DRUGDEX® Evaluations

CARBAMAZEPINE

0.0 Overview

1) Class

a) This drug is a member of the following class(es):

Anticonvulsant
Antimanic
Dibenzazepine Carboxamide
Neuropathic Pain Agent

2) Dosing Information

a) Adult

1) Bipolar I disorder, acute manic and mixed episodes

a) ORAL; (extended-release capsules) initial, 400 mg/day ORALLY in 2 divided doses, may increase dosage 200 mg/day up to a max of 1600 mg/day as needed (Prod Info EQUETRO(TM) oral extended release capsul

2) Epilepsy, Partial, generalized, and mixed types

a) ORAL; (suspension) initial, 1 teaspoon (100 mg) ORALLY 4 times a day for the first week, may increase d mg/day at weekly intervals (usual max dosage 1000 mg/day in children 12-15 years of age, 1200 mg/day in p years of age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablet) initial, 200 mg orally twice daily for the first week, may increase dose by 20 weekly intervals (usual max dosage 1000 mg/day in children 12-15 years of age, 1200 mg/day in patients ab age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral susp TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablet) initial, 200 mg ORALLY twice daily for the first week, may increase dosa at weekly intervals until optimal response is obtained (usual max dosage 1000 mg/day in children 12-15 year mg/day in patients above 15 years of age, and up to 1600 mg/day in adults) (Prod Info TEGRETOL(R) chewa oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) ORAL; maintenance, adjust dosage to the minimum effective level, usually 800-1200 mg/day ORALLY (P TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

3) Glossopharyngeal neuralgia

a) ORAL; (suspension) initial, 50 mg ORALLY 4 times a day on the first day, may increase dosage by 200 m doses/day) as needed for pain control, do not exceed 1200 mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divide needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablet TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divi as needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tab suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) maintenance, 400-800 mg/day ORALLY (range 200-1200 mg/day); at least once every 3 months throughc period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

4) Psychotic disorder

a) 200 to 400 mg/day ORALLY in 3 to 4 divided doses, may increase dosage gradually at weekly intervals u mg/day as needed

5) Trigeminal neuralgia

a) ORAL; (suspension) initial, 50 mg ORALLY 4 times a day on the first day, may increase dosage by 200 m doses/day) as needed for pain control, do not exceed 1200 mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; (regular-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divide needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablet TEGRETOL(R) XR extended-release oral tablets, 2003)

c) ORAL; (extended-release tablets) initial, 100 mg ORALLY every 12 hr, may increase by 200 mg/day (divi as needed for pain control (max dose 1200 mg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tab suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

d) maintenance, 400-800 mg/day ORALLY (range 200-1200 mg/day); at least once every 3 months throughc period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

b) Pediatric

1) Epilepsy, Partial, generalized, and mixed types

a) ORAL; children up to 6 years of age (suspension), initial, 10-20 mg/kg/day ORALLY in 4 divided doses, m dosage by 100 mg/day at weekly intervals as needed, do not exceed 35 mg/kg/day (Prod Info TEGRETOL(R tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)

b) ORAL; children up to 6 years of age (regular-release tablet), initial, 10-20 mg/kg/day ORALLY in 2 or 3 div increase dosage by 100 mg/day at weekly intervals as needed, do not exceed 35 mg/kg/day (Prod Info TEGR chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 2003)
c) ORAL; children up to 6 years of age, maintenance, adjust to the minimum effective dosage, usually 250-3 max 400 mg/day or 35 mg/kg/day) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspens (R) XR extended-release oral tablets, 2003)
d) ORAL; children 6-12 years of age (suspension), initial, 0.5 teaspoon (50 mg) ORALLY 4 times daily (total mg), may increase dosage by 100 mg/day at weekly intervals as needed, do not exceed 1000 mg/day (Prod (R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release oral tablets, 20
e) ORAL; children 6-12 years of age (regular-release tablet), initial, 100 mg twice daily, may increase dosage weekly intervals as needed, doses greater than 200 mg/day should be given in 3 to 4 divided doses, do not e mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR ex oral tablets, 2003)
f) ORAL; children 6-12 years of age (extended-release tablet), initial, 100 mg twice daily, may increase dosa at weekly intervals as needed, doses greater than 200 mg/day may continue to be given twice daily, do not e mg/day (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR ex oral tablets, 2003)
g) ORAL; children 6-12 years of age, maintenance, adjust to the minimum effective dosage, usually 400-800 TEGRETOL(R) chewable oral tablets, oral tablets, oral suspension, TEGRETOL(R) XR extended-release ora

3) Contraindications
a) bone marrow depression, history of previous (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, TEGRETOL(R)-XR extended-release oral tablets, 2007)
b) concomitant use of an MAOI, or use within 14 days of discontinuing an MAOI (Prod Info TEGRETOL(R) oral chewa tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)
c) concomitant use of nefazodone; decreased nefazodone plasma levels may reduce drug effectiveness (Prod Info TE chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)
d) hypersensitivity to carbamazepine or tricyclic compounds (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

4) Serious Adverse Effects
a) Acute intermittent porphyria
b) Acute renal failure
c) Agranulocytosis
d) Angioedema
e) Aplastic anemia
f) Atrioventricular block
g) Bone marrow depression
h) Cardiac dysrhythmia
i) Congestive heart failure
j) Drug-induced eosinophilia
k) Hepatitis
l) Hypocalcemia
m) Hyponatremia
n) Leukocytosis
o) Leukopenia
p) Nephrotoxicity
q) Pancytopenia
r) Stevens-Johnson syndrome
s) Syncope
t) Thrombocytopenia
u) Toxic epidermal necrolysis

5) Clinical Applications
a) FDA Approved Indications
1) Bipolar I disorder, acute manic and mixed episodes
2) Epilepsy, Partial, generalized, and mixed types
3) Glossopharyngeal neuralgia
4) Trigeminal neuralgia
b) Non-FDA Approved Indications
1) Psychotic disorder

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

Carbamazepine

C) Physicochemical Properties

1) Molecular Weight

a) 236.27 (Fleegler & Carolyn A., 1986)

2) pKa

a) 7 (Anon, 1980) (Goodman and Gilman, 1980)

1.2 Storage and Stability

A) Suspension

1) Do not store in temperatures above 86 degrees F (30 degrees C) and dispense in a tight, light-resistant contai Tegretol(R), 2002b). Shake well before using. CARBAMAZEPINE suspension (commercially available) repackage mL aliquots in amber glass vials, polypropylene vials, amber polypropylene syringes and in 2-mL aliquots in ambe syringes were found to be stable for 8 weeks at room temperature under constant fluorescent lighting. These repa suspensions retained at least 86% of the initial carbamazepine concentration (Lowe et al, 1989).

2) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid medicati (Prod Info Tegretol(R), 2002b). In a case report, a man passed an orange rubbery mass after ingesting Tegretol S immediately followed by Thorazine(R) solution (chlorpromazine). The manufacturer reports that mixing Tegretol s chlorpromazine solution (generic and brand name) results in the precipitation of a rubbery orange mass.

B) Tablet

1) Do not store tablets above 86 degrees F (30 degrees C). Protect from moisture and dispense in tight containe Tegretol(R), 2002b).

2) The Food and Drug Administration (FDA) found that carbamazepine, in both its generic and brand-name forms third or more of its potency if stored in humid conditions. Tablets exposed continuously to 97% humidity at room t weeks hardened and dissolved poorly. Patients should be instructed to keep their carbamazepine supply in a tigh prescription container and in a dry location, away from showers, bathrooms, and humidifiers (Anon, 1990).

C) Tablet, Chewable

1) Do not store above 86 degrees F (30 degrees C). Protect from light and moisture; do not keep medicine in the chewable tablets should be dispensed in a tight, light-resistant container (Prod Info Tegretol(R), 2002b).

D) Tablet, Extended Release

1) EXTENDED RELEASE TABLETS

a) Tegretol(R) extended-release tablets should be stored at controlled room temperature between 15 and 30 (59 to 86 degrees Fahrenheit) and protected from moisture. Dispense in a tight container (Prod Info Tegretol(

b) Carbatrol(R) extended-release capsules should be stored at controlled room temperature between 15 and Celsius (59 to 77 degrees Fahrenheit) and protected from moisture. Dispense in a tight, light-resistant contai Carbatrol(R), 2002).

c) Equetro(TM) extended-release capsules should be stored at controlled room temperature between 15 and Celsius (59 to 86 degrees Fahrenheit) and protected from light. (Prod Info Equetro(TM) extended release cap

E) Extemporaneous Formulation - Oral route

1) Carbamazepine oral suspension 200 mg/5 mL was stable for 90 days when prepared with the following vehicle degrees C in amber bottles:

Sucrose	95 g
Sorbitol 70%	49 mL
Glycerin	8.5 mL
Saccharin sodium	170 mg
Methylparaben	340 mg
Methylcellulose 400	4.7 g
Methylcellulose 4000	2.1 g
FD&C Yellow	510 mg
Lemon Lime Flavor	1 mL
Purified Water	QS 500 mL

2) This formulation is easier to pour and produces less foam than simple syrup formulations (Burkart et al, 1981).

3) A carbamazepine 40 mg/mL suspension, 120 mL, may be prepared using 24 carbamazepine 200 mg tablets (and a sufficient quantity of simple syrup to bring the volume to 120 mL. This suspension should be labeled "shake "refrigerate" and is stable for 90 days (Burkart et al, 1981).

4) A carbamazepine 50 mg/mL suspension, 120 mL, may be prepared using 30 carbamazepine 200 mg tablets (Basel), distilled water to levigate, Cologel(R) (methylcellulose; Lilly) 40 mL, and a sufficient quantity of a 2:1 simpl syrup mixture to bring the volume to 120 mL. This suspension should be labeled "shake well" and "refrigerate" an days (Anon, 1987).

5) The palatability of an extemporaneously prepared oral suspension of carbamazepine was reported (Bloomer e suspension was prepared by combining fifty 200 mg carbamazepine tablets (Tegretol(R)) with HSC suspending v syrup 300 mL/L, methylcellulose 1% gel 700 mL/L, and sodium benzoate 0.14%) to yield a volume of 500 mL of s was flavored with banana, tutti-frutti, or grape. A cherry-mint suspension was prepared by using Tegretol(R) in ch The final suspension consisted of 20 mg/mL of carbamazepine. The cherry-mint formulation was judged least pal volunteers, with no trend in preference between the unflavored suspension and other flavors (banana, tutti-frutti, g

F) Extemporaneous Formulation - Rectal route

1) Carbamazepine has also been formulated into a gel for rectal administration without the addition of sorbitol to the associated premature defecation. The preparation consisted of:

2) 200 milligrams (mg) of carbamazepine powder dissolved in 5 milliliters of 20% alcohol and then incorporated w methylhydroxyethylcellulose 250 mg

3) This mixture may be dispensed in syringes as 200 mg doses for rectal administration. The syringes should be degrees Centigrade prior to administration to maintain adequate gelation and discourage microbial growth (Broua

4) The total absorption of a carbamazepine suspension following rectal and oral administration was similar in a a volunteers (Neuvonen PJ & Tokola O, 1987); however, slower absorption was associated with the rectal route. Th mixture consisted of:

5) Carbamazepine 20 milligrams/mL, Sorbitol 300 milligrams/mL, and Water.

1.3 Adult Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage in Geriatric Patients

Dosage Adjustment During Dialysis

Dosage in Other Disease States

1.3.1 Normal Dosage

Oral route

Restless legs syndrome

Tinnitus

1.3.1.A Oral route

Bipolar I disorder, acute manic and mixed episodes

Epilepsy, Partial, generalized, and mixed types

Trigeminal neuralgia

1.3.1.A.1 Bipolar I disorder, acute manic and mixed episodes

a) The recommended initial dose for the treatment of acute manic and mixed episodes associated with b 200 milligrams (mg) twice daily (400 mg/day), and may be taken with or without food. The dose should b increments of 200 mg/day to achieve the optimum clinical response; doses above 1600 mg/day have no Equetro(TM) capsules may be opened and the beads sprinkled over applesauce or other similar food pr Do not crush or chew capsules (Prod Info Equetro(TM) extended release capsules, 2004).

b) The longer-term or prophylactic use of Equetro(TM) capsules for the treatment of bipolar mania has r Physicians who choose to prescribe this medication for extended periods of time should re-evaluate the benefits of the drug for the individual patient at regular intervals (Prod Info Equetro(TM) extended releas

c) Most patients with bipolar disorder have responded to carbamazepine 600 to 1600 milligrams (mg)/da

divided doses, although some patients have required doses as high as 2000 to 3000 mg/day (Ballenger, cycling patients usually require higher doses of 1000 to 2000 mg daily (Perry et al, 1991).

1.3.1.A.2 Epilepsy, Partial, generalized, and mixed types

a) The initial recommended dosage is 200 milligrams (mg) twice a day (tablets or sustained-release tabl four times a day (suspension). The dosage is then increased by adding 200 mg per day in weekly interva daily regimen for sustained-release tablets or a 3 or 4 times a day regimen for conventional tablets or su desired clinical response is obtained (Prod Info Tegretol(R), 2002c). Usual average dose ranges are 17 t mg/kilogram/day (Anon, 1975a). Usual effective maintenance doses reported by the manufacturer are 8((Prod Info Carbatrol(R), 20029)(Prod Info Tegretol(R), 2002c). This medication should be taken with fooc

b) Dosage should generally not exceed 1200 milligrams (mg)/day in adults, although doses of up to 160 been used in rare instances (Prod Info Tegretol(R), 2002c). Serum drug levels should guide dosage requ

1.3.1.A.3 Trigeminal neuralgia

a) The recommended initial dose is 100 milligrams (mg) twice a day of carbamazepine tablets or extend (Prod Info Tegretol(R), 2002c) or one carbamazepine 200 mg extended-release capsule per day (Prod In 2002) or 1/2 teaspoonful 4 times daily of carbamazepine suspension (Prod Info Tegretol(R), 2002c). This increased by up to 200 mg a day using increments of 100 mg every 12 hours for tablets or sustained-rele Info Tegretol(R), 2002c) or by a single 200 mg extended-release capsule (Prod Info Carbatrol(R), 2002) teaspoonsful of carbamazepine suspension administered in divided doses 4 times a day (Prod Info Tegr Effective maintenance doses for most patients have been 400 to 800 mg/day. Do not exceed 1200 mg/d Carbatrol(R), 2002; Prod Info Tegretol(R), 2002c).

b) At 3-month intervals attempts should be made to reduce the dose of the drug to the minimum effectiv discontinue the drug (Prod Info Tegretol(R), 2002c).

1.3.1.B Restless legs syndrome

See Drug Consult reference: RESTLESS LEG SYNDROME - DRUGS OF CHOICE

1.3.1.C Tinnitus

See Drug Consult reference: DRUG THERAPY OF TINNITUS

1.3.1.D IMPORTANT NOTE

1) The dosage of carbamazepine should be adjusted to meet the needs of the individual patient based upon and monitoring of blood levels (Prod Info Tegretol(R), 2002c).

2) To convert patients from regular carbamazepine to the sustained-release formulation (Tegretol(R)-XR or C same total daily milligram dose should be given (Mirza et al, 1998; Prod Info Carbatrol(R), 2002; Prod Info Te When using other formulations besides the Tegretol(R)-XR or Carbatrol(R), please consult the manufacturer's recommendations. The carbamazepine extended release tablets should never be crushed or chewed and sh whole. Damaged tablets or tablets without a release portal should not be consumed (Prod Info Tegretol(R), 2

3) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid mec diluents (Prod Info Tegretol(R), 2002c).

4) The suspension will produce higher peak levels than the same dose given as a tablet; therefore, patients the same number of milligrams/day in smaller, more frequent doses (Prod Info Tegretol(R), 2002c).

1.3.1.E SINGLE DAILY DOSE

1) Single daily carbamazepine doses (mean, 13.7 milligrams/kilogram/day) for 4 weeks maintained carbama epoxide metabolite levels in the therapeutic range, but higher fluctuations of serum carbamazepine levels occ compared to divided dose regimens twice a day, three times daily). Adverse effects or loss of efficacy were n once daily dosing; however, the authors suggest further long-term studies (Ghose et al, 1983; Ghose et al, 19

1.3.1.F Oral loading doses of carbamazepine 8 milligrams (mg)/kilogram given as the suspension or as tablets h (Cohen et al, 1998). Therapeutic concentrations (range=7.1 to 9.9 mg/liter) were reached within 2 hours with the s within 5 hours with the tablets. The 6 patients in this study tolerated it well.

1) WITHDRAWAL OF THERAPY

a) SUMMARY

1) The length of time for and method of anticonvulsant withdrawal is not considered to be a prime fa determining the prognosis of the patient. However, sudden withdrawal of medication may precipitate therefore medication should be withdrawn gradually over a period of at least 3 months. Excellent res achieved by withdrawing each anticonvulsant over a period of 9 months, with downward increments month intervals.

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

1.3.2 Dosage in Renal Failure

A) No dosage reduction is required in patients with renal failure (Bennett et al, 1994).

1.3.3 Dosage in Hepatic Insufficiency

A) Carbamazepine should not be used in cases of aggravated liver dysfunction or active liver disease (Prod Info

2002c).

1.3.4 Dosage in Geriatric Patients

A) The pharmacokinetics of a single 400-milligram carbamazepine dose in 6 young and 5 elderly patients were c (Hockings et al, 1986). No age-related changes in pharmacokinetics or psychomotor function were noted. Dosage not recommended.

1.3.5 Dosage Adjustment During Dialysis

A) No dosage supplementation is required in patients following hemodialysis (Bennett et al, 1994).

B) The half life and apparent clearance of carbamazepine were not changed during hemodialysis in one woman carbamazepine 200 milligrams twice daily. No dosage adjustments are required (Kandrotas et al, 1989).

1.3.6 Dosage in Other Disease States

A) MYOCARDIAL INFARCTION

1) A case of carbamazepine toxicity (carbamazepine levels 18.2 to 21.5 micrograms/milliliter) was reported i two days after cardiothoracic surgery and intraoperative myocardial infarction; levels normalized 10 days afte dosage adjustment (Wright et al, 1990). The authors postulate that the change in levels may relate to change binding and decreased hepatic clearance resulting from both cardiopulmonary bypass surgery and myocardia specific dosage adjustment was recommended.

