-10.9 vs. PBO=-9.8

Wagner et al., 2006: Adverse Event Results

- Discontinuations due to adverse events: OXC=19% vs. PBO=4%
- “Serious” adverse events: OXC=6 vs. PBO=0
  - 3 of the 6 events were suspected to be related to the OXC (worsening of bipolar disorder, aggressive behaviour, and a suicide attempt)
- No clinically significant group differences were noted in physical exam, V.S., lab tests, or ECG
- None of the patients developed hyponatremia

Wagner et al., 2006 (cont.)

- Critique of the study:
  - About 1/3 of subjects in each group were on a stimulant, which may have interfered with mood stabilization (Waslick, 2006 [letter]; Lysne et al., 2006 [letter])
  - Wagner’s response (Wagner et al., 2006 [letter]):
    - The investigators had the option of discontinuing stimulants prior to randomization if they thought that stimulants were exacerbating the subject’s mania
    - The presence of concurrent ADHD and stimulant treatment did not affect baseline ratings of psychopathology or treatment response

Adverse Effects: Common

- Somnolence, fatigue
- Dizziness
- Diplopia, abnormal vision, nystagmus
- Ataxia, abnormal gait
- Tremor
- Headache
- Rash
- Nausea and vomiting
- Abdominal pain, dyspepsia
- Hyponatremia (dose-related)
- Possible lipid abnormalities (Franzoni et al., 2006)
- ↓ T4, ↓ T3, ↓ T3 & ↓ rT3 without a change in TSH, although the clinical significance is uncertain (Cansu et al., 2006)
- ↓ 25-hydroxyvitamin D & possibly ↑ serum parathyroid hormone (Mintzer et al., 2006)

Adverse Effects: Rare but Serious

- Rare cases, some fatal, of serious dermatologic reactions:
  - Include SJS and TEN (median time to onset was 19 days after starting OXC)
  - Reporting rate of SJS and TEN with OXC treatment is considered an underestimate of the actual rate, but it still exceeds the background rate (0.5-6 cases per million-person years) by 3- to 10-fold
  - A strong association has been found between the risk of developing SJS/TEN and the presence of the HLA-B*1502 allele, which is found almost exclusively in individuals with Asian ancestry, especially Han Chinese (see slides 108 & 109)
Adverse Effects:
Rare but Serious (cont.)

- Suicidality (see slides 5-7)
- Rare cases of multi-organ hypersensitivity within 2 months of starting OXC
- Very rare cases of hepatitis and hepatic failure
- Case report of priapism in an adolescent (Negin & Murphy, 2005)

Table 31.8a-1 Comparative Effects of Carbamazepine and Oxcarbazepine

<table>
<thead>
<tr>
<th>CBZ</th>
<th>OXC</th>
<th>Comment on OXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic enzyme induction 3A4</td>
<td>+++ 6.5%</td>
<td>No autoinduction</td>
</tr>
<tr>
<td>Benign decrease in white blood cells</td>
<td>+++ 2.5%</td>
<td>No general white blood cell suppression</td>
</tr>
<tr>
<td>Cross-sensitization from carbamazepine</td>
<td>N/A</td>
<td>Lower rate</td>
</tr>
<tr>
<td>Benign rash</td>
<td>N/A</td>
<td>Low, 25-30%</td>
</tr>
<tr>
<td>Severe rash</td>
<td>N/A</td>
<td>Very rare cases of hepatitis and hepatic failure</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>+/-</td>
<td>Very rare cases of hepatitis and hepatic failure</td>
</tr>
<tr>
<td>Teratogenic (spina bifida)</td>
<td>1-3%</td>
<td>High?</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>1 per million</td>
<td>Low, 25–30%</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1 per million</td>
<td>Low, 25–30%</td>
</tr>
</tbody>
</table>

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)

Contraindications

- Hypersensitivity to OXC
- Caution in patients who have had hypersensitivity reactions to CBZ, as 25-30% will also have hypersensitivity reactions to OXC
- AV block
- Caution in patients with cardiac conduction abnormalities or patients taking medications that depress AV conduction
- Presence of the HLA-B*1502 allele
- Pregnancy (relative contraindication)

Drug Interactions

- OXC has far fewer CYP450 interactions compared with CBZ
- Nonetheless, several AEDs that are CYP450 inducers (e.g., CBZ, phenobarbital, phenytoin) can ↓ plasma levels of OXC and MHD (see slide 153)
- Verapamil also ↓ MHD levels by 20%
Pre-treatment Work-up

• Medical history & physical exam
• Labs:
  – HLA-B*1502 genotyping in individuals of Asian ancestry
  – Serum Na
  – Fasting lipid profile (suggested)
  – (?) TFTs
  – Pregnancy test for menstruating females

Monitoring

• Monitor closely for rash, and if one develops, discontinue OXC because of the risk of progression to SJS or TEN
• Evidence of suicidality or depression (as with all anticonvulsants in all age groups)

Monitoring (cont.)

• For patients with renal conditions or taking sodium lowering drugs, HC and the FDA recommend checking serum Na:
  – 2 weeks after starting OXC
  – Then monthly for 3 months
  – Then as clinically indicated

• For patients without those risk factors, HC and the FDA recommend checking patients’ serum Na only “as part of their routine laboratory studies”

Monitoring (cont.)

