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 I (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 a side effects preclude further increases (give in 2 to 3 divided doses if total daily dose exceeds 250 mg)(M 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 wit serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info 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 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 concern 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 response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DE 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 ser 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed 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 associat 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 i 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 STAVZOR(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 respon mg/kg/day or less with a therapeutic serum range of 50 to 100 mcg/mL); reduce concomitant antiepi 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 c syrup, 2006; Prod Info STAVZOR(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 r ORALLY (give in 2 to 3 divided doses if total daily dose exceeds 250 mg), may increase dosage 5 to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic serum range of 50 t (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release 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 exc may increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day therapeutic serum range of 50 to 100 mcg/mL) (Prod Info DEPAKENE(R) oral capsules, oral syrup, STAVZOR(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 o 2008).

b) 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 DEPAKO 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(total daily doses greater than 250 mg should be given in divided doses for delayed-release and spri 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 a clinical 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 DEPAK release oral tablets, 2006)

b) adjunct, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/kg/week to achiev 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 DE extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf 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 100 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 o 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 DEPAKO 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- seizures are controlled or side effects preclude further increases (MAX 60 mg/kg/day; usual therape 100 mcg/mL; total daily doses greater than 250 mg should be given in divided doses for delayed-rel (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkl 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006)

2) Complex partial epileptic seizure

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

b) 10 yr and older, adjunct, initial, 10 to 15 mg/kg/day ORALLY, may increase dosage 5 to 10 mg/k 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 Inf delayed-release oral tablets, 2006)

c) 10 yr and older, conversion to monotherapy, initial, 10 to 15 mg/kg/day ORALLY, may increase c mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day; therapeutic range, 50 to 100 r concomitant antiepileptic dosage by approximately 25% every 2 weeks (reduction may be started at therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduc DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral caps Info DEPAKOTE(R) delayed-release oral tablets, 2006)

c) Valproate Sodium

1) Adult

a) Absence seizure, Simple and complex

1) 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/day at one week intervals until seizures are cor effects preclude further increases (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/ DEPACON(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 cli (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R) IV ir

2) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 10 mg/kg/week to achi response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL); reduce concomitan dosage by approximately 25% every 2 weeks (reduction may be started at initiation of therapy or delaye there is a concern that seizures are likely to occur with a reduction) (Prod Info DEPACON(R) IV injection

3) adjunct, may be added to the patient's regimen at an initial dosage of 10 to 15 mg/kg/day IV, may inc 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range mcg/mL) (Prod Info DEPACON(R) IV injection, 2006)

c) Seizure, Multiple seizure types; Adjunct

1) 10 to 15 mg/kg/day IV, may increase 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 6 less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(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 optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) DEPACON(R) IV injection, 2006)

b) (10 yr and older) conversion to monotherapy, 10 to 15 mg/kg/day IV, may increase dosage 5 to 1 achieve optimal clinical response (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 r concomitant antiepilepsy drug dosage by approximately 25% every 2 weeks (reduction may be start therapy or delayed by 1 to 2 weeks if there is a concern that seizures are likely to occur with a reduc DEPACON(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 r increase dosage 5 to 10 mg/kg/week to achieve optimal clinical response (MAX 60 mg/kg/day or les therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R) IV injection, 2006)

2) Seizure, Multiple seizure types; Adjunct

a) 10 yr and older, 10 to 15 mg/kg/day IV, may increase 5 to 10 mg/kg/week to achieve optimal clin (MAX 60 mg/kg/day or less with a therapeutic range of 50 to 100 mcg/mL) (Prod Info DEPACON(R)

3) Contraindications

a) Valproic Acid

1) hepatic disease or significant hepatic dysfunction (Prod Info STAVZOR(R) delayed release oral capsules, 200 DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle 2003)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed rele 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAK

oral capsules, 2003)
3) urea cycle disorders, known; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info S delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(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 DEPAK extended-release oral tablets, 2008)
3) urea cycle disorders (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER exte tablets, 2008)

c) Valproate Sodium
1) hepatic disease or significant hepatic dysfunction (Prod Info DEPACON(R) IV injection, 2006)
2) hypersensitivity to valproate sodium, valproic acid, or divalproex sodium (Prod Info DEPACON(R) IV injection,
3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DI injection, 2006)

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 capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

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 Cels 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 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 lacta injection for at least 24 hours in glass or polyvinyl chloride chloride (PVC) bags at 15 to 30 degrees Celsi degrees Fahrenheit) (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 ir mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maximum rec is 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 micrograms/milli 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 sp total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodium doses a 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 DEPAK 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 (r increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or adverse effe clinical response is typically achieved at daily doses below 60 mg/kg/day. If a satisfactory respo obtained, plasma levels should be measured to determine whether or not they are in the accept range (50 to 100 mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAI extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prc (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 therape reached or adverse effects occur. Optimal clinical response is typically achieved at daily doses mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measure whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DE 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 milligram (mg/kg/day) increasing by 5 to 10 mg/kg/week until the desired therapeutic effect is reached or occur. Optimal clinical response is typically achieved at daily doses below 60 mg/kg/day. If a sa has not been obtained, plasma levels should be measured to determine whether or not they are therapeutic range (50 to 100 mcg/mL). The concomitant antiepileptic dosage may be reduced a valproic acid therapy or after 1 to 2 weeks of therapy. The dosage of the concomitant antiepilep reduced by approximately 25% every 2 weeks. Valproic acid doses above 60 mg/kg/day are no (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sp 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. I the target trough plasma level range was 85 to 125 micrograms/milliliter. The maximum recommend 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 inc done as quickly as possible to achieve the desired clinical effect. In clinical studies, the target trough 50 to 125 micrograms/milliliter. The maximum recommended dose is 60 mg/kg/day (Prod Info DEPA release oral tablets, 2006)

3) A divalproex loading dose of 20 milligrams/kilogram/day (mg/kg/day) has been given to achieve s concentrations of 80 milligrams/liter. This dosage strategy has been used to rapidly achieve therape patients with acute psychotic manic symptoms (McElroy et al, 1996).

4) Another accelerated loading regimen used divalproex 30 milligrams per kilogram per day (mg/kg and 2 followed by 20 mg/kg/day for days 3 through 10, which resulted in 16 of 19 (84%) of patients a therapeutic serum valproate levels of 50 micrograms/milliliter by day 3 of the study (Hirschfeld, 1999

1.3.1.A.1.d Migraine; Prophylaxis

1) The recommended initial dose of extended-release tablets is 500 milligrams (mg) orally once a d followed by an increase to 1000 mg orally once daily (Prod Info DEPAKOTE(R) ER extended-releas 2008).

2) The recommended initial dose of delayed-release tablets is 250 milligrams (mg) twice daily. In sc 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 s and dosing schedule. Once stabilized, a schedule of divalproex sodium 2 or 3 times a day may be ir DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

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

Divalproex Sodium Dose Conversion	
Delayed-release (Depakote(R)) total daily dose (mg)	Extended-release (Depakote(R) ER) (mg)
500* - 625	750
750* - 875	1000
1000* - 1125	1250
1250 - 1375	1500

1500 - 1625	1750
1750	2000
1875 - 2000	2250
2125 - 2250	2500
2375	2750
2500 - 2750	3000
2875	3250
3000 - 3125	3500
* these total daily doses cannot be directly converted to extended-release since the required dosing strengths are not available	

In cases where the total daily dose of delayed-release product cannot be directly converted to a release product because the required dosing strengths are not available, consider increasing th the next higher dosage before converting to the appropriate total daily dose of the extended-rele (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 o years 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 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 until the desired therapeutic effect is reached or adverse effects occur. Total daily doses exceeding given in divided doses, and the maximum recommended dosage is 60 mg/kg/day (Prod Info DEPAC 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/k (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until the desired therapeutic e adverse effects occur. Total daily doses exceeding 250 milligrams should be given in divided do 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 regim milligrams/kilogram/day (mg/kg/day), increasing at 1-week intervals by 5 to 10 mg/kg/day until t therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligrar in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON 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, 2

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 in
mg/kg/week to achieve optimal clinical response, which is typically seen at a therapeutic range of 5(
The maximum recommended dose is 60 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 te
use the oral form of valproic acid. Use of valproate sodium injection for periods of more than 14 day
studied. As soon as it is clinically feasible, patients should be switched back to oral valproic acid. Va
injection should be administered as a 60 minute infusion and not faster than 20 milligrams/minute. It
with at least 50 milliliters of a compatible diluent. The same frequency of administration should be us
products. Plasma concentrations should be monitored (Prod Info Depacon(R), 2003).

2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients wi
disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated
1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalp
valproate sodium (Prod Info Depakote(R), 2003; Prod Info Depakote ER(R), 2003; Prod Info Depako
2003; Prod Info Depakene(R), 2003; Prod Info Depacon(R), 2003).

a) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3
milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has bee
21 to 28 mg/kg (mean dose 24.2 mg/kg) were given to 21 patients (2 to 54 years old). Peak ser
concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/milliliter. The ir
tolerated and no cardiac or central nervous system adverse effects were reported (Venkataram
1999).

b) 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 were given over an h
dosages required in the 3 pediatric patients ranged from 120 to 160 mg/kg/day divided every 6
1999).

3) Valproate sodium injection should be administered as a 60 minute infusion and not faster than 2(
milligrams/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The same fr
administration should be used as the oral products. Plasma concentrations should be monitored (Pr
(R), 2003).

e) The total daily dose of valproate sodium injection should be equivalent to the total daily dose of the o
product and should be administered as a 60 minute infusion with the same frequency as the oral product
concentration monitoring and dosage adjustments may be necessary. Infusions should not exceed 20 m
(mg)/minute. If the total daily dose exceeds 250 mg, it should be given in divided doses (Prod Info Depac

f) The manufacturer states that the equivalence shown between valproate sodium injection and oral valp
at steady state was only evaluated in an every 6 hour dosing regimen. If valproate sodium injection is giv
trough levels may fall below those measured using the oral route. Close monitoring of trough plasma lev
if valproate sodium injection is given only 2 or 3 times daily (Prod Info Depacon(TM), 1999).

1.3.1.B.2 Rectal route

a) In one patient, a 65-year-old male, status epilepticus did not respond to commonly used anticonvulsa
completely controlled by SODIUM VALPROATE syrup given rectally (250 to 500 milligrams every 6 to 8
was mixed with 30 milliliters of water and given as a retention enema. It was well-absorbed rectally and c
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 sei
with single agent therapy were evaluated. The dose of each anticonvulsant was reduced by 1 unit at inte
unit equivalent to 200 milligrams of CARBAMAZEPINE or VALPROIC ACID, or 100 milligrams of PHEN
mean follow-up period of 26 months (range, 6 to 62 months). Relapse occurred in 31 patients, with 61 pa
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 maxir
recommended dosage is 60 mg/kg/day . Total daily doses of valproic acid exceeding 250 mg should
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 syru

Pounds (lbs)	Kilograms (kg)	Daily dose
22 to 54.9 lbs	10 to 24.9 kg	250 mg
55 to 87.9 lbs	25 to 39.9 kg	500 mg
88 to 131.9 lbs	40 to 59.9 kg	750 mg
132 to 164.9 lbs	60 to 74.9 kg	1000 mg
165 to 197.9 lbs	75 to 89.9 kg	1250 mg

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

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 belov
a satisfactory response has not been obtained, plasma levels should be measured to determine
they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/d
recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2
(Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed rele
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 wil
desired clinical response or desired range of plasma concentrations. The maximum recommended d
mg/kilogram/day or less with a therapeutic serum range of 50 to 125 micrograms/milliliter (Prod Info
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 (S
milligrams (mg) orally twice daily. Some patients may benefit from doses up to 1000 mg/day. Higher
to 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,

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 Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral ca

1.3.1.C.1.g Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years 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 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.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% reduc 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 unnecessary 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 capsules, 2008).

B) Divalproex Sodium

1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tal Bennett et al, 1994). However, increased free levels of valproic acid have been reported, and monitoring of to 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 creatinir less than 10 milliliters/minute (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

C) Valproate Sodium

1) Dosage 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 misle 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 insufficienc 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 caps

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 insuf 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 concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations m (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral cap Info DEPAKOTE(R) delayed-release oral tablets, 2006).

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 re 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 clearanc a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of f intake, dehydration and adverse effects are also recommended. In patients with decreased food or fluid intak with excessive somnolence, dose reductions or discontinuation of therapy should be considered. Maintenanc 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 patients. Slow dosage titration and close monitoring of fluid and nutritional intake, dehydration, and adverse e recommended. Maintenance doses should be based on clinical response (Prod Info DEPAKOTE(R) ER exte tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-relea 2006).

C) Valproate Sodium

1) The manufacturer recommends that the starting dose be reduced due to a decrease in unbound clearanc a potential increase in sensitivity to somnolence in the elderly. Slow dosage titration and close monitoring of f intake, dehydration and adverse effects are also recommended. Maintenance doses should be based on clin (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 unbou valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefor supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenou Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because prote patients is significantly reduced (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZO release oral capsules, 2008).

B) Divalproex Sodium

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

C) Valproate Sodium

1) No dosage supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuo hemofiltration (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 1994). Hemodialysis typically reduces va concentrations by about 20% and protein binding is substantially reduced. Monitoring total concentrations ma (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 ir mg/kg/day until the desired therapeutic effect is reached or adverse effects occur. The maximum rec dosage is 60 mg/kg/day. The usual therapeutic serum concentration ranges from 50 to 100 microgra however, there is no good correlation between daily dose, serum concentrations, and therapeutic ef patients may experience seizure control with higher or lower serum levels. For the delayed-release t capsules, total daily doses exceeding 250 mg should be given in divided doses. As divalproex sodiu titrated upwards, the blood levels of phenobarbital and/or phenytoin may be affected (Prod Info DEP extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Inf 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 des effect is reached or adverse effects occur. Optimal clinical response is typically achieved at dail mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measure whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Doses above 60 recommended (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DE sprinkle oral capsules, 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 valproic acid to a patient's current regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), incr mg/kg/week until the desired therapeutic effect is reached or adverse effects occur. Optimal clir typically achieved at daily doses below 60 mg/kg/day. If a satisfactory response has not been o levels should be measured to determine whether or not they are in the accepted therapeutic rar mcg/mL). Doses above 60 mg/kg/day are not recommended (Prod Info DEPAKOTE(R) ER exte tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) oral tablets, 2006).

3) Conversion To Monotherapy

a) Conversion to monotherapy (children 10 years of age or older): The recommended initial ora monotherapy is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing by 5 to 10 mg/kg/wee therapeutic effect is reached or adverse effects occur. Optimal clinical response is typically achi doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels sho to determine whether or not they are in the accepted therapeutic range (50 to 100 mcg/mL). Do mg/kg/day are not recommended. The concomitant antiepileptic drug dosage may be reduced a valproic acid therapy or after 1 to 2 weeks of therapy and can be reduced by approximately 25% (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sp capsules, 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 n established (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOT capsules, 2008).

2) The efficacy for use in the pediatric population for the treatment of mania or migraine prophylaxis 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, initiate divalproex sodium sprinkle capsules at the s and dosing schedule. Once stabilized, a schedule of divalproex sodium 2 or 3 times a day may be ir DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

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

Divalproex Sodium Dose Conversion	
Delayed-release (Depakote(R)) total daily dose (mg)	Extended-release (Depakote(R) ER) (mg)
500* - 625	750

750* - 875	1000
1000* - 1125	1250
1250 - 1375	1500
1500 - 1625	1750
1750	2000
1875 - 2000	2250
2125 - 2250	2500
2375	2750
2500 - 2750	3000
2875	3250
3000 - 3125	3500
* these total daily doses cannot be directly converted to extended-release since the required dosing strengths are not available	

In cases where the total daily dose of delayed-release product cannot be directly converted to a release product because the required dosing strengths are not available, consider increasing th the next higher dosage before converting to the appropriate total daily dose of the extended-rel (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 o years 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 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/da week intervals by 5 to 10 mg/kg/day until the desired therapeutic effect is reached or adverse effects doses exceeding 250 mg should be given in divided doses, and the maximum recommended dosag (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 reache effects occur. Total daily doses exceeding 250 milligrams should be given in divided doses, and 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 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to 10 mg/kg/day until t therapeutic effect is reached or adverse effects occur. Total daily doses exceeding 250 milligra in divided doses, and the maximum recommended dose is 60 mg/kg/day (Prod Info DEPACON 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, 2

1.4.1.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 int dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response, which is typicall therapeutic range of 50 to 100 mcg/mL. The maximum recommended dose is 60 mg/kg/day (Prod Ir IV injection, 2006).

1.4.1.B.1.d Important Note

1) Valproate sodium injection is for intravenous use only and should be used in patients who are ter use the oral form of valproic acid. Use of valproate sodium injection for periods of more than 14 days studied. As soon as it is clinically feasible, patients should be switched back to oral valproic acid. Va injection should be administered as a 60 minute infusion and not faster than 20 milligrams/minute. It with at least 50 milliliters of a compatible diluent. The same frequency of administration should be us products. Plasma concentrations should be monitored (Prod Info Depacon(R), 2003).

2) There have been reports of hyperammonemic encephalopathy (including fatalities) in patients wi disorders (UCD) who have received valproate therapy. UCD is a genetic disorder with an estimated 1:8000 to 1:30,000 births. Patients suspected of having UCD should not receive valproic acid, divalp valproate sodium (Prod Info Depakote(R), 2003; Prod Info Depakote ER(R), 2003; Prod Info Depako 2003; Prod Info Depakene(R), 2003; Prod Info Depacon(R), 2003).

e) Two patients (ages 10 years and 34 months) receiving multiple antiepileptic inducing agents including coma required a loading dose of valproate 20 milligrams/kilogram (mg/kg). A maintenance infusion of 4 r required to maintain a level of approximately 75 mg/Liter (Hovinga et al, 1999).

f) To achieve high therapeutic levels of valproic acid, RAPID INTRAVENOUS INFUSION at 3 or 6 millig (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has been used. Doses of 21 to 28 mg 24.2 mg/kg) were given to 21 patients (2 to 54-years-old). Peak serum valproate concentrations measure post-infusion were 105 to 204 micrograms/milliliter. The infusions were well-tolerated and no cardiac or c system adverse effects were reported (Venkataraman & Wheless, 1999).

1.4.1.B.1.g Intravenous valproic acid was used in 4 patients (3 children and 1 adult) for the treatment o WAVE STATUS EPILEPTICUS. Loading doses of 30 milligrams/kilogram 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,

1) Equivalent Doses

a) The total daily dose of valproate sodium injection should be equivalent to the total daily dose valproic acid product and should be administered as a 60 minute infusion with the same freque products. Plasma concentration monitoring and dosage adjustments may be necessary. Infusio exceed 20 milligrams(mg)/minute. If the total daily dose exceeds 250 mg, it should be given in c (Prod Info Depacon(TM), 1999).

b) The manufacturer states that the equivalence shown between valproate sodium injection an products at steady state was only evaluated in an every 6 hour dosing regimen. If valproate soc given less frequently, trough levels may fall below those measured using the oral route. Close m trough plasma levels may be needed if valproate sodium injection is given only 2 or 3 times dail Depacon(TM), 1999).

2) Intravenous Rate of Administration

a) Valproate sodium injection should be administered as a 60 minute infusion and not faster tha milligrams/minute. It should be diluted with at least 50 milliliters of a compatible diluent. The sar administration should be used as the oral products. Plasma concentrations should be monitored Depacon(R), 2003).

b) In a prospective pilot study involving 4 hospitalized and acutely ill children, intravenous sodi safely administered at an infusion rate of 1 milligram/kilogram/minute. The patients ranged from age and weighed between 17.2 to 60 kilograms. Before and during the infusion, vital signs and were recorded every 5 minutes. Blood samples were also collected pre-infusion, at 0.5 hours ar hours post-infusion. Doses ranged between 8.3 to 15.4 milligrams/kilogram (mg/kg) and the dur infusions ranged from 8 to 15 minutes. Intravenous sodium valproate was diluted 1:1 (v/v) with 5 sterile water. The investigators found no clinically significant changes in blood pressure, heart ra rate (values not reported). The only reported adverse reaction was local inflammation at the inje in 1 patient. Unbound valproate acid concentrations were greater at 0.5 hours post-infusion than infusion (median percent of unbound valproate acid 22% vs 15%, respectively). Study investiga being cautious when using rapid infusions to acutely ill patients as higher unbound drug levels r 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 milligrams/kilogram (mg/kg)/minute for a duration of 4.17 or 8.34 minutes, respectively, has bee 21 to 28 mg/kg (mean dose 24.2 mg/kg) were given to 21 patients (2 to 54-years-old). Peak ser concentrations measured 20 minutes post-infusion were 105 to 204 micrograms/milliliter. The in tolerated and no cardiac or central nervous system adverse effects were reported (Venkataram 1999).

d) Two patients (ages 10 years and 34 months) receiving multiple antiepileptic inducing agents phenobarbital, required a loading dose of valproate 20 milligrams/kilogram (mg/kg). A maintena 6 mg/kg/hour was required to maintain a level of approximately 75 mg/Liter (Hovinga et al, 199

1.4.1.B.2 Oral route

1.4.1.B.2.a West syndrome

1) Monotherapy with VALPROIC ACID was effective in the treatment of INFANTILE SPASMS in a p involving 22 children aged 4 to 11 months (Siemes et al, 1988). VALPROIC ACID (as SODIUM VAL given initially in oral doses of 15 milligrams/kilogram/day; this was increased every second day by 1(milligrams/kilogram until seizures ceased or a maximum dose of 100 milligrams/kilogram/day was a(were not controlled or reduced after 4 to 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 m added to the regimen. The doses of SODIUM VALPROATE ranged from 40 to 100 milligrams/kilogra 74).

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 (m 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 exce should be given in 2 to 3 divided doses. Therapeutic valproate serum concentrations for most patien seizures is considered to range from 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral c 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 syru

Pounds (lbs)	Kilograms (kg)	Daily dose
22 to 54.9 lbs	10 to 24.9 kg	250 mg
55 to 87.9 lbs	25 to 39.9 kg	500 mg
88 to 131.9 lbs	40 to 59.9 kg	750 mg
132 to 164.9 lbs	60 to 74.9 kg	1000 mg
165 to 197.9 lbs	75 to 89.9 kg	1250 mg

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 i 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 belov a satisfactory response has not been obtained, plasma levels should be measured to determine they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses above 60 mg/kg/d recommended. Total daily doses of valproic acid exceeding 250 milligrams should be given in 2 (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed rele 2008) .

2) Conversion to Monotherapy

a) When converting to monotherapy in children 10 years and older, the usual recommended ini 10 to 15 milligrams/kilogram/day (mg/kg/day) increasing at 1 week intervals by 5 to 10 mg/kg/w desired therapeutic effect is reached or adverse effects occur. Usually, optimal clinical response daily doses below 60 mg/kg/day. If a satisfactory response has not been obtained, plasma level measured to determine whether or not they are in the accepted therapeutic serum range (50 to Concomitant antiepilepsy drug dosage may be reduced at the initiation of valproic acid therapy weeks of therapy. The dosage of the concomitant antiepilepsy drug can be reduced by approxi 2 weeks. Valproic acid doses above 60 mg/kg/day are not recommended. Total daily doses of v

exceeding 250 milligrams should be given in 2 to 3 divided doses (Prod Info DEPAKENE(R) ora syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) Adjunctive Therapy

a) In children 10 years and older, the usual recommended oral dosage when adding valproic a regimen is 10 to 15 milligrams/kilogram/day (mg/kg/day), increasing at 1 week intervals by 5 to until the desired therapeutic effect is reached. Usually, optimal clinical response is achieved at 60 mg/kg/day. If a satisfactory response has not been obtained, plasma levels should be measu whether or not they are in the accepted therapeutic serum range (50 to 100 mcg/mL). Doses ab are not recommended. Total daily doses of valproic acid exceeding 250 milligrams should be gi divided doses (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R 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 prophy children (Hamalainen, 1998). However, the efficacy has not been confirmed in clinical trials (Prod In delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) ER extended-release oral tablets, 20

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 The dose may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. If total daily 250 mg, give in 2 to 3 divided doses. Maximum daily dose is 60 mg/kg/day or less with a therapeutic 50 to 100 micrograms/milliliter (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info S delayed release oral capsules, 2008).

e) There is an increased risk of fatal hepatotoxicity in patients under 2 years of age (Prod Info DEPAKEN capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsules, 2008). The safety an delayed-release valproic acid (Stavzor(R)) in patients under 18 years of age for the treatment of acute m with bipolar disorder and for the prophylaxis of migraines have not been established (Prod Info STAVZO release oral capsules, 2008).