1.4 Pediatric Dosage

Normal Dosage

Dosage in Renal Failure

Dosage in Hepatic Insufficiency

Dosage Adjustment During Dialysis

1.4.1 Normal Dosage

Oral route

Migraine; Prophylaxis

1.4.1.A Oral route

1.4.1.A.1 Epilepsy, Partial, generalized, and mixed types

a) For children under the age of 6 years, the initial recommended dosage is 10 to 20 milligrams/kilogram administered in divided doses 2 or 3 times a day (chewable or conventional tablets) or 4 times a day (su dose may then be increased in weekly intervals to obtain the desired clinical response; maintenance dos either 3 or 4 times a day for both tablets and suspension. The maximum recommended dose is 35 mg/kg Tegretol(R), 2002c).

b) For children ages 6 to 12 years, the initial recommended dosage is 100 milligrams (mg) twice a day (sustained-release tablets) or 50 mg (one-half teaspoonful) 4 times a day (suspension). The dosage is the adding 100 mg per day in weekly intervals using a twice daily regimen for sustained-release tablets or a regimen for conventional tablets or suspension until the desired clinical response is obtained. The usual dosage is 400 to 800 mg a day; the maximum daily dosage is generally 1000 mg/day or less (Prod Info T 2002c).

c) For children over 12 years of age, the initial recommended dosage is 200 milligrams (mg) twice a day sustained-release tablets) or 100 mg (one teaspoonful) four times a day (suspension). The dosage is the adding 200 mg per day in weekly intervals using a twice daily regimen for sustained-release tablets or a regimen for conventional tablets or suspension until the desired clinical response is obtained (Prod Info T 2002c). Usual effective maintenance doses reported by the manufacturer are 800 to 1000 mg/day in chil years and up to 1200 mg in patients over 15 years old (Prod Info Tegretol(R), 2002c). This medication sh food.

d) In a review of dose-plasma concentration relationships in 196 children, usual pediatric dosage recom to 30 milligrams/kilogram/day were insufficient to achieve therapeutic serum concentrations in many pati on monotherapy. Use of higher dosages requires careful evaluation of efficacy and potential toxicity (Suz

e) Carbamazepine oral suspension was adequately absorbed from the GI tract of newborn infants with a disorders (MacKintosh et al, 1987). All infants were receiving other anticonvulsant agents in addition to c

Maintenance therapy with carbamazepine doses of 5 to 8 milligrams/kilogram orally twice a day resulted carbamazepine serum concentrations in the therapeutic range (10 to 40 micromoles/liter). An elimination from 7.2 to 15.2 hours was observed; carbamazepine oral suspension may be useful for the treatment of SEIZURES, and further study is required to evaluate its efficacy in this age group.

1.4.1.B Migraine; Prophylaxis

1) Carbamazepine 10 to 20 milligrams/kilogram/day divided into 2 daily doses has been used for migraine he prophylaxis (Hamalainen, 1998). Doses should be increased slowly.

1.4.1.C IMPORTANT NOTE

1) The dosage of carbamazepine should be adjusted to meet the needs of the individual patient based upon and monitoring of blood levels (Prod Info Tegretol(R), 2002c).

2) Loss of efficacy has been reported when carbamazepine tablets were exposed to humid conditions (Anon

3) Tegretol suspension(R) (carbamazepine) should not be administered simultaneously with other liquid mec diluents (Prod Info Tegretol(R), 2002c). The suspension will produce higher peak levels than the same dose therefore, patients should be started on lower doses of the suspension and increased slowly (Prod Info Tegre

1.4.1.D MAXIMUM DOSE

1) Dosage of tablets should not exceed 1000 milligrams daily in children 6 to 15 years and 1200 milligrams c or older (Prod Info Tegretol(R), 2002c).

2) The recommended maximum dose of carbamazepine suspension is 1000 milligrams/day in children 6 to 1 1200 milligrams/day in children over 15 years (Prod Info Tegretol(R), 2002c).

1.4.1.E WITHDRAWAL OF THERAPY

1) Withdrawal of anticonvulsant medication in children free of seizures for 2 to 4 years appears to be safe, w children remaining free of seizures after medication withdrawal (Shinnar et al, 1985). In a prospective study, a medications were discontinued in 88 epileptic children who had not had a seizure for 2 to 4 years. Anticonvul withdrawn gradually over 2 to 3 months. The mean age at the time of the first seizure was 5 years (0 to 16 ye mean age at the time of the last seizure being 8.7 years (0 to 22 years). The mean duration of seizures was 3 to 17.4 years). Sixty-six (75%) patients remained free of seizures after withdrawal of anticonvulsants, and the of remaining seizure-free was 79% at 12 months, 77% at 24 months, and 74% at 30 months. The risk of recu was highest within the first few months of initiation of withdrawal. Of 22 patients with recurrence of seizures, 9 the first 3 months, 13 in the first 6 months and 18 (82%) within the first year of withdrawal. The type of seizure and EEG characteristics were considered important in predicting the outcome of anticonvulsant withdrawal. It that anticonvulsants be discontinued in children with good prognostic factors after a 2- year period without se

1.4.2 Dosage in Renal Failure

A) No dosage reduction is required in patients with renal impairment (Bennett et al, 1994).

1.4.3 Dosage in Hepatic Insufficiency

A) DOSAGE IN HEPATIC INSUFFICIENCY

1) Carbamazepine should not be used in cases of aggravated liver dysfunction or active liver disease (Prod 2002c).

1.4.4 Dosage Adjustment During Dialysis

A) No dose supplementation is required in patients following hemodialysis (Bennett et al, 1994).

B) The half life and apparent clearance of carbamazepine were not changed during hemodialysis in one woman carbamazepine 200 milligrams twice daily. No dosage adjustments are required (Kandrotas et al, 1989).

2.0 Pharmacokinetics

Drug Concentration Levels

ADME

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Seizure disorder, 4 to 12 mcg/mL (16 to 50 mmol/L) (Prod Info Tegretol(R), 2002a; Rapeport, 1985).

a) Monitoring of free CARBAMAZEPINE concentrations is indicated in conditions associated with altered bin (Perucca, 1984).

b) Saliva and plasma carbamazepine, total and free levels, have a strong and highly significant correlation (r respectively) (Gorodischer et al, 1997).

c) According to plasma levels, no dosage adjustments are needed during the gestational period (Tomson et al, 1985).

d) Urine levels correlate closely with free plasma levels (Elmquist et al, 1991).

e) Extended-release capsules taken every 12 hours provide steady state plasma levels comparable to imme tablets taken every 6 hours at the same milligram dose (Prod Info Carbatrol(R), 2002a).

f) Some researchers advocate the need for monitoring the carbamazepine-10, 11-epoxide metabolite (Potter

1998).
2) Antidepressant/Antimania, no correlation (Post et al, 1983).
B) Time to Peak Concentration
1) Oral, immediate release: 4 to 5 hours (Prod Info Tegretol(R), 2002a; Sillanpaa, 1981).
2) Oral, chew tablets: 6 hours (Prod Info Tegretol(R), 1990).
3) Oral, extended release: 3 to 12 hours (Prod Info Tegretol(R), 2002a; Prod Info Carbatrol(R), 2002a).
4) Oral, suspension: 1.5 hours (Prod Info Tegretol(R), 2002a).

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

Extracorporeal Elimination

2.3.1 Absorption
A) Bioavailability
1) Oral, tablet: 70% to 79% (Hvidberg & Dam, 1976; Levy et al, 1975).
2) Oral, solution: 95.9% (Levy et al, 1975).
3) Oral, extemporaneously formulated suspension: 94.5% (Bloomer et al, 1987).
a) An extemporaneously prepared oral suspension of carbamazepine had a mean bioavailability of 94.5 tablet formulation. However, peak serum concentrations occurred earlier and were higher as compared t formulation; peak serum concentrations occurred in 3.8 hours and 11.8 hours following administration of tablet, respectively. These data suggest that more frequent administration of lower doses of the suspens indicated to avoid toxicity, as compared to the tablet formulation (Bloomer et al, 1987).
B) Effects of Food
1) increases bioavailability (Levy et al, 1975).

2.3.2 Distribution
A) Distribution Sites
1) Protein Binding
a) 76% (Prod Info Carbatrol(R), 2002a; Prod Info Tegretol(R), 2002a).
1) Unbound drug decreases with increasing total concentrations (Hooper et al, 1975).
2) Tissues and Fluids
a) Cerebrospinal fluid (CSF), the CSF/serum ratio 0.22 (Prod Info Tegretol(R), 2002a).
B) Distribution Kinetics
1) Volume of Distribution
a) 0.8 to 2 L/kg (Graves et al, 1985; Hvidberg & Dam, 1976; Rawlins et al, 1975).

2.3.3 Metabolism
A) Metabolism Sites and Kinetics
1) Liver, 98% (Levy et al, 1975)
a) Carbamazepine induces its own metabolism during prolonged treatment, and is complete in 3 to 5 we dosing regimen (Prod Info Tegretol(R), 2002a).
b) With increasing carbamazepine doses in children, a dose-dependent autoinduction process was seer al, 1997).
c) Metabolism occurs via cytochrome P450 3A4 (Prod Info Tegretol(R), 2002a).
B) Metabolites
1) Carbamazepine-10,11-epoxide, active (Bertilsson, 1978; Tomson et al, 1983)
a) Carbamazepine-10,11-epoxide/CARBAMAZEPINE ratios are higher in infants and preschool children 1985a).
b) Epoxide metabolite exists in a 0.1 to 0.2 ratio to CARBAMAZEPINE 120 hours after administration (E 1975). In 1 study, the carbamazepine epoxide to carbamazepine ratio in serum was 0.12 during monothe et al, 1998). This ratio rose to 0.14 when phenobarbital was added, to 0.18 when phenytoin was added, both phenobarbital and and phenytoin were added. These increased ratios were seen as carbamazepine declined.
c) The epoxide metabolite is partly responsible for CARBAMAZEPINE intoxication (Hvidberg & Dam, 19

d) Higher epoxide levels are seen in patients receiving concomitant valproate or lamotrigine therapy (Pc 1998).

2) 9 hydroxymethyl-10-carbamoyl acridan, active (Wad et al, 1997).

2.3.4 Excretion

A) Kidney

1) Renal Excretion (%)

a) 72% (Prod Info Tegretol(R), 2002a)

B) Total Body Clearance

1) 3.85 L/hr (Graves et al, 1985).

a) Clearance in children was reported to be 2.37 liters/hour (Iribarnegaray et al, 1997). Clearance increa increasing doses. Clearance decreases with increasing age (Gray et al, 1998).

b) Patients 70 years and older had a decreased clearance by approximately 70% (Graves et al, 1985).

C) Other

1) Feces, 28% (Prod Info Tegretol(R), 2002a; Hvidberg & Dam, 1976).

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 12 to 17 hours (Prod Info Carbatrol(R), 2002a; Prod Info Tegretol(R), 2002a; Hvidberg & Dam, 1976)

1) The half-life is 25 to 65 hours with single doses (Prod Info Tegretol(R), 2002a; Hvidberg & Dam,

2) Newborn infants, receiving the drug transplacentally, have half-life values within the same range multiple doses (Rane et al, 1975).

B) Metabolites

1) 10,11-epoxide metabolite, 6.1 hours (Tomson et al, 1983; Bertilsson & Tomson, 1986).

2.3.6 Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Yes, 53.6 mL/min (Lee et al, 1980)

a) Clearance ranges from 40 to 64 mL/min (mean 53.6 mL/min). Calculated total drug removed over a 4 period ranges from 40.5 to 53.1 mg (Lee et al, 1980).

B) Peritoneal

1) Dialyzable: No (Bradley et al, 1984)

a) Carbamazepine is minimally dialyzable during peritoneal dialysis (Bradley et al, 1984).

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Teratogenicity/Effects in Pregnancy/Breastfeeding

Drug Interactions

3.0.A Black Box WARNING

1) Oral (Tablet; Tablet, Chewable; Suspension; Tablet, Extended Release; Capsule, Extended Release)

Serious Dermatologic Reactions and HLA-B*1502 Allele

Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to per 10,000 new users in countries with mainly Caucasian populations, but the risk in some Asian countries is about 10 times higher. Studies in patients of Chinese ancestry have found a strong association between the r SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. HLA-B*1502 is fou exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk p be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

Aplastic Anemia and Agranulocytosis

Aplastic anemia and agranulocytosis have been reported in association with the use of carbamazepine. Data based case control study demonstrate that the risk of developing these reactions is 5-8 times greater than in population. However, the overall risk of these reactions in the untreated general population is low, approxima per one million population per year for agranulocytosis and two patients per one million population per year fo Although reports of transient or persistent decreased platelet or white blood cell counts are not uncommon in the use of carbamazepine, data are not available to estimate accurately their incidence or outcome. However

of the cases of leukopenia have not progressed to the more serious conditions of aplastic anemia or agranulc
Because of the very low incidence of agranulocytosis and aplastic anemia, the vast majority of minor hemato
observed in monitoring of patients on carbamazepine are unlikely to signal the occurrence of either abnormal
complete pretreatment hematological testing should be obtained as a baseline. If a patient in the course of tre
low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation
be considered if any evidence of significant bone marrow depression develops (Prod Info TEGRETOL(R) ora
tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3.1 Contraindications

A) bone marrow depression, history of previous (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, TEGRETOL(R)-XR extended-release oral tablets, 2007)

B) concomitant use of an MAOI, or use within 14 days of discontinuing an MAOI (Prod Info TEGRETOL(R) oral chew tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

C) concomitant use of nefazodone; decreased nefazodone plasma levels may reduce drug effectiveness (Prod Info T chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

D) hypersensitivity to carbamazepine or tricyclic compounds (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

3.2 Precautions

A) dermatologic reactions, serious and sometimes fatal (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; discontinue drug if signs or symptoms develop (Prod Info TEGRETOL(R) oral chewable tablets, tablets, susp Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

B) HLA-B*1502-positive (most common in Asians including South Asian Indians); increased risk of Stevens-Johnson toxic epidermal necrolysis; test for HLA-B*1502 and if positive do not initiate carbamazepine (Prod Info TEGRETOL(R tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

C) adverse hematologic drug reaction, history of; increased risk of bone marrow suppression (Prod Info TEGRETOL(tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

D) (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR exte tablets, 2007a)

E) atypical absence seizures or other mixed seizure disorders, history of; may increase generalized convulsion freque TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral

F) cardiac conduction disturbance, history; increased risk of atrioventricular heart block (Prod Info TEGRETOL(R) ora tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

G) cardiac damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL release oral tablets, 2007)

H) elderly patients; may cause confusion or agitation (Prod Info TEGRETOL(R) oral chewable tablets, tablets, susper Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

I) electrocardiogram abnormalities; increased risk of atrioventricular heart block (Prod Info TEGRETOL(R) oral chewa suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

J) hypersensitivity drug reactions, history of; risk of cross-sensitivity (Prod Info TEGRETOL(R) oral chewable tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

K) hepatic damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL release oral tablets, 2007)

L) hepatic porphyria; acute attacks have been reported and use should be avoided (Prod Info TEGRETOL(R) oral che tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

M) interrupted courses of carbamazepine therapy, history of (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

N) increased intraocular pressure; exacerbation of condition due to cholinergic antagonism (Prod Info TEGRETOL(R) tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

O) mental illness, history; risk of latent psychosis activation (Prod Info TEGRETOL(R) oral chewable tablets, tablets, Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007)

P) renal damage (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(F release oral tablets, 2007)

Q) suicidality, increased risk of; based on data analysis of 199 placebo-controlled studies of 11 antiepileptic drugs, sm occurred as early as 1 week after starting therapy and continued to at least 24 weeks (US Food and Drug Administrati

R) women of childbearing potential; teratogenic effects have been reported and efficacy of oral contraceptives may be Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release

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

Cardiac dysrhythmia

Cardiovascular finding

Congestive heart failure

Heart disease

Vasculitis

3.3.1.A Cardiac dysrhythmia

1) Summary

a) Carbamazepine may suppress both atrioventricular conduction and ventricular automaticity shortly af
administration. bradyarrhythmia and av block occur at therapeutic or mildly elevated carbamazepine bloc
most frequently reported in elderly women. sinus tachycardia has also been reported in overdose situatic
Tegretol(R), 2002b; Kasarskis et al, 1992).

2) Literature Reports

a) Three cases of stokes-adams attacks caused by intermittent AV block, SA block with junctional escap
intermittent asystole secondary to carbamazepine were described (Boesen et al, 1983). Conduction distu
after withdrawal of therapy and recurrence of symptoms was noted after resumption of treatment in 2 pa
pacemaker insertion. Since epileptic seizures and Stokes-Adams attacks are at times difficult to different
suggested that if syncope or changes in seizure patterns occur in patients treated

b) Cardiac conduction abnormalities were reported in an isolated case involving a 13-month-old child, d
serum levels of both carbamazepine and 10,11-epoxide metabolite (Weig & Pollack, 1993). The patient h
tuberous sclerosis and cardiac rhabdomyoma. After two weeks of therapy with carbamazepine, the child
irregular heart rate; EKG and Holter monitor showed intermittent periods of Mobitz type II second-degree
block and occasional premature ventricular beats. Carbamazepine was discontinued with resolution of ca
irregularities.

3.3.1.B Cardiovascular finding

1) Cardiovascular effects reported in patients receiving carbamazepine include AV block, arrhythmias, conge aggravation of hypertension, hypotension, syncope and collapse, edema, vasculitis, aggravation of coronary primary thrombophlebitis, and recurrence of thrombophlebitis. Some of these cardiovascular effects have res

3.3.1.C Congestive heart failure

1) Summary

a) One case of congestive heart failure associated with carbamazepine therapy was reported (Prod Info 2002b; Terrence & Fromm, 1980).

2) Literature Reports

a) A 33-year-old black man with a 12-year history of complex partial and left-sided sensory seizures hac 200 mg added to his anticonvulsant regimen. The dose was subsequently increased to 400 and 600 milli hospital days 4 and 6, respectively. On day 13 the patient complained of pedal edema, shortness of brea Over the next 48 hours the patient received 100 mg furosemide orally and carbamazepine was discontin of diuresis, the patient was asymptomatic and follow-up for 15 months was uneventful with no recurrence symptoms of congestive heart failure (Terrence & Fromm, 1980).

3.3.1.D Heart disease

1) Summary

a) Cardiovascular effects reported in patients receiving carbamazepine include aggravation of hypertens syncope and collapse, edema, aggravation of coronary artery disease, primary thrombophlebitis, and rec thrombophlebitis. Some of these cardiovascular effects have resulted in death (Prod Info Tegretol(R), 20

3.3.1.E Vasculitis

1) Summary

a) A case of leukocytoclastic vasculitis was reported in a 66-year-old male using carbamazepine therap Shant, 1987).

2) Literature Reports

a) Nonthrombocytopenic purpura with histological features of leukocytoclastic vasculitis was described i male with trigeminal neuralgia following carbamazepine 200 milligrams by mouth, three times daily (PO approximately 3 weeks. Withdrawal of carbamazepine and therapy with hydrocortisone IV resulted in gra purpura resolved within 3 months. Rechallenge was not undertaken in this patient (Harats & Shant, 1987

3.3.2 Dermatologic Effects

Acne

Alopecia

Dermatitis

Diaphoresis

Disorder of skin pigmentation

Drug-induced toxic pustuloderma

Eosinophilic pustular folliculitis

Erythema

Erythema multiforme

Fixed drug eruption

Hirsutism

Lichenoid dermatitis

Mycosis fungoides

Onychomadesis

Photosensitivity

Pruritic rash

Rash

Stevens-Johnson syndrome

Summary

Toxic epidermal necrolysis

Urticaria

3.3.2.A Acne

1) Summary

a) The prevalence of acne in patients on anticonvulsant medication compared to those in a control popu different (Greenwood et al, 1983; Harman, 1967; Simpson, 1966).

2) Literature Reports

a) One long-term study has evaluated the incidence of acne in 243 patients with epilepsy receiving varic on a long- term basis. Results were compared with matched controls from a normal population of 2,176 i prevalence of acne or sebum excretion rate was not different in anticonvulsant treated patients as compa group, or in patients taking phenytoin as compared to those who were not taking phenytoin. However, pr regarding length of anticonvulsant treatment, types of drugs administered and doses were not presented 1983; Harman, 1967; Simpson, 1966).