• However, given how frequently OXC causes hyponatremia, strongly consider Na monitoring for ALL children and adolescents treated with this medication:
  – 2 weeks after starting OXC
  – Then monthly for 3 months
  – Then every 3-6 months thereafter

Monitoring (cont.)

• Fasting lipid profile (suggested):
  – At 3 months and every 6 months thereafter

• (?) TFTs

Dosing

• The following dosing recommendations are based on treatment of seizures:
  – Children 4-16 yrs:
    • Start 8-10 mg/kg/day, dosed BID, generally not to exceed 600 mg/day
    • Over 2 weeks, titrate up to the target maintenance dose, which depends on the patient’s weight:
      – 20-29 kg: 900 mg/day
      – 29.1-39 kg: 1200 mg/day
      – >39 kg: 1800 mg/day
Dosing (cont.)

• Dosing for seizures (cont.):
  – Adults:
    • Start 300 mg po BID
    • ↑ by a maximum of 300 mg/day q3 days to 1200 mg/day
    • If patient has inadequate response and is tolerating the medication, consider further titration, at the same rate, to maximum dose of 2400 mg/day
    • However, at 2400 mg/day many patients cannot tolerate the medication, primarily because of CNS side effects

Wagner et al. (2006) used the following dosing strategy for the treatment of PBD (negative DBPC trial):
  – 2-week titration period
  – OXC was titrated upward by 300 mg q2 days to a maximum of 900-2400 mg/day based on body weight, or to the maximum dose tolerated
  – Mean dose for children 7-12 yrs: 1200 mg/day
  – Mean dose for adolescents 13-18 yrs: 2040 mg/day

Lamotrigine

Indications

• LTG is approved for:
  – Monotherapy or adjunctive therapy in adults (≥16 years old) with seizure disorders who have not responded adequately to other AEDs (HC & FDA)
  – Adjunctive therapy in children (≥9 kg per HC, ≥2 years old per the FDA) and adults with Lennox-Gastaut syndrome
  – Adjunctive therapy in children (≥2 years old) with partial seizures (FDA but not HC)
  – Maintenance treatment of bipolar I disorder in adults treated for acute mood episodes with “standard” therapy (FDA but not HC)

Clinical Uses in Psychiatry

• Clinically, LTG is used in adults and—far less often—in children and adolescents for:
  – Maintenance treatment in bipolar disorder
  – Treatment of bipolar depression

• In the current treatment guidelines for PBD, LTG is not included in the pharmacologic algorithm because of the lack of efficacy data and the risk of Stevens-Johnson syndrome (Kowatch et al., 2005)

Pharmacodynamics

• LTG’s mechanisms of action are unclear, but possible effects that have been implicated include:
  – Inhibiting the presynaptic excitatory release of glutamate and aspartate
  – Blocking presynaptic serotonin reuptake
  – Stabilizing neuronal membranes by blocking voltage-sensitive sodium channels
  – Blocking high-voltage-activated N- and P-type calcium channels
  – Preventing amygdala and cortical kindling
Pharmacokinetics

• LTG is rapidly absorbed in adults and children, but the rate of absorption is slightly ↓ when taken with food
• $T_{\text{max}} = 1$-6 hrs in adults and children
• LTG is 55% protein-bound
• LTG does not displace other AEDs from protein binding sites, and other AEDs do not displace LTG from protein binding sites

Pharmacokinetics (cont.)

• In adults, $T_{\frac{1}{2}} = 33$ hrs after a single dose, but 26 hrs after repeated dosing for 2 weeks
• In a study of 296 youths aged 2-19 years, the LTG concentration/dose ratio ↓ by 6% per year of age, not adjusting for weight; therefore, older children need higher doses of LTG to achieve the same serum concentrations as younger children (Reimers et al., 2007)
• In addition, a linear relationship exists between weight and LTG clearance; therefore, heavier children require higher doses of LTG (Chen, 2000)

Pharmacokinetics (cont.)

• LTG is metabolized by glucuronidation, possibly by the UGT 1A4 system:
  – LTG levels are ↓ by UGT inducers (e.g., oral contraceptives, CBZ, phenytoin, phenobarbital, primidone)
  – LTG levels are ↑ by UGT inhibitors (e.g., VPA)
• LTG’s major metabolite is the inactive 2-N-glucuronide conjugate
• 94% is excreted in the urine (mostly as the 2-N-glucuronide conjugate), and 2% is excreted in the feces

Efficacy: LTG for Bipolar Disorder in Adults

• In adults, LTG is efficacious for treating bipolar depression (Calabrese et al., 1999) and rapid cycling (Calabrese et al., 2000)
• In adults, LTG is efficacious for preventing mood episodes in patients with bipolar disorder (Bowden et al., 2003; Goodwin et al., 2004)
• Treatment guidelines recommend LTG (in some circumstances combined with another mood stabilizer) as first-line treatment for adult bipolar depression, followed by quetiapine or olanzapine/fluoxetine combination (Calabrese et al., 2004; TMAP, 2005)

Efficacy: Pediatric Bipolar Depression

• Carandang et al., 2003:
  – Case series of 9 adolescents with refractory depressive disorders, including 6 with bipolar depression, who were treated with LTG
  – 8 responded well to LTG at a mean dose of 142 mg/day
• Thakur et al., 2005:
  – Case report of a 7½-year-old boy with bipolar disorder, mixed episode, who responded to LTG added to VPA and OLZ (the OLZ was subsequently discontinued)

Manic Switching with SRIs in PBD

• Some evidence suggests that SRIs ↑ the risk of manic switching in pediatric bipolar disorder:
  – Biederman et al., 2000
  – Cicero et al., 2003
  – Faedda et al., 2004
• Conflicting evidence, however, has also been reported:
  – Craney & Geller, 2003
• Nonetheless, because of the potential risk of manic switching with SRIs, LTG or Li may be a better choice for youth with bipolar depression
### Efficacy: Pediatric Bipolar Depression (cont.)

