Learning Objectives

1. Clarify the distinction between the various compounds and preparations in the “valproate family”
2. Examine the evidence for the efficacy of valproate as a treatment for pediatric bipolar disorder and aggression paying particular attention to controlled studies
3. Review the side effects and potential adverse effects of valproate. Several serious side effects, which may have been underestimated or not appreciated in the past, will be emphasized.

Outline

• Indications & clinical use
• Compounds and preparations
• Pharmacodynamics & pharmacokinetics
• Efficacy
• Adverse effects (minor and serious)
• Controversies
• Contraindications & drug interactions
• Monitoring
• Dosing

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 PDD or MR

Compounds and Complexity

• 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) and as an extended-release tablet (Epival ER)
- 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<sub>2</sub> receptor density
     d) Possible enhancement of neuronal responsiveness to GABA

Pharmacodynamics (cont.)

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
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<sub>max</sub>=3-4 hrs (absorption slightly delayed when taken with food)
- Epival ER
  - Absorbed over 18-24 hrs
  - T<sub>max</sub>=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<sub>1/2</sub>=6-16 hours
- In adults, Epival ER given QD produces 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.

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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.

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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

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Efficacy: Bipolar Disorder (cont.)

- 5 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 (double-blind, maintenance treatment)
  - Delbello et al., 2006: DVP vs. QUE (double-blind)
  - Barzman et al., 2006: DVP vs. QUE (double-blind)
  - Pavuluri et al., 2010: DVP vs. RISP (double-blind)

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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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Li+DVP for PBD

- Findling et al., 2003 (Study 1 of 3):
  - Open, prospective study of Li+DVP in children and adolescents with bipolar I or II disorder and ≥1 manic or hypomanic episode within the prior 3 months
  - Significant improvement was found on all outcome measures
  - Remission rate: 47%
DVP Maintenance Treatment for PBD

- Findling et al., 2005 (Study 2 of 3):
  - Randomized, double-blind trial of Li vs. DVP maintenance treatment for up to 76 weeks in subjects who were treated initially with Li+DVP and remitted (i.e., either Li or DVP was discontinued)
  - The 2 groups did not differ significantly in:
    - Median time to relapse: Li=114 days, DVP=112 days (p=0.6)
    - Median time to discontinuation from the study for any reason: Li=91 days, DVP=56 days (p=0.7)

Li+DVP for PBD (Revisited)

- Findling et al., 2006 (Study 3 of 3):
  - Open, prospective study of Li+DVP in subjects who previously remitted with Li+DVP but then relapsed on Li or DVP monotherapy (i.e., whichever drug had been stopped was now added back):
    - 90% restabilized with resumption of Li+DVP
    - The remainder required adjunctive antipsychotic treatment to address residual symptoms

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)
  - Rates of adverse events did not differ significantly between groups, and both QUE and DVP were considered to be well tolerated

Barzman et al., 2006

- Post hoc analysis of 33 adolescents who:
  - Participated in a double-blind RCT of QUE vs. DVP for bipolar disorder (Delbello et al., 2006)
  - Had comorbid CD or ODD
- Results:
  - Both groups improved from baseline (p<0.0001)
  - QUE vs. DVP on the primary outcome measure (Positive and Negative Syndrome Scale Excited Component)
  - QUE vs. DVP in PANSS EC rate of improvement
  - Both QUE and DVP were considered to be well tolerated, but sedation was significantly more frequent with QUE

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
- 1st outcome measure – YMRS (2nd-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

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

(ground slide appended)
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

Findling et al., 2007 (cont.)

- Results:
  - 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-Sverity of illness (p=0.02)
      - CGI-Improvement (p=0.0008)
      - Self-reported impulse control (p=0.05)
      - Self-restrain (p=0.06)
    - Analyses comparing outcome by blood VPA level strengthened the results

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: 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>
<tbody>
<tr>
<td>Tremor</td>
<td>Peak dose related; change to formulation with less serum fluctuation (Depakote ER or Depakote SR)</td>
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<tr>
<td>GI upset</td>
<td>Give with food or dose at bedtime, or both; Depakote or Depakote ER has less GI upset than valproate</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>Transient (rare full-blown aspere)</td>
</tr>
<tr>
<td>Weight gain and increased appetite</td>
<td>Some suggestion of dose relationship; diet counseling and exercise</td>
</tr>
<tr>
<td>Hepatic enzyme elevation</td>
<td>Monitor for wasting and wasting vs. continual persistent increase</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

- 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)
Severe Hepatotoxicity (cont.)

• 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).

Pancreatitis

• Gerstner et al., 2007:
  – 16 cases of DVP-induced pancreatitis were identified in Germany from 1994 to 2003 (none had been published previously).
  – “The difference between 90 patients reported worldwide from 1979 to 2005 and the 16 new documented cases from only Germany over 10 years corroborates that the occurrence of this severe side effect is under reported.”