3.3.2.B Alopecia

1) Summary

a) Alopecia has been reported with carbamazepine therapy (Prod Info TEGRETOL(R) oral chewable tab suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007; Ikeda et al, 1997).

2) Literature Reports

a) Two young women developed alopecia after being treated with carbamazepine for partial seizures. O also experienced alopecia with valproic acid. Alopecia began after 2 to 3 months of therapy. The hair los was described as becoming sparse mostly in the front of her head. Hair loss stopped after one woman's decreased and the other woman was switched to phenobarbital (Ikeda et al, 1997).

3.3.2.C Dermatitis

1) Summary

a) Exfoliative dermatitis induced by carbamazepine has been reported in the literature (Prod Info TEGRI chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, Bieder, 1968; Reed et al, 1982). These reactions usually resolve upon withdrawal of carbamazepine.

3.3.2.D Diaphoresis

1) Diaphoresis has been reported with carbamazepine therapy. Discontinuation of therapy may be necessar (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR ext tablets, 2007).

3.3.2.E Disorder of skin pigmentation

1) Alterations in skin pigmentation have been reported with carbamazepine therapy. Discontinuation of thera necessary in some cases (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Ir (R)-XR extended-release oral tablets, 2007).

3.3.2.F Drug-induced toxic pustuloderma

1) Toxic pustuloderma was described in a 24-year-old woman, in association with erythema multiforme, follo carbamazepine therapy 200 milligrams daily for approximately 2 weeks. The patient improved following 4 da wet packs and hydrocortisone topical cream; however, there was a residual post inflammatory hyperpigmenta Fischer, 1988). These data suggest that carbamazepine is capable of producing pustular drug reactions.

3.3.2.G Eosinophilic pustular folliculitis

1) Summary

a) A 58-year-old male developed eosinophilic pustular folliculitis (Ofuji's disease) after taking acetamino carbamazepine for headache and fever (Mizoguchi et al, 1998).

2) Literature Reports

a) A 58-year-old male developed eosinophilic pustular folliculitis (Ofuji's disease) after taking acetamino

carbamazepine for headache and fever (Mizoguchi et al, 1998). Patch testing revealed carbamazepine a drug. Initially, he experienced stomatitis and edematous erythema with papules and pustules. Two montl edema of the upper eyelids, erythema with follicular papules and pustules on the face, neck, chest and u Eosinophil-rich folliculitis with mononuclear cells and neutrophil infiltration was seen on biopsy. He also h and elevated IgE. The eruptions subsided over 2 months with prednisolone 30 milligrams/day.

3.3.2.H Erythema

1) Although prudence suggests the withdrawal of carbamazepine following the occurrence of dermatologic re reactions necessitate permanent carbamazepine (CBZ) withdrawal. Three patients developed an erythemato their face and neck, accompanied by slight fever. Symptoms resolved within 5 to 6 days following CBZ withdr rechallenge with the drug several months later was uneventful (Livingston et al, 1974).

3.3.2.I Erythema multiforme

1) Summary

a) Several cases of erythema multiforme have been noted with carbamazepine therapy. Erythema nodo reported (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRET extended-release oral tablets, 2007; Ward, 1987; Green, 1986; Meisel & North, 1984; Reed et al, 1982; I 1968).

2) Literature Reports

a) Product selection may have a bearing on the occurrence of dermatological reactions secondary to ca 38-year-old woman who had been treated with carbamazepine for several years without incident, develo multiforme a week after receiving a generic version of the drug. Symptoms resolved spontaneously one discontinuation of the drug. Because of her continuing pain from trigeminal neuralgia, carbamazepine (T restarted and there was no recurrence of symptoms (Busch, 1989).

b) A 36-year-old woman receiving chronic carbamazepine therapy experienced facial erythema and ede photocopier for 2 hours. Superficial corneal burns were present one month later (Ward, 1987).

c) Erythema multiforme was described twice in the same patient (43-year-old woman): first in associatio and then with carbamazepine (Green, 1986). The patient developed a seizure disorder secondary to an i malignant neoplasm considered inoperable, and was given phenytoin 300 milligrams by mouth at bedtim betamethasone. A maculopapular rash developed 3 weeks later, which extended to much of the skin sur multiforme was diagnosed and phenytoin was discontinued resulting in improvement despite replacemer carbamazepine 100 milligrams by mouth 3 times a day (PO TID). Approximately one year later, the patie with a severe dull red maculopapular rash covering most of the body surface. Withdrawal of carbamazep subsidence of symptoms, and the patient was treated with valproic acid (and betamethasone) without fu sequelae. It is suggested that concurrent betamethasone therapy in this patient may have prevented a m reaction from occurring. However, based upon data provided in this report, it is unclear if either phenytoi carbamazepine were the sole cause of the erythema multiforme episodes in this patient.

d) Severe erythema multiforme with extreme eosinophilia was described in a 57-year-old Navajo Indian carbamazepine therapy 200 milligrams by mouth 3 times a day (PO TID) for 2 months for partial seizure reaction occurred upon inadvertent reinstitution of drug therapy by the patient (Meisel & North, 1984).

3.3.2.J Fixed drug eruption

1) A case of a fixed drug eruption due to carbamazepine has also been reported (Shuttleworth & Graham-Br

3.3.2.K Hirsutism

1) Isolated cases of hirsutism have been reported although a causal relationship has not been established (F TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-rele 2007)

3.3.2.L Lichenoid dermatitis

1) A 75-year-old male developed a lichenoid reaction (biopsy specimens confirming lichen planus) within 2 w of carbamazepine therapy. The rash resolved 7 days after discontinuation of the drug. On rechallenge with ca lichenoid rash reappeared (Thompson & Skaehill, 1994).

3.3.2.M Mycosis fungoides

1) Summary

a) Mycosis fungoides-like lesions have been reported in association with carbamazepine therapy. Cases several months of therapy and skin lesions were present without evidence of systemic symptoms. Skin b revealed lymphoid infiltrates. Patients responded promptly to discontinuation of the drug and treatment w (Welykyj et al, 1990; Rijlaarsdam et al, 1991).

b) Several different types of skin reactions have been associated with carbamazepine (CBZ), including r pruritic rash, erythema multiforme, light sensitive dermatitis, lichenoid eruptions and mycosis fungoides (Rijlaarsdam et al, 1991).

3.3.2.N Onychomadesis

1) Summary

a) A possible case of onychomadesis induced by carbamazepine in a 31-year-old man with complex-pa reported (Mishra et al, 1989).

2) Literature Reports

a) A possible case of onychomadesis induced by carbamazepine in a 31-year-old man with complex-pa reported (Mishra et al, 1989). Nail detachment and pale color were first reported following 4 months of th discontinuation of carbamazepine, fingernails eventually grew back but had a mild bluish hue.

3.3.2.O Photosensitivity

1) Photosensitivity reactions have been reported with carbamazepine therapy. Discontinuation of therapy ma some cases (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETC extended-release oral tablets, 2007).

3.3.2.P Pruritic rash

1) Purpura has been reported with carbamazepine therapy. Discontinuation of therapy may be necessary in Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007).

3.3.2.Q Rash

1) Summary

a) Reactions including erythematous and pruritic rashes have occurred. Concomitant rashes and blood also been reported associated with carbamazepine therapy (Prod Info TEGRETOL(R) oral chewable tab suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007; Cates & Powers, 1

2) Literature Reports

a) Thirty-three out of 335 (9.9%) children with epilepsy, who were treated with carbamazepine develope Rash was more frequent in children over 6 years old, and appeared on the average, within 2 weeks of in (Konishi et al, 1993).

b) A case of a generalized, pruritic, erythematous rash, which developed after 3 months of carbamazepi been reported. Over the course of a month, this rash developed into florid lichenoid lesions. Biopsy revea hyperkeratosis, localized acanthosis and the presence of eosinophilic infiltrates. Gradual resolution of th following discontinuation of the drug and treatment with betamethasone cream (Atkin et al, 1990).

c) Prednisone 40 milligrams daily was effective in treating carbamazepine-induced skin rash in 3 patient unresponsive to other anticonvulsants. Gradual tapering of prednisone followed by discontinuation succe carbamazepine to be continued in 2 patients. The third patient again experienced a rash after prednison had a permanent response to another course of prednisone therapy after 6 weeks of tapering (Vick, 198

d) Rashes were described in 3 patients who received treatment with carbamazepine. A 75-year-old mar receiving carbamazepine 800 milligrams (mg) daily for 2 weeks for treatment of trigeminal neuralgia dev rash, which rapidly became widespread and involved the limbs. Lichenoid papules were present on his w dorsal surfaces of his feet. Carbamazepine therapy was discontinued with notable improvement in the ra within 7 days. The patient was rechallenged with 800 mg/day of carbamazepine and within 24 hours pru days later, a red, scaly, itchy rash appeared, which was most prominent in light-exposed areas. Two oth developed an exfoliative eczema, which subsequently disappeared when carbamazepine therapy was di (Roberts & Marx, 1981).

e) A skin reaction occurred in a 63-year-old male with a previous history of dermatological disease. Duri therapy, an eruption developed which was identical to his previous eczema. In 3 months, a non-irritant ra different nature developed in his right scapular region and was associated with pain and malaise. The pa developed an eruption of heliotrope color affecting the eyelids, eyebrows, elbows, and wrists. The clinica suggestive of either lupus erythematosus or dermatomyositis. Upon discontinuation of the drug the patie spontaneously. There was prompt recurrence of the skin reaction when therapy was restarted (Simpson,

3.3.2.R Stevens-Johnson syndrome

1) Summary

a) Carbamazepine therapy has been associated with serious and sometimes fatal dermatologic reactior Stevens-Johnson Syndrome (SJS). Over 90% of the patients experience these reactions within the first f carbamazepine therapy. These reactions occurred at an estimated rate of 1 to 6 per 10,000 new users w Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Th correlation between the risk of developing these reactions and the presence of human leukocyte antigen B*1502) allele, an inherited allelic variant of the HLA-B gene, among patients of Asian ancestry, particula ancestry. Based on a case control study, there is an absolute risk of 5% for TEN/Stevens Johnson Syndr B*1502 positive patients on carbamazepine. Individuals not of Asian origin (eg, Caucasians, African-Ame and Native Americans) generally are not HLA-B*1502 positive, yet, are still at risk for fatal dermatologic r Genetically at-risk patients should be screened prior to receiving carbamazepine. Careful assessment of should be conducted among patients tested positive for the allele prior to initiation of carbamazepine. Pa been taking carbamazepine for more than a few months (including HLA-B*1502 positive Asians) are at lo (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR oral tablets, 2007; US Food and Drug Administration, 2007).

2) Human Leukocyte Antigen-B*1502 (HLA-B*1502) Positive

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asian In prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*1502 pos rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and parts of the Phili in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians but may be higher in some gr

than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasians, African-Americans, Hispan Americans) generally are not HLA-B*1502 positive (Prod Info TEGRETOL(R) oral chewable tablets, table 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3) Literature Reports

a) Short-term therapy with carbamazepine has been associated with Stevens Johnson Syndrome (SJS) epidermal necrolysis (TEN) in a case-control study and appears to be a risk factor. Twenty- one cases w either SJS or TEN following a range of therapy of 2 to 4 weeks. The risk is largely confined to the start of therapy (Rzany et al, 1999).

b) Stevens-Johnson syndrome (erythema multiforme major) was described in a 22-year-old male followi 4 weeks of carbamazepine therapy (200 milligrams by mouth 3 times a day). At that time, the patient pre rash, fever, chills, and sore throat of three days duration; carbamazepine as well as previous (lithium and discontinued; however, the rash progressed to multiple confluent bullous lesions about the face, shoulde mucosa. A maculopapular rash extended over the rest of the thorax, anteriorly and posteriorly, and to the Stevens-Johnson syndrome was diagnosed and the patient was eventually treated intensively with IV flu The patient recovered following several months of hospitalization. However, based upon data presented ascertain if carbamazepine was the cause of this patient's skin reaction (Fawcett, 1987).

c) Cases of exfoliative dermatitis, including Steven's-Johnson syndrome, have been reported in patients carbamazepine (CBZ). Generally these patients have been successfully treated with steroids and discon with recovery occurring within 3 weeks (Hoang-Xuan et al, 1990); (Vaillant et al, 1989)(Pagliaro & Paglia

3.3.2.S Summary

1) Various dermatologic reactions have been associated with carbamazepine use in an estimated 4% of trea onset generally occurs at approximately 1 month (range 2 weeks to 5 months) after starting therapy. Reaction erythematous and pruritic rashes, urticaria, toxic epidermal necrolysis, Stevens-Johnson syndrome, photoser alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, alopecia, Hirsutism has been reported in isolated cases. In addition, toxic pustuloderma and onychomadesis were eacl case. Cases of exfoliative dermatitis induced by carbamazepine have been reported in the literature. These r resolve upon withdrawal of carbamazepine. Other reactions such as mild erythema may resolve even with co

3.3.2.T Toxic epidermal necrolysis

1) Summary

a) Carbamazepine therapy has been associated with serious and sometimes fatal dermatologic reaction epidermal necrolysis (TEN). Over 90% of the patients experience these reactions within the first few mon carbamazepine therapy. These reactions occurred at an estimated rate of 1 to 6 per 10,000 new users w Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. Th correlation between the risk of developing these reactions and the presence of human leukocyte antigen B*1502) allele, an inherited allelic variant of the HLA-B gene, among patients of Asian ancestry, particula ancestry. Based on a case control study, there is an absolute risk of 5% for TEN/Stevens Johnson Syndr B*1502 positive patients on carbamazepine. Individuals not of Asian origin (eg, Caucasians, African-Ame and Native Americans) generally are not HLA-B*1502 positive, yet, are still at risk for fatal dermatologic r Genetically at-risk patients should be screened prior to receiving carbamazepine. Careful assessment of should be conducted among patients tested positive for the allele prior to initiation of carbamazepine. Pa been taking carbamazepine for more than a few months (including HLA-B*1502 positive Asians) are at lo (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR oral tablets, 2007; US Food and Drug Administration, 2007).

2) Literature Reports

a) Toxic epidermal necrolysis was reported in a 5 year-old male following treatment with carbamazepine a history of epileptic seizures treated with carbamazepine 100 mg/day. Titration of carbamazepine was b 100 mg weekly. Three weeks later, (1 day after the last increment) the patient was admitted to the hospit of malaise, fever, and erythematous rash on his face and neck. Carbamazepine was immediately discon antihistamine with methylprednisolone 2 mg/kg/day was initiated. His rash and bullae continued to sprea his body within 24 hours and the patient was transferred to the pediatric ICU. Both the antihistamine and methylprednisolone were discontinued. IV immunoglobulin 1 g/kg/day was given for 2 days along with ag replacement, enteral and parenteral nutrition , and appropriate infection and wound management. On da cultures were positive for Escherichia coli, which was treated with cefotaxime and amikacin. A 3-day cou colony-stimulating factor was initiated. From day 10, no new lesions occurred. On day 37 of hospitalizatio epithelialized and the patient was discharged (Sevketoglu et al, 2009).

b) A suspected case of Lyell's syndrome was reported in a 52-year-old male treated with carbamazepin neuralgia. The patient received 200 milligrams (mg) 3 times daily for 15 days and developed a pruritic ra dryness of the oral mucosa. After a 2 day interval, a single 200 mg dose was administered resulting in ge headache and fever with a general exudative erythema. The patient then developed icterus, hepatomega hemorrhage. Tachycardia, hypotension, and respiratory difficulty ensued. Complete epidermal necrolysis followed. Laboratory findings were consistent with those of Lyell's syndrome. The patient also developed septicemia. He was treated with corticosteroids, antihistamines and antibiotics with complete recovery (M Khramtsova, 1976).

3) Human Leukocyte Antigen-B*1502 (HLA-B*1502) Positive

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asian In prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*1502 pos

rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and parts of the Phili in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians but may be higher in some g than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasians, African-Americans, Hispan Americans) generally are not HLA-B*1502 positive (Prod Info TEGRETOL(R) oral chewable tablets, tabl 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

3.3.2.U Urticaria

1) Urticaria has been reported with carbamazepine therapy. Discontinuation of therapy may be necessary in Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007).

3.3.3 Endocrine/Metabolic Effects

Acute intermittent porphyria

Body temperature above normal

Hyperhomocysteinemia

Hypocalcemia

Hyponatremia

Hypophosphatemia

Hypothyroidism due to drugs

Lipids abnormal

Male sex hormones - serum level - finding

Porphyria

Summary

Syndrome of inappropriate antidiuretic hormone secretion

Vitamin D deficiency

Weight gain

3.3.3.A Acute intermittent porphyria

See Drug Consult reference: DRUGS CONSIDERED UNSAFE- ACUTE PORPHYRIAS

3.3.3.B Body temperature above normal

1) A case of recurrent fever was reported in a 62-year-old woman who was receiving carbamazepine 800 mi control of epilepsy. The patient's fever began 2 days after the first dose of carbamazepine and spiked to 40 d daily. Carbamazepine therapy was discontinued and the fever ceased. Carbamazepine was reintroduced at a fever recurred; however, they were not as high as before. The patient's dose was again raised to 800 milligra fever returned to 40 degrees C twice daily. When the medication was discontinued the second time the fever (Stewart et al, 1980).

3.3.3.C Hyperhomocysteinemia

1) In a study of 60 adolescent epileptic patients (aged 14 to 18 years), a one-year course of carbamazepine therapy was found to produce significantly higher plasma concentrations of homocysteine. this was compare levels prior to therapy and compared with levels in a healthy age- and sex-matched control group (n=63; p les comparisons). the finding of hyperhomocysteinemia held true with both fasting and post- methionine homocys measurements. For the patients taking carbamazepine or valproate, serum concentrations of folate and plasr phosphate (PLP) were significantly decreased with respect to pre- treatment values and to values in the cont than 0.01, folate; p less than 0.001, PLP). Levels of vitamin B12 and erythrocyte folate remained in the norma

al, 2000a).

3.3.3.D Hypocalcemia

1) In a study of 21 epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosph noted (Hoikka et al, 1984).

3.3.3.E Hyponatremia

1) Summary

a) The significant antidiuretic actions of carbamazepine have resulted in water intoxication and hyponatr children. Hyponatremia was demonstrated in 4% to 21.7% of patients receiving carbamazepine. Hypona likely to occur in older patients (Dong et al, 2005; Prod Info Tegretol(R), 2002b; Kamiyama et al, 1993; L O'Griofa & Voris, 1991; Rajantie et al, 1984; Hoikka et al, 1984; Kalff et al, 1984; Yeung Laiwah et al, 19 Valikangas, 1983; Uhde & Post, 1983; Byrne et al, 1979; Ashton et al, 1977; Stephens et al, 1977; Henry incidence of hyponatremia appears to be lower with carbamazepine use as compared with the use oxca al, 2005). In a case report, a woman experienced tonic-clonic seizures secondary to carbamazepine-indu (Kuz & Manssourian, 2005).