- **Soutullo et al., 2006:**
  - Chart review of 5 adolescents with bipolar depression treated with LTG for a mean of 28 weeks
  - Results:
    - CGI improved significantly from baseline to endpoint ($p=0.01$)
    - Improvement was marked or moderate in 4 patients and minimal in 1 patient
    - LTG was well tolerated

- **Chang et al., 2006:**
  - 8-week open trial of LTG in 20 adolescents (12-17 years old) with bipolar depression or a mixed episode
  - 7 subjects were taking other psychotropics
  - Primary outcome measure: CGI
  - Secondary outcome measure: CDRS-R

### Chang et al., 2006 (cont.)

- Results:
  - 19/20 subjects completed the trial
  - Mean LTG dose was 131.6 mg/day
  - Response rate:
    - 16/19 (84%) on the CGI
    - 12/19 (63%) on the CDRS-R
  - Remission rate:
    - 11/19 (58%)
  - No significant weight change, rash, or other adverse effects occurred during the trial

### Efficacy: Pediatric Bipolar “bipolar mood elevation”

- **Biederman et al., 2010:**
  - Prospective open trial for 12 weeks of n=39 outpatients aged 6-17 years, 90% bipolar I
  - Measures: YMRS, CGI, CDRS, BPRS
  - Results:
    - Only 22 subjects (56%) completed the trial, n=10 due to adverse effects
    - Statistically significant drop in all measures
    - 13 patients developed a rash, no SJS
  - Conclusion: LTG associated with “antimanic, antidepressant, antipsychotic and anti-ADHD responses in children and adolescents with bipolar and bipolar spectrum disorder”

### Efficacy: Adjunctive Maintenance Therapy for PBD

- **Findling et al., 2015:**
  - Multicentre, randomized withdrawal trial in 10-17 years olds with PBD-1
  - Open-label phase up to 18 weeks (n=298) then randomized to LTG (n=85) vs. PBO (n=87) up to 36 weeks
  - Subjects were already receiving “conventional bipolar disorder treatment” which could include MSs, antipsychotics and stimulants
  - Results:
    - Few subjects completed the trial: LTG n=20 and PBO n=21
    - Primary measure: mean time (days) to occurrence of a bipolar event (TOBE)
    - Depressed: LTG 155 vs. PBO 50
    - Manic/hypomanic: LTG 163 vs. PBO 120
    - Mixed: LTG 137 vs. PBO 107
    - Results did not reach significance
    - Dermatologic reactions (no SJS) and SI higher in LTG group than PBO group

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### Efficacy: Pediatric Bipolar Cognition

- **Pavuluri et al., 2010:**
  - Prospective open trial, n=34 bipolar patients matched to n=24 healthy controls (HC)
  - Neurocognitive battery at baseline and 14 wks
  - Bipolar patients treated with LTG
  - Results:
    - YMRS&CDRS improved significantly (both p<.001)
    - Global cognition improved in bipolar pts relative to HC, but overall performance still impaired
    - working and verbal memory improved in bipolar pts and no longer impaired relative to HC at follow up

### Efficacy: Autism

- **Belsito et al., 2001:**
  - DBPC trial of LTG for 12 weeks in 28 children (3-11 years old) with autistic disorder
  - No significant group differences were found on any outcomes:
    - Autism Behavior Checklist, Aberrant Behavior Checklist, Vineland Adaptability Behavior scales, PL-ADOS, CARS
  - Parent rating scales showed marked improvements in both groups
  - Adverse effects were similar in both groups

### Adverse Effects: General Comments

- LTG is generally well tolerated
- Unlike many other mood stabilizers, LTG typically does **not** cause:
  - Sedation
  - Cognitive dulling
  - Sexual problems
  - Weight gain

### Adverse Effects: Common

- **General:** fatigue, somnolence, insomnia, sweating, anxiety, weight loss, chest pain, flu syndrome, dream abnormality
- **Head & neck:** blurred vision, rhinitis, pharyngitis
- **Neurological:** ataxia, dizziness, diplopia, headache, incoordination
- **GI:** nausea, vomiting, dyspepsia, constipation, diarrhea
- **GYN:** dysmenorrhea
- **Dermatological:** benign rash (~5-10% risk)

### Risk of Benign Rash

- **Hirsch et al., 2006:**
  - 11% in children <13 years old vs. 4% in adolescents and adults (p<0.001)
  - Another anticonvulsant-related rash was the greatest risk factor for developing a rash with LTG:
    - 18% of children <13 years who had developed a rash with another anticonvulsant also developed a rash with LTG

### Risk of Serious Rashes: CPS Warning

"Serious rashes associated with hospitalization have occurred with the use of LTG. The incidence of these rashes in clinical trials was 1% in pediatric patients (age <16 years) [emphasis added] and 0.3% in adults. The incidence of serious rash reported as Stevens-Johnson syndrome in clinical trials was 0.5% in pediatric patients [emphasis added] and 0.1% in adults. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or death associated with rash have been reported, but their numbers are too few to permit a precise estimate of the rate."
Risk of Serious Rash: FDA Black Box Warning
• “...Because the rate of serious rash is greater in pediatric patients than in adults, it bears emphasis that LTG is approved only for use in pediatric patients below the age of 16 years who have seizures associated with the Lennox-Gastaut syndrome or in patients with partial seizures.”

