DRUGDEX® Evaluations

VALPROIC ACID

0.0 Overview
1) Class
   a) This drug is a member of the following class(es):
      Anticonvulsant
      Antimanic
      Antimigraine
      Valproic Acid (class)
2) Dosing Information
   a) Valproic Acid
      1) Adult
         a) Absence seizure, Simple and complex
            1) initial, 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)
            2) maintenance, may increase dosage 5 to 10 mg/kg/day ORALLY at one week intervals until seizures side effects preclude further increases (give in 2 to 3 divided doses if total daily dose exceeds 250 mg)( Rx or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, or Prod Info STAVZOR(R) delayed release oral capsules, 2008)
      b) Complex partial epileptic seizure
         1) monotherapy, initial 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exce increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)
         2) conversion to monotherapy, 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily do mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL); reduce concomitant antiepilepsy drug dosage by approxi 2 weeks (reduction may be started at initiation of therapy or delayed by 1 to 2 weeks if there is a concer likely to occur with a reduction) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STA release oral capsules, 2008)
         3) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day ORALLY (g divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve respo response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)
      c) Manic bipolar I disorder
         1) initial, delayed-release 750 mg ORALLY daily, in divided doses; may increase dose to achieve desire or desired range of plasma concentrations (MAX 60 mg/kg/day or less with a therapeutic serum range of mcg/mL) (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
      d) Migraine; Prophylaxis
         1) delayed-release 250 mg ORALLY twice daily; MAX dose 1000 mg/day (Prod Info STAVZOR(R) delay capsules, 2008)
      e) Seizure, Multiple seizure types; Adjunct
         1) 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may in to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic ses 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayedec capsules, 2008)
2) Pediatric
   a) increased risk of fatal hepatotoxicity in patients under the age of 2 years (Prod Info DEPAKENE(R) oral ca 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) safety and efficacy of delayed-release valproic acid (Stavzor(R)) for the treatment of acute mania associ disorder and for migraine prophylaxis have not been established in pediatric patients (Prod Info STAVZOR(R oral capsules, 2008)
      1) Absence seizure, Simple and complex
         a) (10 yr and older) initial, 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exc (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release 2008)
         b) (10 yr and older) maintenance, may increase dosage 5 to 10 mg/kg/day ORALLY at one week in seizures are controlled or side effects preclude further increases (give in 2 to 3 divided doses if total exceeds 250 mg)(MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) ( DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsu 2) Complex partial epileptic seizure
         a) (10 yr and older) monotherapy, initial 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (M
or less with a therapeutic serum range of 50 to 100 mcg/mL (Prod Info DEPAKENE(R) oral capsule 2006; Prod Info STAZVOR(R) delayed release oral capsules, 2008)

b) (10 yr and older) conversion to monotherapy, 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL; reduce concomitant antiepileptic by approximately 25% every 2 weeks (reduction may be started at initiation of therapy or delayed by there is a concern that seizures are likely to occur with a reduction) (Prod Info DEPAKENE(R) oral capsules, 2006; Prod Info STAZVOR(R) delayed release oral capsules, 2008)

c) (10 yr and older) adjunct, may be added to the patient’s regimen at an initial dosage of 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to 10% achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2008; Prod Info STAZVOR(R) delayed release oral capsules, 2008)

3) Seizure, Multiple seizure types: Adjunct

a) (10 yr and older) 10 to 15 mg/kg/day ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, STAZVOR(R) delayed release oral capsules, 2008)

b) Divalproex Sodium

1) Adult

a) converting from valproic acid: initiate divalproex sodium sprinkle capsules at the same daily dose and dos stabilized, divalproex sodium given 2 or 3 times a day may be instituted (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

b) converting delayed-release to extended-release: administer extended-release tablets (Depakote(R) ER) or 8% to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Prod Info DEPAKOTE(R) extended-release oral tablets, 2008).

1) Absence seizure, Simple and complex

a) initial, 15 mg/kg/day ORALLY, may increase dosage by 5 to 10 mg/kg/day at 1-week intervals un controlled or side effects preclude further increases (MAX 60 mg/kg/day; usual therapeutic range, 5 to total daily doses greater than 250 mg should be given in divided doses for delayed-release and sprin DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral caps Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Complex partial epileptic seizure

a) monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/week to achievemental response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK0 extended-release oral tablets, 2006)

b) adjunct, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/week to achieve se response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) ER oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) oral tablets, 2006)

c) conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 m achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL); reduc antiepileptic dosage by approximately 25% every 2 weeks (reduction may be started at initiation of t by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduction) (Prod Info DEI extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod IntI delayed-release oral tablets, 2006)

3) Manic bipolar I disorder

a) (Depakote (R) ER, extended-release) initial, 25 mg/kg/day ORALLY once daily; increase dose as possible to clinical effect; usual trough plasma level, 85 to 125 mcg/mL; MAX 60 mg/kg/day (Prod In ER extended-release oral tablets, 2008)

b) (Depakote (R), delayed-release) initial, 750 mg ORALLY daily in divided doses; increase dose as possible to clinical effect; usual trough plasma level, 50 to 125 mcg/mL; MAX 60 mg/kg/day (Prod In delayed-release oral tablets, 2006)

4) Migraine; Prophylaxis

a) (Depakote (R) ER, extended-release) initial, 500 mg ORALLY once daily for 1 week, thereafter ir mg once daily (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)

b) (Depakote (R) delayed-release) initial, 250 mg ORALLY twice daily; may increase to a MAX 100i Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Pediatric

a) safety and efficacy for the treatment of epilepsy in children less than 10 years of age have not been estab DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 200( b) efficacy for use in pediatric population for the treatment of mania or migraine prophylaxis has not been es Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) converting from valproic acid: initiate divalproex sodium sprinkle capsules at the same daily dose and dos stabilized, divalproex sodium given 2 or 3 times a day may be instituted (Prod Info DEPAKOTE(R) sprinkle or 2008).

d) converting delayed-release to extended-release: administer extended-release tablets (Depakote(R) ER) o
8% to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Prod Info DEPAKOTE capsules, 2008)

1) Absence seizure, Simple and complex
   a) 10 years and older, initial, 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/day at 1- to
      2-week intervals until seizures are controlled or side effects preclude further increases (MAX 60 mg/kg/day; usual thera
gpe 100 mcg/mL; total daily doses greater than 250 mg should be given in divided doses for delayed-rel  
(Pod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008;  
Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006)
   b) 10 years and older, on monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/day 
      to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info 
(Depakote(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; 
DEPAKOTE(R) delayed-release oral tablets, 2006)
   c) 10 years and older, conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage to 5 to 10 m 
      g/kg/day to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info 
DEPAKOTE(R) delayed-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info 
delayed-release oral tablets, 2006)

2) Complex partial epileptic seizure
   a) 10 or older, on monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/day to achieve  
      optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) 
      sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006)
   b) 10 or older, on adjunct therapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/day to  
      achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) (Prod Info DEP  
      extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info delayed-
      release oral tablets, 2006)

   c) 10 or older, on conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 m  
      g/kg/day to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 mcg/mL) 
      (Prod Info DEPAKOTE(R) delayed-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; 
      Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006)

3) Contraindications
   a) Valproate Sodium
      1) Absence seizure, Simple and complex
         a) 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/day at one week intervals until seizures are controlled or  
             side effects preclude further increases (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL)  
             (Prod Info DEPAKOTE(R) IV injection, 2006)
      b) Complex partial epileptic seizure
         1) monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical  
             response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R)  
             IV injection, 2006)
         2) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve  
             optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info  
             DEPAKOTE(R) IV injection, 2006)
         3) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day IV, may increase  
             dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50  
             to 100 mcg/mL) (Prod Info DEPAKOTE(R) IV injection, 2006)

   c) Seizures, Multiple seizure types; Adjunct
      1) 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 
          mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) IV injection, 2006)

2) Pediatric
   a) Safety and effectiveness in pediatric patients under age 10 have not been established
      1) Complex partial epileptic seizure
         a) (10 yr and older) monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve  
             optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info  
             DEPAKOTE(R) IV injection, 2006)
         b) (10 yr and older) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week  
             to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL)  
             (Prod Info DEPAKOTE(R) IV injection, 2006)
         c) (10 yr and older) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day  
             IV, may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day; therapeu 
             tic range, 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) IV injection, 2006)

2) Seizures, Multiple seizure types; Adjunct
   a) 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 
      mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPAKOTE(R) IV injection, 2006)
oral capsules, 2003)
3) urea cycle disorders, known; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info S delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) oral ca 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releas Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

b) Divalproex Sodium
1) hepatic disease or significant hepatic dysfunction (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Proc (R) ER extended-release oral tablets, 2008)
2) hypersensitivity to divalproex sodium (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
3) urea cycle disorders (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER ext tablets, 2008)

C) Valproate Sodium
1) hepatic disease or significant hepatic dysfunction (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
2) hypersensitivity to valproate sodium, valproic acid, or divalproex sodium (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)

4) Serious Adverse Effects
a) Valproic Acid
1) Coma, Hyperammonemia-induced
2) Hematemesis
3) Hyperammonemia
4) Hyperammonemic encephalopathy
5) Immune hypersensitivity reaction
6) Ototoxicity - deafness
7) Palpitations
8) Pleural effusion
9) Pulmonary hemorrhage
10) Tachycardia
11) Thrombocytopenia, Dose-related

b) Divalproex Sodium
1) Hyperammonemia
2) Hyperammonemic encephalopathy
3) Immune hypersensitivity reaction
4) Liver failure
5) Ototoxicity - deafness
6) Palpitations
7) Pancreatitis
8) Tachycardia
9) Thrombocytopenia, Dose-related

c) Valproate Sodium
1) Liver failure, Children under the age of two years are at increased risk
2) Pancreatitis, Life-threatening
3) Thrombocytopenia, Dose-related

5) Clinical Applications
a) Valproic Acid
1) FDA Approved Indications
   a) Absence seizure, Simple and complex
   b) Complex partial epileptic seizure
   c) Manic bipolar I disorder
   d) Migraine; Prophylaxis
   e) Seizure, Multiple seizure types; Adjunct

b) Divalproex Sodium
1) FDA Approved Indications
   a) Absence seizure, Simple and complex
   b) Complex partial epileptic seizure
   c) Manic bipolar I disorder
   d) Migraine; Prophylaxis

c) Valproate Sodium
1) FDA Approved Indications
   a) Absence seizure, Simple and complex
   b) Complex partial epileptic seizure
   c) Seizure, Multiple seizure types; Adjunct

1.0 Dosing Information

Drug Properties
Storage and Stability

Adult Dosage

Pediatric Dosage

1.1 Drug Properties
   A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product In
   B) Synonyms
      Divalproex Na
      Divalproex Sodium
      Sodium Valproate
      Valproate Na
      Valproate Sodium
      Valproic Acid

1.2 Storage and Stability
   A) Valproic Acid
      1) Preparation
         a) Oral route
            1) Valproic acid capsules should be swallowed whole without chewing to avoid local irritation of the mou
            Divided doses should be given if the total daily dose exceeds 250 milligrams. A slow titration from the ini
giving with food may help to decrease gastrointestinal irritation in patients who experience it (Prod Info D
         B) Divalproex Sodium
         1) Preparation
            a) Oral route
               1) Extended-Release
                  a) Extended-release formulations are for once daily dosing and should be swallowed whole and not
                  chewed. Patients who experience gastrointestinal irritation should take divalproex sodium with food
                  titration from the initial dose (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).
               2) Delayed-Release
                  a) The delayed-release formulation may be taken with or without food. Patients who experience gas
                  irritation should take divalproex sodium with food or utilize slow dose titration from the initial dose (P
                  DEPAKOTE(R) delayed-release oral tablets, 2006).
               3) Sprinkle-Capsules
                  a) The sprinkle-capsules may be swallowed whole, or opened and contents sprinkled on a small an
                  teaspoonful) of soft food such as applesauce or pudding. The drug/food mixture should not be store
                  but should be swallowed immediately without chewing. Patients who experience gastrointestinal irrit
                  divalproex sodium with food or utilize slow dose titration from the initial dose (Prod Info DEPAKOTE
                  capsules, 2008).
               C) Valproic Acid
                  1) Oral route
                     a) Capsule, Delayed Release
                        1) Store delayed-release capsules at controlled room temperature, 25 degrees Celsius (77 degrees Fah
                        excursions permitted between 15 and 30 degrees Celsius (59 and 86 degrees Fahrenheit) (Prod Info ST
                        delayed release oral capsules, 2008).
                     b) Capsule, Liquid Filled
                        1) Store liquid-filled capsules between 15 and 25 degrees Celsius (59 and 77 degrees Fahrenheit) (Proc
                        (R) capsules and syrup, 2003).
                     c) Syrup
                        1) Store syrup below 30 degrees Celsius (86 degrees Fahrenheit) (Prod Info DEPAKENE(R) capsules a
   D) Divalproex Sodium
      1) Oral route
         a) Capsule
            1) Divalproex sodium sprinkle capsules should be stored below 77 degrees Fahrenheit (25 degrees Celsi
            DEPAKOTE(R) oral sprinkle capsule, 2003).
         b) Tablet, Delayed Release
            1) Divalproex sodium delayed-release tablets should be stored below 86 degrees Fahrenheit (30 degree
            Info Depakote(R) Tablets, 2002).
         c) Tablet, Extended Release
            1) Divalproex sodium extended-release tablets should be stored at 77 degrees Fahrenheit (25 degrees Fah
            excursions permitted between 59 and 86 degrees Fahrenheit (15 and 30 degrees Celsius) (Prod Info DE
            Tablets, 2005).
   E) Valproate Sodium
1) Injection route
   a) Solution
      1) Valproate sodium injection should be stored at room temperature, 15 to 30 degrees Celsius (59 to 86 Fahrenheit) (Prod Info Depacon(R), , 2003).
      2) Valproate sodium injection is stable in 5% dextrose injection, 0.9% sodium chloride injection and lact injection for at least 24 hours in glass or polyvinyl chloride chloride (PVC) bags at 15 to 30 degrees Celsius (Prod Info Depacon(R), , 2003).

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

1.3.1 Normal Dosage

Divalproex Sodium

Valproate Sodium

Valproic Acid

1.3.1.A Divalproex Sodium

Oral route

Alcohol withdrawal syndrome

1.3.1.A.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Manic bipolar I disorder

Migraine; Prophylaxis

1.3.1.A.1.a Absence seizure, Simple and complex

1) The recommended initial dose is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals until the desired therapeutic effect is reached or adverse effects occur. The maximum recommended dose is 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 micrograms/milliliter. There is no good correlation between daily dose, serum concentrations, and therapeutic effect. Some experience seizure control with higher or lower serum levels. For the delayed-release tablets and sustained-release capsules, total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodium doses are adjusted upwards, the blood levels of phenobarbital and/or phenytoin may be affected (Prod Info DEPAKOTE release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOT release oral tablets, 2006).

1.3.1.A.1.b Complex partial epileptic seizure
1) Initial Monotherapy
   a) The recommended initial oral dosage for monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day) in increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses above 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy
   a) The recommended oral dosage when adding valproic acid to a patient's regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses above 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

3) Conversion to Monotherapy
   a) When converting to monotherapy, the recommended initial oral dosage is 10 to 15 milligrams/kg/day (mg/kg/day) increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses above 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). The concomitant antiepileptic dosage may be reduced if a valproic acid therapy or after 1 to 2 weeks. The dosage of the concomitant antiepileptic reduced by approximately 25% every 2 weeks. Valproic acid doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.3.1.A.1.c Manic bipolar I disorder

1) Depakote (R) ER, extended-release: The initial dose is 25 milligrams/kilogram/day (mg/kg/day) a once daily with increases in dose done as quickly as possible to achieve the desired clinical effect. The target trough plasma level range was 85 to 125 micrograms/milliliter. The maximum recommended mg/kg/day (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) Depakote (R), delayed-release: The initial dose is 750 mg orally per day in divided doses with increases done as quickly as possible to achieve the desired clinical effect. In clinical studies, the target trough plasma level range was 50 to 125 micrograms/milliliter. The maximum recommended dose is 60 mg/kg/day (Prod Info DEPAKOTE(R) extended-release oral tablets, 2006).

3) A divalproex loading dose of 20 milligrams/kilogram/day (mg/kg/day) has been given to achieve therapeutic serum valproate levels of 50 micrograms/mL by day 3 of the study (Hirschfeld, 1996). Another accelerated loading regimen used divalproex 30 milligrams per kilogram per day (mg/kg/day) twice daily, and 2 followed by 20 mg/kg/day for days 3 through 10, which resulted in 16 of 19 (84%) of patients achieving therapeutic serum valproate levels of 50 micrograms/milliliter by day 3 of the study (Hirschfeld, 1996).

4) Another accelerated loading regimen used divalproex 30 milligrams per kilogram per day (mg/kg/day) twice daily, and 2 followed by 20 mg/kg/day for days 3 through 10, which resulted in 16 of 19 (84%) of patients achieving therapeutic serum valproate levels of 50 micrograms/milliliter by day 3 of the study (Hirschfeld, 1996).

1.3.1.A.1.d Migraine; Prophylaxis

1) The recommended initial dose of extended-release tablets is 500 milligrams (mg) orally once a day followed by an increase to 1000 mg orally once daily (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008). The maximum recommended daily dose is 2000 mg (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) The recommended initial dose of delayed-release tablets is 250 milligrams (mg) twice daily. In some cases, up to 1000 mg/day are beneficial (Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.3.1.A.1.e Conversion From Valproic Acid

1) When converting patients from valproic acid, initiate divalproex sodium sprinkle capsules at the starting dose and titrate the dose during the schedule. Once stabilized, a schedule of divalproex sodium 2 or 3 times a day may be initiated (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2008).

1.3.1.A.1.f Conversion From Delayed-Release To Extended-Release Formulations

1) When converting from divalproex sodium delayed-release tablets (Depakote(R) Tablets), administer sodium extended-release tablets (Depakote(R) ER) once daily in doses 8% to 20% higher than the total daily divalproex sodium delayed-release tablets (Depakote(R) Tablets). Due to pharmacokinetic variation, patients, monitor plasma levels if satisfactory clinical response has not been achieved.

<table>
<thead>
<tr>
<th>Divalproex Sodium Dose Conversion</th>
<th>DEPAKOTE(R) ER Dose Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed-release (Depakote(R))</strong></td>
<td><strong>Total daily dose (mg)</strong></td>
</tr>
<tr>
<td>500 mg - 625</td>
<td>750</td>
</tr>
<tr>
<td>750 mg - 875</td>
<td>1000</td>
</tr>
<tr>
<td>1000 mg - 1125</td>
<td>1250</td>
</tr>
<tr>
<td>1250 - 1375</td>
<td>1500</td>
</tr>
</tbody>
</table>
In cases where the total daily dose of delayed-release product cannot be directly converted to an extended-release product because the required dosing strengths are not available, consider increasing the next higher dosage before converting to the appropriate total daily dose of the extended-release product (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.3.1.A.1.g Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of seizures with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1/2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid or 100 milligrams of Phenobarbital) at a mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.A.2 Alcohol withdrawal syndrome

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

1.3.1.B Valproate Sodium

Intravenous route

Rectal route

1.3.1.B.1 Intravenous route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Seizure, Multiple seizure types; Adjunct

1.3.1.B.1.a Absence seizure, Simple and complex

1) The initial dosage is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 to 10 milligrams/kg/day until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and the maximum recommended dosage is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

1.3.1.B.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) The usual recommended initial intravenous dosage for monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

2) Adjunctive Therapy

a) The usual recommended intravenous dosage when adding valproic acid to a patient’s regimen is 25 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until the therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

3) Conversion to Monotherapy

a) Concomitant antiepilepsy drug dosage may be reduced by approximately 25% every 2 week of valproic acid therapy or after 1 to 2 weeks of therapy (Prod Info DEPACON(R) IV injection, 2006).
1.3.1.B.1.c Seizure, Multiple seizure types: Adjunct
1) Administer 10 to 15 milligrams per kilograms (mg/kg) per day intravenously. The dose may be increased to 10 to 15 milligrams per kilograms (mg/kg) per week to achieve optimal clinical response, which is typically seen at a therapeutic range of 500 to 1000 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

1.3.1.B.1.d Important Note
1) Valproate sodium injection is for intravenous use only and should be used in patients who are unable to use the oral form of valproic acid. Use of valproate sodium injection for periods of more than 14 days has not been studied. As soon as it is clinically feasible, patients should be switched back to oral valproic acid. Valproate sodium injection should be administered as a 60 minute infusion and not faster than 20 milligrams/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The same frequency of administration should be used as the oral products. Plasma concentrations should be monitored (Prod Info Depacon(TM), 2003).
2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients with urea cycle disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated incidence of 1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalproex sodium (Prod Info Depakote(R), 2003; Prod Info Depakote ER(R), 2003; Prod Info Depakene(R), 2003; Prod Info Depacon(TM), 2003).

1.3.1.B.2 Rectal route
a) In one patient, a 65-year-old male, status epilepticus did not respond to commonly used anticonvulsants. He was completely controlled by SODIUM VALPROATE syrup given rectally (250 to 500 milligrams every 6 to 8 hours) was mixed with 30 milliliters of water and given as a retention enema. It was well-absorbed rectally and resulted in less respiratory depression than other agents (Thorpy, 1980).

1.3.1.B.3 Withdrawal Schedule
a) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of seizures for at least 1 year were evaluated. The dose of each anticonvulsant was reduced by 1 unit at intervals of 1 to 2 days. The mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 61% free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.C Valproic Acid

Oral route

Hiccoughs

1.3.1.C.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Manic bipolar I disorder
Migraine; Prophylaxis

Myoclonic seizure

Seizure, Multiple seizure types; Adjunct

1.3.1.C.1.a Absence seizure, Simple and complex

1) The usual recommended dosage is 15 milligrams/kilogram/day (mg/kg/day) orally, increasing at 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maximum recommended dosage is 60 mg/kg/day. Total daily doses of valproic acid exceeding 250 mg should be divided doses. Therapeutic valproate serum concentrations for most patients with absence seizures range from 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006 STAVZOR(R) delayed release oral capsules, 2008).

2) The initial dose should be determined by weight and not age. The manufacturer of (Depakene(R) following dosage schedule based on body weight (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006))

<table>
<thead>
<tr>
<th>Pounds (lbs)</th>
<th>Kilograms (kg)</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 to 54.9 lbs</td>
<td>10 to 24.9 kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>55 to 87.9 lbs</td>
<td>25 to 39.9 kg</td>
<td>500 mg</td>
</tr>
<tr>
<td>88 to 131.9 lbs</td>
<td>40 to 59.9 kg</td>
<td>750 mg</td>
</tr>
<tr>
<td>132 to 164.9 lbs</td>
<td>60 to 74.9 kg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>165 to 197.9 lbs</td>
<td>75 to 89.9 kg</td>
<td>1250 mg</td>
</tr>
</tbody>
</table>

1.3.1.C.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) The usual recommended initial oral dosage for monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until the desired therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Concomitant antiepilepsy drug can be reduced at the initiation of valproic acid therapy or after 1 to 2 weeks of therapy. The dosage can be reduced by approximately 25% every 2 weeks. Valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) Conversion to Monotherapy

a) When converting to monotherapy, the usual recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses below a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Concomitant antiepilepsy drug can be reduced by approximately 25% every 2 weeks. Valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses.

3) Adjunctive Therapy

a) The usual recommended oral dosage when adding valproic acid to a patient's regimen is 10 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to 10 mg/kg/week until therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses below a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.3.1.C.1.c Manic bipolar I disorder

1) The recommended initial dose of delayed-release valproic acid is 750 milligrams (mg) orally daily. The dose should be increased as quickly as possible to achieve the lowest therapeutic dose that will achieve the desired clinical response or desired range of plasma concentrations. The maximum recommended dose is 1500 milligrams (mg)/kilogram/day or less with a therapeutic serum range of 50 to 125 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.3.1.C.1.d Migraine; Prophylaxis

1) For the prophylaxis of migraine, the recommended initial dose of delayed-release valproic acid (5 milligrams (mg) orally twice daily. Some patients may benefit from doses up to 1000 mg/day. Higher doses may be required for greater efficacy in clinical trials (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
1.3.1.C.1.e  Myoclonic seizure

1) A starting dose of 15 milligrams/kilogram/day (mg/kg/day) provided seizure control for 63% of 76 juvenile myoclonic epilepsy. Twenty-five percent of patients were controlled at 20 mg/kg/day, 4% at 8% required addition of a second drug. After a 2-year seizure-free period, 22% of patients could be 5 mg/kg/day, 33% on 6 to 8 mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al, 2009).

1.3.1.C.1.f  Seizure, Multiple seizure types; Adjunct

1) The recommended initial dose is 10 to 15 milligrams/kilogram/day (mg/kg) orally. The dose may to 10 mg/kg/week to achieve optimal clinical response. If total daily dose exceeds 250 mg, give in 2 Maximum daily dose is 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 microgram

1.3.1.C.1.g  Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free c years with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 by 2 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with the remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.3.1.C.2  Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

1.3.2  Dosage in Renal Failure

A) Valproic Acid

1) Renal excretion of sodium valproate as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% redux unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milli however, hemodialysis typically decreases valproate concentrations by about 20%. Therefore, dosage adjust unnecessarily in patients with renal failure. Monitoring total concentrations of valproic acid may be misleading renal failure because protein binding in these patients is significantly reduced (Prod Info DEPAKENE(R) oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral c

B) Divalproex Sodium

1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tab Bennet et al, 1994). However, increased free levels of valproic acid have been reported, and monitoring of tc may be misleading (Lapierre et al, 1999). Renal excretion of sodium valproate as the unchanged drug is 1.8% 1996a). A 27% reduction in the unbound clearance of valproate has been reported in patients with a creatinin less than 10 milliliters/minute (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

C) Valproate Sodium

1) Dose adjustments are not required in renal failure (Prod Info Depakote(R) Tablets, 2002a; Bennett et al increased free levels of valproic acid have been reported and monitoring of total concentrations may be misl al, 1999). Renal excretion of SODIUM VALPROATE as the unchanged drug is 1.8% (Hardman et al, 1996a), in the unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 1 milliliters/minute.

1.3.3  Dosage in Hepatic Insufficiency

A) Valproic Acid

1) Valproic acid should not be administered to patients with hepatic disease or significant hepatic insuffic impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 5 cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin con larger unbound fractions by a 2 to 2.6 fold increase. Monitoring of total concentrations may be misleading sin concentrations may be significantly elevated in patients with hepatic disease, with total concentrations appea (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral c

2) Mean serum half-life of valproic acid was shown to increase in 7 patients with alcoholic cirrhosis or recove hepatitis. Single doses of 450 milligrams orally (solution) were administered (Klotz et al, 1978).

B) Divalproex Sodium

1) Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic insuffi disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreas patients with cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased concentratio

2) Mean serum half-life of valproic acid was shown to increase in 7 patients with alcoholic cirrhosis or recove hepatitis (Klotz et al, 1978). Single doses of 450 milligrams orally (solution) were administered.

C) Valproate Sodium

1) VALPROIC ACID or DIVALPROEX should not be administered to patients with hepatic disease or signific insufficiency (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) Tablets, 2002a). Liver disease impairs th eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in patients with cirrh in patients with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger by a 2 to 2.6 fold increase. Monitoring of total concentrations may be misleading.
2) Mean serum half-life of VALPROIC ACID was shown to increase in 7 patients with alcoholic cirrhosis or recent acute hepatitis (Klotz et al, 1978). Single doses of 450 milligrams orally (solution) were administered.

1.3.4 Dosage in Geriatric Patients

A) Valproic Acid

1) The manufacturer recommends that the starting dose be reduced due to a decrease in unbound clearance and a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of fluid intake, dehydration and adverse effects are also recommended. In patients with decreased food or fluid intake with excessive somnolence, dose reductions or discontinuation of therapy should be considered. Maintenance doses should be based on clinical response (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) oral capsules, 2008).

B) Divalproex Sodium

1) Due to a 39% decrease in intrinsic clearance and a 44% increase in free fraction, decrease the initial dose. Slow dosage titration and close monitoring of fluid and nutritional intake, dehydration, and adverse effects are also recommended. Maintenance doses should be based on clinical response (Prod Info DEPAKOTE(R) ER extended-release tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release tablets, 2008).

C) Valproate Sodium

1) The manufacturer recommends that the starting dose be reduced due to a decrease in unbound clearance and a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of fluid intake, dehydration and adverse effects are also recommended. Maintenance doses should be based on clinical response (Prod Info Depakote(R) Tablets, 2002a).

1.3.5 Dosage Adjustment During Dialysis

A) Valproic Acid

1) Hemodialysis typically reduces valproate concentrations by about 20%, but a 27% reduction in the unbound valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefore, supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenous hemofiltration. Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because protein binding is significantly reduced (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) oral capsules, 2008).

B) Divalproex Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous hemofiltration (Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% as is substantially reduced. Monitoring total concentrations may be misleading (Prod Info DEPAKOTE(R) ER extended-release tablets, 2008).

C) Valproate Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous hemofiltration (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations may be misleading (Prod Info Depakote(R) Tablets, 2002a).

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Divalproex Sodium

Valproate Sodium

Valproic Acid

1.4.1.A Divalproex Sodium
1.4.1.A.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

1.4.1.A.1.a Absence seizure, Simple and complex

1) The recommended initial dose is 15 milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals to a maximum recommended daily dosage of 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 micrograms/mL. However, there is no good correlation between daily dose, serum concentrations, and therapeutic effect. Patients may experience seizure control with higher or lower serum levels. For the delayed-release tablets, total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodium titrated upwards, the blood levels of phenobarbital and/or phenytoin may be affected (Prod Info DEPAKOTE extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.4.1.A.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) Initial monotherapy (children 10 years of age or older): The recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy

a) Adjunctive therapy (children 10 years of age or older): The recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

3) Conversion To Monotherapy

a) Conversion to monotherapy (children 10 years of age or older): The recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Do not exceed 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.4.1.A.1.c Safety and Efficacy

1) The safety and efficacy for the treatment of epilepsy in children less than 10 years of age have been established (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

2) The efficacy for use in the pediatric population for the treatment of mania or migraine prophylaxis has been established (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.4.1.A.1.d Conversion From Valproic Acid

1) When converting patients from valproic acid to a patient's current regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Do not exceed 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

1.4.1.A.1.e Conversion From Delayed-Release To Extended-Release Formulations

1) When converting from divalproex sodium delayed-release tablets (Depakote(R) Tablets), administer sodium extended-release tablets (Depakote(R) ER) once daily in divided doses (600 mg to 20% higher than the total daily dose of divalproex sodium delayed-release tablets (Depakote(R) Tablets). Due to pharmacokinetic variation among patients, monitor plasma levels if satisfactory clinical response has not been achieved.

<table>
<thead>
<tr>
<th>Divalproex Sodium Dose Conversion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed-release (Depakote(R))</td>
<td>Extended-release (Depakote(R) ER)</td>
</tr>
<tr>
<td>Total daily dose (mg)</td>
<td>(mg)</td>
</tr>
<tr>
<td>500* - 625</td>
<td>750</td>
</tr>
</tbody>
</table>

*Conversion to monotherapy (children 10 years of age or older): The recommended initial oral dosage is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).
In cases where the total daily dose of delayed-release product cannot be directly converted to an extended-release product because the required dosing strengths are not available, consider increasing the next higher dosage before converting to the appropriate total daily dose of the extended-release product (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.4.1.A.1.f Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of seizures for 1 year with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 12 weeks (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 6 remaining free of seizures (relapse rate 33.7%) (Callaghan et al, 1988).

1.4.1.B Valproate Sodium

Intravenous route

Oral route

1.4.1.B.1 Intravenous route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Seizure, Multiple seizure types; Adjunct

1.4.1.B.1.a Absence seizure, Simple and complex

1) For children 10 years of age and older, the initial dosage is 15 milligrams/kilogram/day (mg/kg/day) week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 mg should be given in divided doses, and the maximum recommended dosage is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

1.4.1.B.1.b Complex partial epileptic seizure

1) Initial Monotherapy (children 10 years of age or older)
   a) The usual recommended initial dosage for monotherapy is 10 to 15 milligrams/kilogram/day increasing at 1 week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and the recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

2) Adjunctive Therapy (children 10 years of age or older)
   a) The usual recommended dosage when adding valproic acid to a patient's regimen is 10 to 1 mg/kg/day until therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrams in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON(R) IV injection, 2006).

3) Conversion to Monotherapy
   a) Concomitant antiepilepsy drug dosage may be reduced by approximately 25% every 2 week of valproic acid therapy or after 1 to 2 weeks of therapy (Prod Info DEPACON(R) IV injection, 2006).
1.4.1.1.B.1.c  Seizure, Multiple seizure types; Adjunct
1) For children 10 years and older, administer 10 to 15 milligrams per kilograms (mg/kg) per day. This dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response, which is typically therapeutic range of 50 to 100 mcg/mL. The maximum recommended dose is 60 mg/kg/day (Prod Info Depacon(TM), 2003).

1.4.1.1.B.1.d  Important Note
1) Valproate sodium injection is for intravenous use only and should be used in patients who are not using the oral form of valproic acid. Use of valproate sodium injection for perioperative management or as an alternative to the oral form of valproic acid (Prod Info Depacon(TM), 2003).
2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients with disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated prevalence of 1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalproex sodium (Prod Info Depakote(TM), 2003; Prod Info Depakote ER(TM), 2003; Prod Info Depacon(TM), 2003; Prod Info Depakene(TM), 2003; Prod Info Depacon(TM), 2003).

1.4.1.1.B.1.e  Intravenous use
1) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3 or 6 milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has been used. Doses of 21 to 28 mg/kg were given to 21 patients (2 to 54-years-old). Peak serum valproate concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/millimeter. The infusions were well-tolerated and no cardiac or central nervous system adverse effects were reported (Venkataraman & Wheless, 1999).
2) Intravenous valproic acid was used in 4 patients (3 children and 1 adult) for the treatment of WAVE STATUS EPILEPTICUS. Loading doses of 30 milligrams/kilogram (mg/kg) were given over an hour. Main required in the 3 pediatric patients ranged from 120 to 160 mg/kg/day divided every 6 hours (Chez et al, 2003).

1.4.1.1.B.1.f  Intravenous dosing
1) Equivalent Doses
a) The total daily dose of valproate sodium injection should be equivalent to the total daily dose of valproic acid product and should be administered as a 60 minute infusion with the same frequency for the same period of time. Plasma concentration monitoring and dosage adjustments may be necessary. Infusions exceed 20 milligrams (mg)/minute. If the total daily dose exceeds 250 mg, it should be given in 3 equal divided doses (Prod Info Depacon(TM), 1999).
b) The manufacturer states that the equivalence shown between valproate sodium injection and oral products at steady state was only evaluated in an every 6 hour dosing regimen. If valproate sodium injection is given less frequently, trough levels may fall below those measured using the oral route. Close monitoring of plasma levels may be needed if valproate sodium injection is given only 2 or 3 times daily (Depacon(TM), 1999).

2) Intravenous Rate of Administration
a) Valproate sodium injection should be administered as a 60 minute infusion and not faster than 1 milligram/kilogram (mg/kg)/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The same frequency of administration should be used products. Plasma concentrations should be monitored (Prod Info Depacon(TM), 2003).
b) In a prospective pilot study involving 4 hospitalized and acutely ill children, intravenous sodium valproate was administered at an infusion rate of 1 milligram/kilogram/minute. The patients ranged in age and weight between 17.2 to 60 kilograms. Before and during the infusion, vital signs and blood samples were collected pre-infusion, at 0.5 hours at 1 hour post-infusion. Doses ranged between 8.3 to 15.4 milligrams/kilogram (mg/kg) and the duration of infusions ranged from 8 to 15 minutes. Intravenous sodium valproate was diluted 1:1 (v/v) with sterile water. The investigators found no clinically significant changes in blood pressure, heart rate (values not reported). The only reported adverse reaction was localized inflammation at the injection site in 1 patient. Unbound valproate acid concentrations were greater at 0.5 hours post-infusion than concentrations measured before and during the infusion. Vital signs and blood samples were also collected pre-infusion (Birnbaum et al, 2003). Study investigators being cautious when using rapid infusions to acutely ill patients as higher unbound drug levels result in excessive toxicity although total drug levels are within the target range (Birnbaum et al, 2003).

c) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3 to 6 milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has been used. Doses of 21 to 28 mg/kg were given to 21 patients (2 to 54-years-old). Peak serum concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/millimeter. The infusion was well-tolerated and no cardiac or central nervous system adverse effects were reported (Venkataraman & Wheless, 1999).

d) Two patients (ages 10 years and 34 months) receiving multiple antiepileptic inducing agents, including phenobarbital, required a loading dose of valproate 20 milligrams/kilogram (mg/kg). A maintenance dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response, which is typically therapeutic range of 50 to 100 mcg/mL. The maximum recommended dose is 60 mg/kg/day (Prod Info Depacon(TM), 2003).

1.4.1.1.B.1.g Intravenous valproic acid was used in 4 patients (3 children and 1 adult) for the treatment of WAVE STATUS EPILEPTICUS. Loading doses of 30 milligrams/kilogram (mg/kg) were given over an hour. Main required in the 3 pediatric patients ranged from 120 to 160 mg/kg/day divided every 6 hours (Chez et al, 2003).

1.4.1.1.B.2 Oral route

---

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady

Exhibit E.7, page 15
1.4.1.B.2.a West syndrome

1) Monotherapy with VALPROIC ACID was effective in the treatment of INFANTILE SPASMS in a study involving 22 children aged 4 to 11 months (Siemes et al, 1988). VALPROIC ACID (as SODIUM VALPROATE) was given initially in oral doses of 15 milligrams/kilogram/day; this was increased every second day by 1 milligram/kilogram until seizures ceased or a maximum dose of 100 milligrams/kilogram/day was achieved. If seizures were not controlled or reduced after 4 to 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 mg/kg/day was added to the regimen. The doses of SODIUM VALPROATE ranged from 40 to 100 milligrams/kilogram/day.

1.4.1.C Valproic Acid

Oral route

Rectal route

1.4.1.C.1 Oral route

Absence seizure, Simple and complex

Complex partial epileptic seizure

Migraine; Prophylaxis

Seizure, Multiple seizure types; Adjunct

1.4.1.C.1.a Absence seizure, Simple and complex

1) In children, 10 years and older, the usual recommended dosage is 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or occur. The maximum recommended dosage is 60 mg/kg/day. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses. Therapeutic valproate serum concentrations for most patients with absence seizures is considered to range from 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) The initial dose should be determined by weight and not age. The manufacturer of (Depakene(R); following dosage schedule based on body weight (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

<table>
<thead>
<tr>
<th>Pounds (lbs)</th>
<th>Kilograms (kg)</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 to 54.9 lbs</td>
<td>10 to 24.9 kg</td>
<td>250 mg</td>
</tr>
<tr>
<td>55 to 87.9 lbs</td>
<td>25 to 39.9 kg</td>
<td>500 mg</td>
</tr>
<tr>
<td>88 to 131.9 lbs</td>
<td>40 to 59.9 kg</td>
<td>750 mg</td>
</tr>
<tr>
<td>132 to 164.9 lbs</td>
<td>60 to 74.9 kg</td>
<td>1000 mg</td>
</tr>
<tr>
<td>165 to 197.9 lbs</td>
<td>75 to 89.9 kg</td>
<td>1250 mg</td>
</tr>
</tbody>
</table>

1.4.1.C.1.b Complex partial epileptic seizure

1) Initial Monotherapy

a) In children 10 years and older, the usual recommended initial oral dosage for monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until therapeutic effect is reached. Usually, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 divided doses. (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2) Conversion to Monotherapy

a) When converting to monotherapy in children 10 years and older, the usual recommended initial dose is 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/week until therapeutic effect is reached or adverse effects occur. Usually, optimal clinical response is achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured to determine whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 divided doses. (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).
exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) Adjunctive Therapy
   a) In children 10 years and older, the recommended oral dosage when adding valproic acid to the regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to 10 milligrams/kg/day to achieve optimal clinical response. If total daily doses are 60 mg/kg/day or less, a therapeutic effect is reached. Usually, plasma levels should be maintained at about 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.4.1.C.1.c Migraine; Prophylaxis
   1) Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophylaxis of migraines (Hamalainen, 1998). However, the efficacy has not been confirmed in clinical trials (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

1.4.1.C.1.d Seizure, Multiple seizure types; Adjunct
   1) In children, 10 years and older, the recommended initial dose is 10 to 15 milligrams/kilogram/day divided into 2 doses. The dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. If total daily doses are 60 mg/kg/day or less, a therapeutic effect is reached. Usually, plasma levels should be maintained at about 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.4.1.C.1.e Withdrawal Schedule
   1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free of seizures for more than 1 year with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 mg/kg/day (1 unit equivalent to 200 milligrams of carbamazepine or valproic acid, or 100 milligrams of lamotrigine) until the desired therapeutic effect is reached. Usually, optimal clinical response is achieved at about 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

1.4.1.C.2 Rectal route
   a) The bioavailability of diluted valproic acid syrup given rectally is comparable to that following oral administration, therefore, the same for rectal or oral administration. Rectal administration of valproic acid syrup is recommended as an alternative to oral administration when the oral route is not available (Cloyd & Kriel, 1981).
   b) Rectal administration of valproic acid has been successful in the treatment of intractable status epilepticus. Commercially available valproic acid syrup (Depakene(R) 250 mg/5 mL) was diluted 1:1 with tap water to a concentration of 250 mg/L. Maintenance doses were started 8 to 24 hours after the initial loading dose (10 to 15 milligrams/kilogram every 8 hours). The dose may be increased by 5 to 10 milligrams/kg/day to achieve optimal clinical response. If total daily doses are 60 mg/kg/day or less, a therapeutic effect is reached. Usually, plasma levels should be maintained at about 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   c) The successful use of rectal anticonvulsants was described as an alternative route to oral drug therapy in the treatment of status epilepticus. Perioperative rectal therapy was employed for clonazepam in children (Callaghan et al, 1988).

1.4.2 Dosage in Renal Failure
   A) Valproic Acid
      1) Renal excretion of sodium valproate as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% reduction in the unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   B) Divalproex Sodium
      1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tablet, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   C) Valproate Sodium
      1) In children, 10 years and older, the recommended initial dose is 10 to 15 milligrams/kilogram/day divided into 2 doses. The dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. If total daily doses are 60 mg/kg/day or less, a therapeutic effect is reached. Usually, plasma levels should be maintained at about 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measured whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).
1) Renal excretion of SODIUM VALPROATE as the unchanged drug is 1.8% (Hardman et al, 1996a). A 27% unbound clearance of valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Dosage adjustments are not required in renal failure (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1999) increased free levels of valproic acid have been reported and monitoring of total concentrations may be misleading.

1.4.3 Dosage in Hepatic Insufficiency
A) Valproic Acid
1) Valproic acid should not be administered to patients with hepatic disease or significant hepatic insufficiency. The capacity to eliminate valproate is impaired by cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations may be misleading in patients with hepatic disease, with total concentrations appearing increased (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium
1) Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic insufficiency. The capacity to eliminate valproate is impaired by cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations may be misleading in patients with hepatic disease, with total concentrations appearing increased (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 20006).

C) Valproate Sodium
1) VALPROIC ACID or DIVALPROEX should not be administered to patients with hepatic disease or significant hepatic insufficiency (Prod Info Depakene(R), 1999; Prod Info Depakote(R), 1999). Liver disease impairs the capacity to eliminate valproate. In one study, the clearance of free valproate was decreased by 50% in patients with cirrhosis and by 16% in patients with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations may be misleading.

1.4.4 Dosage Adjustment During Dialysis
A) Valproic Acid
1) Hemodialysis typically reduces valproate concentrations by about 20%, but a 27% reduction in the unbound valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefore, supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenous hemofiltration. Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because protein binding is substantially reduced. Monitoring total concentrations may be misleading (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed-release oral capsules, 2008).

B) Divalproex Sodium
1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenous hemofiltration (Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations may be misleading (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

C) Valproate Sodium
1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenous hemofiltration (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1994). Hemodialysis typically reduces valproate concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations may be misleading (Prod Info Depakote(R) Tablets, 2002a).

2.0 Pharmacokinetics

2.1 Onset and Duration
A) Onset
1) Peak Response
a) Epilepsy, oral: 2 weeks (Lance & Anthony, 1977a; Lance & Anthony, 1977b).

2.2 Drug Concentration Levels
A) Therapeutic Drug Concentration
1) Epilepsy, 50 to 100 mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakene(R) Tablets, 2003; Prod Info Depacon(R), 1999; Turnbull et al, 1983a; Rimmer & Richens, 1985d). A free concentration therapeutic range has not been established (Prod Info Depakene(R), 1999).
b) High concentration valproic acid (80 to 150 mcg/mL) may be needed to reduce seizure frequency of some
seizures and secondarily generalized tonic-clonic seizures (Beydoun et al, 1997d).
c) Plasma concentrations fluctuate between doses, varying between 100% and 140% of the steady state con-
(Schobben et al, 1975a; Loiseau et al, 1975).
d) Comparable plasma levels occur when switching from oral valproate to intravenous valproate sodium (Pr-
(R), 1999).
2) Acute mania, 50 to 125 mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Dep-
2003).
B) Peak Concentration
1) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a sing-
divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration-time
noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours vers-
When valproic acid delayed release capsules were administered with food, there was a 23% decrease in Cmax of
median Tmax was increased to 4.8 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
C) Time to Peak Concentration
1) Oral, valproic acid delayed-release capsules, single 500-mg dose, fasted: 2 hr (Prod Info STAVZOR(R) delay-
capsules, 2008)
a) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a
divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration
noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours
(Prod Info STAVZOR(R) delayed release oral capsules, 2008).
2) Oral, valproic acid delayed-release capsules, single 500-mg dose, with food: 4.8 hr (Prod Info STAVZOR(R) di-
capsules, 2008)
a) When a single dose of valproic acid delayed release 500 milligram capsules was administered with food, t
decrease in Cmax of valproic acid and median Tmax was increased to 4.8 hours compared with administrat
state (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
3) Oral, valproic acid capsules (Depakene(R)): 1 to 4 hours (Prod Info Depakene(R), 1999)(Hardman et al, 1996)
4) Oral, divalproex tablet: 4 to 8 hours (Prod Info Depakote(R) Tablets, 2002; Oelkers et al, 1977).
5) Oral, divalproex sprinkle capsule: 3.3 to 4.8 (Prod Info Depakote(R) Sprinkle Capsules, 1999).
6) Oral, divalproex sodium extended-release tablet: 4 - 17 hours (Prod Info Depakote(R) ER, 2003m)
a) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a
divalproex sodium delayed release 500 mg oral tablets under fasted conditions, similar plasma concentration
noted with the exception of median Tmax, which occurred earlier with the delayed release capsules (2 hours
(Prod Info STAVZOR(R) delayed release oral capsules, 2008).
b) Maximum valproate plasma concentration (Cmax) of divalproex sodium extended-release tablets at steady
relative to divalproex sodium delayed-release tablets given twice a day (Prod Info Depakote(R) ER, 2003m).
7) Oral, sodium valproate solution: 1.2 hours (Klotz & Antonin, 1977).
8) Intravenous, Depacon(R): At the end of a 1 hour infusion (Prod Info Depacon(R), 1999).
9) Rectal, diluted valproic acid syrup: 3.1 hours (Holmes et al, 1989).
D) Area Under the Curve
1) When a single dose of valproic acid delayed release 500 milligram (mg) oral capsules was compared to a sing-
divalproex sodium delayed release 500 mg oral tablets under fasted conditions, the plasma concentration-time pr
in terms of valproic acid. Coadministration with food did not alter systemic exposure of valproic acid (Prod Info ST
delayed release oral capsules, 2008).
2) Equivalent areas under the curve were achieved at steady state, when divalproex sodium tablets and valproa-
given as a one hour infusion, were administered at 250 mg every 6 hours for 4 days (Prod Info Depacon(R), 1999)
3) The area under the curve and the maximum concentration resulting from a valproate sodium injection 500 mg
and a 500 mg dose of valproic acid syrup were equivalent (Prod Info Depacon(R), 1999).
4) When extended release divalproex sodium tablets (Depakote(R) ER) are administered once daily in doses 8 t
the total daily dose of delayed release divalproex sodium tablets (Depakote(R) Tablets), equivalent areas under th
achieved (Prod Info Depacon(R) ER, 2003m).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination
2.3.1 Absorption
A) Bioavailability
1) Oral, extended-release tablets: 90% (Prod Info Depakote(R) ER, 2003m)
   a) The absolute bioavailability of divalproex sodium extended-release tablet administered as a single dose was approximately 90% relative to intravenous infusion (Prod Info Depakote(R) ER, 2003m).
   b) Divalproex sodium extended-release tablets given on an empty stomach produced an average bioavailability of 89% relative to divalproex sodium delayed-release tablets given twice a day (Prod Info Depakote(R) ER, 2003m).
B) Effects of Food
1) No significant effect on systemic availability (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   a) When a single dose of valproic acid delayed release 500 milligram capsules was administered with food, Cmax decreased by 23% and median Tmax was increased from 2 hours to 4.8 hours compared to the same dose under fasting conditions (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   b) Coadministration of oral valproate products with food is not expected to have any significant clinical management of patients with epilepsy (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2.3.2 Distribution
A) Distribution Sites
1) Protein Binding
   a) 90% (primarily to albumin) (Prod Info Depakene(R), 1999) (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) Tablets, 2002; Hardman et al, 1996; Klotz & Antonin, 1977).
      1) Protein binding is concentration-dependent and decreases at high valproate concentrations (Prod Info Depakote(R) ER Tablets, 2002; Prod Info Depakote(R) Tablets, 2003).
      2) Tissues and Fluids
         a) CEREBROSPINAL FLUID, 10% (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Pinde
      1) Valproate concentration in cerebrospinal fluid is approximately 10% of the total concentration (Prod Info Depakote(R) delayed release oral capsules, 2008).
B) Distribution Kinetics
1) Volume of Distribution
   a) 0.14 to 0.23 L/kg (Puerta et al, 1999)(Bennett et al, 1994a).
      1) Differences in volume of distribution occur between young and elderly (0.13 and 0.19 L/kg, respectively).
      2) The volume of distribution for total valproate is 11 L/1.73 m(2), free valproate is 92 L/1.73 m(2) (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, rapidly and extensively (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depakote(R) Tablets, 2002).
   a) Valproate undergoes conjugation (30% to 50%), mitochondrial beta oxidation (40%), and microsomal numerous metabolites (15% to 20%). Less than 3% of an administered dose is excreted unchanged in the urine (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m); (Prod Info Depakote(R) Tablets, 2002).
   b) A cytochrome P450 microsomal enzyme appears to metabolize valproic acid (Zaccara et al, 1988).
B) Metabolites
1) 2-propyl-3-keto-pentanoic acid, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) Tablets, 2002).
   a) Approximately 70% of a dose is excreted as the glucuronide (Nau & Loscher, 1984; Loscher, 1981; B 1979).
   b) Approximately 70% of a dose is excreted as the glucuronide (Nau & Loscher, 1984; Loscher, 1981; B 1979).
2) Divalproex sodium extended-release tablets, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) Tablets, 2002).
2) Divalproex sodium extended-release tablets, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R) Tablets, 2002).
   b) Approximately 70% of a dose is excreted as the glucuronide (Nau & Loscher, 1984; Loscher, 1981; B 1979).
   b) Approximately 70% of a dose is excreted as the glucuronide (Nau & Loscher, 1984; Loscher, 1981; B 1979).