1.4.1.C.1.f Withdrawal Schedule

1) The risk factors associated with withdrawal of anticonvulsants in 92 patients who had been free o years 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 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.C.2 Rectal route

a) The bioavailability of diluted valproic acid syrup given rectally is comparable to that following oral adm are, therefore, the same for rectal or oral administration. Rectal administration of valproic acid syrup app 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 epilep Commercially available valproic acid syrup (Depakene(R) 250 mg/5 mL) was diluted 1:1 with tap water a retention enema in a loading dose of 10 to 20 milligrams/kilogram. Maintenance doses were started 8 ho initial loading dose (10 to 15 milligrams/kilogram every 8 hours. Five of 7 children (mean age, 7.7 years) seizures within 24 hours after starting rectal therapy. Duration of therapy ranged from 1 to 8 days (mean authors suggest that loading doses of 20 milligrams/kilogram be administered which will attain plasma le approximately 50 mcg/mL. Marked increases in aspartate aminotransferase activity occurred in 3 of the requiring cessation of valproic acid therapy (Snead & Miles, 1985).

c) The successful use of rectal anticonvulsants was described as an alternative route to oral drug therap seizures undergoing gastrointestinal surgery. Perioperative rectal therapy was employed for clonazepam valproate (retention enema in tap water or saline), and given until the patients could again receive oral m duration of use was generally 48 to 72 hours. All patients maintained excellent seizure control without to rectally administered preparations (Woody et al, 1989).

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% reduc 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 unnecessary 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 capsules, 2008).

B) Divalproex Sodium

1) Dose adjustments are not required in renal failure (Prod Info DEPAKOTE(R) ER extended-release oral tal Bennett et al, 1994). However, increased free levels of valproic acid have been reported and monitoring of to 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) 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 milli Dosage adjustments are not required in renal failure (Prod Info Depakote(R) Tablets, 2002a; Bennett et al, 19 increased free levels of valproic acid have been reported and monitoring of total concentrations may be misle al, 1999).

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 insufficienc 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 caps

B) Divalproex Sodium

1) Divalproex sodium should not be administered to patients with hepatic disease or significant hepatic insuf 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 concentrations and larger unbound fractions by a 2- to 2.6-fold increase. Monitoring of total concentrations m (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral ca Info DEPAKOTE(R) delayed-release oral tablets, 2006).

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), 1999). Liver disease impairs the capacity valproate. In one study, the clearance of free valproate was decreased by 50% in patients with cirrhosis and with acute hepatitis. Patients with liver disease have decreased albumin concentrations and larger unbound f 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 unbou valproate has been reported in patients with a creatinine clearance of less than 10 milliliters/minute. Therefor supplementation is required in patients following hemodialysis, peritoneal dialysis, or continuous arteriovenou Monitoring total concentrations of valproic acid may be misleading in patients with renal failure because prote patients is significantly reduced (Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZO release oral capsules, 2008).

B) Divalproex Sodium

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

C) Valproate Sodium

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

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

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 Depaken Info Depakote(R), Tablets 2003; Prod Info Depacon(R), 1999)(Turnbull et al, 1983a; Rimmer & Richens, 1985d).

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 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 co (Schobben et al, 1975a; Loiseau et al, 1975).

d) Comparable plasma levels occur when switching from oral valproate to intravenous valproate sodium (Pro (R), 1999).

2) Acute mania, 50 to 125 mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depa 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 o 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) delaye 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) d 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 administratio 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 stead 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 valproat 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 t achieved (Prod Info Depakote(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 do 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 bioava 89% relative to divalproex sodium delayed-release tablets given twice a day (Prod Info Depakote(R) ER,

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 fo 23% decrease in Cmax of valproic acid and median Tmax was increased from 2 to 4.8 hours compared v under a fasted state but there was no change in systemic exposure (Prod Info STAVZOR(R) delayed rel capsules, 2008).

b) Coadministration of oral valproate products with food is not expected to have any significant clinical e 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 o 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 (Pro (R), 1999). Free fraction plasm protein concentration increases from approximately 10% at 40 mcg/m mcg/mL (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2

2) Plasma protein binding decreased in the elderly resulting in an increase in the free fraction by 44 Depakote(R) ER Tablets, 2003)(Rimmer & Richens, 1985d). Liver disease is associated with 2 to 2.5 unbound valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depako 2003)(Klotz et al, 1978a). Plasma protein binding is also decreased in patients with renal disease (L (Marbury et al, 1980; Gugler & Mueller, 1978), in hyperlipidemic patients (Prod Info Depakote(R) ER and in the presence of other drugs such as aspirin (Prod Info STAVZOR(R) delayed release oral cap Conversely, valproate may displace other protein-bound medications such as phenytoin, carbamaze tolbutamide (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3) A 108% increase in free valproic acid was observed in the sera of patients with HIV (Dasgupta &

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 (Pr (R) delayed release oral capsules, 2008).

B) Distribution Kinetics

1) Volume of Distribution

a) 0.14 to 0.23 L/kg (Puentas 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, respe et al, 1984; Bryson et al, 1983).

2) The volume of distribution for total valproate is 11 L/1.73 m(2), free valproate is 92 L/1.73 m(2) (F 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 De (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 th STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakote(R) ER, 2003m); (Prod Info Depa (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) T

2) 2-propyl-hydroxypentanoic acids, activity unknown (Prod Info Depakene(R), 1999)(Prod Info Depakote(R)

a) 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 cap

b) Free valproate, adults: 4.6 L/hr/1.73 square meter (Prod Info STAVZOR(R) delayed release oral caps

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 glucu (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 a 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 f years old.

2) Children between 3 months and 10 years have 50% higher clearance rates when compared to a the age of 10, pharmacokinetic parameters of children are similar to those of adults (Prod Info STAV release oral capsules, 2008).

3) Intrinsic clearance in the elderly (age ranged from 68 to 89 years) is reduced by 39% and free fra by 44% when compared with young adults (age ranged from 22 to 26 years) (Prod Info STAVZOR(R 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, 199

6) There are no differences in the body surface area adjusted unbound clearance between male an L/hr/1.73 m(2) and 4.7 L/hr/1.73 m(2), respectively) (Prod Info Depakote(R) ER, 2003m). However, i clearance in female patients is 10% less than in male patients (Yukawa et al, 1997a).

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 hepa 6 healthy subjects (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info Depakot 2002).

8) There is a 27% decrease in the unbound clearance of valproate in patients with a creatinine clea mL/minute (Prod Info STAVZOR(R) delayed release oral capsules, 2008)(Prod Info Depakote(R) EF

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 Depakene(I et al, 1996; 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 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 fro in one study involving 7 patients with cirrhosis and 4 patients with acute hepatitis (Prod Info STAVZOR(R 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, 2

a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to old adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) de capsules, 2008).

4) Neonates greater than 2 months old: 7 to 13 hours (Prod Info STAVZOR(R) delayed release oral capsules

a) Children within the first 2 months of life have decreased ability to eliminate valproate compared to old adults. This is due to reduced clearance and increased volume of distribution (Prod Info STAVZOR(R) de 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); (Frar (Marbury et al, 1980).

a) Hemodialysis of 4 hours duration removed 15% to 22% of valproic acid in chronic renal failure patient 1980).

b) Acute valproic acid overdose (serum concentration greater than 1200 mcg/mL) in a 25-year-old woma suicide attempts was successfully treated with high-flux hemodialysis using a highly permeable polysulfo membrane. High- flux hemodialysis was performed for 4 hours and lowered the valproic acid half-life to 2 increased the calculated elimination rate constant to 0.2522 h(-1). The authors concluded that high-flux h as effective as combination hemodialysis and charcoal hemoperfusion and avoided the attendant risks o hemoperfusion (Kane et al, 2000).

c) A 43-year-old woman who ingested approximately 19 grams of valproic acid had 15.5 grams removed 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.

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 a following a valproic acid overdose (Franssen et al, 1999). The patient was dialyzed during two 3-hour se highly permeable polysulfone hemodialysis membrane. A charcoal hemoperfusion column was added dc first session and a resin column for the second. The hemodialysis was effective while the hemofiltration v in the first hour. This was due to rapid saturation of the column. The resin column appeared to be more e charcoal.

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

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. E indicated that children under the age of two years are at a considerably increased risk of developing fata especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with sever accompanied by mental retardation, and those with organic brain disease. When valproic acid is used in they should be used with extreme caution and as a sole agent. The benefits of therapy should be weighe 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 hepatoto 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.

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 w 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 treatmen 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 requires that the benefits of its use be weighed against the r fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPACON(R) IV injection, 20 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, 200

b) Oral (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, those with congenital metabolic disorders, those with severe seizure disorders accompa retardation, and those with organic brain disease. When valproic acid is used in this patient group, it sho extreme caution and as a sole agent. The benefits of therapy should be weighed against the risks. The ir hepatotoxicity decreases considerably in progressively older patient groups.

These incidents usually have occurred during the first six months of treatment. Serious or fatal hepatoto

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, th
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This is especially important when the treatment of a spontaneously reversible condition not ordinarily ass
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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 w
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, those with congenital metabolic disorders, those with severe seizure disorders accompa
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 (eg, spina bifida). Accordingly, the
sodium in women of childbearing potential requires that the benefits of its use be weighed against the ris
fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar
permanent injury or risk of death (eg, migraine) is contemplated.

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 w
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 treatmen
medical condition should be initiated as clinically indicated (Prod Info DEPAKOTE(R) sprinkle oral capsu
Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

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, those with congenital metabolic disorders, those with sever
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 w
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 treatmen
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 (eg, spina bifida). Accordingly, the

products in women of childbearing potential requires that the benefits of its use be weighed against the r
fetus. This is especially important when the treatment of a spontaneously reversible condition not ordinar
permanent injury or risk of death (eg, migraine) is contemplated (Prod Info DEPACON(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, 200
DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R)
oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle
2003)

2) hypersensitivity to sodium valproate, divalproex sodium, or valproic acid (Prod Info STAVZOR(R) delayed rele
2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info
delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAK
oral capsules, 2003)

3) urea cycle disorders, known; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info S
delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(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 DEPAK
extended-release oral tablets, 2008)

3) urea cycle disorders (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) ER exte
tablets, 2008)

C) Valproate Sodium

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

2) hypersensitivity to valproate sodium, valproic acid, or divalproex sodium (Prod Info DEPACON(R) IV injection,

3) known urea cycle disorders; hyperammonemic encephalopathy, including fatalities, has occurred (Prod Info DI
injection, 2006)

3.2 Precautions

A) Valproic Acid

1) children, especially under the age of 2 years; increased risk of hepatotoxicity; discontinue immediately if signifi
dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV inje
Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Proc
(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

2) concurrent use of multiple anticonvulsants; increased risk of hepatotoxicity; discontinue immediately if significa
dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV inje
Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Proc
(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

3) hepatic disease, prior history of; increased risk of hepatotoxicity; discontinue immediately if significant hepatic
(Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod In
oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R
release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

4) metabolic disorders, congenital; increased risk of hepatotoxicity; discontinue immediately if significant hepatic
(Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod In
oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R
release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

5) organic brain disease; increased risk of hepatotoxicity; discontinue immediately if significant hepatic dysfunctio
Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEP
capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER
tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)

6) pancreatitis, sometimes life-threatening, may occur; discontinuation is recommended (Prod Info STAVZOR(R)
oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 20
DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; P
DEPAKOTE(R) sprinkle oral capsules, 2003)

7) pregnancy; increased risk of birth defects (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod
IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-releas
2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsule

8) seizure disorders, severe and accompanied by mental retardation; increased risk of hepatotoxicity; discontinue
significant hepatic dysfunction occurs (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DE
injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release o
Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 200

9) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info STAVZOR(R) delayed
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; P
DEPAKOTE(R) sprinkle oral capsules, 2003)

10) acute head trauma; IV use is not recommended for prophylaxis of post-traumatic seizures (Prod Info DEPAC 2006)
11) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info STAVZOR(R) delaye 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; F 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 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)
13) elderly; increased incidence of somnolence, especially in the presence of reduced nutritional intake and weig STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
14) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a cont Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
15) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein l related or postpartum encephalopathy; possible undiagnosed urea cycle disorder, which is a contraindication (Pro (R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora 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)
16) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2003)
17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevate (Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPA release oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) capsules, 2003)
18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disor 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) oral tablets, 2006; Prod Info DEPAKOTE(R) ER extended-release tablet, 2006; Prod Info DEPAKOTE(R) sprinkle 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 i 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, 2003)
20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(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)
21) low BUN or protein avoidance; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Ir delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(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)
22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(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)
23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKI capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Info DEPAKOTE(R) ER tablet, 2006; 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 Adı
25) total valproate concentrations of 110 mcg/mL or higher in females, or 135 mcg/mL or higher in males; increas thrombocytopenia (delayed-release capsules) (Prod Info STAVZOR(R) delayed release oral capsules, 2008)
26) unexplained infant deaths (especially males), family history of; possible undiagnosed urea cycle disorder, wh contraindication (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPACON(R) IV injectio DEPAKENE(R) oral capsules, syrup, 2006; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006; Prod Inf ER extended-release tablet, 2006; 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 disa 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, 2
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 o
Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008)
4) abrupt discontinuation in epileptic patients; may precipitate status epilepticus (Prod Info DEPAKOTE(R) sprink
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-rel
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 DEPA
extended-release oral tablets, 2008)
8) multiorgan hypersensitivity reactions have occurred (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Pr
DEPAKOTE(R) ER extended-release oral tablets, 2008)
9) signs and symptoms (eg, encephalopathy; unexplained mental retardation, infant deaths (particularly males), c
elevated plasma ammonia or glutamine; history of cyclical vomiting and lethargy, ataxia, low BUN, or protein avoi
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 Adı
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 bleedir
occur (eg, hemorrhage, bruising, hemostasis/coagulation disorder) (Prod Info DEPAKOTE(R) sprinkle oral capsul
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 injectio
3) metabolic disorders, congenital; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
4) organic brain disease; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
5) pancreatitis, sometimes life-threatening, may occur (Prod Info DEPACON(R) IV injection, 2006)
6) pregnancy; increased risk of birth defects (Prod Info DEPACON(R) IV injection, 2006)
7) seizure disorders, severe, accompanied by mental retardation; increased risk of hepatotoxicity (Prod Info DEP
injection, 2006)
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 i
10) ataxia; possible undiagnosed urea cycle disorder, which is a contraindication (Prod Info DEPACON(R) IV inje
11) cyclical vomiting and lethargy; possible undiagnosed urea cycle disorder, which is a contraindication (Prod In
IV injection, 2006)
12) elderly; increased incidence of adverse effects (ie, somnolence, dehydration), sometimes with reduced nutriti
weight loss (Prod Info DEPACON(R) IV injection, 2006)
13) elevated plasma ammonia or glutamine, history of; possible undiagnosed urea cycle disorder, which is a cont
Info DEPACON(R) IV injection, 2006)
14) encephalopathy, history of unexplained encephalopathy or coma, encephalopathy associated with a protein l
related or postpartum encephalopathy; possible undiagnosed urea cycle disorder, which is a contraindication (Prc
(R) IV injection, 2006)
15) family history of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindication (
DEPACON(R) IV injection, 2006)
16) hepatic disease; prior history of; increased risk of hepatotoxicity (Prod Info DEPACON(R) IV injection, 2006)
17) higher doses (ie, approximately 50 mg/kg/day); increased risk for dose-related thrombocytopenia and elevate
(Prod Info DEPACON(R) IV injection, 2006)
18) hyperammonemia; may be present despite normal liver function tests; possible undiagnosed urea cycle disor
contraindication (Prod Info DEPACON(R) IV injection, 2006)
19) hypersensitivity reactions, multi-organ; have been reported within first 40 days of therapy and may be life-thre
DEPACON(R) IV injection, 2006)
20) irritability, episodic and extreme; possible undiagnosed urea cycle disorder, which is a contraindication (Prod
IV injection, 2006)
21) low blood urea nitrogen or protein avoidance; possible undiagnosed urea cycle disorder, which is a contraind
DEPACON(R) IV injection, 2006)
22) mental retardation, unexplained; possible undiagnosed urea cycle disorder, which is a contraindication (Prod
IV injection, 2006)
23) signs and symptoms of urea cycle disorders; possible undiagnosed urea cycle disorder, which is a contraindi
DEPACON(R) IV injection, 2006)
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 Adı
25) unexplained infant deaths (especially males), history of; possible undiagnosed urea cycle disorder, which is a
(Prod Info DEPACON(R) IV injection, 2006)

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 plac 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

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 p clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas 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 valproate during two clinical trials of valproate treatment of manic episodes associated with bipolar disor STAVZOR(R) delayed release oral capsules, 2008).

c) A mentally retarded 11-year-old girl experienced profound hypotension during an IV valproate infusio given to treat status epilepticus. Upon arrival in the emergency department, the girl was given IV diazepa the seizure temporarily. When the seizures began again, the girl was given IV lorazepam and started on mg. Her blood pressure 5 minutes prior to the start of the valproate infusion was 130/80 mmHg, but decr mmHg 39 minutes after the start of the infusion. She was given IV fluids and her blood pressure ranged mmHg and 60/30 mmHg. She was intubated and given dopamine and recovered 10 days later without fu (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 pl clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas 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 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 dr part of the trial (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 pl clinical trials of acute mania and during monotherapy treatment of complex partial seizures. In many cas 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 DEPAKOT 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 DEPAKOT 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 DEPAKOT 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) com 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).

3.3.1.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 DEPAKOT 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 receivi 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 r

capsules, 2008).
e) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conce
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 valproat
recurred when the patient was switched to carbamazepine. Valproate 500 mg twice daily was ordered af
experienced an extradural hematoma secondary to cranial trauma. His lesion was an itchy infiltrated eryt
histologically mimicking a non-epidermotropic T-cell lymphoma. Applying polymerase chain reaction to th
produced monoclonal rearrangement of the T-cell gamma gene. Valproate was discontinued and replace
carbamazepine 400 mg twice daily (the patient was using no other medications). The lesion became pro
infiltrated, but did not totally disappear. Approximately 6 months later, two additional papules appeared in
Cutaneous biopsy showed a pattern histologically identical to the original papule. Carbamazepine was w
other antiepileptic drugs were prescribed. All 3 skin lesions disappeared after 3 months; no relapse occu
of 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
acid 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 I
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 targ
on the trunk. Liver function tests were elevated with an aspartate aminotransferase level of 3550 units/L,
aminotransferase 5770 units/L and alkaline phosphatase level of 421 units/L. Stevens-Johnson syndrom
and with 2 weeks of prednisolone therapy his skin lesions cleared. After 30 days, liver function tests retu
(Tsai & Chen, 1998). Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have beer
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/TE
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
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 w
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).

3.3.2.B.2 Petechiae
a) Incidence: 1% to less than 5% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) Petechia 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 DEPAKOT
capsules, 2008).

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 alon 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 physica within 24 hours (Barrueto & Hack, 2001).

b) Chronic therapeutic use of valproic acid in young children may cause a carnitine deficiency resulting i symptoms of lethargy, weakness or hypotonia, hepatotoxicity, and hyperammonemia. An incidence of fa 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 a 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 aft 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 valpro between plasma carnitine and blood ammonia values (Ohtani et al, 1982).

3.3.3.A.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 in were 3.3 milliunits/L compared to 2.5 milli-units/L in the co than 0.01). Thyroxine (T4), free thyroxine (FT4), and free triiodothyronine (FT3) levels were not significar between the groups. Patients had been on therapy for a mean of 3 years (range 0.8 to 10.3 years). A se taken a mean of 5.8 years later was performed. Thyroid hormone levels in patients who had discontinue did not significantly differ from the controls. Patients had been off therapy for a mean of 7 years (Vainion

3.3.3.A.4 Hormone level - finding, Sex

a) Antiepileptic agents have been associated with changes in serum concentrations of male reproductiv 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 nanograms carbamazepine; 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 testoste hormone binding globulin, free androgen index, luteinizing hormone, follicle stimulating hormone, prolact 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 determin 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; how were not permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Ve 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- epiandrosterone 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. Su 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 women 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 wom 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, whe 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 le significantly increased compared with controls (n=25) (p less than 0.001), and more than half of the coho (57%) had serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) 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 wer 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 contro 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 o 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.A.5 Hyperammonemia

a) Hyperammonemia, sometimes present despite normal liver function tests, has been reported with val Patients who develop symptoms of hyperammonemia (hypothermia, 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 STAVZOR(R) delayed release o 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

concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentratio
His medication was changed to phenytoin 150 mg twice day and his confusion resolved. One week later
was 63 mcmol/L (reference range 11 to 35 mcmol/L) and his phenytoin and valproate concentrations we
and less than 10 mcg/mL, respectively. He was inadvertently 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).

c) A 37-year-old man with previously unknown ornithine transcarbamylase deficiency developed plasma
of up to 800 mcmol/L (normal less than 40 mcmol/L) after beginning sodium valproate therapy. He had b
with spinocerebellar degeneration and was having severe pain in the region of a sural-nerve biopsy whe
prescribed valproate 200 mg 3 times daily. After 9 days he appeared drowsy and confused with a 3-day
and vomiting. It was noted that plasma ammonia levels were increased and valproate was discontinued.
hospital however, he died. It was not established until after his death that he had ornithine transcarbamy
(Ellaway et al, 1999).

d) One study reported significantly higher postprandial plasma ammonia levels in children who received
other anticonvulsant(s) as compared to the control group (average 34 versus 20 mcg/dL, respectively). T
did find a positive correlation between serum valproic acid and plasma ammonia levels. Oral L-carnitine
reduced ammonia levels to normal within 15 to 45 days of therapy (Altunbasak et al, 1997).

e) The frequency of hyperammonemia in asymptomatic children receiving valproic acid was evaluated. V
concentrations were evaluated in three groups of children (receiving valproic acid only, receiving valproic
anticonvulsants, and control patients receiving other anticonvulsants). Hyperammonemia was reported i
receiving valproic acid alone or in combination with anticonvulsants (ammonia levels exceeding 45 micro
(mcg%)), as compared to 28% of the controlled group. Valproic acid serum concentrations ranged from 2
and there was no correlation with ammonia levels and drug serum concentrations. The authors suggest t
mild elevations in ammonia levels in adults can result in subtle neurologic dysfunction, that monitoring of
concentrations in valproic acid treated patients is desirable (Wyllie et al, 1983).

f) 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 is suggested that valproic acid or its metabolites may decrease the activity on N-acetylg
can decrease the activity of carbamyl phosphate synthetase I, inducing hyperammonemia (Sugimoto et a

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
prior to therapy and compared with levels in a healthy age- and sex-matched control group (p less than 0
comparisons). The finding of hyperhomocystinemia held true with both fasting and post-methionine homo
measurements. For the patients taking carbamazepine or valproate, serum concentrations of folate and
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 t
(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
receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R)
oral capsules, 2008).

3.3.3.A.10 Lipids abnormal

a) In a study evaluating lipids in children and adolescents receiving carbamazepine (n=14), valproic acid
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 (
as compared to the control group. Children receiving phenobarbital had high concentrations of total chol
cholesterol 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, and mg/day was initiated. Symptoms such as hyponatremia, elevated serum concentrations of antidiuretic ho 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 osmosity. Se concentrations were 10.5 mcg/mL. SIADH was diagnosed. The patient was switched from valproate to z 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 v 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 so 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 secretio 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% o 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 s 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 valp 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 tha occurred during the first 16 months of treatment but leveled off with continued treatment. Over the course significant increases in serum triglyceride levels, total serum cholesterol levels, or fasting blood glucose l reported (Grosso et al, 2009).

e) Obesity in children treated with valproate was common in a study of 55 children. Body mass index wa 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 grea 28% had weight gain between 5% and 10% (Corman et al, 1997). In another study of patients treated lon 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 concur 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 val
Patients who develop symptoms of hyperammonemia (hypothermia, unexplained lethargy and vomiting,
changes) while receiving valproate therapy should receive prompt treatment (including discontinuation o
therapy) and be evaluated for underlying urea cyclic disorder (Prod Info DEPAKOTE(R) sprinkle oral cap

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 so
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 DEPAKOT
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
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).

3.3.3.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
divalproex sodium (n=77) compared with 0% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
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, ab reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n= 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) oral capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia abdominal pain was reported in 23% of patients receiving valproate (n=77) compared with 6% of patients (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).

e) During a clinical trial of valproate monotherapy for complex partial seizures, abdominal pain was repo patients receiving high-dose valproate (n=131) compared with 9% of patients receiving low-dose valproa 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).

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 partia constipation was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients rec (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).

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 placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia diarrhea was reported in 13% of patients receiving valproate (n=77) compared with 6% of patients receiv (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).

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=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.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) 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).

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, dy reported in 9% of patients receiving valproate (n=89) compared with 8% of patients receiving placebo (n= STAVZOR(R) delayed release oral capsules, 2008).

c) Dyspepsia was reported in 13% of migraine patients receiving valproate (n=202) compared with 9% o receiving placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) oral capsules, 2008).

d) During a clinical trial of valproate monotherapy for complex partial seizures, dyspepsia was reported i receiving high-dose valproate (n=131) compared with 10% 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).

e) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia dyspepsia was reported in 8% of patients receiving valproate (n=77) compared with 4% of patients receiv (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).