Serious Rash: (cont.)
• Note that the HC and FDA warnings are based on data acquired before current slower titration guidelines were recommended
• More recent data suggest that the incidence of serious rash in children taking LTG may be only 1:10,000 (Messenheimer, 2002)
• Factors that ↑ the risk of serious rashes:
  – More rapid titration
  – Use of concomitant VPA
  – Presence of the HLA-B*1502 allele, which is found almost exclusively in individuals with Asian ancestry, especially Han Chinese (see slides 108 & 109)

Serious Rash: (cont.)
• Nearly all cases of serious rash associated with LTG have occurred within 2-8 weeks of starting it, but some cases have occurred after prolonged treatment (e.g., 6 months)
• Although benign rashes also occur with LTG, it is not possible to predict which rashes will prove to be life threatening; therefore, all patients who develop rash should be promptly evaluated and should discontinue LTG, unless the rash is clearly not drug-related

If You’re Still Not Scared Enough...
• Varghese et al., 2006:
  – Case series:
  1. woman with bipolar I disorder and 2 teenage girls with bipolar II disorder who were treated with LTG, developed TEN, and were admitted to a burn unit
  2. The 3 patients were admitted within a 12-month period to an institution that admits about 10-12 patients with TEN per year
  3. 2 of the 3 required ventilatory support
  4. Fortunately, they all improved within 8-32 days

Other Rare but Serious Risks
• Asceptic meningitis:
  – FDA warning issued based on 40 reported cases between Dec 2004 and Nov 2009 (~46 million scripts)
  – Most Sx resolved with discontinuation, in 15 cases Sx returned with resumption of LTG
  – Sx include: headache, fever, chills, nausea, vomiting, stiff neck, rash, light sensitivity, drowsiness, confusion
• Acute multiorgan or hepatic failure, in some cases fatal or irreversible:
  – 2 of 3,796 adult patients and 4 of 2,435 pediatric patients in clinical trials for treatment of seizures

Other Rare but Serious Risks (cont.)
• Withdrawal seizures:
  – In clinical trials of patients with bipolar disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LTG (confounding factors were present)
• Blood dyscrasias
• Suicidality (see slides 5-7)
• Hypersensitivity reactions, some fatal or life threatening
Contraindications

- Hypersensitivity to LTG
- Presence of the HLA-B*1502 allele
- Pregnancy (relative contraindication)

Pre-treatment Work-up

- Medical history & physical exam
- Labs:
  - HLA-B*1502 genotyping in individuals of Asian ancestry
  - Otherwise, HC and the FDA do not recommend any specific baseline lab tests
  - Some suggest CBC and LFTs
  - Pregnancy test for menstruating females

Drug Interactions

Reference: www.pdr.net

Monitoring

- Monitor closely for rash, and discontinue LTG if one develops
- Evidence of suicidality or depression (as with all anticonvulsants in all age groups)
- LTG levels are not routinely monitored, but if patients attain high doses (e.g., 400 mg/day) without significant benefit, consider checking a 12-hour trough level
- No specific lab monitoring is recommended by HC or the FDA, but consider periodic CBC and LFTs

Dosing

<p>| Table 31.8c-1 Gradual Introduction of Lamotrigine in Adults with Bipolar Disorder |
|----------------------------------|----------------------------------|----------------------------------|</p>
<table>
<thead>
<tr>
<th>Lamotrigine with Valproate (mg/day)</th>
<th>Lamotrigine with Carbamazepine (mg/day)</th>
<th>Lamotrigine with Neither (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1 and 2 dose</td>
<td>12.5</td>
<td>50</td>
</tr>
<tr>
<td>Weeks 3 and 4 dose</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Week 5 dose</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Subsequent weekly dose increments</td>
<td>25–50</td>
<td>100</td>
</tr>
<tr>
<td>FDA target dose</td>
<td>100</td>
<td>400</td>
</tr>
<tr>
<td>Typical final dose range</td>
<td>100–200</td>
<td>400–800</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration.
Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)

N.B. When LTG and DVP are combined, the dose of LTG should be half the usual dose, irrespective of the dose of DVP (Kanner & Frey, 2000)

Dosing (cont.)

- Dosing schedule used by Chang et al. (2006) for adolescents with bipolar disorder:
  - Adolescents not taking VPA:
    - Start LTG 25 mg/day for 2 weeks
    - Then LTG 50 mg/day for 2 weeks
    - Then LTG 100 mg/day
    - If inadequate response, consider increasing by 25 mg/day weekly
    - Target dose: 100-200 mg/day
  - Adolescents taking VPA:
    - Follow above schedule but divide doses in half

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Dosing (cont.)

Note: HC and the FDA do not provide dosing guidelines for LTG monotherapy in children and adolescents, because LTG is approved only for adjunctive treatment of Lennox-Gastaut syndrome (HC and FDA) and partial seizures (FDA only) in youth <16 years.