2.3.4 Excretion
A) Kidney
1) Renal Clearance (rate)
   a) Total valproate, adults: 0.56 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   b) Free valproate, adults: 4.6 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   b) Free valproate, adults: 4.6 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   b) Free valproate, adults: 4.6 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
2) Renal Excretion (%)
   a) 70% to 80% (Bruni & Wilder, 1979; Schobben et al, 1975a).
b) In adult patients on monotherapy, 30% to 50% of an administered dose appears in the urine as glucuronides (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) Less than 3% of an administered dose of valproate is excreted unchanged in the liver total valproate, square meter (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Bile
1) Bile, 7% (Pinder et al, 1977d).

C) Other
1) TOTAL PLASMA CLEARANCE
   a) 0.9 L/hr (Puentes et al, 1999).
      1) Clearance decreases with increasing age (Snachez-Alcaraz et al, 1998). Clearances in specific children were found to be: 24.5 ml/kg/hr for less than 2 years old, 19.9 ml/kg/hr for 2 to 4 years old, 12.7 ml/kg/hr for 6 to 8 years old.
      2) Children between 3 months and 10 years have 50% higher clearance rates when compared to the age of 10, pharmacokinetic parameters of children are similar to those of adults (Prod Info STAVZOR delayed release oral capsules, 2008).
      3) Intrinsic clearance in the elderly (age ranged from 68 to 89 years) is reduced by 39% and free fraction by 44% when compared with young adults (age ranged from 22 to 26 years) (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m).
      4) Clearance is increased by 10% with coadministration of phenobarbital (Yukawa et al, 1997a).
      5) Clearance is increased by coadministration of carbamazepine (dose-related) (Yukawa et al, 1995).
      6) There are no differences in the body surface area adjusted unbound clearance between male an n = 21, body weight = 70 kg, and n = 21, body weight = 100 kg (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) Tablets, 2002).
      7) Clearance of free valproate is decreased in patients with liver disease. One study demonstrated clearance in 7 patients with cirrhosis and a 16% decrease in clearance in 4 patients with acute hepatitis (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote Tablets, 2002).
      8) There is a 27% decrease in the unbound clearance of valproate in patients with a creatinine clearance of less than 1 ml/minute (Prod Info STAVZOR(R) delayed release oral capsules, 2008) (Prod Info Depakote(R) ER, 2003m).

2) OTHER EXCRETION
   a) Lung, 2 to 18% (Pinder et al, 1977d).
      1) Excreted in expired air as carbon dioxide (Pinder et al, 1977d).

2.3.5 Elimination Half-life
A) Parent Compound
1) Adults: 6 to 17 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008) (Prod Info Depakote(R) Tablets, 1996b; Rimmer & Richens, 1985d; Perucca et al, 1984; Bryson et al, 1983).
   a) The mean terminal half-life for valproate monotherapy ranged from 9 to 16 hours following oral dosing to 1000 milligrams (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   b) In one study, the half life of valproate was increased from 12 to 18 hours in patients with liver disease (Prod Info Depakote(R) Tablets, 2002).
2) Adults, liver disease: 18 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   a) Compared with 6 healthy subjects, the half-life of valproate in patients with liver disease increased for one study involving 7 patients with cirrhosis and 4 patients with acute hepatitis (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) Tablets, 2002).
3) Neonates less than 10 days old: 10 to 67 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to older adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
4) Neonates greater than 2 months old: 7 to 13 hours (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to older adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

2.3.6 Extracorporeal Elimination
A) Hemodialysis
1) Dialyzable: Yes (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Johnson et al, 1999); (Franke et al, 1990).
   a) Hemodialysis of 4 hours duration removed 15% to 22% of valproic acid in chronic renal failure patient (Marbury et al, 1980).
   b) Acute valproic acid overdose (serum concentration greater than 1200 mcg/mL) in a 25-year-old woman who attempted suicide was successfully treated with high-flux hemodialysis using a highly permeable polysulfone membrane. High-flux hemodialysis was performed for 4 hours and lowered the valproic acid half-life to 2 hours. The authors concluded that high-flux hemodialysis is as effective as combination hemodialysis and charcoal hemoperfusion and avoided the attendant risks of hemoperfusion (Kane et al, 2000).
   c) A 43-year-old woman who ingested approximately 19 grams of valproic acid had 15.5 grams removed by hemodialysis (high-flux polysulfone hemodialysis membrane) (Johnson et al, 1999). Her valproic acid se
decreased from 940 to 164 micrograms/milliliter. The half-life of valproic acid was reduced from 7.2 to 2.4.

B) Peritoneal
1) Dialyzable: Yes (Orr et al, 1983).
   a) In a 9-year-old boy receiving chronic peritoneal dialysis, only an average of 4.5% of the valproic acid over 12- or 24-hour dialysis periods (Orr et al, 1983).

C) Hemoperfusion
1) Dialyzable: Yes (Franssen et al, 1999).
   a) A 27-year-old male was successfully treated with serial hemodialysis, and hemoperfusion with resin following a valproic acid overdose (Franssen et al, 1999). The patient was dialyzed during two 3-hour sessions with highly permeable polysulfone hemodialysis membrane. A charcoal hemoperfusion column was added during the first session and a resin column for the second. The hemodialysis was effective while the hemofiltration in the first hour. This was due to rapid saturation of the column. The resin column appeared to be more effective than charcoal.

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

3.0.A Black Box WARNING

1) Valproic Acid
   a) Oral (Syrup; Capsule, Liquid Filled)
      Hepatotoxicity
      Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. According to indications that children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe mental retardation, and those with organic brain disease. When valproic acid is used in patients under two years of age, they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicity is considerably lower in progressively older patient groups. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotoxicity preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and vomiting may occur. Patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals thereafter.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. Cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cases reported shortly after initial use as well as after several years of use. Patients and guardians should be informed that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment medical condition should be initiated as clinically indicated.

Teratogenicity
Valproate can produce teratogenic effects such as neural tube defects (eg, spina bifida). Accordingly, the products in women of childbearing potential require that the benefits of its use be weighed against the risk of fetal defects. This is especially important when the treatment of a spontaneously reversible condition not associated with permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2006).

b) Oral (Capsule, Delayed Release)
   Hepatotoxicity
   Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When valproic acid is used in this patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The incidence of fatal hepatotoxicity decreases considerably in progressively older patient groups. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotox
preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there during the first six months.

Teratogenicity
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, ti acid in women of childbearing potential requires that the benefits of its use be weighed against the risk o This is especially important when the treatment of a spontaneously reversible condition not ordinarily ass permanent injury or risk of death (e.g., migraine) is contemplated.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas reported shortly after initial use as well as after several years of use. Patients and guardians should be x abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt r If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the unc condition should be initiated as clinically indicated (Prod Info STAVZOR(R) delayed release oral capsule

2) Divalproex Sodium
a) Oral (Tablet, Enteric Coated; Tablet, Extended Release; Capsule, Delayed Release)

Hepatotoxicity
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. C age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those anticonvulsants, with congenital metabolic disorders, those with severe seizure disorders accompanied retardation, and those with organic brain disease. When divalproex sodium is used in this patient group, with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. T fatal hepatotoxicity decreases considerably in progressively older patient groups. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotox preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there during the first six months.

Teratogenicity
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). According to maternal age, the risk of congenital malformations increases. The risk is higher in women with a history of epilepsy, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. When valproate sodium is used in the patient group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. An information sheet describing the teratogenic potential of valproate is available for patients.

Pancreatitis
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas reported shortly after initial use as well as after several years of use. Patients and guardians should be x abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt r If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment for the unc condition should be initiated as clinically indicated (Prod Info DEPAKOTE(R) sprinkle oral capsu

3) Valproate Sodium
a) Intravenous (Solution)

HEPATOTOXICITY
Hepatic failure resulting in fatalities has occurred in patients receiving valproic acid and its derivatives. E: indicated that children under the age of two years are at a considerably increased risk of developing fata especially those on multiple anticonvulsants, with congenital metabolic disorders, those with severe accompanied by mental retardation, and those with organic brain disease. When valproate sodium is use group, it should be used with extreme caution and as a sole agent. The benefits of therapy should be we risks, Above this age group, experience in epilepsy has indicated that the incidence of fatal hepatotoxicit considerably in progressively older patient groups. These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatotox preceded by non-specific symptoms such as malaise, weakness, lethargy, facial edema, anorexia, and v patients with epilepsy, a loss of seizure control may also occur. Patients should be monitored closely for these symptoms. Liver function tests should be performed prior to therapy and at frequent intervals there during the first six months.(Prod Info DEPACON(R) IV injection, 2006).

PANCREATITIS
Cases of life-threatening pancreatitis have been reported in both children and adults receiving valproate. cases have been described as hemorrhagic with a rapid progression from initial symptoms to death. Cas reported shortly after initial use as well as after several years of use. Patients and guardians should be x abdominal pain, nausea, vomiting and/or anorexia can be symptoms of pancreatitis that require prompt evaluation. If pancreatitis is diagnosed, valproate should ordinarily be discontinued. Alternative treatment medical condition should be initiated as clinically indicated (Prod Info DEPACON(R) IV injection, 2006).

TERATOGENICITY
Valproate can produce teratogenic effects such as neural tube defects (e.g., spina bifida). Accordingly, th
products in women of childbearing potential requires that the benefits of its use be weighed against the risk of permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPAKON(R) IV injection, 20

3.1 Contraindications

A) Valproic Acid

1) hepatic disease or significant hepatic dysfunction (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

3) urea cycle disorders, known; hyperammonemomic encephalopathy, including fatalities, has occurred (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

B) Divalproex Sodium

1) hepatic disease or significant hepatic dysfunction (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKONE(R) delayed-release oral tablets, 2006)

2) hypersensitivity to valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

C) Valproate Sodium

1) hepatic disease or significant hepatic dysfunction (Prod Info DEPACON(R) IV injection, 2006)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

3) known urea cycle disorders; hyperammonemomic encephalopathy, including fatalities, has occurred (Prod Info DEPAKON(R) IV injection, 2006)

3.2 Precautions

A) Valproic Acid

1) children, especially under the age of 2 years; increased risk of hepatotoxicity; discontinue immediately if significant dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

2) concurrent use of multiple anticonvulsants; increased risk of hepatotoxicity; discontinue immediately if significant dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

3) hepatic disease, prior history of; increased risk of hepatotoxicity; discontinue immediately if significant dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

4) metabolic disorders, congenital; increased risk of hepatotoxicity; discontinue immediately if significant dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

5) organic brain disease; increased risk of hepatotoxicity; discontinue immediately if significant hepatic dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

6) pancreatitis, sometimes life-threatening, may occur; discontinuation is recommended (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

7) pregnancy; increased risk of birth defects (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

8) seizure disorders; severe and accompanied by mental retardation; increased risk of hepatotoxicity; discontinue immediately if significant hepatic dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2001)

9) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info STAVZOR(R) delayed release oral capsules, 2001)
10) acute head trauma; IV use is not recommended for prophylaxis of post-traumatic seizures (Prod Info DEPACON 2006)

11) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

12) cyclical vomiting and lethargy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod In delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

13) elderly; increased incidence of somnolence, especially in the presence of reduced nutritional intake and weight (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

14) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

15) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein I related or postpartum encephalopathy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

16) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevated plasma ammonia or glutamine (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disorder contraindication; discontinue if hyperammonemia develops (Prod Info STAVZOR(R) delayed release oral capsule DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

19) hypersensitivity reactions, multi-organ; have been reported within first 40 days of therapy and may be life-thre discontinue treatment (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

21) low BUN or protein avoidance; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

24) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adm (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

25) total valproate concentrations of 110 mcg/mL or higher in females, or 135 mcg/mL or higher in males; increases in plasma ammonia or glutamine (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-releases Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

B) Divalproex Sodium

1) hepatic failure, some cases fatal, has occurred; increased risk in patients with a history of hepatic disease, on anticonvulsant, with congenital metabolic disorders, severe seizure disorder accompanied by developmental disal disease and in children (especially under the age of 2 years); LFT monitoring is recommended (Prod Info DEPAK
oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
2) pancreatitis, sometimes life-threatening, has been reported (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
3) pregnant women; increased risk of birth defects (eg, neural tube defects) (Prod Info DEPAKOTE(R) sprinkle or Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
4) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
5) elderly patients; increased incidence of adverse effects (ie, somnolence, dehydration); slow dosage titration ar recommended (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
6) hypothermia has occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) E release oral tablets, 2008)
7) hyperammonemia has been reported (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
8) multiorgan hypersensitivity reactions have occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
9) signs and symptoms (eg, encephalopathy; unexplained mental retardation, infant deaths (particularly males), elevated plasma ammonia or glutamine; history of cyclical vomiting and lethargy, ataxia, low BUN, or protein avoX history of urea cycle disorders; may indicate an undiagnosed urea cycle disorder which is a contraindication (Proc (R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
10) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adm.
11) thrombocytopenia has occurred; higher doses (ie, approximately 50 mg/kg/day or higher) may increase risk; coagulation test monitoring is recommended; dose reduction or withdrawal of therapy may be warranted if bleeding occur (eg, hemorrhage, bruising, hemostasis/coagulation disorder) (Prod Info DEPAKOTE(R) sprinkle oral capsules DEPAKOTE(R) ER extended-release oral tablets, 2008)

C) Valproate Sodium
1) children, especially under the age of 2 years; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injec
2) concurrent use of multiple anticonvulsants; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injec
3) metabolic disorders, congenital; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injec, 2006)
4) organic brain disease; increased risk of hepatotoxicity (Proc (R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
5) pancreatitis, sometimes life-threatening, may occur (Prod Info DEPAKOTE(R) IV injec, 2006)
6) pregnancy; increased risk of birth defects (Prod Info DEPACON(R) IV injec, 2006)
7) seizure disorders, severe, accompanied by mental retardation; increased risk of hepatotoxicity (Prod Info DEP
8) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info DEPACON(R) IV injec
9) acute head trauma; not recommended for prophylaxis of post-traumatic seizures (Prod Info DEPACON(R) IV inj
10) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV injec
11) cyclical vomiting and lethargy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod In
12) elderly; increased incidence of adverse effects (ie, somnolence, dehydration), sometimes with reduced nutriti
13) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a cont
14) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein I
15) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (DEPAKOTE(R) IV injec, 2006)
16) hepatic disease; prior history of; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injec, 2006)
17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevat
18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disor contraindication (Prod Info DEPACON(R) IV injec, 2006)
19) hypersensitivity reactions, multi-organ; have been reported within first 40 days of therapy and may be life-thr
20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod IV injec, 2006)
21) low blood urea nitrogen or protein avoidance; possible undiagnosed urea cycle disorder, which is a contrain
22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod IV injec, 2006)
23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi
24) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drug risk occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Adm
25) unexplained infant deaths (especially males), history of; possible undiagnosed urea cycle disorder, which is a
3.3 Adverse Reactions

Cardiovascular Effects
Dermatologic Effects
Endocrine/Metabolic Effects
Gastrointestinal Effects
Hematologic Effects
Hepatic Effects
Immunologic Effects
Musculoskeletal Effects
Neurologic Effects
Ophthalmic Effects
Otic Effects
Psychiatric Effects
Renal Effects
Reproductive Effects
Respiratory Effects
Other

3.3.1 Cardiovascular Effects

Valproic Acid
Divalproex Sodium

3.3.1.A Valproic Acid

Chest pain
Hypertension
Hypotension
Palpitations
Peripheral edema
Tachycardia
3.3.1.A.1 Chest pain
   a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Chest pain was reported in more than 1% but less than 5% of patients receiving valproate during pla
   c) Clinical trials of migraine and acute mania and during monotherapy treatment of complex partial seizures
   causality could not be attributed to valproate alone in the complex partial seizures trial, as patients were
   another antiepilepsy drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.2 Hypertension
   a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Hypertension was reported in more than 1% but less than 5% of patients receiving valproate during pla
   c) Clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cases
   not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an
   drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.3 Hypotension
   a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Hypotension and postural hypotension was reported in more than 1% but less than 5% of 89 patients receiv
   c) Clinical trials of valproate treatment of manic episodes associated with bipolar disorder and during monothera
   treatment of complex partial seizures (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   c) A mentally retarded 11-year-old girl experienced profound hypotension during an IV valproate infusion
given to treat status epilepticus. Upon arrival in the emergency department, the girl was given IV diazepam
to maintain her blood pressure. Her blood pressure 5 minutes prior to the start of the infusion was 130/80 mmHg,
decreased to 90/60 mmHg 39 minutes after the start of the infusion. She was given IV fluids and her blood pressure ranged from 60/40 to 90/60 mmHg. She was intubated and given dopamine and recovered 10 days later without further complications (White & Santos, 1999).

3.3.1.A.4 Palpitations
   a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Palpitations were reported in more than 1% but less than 5% of patients receiving valproate during pla
   c) Clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cases
   not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an
   drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.5 Peripheral edema
   a) Incidence: 3% to 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) During a clinical trial of valproate monotherapy for complex partial seizures, peripheral edema was re
   c) Patients receiving high-dose valproate (n=131) compared with 3% of patients receiving low-dose valproa
   many cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.A.6 Tachycardia
   a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Tachycardia was reported in more than 1% but less than 5% of patients receiving valproate during pla
   c) Clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cases
   not be attributed to valproate alone in the complex partial seizures trial, as patients were titrated off of an
   drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.1.B Divalproex Sodium

   Chest pain
   Hypertension
   Palpitations
   Peripheral edema
   Tachycardia

3.3.1.B.1 Chest pain
   a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) Chest pain was reported in more than 1% but less than 5% of patients receiving divalproex sodium (r
monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKO1 capsules, 2008).

3.3.1.B.2 Hypertension
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Hypertension was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.1.B.3 Palpitations
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Palpitations were reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.1.B.4 Peripheral edema
a) Incidence: 3% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Peripheral edema was reported in 8% of patients receiving high-dose divalproex sodium (n=131) cor patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antie the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.1.B.5 Tachycardia
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Tachycardia was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.2 Dermatologic Effects

Valproic Acid

Divalproex Sodium

3.3.2.A Valproic Acid

Alopecia

Cutaneous pseudolymphoma

Injection site disorder

Rash

Stevens-Johnson syndrome

3.3.2.A.1 Alopecia
a) Incidence: 6% to 24% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia alopecia was reported in 6% of patients receiving valproate (n=77) compared with 1% of patients receive In most cases, causality could not be determined as patients also received other antiepilepsy drugs conc valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) During a clinical trial of valproate monotherapy for complex partial seizures, alopecia was reported in receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) Alopecia was reported in 7% of migraine patients receiving valproate (n=202) compared with 1% of p placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed n
capsules, 2008).

e) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high concen-
tration valproic acid (n=96, target level 80 to 150 mcg/mL) caused alopecia in 27 patients (28%) versus 2 patients (4%)
to low concentration valproic acid (n=47, target range of 25 to 50 mcg/mL) (Beydoun et al, 1997c).

3.3.2.A.2 Cutaneous pseudolymphoma

a) Cutaneous pseudolymphoma erupted on the left shoulder of a 41-year-old man after sodium valproate recurred when the patient was switched to carbamazepine. Valproate 500 mg twice daily was ordered after experienced an extradural hematoma secondary to cranial trauma. His lesion was an itchy infiltrated erythematous plaque histologically mimicking a non-epidermotropic T-cell lymphoma. Applying polymerase chain reaction to the lesion produced monoclonal rearrangement of the T-cell gamma gene. Valproate was discontinued and replaced with carbamazepine 400 mg twice daily (the patient was using no other medications). The lesion became pro-
inflamed, but did not totally disappear. Approximately 6 months later, two additional papules appeared on the back and shoulders. Infiltration decreased and the lesion was biopsied. Histology showed a pattern histologically identical to the original papule. Carbamazepine was withdrawn and other antiepileptic drugs were prescribed. All 3 skin lesions disappeared after 3 months; no relapse occurred after follow-up (Cogrel et al, 2001).

3.3.2.A.3 Injection site disorder

a) The manufacturer reports that injection site reactions including inflammation and pain have been repo-
sed with intravenous therapy (Prod Info Depacon(TM), 1999).

3.3.2.A.4 Rash

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, ra-
6% of patients receiving valproate (n=89) compared with 3% of patients receiving placebo (n=97) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.2.A.5 Stevens-Johnson syndrome

a) After 45 days of valproate 400 mg 3 times daily, a 20-year-old man developed lip ulcerations and target lesions on the trunk. Liver function tests were elevated with an aspartate aminotransferase level of 3550 units/L, alanine aminotransferase 5770 units/L and alkaline phosphatase level of 421 units/L. Stevens-Johnson syndrome and with 2 weeks of prednisolone therapy his skin lesions cleared. After 30 days, liver function tests retu-
red normal. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been repo-
sed occasionally during the early stages of valproic acid therapy. In a case-control study of patients taking va-
 agents, 73 cases of SJS or TEN were identified; of these, 13 were due to valproic acid ingestion. SJS/TEN occurred during the first 8 weeks of valproic acid therapy (Rzany et al, 1999).

3.3.2.B Divalproex Sodium

Alopecia

Petechiae

Rash

3.3.2.B.1 Alopecia

a) Incidence: 6% to 24% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, alopecia was reported in 6% of pa-
patients receiving high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Alopecia was reported in 24% of patients receiving high-dose divalproex sodium (n=131) compared with patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei-
 cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antie-
 the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.2.B.2 Petechiae

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Petechiae was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=30 of 142MICROMEDEX® Healthcare Series Document: Page 30 of 142)

3.3.2.B.3 Rash

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Rash was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=358
treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle 2008).

3.3.3 Endocrine/Metabolic Effects

Valproic Acid

Divalproex Sodium

3.3.3.A Valproic Acid

Acute intermittent porphyria

Carnitine nutritional deficiency

Finding of thyroid function

Hormone level - finding, Sex

Hyperammonemia

Hyperglycinemia

Hyperhomocysteinemia

Hyperprolactinemia

Increased appetite

Lipids abnormal

Syndrome of inappropriate antidiuretic hormone secretion

Weight gain

Weight loss

3.3.3.A.1 Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.A.2 Carnitine nutritional deficiency

a) A case of carnitine deficiency associated with hyperammonemia (venous ammonia level of 377 mcm (Glasgow Coma Scale score 8) without hepatic dysfunction, and with a therapeutic serum valproic acid c reported in a 41-year-old male on chronic valproic acid therapy. His venous ammonia level dropped to 4 after the administration of 10 g of L-carnitine IV over 1 hour. The patient was alert, with a normal physics within 24 hours (Barrueto & Hack, 2001).

b) Chronic therapeutic use of valproic acid in young children may cause a carnitine deficiency resulting in symptoms of lethargy, weakness or hypotonia, hepatotoxicity, and hyperammonemia. An incidence of fat children under the age of two years of 1/800 has been reported (Raskind & El-Chaar, 2000).

c) Decreased plasma carnitine was reported in 14 children. Thirteen children were symptomless, yet on signs of valproic acid hepatotoxicity (appearing as a Reye's-like syndrome). After withdrawal of valproic acid symptomatic patient recovered. The mechanism is believed to be increased excretion of carnitine in the and valproyl metabolites (Murphy et al, 1985).

d) A 3-year-old girl developed acute liver disease along with the typical features of Reye's syndrome after valproate for 6 months. Serum free carnitine was decreased as well as 3-keto-valproic acid, the main me oxidation of valproate. The possible importance of carnitine in the pathogenesis of liver disease induced (Bohles et al, 1982).
e) An inverse relationship was found between plasma carnitine concentrations and the dosage of valproic acid between plasma carnitine and blood ammonia values (Ohtani et al, 1982).

3.3.3.3 Finding of thyroid function

a) One study found valproic acid slightly increased serum thyrotropin hormone (TSH) levels in girls with effects were reversible upon discontinuation of therapy. Patients, between the ages of 8 and 18 years, w 54 age-matched controls. Mean TSH levels were 3.3 milliunits/L compared to 2.9 milliunits/L in the control group (2.2 nanograms/mL; p less than 0.001). No statistically significant differences in dehydroepiandrosterone lev between controls and oxcarbazepine treated (n=13) or valproic acid treated (n=27) men with generalized also found that men in the valproic acid group had higher androstenedione levels (5.9 nanograms/mL) w the control group (2.2 nanograms/mL; p less than 0.001) whereas the other arms did not. Serum thyroid hormone binding globulin, free androgen index, luteinizing hormone, follicle stimulating hormone, prolactin measurements were not statistically significantly different between all 4 groups. Whether the differences hormones are epilepsy-induced changes or antiepileptic agent-induced changes remains to be determine (2004).

b) Carbamazepine and (to a lesser extent) valproic acid were found to alter serum concentrations of sex young male epileptic patients (aged 15 to 18 years; n=48) treated at least 2 years with these drugs; howe were not permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Vt Compared with concentrations in normal healthy male controls, subjects treated with carbamazepine mo had decreased levels of free testosterone (FT) (p less than 0.05) and dehydro- epitestosterone sulphate than 0.001); concentrations of sex hormone-binding globulin were significantly increased (p less than 0.0 treated with valproic acid monotherapy (n=18) had insignificantly decreased levels of FT and DHEAS. Si combination carbamazepine and valproic acid (n=10) had the same significant alterations as those on ca monotherapy. At least four months after withdrawal of these drugs, all values had returned to normal. Le testosterone, luteinizing hormone, follicle stimulating hormone, and prolactin were normal throughout the ovaries, hyperandrogenism, and menstrual disorders were more common among women being treated f valproate (n=37) than among men being treated for epilepsy with carbamazepine (n=35) or among co (n=52). Seventy-nine percent of obese valproate-treated women and 65% of lean valproate- treated won ovaries or hyperandrogenism or both, compared to 20% of carbamazepine-treated women and 19% of c Seventy-nine percent of obese and 48% of lean valproate- treated women had menstrual disorders, who and 17% of lean control women had menstrual disorders (p less than 0.001) (Isojarvi et al, 2001).

c) Reproductive hormone levels in men with epilepsy may be affected by use of valproic acid or carbam some effect shown by oxcarbazepine at high doses. In valproate-treated men (n=21), androstenedione k significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the cohc (57%) had serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) i reference range (p less than 0.001). Follicle stimulating hormone levels were abnormally low in valproate less than 0.05). Among carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p and sex hormone-binding globulin (SHBG) levels were high (p less than 0.05). In men taking high doses (900 milligrams/day or more), serum concentrations of testosterone, luteinizing hormone, and SHBG were p=0.02, p=0.005, respectively). The authors noted that serum insulin levels were high across all groups (2001).

d) Hyperandrogenism has been reported in girls taking valproic acid. Evaluation of testosterone levels ir years old, taking valproic acid revealed significantly higher serum testosterone levels compared to contrc same pubertal stage. Of girls receiving valproic acid, 38% of prepubertal girls, 36% of pubertal girls, and postpubertal girls were hyper-androgenic (Vainionpaa et al, 1999).

e) Evidence is strongly suggestive of a causative link between reproductive endocrine disorders and val treatment in women with epilepsy. In a study of 238 adult epileptic women, 27% of those who received v 20 or later, and 80% of those who received valproic acid before the age of 20, demonstrated polycystic c serum testosterone levels. In both age groups, the incidence of hyper-androgenic effects was significantl valproic acid than for other antiepileptic medications (p less than 0.01) (Isojarvi et al, 1993).

3.3.3.4 Hormone level - finding, Sex

a) Antiepileptic agents have been associated with changes in serum concentrations of male reproductive compared to healthy controls (n=41), carbamazepine-treated men with partial epilepsy (n=15) had lower dehydroepiandrosterone sulfate concentrations (3068 nanogram/mL for controls versus 1952 nanogram Carmazepine; p less than 0.001). No statistically significant differences in dehydroepiandrosterone lev between controls and oxcarbazepine treated (n=18) or valproic acid treated (n=27) men with generalized also found that men in the valproic acid group had higher androstenedione levels (5.9 nanograms/mL) w the control group (2.2 nanograms/mL; p less than 0.001) whereas the other arms did not. Serum testost hormone binding globulin, free androgen index, luteinizing hormone, follicle stimulating hormone, prolactin measurements were not statistically significantly different between all 4 groups. Whether the differences hormones are epilepsy-induced changes or antiepileptic agent-induced changes remains to be determine (2004).

b) Carbamazepine and (to a lesser extent) valproic acid were found to alter serum concentrations of sex young male epileptic patients (aged 15 to 18 years; n=48) treated at least 2 years with these drugs; howe were not permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Vt Compared with concentrations in normal healthy male controls, subjects treated with carbamazepine mo had decreased levels of free testosterone (FT) (p less than 0.05) and dehydro- epitestosterone sulphate than 0.001); concentrations of sex hormone-binding globulin were significantly increased (p less than 0.0 treated with valproic acid monotherapy (n=18) had insignificantly decreased levels of FT and DHEAS. Si combination carbamazepine and valproic acid (n=10) had the same significant alterations as those on ca monotherapy. At least four months after withdrawal of these drugs, all values had returned to normal. Le testosterone, luteinizing hormone, follicle stimulating hormone, and prolactin were normal throughout the ovaries, hyperandrogenism, and menstrual disorders were more common among women being treated f valproate (n=37) than among men being treated for epilepsy with carbamazepine (n=35) or among co (n=52). Seventy-nine percent of obese valproate-treated women and 65% of lean valproate- treated won ovaries or hyperandrogenism or both, compared to 20% of carbamazepine-treated women and 19% of c Seventy-nine percent of obese and 48% of lean valproate- treated women had menstrual disorders, who and 17% of lean control women had menstrual disorders (p less than 0.001) (Isojarvi et al, 2001).

c) Reproductive hormone levels in men with epilepsy may be affected by use of valproic acid or carbam some effect shown by oxcarbazepine at high doses. In valproate-treated men (n=21), androstenedione k significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the cohc (57%) had serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) i reference range (p less than 0.001). Follicle stimulating hormone levels were abnormally low in valproate less than 0.05). Among carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p and sex hormone-binding globulin (SHBG) levels were high (p less than 0.05). In men taking high doses (900 milligrams/day or more), serum concentrations of testosterone, luteinizing hormone, and SHBG we p=0.02, p=0.005, respectively). The authors noted that serum insulin levels were high across all groups (2001).

d) Hyperandrogenism has been reported in girls taking valproic acid. Evaluation of testosterone levels ir years old, taking valproic acid revealed significantly higher serum testosterone levels compared to contrc same pubertal stage. Of girls receiving valproic acid, 38% of prepubertal girls, 36% of pubertal girls, and postpubertal girls were hyper-androgenic (Vainionpaa et al, 1999).

e) Evidence is strongly suggestive of a causative link between reproductive endocrine disorders and val treatment in women with epilepsy. In a study of 238 adult epileptic women, 27% of those who received v 20 or later, and 80% of those who received valproic acid before the age of 20, demonstrated polycystic c serum testosterone levels. In both age groups, the incidence of hyper-androgenic effects was significantl valproic acid than for other antiepileptic medications (p less than 0.01) (Isojarvi et al, 1993).
concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentra-
tic and his phenytoin and valproate concentrations we-
and less than 10 mcg/mL, respectively. He was inadver-
tently started on valproate again at the former do-
days his ammonia concentration increased to 130 mcmol/L. He became confused and lethargic and his l-
bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate wa-
his ammonia concentration decreased to 60 mcmol/L after one day and on the second day his confusion 
baseline (Feil et al, 2002).

3.3.3.A.6 Hyperglycinemia

a) In a patient with preexistent nonketotic hyperglycinemia, hyperglycinemia occurred with valproic acid 
associated with a fatal outcome (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.3.A.7 Hyperhomocysteinemia

a) In a study of 60 adolescent epileptic patients (aged 14 to 18 years), a one-year course of carbamaze-
therapy was found to produce significantly higher plasma concentrations of homocysteine compared with 
therapy and compared with levels in a healthy age- and sex-matched control group (p less than \( \leq 0.01 \) comparisons). The finding of hyperhomocysteinemia held true with both fasting and post-methionine home 
measurements. For the patients taking carbamazepine or valproate, serum concentrations of folate and j 
5-phosphate (PLP) were significantly decreased with respect to pretreatment values and to values in the 
less than 0.01, folate; p less than 0.001, PLP). Levels of vitamin B12 and erythrocyte folate remained in l 
(Verrotti et al, 2000a).

3.3.3.A.8 Hyperprolactinemia

a) Sodium valproate was given to 20 normal and 15 hyperprolactinemic patients. Prolactin levels were s 
lowered in both groups following valproate administration; however, prolactin levels in the hyperprolactin-
decreased in those patients without evidence of prolactinoma. This study suggests that enhancement of 
is followed by inhibition of prolactin secretion (Melis et al, 1982).

3.3.3.A.9 Increased appetite

a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased appetite was reported in 6% of migraine patients receiving valproate (n=202) compared wi 
valproic acid serum concentrations ran 

3.3.3.A.10 Lipids abnormal

a) In a study evaluating lipids in children and adolescents receiving carbamazepine (n=14), valproic acic 
phenobarbital (n=20), serum lipid and lipoprotein levels returned completely to normal at 1 to 1.5 years a 
discontinued. During therapy patients receiving carbamazepine demonstrated increased levels of total ch 
triglycerides, LDL cholesterol, and HDL as compared to a control group (n=110)(all p less than 0.01). Ch 
valproic acid had low triglycerides (p less than 0.05) and LDL (p less than 0.05) and high levels of HDL (l 
as compared to the control group. Children receiving phenobarbital had high concentrations of total chole 
sterol and low concentrations of triglycerides as compared to the control group (all p less than 0.01; 1998).

b) Serum lipids and lipoproteins in 33 epileptic children were measured. All of the children were being cl
with phenobarbital, valproate and carbamazepine. HDL cholesterol was significantly higher in the epilept 2 control groups (healthy nonepileptic children and epileptic children before starting anticonvulsant thera indicate that anticonvulsant drugs should be added to the list of substances that affect serum HDL (Held 1983).

### 3.3.3.A.11 Syndrome of inappropriate antidiuretic hormone secretion

#### a) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in a 62-year-old man was attrib long-term use of sodium valproate. At age 56, the man had his first generalized tonic-clonic seizure. Symptoms such as hyponatremia, elevated serum concentrations of antidiuretic hc cloudiness of consciousness, disorientation, psychomotor excitement, and a tonic-clonic seizure occurre year. These episodes were different from his original tonic-clonic convulsion, as originally hyponatremia, and cloudiness of consciousness were not present. Laboratory findings included serum sodium of 127 m picograms (pg)/mL, an increase in urinary sodium excretion, and slight elevation of urinary osmolarity. Se concentrations were 10.5 mcg/mL. SIADH was diagnosed. The patient was switched from valproate to zi 18 months, his serum ADH had normalized (0.8 pg/mL); he had no symptoms of SIADH and he no longe type of seizures. The authors concluded that SIADH in this case was due to long-term administration of \ weakness in the CNS (bilateral hippocampal atrophy) (Miyaoka et al, 2001).

#### b) A 50-year-old male with Henoch-Schonlein nephritis was discovered to have hyponatremia (serum sc mEq/L) during a routine follow-up. His only medication was valproate 2000 mg/day. He had no complaint volume depletion, hypothyroidism, or renal or adrenal insufficiency. His plasma osmolality was low at 26. Repeated water loading at different valproate doses confirmed the ability to excrete water was reduced i dependent manner. The authors concluded that the valproate caused syndrome of inappropriate secretory hormone (SIADH). Water restriction corrected the hyponatremia (Branten et al, 1998).

### 3.3.3.A.12 Weight gain

#### a) Incidence: 4% to 9% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

#### b) Weight gain was reported in 8% of migraine patients receiving valproate (n=202) compared with 2% c receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).

#### c) During a clinical trial of valproate monotherapy for complex partial seizures, weight gain was reported receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

#### d) A retrospective, longitudinal study revealed that epileptic children between the ages of 2 and 8 years 0.8 yr; 53% male) experienced a significant increase in BMI z-scores following valproic acid treatment. H percentage of patients who were overweight or obese at the end of 3.1 yr follow-up was not statistically BMI z-score of 0.1 was calculated at initiation of treatment, which increased to 0.8 (p=0.001) at 3.1 years therapy, 6.9% of the patients were overweight, which increased to 16% (p=0.081) following 3.1 yr of val treatment. A total of 3.5% of patients were obese at baseline, which increased to 5.7% following 3.1 yr of however this increase in weight was also not statistically significant (p=0.8). This study data suggests the occurred during the first 16 months of treatment but leveled off with continued treatment. Over the cours significant increases in serum triglyceride levels, total serum cholesterol levels, or fasting blood glucose I reported (Grosso et al, 2009).

#### e) Obesity in children treated with valproate was common in a study of 55 children. Body mass index we 90th percentile-for-age in 14 patients at baseline which increased to 20 patients at follow-up. The risk of gain with valproate was significant as seen in changes in weight Z-score and in body mass index (p=0.0 respectively). Also seen was impaired growth in girls as measured by height Z-score (p=0.001) (Novak e et al, 1977c).

#### f) In a retrospective study of 70 epileptic patients treated with long-term valproic acid (mean 27 months) weight gain in excess of 10% over their baseline measurement, and another 24% gained an additional 5 control group of patients treated with carbamazepine monotherapy, 14% of patients had weight gain gre 28% had weight gain between 5% and 10% (Corman et al, 1997). In another study of patients treated lor valproic acid for epilepsy (female patients only), 11 of 22 (50%) experienced marked weight gain (mean : indisputable despite preexisting obesity. Weight gain was frequently associated with hyperinsulinemia ar growth factor-binding protein 1 (Isojarvi et al, 1996).

### 3.3.3.A.13 Weight loss

#### a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

#### b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia loss was reported in 6% of patients receiving valproate (n=77) compared with 0% of patients receiving pl most cases, causality could not be determined as patients also received other antiepilepsy drugs concurre valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

### 3.3.3.B Divalproex Sodium

Hyperammonemia
Increased appetite

Weight gain

Weight loss

3.3.3.B.1 Hyperammonemia

a) Hyperammonemia, sometimes present despite normal liver function tests, has been reported with valproate therapy. Patients who develop symptoms of hyperammonemia (hypothesis, unexplained lethargy and vomiting, changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of therapy) and be evaluated for underlying urea cyclic disorder (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.3.B.2 Increased appetite

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased appetite was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.3.B.3 Weight gain

a) Incidence: 4% to 9% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Weight gain was reported in 9% of patients receiving high-dose divalproex sodium (n=131) compared with 4% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.3.B.4 Weight loss

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, weight loss was reported in 6% of patients receiving divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.4 Gastrointestinal Effects

Valproic Acid

Divalproex Sodium

3.3.4.A Valproic Acid

Abdominal pain

Constipation

Diarrhea

Hematemesis

Indigestion

Loss of appetite

Nausea

Pancreatitis

Vomiting
3.3.4.A.1 Abdominal pain
a) Incidence: 9% to 23% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, abdominal pain was reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n=81) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) Abdominal pain was reported in 9% of migraine patients receiving valproate (n=202) compared with 4 receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, abdominal pain was reported in 23% of patients receiving valproate (n=77) compared with 6% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
e) During a clinical trial of valproate monotherapy for complex partial seizures, abdominal pain was reported in 9% of patients receiving high-dose valproate (n=131) compared with 9% of patients receiving low-dose valproate (n=130). In many cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.2 Constipation
a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, constipation was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.3 Diarrhea
a) Incidence: 12% to 23% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) Diarrhea was reported in 12% of migraine patients receiving valproate (n=202) compared with 7% of patients receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, diarrhea was reported in 13% of patients receiving valproate (n=77) compared with 6% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) During a clinical trial of valproate monotherapy for complex partial seizures, diarrhea was reported in receiving high-dose valproate (n=131) compared with 19% of patients receiving low-dose valproate (n=130). In most cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.4 Hematemesis
a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) Hematemesis was reported in more than 1% but less than 5% of patients receiving valproate (n=265) during treatment of complex partial seizures. In many cases, causality could not be attributed to valproate alone but was observed during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.5 Indigestion
a) Incidence: 8% to 13% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, dyspepsia was reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n=81) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) Dyspepsia was reported in 13% of migraine patients receiving valproate (n=202) compared with 9% receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) During a clinical trial of valproate monotherapy for complex partial seizures, dyspepsia was reported in receiving high-dose valproate (n=131) compared with 10% of patients receiving low-dose valproate (n=130). In most cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
e) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, dyspepsia was reported in 8% of patients receiving valproate (n=77) compared with 4% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.A.6 Loss of appetite
a) Incidence: 4% to 12% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, anorexia was reported in 12% of patients receiving valproate (n=77) compared with 0% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) During a clinical trial of valproate monotherapy for complex partial seizures, anorexia was reported in receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

### 3.3.4.A.7 Nausea

a) Incidence: 22% to 48% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, ne in 22% of patients receiving valproate (n=89) compared with 15% of patients receiving placebo (n=97) (F STAVZOR(R) delayed release oral capsules, 2008).

c) Nausea was reported in 31% of migraine patients receiving valproate (n=202) compared with 10% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed n capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 48% of patients receiving valproate (n=77) compared with 14% of patients receiving plac most cases, causality could not be determined as patients also received other antiepilepsy drugs concur valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial of valproate monotherapy for complex partial seizures, nausea was reported in 3 receiving high-dose valproate (n=131) compared with 26% of patients receiving low-dose valproate (n=1 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug du the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

### 3.3.4.A.8 Pancreatitis

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Life-threatening pancreatitis has been reported with valproate use in both children and adults shortly after several years of therapy. Some cases of hemorrhagic pancreatitis with rapid progression from initia death have been described. Symptoms of pancreatitis requiring prompt medical evaluation include abdo seizures. Serum markers of pancreatitis normalized by 4 days and she was discharged on day 22. A da after several years of therapy. Some cases of hemorrhagic pancreatitis with rapid pro

c) Pancreatitis was reported in more than 1% but less than 5% of patients receiving valproate (n=265) for treatment of complex partial seizures. In many cases, causality could not be attributed to valproate alone titrated off of another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed re capsules, 2008).

d) Of 45 published cases of valproic acid-induced pancreatitis, 3 cases were found to be definite (by the drug reaction probability scale), 32 probable, and 10 possible. There was no correlation between valpro plasma concentration and development of pancreatitis. Thirty percent of patients developed symptoms w starting valproic acid, 58% within 12 months, and 30% 2 years or more after starting valproic acid. Many with discontinuation of valproic acid. However, 13 (29%) died (Chapman et al, 2001).

e) A 22-year-old woman who been taking valproic acid for 19 years for epilepsy developed an acute exac pancreatitis. At the time, her valproic acid dosage was 25 mg/kg/day. She also took other medications f She was treated conservatively, with discontinuation of valproic acid and increased doses of other agent seizures. Serum markers of pancreatitis normalized by 4 days and she was discharged on day 22. A day readmitted because of recurrent pancreatitis, which required surgical resection of the pancreatic head and preservation of the stomach and pyloric ring. The resected specimens were notable for a large volume in the pancreatic head and fibrosis around the main pancreatic duct. Findings suggested that the cause was flow disturbance of pancreatic juice due to calculi in the main pancreatic duct. There had been no re pancreatitis at 2 years postsurgery (Taira et al, 2001).

f) A 35-year-old man demonstrated signs and symptoms of pancreatitis 17 months after beginning valpr and again upon rechallenge. Signs and symptoms included abdominal pain, increased enzymes, and ultra computed tomographic scan showing thickening of the body and tail of the pancreas. Rechallenge was c after valproic acid discontinuance due to increased seizure frequency and irritability. Pancreatitis develop restarting valproic acid (Fecik et al, 1999).

g) A 23-year-old male, on hemodialysis for endstage renal disease secondary to hemolytic uremic syndi pancreatitis following a 3 month course of valproic acid (2500 mg/day) and phenobarbital (200 mg/day) . valproic acid and administering symptomatic therapy, the pancreatitis resolved. Phenobarbital was conti further pancreatic symptoms (Plaza et al, 1999).

h) Two pediatric cases of valproic acid-associated pancreatitis occurred in the presence of endstage rr amylose levels were 232 units/L and 465 units/L, respectively, in a 14-year-old female on peritoneal dial figures were 880 units/L and 530 units/L in a 12-year-old male on hemodialysis. Both had received valpn for seizure disorder (doses not given). The 14-year-old also developed hepatotoxicity and subsequently old recovered with valproic acid discontinuation (Levin et al, 1997).

i) Development of VPA (valproic acid)-associated pancreatitis is a relative contraindication to further tre routine monitoring of serum amylose is not necessary in asymptomatic patients. Other cases of fatal and induced pancreatitis have been described (Evans et al, 1995)(Pinkston & Walker, 1997).

j) Four cases of pancreatitis secondary to valproic acid were described. Doses of valproic acid were ran mg/kg/day for 7 months to 4.5 years (age of patients, 3, 7, 18, and 27 years). Complications of pancreat pseudocyst, pericardial effusion, laparotomy wound infection, and coagulopathy occurred in one patient;
one other patient. Withdrawal of valproic acid resulted in recovery (Wyllie et al, 1984).

k) Fourteen cases of valproate-associated pancreatitis are reviewed. None of the cases experienced other effects and pancreatitis was not dose-related. It developed as early as one week and as late as 4.5 years after the start of treatment. Two of 14 patients died. Of 7 rechallenged with valproic acid, 6 had recurrence of pancreatitis (1984).

l) Attacks of pancreatitis were described in an 11-year-old girl receiving valproic acid 15 mg/kg/day. Trar discomfort occurred at this dosage (exact duration of therapy unspecified), and 2 days after beginning 45 mg/kg/day daily the patient developed severe abdominal pain. Laparotomy for suspected appendicitis was institute. Mesenteric fat necrosis. Postoperative serum amylase was 225 units/dL (normal less than 160). The patient recovered fully after a period of 2 weeks. Valproic acid was initiated again after a period of 4 weeks and was again associated with abdominal pain and elevated serum amylase (696 units/dL) after the dosage was increased from 20 to 200 mg/kg/day, patient recovered fully upon discontinuation of valproic acid. The second case, a 1-year-old boy, develop abdominal pain following meals at doses of 55 mg/kg/day (900 mg daily) with serum amylase increasing units/dL. The patient recovered 2 weeks after discontinuation of valproic acid. It is not possible to attribute pancreatitis in these children to the use of valproic acid. However, signs of unusual abdominal discomfort were followed by serum amylase examination in order to rule out the possibility of acute pancreatitis (Camfield 1989).