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 partia anorexia was reported in 12% of patients receiving valproate (n=77) compared with 0% of patients receiv (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).

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, na in 22% of patients receiving valproate (n=89) compared with 15% of patients receiving placebo (n=97) (P 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 r 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 nausea, vomiting, and anorexia. There were 2 cases of pancreatitis reported among 2416 patients receiv during clinical trials, representing 1044 patient-years of experience. Pancreatitis has recurred upon recha valproate (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

c) Pancreatitis was reported in more than 1% but less than 5% of patients receiving valproate (n=265) fo 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 valproic 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 epiloia developed an acute exac pancreatitis. At the time, her valproic acid dosage was 25 mg/kg/day. She also took other medications fo 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 ar preservation of the stomach and pyloric ring. The resected specimens were notable for a large volume o 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 ult 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 syndr 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 contin further pancreatic symptoms (Plaza et al, 1999).

h) Two pediatric cases of valproic acid-associated pancreatitis occurred in the presence of endstage ren amylase levels were 232 units/L and 465 units/L, respectively, in a 14-year-old female on peritoneal dialy figures were 880 units/L and 530 units/L in a 12-year-old male on hemodialysis. Both had received valpr 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 trea routine monitoring of serum amylase 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 pancreati 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 oth effects and pancreatitis was not dose-related. It developed as early as one week and as late as 4.5 years 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. Trai discomfort occurred at this dosage (exact duration of therapy unspecified), and 2 days after beginning 45 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 pat after a period of 2 weeks. Valproic acid was initiated again after a period of 4 weeks and was again asso abdominal pain and elevated serum amylase (696 units/dL) after the dosage was increased from 20 to 2 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 attribut pancreatitis in these children to the use of valproic acid. However, signs of unusual abdominal discomfor followed by serum amylase examination in order to rule out the possibility of acute pancreatitis (Camfield

3.3.4.A.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, vo reported in 12% of patients receiving valproate (n=89) compared with 3% of patients receiving placebo (r 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 r capsules, 2008).
d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia vomiting was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiv (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).
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=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.B Divalproex Sodium

Abdominal pain

Constipation

Diarrhea

Hematemesis

Indigestion

Loss of appetite

Nausea

Pancreatitis

Vomiting

3.3.4.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 DI sprinkle oral capsules, 2008).
c) Abdominal pain was reported in 12% of patients receiving high-dose divalproex sodium (n=131) comp 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).

3.3.4.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 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 pa divalproex sodium (n=77) compared with 6% 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 w 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).

3.3.4.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 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 DEPAKOT 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 p 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 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).

3.3.4.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 p 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 w 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 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 pa divalproex sodium (n=77) compared with 14% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).

c) Nausea was reported in 34% of patients receiving high-dose divalproex sodium (n=131) compared wi 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 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 nausea, vomiting, and anorexia. There were 2 cases of pancreatitis reported among 2416 patients receiv during clinical trials, representing 1044 patient-years of experience. Pancreatitis may recur upon rechalle (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 (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 DEPAKOT 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 pa 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 w 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).

3.3.5 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 year-old Native American female. The patient had received 65 mg/kg/day for seizure disorder for 1 year presentation with anemia, thrombocytopenia, leukocytosis, and coagulopathy. The valproic acid serum le normal range (82 mcg/mL). Abnormal/immature myeloid precursor cells appeared in the bone marrow ar Although the diagnosis of APML was considered, the patient gradually recovered after valproic acid disc (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 ca increased bleeding times and hemorrhage (Prod Info STAVZOR(R) delayed release oral capsules, 2 Bruni & Wilder, 1979a; Gerber et al, 1979; Addison & Gordon, 1980; Hintze et al, 1987; Gidal et al, 1 inhibition of platelet aggregation is usually of no clinical significance unless patients are receiving otl

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 dail
3 years for grand mal epilepsy. During valproate therapy, the patient developed an acute pulmonary infe
resulted in severe nasal bleeding, hemoptysis, thrombocytopenia and abnormal clotting tests. Partial thro
74.8 seconds (normal 50), fibrinogen was 420 mg% (normal 160 to 400) and hemoglobin was 6 gram%.
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 reporte
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
with valproate 20 mg/kg for 7 months. There was no reported personal or family history of hematologic 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, 2008).

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 valproic 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 pancyto
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 mcmol/L (therapeutic range, 347 to 693 mcmol/L). Severe pancytopenia occurr
and a diagnosis of dysmyelopoiesis was made following examination of her bone marrow aspirate. She v
carbamazepine and her blood counts normalized in 6 weeks (So & Wong, 2002).

b) Valproic acid therapy resulted in myelodysplastic hematologic changes including macrocytosis, throm
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
mcg/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 a
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, valproic 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
titrated 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. Th

was then discontinued. The next day, the ANC dropped to its nadir of 47 cells/mm(3) and the patient rec
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 ta
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 functior
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; Covanis et al, 1982; Barr et al, 1982). The inci
induced thrombocytopenia has been reported to vary from 1% to 30% (Allarakhia et al, 1996a; Hoffr
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 8
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 5
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
mcg/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 r
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 importa
1999).

e) The incidence of thrombocytopenia (defined as a platelet count of less than 200,000/mm(3)) in childre

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 th 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 anticonvul cases of thrombocytopenia (defined as a platelet count less than 150,000/mm(3) occurring 3 to 8 months of valproate) were noted that were reported to be transient and self-limited. In 82% of cases, thrombocyt associated with an increase in platelet-associated IgG antibodies. There was an inverse relationship in t and the serum concentration of platelet-associated IgG antibody. There was not a significant difference b 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 fema valproate monotherapy. Its 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 tota concentrations (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significantl 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 valproa 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).

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 "acc Willebrand's Disease." No correlation was found between von Willebrand factor activity and dose or bloo acid or duration of therapy. The authors cautioned that when surgery is necessary, factor VIII von Willebr 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 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).

3.3.5.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/k counts returned to normal in all patients regardless of whether the drug was withdrawn or continued. Hig concentrations (110 mcg/mL or greater in females and 135 mcg/mL or greater in males) were significantl 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 discontinuatio 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) co 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 antiep 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 durir (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causalit attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first par 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 durir (n=202) and during monotherapy treatment of complex partial seizures (n=265). In many cases, causalit attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first par 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 hepa acquired from his sister. The boy presented with jaundice, decreased consciousness, lethargy, hyperam 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 da to the hospital. The authors postulate that the additive hepatotoxicity associated with the increased valpr 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 thera acid. It is suggested that valproic acid may induce a carnitine deficiency in young children and result in n symptoms of deficiency, hepatotoxicity, and hyperammonemia. Carnitine supplementation may help prev hepatotoxicity (Raskind & El-Chaar, 2000).

b) A 52-year-old male with no known risk factors developed fulminant hepatotoxicity that progressed to while taking valproic acid 500 mg twice daily for migraine prophylaxis. He presented with altered mental jaundice and anuria. An exhaustive diagnostic work-up failed to reveal an etiology. The patient had asso as well as acute tubular necrosis with renal failure and rhabdomyolysis. He fully recovered after 16 days and supportive care (Pinkston & Walker, 1997).

c) One study indicated that the greatest risk of fatal hepatotoxicity occurred in children between the age who were receiving multiple anticonvulsant therapy. The incidence of fatal hepatotoxicity in this group wa greater than the overall incidence of fatal hepatotoxicity of 1/10,000). The incidence of fatal hepatotoxicit age group was 1/7000. No hepatic fatalities were described in patients over the age of 10 years who rec as monotherapy. The risk of fatal hepatotoxic reactions in children over the age of 2 years receiving poly considerably lower (1/12,000), with the risk of fatal hepatic dysfunction in patients above 2 years of age r acid as monotherapy being 1/45,000. Thus, the risk of fatal hepatic reactions appears to be greatest in v (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, 198 elevations in transaminases (aspartate aminotransferase (AST; SGOT) and alanine aminotransferas 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 val normally toxic substance, but in the presence of metabolic abnormalities such as an inborn error of administration with other drugs, it may become toxic (Rimmer & Richens, 1985f).

3.3.6.A.6 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 lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). Mo function tests should be initiated prior to therapy and at frequent intervals during treatment, mainly during months. However, abnormal serum biochemistry may not be present in all cases. Children under the age increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have co disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain dise dysfunction has progressed in some cases, even with the discontinuation of drug (Prod Info STAVZOR(R oral capsules, 2008).

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

c) It is speculated that valproic acid is not 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 & Rich one case, medium chain acyl-CoA dehydrogenase deficiency, resulting in abnormal fatty acid beta-oxida 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 epilepsy. The patient had also been receiving phenytoin and phenobarbital. The patient developed cereb in a 24-hour period. These data suggest that hepatic failure secondary to valproic acid can also occur aft 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 months and 250 mg to 1000 mg daily over approximately 7 weeks (with other anticonvulsants), respectiv described. Autopsy revealed mixed toxic cholestatic hepatitis with diffuse hepatocellular injury which tern centrolobular microvesicular fatty changes and submassive necrosis. The site of injury appeared to be bi 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 (SGPT) level raised

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

b) Increased SGPT was reported in more than 1% but less than 5% of patients receiving divalproex sod 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 DEPAKOT capsules, 2008).

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 soc 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 DEPAKOT capsules, 2008).

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 lethargy, anorexia, malaise, facial edema, weakness, or loss of seizure control (in epileptic patients). Mo function tests should be initiated prior to therapy and at frequent intervals during treatment, mainly during months. However, abnormal serum biochemistry may not be present in all cases. Children under the age increased risk of developing hepatotoxicity, especially if they are taking multiple anticonvulsants, have co disorders, have severe seizure disorders accompanied by mental retardation, or have organic brain dise dysfunction 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 redu red blood cells. There may be a link between intracellular levels of glutathione and the progression of hu immunodeficiency virus (HIV) disease. Decreased glutathione levels may activate the replication of HIV. with cell lines infected with HIV showed the addition of valproate increased viral expression and replicati 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 associate with other organ system involvem 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, disconti therapy and begin an 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 mon 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, lymp monocytosis, and stimulated lymphocytes. Liver enzymes were also slightly elevated. Since the authors infections may contribute to the pathogenesis of hypersensitivity, the child was tested for reactivation of l 6. Titers were significantly increased within 15 days. Patch testing revealed hypersensitivity to both valpr 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 (valpr phenytoin, phenobarbital, carbamazepine) was reported. Patients receiving valproate sodium exhibited s mean 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 treatm acid. The laboratory and clinical symptoms disappeared after discontinuation of valproic acid (Gigli et al, 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 associate with other organ system involvem

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, disconti 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

a) Incidence: 10% 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, as reported in 10% of patients receiving valproate (n=89) compared with 7% of patients receiving placebo (n STAVZOR(R) delayed release oral capsules, 2008).

c) 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 re capsules, 2008).

d) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia asthenia was reported in 27% of patients receiving valproate (n=77) compared with 7% of patients receiv (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).

e) During a clinical trial of valproate monotherapy for complex partial seizures, asthenia was reported in receiving high-dose valproate (n=131) compared with 10% 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).

3.3.8.A.2 Backache

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

b) 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 re capsules, 2008).

3.3.8.A.3 Osteomalacia

a) A 2-year cross-sectional and retrospective study concluded that lumbar spine bone mineral density va significantly reduced in prepubertal children treated with valproic acid and carbamazepine compared to c children treated with antiepileptics (valproic acid: 17 boys, 16 girls; mean age 8.8 +/- 2 years; carbamaze girls; mean age 9.7 +/-1.6 years) were compared to age- and sex-matched controls (13 boys, 9 girls; me 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 insu factor (IGF)-I and IGF binding protein (IGFBP)-3 levels, which affect bone metabolism and BMD, betwee receiving antiepileptics compared to controls were not significant (Kumandas et al, 2006).

3.3.8.A.4 Secondary myopathy

a) A 4-year-old male child developed myopathy with symptoms of progressive weakness in all limbs 16 starting valproate sodium for epilepsy. Over 1 year the valproate sodium dose was gradually increased fr 40 mg/kg. Four months after starting on 40 mg/kg, he developed lower limb weakness resulting in difficu 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 initiate there was improvement and within 2 months complete recovery. Complete recovery was further demons months later (Kasturi & Sawant, 2005).

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

c) The syndrome known as MELAS, including mitochondrial myopathy, encephalopathy, lactic acidosis 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 infar 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= 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 DEPAKOT 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= 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 DEPAKOT 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 (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 DEPAKOT 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 DEPAKOT 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 monothe included irritability, longer and deeper sleep, superficial sleep, hyperactivity, increased alertness, lassitu 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 partia was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients receiving placeb cases, causality could not be determined as patients also received other antiepilepsy drugs concurrently (Prod Info STAVZOR(R) delayed release oral capsules, 2008).

3.3.9.A.4 Cerebral atrophy

a) In a series of 16 patients treated with valproate in whom cranial computer tomography (CT) were perf demonstrated new or progressive cerebral atrophy. The atrophy improved in the two patients in whom cr 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 dos divalproex sodium. The patient had been poorly controlled while receiving divalproex sodium for 6 years

phenobarbital, phenytoin, carbamazepine, and gabapentin. The divalproex sodium dose was increased f to 2500 mg/day, and the phenobarbital, phenytoin, carbamazepine and gabapentin were slowly discontir 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 pat after 10 hours of the dose escalation. Her venous ammonia level was 921 mcg/dL, and the arterial amm mcg/dL (reference range 22 to 78). Possible causes of hyperammonemia and coma were excluded by e gastrointestinal bleeding or portosystemic shunt and other metabolic, toxic, and structural factors respec divalproex sodium was discontinued and within 48 hours, the ammonia level normalized to 69 mcg/dL ar regained consciousness. A possible urea enzyme deficiency may have contributed to the development o hyperammonemic coma. The Naranjo probability scale conducted stated that the causal relationship bet and 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 a with epilepsy. Withdrawal of the drug resulted in dramatic improvement in memory and other tasks of int It is suggested that valproic acid may induce a dementia-like syndrome via either a direct toxic central ne (CNS) effect, a paradoxical epileptogenic effect, or an indirect CNS effect via production of hyperammon 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 e valproate-induced hyperammonemic encephalopathy. He had been experiencing uncontrolled seizures v phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 da progressively lethargic and was eventually unresponsive. His venous ammonia level was 524 mcmol/L (r mcmol/L) with normal liver enzymes. Serum carnitine levels were also low. After 15 days, a repeat crania extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors specula hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoide of seizures 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 ir 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).

c) During two clinical trials of valproate treatment of manic episodes associated with bipolar disorder, diz reported in 12% of patients receiving valproate (n=89) compared with 4% of patients receiving placebo (r STAVZOR(R) delayed release oral capsules, 2008).

d) Dizziness was reported in 12% of migraine patients receiving valproate (n=202) compared with 6% o placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

e) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia dizziness was reported in 25% of patients receiving valproate (n=77) compared with 13% of patients rec (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).

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 Pa movement disorder 1 week after starting valproate therapy. This man, who had no prior history of m was started on valproate due to an increase in aggressive and violent behaviors. The valproate dos increased to 300 mg per day over one week and resulted in a serum level of 11 mcg/mL. At this time experienced resting tremors, rigidity, gait disturbance, and bradykinesis and his Unified Parkinson's Scale (UPDRS) score increased from 18 to 59. Valproate was discontinued 2 weeks later when ther lessening in the Parkinsonian symptoms. Movement disorder signs gradually resolved following disc valproate (Iijima, 2002).

2) Parkinson's syndrome has been associated with chronic valproate therapy. In a series of 36 patie 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 abulia and 16 (44%) had upper motor neuron signs (Armon et al, 1996). Most patients im valproate was discontinued. An extrapyramidal syndrome, unresponsive to antiparkinson medicatior developed in a 52-year-old man with schizophrenia who was given sodium valproate 1 to 2 g/day (L

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 reporte patients receiving high-dose valproate (n=131) compared with 7% of patients receiving low-dose valproa 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).

3.3.9.A.11 Headache

a) Incidence: 5% to 31% (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 headache was reported in 31% of patients receiving valproate (n=77) compared with 21% of patients rec (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).

c) During a clinical trial of valproate monotherapy for complex partial seizures, headache was the only a reported in at least 5% of patients receiving high-dose (n=131) valproate and occurring at an equal or gr patients receiving low-dose valproate (n=134). In many cases, causality could not be determined as pati titrated off another antiepilepsy drug during the first part of the trial (Prod Info STAVZOR(R) delayed rele 2008).

3.3.9.A.12 Hyperammonemic encephalopathy

a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in pati cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of hyperammonemic encephalopathy (unexplained lethargy and vomitin 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 topira resolution of hyperammonemia upon discontinuation of either drug (Prod Info STAVZOR(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 concentration of 836 mcg/dL (reference range 19 to 60 mcg/dL). His trough valproate serum concentratio His medication was changed to phenytoin 150 mg twice day and his confusion resolved. One week later was 63 mcmol/L (reference range 11 to 35 mcmol/L) and his phenytoin and valproate concentrations we and less than 10 mcg/mL, respectively. He was inadvertently started on valproate again at the former do days his ammonia concentration increased to 130 mcmol/L. He became confused and lethargic and his E 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 1 day and on the second day his confusion de baseline (Feil et al, 2002).

c) Clinicians reported two adult cases of valproate-induced hyperammonemic encephalopathy, which oc combination therapy including valproate and topiramate. The patients were a 32-year-old man who had l epilepsy with complex partial and secondarily generalized seizures and a 37-year-old woman with focal e 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 experienced 2 secondarily generalized tonic-clonic seizures (the first time in 10 years for the woman). EE revealed continuous generalized slowing for both. The patients had previously tolerated valproate in com medications (phenobarbital, carbamazepine, lamotrigine). The encephalopathy occurred in both instance and topiramate were given concurrently in a combination regimen. Both had serum levels of valproate be therapeutic range (ie, 38 and 47 mcg/mL, respectively; therapeutic range, 50 to 100 mcg/mL) and elevat ammonia concentrations (116 and 88 mcmol/L, respectively; normal range 11 to 60 mcmol/L). One patie by discontinuation of valproate and the other, by withdrawal of topiramate. The authors suggested that to increase ammonia levels by its inhibition of carbonic anhydrase and cerebral glutamine synthetase (Ham

d) Ten days following initiation of valproic acid (10 mg/kg/day), a 51-year-old female presented with a ra level of consciousness (Glasgow coma score 5/15). EEG showed triphasic waves consistent with hepatic Serum valproic acid and liver enzyme levels were normal; blood arterial ammonia concentration was sign (234 mcmol/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) devel hyperammonemic encephalopathy after valproic acid therapy. OTC deficiency is an X-linked disorder wh common inherited cause of hyperammonemia. The child was experiencing frequent seizures and had va to her carbamazepine therapy. After 7 days, she became deeply somnolent. Her plasma ammonia level (normal less than 50 mcmol) with normal serum transaminases and fibrinogen. Valproic acid was discon deficiency diagnosis was based on non-detectable serum citrulline and high urinary excretion of orotic ac treated with a low-protein diet, sodium benzoate, sodium phenylbutyrate, and substitution of L-arginine. A ammonia levels fell to 55 mcmol (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 v phenytoin and phenobarbital when valproic acid 500 mg twice daily was added to his regimen. After 3 da progressively lethargic and was eventually unresponsive. His venous ammonia level was 524 mcmol/L (r mcmol/L) with normal liver enzymes. Serum carnitine levels were also low. After 15 days, a repeat crania extensive progression of his demyelinating disease. He expired 3 weeks thereafter. The authors specula hyperammonemia may have exacerbated his disease. They conclude that valproic acid should be avoide of seizures in patients with demyelinating disease (Blindauer et al, 1998).

g) A 31-year-old woman with systemic lupus erythematous and a seizure disorder treated with valproic a 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 mcmol/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 ir
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

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 a
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 discontinue
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
generalized 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 mcmol/L. Valproic acid was discontinued and la
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 occurr
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, and
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=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).

c) During a clinical trial where valproate was given as adjunctive therapy for treatment of complex partia was reported in 25% of patients receiving valproate (n=77) compared with 6% of patients receiving place 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 pa placebo (n=81) during two clinical trials and their long-term extension (Prod Info STAVZOR(R) delayed r capsules, 2008).

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

f) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high conce 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, benztropine, and cyproheptadine on valpro patients were studied. Propranolol was clearly the most therapeutic. Amantadine was moderately effecti cyproheptadine, diphenhydramine and benztropine 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 pa divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Amnesia was reported in 7% of patients receiving high-dose divalproex sodium (n=131) compared wi 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 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 p divalproex sodium (n=77) compared with 7% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).
c) Asthenia was reported in 21% of patients receiving high-dose divalproex sodium (n=131) compared v 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).

3.3.9.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 patie divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE 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 p divalproex sodium (n=77) compared with 13% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).
c) Dizziness was reported in 18% 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).

3.3.9.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) compa 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).

3.3.9.B.6 Headache
a) Incidence: 31% (Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008)
b) In a clinical trial of adjunctive therapy for complex partial seizures, headache was reported in 31% of divalproex sodium (n=77) compared with 21% of patients receiving placebo (n=70) (Prod Info DEPAKOT capsules, 2008).

3.3.9.B.7 Hyperammonemic encephalopathy
a) Hyperammonemic encephalopathy, sometimes fatal, has been reported with valproic acid use in patie cycle disorders (particularly ornithine transcarbamylase deficiency) and in patients receiving concomitant Patients who develop symptoms of unexplained hyperammonemic encephalopathy (unexplained letharg mental status changes) while receiving valproate therapy should receive prompt treatment (including dis valproate therapy) and be evaluated for underlying urea cyclic disorder. Most patients receiving concomi experienced resolution of hyperammonemia upon discontinuation of either drug (Prod Info DEPAKOTE(R 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 v 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 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) In a clinical trial of adjunctive therapy for complex partial seizures, nystagmus was reported in 8% of divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).
c) Nystagmus was reported in 7% 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).

3.3.9.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 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 DEPAKOT

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% receiving divalproex sodium (n=77) compared with 11% of patients receiving placebo (n=70) (Prod Info D sprinkle oral capsules, 2008).

c) Somnolence was reported in 30% of patients receiving high-dose divalproex sodium (n=131) compar 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).

d) Due to a higher risk of somnolence among the elderly, the starting dose should be reduced and dose 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 pati divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

c) Tremor was reported in 57% of patients receiving high-dose divalproex sodium (n=131) compared wi 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 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 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose v In many cases, causality could not be determined as patients were being titrated off another antiepilepsy 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 partia amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% receiving placebo (n=70). In most cases, causality could not be determined as patients also received oth drugs 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 8% of patients receiving high-dose valproate (n=131) compared with 4% of patients receiving low-dose v In many cases, causality could not be determined as patients were being titrated off another antiepilepsy 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 partia amblyopia/blurred vision was reported in 12% of patients receiving valproate (n=77) compared with 9% receiving placebo (n=70). In most cases, causality could not be determined as patients also received oth drugs 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 partia was reported in 16% of patients receiving valproate (n=77) compared with 9% of patients receiving place 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 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 partia nystagmus was reported in 8% of patients receiving valproate (n=77) compared with 1% of patients rece (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).

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 sodi 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 DEPAKOT capsules, 2008).

3.3.10.B.2 Amblyopia

a) In a clinical trial of adjunctive therapy for complex partial seizures, amblyopia/blurred vision was repo patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Pro (R) sprinkle oral capsules, 2008).

b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=13 4% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex part many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another 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 repo patients receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Pro (R) sprinkle oral capsules, 2008).

b) Amblyopia/blurred vision was reported in 8% of patients receiving high-dose divalproex sodium (n=13 4% of patients receiving low-dose divalproex sodium (n=134) for monotherapy treatment of complex part many cases, causality could not be attributed to divalproex alone, as patients were titrated off of another 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 pa divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DEPAKOTE capsules, 2008).

3.3.11 Otic Effects

Valproic Acid

Divalproex Sodium

3.3.11.A Valproic Acid

Ototoxicity - deafness

Tinnitus

3.3.11.A.1 Ototoxicity - 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 spe 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 increa ears. At that time, his serum valproic acid level was 67.5 mcg/mL (within the therapeutic range). The pati 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

Ototoxicity - 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 DEPAKOT capsules, 2008).

3.3.11.B.2 Ototoxicity - 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= 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 DEPAKOT 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 wit 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 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 during 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 partia 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 antiepil 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 receiving valproate (n=77) compared with 4% of patients receiving placebo (n=70). In most cases, causa determined as patients also received other antiepilepsy drugs concurrently with valproate (Prod Info STA 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 receiv valproic acid per day as part of a controlled study. The valproic acid was discontinued and 5 days later th 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 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 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=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 DEPAKOT
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 DEPAKOT
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 antiep
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 6
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-co
studies covering 11 different AEDs used for several different indications such as epilepsy, selected psyc
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.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 behavic 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 psyc 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 placebc 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).