2) Incidence: 4% to 21.7% (Dong et al, 2005; Lahr, 1985; Kalff et al, 1984)

3) The results of one study indicate that oxcarbazepine use is associated with a greater incidence of hypona compared with the use of carbamazepine. In a cross-sectional study, the sodium levels of patients receiving t either oxcarbazepine (n=97; mean age, 36.3 years) or carbamazepine (n=451; mean age, 38.2 years) were e presence of hyponatremia. Hyponatremia was defined as a sodium level less than or equal to 134 milliequiva severe hyponatremia was defined as a sodium level less than or equal to 128 mEq/L. Hyponatremia was obs significantly greater number of oxcarbazepine-treated patients, as compared with those receiving carbamaze (29.9% (29/97) vs 13.5% (61/451), respectively; p less than 0.0001). The incidence of severe hyponatremia v the oxcarbazepine group as compared with the carbamazepine group (12.4% (12/97) vs 2.8%(13/451), respe hyponatremia accounted for 41% (12/29) of all hyponatremia cases in oxcarbazepine-treated patients, while 21.3% (13/61) of all hyponatremia cases reported in patients receiving carbamazepine therapy (p less than 0 investigators also found that, for both groups, hyponatremia was more likely to occur in older patients. Hypon observed in 62.2% and 20.6% of oxcarbazepine- and carbamazepine-treated patients 40 years of age or olde with 10% and 7.9% of oxcarbazepine- and carbamazepine-treated patients less than 40 years of age, respec 0.0001, both values) (Dong et al, 2005).

4) In a case report, a 44-year-old woman experienced new-onset, tonic-clonic seizures secondary to hypona a larger than her usual dose of carbamazepine. Concomitant medications include paroxetine, risperidone, bu and hydroxyzine. The night before the seizures she took double the bedtime dose of carbamazepine (1200 m instead of 600 mg). The next day, symptoms experienced were faintness, dizziness, light-headedness, and th blood rushing to her head and immediately prior to seizures were vision "began narrowing" and loss of consc emergency room, serum sodium concentration was 122 milliequivalent/liter and serum carbamazepine was 1 microgram/milliliter. Past medical history includes a similar event after she took a large dose of carbamazepir Manssourian, 2005).

5) Sixty patients receiving carbamazepine and 61 age-matched controls were studied to determine the preva hyponatremia. There was a significant difference between the mean serum sodium levels of the subjects (138 milliequivalents/liter) and the controls (141.7+/-0.4 milliequivalents/liter). Thirteen (21.7%) of the subjects, but controls, had sodium levels less than 135 milliequivalents/liter. The risk of hyponatremia increased with age a serum level (Lahr, 1985).

6) In 1 study, hyponatremia was demonstrated in 28 of 674 (4%) of patients receiving carbamazepine for sei patients, 113 were on carbamazepine monotherapy and 460 were receiving carbamazepine in combination w anticonvulsant medications. Of the 23 patients available for long-term follow- up, 10 were consistently hypona remainder were intermittently hyponatremic. All patients who developed hyponatremia were receiving carbam these were on monotherapy. In all patients, the hyponatremia was slight and did not cause clinical symptoms

3.3.3.F Hypophosphatemia

1) In a study of 21 epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosph noted (Hoikka et al, 1984)

3.3.3.G Hypothyroidism due to drugs

1) One study found that carbamazepine and oxcarbazepine both decrease serum thyroxine (T4) and free thy girls with epilepsy. These effects were reversible upon discontinuation of therapy. Patients, between the ages years, were compared to 54 age-matched controls. Mean T4 and FT4 levels in patients receiving carbamaze 11.5 nM and 70.2 nM compared to 14.4 nM and 96.6 nM in the control group (p less than 0.01 and 0.001, res T4 and FT4 in patients receiving oxcarbazepine (n=18) were 11.3 nM and 74.9 nM (p less than 0.001 for both compared control). Thyrotropin and free triiodothyronine levels were not significantly different. A second evalu mean of 5.8 years later, was performed. Thyroid hormone levels in patients who had discontinued therapy (1 patients and 10 oxcarbazepine patients) did not significantly differ from the controls. Patients had been off the 5 and 4.8 years, respectively (Vainionpaa et al, 2004).

2) Carbamazepine may increase the hepatic clearance of thyroid hormones as well as having an inhibitory e hypothalamic level. The effect of carbamazepine on thyroid function was examined in 40 epileptic patients. A levels of thyroxine, free thyroxine and thyroxine binding globulin were decreased at both 2 and 12 months foll therapy; low serum thyroxine and free thyroxine concentrations were also found after long-term therapy. No p

demonstrated clinical signs of hypothyroidism. Thyrotropin levels were not changed although the response to releasing hormone increased slightly. The decreased thyroid function tests did not correlate with serum carba (Prod Info Tegretol(R), 2002b; Isojarvi et al, 1989).

3.3.3.H Lipids abnormal

1) Significant increases in atherogenic lipids (total cholesterol, very-low-density lipoprotein (VLDL), LDL, and noted after 3 months of carbamazepine therapy in a prospective study of children with partial epilepsy. Over a 29 children (mean age 7.3 years (yr); range 3 to 12 yr; 16 male) were enrolled within 48 hours of presentation seizures, placed on carbamazepine monotherapy, and followed up monthly for 3 months to study the effect o therapy on serum lipids. Family histories, weight, height, and body mass index were recorded. Participants w carbamazepine at a dose of 10 mg/kg per day, with doses increased by 5 mg/kg per day if required, up to a m 30 mg/kg/day. Participants were advised against dietary changes. After 12 hours of fasting, venous blood sam lipid levels were taken. Participants were monitored monthly and compliance was noted. Blood samples were months for lipid profiles and carbamazepine levels. Correlation of lipid levels with carbamazepine was determ of correlation. A p-value of less than 0.05 was taken as significant. Results for the study participants were an liver function tests and lipid levels. Baseline lipid and liver function levels were compared with 3-month finding increased 10% during the study period with mean total cholesterol at baseline 130.6 +/- 27.4 mg/dL and 144. 3 months (p=0.018). Significant increases were also noted in LDL, VLDL, total cholesterol/HDL ratio, and LDL There was no significant change in HDL levels, alkaline phosphate or serum glutamine transaminase. At 3 m the mean dose of carbamazepine was 10.3 +/- 1.1 mg/kg per day, and the mean carbamazepine levels were mcg/dL. There was no correlation of carbamazepine level with lipid levels at 3 months, and no correlation wa the change in lipids and carbamazepine levels. Lipid monitoring should be advised for high-risk patients on ca therapy. Long-term implications of increased risk of atherosclerosis needs further study (Aggarwal et al, 2009

2) In a study evaluating lipids in children and adolescents receiving carbamazepine (n=14), valproic acid (n= phenobarbital (n=20), serum lipid and lipoprotein levels returned completely to normal at 1 to 1.5 years after t discontinued (Verrotti et al, 1998). During therapy patients receiving carbamazepine demonstrated increased cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein as compared to a co (n=110) (all p less than 0.01). Children receiving valproic acid had low triglycerides (p less than 0.05) and low lipoproteins (p less than 0.05) and high levels of high-density lipoproteins (p less than 0.01) as compared to t Children receiving phenobarbital had high concentrations of total cholesterol and low-density lipoprotein chole concentrations of triglycerides as compared to the control group (all p less than 0.01).

3) Carbamazepine was shown to adversely affect serum lipids in a study comparing 57 healthy children to 23 treated children (Sozuer et al, 1997). The carbamazepine-treated children had significantly higher levels of m cholesterol (p less than 0.01), mean low-density lipoprotein (p less than 0.005), and mean total cholesterol/hi lipoprotein (p less than 0.05).

4) High-density lipoprotein cholesterol levels were significantly elevated in epileptic children receiving carban as phenobarbital and valproic acid (Heldenberg et al, 1983); however, this effect may be protective against th heart disease.

5) The effects of valproic acid, carbamazepine or phenobarbital on serum lipids, lipoproteins and apolipoprot examined in 101 epileptic patients and 75 age-matched controls (Calandre et al, 1991). Patients treated with demonstrated significantly higher high-density lipoprotein and apolipoprotein A concentrations. The total chol cholesterol ratio was also significantly lower in patients receiving carbamazepine. The change in serum lipid p correlate with drug concentrations or with duration of therapy.

3.3.3.I Male sex hormones - serum level - finding

1) Antiepileptic agents have been associated with changes in serum concentrations of male reproductive hor compared to healthy controls (n=41), carbamazepine treated men with partial epilepsy (n=15) had lower seru dehydroepiandrosterone sulfate concentrations (3068 ng/mL for controls versus 1952 ng/mL for carbamazep 0.001). No statistically significant differences in dehydroepiandrosterone levels were detected between contro oxcarbazepine treated (n=18) or valproic acid treated (n=27) men with generalized epilepsy. It was also found valproic acid group had higher androstenedione levels (5.9 ng/mL) when compared to the control group (2.2 0.001) whereas the other arms did not. Serum testosterone, sex hormone binding globulin, free androgen inc hormone, follicle stimulating hormone, prolactin and inhibin B measurements were not statistically significantl all 4 groups. Whether the differences in reproductive hormones are epilepsy-induced changes or antiepileptic changes remains to be determined (Isojarvi et al, 2004).

2) Reproductive hormone levels in men with epilepsy may be affected by use of valproic acid or carbamazep effect shown by oxcarbazepine at high doses. In valproate-treated men (n=21), androstenedione levels were increased compared with controls (n=25) (p less than 0.001), and more than half of the cohort taking valproat serum concentrations of testosterone, androstenedione, or dehydroepiandrosterone (DHEA) above the refere than 0.001). Follicle stimulating hormone levels were abnormally low in valproate- treated men (p less than 0. carbamazepine-treated men (n=40), serum concentrations of DHEA were low (p less than 0.001) and sex hor globulin (SHBG) levels were high (p less than 0.05). In men taking high doses of oxcarbazepine (900 mg/day concentrations of testosterone, luteinizing hormone, and SHBG were high (p=0.008, p=0.02, p=0.005, respec authors noted that serum insulin levels were high across all groups (Rattya et al, 2001).

3) Carbamazepine and (to a lesser extent) valproic acid were found to alter serum concentrations of sex hor male epileptic patients (aged 15 to 18 years; n=48) treated at least 2 years with these drugs; however, serum permanently changed and soon after the drugs were withdrawn, hormone levels normalized (Verrotti et al, 20 with concentrations in normal healthy male controls, subjects treated with carbamazepine monotherapy (n=2

levels of free testosterone (FT) (p less than 0.05) and dehydro- epiandrosterone sulphate (DHEAS) (p less th concentrations of sex hormone-binding globulin were significantly increased (p less than 0.01). Subjects treat acid monotherapy (n=18) had insignificantly decreased levels of FT and DHEAS. Subjects on combination ca valproic acid (n=10) had the same significant alterations as those on carbamazepine monotherapy. At least f withdrawal of these drugs, all values had returned to normal. Levels of testosterone, luteinizing hormone, folli hormone, and prolactin were normal throughout the study.

3.3.3.J Porphyria

1) Carbamazepine has been associated with the development of nonhereditary acute porphyria, similar to ac porphyria, in a 38-year-old male during treatment of epilepsy. Carbamazepine reportedly produces direct sup on the enzyme uroporphyrinogen I synthase. Decreases in this enzyme are also present in hereditary acute i porphyria (Yeung Laiwah et al, 1983).

3.3.3.K Summary

1) The significant antidiuretic actions of carbamazepine have resulted in water intoxication and hyponatremia children. Hyponatremia was demonstrated in 4% to 21.7% of patients receiving carbamazepine. Hyponatrem to occur in older patients (Dong et al, 2005; Prod Info Tegretol(R), 2002b; Kamiyama et al, 1993; Lampl et al, Voris, 1991; Rajantie et al, 1984; Hoikka et al, 1984; Kalff et al, 1984; Yeung Laiwah et al, 1983; Koivikko & V Uhde & Post, 1983; Byrne et al, 1979; Ashton et al, 1977; Stephens et al, 1977; Henry et al, 1977). In a study epileptic patients, hyperhomocystinemia was reported (Verrotti et al, 2000a). Reproductive hormone levels in may be affected by carbamazepine use (Rattya et al, 2001). Soon after the drug is withdrawn, the hormone le normal (Verrotti et al, 2000). Serum calcium concentrations and 25-hydroxyvitamin D levels were found to be in mentally retarded patients and patients on chronic carbamazepine monotherapy (Rajantie et al, 1984). In a epileptic patients, hypocalcemia, hypophosphatemia, and elevated serum alkaline phosphatase levels were r 1984). Carbamazepine may increase the hepatic clearance of thyroid hormones as well as having an inhibito hypothalamic level(Prod Info Tegretol(R), 2002b; Isojarvi et al, 1989). Carbamazepine has been shown to ad serum lipids and lipoprotein levels in children (Prod Info Tegretol(R), 2002b; Verrotti et al, 1998) (Souzuer et et al, 2009). Syndrome of inappropriate antidiuretic hormone secretion has been reported (Prod Info Tegretol
2) There have been case reports of recurrent fever (Stewart et al, 1980), nonhereditary acute porphyria, simi intermittent porphyria (Yeung Laiwah et al, 1983), and weight gain (Lampl et al, 1991).

3.3.3.L Syndrome of inappropriate antidiuretic hormone secretion

1) Syndrome of inappropriate antidiuretic hormone secretion has been reported (Prod Info Tegretol(R), 2002

3.3.3.M Vitamin D deficiency

1) A 2-year cross-sectional and retrospective study reported lower 25-hydroxy vitamin D serum levels in prep treated with carbamazepine when compared to children treated with valproic acid and controls. Sixty-six childc antiepileptics (carbamazepine: 20 boys, 13 girls; mean age 9.7 +/-1.6 years; valproic acid: 17 boys, 16 girls; r years) were compared to age- and sex-matched controls (13 boys, 9 girls; mean age 8.9 +/- 2.3 years). Mear treatment was 35.52 +/- 12.84 months for carbamazepine and 33.72 +/- 15 months for valproic acid. Serum 2 D levels in patients treated with carbamazepine were significantly lower than those of patients treated with va controls (9.8 +/- 3.6 micrograms per liter (mcg/L), 15.1 +/- 3.5 mcg/L, and 16.6 +/- 4.7 mcg/L, respectively; p< carbamazepine) (Kumandas et al, 2006).
2) Serum calcium concentrations and 25-hydroxyvitamin D levels were reported to decrease in mentally reta receiving carbamazepine, as compared to a control group. Alkaline phosphatase levels were higher in patien carbamazepine and administration of vitamin D in the diet abolished the syndrome. It is suggested that hypov occur during long-term carbamazepine treatment especially if other risks for vitamin D deficiency exist (Rajan
3) Bone mineral metabolism was studied in 21 epileptic patients on chronic carbamazepine monotherapy at of 505 milligrams. In 3 cases, hypocalcemia was identified; hypophosphatemia was noted in 1 patient and 4 p demonstrated elevated serum alkaline phosphatase levels. Serum 25-hydroxyvitamin D levels were significar controls. No significant difference was noted in bone mineral density or in the amount of trabecular bone betv controls. Two patients were found to have histological evidence of osteomalacia (Hoikka et al, 1984).

3.3.3.N Weight gain

1) Weight gain induced by carbamazepine has been reported in 4 adolescent patients taking the drug at usu doses for control of seizures. Over a 2-month period, all patients developed an increase in appetite with conc increased food intake; body weight increased by 7 to 15 kilograms. Dietary restriction was ineffective in achie while the patients remained on the drug; a return to original body weight was achieved 2 to 3 months followin of the drug (Lampl et al, 1991).

3.3.4 Gastrointestinal Effects

Diarrhea

Disease of mouth

Disorder of gastrointestinal tract

Gastrointestinal tract finding

Nausea and vomiting

Pancreatitis

3.3.4.A Diarrhea

1) Summary

a) Several cases of intractable diarrhea have been reported with therapeutic carbamazepine therapy (P
(R), 2002b; Mahajan et al, 1997; Iyer et al, 1992).

2) Literature Reports

a) An 8-year-old boy with Lennox-Gastaut syndrome developed protracted watery diarrhea while receivi
(Mahajan et al, 1997). The diarrhea started approximately 3 weeks after beginning carbamazepine. A ra
biopsy was consistent with the diagnosis of LYMPHOCYTIC COLITIS. No improvement was noted after
of sulfasalazine. The diarrhea gradually resolved over a 2-month period while the carbamazepine was ta

b) Three cases of intractable diarrhea were reported following initiation of carbamazepine therapy (Iyer
three cases, the patients experienced frequent loose stools approximately one week after starting carba
abdominal pain or discomfort were noted, and antidiarrheal medications were ineffective. The diarrhea c
carbamazepine was discontinued.

3.3.4.B Disease of mouth

1) Summary

a) Dryness of the mouth and pharynx, glossitis, stomatitis, and loss of taste have been reported in patie
carbamazepine therapy (Prod Info Tegretol(R), 2002b).

3.3.4.C Disorder of gastrointestinal tract

1) Summary

a) Constipation, abdominal cramps, and anorexia have been reported in patients receiving carbamazepi
Info Tegretol(R), 2002b).

3.3.4.D Gastrointestinal tract finding

1) Nausea and vomiting are two of the most frequent adverse effects associated with carbamazepine therap
usually occur during the initiation of therapy. Diarrhea, constipation, abdominal cramps, anorexia, and drynes
pharynx, glossitis, stomatitis, pancreatitis, and loss of taste have been reported in patients receiving carbama

3.3.4.E Nausea and vomiting

1) Summary

a) Nausea and vomiting are two of the most frequent adverse effects associated with carbamazepine th
effects usually occur during the initiation of therapy (Prod Info Tegretol(R), 2002b).

3.3.4.F Pancreatitis

1) Summary

a) Pancreatitis has been reported in one case during carbamazepine therapy (Soman & Swenson, 1985

2) Literature Reports

a) A 73-year-old female receiving carbamazepine 200 mg twice a day for partial seizures developed nau
anorexia, malaise, headache, and increased thirst 4 weeks after starting therapy. Her symptoms continu
the addition of lower abdominal pain. Her serum amylase rose to 429 units/dL (normal 60 to 160). The ca
discontinued with an immediate decrease in symptoms. Ten days after stopping the carbamazepine, the
was 172 units/dL and the patient was free of symptoms (Soman & Swenson, 1985).

3.3.5 Hematologic Effects

Agranulocytosis

Aplastic anemia

Disorder of hematopoietic structure

Drug-induced eosinophilia

Hematology finding

Hemolytic anemia

Leukemoid reaction

Leukopenia

Malignant lymphoma

Pancytopenia

Pure red cell aplasia

Thrombocytopenia

3.3.5.A Agranulocytosis

1) Summary

a) Agranulocytosis is one of the most severe hematologic effects. It is reported to occur 5 to 8 times mo patients treated with carbamazepine than in the general population. While agranulocytosis is a low risk e untreated general population (6 patients/1 million population/year), a fatal case has been associated with therapy (Prod Info Tegretol(R), 2002b; Luchins, 1984; Owens et al, 1980; Hawson et al, 1980; Murphy e Agranulocytosis can occur after different periods of exposure and is not clearly related to the total dose c cases over 12 years have been reported during chronic therapy. It appears to be an idiosyncratic respon 1995; Pellock, 1998a; Owens et al, 1980).