3.3.4.4.9 Vomiting

a) Incidence: 11% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, vomiting was reported in 12% of patients receiving valproate (n=89) compared with 3% of patients receiving placebo (n=81) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) Vomiting was reported in 11% of migraine patients receiving valproate (n=202) compared with 1% of placebo (n=81 during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, vomiting was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) During a clinical trial of valproate monotherapy for complex partial seizures, vomiting was reported in receiving high-dose valproate (n=131) compared with 15% of patients receiving low-dose valproate (n=134) for monotherapy treatment of complex partial seizures. Causality could not be attributed to valproate alone, as patients were titrated off another antiepilepsy drug du to the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.4.4.B Divalproex Sodium

Abdominal pain

Constipation

Diarrhea

Hematemesis

Indigestion

Loss of appetite

Nausea

Pancreatitis

Vomiting

3.3.4.4.B.1 Abdominal pain

a) Incidence: 9% to 23% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, abdominal pain was reported in 23 receiving divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info Divalproex Sodium Delayed Release Oral Capsules, 2008).

c) Abdominal pain was reported in 12% of patients receiving high-dose divalproex sodium (n=131) compared with 8% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. Causality could not be attributed to divalproex alone, as patients were titrated off another antiepilepsy drug du to the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.2 Constipation

**a)** Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** In a clinical trial of adjunctive therapy for complex partial seizures, constipation was reported in 5% of high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

### 3.3.4.B.3 Diarrhea

**a)** Incidence: 13% to 23% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** In a clinical trial of adjunctive therapy for complex partial seizures, diarrhea was reported in 13% of patients receiving high-dose divalproex sodium (n=77) compared with 8% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

**c)** Diarrhea was reported in 23% of patients receiving high-dose divalproex sodium (n=131) compared with patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.4 Hematemesis

**a)** Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** Hematemesis was reported in more than 1% but less than 5% of patients receiving divalproex sodium for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.5 Indigestion

**a)** Incidence: 8% to 11% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** In a clinical trial of adjunctive therapy for complex partial seizures, dyspepsia was reported in 8% of patients receiving high-dose divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

**c)** Dyspepsia was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compared with patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.6 Loss of appetite

**a)** Incidence: 4% to 12% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** In a clinical trial of adjunctive therapy for complex partial seizures, anorexia was reported in 12% of patients receiving high-dose divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

**c)** Anorexia was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compared with patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.7 Nausea

**a)** Incidence: 26% to 48% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** In a clinical trial of adjunctive therapy for complex partial seizures, nausea was reported in 48% of patients receiving high-dose divalproex sodium (n=77) compared with 14% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

**c)** Nausea was reported in 34% of patients receiving high-dose divalproex sodium (n=131) compared with patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.4.B.8 Pancreatitis

**a)** Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

**b)** Life-threatening pancreatitis has been reported with valproate use in both children and adults shortly after several years of therapy. Some cases of hemorrhagic pancreatitis with rapid progression from initia death have been described. Symptoms of pancreatitis requiring prompt medical evaluation include abdo pain, vomiting, and anorexia. There were 2 cases of pancreatitis reported among 2416 patients received during clinical trials, representing 1044 patient-years of experience. Pancreatitis may recur upon rechallenge (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

**c)** Pancreatitis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
3.3.4.B.9 Vomiting
   a) Incidence: 15% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) In a clinical trial of adjunctive therapy for complex partial seizures, vomiting was reported in 27% of patients receiving divalproex sodium (n=77) compared with 7% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).
   c) Vomiting was reported in 23% of patients receiving high-dose divalproex sodium (n=131) compared with 12% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. Causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic medication prior to the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.5 Hematologic Effects

Valproic Acid

Divalproex Sodium

3.3.5.A Valproic Acid

Acute promyelocytic leukemia, FAB M3

Blood coagulation disorder

Ecchymosis

Factor VII deficiency

Hematology finding

Myelosuppression

Neutropenia

Pancytopenia

Protein C deficiency disease

Pure red cell aplasia

Thrombocytopenia

Thrombocytopenia, Dose-related

von Willebrand factor inhibitor disorder

3.3.5.A.1 Acute promyelocytic leukemia, FAB M3
   a) Valproic acid therapy produced hematopoietic changes consistent with acute promyelocytic leukemia in a 17-year-old Native American female. The patient had received 65 mg/kg/day for seizure disorder for 1 year prior to the presentation with anemia, thrombocytopenia, leukocytosis, and coagulopathy. The valproic acid serum level was within the normal range (82 mcg/mL). Abnormal/immature myeloid precursor cells appeared in the bone marrow at presentation. Although the diagnosis of APML was considered, the patient gradually recovered after valproic acid discontinuation (Bottom et al, 1997).

3.3.5.A.2 Blood coagulation disorder
   a) Summary
      1) Sodium valproate has been shown to inhibit the secondary phase of platelet aggregation. This effect is dose-related and was observed at concentrations ranging from 15 to 200 mcg/mL (Bruni & Wilder, 1979a; Gerber et al, 1979; Addison & Gordon, 1980; Hintze et al, 1987; Gidal et al, 1988). The inhibition of platelet aggregation is usually of no clinical significance unless patients are receiving other anticoagulants.
affect hemostasis (aspirin, warfarin) or undergoing surgery. Children appear to be particularly susce
1977c). 

b) Hemostatic disturbances occurred in a 9-year-old female receiving oral valproate sodium 600 mg daily 3 years for grand mal epilepsy. During valproate therapy, the patient developed an acute pulmonary infec
tioned bleeding, heparinization, thrombocytopenia and abnormal clotting tests. Partial thr
74.8 seconds (normal 50), fibrinogen was 420 mg/dL (normal 160 to 400) and hemoglobin was 6 grams.
and antibiotics were administered resulting in complete recovery (Klose et al, 1977). 

c) The effects of sodium valproate on platelet function in 20 children with seizures was evaluated. Clinic hemorrhagic disease including petechiae, epistaxis, otorrhagia, and prolonged bleeding after surgery we
several patients. Bleeding time was increased in 6 patients and platelet adhesiveness was found to be d
patients (von Voss et al, 1976).

3.3.5.A.3 Ecchymosis 

a) Incidence: 4% to 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, ecchymosis was reportec
receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13)
causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.5.A.4 Factor VII deficiency 

a) A 3-year-old boy with a history of afebrile convulsions developed acquired factor VII deficiency while i
with valproate 20 mg/kg for 7 months. There was no reported personal or family history of hemostatic d
other drug treatments, toxic compound exposure, infection, or immunization. The child had experienced bruising over his body 1 month after beginning valproate treatment. Neurological examination revealed h
tendon reflexes in both lower extremities and positive Babinski sign and clonus. The patient's laboratory normal with the exception of prolonged prothrombin time (PT, 15.6 sec) and reduced factor VII concentra
the parents had factor VII levels within normal range. Twelve months following discontinuation of valproa
institution of phenobarbital), bruising resolved and factor VII concentrations and PT intervals returned to range (50% and 13 sec, respectively) (Unalp et al, 2009).

3.3.5.A.5 Hematology finding 

a) Valproic acid therapy resulted in myelodysplastic hematologic changes including macrocytosis, throm
pelger-huet neutrophils in two case reports. Neither had folate or vitamin B12 deficiencies. The patients i
48-year-old female on valproac acid 6000 mg/day for 3 years for refractory bipolar disorder, with a serum of 95.4 mcg/mL, and a 2-year-old female with congenital anomalies and seizure disorder on valproic acid (duration unknown), with a serum level of 125 mcg/mL. Hematology profiles improved in both cases with Fawcett, 1997; Hongeng et al, 1997).

b) In a cohort study involving 29,357 recipients of anticonvulsive therapy (receiving 684,706 prescription drugs, one being valproate), serious blood dyscrasias were rarely found in these patients. Among the 4 c
appear different. An overall rate of blood dyscrasias was reported to be 3 to 4 per 100,000 prescriptions (Blackburn et al, 1998).

3.3.5.A.6 Myelosuppression 

a) Valproate-associated dysmyelopoiesis was reported in a 62-year-old man and in a 62-year-old woma
received valproate 200 mg twice a day for seizure control. Two weeks later he developed a mild pancyt
bone marrow aspirate showed mild dysmyelopoiesis. His blood cell counts normalized 12 days after disc
valproate. The woman had received valproate 1500 mg/day for 10 years and developed a mild, persister
thrombocytopenia. Following an increase in dosage to 1500 mg twice a day her valproate concentration therapeutic level to 1447 mcg/L (therapeutic range, 347 to 693 mcg/L). Severe pancytopenia occur
and a diagnosis of dysmyelopoiesis was made following examination of her bone marrow aspirate. She s
 carbamazepine and her blood counts normalized in 6 weeks (So & Wong, 2002).

b) Valproic acid therapy resulted in myelodysplastic hematologic changes including macrocytosis, thorr
Pelger-Huet neutrophils in two case reports. Neither had folate or B12 deficiencies. The patients involve
old female on valproic acid 6000 mg/day for 3 years for refractory bipolar disorder, with a serum valproic m
cmg/mL; and a 2-year-old female with congenital anomalies and seizure disorder on valproic acid 90 mg unknown), with a serum level of 125 mcg/mL. Hematology profiles improved in both cases with valproic z
reduction (Fawcett, 1997; Hongeng et al, 1997).

c) In a study of 1,251 hospitalized patients receiving valproate therapy, 6 developed moderate to severe less than 4000/mm(3)); 2 of these patients were also taking carbamazepine (Tohen et al, 1995).

3.3.5.A.7 Neutropenia 

a) In a case report, valproaic acid use was associated with severe neutropenia that resolved after drug di
56-year-old female was hospitalized for seizure activity secondary to a superior frontoparietal cortex abs
initially treated with phenytoin, however it was replaced with valproic acid due to an adverse reaction. Va
titated to a dose of 500 mg 3 times daily. Concomitant medications included ceftriaxone and metronidaz
absolute neutrophil count (ANC) prior to the administration of valproic acid was 2064 cells/mm(3). Two d
patient's ANC decreased to 735 cells/mm(3). The following day the ceftriaxone was discontinued and lev
started. On day 4 of valproic acid use the ANC dropped to 56 cells/mm(3) despite a dose of filgrastim. Ti

3.3.5.A.8 Hemorrhagic diathesis 

a) The rare occurrence of coagulopathy with valproic acid was evaluated in 14 children with afebrile convulsions and in 12 children with acquired factor VII deficiency. Valproic acid was associated with a
}\n

\[2.1.5.1.\text{3.3.5.A.7 Neutropenia}\]
\[2.1.5.1.\text{3.3.5.A.8 Hemorrhagic diathesis}\]
\[2.1.5.1.\text{3.3.5.A.9 Myelosuppression}\]
\[2.1.5.1.\text{3.3.5.A.10 Hemato}\]
was then discontinued. The next day, the ANC dropped to its nadir of 47 cells/mm(3) and the patient reo of filgrastim. From that point forward the ANC continued to rise and the neutropenia resolved (Vesta & M

3.3.5.A.8 Pancytopenia
a) Pancytopenia occurred in a 65-year-old man taking valproate 1000 mg daily for bipolar mood disorde of therapy his WBC count was 6.8, RBC count was 4.52 and platelets (PLT) were 160. He then started ti 750 mg daily. At 10 weeks of treatment his hematological values were: WBC 4.7, RBC 4.21, PLT 137. H increased to 1000 mg daily and at 14 weeks the hematologic values were: WBC 3.5, RBC 4.18, PLT 132 valproate was discontinued, the indices were: WBC 3.2, RBC 3.83, and PLT 106. The pancytopenia app related and reversible, disappearing on the valproate was stopped (Oluboka et al, 2000).

b) Fatal pancytopenia developed in a 3-year-old child administered high-dose valproate therapy (Rajant

3.3.5.A.9 Protein C deficiency disease
a) Protein C deficiency may be associated with use of valproic acid, based on a comparison of children (n=20) and those using other anticonvulsants (n=20), such as carbamazepine, phenytoin, and lamotrigin group, 19 of 20 children had normal values for coagulation proteins (protein C antigen, protein C function protein S free, antithrombin). In the valproic acid group, 45% (9 of 20) had abnormally low values for prot (p=0.001 compared with other anticonvulsant group), and 40% (8 of 20) had abnormally low values for p (p=0.002). The authors decided to investigate a potential relationship between valproic acid and protein a stroke occurred in an 18-month-old child being treated with valproic acid for a seizure disorder. Ruling which might have caused the child’s stroke (a stroke seemingly consistent with ischemic injury) led to a f abnormally low protein C and related low anticoagulation activity seemed to be the most plausible cause (Gruppo et al, 2000).

3.3.5.A.10 Pure red cell aplasia
a) Pure red cell aplasia has been associated with sodium valproate therapy. A case of pure red cell apla 9-year-old girl following sodium valproate therapy with 200 mg three times a day for a period of 6 months previously, the girl had an attack of measles followed immediately by severe chicken pox. It has been su infective episodes may have sensitized the patient to a potentially hematotoxic drug (valproic acid) that h been well tolerated. Within one month of drug withdrawal regeneration of bone marrow erythroid precurs The patient was rechallenged with sodium valproate 200 mg 3 times daily. Within 6 weeks there was evi aplasia, and the drug was withdrawn. Over the next 6 weeks, the child improved, and red cell aplasia res (MacDougall, 1982).

3.3.5.A.11 Thrombocytopenia
a) Summary
1) The most common hematologic abnormality with valproic acid is thrombocytopenia, possibly rela autoimmune mechanism (Rimmer & Richens, 1985f; Covaris et al, 1982; Barr et al, 1982). The inci induced thrombocytopenia has been reported to vary from 1% to 30% (Allarakha et al, 1996a; Hoffer al, 1982; Morris et al, 1981; Smith & Boots, 1980). The rate of occurrence of thrombocytopenia amo was nearly double that among younger patients (Conley et al, 2001). The risk of thrombocytopenia i increasing doses of valproic acid and with coadministration of aspirin (Conley et al, 2001). The risk i total valproate plasma trough levels above 110 mcg/mL in females and 135 mcg/mL in males (Prod Tablets, 2002a). Nadir platelet counts after valproate administration ranged from 15,000/mm(3) to 8i the time course was variable. A thrombocytopenia rate of 1.6 per 100,000 valproic acid prescriptions reported by the United Kingdom Department of Health’s General Practice Research Database with £ 6465 valproic acid recipients (Blackburn et al, 1998). Valproate-induced thrombocytopenia may be t related. Platelet aggregation inhibition has also been described (Rimmer & Richens, 1985f; Prod Inf Tablets, 2002a).

b) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conc acid (n=96, target level 80 to 150 mcg/mL) caused thrombocytopenia (platelet count of less than 75,000 patients (31%) versus 0 patients in those assigned to low concentration valproic acid (n=47, target range mcmg/mL). Although none of the patients were symptomatic, 12 patients were withdrawn for this adverse (al, 1997c).

c) The effects of valproate in 30 patients ranging in age from 26 years to 76 years were studied. Patient valproate doses of 1200 mg to 3000 mg. No other anticonvulsants were administered. Following valproa significant reductions in platelet counts of 49,000/mm(3) from baseline was reported with moderate dose 1700 mg) and a reduction of 69,000/mm(3) was reported with high doses (2100 mg to 3000 mg). Platele reduced to the lower limit of normal in 10 patients. All patients were asymptomatic. After discontinuation platelet counts returned to baseline within 4 to 12 days (Neophytides et al, 1979).

d) Children receiving valproic acid had lower platelet counts as compared to control subjects. Patients acid mean dose of 20 mg/kg and mean level of 60 mcg/mL. After 6 months of therapy, children receiving n=20) had significantly lower platelet counts than age-matched controls (n=15) (194,000/mcL versus 29 than 0.01). Platelet counts were significantly correlated with dose (r=-0.49, p less than 0.05) and plasma 0.52, p less than 0.01). Decreased platelet aggregation and ATP release impairment was also noted in t group. Discontinuation of valproic acid was not necessary since the decreases were not clinically import 1999).

e) The incidence of thrombocytopenia (defined as a platelet count of less than 200,000/mm(3)) in childr
Serum valproic acid concentrations of greater than 90 mcg/mL and older adolescent age (16 to 21 years predictive of thrombocytopenia. The degree of thrombocytopenia was mild; the authors concluded that if thrombocytopenia with valproic acid therapy is low and that drug discontinuation is not necessary in the (Allarakhia et al. 1996).

f) A one-year prospective study of 45 children (median age of 6 years) was conducted in which the incid induced thrombocytopenia was evaluated. Twelve patients also received treatment with other anticonvuls cases of thrombocytopenia (defined as a platelet count less than 150,000/mm³ occurring 3 to 8 months of valproate) were noted that were reported to be transient and self-limited. In 82% of cases, thrombocyta associated with an increase in platelet-associated IgG antibodies. There was an inverse relationship in that the serum concentration of platelet-associated IgG antibody. There was not a significant difference in serum concentrations in patients with or without thrombocytopenia. It was concluded that immune-media thrombocytopenia may be common, but appears to be transient and self-limited despite continuations of (Barr et al, 1982).

g) A case of thrombocytopenia-induced fatal pulmonary hemorrhage was reported in a 30-year-old female valproate monotherapy. It has been suggested that viral infections may be associated with thrombocytopeni receiving valproate therapy (Sleiman et al, 2000).

3.3.5.A.12 Thrombocytopenia, Dose-related
a) Incidence: 1% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During clinical trials of patients with epilepsy, thrombocytopenia (at least 1 platelet value of 75 x 10^9 reported in 27% (34/126) of patients receiving valproate monotherapy at approximately 50 mg/kg/day. Pl returned to normal in all patients regardless of whether the drug was withdrawn or continued. Higher total concentrations (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significant thrombocytopenia occurrence. Monitoring of platelet counts and coagulation is recommended prior to va and at periodic intervals during therapy (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) During a clinical trial of valproate monotherapy for complex partial seizures, thrombocytopenia was re patients receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valpro many cases, causality could not be determined as patients were being titrated off another antiepilepsy d part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.5.A.13 von Willebrand factor inhibitor disorder
a) Below-normal levels of von Willebrand factor activity was observed in 6 of 29 (21%) children who had valproic acid for at least 6 months for treatment of epilepsy. The 6 children were regarded as having "ac Willebrand's Disease." No correlation was found between von Willebrand factor activity and dose or blo acid or duration of therapy. The authors cautioned that when surgery is necessary, factor VIII von Wille concentrations should be supplemented (Serdaroglu et al, 2002).

3.3.5.B Divalproex Sodium

Ecchymosis

Thrombocytopenia, Dose-related

3.3.5.B.1 Ecchymosis
a) Incidence: 4% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Ecchymosis was reported in 5% of patients receiving high-dose divalproex sodium (n=131) compared cas patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antie first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.5.B.2 Thrombocytopenia, Dose-related
a) Incidence: 1% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) During clinical trials of patients with epilepsy, thrombocytopenia (at least 1 platelet value of 75 x 10^9 reported in 27% (34/126) of patients receiving divalproex sodium monotherapy at approximately 50 mg/kg/di h concentration (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significant thrombocytopenia occurrence. Monitoring of platelet counts and coagulation is recommended prior to div initiation and at periodic intervals during therapy, especially prior to planned surgery. Drug discontinuation reduction is recommended if patient experiences hemorrhage, bruising, or a hemostasis/coagulation disc divalproex sodium therapy (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
c) Thrombocytopenia was reported in 24% of patients receiving high-dose divalproex sodium (n=131) of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial s cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antie the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
3.3.6 Hepatic Effects

Valproic Acid

Divalproex Sodium

3.3.6.A Valproic Acid

ALT (SGPT) level raised

AST/SGOT level raised

Hepatitis

Hepatotoxicity

Increased liver function test

Liver failure

3.3.6.A.1 ALT (SGPT) level raised

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased SGPT was reported in more than 1% but less than 5% of patients receiving valproate during complex partial seizures (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causality attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.6.A.2 AST/SGOT level raised

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Increased SGOT was reported in more than 1% but less than 5% of patients receiving valproate during complex partial seizures (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causality attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.6.A.3 Hepatitis

a) An 8-year-old boy taking valproate 40 mg/kg daily for epilepsy died from a normally benign viral hepatitis acquired from his sister. The boy presented with jaundice, decreased consciousness, lethargy, hyperammonemia, increased valproate level. Despite aggressive medical treatment and discontinuation of the valproate the liver enzymes decreased while his bilirubin level and bleeding time increased and the patient died 12 days to the hospital. The authors postulate that the additive hepatotoxicity associated with the increased valproate have contributed to the development of fulminant liver failure and death in this patient (Fayad et al, 2000).

3.3.6.A.4 Hepatotoxicity

a) Fatal hepatotoxicity is reported in 1/800 children under the age of 2 years following antiepileptic therapy. It is suggested that valproic acid may induce a carnitine deficiency in young children and result in symptoms of deficiency, hepatotoxicity, and hyperammonia. Carnitine supplementation may help prevent hepatotoxicity (Raskind & El-Chaar, 2000).

b) A 52-year-old male with no known risk factors developed fulminant hepatotoxicity that progressed to liver failure. He presented with altered mental status, jaundice and anuria. An exhaustive diagnostic work-up failed to reveal an etiology. The patient had associated acute tubular necrosis with renal failure and rhabdomyolysis. He fully recovered after 16 days of supportive care (Pinkston & Walker, 1997).

c) One study indicated that the greatest risk of fatal hepatotoxicity occurred in children between the age of 0 to 2 years who were receiving multiple anticonvulsant therapy. The incidence of fatal hepatotoxicity in this group was greater than the overall incidence of fatal hepatotoxicity of 1/10,000. The incidence of fatal hepatotoxicity age group was 1/700. No hepatic fatalities were described in patients over the age of 10 years who received monotherapy. The risk of fatal hepatotoxic reactions in children over the age of 2 years receiving polytherapy was considerably lower (1/12,000), with the risk of fatal hepatic dysfunction in patients above 2 years of age receiving valproate as monotherapy being 1/45,000. Thus, the risk of fatal hepatic reactions appears to be greatest in very young children (0 to 2 years of age) and declines significantly with age (Dreifuss et al, 1987).
3.3.6.A.5 Increased liver function test

a) Summary

1) Elevated liver enzymes have been reported following chronic administration of valproate (Lewis, Wilder, 1979a; Gerber et al, 1979; Addison & Gordon, 1980; Coulter & Allen, 1981; Rawat et al, 1986) elevations in transaminases (aspartate aminotransferase (AST; SGOT) and alanine aminotransferase and lactate dehydrogenase are frequently seen and are dose-related. Increased serum bilirubin and function tests may also be seen. These may reflect a more serious problem. It is speculated that valproic acid is normally toxic substance, but in the presence of metabolic abnormalities such as an inborn error of metabolism or administration with other drugs, it may become toxic (Rimmer & Richens, 1985).

3.3.6.A.6 Liver failure

a) Serious hepatotoxicity and hepatic failure have been reported in patients receiving valproic acid and in usually in the first 6 months of treatment. Serious or fatal hepatic toxicity may be preceded by symptoms of lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). More commonly, elevated liver enzymes should be initiated prior to therapy and at frequent intervals during treatment, mainly during the first 6 months. However, abnormal serum biochemistry may not be present in all cases. Children under the age of 5 have an increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have cc disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain disease. Failure to discontinue the drug has progressed in some cases, even with the discontinuation of drug (Prod Info STAVZOR(R) sprinkle oral capsules, 2008).

b) A case of fulminant liver failure induced by valproate therapy was reported in a 39-year-old woman with bilateral ptosis and chronic progressive external ophthalmoplegia (CPEO). The patient developed fulminant liver failure 2 months after she was treated with valproate for status epilepticus and died due to multorgan failure and syndrome. The patient’s 2 siblings also had congenital bilateral ptosis and CPEO, a typical sign of mitochondrial cytopathies, but none of them had any previous signs of liver disease. This report suggested that mitochondrial dysfunction should be considered a risk factor for valproate-induced liver failure and should be excluded before valproate therapy (Krahenbuhl et al, 2000).

c) It is speculated that valproic acid is a normally toxic substance, but in the presence of metabolic a as an inborn error of metabolism or administration with other drugs, it may become toxic (Rimmer & Richens, 1985). One case, medium chain acyl-CoA dehydrogenase deficiency, resulting in abnormal fatty acid beta-oxidation in a 10-year-old male who died of liver failure 3 months after valproic acid initiation (Njolstad et al, 1997).

d) In one report, hepatic failure occurred in a 15-year-old boy following approximately 5 years of valproic acid therapy. The patient had also been receiving phenytoin and phenobarbital. The patient developed cerebrohepatic encephalopathy in a 24-hour period. These data suggest that hepatic failure secondary to valproic acid can also occur after therapy (van Egmond et al, 1987).

e) Acute hepatic failure resulting in fatality in 2 children (5 years and 11.5 years) following 650 mg daily doses of valproic acid over approximately 7 weeks (with other anticonvulsants), respectively described. Autopsy revealed mixed toxic cholestatic hepatitis with diffuse hepatocellular injury which term centrolobular microvesicular fatty changes and submassive necrosis. The site of injury appeared to be the liver apparatus, canaliculi and ducts of Hering (Suchy et al, 1979).

3.3.6.B Divalproex Sodium

ALT (SGPT) level raised

AST/SGOT level raised

Liver failure

3.3.6.B.1 ALT (SGOT) level raised

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased SGOT was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex sodium treatment being a risk factor for valproate-induced liver failure and should be excluded before valproate therapy (Krahenbuhl et al, 2000).

3.3.6.B.2 AST/SGOT level raised

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Increased SGOT was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex sodium treatment being a risk factor for valproate-induced liver failure and should be excluded before valproate therapy (Krahenbuhl et al, 2000).

3.3.6.B.3 Liver failure

a) Serious hepatotoxicity and hepatic failure have been reported in patients receiving valproic acid and i
usually in the first 6 months of treatment. Serious or fatal hepatic toxicity may be preceded by symptoms of lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). Monitoring tests should be initiated prior to therapy and at frequent intervals during treatment, mainly during the first 6 months. However, abnormal serum biochemistry may not be present in all cases. Children under the age of 10 years have an increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have comorbid disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain dysfunction that has progressed in some cases, even with the discontinuation of drug (Prod Info DEPAKOTE capsules, 2008).

3.3.7 Immunologic Effects

Valproic Acid

Divalproex Sodium

3.3.7.A Valproic Acid

HIV infection, Progression

Immune hypersensitivity reaction

Immunology finding

Systemic lupus erythematosus

3.3.7.A.1 HIV infection, Progression

a) Valproate therapy may reduce intracellular levels of glutathione and inhibit activity of glutathione reduced blood cells. There may be a link between intracellular levels of glutathione and the progression of human immunodeficiency virus (HIV) disease. Decreased glutathione levels may activate the replication of HIV. Studies with cell lines infected with HIV showed the addition of valproate increased viral expression and replication over drug concentrations (Hardy & Nardacci, 1999).

3.3.7.A.2 Immune hypersensitivity reaction

a) Incidence: rare (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) Multiorgan hypersensitivity reactions (eg, fever and rash associated with other organ system involvement) are rarely reported between 1 and 40 days following initiation of valproate therapy in both adult and pediatric reactions have led to hospitalization and at least one death. If a hypersensitivity reaction occurs, discontinue therapy and begin alternative treatment (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

c) A 6-year-old boy developed hypersensitivity syndrome after receiving valproic acid for about 1.5 months of ethosuximide for 1 month. Both drugs were in the therapeutic range. He developed a diffuse morbilliform edema of the face, high fever, and enlarged lymph nodes. He also had a leukocytosis, eosinophilia, lymph monocytosis, and stimulated lymphocytes. Liver enzymes were also slightly elevated. Since the authors hypothesize that infections may contribute to the pathogenesis of hypersensitivity, the child was tested for reactivation of 6. Titers were significantly increased within 15 days. Patch testing revealed hypersensitivity to both valproic acid and ethosuximide (Conilleau et al, 1999).

3.3.7.A.3 Immunology finding

a) IgA deficiency was reported in 29% of 41 epileptic patients receiving 1 or more anticonvulsants (valproate, phenytoin, phenobarbital, carbamazepine) was reported. Patients receiving valproate sodium exhibited slightly lower IgA levels than nonusers of valproate sodium (Joubert et al, 1977).

3.3.7.A.4 Systemic lupus erythematosus

a) A case of systemic lupus erythematosus, marked by increased antihistone antibody level, arthralgias, weakness, fatigue and fever, was reported in a 30-year-old female epileptic patient after 1 year of treatment with valproic acid. The laboratory and clinical symptoms disappeared after discontinuation of valproic acid (Gigli et al, 2008). See Drug Consult reference: DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

3.3.7.B Divalproex Sodium

3.3.7.B.1 Immune hypersensitivity reaction

a) Incidence: rare (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Multi-organ hypersensitivity reactions (eg, fever and rash associated with other organ system involvement) are rarely reported between 1 and 40 days following initiation of valproate therapy in both adult and pediatric reactions have led to hospitalization and at least one death. If a hypersensitivity reaction occurs, discontinue therapy and begin alternative treatment (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
rarely reported between 1 and 40 days following initiation of valproate therapy in both adult and pediatric reactions have led to hospitalization and at least one death. If a hypersensitivity reaction occurs, discontinue therapy and begin an alternative treatment (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

### 3.3.8 Musculoskeletal Effects

**Valproic Acid**

**Divalproex Sodium**

#### 3.3.8.A Valproic Acid

- **Asthenia**
- **Backache**
- **Osteomalacia**
- **Secondary myopathy**

##### 3.3.8.A.1 Asthenia

- **Incidence:** 10% to 27% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
- **During** two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, as reported in 10% of patients receiving valproate (n=89) compared with 7% of patients receiving placebo (STAVZOR(R) delayed release oral capsules, 2008).
- **Asthenia** was reported in 20% of migraine patients receiving valproate (n=202) compared with 9% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed n capsules, 2008).
- **During** a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, asthenia was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiving low-dose valproate (n=39) during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

##### 3.3.8.A.2 Backache

- **Incidence:** 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
- **Back pain** was reported in 8% of migraine patients receiving valproate (n=202) compared with 6% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed n capsules, 2008).

##### 3.3.8.A.3 Osteomalacia

- **A 2-year cross-sectional and retrospective study concluded** that lumbar spine bone mineral density v significantly reduced in prepubertal children treated with valproic acid and carbamazepine compared to children treated with antiepileptics (valproic acid: 17 boys, 16 girls; mean age 9.7 +/- 1.6 years) compared to age- and sex-matched controls (13 boys, 9 girls; mean age 9.7 +/- 1.6 years). Patients were ambulatory with normal activity and had adequate nutritional intake, which exclude could reduce BMD or biochemical markers of bone turnover. Mean length of treatment was 33.72 +/- 15 acid and 35.52 +/- 12.84 months for carbamazepine. Mean BMD z-scores at lumbar spine were -1.28 +/- acid, -1.69 +/- 0.85 for carbamazepine, and -0.23 +/- 0.87 for the control group. Differences in serum ins factor (IGF)-1 and IGF binding protein (IGFBP)-3 levels, which affect bone metabolism and BMD, between receiving antiepileptics compared to controls were not significant (Kumandas et al, 2006).

##### 3.3.8.A.4 Secondary myopathy

- **A 4-year-old male child developed myopathy with symptoms of progressive weakness in all limbs starting valproate sodium for epilepsy. Over 1 year the valproate sodium dose was gradually increased to 40 mg/kg. Four months after starting on 40 mg/kg, he developed lower limb weakness resulting in difficult jumping, climbing up stairs, and standing from a sitting position. Examination revealed weakness in prox muscles of all four limbs (more pronounced in the lower limbs), lordosis, a waddling gait, and normal sen tendon reflexes. No hypertrophy or atrophy was noted. Serum valproate and creatinine phosphokinase c
were within normal limits. The findings on electromyogram (EMG) were suggestive of myopathy. Plasma was below normal at 16 mcmol/L (normal, 20 to 43 mcmol/L). Valproate-induced-myopathy secondary to deficiency was suspected. Carbamazepine replaced valproate and L-carnitine 100 mg/kg/day was initiated there was improvement and within 2 months complete recovery. Complete recovery was further demonstrated months later (Kasturi & Sawant, 2005).

b) Chronic therapeutic use of valproic acid in young children may cause a carnitine deficiency resulting in symptoms of lethargy, weakness or hypotonia, hepatotoxicity, and hyperammonemia. An incidence of 1 in 800 children under the age of two years has been reported (Raskind & El-Chaar, 2000). An inverse found between plasma carnitine concentrations and the dosage of valproic acid, and between plasma carnitine concentrations and the dosage of valproic acid, and between plasma ammonia values (Ohtani et al, 1982).

c) The syndrome known as MELAS, including mitochondrial myopathy, encephalopathy, lactic acidosis and episodes, was precipitated by valproic acid therapy in a 12-year-old male. Signs and symptoms included exacerbation, hemiparesis, hypotonia, elevated deproteinized blood lactate and pyruvate, and brain infarction was found to have a point mutation in mitochondrial DNA. He stabilized upon valproic acid withdrawal (L

3.3.8.B Divalproex Sodium

Arthralgia

Backache

Generalized myasthenia

Myalgia

3.3.8.B.1 Arthralgia
a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Arthralgia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3) monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKO1 capsules, 2008).

3.3.8.B.2 Backache
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Back pain was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3) monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKO1 capsules, 2008).

3.3.8.B.3 Generalized myasthenia
a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Myasthenia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3) monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKO1 capsules, 2008).

3.3.8.B.4 Myalgia
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Myalgia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3) monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKO1 capsules, 2008).

3.3.9 Neurologic Effects

Valproic Acid

Divalproex Sodium

3.3.9.A Valproic Acid

Abnormal behavior
Amnesia
Ataxia
Cerebral atrophy
Coma, Hyperammonemia-induced
Dementia
Demyelinating disease of central nervous system
Dizziness
Extrapyramidal disease
Feeling nervous
Headache
Hyperammonemic encephalopathy
Insomnia
Paresthesia
Seizure
Somnolence
Tremor

3.3.9.A.1 Abnormal behavior
   a) Behavioral changes were seen in 56 out of 88 pediatric patients receiving sodium valproate monotherapy included irritability, longer and deeper sleep, superficial sleep, hyperactivity, increased alertness, lassitude, increased sociability, calmness, increased sadness, happiness, and aggression. It was emphasized that reactions with valproic acid were as frequent as depressive effects (Herranz et al, 1984b).

3.3.9.A.2 Amnesia
   a) Incidence: 4% to 7% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) During a clinical trial of valproate monotherapy for complex partial seizures, amnesia was reported in receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=13). Causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.3 Ataxia
   a) Incidence: 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, ataxia was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients receiving placebo. Causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.4 Cerebral atrophy
   a) In a series of 16 patients treated with valproate in whom cranial computer tomography (CT) were performed demonstrated new or progressive cerebral atrophy. The atrophy improved in the two patients in whom cranial computer tomography was repeated after valproate was discontinued (Armon et al, 1996).

3.3.9.A.5 Coma, Hyperammonemia-induced
   a) A 56-year-old woman experienced life-threatening hyperammonemic coma following a moderate dose of valproate sodium. The patient had been poorly controlled while receiving valproate for 6 years.
phenobarbital, phenytoin, carbamazepine, and gabapentin. The divalproex sodium dose was increased from 2500 mg/day, and the phenobarbital, phenytoin, carbamazepine and gabapentin were slowly discontinued initially presented with a 3-hour period of unresponsiveness on divalproex sodium monotherapy. Her am mcg/dL (reference range 22 to 78). The divalproex sodium dose was increased to 3000 mg/day. The patient after 10 hours of the dose escalation. Her venous ammonia level was 921 mcg/dL, and the arterial ammonia mcg/dL (reference range 22 to 78). Possible causes of hyperammonemia and coma were excluded by gastrointestinal bleeding or portosystemic shunt and other metabolic, toxic, and structural factors. After one week of divalproex sodium was discontinued and within 48 hours, the ammonia level normalized to 69 mcg/dL as regained consciousness. A possible urea enzyme deficiency may have contributed to the development of hyperammonemic coma. The Naranjo probability scale conducted stated that the causal relationship between hyperammonemic coma was probable (Cuturic, 2005).

3.3.9.A.6 Dementia

a) Long-term therapy with valproic acid was associated with the occurrence of a reversible dementia in patients with epilepsy. Withdrawal of the drug resulted in dramatic improvement in memory and other tasks of intellect. It is suggested that valproic acid may induce a dementia-like syndrome via either a direct toxic central nervous system (CNS) effect, a paradoxical epileptogenic effect, or an indirect CNS effect via production of hyperammonemia (Cohen, 1986).

3.3.9.A.7 Demyelinating disease of central nervous system

a) A 23-year-old male with fulminant demyelinating disease experienced an acute progression after an exacerbation of relapsing-remitting multiple sclerosis. He had been experiencing uncontrolled seizures with phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 days of progressively lethargic and was eventually unresponsive. His venous ammonia level was 524 mcmol/L (reference range 7 to 38 mcmol/L) with normal liver enzymes. Serum creatinine levels were also low. After 15 days, a repeat cranial magnetic resonance imaging (MRI) showed extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors speculate that hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoided in patients with demyelinating disease (Blindauer et al, 1998).

3.3.9.A.8 Dizziness

a) Incidence: 12% to 25% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial of valproate monotherapy for complex partial seizures, dizziness was reported in 12% of patients receiving high-dose valproate (n=131) compared with 7% of patients receiving low-dose valproate (n=70). In most cases, causality could not be determined as patients were also receiving other antiepilepsy drugs.

c) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, dizziness was reported in 12% of patients receiving valproate (n=89) compared with 4% of patients receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) Dizziness was reported in 12% of male patients receiving valproate (n=202) compared with 6% of placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
e) Dizziness was reported in 12% of patients receiving valproate (n=77) compared with 13% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs.

3.3.9.A.9 Extrapyramidal disease

a) Summary

1) A 77-year-old man, with a diagnosis of dementia of the Alzheimer's type, developed an acute Parkinsonian syndrome 1 week after starting valproate therapy. This man, who had no prior history of movement disorder, was started on valproate due to an increase in aggressive and violent behaviors. The valproate dose increased to 300 mg per day over one week and resulted in a serum level of 11 mcg/mL. At this time, he experienced resting tremors, rigidity, gait disturbance, and bradykinesia and his Unified Parkinson's Disease Rating Scale (UPDRS) score increased from 18 to 59. Valproate was discontinued 2 weeks later when his Unified Parkinson's Disease Rating Scale (UPDRS) score decreased from 59 to 18. He experienced lessening in the Parkinsonian symptoms. Movement disorder signs gradually resolved following discontinuation of valproate (Iijima, 2002).

2) Parkinson’s syndrome has been associated with chronic valproate therapy. In a series of 36 patients on valproate, 27 (75%) had clinical evidence of Parkinsonism (Armon et al, 1996). Of these patients 19 of instability, 16 (44%) reported tremor, 30 (80%) demonstrated cognitive impairment, 22 (62%) had 55% had abnormal upper motor neuron signs (Armon et al, 1996). Most patients on valproate were discontinued. An extrapyramidal syndrome, unresponsive to antiparkinsonian medication, developed in a 52-year-old man with schizophrenia who was given sodium valproate 1 to 2 g/day (L. 2000).

3.3.9.A.10 Feeling nervous

a) Incidence: 7% to 11% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial of valproate monotherapy for complex partial seizures, nervousness was reported in 7% of patients receiving high-dose valproate (n=131) compared with 7% of patients receiving low-dose valproate. In many cases, causality could not be determined as patients were being titrated off another antiepilepsy drug.
Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in path cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of hyperammonemic encephalopathy (unexplained lethargy and vomiting changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of therapy) and be evaluated for underlying urea cyclic disorder. Most patients receiving concomitant topiramate resolution of hyperammonemia upon discontinuation of either drug (Prod Info STAZVOR(R) delayed rele 2008).

Clinicians reported two adult cases of valproate-induced hyperammonemic encephalopathy, which occurred in combination therapy including valproate and topiramate. The patients were a 32-year-old man who had in epilepsy with complex partial and secondarily generalized seizures and a 37-year-old woman with focal right parietal angioma. Among the patient's symptoms were sudden somnolence, slurred speech, ataxia, horizontal nystagmus, and nausea. One day after admission, the man was reacting only to strong stimuli and he was found to have a 2-second generalized tonic-clonic seizure. His ammonia concentration increased to 130 mmol/L. He became confused and lethargic and his I bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate was stopped, and ammonia concentration decreased to 60 mmol/L after 1 day and on the second day his confusion decreased to baseline (Feil et al, 2002).

d) Ten days following initiation of valproic acid (10 mg/kg/day), a 51-year-old female presented with a rapid level of consciousness (Glasgow coma score 5/15). EEG showed triphasic waves consistent with hepatic coma. Serum valproic acid and liver enzyme levels were normal; blood arterial ammonia concentration was sign (234 mmol/L) 10 hours after presentation. Following discontinuation of valproic acid and administration her neurological condition improved within 18 hours (Borbath et al, 2000).

e) A 16-year-old girl with undiagnosed heterozygous ornithine transcarbamylase deficiency (OTC) developed hyperammonemic encephalopathy after valproic acid therapy. OTC deficiency is an X-linked disorder which is common inherited cause of hyperammonemia. The child was experiencing frequent seizures and had vomiting due to her carbamazepine therapy. After 7 days, she became deeply somnolent. Her plasma ammonia level (normal less than 50 mmol) with normal serum transaminases and fibrinogen. In Valproic acid was discontinued. Deficiency diagnosis was based on non-detectable serum citrulline and high urinary excretion of orotic acid treated with a low-protein diet, sodium benzoate, sodium phenytoin, and substitution of L-arginine. Plasma ammonia levels fell to 55 mmol/L (Ochsner et al, 1998).

"part of the trial (Prod Info STAZVOR(R) delayed release oral capsules, 2008).

3.3.9.A.12 Hyperammonemic encephalopathy

a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in path cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of hyperammonemic encephalopathy (unexplained lethargy and vomiting changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of therapy) and be evaluated for underlying urea cyclic disorder. Most patients receiving concomitant topiramate resolution of hyperammonemia upon discontinuation of either drug (Prod Info STAZVOR(R) delayed rele 2008).

b) An 88-year-old man developed hyperammonemia and worsening confusion two months after starting four times a day for a presumed seizure disorder. His liver function tests were within normal limits except for concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentration was 150 mcg/mL. His condition slowly worsened. One week later his ammonia concentration increased to 130 mmol/L. He became confused and lethargic and his I bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate was stopped, and ammonia concentration decreased to 60 mmol/L after 1 day and on the second day his confusion decreased to baseline (Feil et al, 2002).

c) Clinicians reported two adult cases of valproate-induced hyperammonemic encephalopathy, which occurred in combination therapy including valproate and topiramate. The patients were a 32-year-old man who had in epilepsy with complex partial and secondarily generalized seizures and a 37-year-old woman with focal right parietal angioma. Among the patient's symptoms were sudden somnolence, slurred speech, ataxia, horizontal nystagmus, and nausea. One day after admission, the man was reacting only to strong stimuli and he was found to have a 2-second generalized tonic-clonic seizure. His ammonia concentration increased to 130 mmol/L. He became confused and lethargic and his I bilateral 5 to 7 hertz (Hz) slowing and abnormal, irregular 2-Hz to 3-Hz activity on the right. Valproate was stopped, and ammonia concentration decreased to 60 mmol/L after 1 day and on the second day his confusion decreased to baseline (Feil et al, 2002).

d) Ten days following initiation of valproic acid (10 mg/kg/day), a 51-year-old female presented with a rapid level of consciousness (Glasgow coma score 5/15). EEG showed triphasic waves consistent with hepatic coma. Serum valproic acid and liver enzyme levels were normal; blood arterial ammonia concentration was sign (234 mmol/L) 10 hours after presentation. Following discontinuation of valproic acid and administration her neurological condition improved within 18 hours (Borbath et al, 2000).

e) A 16-year-old girl with undiagnosed heterozygous ornithine transcarbamylase deficiency (OTC) developed hyperammonemic encephalopathy after valproic acid therapy. OTC deficiency is an X-linked disorder which is common inherited cause of hyperammonemia. The child was experiencing frequent seizures and had vomiting due to her carbamazepine therapy. After 7 days, she became deeply somnolent. Her plasma ammonia level (normal less than 50 mmol) with normal serum transaminases and fibrinogen. In Valproic acid was discontinued. Deficiency diagnosis was based on non-detectable serum citrulline and high urinary excretion of orotic acid treated with a low-protein diet, sodium benzoate, sodium phenytoin, and substitution of L-arginine. Plasma ammonia levels fell to 55 mmol/L (Ochsner et al, 1998).

f) A 23-year-old male with fulminant demyelinating disease experienced an acute progression after an e valproate-induced hyperammonemic encephalopathy. He had been experiencing uncontrolled seizures with phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 days his ammonia concentration increased to 130 mmol/L. He became confused and lethargic and was eventually unresponsive. His venous ammonia level was 524 mmol/L (normal range 11 to 60 mmol/L) with normal liver enzymes. Serum creatinine levels were also low. After 15 days, a repeat cranial imaging showed extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors speculate hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoided in patients with demyelinating disease (Blindauer et al, 1998).

g) A 31-year-old woman with systemic lupus erythematosus and a seizure disorder treated with valproic acid developed fatal hyperammonemia. The woman had also been receiving aspirin 81 mg and cimetidine 40
elevation in anti-cardiolipin-beta2-glycoprotein-1Ab. After 15 months of valproic acid therapy, she was di nephritis and treated with repeated steroid pulse therapy. This was ineffective and hemodialysis was inst and finally coma developed and she was found to have a serum ammonia level of 500 mc/mol/L. Despite her ammonia level continued to rise and she died of hyperammonemic encephalopathy (Ichikawa et al, 1

3.3.9.A.13 Insomnia
a) Incidence: 9% to 15% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial of valproate monotherapy for complex partial seizures, insomnia was reported in receiving high-dose valproate (n=131) compared with 9% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.14 Paresthesia
a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) Paresthesia was reported in more than 1% but less than 5% of patients receiving valproate during pla clinical trials of migraine and acute mania and during monotherapy treatment of complex partial seizures causality could not be attributed to valproate alone in the complex partial seizures trial, as patients were another antiepilepsy drug during the first part of the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.15 Seizure
a) In 2 children, ages 5 and 10 years old, valproic acid therapy for infrequent absence seizures resulted deterioration to absence status with atonic generalized seizures, along with drop attacks in the younger c experienced an increase in the frequency and duration of absences and progressive disorientation. The effects of valproic acid occurred at doses of 80 to 120 mg twice per day for the 5-year-old patient and 50 for the 10-year-old patient. After valproic acid administration was stopped, both patients experienced a d absence frequency and duration (to pretreatment levels) along with a clearing of disorientation (Shahar e b) A 14-year-old boy receiving phenobarbital for tonic-clonic seizures presented with status epilepticus valproic acid added. Initially, tonic seizures occurred which increased after 13 days to status. Serum plas of both valproic acid and phenobarbital were within the therapeutic range. Valproic acid was discontinued a later date with similar results (Capocchi et al, 1998).
c) Increasing generalized spike and wave activity with increasing somnolence to the point of absence st 25-year-old woman after beginning valproic acid therapy. The woman suffered from multiple seizure type generalization of tonic-clonic, gelastic, absence, and drop attacks. She was being treated with carbamazepine and fluphenazine. Valproic acid (maximum dose 2500 mg after 4 days) was added for hallucinations ass frequent seizures. Spike and wave activity during wakefulness was noted to increase as the blood conce acid increased. Her ammonia level also increased to 104 mc/mol/L. Valproic acid was discontinued and i started (Stecker & Kita, 1998).
d) A breakthrough seizure occurred in a 19-year-old epileptic girl following substitution of Depakene(R) generic form of valproic acid capsules. Re-initiation of Depakene(R) therapy resulted in no recurrence of months of follow-up (MacDonald, 1987).

3.3.9.A.16 Somnolence
a) Incidence: 17% to 30% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) In a double-blinded study involving elderly patients with dementia (mean age of 83 years), the occur somnolence was significantly higher in the valproate arm (target dose of 20 mg/kg/day) compared with p approximately half of the affected patients, somnolence was associated with reduced nutritional intake, v baseline albumin concentration, lower valproate clearance, and higher BUN. When dosing elderly patien recommended to increase doses more slowly and to monitor fluid and nutritional intake, dehydration, ax adverse reactions (including somnolence) on a regular basis. Consider dose reductions or discontinuatio excessive somnolence or in patients with reduced fluid or nutritional intake (Prod Info STAVZOR(R) dela capsules, 2008).
c) During a clinical trial of valproate monotherapy for complex partial seizures, somnolence was reporte patients receiving high-dose valproate (n=131) compared with 18% of patients receiving low-dose valpro many cases, causality could not be determined as patients were being titrated off another antiepilepsy dr part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
d) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, so reported in 19% of patients receiving valproate (n=89) compared with 12% of patients receiving placebo STAVZOR(R) delayed release oral capsules, 2008).
e) Somnolence was reported in 17% of migraine patients receiving valproate (n=202) compared with 5% receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).
f) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial somnolence was reported in 27% of patients receiving valproate (n=77) compared with 11% of patients r (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy dru with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
g) Due to a higher risk of somnolence among the elderly, the valproate starting dose should be reduced adjustment should be conservative (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
3.3.9.A.17   Tremor

a) Incidence: 9% to 57% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, tremor was reported in 5% receiving high-dose valproate (n=131) compared with 19% of patients receiving low-dose valproate (n=110) cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, tremor was reported in 25% of patients receiving valproate (n=131) compared with 6% of patients receiving placebo (n=134) cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

d) Tremor was reported in 9% of migraine patients receiving valproate (n=202) compared with 0% of patients receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

e) In 28 consecutive valproic acid-treated patients (mean duration: 3.8 years, mean dose: 1259 mg), 3 had parkinsonism, 15 had intentional tremor, and 16 had postural tremor. None of the patients with parkinsonism had levodopa (Nouzeilles et al, 1999).

f) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high concentration valproic acid (n=96, target level 80 to 150 mcg/mL) caused tremor in 61 patients (64%) versus 3 patients (6%) in low concentration valproic acid (n=47, target range of 25 to 50 mcg/mL) (Beydoun et al, 1997c).

g) The effects of propranolol, amantadine, diphenhydramine, benzotropine, and cyproheptadine on valproate patients were studied. Propranolol was clearly the most therapeutic. Amantadine was moderately effectivc, cyproheptadine, diphenhydramine and benzotropine gave little or no relief (Karas et al, 1983).