3.3.13 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 delayed 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, phospha glycosuria, mild metabolic acidosis, aminoaciduria, and evidence of rickets. Symptoms slowly improved follov discontinuation of both drugs. It is difficult to determine from this report whether this adverse reaction occurre therapy 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 c 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 freque morphologically normal sperm was found in carbamazepine treated men with partial epilepsy (n=15), in valpr men with generalized epilepsy and in oxcarbazepine treated men with partial epilepsy (n=18) (p less than 0.0 carbamazepine and valproic acid and p less than 0.05 for oxcarbazepine) compared to healthy controls (n=4 significant decrease in the frequency of motile sperm was also found with all treatment groups combined whe healthy controls (p less than 0.05). Within the various treatment groups, valproic acid treated patients had a s significant decrease in the frequency of motile sperm than in the control group (p less than 0.05). Carbamaze had high frequencies of abnormally low sperm concentration (p less than 0.001) and poorly motile sperm (p l 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) ha 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 furth valproic acid treated men with abnormal sperm morphology had smaller testicular volumes than control wher 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 partia bronchitis was reported in 5% of patients receiving valproate (n=77) compared with 1% of patients receiv (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).

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 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 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 erythro 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 c was switched from sodium valproate to gabapentin 300 mg/day and the patient had no recurrence of ple months follow-up. After 7 months, an epileptic episode caused the patient to resume sodium valproate th month later the patient experienced a recurrence of right-sided pleural effusion with transudative effusion relapse, gabapentin was increased to 400 mg twice daily and no pleural fluid recurrence was observed u (Tryfon et al, 2009).

c) Eosinophilic pleural effusion developed in a 34-year-old male treated with valproic acid 1500 mg/day. months after the initiation of therapy, the patient presented with fever and nonproductive cough. Upon ho medications were discontinued and a full medical workup was conducted. There was no evidence of pne hemothorax, pulmonary infiltrates, lymphadenopathy or infection. The symptoms resolved and the patien Rechallenge with valproic acid resulted in the reappearance of symptoms (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 fema 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 thrombo 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 partia 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 oth 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 20% of patients receiving high-dose valproate (n=131) compared with 13% of patients receiving low-dos (n=134). In many cases, causality could not be determined as patients were being titrated off another an 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 patie valproate (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info STAVZOR(R) delaye 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 p divalproex sodium (n=77) compared with 1% of patients receiving placebo (n=70) (Prod Info DEPAKOTE 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 wi 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 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 d patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT 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 d
patients were titrated off of another antiepilepsy drug during the first part of the trial (Prod Info DEPAKOT
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 patie
divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
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=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 DEPAKOT
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 patien
valproate (n=77) compared with 4% of patients receiving placebo (n=70). In many cases, causality could
to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part of the tria
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%
receiving valproate (n=77) compared with 9% of patients receiving placebo (n=70). In many cases, causa
attributed to valproate alone, as patients were titrated off of another antiepilepsy drug during the first part
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 rev
fatal outcomes. Most patients presented with nausea, vomiting and apathy. Increase in seizure frequ
concurrent febrile illness also occur. Patients developing any signs of RLS should have valproic acid
immediately (Sugimoto et al, 1983; Gerber et al, 1979).

b) 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-indu
hepatotoxicity. Laboratory values revealed increased plasma ammonia levels, increased liver enzymes a
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-acet
can decrease the activity of carbamyl phosphate synthetase I, inducing hyperammonemia (Sugimoto et a
d) Features of Reye's syndrome were reported in a 3-year-old girl receiving valproic acid 600 mg daily.
attack, which caused unconsciousness and subsequent recovery, the patient became increasingly drows
Blood ammonia levels and bilirubin were elevated, but liver enzymes were within a normal to slightly elev
serum carnitine was decreased. Postmortem liver biopsy revealed microvesicular steatosis of hepatocyte
suggested that valproic acid and its metabolites needed to be investigated for their influence on carnitine
the resultant storage of free fatty acids as lipid particles (Bohles et al, 1982).
e) Reye-like syndrome (RLS) associated with valproic acid was reported in a 40-month-old mentally reta
severe refractory multifocal seizure disorder. The patient was receiving phenytoin and ethosuximide in a
acid. Increased liver enzymes were noted 2 weeks prior to admission. A low-grade fever and loose, foul
were noted shortly before onset of generalized seizure activity. Blood ammonia levels were increased. Li
widespread disorganization of the parenchyma with swelling of the hepatocytes and compression of the
diffuse fatty infiltration, including macrovacuoles and microvacuoles was also identified (Keene et al, 198
f) A fatal case of Reye-like syndrome was reported in an 8-year-old boy receiving valproic acid 375 mg t
seizure episode, the boy became febrile and tachypneic; liver enzymes and blood ammonia levels were
Postmortem examination revealed panlobular microvesicular fatty changes in the liver and renal tubules.
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 patien
multiple medications including valproic acid 250 mg three times daily, phenobarbital 60 mg daily, phenyto
and acetazolamide 125 mg twice daily. The patient developed a viral respiratory infection and steadily de
increasing temperature and loss of consciousness. Liver enzymes and blood ammonia levels were eleva
examination revealed a bronchopneumonia and an enlarged, yellow, greasy liver with a mottled appeara
of venous congestion. Biopsy showed marked fatty changes in the liver with fat formed vacuoles which fi
in 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 patien
divalproex sodium (n=77) compared with 4% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
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 pa
divalproex sodium (n=77) compared with 6% of patients receiving placebo (n=70) (Prod Info DEPAKOTE
capsules, 2008).
c) Infection was reported in 20% of patients receiving high-dose divalproex sodium (n=131) compared w
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).

3.3.16.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%
receiving divalproex sodium (n=77) compared with 9% of patients receiving placebo (n=70) (Prod Info DI
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 DEPAKOT 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 extende tablets, 2006) (All Trimesters)

a) There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be accep 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, cons 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 un folic 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, 200 DEPAKOTE(R) delayed-release oral tablets, 2006a; Prod Info DEPACON(R) IV injection, 2006; Prod Info DE capsules, oral syrup, 2006). 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 malformatic (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; P DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) oral capsules, oral syrup, 2006).

b) 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 monotherapy w to 1.6% (RR 6.0; 95% CI 3.5 to 10.2) of an external comparison group. Anomalies reported in order of freque neural tube, hypospadias, polydactyly, 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 offspri 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 hypospadia was similarly higher in the monotherapy and combination therapy groups (RR 4.8, p=0.05; respectively).

c) Numerous cases have been reported of fetal neural tube defects, primarily spina bifida, and/or cardiac def of Fallot, patent ductus arteriosus, valvular aortic stenosis, and ventricular septal defect). There is an increas neural tube defects with exposure during the first trimester of pregnancy. Risk of spina bifida in children of wo valproic acid during pregnancy 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 DE delayed-release oral tablets, 2006a; Prod Info DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora 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).

d) 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 sprinkle 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, 198

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 afte prenatal exposure to valproic acid. The types of limb deficiencies reported included overlapping digits, talipes clinodactyly, 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 third 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 i infants exhibited withdrawal symptoms within 12 to 24 hours including irritability, jitteriness, hypertonia, seizu 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 prodrugs) is used in pregnant women, there is a substantially incre teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is largely o 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 each otl drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, su acid, progabide, and lamotrigine (Bianchetti et al, 1987c; Ramsay et al, 1990c; Spina et al, 1996c). Such com 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, 2

2) World Health Organization Rating: Compatible with breastfeeding. Monitor infant for side effects. (Anon, 2002)

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 wh breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this dr 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 DEPACON(R) IV injection, 2006; Prod Info DEPAKENE(R) ora 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 inf 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 breastfeed (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 sodiu 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

Fosphenytoin

Ginkgo

Imipenem

Isoniazid

Lamotrigine

L-Methylfolate

Lopinavir

Lorazepam

Mefloquine

Meropenem

Nifedipine

Nimodipine

Nortriptyline

Oxcarbazepine

Panipenem

Phenobarbital

Phenytoin

Primidone

Rifampin

Rifapentine

Risperidone

Ritonavir

Rufinamide

Tipranavir

Topiramate

Vorinostat

Zidovudine

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 and valproic acid when combined with acyclovir treatment. This reduction resulted in increased seizure activi approximately one per month to 25 in one day. Phenytoin dosage was increased and plasma levels returned 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 an

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 histor experienced increased seizure activity after being treated with acyclovir in addition to his antiepileptic me patient's trough plasma levels of phenytoin and valproic acid were 17 and 32 mcg/mL, respectively, 10 d acyclovir treatment for viral throat and mouth lesions. Four days after initiation of acyclovir treatment, the were 5.0 and 22 mcg/mL, respectively. Acyclovir treatment was discontinued after six days. Three and si acyclovir withdrawal, phenytoin and valproic acid plasma levels were still low, and the patient experience seizures five days after discontinuation. Phenytoin dosage was increased to reach therapeutic plasma le frequency of seizures was reduced to two or three per week. The authors suggest that further study of th 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) ar concentration (Cmax) for amitriptyline and its active metabolite, nortriptyline, when given concurrently with div (Wong et al, 1996a). Monitor amitriptyline levels in patients taking valproate concomitantly. Consideration sho 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 nortripyline concentrations in patients taking valproa 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 amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving n divalproex sodium 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalp resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the an under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was coadministration with divalproex sodium. For nortriptyline, the metabolite of amitriptyline, AUC was increa Cmax 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, 1
b) The addition of valpromide to a stable amitriptyline regimen may result in an increase of antidepressa concentrations. Twenty patients with major depressive illness (DSM - III criteria) were divided into two gr with amitriptyline alone and one treated with both amitriptyline and valpromide. All patients received oral mg once daily in the evening for 20 days. Only benzodiazepines (diazepam, lorazepam, bromazepam, cl dipotassique), 5-30 mg/day, were also administered. Ten patients also received 600 mg valpromide daily amitriptyline to avoid relapses and/or to decrease irritability and agitation. No statistically significant differ amitriptyline and nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patie amitriptyline 125 mg daily. In the ten patients who received valpromide 600 mg, amitriptyline and nortript 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 1(less than 0.01). No significant relationship was seen between the percentage increase of amitriptyline lev 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 betwee plasma levels before and after valpromide (r equal to 0.87, p less than 0.001). Tricyclic antidepressant pl increase above the therapeutic window after addition of valpromide. Monitoring of plasma levels of tricyc 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. in increased free valproate free fractions (Prod Info Depakote(R) ER, 2003j) by 30% to 65% (Abbott et al, 198 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, w doses, monitoring of valproic acid concentrations might be considered. An alternative analgesic such as acet 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-s of valproate rose from 12% to 43% in the presence of salicylate in five of these patients. Half-life of valpr total and free valproate concentrations, increased. Renal excretion of unchanged valproate decreased w 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 panipener therapy 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 admitted to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while was decreased to 4.5 mg/kg/day. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three 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 carbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission f pneumonia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamipr and 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 treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of disc panipenem/betamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipror carbamazepine level was not significantly altered (Yamagata et al, 1998).

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 fro 108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 m the valproic acid dose 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 concentrat 55 mg/mL and the frequency of the seizures was decreased. Incidentally, in this patient, the phenytoin a levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

3.5.1.E Carbamazepine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur decreased valproic acid effectiveness

2) Summary: The literature contains conflicting data regarding the effects of combined carbamazepine and v 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 va ene-VPA (thought to be the most toxic metabolite with potential for hepatotoxicity and teratogenicity) is signifi with coadministration of carbamazepine (Kondo et al, 1990a). Valproic acid may increase, decrease, or caus carbamazepine concentrations (Mattson et al, 1982a; Levy et al, 1984a; Pisani et al, 1990a; Anderson et al, 1

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drow when valproic acid is added. Serum carbamazepine concentrations should also be measured, though clinicia aware of the increase in the concentration of the active metabolite, carbamazepine-epoxide, which is not rout but does contribute to the efficacy and toxicity of the drug. If carbamazepine is added to valproic acid therapy acid levels; increased 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 w 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 (Ri 1985a; Flachs et al, 1979; Adams et al, 1978). In an in vitro study of protein binding, valproic acid compe carbamazepine plasma protein binding sites, resulting in significant increases in free carbamazepine (Ma Concurrent therapy of valproic acid and carbamazepine in seven patients was found to decrease levels o by 3% to 59% and protein binding decreased. The plasma concentration ratio of carbamazepine-10,11-e carbamazepine increased in all patients by 11% to 500% (Levy et al, 1984; Pisani et al, 1990) probably d epoxide hydroxylase by valproic acid (Robbins et al, 1990). In addition, carbamazepine may cause a red valproic acid half-life with increased clearance secondary to enzyme induction and increased hepatic me et al, 1979; Rimmer & Richens, 1985a; Mahaly et al, 1979). Infrequent reports have indicated symptoms nausea, or confusion when valproic acid was added to carbamazepine therapy (Lhermitte et al, 1978; Ha A single case of psychosis following the addition of carbamazepine to valproic acid has been reported in refractory epilepsy (McKee et al, 1989).

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-valpro these individuals (Anderson et al, 1994a).

d) The pharmacokinetics of valproic acid and its metabolites when coadministered with carbamazepine epileptic patients. The ratio of valproic acid concentration to dose was significantly lower in those patient acid with carbamazepine compared with those receiving only valproic acid. Additionally, the ratio of 4-en concentration to valproic acid concentration was significantly higher in those receiving combined carbam acid compared with those on valproic acid monotherapy. 4-ene-VPA, reported to be the most toxic of val metabolites, may manifest as hepatotoxicity and teratogenicity (Kondo et al, 1990).

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; Fir 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 hyc valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ov

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 cholestyram significantly reduced valproic acid area under the concentration-time curve (AUC) and maximum concentratic However, administration of valproic acid three hours before taking cholestyramine resulted in no significant pl changes (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 cholestyramin serum valproic acid concentrations. If these drugs are to be given together, administer cholestyramine at leas 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 concentrati were investigated in six healthy volunteers. Subjects participated in three treatment phases, with a minim washout period between phases. During phase 1, the subjects received a single dose of valproic acid 25 phase 2, subjects received cholestyramine 4 g twice daily for one day, followed by valproic acid 250 mg dose of cholestyramine. Phase 3 was identical to phase 2 except that the valproic acid 250 mg was take before the morning dose of cholestyramine. When valproic acid was given concurrently with cholestyram acid area under the concentration-time curve (AUC) decreased by 21% and the valproic acid maximum c (Cmax) decreased by 15% compared to valproic acid alone. When valproic acid was given three hours b cholestyramine, no significant changes in AUC or Cmax were observed. Based on this data, decreases i concentrations can be partially avoided by taking the cholestyramine three hours after valproic acid (Mall

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 metaboli 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 concomitar therapy.

7) Probable Mechanism: unknown

3.5.1.H Clomipramine

1) Interaction Effect: an increased risk of clomipramine toxicity (agitation, confusion, hallucinations, urinary re tachycardia, seizures, coma)

2) Summary: Comedication with clomipramine and valproic acid may increase serum levels of clomipramine increased side effects. Clomipramine toxicity developed in a patient twelve days after valproic acid therapy w Metabolism of clomipramine is mediated through N-demethylation, hydroxylation, and glucuronidation, and va 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 overdosing as a result of elevated conc clomipramine when comedicating with valproic acid. The clomipramine dose may need to be reduced when v 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 cc became elevated after she began concomitant therapy with valproic acid. Antidepressant therapy with cl lorazepam was initiated while being hospitalized for treatment of her psychiatric disorder. These two age reduce the frequency of panic attacks and to improve symptoms of suicidal and self-destructive behavior clomipramine 150 mg/day resulted in serum clomipramine levels in the normal range. Lorazepam was in 2 mg/day After two weeks of therapy valproate was initiated at 1000 mg/day because emotional instabilit destructive behavior remained unimproved. After five days of therapy the serum levels of clomipramine a desmethylclomipramine increased to 447 ng/mL and 85 ng/mL, respectively. Valproate serum concentra mcg/mL. The valproate dose was subsequently adjusted to 1400 mg/day. Seven days after the increase clomipramine and desmethylclomipramine serum concentrations were 479 ng/mL and 269 ng/mL respec the valproate serum level was 55 mcg/mL. The patient noted a feeling of numbness and exaggerated sle After the clomipramine dose was reduced to 75 mg/day, these symptoms resolved. The author conclude in serum clomipramine concentrations was primarily due to comedication with valproate (Fehr et al, 200

3.5.1.I Dehydroepiandrosterone

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 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 dehydroepian (DHEA) may cause a return of symptoms. Patients with a personal or family history of bipolar disorder should avoid DHEA use.
7) Probable Mechanism: proserotonergic activity of dehydroepiandrosterone may predispose patients to mar dehydroepiandrosterone is a precursor to androgenic steroids, which in high doses may precipitate mania
8) Literature Reports
a) A 68-year-old male with no documented psychiatric history initiated 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 inpatient admission secondary to rapid, loud, pressured 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. Urinary drug scree Over the seven-day hospital stay, with the institution of valproic acid 500 mg twice daily, the patient's beh patterns improved, and the patient believed DHEA led to his symptoms. There were no ethanol withdraw 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 re valproic acid concentrations and may result in loss of seizure control. If valproic acid concentrations cannot b within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy should be con 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 coadmi result in reduced valproic acid concentrations and possibly a loss of seizure control. If valproic acid concentra maintained within the therapeutic range or a seizure occurs, alternative antibiotic or anticonvulsant therapy sh considered (Prod Info 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 rec carbapenem antibiotics concomitantly. Two case reports describe significant decreases in serum valproic aci with coadministration of ertapenem, leading to seizures in one (Lunde et al, 2007; CabanesMariscal et al, 20 exact mechanism is not understood, in vitro and animal data suggest that carbapenems may inhibit valproic a hydrolysis. If ertapenem is initiated in patients receiving valproic acid, frequent monitoring of valproic acid lev recommended. Use alternative antibacterial or anticonvulsant therapy if valproic acid blood levels drop below or if 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 va concentration frequently. Consider alternative antibiotic or anticonvulsant therapy if serum valproic acid levels 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 to on day 7 of concomitant ertapenem (1000 mg) every 24 hours) therapy. His medical history was significa 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 conc therapeutic at 130 mcg/mL while taking divalproex sodium 2000 mg/day. He was admitted to the emerge 3 seizure episodes, the last of which was 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 was discharged. He returned 4 days later with recurrent seizures and a serum valproic acid concentratio Intravenous valproic acid 1000 mg 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 followin 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 ertapenem 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 partia secondary to severe cerebrovascular disease, experienced significantly reduced serum valproic acid cor beginning 4 days after the initiation of ertapenem 1000 mg every 24 hours. Approximately, 1.5 months p exposure, her total serum valproic acid concentration was 72 mcg/mL. Admitted to the hospital for aspira the patient was treated with ertapenem. Four days later serum valproic acid concentration was reported mcg/mL, and her valproic acid dose was increased to 1600 mg/day. Two days later serum valproic acid mcg/mL and the drug dose increased to 2000 mg/day. A level of 1.04 mcg/mL was measured 4 days afte increase. Ertapenem 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 th She was subsequently maintained on oral valproic acid 1400 mg/day (CabanesMariscal et al, 2006).

3.5.1.L Erythromycin

1) Interaction Effect: valproic acid toxicity (CNS depression, seizures)

2) Summary: One case report described the concurrent use of erythromycin and valproic acid resulting in inc acid concentration and symptoms of valproate toxicity. Discontinuation of erythromycin led to lowered valproa resolution of the symptoms (Redington et al, 1992a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: If erythromycin and valproic acid are used concurrently, monitor patient for signs of (CNS depression, seizures). Monitor valproic acid serum concentrations during and after erythromycin therap

7) Probable Mechanism: decreased valproic acid metabolism

8) Literature Reports

a) One study describes a 38-year-old female outpatient receiving valproate 3500 mg daily, clorazepate mg four times daily, and lithium carbonate 300 mg twice daily; her valproate level was 88.8 mg/L (therap 100 mg/L). Erythromycin 250 mg four times daily was prescribed for a respiratory infection; within a weel difficulty in walking, confusion, lethargy, slurred speech, and poor concentration. Her valproate level was admission; at that time both erythromycin and valproate were discontinued. Fifteen hours later the valpro mg/L, and valproate was restarted at the original dosage. All signs of adverse reaction resolved (Redingt

3.5.1.M Ethosuximide

1) Interaction Effect: an increased risk of ethosuximide toxicity

2) Summary: Concomitant valproic acid and ethosuximide therapy does not appear to influence the pharmac parameters of ethosuximide. This was demonstrated in an evaluation in which valproic acid was added to a c ethosuximide regimen. There was no apparent change in total or nonrenal clearance of ethosuximide (Bauer However, the above combination did result in elevated ethosuximide levels (Mattson & Cramer, 1980). Admir ethosuximide in patients receiving valproic acid therapy was reported to result in significant increases in etho (from 44 to 54 hours) and a significant decrease in total body clearance (11.2 to 9.5 mL/minute) (Pisani et al, suggest that valproic acid is capable of inhibiting the metabolism of ethosuximide.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients receiving valproate and ethosuximide concomitantly for alterations concentrations of both drugs.

7) Probable Mechanism: inhibition of ethosuximide metabolism

8) Literature Reports

a) Valproate inhibits the metabolism of ethosuximide. Administration of a single ethosuximide 500 mg d (800 to 1600 mg/day) to six healthy volunteers resulted in a 25% increase in elimination half-life of ethos 15% decrease in valproate total clearance compared to ethosuximide alone. Patients on concomitant val ethosuximide should be monitored for alterations in serum concentrations of both drugs (Prod Info Depal 2003k).

3.5.1.N Evening Primrose

1) Interaction Effect: reduced anticonvulsant effectiveness

2) Summary: Theoretically, evening primrose oil may reduce the effectiveness of anticonvulsants by lowering threshold. Evening primrose oil is contraindicated in patients with epilepsy (Barber, 1998; Newall et al, 1996).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant use of evening primrose oil with anticonvulsants.

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 incr valproic acid AUC (28% and 54%), peak concentrations (34% and 55%), and average steady-state concentra 54%) (Wagner et al, 1992; Prod Info Felbatol(R), 2000). A decrease in valproate dosage may be necessary v 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, irrita 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 are occur with fosphenytoin (Prod Info Cerebyx(R), 1999). Valproic acid may initially cause a decrease in total ph displacement of phenytoin from protein binding sites (Levy & Koch, 1982; Bruni et al, 1980; Monks et al, 1978 decrease in the bound fraction of phenytoin; the phenytoin which is displaced by valproic acid re-equilibrates capacity of the tissue compartment such that the unbound plasma concentration remains unchanged (Winter al, 1978). The degree of displacement appears to be valproic acid dose related (Monks & Richens, 1980). Va also inhibit phenytoin metabolism (Levy & Koch, 1982; Bruni et al, 1980; Patel et al, 1980; Winter, 1988; de W

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 phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to p 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 i 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 epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with eac drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase acid, progabide, and lamotrigine (Bianchetti et al, 1987; Ramsay et al, 1990; Spina et al, 1996). Such co 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 develo of seizures after ingesting ginkgo extract. Seizure control was regained after ginkgo was withdrawn (Granger developed seizures after exposure to 4'-O-methylpyridoxine arising from ingestion of ginkgo seeds (Yagi et a compound 4'-O-methylpyridoxine, a neurotoxin, is found in ginkgo seeds (used as food in Japan) as well as i ginkgo component from which commercially available extracts are derived (Arenz et al, 1996a). The majority products should not contain sufficient amounts of 4'-O-methylpyridoxine to cause seizures. However, ginkgo commonly assayed to assure that 4'-O-methylpyridixone is not contained in the commercial product. Of conc instances where, depending on the harvest season and the potential introduction of contamination, 4'-O-meth be present in sufficient amounts to be problematic in vulnerable populations (eg, infants or those with known

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Avoid concomitant use of ginkgo and anticonvulsants in patients with epilepsy. If se the first time or recur in patients previously controlled by anticonvulsant medication, inquire about the use of g extract. If possible, an assay should be conducted on the specific product to ascertain if 4'-O-methylpyridoxin

7) Probable Mechanism: neurotoxin 4'-O-methylpyridoxine (found in leaves and seeds of ginkgo biloba) may

8) Literature Reports

a) The serum of a 21-month-old patient with gin-nan food poisoning was assayed for 4'-O-methylpyridox 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 fo convulsions and loss of consciousness observed. They further observed that infants are particularly vuln 1993).

b) Four to six milligrams of 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 (85 (mcg)/seed) and leaves (5 mcg/leaf) derived from the tree at the end of July and beginning of August. Th seed can contain 105.15 mcg/gram dry weight, but this is reduced to 0.75-1.32 mcg/gram dry weight whe 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-m was found in Tebonin Forte(R), 9.77 mcg/mL in Rokan(R), 3.80 mcg/mL in Kaveri Forte(R), and 7.18 mc (R). Based on recommended daily intake, this translates into a maximum daily intake of 4'-O-methylpyrid mcg, 58.62 mcg, 11.40 mcg, and 43.08 mcg for Tebonin Forte(R), Rokan(R), Kaveri Forte(R), and Gingi respectively. Among the homeopathic products, Ginkgo biloba Urtinktur Hanosan(R) and Ginkgo biloba U contained 0.301 mcg/mL and 0.589 mcg/mL of 4'-O-methylpyridoxine, respectively. However, the author 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 har al, 1996).

c) Seizures recurred in 2 patients, both with epilepsy that was well controlled prior to ingesting ginkgo bi patients (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 Imipenem

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 rec carbapenem antibiotics concomitantly. If imipenem is initiated in patients receiving valproic acid, frequent mo acid levels is recommended. Use alternative antibacterial or anticonvulsant therapy if valproic acid blood leve therapeutic range or if a seizure occurs (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: If concomitant administration of valproic acid and imipenem is required, monitor val concentration frequently. Consider alternative antibiotic or anticonvulsant therapy if serum valproic acid levels therapeutic range or if a seizure occurs (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008).