2) Literature Reports

a) A 49-year-old asthmatic epileptic woman began receiving carbamazepine 200 milligrams three times epilepsy, and within a week she developed an erythematous non-itchy rash which resolved spontaneous recurred and was itchy 3-1/2 weeks later. Twenty days after commencing therapy, routine blood count sh 1.8 x 10(9)/liter with neutrophil count of 0.4 x 10(9)/liter. Three days later the patient became febrile and (9)/liter with 1% myelocytes but no neutrophils was seen. Carbamazepine was discontinued and a bone examination two days later showed normal cellularity with 3% promyelocytes, 25% myelocytes and 34% and band cells and virtually no mature neutrophils. The patient made an uneventful recovery (Hawson et

b) A case of fatal agranulocytosis was reported in a 48-year-old chronic schizophrenic patient after carb milligrams twice daily for 1 month for aggression (Luchins, 1984). Routine hematological monitoring was prior to or during carbamazepine therapy.

3.3.5.B Aplastic anemia

1) Summary

a) Aplastic anemia is one of the most severe hematological effects and it occurs rarely during carbamaz (Gerson et al, 1983; Donaldson & Graham, 1965). Aplastic anemia is reported to occur 5 to 8 times more patients treated with carbamazepine than in the general population. It has also been reported during chr cases over 12 years) (Prod Info Tegretol(R), 2002b; Tohen et al, 1995; Pellock, 1998a).

2) Literature Reports

a) Aplastic anemia is one of the most severe hematologic effects. Aplastic anemia is reported to occur 5 frequently in patients treated with carbamazepine than in the general population. The risk of aplastic ane low with approximately 2 persons per 1,000,000 population per year likely to develop the disorder (Prod 2002b).

b) Clinically significant hematological toxicity with carbamazepine is uncommon in adults (Hart & Easton review indicated the occurrence of aplastic anemia in 20 patients since 1964, with leukopenia and throm occurring in about 2% of patients treated.

1) Monitoring - The authors suggested a conservative approach to hematological monitoring during complete blood and platelet count performed prior to therapy; 2) CBC performed every 2 weeks for t (if no abnormalities are present, CBC should be obtained quarterly or with the appearance of signs bone marrow depression); 3) if leukopenia develops, white blood cell count should be monitored at 2 seeking the expected return to baseline (withdrawal is indicated in the presence of WBC less than 3 millimeters) (Hart & Easton, 1982).

c) A low incidence of hematologic toxicity with carbamazepine in children has been reported (Silverstein

1) Monitoring - The authors recommend the following monitoring guidelines: 1) hemoglobin, hemato platelet count prior to therapy, monthly for 6 months, then every 3 months; 2) obtain neutrophil, plate reticulocyte count if WBC falls less than 4000; 3) if neutrophil count decreases to 1000 to 1500/cubi in 2 weeks, and consider withdrawal of therapy if remains in this range (neutrophil counts below 100 decreased dosage or drug withdrawal); 4) request hematologic consultation if depression in platelet count occurs in addition to neutropenia (Silverstein et al, 1983).

3.3.5.C Disorder of hematopoietic structure

1) Summary

a) Rates of blood dyscrasias per 100,000 anticonvulsant prescriptions have been reported as 2.8 for ne thrombocytopenia, and 0.5 for hemolytic anemia. These were determined using the United Kingdom Dep Health's General Practice Research Database with 5-year records of 16,686 carbamazepine recipients. differ between phenytoin, phenobarbital, carbamazepine, or valproate throughout all age groups (Blackb

3.3.5.D Drug-induced eosinophilia

1) Summary

a) A slight increase of eosinophilia was reported in patients taking carbamazepine (De Marco & Melchio

2) Literature Reports

a) A 5% increase of eosinophilia with normal leukocyte counts was reported in 653 patients taking carba 48 months. Blood levels ranged from 3 to 12 milligrams/milliliter (Prod Info Tegretol(R), 2002b; Perry et a & Melchiori, 1986; Killian & Fromm, 1968).

b) A 13-year-old boy developed fever, rash, and eosinophilia (white blood cell count of 20,400 cells/cubi eosinophils) weeks after starting carbamazepine therapy. He developed chest pain and died from uncon dysrhythmias. Autopsy revealed severe eosinophilic myocarditis Salzman & Valderrama, 1997).

3.3.5.E Hematology finding

1) Hematopoietic toxicity (neutropenia, thrombocytopenia, and aplastic anemia) has been reported following but not acute overdose. Pancytopenia, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, agranulocy dyscrasia, hemolytic anemia, and pure red cell aplasia have also been reported in patients receiving carbama

3.3.5.F Hemolytic anemia

1) Summary

a) CASE REPORT - Hemolytic anemia was reported in a 63-year-old male following carbamazepine ad milligrams daily for approximately 20 days). Withdrawal of the drug resulted in

3.3.5.G Leukemoid reaction

1) Summary

a) CASE REPORT - A case of leukocytosis induced by carbamazepine has been reported. A 26-year-ol receiving carbamazepine for the treatment of epilepsy had a white blood cell count of 21.2 x 10(3)/cubic patient's medication was changed from carbamazepine 600 milligrams/day to phenytoin 400 milligrams/c phenobarbital 120 milligrams/day and her white count decreased to a normal range. The patient experie ataxia and the phenytoin and phenobarbital were replaced with carbamazepine 600 milligrams/day. Whit performed 11 and 13 days later were significantly elevated (Murphy et al, 1980).

3.3.5.H Leukopenia

1) Summary

a) Carbamazepine may produce leukopenia in 10% of patients for whom it is prescribed. Usually the rea transient although a few cases of persistent neutropenia have been described. In some patients, the rea dose-related (Prod Info Tegretol(R), 2002b; Perry et al, 1991); (de Marco & Melchiori, 1986)(Killian & Fro

b) Transient leukopenia is not an absolute indication to stop the drug although it is an indication to moni Upon continuation of therapy, the WBC has returned to normal in some patients, while in others it has flu normal and low values. Where the drug is discontinued, the WBC returns to normal within a period of 1 v Cook, 1977).

c) In an evaluation of chronic leukopenia resulting from antiepileptic drug use, it was demonstrated that antiepileptic drug regimen was safe to continue despite asymptomatic leukopenia when the percentage polymorphonuclear leukocytes (PMN) remained normal. If the absolute PMN count dropped to less than cells/microliter, a bone marrow aspirate should be obtained and the ratio of myeloid to erythroid precurso ratio is reduced, or the absolute PMN count remains less than 500, the antiepileptic agent should be disc (O'Connor et al, 1994). Several authors have suggested that carbamazepine be discontinued when the t count is less than 3000/cubic millimeter or neutrophils are less than 1500/cubic millimeter (Hart & Easter al, 1985).

2) Literature Reports

a) A 66-year-old woman with bipolar disorder developed an initial drop in white blood cell count to a leve millimeter. The drug was discontinued for a 2-week period and then gradually titrated from a dose of 100 carbamazepine daily to 800 mg daily. Although leukopenia occurred, the dosage of carbamazepine was time the white blood cell count reached 3000/cubic millimeter. Her hematologic indices remained normal to the therapeutic dosage (Regan, 1987).

b) Leukopenia and neutropenia occurred in a 27-year-old female who received carbamazepine for at lea time of presentation, the carbamazepine dosage was 1200 milligrams (mg)/day. A reduction in dose to 1 an increase in white cell count. The patient's dose was further reduced to 900 mg/day 21 days later, but carbamazepine serum level rose and white cell count fell again. Approximately 3 months later, the patier carbamazepine and her white cell count rose when the serum concentration of carbamazepine fell to 11 patient's white cell counts showed a relationship to serum concentrations of the drug. The authors sugge important to determine if the hematologic side effects of carbamazepine are dose-related or idiosyncratic particular patient. If it is dose-related, carbamazepine can be continued provided the patient is closely m Beran, 1984).

3.3.5.I Malignant lymphoma

1) Summary

a) An 81-year-old man experienced lymphoma after 50 days of carbamazepine therapy (Lombardi et al, pseudolymphoma induced by carbamazepine in a 78-year-old woman was reported (Sinnige et al, 1990)

2) Literature Reports

a) CD30+ primary cutaneous anaplastic large-cell lymphoma was associated with carbamazepine thera girl. the patient started on carbamazepine, titrated to a dose of 600 mg/day, for lipothymic episodes durir Eight months later she was admitted for an erythematous macular eruption diagnosed as pityriasis rosea regressing, until 1 month later, the patient suddenly developed multiple painless reddish skin nodules on and arms. The nodules were 0.5 to 6 cm, and quickly grew and ulcerated. Histologic examination reveale pseudoepitheliomatous hyperplasia overlying a diffuse lymphoid infiltrate of large anaplastic cells, scatte cohesive clusters. Most of the anaplastic cells expressed the CD30/Ki-1 antigen, the TIA-1 antigen, and antigens. Carbamazepine was tapered and withdrawn. Lesions regressed with radiotherapy; some untre regressed after 4 months, though prominent scarring remained. After 3 years, the patient was healthy, w in remission (Di Lernia et al, 2001).

b) An 81-year-old man experienced lymphoma after 50 days of carbamazepine therapy (Lombardi et al, presented with fever, morbilliform pruritic rash, and jaundice with dark urine and acholic feces. He also h liver and mildly enlarged spleen. Carbamazepine was discontinued. The maculopapular rash progressec erythroderma. The patient also developed oliguria. Leukocyte count fell to 2400/cubic millimeter and hen grams/decaliter. The bone marrow aspirate showed anemia associated with bone marrow hypercellularit dyserythropoietic changes. Lab values improved but a repeat bone marrow aspirate confirmed a low-gra (non-Hodgkin's) and the absence of myelodysplastic changes.

c) A 44-year-old woman, who was allergic to phenytoin, developed anticonvulsant hypersensitivity syndi pseudolymphoma after 1 month of carbamazepine therapy (Nathan & Belsito, 1998). Her symptoms inclu lymphadenopathy, pneumonitis, hepatitis, and a morbilliform eruption. The skin biopsy showed atypical l dermis that were CD-3(+), CD-30(+), and L26(-). Her symptoms resolved 3 weeks after carbamazepine

d) A case of pseudolymphoma induced by carbamazepine in a 78-year-old woman was reported (Sinnig condition was characterized by generalized lymphadenopathy, hepatosplenomegaly, an abnormal differe cell count, hypergammaglobulinemia and anemia with evidence of severe immune dysregulation. Withdr carbamazepine resulted in resolution of all symptoms within a few days.

3.3.5.J Pancytopenia

1) Summary

a) Neutropenia (75 to 100 cases over 12 years) and pancytopenia (8 cases over 12 years), have been r chronic carbamazepine therapy (Tohen et al, 1995; Pellock, 1998a; Prod Info Tegretol(R), 2002b; Perry Marco & Melchiori, 1986)(Killian & Fromm, 1968). (Cates & Powers, 1998) reported concomitant rashes, thrombocytopenia associated with carbamazepine therapy, in 2 geriatric patients.

3.3.5.K Pure red cell aplasia

1) Summary

a) Two cases of pure red cell aplasia were reported in young girls taking carbamazepine for seizures (T Buitendag, 1990).

2) Literature Reports

a) A case of pure red cell aplasia was reported in a 3-year-old girl taking carbamazepine 150 milligrams control. Recovery followed drug discontinuation (Buitendag, 1990). A 7-year-old girl developed pure red months of carbamazepine monotherapy (Tagawa et al, 1997). She began to recover within 1 week of ca discontinuation.

3.3.5.L Thrombocytopenia

1) Summary

a) Thrombocytopenia is an infrequent but potentially serious side effect of carbamazepine and its occurr discontinuation of the drug. The mechanism of this effect is unknown, but has been postulated to be imm due to the identification of carbamazepine-dependent antiplatelet antibodies (Tohen et al, 1991). Thromb often develops 2 weeks after initiating carbamazepine treatment, but there have also been cases reporte therapy (Tohen et al, 1995; Pellock, 1998a; Ishikita et al, 1999; Prod Info Tegretol(R), 2002b); (Tohen et al, 1991); (de Marco & Melchiori, 1986)(Killian & Fromm, 1968). Some cases are asymptomatic while oth fever, skin rash, arthralgia or swollen joints. Recovery usually occurs within 1 week of carbamazepine dis (Ishikita et al, 1999). There have been 31 cases reported to the manufacturer over a 12-year span (Pello incidence rate for thrombocytopenia of 0.5 per 100,000 prescriptions was reported by the United Kingdor Health's General Practice Research Database (Blackburn et al, 1998).

2) Literature Reports

a) ADULT

1) A 67-year-old woman, with Lennox-Gasteau syndrome, developed severe, isolated thrombocyto placed on a combination of carbamazepine and valproate for the treatment of generalized tonic-clon patient received carbamazepine 150 milligrams (mg) per day for 7 days, 600 mg/day on day eight, a mg/day by day nine. On day 10, valproate 300 mg/day was added because of nonconvulsive status valproate was discontinued 5 days later because the patient developed urticaria and a maculopapul

The thrombocyte count was 262 GIGA/L (normal: 150-360 GIGA/L) on day 5 and had dropped to 5 G at which time carbamazepine was also discontinued. The patient received two thrombocyte transfus thrombocyte count was within normal limits 3 days after the carbamazepine was discontinued. It cou determine whether it was carbamazepine alone or the combination of carbamazepine and valproate responsible for the severe thrombocytopenia (Finsterer et al, 2001).

2) Four cases of thrombocytopenia were reported in patients taking carbamazepine for bipolar diso the drop in platelet count occurred 14 to 16 days following the initiation of therapy and resolved with discontinuation. Carbamazepine doses in all patients were 400 to 600 milligrams daily. These cases somewhat by the presence of concomitant drug therapy including antipsychotics, lithium and benzoc et al, 1991).

3) A 31-year-old epileptic, female developed thrombocytopenia after receiving carbamazepine thera The patient was admitted with diffuse purpura and ecchymoses and her platelet count was 5000/ cu (3)). A migration inhibition factor test for carbamazepine was positive. Following withdrawal of the dr with phenytoin, her platelet count rose to 210,000/mm(3) (Schoenfeld et al, 1982).

4) In one study, 1 patient out of a total of 79 (1.5%) was reported with a platelet count of less than 8 millimeter and no evidence of bruising. The average doses given in the study were 600 to 800 millig although the specific dose and duration of treatment was not mentioned for this patient. After discon drug, a normal platelet count was measured within 1 week (Davis, 1969).

5) Thrombocytopenia was reported a patient receiving carbamazepine 800 milligrams daily for trige over a 10 month period. The platelet count was 50,000/cubic millimeter and a sternal biopsy reveale megakaryocytes with decreased platelet production. The patient's platelet count returned to normal carbamazepine discontinuation (Pearce & Ron, 1968).

b) PEDIATRIC

1) A 12-year-old boy developed thrombocytopenia 10,000/cubic millimeter with petechial rash after carbamazepine therapy. His platelet count recovered 7 days after withdrawal of carbamazepine and prednisone therapy. The boy was subsequently rechallenged with a single oral dose of carbamazep milligrams/kilogram. After 4 hours he developed fever, flushing, and conjunctival hyperemia. Leukoc increased with a left shift in the neutrophilic series. On the second day, platelet counts decreased ar increased. Levels of platelet glycoprotein IIb/IIIa or Ib were detected in plasma (Ishikita et al, 1999).

2) A 12-year-old girl developed thrombocytopenia and petechiae 2 weeks after starting carbamazep milligrams/kilogram/day. Her platelet count was noted to have decreased from 300,000/cubic millime 100,000/mm(3). Carbamazepine was discontinued with resolution of petechiae and an increase in p days (Ueda et al, 1998).

3) A case of carbamazepine-induced thrombocytopenia was reported in a young child. The child wa hospital with a diagnosis of scattered petechiae, 2 weeks after starting carbamazepine 100 milligram All of the patient's laboratory values were within normal limits except for a platelet count of 14,000/ c (mm(3)). Carbamazepine was withdrawn and the patient's platelet count rose to 239,000/mm(3) by c was not rechallenged (Bradley et al, 1985).

3.3.6 Hepatic Effects

Cholangitis

Hepatotoxicity

Injury of bile duct

Liver finding

3.3.6.A Cholangitis

1) Summary

a) Cholangitis has been reported in patients receiving carbamazepine (La Spina et al, 1994)(Larrey et a

2) Literature Reports

a) Cholangitis was described in a 79-year-old woman following carbamazepine 200 mg daily for approxi the treatment of facial neuralgia. A marked hypereosinophilia (54%) was associated with the hepatic lesi cholestasis was observed in the centrilobular areas on liver biopsy. However, granuloma or hepatocellul observed. Withdrawal of carbamazepine resulted in resolution of symptoms over a period of 2 weeks wit tests and eosinophils returning to normal over 3 months (Larrey et al, 1987). This patient had also been vincamine and clonazepam at the time of acute cholangitis, and these drugs were also discontinued with however, readministration of these 2 latter agents did not result in recurrence of symptoms. A second ca has been reported (La Spina et al, 1994).

3.3.6.B Hepatotoxicity

1) Summary

a) Hepatitis, cholestatic and hepatocellular jaundice, abnormal liver function tests and hepatic failure (ve have been reported in patients receiving carbamazepine. Several cases of hepatotoxicity were reported carbamazepine therapy. Symptoms were alleviated with the discontinuation of the drug (Prod Info Tegre Morales-Diaz et al, 1999; Horowitz et al, 1988; Larrey et al, 1987; Luke et al, 1986).

2) Literature Reports

a) A 9-year-old girl developed hepatotoxicity after 5 months of carbamazepine 500 milligrams per day (M 1999). She presented with persistent vomiting, fever, headache, jaundice and dark urine. Her aspartate a was level 550 International units/liter, alanine aminotransferase 570 International units/liter, alkaline phos International units/liter, and ammonia 148 micrograms/decaliter. She also had hypoprothrombinemia not intravenous vitamin K. Her carbamazepine was discontinued and she received prednisone 50 mg/day wi over the next 8 days.

b) Dose-related carbamazepine hepatotoxicity was reported in a 2-year-old child treated with carbamaz disorder (Luke et al, 1986). In one instance, she received an excessive dose of medication with a resulti blood level of 28 micrograms/milliliter; the concentration of the 10,11-epoxide metabolite was also signifi the second situation, the patient had been maintained on carbamazepine 150 milligrams twice daily for a months. In each situation, the patient developed severe neurological symptoms, significant elevations in (100 to 200 times baseline values) and elevated serum ammonia levels. All evidence of hepatotoxicity di discontinuation of the drug.

c) A 6-year-old, 13-kilogram boy with cerebral palsy suffered hepatorenal failure secondary to carbamaz milligrams/kilogram/day. He presented with fever, flaccidness, lethargy, and seizures. His blood urea nitr milligrams/decaliter, serum creatinine 3 milligrams/decaliter, aspartate aminotransferase 5168 Internatio alanine aminotransferase 6166 International units/liter, and lactate dehydrogenase 7378 International un carbamazepine level was elevated at 17.7 micrograms/milliliter after missing 2 doses. Carbamazepine w and fluid challenges were initiated. Serum creatinine peaked at 5.3 milligrams/decaliter on day 6, and dia on days 3 through 5. He slowly recovered during the next 13 days (Haase, 1999).

3.3.6.C Injury of bile duct

1) Summary

a) Severe bile duct injury and vanishing bile-duct syndrome have been reported with carbamazepine us Johnston, 1999)(de Galoscy et al, 1994; Forbes et al, 1992).