Encephalopathy

• Rare complication of DVP treatment.

• Typical signs:
  – Impaired consciousness
  – Marked EEG background slowing (sometimes)
  – ↑ seizure frequency
  – Hyperammonemia may be present or absent

• 19 cases of DVP-associated encephalopathy were identified in Germany from 1994 to 2003 (Gerstner et al., 2006).

Controversy #1: 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.

• These actions were based on an analysis of suicide-related events (SREs) in PBO-controlled trials of 11 anticonvulsants (valproate, carbamazepine, oxcarbazepine, lamotrigine, topiramate, gabapentin, felbamate, levetiracetam, pregabalin, tiagabine, and zonisamide).

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.

Suicidality and AEDs: Unanswered questions

• Association or causation?

• Is there equal risk with all anticonvulsants?

• Which patients are at greatest risk - those with epilepsy, bipolar disorder, depression or other conditions (e.g. pain disorders)?

• Are pediatric patients at equal risk?

• See:
  – Gibbons et al., 2009
  – Patomo et al., 2010
  – Arana et al., 2010
  – And many letters and rebuttals.
Other Adverse Effects

• Possible ↑ 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: 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 Controversy #2: 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 Controversy #3: 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 Now Available!

• 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

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, 2006)

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)

Drug Interactions: General Considerations

• Drugs that ↑ the expression of hepatic enzymes, particularly those that elevate levels of glucuronyl 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
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.

**TABLE 5**

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Baseline</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Divalproex</td>
</tr>
<tr>
<td>Platelet count</td>
<td>281.9</td>
<td>277.2</td>
</tr>
<tr>
<td>White blood cells (×10⁹/L)</td>
<td>6.24</td>
<td>6.12</td>
</tr>
<tr>
<td>Monocytes, %</td>
<td>6.00</td>
<td>5.39</td>
</tr>
<tr>
<td>BUN, mmol/L</td>
<td>3.88</td>
<td>4.23</td>
</tr>
<tr>
<td>Total protein, g/L</td>
<td>73.57</td>
<td>73.12</td>
</tr>
<tr>
<td>Albumin, g/L</td>
<td>45.40</td>
<td>45.72</td>
</tr>
<tr>
<td>Total</td>
<td>7.59</td>
<td>9.19</td>
</tr>
<tr>
<td>Bilirubin, μmol/L</td>
<td>22.07</td>
<td>22.81</td>
</tr>
<tr>
<td>SGOT/AST, U/L</td>
<td>15.57</td>
<td>16.27</td>
</tr>
<tr>
<td>Total protein, g/L</td>
<td>4.39</td>
<td>4.36</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.43</td>
<td>2.44</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.34</td>
<td>4.47</td>
</tr>
<tr>
<td>Ammonia, μmol/L</td>
<td>39.05</td>
<td>34.37</td>
</tr>
</tbody>
</table>

*Note: Sample sizes range from 67 to 68 for placebo and from 66 to 68 for divalproex ER. BUN = blood urea nitrogen; SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase; SGPT/ALT = serum glutamic pyruvic transaminase/alanine aminotransferase.

*n = 57 for placebo, n = 54 for divalproex.*
# 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>
<tbody>
<tr>
<td>Tremor</td>
<td>• Peak dose related&lt;br&gt;• Decrease dose, change to formulation with less serum fluctuation (Depakote ER or Depakote Sprinkle)&lt;br&gt;• Adjunctive β-blocker or benzodiazepine</td>
</tr>
<tr>
<td>GI upset</td>
<td>• Give with food or dose at bedtime, or both&lt;br&gt;• Depakote or Depakote ER has less GI upset than valproate&lt;br&gt;• Adjunctive histamine 2 antagonist</td>
</tr>
<tr>
<td>Hair thinning</td>
<td>• Transient (rare full-blown alopecia)&lt;br&gt;• Anecdotal evidence of zinc and selenium supplements</td>
</tr>
<tr>
<td>Weight gain and increased appetite</td>
<td>• Some suggestion of dose relationship&lt;br&gt;• Diet counseling and exercise&lt;br&gt;• Adjunctive pharmacotherapy (i.e., topiramate [Topamax], zonisamide [Zonegran], orlistat [Xenical], sibutramine [Meridia]) not systematically studied</td>
</tr>
<tr>
<td>Hepatic enzyme elevation (less than three times normal)</td>
<td>• Monitor for waxing and waning vs. continual persistent increase&lt;br&gt;• Inquire about symptoms (right upper quadrant pain, malaise, urine color change)&lt;br&gt;• Dose decrease recommend for elevation or side effects</td>
</tr>
</tbody>
</table>

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) |

Adapted from *Physician’s Desk Reference*. Oradell, NJ: Medical Economics Company; 2002.

*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)