7) Probable Mechanism: unknown

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 l and a higher incidence of tonic-clonic seizures. Isoniazid may inhibit the metabolism of valproic acid, or valpr increase the risk of isoniazid toxicity (Dockweiler, 1987).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Consider monitoring liver function tests periodically with therapy, as well as continu 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, drow an increased risk of life-threatening rashes

2) Summary: Valproic acid interferes with the metabolic clearance of lamotrigine. The normal elimination half is approximately 24 hours; in patients receiving concomitant valproic acid therapy, the half-life increases to ap 60 hours. The mechanism of this interaction is thought to be competition of the two drugs for hepatic metabol 1986; Peck, 1991; Eriksson et al, 1996; Sallustio & Morris, 1997). Fever, rash, multiorgan dysfunction, dissem intravascular coagulation, and fatal toxic necrolysis have been reported with this combination in adults and pe (Chattergoon et al, 1997a; Page II et al, 1998a). Given the increased risk of rash in pediatric patients, careful lamotrigine serum concentrations may be advisable for children younger than 16 years of age, for whom the i lamotrigine is restricted to those who have been diagnosed with either partial seizures or Lennox-Gastaut syn of lamotrigine should be reduced when coadministered with valproate (Prod Info Depakote(R) ER, 2003c; Pro oral tablets, 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Dosage reductions of lamotrigine are necessary with concurrent valproic acid thera in conjunction with other enzyme-inducing medications. The manufacturer recommends a lamotrigine dose o other day for the first two weeks, increasing to 25 mg once daily for the next two weeks, advancing to a maint 100 mg to 400 mg daily in increments of 25 mg to 50 mg daily every one to two weeks. If valproic acid is the antiepileptic medication, the usual maintenance dose of lamotrigine is 100 to 200 mg daily. Discontinue use o first sign of a rash unless the rash is clearly not drug related (Prod Info lamotrigine oral tablets, 2006).

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-epilepsy initial regimen consisted of carbamazepine 400 mg twice a day. Valproic acid 500 mg twice daily was ad lamotrigine 50 mg twice daily was added 3 weeks prior to current presentation. The patient had an eleva 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-induc 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 i developing SJS may have potentially been a result of either the combination of lamotrigine and valproic a decreased metabolism of lamotrigine, or due to initiation of lamotrigine at a dose higher than the manufa 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. La 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 feve and pruritic rash on the chest, upper extremities, neck, and back. He had been taking allopurinol 100 mg 50 mg daily for four 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 e 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 adve 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 th 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 lamotrigi stable lamotrigine Css. Seizure-free periods were significantly longer during treatment with both lamotrig acid than during lamotrigine monotherapy, an indication that therapeutic synergism exists between lamot 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 a mg/day resulted in mean increases in lamotrigine AUC of more than 2.5-fold. Even low doses of valproic resulted in significant increases in lamotrigine AUC (mean 84%). Significant increases in plasma lamotrig by inhibiting lamotrigine metabolism and increased half-life has been achieved with the use of low to mod 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 valproat in adult or pediatric patients in controlled clinical trials. The addition of valproate increased lamotrigine st concentrations in normal volunteers by more than 2-fold (Prod Info Lamictal(R), 2004).
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 may lead to decreased serum levels of the anticonvulsant, thereby decreasing valproic acid efficacy and incre seizures. Although there have been no such reports with the use of l-methylfolate and valproic acid, caution is agents are used concomitantly (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tablets, 20 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 a 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 Zervalx(R) oral tablets, 2008). If used concomitantly, monitor patients for loss of valproic acid efficacy.
7) Probable Mechanism: unknown

3.5.1.V Lopinavir

1) Interaction Effect: decreased valproic acid serum concentrations
2) Summary: Coadministering lopinavir/ritonavir with valproic acid may decrease the plasma concentration o
case report suggests the mechanism may be due to ritonavir induction of VPA metabolism via glucuronidatio
2006). 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 lopin
valproic 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 mcmol/L, when the antiretrovirals were prescribed during a hospital admission for m
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
became increasingly manic and was again admitted. He had continued all medications except sertraline
including 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.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 clea
compared to controls (Anderson et al, 1994). When lorazepam and valproic acid are coadministered, the dos
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 shou
50%. The patient should then still be monitored for evidence of lorazepam toxicity, including excessive sedati
depression.
7) Probable Mechanism: decreased lorazepam metabolism
8) Literature Reports
a) In a study involving six healthy male subjects, the coadministration of intravenous lorazepam 2 mg wi
acid 250 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 appro
times higher for at least 12 hours following concurrent administration. The manufacturer of lorazepam re
reducing the dose of lorazepam by 50% during valproic acid coadministration (Prod Info Ativan(R), 1997

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 se
lowering plasma levels of the anticonvulsant (Prod Info Lariam(R), 2003). One case report describes a male
an increase in the frequency of his seizures after he was prescribed mefloquine for malaria prophylaxis. His a
medication included carbamazepine and sodium valproate. Pharmacokinetic studies determined that the half
valproate was significantly reduced by the administration of mefloquine, while carbamazepine was not affecte
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If mefloquine and valproic acid must be administered concurrently, monitor the leve
Adjustments of the valproic acid dose may be required. Also monitor the patient for seizure control.
7) Probable Mechanism: unknown
8) Literature Reports
a) A 38-year old male epileptic controlled by carbamazepine 1200 mg daily and sodium valproate 1 grar
mefloquine 250 mg weekly. The patient began to experience multiple partial seizures. The pharmacokine
antiepileptic drugs were studied to determine the cause of this patient's seizures. A reduction in the half-
valproate (from 8-20 hours to 5.6 hours) was observed, although that of carbamazepine was unchanged
mefloquine accelerated the metabolism of sodium valproate, since they both share the same hepatic me
(Jallon, 1988).

3.5.1.Y Meropenem

1) Interaction Effect: decreased valproic acid plasma concentrations and loss of anticonvulsant effect

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 Turck 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 v Consider an alternative antibiotic which does not affect valproic acid serum levels. If concomitant administrati and meropenem is unavoidable, monitor valproic acid serum concentration closely (Spriet et al, 2007).
7) Probable Mechanism: unknown
8) Literature Reports

a) A retrospective study of 39 patients with concurrent treatment with valproic acid (VPA) and meropene an average decrease of valproic acid levels of 66% within 24 hours. In patients receiving meropenem aft 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 ma 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 releva 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 et al, 2007).

b) The coadministration of meropenem with valproic acid produced a pronounced decline in valproic aci concentrations. In a case report, a 21-year-old woman was administered valproic acid (VPA) 1920 milligı 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 intı 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 I.V. infusion over 24 hours), yet tonic-clonic seizures recurred 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 serun 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 cessation of seizure activity (Coves-Orts et al, 2005).

c) As described in a series of case reports, serum concentration levels of valproic acid were substantiall 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 tobramyc 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 patient was a 7-month-old girl with West syndrome, receiving anticonvulsant treatment with VPA 75 mg/k VPA plasma concentrations were within therapeutic range (69 to 90 mcg/mL) prior to receiving concomit meropenem and vancomycin to treat an Acinetobacter nosocomial pneumonia. VPA was increased to 13 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 anticonv West syndrome symptoms. Baseline VPA serum concentrations were 85 mcg/mL. The patient received ı therapy 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 day 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 d approximately 55 mg/mL to 25 mg/L (per graphic analysis), despite supplementation of VPA dose. In the report, a 57-year-old woman was given a prophylactic infusion of intravenous VPA (dose unspecified) alc 100 mg 3 times daily administered on postop days 9-15. Due to development of a lung infection with Klel 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 this second patient, the plasma elimination half life of VPA was found to have declined from an expected to only 4 hours (De Turck 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 n 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 t Monitor for clinical signs of nifedipine toxicity, including hypotension, peripheral edema, and bradycardia. Cor 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 ir 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). Downv 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 was comprised of healthy s had epileptic patients treated at least four months with carbamazepine, phenobarbital, phenytoin (all enz a combination, and group 3 included epileptic patients treated for at least four months with sodium valpro the control group, nimodipine AUCs averaged a 7-fold decrease in the enzyme inducer group, probably d 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% decr clearance of amitriptyline following the administration of amitriptyline 50 mg (single dose) and valproate 500 r 15 healthy volunteers. However, concurrent use of valproate and amitriptyline (nortriptyline precursor) has ra associated with overt toxicity (Prod Info Depacon(R), 2002). Monitor nortriptyline levels in patients taking valp concomitantly. Consider lowering the dose of nortriptyline in the presence of valproate (Prod Info Depakote(R

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor nortriptyline levels in patients taking valproate concomitantly. Consider lowe 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 amitriptyline were studied. Subjects were given amitriptyline 50 mg alone and two hours after receiving n divalproex sodium 500 mg, which was given every 12 hours. Coadministration of amitriptyline with divalp resulted in a 17% increase in amitriptyline maximum concentration (Cmax) and a 31% increase in the an under the concentration-time curve (AUC). Time to maximum concentration (Tmax) for amitriptyline was coadministration with divalproex sodium. For nortriptyline, the metabolite of amitriptyline, AUC was increa Cmax 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, 1

b) The combination of valproic acid and nortriptyline has resulted in toxic levels of nortriptyline. A 33-yea bipolar disorder had elected to discontinue her lithium treatment which she had been maintained on for 8 developed severe depression two months later. Nortriptyline 25 mg at bedtime was initiated on day 1 of l day 10, the dosage was increased to nortriptyline 100 mg at bedtime. Valproate 250 mg three times daily day 7 and increased to 500 mg twice daily on day 10. On day 13 of the patient noticed marked tremulous and fingers, which worsened over the next 3 days. After 15 days of nortriptyline treatment the nortriptylin ng/nL (range, 40 to 130 ng/mL). The valproate level was 105 mg/liter (range, 50 to 100 mg/liter). Both me 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 of suspected lithium-induced hypothyroidism. His current regimen consisted of thioridazine 75 mg/day ar mg/day. His nortriptyline level at that time was 146 ng/mL. His thioridazine dose was tapered over a 20-d then discontinued due to difficulties with sexual dysfunction. One month later his mood became dysphori presentation to the emergency room, he was restarted on thioridazine 75 mg/day and nortriptyline was ir mg/day. His nortriptyline level was 218 ng/mL, and his nortriptyline was decreased to 75 mg/day. Valproa times daily was subsequently added to the patient's regimen to provide mood stabilization. Valproate wa 1250 mg/day within a few weeks. The patient then stopped thioridazine and started loxapine 10 mg/day. level of nortriptyline was 345 ng/mL. Nortriptyline was titrated down to 25 mg/day and a subsequent drug

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 treate
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 amitrip
nortriptyline plasma levels were determined on days 10 and 20, respectively in ten patients treated with a
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 plas
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 less than 0.001) and between the nortriptylin
before and after valpromide (r equal to 0.87, p less than 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 oxcarbaze
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
oxcarbazepine and valproic acid are administered concurrently, clinical response to oxcarbazepine may need
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Coadministration of oxcarbazepine and valproic acid may result in a decreased con
active 10-monohydroxy metabolite of oxcarbazepine. Monitor patients for clinical response to oxcarbazepine.
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
therapy 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
admitted to the hospital for pneumonia, and her valproic acid dose was increased to 30 mg/kg/day while
was decreased to 4.5 mg/kg/day. Panipenem/betamipron therapy was initiated at 60 mg/kg/day in three
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
carbamazepine 11 mg/kg/day, and phenytoin 10 mg/kg/day for two months before a hospital admission f
pneumonia. Valproic acid serum concentration was 88.7 mg/mL prior to the start of panipenem/betamipr
and 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
treatment with panipenem/betamipron. The valproic acid level started to increase within 24 hours of disc
panipenem/betamipron. The phenytoin serum level was undetectable on day 3 of panipenem/betamipror
carbamazepine level was not significantly altered (Yamagata et al, 1998).
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 fro
108.9 mg/mL. However, by day 5 of panipenem/betamipron treatment, the valproic acid level was 26.7 m
the valproic acid dose 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 concentrat
55 mg/mL and the frequency of the seizures was decreased. Incidentally, in this patient, the phenytoin a

levels were not significantly altered by the presence of panipenem/betamipron (Yamagata et al, 1998).

3.5.1.AE Phenobarbital

1) Interaction Effect: phenobarbital toxicity or decreased valproic acid effectiveness

2) Summary: Concurrent administration of valproic acid and phenobarbital results in decreased phenobarbita increased serum concentrations (Prod Info Depakote(R) ER, 2003g; Bourgeois, 1988; Fernandez de Gatta et al, 1980a). It may be necessary to decrease the phenobarbital dosage with concomitant use. Conversely, val may decrease significantly with concurrent use (May & Rambeck, 1985).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: With the addition of valproic acid therapy in a patient stabilized on phenobarbital, th be monitored for signs of phenobarbital toxicity and a serum phenobarbital level obtained. Phenobarbital dos be decreased in some cases. Due to increased valproic acid metabolism, periodic determinations of valproic barbiturate concentrations should be considered.

7) Probable Mechanism: decreased phenobarbital metabolism or increased valproic acid metabolism

8) Literature Reports

a) Elevations in serum phenobarbital levels have occurred with concurrent sodium valproate administrat secondary to inhibition of phenobarbital metabolism (Schobben et al, 1975; Johannessen, 1977; Richens Suganuma et al, 1981; Kapetanovic et al, 1981; Bruni et al, 1980a; Anon, 1978). Conversely, phenobarb the serum half-life of sodium valproate due to the induction of liver enzymes (Pinder et al, 1977; Rimmer Furlanut et al, 1982). A 10% increase in clearance of valproic acid has been observed in patients taking (Yukawa et al, 1997).

b) Phenobarbital metabolism is inhibited by valproate. Six subjects received valproate 250 mg twice dail phenobarbital which resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of p mg single dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence Info Depakote(R) ER, 2003f).

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 phenytc binding sites (Prod Info Depakote(R) ER, 2003l; Levy & Koch, 1982a; Bruni et al, 1980a; Monks et al, 1978a) decrease in the bound fraction of phenytoin; the phenytoin which is displaced by valproic acid re-equilibrates capacity of the tissue compartment such that the unbound plasma concentration remains unchanged (Winter et al, 1978a). The degree of displacement appears to be valproic acid dose related (Monks & Richens, 1980a may also inhibit phenytoin metabolism (Levy & Koch, 1982a; Bruni et al, 1980a; Patel et al, 1980b; Winter, 19 al, 1982a).

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 phenytoin toxicity and therapeutic efficacy. Free plasma phenytoin levels should be measured if possible to p 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 i 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, 1990b; Van Dyke et al, 1991b; Fir 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 hyc valproic acid, progabide, and lamotrigine (Spina et al, 1996b; Bianchetti et al, 1987b; Ramsay et al, 1990 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

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 sys 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 possibl Depakote(R) ER, 2003b; Prod Info Depakene(R), 1998).

3) Severity: major

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: All patients receiving concurrent primidone and valproic acid therapy should be mor excessive central nervous system depression and neurological toxicity. Serum primidone and derived phenob 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 w studied (Yukawa et al, 1989). Primidone doses ranged from 1.45 mg per kg to 27.03 mg per kg. All patie taking the same dosage for at least three weeks prior to blood sampling. Results showed no significant c primidone serum level when given concomitantly with valproate sodium, but there was a significant incre 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 admini dose of valproate (7 mg per kg) 36 hours after five nights of daily dosing with rifampin (600 mg) (Prod Info De 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 do 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. Rifapentir the metabolism of other coadministered drugs that are metabolized by cytochrome P450 3A4 or 2C8/9. Dosa 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 ac
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 al, 2007). The high protein 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 Wat However, Valproic acid can be added safely to a treatment regimen consisting of risperidone (Spina et al, 20(ammonia levels may be warranted in patients who exhibited new or increased manic behavior when taking va risperidone, 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 ca al, 2007). In patients prescribed this combination of drugs, monitoring of plasma risperidone or 9-OH-risperid does not appear to be warranted.
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 serum ammonia levels when risperidone and valproic acid were concomitantly administered. The first pa history of Asperger's disorder, attention-deficit/hyperactivity disorder (ADHD), psychosis, and manic sym admitted for increasing aggressive behavior. Chlorpromazine was added as needed and risperidone was his aripiprazole. Following the initiation of valproic acid 250 mg twice daily, the patient experienced a qua exacerbation of manic behavior. The risperidone dosage was eventually adjusted to 2 mg/day and valpro mg/day. The patient's valproate level ranged from 87 to 90 and ammonia level was 213. When valproic a discontinued, and the ammonia level fell to 55, his manic behavior stopped. The second patient, with a h epilepsy and ADHD, was on stable doses of valproic acid. Because of his psychotic symptoms, risperido and increased to 1.125 mg/day over 5 weeks. The patients exhibited markedly pronounced manic behav serum ammonia level of 113, despite a normal valproic acid level of 71. Upon discontinuation of risperido acid, the ammonia level normalized to 55 and the manic behavior resolved. One month later when the pa rechallenged with risperidone (in the absence of valproic acid), there was no return of either mania or hy (Carlson et al, 2007).
b) A study was performed to evaluate the pharmacokinetic interaction between risperidone and valproic plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were compared in pa risperidone alone or in patients comedicated with valproic acid. Thirty-three patients with a DSM-IV diagr schizophrenia, schizoaffective disorder or bipolar disorder, were stabilized with risperidone alone or in co

valproic acid. The results demonstrate that valproic acid given at doses up to 1200-1500 mg/day had clir effects on plasma concentrations of risperidone and its active metabolite. Valproic acid can be added sat 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 treatm mg/day was added, which was increased to 3 mg/day on day 4. On day 5 after risperidone was started, t symptoms improved but valproic acid levels were above the therapeutic range at 191 mg/L. Valproic acic 1000 mg/day and the level normalized to 108 mg/L within 3 days and subsequently stabilized. The autho the high-protein-binding capacity of risperidone could lead to a competition for protein-binding with the hi 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 risperidc 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 (Sh 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 ritona 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 mcmol/L, when the antiretrovirals were prescribed during a hospital admission for m 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 became increasingly manic and was again admitted. He had continued all medications except sertraline including 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 resul 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 concentra 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 hyperammo encephalopathy

2) Summary: Controlled, clinical pharmacokinetic studies in patients with epilepsy showed an 11% decrease 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 sprin 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 implicate development of hyperammonemic encephalopathy (Hamer et al, 2000a). As described in a series of case rep 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 i completely withdrawn (Latour et al, 2004). Although not studied, concomitant use of topiramate and valproic a exacerbate existing defects or unmask deficiencies in susceptible patients. Patients with inborn errors of met hepatic mitochondrial activity may be at an increased risk for hyperammonemia with or without encephalopat 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 a encephalopathy. It may also result in decreased plasma concentrations of one or both drugs (Prod Info TOPA tablets, oral sprinkle capsules, 2008). Upon the coadministration of topiramate and valproic acid, dosing adju 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 takir three 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 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 beginnir anticonvulsant regimens comprising topiramate (TPM) and valproic acid (VPA). Hyperammonemia was d the patients (age ranging from 29 to 41 years). Blood ammonia levels ranged from 62 to 146 mcmol/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-transfera phosphatase. 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 conce mcg/mL (therapeutic range 15 mcg/mL to 40 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 mcmol/ mcmol/L to 60 mcmol/L), as was the gamma glutamyl transpeptidase (GGT) level. Acute valproic acid er 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 sho acid level of 47 mcg/mL (therapeutic range 50 mcg/mL to 100 mcg/mL) and a carbamazepine level of 5.2 (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 zidovu (Lertora et al, 1994a; Prod Info Retrovir(R), 2003). In six patients who were seropositive for HIV, the clearanc (100 mg q8h) was decreased by 38% after administration of valproate (250 or 500 mg q8h) (Prod Info Depak
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs and symptoms of zidovudine toxicity (asthenia, fatigue, na hematologic abnormalities). It may be necessary to reduce zidovudine doses when valproic acid is added to t 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 zi and four days of zidovudine combined with valproic acid. Study subjects received zidovudine 100 mg ora hours and valproic acid 250 mg orally every eight hours (one patient was given 500 mg of valproic acid e The area under the concentration-time curve of zidovudine increased by 80%, from 0.65 to 1.17 mcg/hr/r concomitant valproic acid was given. Zidovudine oral clearance decreased 38% from 2351 to 1449 mL/m life of zidovudine was not significantly altered during coadministration. In this short-term study, no chang hematologic parameters or renal and hepatic function tests. The clinical impact of long-term use of this c date unknown. Effects on valproic acid concentrations were not studied. The mechanism of the interactio be inhibition by valproic acid of first-pass glucuronidation of zidovudine (Prod Info Depakote(R) ER, 2003 1994).

3.5.3 Drug-Lab Modifications

Plasma free fatty acid measurement

Urinalysis, acetone or ketone bodies measurement

3.5.3.A Plasma free fatty acid 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 colorime therapeutic concentrations of valproic acid were added (Albani et al, 1982). Consider using a more specific m 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 ir 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 valproic acid, a short branched-chain organic acid. In a controlled plasma mixing experiment, the additio micrograms/milliliter valproic acid increased the apparent FFA by an average 246 micromole/liter in 10 re to 705 micromole/liter). Using more specific methods to determine FFA concentrations in patients receivi should avoid this interference (Albani et al, 1982). The concentration of valproic acid used in the experim within the approved therapeutic ranges used for epilepsy (50 to 100 micrograms/milliliter) and acute mar micrograms/milliliter trough concentration), respectively (Prod Info Depakote(R), valproic acid, 2000).

3.5.3.B Urinalysis, acetone or 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 b acid is partially eliminated in the urine as a keto-metabolite (Prod Info DEPAKOTE(R) ER extended-release c Use caution when interpreting urine ketone test results in patients receiving concurrent therapy with valproic a
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 res reactions for ketones in the urine (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008). Interpre 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 ter
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 frequency
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.

1) 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 inte 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 beca induced pancreatitis has low occurrence, there is wide variability in time to onset, and mild, asymptomatic ele pancreatic enzyme markers occurs frequently without progression to pancreatitis. Those healthcare providers counseling of patients to recognize the signs and symptoms of pancreatitis and advising them to seek immed 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 w an AED and continued to at least 24 weeks. Patients treated for epilepsy, psychiatric disorders, or other cond an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emergen of depression, suicidality, and other unusual changes in behavior, which may include symptoms such as anxi 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 t 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, c severe liver disease, a urea cycle disorder (a disease that causes too much ammonia in the blood), or are pregna get 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 order to find out what works best for you. Do not use more medicine or use it more often than your doctor tells 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 so 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 d 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:

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, a products.

Make sure your doctor knows if you or your child are taking a blood thinner (such as aspirin, warfarin, or Cou medicines that could make you sleepy, such as sleeping pills (such as alprazolam, lorazepam, Ativan®, Xana medicines (Lorcet®, Percocet®, Tylenol® with Codeine, Vicodin®, Vicoprofen®), or cold medicines. Tell your your child are using any other medicine for seizures.