Reference: Lamictal product monograph (Canada, Oct. 4, 2005)

Dosing (cont.)

- If patients do not take LTG for ≥5 days, it needs to be restarted according to the initial gradual titration schedule, as serious rashes can occur with abruptly restarting the medication at a higher dose.

- Abrupt discontinuation of LTG may ↑ the risk of seizures in patients with and without epilepsy; therefore, when LTG is discontinued, it should be tapered gradually over at least 2 weeks (about 50% per week) unless safety concerns (e.g., a serious rash) require a more rapid withdrawal.
Long-term study:

- Mean changes from open-label baseline to final value for each lab parameter were generally small, except for ↓ platelets and ↑ NH$_3$

- 7/66 (11%) subjects had platelet counts below normal

- 11/66 (17%) subjects had clinically significant elevations in NH$_3$
## Adverse Effects: Minor

**Table 31.8e-5 Non-Life-Threatening Side Effects Associated with Valproate**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Management Considerations</th>
</tr>
</thead>
</table>
| Tremor                                | • Peak dose related  
• Decrease dose, change to formulation with less serum fluctuation (Depakote ER or Depakote Sprinkle)  
• Adjunctive β-blocker or benzodiazepine |
| GI upset                              | • Give with food or dose at bedtime, or both  
• Depakote or Depakote ER has less GI upset than valproate  
• Adjunctive histamine 2 antagonist |
| Hair thinning                         | • Transient (rare full-blown alopecia)  
• Anecdotal evidence of zinc and selenium supplements |
| Weight gain and increased appetite    | • Some suggestion of dose relationship  
• Diet counseling and exercise  
• Adjunctive pharmacotherapy (i.e., topiramate [Topamax], zonisamide [Zonegran], orlistat [Xenical], sibutramine [Meridia]) not systematically studied |
| Hepatic enzyme elevation (less than three times normal) | • Monitor for waxing and waning vs. continual persistent increase  
• Inquire about symptoms (right upper quadrant pain, malaise, urine color change)  
• Dose decrease recommend for elevation or side effects |

**Reference:** Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)
Adverse Effects: Serious

Table 31.8e-4 Black Box Warnings and Other Warnings

<table>
<thead>
<tr>
<th>More Serious Side Effect</th>
<th>Management Considerations</th>
</tr>
</thead>
</table>
| Hepatotoxicity           | • Rare, idiosyncratic event  
                          | • Estimated risk 1:118,000 (adults)  
                          | • Greatest risk profile (polypharmacy, younger than 2 yrs of age, mental retardation) ↑ 1:800 |
| Pancreatitis             | • Rare, similar pattern to hepatotoxicity  
                          | • Incidence in clinical trials data is 2 of 2,416 (0.0008%)  
                          | • Postmarketing surveillance shows no increased incidence  
                          | • Relapse with rechallenge  
                          | • Asymptomatic amylase not predictive |
| Hyperammonemia           | • Rare*—more common in combination with carbamazepine (Tegretol)  
                          | • Associated with coarse tremor and may respond to L-carnitine administration  
                          | • Associated with urea cycle disorders: divalproex is contraindicated in patients with urea cycle disorders; discontinue valproate and protein intake; assess underlying urea cycle disorder |
| Teratogenicity           | • Neural tube defect: 1–4% with valproate  
                          | • Preconceptual education and folate–vitamin B complex supplementation for all young women of childbearing potential |
| Somnolence in the elderly | • Slower titration than conventional doses  
                         | • Regular monitoring of fluid and nutritional intake |
| Thrombocytopenia         | • Decrease dose if clinically symptomatic (i.e., bruising, bleeding gums)  
                          | • Thrombocytopenia more likely with valproate levels ≥110 µg/mL (women) and ≥135 µg/mL (men) |


*Asymptomatic hyperammonemia is NOT rare: it was found in 51% of psychiatric patients receiving DVP, compared to 22% in controls (Raja & Azzoni, 2002; Carr & Shrewsbury, 2007)

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)
<table>
<thead>
<tr>
<th>Anti-depressants</th>
<th>Antipsychotics</th>
<th>Anxiolytics/sedatives</th>
<th>Statins</th>
<th>Anti-convulsants</th>
<th>Analgesics</th>
<th>Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Aripiprazole</td>
<td>Alprazolam (?)</td>
<td>Atorvastatin</td>
<td>Carbamazepine</td>
<td>Alfentanil</td>
<td>Dicumarol (?)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Clozapine</td>
<td>Buspirone</td>
<td>Simvastatin</td>
<td>Ethosuximide</td>
<td>Buprenor-</td>
<td>Phenprocoumon</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Fluphenazine (?)</td>
<td>Clonazepam</td>
<td>Lovastatin (but not Pravastatin)</td>
<td>Felbamate</td>
<td>Fentanyl (?)</td>
<td>Warfarin b</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Haloperidol b</td>
<td>Midazolam</td>
<td></td>
<td>Lamotrigine b</td>
<td>Levobupiva-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>Zopiclone?</td>
<td></td>
<td>Oxcarbama-</td>
<td>Methadone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quetiapine (?)</td>
<td></td>
<td></td>
<td>zepine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td></td>
<td></td>
<td>Phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thiothixene (?)</td>
<td></td>
<td></td>
<td>Primidone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ziprasidone</td>
<td></td>
<td></td>
<td>Tiagabine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Topiramate a          | Valproate a    | Zonisamide           |                   |                  |            |                |