3.3.9.B   Divalproex Sodium

- Amnesia
- Asthenia
- Ataxia
- Dizziness
- Feeling nervous
- Headache
- Hyperammonemic encephalopathy
- Insomnia
- Nystagmus
- Paresthesia
- Somnolence
- Tremor

3.3.9.B.1   Amnesia

a) Incidence: 4% to 7% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, amnesia was reported in 5% of patients receiving high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Amnesia was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared with 1% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.2   Asthenia

a) Incidence: 10% to 27% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, asthenia was reported in 27% of patients receiving high-dose divalproex sodium (n=77) compared with 7% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Asthenia was reported in 21% of patients receiving high-dose divalproex sodium (n=131) compared with 7% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic agent during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.3 Ataxia

a) Incidence: 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, ataxia was reported in 8% of patients receiving high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.4 Dizziness

a) Incidence: 13% to 25% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, dizziness was reported in 25% of patients receiving high-dose divalproex sodium (n=77) compared with 13% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Dizziness was reported in 18% of patients receiving high-dose divalproex sodium (n=131) compared with 13% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic agent during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.5 Feeling nervous

a) Incidence: 7% to 11% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Nervousness was reported in 11% of patients receiving high-dose divalproex sodium (n=131) compared with 7% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic agent during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.6 Headache

a) Incidence: 31% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Headache was reported in 31% of patients receiving high-dose divalproex sodium (n=77) compared with 21% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.7 Hyperammonemic encephalopathy

a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in patients with urea cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant therapy for hyperammonemia. Patients who develop symptoms of unexplained hyperammonemic encephalopathy (unexplained lethargy, ataxia, mental status changes) while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying urea cycle disorder. Most patients receiving concomitant therapy for hyperammonemia upon discontinuation of either drug (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.8 Insomnia

a) Incidence: 9% to 15% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Insomnia was reported in 15% of patients receiving high-dose divalproex sodium (n=131) compared with 13% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic agent during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.9 Nystagmus

a) Incidence: 1% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Nystagmus was reported in 8% of patients receiving high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Nystagmus was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared with 7% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic agent during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.10 Paresthesia

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Paresthesia was reported in more than 1% but less than 5% of patients receiving high-dose valproic acid monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
capsules, 2008).

3.3.9.B.11 Somnolence

a) Incidence: 18% to 30% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, somnolence was reported in 27% of patients receiving divalproex sodium (n=77) compared with 11% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
c) Somnolence was reported in 30% of patients receiving high-dose divalproex sodium (n=131) compared with 27% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In most cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
d) Due to a higher risk of somnolence among the elderly, the starting dose should be reduced and dose titration should be conservative (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.9.B.12 Tremor

a) Incidence: 19% to 57% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, tremor was reported in 25% of patients receiving divalproex sodium (n=77) compared with 11% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
c) Tremor was reported in 57% of patients receiving high-dose divalproex sodium (n=131) compared with 30% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In most cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10 Ophthalmic Effects

Valproic Acid

Divalproex Sodium

3.3.10.A Valproic Acid

Amblyopia

Blurred vision

Diplopia

Nystagmus

3.3.10.A.1 Amblyopia

a) During a clinical trial of valproate monotherapy for complex partial seizures, amblyopia/blurred vision was reported in 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=77). In many cases, causality could not be determined as patients were being titrated off of another antiepileptic first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepileptics concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.2 Blurred vision

a) During a clinical trial of valproate monotherapy for complex partial seizures, amblyopia/blurred vision was reported in 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose valproate (n=77). In many cases, causality could not be determined as patients were being titrated off of another antiepileptic first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepileptics concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.3 Diplopia

a) Incidence: 16% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, nystagmus was reported in 16% of patients receiving valproate (n=77) compared with 9% of patients receiving placebo cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.A.4 Nystagmus
a) Incidence: 1% to 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) During a clinical trial of valproate monotherapy for complex partial seizures, nystagmus was reported receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13 cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, nystagmus was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients receiving placebo (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.10.B Divalproex Sodium

Abnormal vision

Amblyopia

Blurred vision

Diplopia

3.3.10.B.1 Abnormal vision
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Abnormal vision was reported in more than 1% but less than 5% of patients receiving divalproex sodium monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10.B.2 Amblyopia
a) In a clinical trial of adjunctive therapy for complex partial seizures, amblyopia/blurred vision was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures, many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10.B.3 Blurred vision
a) In a clinical trial of adjunctive therapy for complex partial seizures, amblyopia/blurred vision was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).
b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures, many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.10.B.4 Diplopia
a) Incidence: 16% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, diplopia was reported in 16% of patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.11 Otic Effects

Valproic Acid

Divalproex Sodium
3.3.11.A Valproic Acid

Otitotoxicity - deafness

Tinnitus

3.3.11.A.1 Otitotoxicity - deafness

a) Incidence: 1% to less than 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) Deafness was reported in more than 1% but less than 5% of patients receiving valproate during acute (n=89) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causality attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part monotherapy trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.11.A.2 Tinnitus

a) Incidence: 1% to 7% (Prod Info STAVZOR(R) delayed release oral capsules, 2008) 
b) During a clinical trial of valproate monotherapy for complex partial seizures, tinnitus was reported in 7 receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13 causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008). 
c) A 52-year-old man experienced tinnitus after receiving valproic acid for treatment of bipolar disorder. admitted to a psychiatric unit for bipolar disorder; symptoms included agitation, loudness, pressured speech, grandiose delusions, and paranoia. His treatment included olanzapine 10 mg and divalproex sodium 500 day, and lorazepam as needed. Two days later, he complained of noises in his head. This complaint was worsening of his psychotic symptoms. By day 8, he was calm and coherent but continued to report increased hearing. At that time, his serum valproic acid level was 67.5 mcg/mL (within the therapeutic range). The patient that he had experienced the same problem when he had taken valproate several years earlier. Valproate and his tinnitus resolved over a period of 10 days (Reeves et al, 2000).

3.3.11.B Divalproex Sodium

Otitis media

Otitotoxicity - deafness

Tinnitus

3.3.11.B.1 Otitis media

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Otitis media was reported in more than 1% but less than 5% of patients receiving divalproex sodium (monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.11.B.2 Otitotoxicity - deafness

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Deafness was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.11.B.3 Tinnitus

a) Incidence: 1% to 7% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Tinnitus was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared with receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12 Psychiatric Effects

Valproic Acid
Divalproex Sodium
Valproate Sodium

3.3.12.A Valproic Acid

Depression
Disturbance in thinking
Mood swings
Psychiatric sign or symptom
Suicidal thoughts

3.3.12.A.1 Depression
a) Incidence: 4% to 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) Depression was reported in 5% of patients receiving high-dose valproate (n=131) compared with 4%
      receiving low-dose valproate (n=134) for monotherapy treatment of complex partial seizures. In many ca
      could not be attributed to valproate alone, as patients were titrated off of another antiepilepsy drug durin
      the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.12.A.2 Disturbance in thinking
a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex parti
      abnormal thinking was reported in 6% of patients receiving valproate (n=77) compared with 0% of patien
      placebo (n=70). In most cases, causality could not be determined as patients also received other antiepi
      concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.12.A.3 Mood swings
a) Incidence: 6% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) In a clinical trial of adjunctive therapy for complex partial seizures, emotional lability was reported in 6
      of patients receiving valproate (n=77) compared with 4% of patients receiving placebo (n=70). In most cases, caus
      determined as patients also received other antiepileptic drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.12.A.4 Psychiatric sign or symptom
a) Behavioral changes were reported 1 week after starting therapy in a 34-year-old male who was recei
      valproic acid per day as part of a controlled study. The valproic acid was discontinued and 5 days later t
      recovered (Alvarez et al, 1982).
   b) A psychotic reaction in a 14-year-old male who received valproate sodium 1600 mg daily for 14 days
      described. The patient at this time was seizure-free but experienced confusion, bizarre behavior, and hal
      Plasma levels of valproate at the time were 13 mcg/mL. The drug was discontinued and restarted at 800
      patient remained seizure-free with no further psychotic episodes (Bellman & Ross, 1977).

3.3.12.A.5 Suicidal thoughts
a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavio
   exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-co
   studies covering 11 different AEDs used for several different indications such as epilepsy, selected psyd
   and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863
   with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There
   suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal b
   occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo
   corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AE
   groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality wa
   after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene
   among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric
   conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients trea
   emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in
   such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).
3.3.12.B  Divalproex Sodium

Anxiety

Confusion

Depression

Disturbance in thinking

Mood swings

Suicidal thoughts

3.3.12.B.1 Anxiety

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Anxiety was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=355 monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12.B.2 Confusion

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Confusion was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12.B.3 Depression

a) Incidence: 4% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) Depression was reported in 5% of patients receiving high-dose divalproex sodium (n=131) compared patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antie the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.12.B.4 Disturbance in thinking

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, abnormal thinking was reported in receiving divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DI sprinkle oral capsules, 2008).

3.3.12.B.5 Mood swings

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, emotional lability was reported in receiving divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DI sprinkle oral capsules, 2008).

3.3.12.B.6 Suicidal thoughts

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavio exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled studies covering 11 different AEDs used for several different indications such as epilepsy, selected psych and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There suicides among patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal b occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AED groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality wa after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients for emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

3.3.12.C  Valproate Sodium
3.3.12.C.1 Suicidal thoughts

a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior exist in patients receiving therapy with antiepileptic drugs (AEDs). The analysis included 199 placebo-controlled studies covering 11 different AEDs used for several different indications such as epilepsy, selected psychosocial and other conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 with AEDs and 16,029 patients who received placebo, and patients were aged 5 years and older. There suicides among patients in the AED treatment groups versus none in the placebo groups. Suicidal behavior occurred in 0.43% of patients in the AED treatment groups compared to 0.22% of patients in the placebo groups. Corresponded to an estimated 2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AED groups having suicidal behavior or ideation than the placebo groups. The increased risk of suicidality was after starting an AED and continued to at least 24 weeks. When compared to placebo, results were gene among the drugs and were seen in all demographic subgroups. Patients treated for epilepsy, psychiatric conditions were all at an increased risk for suicidality compared to placebo. Closely monitor patients treated for emergence or worsening of depression, suicidality and other unusual changes in behavior, which may in such as anxiety, agitation, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

3.3.13 Renal Effects

Fanconi syndrome

Nocturnal enuresis

3.3.13.A Fanconi syndrome

1) The manufacturer reports that rare reports of Fanconi's syndrome have occurred mainly in children (Prod delay release oral capsules, 2008). A case of Fanconi's syndrome occurred in a young girl following 18 an therapy of valproic acid and clobazam, respectively. The patient presented with hypophosphatemia, phosphataemia, mild metabolic acidosis, aminoaciduria, and evidence of rickets. Symptoms slowly improved follow discontinuation of both drugs. It is difficult to determine from this report whether this adverse reaction occurred with one of the drugs, or possibly, a combination of both agents (Smith et al, 1995).

3.3.13.B Nocturnal enuresis

1) Summary

a) Enuresis has occurred with valproic acid therapy (Prod Info STAVZOR(R) delayed release oral capsu et al, 1979; Suchy et al, 1979). Nocturnal enuresis was described as a side effect of valproic acid in 2 Gr treated for seizures. Enuresis developed within 2 to 3 days after initiation of valproic acid treatment and a seizure-free period; enuresis remitted upon reduction of the dose or withdrawal of valproic acid (Panayio

3.3.14 Reproductive Effects

Semen finding

Testicular hypofunction

3.3.14.A Semen finding

1) Antiepileptic agents have been associated with changes in sperm morphology and motility. A lower frequency of morphologically normal sperm was found in carbamazepine treated men with partial epilepsy (n=15), in valproate treated men with generalized epilepsy and in oxcarbazepine treated men with partial epilepsy (n=18) (p less than 0.05) compared to healthy controls (n=41). A significant decrease in the frequency of motile sperm was also found with all treatment groups compared to controls (p less than 0.05). Carbamazepine had high frequencies of abnormally low sperm concentration (p less than 0.001) and poorly motile sperm (p less than 0.05) when compared to controls (Isojarvi et al, 2004).

3.3.14.B Testicular hypofunction

1) When compared to healthy controls (n=41), valproic acid treated men with generalized epilepsy (n=27) had lower volumes (p=0.01). Within the same study however, the testicular volumes of carbamazepine treated men with (n=15) or oxcarbazepine treated men with generalized epilepsy (n=18) did not differ from controls. When further valproic acid treated men with abnormal sperm morphology had smaller testicular volumes than control when volumes of valproic acid treated men with normal sperm were similar to controls (Isojarvi et al, 2004).

3.3.15 Respiratory Effects
Valproic Acid

Divalproex Sodium

3.3.15.A Valproic Acid

Bronchitis

Dyspnea

Pharyngitis

Pleural effusion

Pulmonary hemorrhage

Respiratory tract infection

Rhinitis

3.3.15.A.1 Bronchitis

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial bronchitis was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients receiving valproate (n=70). In most cases, causality could not be determined as patients also received other antiepilepsy drugs with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.2 Dyspnea

a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, dyspnea was reported in receiving high-dose valproate (n=131) compared with 1% of patients receiving low-dose valproate (n=13). Causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.3 Pharyngitis

a) Incidence: 8% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)

b) During a clinical trial of valproate monotherapy for complex partial seizures, pharyngitis was reported receiving high-dose valproate (n=131) compared with 2% of patients receiving low-dose valproate (n=13). Causality could not be determined as patients were being titrated off another antiepilepsy drug during the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.4 Pleural effusion

a) Incidence: rare

b) Recurrent transudative pleural effusion associated with sodium valproate therapy was diagnosed in a patient with a history of smoking, atrial fibrillation (treated with digoxin), and posttraumatic epilepsy (treated with 500 mg/day for one year). The patient had his first occurrence 8 months earlier when he was diagnosed with pleural effusion containing 700 mL of neutrophilic transudate. Current symptoms included a 5-day fever, dry cough, and dyspnea and laboratory examination revealed mild anemia and slightly increased erythrocyte sedimentation rate and C-reactive protein. Chest X-ray and thoracentesis revealed a right-sided pleural effusion with 12% neutrophilic transudative. One day after the fluid was drained, a CT showed pleural fluid in both pleural clefts. The patient was switched from sodium valproate to gabapentin 300 mg/day and the patient had no recurrence of pleural effusion for 2 months follow-up. After 7 months, an epileptic episode caused the patient to resume sodium valproate therapy. One month later the patient experienced a recurrence of right-sided pleural effusion with transudative effusion of 12% neutrophilic transudative. Gabapentin was increased to 400 mg twice daily and no pleural fluid recurrence was observed (Tryfon et al, 2009).

c) Eosinophilic pleural effusion developed in a 34-year-old male treated with valproic acid 1500 mg/day. After the initiation of therapy, the patient presented with fever and nonproductive cough. Upon IHC, medications were discontinued and a full medical workup was conducted. There was no evidence of pneumothorax, pulmonary infiltrates, lymphadenopathy or infection. The symptoms resolved and the patient's disease relapse, gabapentin was increased to 400 mg twice daily and no pleural fluid recurrence was observed (Kravetz & Federman, 2003).
3.3.15.A.5 Pulmonary hemorrhage
   a) Incidence: rare
   b) A case of thrombocytopenia-induced fatal pulmonary hemorrhage was reported in a 30-year-old female on valproate monotherapy, with a history of a viral illness 3 weeks earlier. Initial serum valproate level was 1 (normal 50 to 100 mcg/mL). The authors suggested that viral infections may be associated with thrombocytopenia in patients on valproate therapy (Sleiman et al, 2000).

3.3.15.A.6 Respiratory tract infection
   a) Incidence: 12% to 20% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partial seizures, respiratory tract infection was reported in 12% of patients receiving valproate (n=77) compared with 6% receiving placebo (n=70). In most cases, causality could not be determined as patients also received other drugs concurrently with valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   c) During a clinical trial of valproate monotherapy for complex partial seizures, respiratory tract infection was reported in 20% of patients receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dose valproate (n=134). In many cases, causality could not be determined as patients were being titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.A.7 Rhinitis
   a) Incidence: 5% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
   b) In a clinical trial of adjunctive therapy for complex partial seizures, rhinitis was reported in 5% of patients receiving high-dose valproate (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.15.B Divalproex Sodium

Bronchitis
Dyspnea
Epistaxis
Pharyngitis
Pneumonia
Rhinitis
Sinusitis

3.3.15.B.1 Bronchitis
   a) Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) In a clinical trial of adjunctive therapy for complex partial seizures, bronchitis was reported in 5% of patients receiving high-dose divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.2 Dyspnea
   a) Incidence: 1% to 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) Dyspnea was reported in 1% of patients receiving high-dose divalproex sodium (n=131) compared with 1% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.3 Epistaxis
   a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) Epistaxis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.4 Pharyngitis
   a) Incidence: 2% to 8% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
   b) Pharyngitis was reported in 8% of patients receiving high-dose divalproex sodium (n=131) compared
patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial sei
cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiep
the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.5 Pneumonia
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Pneumonia was reported in more than 1% but less than 5% of patients receiving divalproex sodium (monotherapy treatment of complex partial seizures). In many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.6 Rhinitis
a) Incidence: 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, rhinitis was reported in 5% of patients receiving divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.15.B.7 Sinusitis
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Sinusitis was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.16 Other
Valproic Acid
Divalproex Sodium

3.3.16.A Valproic Acid

Fever
Influenza
Reye’s syndrome

3.3.16.A.1 Fever
a) Incidence: 2% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, fever was reported in 6% of patients receiving valproate (n=77) compared with 4% of patients receiving placebo (n=70). In many cases, causality could not be attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.16.A.2 Influenza
a) Incidence: 12% (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, flu syndrome was reported in 12% of patients receiving valproate (n=77) compared with 9% of patients receiving placebo (n=70). In many cases, causality could not be attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.16.A.3 Reye’s syndrome
a) Summary
1) Valproic acid has been associated with a Reye-like syndrome (RLS). In some reports, there was decreased serum carnitine levels. Clinical signs and symptoms were similar among patients with renal failure outcomes. Most patients presented with nausea, vomiting and apathy. Increase in seizure frequency, concurrent febrile illness also occur. Patients developing any signs of RLS should have valproic acid immediately (Sugimoto et al, 1983; Gerber et al, 1979).
2) A case of Reye-like syndrome (RLS) was reported in a 6-month-old infant who received valproic acid. This infant became unresponsive to therapy for seizure control and developed signs of valproic acid-induced hepatotoxicity. Laboratory values revealed increased plasma ammonia levels, increased liver enzymes and plasma carnitine. Valproic acid was discontinued and the patient recovered. This report supported the vi
acid-associated RLS may be mediated by carnitine depletion (Murphy et al., 1985).

c) A case of a Reye-like syndrome was reported in a 13-year-old female who had received valproic acid. Hyperammonemia and severe hepatic damage, as well as diffuse small droplets in liver biopsy material, demonstrated. It was suggested that valproic acid or its metabolites may decrease the activity on N-acetylglutamate, inducing hyperammonemia (Sugimoto et al., 1979).

d) Features of Reye's syndrome were reported in a 3-year-old girl receiving valproic acid 600 mg daily. A febrile attack, which caused unconsciousness and subsequent recovery, the patient became increasingly drowsy. Blood ammonia levels and bilirubin were elevated, but liver enzymes were within a normal to slightly elevated range. Serum carnitine was decreased. Postmortem liver biopsy revealed microvesicular steatosis of hepatocytes. It was suggested that valproic acid and its metabolites needed to be investigated for their influence on carnitine metabolism (Bohles et al., 1982).

e) Reye-like syndrome (RLS) associated with valproic acid was reported in a 40-month-old mentally retarded girl with a severe refractory multifocal seizure disorder. The patient was receiving phenytoin and ethosuximide in a 50:1 ratio. Increased liver enzymes were noted 2 weeks prior to admission. A low-grade fever and loose, foul-smelling stools were noted shortly before onset of generalized seizure activity. Blood ammonia levels were increased. Liver biopsy revealed widespread disorganization of the parenchyma with swelling of the hepatocytes and compression of the hepatic cords. Diffuse fatty infiltration, including macrovacuoles and microvacuoles was also identified (Keene et al., 1982).

f) A fatal case of Reye's syndrome was reported in an 8-year-old boy receiving valproic acid 375 mg three times daily for a generalized seizure episode. The boy became febrile and tachypneic; liver enzymes and blood ammonia levels were elevated. Postmortem examination revealed panlobular microvesicular fatty changes in the liver and renal tubules. The liver appeared swollen, but did not have other gross or microscopic pathological changes (Young et al., 1980).

g) Reye-like syndrome (RLS) associated with valproic acid was reported in a 12-year-old girl. The patient was receiving multiple medications including valproic acid 250 mg three times daily, phenobarbital 60 mg daily, phenytoin 100 mg twice daily, and acetazolamide 125 mg twice daily. The patient developed a viral respiratory infection and steadily deteriorated with increasing temperature and loss of consciousness. Liver enzymes and blood ammonia levels were elevated. Postmortem examination revealed a bronchopneumonia and an enlarged, yellow, greasy liver with a mottled appearance of venous congestion. Biopsy showed marked fatty changes in the liver with fat formed vacuoles which filled most of the cells; kidney biopsy revealed numerous small lipid vacuoles in most proximal tubular cells (1979).

3.3.16.B Divalproex Sodium

Fever

Infectious disease

Influenza

Malaise

3.3.16.B.1 Fever

a) Incidence: 6% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, fever was reported in 6% of patients receiving divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.16.B.2 Infectious disease

a) Incidence: 12% to 20% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, infection was reported in 12% of patients receiving divalproex sodium (n=77) compared with 8% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

c) Infection was reported in 20% of patients receiving high-dose divalproex sodium (n=131) compared with 14% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex partial seizures; causality could not be attributed to divalproex alone, as patients were titrated off of another antiepileptic medication in the first part of the trial (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.16.B.3 Influenza

a) Incidence: 12% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)

b) In a clinical trial of adjunctive therapy for complex partial seizures, flu syndrome was reported in 12% of patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008).

3.3.16.B.4 Malaise

a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Malaise was reported in more than 1% but less than 5% of patients receiving divalproex sodium (n=3 monotherapy treatment of complex partial seizures. In many cases, causality could not be attributed to d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOTE capsules, 2008).

3.4 Teratogenicity/Effects in Pregnancy/Breastfeeding
A) Teratogenicity/Effects in Pregnancy
1) U.S. Food and Drug Administration’s Pregnancy Category: Category D (Prod Info DEPAKOTE(R) ER extended tablets, 2006) (All Trimesters)
a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be accept risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs car ineffective).

2) Australian Drug Evaluation Committee’s (ADEC) Category: D (Batagol, 1999)
a) Drugs which have caused, are suspected to have caused, or may be expected to cause an increased inci fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Acc should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES
3) Crosses Placenta: Yes
4) Clinical Management
a) As valproic acid can be teratogenic and cause congenital malformations such as neural tube defects, conc valproic acid or its salt form, sodium divalproex in women of childbearing potential only after the risks have be discussed with the patient and the potential benefits outweigh the risk of injury to the fetus. This is particularly treating a spontaneously reversible condition which does not bear a risk of permanent injury or risk of death ( cases where the severity and frequency of the seizure disorder may permit removal of the drug without posin therapy to the patient, clinicians may consider discontinuation of the drug prior to or during pregnancy. Where unavoidable or unanticipated, the pregnant mother should be advised of possible consequences to the fetus. neural tube defects is recommended and clotting parameters should be routinely monitored. Although it is a unfollic acid supplementation in pregnant women receiving valproate can reduce risk of neural tube defects in th should be routinely recommended in patients contemplating pregnancy, both prior to and during pregnancy (f DEPAKOTE(R) ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; DEPAKOTE(R) delayed-release oral tablets, 2006a; Prod Info DEPAKOTE(R) oral capsule, 2006; Prod Info DEPAKOTE(R) oral capsule, oral syrup, 2006a). Infants born to mothers treated with valproate during pregnancy should have blo monitored during the first several hours of life (Ebbesen et al, 2000).

5) Literature Reports
a) Data collected from the Antiepileptic Drug (AED) Pregnancy Registry revealed 16 cases of congenital mal infants born of pregnant women (n=149) exposed valproate monotherapy (doses of approximately 1,000 mg/ first trimester. The prevalence rate of birth defects was 10.7% (95% confidence interval (CI), 6.3% to 16.9%). defects occurred in 2% of the infants (n=3/149) while 4% of the infants (n=6/149) had less severe malformat (n=1,048) exposed to other AED monotherapies, the malformation rate was 2.9% (95% CI, 2% to 4.1%). Con malformations in valproic acid-exposed mothers was 4-fold higher compared to those treated with other AED a group (odds ratio, 4.0; 95% CI, 2.1% to 7.4%) (Prod Info DEPAKOTE(R) ER extended-release oral tablets, DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006a; DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006). Data collected from the Antiepileptic Drug (AED) Pregnancy Registry for over 3,000 pregnant women exp included 123 completed pregnancies exposed to valproate monotherapy (Holmes et al, 2003). The prevalenc was 8.9% in this subset compared to 2.8% (RR 3.5; 95% CI 2.0 to 6.2%) of women exposed to other AED mono therapies, polyacetyls, polyacytly, bilateral inguinal hernia, dysplastic kidneys, and club foot. Similarly, a retrospective cohort study (n=1411) showed an increased risk of major congenital abnormalities in the offspring treated with either carbamazepine (relative risk (RR) 2.6) or valproate (RR 4.1) monotherapy during the first t pregnancy (Samren et al, 1999). Risk associated with valproate was dose-dependent. Valproate alone and in other AEDs were associated with an increased risk of neural tube defects (RR 4.0, p=0.03; RR 5.4, p=0.004, risk of hypospadias was similarly higher in the monotherapy and combination therapy groups (RR 4.8, p=0.05 respectively).

b) Numerous cases have been reported of fetal neural tube defects, primarily spina bifida, and/or cardiac del of Fallot, patent ductus arteriosus, valvarular aortic stenosis, and ventricular septal defect). There is an incre neural tube defects with exposure is estimated to be 1% to 2% by the CDC. While the American College of Obst Gynecologists estimates the general risk for congenital neural tube defects to be 0.14% to 0.2%, data from th Drug (AED) Pregnancy Registry showed that neural tube defects occurred at a rate of 2% (n=3/149) (Prod In ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DEPAKOTE delayed-release oral tablets, 2006a; Prod Info DEPAKONE(R) oral capsule, oral syrup, 2006; Ardinger et al, 1988; Bertollini et al, 1987; Jager-Roman et al, 1986; Bailey et al, 1983; Jeavons Guibaud, 1982; Thomas & Buchanan, 1981; Clay et al, 1981; Dalens et al, 1980).

c) Various other reports of fetal abnormalities resemble those seen in fetal hydantoin syndrome, including cr skeletal or limb defects (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2006; Prod Info DEPAK sparkie capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006a; Prod Info DEPACON 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Diliberti et al, 1984; Jager-Roman et al, 1988;
1988). It is not clearly established, however, whether these anomalies constitute a fetal valproic acid syndrom of other factors such as genetic or environmental factors, combination therapy with other anticonvulsants, an episodes during gestation. A case-control study in which 57 of 22,294 malformed infants and 10 of 21,937 co exposed to valproic acid estimated a risk for limb deficiencies to be about 0.42% (Rodriguez-Pinilla et al, 200 analysis calculated an odds ratio of 6.17 (confidence interval 1.28-29.66, p = 0.023) for limb deficiencies after prenatal exposure to valproic acid. The types of limb deficiencies reported included overlapping digits, talipes clinicodactyly, arachnodactyly, hip dislocation, and others.

e) The relationship of first-trimester plasma antiepileptic drug (AED) concentrations and pregnancy outcome: women was assessed, including 44 women on valproic acid monotherapy (Canger et al, 1999). Valproic acid significantly higher rate of malformations (p less than 0.02) compared to monotherapy with other AEDs such: carbamazepine, phenobarbital, phenytoin, and clonazepam. In addition, the mothers of malformed fetuses us valproic acid during their first trimester than did mother of nonmalformed fetuses.

f) Twenty-two infants with in utero exposure to a median daily dose of 1 g valproate in the first trimester and the first trimester were described by (Ebbesen et al, 2000). In 13 of the 22 infants, blood glucose dropped below the first hypoglycemic episode occurring within one hour of birth in seven infants and within 2 hours in three infants exhibited withdrawal symptoms within 12 to 24 hours including irritability, jitteriness, hypotonia, seizure problems.

g) Other reported fetotoxic effects include a case of an infant with afibrinogenemia who died of hemorrhage, hepatic failure that resulted in death of a newborn infant (Prod Info DEPAKOTE(R) ER extended-release oral Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006).

h) If phenytoin or carbamazepine (or any produgs) is used in pregnant women, there is a substantially increase teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is largely due to the levels of the reactive epoxide metabolites (Buehler et al, 1990c; Van Dyke et al, 1991c; Finnell et al, 1992). Epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, such as acid, pro gabide, and lamotrigine (Bianchetti et al, 1987c; Ramsay et al, 1990c; Spina et al, 1998c). Such cor the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background rates.

B) Breastfeeding

1) American Academy of Pediatrics Rating: Maternal medication usually compatible with breastfeeding. (Anon, 20


3) Thomson Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk with breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug breastfeeding.

4) Clinical Management

a) Valproate is excreted into breast milk, with levels reported to be 1% to 10% of maternal serum levels. The recommends to consider discontinuing nursing when valproic acid is administered to a nursing woman (Prod (R) ER extended-release oral tablets, 2006; Prod Info DEPAKOTE(R) oral sprinkle capsules, 2006; Prod Info delayed-release oral tablets, 2006a; Prod Info DEPAKONE(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006). However, valproic acid is considered to be compatible with breastfeeding by the American Acad (Anon, 2001). Children younger than two years of age who use valproic acid may, however, be at risk of fatal (Zimmerman, 1993). Additionally, a case report described thrombocytopenia and anemia in a 3-month-old in mother received sodium valproate (Stahl et al, 1997). Therefore, nursing mothers should monitor their infants toxicity such as drowsiness, petechiae, vomiting, and/or diarrhea (Iqbal et al, 2001).

5) Literature Reports

a) Early data indicated that valproic acid was excreted in breast milk in significant levels (approximately 10% levels) (Pinder et al, 1977a), but the number of women studied was low (16 in the largest study) (Chaudron & Data from other studies have supported the findings that the drug is not contraindicated during the breastfeec (Rimmer & Richens, 1985c; Von Uhruh et al, 1984; Dickinson et al, 1979).

b) One report describes a 3-month-old infant presenting with thrombocytopenia and anemia caused by sodi administration to the nursing mother. The infant's serum valproate level was 6.6 mcg/mL. Breastfeeding was hematologic abnormalities resolved within 35 days(Stahl et al, 1997).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.1-0.42 (Lawrence & Lawrence, 1999)

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Lab Modifications

Intravenous Admixtures
3.5.1 Drug-Drug Combinations

Acyclovir
Amitriptyline
Aspirin
Betamipron
Carbamazepine
Cholestyramine
Clarithromycin
Clomipramine
Dehydroepiandrosterone
Doripenem
Ertapenem
Erythromycin
Ethosuximide
Evening Primrose
Felbamate
Felbamate
Ginkgo
Imipenem
Isoniazid
Lamotrigine
L-Methylfolate
Lopinavir
Lorazepam
Mefloquine
Meropenem
Nifedipine
Nimodipine
3.5.1.A  Acyclovir
1) Interaction Effect: decreased valproic acid plasma concentrations and potential increased seizure activity
2) Summary: A case report from the University of Bologna in Italy documents a reduction in plasma levels of valproic acid when combined with acyclovir treatment. This reduction resulted in increased seizure activity approximately one per month to 25 in one day. Phenytoin dosage was increased and plasma levels returned to normal ranges after 10 days (Parmeggiani et al, 1995a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for reduction in antiepileptic plasma levels. Consider alternative antiepileptics.
7) Probable Mechanism: increased gastrointestinal transit or change in gastrointestinal fluid pH
8) Literature Reports
   a) According to a case report from the University of Bologna in Italy, a seven-year-old child with a history of increased seizure activity after being treated with acyclovir in addition to his antiepileptic medication, the patient's trough plasma levels of phenytoin and valproic acid were 17 and 32 mcg/mL, respectively, 10 days after the initiation of acyclovir treatment. Four days after initiation of acyclovir treatment, the trough plasma levels of phenytoin and valproic acid were 5.0 and 22 mcg/mL, respectively. Acyclovir treatment was discontinued after six days. Three and six months after acyclovir withdrawal, phenytoin and valproic acid plasma levels were still low, and the patient experienced seizures five days after discontinuation. Phenytoin dosage was increased to reach therapeutic plasma levels. The frequency of seizures was reduced to two or three per week. The authors suggest that further study of this interaction is warranted (Parmeggiani et al, 1995).

3.5.1.B  Amitriptyline
1) Interaction Effect: increased serum concentrations of amitriptyline and its metabolite nortriptyline
2) Summary: A controlled study observed increases in the area under the concentration-time curve (AUC) or concentration (Cmax) for amitriptyline and its active metabolite, nortriptyline, when given concurrently with diazepam (Wong et al, 1996a). Monitor amitriptyline levels in patients taking valproate concomitantly. Consideration should be given to lowering the dose of amitriptyline in the presence of valproate (Prod Info Depakote(R) ER, 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor amitriptyline levels and nortriptyline concentrations in patients taking valproic acid with amitriptyline. A lower dose of amitriptyline may be necessary if given concurrently with valproate.
7) Probable Mechanism: decreased amitriptyline plasma clearance
8) Literature Reports
   a) In an open-label study of 15 healthy volunteers, the pharmacokinetic interactions between divalproex sodium amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving n-valproic acid 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalproex resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the area under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was unaffected. For nortriptyline, the metabolite of amitriptyline, AUC was increased by 28%, and Tmax was unaffected. The authors postulated that divalproex sodium amitriptyline and nortriptyline disposition, possibly through inhibition of hepatic metabolism (Wong et al., 1987).
   b) The addition of valpromide to a stable amitriptyline regimen may result in an increase of antidepressant plasma concentrations. Twenty patients with major depressive illness (DSM - III criteria) were divided into two groups with amitriptyline alone and one treated with both amitriptyline and valpromide. All patients received oral amitriptyline daily once in the evening for 20 days. Only benzodiazepines (diazepam, lorazepam, bromazepam, clonazepam, clobazam) were allowed. Ten patients also received 600 mg valpromide daily amitriptyline to avoid relapses and/or to decrease irritability and agitation. No statistically significant difference in amitriptyline and nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patients amitriptyline 125 mg daily. In the ten patients who received valpromide 600 mg, amitriptyline and nortriptyline increased. The mean amitriptyline level increased from 70.5 +/- 35.9 nanograms/milliliter (ng/mL) to 105. (p less than 0.0003, paired Student’s t test), and the mean nortriptyline level rose from 61.0 +/- 34.3 to 115.0 +/- 34.3 (less than 0.01). No significant relationship was seen between the percentage increase of amitriptyline vs. plasma level of valproic acid, the main valpromide metabolite. There was a significant linear relationship plasma levels of amitriptyline before and after valpromide (r equal to 0.94, p less than 0.001) and between plasma levels before and after valpromide (r equal to 0.87, p less than 0.001). Tricyclic antidepressants plasm increase above the therapeutic window after addition of valpromide. Monitoring of plasma levels of triyclic antidepressants is advisable to control this interaction (Vandel et al., 1988).

3.5.1.C Aspirin
1) Interaction Effect: increased free valproic acid concentrations
2) Summary: Salicylates have been shown to alter both the metabolism and protein binding of valproic acid. Increase in free valproate free fractions (Prod Info Depakote(R) ER, 2003) by 30% to 65% (Abbott et al., 1987).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: An occasional single dose of aspirin would not likely present a problem; however, with multiple doses, monitoring of valproic acid concentrations might be considered. An alternative analgesic such as acetaminophen may be considered if appropriate.
7) Probable Mechanism: altered binding and metabolism
8) Literature Reports
   a) Six epileptic children who were taking valproic acid received antipyretic doses of aspirin. The steady-state of valproate rose from 12% to 43% in the presence of salicylate in five of these patients. Half-life of valproate total and free valproate concentrations, increased. Renal excretion of unchanged valproate decreased with Salicylates appear to displace valproate from serum protein binding sites and alter valproate metabolism (Farrell et al., 1982).

3.5.1.D Betamipron
1) Interaction Effect: decreased valproic acid efficacy
2) Summary: Three case reports describe a decrease in valproic acid serum concentrations when panipenem/betamipron was started, resulting in the recurrence of seizures in two patients. Although the exact mechanism is not known, panipenem/betamipron should be avoided in patients treated with valproic acid (Yamagata et al., 1987).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should not be treated with panipenem/betamipron. An alternative antibiotic which does not affect valproic acid serum levels should be considered.
7) Probable Mechanism: unknown
8) Literature Reports
   a) A 4-year-old female with spastic quadriplegia, epilepsy, and mental retardation was receiving valproic acid 500 mg/kg/day and phenobarbital 5 mg/kg/day with serum levels of 55.1 mg/dL and 28.4 mg/dL, respectively. She was admitted to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while she was receiving a therapeutic dose of valproate. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three divided doses, and the serum valproic acid level decreased to 22.9 mg/mL by day 6. Although no seizures developed as a result of this decrease, panipenem/betamipron was discontinued, and the valproic acid serum concentration increased to 60 mg/dL (Yamagata et al., 1998).
b) A 3-year-old girl with quadriplegia, epilepsy, and mental retardation was receiving valproic acid 35 mg/carbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission for pneumonia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamipron and amikacin 5 mg/kg/day. Three days later, generalized tonic-clonic seizures began to occur once or twice daily. Valproic acid level had decreased to 30.9 mg/mL and further dropped to 26.8 mg/mL two days later. Desiccation of the valproic acid dose to 42 mg/kg/day, the serum concentration continued to decrease to 15.3 mg/mL over treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of discontinuing the treatment with panipenem/betamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipron therapy. Carbamazepine level was not significantly altered (Yamagata et al, 1998).

c) Panipenem/betamipron 30 mg/kg/day resulted in intense, generalized seizures and frequent myoclonus in a 61-year-old male who had previously been stabilized on valproic acid 32 mg/kg/day, clonazepam 0.9 mg/kg, phenytoin 5 mg/kg/day. Prior to panipenem/betamipron therapy, his valproic acid serum level ranged from 108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 μg/mL. The dose of the valproic acid was increased to 34 mg/kg/day, serum levels were undetectable by day 25 of panipenem/betamipron therapy. After the antibiotic was discontinued, the serum valproic acid concentration was 55 mg/mL and the frequency of the seizures was decreased. Incidentally, in this patient, the phenytoin concentration levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

3.5.1.5 Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizure decreased valproic acid effectiveness 2) Summary: The literature contains conflicting data regarding the effects of combined carbamazepine and valproate. Carbamazepine may decrease valproic acid levels by 15% to 25% while increasing clearance by up to 30% (1979a; Rimmer & Richens, 1985b; Mahaly et al, 1979a; Jann et al, 1988a). Furthermore, the conversion of valproic acid to 4-ene-VPA (thought to be the most toxic metabolite with potential for hepatotoxicity and teratogenicity) is significantly decreased with coadministration of carbamazepine (Kondo et al, 1990a). Valproic acid may increase, decrease, or cause carbamazepine concentrations (Mattson et al, 1982a; Levy et al, 1984a; Pisani et al, 1990a; Anderson et al, 1993).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drowsiness when valproic acid is added. Serum carbamazepine concentrations should also be measured, though clinical correlation of the active metabolite, carbamazepine-epoxide, which is not routinely measured in clinical practice, does contribute to the efficacy and toxicity of the drug. If carbamazepine is added to valproic acid therapy, plasma concentrations should be monitored, and valproic acid dosage may be required.

7) Probable Mechanism: increased valproic acid clearance; variable effects on carbamazepine metabolism

8) Literature Reports

a) Significant increases (59%) in valproic acid serum concentrations have been reported following the withdrawal of carbamazepine in six epileptic patients. A new plateau for the valproic acid serum level was observed at weeks after withdrawal of the carbamazepine (Jann et al, 1988).

b) Several reports have indicated conflicting effects of valproic acid on carbamazepine serum levels (Rimmer & Richens, 1985a; Flachs et al, 1979; Adams et al, 1978). In an in vitro study of protein binding, valproic acid competes with carbamazepine plasma protein binding sites, resulting in significant decreases in free carbamazepine (McKee et al, 1989). Concurrent therapy of carbamazepine and valproate in seven patients found to decrease levels by 3% to 59% and carbamazepine protein binding decreased. The plasma concentration ratio of carbamazepine-10,11-epoxide increased in all patients by 11% to 500%. (Levy et al, 1984; Pisani et al, 1990) probably due to carbamazepine increased in all patients by 11% to 500%. (Levy et al, 1984; Pisani et al, 1990) probably due to carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990) probably due to carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990) probably due to carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990)

c) Select patients with suspected genetic deficiencies may tolerate poorly the effects of valproic acid on certain amino and fatty acids, which may impact anticonvulsant therapy based on carbamazepine-valproic acid combinations (Kondo et al, 1990).

d) The pharmacokinetics of valproic acid and its metabolites when coadministered with carbamazepine in epileptic patients. The ratio of valproic acid concentration to dose was significantly lower in those patient with carbamazepine compared with those receiving only valproic acid. Additionally, the ratio of 4-en-10,11-epoxide hydroxylase by valproic acid (Robbins et al, 1990). In addition, carbamazepine may cause a reduced valproic acid half-life with increased clearance secondary to enzyme induction and increased hepatic clearance (Rimmer & Richens, 1985a; Mahaly et al, 1979). Infrequent reports have indicated symptoms of nausea, or confusion when valproic acid was added to carbamazepine therapy (Lhermitte et al, 1978; Henry et al, 1979).

e) If phenytoin or carbamazepine (or any prodrug) is used in pregnant women, there is a substantially in teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990a; Van Dyke et al, 1991a). For the epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase (Buehler et al, 1987a; Ramsay et al, 1990a; Spina et al, 1996).
rates.

### 3.5.1.F Cholestyramine

1. **Interaction Effect:** decreased serum valproic acid concentrations
2. **Summary:** A controlled study observed that the concurrent administration of valproic acid and cholestyramine significantly reduced valproic acid area under the concentration-time curve (AUC) and maximum concentration. However, administration of valproic acid three hours before taking cholestyramine resulted in no significant change (Malloy et al., 1996a).
3. **Severity:** moderate
4. **Onset:** rapid
5. **Substantiation:** probable
6. **Clinical Management:** Clinicians should be aware that valproic acid taken concurrently with cholestyramine serum valproic acid concentrations. If these drugs are to be given together, administer cholestyramine at least three hours after the valproic acid, and monitor patients for valproic acid therapeutic efficacy.
7. **Probable Mechanism:** decreased absorption of valproic acid
8. **Literature Reports**
   a) In an open-label, three-way crossover study, the effects of cholestyramine on the plasma concentration were investigated in six healthy volunteers. Subjects participated in three treatment phases, with a minimum washout period between phases. During phase 1, the subjects received a single dose of valproic acid 25 mg, followed by valproic acid 250 mg dose of cholestyramine. Phase 3 was identical to phase 2 except that the valproic acid 250 mg was taken before the morning dose of cholestyramine. When valproic acid was given concurrently with cholestyramine, area under the concentration-time curve (AUC) decreased by 21% and the valproic acid maximum concentration (Cmax) decreased by 15% compared to valproic acid alone. When valproic acid was given three hours before cholestyramine, no significant changes in AUC or Cmax were observed. Based on this data, decreases in concentrations can be partially avoided by taking the cholestyramine three hours after valproic acid (Mallory et al., 1996b).

### 3.5.1.G Clarithromycin

1. **Interaction Effect:** increased serum levels of valproate
2. **Summary:** There have been reports of interactions of clarithromycin with drugs not thought to be metabolized by P450 3A4, such as valproate (Prod Info Biaxin(R), 2002).
3. **Severity:** moderate
4. **Onset:** delayed
5. **Substantiation:** theoretical
6. **Clinical Management:** Monitor plasma concentrations of valproate closely in patients receiving concomitant therapy.
7. **Probable Mechanism:** unknown

### 3.5.1.H Clomipramine

1. **Interaction Effect:** an increased risk of clomipramine toxicity (agitation, confusion, hallucinations, urinary retention, tachycardia, seizures, coma)
2. **Summary:** Comedication with clomipramine and valproic acid may increase serum levels of clomipramine and its metabolites. Clomipramine toxicity developed in a patient twelve days after valproic acid therapy, where metabolism of clomipramine is mediated through N-demethylation, hydroxylation, and glucuronidation, and vitamin B6 appears to inhibit the enzymes responsible for this mode of metabolism (Fehr et al., 2000a).
3. **Severity:** moderate
4. **Onset:** delayed
5. **Substantiation:** probable
6. **Clinical Management:** Monitor serum clomipramine levels to avoid overdose as a result of elevated conc levels when comedicating with valproic acid. The clomipramine dose may need to be reduced when valproic acid is added to therapy.
7. **Probable Mechanism:** inhibition of cytochrome P450 2C-mediated metabolism of clomipramine
8. **Literature Reports**
   a) A case report describes a 46-year-old female with personality disorder whose serum clomipramine concentration was elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with clomipramine and desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentrations of clomipramine and desmethylclomipramine both decreased by 15% compared to valproic acid alone. When valproic acid was given three hours before cholestyramine, no significant changes in AUC or Cmax were observed. Based on this data, decreases in concentrations can be partially avoided by taking the cholestyramine three hours after valproic acid (Mallory et al., 1996b).

### 3.5.1.J Dehydroepiandrosterone

A case report describes a 46-year-old female with personality disorder whose serum clomipramine concentration was elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with clomipramine and desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentrations of clomipramine and desmethylclomipramine both decreased by 15% compared to valproic acid alone. When valproic acid was given three hours before cholestyramine, no significant changes in AUC or Cmax were observed. Based on this data, decreases in concentrations can be partially avoided by taking the cholestyramine three hours after valproic acid (Mallory et al., 1996b).
1) Interaction Effect: reduced effectiveness of valproic acid
2) Summary: Dehydroepiandrosterone (DHEA) in a single case report was noted to cause mania in a patient personal or family history of bipolar disorder (Markowitz et al, 1999a). Elevated DHEA levels have been found in mental disorders; DHEA suppression has lead to improvement in psychotic symptoms (Howard, 1992). Patie medication for bipolar disorder or patients with a personal and/or family history of bipolar disorder should not further data is available to characterize this drug-herb interaction.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If valproic acid is being used for manic symptoms, concomitant use of dehydroepiandosterone (DHEA) may cause a return of symptoms. Clinically significant reductions in serum valproic acid levels have been reported in patients receiving dehydroepiandrosterone (DHEA) (mg) daily and increased the dose to 200 to 300 mg daily for 6 months. Within 3 months, family members of odd behavior with prominent symptoms of agitation, delusional thinking, decreased sleep and appetite sprees. The patient was not taking any prescribed medication but did ingest alcohol in amounts up to 1 c Another 3 months elapsed, leading to involuntary patient admission secondary to rapid, loud, pressure grandiose thoughts. At admission, the patient reported that he had decreased alcohol intake to 2 beers c concerns about his behavior changes. There was no family history of bipolar disorder. Oral prednisone was initiated. Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient's behavioral patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdrawal symptoms, and the patient was discharged with follow-up care from his primary care physician with a diagnosis of substance disorder (Markowitz et al, 1999).

3.5.1.J Doripenem
1) Interaction Effect: reduced valproic acid serum concentrations
2) Summary: Frequently monitor valproic acid concentrations after starting doripenem as coadministration of valproic acid concentrations and may result in loss of seizure control. If valproic acid concentrations cannot be maintained within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy should be considered (DORIBAX(R) IV injection, 2009).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Frequently monitor valproic acid concentrations after starting doripenem as coadministration of valproic acid concentrations and possibly a loss of seizure control. If valproic acid concentrations cannot be maintained within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy should be considered (DORIBAX(R) IV injection, 2009).
7) Probable Mechanism: unknown
8) Literature Reports
   a) Valproic acid AUC was reduced by 63% in healthy volunteers following coadministration of doripenem (DORIBAX(R) IV injection, 2009).