Tell your doctor if you or your child are taking meropenem (Merrem®), rifampin (Rifadin®, Rimactane®), amit Vanatrip®), topiramate (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 contro 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 dis 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 docto

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 th stool. This is normal.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou you are not alert.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may 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, c 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.
Swelling on your face, hands, ankles, or feet.
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 p should not receive this medicine if you have a genetic (inherited) urea cycle disorder, which causes the body to ha rid of 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 d 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, a 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 me 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 you have a history of coma, unexplained mental or behavior problems, frequent vomiting, a family history of u 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 y
using other medicine to treat seizures. Tell the doctor if your child was born with a disease that affects his me
making process of the body). Make sure the doctor knows if your child has mental retardation or a brain disea
Using this medicine while you are pregnant can harm your unborn baby. Use an effective form of birth contro
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 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
This medicine may make you drowsy or less alert. Avoid driving, using machines, or doing anything else that
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, c
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 clas
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 se
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 c
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 m
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or n
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, a 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, kidn blood disorder.
Talk to your doctor before taking this medicine if you are pregnant. If you become pregnant while being treate 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 wit
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 multip 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, simp and complex partial seizures, carbamazepine is generally preferred due to its lesser toxicity. Valproic acid is agent for the treatment of absence seizures; ethosuximide is generally preferred, however (Young & Koda-Ki 1989).

c) Valproic acid and carbamazepine appear to have less of an effect on cognitive function and behavioral dis comparison with phenobarbital, phenytoin, and primidone. For this reason, both valproic acid and carbamaze 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 disc week, placebo-controlled, parallel-group studies, valproate had significantly superior results on all measures outcomes for acute mania compared with placebo (Prod Info STAVZOR(R) delayed release oral capsules, 2(

b) Valproic acid has been effective in treating mania associated with bipolar disorder in clinical studies (Faw 1989; Post, 1989; McElroy et al, 1989; Calabrese & Delucchi, 1989; Pope et al, 1988; Grunze et al, 1999; Pra

c) Valproic acid has been shown to be effective for the treatment of acute mania. Response has been seen i unresponsive to lithium therapy and to those with mixed mania and rapid cycling (Keck et al, 1998). A greate reduction is seen in approximately 50% of patients. The therapeutic onset correlates with therapeutic plasma 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 olde randomized, placebo-controlled clinical trials established the efficacy of valproate for prophylaxis of migraine 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 prophyl patients with bipolar disorder over a one-year time period. Four attributes of overall patient management were

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 tha treatment with lithium, most likely due to a more rapid response with divalproex and shorter length of hospital were most significant in patients with mixed mania and rapid cycling; however, cost savings with lithium thera 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 it is clinically feasible, patients should be switched back to oral valproic acid (Prod Info valproate sodium injec

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 th the function of brain gamma-aminobutyric acid (GABA), specifically by increasing brain concentrations of this inhil (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Beckner, 1979; Godin et al, 1969; Simler et al, 197

2) The drug has been shown to be an inhibitor of GABA-aminotransferase and succinic semialdehyde dehydroge involved in the synthesis and degradation of GABA (Simler et al, 1973; Loscher, 1980; Sawaya et al, 1975), and s of GABA have been reported to occur in synaptosomes, primarily in areas of high GABA activity (Iadarola & Gale, Richens, 1985d). However, this proposed mechanism of action has been disputed (Rimmer & Richens, 1985d; Hc Concentrations of the drug are reportedly too low for enzyme effects to occur with therapeutic doses, and increas GABA are reportedly too small to account for anticonvulsant effects (Rimmer & Richens, 1985d). Alternately, it ha that valproic acid may selectively enhance postsynaptic GABA responses (Rimmer & Richens, 1985d; MacDonalc Other hypotheses which have been advanced are: (1) direct effect of the drug on neuronal membranes and (2) re excitatory transmission by aspartate (Rimmer & Richens, 1985d; Slater & Johnston, 1978). However, no mechani 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 (E

B) REVIEW ARTICLES

1) Basic reviews of the treatment of seizures have been written; these include treatment of first seizure and statu (Willmore, 1998), treatment of the elderly (Rowan, 1998), and management of epilepsy in adults (Feely, 1999; Ma Pediatric seizure management has also been reviewed (Wolf et al, 1998; Pellock, 1995).

2) A comprehensive review concerning the use of valproate in psychiatric conditions is available (Davis et al, 200

3) The association between valproate therapy and the development of polycystic ovarian syndrome is discussed 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 extens (Bruni & Albright, 1984).

7) An extensive study of first-dose and steady-state pharmacokinetics with valproic acid in children with seizures al, 1983). A detailed case review of the kinetics of valproic acid in neonates is provided (Irvine-Meek et al, 1982).

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, 19

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 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 adjunct or monotherapy for patients with simple and complex absence s
DEPAKENE(R) oral capsules, oral syrup, 2006; Prod Info STAVZOR(R) delayed release oral capsu

c) Adult:

1) Valproic acid is indicated for use as sole and adjunctive therapy in the treatment of simple and compl 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). Result involving 354 patients indicate there is at least a 75% reduction in seizure frequency in about 66% of pat 45 (13%) patients failed to show any significant improvement in this review (Pinder et al, 1977e). Ethosu preferred over valproic acid for treatment of absence seizures as it is equally effective and better tolerate Kimble, 1995a). Combination therapy with valproic acid and ethosuximide was successful in treating abs patients who were refractory to either drug alone (Rowan et al, 1983).

d) Pediatric:

1) Valproic acid monotherapy was reported effective in the treatment of absence epilepsy in 6 of 7 childr patient also responded when clonazepam was added to valproic acid. Prior to therapy, 3 patients had be unsatisfactorily with ethosuximide, alone or in combination with carbamazepine. Valproic acid was given 15 milligrams/kilogram/day for 7 days, followed by 20 to 25 milligrams/kilogram/day for a further 14 days 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 disch 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 altern seizures 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, was effective and well-tolerated for the treatment of acute a in a randomized, double-blind, placebo-controlled study of 40 men. Within 24 hours of hospital admissior 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 (sc 7 being the most severe), with response defined as at least 50% improvement from baseline after 10 day Study subjects consumed an average of 200 to 300 grams of ethanol per day, and had a history of 10 +/ abuse. At 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 valpro patients at the end of 10 days improved to 2 +/- 0.9 and 5 +/-1.4 for the placebo group (p=0.001). Secon of response based on the Clinical Global Impression (CGI) determined that 73.68% of valproate-treated "much" or "very much" improved compared to 26.31% of placebo-treated patients (p less than 0.001) (Al 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 wit (Herrmann, 1998).

Valproic acid decreased behavioral disturbances in 5 of 10 elderly subjects with dementia in an oper (Kasckow et al, 1997).

Benefit was shown in a retrospective chart review of 25 elderly patients with dementia who received 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 Agitated patients (n=16, 68 to 95 years old) with Alzheimer's disease, vascular dementia, or Lewy body d valproic acid 125 milligrams (mg) twice daily. Doses were increased to target serum levels of 350 to 700 Average daily doses were 1438 mg over the average trial length of 9 weeks. Benefits were seen within 4 the Clinical Global Impression Scale, 1 patient was rated as very much improved, 3 patients were much minimally improved and 8 were unchanged (Herrmann, 1998).

2) Valproic acid, initiated at 250 milligrams daily and titrated upward for a 2- to 5-week treatment duratio

behavioral disturbances in 5 of 10 elderly subjects with dementia in an open-label pilot study. The remai
either no change (n=3) or worsened behavior (n=2) (Kasckow et al, 1997).
3) According to a retrospective chart review of 25 elderly patients with dementia who received valproic a
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 tha
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 m
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 valproi
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 S
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 (E

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 follo
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 valp
Within 24 hours of injury, patients (ages 14 years and older) were randomized to receive either phenytoi
(n=132), valproic acid for 1 month (n=120), or valproic acid for 6 months (n=127). A phenytoin loading do
administered at 20 milligrams/kilogram (mg/kg) intravenously (IV) followed by maintenance dosing at 5 m
into 2 doses. A valproic acid loading dose was given at 20 mg/kg intravenously followed by a maintenan
mg/kg/day divided into 4 doses. Plasma concentrations of each drug were followed and adjusted to thera
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, su
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 (Dhanara
Valproic acid was found to be safe and effective in the treatment of choreic movements in 7 pediatri
Sydenham's chorea in an open-label trial (Genel 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, 19
1500 milligrams/day successfully treated a recurrence of Sydenham's chorea in a 74-year-old male with
(Black 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 t
kilogram 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. There
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 mi
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 con
acid (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

c) Adult:

1) Monotherapy

a) In a dose-comparison study of valproate monotherapy in 265 patients converted from other antie
was either no change or a reduction in complex partial seizure rates in 54% and 64% of patients on
high-dose valproate monotherapy, respectively. Patients who experienced 2 or more CPS per 4 wee
adequate doses of carbamazepine, phenobarbital, primidone, or phenytoin monotherapy were rando
valproate with either low-dose (mean concentration, 71 micrograms/milliliter (mcg/mL); n=134) or hig
concentration, 123 mcg/mL; n=131) monotherapy. Following a 2-week transition period of conversio
results at 8 weeks demonstrated a greater reduction in seizures in the high-dose group (13.2 seizure
10.7) compared to the low-dose group (14.2 seizures at baseline to 13.8) (p less than 0.05). It shoul
there was no control group in this study, and less than 50% of the patients randomized completed th
STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKENE(R) oral capsules, oral syr
b) In a double-blind, concentration-response clinical trial using valproic acid as monotherapy, high c
valproic acid (target level 80 to 150 micrograms/milliliter) reduced seizure frequency of complex part
(p=0.001) and secondarily generalized tonic-clonic seizures (p=0.018) better than those assigned to
valproic acid (target range of 25 to 50 micrograms/milliliter). Participating patients had partial epileps
at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic sei
maintained on a therapeutic level of another antiepileptic drug. They were randomly assigned to high
valproic acid (n=96) or low concentration valproic acid (n=47) with an 8 week dosage adjustment pe
was started and the other drug was tapered off) followed by a 16-week dosage maintenance period.
baseline, there was a 30% median reduction in complex partial seizures for patients in the high grou
increase for those in the low group. The median reduction for secondarily generalized tonic-clonic se
for patients in the high group compared with a 22% increase in the low group. The authors conclude
is efficacious as monotherapy for partial-onset seizures and that it should be considered as first-line
et al, 1997e).

2) Adjunctive Therapy

a) In a 16 week, placebo-controlled study of 144 patients with complex partial seizures (CPS), the u
adjunctive therapy was more effective in reducing the incidence of seizure compared with placebo. P
experienced 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or phenytoin r
randomized to add-on therapy with either valproate (n=75) or placebo (n=69). The results at 16 wee
reduction from baseline of 16 seizures to 8.9 for valproate, compared with 14.5 seizures at baseline
than or equal to 0.05) for placebo. Comparing valproate to placebo, there were 45% vs 23% of patie
least a 50% reduction in CPS rate, respectively (Prod Info STAVZOR(R) delayed release oral capsu
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-te
both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepa
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
(Herranz et al, 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980).

c) Pediatric:

1) The American Academy of Pediatrics (AAP) Clinical Practice Guideline does not recommend long-ter
both daily use of phenobarbital, primidone, or valproic acid and intermittent therapy with oral diazepam ir
months to 5 years with 1 or more simple febrile seizures even though there is evidence that both are effe
the risk of recurrence. The rationale behind the lack of recommendation is because the number of childre
seizures in the first few years of life is extremely high but the associated risks are benign, and there are r
term effects in these children identified up to date. With the exception of the high rate of recurrence, febr
harmful, they do not cause a decline in IQ nor behavioral abnormalities, and do not significantly increase
development of future epilepsy. The use of anticonvulsants has high potential for adverse effects and the
demonstrated improvement in children's long-term outcomes. Adverse effects of anticonvulsant therapy
hepatotoxicity, especially children less than 2 years of age who are also at greater risk of febrile seizures
thrombocytopenia, weight loss, weight gain, gastrointestinal disturbances, and pancreatitis with valproic
irritability, lethargy, and sleep disturbances with phenobarbital and primidone; lethargy, drowsiness and a

intermittent diazepam as well as the risk of masking an evolving central nervous system infection, such a
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 (St
on Quality Improvement and Management,Subcommittee on Febrile Seizures American Academy of Ped
2) Valproic acid has been as effective as phenobarbital for prophylaxis of febrile seizures, with a lower o
(Herranz et al, 1984c; Lee & Melchior, 1981a; Wallace & Aldridge-Smith, 1980). However, phenobarbital
of choice (despite its propensity to cause behavioral abnormalities) due to the hepatotoxic potential of va
Richens, 1985g; Addy, 1981). In general, use of anticonvulsant agents for febrile seizures remains contr

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, aft
had failed (Jacobson et al, 1981a).

c) Adult:

1) Five patients with incapacitating, intractable hiccups were successfully treated with valproic acid, afte
granulated sugar, carbamazepine, chlorpromazine, and nasopharyngeal stimulation had failed. Valproic
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 imp
patient; however, therapy was discontinued after 6 weeks in the fifth patient due to mild gastrointestinal b
patient, hiccups returned to pretreatment levels following withdrawal of valproic acid. Two patients were
off valproic acid; however, 2 patients required continued therapy. Effective peak valproic acid plasma lev
to 96 mcg/mL. It appears that some patients may be successfully treated with valproic acid therapy and
this agent (Jacobson et al, 1981a).

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, 19
Valproic acid may reduce the frequency, number, and severity of manic episodes in patients with sc
disorders (Puzynski & Klosiewicz, 1984).
Valproic acid was effective in the treatment of severe kleptomania and mixed mania refractory to flu
report (Kmetz et al, 1997).

c) Adult:

1) During the 26 to 51 months of valproic acid treatment of 15 patients with affective and schizoaffective
authors observed reduction in the number, length and severity of affective episodes especially mania. In
fragmentation of long and severe relapses into short and mild mania or depression occurred. The numbe
hospital admissions dropped in all patients (Puzynski & Klosiewicz, 1984).
2) Valproic acid, titrated to a serum level of 94 to 110 micrograms/milliliter, successfully treated AIDS-re
case reports (RachBeisel & Weintraub, 1997).
3) Valproic acid 2000 milligrams/day was effective in the treatment of severe kleptomania and mixed ma
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 ass
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 rel 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; Grunz Prasad, 1984).
Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established outpatient, double-blind, placebo controlled trial (n=150; 76 on valproate) (Prod Info STAVZOR(R) d 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 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 stuc receiving a mean dose of 2402 mg/day in study 1 and a mean dose of 2006 mg/day in study 2. The perc who achieved a 30% or greater reduction from baseline in symptom scores in the valproate group compa was 60% vs 26% in study 1, and 58% vs 29% in study 2 (p less than 0.05 for each valproate group comp (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 bi adults (Prod Info STAVZOR(R) delayed release oral capsules, 2008). Valproic acid is effective in the trea suffering from bipolar disorder, even in those who have failed conventional therapy (Fawcett, 1989; Brow 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. Fiv received valproate 1200 or 1800 milligrams on day 1 followed by dosage individualization based on side mean baseline Bech-Rafaelson Mania Rating Scale score was 30.2 which improved to 8 by day 5. One p been unresponsive to oral valproate. On day 5 most were switched to oral dosing. The authors believe th intravenous loading a quick saturation of plasma-binding proteins occurred which could have contributed action (Grunze et al, 1999).

4) One uncontrolled study reported improvement in 5 of 7 patients with mania given valproic acid (up to daily) for 6 weeks. All patients had not responded to previous therapy with lithium and neuroleptics (Pras

d) Pediatric:

1) Efficacy of valproate for the treatment of children with pediatric bipolar disorder was not established in outpatient, double-blind, placebo controlled trial (n=150; 76 on valproate). Children 10 to 17 years of age bipolar disorder received an initial daily dose of valproate of 15 milligrams/kilogram (mg/kg)(max 750 mg dosing used to achieve a clinical response and/or target serum valproate level of 80 to 125 mcg/mL with of 35 mg/kg. Change from baseline on the YMRS scale at final evaluation was the primary efficacy endp maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum valproate concentration of 80 mcg/m during the study (Prod Info STAVZOR(R) delayed release oral capsules, 2008; Prod Info DEPAKOTE(R) 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 me 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 mer 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, incor impairment, worsening of mood, and increased seizures associated with other classes of medication (Ka Sovner, 1989).

2) Valproic acid was useful in 5 cases of bipolar disorder in mentally deficient adults (1 patient with Frag with autistic disorder, two with rapidly cycling illness) . Valproic acid was used in doses of 1000 to 2000 r 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 valproi 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).

d) Pediatric:

1) Significant improvement was seen with valproic acid in 3 mentally deficient children and adolescents disorders characterized by irritability, aggressiveness, self-injurious behavior, hyperactivity and sleep dis symptoms had been unresponsive to previous therapy or the patient had been unable to tolerate side eff with previous medications. Valproic acid 1500 to 3000 milligrams daily, at blood levels of 78 to 111 mcg/

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 Ir
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 at 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) (S
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=304
valproate) in pediatric patients ages 12 to 17 years old (Prod Info STAVZOR(R) delayed release ora
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 mo
who were experiencing at least 2 migraine headaches a month during the previous 3 months were recrui
following a 4-week single-blind placebo baseline period, patients were randomized to valproate or placeb
treatment 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 t
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 adj
differences in baseline rates, were 4.5 in the placebo group compared to 3.3, 3, and 3.3 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/lite
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 patien
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
to 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 ed
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 micromol/liter in the morning before the first daily dose. Eleven patients wer
attacks during the duration of follow-up (mean, 6.5 months; range, from 3 to 12 months). Six patients had
headache frequency, and no effect was observed in 1 patient. Four patients were withdrawn from the stu
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) (S

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 l
week migraine headache rate was the primary efficacy endpoint (Prod Info STAVZOR(R) delayed releas
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
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 sy
(Kuendgen et al, 2004).

c) Adult:

1) A 44% response rate was achieved with valproic acid (VPA) monotherapy in 23 patients with myelody
syndromes (MDS) and acute myelogenous leukemia secondary to MDS (sAML/MDS). In an open-label,
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/m(2)) daily (in two divid
1 through 7 every other week (n=5). VPA dose was titrated to maintain serum levels between 50 and 10
micrograms/milliliter (mcg/mL). Patients who failed monotherapy or relapsed were switched to combinati
Response was rated according to the International Working Group (IWG) criteria. A response was obser
(44%) patients receiving VPA monotherapy. The median time to response was 30 days (range, 14 to 38
median VPA dose of 1250 mg (range, 900 to 2550 mg) and median duration of 6 months (range, 2 to 23
Hematologic improvement was observed in 7 patients and a partial response in 1 patient. Relapse occur
a median of 4 months, of which, 4 patients were switched to combination therapy. Two of these 4 patient
therapy for another 11 and 16 months. Stable disease was seen in 4 patients at a median duration of 5 r
patients had progressive disease and were switched to combination therapy without success. None of th
receiving combination therapy initially responded to therapy. Of note, all 3 patients considered low-risk a
international prognostic scoring system showed a major response, while only 1 patient considered high-r
minor response. Furthermore, 3 of 9 patients with an elevated blast count achieved a significant reductio
marrow blasts. Therapy was well tolerated as only one patient discontinued VPA because of vertigo and
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 us
valproic acid, and after a period of 2 years free from seizures, could be maintained on still lower dos
al, 2001).
Combination therapy with valproic acid (1500 to 1800 mg daily), clonazepam (6 to 10 mg daily) and
to 100 mg daily) was effective in improving severe progressive myoclonus epilepsy in adults in a lon
clinical study (Iivanainen & Himberg, 1982).

c) Adult:

1) Patients with juvenile myoclonic epilepsy (JME) were successfully treated with lower than usual dose
and after a period of 2 years free from seizures, could be maintained on still lower doses. Seventy-six pa
diagnosed with JME, were initially treated with sodium valproate 15 milligrams/kilogram/day (mg/kg/day)
controlled at that dose continued with the same dose. Doses were increased to 20 to 40 mg/kg/day in th
controlled. In those who were not controlled at 40 mg/kg/day, a second drug was added. Sixty-three perc
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%
mg/kg/day, and 42% required more than 9 mg/kg/day (Panagariya et al, 2001).
2) Combination therapy with valproic acid (1500 to 1800 milligrams (mg) daily), clonazepam (6 to 10 mg
phenobarbital (50 to 100 mg daily) was effective in improving severe progressive myoclonus epilepsy in
term prospective clinical study. All previous medications (phenytoin and other antiepileptic agents) were
to initiation of combination therapy. After 6 years of continuous follow-up, improvement was still observe
not benefited from previous anticonvulsant therapy at optimal doses. Effective plasma levels evaluated i
28 milligrams/liter (mg/L) for valproic acid, 0.05 mg/L for clonazepam, and 19 mg/L for phenobarbital (Iiva
Himberg, 1982).

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 myocl with post-anoxic myoclonus and 2 with nocturnal myoclonus). These patients had no epileptic manifestat seizure activity and no other medications were given. Valproic acid may have a role in the treatment of m however further studies are warranted. The mechanism of action in the condition is unclear (Sotaniemi, 1

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 et al, 1984; Buckingham, 1983; Jones et al, 1981; Mercado-Asis et al, 1997a; Loli et al, 1988; Loli et

c) Adult:

1) Numerous studies have documented the efficacy of valproic acid in the treatment of Nelson's syndror Cushing's disease. Decreases in circulating ACTH levels have been documented in patients receiving va or in combination with diazepam, cyproheptadine, or metyrapone (Glaser et al, 1984; Buckingham, 1983 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 adrenocorticotro (ACTH) secretion in Nelson's Syndrome. Six women with Nelson's Syndrome had their ACTH measured placebo, cyproheptadine, valproic acid, bromocriptine; and the combination of cyproheptadine and valpro combination of bromocriptine, cyproheptadine and valproic acid. Only bromocriptine caused a significant plasma ACTH (P less than 0.05), as did the combination of the 3 drugs (P less than 0.05). However, the the 3 drugs 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 adren hormone (ACTH)-secreting pituitary macroadenoma in a patient with Nelson's syndrome (Loli et al, 1988 1.5 years, the patient received 2 courses of therapy with valproic acid lasting 4 months each; both treatm tumor reduction that was documented by computed tomography. More studies are required to evaluate t valproic acid in this clinical setting.

4) Another study failed to show the effectiveness of valproic acid in 8 patients with Nelson's syndrome. A 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, 199

c) Adult:

1) Valproate was effective for obsessive compulsive disorder in a 35-year-old man who stopped working obsessed with touching his parents 70 to 80 times per day. He had previously discontinued fluoxetine du agitation. Fluoxetine 5 mg was restarted along with valproate 250 milligrams (mg) in the morning and 50 evening to alleviate side effects. After 2 weeks he was able to resume work and felt less anxious and mo control" (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

b) Summary:

Valproic acid was effective in a case report of a patient with panic disorder associated with multiple s & Cassano, 1996).

c) Adult:

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

4.5.A.23 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:

Sleep quality and duration were improved in 6 outpatients given long-term valproate for periodic limb disorder (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) giv valproate for periodic limb movement disorder. After a mean 6 months of therapy, dosages of valproate r 600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep effic 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 hou 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 discontinue the end of the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other du side effects (Ehrenberg et al, 2000).

4.5.A.24 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:

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

c) Adult:

1) Four controlled studies and several case reports and case series suggest that valproate may be effec and 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 alc symptoms between valproate- and phenobarbital-treated patients, nor were there differences in blood pr rate responses associated with the 2 agents. In another comparative study, valproate and chlormethiazo have similar efficacy in ethanol withdrawal, but physiological effects were poorly documented. A double-l 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 com and lorazepam, valproate was found to be effective and well-tolerated in the treatment of ethanol withdra 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 b clonazepam until valproate was added to therapy. Another report describes 4 cases of protracted withdra during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Tw reported in which valproate prevented alcohol or benzodiazepine relapse (Harris et al, 2000).

4.5.A.25 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 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 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

withdrawal of anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnost purposes (Rosenfeld et al, 1987).
Valproic acid has been demonstrated effective in a variety of seizure types which include absence s seizures, and tonic-clonic seizures (grand mal), including patients who have been unresponsive to o 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 ge Valproic acid has been effective in generalized epilepsy (Rimmer & Richens, 1985g; AMA Departme Sato et al, 1982a; Jeavons et al, 1977); however, carbamazepine is generally preferred because of (Young & Koda-Kimble, 1995a).

2) Clinical Trials

a) Valproic acid in loading doses of approximately 12.5 milligrams/kilogram (mg/kg), orally or rectall 15.9 mg/kg) was reported effective in preventing generalized tonic-clonic seizures following withdrav anticonvulsant agents in seizure patients undergoing intensive monitoring for diagnostic and therape Seizure activity was prevented in 23 of 35 patients (66%) following a single loading dose. Serum co ranging from 284 to 458 micromole/L were observed 1.5 hours following administration in 6 of 8 pati These data suggest the benefits of valproic acid given orally or rectally in patients undergoing anticc withdrawal. The rectal route appears to have a place in the treatment of patients unable to take oral to GI disorders, surgery or coma (Rosenfeld et al, 1987).

b) Valproic acid is indicated as adjunctive therapy in patients with multiple seizure types. Valproic a demonstrated effective in a variety of seizure types which include absence seizures, partial seizures 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 treatme absence seizures (petit mal) and photosensitive epilepsy (Rimmer & Richens, 1985g; Sato et al, 198 1977). Although valproic acid is considered a first-line therapy for treating generalized tonic-clonic s or complex partial seizures, carbamazepine is generally preferred because of its lesser toxicity. Etho generally preferred over valproic acid for treatment of absence seizures because it is equally effectiv tolerated (Young & Koda-Kimble, 1995a). Oral and rectal valproic acid have been effective in refract epilepticus (Vajda et al, 1977; Manhire & Espir, 1974). The drug is usually combined with other antic producing seizure reduction in 75 to 100% in greater than 40% of patients with intractable epilepsy, improvement being seen in myoclonic seizures, absence seizures and grand mal seizures (Simon & However, single-agent therapy has also been effective (Rimmer & Richens, 1985g; Turnbull et al, 19 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 aci their drug regimens. Sixty-one percent improved clinically. Valproic acid significantly reduced the fre generalized tonic-clonic seizures, generalized myoclonus, absence and atonic seizures. There was correlation between clinical improvement and reduction of EEG paroxysmal activity (Chayasirisobho 1983).