2) Literature Reports

a) A 52-year-old woman developed severe bile duct injury 4 weeks after starting carbamazepine 600 mg Johnston, 1999). She presented with fever and jaundice. Her aspartate aminotransferase level was 166 aminotransferase 122 units/L, alkaline phosphatase 2906 units/L, gamma-glutamyl transferase 4026 uni total/direct serum bilirubin 4.2/4. Histology from a percutaneous liver biopsy showed intact lobular archite few severely damaged bile ductules. Carbamazepine was discontinued and liver enzymes gradually dec next month.

b) Two cases of vanishing bile duct-syndrome occurred following carbamazepine administration (de Gal Forbes et al, 1992). Both patients presented with fever, skin rash, eosinophilia, and disappearance of int on liver biopsy.

3.3.6.D Liver finding

1) Hepatitis, cholangitis, cholestatic and hepatocellular jaundice, hepatorenal failure, abnormal liver function failure (very rare cases) have been reported in patients receiving carbamazepine. The hepatotoxic reaction to generally appears within the first month of therapy and usually improves upon withdrawal of the drug; the me presumed to be an idiosyncratic hypersensitivity reaction. Symptoms occur with usual therapeutic doses and the therapeutic range.

3.3.7 Immunologic Effects

Cross sensitivity reaction

Drug hypersensitivity syndrome

Hypogammaglobulinemia

Immune hypersensitivity reaction

Lymphadenopathy

Summary

Systemic lupus erythematosus

3.3.7.A Cross sensitivity reaction

1) Cross-sensitivity is reported in an 18-year-old male treated with carbamazepine for generalized tonic-clon
treatment with phenytoin resulted in an anticonvulsant hypersensitivity syndrome consisting of fever, rash, my
neck glands. Treatment with switched to carbamazepine 200 milligrams (mg) twice daily (BID), but the patien
following day with worsening symptoms. Physical examination revealed a maculopapular rash and painful lyn
Laboratory tests demonstrated an elevated white blood cell count (17,000 per cubic millimeter) with 9% eosir
elevated hepatic enzymes. Valproic acid 500 mg BID was started, as was intravenous methylprednisolone. T
patient's symptoms resolved and hepatic enzymes began to normalize. The patient was discharged; follow-up
recurrence of symptoms on valproic acid therapy. Cross-sensitivity with phenytoin, carbamazepine, and pher
explained by metabolism of the aromatic ring compounds to a toxic arene oxide intermediate, which stimulate
response. Valproic acid and benzodiazepines, structurally and metabolically different, are suitable alternative
seizures who experience the anticonvulsant hypersensitivity syndrome. Treatment involves discontinuation of
anticonvulsant, supportive care, and corticosteroids (Moss, et al, 1999). Cross sensitivity has been reported b
carbamazepine and phenytoin. Although the drugs are chemically dissimilar, they share the formation of arer
intermediate metabolites which may be responsible for toxicity, including hypersensitivity (Nathan & Balsito, 1
et al, 1991; Reents et al, 1989).

3.3.7.B Drug hypersensitivity syndrome

1) Carbamazepine treatment is suspected to be the cause of Drug Reaction with Eosinophilia and Systemic
(DRESS) syndrome in this 35-year-old male patient who presented with a 1-week history of jaundice, dark-co
lethargy, rash, vomiting, and high-fever. He had been taking phenytoin 200 mg twice daily for 14 months to tr
carbamazepine had been added 8 weeks prior to admission for uncontrolled seizures. The patient had no oth
relevance. Examination revealed a temperature of 104 degrees, jaundice, some facial edema, and a diffuse r
rash on his trunk, limbs, and face. Over the next few days, the rash became exfoliative, and the patients conc
He was screened for infection and started on benzylpenicillin and doxycycline for suspected leptospiral and ri
infections. Blood cultures, serology, cytomegalovirus, and herpes virus 6 screenings were negative. Total wh
was 4.2 X10(9)/L with a normal differential, and eosinophil count was normal. Echocardiogram and CT scan c
were normal. Despite adequate carbamazepine and phenytoin levels, the patient had a grand mal seizure du
A carbamazepine-induced reaction was suspected, therefore carbamazepine was stopped and a high-dose c
was started. Fever lowered, liver function tests that had been 10 times the upper limit of normal improved, an
discharged on a tapering dose of steroids. Follow-up indicated that the jaundice had gradually resolved and h
continued to demonstrate a downward trend. Study authors suspect that phenytoin may have sensitized the p
carbamazepine, and that carbamazepine was likely the causative agent of the clinical manifestation of DRES
2008).

3.3.7.C Hypogammaglobulinemia

1) A 49-year-old woman developed bronchiolitis obliterans organizing pneumonia (BOOP) secondary to carb
induced hypogammaglobulinemia after two years of carbamazepine therapy for epilepsy. The woman presen
progressive exertional dyspnea and prolonged productive cough. BOOP was diagnosed via computerize tom
and transbronchial biopsy. Laboratory analysis revealed severe hypogammaglobulinemia including immunog
milligrams/deciliter (mg/dL), Ig A 20 mg/dL, and Ig M 51 mg/dL. After carbamazepine withdrawal, gammaglob
and roentgenogram findings improved (Tamada et al, 2007).

3.3.7.D Immune hypersensitivity reaction

1) A 62-year-old woman developed a hypersensitivity syndrome associated with carbamazepine therapy. Sh
her first epileptic seizure in a neurological emergency unit. No intracranial pathology was found after an EEG
Cerebral spinal fluid and serum tested negative for parasitic, fungal, viral, or bacterial pathogens, and blood a
fluids were unremarkable. Epilepsy was suspected to cause the seizure; therefore, the patient was started or
carbamazepine 200 mg twice daily. Ten days after starting carbamazepine, she developed a fever, watery di
reddish, pruritic, maculopapulous rash on her entire body except her face and legs. Diarrhea improved, temp
normalized, and skin lesions disappeared after decreasing carbamazepine to 200 mg once daily and institutir
and antipyretic drugs; however, her condition dramatically worsened 20 days later. The patient experienced g
exanthema, watery diarrhea, and an increased temperature. Carbamazepine was discontinued and valproic a
admission, lab tests indicated a normal white blood cell count with relative eosinophilia and elevated transam
reactive protein level of 2.2 mg/dL, elevated serum creatinine of 1.3 mg/dl, and elevated serum potassium wa
ECG indicated terminal negative T waves in I, II, aVL, V(5), and V(6) with normalizing tendency after strain. M
scintigraphy, negative angina history, and normal troponine T and creatinine kinase ruled out an ischemic cau
condition improved, fever and diarrhea stopped, and the ECG normalized after treatment with IV methylpredr
for 1 week and antihistamines. Antiepileptic drug-induced hypersensitivity syndrome (AEDHS) was the plausi
the patient had no previous history of drug related side effects, cardiac, gastrointestinal, or dermatologic diso
apparent acute infection (Aigner et al, 2008).

2) A 5-year-old boy developed a hypersensitivity to carbamazepine after 3 weeks of therapy (Brown et al, 19
with fever, lethargy, diarrhea, abdominal pain, and macular rash. Lab tests showed hyponatremia and elevate
Carbamazepine was discontinued. Over the next few days, he developed edema and right-sided pleural effus
intubation. He improved over a 2-week period during which he required 12 days of ventilation. He also had 5
parenteral nutrition. The patient's peripheral blood monocyte proliferation response in vitro to carbamazepine
diagnosis of carbamazepine hypersensitivity.

3) A patient who had developed fever, headache, and a maculopapular rash while receiving carbamazepine from therapy and her symptoms resolved. Two years later, carbamazepine was reinstituted along with predni milligrams/day. After 10 days of carbamazepine therapy, the patient experienced fever, headache, photophol elevations of transamidase levels, and EEG findings consistent with toxic or metabolic encephalopathy. Altho occurred, no rash developed. All symptoms resolved within 72 hours of discontinuing the carbamazepine. Alt suppressed the rash associated with carbamazepine, the other manifestations of carbamazepine hypersensit prevented (Hampton et al, 1985).
4) A hypersensitivity reaction to carbamazepine, characterized by generalized erythroderma, a severe leuke hyponatremia, marked eosinophilia, and renal failure, was described in a 35-year-old woman with late-onset receiving carbamazepine therapy for approximately 3 weeks (Ray-Chaudhuri et al, 1989). The patient improv of carbamazepine and steroid therapy; however, introduction of sodium valproate resulted in development of leukocytosis, and eosinophilia; valproate was discontinued. The patient was not treated further with anticonvu seizures did not recur. A multisystemic hypersensitivity reaction after 50 days of chronic carbamazepine thera a 81-year-old man. His reaction was characterized by generalized erythroderma and renal, hepatic and bone (dyserythropoietic anemia)(Lombardi et al, 1999). A positive proactive test implicated carbamazepine as the

3.3.7.E Lymphadenopathy

1) A 17-year-old male with seizures secondary to a right parietal abscess developed cervical lymphadenopat of carbamazepine therapy titrated up to 600 milligrams per day (Ganga et al, 1998). He developed fever, mac and painful lymph nodes that were 1 to 2 centimeters, solid and round. Biopsies revealed kikuchi disease witl immunohistochemistry positive for CD68 and CD43. Liver transaminases were elevated with normal leukocyt lymphopenia, monocytosis and eosinophilia. Antibiotics were unsuccessful. Symptoms resolved 1 week after withdrawal.

3.3.7.F Summary

1) Multisystemic hypersensitivity and cross sensitivity has transpired in a variety of carbamazepine treated p al, 1999; Lombardi et al, 1999; Ray-Chaudhuri et al, 1989; Hampton et al, 1985; Moss et al, 1999); (Nathan & (Pirmohamed et al, 1991; Reents et al, 1989). Carbamazepine is suspected to be the most likely cause of a D Eosinophilia and Systemic Symptoms (DRESS) syndrome in a 35-year-old male patient (Fsadni et al, 2008). erythematosus (SLE) has been reported in several cases with varying length of carbamazepine therapy (Toe (Reiffers-Mettelock et al, 1997; Jain, 1991; Drory et al, 1989; Bateman, 1985)

3.3.7.G Systemic lupus erythematosus

1) Systemic lupus erythematosus (SLE) occurred in a 34-year-old male after 8 years of carbamazepine thera occurs after only months of therapy, however, this patient exhibited all of the clinical symptoms (rash, enlarge joint involvement, myalgia, fever, leukopenia, and positive antinuclear antibody titer) associated with SLE (To
2) A syndrome resembling systemic Lupus erythematosus (SLE) was induced by carbamazepine in a 40-yea a paralyzed left arm following an aneurysm. After one year of carbamazepine therapy, she developed red fac Raynaud's phenomenon of the extremities, the left-paralyzed arm being more affected. Her ANA was positive Later she developed a lichen-planus- like eruption with an increased ANA titer of 1/1280. Valproate was subs carbamazepine and after 6 months, the ANA titer was unchanged but anti-DNA antibodies and antihistone ar negative. The cutaneous lichenoid lesions improved (Reiffers-Mettelock et al, 1997).
3) Lupus erythematosus was described in a 30-year-old woman with complex partial seizures following carba daily (plus phenobarbital 120 milligrams daily) for approximately 1 year. At that time, the patient developed st the joints, a blotchy rash on her hands and feet, and eye symptoms (soreness and pruritus). Pleuritic chest pa leukopenia, as well as a positive ANA titer, were observed and the drug was withdrawn with continuance of p therapy and the addition of prednisolone 30 mg daily. Improvement occurred rapidly; however, the ANA titer r at 1:160 (Bateman, 1985).
4) Systemic lupus erythematosus (SLE) was described in an 18- year-old male after receiving carbamazepin each day for approximately 5 months in the treatment of complex partial seizures and secondary generalizati developed severe migrating arthralgia 5 months after initiation of therapy; low-grade fever and profuse sweat weeks later. Antinuclear factor was positive at that time, and anti-DNA was 74% (normal, 14%); a few LE cell Withdrawal of carbamazepine and institution of prednisone therapy (60 milligrams daily) resulted in abatemer However, seizure activity recurred and phenytoin was initiated, resulting in a severe relapse of SLE symptom despite continued steroid therapy. Substitution of phenytoin with sodium valproate, with continued steroid the recovery within 3 weeks. The patient was treated subsequently with sodium valproate and primidone without systemic manifestations. This case report suggests that carbamazepine may be associated with SLE, and tha phenytoin therapy can induce relapse in these patients. Based upon this case report, Ciba-Geigy has include potential adverse effect of carbamazepine in the product data (Drory et al, 1989). However, in the absence of impossible to establish a definite cause-effect relationship between carbamazepine and SLE in this patient. A cases of systemic lupus erythematosus induced by carbamazepine was provided (Jain, 1991).
5) (Verma et al, 2000) report a carbamazepine-induced systemic lupus erythematosus syndrome presenting tamponade after 8 months of therapy in a 45-year-old male. Blood serologic studies revealed a positive ANA Pericardicenteses was performed with immediate relief and carbamazepine was discontinued. The patient ful
See Drug Consult reference: DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

3.3.8 Musculoskeletal Effects

Disorder of connective tissue

Musculoskeletal finding

Myasthenia gravis

Osteomalacia

3.3.8.A Disorder of connective tissue

1) Summary

a) The occurrence of connective tissue disorders is 6% of patients who were treated with a single barbit monotherapy (Mattson et al, 1989). It is suggested that switching to an alternative antiepileptic should be patients presenting with symptoms of musculoskeletal problems who are receiving barbiturates.

2) Literature Reports

a) The occurrence of connective tissue disorders in 10 of 178 patients (6%) who were treated with a sin (phenobarbital or primidone) as monotherapy for 6 months or longer were reported in a prospective stud 1989). The disorders occurred in 7 of the 10 patients during the first year of treatment. The connective tis associated with primidone in these patients were frozen shoulder, arthralgias, Dupuytren's contractures; shoulder pain, Dupuytren's contractures, Peyronie's disease were observed. In this study, no associatior between new-onset connective tissue disorders and carbamazepine or phenytoin therapy (for 6 months data support the association between barbiturate use and the development of connective tissue disorder that switching to an alternative antiepileptic (carbamazepine, phenytoin, valproic acid) should be conside presenting with symptoms of musculoskeletal problems who are receiving barbiturates.

3.3.8.B Musculoskeletal finding

1) Summary

a) Aching joints, sore muscles and leg cramps have been reported in patients receiving carbamazepine (R), 2002b).

2) Aching joints and muscles, leg cramps and general connective tissue disorders have been reported in pat carbamazepine. The data is conflicting with regard the propensity of carbamazepine to induce osteomalacia . systemic lupus erythematosus have also been reported.

3.3.8.C Myasthenia gravis

See Drug Consult reference: DRUG-INDUCED MYASTHENIA GRAVIS

3.3.8.D Osteomalacia

1) Summary

a) There are conflicting data regarding the effects of carbamazepine on bone mineral density in children identified reduced bone mineral density in children treated with carbamazepine for an average of approx (Kumandas et al, 2006). Another showed an association between carbamazepine use and increased bor collagen metabolism in young male patients (Verotti et al, 2000). However, earlier studies differed by cor mineral density in the lumbar region of children receiving carbamazepine was not significantly different fr group (Akin et al, 1998; Hoikka et al, 1984; Tjellesen et al, 1983; Zerwekh et al, 1982).

2) A 2-year cross sectional and retrospective study concluded that lumbar spine bone mineral density values reduced in prepubertal children treated with carbamazepine and valproic acid compared to controls. Sixty-six with antiepileptics (carbamazepine: 20 boys, 13 girls; mean age 9.7 +/-1.6 years; valproic acid: 17 boys, 16 g +/- 2 years) were compared to age- and sex-matched controls (13 boys, 9 girls; mean age 8.9 +/- 2.3 years). ambulatory with normal activity and had adequate nutritional intake, which excluded factors that could reduce biochemical markers of bone turnover. Mean length of treatment was 35.52 +/- 12.84 months for carbamazep 15 months for valproic acid. Mean BMD z-scores at lumbar spine were -1.69 +/- 0.85 for carbamazepine, -1.2 valproic acid, and -0.23 +/- 0.87 for the control group. Differences in serum insulin-like growth factor (IGF)-I a protein (IGFBP)-3 levels, which affect bone metabolism and BMD, between children receiving antiepileptics c controls were not significant. It is thought that the mechanism of carbamazepine-associated reduction in BMD altered hepatic conversion of vitamin D or excessive enzymatic degradation of vitamin D (Kumandas et al, 20

3) Carbamazepine has been associated with increased bone turnover and collagen metabolism in young ma et al, 2000). Bone mineral density in the lumbar region in children receiving carbamazepine was not significar the control group (Akin et al, 1998; Hoikka et al, 1984; Tjellesen et al, 1983; Zerwekh et al, 1982).

4) A prospective evaluation demonstrated that carbamazepine therapy was associated with increased bone collagen metabolism in young male patients receiving the drug for idiopathic partial epilepsy. Markers of bone (alkaline phosphatase, Osteocalcin, and propeptides of type I and III procollagen) were significantly higher at carbamazepine-treated patients as compared to those in 15 healthy, age-matched volunteers. Similarly, mark resorption (serum telopeptide of type I collagen and urinary N- telopeptides of type I collagen) were significar patients. Serum levels of calcium, phosphate, magnesium, parathyroid hormone, and vitamin D metabolites v normal range before and after carbamazepine treatment. Carbamazepine-treated patients received usual dos milligrams per kilogram per day and had therapeutic serum concentrations (Verotti et al, 2000).

5) Bone mineral density at L2-L4 levels of lumbar vertebrae in children receiving carbamazepine (n=28, aver micrograms/milliliter (mcg/mL)) for an average of 2.6 years were not significantly different from a control grou than 0.05). Bone mineral density measured by dual-energy x-ray absorptiometry was 0.611 grams per centim the carbamazepine group and 0.568 grams per centimeter squared in the control group (Akin et al, 1998).
6) Bone mineral metabolism was studied in 21 epileptic patients on chronic carbamazepine monotherapy at of 505 milligrams. In 3 cases, hypocalcemia was identified; hypophosphatemia was noted in 1 patient and 4 p demonstrated elevated serum alkaline phosphatase levels. Serum 25-hydroxy vitamin D levels were significa controls in all patients. No significant difference was noted in bone mineral density or in the amount of trabec patients and controls. Two patients were found to have histological evidence of osteomalacia (Hoikka et al, 1
7) Data are conflicting with regard to the propensity of carbamazepine to induce osteomalacia to a similar de Reductions in 24,25-dihydroxycholecalciferol concentrations during carbamazepine, phenytoin and phenobar been reported (Zerwekh et al, 1982). This deficiency may play an important role in the pathogenesis of anticc osteomalacia induced by carbamazepine. Reduction in 25-hydroxycholecalciferol occurred only in patients tre phenobarbital. Calcium metabolism was evaluated in 30 adult epileptic patients receiving carbamazepine as therapy for 1 to 10 years (serum levels, 3 to 11 micrograms/milliliter) (Tjellesen et al, 1983). Their examinatio normal bone mass in these patients as well as normal serum concentrations of 25-hydroxycholecalciferol. Se were decreased and alkaline phosphatase levels were increased. The authors suggest that single agent ther carbamazepine is not associated with adverse effects on bone metabolism (anticonvulsant osteomalacia). In 25- hydroxycholecalciferol levels were decreased significantly only in patients treated with phenobarbital, anc receiving carbamazepine, suggesting that this deficiency is not the abnormality in anticonvulsant osteomalaci reductions in 24,25- dihydroxycholecalciferol may be implicated (Zerwekh et al, 1982). Serum levels of 24,25,dihydroxycholecalciferol were not performed in the other study (Tjellesen et al, 1983).