3.5.1.K Ertapenem
1) Interaction Effect: decreased valproic acid plasma concentrations and loss of anticonvulsant effect
2) Summary: Clinically significant reductions in serum valproic acid levels have been reported in patients receiving carbapenem antibiotics concomitantly. Two case reports describe significant decreases in serum valproic acid concentrations and a return of seizures in one (Lunde et al, 2007; CabanesMariscal et al, 2009). The exact mechanism is not understood, in vitro and animal data suggest that carbapenems may inhibit valproic acid hydrolisis. If ertapenem is initiated in patients receiving valproic acid, frequent monitoring of valproic acid concentrations is recommended. Use alternative antibacterial or anticonvulsant therapy if valproic acid blood levels drop below the therapeutic range or a seizure occurs (Prod Info INVANZ(R) IV, IM injection, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: If concomitant administration of valproic acid and ertapenem is required, monitor valproic acid concentration frequently. Consider alternative antibiotic or anticonvulsant therapy if serum valproic acid levels are below the therapeutic range or if a seizure occurs (Prod Info INVANZ(R) IV, IM injection, 2008).
7) Probable Mechanism: unknown
8) Literature Reports
   a) A 41-year-old man maintained on divalproex sodium for seizure prophylaxis experienced recurrent tonic-clonic seizures on day 7 of concomitant ertapenem (1000 mg) therapy. His medical history was significant for hypertension controlled with metoprolol, seizure disorder secondary to traumatic brain injury, and chronic osteomyelitis. Approximately 3 months prior to starting ertapenem, the patient's serum valproic acid concentration was 130 mcg/mL while taking divalproex sodium 2000 mg/day. He was admitted to the emergency department with a witnessed tonic-clonic seizure lasting longer than one minute...
valproic acid concentration was 70 mcg/mL. The dose of divalproex sodium was increased to 2750 mg/d and was discharged. He returned 4 days later with recurrent seizures and a serum valproic acid concentration 1000 mcg/mL was administered along with one oral dose of divalproex sodium 100 was discontinued, and intravenous ampicillin-sulbactam 3 grams every 6 hours was begun. The following serum valproic acid concentration increased to 55 mcg/mL. Oral divalproex sodium was again increased and 2 days later his level was 88.1 mcg/mL. Five days after erthropenem was discontinued his serum valp concentration reached 146 mcg/mL, necessitating a decrease in divalproex sodium dose. He subsequen seizure-free (Lunde et al, 2007; Personal Communication, 04/28/2008).
b) An 80-year-old woman, chronically treated with valproic acid solution 1100 mg/day for complex partial to severe cerebrovascular disease, experienced significantly reduced serum valproic acid concentration 4 days after the initiation of erthropenem 1000 mg every 24 hours. Approximately, 1.5 months after exposure, her total serum valproic acid concentration was 72 mcg/mL. Admitted to the hospital for aspiration the patient was treated with erthropenem. Four days later serum valproic acid concentration was reported 1 mcg/mL, and her valproic acid dose was increased to 1600 mg/day. Two days later serum valproic acid concentration was 1 mcg/mL and the drug dose increased to 2000 mg/day. A level of 1.04 mcg/mL was measured 4 days after increase. Erthropenem was discontinued. With intravenous administration of valproic acid (800 mg loading 400 mg every 6 hours), the patient's serum concentration gradually returned to therapeutic range over the 4 weeks. She was subsequently maintained on oral valproic acid 1400 mg/day (CabanesMariscal et al, 2006).

3.5.1.1 Evening Primrose

<table>
<thead>
<tr>
<th>Interaction Effect</th>
<th>Summary</th>
<th>Probable Mechanism</th>
<th>Substantiation</th>
<th>Onset</th>
<th>Severity</th>
<th>Literature Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic acid toxicity (CNS depression, seizures)</td>
<td>One case report described the concurrent use of evening primrose and valproic acid resulting in increased serum valproic acid concentration and symptoms of valproic acid toxicity. Discontinuation of evening primrose led to lowered serum valproic acid concentration and resolution of the symptoms (Redington et al, 1992a).</td>
<td>Monitor patients receiving valproic acid and evening primrose concomitantly for alterations in serum concentrations of both drugs.</td>
<td>Theoretical</td>
<td>Delayed</td>
<td>Moderate</td>
<td>No literature reports found for evening primrose and valproic acid.</td>
</tr>
</tbody>
</table>

3.5.1.2 Ethosuximide

<table>
<thead>
<tr>
<th>Interaction Effect</th>
<th>Summary</th>
<th>Probable Mechanism</th>
<th>Substantiation</th>
<th>Onset</th>
<th>Severity</th>
<th>Literature Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>An increased risk of ethosuximide toxicity</td>
<td>Concomitant valproic acid and ethosuximide therapy does not appear to influence the pharmacokinetics of ethosuximide. This was demonstrated in an evaluation in which valproic acid was added to a ethosuximide regimen. There was no apparent change in total or nonrenal clearance of ethosuximide (Bauer et al, 1998).</td>
<td>Administer ethosuximide in patients receiving valproic acid and ethosuximide therapy was reported to result in significant increases in ethosuximide concentration (from 44 to 54 hours) and a significant decrease in total body clearance (11.2 to 9.5 mL/minute) (Pisani et al, 1992).</td>
<td>Theoretical</td>
<td>Delayed</td>
<td>Moderate</td>
<td>No literature reports found for valproic acid and ethosuximide.</td>
</tr>
</tbody>
</table>

3.5.1.3 Evening Primrose

<table>
<thead>
<tr>
<th>Interaction Effect</th>
<th>Summary</th>
<th>Probable Mechanism</th>
<th>Substantiation</th>
<th>Onset</th>
<th>Severity</th>
<th>Literature Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced anticonvulsant effectiveness</td>
<td>Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering the threshold. Evening primrose oil is contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).</td>
<td>Avoid concomitant use of evening primrose oil with anticonvulsants.</td>
<td>Theoretical</td>
<td>Delayed</td>
<td>Moderate</td>
<td>No literature reports found for evening primrose and valproic acid.</td>
</tr>
</tbody>
</table>
7) Probable Mechanism: evening primrose oil may reduce the seizure threshold

3.5.1.O Felbamate

1) Interaction Effect: increased valproic acid concentrations
2) Summary: Coadministration of felbamate (1200 mg to 2400 mg daily) and valproic acid resulted in an increase in valproic acid AUC (28% and 54%), peak concentrations (34% and 55%), and average steady-state concentrations (54%) (Wagner et al, 1992; Prod Info Felbatol(R), 2000). A decrease in valproic acid dosage may be necessary if therapy is initiated (Prod Info Depakote(R) ER, 2003e).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor valproic acid levels when initiating or discontinuing felbamate. Tremor, irritability, and restlessness are more common when valproic acid serum levels exceed 100 mcg/mL. A decrease in the acid may be necessary.
7) Probable Mechanism: decreased valproic acid clearance

3.5.1.P Fosphenytoin

1) Interaction Effect: altered valproate levels or altered phenytoin levels
2) Summary: Fosphenytoin is a prodrug of phenytoin and the same interactions that occur with phenytoin also occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Valproic acid may initially cause a decrease in total phenytoin concentration, resulting in displacement of phenytoin from protein binding sites (Levy & Koch, 1982; Bruni et al, 1980; Monks et al, 1978). A decrease in the bound fraction of phenytoin, the phenytoin which is displaced by valproic acid re-equilibrates with the tissue compartment such that the unbound plasma concentration remains unchanged (Winter et al, 1978). The degree of displacement appears to be related to the rate of valproic acid dose related (Monks & Richens, 1980). Valproic acid may also inhibit phenytoin metabolism (Levy & Koch, 1982; Bruni et al, 1980; Patel et al, 1980; Winter, 1988; de Vries et al, 1993).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the complex situation involving displacement of protein-bound phenytoin and altered clearance and protein binding of both drugs, plasma phenytoin levels should be measured if possible to provide accurate assessment of phenytoin activity early in therapy. At steady-state free phenytoin concentrations and concentrations should be normalized.
7) Probable Mechanism: altered clearance and protein binding of both drugs
8) Literature Reports
   a) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially increased teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is large related to the levels of the reactive epoxide metabolites (Buehler et al, 1990; Van Dyke et al, 1991; Finne et al, 1991). Finne demonstrated that the epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with each drug that induces cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase activity of 6-arylpropionic acid, progabide, and lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996). Such coadministration may increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background

3.5.1.Q Ginkgo

1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: In a case report, 2 patients with epilepsy previously well controlled by valproate sodium developed seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn. Granger et al (1987) developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et al, 1993). Four to six milligrams of the neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known sensitivity of these drugs). Such coadministration may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known sensitivity of these drugs).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of ginkgo extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxine is present. A decrease in the bound fraction of phenytoin, the phenytoin which is displaced by valproic acid re-equilibrates with the tissue compartment such that the unbound plasma concentration remains unchanged (Winter et al, 1978). The degree of displacement appears to be related to the rate of valproic acid dose related (Monks & Richens, 1980). Valproic acid may also inhibit phenytoin metabolism (Levy & Koch, 1982; Bruni et al, 1980; Patel et al, 1980; Winter, 1988; de Vries et al, 1993).
7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known sensitivity of these drugs).
8) Literature Reports
   a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridoxine serum concentration was 0.9 micrograms/milliliter (mcg/mL) at 8.5 hours after ingesting ginkgo seeds, de mcg/mL at 15.5 hours. The authors concluded that the 4'-O-methylpyridoxine content was responsible for convulsions and loss of consciousness observed. They further observed that infants are particularly vulnerable when the neurotoxin 4'-O-methylpyridoxine have been isolated from 2 kilograms of
leaves which is the source of commercially-available products. Highest amounts were found in seeds (8 mcg/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. The seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight when unprocessed seed coats contain from 5.44-7.15 mcg/gram dry weight. The neurotoxin in ginkgo leaf was medications and it was even detectable in homeopathic preparations. Specifically, 8.13 mcg/mL of 4'-O+ was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mcg/mL in Gingko respectively. Among the homeopathic products, Ginkgo biloba Urtinkur HanoSan(R) and Ginkgo biloba contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Co the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested, 1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo biloba (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after di (Granger, 2001).

3.5.1.R Lamotrigine

1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drowsiness increased risk of life-threatening rashes
2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half-life is approximately 24 hours; in patients receiving concomitant valproic acid therapy, the half-life increases to a maximum of 100-200 mg daily. Discontinue use c first sign of a rash unless the rash is clearly not drug related (Prod Info lamotrigine oral tablets, 2006).

3.5.1.S Isoniazid

1) Interaction Effect: valproic acid or isoniazid toxicity
2) Summary: In a case report, the concurrent use of valproic acid and isoniazid resulted in increased SGPT and a higher incidence of tonic-clonic seizures. Isoniazid may inhibit the metabolism of valproic acid, or valproic acid may increase the risk of isoniazid toxicity (Dockweiler, 1987).

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consider monitoring liver function tests periodically with therapy, as well as continuous therapeutic efficacy of valproic acid. Monitor serum valproic acid trough concentrations as indicated. If toxicity alternative anticonvulsant may be appropriate.
7) Probable Mechanism: altered metabolism

3.5.1.T Lamotrigine

1) Interaction Effect: increased elimination half-life of lamotrigine leading to lamotrigine toxicity (fatigue, drowsiness increased risk of life-threatening rashes
2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half-life is approximately 24 hours; in patients receiving concomitant valproic acid therapy, the half-life increases to a maximum of 60 hours. The mechanism of this interaction is thought to be competition of the two drugs for hepatic metabolidyne. Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyridoxine mg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingko respectively. Among the homeopathic products, Ginkgo biloba Urtinkur HanoSan(R) and Ginkgo biloba contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the amount contained in medicinal extracts of ginkgo leaves may be too low to be of clinical significance. Co the variance in 4'-O-methylpyridoxine content depending on the season during which the ginkgo was harvested, 1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo biloba (an 84-year-old woman and a 78-year-old man) had been free of seizures for at least 18 months therapy with Gb 120 milligrams daily to treat cognitive decline. Both patients developed seizures within 2 beginning Gb therapy, and both remained seizure-free (without changing anticonvulsant therapy) after di (Granger, 2001).
7) Probable Mechanism: decreased lamotrigine metabolism

8) Literature Reports

a) A 23-year-old woman presented to the emergency room with generalized rash, redness and swelling lips, fever, weakness, blisters, and a sore throat 3 weeks after lamotrigine was added to her anti-epileptic initial regimen consisted of carbamazepine 400 mg twice a day. Valproic acid 500 mg twice daily was added lamotrigine 50 mg twice daily was added 3 weeks prior to current presentation. The patient had an elevated sedimentation rate and C-reactive protein. However, serum carbamazepine and valproic acid levels were range. Serum lamotrigine concentrations were not measured. She was diagnosed with lamotrigine-induced Johnson syndrome (SJS), with a Naranjo Adverse Drug Reactions Probability Scale score of 6 (probably Lamotrigine was discontinued and treatment was initiated for the SJS. She was discharged on day 18 or carbamazepine 400 mg twice daily and oral valproic acid 1500 mg/day. At the one month follow-up, she significant improvement in oromucosal and skin lesions, with areas of hyperpigmentation. The patient's developing SJS may have potentially been a result of either the combination of lamotrigine and valproic acid; decreased metabolism of lamotrigine, or due to initiation of lamotrigine at a dose higher than the manufacturer recommended starting dose of 25 mg per day (Kocak et al, 2007).

b) Fever, rash, multiorgan dysfunction, and disseminated intravascular coagulation were reported in two with valproic acid and lamotrigine. Both children were receiving valproic acid for treatment of seizures. Lm was added because of poor control. Symptoms developed within nine days of starting lamotrigine, but did not lamotrigine was discontinued (Chattergoon et al, 1997).

c) A 54-year-old male presented to the hospital with a five-day history of facial swelling, intermittent fever and pruritic rash on the chest, upper extremities, neck, and back. He had been taking allopurinol 100 mg 50 mg daily for 4 years prior to admission. Because of a glioblastoma multiforme brain tumor, valproic lamotrigine therapy was begun and the doses were titrated to valproic acid 500 mg three times daily and twice daily approximately four weeks prior to his hospital admission. By hospital day 7, the patient was extensive sloughing of his skin along his back, face, and trunk, accounting for more than 60% of his total area. He continued to deteriorate and was withdrawn from life support on hospital day 12. His death was epidermal necrolysis probably due to lamotrigine therapy and possibly enhanced by valproic acid (Page d) A study including 28 patients with intractable epilepsy was conducted to determine whether the dose serum concentrations (Css) of valproic acid were inversely related to lamotrigine clearance. Valproic acid 500 mg/day for 3 days and increased to 750 mg/day on day 4, depending on tolerance and response. Th dose was increased 125 to 250 mg every 3 weeks, until patients became seizure-free or developed adverse initiation of valproic acid, the dose of lamotrigine was decreased by 50%, so as to maintain lamotrigine C levels to those reached during monotherapy. A 50% reduction in lamotrigine clearance was reported in the dose of lamotrigine needs to be decreased by 50% at the start of valproic acid therapy to maintain comp Css. However, additional increases in valproic acid dose would not require further reductions of lamotrigine stable lamotrigine C. Seizure-free periods were significantly longer during treatment with both lamotrigic acid than during lamotrigine monotherapy, an indication that therapeutic synergism exists between lamotrigic acid (Kanner & Frey, 2000).

e) A study involving eight patients with epilepsy found a significant increase in lamotrigine area under th time curve (AUC) and longer half-life with concomitant valproic acid administration. Dosages of valproic 2 mg/day resulted in mean increases in lamotrigine AUC of more than 2.5-fold. Even low doses of valproic acid resulted in significant increases in lamotrigine AUC (mean 84%). Significant increases in plasma lamotrigic by inhibiting lamotrigine metabolism and increased half-life has been achieved with the use of low to moderate valproic acid (Morris et al, 2000).

f) Lamotrigine decreased valproic acid steady-state concentrations by 25% in 18 healthy volunteers ove and then stabilized. Adding lamotrigine to the existing therapy did not cause a change in plasma valproic acid in adult or pediatric patients in controlled clinical trials. The addition of valproic acid increased lamotrigine concentrations in normal volunteers by more than 2-fold (Prod Info Lamictal(R), 2004). Valproic acid (Pa)

g) In a black box warning from the manufacturer, the incidence of severe rash may be higher in patients administered valproic acid and lamotrigine (Prod Info Lamictal(R), 2003).

3.5.1.U L-Methylfolate

1) Interaction Effect: decreased valproic acid serum levels

2) Summary: Concomitant administration of first-generation anticonvulsants, including valproic acid, with high lipid ratio may lead to decreased serum levels of the anticonvulsant, thereby decreasing valproic acid efficacy and increasing seizures. Although there have been no such reports with the use of L-methylfolate and valproic acid, caution is advised if these agents are used concomitantly (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervax(R) oral tablets, 2006) patients for loss of valproic acid efficacy.

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Caution is advised if L-methylfolate is prescribed to patients receiving valproic acid folate may theoretically result in decreased serum valproic acid levels, thereby reducing valproic acid efficacy the frequency of seizures (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervax(R) oral tablets, 2008). If used concomitantly, monitor patients for loss of valproic acid efficacy.

7) Probable Mechanism: unknown

3.5.1.V Lopinavir

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
3.5.1.W Lorazepam

1) Interaction Effect: increased lorazepam concentrations
2) Summary: In a small study of healthy subjects (n=8), valproic acid was found to decrease lorazepam clear compared to controls (Anderson et al, 1994). When lorazepam and valproic acid are coadministered, the dosage should be reduced by 50% (Prod Info Ativan(R), 1997a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: When lorazepam and valproic acid are coadministered, the dose of lorazepam should be reduced by 50%. The patient should then still be monitored for evidence of lorazepam toxicity, including excessive sedation. This can be managed by reducing the dose of lorazepam by 50% during valproic acid coadministration (Prod Info Ativan(R), 1997).

8) Literature Reports
   a) A case report describes a 30-year-old man with bipolar disorder and HIV who became increasingly manic after the addition of lamivudine 150 mg zidovudine 300 mg twice a day and lopinavir 133 mg ritonavir 33 mg (3 times a day) to his drug regimen. The patient had been maintained on valproic acid (VPA) 250 mg 3 times a day. The dose was increased to 375 mg twice a day and lorazepam 1 mg/day was administered for depression. The patient was switched to sertraline 50 mg/day. Twenty-one days after the initiation of antiretroviral therapy, the patient became more manic and was again admitted. He had continued all medications except sertraline and received the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1 g/day effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre-antiretroviral regimen, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 mg/dL. The patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesized that there may be a decrease in VPA concentrations due to ritonavir induction of VPA metabolism (via glucuronidation).

3.5.1.X Mefloquine

1) Interaction Effect: loss of seizure control
2) Summary: The concomitant use of mefloquine in patients taking an anticonvulsant may cause reduced serum levels of the anticonvulsant (Prod Info Lariam(R), 2003). One case report describes a man with epilepsy who was maintained on carbamazepine 1200 mg daily and sodium valproate 1 g to treat his seizures. His medication included carbamazepine and sodium valproate. Pharmacokinetic studies determined that the half-life of carbamazepine was significantly reduced by the administration of mefloquine, while carbamazepine was not affected. The half-life of mefloquine was also decreased by 55%. Plasma concentrations of mefloquine were appreciably lower for at least 12 hours following concurrent administration. The manufacturer of mefloquine recommended reducing the dose of mefloquine by 50% during valproic acid coadministration (Prod Info Lariam(R), 1997).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If mefloquine and valproic acid must be administered concurrently, monitor the levels of the anticonvulsant acid dose may be required. Also monitor the patient for seizure. The patient may need to effectively manage the manic episode. The patient adhered to this new drug regimen, including the pre-antiretroviral regimen, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 mg/dL. The patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesized that there may be a decrease in VPA concentrations due to ritonavir induction of VPA metabolism (via glucuronidation).

8) Literature Reports
   a) A 38-year-old male epileptic controlled by carbamazepine 1200 mg daily and sodium valproate 1 g. Mefloquine 250 mg weekly was added to control seizures. The patient began to experience multiple partial seizures. The pharmacokinetics of antiepileptic drugs were studied to determine the cause of this patient's seizures. A reduction in the half-life of valproate (from 8 to 20 hours to 5.6 hours) was observed, although that of carbamazepine was unchanged. Mefloquine accelerated the metabolism of sodium valproate, since both share the same hepatic metabolic pathways. The patient had a significant increase in the frequency of his seizures after he was prescribed mefloquine for malaria prophylaxis. His seizures were effectively managed with the addition of lamotrigine 150 mg twice daily. The patient was maintained on valproic acid (VPA) 250 mg twice daily for three days resulted in a decrease of 40% in the total clearance of lorazepam. The glucuronide formation rate was also decreased by 55%. Plasma concentrations of lorazepam were approximately 50% of the initial values. The patient became increasingly manic and was again admitted. He had continued all medications except sertraline and received the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1 g/day effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre-antiretroviral regimen, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 mg/dL. The patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesized that there may be a decrease in VPA concentrations due to ritonavir induction of VPA metabolism (via glucuronidation).

3.5.1.Y Meropenem

1) Interaction Effect: decreased valproic acid serum concentrations
2) Summary: Coadministration of lopinavir/ritonavir with valproic acid may decrease the plasma concentration of valproic acid. Monitoring of valproic acid plasma concentrations is recommended (Prod Info NORVIR(R), 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic concentrations of valproic acid when coadministering with lopinavir/ritonavir. The dose of valproic acid may need to be reduced by 50% (Prod Info Lariam(R), 2003). One case report describes a male patient who was maintained on paroxetine 10 mg day and lopinavir 133 mg/ritonavir 33 mg (3 times a day) to his drug regimen. The patient had been maintained on valproic acid (VPA) 250 mg 3 times a day. The dose was increased to 375 mg twice a day and lorazepam 1 mg/day was simultaneously given for the depressive episode. The patient became hypomotivated and the paroxetine was switched to sertraline 50 mg/day. Twenty-one days after the initiation of antiretroviral therapy, the patient became more manic and was again admitted. He had continued all medications except sertraline and received the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1 g/day effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre-antiretroviral regimen, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 mg/dL. The patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesized that there may be a decrease in VPA concentrations due to ritonavir induction of VPA metabolism (via glucuronidation).
2) Summary: As described in a case report, the coadministration of meropenem with valproic acid produced in valproic acid (VPA) plasma concentrations, causing recurrent seizure activity (Coves-Orts et al, 2005). Sin VPA serum concentrations were reported in several other patients receiving concomitant treatment with VPA. No patient developed seizures (Nacarkucuk et al, 2004; De Turk et al, 1998). A single retrospective study of confirms that the concurrent use of valproic acid with meropenem results in subtherapeutic VPA plasma conc
corresponding increases in seizure activity and electroencephalogram changes (Spriet et al, 2007).

3) Severity: major
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should avoid being treated with meropenem. Consider an alternative antibiotic which does not affect valproic acid serum levels. If concomitant administratio
7) Probable Mechanism: unknown
8) Literature Reports

a) A retrospective study of 39 patients with concurrent treatment with valproic acid (VPA) and meropenem an average decrease of valproic acid levels of 66% within 24 hours. In patients receiving meropenem after the mean plasma concentrations of VPA decreased from 64.3 milligrams/liter (mg/L) to 22.5 mg/L. Thera plasma concentrations range from 50 to 100 (mg/L). Patients receiving VPA after meropenem did not ac plasma levels of VPA, with mean levels of 11.8 mg/L. Despite additional loading doses and increased mi
only one patient achieved therapeutic plasma levels after the maintenance dose was increased to 12 gra adverse patient outcomes or incomplete data, 20 patients were evaluated for causality and clinical rele
interaction. The interaction was rated probable in 16 and possible in 4 of the 20 patients. Eleven of these experienced an increase in seizures, electroencephalogram changes, or both. VPA concentrations achie
range approximately 8 days after concurrent use of the two medications ceased, and seizure activity was

b) The coadministration of meropenem with valproic acid produced a pronounced decline in valproic ac
concentrations. In a case report, a 21-year-old woman was administered valproic acid (VPA) 1920 milli
continuous intravenous (I.V.) infusion over 24 hours in an attempt to control recurrent tonic-clonic seizure concentration of 52.5 micrograms/milliliter (mcg/mL) was attained on treatment day 6, with therapeutic se concentrations maintained on days 8, 10, and 12. On day 13, the patient developed a fever for which intr meropenem 1 gram 3 times daily was started. Two days later, numerous myoclonic events were observe
arms and face; VPA serum concentration was measured at 42 mcg/mL. VPA dose was increased to 288 l.V. infusion over 24 hours), yet tonic-clonic seizures occurred on day 17 in conjunction with a further dec
concentration to 7 mcg/mL. VPA dose was increased the following day to 3600 mg; however, VPA serum did not exceed 10 mcg/mL. Intravenous ceftazidime and ciprofloxacin were substituted for meropenem o which serum concentration of VPA increased over the next several days, eventually attaining therapeutic cessa
tion of seizure activity (Coves-Orts et al, 2005).

c) As described in a series of case reports, serum concentration levels of valproic acid were substantial
the concurrent administration of meropenem. In the first case, a 14-year-old boy with epilepsy had been with valproic acid (VPA) 50 milligrams/kilogram (mg/kg)/day, prior to receiving meropenem and tobramycin unspecified) for treatment of Acinetobacter pneumonia. VPA serum concentrations subsequently decline therapeutic levels (nadir of 15 micrograms/milliliter (mcg/mL) despite an increase in VPA dose to 200 m after completing meropenem therapy. VPA serum concentrations returned to therapeutic levels (114 mcg/mL); patient was a 7-month-old girl with West syndrome, receiving anticonvulsant treatment with VPA 75 mg/L VPA plasma concentrations were within therapeutic range (69 to 90 mcg/mL) prior to receiving concurrent meropenem and vancomycin to treat an Acinetobacter nosocomial pneumonia. VPA was increased to 12 plasma VPA declined to as low as 18 mcg/mL. The patient continued to receive meropenem for 14 days, activity, and sustained an increase in plasma VPA concentrations to 81 mcg/mL on the third day after co meropenem therapy. The third patient, a 14-month-old girl, was receiving VPA 75 mg/kg/day for anticon West syndrome symptoms. Baseline VPA serum concentrations were 85 mcg/mL. The patient received meropenem for treatment of an Acinetobacter urinary tract infection; within 3 days of beginning meropenem t plasma concentrations decreased to a nadir of 10 mcg/mL, yet returned to within therapeutic range 3 da
the course of meropenem treatment (Nacarkucuk et al, 2004).

d) In 2 patients, substantial reductions occurred in valproic acid (VPA) plasma concentrations when mer added to previously stable dose regimens of VPA. The first patient, a 65-year-old woman, received an in intravenous VPA 1200 milligrams (mg) over 24 hours following shunt placement for management of a su hemorrhage. Therapeutic VPA concentration levels were maintained with a dose range of 1200 mg to 16 approximately 23 days, intravenous meropenem 1 gram 3 times daily was administered with amikacin to negative bacillus infection. On the day following initiation of meropenem, the VPA serum concentration of approximately 55 mg/mL to 25 mg/L (per graphic analysis), despite supplemenation of VPA dose. In the report, a 57-year-old woman was given a prophylactic infusion of VPA (dose unspecified), all 100 mg 3 times daily administered on postop days 9-15. Due to development of a lung infection with Kiel Pseudomonas organisms, intravenous meropenem and amikacin were administered at an indeterminate during the postoperative course, accompanied by an unspecified supplementation of VPA dose. Despite augmentation, serum concentration of VPA declined from 44 mg/L to 5 mg/L within 24 hours of beginning second patient, the plasma elimination half life of VPA was found to have declined from an expected to only 4 hours (De Turk et al, 1998).
3.5.1.Z Nifedipine

1) Interaction Effect: increased plasma concentration of nifedipine
2) Summary: Nifedipine plasma concentrations may be increased by the presence of valproic acid. Clinical nifedipine toxicity is recommended (Prod Info Adalat(R) CC Extended Release Tablets, 2004).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of nifedipine and valproic acid may increase exposure to nifedipine. Monitor for clinical signs of nifedipine toxicity, including hypotension, peripheral edema, and bradycardia. Consider reduction of nifedipine.
7) Probable Mechanism: unknown

3.5.1.AA Nimodipine

1) Interaction Effect: nimodipine toxicity (dizziness, headache, flushing, peripheral edema)
2) Summary: A single dose study has shown that concurrent use of valproic acid with nimodipine results in increased nimodipine AUC with no change in half-life (Tartara et al, 1991a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical or toxic effects of nimodipine (hypotension is most likely). Downward adjustment may be necessary to maintain desired cardiovascular response.
7) Probable Mechanism: decreased nimodipine metabolism
8) Literature Reports
   a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 included healthy subjects with epilepsy treated for at least four months with carbamazepine, phenobarbital, phenytoin (all at the same dose) and group 3 included patients treated for at least four months with sodium valproate for the control group. Nimodipine AUCs averaged a 7-fold decrease in the enzyme inducer group, probably due to first-pass metabolism. The nimodipine AUCs were increased by 50% in the valproate-treated group.

3.5.1.AB Nortriptyline

1) Interaction Effect: increased serum nortriptyline levels
2) Summary: The manufacturer reports a 34% decrease in plasma clearance of nortriptyline and a 21% decrease in amitriptyline clearance following administration of amitriptyline 50 mg (single dose) and valproate 500 mg/day in 15 healthy volunteers. However, concurrent use of valproate and amitriptyline (nortriptyline precursor) has resulted in overt toxicity (Prod Info Depacon(R), 2002). Nimodipine levels in patients taking valproate concomitantly. Consider lowering the dose of nortriptyline in the presence of valproate (Prod Info Depakote(R), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor nortriptyline levels in patients taking valproate concomitantly. Consider lowering the dose of nortriptyline in the presence of valproate.
7) Probable Mechanism: inhibition of nortriptyline metabolism
8) Literature Reports
   a) In an open-label study of 15 healthy volunteers, the pharmacokinetic interactions between divalproex sodium and amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving a single dose of divalproex sodium 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalproex resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the area under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was prolonged compared to amitriptyline alone. Nimodipine levels in patients taking valproate concomitantly. Consider lowering the dose of nortriptyline in the presence of valproate (Prod Info Depakote(R), 2002).
   b) The combination of valproic acid and nortriptyline has resulted in toxic levels of nortriptyline. A 33-year-old bipolar patient who had elected to discontinue her lithium treatment which had been maintained on for 8 developed severe depression two months later. Nortriptyline 25 mg at bedtime was initiated on day 1 of a 14-day dosing regimen. On day 8, the dosage was increased to nortriptyline 100 mg at bedtime. Valproate 250 mg 3 times daily was added on day 7 and increased to 500 mg twice daily on day 10. On day 13 of the patient noticed marked tremulousness and fingers, which worsened over the next 3 days. After 15 days of nortriptyline treatment the nortriptyline plasma level was 105 ng/liter (range, 40 to 130 ng/mL). The valproate level was 105 mg/liter (range, 50 to 100 mg/liter). Both medications were discontinued and the patient's tremulousness decreased over the next 2 days (Fu et al, 1994).
   c) A 36-year old male with bipolar disorder was treated initially with lithium but had terminated his lithium treatment due to difficulties with sexual dysfunction. One month later he developed suspected lithium-induced hypothyroidism. His current regimen consisted of lithium 75 mg/day for 10 days, followed by valproate 250 mg/day for 10 days, and then discontinued due to difficulties with sexual dysfunction. On day 2 of valproate treatment he was restarted on thioridazine 75 mg/day and nortriptyline was increased to 100 mg/day. His nortriptyline level at that time was 146 ng/mL. His thioridazine dose was tapered over 3 weeks. The combination of valproic acid and nortriptyline has resulted in toxic levels of nortriptyline. A 33-year-old bipolar patient who had elected to discontinue her lithium treatment which had been maintained on for 8 developed severe depression two months later. Nortriptyline 25 mg at bedtime was initiated on day 1 of a 14-day dosing regimen. On day 8, the dosage was increased to nortriptyline 100 mg at bedtime. Valproate 250 mg 3 times daily was added on day 7 and increased to 500 mg twice daily on day 10. On day 13 of the patient noticed marked tremulousness and fingers, which worsened over the next 3 days. After 15 days of nortriptyline treatment the nortriptyline plasma level was 105 ng/liter (range, 40 to 130 ng/mL). The valproate level was 105 mg/liter (range, 50 to 100 mg/liter). Both medications were discontinued and the patient's tremulousness decreased over the next 2 days (Fu et al, 1994).
ng/mL. This was within the therapeutic range (Fu et al., 1994).

d) The addition of valpromide to a stable amitriptyline regimen may result in an increase of antidepressa
Twenty patients with major depressive illness (DSM - III criteria) were divided into two groups, one treat
alone and one treated with both amitriptyline and valpromide. All patients received oral amitriptyline 125
the evening for 20 days. Only benzodiazepines (diazepam, lorazepam, bromazepam, clorazepate dipota
mg/day, were also administered. Ten patients also received 600 mg valpromide daily after 10 days on ar
relapses and/or to decrease irritability and agitation. No statistically significant difference between amitri
nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patients treated with 1
mg daily. In the ten patients who received valpromide 600 mg, amitriptyline and nortriptyline plasma leve
mean amitriptyline level increased from 70.5 +/- 35.9 nanograms/milliliter (ng/mL) to 105.5 +/- 49.4 ng/m
0.0003, paired Student's t test), and the mean nortriptyline level rose from 61.0 +/- 34.3 to 100.5 +/- 65.1.
No significant relationship was seen between the percentage increase of amitriptyline levels and the pla
valproic acid, the main valpromide metabolite. There was a significant linear relationship between the pla
amitriptyline before and after valpromide (r equal to 0.94, p < 0.001) and between the nortriptylin
before and after valpromide (r equal to 0.87, p < 0.001). Tricyclic antidepressant plasma levels m
the therapeutic window after addition of valpromide. Monitoring of plasma levels of tricyclic antidepressa
control this interaction (Vandel et al., 1988a).

3.5.1.AC Oxcarbazepine
1) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of oxcarba
2) Summary: Concurrent administration of oxcarbazepine (600 to 1,800 milligrams (mg)/day) in patients rece
with valproic acid (400 to 2,800 mg/day) resulted in a 18% decrease (90% confidence interval, 13% decrease
in the plasma concentration of oxcarbazepine's 10-monohydroxy derivative (MHD) and a less than 10% chan
acid concentration (Prod Info TRILEPTAL(R) oral tablets, oral suspension, 2005). Although, the clinical signif
interaction is unknown, decreased plasma MHD concentrations may result in a potential loss of oxcarbazepin
oxcarbazepin and valproic acid are administered concurrently, clinical response to oxcarbazepine may neec
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of oxcarbazepine and valproic acid may result in a decreased co
7) Probable Mechanism: unknown

3.5.1.AD Panipenem
1) Interaction Effect: decreased valproic acid efficacy
2) Summary: Three case reports describe a decrease in valproic acid serum concentrations when panipener thera
was instituted, resulting in the recurrence of seizures in two patients. Although the exact mechanism is not known, panipenem/betamipron should be avoided in patients treated with valproic acid (Yamagata et a
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving valproic acid anticonvulsant therapy should not be treated with panipenem/betamipron. An alternative antibiotic which does not affect valproic acid serum levels should be c
7) Probable Mechanism: unknown
8) Literature Reports
   a) A 4-year-old female with spastic quadriplegia, epilepsy, and mental retardation was receiving valproic mg/kg/day and phenobarbital 5 mg/kg/day with serum levels of 55.1 mg/dL and 28.4 mg/dL, respectively ad
   nimed to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while wa
   decreased to 4.5 mg/kg/day. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three d
   daily, and the serum valproic acid level decreased to 22.9 mg/mL by day 6. Although no seizures develo
   this decrease, panipenem/betamipron was discontinued, and the valproic acid serum concentration incre
   mg/dL (Yamagata et al., 1998).
   b) A 3-year-old girl with quadriplegia, epilepsy, and mental retardation was receiving valproic acid 35 mg
arbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission f
nia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamip
amikacin 5 mg/kg/day. Three days later, generalized tonic-clonic seizures began to occur once or tw
valproic acid level had decreased to 30.9 mg/mL and further dropped to 26.8 mg/mL two days later. Des
the valproic acid dose to 42 mg/kg/day, the serum concentration continued to decrease to 15.3 mg/mL o
fani treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of disco
etamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipron thera
4) Severity: moderate
   c) Panipenem/betamipron 30 mg/kg/day resulted in intense, generalized seizures and frequent myoclon
year-old male who had previously been stabilized on valproic acid 32 mg/kg/day, clonazepam 0.9 mg/kg
phenytoin 5 mg/kg/day. Prior to panipenem/betamipron therapy, his valproic acid serum level ranged fr
108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 mg/kg/day. The valproic acid dose was increased to 34 mg/kg/day, serum levels were undetectable by day 25 of the se
bined therapy. After the antibiotic was discontinued, the seru
levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

### 3.5.1.AF Phenytoin

1. **Interaction Effect:** altered valproate levels or altered phenytoin levels
2. **Summary:** Valproic acid may initially cause a decrease in total phenytoin level by displacement of phenytoin from protein binding sites (Prod Info Depakote(R) ER, 2003f; Levy & Koch, 1982a; Bruni et al, 1980a; Monks et al, 1978a) or increase in the bound fraction of phenytoin; the phenytoin which is displaced by valproic acid re-equilibrates with the tissue compartment such that the unbound plasma concentration remains unchanged (Winter et al, 1982a). The degree of displacement appears to be valproic acid dose related (Monks & Richens, 1980a), with a proportional increase in phenytoin levels. A 10% increase in clearance of valproic acid has been observed in patients taking valproate 250 mg twice daily (Prod Info Depakote(R) ER, 2003f).

3. **Severity:** moderate
4. **Onset:** delayed
5. **Substantiation:** probable
6. **Clinical Management:** Due to the complex situation involving displacement of protein-bound phenytoin and phenytoin metabolism, as well as the potential for decreased valproic acid concentrations, patients should be monitored for signs of phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to accurately assess phenytoin activity early in therapy. At steady-state free phenytoin concentrations are used to monitor phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to accurately assess phenytoin activity early in therapy.

#### Literature Reports

1. **Elevations in serum phenobarbital levels have occurred with concurrent sodium valproate administration (Sobben et al, 1975; Johanssens, 1977; Richens, 1981; Kapetanovic et al, 1981; Bruni et al, 1980a; Anon, 1978). Conversely, phenobarbital serum half-life of sodium valproate due to the induction of liver enzymes (Pinder et al, 1977; Rimmer & Furlanet al, 1982). A 10% increase in clearance of valproic acid has been observed in patients taking valproate 250 mg twice daily (Prod Info Depakote(R) ER, 2003f).

2. **Phenobarbital metabolism is inhibited by valproate. Six subjects received valproate 250 mg twice daily and showed a significant increase in serum phenobarbital levels (Prod Info Depakote(R) ER, 2003f). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence (Prod Info Depakote(R) ER, 2003f).**

3. **Summary:** Concurrent administration of valproic acid and phenobarbital results in decreased phenobarbital levels due to the potential for decreased valproic acid concentrations, patients should be monitored for signs of phenobarbital toxicity and a serum phenobarbital level obtained. Phenobarbital dosing may decrease in some cases. Due to increased valproic acid metabolism, periodic determinations of valproic acid concentrations should be considered.

4. **Probable Mechanism:** decreased phenobarbital metabolism or increased valproic acid metabolism

5. **Literature Reports**

   - **Elevations in serum phenobarbital levels have occurred with concurrent sodium valproate administration (Sobben et al, 1975; Johanssens, 1977; Richens, 1981; Kapetanovic et al, 1981; Bruni et al, 1980a; Anon, 1978). Conversely, phenobarbital serum half-life of sodium valproate due to the induction of liver enzymes (Pinder et al, 1977; Rimmer & Furlanet al, 1982). A 10% increase in clearance of valproic acid has been observed in patients taking valproate 250 mg twice daily (Prod Info Depakote(R) ER, 2003f).**

   - **Phenobarbital metabolism is inhibited by valproate. Six subjects received valproate 250 mg twice daily and showed a significant increase in serum phenobarbital levels (Prod Info Depakote(R) ER, 2003f). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence (Prod Info Depakote(R) ER, 2003f).**

### 3.5.1.AG Primidone

1. **Interaction Effect:** severe central nervous system depression
2. **Summary:** The concurrent use of valproic acid and phenobarbital may result in severe central nervous system depression possibly due to the impairment of non-renal phenobarbital clearance. Serum concentrations of phenobarbital significantly increased. Since primidone is metabolized to phenobarbital, the same interaction may be possible (Sobben et al, 1975; Johanssens, 1977; Richens, 1981; Kapetanovic et al, 1981; Bruni et al, 1980a; Anon, 1978). Conversely, phenobarbital serum half-life of sodium valproate due to the induction of liver enzymes (Pinder et al, 1977; Rimmer & Furlanet al, 1982). A 10% increase in clearance of valproic acid has been observed in patients taking valproate 250 mg twice daily (Prod Info Depakote(R) ER, 2003f).

3. **Severity:** major
4. **Onset:** rapid
5. **Substantiation:** probable
6. **Clinical Management:** All patients receiving concurrent primidone and valproic acid therapy should be monitored for signs of phenobarbital toxicity and neurological toxicity. Serum primidone and derived phenotol levels should be monitored and the dosage of primidone decreased, if necessary.
7) Probable Mechanism: impairment of phenobarbital clearance
8) Literature Reports
   a) One hundred epileptic patients taking primidone alone or in combination with other anticonvulsants were studied (Yukawa et al, 1989). Primidone doses ranged from 1.45 mg per kg to 27.03 mg per kg. All patients taking the same dosage for at least three weeks prior to blood sampling. Results showed no significant change in phenobarbital serum level when given concomitantly with valproate sodium, but there was a significant increase in phenobarbital serum level.

3.5.1.AH Rifampin
1) Interaction Effect: reduced valproate levels
2) Summary: A 40% increase in the oral clearance of valproate was observed in a study involving the administration of valproate (7 mg per kg) 36 hours after five nights of daily dosing with rifampin (600 mg) (Prod Info Depakote(R) E). When coadministered with rifampin, valproate dosage adjustment may be required (Prod Info Depakote(R) E).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor valproate levels and the patient for seizure control. An adjustment in the dose may be necessary when coadministered with rifampin.
7) Probable Mechanism: increased valproate oral clearance

3.5.1.AI Rifapentine
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: The efficacy of anticonvulsants may be impaired with concomitant use of rifapentine. Rifapentine may decrease the metabolism of other coadministered drugs that are metabolized by cytochrome P450 3A4 or 2C8/9. Dose reductions of anticonvulsants may be necessary if given concurrently with rifapentine (Prod Info Priftin(R), 2000).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor serum anticonvulsant levels and with concomitant use and adjust doses accordingly.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.AJ Risperidone
1) Interaction Effect: increased plasma valproic acid concentrations
2) Summary: The addition of risperidone to valproic acid produces a significant increase in the peak plasma (Cmax) of valproic acid (Prod Info Risperdal(R) Consta(TM), 2003a) as well as marked increases in ammonia levels. The high protein capacity of risperidone could lead to a competition for protein-binding with the high capacity of valproic acid, leading to a decrease in valproic acid plasma protein-binding sites (van Walt. However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 2007). Ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking valproate, especially in patients vulnerable to valproic acid-induced hyperammonemia, including the young, polytherapy, severely handicapped, or suffering from malnutrition, protein load, and decreased free serum calcium levels. In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone levels may be necessary.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor for increased ammonia levels and plasma valproic acid concentrations with risperidone to drug therapy or changes in risperidone dose.
7) Probable Mechanism: unknown
8) Literature Reports
   a) In 2 case reports of 11 year-old boys, there were marked exacerbations in manic behavior and a 2 to 3-fold increase in the peak plasma (Cmax) of valproic acid. The high protein capacity of risperidone could lead to a competition for protein-binding with the high capacity of valproic acid, leading to a decrease in valproic acid plasma protein-binding sites (van Walt, However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 2007). Ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking valproate, especially in patients vulnerable to valproic acid-induced hyperammonemia, including the young, polytherapy, severely handicapped, or suffering from malnutrition, protein load, and decreased free serum calcium levels. In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperidone levels may be necessary.
   b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic acid. Plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH-risperidone) were compared in patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder, were stabilized with risperidone alone or in combination with valproic acid. The patients exhibited markedly pronounced manic behavior when taking valproate sodium, but there was a significant increase in phenobarbital serum level when given concomitantly with valproate sodium, but there was a significant increase in phenobarbital serum level.

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
Exhibit E.7, page 82
7/1/2009
valproic acid. The results demonstrate that valproic acid given at doses up to 1200-1500 mg/day had circl effects on plasma concentrations of risperidone and its active metabolite. Valproic acid can be added sal regimen consisting of risperidone. In patients prescribed this combination of drugs, monitoring of plasma OH-risperidone concentrations does not appear to be warranted (Spina et al, 2000).

c) The combination of valproic acid and risperidone led to significantly increased levels of valproic acid i-year-old male suffered from mood swings and increasingly aggressive behavior. Valproic acid treatment titrated up to 1750 mg/day. Valproate serum levels were in the therapeutic range. After 10 days of treatment mg/day was added, which was increased to 3 mg/day on day 4. On day 5 after risperidone was started, the symptoms improved but valproic acid levels were above the therapeutic range at 191 mg/L. Valproic acid aci 1000 mg/day and the level normalized to 108 mg/L within 3 days and subsequently stabilized. The author a high-protein-binding capacity of risperidone could lead to a competition for protein-binding with the high capacity of valproic acid, leading to displacement of valproic acid from plasma protein-binding sites (Van d) In 21 patients, repeated oral doses of risperidone 4 mg daily did not affect the pre-dose or average pl concentrations or exposure (area under the concentration-time curve) of valproate 1000 mg daily compa There was, however, a 20% increase in valproate maximum plasma concentration (Cmax) after risperidic coadministration (Prod Info Risperdal(R) Consta(TM), 2003).

3.5.1.AK  Ritonavir  
1) Interaction Effect: decreased valproic acid serum concentrations  
2) Summary: Coadministering ritonavir with valproic acid may decrease the plasma concentration of valproic report suggests the mechanism may be due to ritonavir induction of VPA metabolism via glucuronidation (Shi Monitoring of valproic acid plasma concentrations is recommended (Prod Info NORVIR(R), 2005).  
3) Severity: moderate  
4) Onset: delayed  
5) Substantiation: probable  
6) Clinical Management: Monitor therapeutic concentrations of valproic acid when coadministering with ritonav acid dose increase may be needed.  
7) Probable Mechanism: ritonavir-induced metabolism of valproic acid  
8) Literature Reports  
   a) A case report describes a 30-year-old man with bipolar disorder and HIV who became increasingly m addition of lamivudine 150 mg/zidovudine 300 mg twice a day and lopinavir 133 mg/ritonavir 33 mg (3 ca day) to his drug regimen. The patient had been maintained on valproic acid (VPA) 250 mg 3 times a day concentration of 495 mcg/mL, when the antiretrovirals were prescribed during a hospital admission for n Paroxetine 10 mg/day was simultaneously given for the depressive episode. The patient became hypom and the paroxetine was switched to sertraline 50 mg/day. Twenty-one days after the initiation of antiretro become increasingly manic and was again admitted. He had continued all medications except sertraline includin the same VPA dose. Serum VPA concentration 6 to 10 hours post-dose was subtherapeutic at decrease of 48% from the previous documented concentration. Olanzapine and an increase in VPA to 1 effectively managed the manic episode. The patient adhered to this new drug regimen, including the pre antiretrovirals, and 10 days later a 14-hour post-dose VPA level measured in the therapeutic range at 39 the patient was not taking concomitant medications known to affect VPA metabolism, it was hypothesize decrease in VPA concentrations was due to ritonavir induction of VPA metabolism (via glucuronidation) 2006).