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 anxie open-label, 12-week study (Kinrys et al, 2003).

c) Adult:

1) Valproic acid improved Liebowitz Social Anxiety Scale (LSAS) scores in 17 patients with social anxiet open-label, 12-week study. Valproic acid therapy was initially dosed at 250 milligrams (mg) twice daily, w tolerated, doses were increased to 1000 mg daily. Doses were adjusted according to tolerability and ther however doses were kept between 500 mg daily and 2500 mg daily. Intent to treat analysis demonstrate decrease in the total LSAS score of 19.1 (p less than 0.0001). Individual LSAS scores also showed a sig improvement in fear and avoidance symptoms (p less than 0.0001). Mild cases of nausea, headache, so dizziness, and fatigue were reported with the use of valproic acid in this study group. The authors ackno sample size, and the lack of placebo control and blinding were limitations in study design (Kinrys et al, 2(

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 r clonazepam 18 mg, and baclofen 60 mg in divided doses each day. Valproate was gradually added to th increased to a dose of 2 grams daily. The patient showed marked improvement and was able to walk wit and without his cane. Although the effectiveness of sodium valproate is only cited in one case report, it d 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 syn reports (Hori et al, 2000).

c) Adult:

1) Two psychologically normal elderly women (ages 73 and 77) experiencing complex visual hallucinatic sensory deprivation (decreased visual acuity) and mild cerebral dysfunction were successfully treated wi 400 milligrams (mg) to 800 mg daily. The 73-year-old had partial resolution of symptoms at 400 mg daily disappearance of all hallucinations with 800 mg daily. The 77-year-old woman was started on 200 mg da increased to 400 mg daily, at which point she was able to sleep and experienced no more hallucinations. 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 sir absence seizures occurring in isolation and as adjunctive therapy for simple and complex absence s in association with other types of seizures (Prod Info DEPAKOTE(R) ER extended-release oral table DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets,

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;

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

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, plac study. All patients received an initial 30 milligram (mg) dose of oxazepam; additional 30 mg doses of oxa every hour if the subject's CIWA-Ar score was 10 or higher. The divalproex group received 500 mg of div (sprinkle formulation) three times a day in addition to the oxazepam. The divalproex group required signi (p=0.033) oxazepam than the placebo group (85 +/- 63.64 mg vs. 111.7 +/- 119.5 mg, respectively) to m withdrawal symptoms. Six percent (1 of 18) of subjects in the divalproex group and 40% (7 of 18) of the p had an increase in withdrawal symptoms (1 point and 3 points respectively) compared to baseline. Adver similar between groups with somnolence reported significantly more frequently (p less than 0.05) in the d (Reoux et al, 2001a).

2) A 51-year-old man with a 30-year history of heavy drinking was successfully withdrawn from alcohol u sodium. On admission, he was found to meet diagnostic criteria for alcohol dependency (DSM-IV), and e liver enzymes and an increased mean corpuscular volume. He had no other mental or physical co-morbi the Clinical Institute Withdrawal Assessment-Alcohol revised instrument (CIWA-Ar) increased from an ini at 8 hours post-admission. He began divalproex detoxification with a loading dose of 750 milligrams (mg) mg/kilogram body weight; the second half of his loading dose 750 mg was given 6 hours later. During the his CIWA-Ar score decreased to below 6, where it remained for the duration of his hospital stay. He was 4 (divalproex level 83 mg/milliliter), and maintained on a dose of divalproex 750 mg twice daily for 6 wee abstinence during the 6 weeks of follow-up. His laboratory results improved. Divalproex was tapered and patient remained abstinent. According to the author, advantages of divalproex over benzodiazepines for include its lack of abuse potential and absence of synergistic reaction with alcohol, and, in contrast to oth anticonvulsants, divalproex can be initiated with an oral loading dose to effect a rapid onset of action (Lo

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 patie
48.2 years; range, 13 to 89 years) who had suffered acute brain injury and were recovering in a brain inju
unit. All subjects had agitation unsuccessfully controlled on prior benzodiazepine therapy, with or without
Overall, 18 of 29 (62%) were recorded 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 w
dose of 714 mg divalproex and no other psychotropic medications. Divalproex was soon discontinued in
recurrence of agitation. Most patients (93%) were discharged to their home or community sites. One pati
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 childre
2005)

c) Pediatric:

1) Divalproex sodium may be effective for mixed manic episodes associated with bipolar I disorder, as e
open-label, time-series study. Patients (n=35; mean age 12.3 +/-3.7 years) with a diagnosis of mixed epi
disorder and greater than 20 on the Young Mania Rating Scale (YMRS) were offered divalproex treatme
up to 6 months. The treatment protocol consisted of divalproex sodium at an initial dose of 250 to 500 m
to achieve target doses of 15 to 20 mg/kg/day and serum concentrations of 50 to 120 micrograms/millilite
Risperidone, benztropine, and trazodone were allowed for limited treatment of breakthrough symptoms a
Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulants at a s
Response was defined as at least a 50% change from baseline on YMRS and no more than 40 on the C
Rating Scale-Revised (CDRS-R). Remission was defined as at least a 50% change from baseline on YM
40 on CDRS-R, no more than 2 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 sar
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 approx
months of treatment ($p < 0.001$). The response rate was 73.5% and the remission rate was 52.9%. An ov
size of 2.9 was calculated by Cohen's d, with 0.8 generally considered to be large in magnitude. Seventee
required risperidone (mean length, 7 +/- 1 day), 5 patients received trazodone (mean length, 5 +/- 2 days
continued to receive methylphenidate. Common adverse events encountered were: weight gain (58.8%),
increased appetite (47.1%), cognitive dulling (41.2%), nausea (26.5%), stomach pain (23.5%), agitation (
tremor (14.7%). Six patients had elevated alanine transferase levels that normalized after 2 months of tre
et al, 2005).

2) No difference in efficacy was found between divalproex sodium and lithium sodium for the maintenan
pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/-
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 tar
mg/kg/day and adjusted to maintain serum levels of 0.6 to 1.2 millimoles/liter (mmol/L). Divalproex was ti
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 c
and were able to tolerate the minimum serum concentration levels of lithium or divalproex while receiving
stabilizers, antipsychotics, or antidepressants were eligible for enrollment in phase II (double-blind maint
phase II, patients were randomized to receive either lithium or divalproex, maintaining desired serum lev
weeks. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulan
(maximum dosage 6 micrograms/kg/day) at stable doses 4 weeks prior to phase II. One hundred thirty-n
treated in phase I, 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 (standa
57.4 days) for patients treated with lithium and 112 days (SE +/- 56 days) for patients treated with divalpr
Median time to discontinuation for any reason was 91 days (SE +/- 30.1 days) for patients treated with lit
(SE +/- 19.9 days) for patients treated with divalproex (p=0.72). Statistically significant differences were r
frequency of reported emesis (30% lithium versus 10% divalproex; p=0.05), enuresis (30% lithium versus
p=0.02), and increased thirst (16.7% lithium versus 0% divalproex). Differences in frequency of headach
versus 23.3% divalproex) and stomach pain (10% lithium versus 23.3% divalproex) were also noted, but
significant. Other adverse events reported in over 5% of patients in phase II were tremor, nausea, diarrh
appetite, upper respiratory congestion, fever and sore throat. Five patients withdrew from the study due t
(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 IIb
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 maintena 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 maintenan pediatric bipolar I or II disorder in a double-blind, randomized study. Patients (n=139; mean age 10.8 +/- 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 tar mg/kg/day and adjusted to maintain serum levels of 0.6 to 1.2 millimoles/liter (mmol/L). Divalproex was ti 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 c and were able to tolerate the minimum serum concentration levels of lithium or divalproex while receiving stabilizers, antipsychotics, or antidepressants were eligible for enrollment in phase II (double-blind maint phase II, patients were randomized to receive either lithium or divalproex, maintaining desired serum lev weeks. Patients with attention-deficit/hyperactivity disorder were allowed to continue prescribed stimulan (maximum dosage 6 micrograms/kg/day) at stable doses 4 weeks prior to phase II. One hundred thirty-n treated in phase I, 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 (stand 57.4 days) for patients treated with lithium and 112 days (SE +/- 56 days) for patients treated with divalpr Median time to discontinuation for any reason was 91 days (SE +/- 30.1 days) for patients treated with lit (SE +/- 19.9 days) for patients treated with divalproex (p=0.72). Statistically significant differences were r frequency of reported emesis (30% lithium versus 10% divalproex; p=0.05), enuresis (30% lithium versus p=0.02), and increased thirst (16.7% lithium versus 0% divalproex). Differences in frequency of headach versus 23.3% divalproex) and stomach pain (10% lithium versus 23.3% divalproex) were also noted, but significant. Other adverse events reported in over 5% of patients in phase II were tremor, nausea, diarrh appetite, upper respiratory congestion, fever and sore throat. Five patients withdrew from the study due t (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.6 Borderline personality 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:

Preliminary results suggest possible efficacy; more studies in larger trials needed (Townsend et al, 2

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 enrolle 8-week study; one each completed weeks 3, 4, 5, and 6; one dropped out after the initial visit. Divalproex initiated at 250 milligrams (mg) twice daily, and could be increased by 250 to 500 mg at weekly visits if in not seen. At their last visit (whenever it occurred), mean dose of responders was 1125 mg/day compared for non-responders. Six of nine evaluable subjects were rated as "much improved" or better on the Clinic Impression Scale (CGI) at their last weekly visit. Scores on the Mania Rating Scale (MRS) declined, but extent. 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 improve with borderline personality disorders (DSM-IV axis II); however, the validity of these results are limited du out rate and small sample size. In a double- blind, randomized (2:1 ratio) manner, 16 patients were assig sodium or placebo. Six patients completed the study and 10 dropped out. Overall, 100% of those assigne withdrew, while 50% allocated to divalproex sodium withdrew. No one withdrew due to side effects. Com baseline, divalproex sodium-treated patients had significantly improved scores on the Clinical Global Imp Improvement scale (CGI-I) (p=0.006). Of the 6 patients, 5 were considered to be responders, ie, were m very much improved, based on the CGI-I. On the Global Assessment Scale (assessment of overall funct treated with divalproex sodium had significantly improved scores compared with baseline (p=0.003). Son

among those in the divalproex sodium group was shown on the Beck Depression Inventory (BDI) and sli
occurred on the Aggression Questionnaire (AQ), related to aggressive feelings and actions. Divalproex s
as 250 milligrams at bedtime and gradually titrated to doses sufficient to maintain serum levels of 80 mic
the highest tolerated dose. The authors concluded that more study of divalproex sodium in this patient p
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 7
newly-diagnosed brain tumors, divalproex or placebo was given within 14 days of diagnosis. Divalproex
adjusted to achieve trough levels in the range of 50 to 100 mcg/mL; the median duration of follow-up wa
five percent of patients treated with divalproex suffered seizures compared to 24% of patients treated wi
authors conclude that anticonvulsant therapy is not indicated in patients with brain tumors unless they su
(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 v
use (Wheeler, 1998). Both patients had been unresponsive to multiple medications and one to surgical i
first, a 37-year-old man with a 15-year history of cluster headaches with an atypical visual aura, received
milligrams (mg) twice daily. Headache remission occurred within 2 months. Divalproex was tapered after
remained in remission. The second, a 55-year-old man with a 16-year history of cluster headaches alon
without aura, was given divalproex 250 mg 3 times daily with 750 mg nightly. Headache remission occur
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 co
seizures occurring in isolation or in association with other types of seizures (Prod Info DEPAKOTE(R
release oral tablets, 2008; Prod Info DEPAKOTE(R) sprinkle oral capsules, 2008; Prod Info DEPAK
release oral tablets, 2006)

c) Adult:

1) Monotherapy

a) In a dose-comparison study of divalproex sodium monotherapy in 265 patients converted from ot
there was either no change or a reduction in complex partial seizure rates in 54% and 64% of patien
and high-dose divalproex sodium monotherapy, respectively. Patients who experienced 2 or more C
despite adequate doses of carbamazepine, phenobarbital, primidone, or phenytoin monotherapy we
receive divalproex sodium with either low-dose (mean concentration, 71 micrograms/milliliter (mcg/m
high-dose (mean concentration, 123 mcg/mL; n=131) monotherapy. Following a 2-week transition p
to divalproex sodium, the results at 8 weeks demonstrated a greater reduction in seizures in the high
seizures at baseline to 10.7) compared to the low-dose group (14.2 seizures at baseline to 13.8) (p
should be noted that there was no control group in this study, and less than 50% of the patients ran
the study (Prod Info DEPAKOTE(R) ER extended-release oral tablets, 2008; Prod Info DEPAKOTE(
capsules, 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 u sodium as adjunctive therapy was more effective in reducing the incidence of seizure compared with who experienced 8 or more CPS per 8 weeks despite therapeutic levels of carbamazepine or pheny were randomized to add-on therapy with either divalproex sodium (n=75) or placebo (n=69). The res demonstrated a reduction from baseline of 16 seizures to 8.9 for divalproex sodium, compared with seizures at baseline to 11.5 (p less than or equal to 0.05). Comparing divalproex sodium to placebo, vs 23% of patients who had at least a 50% reduction in CPS rate, respectively (Prod Info DEPAKOT 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 pat partial seizures. Patients taking either carbamazepine or phenytoin, whose seizures were inadequat monotherapy, were randomized to either divalproex sodium or placebo after optimization of their mo regimen. The dose of divalproex was slowly adjusted to a maximum of 90 milligrams/kilogram/day. T divalproex resulted in a median seizure reduction of 7.9 seizures in eight weeks compared to 2.5 in treated with placebo. Six of the divalproex-treated patients became seizure-free during the study pe al, 1996).

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 h retrospective study (Freitag et al, 2001).

c) Adult:

1) Results from a retrospective study (n=138) indicated that divalproex sodium was effective in the treat patients with chronic daily headache. In this study, 67% (93 of 138) of the patients had at least a 50% re 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 DE delayed-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 outpa placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorc DEPAKOTE(R) ER extended-release oral tablets, 2008).

c) Adult:

1) In two 3-week, placebo-controlled, parallel-group studies, divalproex sodium had significantly superio measures of assessed outcomes for acute mania compared with placebo. In both studies, patients were divalproex sodium delayed-release 250 milligrams (mg) orally three times a day and adjusted to achieve levels in the range of 50 to 100 micrograms/milliliter (mcg/mL) in study 1, and 40 to 150 mcg/mL in study completion of the study, patients were receiving a mean dose of 2402 mg/day in study 1 and a mean dos in study 2. The percentage of patients who achieved a 30% or greater reduction from baseline in sympto divalproex sodium group compared with placebo was 60% vs 26% in study 1, and 58% vs 29% in study for each divalproex group compared to placebo) (Prod Info DEPAKOTE(R) delayed-release oral tablets,

2) In a 3-week, randomized, double-blind, parallel-group study, adult patients diagnosed with bipolar I di mixed type, hospitalized with acute mania treated with divalproex sodium extended-release had significa Mania Rating Scale (MRS) scores compared with placebo. Patients received an initial dose of divalproex release 25 milligrams/kilogram (mg/dg) orally once a day, increased by 500 mg/day on day 3, and then a a plasma valproate level of 85 to 125 microgram/milliliter (mcg/mL). At the end of the study, the mean da mg (range, 1500 to 5500 mg), and mean valproate plasma levels were 89.5 mcg/mL (Prod Info DEPAKC extended-release oral tablets, 2008).

3) Divalproex sodium (target dosage of 20 milligrams/kilogram/day) did not improve signs and symptom associated with dementia in elderly patients during a double-blind, 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) Inv

significant improvement in the divalproex sodium-treated group. Twenty-two percent of divalproex sodiur and 4% of patients who received placebo withdrew from the study because of adverse effects, primarily s et al, 2001).

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets was not established in a single 4-week outpat placebo controlled trial (n=150; 76 on divalproex sodium) for the treatment of pediatric bipolar disorder. C years of age, with pediatric bipolar disorder received an initial daily dose of divalproex sodium of 15 milli (mg/kg)(max 750 mg) with flexible dosing used to achieve a clinical response and/or target serum valpro 125 mcg/mL with a maximum dose of 35 mg/kg. Change from baseline on the YMRS scale at final evalu primary efficacy endpoint. A mean maximum daily dose of 1457 mg (27.1 mg/kg) and mean final serum v concentration of 80 mcg/mL were attained during the study (Prod Info DEPAKOTE(R) ER extended-relea 2008).

2) Oral loading doses of divalproex sodium 15 milligrams/kilogram/day (in divided doses) produced troug 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 the defined as 50 to 120 micrograms/milliliter (mcg/mL). These doses were well tolerated by the normal-weig more side effects seen at plasma concentrations above 90 mcg/mL. Overweight subjects benefited from the formula: ideal body weight (IBW) plus 40% multiplied by actual weight minus IBW (Good et al, 2001).

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 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 is indicated for the prophylaxis of migraine headache in adults (Prod Info DEPAK extended-release oral tablets, 2008; Prod Info DEPAKOTE(R) delayed-release oral tablets, 2006).
Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established double-blind, placebo-controlled, parallel-group, four equal armed (placebo, 250 milligrams (mg), 50 mg) study (n=304; 231 on divalproex sodium) in pediatric patients ages 12 to 17 years old (Prod Info ER extended-release oral tablets, 2008).
In an open-label, retrospective study in 42 adolescents and children, divalproex sodium provided a 5 reduction in migraine frequency (Caruso et al, 2000).

c) Adult:

1) The average incidence of migraine headache attacks was reduced following once-daily prophylactic t divalproex sodium extended-release (ER) tablets. In a randomized, controlled, double- blind, multicenter at least a 6-month history of migraine headache attacks and experiencing an average of 2 or more migra 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= milligrams (mg)/day for 1 week titrated to 1000 mg/day; mean dose, 871 mg/day) or placebo (n=115) for Following 12 weeks of treatment, a significantly greater reduction in the mean baseline migraine headacl in patients who took divalproex sodium-ER as compared with placebo (mean reduction, 1.2 vs 0.6, respe This reduction from baseline reached significance during the first 4 weeks of treatment (p=0.035) and rer throughout the second and third 4-week periods (p=0.006 and p=0.045, respectively). Adverse events w between treatment groups (Freitag et al, 2002).

2) A case report describes how divalproex brought dramatic relief of migraine headaches induced by se serotonin reuptake inhibitor (SSRI), in a 44-year-old woman with a history of refractory major depression 2000). Divalproex 750 milligrams (mg)/day immediately reduced the frequency, severity, and duration of (valproate serum level was 240 micromoles/liter). After 3 months, the patient was headache-free most of months, the dose of divalproex was increased to 1500 mg/day as the migraines had become more frequ patient was successfully maintained on a daily regimen of sertraline 100 mg, divalproex 1500 mg, and ox needed. The authors suggest that valproate be considered for patients who have a history of migraine or experience migraine while being treated with a selective serotonin reuptake inhibitor.

d) Pediatric:

1) Efficacy of divalproex sodium extended-release tablets for migraine prophylaxis was not established i blind, placebo-controlled, parallel-group, four equal armed (placebo, 250 milligrams (mg), 500 mg, and 1 (n=304; 231 on divalproex sodium) in pediatric patients ages 12 to 17 years old. The study consisted of a period followed by a 12 week experimental period (including an initial 2 week titration period) with placeb each dose. Reduction from baseline in the 4 week migraine headache rate was the primary efficacy endp DEPAKOTE(R) ER extended-release oral tablets, 2008).

2) In an open-label, retrospective study (n=42), divalproex sodium was shown to be safe and effective fo treatment of migraine headache in adolescents and children (aged 7 to 16 years, mean 11.3 years) (Car Study subjects had a history of 1 to 4 headaches per month. After a 4-month course of divalproex treatm in headache frequency occurred in 33 (78.5%), 75% reduction in headache frequency in 6 (14.2%), and were virtually headache-free (p less than 0.05). Initial doses of divalproex were 15 milligrams/kilogram (n

(divided into 2 doses) with titration upward over 6 weeks based on response. Daily doses over the 4-mor
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
were gastrointestinal upset, weight gain, somnolence, dizziness, and tremor; mild transient elevation of li
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 unres
disorder and mood instability (Baetz & Bowen, 1998). Patients (18 to 65 years old) received divalproex 2
twice daily and increased by 250-mg increments to a target level of 300 to 600 micromoles/L (45 to 90 m
patients completed the study and 2 dropped out due to side effects. Panic attacks decreased significantly
2.6/week (p=0.0318). Also decreased were the Hamilton Anxiety Rating Scale (p=0.0001) and the Beck
(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) giv
valproate for periodic limb movement disorder. After a mean 6 months of therapy, dosages of valproate r
600 milligrams taken at bedtime. Polysomnographic findings included a significant increase in sleep effic
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 ho
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 discontinue
the end of the study; subsequently 2 patients terminated the drug, 1 due to weight gain and the other du
side effects (Ehrenberg et al, 2000).

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 treatmen
2001).

c) Adult:

1) Divalproex sodium therapy was associated with some improvement of social interaction skills, repetiti
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 dis
otherwise specified (2). Ten were children/adolescents and 4 were adults (age range 5 to 40 years, mea
scores ranged from 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 milligra
Mean final dose was 768 mg/day (range 125 to 2500 mg/day) and mean duration of valproate treatment
Concomitant medications were taken by 10 patients, and included antidepressants, atypical neuroleptics
and alpha-1 agonists. Based on the Clinical Global Impressions-Improvement scale (CGI-I), 10 of 14 sub
sustained responders, with ratings of much or very much improved. Four patients showed improvement i
interactions. Four showed improvement related to repetitive behavior (ie, reduced obsessive-compulsive
subject improved in language and communication skills. Five became less impulsive, and 4 were less ag
patients were discontinued in the first 2 weeks due to severe behavioral activation. Other adverse effects
(5), digestive disturbances (3), weight gain (3), hair loss (2), mood lability (1), and elevated liver enzymes
recommend 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= (patient-rated) after at least 1 month of divalproex sodium, based on a retrospective chart review; the dru well tolerated, with no serious side effects. Mild improvement was defined as 25% to 50% better, and mo than 50% improvement. In all subjects, headache was the result of mild head injury and had persisted fo months. Six patients became headache-free for 1 month or more, and 35 patients reported that their dail 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 p response, 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, 200 Standard preparations and extended-release formulations of divalproex sodium are equally efficacio schizoaffective disorders; however, higher daily doses of extended-release formulations are require 2003).

c) Adult:

1) In a retrospective study (n=20), add-on divalproex therapy appeared to be well-tolerated and efficacic with schizoaffective disorder, bipolar type (aged 23 to 52 years, mean 38 years). Improvement in the Clir Impression (CGI) Scale scores occurred in 15 of 20 (75%) patients (p=0.0001); no change in CGI scores patients. None of the cohort showed worsening of their disorder; and no one discontinued divalproex due effects. Most common side effects were anxiety (n=2) and agitation (n=2); 1 person experienced extrapy symptoms/tremors. Other concurrent medications were most frequently antipsychotics (n=19), antidepre lithium (n=6). Mean daily dose of divalproex was 986 milligrams (mg) (range, 375 to 1750 mg); mean pea 61 micrograms/milliliter. Mean follow-up was 24 weeks (Bogan et al, 2000).

2) In a 6-week, open-label pilot study, dose-adjusted extended-release divalproex was equally efficaciou the standard preparation in bipolar and schizoaffective disorders. Twelve euthymic and clinically stable p enrolled into the study. Eight of these patients had been diagnosed with bipolar I or II disorder and 4 wer bipolar-type schizoaffective disorder. Each patient had received regular divalproex sodium twice daily for weeks and were maintained at serum valproic acid concentrations between 50 to 120 micrograms/millilit dose. Patients were switched to extended-release divalproex at doses rounded to the nearest 500 milligr Extended-release divalproex doses were administered once daily at bedtime. Doses were adjusted to at valproic acid levels achieved with the standard preparation. Average daily doses of the extended-release 20.7% higher than those of the standard preparation (1.19 grams versus 1.5 grams, p=0.0009). Clinical s evaluated using the Young Mania Rating Scale, the Hamilton Depression Rating Scale, Clinical Global Ir severity and improvement, the Global Assessment of Functioning Scale and the Brief Psychiatric Rating no significant differences between the baseline and endpoint ratings. Reported adverse effects were also an increase in polyuria-polydipsia (p=0.03) (Centorrino et al, 2003).