3.3.9 Neurologic Effects

Aseptic meningitis

Finding related to coordination / incoordination

Impaired cognition

Motor dysfunction

Movement disorder

Myoclonus

Neuroleptic malignant syndrome

Neurological finding

Nystagmus

Seizure

Somnolence

3.3.9.A Aseptic meningitis

1) Summary
a) Aseptic meningitis has been associated with the use of carbamazepine in 2 cases (Simon et al, 1990 1989).
2) Literature Reports
a) Aseptic meningitis, confirmed on rechallenge, has been described in a 45-year-old female during carb therapy (Hilton & Stroh, 1989). Three days after beginning therapy with carbamazepine 100 milligrams tv patient developed a fever, sore throat, and rhinorrhea. Carbamazepine was discontinued and therapy wi milligrams 3 times a day was initiated. The patient's symptoms resolved over 5 days and carbamazepine restarted. Within 1 day, the patient developed perioral numbness, which progressed over 2 days to perip paresthesias. Fever developed and a malar rash was noted. The patient was diagnosed wish aseptic me basis of physical examination and laboratory findings. Symptoms again resolved over 7 to 10 days follow discontinuation of carbamazepine. A similar case without rechallenge has been reported (Simon et al, 19

3.3.9.B Finding related to coordination / incoordination

1) Summary

a) Vertigo, unsteadiness and dizziness are relatively common side effects of carbamazepine therapy, ge with the initiation of therapy (Prod Info Tegretol(R), 2002b).

3.3.9.C Impaired cognition

1) Summary

a) Carbamazepine did not impair the elderly patient's reflexes while driving (Etminan et al, 2004). Cogni memory tests performed in 7 children during carbamazepine therapy demonstrated that therapeutic dose associated with adverse neurologic effects (Riva & Devoti, 1999).

2) Literature Reports

a) Elderly users of lithium (but not carbamazepine) are at increased risk of having an injurious car accid than age-matched controls. A case-control study nested within a cohort was conducted. The cohort cons drivers between the age of 67 and 84 years living in Quebec providence for at least two years. Cohort su followed until they reached 85 years of age, left the providence, or the end of study date, May 31, 1993. vehicle crash was defined as one person in the car sustaining a physical injury. Drug exposure was defir prescription dispensed within the 60 days before the date of car accident. Of the 5579 subjects that had during the study period, 20 were prescribed lithium and 18 carbamazepine. A random sample of 6% (13, subjects within the cohort showed 27 and 48 were prescribed lithium and carbamazepine, respectively. I accidents were more likely to occur with elderly drivers who were prescribed lithium (rate ratio 2.08 (95% interval (CI), 1.11 to 3.9)). The rate of injurious car accidents with drivers prescribed carbamazepine, wa different from controls (rate ratio 0.83 (95% CI, 0.48 to 1.44)) (Etminan et al, 2004).

b) Cognitive function and memory tests performed in 7 children during carbamazepine therapy demonst therapeutic doses were not associated with adverse neurologic effects. Patients with symptomatic partia carbamazepine for 4 to 15 years, with measured serum concentrations consistently within the therapeuti Withdrawal of treatment was allowed if patients were seizure- free for 2 years and demonstrated no electroencephalographic abnormalities for 1 year. At a mean of 17 months following carbamazepine with testing showed improvement in all scores, but significant improvement occurred only in tests assessing f more complete tasks. This potentially suggests that the effects of carbamazepine on decreasing neuron excitability may impair information circuitry in the front areas of the brain. However, in patients' studies, c testing scores never fell below the normal range (Riva & Devoti, 1999).

3.3.9.D Motor dysfunction

1) Summary

a) Carbamazepine has been associated with episodes of dystonia possibly due to its antagonism of dop Tegretol(R), 2002b); (Bradbury & Bentick, 1982; Larazo, 1982)(Crosley & Swender, 1979; Jacome, 1979

2) Literature Reports

a) Four episodes of dystonia in 3 children with generalized tonic-clonic seizures occurred in association carbamazepine use. Carbamazepine dosage was increased to a maximum of 25 milligrams/kilogram/da symptoms beginning 2 to 3 weeks after start of therapy. Symptoms subsided within 3 weeks following di second course of carbamazepine in 1 child resulted in dystonia (Crosley & Swender, 1979).

b) Carbamazepine produces dyskinesias similar to those induced by neuroleptic agents (Chadwick et al asterixis and cerebellar syndrome is reported in a 66-year-old patient receiving doses of 800 to 1200 mil decreasing the dose to 800 milligrams daily, the asterixis improved markedly and only minor nystagmus discontinuation of therapy, asterixis and nystagmus subsided completely.

c) Treatment with carbamazepine in ordinary doses can cause motor impairment in children (Braathen e Nineteen children were tested while receiving carbamazepine and 6 months later without treatment. Sign improvements were found in response speed (p less than 0.05), composite fine-motor tests (p less than test battery (p less than 0.05).

3.3.9.E Movement disorder

1) Summary

a) The appearance or worsening of tics has been reported in 9 cases. With the withdrawal of carbamaze patients with a previous history, the tics did not resolve, suggesting the drug may trigger the onset of Tou Tics did subside in patients without a history of movement disorders after discontinuation of carbamazep (Robertson et al, 1993; Kurlan et al, 1989; Neglia et al, 1984).

2) Literature Reports

a) The appearance or worsening of tics was reported in 3 patients with underlying movement disorders chorea, tardive dyskinesia and tourette's syndrome) following initiation of low doses of carbamazepine (K The tics included vocalizations, facial tics and generalized motor tics; these disappeared or returned to b discontinuation of the drug.

b) Three similar cases of a syndrome like Tourette's associated with carbamazepine for control of seizu reported (Neglia et al, 1984). Tics and vocalizations did not resolve upon discontinuation of the carbama that the drug might trigger the onset of Tourette's syndrome in susceptible patients.

c) Transient facial tics were reported in 3 children with no previous history of involuntary movements (R 1993). The tics, characterized by abnormal movements of the eyes and mouth, began about two weeks carbamazepine and despite therapeutic serum levels. In 2 of the cases the tics gradually subsided after continuous therapy; in the third case, carbamazepine was discontinued with resolution of symptoms.

3.3.9.F Myoclonus

1) Summary

a) Myoclonus was reported secondary to carbamazepine. Withdrawal of therapeutic levels of carbamaz involuntary movements (Nanba & Maegaki, 1999; Aguglia et al, 1987).

2) Literature Reports

a) A case of epileptic negative myoclonus is reported in a 7- year-old child treated with carbamazepine f childhood epilepsy with centrotemporal spikes. Carbamazepine was increased to 300 milligrams per day frequency did not decrease. In addition, several weeks after beginning carbamazepine treatment, the pa brief episodes of loss of tone in one or both arms, accompanied by eye blinking. Electroencephalograms spike and wave discharges that tended to spread diffusely. This activity ceased when carbamazepine wa (Nanba & Maegaki, 1999).

b) A further report of myoclonus secondary to carbamazepine was described in a 11-year-old boy with b epilepsy (Aguglia et al, 1987). Nonepileptic myoclonus and tic-like movements were observed after 2 we carbamazepine therapy (15 milligrams/kilogram/day). Withdrawal of the drug resulted in resolution of inv movements within several days; rechallenge with carbamazepine again produced myoclonic symptoms. occurred in the presence of therapeutic serum levels of carbamazepine.

3.3.9.G Neuroleptic malignant syndrome

1) Summary

a) A case of neuroleptic malignant syndrome (NMS) induced by carbamazepine was reported in a schiz a history of classic NMS secondary to antipsychotics (O'Griofa & Voris, 1991).

2) Literature Reports

a) A case of neuroleptic malignant syndrome (NMS) induced by carbamazepine was reported in a schiz a history of classic NMS secondary to antipsychotics (O'Griofa & Voris, 1991). Following 3 weeks of carb milligrams 3 times daily (serum level 10.8 micrograms/milliliter), the patient developed fever, increased c phosphokinase, tachycardia, hypertension, diaphoresis and leukocytosis; there was no evidence of musc Symptoms of NMS resolved within 10 days following discontinuation of the carbamazepine despite conti intramuscular lorazepam and amobarbital.

3.3.9.H Neurological finding

1) Summary

a) Other central nervous system effects that have been reported carbamazepine therapy include headac disturbances, confusion, peripheral neuritis, and paresthesias, (Bradbury & Bentick, 1982)(Lazaro, 1982 O'Donnell, 1984)(Aguglia et al, 1987; Silverstein et al, 1982; Shields & Saslow, 1983; Kurlan et al, 1989; (R), 2002b).

2) Symptoms of vertigo, drowsiness, unsteadiness and dizziness are relatively common side effects of carba Other central nervous system effects that have been reported include aseptic meningitis, headache, speech confusion, depression with agitation, psychosis, mania, nystagmus, visual hallucinations, peripheral neuritis, worsening of tics, dystonic reactions such as dyskinesias and myoclonus, and neuroleptic malignant syndrom seizures in children has also occurred. Patients with chronic focal epilepsy who exhibited cerebellar atrophy c resonance imaging were at increased risk of cerebellar adverse effects of carbamazepine.

3.3.9.I Nystagmus

1) Summary

a) Nystagmus occurs often with therapeutic levels of carbamazepine (Prod Info Tegretol(R), 2002b; Rar (Weeler et al, 1982).

2) Literature Reports

a) In a controlled trial, nystagmus occurred in 52% of 35 adult epileptic patients treated with carbamaze sufficient to maintain therapeutic serum concentrations (Ramsay et al, 1983a). Nystagmus was consider effect and did not interfere with daily functioning and in some cases was transient. Nystagmus did not ne discontinuation in any patient. Nystagmus may also occur in overdosage or acute toxic reactions (Fraunf 1982).

b) DOWNBEAT NYSTAGMUS was reported following several weeks of carbamazepine therapy in a 23- (Wheeler et al, 1982). The occurrence of nystagmus was associated with a high unbound concentration (2.6 micrograms/milliliter). Downbeat nystagmus with oscillopsia and reduced visual acuity has also beer patients taking carbamazepine with blood levels of 9 to 12 micrograms/milliliter. Symptoms reversed upo reduction (Chrousos et al, 1987).

c) Patients with chronic focal epilepsy who exhibited cerebellar atrophy on magnetic resonance imaging increased risk of cerebellar adverse effects of carbamazepine. These patients exhibited gaze-evoked ny than 0.001), dizziness (p less than 0.008), and ataxia of stance (p less than 0.02) at significantly lower se concentrations as compared to patients without cerebellar atrophy (Specht et al, 1997).

3.3.9.J Seizure

1) Summary

a) Carbamazepine increases the risk of exacerbation of seizures in children and adolescents (Prasad et al, 1986; Snead & Hosey, 1985). Patients developing uncontrolled, generalized seizures during carbama should be examined for possible carbamazepine exacerbation of epilepsy (Dhuna et al, 1991).

2) Literature Reports

a) Exacerbation of seizures may occur in children receiving carbamazepine monotherapy (Prasad et al, 1998; Shields & Saslow, 1983). Exacerbations occur when children with absence seizures are erroneous carbamazepine. Patients have experienced increased absences or myoclonic jerking. One study noted t children (28.5%) beginning carbamazepine therapy experienced a clinical or electroencephalographic de seizure disorder regardless of type (Prasad et al, 1998).
b) Fifteen children were evaluated with complex partial seizures where 1 or more seizure type was exac carbamazepine therapy (Snead & Hosey, 1985). The most common seizure type exacerbated by the dru atypical absence seizures in 11 children. in 4 patients, more frequent and severe generalized convulsive the use of video-electroencephalographic monitoring enabled evaluation of risk factors for seizures induc carbamazepine. a bilaterally synchronous spike and wave discharge of 2.5 to 3 cycles/second was consi an increase in atypical absence seizures with carbamazepine. generalized bursts of spikes and slow wa cycles/second were suggestive of a risk of increased generalized convulsive seizures. A generalized par wave discharge was observed in all children who had exacerbated seizures induced by carbamazepine.
c) It is suggested that carbamazepine be used cautiously to treat a complex partial component of mixed in children, as the risk of seizure exacerbation was approximately 12% in this series of patients. Children of generalized absence or atypical absence seizures appear to be at a particularly high risk. The drug sh when generalized, synchronous, spike and wave discharges of 2.5 to 3 cycles/second are observed rega clinical manifestation. Prolonged video-EEG monitoring is suggested prior to carbamazepine therapy in c seizure disorders to identify patients at risk of developing seizure exacerbation during treatment. The occ worsening of atypical absence or generalized convulsive seizures following the addition of carbamazepir be an indication that seizure activity may be a result of carbamazepine rather than the natural history of Hosey, 1985).
d) Myoclonic, atypical absence and/or atonic (minor motor) seizures were reported within a few days of carbamazepine treatment for epilepsy in 5 children (3 to 11 years of age) (Shields & Saslow, 1983). With resulted in resolution of symptoms in 2 children, whereas in 2 others, minor motor seizures resolved in 3 the remaining child, seizures persisted, and this child was later found to have ceroid lipofuscinosis. The a that carbamazepine can in some cases precipitate or exacerbate minor motor seizures and their occurre days of initiation of therapy requires withdrawal of the drug.
e) Exacerbation of epilepsy was reported in 26 adolescents and children receiving carbamazepine (Horr epileptic syndromes were affected by carbamazepine: childhood absence seizures; focal symptomatic, fi epilepsy; Lennox-Gastaut syndrome; and severe myoclonic epilepsy of infancy. New-onset absence seiz of the 26 patients, and 3 patients with established absence seizures experienced absence status. It is su caution be exercised when carbamazepine is administered to children or adolescents with absence or m Patients developing uncontrolled, generalized seizures during carbamazepine therapy should be examin carbamazepine exacerbation of epilepsy. Withdrawal of the drug in these patients may result in marked i
f) Seizure exacerbation was attributed to high levels of carbamazepine-10,11-epoxide in a series of 6 pa condition unexpectedly deteriorated (So et al, 1994). In all 6 cases, the patients were taking other drugs serum carbamazepine- epoxide levels. Status epilepticus did not respond to intravenous phenytoin, and after withholding carbamazepine. While routine monitoring of serum carbamazepine-epoxide levels is no the authors suggest obtaining a level when the cause of seizure exacerbation or drug toxicity is not appa
g) The development of frequent complex partial seizures and nonepileptic multifocal myoclonus was rep month-old child started on carbamazepine therapy for generalized tonic-clonic seizures previously unres phenobarbital and valproic acid. Carbamazepine blood levels reached 8.2 micrograms/milliliter and carba epoxide levels were 8.9 micrograms/milliliter. Within 24 hours of carbamazepine discontinuation, seizure myoclonus disappeared within 5 days. The authors postulate that symptoms may have related to toxic co the epoxide metabolite (Dhuna et al, 1991).

3.3.9.K Somnolence

1) Summary

a) Marked drowsiness is a common adverse effect of carbamazepine therapy (Prod Info Tegretol(R), 20 1997; Smith, 1991; Levy et al, 1985).

2) Literature Reports

a) Daytime sleepiness was worse in carbamazepine patients as compared with controls (Bonanni et al, carbamazepine monotherapy (n=26) and controls (n=12) were tested for sleepiness using the multiple sl Compared with controls, the carbamazepine group showed statistically significant shorter sleep latencies 0.001).
b) Profound drowsiness was reported in a 19-month-old boy receiving carbamazepine for seizure activit receiving carbamazepine 100 milligrams 4 times a day (35 milligrams/kilogram/day) which produced sev 17 days. Serum levels of carbamazepine were within therapeutic range upon admission. Further investig normal behavior when serum levels of carbamazepine had decreased to 4 micrograms/milliliter (10 hours dose) and severe drowsiness occurred immediately following a test dose of 100 mg carbamazepine (Lev
c) Carbamazepine 800 mg daily in combination with phenytoin 500 mg daily was prescribed for symptor neuralgia in a 66-year-old woman. Maximum blood levels were 2.6 micrograms/milliliter and 16.5 microg respectively. After 2 weeks of combined therapy, the patient developed drowsiness, confusion, staggerin disorientation and confusion. The EEG indicated diffuse cerebral dysfunction. Within 48 hours of drug dis encephalomyelopathy disappeared and facial pain returned. A retrial of carbamazepine resulted in hyper spasticity without evidence of mental status change. Discontinuation resulted in complete resolution of sy 1991).

3.3.10 Ophthalmic Effects

Disorder of oculomotor system

Eye / vision finding

Oculogyric crisis

Retinopathy

3.3.10.A Disorder of oculomotor system

1) Summary

a) Oculomotor disturbances have been reported with carbamazepine therapy (Prod Info Tegretol(R), 20

3.3.10.B Eye / vision finding

1) Summary

a) Diplopia, esotropia, blurred vision and impaired visual contrast sensitivity occasionally occur with carb therapy (Fukuo et al, 1998; Tomson et al, 1988; Fraunfelder & Meyer, 1982; Livingston et al, 1974). In ac opacities and conjunctivitis have been reported; a direct causal relationship has not been established (Pr (R), 2002b)

2) The following ocular effects have been reported during carbamazepine therapy: blurred vision, transient d oculomotor disturbances. In addition, lens opacities and conjunctivitis have been reported; a direct causal rel been established. An oculogyric crisis has been reported in 1 case and ophthalmoplegia was reported in 2 pa elevated carbamazepine blood levels. Visual disturbances are reversible and may clear without reduction of c however, such problems are most common with high doses and typically respond to dosage decreases.

3) Literature Reports

a) An 11-year-old boy with head trauma and postsurgical convulsions developed diplopia associated wit his carbamazepine had been increased to 700 milligrams per day and his level was 12.5 micrograms/mil examination he was also noted to have esotropia and lateral gaze nystagmus. Carbamazepine was decr milligrams and the symptoms disappeared (Fukuo et al, 1998).

b) Blurred vision, most often manifested as diplopia, occurs occasionally during therapy with carbamaze figures have varied from 0% of patients in 1 series (n=280) (Andersen et al, 1983) to as many as 17% wi another 5.5% with transient blurred vision in another series (n=255) (Livingston et al, 1974). Visual distur reversible and may clear without reduction of drug dosage although such problems are most common wi typically respond to dosage decreases. Vision changes generally are not serious; a small number of lens resembling cataracts have been reported, but an association with carbamazepine is unproved (Fraunfelc 1982).

c) Impaired visual contrast sensitivity has been reported in a study of 27 epileptic patients receiving carb monotherapy. These patients had no subjective complaints of visual disturbance and critical flicker-fusion not affected. The effect upon visual contrast sensitivity appeared to be dose-related, with higher blood le greater impairment (Tomson et al, 1988).

3.3.10.C Oculogyric crisis

1) Summary

a) A case report of an oculogyric crisis in an 8-year-old girl was also reported with carbamazepine thera 1979).

2) Literature Reports

a) One case of oculogyric crisis in a 8-year-old girl was reported (Fallat & Norris, 1979). Oculogyric crisis carbamazepine was added to her regimen of phenytoin and phenobarbital. There was temporary cessati when treated with 25 milligrams of oral diphenhydramine and permanent cessation when the carbamaze completely withdrawn. The highest serum level of carbamazepine recorded was 4.3 micrograms/milliliter

3.3.10.D Retinopathy

1) Summary

a) Two cases of retinopathy in patients treated with long-term carbamazepine therapy have been report Syversen, 1986).