3.5.1.AL  Rufinamide  
1) Interaction Effect: increased rufinamide plasma concentrations  
2) Summary: Concomitant administration of rufinamide and valproate may result in rufinamide concentration 70%. Larger increases in rufinamide plasma concentrations were observed in children with higher valproate doses/concentrations (Prod Info BANZEL(TM) oral tablets, 2008).  
3) Severity: moderate  
4) Onset: unspecified  
5) Substantiation: probable  
6) Clinical Management: Caution is advised if rufinamide and valproate are coadministered as this may resu rufinamide plasma concentrations. Risk is increased in children with higher valproate doses/concentrations (f (TM) oral tablets, 2008).  
7) Probable Mechanism: unknown  

3.5.1.AM  Tipranavir  
1) Interaction Effect: decreased valproic acid plasma concentrations and potential for decreased efficacy  
2) Summary: Coadministration of tipranavir and valproic acid may result in decreased valproic acid concentr decrease the efficacy of valproic acid (Prod Info APTIVUS(R) oral capsules, 2007). Valproic acid doses may adjusted and frequent monitoring of valproic acid levels for efficacy may be required.  
3) Severity: moderate  
4) Onset: unspecified  
5) Substantiation: theoretical  
6) Clinical Management: Use caution when prescribing valproic acid to patients who are taking tipranavir. Va less effective due to decreased valproic acid concentrations in patients taking concomitant tipranavir (Prod In oral capsules, 2007). Monitor patients for loss of valproic acid efficacy and adjust doses as necessary.
7) Probable Mechanism: unknown

3.5.1.AN Topiramate

1) Interaction Effect: decreased topiramate or valproic acid concentrations, and increased risk of hyperammonemic encephalopathy

2) Summary: Controlled, clinical pharmacokinetic studies in patients with epilepsy showed an 11% decrease in concentration of valproic acid when topiramate was added. However, when topiramate was given alone, the topiramate decreased by 14% when valproic acid was added (Prod Info TOPAMAX(R) oral tablets, oral sprinkle 2008). In two controlled studies involving a total of seven epileptic patients already receiving valproic acid, the topiramate did not significantly change the serum concentration of valproic acid or valproic acid trough conce et al, 1996; Floren et al, 1989a). The coadministration of valproic acid and topiramate has also been implicated in development of hyperammonemic encephalopathy (Hamer et al, 2000a). As described in a series of case reports, encephalopathy developed in 5 patients with drug-resistant epilepsy, shortly after beginning a combination ar regimen comprising topiramate and valproic acid. Symptoms largely resolved after either drug was reduced or completely withdrawn (Latour et al, 2004). Although not studied, concomitant use of topiramate and valproic acid has been implicated in exacerbate existing defects or unmask deficiencies in susceptible patients. Patients with inborn errors of met hepat mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopathy TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concomitant use of topiramate and valproic acid may result in hyperammonemia or encephalopathy. It may also result in decreased plasma concentrations of one or both drugs (Prod Info TOPAMAX(R) tablets, oral sprinkle capsules, 2008). Upon the coadministration of topiramate and valproic acid, dosing adj required for either or both drugs. Consider monitoring patients for seizure control and excessive adverse effe

7) Probable Mechanism: unknown

8) Literature Reports

a) In a controlled study, interactions with topiramate were assessed in six epileptic patients already taking valproic acid. The patients were given topiramate 100 mg every m increased to the maximum tolerated dose (no greater than 1200 mg per day). Plasma concentration-time observed over the next eight weeks. No apparent changes were observed in either phenytoin or valproic acid the concentration-time curve (AUC) profiles or trough plasma concentrations (Floren et al, 1989).

b) Stuporous encephalopathy developed in 5 patients with drug-resistant epilepsy, shortly after beginnin anticonvulsant regimens comprising topiramate (TPM) and valproic acid (VPA). Hyperammonemia was c the patients (age ranging from 29 to 41 years). Blood ammonia levels ranged from 62 to 146 mc mol/L. A dose or withdrawal of TPM or VPA, blood ammonia levels returned to normal. In the 5th case report, a 1 developed impaired consciousness, 10 days after VPA 1500 mg/day was added to a stable dose regime 300 mg/day, phenytoin (PHT) 300 mg/day, and carbamazepine 6 mg/day. Blood ammonia concentration normal limits; however, elevations were observed in plasma concentrations of gamma glutamyl-transferase (GGT) level. The patient's cognitive status returned to baseline after TPM was tapered and withdrawn, a reduction of PHT dose (Latour et al, 2004).

c) A 32-year-old male with centro-temporal epilepsy was controlled on phenobarbital 200 mg daily and t daily when valproic acid was added to his regimen. Two days prior to hospital admission, valproic acid w 1500 mg daily and the patient became drowsy with nausea and slurred speech. The phenobarbital conc mcg/mL (therapeutic range 8 mcg/mL to 20 mcg/mL) and the valproic acid level was 38 mcg/mL (therap mcg/mL to 100 mcg/mL) at hospital admission. The ammonia concentration was elevated at 116 mc mol/L, to 60 mcmol/L), as was the gamma glutamyl transpeptidase (GGT) level. Acute valproic acid or suspected, and valproic acid was discontinued. The patient recovered within the next three days and the concentration decreased to within normal limits (Hamer et al, 2000).

d) A 37-year-old female with focal epilepsy was receiving topiramate 400 mg daily, carbamazepine 1000 lamotrigine 150 mg daily with little effect on her seizure frequency. Valproic acid 1200 mg daily was slow lamotrigine, and the patient became somnolent and dysarthric within three weeks. Laboratory results sh acid level of 47 mcg/mL (therapeutic range 50 mcg/mL to 100 mcg/mL) and a carbamazepine level of 52 (therapeutic range 8 mcg/mL to 12 mcg/mL). The ammonia level was increased to 88 mmol/L and valpro hyperammonemic encephalopathy was suspected. Topiramate was slowly discontinued over a seven-da patient completely recovered, although the ammonia level remained elevated. Valproic acid was then als and the ammonia concentration returned to a normal range (Hamer et al, 2000).

3.5.1.AO Vorinostat

1) Interaction Effect: severe thrombocytopenia and gastrointestinal bleeding

2) Summary: Severe thrombocytopenia and gastrointestinal bleeding have occurred with the concomitant us other histone deacetylase inhibitors, such as valproic acid. Caution is advised if these agents are coadministe platelet count every 2 weeks for the first 2 months of therapy (Prod Info ZOLINZA(TM) oral capsules, 2006).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant use of vorinostat with other histone deacetylase inhibitors, such as val resulted in severe thrombocytopenia and gastrointestinal bleeding. Use caution if these agents are coadminis
platelet count every 2 weeks for the first 2 months of therapy (Prod Info ZOLINZA(TM) oral capsules, 2006).

7) Probable Mechanism: unknown

3.5.1.AP Zidovudine

1) Interaction Effect: increased zidovudine plasma concentrations and potential zidovudine toxicity (asthenia, hematologic abnormalities)
2) Summary: Coadministered valproic acid increases the bioavailability of zidovudine and may lead to zidovudine toxicity (asthenia, hematologic abnormalities). In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h) (Prod Info Depakote(R), 2003). In this short-term study, no change in hematologic parameters was noted during coadministration. The clinical impact of long-term use of this combination is unknown. Effects on valproic acid concentrations were not studied. The mechanism of the interaction is inhibition by valproic acid of zidovudine metabolism.

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of zidovudine toxicity (asthenia, fatigue, nausea, hematologic abnormalities). It may be necessary to reduce zidovudine doses when valproic acid is added to or increase doses when valproic acid is discontinued.
7) Probable Mechanism: Inhibition by valproic acid of zidovudine metabolism
8) Literature Reports
   a) Zidovudine pharmacokinetics were studied in six HIV-infected volunteers administered four days of zidovudine 100 mg orally and four days of zidovudine combined with valproic acid. Study subjects received zidovudine 100 mg q8h and valproic acid 250 mg orally every eight hours (one patient was given 500 mg of valproic acid q8h). The area under the concentration-time curve of zidovudine increased by 80%, from 0.65 to 1.17 mcg/hr/l, when concomitant valproic acid was given. Zidovudine oral clearance decreased 38% from 2351 to 1449 mL/hr/l. The half-life of zidovudine was not significantly altered during coadministration. In this short-term study, no change in hematologic parameters or renal and hepatic function tests was noted. The clinical impact of long-term use of this combination is unknown. Effects on valproic acid concentrations were not studied. The mechanism of the interaction is inhibition by valproic acid of first-pass glucuronidation of zidovudine (Prod Info Depakote(R), 1994).

3.5.3 Drug-Lab Modifications

3.5.3.A Plasma free fatty acid measurement

Plasma free fatty acid measurement

Urinalysis, acetone or ketone bodies measurement

3.5.3.3.B Urinalysis, acetone or ketone bodies measurement

1) Interaction Effect: falsely elevated plasma free fatty acid levels
2) Summary: In a plasma mixing experiment, free fatty acids falsely increased when measured by a colorimetric therapeutic concentrations of valproic acid were added (Albani et al, 1982). Consider using a more specific method to determine FFA concentration in patients receiving valproic acid.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider avoiding calorimetric methods to determine plasma free fatty acid levels in patients receiving valproic acid. More specific methods for free fatty acid determination should be used.
7) Probable Mechanism: assay interference
8) Literature Reports
   a) When free fatty acids (FFA) are measured by colorimetric methods, false elevations may occur due to the presence of valproic acid, a short branched-chain organic acid. In a controlled plasma mixing experiment, the addition of micrograms/milliliter of valproic acid increased the apparent FFA by an average 246 micromole/liter in 10 patients receiving valproic acid. Using more specific methods to determine FFA concentrations in patients receiving valproic acid should avoid this interference (Albani et al, 1982). The concentration of valproic acid used in the experiment was 50 to 100 micrograms/milliliter (concentrations used for epilepsy) and acute mania micrograms/milliliter (treatment of bipolar disorder). The clinical impact of long-term use of this combination is unknown. Effects on valproic acid concentrations were not studied. The mechanism of the interaction is inhibition by valproic acid of first-pass glucuronidation of zidovudine (Prod Info Depakote(R) ER, 2003).

3.5.3.3.C Urinary ketone bodies measurement

1) Interaction Effect: a false-positive urine ketone test
2) Summary: In patients receiving valproic acid, false-positive reactions for ketones in the urine may occur because the urine is partially eliminated in the urine as a keto-metabolite (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008). Interpret results with caution in patients receiving valproic acid therapy.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Valproic acid is partially eliminated in the urine as a keto-metabolite, which may result in false-positive reactions for ketones in the urine (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008). Interpret results with caution in patients receiving valproic acid therapy.
7) Probable Mechanism: valproic acid being partially eliminated in the urine as a keto-metabolite

3.5.5 Intravenous Admixtures

3.5.5.2 Solutions

3.5.5.2.A Valproate Sodium

DEXTROSE 5%

Lactated Ringer’s Injection

SODIUM CHLORIDE 0.9%

3.5.5.2.A.1 DEXTROSE 5%
   a) Compatible
      1) Valproate sodium injection was found to be physically compatible and chemically stable in d
         least 24 hours when stored in glass or polyvinyl chloride bags at controlled room temperature, 1
         Celsius (Prod Info Depacon(R), 1999).

3.5.5.2.A.2 Lactated Ringer’s Injection
   a) Compatible
      1) Valproate sodium injection was found to be physically compatible and chemically stable in la
         injection for at least 24 hours when stored in glass or polyvinyl chloride bags at controlled room
         30 degrees Celsius (Prod Info Depacon(R), 1999).

3.5.5.2.A.3 SODIUM CHLORIDE 0.9%
   a) Compatible
      1) Valproate sodium injection was found to be physically compatible and chemically stable in s
         0.9% for at least 24 hours when stored in glass or polyvinyl chloride bags at controlled room ten
         degrees Celsius (Prod Info Depacon(R), 1999).

4.0 Clinical Applications

   Monitoring Parameters

   Patient Instructions

   Place In Therapy

   Mechanism of Action / Pharmacology

   Therapeutic Uses

   Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

   A) Therapeutic
      1) Monitor the reduction in the incidence and severity of seizures.
         a) SERUM LEVELS
            1) The therapeutic range in epilepsy is 50 to 100 mcg/mL of total valproate (Prod Info Depakene(R), 19
               Depakote(R) Tablets, 2002a); (Prod Info Depacon(R), 1999)(Turnbull et al, 1983aa; Rimmer & Richens,
               a) A free concentration therapeutic range has not been established (Prod Info Depakene(R), 1999).
               b) High concentration valproic acid (80 to 150 mcg/mL) may be needed to reduce seizure frequenc,
                  partial seizures and secondarily generalized tonic-clonic seizures (Beydoun et al, 1997c).
            2) Studies with valproate in acute mania utilized the following therapeutic range: 50 to 125 mcg/mL (Pro
               Tablets, 2002a).

   B) Toxic
      1) Laboratory Parameters
         a) Liver function tests should be monitored prior to the initiation of therapy and at frequent intervals. Liver tox
            mainly during the first 6 months of therapy.
Ammonia concentrations should be monitored in cases of mental confusion

b) Complete Blood Count
   1) Platelet counts and coagulation tests should be undertaken before and during therapy at periodic intervals planned surgeries.

c) Amylase levels (serum)
   d) Monitor concentrations; increase frequency of monitoring when concomitant antiepileptics are introduced

e) Some healthcare providers recommend against routine monitoring of serum for pancreatic enzymes because induced pancreatitis has low occurrence, there is wide variability in time to onset, and mild, asymptomatic elevation of pancreatic enzyme markers occurs frequently without progression to pancreatitis. Those healthcare providers counsel patients to recognize the signs and symptoms of pancreatitis and advising them to seek immediate assistance if those symptoms occur (Chapman et al, 2001).

2) Physical Findings
   a) Data reviewed by the US Food and Drug Administration suggest an increased risk of suicidal behavior or in patients receiving therapy with antiepileptic drugs (AEDs). The increased risk of suicidality was noted at 1 week at an AED and continued to at least 24 weeks. Patients treated for epilepsy, psychiatric disorders, or other conditions have an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emergence of depression, suicidality, and other unusual changes in behavior, which may include symptoms such as anxiety, hostility, mania, and hypomania (US Food and Drug Administration, 2008).

4.2 Patient Instructions

A) Divalproex (By mouth)
   Divalproex Sodium

   Treats seizures (epilepsy). Also used to treat the manic phase of bipolar disorder (manic-depressive illness) and tension headaches. Belongs to a class of drugs called anticonvulsants.

   When This Medicine Should Not Be Used:
   You or your child should not use this medicine if you have had an allergic reaction to valproic acid or divalproex, or if you have severe liver disease, a urea cycle disorder (a disease that causes too much ammonia in the blood), or are pregnant.

   How to Use This Medicine:
   Long Acting Tablet, Delayed Release Tablet, Coated Tablet, Delayed Release Capsule
   Your doctor will tell you how much of this medicine to use and how often. Your dose may need to be changed to find out what works best for you. Do not use more medicine or use it more often than your doctor tells you. May be taken with food to decrease stomach upset.
   Swallow the capsule or tablet whole. Do not crush, break or chew it.
   You may open the sprinkle capsule and mix the medicine beads with a small amount (about a spoonful) of applesauce or pudding. Swallow the mixture whole. Do not chew.
   If a Dose is Missed:
   If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next dose, do not use extra medicine to make up for a missed dose. If you miss two or more doses, call your doctor.

   How to Store and Dispose of This Medicine:
   Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
   Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine after your treatment. You will also need to throw away old medicine after the expiration date has passed.
   Keep all medicine away from children and never share your medicine with anyone.

   Drugs and Foods to Avoid:
   Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, or products.
   Make sure your doctor knows if you or your child are taking a blood thinner (such as aspirin, warfarin, or Coumadin®), or Conjugated estrogens that could make you sleepy, such as sleeping pills (such as alprazolam, lorazepam, Ativan®, Xanax®), or Xanex® medicines (Loracet®, Percocet®, Tylenol® with Codeine, Vicodin®, Vicoprofen®), or cold medicines. Tell your child if you are using any other medicine for seizures.
   Your doctor if you or your child are taking meropenem (Merrem®), rifampin (Rifadin®, Rimactane®), amitriptyline (Topamax®), or zidovudine (Retrovir®).
   Do not drink alcohol while you are using this medicine.

   Warnings While Using This Medicine:
   Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away. Make sure your doctor knows if you are breastfeeding, or if you or your child have liver disease, pancreas disorders. Tell your doctor if you have a family history of urea cycle disorders or unexplained infant deaths. Because of the risk of increased seizures, do not stop using this medicine suddenly without asking your doctor.
to slowly decrease your dose before stopping it completely. If you or your child are taking this medicine in the form of sprinkle capsules, you may see small amounts of the stool. This is normal.

This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could you are not alert.

Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may be a certain medical tests.

Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

- Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, trouble breathing.
- Changes in vision.
- Chest pain.
- Dark-colored urine or pale stools.
- Fast, pounding heartbeat.
- Fever, chills, cough, sore throat, runny or stuffy nose, and body aches.
- Lightheadedness, dizziness, drowsiness, or fainting.
- Sudden and severe stomach pain, nausea, vomiting, loss of appetite.
- Tremors or loss of seizure control.
- Trouble breathing.
- Unusual bleeding or bruising.
- Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:

- Back pain.
- Diarrhea, constipation, or upset stomach.
- Hair loss.
- Headache.
- Increase in appetite.
- Mood changes, unusual thoughts, or memory loss.
- Nervousness or depression.
- Rash or hives with itching.
- Restlessness or irritability.
- Ringing in the ears.
- Trouble sleeping.
- Weight gain or weight loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

B) Valproate Sodium (Injection)

Valproate Sodium

Treats different types of seizures (epilepsy). This medicine is an anticonvulsant.

When This Medicine Should Not Be Used:

You should not receive this medicine if you have had an allergic reaction to valproate, or if you have certain liver problems. You should not receive this medicine if you have a genetic (inherited) urea cycle disorder, which causes the body to handle ammonia (a waste product in the blood).

How to Use This Medicine:

Injectable

A nurse or other trained health professional will give you this medicine. Your doctor will prescribe your exact dose and how often it should be given. This medicine is given through a needle placed in one of your veins.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and products.

Do not use aspirin without your doctor's OK.

There are many other drugs that can interact with valproate. Make sure your doctor knows about all other medicines you may be using, especially blood thinners, and medicine to treat seizures, depression, or mood problems.

Do not drink alcohol while you are using this medicine.

Warnings While Using This Medicine:

Tell your doctor if you are pregnant or breast feeding, or if you have had a recent head injury. Make sure you have a history of coma, unexplained mental or behavior problems, frequent vomiting, a family history of liver disorders, or a family history of unexplained infant deaths. Tell your doctor if you have HIV or AIDS, or if you...
caused by cytomegalovirus (CMV).
If this medicine is to be given to your child, make sure the doctor knows if your child is under the age of two years using other medicine to treat seizures. Tell the doctor if your child was born with a disease that affects his or her bone-making process of the body. Make sure the doctor knows if your child has mental retardation or a brain disease. Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth control before getting pregnant. If you think you have become pregnant while using the medicine, tell your doctor right away. Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may affect certain medical tests.
Your doctor will need to check your blood at regular visits while you are using this medicine. Be sure to keep this medicine may make you drowsy or less alert. Avoid driving, using machines, or doing anything else that is dangerous if you are not alert.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, trouble breathing.
Chest pain or slow heartbeat.
Confusion or hallucinations (sensing things that are not there).
Fever or new coughing.
Lightheadedness, dizziness, severe tiredness, or fainting.
Nausea, vomiting, or sudden and severe stomach pain.
Poor seizure control.
Redness, pain, or swelling at the injection site.
Swelling in your arms or legs, skin rash, or blistering, peeling skin.
Tremors (shaking), or problems with coordination (movement) or posture (remaining upright).
Unusual bleeding or bruising.
Vision changes.
Weakness, loss of appetite, unexplained weight loss, or rapid weight gain.

If you notice these less serious side effects, talk with your doctor:
Dark or bloody urine, pain or burning with urination, or a change in how much or how often you urinate.
Heartburn, diarrhea, or constipation.
Headache.
Hair loss.
Mood changes.
Menstrual (period) changes.
Tiredness or feeling generally unwell.

If you notice other side effects that you think are caused by this medicine, tell your doctor.
C) Valproic Acid (By mouth)
Valproic Acid
Treats seizures (epilepsy). Also used to treat mood disorders and prevent migraine headaches. Belongs to a class of anticonvulsants.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to valproic acid or divalproex, if you have severe or if you are pregnant.

How to Use This Medicine:
Liquid, Liquid Filled Capsule, Delayed Release Capsule
Your doctor will tell you how much of this medicine to use and how often. Do not use more medicine or use it your doctor tells you to.
May be taken with food to lessen stomach upset.
Swallow the capsule whole. Do not crush, break or chew.
Measure the oral liquid medicine with a marked measuring spoon, oral syringe, or medicine cup.

If a Dose is Missed:
If you miss a dose or forget to use your medicine, use it as soon as you can. If it is almost time for your next (then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose. If you miss two or more doses, call your doctor.

How to Store and Dispose of This Medicine:
Keep this medicine in the original tightly closed container. Store at room temperature, away from heat and moisture.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or if needed.
Keep all medicine away from children and never share your medicine with anyone.
Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, or products.

Avoid drinking alcohol.
Make sure your doctor knows if you are taking "blood thinners" (medicines such as aspirin or Coumadin®) or other medicines that could make you sleepy such as sleeping pills, cold medicine, or sedatives.

Warnings While Using This Medicine:
Check with your doctor before taking this medicine if you are breastfeeding, or if you have liver disease, kidney blood disorder.
Talk to your doctor before taking this medicine if you are pregnant. If you become pregnant while being treated with this medicine, tell your doctor right away. This medicine may be harmful to your unborn baby.
Because of the risk of increased seizures, do not suddenly stop taking this medicine without first checking with your doctor.
This medicine may cause drowsiness. Be careful when driving or using machinery.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Loss of seizure control
Severe weakness or dizziness
Severe vomiting that doesn't go away
Unusual bleeding or bruising
Yellowing of the skin or eyes
Rash or hives with itching

If you notice these less serious side effects, talk with your doctor:
Nausea, vomiting, or stomach cramps
Drowsiness or dizziness
Restlessness or irritability
Diarrhea or constipation
Trembling of hands or arms
Hair loss

If you notice other side effects that you think are caused by this medicine, tell your doctor.

4.3 Place In Therapy
A) Valproic Acid
1) Seizures
a) Valproic acid is indicated as monotherapy and adjunctive therapy for complex partial seizures occurring in association with other types of seizures in patients 10 years and older. Valproic acid is also indicated for use and adjunctive therapy in the treatment of complex absence seizures, and adjunctively in patients with multiple seizures that include absence seizures (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPA capsules, oral syrup, 2006).
b) Although valproic acid is considered a first-line therapy for treating generalized tonic-clonic seizures, simple and complex partial seizures, carbamazepine is generally preferred due to its lesser toxicity. Valproic acid is a preferred agent for the treatment of absence seizures; ethosuximide is generally preferred, however (Young & Koda-Kim, 1989).
c) Valproic acid and carbamazepine appear to have less of an effect on cognitive function and behavioral disorders when compared with phenobarbital, phenytoin, and primidone. For this reason, both valproic acid and carbamazepine are preferred over these other agents for treating seizure disorders in children (Trimble, 1988; Anon, 1985).

2) Bipolar disorder
a) Valproic acid (Stavzor(R)) is indicated for the treatment of the manic episodes associated with bipolar disorder over a one-year time period. Valproate has significantly superior results on all measures outcomes for acute mania compared with placebo (Prod Info STAVZOR(R) delayed release oral capsules, 2008). b) Valproic acid has been effective in treating mania associated with bipolar disorder in clinical studies (Fawcett, 1989; Post, 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989; Pope et al, 1988; Grunze et al, 1999; Prasad, 1999).
c) Valproic acid has been shown to be effective for the treatment of acute mania. Response has been seen in approximately 50% of patients. The therapeutic onset correlates with therapeutic plasma levels. Controlled studies are needed to assess valproic acid in the treatment of acute bipolar depression and maint of bipolar disorder.

3) Migraine prophylaxis
a) Valproic acid (Stavzor(R)) is indicated for prophylaxis of migraine in adults and children 16 years and older. Randomized, placebo-controlled clinical trials established the efficacy of valproate for prophylaxis of migraine (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

B) Divalproex Sodium
1) BIPOLAR DISORDER
a) In a decision analysis model, divalproex was found to be less costly than lithium for the acute and prophylactic treatment of bipolar disorder over a one-year time period. Four attributes of overall patient management were considered.
model: the response rate to initial therapy; the mean length of hospital stay; the rates of adverse effects; and treatment costs. In the overall analysis, initial therapy with divalproex resulted in costs that were 9% lower than treatment with lithium, most likely due to a more rapid response with divalproex and shorter length of hospital stay. These savings were most significant in patients with mixed mania and rapid cycling; however, cost savings with lithium therapy were recognized in patients with classic mania (Keck et al, 1996).

C) Valproate Sodium

1) SEIZURES

   a) Valproate sodium injection should be used in patients who temporarily cannot use the oral form of valproic acid (Prod Info valproate sodium injection). If it is clinically feasible, patients should be switched back to oral valproic acid (Prod Info valproate sodium injection).

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION

1) Although the mechanism of action is presently unknown, it is postulated that the drug's effects are mediated through the function of brain gamma-aminobutyric acid (GABA), specifically by increasing brain concentrations of this inhibitory neurotransmitter (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Beckner, 1979; Godin et al, 1969; Simler et al, 1973).

2) The drug has been shown to be an inhibitor of GABA-aminotransferase and succinic semialdehyde dehydrogenase involved in the synthesis and degradation of GABA (Simler et al, 1973; Loscher, 1980; Sawaya et al, 1975), and its effects on GABA have been reported to occur in synaptosomes, primarily in areas of high GABA activity (Iadarola & Gale, 1985d). However, this proposed mechanism of action has been disputed (Rimmer & Richens, 1985d; MacDonald, 1985d). Other hypotheses which have been advanced are: (1) direct effect of the drug on neuronal membranes and (2) reexcitatory transmission by aspartate (Rimmer & Richens, 1985d; Slater & Johnston, 1978). However, no mechanism is adequately supported by experimental data (Rimmer & Richens, 1985d).

3) There is some evidence that valproic acid may inhibit the re-uptake of GABA into the glia and nerve endings (Buckley & Haram, 1984).

B) REVIEW ARTICLES

1) Basic reviews of the treatment of seizures have been written; these include treatment of first seizure and status epilepticus (Willmore, 1998), treatment of the elderly (Rowan, 1998), and management of epilepsy in adults (Feely, 1999; MacDonald, 1985d; MacDonald, 1985d).

2) A comprehensive review concerning the use of valproic acid in psychiatric conditions is available (Davis et al, 2000).

3) The association between valproate therapy and the development of polycystic ovarian syndrome is discussed (Shweizer, 1999).

4) A review of clinical trial data on valproic acid's efficacy in migraine prophylaxis is available (Rothrock, 1997).

5) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy is being revisited (Schneiderman, 1998).

6) The clinical pharmacology, pharmacokinetics, and kinetics of valproic acid in disease states have been extensively reviewed (Bruni & Albright, 1984).

7) An extensive study of first-dose and steady-state pharmacokinetics with valproic acid in children with seizures is available. A detailed case review of the kinetics of valproic acid in neonates is provided (Irvine-Meek et al, 1983).

8) Pharmacokinetics of valproic acid has been reviewed (Zaccara et al, 1988).

9) The treatment of pediatric malignant glioma with valproic acid has been reviewed (Driever et al, 1999).

10) The clinical studies evaluating the efficacy of valproic acid in bipolar disorder have been reviewed (Guay, 1999).

4.5 Therapeutic Uses

Valproic Acid

Divalproex Sodium

Valproate Sodium

4.5.A Valproic Acid

Absence seizure, Simple and complex

Alcohol hallucinosis

Behavioral syndrome - Dementia

Bipolar disorder

Brain injury; Prophylaxis - Seizure
Chorea
Cluster headache
Complex partial epileptic seizure
Dementia
Febrile seizure
Hiccoughs
Hiccoughs, Intractable
Mania
Manic bipolar I disorder
Mental disorder - Mood disorder
Migraine; Prophylaxis
Myelodysplastic syndrome
Myoclonic seizure
Myoclonus
Nelson syndrome
Obsessive-compulsive disorder
Panic disorder
Periodic limb movement disorder
Sedative withdrawal delirium
Seizure, Multiple seizure types; Adjunct
Social phobia
Stiff-man syndrome
Tinnitus
Visual hallucinations

4.5.A.1  Absence seizure, Simple and complex
FDA Labeled Indication
  a) Overview
      FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
      Efficacy: Adult, Effective; Pediatric, Effective
      Recommendation: Adult, Class Ila; Pediatric, Class Ila
      Strength of Evidence: Adult, Category B; Pediatric, Category B
      See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
  b) Summary:
Valproic acid is indicated as adjunct or monotherapy for patients with simple and complex absence seizures. Results of several clinical studies have shown that sodium valproate is effective in patients with seizures (petit mal seizures) with response rates approaching 100% (Rimmer & Richens, 1985g). Results involving 354 patients indicate there is at least a 75% reduction in seizure frequency in about 66% of patients (Herrmann, 1998). Ethosuximide was subsequently adjusted based upon seizure response (maximum plasma levels of 700 micromoles/liter). I responding to monotherapy, the EEG normalized completely in 4, with a 95% reduction in epileptic discharges remaining two. In these patients, a valproic acid serum level of 440 to 660 micromoles/liter was required 50% reduction of seizures (Braathen et al, 1988). It is suggested that valproic acid is a reasonable alternative in children when ethosuximide has failed.

**4.5.A.2 Alcohol hallucinosis**

a) **Overview**

- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence favors efficacy
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) **Summary**

Valproate was effective for the treatment of acute alcohol hallucinosis in a randomized, double-blind conducted in 40 patients (Aliyev & Aliyev, 2008).

c) **Adult**

1) Valproate, in the form divalproex sodium, is effective and well-tolerated for the treatment of acute alcohol hallucinosis. In a randomized, double-blind, placebo-controlled study of 40 men. Within 24 hours of hospital admission initiated with valproate or placebo, increasing over 3 days from 1000 mg to 3000 mg in 3 divided doses. Evaluated using the Positive and Negative Syndrome Scale (PANSS) subscale for verbal hallucinosis (scale 7 being the most severe), with response defined as at least 50% improvement from baseline after 10 days. Study subjects consumed an average of 200 to 300 grams of ethanol per day, and had a history of 10+/+ abuse. Baseline, the mean PANSS verbal hallucinosis subscale scores were 6 +/− 2.3 and 5.9 +/− 0.6 and placebo group, respectively. Based on an intent-to-treat analysis, the mean PANSS score for valproate was lower (p=0.001). Secon of response based on the Clinical Global Impression (CGI) determined that 73.68% of valproate-treated patients were considered “much” or “very much” improved compared to 26.31% of placebo-treated patients (p less than 0.001) (Aliyev & Aliyev, 2008).

**4.5.A.3 Behavioral syndrome - Dementia**

a) **Overview**

- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence is inconclusive
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) **Summary**

In an open study, valproic acid therapy provided some improvement in 50% of dementia patients with Alzheimer’s disease, vascular dementia, or Lewy body dementia. Valproic acid was initiated at 250 milligrams daily and titrated upward for a 2- to 5-week treatment duration. Valproic acid decreased behavioral disturbances in 5 of 10 elderly subjects with dementia in an open-label trial (Kasckow et al, 1997). Benefit was shown in a retrospective chart review of 25 elderly patients with dementia who received valproic acid alone or in addition to a neuroleptic for behavioral disturbances (Narayan & Nelson, 1997).

c) **Adult**

1) In an open study, valproic acid therapy provided some improvement in 50% of dementia patients with Alzheimer’s disease, vascular dementia, or Lewy body dementia. Valproic acid was initiated at 250 milligrams daily and titrated upward for a 2- to 5-week treatment duration. Valproic acid decreases behavioral disturbances in 5 of 10 elderly subjects with dementia in an open-label trial (Kasckow et al, 1997). Benefit was shown in a retrospective chart review of 25 elderly patients with dementia who received valproic acid alone or in addition to a neuroleptic for behavioral disturbances (Narayan & Nelson, 1997).

2) Valproic acid, initiated at 250 milligrams daily and titrated upward for a 2- to 5-week treatment duration.
behavioral disturbances in 5 of 10 elderly subjects with dementia in an open-label pilot study. The remain
either no change (n=3) or worsened behavior (n=2) (Kascokw et al, 1997).
3) According to a retrospective chart review of 25 elderly patients with dementia who received valproic
addition to a neuroleptic for behavioral disturbances, 56% showed much or very much improvement on t
Impressions (CGI) scale. The average valproic acid dose and serum level was 1650 milligrams/day and 
micrograms/milliliter, respectively (Narayan & Nelson, 1997).

4.5.A.4 Bipolar disorder
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence favors efficacy
   Recommendation: Adult, Class IIb
   Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
   A randomized, partially blinded trial reported improved efficacy with the combination of valproic acid 
   serum level of 50 to 125 micrograms/milliliter) and lithium as compared to lithium alone in 12 subject 
   disorder (Solomon et al, 1997).
   A retrospective review of 36 patients with documented bipolar disorders refractory to lithium, neurole 
   antidepressants, and electroconvulsive treatments who had received valproic acid demonstrated the 
   showed a marked response after the addition of valproic acid (McElroy et al, 1987).
   Valproic acid was effective in bipolar disorder in mentally retarded adults (Sovner, 1989).
   Twelve lithium non-responders suffering from bipolar disorder improved with the addition of valproic 
   1985).

c) Adult:
   1) A randomized, partially blinded trial reported improved efficacy with the combination of valproic acid ( 
   level of 50 to 125 micrograms/milliliter) and lithium as compared to lithium alone in 12 subjects with bipol 
   the time of enrollment, 50% had depression and 50% had mania. After at least 40 weeks average follow-
   combination therapy were significantly less likely to experience a relapse or recurrence, but more likely t 
   to severe adverse effect(s) than patients on lithium monotherapy (Solomon et al, 1997).
   2) Valproic acid was useful in 5 cases of bipolar disorder in mentally retarded adults (1 patient with Frag 
   with autistic disorder, two with rapidly cycling illness). Valproic acid was used in doses of 1000 to 2000 mg 
   maintain blood levels in the usual therapeutic serum range of 50 to 100 mcg/mL. In 4 of these cases, the 
   antipsychotic medications was continued. Four of the 5 patients showed a significant response to valpro 
   improvements in sleep cycle, maladaptive behaviors, distractibility and assaultiveness; the other patient 
   a moderate response. Antipsychotic medications were successfully tapered or discontinued in all of the p 
   1989).
   3) A retrospective review of 36 patients with documented bipolar disorders refractory to lithium, neurolep 
   antidepressants, and electroconvulsive treatments who had received valproic acid demonstrated that 44% 
   showed a marked response after the addition of valproic acid . A therapeutic response was generally see 
   after attaining therapeutic levels (50 to 100 milligrams/liter) (McElroy et al, 1987).
   4) Twelve lithium non-responders suffering from bipolar disorder improved with the addition of valproic a 
   received valproic acid alone as he did not tolerate lithium) . Initial Inpatient Multidimensional Psychiatric 
   scores were reduced by an average of 49.6%, and the average improvement ratio comparing the course 
   valproic acid treatment with prior lithium prophylaxis was 5.3; ratios greater than 1 reflect improvement (I 

4.5.A.5 Brain injury; Prophylaxis - Seizure
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence is inconclusive
   Recommendation: Adult, Class III
   Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
   Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures follow 
   brain injury in a randomized study (n=379); however, there was a trend towards increased mortality 
   groups (Temkin et al, 1999).

c) Adult:
   1) Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures follow 
   injury in a randomized study (n=379); however, there was a trend towards increased mortality in the val 
   Within 24 hours of injury, 24 patients (ages 14 years and older) were randomized to receive either phenyto 
   (n=132), valproic acid for 1 month (n=120), or valproic acid for 6 months (n=127). A phenytoin loading dc 
   administered at 20 milligrams/kilogram (mg/kg) intravenously (IV) followed by maintenance dosing at 5 n 
   into 2 doses. A valproic acid loading dose was given at 20 mg/kg intravenously followed by a maintainan 
   mg/kg/day divided into 4 doses. Plasma concentrations of each drug were followed and adjusted to ther 
   Early seizures occurred in 1.5% of the phenytoin treated patients and in 4.5% of the combined valproic a 
   significant). There was also no significant difference in the occurrence of late seizures. The death rate af 
   13.4% for the combined valproic acid groups and 7.2% for the phenytoin group (p=0.07). The authors co
lack of any additional benefit from valproic acid over phenytoin, and the possibly higher mortality rate, suc
d acid should not be routinely used for prevention of posttraumatic seizures (Temkin et al, 1999).

4.5.A.6 Chorea
a) Overview
   - FDA Approval: Adult, no; Pediatric, no
   - Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence favors efficacy
   - Recommendation: Adult, Class IIb; Pediatric, Class IIb
   - Strength of Evidence: Adult, Category C; Pediatric, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Valproic acid was reported effective in the treatment of 5 patients with Sydenham's chorea (Dhanaraj et al, 2002).
c) Adult:
   1) Valproic acid in doses of 15 to 25 milligrams/kilogram/day was reported effective in the treatment of 5
Sydenham's chorea, resulting in disappearance of choreic movements within 10 days (Dhanaraj et al, 1997).
d) Pediatric:
   1) Valproic acid was found to be safe and effective in the treatment of choreic movements in 7 pediatric
female; 12.4 +/- 1.5 years old) with Sydenham's chorea in an open-label trial. The children received 20 to
25 milligram per day of sodium valproate. Onset of clinical improvement was 8 +/- 4 days; time to complete r
choreic movements was 10.1 +/- 8.5 weeks; and the duration of treatment was 4.3 +/- 2.8 months. Ther
rate of 14.3% and no adverse drug events were reported during the trial (Genel et al, 2002).

4.5.A.7 Cluster headache
a) Overview
   - FDA Approval: Adult, no; Pediatric, no
   - Efficacy: Adult, Evidence favors efficacy
   - Recommendation: Adult, Class IIb
   - Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Valproic acid was effective in 2 case reports of patients with cluster headaches with migraine-like fe
1998).
c) Adult:
   1) Two patients with cluster headache and prominent migraine-like features had their headaches remit v
use. Both patients had been unresponsive to multiple medications and one to surgical interventions. The
man with a 15-year history of cluster headaches with an atypical visual aura, received divalproex 500 mil
daily. Headache remission occurred within 2 months. Divalproex was tapered after 9 months and he rem
The second, a 55-year-old man with a 16-year history of cluster headaches along with migraine without a
divalproex 250 mg 3 times daily with 750 mg nightly. Headache remission occurred within 2 months. He
tapered down to 375 mg daily (Wheeler, 1998).
   2) Sodium valproate (600 to 1200 milligrams/day in divided doses) has also been effective in a small se
the treatment of cluster headache (Kuritzky & Hering, 1987).

4.5.A.8 Complex partial epileptic seizure
FDA Labeled Indication
a) Overview
   - FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
   - Efficacy: Adult, Effective; Pediatric, Effective
   - Recommendation: Adult, Class IIA; Pediatric, Class IIa
   - Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Valproic acid is indicated as monotherapy and adjunctive therapy for complex partial seizures occur
in association with other types of seizures (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006
STAVZOR(R) delayed release oral capsules, 2008).
In a dose-comparison study of valproate monotherapy in 265 patients converted from other antiepile
either no change or a reduction in complex partial seizure rates in 54% and 64% of patients on low-
dose valproate monotherapy, respectively (Prod Info STAVZOR(R) delayed release oral capsules, 2
DEPAKENE(R) oral capsules, oral syrup, 2006).
In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conc
(target level 80 to 150 micrograms/milliliter) reduced seizure frequency of complex partial seizu
secondarily generalized tonic-clonic seizures (p=0.018) better than those assigned to low concentra
(target range of 25 to 50 micrograms/milliliter)(Beydoun et al, 1997e).
In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the use
adjunctive therapy was more effective in reducing the incidence of seizure compared with placebo (I STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKENE(R) oral capsules, oral syr
1. Monotherapy

1) In a dose-comparison study of valproate monotherapy in 265 patients converted from other antiepileptic drugs, the incidence of partial complex partial seizures in the high-dose group was significantly reduced compared to placebo (p<0.001) and secondarily generalized tonic-clonic seizures (p<0.018) better than those assigned to placebo (target range of 25 to 50 micrograms/milliliter). Participating patients had partial epileptic seizures at least 2 complex partial seizures per month, with or without secondarily generalized tonic-clonic seizures, maintained on a therapeutic level of another antiepileptic drug. They were randomly assigned to high or low concentration of valproate (n=96) or low concentration valproate (n=47) with an 8-week dosage adjustment period. At baseline, there was a 30% median reduction in complex partial seizures for patients in the high group compared with a 22% increase in the low group. The authors conclude that the efficacy of valproate is comparable to other antiepileptic drugs.

2) Adjunctive Therapy

a) In a 16-week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the use of valproate was more effective in reducing the incidence of seizures compared with placebo. Patients who experienced 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or phenytoin randomized to add-on therapy with either valproate (n=75) or placebo (n=69). The results at 16 weeks demonstrated a greater reduction in seizures in the high-dose group (13.2 seizures at baseline to 8.6 seizures at endpoint) compared to the low-dose group (14.2 seizures at baseline to 13.8) (p<0.05). It should be noted that there was no control group in this study, and less than 50% of the patients randomized completed the study. STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006.

4.5. A.9 Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5. A.10 Febrile seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence is inconclusive
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary

The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-term both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam 6 months to 5 years with 1 or more simple febrile seizures even though there is evidence that both a reducing the risk of recurrence (Steering Committee on Quality Improvement and Management, Sub Febrile Seizures American Academy of Pediatrics, 2008).

Valproic acid has been as effective as phenobarbital for prophylaxis of febrile seizures, with a lower rate of recurrence (Herranz et al, 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980).

1. The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-term both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam in months to 5 years with 1 or more simple febrile seizures even though there is evidence that both are efficacious and safe.

2. The risk of recurrence is high, and there is evidence that both drugs are effective in reducing the risk of recurrence. The rationale behind the lack of recommendation is because the number of children with febrile seizures in the first few years of life is extremely high but the associated risks are benign, and there is evidence that both drugs are effective in reducing the risk of recurrence.

3. The use of antiepileptic drugs has high potential for adverse effects and the development of future epilepsy. The use of antiepileptic drugs has high potential for adverse effects and the development of future epilepsy.
intermittent diazepam as well as the risk of masking an evolving central nervous system infection, such as meningitis. Therefore, the AAP does not recommend either continuous or intermittent anticonvulsant therapy due to toxicities associated with these agents outweigh the low risks associated with simple febrile seizures (Steinon Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics, 1995).

2) Valproic acid has been as effective as phenobarbital for prophylaxis of febrile seizures, with a lower incidence of side effects (Herranz et al., 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980). However, phenobarbital is often the agent of choice (despite its propensity to cause behavioral abnormalities) due to the hepatotoxic potential of valproic acid (Richens, 1985g; Addy, 1981). In general, use of anticonvulsant agents for febrile seizures remains contraindicated.

4.5.A.11 Hiccoughs

See Drug Consult reference: HICCUPS - ETIOLOGY AND TREATMENT

4.5.A.12 Hiccoughs, Intractable

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Five patients with incapacitating, intractable hiccups were successfully treated with valproic acid, after granulated sugar, carbamazepine, chlorpromazine, and nasopharyngeal stimulation had failed. Valproic acid was initiated with 15 milligrams/kilogram/day in divided doses. The dose was gradually increased by 250 mg until hiccups ceased or side effects occurred. Symptoms were eliminated in 4 patients and markedly improved in the 5th patient; however, therapy was discontinued after 6 weeks in the fifth patient due to mild gastrointestinal side effects. Valproic acid was also effective in the treatment of severe kleptomania and mixed mania refractory to fluoxetine in a 36-year-old female (Kmetz et al., 1997).

c) Adult:

1) Five patients with incapacitating, intractable hiccups were successfully treated with valproic acid, after granulated sugar, carbamazepine, chlorpromazine, and nasopharyngeal stimulation had failed. Valproic acid was initiated with 15 milligrams/kilogram/day in divided doses. The dose was gradually increased by 250 mg until hiccups ceased or side effects occurred. Symptoms were eliminated in 4 patients and markedly improved in the 5th patient; however, therapy was discontinued after 6 weeks in the fifth patient due to mild gastrointestinal side effects. Valproic acid was also effective in the treatment of severe kleptomania and mixed mania refractory to fluoxetine in a 36-year-old female (Kmetz et al., 1997).

4.5.A.13 Mania

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class III
Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid was successful in treating AIDS-related mania in 2 cases (RachBeisel & Weintraub, 1997). Valproic acid may reduce the frequency, number, and severity of manic episodes in patients with schizoaffective disorders (Puzynski & Klosiewicz, 1984).

Valproic acid was effective in the treatment of severe kleptomania and mixed mania refractory to fluoxetine in a 36-year-old female (Kmetz et al., 1997).

c) Adult:

1) During the 26 to 51 months of valproic acid treatment of 15 patients with affective and schizoaffective disorders, the number of manic episodes was reduced. In all patients, the number of hospital admissions dropped from 10 in 2000 to 96 in 2004 (Puzynski & Klosiewicz, 1984).

2) Valproic acid, titrated to a serum level of 94 to 110 micrograms/mL, successfully treated AIDS-related mania in 2 cases (RachBeisel & Weintraub, 1997).

3) Valproic acid 2000 milligrams/day was effective in the treatment of severe kleptomania and mixed mania refractory to fluoxetine in a 36-year-old female (Kmetz et al., 1997).

4.5.A.14 Manic bipolar I disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Stavzor(R) only); Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid, delayed-release ((Stavzor(R)) is indicated for the treatment of the manic episodes of bipolar disorder in adults (Prod Info STAVZOR(R) delayed release oral capsules, 2008). In two 3-week, placebo-controlled, parallel-group studies, valproate had significantly superior results.
of assessed outcomes for acute mania compared with placebo (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

Valproic acid has been effective in treating mania associated with bipolar disorder in clinical studies (Brown, 1989; Post, 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989; Pope et al, 1988; Grunze Prasad, 1984).

Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established in an open study, double-blind, placebo controlled trial (n=150; 76 on valproate) (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) Adult:
1) In two 3-week, placebo-controlled, parallel-group studies, valproate had significantly superior results in assessed outcomes for acute mania compared with placebo. In both studies, patients were initiated with milligrams (mg) orally three times a day and adjusted to achieve serum valproate levels in the range of 5 micrograms/milliliter (mcg/mL) in study 1, and 40 to 150 mcg/mL in study 2. At the completion of the study, receiving a mean dose of 2402 mg/day in study 1 and a mean dose of 2006 mg/day in study 2. The percent who achieved a 30% or greater reduction in baseline in symptom scores in the valproate group compared to the placebo group was 60% vs 26% in study 1, and 58% vs 29% in study 2 (p less than 0.05 for each valproate group compared to placebo group) (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
2) Valproic acid, delayed-release is indicated for the treatment of the manic episodes associated with bipolar disorder in adults (Prod Info STAVZOR(R) delayed release oral capsules, 2008). Valproic acid is effective in the treatment of bipolar disorder, even in those who have failed conventional therapy (Fawcett, 1989; Brown 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989), and in bipolar disorder secondary to head injury (1988).
3) Four out of 5 acutely manic patients responded to intravenous valproate loading in an open study. Four patients received valproate 1200 or 1800 milligrams on day 1 followed by dosage individualization based on side effects (mean baseline Bech-Rafaelsen Mania Rating Scale score was 30.2 which improved to 8 by day 5. One patient was unresponsive to oral valproate. On day 5 most were switched to oral dosing. The authors believe that intravenous loading a quick saturation of plasma-binding proteins occurred which could have contributed to the efficacy (Grunze et al, 1999).
4) One uncontrolled study reported improvement in 5 of 7 patients with mania given valproic acid (up to 1800 mg) daily for 6 weeks. All patients had not responded to previous therapy with lithium and neuroleptics (Prasad et al, 1999).

d) Pediatric:
1) Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established in an open study, double-blind, placebo controlled trial (n=150; 76 on valproate). Children 10 to 17 years of age with bipolar disorder received an initial daily dose of valproate of 15 milligrams/kilogram (mg/kg)(max 750 mg daily) dosing used to achieve a clinical response and/or target serum valproate level of 80 to 125 mcg/mL with a mean baseline Bech-Rafaelsen Mania Rating Scale score at baseline of 86.9. Change from baseline on the YMRS scale at final evaluation was the primary efficacy end point (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

4.5.A.15 Mental disorder - Mood disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class IIb; Pediatric, Class IIb

Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Although data is limited, valproic acid appears useful in the management of affective disorders in mentally retarded children and adults (Kastner et al, 1990; Sovner, 1989).

c) Adult:

1) Although data is limited, valproic acid appears useful in the management of affective disorders in mentally retarded children and adults. Valproic acid was noted in studies to have advantages over carbamazepine, lithium, antipsychotics for use in mentally retarded patients since it does not carry the same risks of tremor, inco-ordination, worsening of mood, and increased seizures associated with other classes of medication (Kastner et al, 1990; Sovner, 1989).

2) Valproic acid was useful in 5 cases of bipolar disorder in mentally deficient adults (1 patient with Fragile X syndrome, 2 with rapidly cycling illness). Valproic acid was used in doses of 1000 to 2000 mg/day maintain blood levels in the usual therapeutic serum range of 50 to 100 mcg/mL. In 4 of these cases, the antipsychotic medications was continued. Four of the 5 patients showed a significant response to valproic acid with improvements in sleep cycle, maladaptive behaviors, distractibility and assaultiveness; the other patient showed a moderate response. Antipsychotic medications were successfully tapered or discontinued in all of the other cases (Kastner et al, 1990; Sovner, 1989).

d) Pediatric:

1) Significant improvement was seen with valproic acid in mentally deficient children and adolescents with bipolar disorder characterized by irritability, aggressiveness, self-injurious behavior, hyperactivity and sleep disturbances. Valproic acid symptoms had been unresponsive to previous therapy or the patient had been unable to tolerate side effects with previous medications. Valproic acid 1500 to 3000 milligrams daily, at blood levels of 78 to 111 mcg/mL
significant improvement in all 3 patients (Kastner et al, 1990).