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 effec withdrawal and benzodiazepine withdrawal. In contrast, one double-blind, controlled trial failed to suppor

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 chlor 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) b 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 ethar another report, two manic schizoaffective patients had successful withdrawal from ethanol when valproat 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 withdra during tapering of benzodiazepines; the symptoms were notably eased after the addition of valproate. Tw 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 administr 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 a
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 w
Sodium valproate was no more effective than placebo in the treatment of aggression in this group of pati
2003).
2) In a randomized, placebo-controlled, double-blind study of 42 elderly patients (mean age=80.4 years)
had no effect versus placebo in the treatment of aggressive behavior in dementia. Sodium valproate was
three weeks at a fixed dose of 6 milliliters (mL) of a 40 milligram per milliliter (mg/mL) oral suspension tw
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
seizures. In a study evaluating the effect of valproate sodium injection in the prevention of post-traumatic
patients with acute head injuries, patients were assigned to receive either valproate sodium injection for
by oral valproate for either one or six months, or phenytoin intravenous given for one week followed by p
incidence of death was found to be higher in the 2 groups assigned to the valproic acid treatment compa
those assigned to the phenytoin treatment group (13% versus 8.5%). Evaluation of the cause of death di
specific drug-related causation. Furthermore, without a placebo group it is difficult to determine the actua
these head trauma patients. Until further information is available, the manufacturer recommends not usir
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 intrave
VALPROIC ACID (Kruger & Braunig, 2001). The patient required an average of 10 hospital admissions p
acute phases of his illness. In the acute phases, he would exhibit motor excitement, impulsive aggressio
iterations, screaming, negativism, gegenhalten, and impulsive behavior (such as binge eating, pica, and
masturbation). Between acute phases, he had severe negative symptoms, along with bizarre behaviors.
unsuccessfully treated with typical and atypical neuroleptics. On the index admission, he could not be giv
because he was unable to open his mouth due to extreme rigidity. He was started on high-dose IV valpro
milligrams (mg)/day, followed on the succeeding days by 3000 mg, 2500 mg, and 1800 mg. Each day his
symptoms were reduced from the previous day (90% symptom reduction over 4 days). After day 4, he w
valproate orally (900 mg/day for a plasma level of 60 micrograms/liter maintenance dosing). He required
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)

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:

Intravenous sodium valproate is indicated as monotherapy and adjunctive therapy for complex partia occurring in isolation or in association with other types of seizures when administration of oral valpro possible (Prod Info DEPACON(R) IV injection, 2006)
Carbamazepine is generally the first line agent for complex partial seizures

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:

As effective as PHENOBARBITAL

c) Pediatric:

1) Recurrence rates of febrile convulsions during one year were not statistically different among 196 chil convulsions treated with either PHENOBARBITAL, PRIMIDONE or SODIUM VALPROATE (Minagawa & The children on SODIUM VALPROATE received either 20 to 25 milligrams/kilogram/day (mg/kg/day) twi mg/kg/day three times 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 eff regimens were of equal efficacy in the long-term prophylaxis of febrile convulsions in children.

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 individua side effects. Their mean baseline Bech-Rafaelson Mania Rating Scale score was 30.2 which improved t patient had actually been unresponsive to oral valproate. On day 5 most were switched to oral dosing. T that with the intravenous loading a quick saturation of plasma-binding proteins occurred which could hav beneficial action.

2) One uncontrolled study reported improvement in 5 of 7 patients with MANIA given VALPROIC ACID (milligrams daily) for 6 weeks. All patients had not responded to previous therapy with LITHIUM and neur 1984).

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 (Math (Tanen, 2003)

c) Adult:

1) Results from an open-label, prospective study (n=61) indicate that intravenous valproate sodium (300 effective for the acute treatment of migraine headache. In this preliminary report, significant improvemen 0.001) (decreased headache severity) occurred in 73% of the migraine sufferers. Mean time to onset of r complete relief were 8 minutes and 25 minutes, respectively (Mathew et al, 2000).

2) In a randomized, double-blinded trial, intravenous prochlorperazine was more effective than intraven treating acute migraine headaches. Forty patients presented to emergency with a migraine headache wi and were recruited into the trial. Patients received either 500 milligrams (mg) of sodium valproate or 10 m 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 less than 0.001). Median nausea

35.5 mm in prochlorperazine patients and 2 mm in valproate patients (p less than 0.001). Median sedatic
4 mm in prochlorperazine patients and 0 mm in valproate patients (p=0.603). Over time, prochlorperazin
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 conclu
minute follow-up period, 79% of valproate patients and 25% of prochlorperazine patients required rescue
insufficient symptom relief (p=0.001). Extrapyramidal reactions were reported in 2 prochlorperazine patie

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 MYOCLONIC ASTATIC ATTACKS and sudden falls in 18 parkinsonian
(Henneberg et al, 1998). These patients also had polyspikes or polyspike-wave complexes on electroenc
(EEG). Sodium valproate 600 to 1800 milligrams/day was administered to achieve a level of at least 60 u
and EEG readings improved in 16 patients. The authors suspect that a generalized epilepsy may have c
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 r
with cancer-related neuropathic pain. Valproate was initiated at 200 milligrams (mg) twice a day with titra
not controlled and toxicity was not present) of 200 mg at intervals of 2 to 3 days to a maximum of 600 mg
Nineteen of 25 patients completed the study and the median valproate dose at day 15 was 600 mg twice
55.6% of those completing the study had a reduction in average pain by at least one category (eg, from s
moderate, or from moderate to mild), and 66.7% also had a decline in pain category for their worst pain.
timeframe, 66.7% had a decline in their absolute pain score (scale of 1 to 10 based on the Brief Pain Inv
average and worst pain. The proportion reporting a 50% reduction in pain score was 27.8% for both aver
pain. Most common side effects were drowsiness, unsteadiness, nausea, and decreased appetite; one p
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 IIa; Pediatric, Class IIa
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 adm
valproate products is not possible (Prod Info DEPACON(R) IV injection, 2006)

c) Adult:

1) General Information

a) Results of several clinical trials indicate that SODIUM VALPROATE alone or in combination with
anticonvulsants is effective in GRAND MAL SEIZURES (Covanis et al, 1982a; Pinder et al, 1977e; F
1975a; Simon & Penry, 1975). Of 519 patients who received SODIUM VALPROATE, mostly as an a
anticonvulsant agents, 239 (46%) experienced a 75% or more reduction in seizure frequency. Howe
ineffective in about 33% of these patients (Pinder et al, 1977e). Other studies have reported respons
100% when used as single-agent therapy (Rimmer & Richens, 1985g; Fuerstein, 1983; Covanis et a

2) The efficacy of VALPROATE SODIUM in 10 patients (21 to 50 years of age) with INTRACTABLE SE
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 anticor
responses were observed in general seizure disorders including tonic, tonic-clonic, atonic-akinetic and si

types. The most impressive results were observed in ATONIC-AKINETIC SPELLS. Considerable variatic
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 myocl
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 s
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 greater than 125 mi
(mg)/milliliter to control her seizures. During a previous episode, she had been treated with intravenous l
lethargy had led to a hospital admission. Intravenous valproate 500 mg was administered at 20 mg/minu
minutes. There were no adverse effects locally or on pulse or blood pressure. The patient was able to re
afterwards.

3) Two mentally retarded patients with intractable status epilepticus were treated with SODIUM VALPRO
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 withdrawn
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 milli
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 neura patients had no attacks for 6 to 18 months, while in 3 patients the frequency and severity of attacks were least 50%. Four patients responded well when SODIUM VALPROATE was used in combination with oth patients showed little or no response while one patient showed poor tolerance to SODIUM VALPROATE 1980).

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 in a prospectiv 22 children aged 4 to 11 months (Siemes et al, 1988a). VALPROIC ACID (as SODIUM VALPROATE) w oral doses of 15 milligrams/kilogram/day; this was increased every second day by 10 milligrams/kilogram ceased or a maximum dose of 100 milligrams/kilogram/day was achieved. If seizures were not controlled to 6 weeks of treatment, oral DEXAMETHASONE 0.4 to 0.5 mg/kg/day was added to the regimen. The d VALPROATE ranged from 40 to 100 milligrams/kilogram/day (mean, 74). Total seizure control was achie patients within 3 months of starting VALPROATE; after 6 to 12 months, 73% of patients were free of seiz monotherapy, and at 18 to 24 months, 88% of children remained seizure free. Developmental status afte treatment demonstrated severe and very severe retardation in approximately 40% of children, with mode 25% and no or slight retardation in approximately 35%.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Biperiden

Bromocriptine

Carbamazepine

Cyproheptadine

Ethosuximide

Haloperidol

Lithium

Olanzapine

Phenobarbital

Phenytoin

Primidone

Prochlorperazine

Progabide

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 psychi neuroleptic-induced extrapyramidal symptoms (Friis et al, 1983). Biperiden therapy was superior to valproic a 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 wome 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 the combination of the 3 drugs (P less than 0.05). However, the combined effect of the 3 drugs did not signifi 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, phe carbamazepine as monotherapy and followed for 14 to 24 months. All 3 drugs were highly effective in the cor seizures but less effective for partial seizures. There was no significant difference between the overall incider 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 t 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 seconc tonic-clonic seizures. However, for complex partial seizures, carbamazepine was more effective and was ass adverse reactions (Mattson et al, 1992). Long-term side effects associated with valproate therapy included w loss or change in texture, and tremor. Hypersensitivity, characterized by rash, occurred more frequently in tho carbamazepine.

d) Patients switched to high dose valproic acid (target serum level 80 to 150 micrograms/milliliter) demonstra improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had pa history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-clonic se maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone. A 30% me complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic seizures over p occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-onset seizures an considered as first-line therapy (Beydoun et al, 1997).

e) 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 trea 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%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca 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, 2003a).

4.6.C.2 Epilepsy, Children

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea 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 t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem However, randomization to phenobarbital was discontinued early in the study period due to unacceptable sid Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatmer 9% of children treated with phenytoin.

4.6.C.3 Rheumatic chorea

a) Carbamazepine and valproic acid were found to be safe and equally effective in the treatment of choreic r of clinical improvement, time to complete remission, duration of treatment, and recurrence rates in a group of patients with Sydenham's chorea. In this open-label trial, 7 children received 20 to 25 milligrams per kilogram sodium valproate and a matched group of 17 children received 15 mg/kg/day of carbamazepine. No adverse reported by either group.

Demographics and Response to Treatment			
	Sodium valproate	Carbamazepine	P
Female sex (%)	71.4	58.8	0.56
Age (years)	12.4 +/- 1.5	10.9 +/- 2.4	0.13
Onset of improvement (days)	8.0 +/- 4.0	7.4 +/- 8.2	0.88
Time to remission (weeks)	10.1 +/- 8.5	6.7 +/- 6.3	0.36
Duration of treatment (months)	4.3 +/- 2.8	5.0 +/- 2.4	0.56
Recurrences (%)	14.3	17.6	0.84
Generalized chorea (%)	71.4	64.7	0.75
(Genel et al, 2002)			

4.6.D Cyproheptadine

4.6.D.1 Nelson syndrome

a) Bromocriptine significantly suppressed plasma adrenocorticotropin hormone (ACTH) secretion in Nelson's women with Nelson's Syndrome had their ACTH measured after receiving therapy with each of the following: cyproheptadine, valproic acid, and bromocriptine. Also they received each of the following combinations: cypr valproic acid; and bromocriptine, cyproheptadine and valproic acid. Only bromocriptine caused a significant d ACTH (P less than 0.05), as did the combination of the 3 drugs (P less than 0.05). However, the combined ef 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 (P Suzuki et al, 1972; Sato et al, 1982; Callaghan et al, 1982). Sodium valproate 500 to 2400 mg daily (mean, 8 been as effective as ethosuximide 200 to 1200 mg daily (mean, 438 mg daily) (Pinder et al, 1977b).

b) Valproic acid and ethosuximide were compared in a double-blind, response-conditional crossover study o in 16 previously untreated patients and 29 refractory patients (18 male and 27 female; 4 to 18 years of age) (In the previously untreated patients, valproic acid was as effective as ethosuximide in reducing generalized s discharges on the telemetered EEG. Adverse reactions to valproic acid or ethosuximide were generally mild a

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 ma bipolar disorder. In this study, patients (n=36) were randomized to therapy with divalproex (20 mg/kg/day) or mg/kg/day) for a period of six days. Divalproex was given at a dosage considered to be a loading dose to pro concentrations of approximately 80 mg/L after one day of treatment. Improvement was greatest during the fir 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 depress episodes; therapeutic serum levels of either drug may help predict clinical response and outcome. Limited ev that suicide risk may be lower with lithium than with divalproex.

b) A review of 3 randomized, double-blinded, placebo-controlled studies concluded that a more rapid antima achieved with olanzapine or oral loading of divalproex than with standard titration divalproex, lithium or placel term studies, oral-loaded divalproex (n=80) was either initiated at 30 milligrams/kilogram/day (mg/kg/day) for and maintained at 20 mg/kg/day or it was initiated at 20 mg/kg/day for the first 2 days and gradually increase 20 mg/kg/day plus 1000 mg by day 6. This regimen was compared to divalproex (n=87) initiated at 250 mg 3 titrated to serum levels of 40 to 150 micrograms/milliliter (mcg/mL), lithium (n=54) initiated at 300 mg 3 times to 0.4 to 1.5 milliequivalents per liter, and olanzapine (n=55) initiated at 10 mg/day and titrated to a maximum placebo (n=72). Patients were followed for 10 days and efficacy was assessed using the change from baselir 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 differer 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 inc was more commonly reported with divalproex load compared to standard titration (p less than 0.05). Howeve divalproex was associated with an increased incidence of dizziness, general pain and back pain (p less than overall was 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 ad as dry mouth, weight gain, edema, speech disorder, rhinitis, increases in total cholesterol and increases in se aminotransferase) overall (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 s death compared to the same risks while on divalproex. Health plan data from two managed care organizatior identify 20638 health plan members with type 1 or type 2 bipolar disorder, who had received 1 or more presc divalproex, or carbamazepine. Over an 8-year follow-up period and using lithium as a referent, patients on di hazard ratios of 2.7 for suicide death (event rate per 1000 person-years 1.7, versus 0.7 for lithium); 1.7 for att hospitalization (event rate per 1000 person-years 10.5, versus 4.2 for lithium); and 1.8 for attempts ascertaine emergency department (event rates not reported for both study sites). Comparisons of lithium to carbamazep drug therapy, or no drug treatment were less consistent or stable (Goodwin et al, 2003). Confounding factors interpretation of these results include underrepresentation of certain patient populations in managed care mo diagnoses that might influence drug choice, and reliance on diagnostic coding rather than evaluative researcl outcomes.

d) Response to lithium, but not to valproic acid, worsened with increased numbers of depressive or manic ep hospitalized for the treatment of 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 Schizophren conducted of the relationship between treatment response and the number of previous episodes. It was note episodes, the 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 ma response to lithium decreased and differed significantly from that to divalproex (p=0.007). Similarly, in patient depressive episodes, patients were less likely to respond to lithium as compared to divalproex (p=0.004)(Swa

e) In a retrospective review, lithium appeared to be more effective than valproic acid in the treatment of mani 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=2 Global Impression rating scale was used to assess outcomes on day 5 and at discharge. Overall more patien with lithium than valproic acid at day 5 (p=0.033) and at discharge (p=0.011). However, patients with a lithium millimoles/liter or greater, or with valproic acid levels of 65 to 90 micrograms/milliliter had similar outcomes. T suggest that there may be no difference in outcome if appropriate drug serum levels are achieved in elderly p

f) In a 3-week parallel, double-blind study, a history of multiple (greater than 10) pervious episodes of mania with a poor response to lithium but not to valproic acid (Swann et al, 1999). Patients with acute mania (n=154 to lithium, valproic acid or placebo. The primary efficacy measure was the manic syndrome score from the Sc Disorder and Schizophrenia scale. A relationship between response to medication and number of previous m apparent at approximately greater than or less than 10 episodes. For a low number of previous episodes (les lithium and valproic acid were significantly more effective than placebo (p less than 0.005 for both). For patie

episodes (greater than 10) only the response to valproic acid was significantly better than placebo (p less tha
g) Pretreatment depression-related symptoms were a strong predictor of a better response to valproic acid tl
179 patients hospitalized with an acute manic episode, patients were randomized to receive a 3 week treatm
valproic acid, lithium, or placebo. Patients had comprehensive evaluations of behavior and symptoms with th
measure being the change in mania factor scores on the Schedule for Affective Disorders and Schizophrenia
This study also noted that: lithium was substantially more effective in classic mania than in depressive mania
valproic acid did not differ between classic and depressive mania; and lithium resistance in depressive mania
gender, age, substance abuse, or overall severity of illness (Swann et al, 1997).
h) The efficacy of lithium carbonate was compared with that of valproate in 27 patients with DSM-III-R acute
(Freeman et al, 1992). The study was a 3-week, randomized, double-blind, parallel groups design in which se
symptoms was measured with the Schedule for Affective Disorders and Schizophrenia, change version (SAD
Assessment Scale (GAS), and the Brief Psychiatric Rating Scale (BPRS). Nine of 14 patients treated with val
13 treated with lithium responded favorably at the end of the study. Elevated pre-treatment SADS-C depressi
associated with good response to valproate but not to lithium. Lithium and valproate were both effective in im
symptoms, and lithium was slightly more efficacious overall. Treatment with valproate alone may be particula
manic patients with mixed affective states.
i) In a decision analysis model, divalproex was found to be less costly than lithium for the acute and prophyla
patients with bipolar disorder over a one-year time period. Four attributes of overall patient management were
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 tha
treatment with lithium, most likely due to a more rapid response with divalproex and shorter length of hospital
were most significant in patients with mixed mania and rapid cycling; however, cost savings with lithium thera
recognized in patients with classic mania (Keck et al, 1996a).

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 plac
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 milliequivalents 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 signi
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 groups
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 improvemen
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 psy
(p=0.06), but there was no difference between treatments among patients with psychotic features. Clinical res
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.I Phenobarbital

Epilepsy

Febrile seizure

4.6.I.1 Epilepsy

a) The efficacy and tolerability of phenobarbital, phenytoin, carbamazepine, and sodium valproate in the trea 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 t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem
b) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/mililiter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-c that it should be considered as first-line therapy (Beydoun et al, 1997a).

4.6.I.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 (Wallas et al, 1980; Cavazzuti, 1975), whereas a more indicated that, in these doses, valproic acid was superior to phenobarbital with a lower order of toxicity (Lee &
b) Phenobarbital in doses of approximately 5 milligrams/kilogram/day was as effective as valproic acid in dos approximately 35 milligrams/kilogram/day in prevention of febrile convulsions (Herranz et al, 1984). These do plasma levels of approximately 16 mcg/mL for phenobarbital and 57 mcg/mL for valproic acid, resulting in effi 91% of children, respectively. Side effects occurred in 77% of phenobarbital-treated children as opposed to 4 acid-treated children; phenobarbital toxicity was primarily irritability, hyperactivity and sleep disorders, wherea 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 p effective as phenobarbital in the prophylaxis of febrile convulsions. Although side effects were higher with phe therapy, valproic acid required dosage change and withdrawal of treatment in 10% and 4% of patients, respe no withdrawal of therapy was required in phenobarbital-treated patients. Changes in dose were required in 1 phenobarbital-treated patients.
c) Although valproic acid may be as effective as phenobarbital in prevention of febrile convulsions, the poten of the drug would preclude its routine initial use (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 ton (Rimmer & Richens, 1985e; Wilder et al, 1983; Turnbull et al, 1983).
b) One hundred eighty-one patients with previously untreated epilepsy were randomized to valproic acid, phe carbamazepine as monotherapy and followed for 14 to 24 months (Callaghan et al, 1985). The oral drug dose phenytoin 300 mg/day (adults) and 5 to 10 mg/kg/day (children), carbamazepine 600 mg/day (adults) and 5 t (children), and valproic acid 600 mg/day (adults) and 5 to 10 mg/kg/day (children). All 3 drugs were highly eff control of generalized seizures but less effective for partial seizures. There was no significant difference betw incidence of side effects between the 3 drugs.
c) No difference was reported in efficacy between valproic acid and phenytoin therapy in previously untreate or partial seizures (Turnbull et al, 1985).
d) One study reported the similar efficacy of phenytoin and valproate in newly diagnosed complex partial sei al, 1983).
e) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-c that 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 trea epilepsy were compared in a long-term, prospective, randomized trial (de Silva et al, 1996). Children aged 3 t (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in t drugs were equally efficacious with 20% of the patients remaining seizure free and 73% achieving 1-year rem

4.6.J.3 Seizure; Prophylaxis

a) In a double-blind, 1-year study, phenytoin and valproate were equally effective in preventing seizures afte (Beenen, 1999). Patients undergoing surgery for brain tumor, trauma, or vascular lesions were randomized p 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 se There was also no significant difference in the number of patients having to discontinue therapy due to adver phenytoin group, 2 in the valproate group). Neuropsychological testing also showed no significant differences 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 st the week 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 t injury, however there was a trend seen towards increased mortality in the valproic acid groups (Temkin et al, hours of injury, patients (ages 14-years and older) were randomized to receive either phenytoin for 1 week (n acid for 1 month (n=120), or valproic acid for 6 months (n=127). A phenytoin loading dose was administered a milligrams/kilogram (mg/kg) intravenously (IV) followed by maintenance dosing at 5 mg/kg/day divided into 2 acid loading dose was given at 20 mg/kg intravenously followed by a maintenance dose of 15 mg/kg/day divi Plasma concentrations of each drug were followed and adjusted to therapeutic levels. Early seizures occurre phenytoin treated patients and in 4.5% of the combined valproic acid groups (p not significant). There was als difference in the occurrence of late seizures. The death rate after 2 years was 13.4% for the combined valpro 7.2% for the phenytoin group (p=0.07). The authors conclude that the lack of any additional benefit from valp phenytoin, and the possibly higher mortality rate, suggest that valproic acid should not be routinely used for p posttraumatic seizures.

c) The incidence of death was higher in patients receiving valproate sodium injection followed by oral valproa receiving phenytoin intravenous followed by placebo for the prophylaxis of post-traumatic seizures in patients trauma. In a study evaluating the effect of valproate sodium injection in the prevention of post- traumatic seizu assigned to receive either valproate sodium injection for one week followed by oral valproate for either one or phenytoin intravenous given for one week followed by placebo. The incidence of death was found to be highe assigned to the valproate treatment compared to the rate in those assigned to the phenytoin treatment group 8.5%). Evaluation of the cause of death did not reveal any specific drug-related causation. Furthermore, witho group, it is difficult to determine the actual mortality rate of these head trauma patients. Until further informatio manufacturer recommends not using valproate sodium injection in patients with acute head trauma for the pr traumatic seizures (Prod Info Depacon(R), 1999).

4.6.K Primidone

Epilepsy

Febrile seizure

4.6.K.1 Epilepsy

a) Patients switched to high concentration valproic acid (target level 80 to 150 micrograms/milliliter) demonst or improved seizure control versus treatment with their baseline antiepileptic drug. Participating patients had and a history of at least 2 complex partial seizures per month with or without secondarily generalized tonic-cl while being maintained on therapeutic levels of either carbamazepine, phenytoin, phenobarbital or primidone reduction in complex partial seizures and a 70% median reduction for secondarily generalized tonic-clonic se baseline therapy occurred. The authors conclude that valproic acid is efficacious as monotherapy for partial-o that it should be considered as first-line therapy (Beydoun et al, 1997b).

4.6.K.2 Febrile seizure

a) Primidone, phenobarbital and valproic acid were equally effective over a 1-year period in the prophylaxis o convulsions in 95 children (Herranz et al, 1984a). Inclusion criteria included complicated febrile convulsions (than 15 minutes, focal or followed by transient or permanent neurological changes) or simple febrile convulsi factors (convulsions before 12-months-old, 3 or more seizures, history of neurological disorder, delay in move deficiency, microcephaly, or a history of febrile convulsions in parents or siblings). Patients were not randomi disclosed if therapy was blinded. All groups of patients presented with similar clinical characteristics and risk significantly difference between the groups was that the primidone group contained patients who all had expe seizure attacks while the other 2 groups only had approximately 70% of patients experience that many attack distribution was also uneven with 30 phenobarbital patients, 17 primidone patients and 48 valproic acid patie phenobarbital were dosed to achieve phenobarbital levels of 15 mcg/mL and valproic acid was dosed to achi plasma levels of 50 mcg/mL. Successful therapy was determined if there was no recurrence of febrile convul first year. The percentages of patients without recurrence of febrile convulsions were 80%, 88%, and 92% of with phenobarbital, primidone, and valproic acid, respectively. The differences between the groups were not s Adverse effects were experienced by 77%, 53%, and 45% of the patients treated with phenobarbital, primido acid, respectively. The adverse effects experienced with primidone were relatively less severe than with pher

valproic acid. None of the children on primidone had to change doses or withdraw from the study because of while 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 convu method for dividing the patients into the drug therapy groups and any differences between them were not dis dosage regimen of valproic acid 20 to25 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 prochlo and 9 mm in the valproate group (p less than 0.001). Median nausea scores improved 35.5 mm in prochlorpe 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 p 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, 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 signific 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 trea 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%), langua 7%), confusion (3 to 6%), nausea (7 to 14%) and abdominal pain (3 to 7%) were reported with topiramate. Ca 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).

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