Table 31.8a-2 Carbamazepine Decreases Serum Concentrations of Other Drugs Via Prominent Induction of CYP3A4

**Bold** indicates clinically most important drugs. **Of some medical consequence**

? , uncertain; (?) inconsistent or questionable

b Of particular medical consequence

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)
Table 31.8a-2 Carbamazepine Decreases Serum Concentrations of Other Drugs Via Prominent Induction of CYP3A4 (continued)

**Bold** indicates clinically most important drugs.  
*a* Of some medical consequence  
?*, uncertain; (?) inconsistent or questionable  
*b* Of particular medical consequence

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>Antivirals</th>
<th>Immuno-suppressants</th>
<th>Muscle relaxants</th>
<th>Steroids</th>
<th>Stimulants</th>
<th>Others*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>Delavirdine</td>
<td>Cyclosporine (?)</td>
<td>Doxacurium</td>
<td>Mifepristone</td>
<td>Methylphenidate</td>
<td>Bepridil</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Protease inhibitors</td>
<td>Sirolimus</td>
<td>Pancuronium</td>
<td>Prednisolone</td>
<td>Modafinil</td>
<td>Dihydropyridine calcium channel blockers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tacrolimus</td>
<td>Rapacuronium</td>
<td>Estrogen in hormonal contraceptives</td>
<td></td>
<td>Oxiracetam (?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rocuronium</td>
<td>Dexamethasone</td>
<td></td>
<td>Paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vecuronium</td>
<td></td>
<td></td>
<td>Quinidine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Remacemide?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Repaglinide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Theophylline (?)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thyroid hormones</td>
</tr>
</tbody>
</table>

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)

*Also oral contraceptives (added by DG)
Table 31.8a-5 Drugs That Increase Serum Concentrations of Carbamazepine

<table>
<thead>
<tr>
<th>Antidepressants</th>
<th>Hypolipidemics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine(^{b})</td>
<td>Gemfibrozil</td>
</tr>
<tr>
<td>Fluvoxamine(^{e})</td>
<td>Nicotinamide</td>
</tr>
<tr>
<td><strong>Nefazodone</strong>(^{b})</td>
<td>Others</td>
</tr>
<tr>
<td>Antimicrobials</td>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Isoniazid(^{e})</td>
<td><strong>Cimetidine</strong>(^{a})</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>Danazol</td>
</tr>
<tr>
<td>Macrolide antibiotics</td>
<td>Omeprazole</td>
</tr>
<tr>
<td>Clarithromycin(^{e})</td>
<td><strong>D-Propoxyphene</strong>(^{b})</td>
</tr>
<tr>
<td>Erythromycin(^{e})</td>
<td>Ticlopide</td>
</tr>
<tr>
<td>Flurithromycin(^{e})</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>Josamycin(^{e})</td>
<td>Saquinavir(^{e})</td>
</tr>
<tr>
<td>Ponsinomycin(^{e})</td>
<td>Ritonavir(^{e})</td>
</tr>
<tr>
<td>Triacetyloleandromycin(^{e})</td>
<td>Helfinar(^{e})</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Reverse transcriptase inhibitors</td>
</tr>
<tr>
<td>Valproic acid(^{e}) (increases CBZ-E)</td>
<td>Delavirdine(^{e})</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Efavirenz (^\uparrow, \downarrow)</td>
</tr>
<tr>
<td>Diltiazem(^{e}) (but not nifedipine or nimodipine)</td>
<td></td>
</tr>
<tr>
<td>Verapamil(^{e})</td>
<td></td>
</tr>
</tbody>
</table>

Note: **Bold** indicates potential for toxicity.

CBZ-E, carbamazepine-10,11-epoxide.

\(^{a}\)Weak.

\(^{b}\)Mild to moderate.

\(^{c}\)Important to severe.

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)
FIGURE 31.8a-11 Carbamazepine (CBZ) metabolism. Bottom left: Drugs that inhibit cytochrome P450 increase CBZ. ++, Drugs that decrease the level of carbamazepine through induction of its oxidative metabolic pathway cytochrome P450; +, drugs that decrease the level of the active metabolite carbamazepine-10,11-epoxide (CBZ-E) through induction of the epoxide hydroxylase and production of the inactive dihydroxy metabolite (CBZ-D); -, drugs that increase the level of carbamazepine-10,11-epoxide through blockade of the epoxide catabolism. Drug names in capital letters indicate common or more important interactions.

Reference: Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 8th ed. (online)
FIGURE 31.8a-1 Comparative metabolism of carbamazepine and oxcarbazepine. Both parent and first metabolite are active anticonvulsants—the top two are potent enzyme inducers; the bottom two are not.