4.5.A.16 Migraine; Prophylaxis
FDA Labeled Indication
a) Overview
   FDA Approval: Adult, yes (Stavzor(R) only); Pediatric, no
   Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy
   Recommendation: Adult, Class IIb; Pediatric, Class IIb
   Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Valproic acid, delayed-release (Stavzor(R)) is indicated for prophylaxis of migraine in adults (Prod lr
delayed release oral capsules, 2008).
   Two multicenter, randomized, placebo-controlled clinical trials established the efficacy of valproate f
migraine headache (Prod Info STAVZOR(R) delayed release oral capsules, 2008).
   Valproic acid in doses adjusted to produce trough valproate concentrations of 70 to 120 milligrams/li
effective in the prophylaxis of migraine headache in a double-blind trial (n=107) (Mathew et al, 1995
A 12-week controlled study (n=176) demonstrated that 44% of valproic acid-treated patients had a l
reduction in migraine frequency, as compared to 21% of placebo-treated patients (Mathew, 1997).
Valproic acid has been effective as prophylaxis against migraine headache (common and classic) (§
Efficacy of valproate was not established for migraine prophylaxis in a single, double-blind, placebo-
parallel-group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1000 mg) study (n=30c
valproate) in pediatric patients ages 12 to 17 years old (Prod Info STAVZOR(R) delayed release oral
Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophylax
children (Hamalainen, 1998).
See Drug Consult reference: MIGRAINE - RECOMMENDATIONS FOR TREATMENT IN CHILDREN AN
ADOLESCENTS
c) Adult:
   1) Two multicenter, randomized, placebo-controlled clinical trials established the efficacy of valproate fo
migraine headache. In both trials, patients with a history of migraine with or without aura (of at least 6 mc
who were experiencing at least 2 migraine headaches a month during the previous 3 months were recru
following a 4-week single-blind placebo baseline period, patients were randomized to valproate or pl ace
reatment phase, comprised of a 4-week dose titration followed by an 8-week maintenance period. In the
aged 26 to 73 years), 90 patients completed the 8-week maintenance period. Patients in the valproate gr
with doses ranging from 500 to 2500 milligrams (mg) with a mean treatment dose of 1087 mg/day resulti
trough total valproate level of 72.5 micrograms/milliliter (mcg/mL)(range, 31 to 133 mcg/mL). During the l
the mean 4-week migraine headache rate was 5.7 in the placebo group compared to 3.5 in the valproate
significantly different). In the second study (n=176; aged 17 to 76 years), 137 patients completed the 8-w
period. Patients were randomized equally to one of 3 valproate groups (500, 1000, or 1500 mg/day) or p
were initialized with 250 mg and titrated up every 4 to 8 days to the randomized target dose. The mean t
valproate levels during the treatment period were 39.6, 62.5, and 72.5 mcg/mL in the valproate 500, 100
mg/day groups, respectively. During the treatment phase, the mean 4-week migraine headache rates ad
differences in baseline rates, were 4.5 in the placebo group compared to 3.3, 3, and 3 in the valproate
1500 mg/day groups, respectively, based on intent-to-treat results. Migraine headache rates in the comb
1000/1500 mg group were significantly lower than in the placebo group (Prod Info STAVZOR(R) delayed
capsules, 2008).
   2) Valproic acid in doses adjusted to produce trough valproate concentrations of 70 to 120 milligrams/lit
effective in the prophylaxis of migraine headache. In a double-blind trial, 107 patients were randomized t
either divalproex or placebo for a period of 12 weeks. Forty-eight percent of divalproex-treated patients e
or greater reduction in the frequency of migraine headaches compared to 14% of placebo-treated patient
common side effects noted in patients treated with divalproex were weakness, fatigue, nausea, and vom
only 13% of patients required discontinuation of therapy (Mathew et al, 1995). Another 12-week controlle
 demonstrated that 44% of valproic acid-treated patients had at least a 50% reduction in migraine frequer
21% of placebo-treated patients. This dose-ranging trial also found no significant difference between t
(mg), 1000 mg, or 1500 mg daily dose in preventing migraine (Klapper et al, 1997). An accompanying ec
that valproic acid be considered for migraine prophylaxis in patients with coexisting epilepsy or mania, or
(s) to beta-blockers (Mathew, 1997).
   3) Valproic acid has been effective as prophylaxis against migraine headache (common and classic) . T
in open fashion to 22 patients. Initial doses were 600 milligrams orally twice daily, followed by dosing adj
achieve serum levels of 700 micromilliliter in the morning before the first daily dose. Eleven patients wen
attacks during the duration of follow-up (mean, 6.5 months; range, from 3 to 12 months). Six patients had h
headache frequency, and no effect was observed in 1 patient. Four patients were withdrawn from the st
cooperation. Adverse effects consisted of hepatotoxicity (1 patient), weight gain (3 patients), drowsiness
paresthesias (2 patients who had also used ergotamine suppositories chronically prior to valproic acid) (I
d) Pediatric:
   1) Efficacy of valproate was not established for migraine prophylaxis in a single, double-blind, placebo-c
group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1000 mg) study (n=304; 231 on val
patients ages 12 to 17 years old. The study consisted of a 4 week baseline period followed by a 12 week
period (including an initial 2 week titration period) with placebo compared to each dose. Reduction from 1 week migraine headache rate was the primary efficacy endpoint (Prod Info STAVZOR(R) delayed release 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) Valproic acid 15 to 30 milligrams/kilogram/day divided into 2 doses has been used for the prophylaxis of children. Monitor valproic acid concentrations after 2 to 3 weeks of therapy and after dosage increases. Follow-up should be done with height and weight observations (Hamalainen, 1998).

4.5.A.17 Myelodysplastic syndrome

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Valproic acid monotherapy resulted in a response rate of 44% in 23 patients with myelodysplastic syndrome (Kuendgen et al, 2004).

c) Adult:

1) A 44% response rate was achieved with valproic acid (VPA) monotherapy in 23 patients with myelodysplastic syndromes (MDS) and acute myelogenous leukemia secondary to MDS (sAML/MDS). In an open-label, randomized study, patients, aged 35 to 78 years, with MDS for 3 to 122 months, received daily VPA monotherapy (n=18) or combination with all trans retinoic acid (ATRA) 80 milligrams/meter squared (mg/m2) daily (in two divided doses) for 2 years (n=5). VPA dose was titrated to maintain serum levels between 50 and 100 micromgrams/milliliter (mcg/mL). Patients who failed monotherapy or relapsed were switched to combination therapy. Response was rated according to the International Working Group (IWG) criteria. A response was obsered in patients receiving VPA monotherapy. The median time to response was 30 days (range, 14 to 78 days). The median VPA dose was 1250 mg (range, 900 to 2550 mg) and median duration of 6 months (range, 2 to 15 months). Hematologic improvement was observed in 7 patients and a partial response in 1 patient. Relapse occurred in a median of 4 months, of which, 4 patients were switched to combination therapy. Two of these 4 patients regressed to complete remission after 11 and 16 months. Stable disease was seen in 4 patients at a median duration of 5 months. Patients who failed combination therapy and were switched to combination therapy without success. None of the patients receiving combination therapy initially responded to therapy. Of note, all 3 patients considered low-risk according to the international prognostic scoring system showed a major response, while only 1 patient considered high-risk showed a minor response. Furthermore, 3 of 9 patients with an elevated blast count achieved a significant reduction in blast count. Therapy was well tolerated as one patient discontinued VPA because of vertigo and thrombocytopenia were attributed to study medication in 2 patients (Kuendgen et al, 2004).

4.5.A.18 Myoclonic seizure

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Patients with juvenile myoclonic epilepsy (JME) (n=76) were successfully treated with lower than usual doses of valproic acid, and after a period of 2 years free from seizures, could be maintained on still lower doses (Panagariya et al, 2001).

Combination therapy with valproic acid (1500 to 1800 milligrams of valproic acid daily), clonazepam (6 to 10 mg daily) and phenobarbital (50 to 100 mg daily) was effective in improving severe progressive myoclonic epilepsy in adults in a long clinical study (Iivanainen & Himberg, 1982).

c) Adult:

1) Patients with juvenile myoclonic epilepsy (JME) were successfully treated with lower than usual doses, and after a period of 2 years free from seizures, could be maintained on still lower doses. Seventy-six patients diagnosed with JME, were initially treated with sodium valproate 15 milligrams/kg/day in a double-blind, placebo-controlled study. In those who were not controlled at 40 mg/kg/day, a second drug was added. Sixty-three percent were controlled at the 15 mg/kg/day dose, 25% at 20 mg/kg/day, 4% at 40 mg/kg/day, and 8% required a second drug. After a seizure-free period of 2 years, 22% could be maintained on 3 to 5 mg/kg/day, 33% on 5 to 10 mg/kg/day, and 42% required more than 10 mg/kg/day (Panagariya et al, 2001).

2) Combination therapy with valproic acid (1500 to 1800 milligrams of valproic acid daily), clonazepam (6 to 10 mg daily) and phenobarbital (50 to 100 mg daily) was effective in improving severe progressive myoclonic epilepsy in adults in a long-term prospective clinical study. All previous medications (phenytoin and other antiepileptic agents) were continued at that dose duration with the same dose. Doses were increased to 20 to 40 mg/kg/day in the controlled. In those who were not controlled at 40 mg/kg/day, a second drug was added. Sixty-three percent were controlled at the 15 mg/kg/day dose, 25% at 20 mg/kg/day, 4% at 40 mg/kg/day, and 8% required a second drug. After a seizure-free period of 2 years, 22% could be maintained on 3 to 5 mg/kg/day, 33% on 5 to 10 mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al, 2001).

3) Combination therapy with valproic acid (1500 to 1800 milligrams of valproic acid daily), clonazepam (6 to 10 mg daily) and phenobarbital (50 to 100 mg daily) was effective in improving severe progressive myoclonic epilepsy in adults in a long-term prospective clinical study. All previous medications (phenytoin and other antiepileptic agents) were continued at that dose duration with the same dose. Doses were increased to 20 to 40 mg/kg/day in the controlled. In those who were not controlled at 40 mg/kg/day, a second drug was added. Sixty-three percent were controlled at the 15 mg/kg/day dose, 25% at 20 mg/kg/day, 4% at 40 mg/kg/day, and 8% required a second drug. After a seizure-free period of 2 years, 22% could be maintained on 3 to 5 mg/kg/day, 33% on 5 to 10 mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al, 2001).
4.5.A.19 Myoclonus

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Valproic acid was reported effective in 3 patients with nonepileptic myoclonus (Sotaniemi, 1982).

c) Adult:
1) Valproic acid 900 to 1200 milligrams daily was reported effective in 3 patients with nonepileptic myoclonus and 2 with nocturnal myoclonus. These patients had no epileptic manifestations, no other medications were given. Valproic acid may have a role in the treatment of myoclonus; however, further studies are warranted. The mechanism of action in the condition is unclear (Sotaniemi, 1982).

4.5.A.20 Nelson syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Clinical outcomes have varied in studies on the efficacy of valproic acid in the treatment of Nelson's syndrome. Decreases in circulating ACTH levels have been documented in patients receiving valproic acid alone or in combination with diazepam, cyproheptadine, or metyrapone (Glaser et al, 1984; Buckingham, 1983; Jones et al, 1981; Mercado-Asis et al, 1997a; Loli et al, 1988; Loli et al, 1984). Other studies have failed to find any effects with valproic acid.

c) Adult:
1) Numerous studies have documented the efficacy of valproic acid in the treatment of Nelson's syndrome. Decreases in circulating ACTH levels have been documented in patients receiving valproic acid alone or in combination with diazepam, cyproheptadine, or metyrapone (Glaser et al, 1984; Buckingham, 1983; Jones et al, 1981). Other studies have failed to find any effects with valproic acid.
2) Valproic acid alone or in combination with cyproheptadine failed to suppress plasma adrenocorticotropic hormone (ACTH) secretion in Nelson's syndrome. Six women with Nelson's syndrome had their ACTH measured before, during, and after treatment with valproic acid or in combination with cyproheptadine and bromocriptine. Only bromocriptine caused a significant decrease in plasma ACTH (P < 0.05), as did the combination of the 3 drugs (P < 0.05). However, the combination of bromocriptine, cyproheptadine, and valproic acid did not significantly exceed the effect of bromocriptine alone (Mercado-Asis et al, 1997a).
3) Chronic valproate acid therapy with 600 milligrams/day was effective in reducing the size of an adrenocorticotrophic hormone (ACTH)-secreting pituitary macroadenoma in a patient with Nelson's syndrome (Loli et al, 1988). The patient received 2 courses of therapy with valproic acid lasting 4 months each; both treatments resulted in tumor reduction that was documented by computed tomography. More studies are required to evaluate the efficacy of valproic acid in this clinical setting.
4) Another study failed to show the effectiveness of valproic acid in 8 patients with Nelson's syndrome. Four patients were unaffected by valproic acid administration. They concluded that the GABAergic system plays a role in the ACTH hypersecretion in Nelson's syndrome (Loli et al, 1984).

4.5.A.21 Obsessive-compulsive disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Valproate was effective for obsessive compulsive disorder in 1 case report (Cora-Locatelli et al, 1998).

c) Adult:
1) Valproate was effective for obsessive compulsive disorder in a 35-year-old man who stopped working and was obsessed with touching his parents 70 to 80 times per day. He had previously discontinued fluoxetine due to agitation. Fluoxetine 5 mg was restarted along with valproate 250 milligrams (mg) in the morning and 500 mg at bedtime to alleviate side effects. After 2 weeks he was able to resume work and felt less anxious and more able to control his obsessions (Cora-Locatelli et al, 1998).

4.5.A.22 Panic disorder

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
Valproic acid was effective in a case report of a patient with panic disorder associated with multiple sclerosis. After alprazolam, imipramine, and clonazepam was ineffective, valproic acid titrated to a dose of 1500 mg caused a complete disappearance of symptoms after two months. The patient remained symptom-free (Marazziti & Cassano, 1996).

Sleep quality and duration were improved in 6 outpatients given long-term valproate for periodic limb movement disorder (Ehrenberg et al, 2000).

Sleep quality and duration were improved in 6 outpatients (aged 28 to 62 years, mean 41.5 years) given valproate for periodic limb movement disorder. After a mean 6 months of therapy, doses of valproate 600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep efficiency, significant decrease in stage 1 (light) sleep (p=0.04), significant increases in stages 3 and 4 (deep) sleep change in stage 2 (rapid eye movement-REM) sleep. Mean total sleep time increased from 5.8 to 6.4 hours, trend toward a reduction in the number of periodic limb movements per hour of sleep and in the number arousals (p=0.062). Daytime alertness was subjectively reported to be improved. No subject discontinued the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other due to side effects (Ehrenberg et al, 2000).

Four controlled studies and several case reports and case series suggest that valproate may be effective and benzodiazepine withdrawal (Harris et al, 2000).

Four controlled studies and several case reports and case series suggest that valproate may be efficacious for benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to support the use of benzodiazepine withdrawal. In an open-label study, there were no significant differences in subjective or objective symptoms between valproate- and phenobarbital-treated patients, nor were there differences in blood pressure responses associated with the 2 agents. In another comparative study, valproate and clormethiazole have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented. A double-blind trial might have supported this use of valproate, but dismissed the treatment drug (valproate) because of association with GI distress (probably related to use of the valproic acid form of the drug). In a study, corr and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ethanol withdrawal report, two manic schizoaffective patients had successful withdrawal from ethanol when valproate 20 milligrams/kilogram/day was combined with low-dose lorazepam. A patient with panic disorder failed to clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdrawal during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Two reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

Valproic acid is indicated as adjunctive therapy for multiple seizure types (Prod Info DEPAKENE(R) syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008). Valproic acid, orally or rectally, was reported effective in preventing generalized tonic-clonic seizures and multiple seizure types; Adjunct

Valproic acid was effective in a case report of a patient with panic disorder associated with multiple sclerosis. After alprazolam, imipramine, and clonazepam was ineffective, valproic acid titrated to a dose of 1500 mg caused a complete disappearance of symptoms after two months. The patient remained symptom-free (Marazziti & Cassano, 1996).

Sleep quality and duration were improved in 6 outpatients given long-term valproate for periodic limb movement disorder (Ehrenberg et al, 2000).

Sleep quality and duration were improved in 6 outpatients (aged 28 to 62 years, mean 41.5 years) given valproate for periodic limb movement disorder. After a mean 6 months of therapy, doses of valproate 600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep efficiency, significant decrease in stage 1 (light) sleep (p=0.04), significant increases in stages 3 and 4 (deep) sleep change in stage 2 (rapid eye movement-REM) sleep. Mean total sleep time increased from 5.8 to 6.4 hours, trend toward a reduction in the number of periodic limb movements per hour of sleep and in the number arousals (p=0.062). Daytime alertness was subjectively reported to be improved. No subject discontinued the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other due to side effects (Ehrenberg et al, 2000).

Four controlled studies and several case reports and case series suggest that valproate may be efficacious and benzodiazepine withdrawal (Harris et al, 2000).

Four controlled studies and several case reports and case series suggest that valproate may be efficacious for benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to support the use of benzodiazepine withdrawal. In an open-label study, there were no significant differences in subjective or objective symptoms between valproate- and phenobarbital-treated patients, nor were there differences in blood pressure responses associated with the 2 agents. In another comparative study, valproate and clormethiazole have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented. A double-blind trial might have supported this use of valproate, but dismissed the treatment drug (valproate) because of association with GI distress (probably related to use of the valproic acid form of the drug). In a study, corr and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ethanol withdrawal report, two manic schizoaffective patients had successful withdrawal from ethanol when valproate 20 milligrams/kilogram/day was combined with low-dose lorazepam. A patient with panic disorder failed to clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdrawal during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Two reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

Valproic acid is indicated as adjunctive therapy for multiple seizure types (Prod Info DEPAKENE(R) syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008). Valproic acid, orally or rectally, was reported effective in preventing generalized tonic-clonic seizures and multiple seizure types; Adjunct
withdrawal of anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnostic purposes (Rosenfeld et al, 1987). Valproic acid has been demonstrated effective in a variety of seizure types which include absence seizures, and tonic-clonic seizures (grand mal), including patients who have been unresponsive to other anticonvulsants (Rimmer & Richens, 1985g; Sato et al, 1982a; Jeavons et al, 1977).

c) Adult:
   1) General Information
      a) Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types such as generalized epilepsy (Rimmer & Richens, 1985g; AMA Department of Cerebral Palsy Committee, 1985). Valproic acid has been effective in preventing generalized tonic-clonic seizures following withdrawal of anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnostic and therapeutic purposes (Rimmer & Richens, 1985g; Sato et al, 1982a; Jeavons et al, 1977); however, carbamazepine is generally preferred because of improved tolerability and the lower incidence of side effects (Young & Koda-Kimble, 1995a).

   2) Clinical Trials
      a) Valproic acid in loading doses of approximately 12.5 milligrams/kilogram (mg/kg), orally or rectally (Young & Koda-Kimble, 1995a) twice daily, was reported effective in preventing generalized tonic-clonic seizures following withdrawal of anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnostic and therapeutic purposes (Rimmer & Richens, 1985g; Sato et al, 1982a; Jeavons et al, 1977). Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types. Valproic acid was demonstrated effective in a variety of seizure types which include absence seizures, partial seizures (grand mal), including patients who have been unresponsive to other anticonvulsants. The more effective in generalized epilepsy than partial seizures, and appears most useful for the treatment of absence seizures (petit mal) and photosensitive epilepsy (Rimmer & Richens, 1985g; Sato et al, 1982a; Jeavons et al, 1977). Although valproic acid is considered a first-line therapy for treating generalized tonic-clonic seizures or complex partial seizures, carbamazepine is generally preferred because of its lesser toxicity. Ethosuximide is generally preferred over valproic acid for treatment of absence seizures because it is equally effective and better tolerated (Young & Koda-Kimble, 1995a). Oral and rectal valproic acid have been effective in refractory epilepsy (Vajda et al, 1977; Manhire & Espir, 1974). The drug is usually combined with other anticonvulsants to produce seizure reduction in 75 to 100% in greater than 40% of patients with intractable epilepsy, as improvement being seen in myoclonic seizures, absence seizures and grand mal seizures (Simon & Seidenberg, 1983; Covanis et al, 1982a; Callaghan et al, 1982a; Shakir et al, 1981).

c) In 52 severely brain damaged (mental retardation) patients with intractable seizures, valproic acid was more effective than sodium valproate in improving seizure control (Young & Koda-Kimble, 1995a). Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types. Valproic acid has been demonstrated effective in a variety of seizure types which include absence seizures, partial seizures (grand mal), including patients who have been unresponsive to other anticonvulsants.

4.5.A.26 Social phobia
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence favors efficacy
   Recommendation: Adult, Class III
   Strength of Evidence: Adult, Category B

   See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
   Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxiety disorder (Kinrys et al, 2003).

c) Adult:
   1) Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxiety disorder (Kinrys et al, 2003). Valproic acid therapy was initially dosed at 250 milligrams (mg) twice daily, with tolerated, doses were increased to 1000 mg daily. Doses were adjusted according to tolerability and therapeutic response. The rectal route appears to have a place in the treatment of patients unable to take oral agents (Rosenfeld et al, 1987). Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxiety disorder (Kinrys et al, 2003).

4.5.A.27 Stiff-man syndrome
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence is inconclusive
   Recommendation: Adult, Class IIb
   Strength of Evidence: Adult, Category C

   See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Sodium valproate showed efficacy for stiff man syndrome in one case report (Spehlmann et al, 1981).

c) Adult:
1) Stiff man syndrome was described in a 55-year-old male which was poorly treated by diazepam 130 mg, clonazepam 18 mg, and baclofen 60 mg in divided doses each day. Valproate was gradually added to the increased to a dose of 2 grams daily. The patient showed marked improvement and was able to walk without his cane. Although the effectiveness of sodium valproate is only cited in one case report, it did trials for this indication (Spehlmann et al, 1981).

4.5.A.28 Tinnitus
See Drug Consult reference: DRUG THERAPY OF TINNITUS

4.5.A.29 Visual hallucinations
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence is inconclusive
   Recommendation: Adult, Class III
   Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
   Valproic acid was efficacious in controlling visual hallucinations associated with Charles Bonnet syndromes (Hori et al, 2000).

c) Adult:
1) Two psychologically normal elderly women (ages 73 and 77) experiencing complex visual hallucinations due to sensory deprivation (decreased visual acuity) and mild cerebral dysfunction were successfully treated with 400 milligrams (mg) to 800 mg daily. The 73-year-old had partial resolution of symptoms at 400 mg daily and disappearance of all hallucinations with 800 mg daily. The 77-year-old woman was started on 200 mg daily increased to 400 mg daily, at which point she was able to sleep and experienced no more hallucinations. She experienced adverse effects (Hori et al, 2000).

4.5.B Divalproex Sodium

Absence seizure, Simple and complex

Alcohol withdrawal syndrome

Behavioral syndrome - Dementia

Bipolar I disorder, Maintenance

Bipolar II disorder, Maintenance

Borderline personality disorder

Brain injury - Seizure; Prophylaxis

Cluster headache

Complex partial epileptic seizure

Headache disorder, chronic

Manic bipolar I disorder

Migraine; Prophylaxis

Panic disorder

Periodic limb movement disorder

Pervasive developmental disorder
Posttraumatic headache
Schizoaffective disorder, bipolar type
Sedative withdrawal delirium

4.5.B.1 Absence seizure, Simple and complex
FDA Labeled Indication
a) Overview
   FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
   Efficacy: Adult, Effective; Pediatric, Effective
   Recommendation: Adult, Class IIa; Pediatric, Class IIa
   Strength of Evidence: Adult, Category B; Pediatric, Category B
   See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Indicated in adults and children age 10 years and older as monotherapy or adjunctive therapy for simple absence seizures occurring in isolation and as adjunctive therapy for simple and complex absence seizures in association with other types of seizures (Prod Info DEPAKOTE(R) ER extended-release oral tablet, DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2008).

4.5.B.2 Alcohol withdrawal syndrome
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence favors efficacy
   Recommendation: Adult, Class IIb
   Strength of Evidence: Adult, Category B
   See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   May be effective for treatment of alcohol withdrawal and prevention of relapse (Reoux et al, 2001a; Le Grange et al, 2001b).
   c) Adult:
      1) Divalproex sodium was more effective than placebo in decreasing the need for oxazepam during moc withdrawal. Thirty-six subjects (75% white, 97% male) with a score of at least 10 on the Clinical Institute Assessment-Alcohol revised instrument (CIWA-Ar) completed this 7-day, randomized, double-blind, placebo-controlled study. All patients received an initial 30 milligram (mg) dose of oxazepam; additional 30 mg doses of oxazepam were given every hour if the subject's CIWA-Ar score was 10 or higher. The divalproex group received 500 mg of divalproex sodium (sprinkle formulation) three times a day in addition to the oxazepam. The divalproex group required significantly less oxazepam than the placebo group (85 +/- 63.64 mg vs. 111.7 +/- 119.5 mg, respectively) to manage withdrawal symptoms. Six percent (1 of 18) of subjects in the divalproex group and 40% (7 of 18) of the placebo group had an increase in withdrawal symptoms (1 point and 3 points respectively) compared to baseline. Advantages of divalproex over benzodiazepines for the treatment of alcohol withdrawal include its lack of abuse potential and absence of synergistic reactions with alcohol, and, in contrast to other anticonvulsants, divalproex can be initiated with an oral loading dose to effect a rapid onset of action (Lo 3d et al, 2001a).
      2) A 51-year-old man with a 30-year history of heavy drinking was successfully withdrawn from alcohol through divalproex detoxification. On admission, he was found to meet diagnostic criteria for alcohol dependency (DSM-IV), and had no other mental or physical co-morbidities. His laboratory results revealed elevated liver enzymes and an increased mean corpuscular volume. He had no other mental or physical co-morbidities. According to the author, advantages of divalproex over benzodiazepines for the treatment of alcohol withdrawal include its lack of abuse potential and absence of synergistic reactions with alcohol, and, in contrast to other anticonvulsants, divalproex can be initiated with an oral loading dose to effect a rapid onset of action (Lo 3d et al, 2001a).

4.5.B.3 Behavioral syndrome - Dementia
a) Overview
   FDA Approval: Adult, no; Pediatric, no
   Efficacy: Adult, Evidence is inconclusive
   Recommendation: Adult, Class IIb
   Strength of Evidence: Adult, Category B
   See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   Benefit was shown in a retrospective review (Showalter & Kimmel, 2000).
c) Adult:
1) In a retrospective chart review (n=29), divalproex was found to improve symptoms of agitation in patients 48.2 years; range, 13 to 89 years) who had suffered acute brain injury and were recovering in a brain injury unit. All subjects had agitation unsuccessfully controlled on prior benzodiazepine therapy, with or without Overall, 18 of 29 (62%) were rated as having significantly improved or decreased agitation symptoms resolution of symptoms within 7 days after reaching a mean daily divalproex dose of 1257 milligrams (mg) doses in this group showed a wide range: 250 (n=1), 750 (n=1), 1000 (n=5), 1125 (n=1), 1250 (n=2), 150 mg (n=2). In another subgroup (n=8, 28%), rapid resolution of agitation to near total recovery occurred with dose of 714 mg divalproex and no other psychoactive medications. Divalproex was soon discontinued in recurrence of agitation. Most patients (93%) were discharged to their home or community sites. One patient response to divalproex and in 2 cases, lethargy was worsened and the drug was withdrawn (Showalter &

4.5.B.4 Bipolar I disorder, Maintenance
a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Divalproex may be effective for mania or mixed episodes associated with bipolar I disorder in children (2005)

b) Pediatric:
1) Divalproex sodium may be effective for mixed manic episodes associated with bipolar I disorder, as an open-label, time-series study. Patients (n=35; mean age 12.3 +/-3.7 years) with a diagnosis of mixed episode disorder and greater than 20 on the Young Mania Rating Scale (YMRS) were offered divalproex treatment up to 6 months. The treatment protocol consisted of divalproex sodium at an initial dose of 250 to 500 mg to achieve target doses of 15 to 20 mg/kg/day and serum concentrations of 50 to 120 micrograms/milliliter. Risperidone, benzotriazine, and trazodone were allowed for limited treatment of breakthrough symptoms. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulants at a stable dose. The response was defined as at least a 50% change from baseline on YMRS and no more than 40 on the CDRS-R. Remission was defined as at least a 50% change from baseline on YMRS and no more than 12 on the Clinical Global Impression Scale for Bipolar Disorder (CGI-BP; 1 improved, 2 = much improved) and at least 51 on the Children's Global Assessment of Functioning Scale. Subject dropped out of the study due to worsening of symptoms prior to follow-up; therefore, the final sample size was 34 patients. The mean YMRS score decreased from approximately 30 at baseline to approximately 12 at treatment (p < 0.001). The mean CDRS-R score decreased from approximately 55 at baseline to approximately 40 months of treatment (p < 0.001). The response rate was 73.5% and the remission rate was 52.9%. An alpha size of 2.9 was calculated by Cohen's d, with 0.8 generally considered to be large in magnitude. Sevente require risperidone (mean length, 7 +/- 1 day), 5 patients required trazodone (mean length, 5 +/- 2 days) continued to receive methyphenidate. Common adverse events encountered were: weight gain (58.8%), increased appetite (47.1%), cognitive dulling (41.2%), nausea (26.7%), stomach pain (23.5%), agitation (14.7%). Six patients had elevated alanine transferase levels that normalized after 2 months of treatment (et al, 2005).

2) No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenance pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/-3 years) were enrolled if they had a primary diagnosis of bipolar I or II disorder and had experienced at least one manic episode within the past 3 months. In phase I (stabilization phase), all patients received open-label combi immediate release lithium sodium and divalproex sodium for up to 20 weeks. Lithium was titrated to a target dose of 20 mg/kg/day and adjusted to maintain serum levels of 50 to 100 micrograms/milliliter (mcg/mL). Divalproex was titrated to a target dose of 714 mg (n=2) and other psychotropic medications. Divalproex was soon discontinued in the event of symptom recurrence. Most patients (93%) were discharged to their home or community sites. One patient withdrew from the study due to alopecia, one from each; abnormal thyrotropin blood level, one on divalproex; thrombocytopenia, one or
enuresis, one on lithium) (Findling et al, 2005).

4.5.B.5 **Bipolar II disorder, Maintenance**

a) **Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class Ib

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) **Summary:**

No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenance pediatric bipolar I or II disorder (Findling et al, 2005).

c) **Pediatric:**

1) No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenance pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/- 1) enrolled if they had a primary diagnosis of bipolar I or II disorder and had experienced at least one manic episode within the past 3 months. In phase I (stabilization phase), all patients received open-label combination immediate release lithium and divalproex sodium for up to 20 weeks. Lithium was titrated to a target dose of 20 mg/kg/day and adjusted to maintain serum levels of 0.6 to 1.2 millimoles/liter (mmol/L). Divalproex was titrated to a target dose of 20 mg/kg/day and adjusted to maintain serum levels of 50 to 100 micrograms/milliliter (mcg/mL). Remission criteria (40 or less on the Children’s Depression Rating Scale-Revised (CDRS-R), 12.5 or less Mania Rating Scale (YMRS), and at least 51 on the Children’s Global Assessment Scale (CGAS)) for 4 consecutive weeks and were able to tolerate the minimum serum concentration levels of lithium or divalproex while receiving mood stabilizers, antipsychotics, or antidepressants were eligible for enrollment in phase II (double-blind maintenance phase). Patients were randomized to receive either lithium or divalproex, maintaining desired serum levels for up to 8 weeks. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulants (maximum dosage 6 micrograms/kg/day) at stable doses 4 weeks prior to phase II. One hundred thirty-nine patients were enrolled in phase II, with 60 continuing into phase II (lithium, n=30; divalproex, n=30). Sixty-three percent discontinued the study due to mood-related reasons. Median time to mood relapse was 114 days (standard deviation 57.4 days) for patients treated with lithium and 112 days (SE +/- 56 days) for patients treated with divalproex. Median time to discontinuation for any reason was 91 days (SE +/- 30.1 days) for patients treated with lithium (SE +/- 19.9 days) for patients treated with divalproex (p=0.72). Statistically significant differences were reported for frequency of reported emesis (30% lithium versus 10% divalproex; p=0.05), enuresis (30% lithium versus 0% divalproex; p=0.02), and increased thirst (16.7% lithium versus 0% divalproex). Differences in frequency of headache versus 23.3% (divalproex) and stomach pain (10% lithium versus 23.3% divalproex) were also noted, but not significant. Other adverse events reported in over 5% of patients in phase II were tremor, nausea, diarrhea, appetite, upper respiratory congestion, fever and sore throat. Five patients withdrew from the study due to adverse effects (alopecia, one from each; abnormal thyrotropin blood level, one on divalproex; thrombocytopenia, one on lithium, one on lithium) (Findling et al, 2005).

4.5.B.6 **Borderline personality disorder**

a) **Overview**

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class Ib

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) **Summary:**

Preliminary results suggest possible efficacy; more studies in larger trials needed (Townsend et al, 2001).

c) **Adult:**

1) In a small, prospective, open-label case series, some patients with borderline personality disorder an (DSM-IV) showed improvement during a course of divalproex sodium therapy. Of the 10 patients enrolled in an 8-week study; one each completed weeks 3, 4, 5, and 6; one dropped out after the initial visit. Divalproex was initiated at 250 milligrams (mg) twice daily, and could be increased by 250 to 500 mg at weekly visits if improvement was not seen. At their last visit (whenever it occurred), mean dose of responders was 1125 mg/day compared to baseline. Six of nine evaluable subjects were rated as "much improved" or better on the Clinical Impression Scale (CGI) at their last weekly visit. Scores on the Mania Rating Scale (MRS) declined, but not significantly. In 3 responders, serum valproic acid concentrations ranged from 51 to 113 nanograms/milliliter. f studies were suggested by the investigators (Townsend et al, 2001).

2) A pilot study suggests that a 10-week course of divalproex sodium may provide symptomatic improvement for borderline personality disorders (DSM-IV axis II); however, the validity of these results are limited due to small sample size. In a double-blind, randomized (2:1 ratio) manner, 16 patients were assigned to divalproex sodium or placebo. Six patients completed the study and 10 dropped out. Overall, 100% of those assigned to divalproex sodium withdrew. No one withdrew due to side effects. Compared to placebo, patients treated with divalproex sodium had significantly improved scores compared to baseline (p=0.003). Son
among those in the divalproex sodium group was shown on the Beck Depression Inventory (BDI) and six participants occurred on the Aggression Questionnaire (AQ), related to aggressive feelings and actions. Divalproex was administered as 250 milligrams at bedtime and gradually titrated to doses sufficient to maintain serum levels of 80 micrograms per milliliter (mcg/mL) at the highest tolerated dose. The authors concluded that more study of divalproex sodium in this patient population was warranted (Hollander et al, 2001).

4.5.B.7 Brain injury - Seizure; Prophylaxis
a) Overview
   - FDA Approval: Adult, no; Pediatric, no
   - Efficacy: Adult, Evidence is inconclusive
   - Recommendation: Adult, Class III
   - Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   - Not effective prophylaxis (Glantz et al, 1996)

c) Adult:
   1) Divalproex is not effective for the prophylaxis of seizures in patients with brain tumors. In a study of 76 newly-diagnosed brain tumors, divalproex or placebo was given within 14 days of diagnosis. Divalproex was adjusted to achieve trough levels in the range of 50 to 100 mcg/mL; the median duration of follow-up was 52 months. Five percent of patients treated with divalproex suffered seizures compared to 24% of patients treated with placebo. The authors conclude that anticonvulsant therapy is not indicated in patients with brain tumors unless they suffer seizures (Glantz et al, 1996).

4.5.B.8 Cluster headache
a) Overview
   - FDA Approval: Adult, no; Pediatric, no
   - Efficacy: Adult, Evidence favors efficacy
   - Recommendation: Adult, Class IIb
   - Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   - Effective in 2 cases of cluster headaches with migraine-like features (Wheeler, 1998)

c) Adult:
   1) Two patients with cluster headache and prominent migraine-like features had their headaches remit with divalproex use (Wheeler, 1998). Both patients had been unresponsive to multiple medications and one to surgical intervention. The first, a 37-year-old man with a typical cluster headache aura, received divalproex 250 mg twice daily. Headache remission occurred within 6 weeks. The second, a 55-year-old man with a typical cluster headache aura, was given divalproex 500 mg three times daily with 750 mg nightly. Headache remission occurred within 6 months. He was then slowly tapered down to 375 mg daily.

4.5.B.9 Complex partial epileptic seizure
FDA Labeled Indication
a) Overview
   - FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
   - Efficacy: Adult, Effective; Pediatric, Effective
   - Recommendation: Adult, Class IIa; Pediatric, Class IIa
   - Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS
b) Summary:
   - Indicated in adults and children age 10 years and older as monotherapy or adjunctive therapy for complex partial seizures occurring in isolation or in association with other types of seizures (Prod Info DEPAKOTE extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

c) Adult:
   1) Monotherapy
      a) In a dose-comparison study of divalproex sodium monotherapy in 265 patients converted from carbamazepine, phenobarbital, primidone, or phenytoin monotherapy we receive divalproex sodium with either low-dose (mean concentration, 71 micrograms/milliliter (mcg/mL)) or high-dose (mean concentration, 123 mcg/mL; n=131) monotherapy. Following a 2-week transition period to divalproex sodium, the results at 8 weeks demonstrated a greater reduction in seizures in the high-dose group (mean concentration, 123 mcg/mL; n=131) compared to the baseline group (mean concentration, 71 micrograms/milliliter (mcg/mL)). It should be noted that there was no control group in this study, and less than 50% of the patients randomized to the study (Prod Info DEPAKOTE(R) extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).

2) Adjunctive Therapy
a) In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the use of sodium as adjunctive therapy was more effective in reducing the incidence of seizure compared with placebo for patients with 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or phenytoin monotherapy. Patients taking either carbamazepine or phenytoin, whose seizures were inadequately controlled, were randomized to either divalproex sodium or placebo after optimization of their medication regimen. The dose of divalproex was slowly adjusted to a maximum of 90 milligrams/kilogram/day. The percentage of patients who achieved a seizure-free status and had a greater than 50% reduction in seizure frequency in a group of 137 patients treated with divalproex sodium was 60% vs 26% in study 1, and 58% vs 29% in study 2. The percentage of patients who achieved a 50% or greater reduction from baseline in symptomatic seizures at baseline to 11.5 (p less than or equal to 0.05). Comparing divalproex sodium to placebo, 23% of patients who had at least a 50% reduction in CPS rate, respectively (Prod Info DEPAKOTE extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf delayed-release oral tablets, 2006).

b) Add-on therapy with divalproex was effective in reducing seizure frequency in a group of 137 patients with complex partial seizures. Results from a retrospective study (n=138) indicated that divalproex sodium was effective in the treatment of adult patients with chronic daily headache. In this study, 67% (93 of 138) of the patients had at least a 50% reduction in headache frequency (Freitag et al, 2001).

4.5.B.10 Headache disorder, chronic

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Divalproex sodium demonstrated effectiveness in the treatment of adult patients with chronic daily headache in a double-blind, placebo-controlled study (Freitag et al, 2001).

c) Adult:

1) Results from a retrospective study (n=138) indicated that divalproex sodium was effective in the treatment of adult patients with chronic daily headache. In this study, 67% (93 of 138) of the patients had at least a 50% reduction in headache frequency (Freitag et al, 2001).

4.5.B.11 Manic bipolar I disorder

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (tablets, delayed-release tablets, extended-release tablets); Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder (with psychotic features) (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE ER extended-release oral tablets, 2006)

Ineffective in the treatment of manic symptoms in elderly patients with dementia (Tariot et al, 2001)

Efficacy of divalproex sodium extended-release tablets was not established in a single 4-week open-label placebo-controlled study (n=150: 76 on divalproex sodium) for the treatment of pediatric bipolar disorder (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

4.5.B.13 Tardive dyskinesia

a) Overview

FDA Approval: Adult, yes (tablets, delayed-release tablets, extended-release tablets); Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category B; Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Divalproex sodium (target dosage of 20 milligrams/kilogram/day) did not improve symptoms and did not worsen symptoms and symptomatology in a 16 week, placebo-controlled study (n=172), but symptoms of agitation. In this 6-week trial, there was no significant difference between drug and placebo from the Brief Psychiatric Rating Scale (BPRS), but scores on the Cohen-Mansfield Agitation (CMAI) Inventory...
significant improvement in the divalproex sodium-treated group. Twenty-two percent of divalproex sodium for 4% of patients who received placebo withdrew from the study because of adverse effects, primarily nausea (et al, 2001).

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets was not established in a single 4-week outpatient placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorder. Of patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively). This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and remained significant throughout the second and third 4-week periods (p=0.006 and p=0.045, respectively). Adverse events were equally distributed between treatment groups (Freitag et al, 2002).

2) Oral loading doses of divalproex sodium 15 milligrams/kilogram/day (in divided doses) produced trough concentrations in the therapeutic range by day 5 of dosing in male pediatric psychiatry inpatients (n=16; years). All subjects in this retrospective study received concomitant atypical neuroleptics. Divalproex was defined as 50 to 120 micrograms/milliliter (mcg/mL). These doses were well tolerated by the normal-weight children with migraine who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively) and patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively). Adverse events were equally distributed between treatment groups (Freitag et al, 2002).

4.5.B.12 Migraine; Prophylaxis

FDA Labeled Indication

a) Overview

- FDA Approval: Adult, yes (tablets, delayed-release tablets, extended-release tablets); Pediatric, no
- Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence is inconclusive
- Recommendation: Adult, Class Ib; Pediatric, Class IIb
- Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

- Divalproex sodium is indicated for the prophylaxis of migraine headache in adults (Prod Info DEPATEK(R) extended-release oral tablets, 2008; Prod Info DEPATEK(R) delayed-release oral tablets, 2006). Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established in a single 4-week outpatient placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorder. Of patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively). This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and remained significant throughout the second and third 4-week periods (p=0.006 and p=0.045, respectively). Adverse events were equally distributed between treatment groups (Freitag et al, 2002). A case report describes how divalproex brought dramatic relief of migraine headaches induced by selective serotonin reuptake inhibitor (SSRI), in a 44-year-old woman with a history of refractory major depression (Prod Info DEPATEK(R) extended-release oral tablets, 2008).

- In an open-label, retrospective study in 42 adolescents and children, divalproex sodium provided a 50% reduction in migraine frequency (Caruso et al, 2000).

c) Adult:

1) The average incidence of migraine headache attacks was reduced following once-daily prophylactic treatment with divalproex sodium extended-release (ER) tablets. In a randomized, controlled, double-blind, multicenter study with at least 6-month history of migraine headache attacks and experiencing an average of 2 or more migraine attacks per month, the previous 3 months entered a 4-week baseline phase during which they maintained a headache diary reported at least 2 migraine attacks during the baseline period received either divalproex sodium-ER (n=304; 231 on divalproex sodium) or placebo (n=115) for 12 weeks of treatment, a significantly greater reduction in the mean baseline migraine headache frequency occurring in patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively) and patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively). This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and remained significant throughout the second and third 4-week periods (p<0.006 and p<0.045, respectively). Adverse events were equally distributed between treatment groups (Freitag et al, 2002).

2) A case report describes how divalproex brought dramatic relief of migraine headaches induced by selective serotonin reuptake inhibitor (SSRI), in a 44-year-old woman with a history of refractory major depression (Prod Info DEPATEK(R) extended-release oral tablets, 2008).

- In an open-label, retrospective study (n=42), divalproex sodium showed to be safe and effective for treatment of migraine headache in adolescents and children (aged 7 to 16 years, mean 11.3 years) (Caruso et al, 2000). The study consisted of an initial 2-week period followed by a 12 week experimental period (including an initial 2-week titration period) with placebo each dose. A mean maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum valproic acid concentration of 80 mcg/mL were attained during the study (Prod Info DEPATEK(R) ER extended-release tablets, 2008).

- In an open-label, retrospective study in 42 adolescents and children, divalproex sodium provided a 50% reduction in migraine frequency (Caruso et al, 2000).

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established in a single 4-week outpatient placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorder. Of patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respectively). This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and remained significant throughout the second and third 4-week periods (p<0.006 and p<0.045, respectively). Adverse events were equally distributed between treatment groups (Freitag et al, 2002).

2) In an open-label, retrospective study (n=42), divalproex sodium was shown to be safe and effective for treatment of migraine headache in adolescents and children (aged 7 to 16 years, mean 11.3 years) (Caruso et al, 2000). The study consisted of an initial 2-week period followed by a 12 week experimental period (including an initial 2 week titration period) with placebo each dose. A mean maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum valproic acid concentration of 80 mcg/mL were attained during the study (Prod Info DEPATEK(R) ER extended-release oral tablets, 2008).

- In an open-label, retrospective study (n=42), divalproex sodium was shown to be safe and effective for treatment of migraine headache in adolescents and children (aged 7 to 16 years, mean 11.3 years) (Caruso et al, 2000). The study consisted of an initial 2-week period followed by a 12 week experimental period (including an initial 2-week titration period) with placebo each dose. A mean maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum valproic acid concentration of 80 mcg/mL were attained during the study (Prod Info DEPATEK(R) ER extended-release oral tablets, 2008).
(divided into 2 doses) with titration upward over 6 weeks based on response. Daily doses over the 4-mo period included 15 mg/kg (n=9), 25 mg/kg (n=16), 35 mg/kg (n=10), and 45 mg/kg (n=7). Most common side effects were gastrointestinal upset, weight gain, somnolence, dizziness, and tremor. Mild transient elevation of liver enzymes occurred in 4 patients. Doses were decreased but no one discontinued divalproex due to side effects.

### 4.5.B.13 Panic disorder

**a) Overview**
- **FDA Approval:** Adult, no; Pediatric, no
- **Efficacy:** Adult, Evidence favors efficacy
- **Recommendation:** Adult, Class IIb
- **Strength of Evidence:** Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**
- Efficacy in small, open-label studies only (Baetz & Bowen, 1998)

**c) Adult:**
- 1) In an 8-week, open-label study, divalproex was shown to be effective in patients with previously unresponsive panic disorder and mood instability (Baetz & Bowen, 1998). Patients (18 to 65 years old) received divalproex 2 to 6 times daily and increased by 250-mg increments to a target level of 300 to 600 micromoles/L (45 to 90 mg/kg). Mean final dose was 768 mg/day (range 125 to 2500 mg/day) and mean duration of valproate treatment was 19 weeks. Significant decrease in stage 1 (light) sleep (p=0.04), significant increases in stages 3 and 4 (deep) sleep change in stage 2 (rapid eye movement-REM) sleep. Mean total sleep time increased from 5.8 to 6.4 hours. Doses were adjusted to maintain concentrations within the therapeutic range (between 50 and 100 micromoles/L, or 45 to 90 mg/kg).

**2.6/week (p=0.0318). Also decreased were the Hamilton Anxiety Rating Scale (p=0.0001) and the Beck Depression Inventory Scale (p=0.003).**

### 4.5.B.14 Periodic limb movement disorder

**a) Overview**
- **FDA Approval:** Adult, no; Pediatric, no
- **Efficacy:** Adult, Evidence favors efficacy
- **Recommendation:** Adult, Class IIb
- **Strength of Evidence:** Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**
- Improvement in sleep occurred in a small study cohort receiving valproate (Ehrenberg et al, 2000)

**c) Adult:**
- 1) Sleep quality and duration were improved in 6 outpatients (aged 28 to 62 years, mean 41.5 years) given valproate for periodic limb movement disorder. After a mean 6 months of therapy, dosages of valproate ranged from 600 to 800 milligrams taken at bedtime. Polysomnographic findings included a significant decrease in sleep efficiency, significant decrease in stage 1 (light) sleep, significant increase in stage 2 (rapid eye movement-REM) sleep, significant increase in stage 3 and 4 (deep) sleep. Mean total sleep time increased from 5.8 to 6.4 hours. Doses were adjusted to maintain concentrations within the therapeutic range (between 50 and 100 micromoles/L, or 45 to 90 mg/kg).

**2) A small cohort of patients with autism disorders showed some improvement with valproate treatment (Baetz et al, 2001).**

### 4.5.B.15 Pervasive developmental disorder

**a) Overview**
- **FDA Approval:** Adult, no; Pediatric, no
- **Efficacy:** Adult, Evidence is inconclusive
- **Recommendation:** Adult, Class IIb
- **Strength of Evidence:** Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

**b) Summary:**
- A small cohort of patients with autism disorders showed some improvement with valproate treatment.

**c) Adult:**
- 1) Divalproex sodium therapy was associated with some improvement of social interaction skills, repetitive impulsivity, and other traits related to autism in an open-label, retrospective study (n=14). Included in the consecutive patients with autism (10; DSM-IV), Asperger's disorder (2), and pervasive developmental disorder otherwise specified (2). Ten were children/adolescents and 4 were adults (age range 5 to 40 years, mean 20 to 105, mean 69.1). Three subjects had a history of seizures. Divalproex sodium doses and adjusted to maintain concentrations within the therapeutic range (between 50 and 100 milligrams/L). Mean final dose was 768 mg/day (range 125 to 2500 mg/day) and mean duration of valproate treatment was 19 weeks. Significant decrease in stage 1 (light) sleep, significant increases in stages 3 and 4 (deep) sleep. Mean total sleep time increased from 5.8 to 6.4 hours. Doses were decreased but no one discontinued divalproex due to side effects.

2.6/week (p=0.0318). Also decreased were the Hamilton Anxiety Rating Scale (p=0.0001) and the Beck Depression Inventory Scale (p=0.003).