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)
<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>OXC</th>
<th>Comment on OXC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic enzyme induction 3A4</td>
<td>+++</td>
<td>±</td>
<td>No autoinduction</td>
</tr>
<tr>
<td>Benign decrease in white blood cells</td>
<td>+++</td>
<td>±</td>
<td>No general white blood cell suppression</td>
</tr>
<tr>
<td>Rash</td>
<td>6.5%</td>
<td>2.5%</td>
<td>Lower rate</td>
</tr>
<tr>
<td>Cross-sensitization from carbamazepine</td>
<td>N/A</td>
<td>Low, 25–30%</td>
<td>83/106 did not re-rash</td>
</tr>
<tr>
<td>Benign rash</td>
<td>N/A</td>
<td>Low, 25–30%</td>
<td>3/3 with exfoliative rash on carbamazepine re-rashed on oxcarbazepine</td>
</tr>
<tr>
<td>Severe rash</td>
<td>N/A</td>
<td>High?</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>+a</td>
<td>++b</td>
<td>The one side effect more common with oxcarbazepine</td>
</tr>
<tr>
<td>↑Liver function tests</td>
<td>+</td>
<td>±</td>
<td></td>
</tr>
<tr>
<td>Teratogenic (spina bifida)</td>
<td>1–3%</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>5 per million</td>
<td>?</td>
<td>Hematological monitoring not indicated</td>
</tr>
<tr>
<td>Agranulocytosis</td>
<td>1 per million</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>

N/A, not applicable.

Reference: Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)

\(^a\)13.5% Na<134 mEq/L, 2.8% Na<128 mEq/L
\(^b\)29.9% Na<134 mEq/L, 12.4% Na<128 mEq/L
(Dong et al., 2005)
### Table 2  
Summary of AED Interactions with *(Trileptal)*®

| AED Coadministered | Dose of AED (mg/day) | *(Trileptal)*® Dose (mg/day) | Influence of *(Trileptal)*® on AED Concentration (Mean Change, 90% Confidence Interval) | Influence of AED on MHD Concentration (Mean Change, 90% Confidence Interval) |
|---------------------|----------------------|-------------------------------|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------
| Carbamazepine       | 400-2000             | 900                           | nc ¹                                                                             | 40% decrease [CI: 17% decrease, 57% decrease]                                      |
| Phenobarbital       | 100-150              | 600-1800                      | 14% increase [CI: 2% increase, 24% increase]                                      | 25% decrease [CI: 12% decrease, 51% decrease]                                      |
| Phenytoin           | 250-500              | 600-1800 up to 1200-2400      | nc ¹, ² up to 40% increase ³ [CI: 12% increase, 60% increase]                    | 30% decrease [CI: 3% decrease, 48% decrease]                                      |
| Valproic acid       | 400-2800             | 600-1800                      | nc ¹                                                                             | 18% decrease [CI: 13% decrease, 40% decrease]                                      |

¹ nc denotes a mean change of less than 10%

² Pediatrics

³ Mean increase in adults at high *(Trileptal)*® doses

Reference: www.pdr.net
<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug Plasma Concentration With Adjunctive Lamictal *</th>
<th>Lamotrigine Plasma Concentration With Adjunctive Drugs *<em>/</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin (PHT)</td>
<td>[harr]</td>
<td>down</td>
</tr>
<tr>
<td>Carbamazepine (CBZ)</td>
<td>[harr]</td>
<td>down</td>
</tr>
<tr>
<td>CBZ epoxide <strong>/</strong></td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>down</td>
<td></td>
</tr>
<tr>
<td>Valproate + PHT and/or CBZ</td>
<td>Not assessed</td>
<td>[harr]</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>[harr]</td>
<td>[harr]</td>
</tr>
<tr>
<td>10-monohydroxy oxcarbazepine metabolite §</td>
<td>[harr]</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>[harr]</td>
<td>[harr]</td>
</tr>
<tr>
<td>Lithium</td>
<td>[harr]</td>
<td>Not assessed</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Not assessed</td>
<td>[harr ]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>[harr ]</td>
<td>[harr ] [Verbar]</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Ethinylestradiol/levonorgesterol ¶</td>
<td>[harr ] ¶</td>
<td>down</td>
</tr>
</tbody>
</table>

*From adjunctive clinical trials and volunteer studies.

**/* Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteers studies.

**/** Not administered, but an active metabolite of carbamazepine.

§ Not administered, but an active metabolite of oxcarbazepine.

[harr ] = No significant effect.

? = Conflicting data.

[Verbar] Slight decrease, not expected to be clinically relevant.

¶ The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been evaluated, although the effect may be similar.

# Modest decrease in levonorgesterol (see PRECAU-TIONS: Drug Interactions: Effect of Lamictal on Oral Contraceptives).
## Dosing

### Table 31.8c–1 Gradual Introduction of Lamotrigine in Adults with Bipolar Disorder

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine with Valproate (mg/day)</th>
<th>Lamotrigine with Carbamazepine (mg/day)</th>
<th>Lamotrigine with Neither (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weeks 1 and 2 dose</strong></td>
<td>12.5</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td><strong>Weeks 3 and 4 dose</strong></td>
<td>25</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td><strong>Week 5 dose</strong></td>
<td>50</td>
<td>200</td>
<td>100</td>
</tr>
<tr>
<td><strong>Subsequent weekly dose increments</strong></td>
<td>25–50</td>
<td>100</td>
<td>50–100</td>
</tr>
<tr>
<td><strong>FDA target dose</strong></td>
<td>100</td>
<td>400</td>
<td>200</td>
</tr>
<tr>
<td><strong>Typical final dose range</strong></td>
<td>100–200</td>
<td>400–800</td>
<td>200–400</td>
</tr>
</tbody>
</table>

FDA, U.S. Food and Drug Administration.