Concomitant medications were taken by 10 patients, and included antidepressants, atypical neuroleptics, mood stabilizers, and alpha-1 agonists. Based on the Clinical Global Impressions-Improvement scale (CGI-I), 10 of 14 subjects showed a significant decrease in symptoms, and 4 showed no change. Four showed improvement related to repetitive behavior (ie, reduced obsessive-compulsive behaviors) and improved social interaction. One patient improved in language and communication skills. Five became less impulsive, and 4 were less aggressive. Four patients showed improvement in social interactions. Four showed improvement related to repetitive behavior (ie, reduced obsessive-compulsive behaviors). Five became less impulsive, and 4 were less aggressive. Four patients were discontinued in the first 2 weeks due to severe behavioral activation. Other adverse effects included digestive disturbances, weight gain, mood lability, and elevated liver enzymes. The recommendation is that controlled studies be undertaken (Hollander et al, 2001).
4.5.B.16  Posttraumatic headache  

a) Overview  
- FDA Approval: Adult, no; Pediatric, no  
- Efficacy: Adult, Evidence favors efficacy  
- Recommendation: Adult, Class IIb  
- Strength of Evidence: Adult, Category B  

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:  
Effective in some patients based on a retrospective study (Packard, 2000)

c) Adult:  
1) Of 100 patients with chronic daily posttraumatic headache, 60% showed mild (n=44) to moderate (n=23) (patient-rated) after at least 1 month of divalproex sodium, based on a retrospective chart review: the drug was well tolerated, with no serious side effects. Mild improvement was defined as 25% to 50% better, and moderate improvement as greater than 50% improvement. In all subjects, headache was the result of mild head injury and had persisted for more than 6 months. Six patients became headache-free for 1 month or more, and 35 patients reported that their daily headache became episodic, with headache-free days between episodes. Twenty-six patients had no improvement, discontinued therapy due to side effects (nausea, weight gain, hair loss, tremor). Divalproex dosing was generally started as 250 milligrams (mg) daily (sometimes as 125 mg twice daily), increased by 250 mg/week, and peaked at a maximum of 500 mg 3 times a day (Packard, 2000).

4.5.B.17  Schizoaffective disorder, bipolar type  

a) Overview  
- FDA Approval: Adult, no; Pediatric, no  
- Efficacy: Adult, Evidence favors efficacy  
- Recommendation: Adult, Class IIb  
- Strength of Evidence: Adult, Category B  

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:  
Adjunctive use may produce improvements in bipolar type schizoaffective disorder (Bogan et al, 2000). Standard preparations and extended-release formulations of divalproex sodium are equally efficacious in schizoaffective disorders; however, higher daily doses of extended-release formulations are required (2003).

c) Adult:  
1) In a retrospective study (n=20), add-on divalproex therapy appeared to be well-tolerated and efficacious. Divalproex doses were administered once daily at bedtime. Doses were adjusted to at least 1 month of divalproex sodium, based on a retrospective chart review: the drug was generally well tolerated, with no serious side effects. Mild improvement was defined as 25% to 50% better, and moderate improvement as greater than 50% better. In all subjects, headache was the result of mild head injury and had persisted for more than 6 months. Six patients became headache-free for 1 month or more, and 35 patients reported that their daily headache became episodic, with headache-free days between episodes. Twenty-six patients had no improvement, discontinued therapy due to side effects (nausea, weight gain, hair loss, tremor). Divalproex dosing was generally started as 250 milligrams (mg) daily (sometimes as 125 mg twice daily), increased by 250 mg/week, and peaked at a maximum of 500 mg 3 times a day (Packard, 2000).

4.5.B.18  Sedative withdrawal delirium  

a) Overview  
- FDA Approval: Adult, no; Pediatric, no  
- Efficacy: Adult, Evidence is inconclusive  
- Recommendation: Adult, Class III  
- Strength of Evidence: Adult, Category B  

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:  
May reduce symptoms associated with sedative-hypnotic withdrawal (Harris et al, 2000)

c) Adult:  
1) Four controlled studies and several case reports and case series suggest that valproate may be effective in the treatment of sedative withdrawal and benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to support the efficacy of valproate in the treatment of sedative withdrawal delirium (Centorrino et al, 2003).
valproate for benzodiazepine withdrawal. In an open-label study, there were no significant differences in withdrawal symptoms between valproate- and phenobarbital-treated patients, nor were there differences or pulse rate responses associated with the 2 agents. In another comparative study, valproate and clonazepam reported to have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented controlled trial might have supported this use of valproate, but dismissed the treatment drug (valproate) frequent association with GI distress (probably related to use of the valproic acid form of the drug). In a s valproate and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ether another report, two manic schizoaffective patients had successful withdrawal from ethanol when valproal milligrams/kilogram/day was combined with low-dose lorazepam. A patient with panic disorder failed to b clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdr during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Tv reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

4.5.C Valproate Sodium

Absence seizure, Simple and complex

Behavioral syndrome - Dementia

Brain injury; Prophylaxis - Seizure

Catatonia

Complex partial epileptic seizure

Febrile seizure

Manic bipolar I disorder

Migraine

Myoclonus

Neuropathic pain

Seizure, Multiple seizure types; Adjunct

Status epilepticus

Tardive dyskinesia

Trigeminal neuralgia

West syndrome

4.5.C.1 Absence seizure, Simple and complex

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (10 years and older)

Efficacy: Adult, Effective; Pediatric, Evidence is inconclusive

Recommendation: Adult, Class Iia; Pediatric, Class Iib

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Intravenous sodium valproate is indicated for simple and complex absence seizures when administer valproate products is not possible (Prod Info DEPACON(R) IV injection, 2006)

4.5.C.2 Behavioral syndrome - Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Conflicting results reported regarding the effectiveness of valproic acid in the treatment of dementia-AGITATION (Sival et al, 2003) (Sival et al, 2002)

c) Adult:
1) Sodium valproate treatment offered no advantage over placebo in the treatment of dementia-related behavior in forty-two patients. In a randomized, double-blind, placebo-controlled, cross-over trial, patient behavior and senile dementia received oral doses of either placebo or sodium valproate suspension 480 divided doses) for three weeks and then crossed over to the other treatment arm following a one-week washout period. Sodium valproate was no more effective than placebo in the treatment of aggression in this group of patients (Sival et al, 2003).
2) In a randomized, placebo-controlled, double-blind study of 42 elderly patients (mean age=80.4 years) there was no advantage of sodium valproate compared to placebo in the treatment of aggression in dementia. Sodium valproate was given for three weeks at a fixed dose of 6 milliliters (mL) of a 40 milligram per milliliter (mg/mL) oral suspension twice daily dose was 480 mg. Significant improvements in other measures, such as restlessness, melancholic behaviors, suggest that treatment duration was sufficient to produce therapeutic effects (Sival et al, 2002).

4.5.C.3 Brain injury; Prophylaxis - Seizure

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Not effective prophylaxis

c) Adult:
1) Valproate sodium injection should not be used in patients with acute head trauma for the prophylaxis of post-traumatic seizures. In a study evaluating the effect of valproate sodium injection in the prevention of post-traumatic seizures in patients with acute head injuries, patients were assigned to receive either valproate sodium injection for 3 weeks or oral valproate for either one or six months, or phenytoin intravenously given for one week followed by a maintenance dose of 200 mg daily. A significantly higher incidence of death was found to be higher in the 2 groups assigned to the valproic acid treatment compared with those assigned to the phenytoin treatment group (13% versus 8.5%). Evaluation of the cause of death did not support specific drug-related causation. Furthermore, without a placebo group it is difficult to determine the actual incidence of death in these head trauma patients. Until further information is available, the manufacturer recommends not using sodium injection in patients with acute head trauma for the prophylaxis of post-traumatic seizures (Prod I 1999).

4.5.C.4 Catatonia

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category C
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Several cases of catatonia were improved with intravenous VALPROIC ACID

c) Adult:
1) A 38-year-old man with severe catatonic schizophrenia was markedly improved after receiving intravenous VALPROIC ACID (Kruger & Braunig, 2001). The patient required admission to the hospital but was unable to open his mouth due to extreme rigidity. He was started on high-dose IV valproic acid (900 mg/day) followed by oral maintenance dosing (900 mg/day for a plasma level of 60 micrograms/liter maintenance dosing). He required hospital admissions for the following 6 months. The authors noted that since this case, they have treated 3 more successfully with a similar regimen.

4.5.C.5 Complex partial epileptic seizure

FDA Labeled Indication

a) Overview
FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
**4.5.C.6 Febrile seizure**

**a) Overview**
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Pediatric, Evidence is inconclusive
- Recommendation: Pediatric, Class IIb
- Strength of Evidence: Pediatric, Category B

**See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS**

**b) Summary:**
Intravenous sodium valproate is indicated as monotherapy and adjunctive therapy for complex partial seizures occurring in isolation or in association with other types of seizures when administration of oral valproate is not possible (Prod Info DEPACON(R) IV injection, 2006). Carbamazepine is generally the first line agent for complex partial seizures.

**4.5.C.7 Manic bipolar I disorder**

**a) Overview**
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence favors efficacy
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category B

**See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS**

**b) Summary:**
Valproate has been used for mania secondary to bipolar disorder.

**c) Adult:**
1) Four out of 5 acutely manic patients responded to intravenous valproate loading in an open study (Gr. Five bipolar I patients received valproate 1200 or 1800 milligrams on day 1 followed by dosage individual side effects. Their mean baseline Bech-Rafaelsen Mania Rating Scale score was 30.2 which improved to 11.7 following the intravenous loading a quick saturation of plasma-binding proteins occurred which could have beneficial action.
2) One uncontrolled study reported improvement in 5 of 7 patients with MANIA given VALPROIC ACID (valproate) for 6 weeks. All patients had not responded to previous therapy with LITHIUM and other antidepressants (minagawa & The children on SODIUM VALPROATE received either 20 to 50 milligrams/kilogram/day (mg/kg/day) twice daily or 30 mg/kg/day twice daily. However, the dosage regimen of VALPROATE mg/kg/day twice daily was relatively inferior to the other regimens of VALPROATE in the prophylactic efficacy of febrile convulsions in children.

**4.5.C.8 Migraine**

**a) Overview**
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence is inconclusive
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category B

**See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS**

**b) Summary:**
Valproate sodium has been used with mixed results for acute treatment of migraine headache (Mathew et al, 2000).

**c) Adult:**
1) Results from an open-label, prospective study (n=61) indicate that intravenous valproate sodium (300 mg effective for the acute treatment of migraine headache). In this preliminary report, significant improvement occurred in 73% of the migraine sufferers. Mean time to onset of complete relief was 8 minutes and 25 minutes, respectively (Mathew et al, 2000).
2) In a randomized, double-blinded trial, intravenous prochlorperazine was more effective than intravenous treating acute migraine headaches. Forty patients presented to emergency with a migraine headache and were recruited into the trial. Patients received either 50 milligrams (mg) of sodium valproate or 10 mg prochlorperazine diluted to 10 milliliters in normal saline. After the 2 minute infusion, patients used visual grade their pain, nausea and sedation every 15 minutes for 60 minutes. Median pain scores improved 64 (mm) in the prochlorperazine group and 9 mm in the valproate group (p < 0.001). Median nausea scores
35.5 mm in prochlorperazine patients and 2 mm in valproate patients (p less than 0.001). Median sedative improvement in patient pain 30 minutes post dose (p less than 0.001) and in patient nausea 15 minutes (p=0.002). Sodium valproate did not show significant improvement in symptoms over time. At the conclusion of the study period, 79% of valproate patients and 25% of prochlorperazine patients required rescue due to insufficient symptom relief (p=0.001). Extrapyramidal reactions were reported in 2 prochlorperazine patients.

4.5.C.9 Myoclonus

a) Overview
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence favors efficacy
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
In case reports, valproic acid was useful for myoclonus.

c) Adult:
1) Sodium valproate diminished MYOCLOMATIC ASTATIC ATTACKS and sudden falls in 18 parkinsonian patients (Henneberg et al, 1998). These patients also had polyspikes or polyspike-wave complexes on electroencephalogram (EEG). Sodium valproate 600 to 1800 milligrams/day was administered to achieve a level of at least 60 μg/mL, and EEG readings improved in 16 patients. The authors suspect that a generalized epilepsy may have caused myoclonus and falls.

4.5.C.10 Neuropathic pain

a) Overview
- FDA Approval: Adult, no; Pediatric, no
- Efficacy: Adult, Evidence favors efficacy
- Recommendation: Adult, Class IIb
- Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Some pain reduction in patients with cancer-related neuropathic pain in a pilot study.

c) Adult:
1) According to an open-label phase II study, a 2-week course of sodium valproate brought some pain relief for cancer-related neuropathic pain. Valproate was initiated at 200 milligrams (mg) twice a day with titrations to a maximum of 600 mg four times daily. Nineteen of 25 patients completed the study and the median valproate dose at day 15 was 600 mg twice daily. Nineteen of 25 patients experienced at least a 50% reduction in pain score, and 66.7% also had a decline in pain category for their worst pain. The proportion reporting a 50% reduction in pain score was 27.8% for both average and worst pain. Most common side effects were drowsiness, unsteadiness, nausea, and decreased appetite; one patient had a side effect due to toxicity. It was noted that after the study period ended, 89% of subjects continued on valproate as the patient or doctor to be of benefit (Hardy et al, 2001).

4.5.C.11 Seizure, Multiple seizure types; Adjunct

FDA Labeled Indication

a) Overview
- FDA Approval: Adult, yes; Pediatric, yes (10 years and older)
- Efficacy: Adult, Effective; Pediatric, Effective
- Recommendation: Adult, Class Ila; Pediatric, Class Ila
- Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Intravenous sodium valproate is indicated as adjunctive therapy for multiple seizure types when adjuvant use of other anticonvulsants is ineffective in GRAND MAL SEIZURES (Covanis et al, 1982a; Pinder et al, 1977e; Rimmer & Richens, 1985; Simon & Penny, 1975). Of 519 patients who received SODIUM VALPROATE, mostly as an anticonvulant agent, 239 (46%) experienced a 75% or more reduction in seizure frequency. However, in about 33% of these patients (Pinder et al, 1977e). Other studies have reported response rates of 100% when used as a single-agent therapy (Rimmer & Richens, 1985; Fuerstein, 1983; Covanis et al, 1982a).

2) The efficacy of VALPROATE SODIUM in 10 patients (21 to 50 years of age) with INTRACTABLE SEIZURE DISORDERS was evaluated (Adams et al, 1978a). VALPROATE was administered initially in doses of 3 every 8 hours and increased weekly over a period of 12 weeks. All patients received concomitant anticonvulsant therapy observed in general seizure disorders including tonic, tonic-clonic, atonic-kinetic, and atonic-kinetic seizures.
types. The most impressive results were observed in ATONIC-AKINETIC SPELLS. Considerable varietic partial seizures, with 0% to 75% decrease in seizure frequency. EEG reading revealed the degree of epi roughly correlated with the decrease in seizure frequency. Plasma levels of VALPROATE SODIUM of ap mcg/mL in 5 patients was associated with a 50% decrease in seizure frequency.

d) Pediatric:

1) Successful results were reported in 22 of 27 children with grand mal seizures given SODIUM VALPR.
600 and 2000 milligrams daily (dose depended upon age), for 4 to 5 weeks (Forster, 1972).
2) Good results were reported in one 17-year-old female with status epilepticus administered initial dose
milligrams 4 times daily followed by an increase to 600 mg 4 times daily for greater than 6 weeks (Manhi.
The patient responded well to gradually increasing doses of sodium valproate and made a rapid recover.
discharged and a follow-up 6 weeks later revealed the patient was much improved with relatively few sei

4.5.C.12 Status epilepticus

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy
Recommendation: Adult, Class IIb; Pediatric, Class IIb
Strength of Evidence: Adult, Category C; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Oral, rectal and intravenous VALPROIC ACID have been effective treating status epilepticus refract
anticonvulsants

c) Adult:

1) Two female patients were successfully treated with 500 milligrams of intravenous valproate for myoch
epilepticus. Each girl presented with a history of epilepsy treatment and chief complaints of 24 hours or r
spells, jerking, shuddering, and confusion. Mental status returned to normal and jerking and shuddering r
approximately 5 minutes after the infusion was completed in each girl (Sheth et al, 2000).
2) A 25-year-old woman with generalized nonconvulsive status epilepticus was successfully treated with
valproate (Kaplan, 1999). She had been receiving oral valproate and required levels
2) Approximately 5 minutes after the infusion was completed in each girl (Sheth et al, 2000).

3) Two mentally retarded patients with intractable status epilepticus were treated with SODIUM VALPR
1977). The first patient was given SODIUM VALPROATE via nasogastric tube and then 400 mg by recta
days. The second patient was given 600 mg every 6 hours as a rectal suppository for 5 days. Prior to ad
patients were receiving DIAZEPAM, PHENYTOIN, SODIUM AMOBARBITAL, and 1 patient was also rec
clonazepam. Seizures were controlled in both patients and AMOBARBITAL was subsequently withdraw
in seizure activity. The authors suggest that rectal administration may be a practical and effective metho
epilepticus when the oral route is not available.
4) One adult patient in focal spike-and-wave status epilepticus responded to valproic acid 30 milligrams/
intravenously (Chez et al, 1999).

d) Pediatric:

1) Three pediatric patients in slow spike-and-wave status epilepticus responded to valproic acid 30 millig
intravenously (Chez et al, 1999).
2) Good results were reported in one 17-year-old female with status epilepticus administered initial dose
milligrams 4 times daily by an increase to 600 mg 4 times daily for greater than 6 weeks. (Manhire & Esp.
patients responded well to gradually increasing doses of SODIUM VALPROATE and made a rapid recov
was discharged and a follow-up 6 weeks later revealed the patients was much improved with relatively fe

4.5.C.13 Tardive dyskinesia

a) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Mixed results have occurred

c) Adult:

1) Tardive dyskinesia improved in some patients receiving VALPROATE SODIUM at 300 milligrams 3 ti
over a period of 2 weeks in a controlled study. All patients received concomitant neuroleptic therapy. Res
VALPROATE SODIUM produced improvement in 14 of 32 patients with oro-facial dyskinesia, with impro
in akinesia, rigidity, akathisia and dystonic spasms (Linnoila & Viukari, 1979). Further data are required t
efficacy of VALPROATE in tardive dyskinesia.

4.5.C.14 Trigeminal neuralgia

a) Overview


FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence is inconclusive
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Produces mixed results

c) Adult:
1) Mixed outcomes occurred when SODIUM VALPROATE was tried in 20 patients with trigeminal neuralgia. Patients had no attacks for 6 to 18 months, while in 3 patients the frequency and severity of attacks were at least 50%. Four patients responded well when SODIUM VALPROATE was used in combination with other therapies. Patients showed little or no response while one patient showed poor tolerance to SODIUM VALPROATE.

4.5.C.15  West syndrome

a) Overview
FDA Approval: Adult, no; Pediatric, no
Efficacy: Pediatric, Evidence favors efficacy
Recommendation: Pediatric, Class IIb
Strength of Evidence: Pediatric, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:
Effective in INFANTILE SPASMS (40% of patients) (Siemes et al, 1988a)

c) Pediatric:
1) Monotherapy with VALPROIC ACID was effective in the treatment of infantile spasms. A prospective study of 22 children aged 4 to 11 months (Siemes et al, 1988a). VALPROIC ACID (as SODIUM VALPROATE) was administered in oral doses of 15 milligrams/kilogram/day; this was increased every second day by 10 milligrams/kilogram until a maximum dose of 100 milligrams/kilogram/day was achieved. If seizures were not controlled after 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 mg/kg/day was added to the regimen. The total dose of VALPROATE ranged from 40 to 100 milligrams/kilogram/day (mean, 74). Total seizure control was achieved in patients within 3 months of starting VALPROATE; after 6 to 12 months, 73% of patients were free of seizures with monotherapy, and at 18 to 24 months, 88% of children remained seizure free. Developmental status after treatment demonstrated severe and very severe retardation in approximately 40% of children, with moderate to mild retardation in approximately 35%.

4.6  Comparative Efficacy / Evaluation With Other Therapies

Biperiden
Bromocriptine
Carbamazepine
Cyproheptadine
Ethosuximide
Haloperidol
Lithium
Olanzapine
Phenobarbital
Phenytoin
Primidone
Prochlorperazine
Protaglandin
Propranolol

Topiramate

4.6.A Biperiden

4.6.A.1 Extrapyramidal disease

a) A double-blind crossover comparison of valproic acid, biperiden, and placebo was conducted in 15 psychoneuroleptic-induced extrapyramidal symptoms (Friis et al, 1983). Biperiden therapy was superior to valproic acid in decreasing symptoms. Valproic acid had no significant effects on akathisia, a slight beneficial effect on hyper movements, and aggravated parkinsonism-like symptoms.

4.6.B Bromocriptine

4.6.B.1 Nelson syndrome

a) Bromocriptine significantly suppressed plasma adrenocorticotropin hormone (ACTH) secretion in 6 women with Nelson Syndrome. ACTH was measured after receiving therapy with each of the following: placebo, cyproheptadine, bromocriptine. Also they received each of the following combinations: cyproheptadine and valproic acid; and cyproheptadine and valproic acid. Only bromocriptine caused a significant decrease in plasma ACTH (P less than 0.05). However, the combined effect of the 3 drugs did not significantly affect the effect of bromocriptine alone (Mercado-Asis et al, 1997a).

4.6.C Carbamazepine

Epilepsy

Epilepsy, Children

Rheumatic chorea

4.6.C.1 Epilepsy

a) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phenytoin, carbamazepine as monotherapy and followed for 14 to 24 months. All 3 drugs were highly effective in the control of seizures but less effective for partial seizures. There was no significant difference between the overall incidence between the 3 drugs (Callaghan et al, 1985a).
b) Carbamazepine and sodium valproate were shown to be equally effective in controlling seizures in patient diagnosed primary generalized or partial seizures (Richens et al, 1994). In this large multicenter study patient randomized to either carbamazepine or valproate and followed for a period of three years. Although long-term similar in the two groups, significantly more patients in the carbamazepine group (15% vs 5%) discontinued therapy first six months due to adverse reactions (predominantly rash). Headache and dizziness were also reported n the carbamazepine group; weight gain was reported more often in patients receiving sodium valproate.
c) Results from a large multicenter trial comparing valproate with carbamazepine in the treatment of complex secondarily generalized tonic-clonic seizures indicate similar effectiveness of both drugs for control of secondarily generalized tonic-clonic seizures. However, for complex partial seizures, carbamazepine was more effective and was associated with adverse reactions (Mattson et al, 1992). Long-term side effects associated with valproate therapy included weight loss or change in texture, and tremor. Hypersensitivity, characterized by rash, occurred more frequently in the carbamazepine group.
d) Patients switched to high dose valproic acid (target serum level 80 to 150 micrograms/milliliter) demonstrated improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had pri history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic seizures maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone. A 30% mean complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-onset seizures and considered as first-line therapy (Beydoun et al, 1997).
e) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstrated to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months. Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician's treatment choice. Patients were enrolled. Of the total 285 patients, 46% completed the study. Adverse event rates of 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective treatment for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who...
experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), language (7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Carbamazepine was associated with concentration and attention difficulty (4% and 1%), and language problems (6%).

4.6.C.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the treatment of epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996a). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in the trial. The efficacy of the drugs was equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year remission. However, randomization to phenobarbital was discontinued early in the study period due to unacceptable side effects. Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatment due to adverse effects.

4.6.C.3 Rheumatic chorea

a) Carbamazepine and valproic acid were found to be safe and equally effective in the treatment of choreic movements of clinical improvement, time to complete remission, duration of treatment, and recurrence rates in a group of children with Sydenham's chorea. In this open-label trial, 7 children received 20 to 25 milligrams per kilogram of sodium valproate and a matched group of 17 children received 15 mg/kg/day of carbamazepine. No adverse events were reported by either group.

### Demographics and Response to Treatment

<table>
<thead>
<tr>
<th></th>
<th>Sodium valproate</th>
<th>Carbamazepine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex (%)</td>
<td>71.4</td>
<td>58.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.4 +/- 1.5</td>
<td>10.9 +/- 2.4</td>
<td>0.13</td>
</tr>
<tr>
<td>Onset of improvement (days)</td>
<td>8.0 +/- 4.0</td>
<td>7.4 +/- 8.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Time to remission (weeks)</td>
<td>10.1 +/- 8.5</td>
<td>6.7 +/- 6.3</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of treatment (months)</td>
<td>4.3 +/- 2.8</td>
<td>5.0 +/- 2.4</td>
<td>0.56</td>
</tr>
<tr>
<td>Recurrences (%)</td>
<td>14.3</td>
<td>17.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Generalized chorea (%)</td>
<td>71.4</td>
<td>64.7</td>
<td>0.75</td>
</tr>
</tbody>
</table>

(Revised: Genel et al, 2002)

4.6.D Cyproheptadine

4.6.D.1 Nelson syndrome

a) Bromocriptine significantly suppressed plasma adrenocorticotropic hormone (ACTH) secretion in Nelson's syndrome patients. The ACTH levels were measured after receiving therapy with each of the following: cyproheptadine, valproic acid, and bromocriptine. Also they received each of the following combinations: cyproheptadine and valproic acid; bromocriptine, cyproheptadine and valproic acid. Only bromocriptine caused a significant decrease in ACTH (P less than 0.05), as did the combination of the 3 drugs (P less than 0.05). However, the combined effect did not significantly exceed the effect of bromocriptine alone (Mercado-Asis et al, 1997).

4.6.E Ethosuximide

4.6.E.1 Absence seizure

a) SUMMARY: Sodium valproate has been as effective as ethosuximide in children with petit mal seizures (Suzuki et al, 1972; Sato et al, 1982; Callaghan et al, 1982). Sodium valproate 500 to 2400 mg daily (mean, 800 mg daily) has been as effective as ethosuximide 200 to 1200 mg daily (mean, 438 mg daily) (Pinder et al, 1977b). Valproic acid and ethosuximide were compared in a double-blind, response-conditional crossover study in 16 previously untreated patients and 29 refractory patients (18 male and 27 female; 4 to 18 years of age) (Suzuki et al, 1977a). In the previously untreated patients, valproic acid was as effective as ethosuximide in reducing generalized epileptiform discharges on the telemetered EEG. Adverse reactions to valproic acid or ethosuximide were generally mild;
withdrawal or dosage reduction.

4.6.F Haloperidol

4.6.F.1 Mania

a) Divalproex and haloperidol were found to be equally efficacious in the management of acute psychotic manic bipolar disorder. In this study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or haloperidol (20 mg/kg/day) for a period of six days. Divalproex was given at a dosage considered to be a loading dose to produce concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the first treatment; extrapyramidal side effects were observed much more often in patients treated with haloperidol (M 1996).

4.6.G Lithium

4.6.G.1 Bipolar disorder - Mania

a) SUMMARY: Valproic acid may be superior to lithium in managing patients with higher numbers of depressive episodes; therapeutic serum levels of either drug may help predict clinical response and outcome. Limited evidence suggests that suicide risk may be lower with lithium than with divalproex.

b) A review of 3 randomized, double-blind, placebo-controlled studies concluded that a more rapid antimania was achieved with olanzapine or oral loading of divalproex than with standard titration divalproex, lithium or placebo term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kd) for and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually increased 20 mg/kg/day plus 1000 mg/day by day 6. This regimen was compared to divalproex (n=87) initiated at 250 mg 3 times per day to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times per day to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum of 20 mg/day. Patients were followed for 10 days and efficacy was assessed using the change from baselin the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS) analyses showed that MRS measurements from oral-loaded divalproex patients were not significantly different from placebo patients. However, it showed significant differences from standard titration divalproex and placebo by day 5 a days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements. Dry mouth and increased appetite were more commonly reported with divalproex load compared to standard titration (p less than 0.05). However, divalproex was associated with an increased incidence of dizziness, general pain and back pain (p less than 0.05) overall more associated with greater decreases in platelet counts than other groups (p less than 0.05). Lithium with greater reports of headache and fever (p less than 0.05) and olanzapine was associated with greater adverse effects as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in total cholesterol and increases in serum transaminase (p less than 0.05) (Hirschfeld et al, 2003a).

c) In a large-scale retrospective review of claims data, lithium treatment was associated with a lower risk of death compared to the same risks while on divalproex. Health plan data from two managed care organizations identified 20638 health plan members with type 1 or type 2 bipolar disorder, who had received 1 or more prescriptions for divalproex, or carbamazepine. Over an 8-year follow-up period and using lithium as a referent, patients on divalproex had hazard ratios of 2.7 for suicide death (event rate per 1000 person-years 1.7, versus 0.7 for lithium); 1.7 for all-cause death (event rate per 1000 person-years 10.5, versus 4.2 for lithium); and 1.8 for attempts at self-harm (event rates not reported for both study sites). Comparisons of lithium to carbamazepine showed no difference in outcomes. Drug therapy for bipolar disorder, or no drug treatment were less consistent or stable (Goodwin et al, 2003). Confounding factors were considered in this study, the possibility of underrepresentation of certain patient populations in managed care settings and the treatment was relatively new.

d) Response to lithium, but not to valproic acid, worsened with increased numbers of depressive or manic episodes. The treatment for manic episodes had their records reviewed for their illness histories. Using a fitting equation for change in Manic Syndrome Score of the Schedule of Affective Disorders and Schizophrenia conduct of the relationship between treatment response and the number of previous episodes. It was noted that the therapeutic response to lithium dropped for subjects having at least 11 or more episodes. For subjects with manic episodes, response to lithium and divalproex was identical. However, in subjects with more than 11 manic episodes, response to lithium decreased and differed significantly from that to divalproex (p=0.007). Similarly, in patients with depressive episodes, patients were less likely to respond to lithium as compared to divalproex (p=0.004) (Swann et al, 1999).

e) In a retrospective review, lithium appeared to be more effective than valproic acid in the treatment of manic episodes however, when only patients with therapeutic levels were reviewed, results were similar (Chen et al, 1999). C patients (55-years-old or older) were reviewed to assess the efficacy of lithium (n=30) and valproic acid (n=28). A Global Impression rating scale was used to assess outcomes on day 5 and at discharge. Overall more patients with lithium than valproic acid at day 5 (p=0.033) and at discharge (p=0.011). However, patients with a lithium level of 65 to 90 micrograms/milliliter had similar outcomes. T suggests that there may be no difference in outcome if appropriate drug serum levels are achieved in elderly patients.

f) In a 3-week parallel, double-blind study, a history of multiple (greater than 10) previous episodes of mania with a poor response to lithium but not to valproic acid (Swann et al, 1999). Patients with acute mania (n=154) were randomly assigned to lithium, valproic acid or placebo. The primary efficacy measure was the Manic Syndrome Score from the Schedule of Affective Disorders and Schizophrenia scale. A relationship between response to medication and number of previous manic episodes was identified. However, no group showed a significant difference in outcome, the placebo group had similar outcomes.

4.6.G.2 Schizophrenia

a) In a 3-week parallel, double-blind study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or haloperidol (20 mg/kg/day) for a period of six days. Divalproex was given at a dosage considered to be a loading dose to produce concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the first treatment; extrapyramidal side effects were observed much more often in patients treated with haloperidol (M 1996).
4.6.H Olanzapine

4.6.H.1 Mania

a) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima achieved with olanzapine and oral loading of divalproex than with standard titration divalproex, lithium or place short-term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/da days and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually incr maximum of 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated daily and titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 m and titrated to 0.4 to 1.5 millequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to mg/day and placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change measurement of the Mania Rating Scale (MRS), the Manic Syndrome Scale (MSS) and the Behavior and Ide Intent-to-treat analyses showed that MRS measurements from oral-loaded divalproex patients were not signif from olanzapine patients. However, it showed significant differences from standard titration divalproex and pl and from lithium by days 7 to 8 (p less than 0.02). Similar results were found for MSS and BIS measurements increased appetite was more commonly reported with divalproex load compared to standard titration (p less t However, standard titration divalproex was associated with an increased incidence of dizziness, general pain less than 0.05). Divalproex overall was associated with greater decreases in platelet counts than other group: 0.05). Lithium was associated with greater reports of headache and fever (p less than 0.05) and olanzapine v with greater adverse events (such as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in t and increases in serum alanine aminotransferase) overall (p less than 0.05) (Hirschfeld et al, 2003).

b) Olanzapine was superior to divalproex for the treatment of acute mania in a 3-week, randomized, double-hundred fifty one patients with bipolar I disorder, manic or mixed episode, and with or without psychotic featu flexibly dosed olanzapine (5 to 20 milligrams (mg) per day) or divalproex (500 to 2500 mg/day). Modal doses for olanzapine and 1401 mg/day for divalproex. A divalproex blood level of 50 microgram/liter (mcg/L) or grea therapeutic range) was attained by approximately 87% of divalproex-treated patients. The mean improvement Mania Rating Scale total score was 13.4 points for the olanzapine group and 10.4 points for the divalproex gr 0.03). In subgroup analysis, the difference was significant (in favor of olanzapine) among patients without p5 (p=0.06), but there was no difference between treatments among patients with psychotic features. Clinical re: greater improvement in they Young Mania Rating Scale score) was achieved by 54% of olanzapine-treated p divalproex-treated patients (p=0.058). Time-to- remission was significantly shorter with olanzapine (3 days vs than 0.04). There were more adverse events with olanzapine, mainly somnolence, dry mouth, and weight gai occurred more frequently in the divalproex group (Tohen et al, 2002).

4.6.1 Phenobarbital

Epilepsy

Febrile seizure

4.6.1.1 Epilepsy

http://www.thomsonhc.com/hcs/librarian/PFDefaultActionId/pf.PrintReady
a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the treatment of epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al., 1996b). Children aged 3 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in the study. Drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year remission.

b) Patients switched to high-concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonstrated improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had a history of at least two complex partial seizures per month with or without secondarily generalized tonic-clonic seizures. While being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone, and sodium valproate, they demonstrated reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures. Baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial seizures, and it should be considered as first-line therapy (Beydoun et al., 1997a).

4.6.2 Febrile seizure

a) Phenobarbital in doses of 3 to 5 milligrams/kilogram/day was reported as effective as valproic acid 20 to 3 milligrams/kilogram/day in preventing febrile seizures (Wallis et al., 1980; Cavazzuti, 1975), whereas a more recent study indicated that, in these doses, valproic acid was superior to phenobarbital with a lower order of toxicity (Lee & Rimmer, 1985). In another study, phenobarbital in doses of approximately 5 milligrams/kilogram/day was as effective as valproic acid in decreasing plasma levels of approximately 16 mcg/mL for phenobarbital and 57 mcg/mL for valproic acid, resulting in efficacy rates of 91% in children, respectively. Side effects occurred in 77% of phenobarbital-treated children. Phenobarbital toxicity was primarily irritability, hyperactivity, and sleep disorders, whereas valproic acid produced gastrointestinal symptoms. In this study, primidone in doses of approximately 18 mg/kg/day (serum phenobarbital, 14 mcg/mL) was effective in 88% of patients. These data suggest that both valproic acid and phenobarbital are effective for febrile seizures. Although side effects were higher with phenobarbital therapy, valproic acid required dosage change and withdrawal of treatment in 10% and 4% of patients, respectively.

b) Although valproic acid may be as effective as phenobarbital in the prophylaxis of febrile convulsions, the potential for drug interactions and side effects should be considered (Lott, 1982).

4.6.J Phenytoin

Epilepsy

Epilepsy, Children

Seizure; Prophylaxis

4.6.J.1 Epilepsy

a) SUMMARY: Valproic acid is as effective as phenytoin in the treatment of newly diagnosed generalized or partial seizures (Rimmer & Richens, 1985; Wilder et al., 1983; Turnbull et al., 1983).

b) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phenytoin, carbamazepine as monotherapy and followed for 14 to 24 months (Callaghan et al., 1985). The oral drug dose of phenytoin was 300 mg/day for adults and 5 to 10 mg/kg/day for children, carbamazepine was 600 mg/day for adults and 5 mg/kg for children, and valproic acid was 600 mg/day for adults and 5 to 10 mg/kg/day for children. All 3 drugs were highly effective in controlling seizures but less effective for partial seizures. There was no significant difference between the incidence of side effects between the 3 drugs.

c) No difference was reported in efficacy between valproic acid and phenytoin therapy in previously untreated or partial seizures (Turnbull et al., 1985).

d) One study reported the similar efficacy of phenytoin and valproate in newly diagnosed complex partial seizures (Turnbull et al., 1983).

e) Patients switched to high-concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonstrated improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic seizures. While being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone, and sodium valproate, they demonstrated reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures. Baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial seizures, and it should be considered as first-line therapy (Beydoun et al., 1997).

4.6.J.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the treatment of epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al., 1996). Children aged 31 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in the study. Drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year remission.
4.6.3 Seizure; Prophylaxis

a) In a double-blind, 1-year study, phenytoin and valproate were equally effective in preventing seizures after surgery for brain tumor, trauma, or vascular lesions were randomized to receive either phenytoin 100 milligrams (mg) 3 times daily (n=50) or valproate 500 mg 3 times daily (n=50). A started intravenously after surgery and switched to oral dosing (or via nasogastric tube) as soon as possible. Each group experienced a seizure. There was no difference found in the 2 groups in time to first seizure or seizure frequency. There was also no significant difference in the number of patients having to discontinue therapy due to adverse effects. (Beenen, 1999). Neuropsychological testing also showed no significant differences between phenytoin and valproate groups on cognitive functioning. This study verifies that either drug may be used for prophylaxis. Since 4 patients experienced their first seizure on the day of surgery, the authors recommend starting the prophylactic regimen 24 hours before surgery or giving a loading dose after surgery.

b) Valproic acid was as effective as phenytoin for the prophylaxis of short- and long-term seizures following traumatic brain injury, however there was a trend seen towards increased mortality in the valproic acid groups (Temkin et al, 1999). Patients (ages 14-years and older) were randomized to receive either phenytoin for 1 week (n=120), or valproate for 6 months (n=127). A phenytoin loading dose was administered at 5 mg/kg intravenously (IV) followed by maintenance dosing at 10 mg/kg/day divided into 2 doses. Valproic acid loading dose was given at 20 mg/kg intravenously followed by a maintenance dose of 15 mg/kg/day divided to achieve therapeutic levels. Early seizures occurred in 5% of the phenytoin treated patients and in 4.5% of the combined valproic acid groups (p not significant). There was also no difference in the occurrence of late seizures. The death rate after 2 years was 13.4% for the combined valproate groups, 7.2% for the phenytoin group (p=0.07). The authors conclude that the lack of any additional benefit from valproic acid, and the possibly higher mortality rate, suggest that valproic acid should not be routinely used for prophylaxis after traumatic brain injury.

c) The incidence of death was higher in patients receiving valproate sodium injection followed by oral valproic acid in those with head trauma. In a study evaluating the effect of valproate sodium injection in the prevention of post-traumatic seizures, patients were randomized to receive either valproate sodium injection for one week followed by oral valproate for either one or two weeks. Ten patients (ages 14-years and older) were assigned to receive either valproate sodium injection for one week followed by placebo. The incidence of death was found to be higher assigned to the valproate treatment compared to the placebo (p=0.004). Evaluation of the cause of death did not reveal any specific drug-related causation. Furthermore, with the 1-year follow-up, it is difficult to determine the actual mortality rate of these head trauma patients. Until further information is available, the manufacturer recommends not using valproate sodium injection in patients with acute head trauma for the prophylaxis of post-traumatic seizures. (Prod Info Depacon(R), 1999).

4.6 K Primidone

Epilepsy

Febrile seizure

4.6.1 Epilepsy

a) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonstrated improvement in seizure control versus their baseline antiepileptic drug. Participating patients had a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic seizures while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone. Plasma concentrations of each drug were followed and adjusted to therapeutic levels. Early seizures occurred in 29% of the up to 150 mg/milliliter dosing group and 25% of the 150 mg/milliliter dosing group. The authors conclude that valproic acid is efficacious as monotherapy for partial-onset seizures (Prod Info Depacon(R), 1999).

4.6.2 Febrile seizure

a) Primidone, phenobarbital and valproic acid were equally effective over a 1-year period in the prophylaxis of febrile seizures in 95 children (Herranz et al, 1984a). Inclusion criteria included complicated febrile convulsions (febrile convulsions before 12-months-old, 3 or more seizures, history of neurological disorder, delay in movement, delay in speech, microcephaly, a history of febrile convulsions in parents or siblings). Patients were not randomized but revealed if therapy was blinded. All groups of patients presented with similar clinical characteristics and risk factors. There was no significant difference between the groups was that the primidone group contained patients who all had experienced febrile seizures while the other groups contained only approximately 70% of patients who experienced that many attacks. The incidence of first seizure was also uneven with 30% of patients having 1 febrile seizure, 17 primidone patients and 48 valproic acid patients having 2 febrile seizures and 35% of valproic acid patients and 48 valproic acid patients having 3 febrile seizures. The percentage of patients without recurrence of febrile convulsions were 80%, 88%, and 92% of patients treated with carbamazepine, phenytoin, and valproic acid, respectively. The differences between the groups were not statistically significant. The adverse effects experienced with primidone were relatively less severe than with phenobarbital, phenytoin, and valproic acid, respectively. The adverse effects experienced with phenobarbital were frequency of 77%, 53%, and 45% of the patients treated with phenobarbital, phenytoin, and valproic acid, respectively.
valproic acid. None of the children on primidone had to change doses or withdraw from the study because of white 10% and 4% of the children on valproic acid and phenobarbital, respectively, did so. The most common with primidone and phenobarbital included hyperactivity, irritability, and disturbances of sleep, while with valp gastrointestinal effects (nausea, vomiting, and anorexia) were most common.

b) The recurrence rate of febrile convulsions over a one year period in 196 children under 3-years-old were r different between phenobarbital, primidone, or valproic acid prophylaxis therapy (Minagawa & Miura, 1981). f 5 mg/kg/day in 2 doses, primidone 15 to 20 mg/kg/day in 2 doses, valproic acid 20 to 25 mg/kg/day in 2 or 3 acid 30 mg/kg/day in 2 doses were administered to 196 children who had experienced at least 2 febrile convulsive method for dividing the patients into the drug therapy groups and any differences between them were not dose dosage regimen of valproic acid 20 to 25 mg/kg/day in 2 doses was noted to be relatively inferior to the other dosing regimens for prophylactic effect. The remaining regimens appeared to be of equal efficacy in the long- of febrile convulsions.

4.6.L Prochlorperazine

4.6.L.1 Migraine, acute

a) In a randomized, double-blinded trial, intravenous prochlorperazine was more effective than intravenous v acute migraine headaches. Forty patients presented to emergency with a migraine headache with or without recruited into the trial. Patients received either 500 milligrams (mg) of sodium valproate or 10 mg of prochlorp 10 milliliters in normal saline. After the 2 minute infusion, patients used visual analog scales to grade their pa sedation every 15 minutes for 60 minutes. Median pain scores improved 64.5 millimeters (mm) in the prochloro and 9 mm in the valproate group (p less than 0.001). Median nausea scores improved 35.5 mm in prochlorper and 2 mm in valproate patients (p less than 0.001). Median sedation scores improved 4 mm in prochlorperaz mm in valproate patients (p=0.603). Over time, prochlorperazine led to marked improvement in patient pain 3 dose (p less than 0.001) and in patient nausea 15 minutes post dose (p=0.002). Sodium valproate did not sh improvement in symptoms over time. At the conclusion of the 60 minute follow-up period, 79% of valproate pr prochlorperazine patients required rescue therapy due to insufficient symptom relief (p=0.001). Extrapyramid reported in 2 prochlorperazine patients (Tanen et al, 2003).

4.6.M Progabide

4.6.M.1 Epilepsy

a) In a single-blind, cross-over study, progabide (median maximal dose of 2.4 grams (g) daily) was reported acid (median maximal dose of 1.8 g daily) as add-on therapy in patients with refractory epilepsy. In addition, t associated with increases in serum glutamic-oxaloacetic transaminase (SGOT) levels (more than twice the u 62 patients treated; an adverse interaction with phenytoin and progabide resulted in phenytoin intoxication ar phenytoin dosage in 9 patients (Crawford & Chadwick, 1986).

4.6.N Propranolol

4.6.N.1 Migraine; Prophylaxis

a) Valproic acid exhibited equivalent efficacy to propranolol in the prophylaxis of migraine without aura in a s crossover study (n=37). Each 12-week treatment phase, separated by a 4-week placebo washout, consisted divalproex sodium 125 milligrams (mg) twice daily titrated to a goal 1500 mg/day, or propranolol sustained-re titrated to a goal 180 mg/day. Significant (at least 50%) reductions in migraine frequency occurred in 19%, 63 placebo, valproic acid and propranolol groups, respectively. Active treatments were well-tolerated and signif efficacious than placebo, but did not differ statistically from each other (Kaniecki, 1997).

4.6.O Topiramate

4.6.O.1 Epilepsy

a) In a double-blinded, randomized study, topiramate, carbamazepine and valproate monotherapy demonstr to study exit, times to first seizure and proportions of patients who were seizure-free during the final 6 months Newly diagnosed epilepsy patients were randomized to receive topiramate 100 milligrams (mg) daily (n=210) mg daily (n=199), or traditional therapy (n=204). Patients in the traditional therapy arm were prescribed either 600 mg/day or valproate 1250 mg/day depending on the prescribing physician’s treatment choice. Patients w months after the final patient was enrolled. Of the total 285 patients, 46% completed the study. Adverse even 19% and 23% of discontinuations in the topiramate and traditional therapy arms, respectively. Ineffective tre for 11% and 12% of discontinuations in the topiramate and traditional therapy arms, respectively. The time to first seizure between the arms did not differ (p=0.53 and 0.35, respectively). The proportion of patients who experience a seizure during the last 6 months of the study was 49% of topiramate-100 mg patients and 44% other arms. Dose related paresthesia (25 to 33%), difficulty with concentration or attention (4 to 11%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. C valproate were associated with concentration and attention difficulty (4% and 1%), and language problems (6 Carbamazepine was also associated with confusion (3%) (Privitera et al, 2003).

6.0 References
11. Albi F, Riva R, Perucca E, et al: Interference of valproic acid in the colorimetric determination of free fatty acids in 
Chem 1982; 28(6):1398-.
12:461-463.
17. Anderson GD, Acheampong AA, & Levy RH: Interaction between valproate and branched-chain amino acid metabolic 
1994a; 44:742-744.
18. Anderson GD, Acheampong AA, & Levy RH: Interaction between valproate and branched-chain amino acid metabolic 
1994b; 44:742-744.
Epilepsia 1994; 35:221-225.
21. Anon: American Academy of Pediatrics Committee on Drugs. Behavioral and cognitive effects of anticonvulsant the 
1985; 76:644-647.
22. Anon: American Academy of Pediatrics Committee on Drugs: The transfer of drugs and other chemicals into humar 
185.
47:626-635.
33. Baetz M & Bowen RC: Efficacy of divalproex sodium in patients with panic disorder and mood instability who have i 
38. Barrueto F & Hack JB: Hyperammonemia and coma without hepatic dysfunction induced by valproate therapy. Aca 
33:36-39.
30:264-268.
31:741-745.


300. Lance JW & Anthony M: The anticonvulsant action of sodium valproate (Epilim(R)) in 100 patients with forms of epilepsy 1977b; 11:911-915.
338. MacDonald JT: Breakthrough seizure following substitution of depakene capsules (Abbott) with a generic product. 37:1888.
408. Panagariya A, Surek Ra RK, & Sardana V: Juvenile myoclonic epilepsy - an experience from north western India. Act 2001; 104:12-16.
518. Puentes E, Puzantian T, & Lum BL: Prediction of valproate serum concentrations in adult psychiatric patients using estimations with NPEM2 population pharmacokinetic parameters. Ther Drug Monit 1999; 21(3):351-354.
529. Raskind MA & El-Chaar GM: The role of carnitine supplementation durin...


598. Smith GC, Balfe JW, & Kooh SW: Anticonvulsants as cause of Fanconi syndrome. Nephrol Dial Transplant 1995; 10:97-


611. Stahl MMS, Neiderud J, & Vinge E: Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was taking valproic acid. J Pediatr 1997; 130:1001-1003.


14:38-42.

14:38-42.


Administration. Rockville, MD. 2009. Available from URL:

647. US Food and Drug Administration: Information for healthcare professionals suicidality and antiepileptic drugs. US F


652. Vainionpaa LK, Mikkonen K, Rattyja J, et al: Thyroid function in girls with epilepsy with carbamazepine, oxcarbaze
monotherapy and after withdrawal of medication. Epilepsia 2004; 45(3):197-203.

Neurol 1999; 45:444-450.


655. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congentinal m-

656. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital m-

657. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital m-

658. Van Dyke DC, Berg MJ, & Olson CH: Differences in phenytoin biotransformation and susceptibility to congenital m-


661. Vandel S, Bertschy G, Jounet J, et al: Valpromide increases the plasma concentrations of amitriptyline and its met-


666. Verrotti A, Basciani F, Morresi S, et al: Serum sex hormone levels in youn-
girls with epilepsy with carbamazepine, oxcarbaze
monotherapy and after withdrawal of medication. Epilepsia 2004; 45(3):197-203.

667. Verrotti A, Basciani F, Morresi S, et al: Serum sex hormone levels in youn-
girls with epilepsy with carbamazepine, oxcarbaze
monotherapy and after withdrawal of medication. Epilepsia 2004; 45(3):197-203.

668. Verrotti A, Basciani F, Morresi S, et al: Serum sex hormone levels in youn-
girls with epilepsy with carbamazepine, oxcarbaze
monotherapy and after withdrawal of medication. Epilepsia 2004; 45(3):197-203.

12:260.

670. Wallace SJ & Aldridge-Smith J: Successful prophylaxis against febrile convulsions with valproic acid or pheno-


673. White JK & Santos CS: Intravenous valproate associated with significant hypotension in the treatment of status epi
Neurol 1999; 14:822-823.


115.