**Reference:** Kaplan & Sadock’s Comprehensive Textbook of Psychiatry, 8th ed. (online)

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**N.B.** When LTG and DVP are combined, the dose of LTG should be **half** the usual dose, irrespective of the dose of DVP (Kanner & Frey, 2000)
**Dosing (cont.)**

### Table 10

**Pediatric Dosing with LAMICTAL® for patients receiving Valproic Acid with or without Enzyme-inducing1 AEDs**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Weeks 5 and onwards to Usual Maintenance Dose2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.15mg/kg once a day</td>
<td>0.3mg/kg once a day</td>
<td>To achieve maintenance, doses may be increased by 0.3 mg/kg every 1-2 weeks, to a maximum of 200mg/day. Usual dose is between 1-5mg/kg once a day3</td>
</tr>
<tr>
<td>&lt;9kg</td>
<td>&lt;20 lbs</td>
<td>Do not take LAMICTAL® since there is insufficient experience in children weighing less than 9 kg</td>
<td></td>
</tr>
<tr>
<td>9-13kg</td>
<td>20-28 lbs</td>
<td>2mg every other day</td>
<td>2mg/day</td>
</tr>
<tr>
<td>14-16kg</td>
<td>31-35 lbs</td>
<td>2mg/day</td>
<td>4mg/day</td>
</tr>
<tr>
<td>17-33kg</td>
<td>37-79 lbs</td>
<td>5mg every other day</td>
<td>5mg/day</td>
</tr>
<tr>
<td>34-49kg</td>
<td>75-108 lbs</td>
<td>5mg/day</td>
<td>10mg/day</td>
</tr>
<tr>
<td>&gt;50kg4</td>
<td>&gt;110 lbs</td>
<td>5mg/day</td>
<td>15mg/day</td>
</tr>
</tbody>
</table>

1= enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone
2= It may take several weeks to months to achieve an individualized maintenance dose
3= can be given as two divided doses
4= insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 50kg

**Note:** HC and the FDA do not provide dosing guidelines for LTG monotherapy in children and adolescents, because LTG is approved only for adjunctive treatment of Lennox-Gastaut syndrome (HC and FDA) and partial seizures (FDA only) in youth <16 years.

### Table 11

**Pediatric Dosing with LAMICTAL® for patients receiving Enzyme-inducing1,2,3 AEDs without Valproic Acid**

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Weeks 1 + 2</th>
<th>Weeks 3 + 4</th>
<th>Week 5 and onwards to Usual Maintenance Dose3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.3mg/kg twice a day</td>
<td>0.6 mg/kg twice a day</td>
<td>To achieve maintenance, doses may be increased by 1.2mg/kg every 1-2 weeks, to a maximum of 400mg/day. Usual dose is between 2.5 - 7.5mg/kg twice a day</td>
</tr>
<tr>
<td>&lt;9kg</td>
<td>&lt;20 lbs</td>
<td>Do not take LAMICTAL® since there is insufficient experience in children weighing less than 9 kg</td>
<td></td>
</tr>
<tr>
<td>9-12kg</td>
<td>26-26 lbs</td>
<td>5mg/day</td>
<td>10mg/day</td>
</tr>
<tr>
<td>13-16kg</td>
<td>29-35 lbs</td>
<td>5mg/day</td>
<td>15mg/day</td>
</tr>
<tr>
<td>17-20kg</td>
<td>37-44 lbs</td>
<td>10mg/day</td>
<td>20mg/day</td>
</tr>
<tr>
<td>21-24kg</td>
<td>46-53 lbs</td>
<td>10mg/day</td>
<td>25mg/day</td>
</tr>
<tr>
<td>25-29kg</td>
<td>56-64 lbs</td>
<td>15mg/day</td>
<td>30mg/day</td>
</tr>
<tr>
<td>30-33kg</td>
<td>66-73 lbs</td>
<td>15mg/day</td>
<td>35mg/day</td>
</tr>
<tr>
<td>34-37kg</td>
<td>75-81 lbs</td>
<td>20mg/day</td>
<td>40mg/day</td>
</tr>
<tr>
<td>38-41kg</td>
<td>84-90 lbs</td>
<td>20mg/day</td>
<td>45mg/day</td>
</tr>
<tr>
<td>42-45kg</td>
<td>92-99 lbs</td>
<td>25mg/day</td>
<td>50mg/day</td>
</tr>
<tr>
<td>46-49kg</td>
<td>101-108 lbs</td>
<td>25mg/day</td>
<td>55mg/day</td>
</tr>
<tr>
<td>50-54kg</td>
<td>110-119 lbs</td>
<td>30mg/day</td>
<td>60mg/day</td>
</tr>
<tr>
<td>55-58kg</td>
<td>121-128 lbs</td>
<td>30mg/day</td>
<td>65mg/day</td>
</tr>
<tr>
<td>&gt;59kg4</td>
<td>&gt;130 lbs</td>
<td>35mg/day</td>
<td>70mg/day</td>
</tr>
</tbody>
</table>

1= enzyme-inducing AEDs include carbamazepine, phenobarbital, phenytoin, and primidone
3= can be given as two divided doses
3= it may take several weeks to months to achieve an individualized maintenance dose
4= insufficient data are available to be able to support the mg/kg dosing in patients weighing more than 59kg

* total daily dose can be divided

Reference: Lamictal product monograph (Canada, Oct. 4, 2005)