2) Literature Reports

a) Two cases of retinopathy in patients treated with long-term carbamazepine therapy have been report Syversen, 1986). Despite the absence of systemic toxicity, both patients developed decreases in visual a disturbances. Examination revealed lesions of the retinal pigment epithelium, which partially resolved in discontinuation of the drug.

3.3.11 Otic Effects

Auditory dysfunction

Ear and auditory finding

3.3.11.A Auditory dysfunction

1) Summary

a) Several case reports of a lowered pitch perception shift have been identified following the administrat carbamazepine (Kobayaski et al, 2001)(Kashihara et al, 1998).

2) Literature Reports

a) In two separate case reports, a 17-year-old girl and a 10-year-old boy experienced a downwards pitcl of one semitone after receiving carbamazepine 400 milligrams per day. In addition to carbamazepine, th receiving sulpiride and bromazepam, and the boy was taking imipramine and bromazepam. The girl noti two days following the carbamazepine, and the boy noticed the pitch perception change 3 to 4 hours afte drug. Neither patient demonstrated any other signs of carbamazepine toxicity. The girl's pitch perception one week after discontinuing carbamazepine, and the boy stopped complaining of the pitch perception c remaining on carbamazepine (Kobayashi et al, 2001).

b) Within 3 days of beginning carbamazepine 200 milligrams (mg)/day, an 18-year-old woman with gene noticed a false lowering of perceived pitch (Kashihara et al, 1998). She noted false pitches of the telepho sounds, and mechanical noises. After 2 weeks, her carbamazepine dose was increased to 300 mg and s TINNITUS (noted in approximately 0.2% of carbamazepine patients). Carbamazepine was subsequently auditory symptoms disappearing in 2 days.

3.3.11.B Ear and auditory finding

1) Several cases of lowered pitch perception shift have been reported in association with carbamazepine the

3.3.12 Psychiatric Effects

Mania

Psychiatric sign or symptom

Psychotic disorder

Suicidal thoughts

3.3.12.A Mania

1) Summary

a) Carbamazepine has been associated with mania in a few cases (Prod Info Tegretol(R), 2002b; Kurla Aguglia et al, 1987; Drake & Peruzzi, 1986; Reiss & O'Donnell, 1984; Reiss & O'Donnell, 1984); (Shields 1983; Bradbury & Bentick, 1982)(Lazaro, 1982; Silverstein et al, 1982).

2) Literature Reports

a) Mania attributable to carbamazepine was described in 2 children (Reiss & O'Donnell, 1984). In 1 chil had also developed after receiving imipramine and dextroamphetamine. The authors suggest that, due t similarities between carbamazepine and tricyclic antidepressants, this reaction may be similar to that ind antidepressants.

b) Carbamazepine was associated with the occurrence of an acute manic state in a 40-year-old seizure days of therapy for complex partial seizures (200 milligrams 4 times a day). Withdrawal of the drug result of psychiatric symptoms within the ensuing 24 hours. Inadvertent readministration of carbamazepine 200 times a day reproduced acute manic symptoms, which again subsided upon withdrawal of the drug. It is carbamazepine may have produced a paradoxical effect; the patient recalled brief euphoric episodes foll occurrence of seizures, at which time carbamazepine was administered, and exacerbation or prolongatic cerebral dysfunction may have occurred (Drake & Peruzzi, 1986).

3.3.12.B Psychiatric sign or symptom

1) Psychiatric effects that have been reported with carbamazepine therapy include depression with agitation and visual hallucinations.

3.3.12.C Psychotic disorder

1) Summary

a) Acute adverse behavioral changes were noted with both the initiation and withdrawal of carbamazepi Depression with agitation has also been reported (Heh et al, 1988); (Reiss &O'Donnell, 1984)(Silverstein Berger, 1971).

2) Literature Reports

a) Acute adverse behavioral changes were reported in 7 children following initiation of carbamazepine th
et al, 1982). Symptoms of irritability, agitation, insomnia, aggressive outbursts, delirium, confusion, and h
appeared within 4 days to several weeks after initiation of therapy. Serum concentrations at the time of th
ranged from 5.8 to 11.8 micrograms/milliliter. The 3 most severe reactions occurred in children who were
retarded, suggesting that prior psychopathological problems may predispose to adverse reactions. In all
behavior changes resolved upon drug discontinuation, and 5 of the 7 patients were eventually able to tol
when lower doses were used.
b) Abrupt discontinuation of carbamazepine 600 to 800 mg daily resulted in exacerbations of psychotic s
including paranoia, hostility and agitation in 2 of 20 schizophrenic patients treated with carbamazepine in
an antipsychotic. The authors postulate the possibility of a withdrawal syndrome caused by carbamazepi
rebound or a hyperdopaminergic state (Heh et al, 1988).
c) At least 1 case of visual hallucinations has been reported secondary to carbamazepine therapy (Berg
year-old female developed visual hallucinations after 2 weeks of carbamazepine 100 milligrams 4 times a
neuralgia. Specifically, she complained of strangers in her apartment and insects on walls. The patient w
hospital and all drugs were discontinued including pentazocine, corticosteroids, carisoprodol, and analge
Hallucinations disappeared gradually and the neuralgia did not occur. A test dose of carbamazepine 60 m
a day was administered and visual hallucinations recurred within 2 days. They again subsided when the
withdrawn.

3.3.12.D Suicidal thoughts

1) 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 analysis included 199 placebo-controlled cli
covering 11 different AEDs used for several different indications such as epilepsy, selected psychiatric illness
conditions, including migraine and neuropathic pain syndromes. The analysis included 27,863 patients treate
16,029 patients who received placebo, and patients were aged 5 years and older. There were 4 completed su
patients in the AED treatment groups versus (vs) none in the placebo groups. Suicidal behavior or ideation oc
patients in the AED treatment groups compared to 0.22% of patients in the placebo groups. This corresponde
2.1 per 1000 (95% confidence interval, 0.7 to 4.2) more patients in the AED treatment groups having suicidal
ideation than the placebo groups. The increased risk of suicidality was noted at 1 week after starting an AED
at least 24 weeks. When compared to placebo, results were generally consistent among the drugs and were
demographic subgroups. Patients treated for epilepsy, psychiatric disorders, or other conditions were all at ar
suicidality compared to placebo. Closely monitor patients treated with AEDs for emergence or worsening of d
suicidality and other unusual changes in behavior, which may include symptoms such as anxiety, agitation, h
hypomania (US Food and Drug Administration, 2008).

3.3.13 Renal Effects

Drug-induced tubulointerstitial nephritis, acute

Kidney finding

Necrotizing arteritis, Granulomatous

Renal failure

Urogenital finding

3.3.13.A Drug-induced tubulointerstitial nephritis, acute

1) Summary

a) Infrequent cases of tubulointerstitial nephritis and tubular necrosis have occurred with therapeutic car
(Hogg et al, 1981; Jubert et al, 1994).

2) Literature Reports

a) A case of acute renal failure secondary to tubulointerstitial nephritis in a 7-year-old boy receiving carb
reported (Hogg et al, 1981). Because of worsening control of grand mal seizures, carbamazepine 200 m
milligrams/kilogram/day) was initiated, phenobarbital was discontinued, and the dosage of phenytoin was
25 days treatment with carbamazepine, he developed a fever and patchy erythematous rash. Relevant la
included bilirubin 0.9 nanograms/decaliter, SGOT 89 International units/liter, alkaline phosphatase 393 In
units/liter, and a white blood cell count of 3500/cubic millimeter with a normal differential. His carbamaze
decreased, but 3 days later, spiking fevers occurred with development of a generalized swelling and eryt
over his entire body. Over the next 7 days, urinalysis revealed 1+ proteinuria with coarse granular casts.
increased to 3.4 nanograms/decaliter. Urine output decreased and the patient became anuric over the ne
Peritoneal dialysis was begun. Sonography revealed enlarged kidneys and renal biopsy showed tubular
infiltration of lymphocytes and plasma cells. High dose parenteral methylprednisolone was begun and co
with gradual improvement leading to a return of renal function to normal over the following 4 weeks.

3.3.13.B Kidney finding

1) Summary

a) Urinary frequency, acute urinary retention, oliguria, azotemia, albuminuria, glycosuria, elevated bun, a in the urine have been reported in patients receiving carbamazepine (Prod Info Tegretol(R), 2002b).

3.3.13.C Necrotizing arteritis, Granulomatous

1) Summary

a) CASE REPORT- Granulomatous necrotizing angiitis accompanying acute renal failure was describec male with schizophrenia following carbamazepine therapy (150 milligrams daily) for approximately 3 mor 1989). The patient developed a skin eruption initially, followed by acute renal failure. On admission, signi and eosinophilia were observed, suggesting an allergic reaction. Renal biopsy demonstrated granulomat angiitis, differing from classic periarteritis nodosa and hypersensitivity angiitis. The patient was also rece zometapine and profenamine. After withdrawal of all drugs and with conservative therapy renal function i gradually. A carefully performed provocation test identified carbamazepine as the causative agent.

3.3.13.D Renal failure

1) Summary

a) Renal failure has been reported in patients. Acute renal failure was described in a 59-year-old male w carbamazepine 200 to 400 milligrams four times daily for 8 weeks for trigeminal neuralgia. Also, a case c hypersensitivity reaction to carbamazepine was described in a 35-year-old woman with late-onset epilep Tegretol(R), 2002b; Nicholls & Yasin, 1972); (Ray- Chaudhuri et al, 1989).

2) Literature Reports

a) A 79-year-old man developed kidney failure within 4 weeks of starting carbamazepine therapy for cor seizures. He first manifested a rash (within 2 weeks), which led to discontinuation of all other medication his carbamazepine dose to 200 milligrams (mg) twice daily. Two weeks later, his rash had worsened anc hospitalized. Carbamazepine was replaced by sodium valproate and he was given topical hydrocortisone rash. Laboratory results showed liver dysfunction, which improved over the next 6 days. However, he wa acute renal failure. Biopsy showed a giant cell granuloma. He became anuric and was treated with hemc steroids. He was discharged 15 days after admission with normal liver function, normal renal function, re rash, and on prednisone 60 mg, which was eventually reduced and withdrawn (Hegarty et al, 2002).

b) Acute renal failure was described in a 59-year-old male who had received carbamazepine 200 to 400 times daily for 8 weeks for trigeminal neuralgia (Nicholls & Yasin, 1972). The patient developed symptom sweating, and passing of dark urine. The eyes and face became swollen, and the patient passed large v urine. BUN was 285 milligrams/100 milliliters and serum creatinine was 6.5 milligrams/100 milliliters. Urir trace of protein and some hyaline casts. The drug was withdrawn and the patient rapidly improved, not r and BUN levels fell to 60 milligrams/100 milliliters in the next 2 weeks and serum electrolytes normalized revealed a non-specific tubular damage. A similar case has been reported (Prod Info Tegretol(R), 2002b 1993).

c) A hypersensitivity reaction to carbamazepine, characterized by generalized erythroderma, a severe le hyponatremia, marked eosinophilia, and renal failure, was described in a 35-year-old woman with late-or receiving carbamazepine therapy for approximately 3 weeks (Ray-Chaudhuri et al, 1989). The patient im withdrawal of carbamazepine and steroid therapy; however, introduction of sodium valproate resulted in new skin rash, leukocytosis, and eosinophilia; valproate was discontinued. The patient was not treated fu anticonvulsants, and seizures did not recur. This appears to be the first report of this type of reaction to c

3.3.13.E Urogenital finding

1) Renal failure, urinary frequency, acute urinary retention, oliguria, azotemia, albuminuria, glycosuria, eleva deposits in the urine, and impotence have been reported in patients receiving carbamazepine. Ejaculatory fai granulomatous necrotizing angitis has also been reported. Infrequent cases of tubulointerstitial nephritis and have occurred.

2) 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 furtl 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).

3.3.14 Reproductive Effects

Impotence

Semen finding

3.3.14.A Impotence

1) Summary

a) Sexual dysfunction has been reported in patients receiving carbamazepine (Prod Info Tegretol(R), 20

2) Literature Reports

a) A 61-year-old man developed ejaculatory failure and associated loss of sensation of orgasm shortly a taking carbamazepine (Leris et al, 1997). His symptoms returned to normal after discontinuation of carba returned upon rechallenge.

3.3.14.B 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).

3.3.15 Respiratory Effects

Cryptogenic organizing pneumonia

Pulmonary eosinophilia

Pulmonary hypersensitivity

3.3.15.A Cryptogenic organizing pneumonia

1) A 49-year-old woman developed bronchiolitis obliterans organizing pneumonia (BOOP) secondary to carb induced hypogammaglobulinemia after two years of carbamazepine therapy for epilepsy. The woman presen progressive exertional dyspnea and prolonged productive cough. BOOP was diagnosed via computerize tom and transbronchial biopsy. Laboratory analysis revealed severe hypogammaglobulinemia including immunog milligrams/deciliter (mg/dL), Ig A 20 mg/dL, and Ig M 51 mg/dL. After carbamazepine withdrawal, gammaglob and roentgenogram findings improved (Tamada et al, 2007).

2) A 52-year-old woman developed Bronchiolitis obliterans organizing pneumonia (BOOP) and lupus while ta carbamazepine (Milesi-Lecat et al, 1997). Her symptoms included facial erythema, arthralgia, dyspnea and m rounded masses and nodules. BOOP was diagnosed via pulmonary histologic examination. Antinuclear antib antihistone antibodies were present without antibodies to double-stranded DNA. All symptoms disappeared 1 carbamazepine withdrawal.

3.3.15.B Pulmonary eosinophilia

1) Summary

a) A few cases of pulmonary eosinophilia have been described following carbamazepine therapy (Tolmi Lewis & Rosenbloom, 1982).

2) Literature Reports

a) Pulmonary eosinophilia was described in an 8-year-old girl following carbamazepine (elixir) 300 millig approximately 12 weeks. The patient presented with eczema and wheezing; a chest X-ray revealed colla of the right middle lobe accompanied by a diffuse increase in bronchovascular markings. The absolute e was 11 x 10(9)/liter. valproic acid was substituted for carbamazepine, and the eosinophil count dropped later; the patient recovered in 1 month. Rechallenge with 20 mg of oral carbamazepine elixir resulted in a expiratory flow rate, wheezing, and pruritus (Tolmie et al, 1983).

b) A hypersensitivity reaction to carbamazepine was described in an 8-year-old boy who received carba milligrams orally, twice daily for approximately 5 weeks. The child developed symptoms of both pulmona asthma and fever, rash, lymphadenopathy, and hepatosplenomegaly. Symptoms improved within 3 days carbamazepine (Lewis & Rosenbloom, 1982).

3.3.15.C Pulmonary hypersensitivity

1) Summary

a) Acute pulmonary hypersensitivity was reported in patients receiving carbamazepine (Prod Info Tegret et al, 1994; Tolmie et al, 1983; Lewis & Rosenbloom, 1982; Cullinan & Bower, 1975).

2) Literature Reports

a) A case of acute pulmonary hypersensitivity was reported in a 55-year-old woman receiving carbamaz milligrams (mg) twice daily for trigeminal neuralgia (Cullinan & Bower, 1975). After 5 weeks of drug thera developed symptoms of shortness of breath, cough, and skin rash on the forearms, thighs and trunk. Exa chest disclosed crackling RALES throughout both lungs associated with a white blood cell count of 17,40 millimeter (mm(3)) with 58% eosinophils. Carbamazepine was discontinued and the patient was treated corticosteroids and diphenhydramine 25 mg every 6 hours. Within 1 to 2 weeks, the patient improved an

with a white blood cell count of 8,100 per mm(3) (8% eosinophils). Three months after discharge, the pat and blood studies were normal.

3.3.16 Other

Summary

Angioedema

Desensitization therapy

Drug withdrawal

Toxic shock syndrome

3.3.16.A Summary

1) OTHER EFFECTS

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures.

3.3.16.B Angioedema

1) Carbamazepine-associated angioedema and maculopapular eruptions occurred in a 27 year-old Indian w history of postpartum psychosis. The patient presented with symptoms of mania and aggressive behavior an carbamazepine 400 milligrams each day after failing to adequately respond to lithium and valproic acid. Carb discontinued on the second day after she developed mild palpebral edema, itching, and discoloration of the s giddiness, syncope, vomiting, and fever. Her palpebral edema became worse on the third day. Her blood cou white blood cells of 13,800 cells/cubic millimeter, with 70% neutrophils, 27% lymphocytes, 3% eosinophils, 0 0% basophils. Her serum chemistry was essentially normal with the exception of serum sodium (133 milliequ A dermatological examination indicated she had angioedema and maculopapular rash. The angioedema resp treatment with pheniramine and oral hydroxyzine hydrchloride, and her skin rash resolved gradually. The autl subsidence of angioedema with carbamazepine cessation and continued use of her other drugs suggests tha did not account or contribute to this adverse reaction (Elias et al, 2006).

3.3.16.C Desensitization therapy

1) Summary

a) The use of desensitization to carbamazepine was described in a 12-year-old epileptic boy with multip allergies (Smith & Newton, 1985).

2) Literature Reports

a) The use of desensitization to carbamazepine was described in a 12-year-old epileptic boy with multip allergies. Desensitization was accomplished by initiating 0.1 milligrams (mg) carbamazepine daily and do every 2 days until the patient had reached a therapeutic dosage of 200 milligrams twice daily (Smith & N

3.3.16.D Drug withdrawal

1) Summary

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures in patients with refra epilepsies who had incompletely controlled seizures compared to rebound seizure occurrence rates in pa from other antiepileptic drugs (DeToledo et al, 2000).

2) Literature Reports

a) Withdrawal of carbamazepine was found to increase the risk of rebound seizures in patients with refra epilepsies who had incompletely controlled seizures compared to rebound seizure occurrence rates in pa from other antiepileptic drugs (AEDs); patients who had NOT had seizures for several years on carbama seemed not to have a higher risk of recurring seizures than patients who had used other AEDs. The stud seizure occurrence rates in patients with epilepsy who had all AEDs discontinued during an 8-week perio converted to gabapentin monotherapy and observed on gabapentin for 26 weeks (n=275). Seizure rates the first 2 weeks after discontinuation of CBZ, and the state of activation of seizures was found to possib 10 weeks. Patients discontinuing CBZ had more seizures and earlier seizures than patients tapered from VALPROATE. When CBZ was part of combination treatment, the sequence in which CBZ was withdrawn inconsequential (ie, CBZ withdrawn first versus CBZ withdrawn second). No new types of seizures were CBZ withdrawal (DeToledo et al, 2000).

3.3.16.E Toxic shock syndrome

1) Summary

a) A case of pseudo-toxic shock syndrome was attributed to carbamazepine in a 13-year-old girl after 1 for temporal lobe seizures (Burnstein et al, 1983).

2) Literature Reports

a) A case of pseudo-toxic shock syndrome was attributed to carbamazepine in a 13-year-old girl after 1 for temporal lobe seizures (Burnstein et al, 1983). One week prior to admission, the patient experienced malaise, vomiting, anorexia and a facial rash had progressed to the entire body. Diarrhea, elevations in h tests and white blood cells in the urine were observed. S aureus was recovered from the patient's blood Leukopenia was also present. The patient was treated with methicillin IV and became afebrile within 48 h with oral carbamazepine resulted in recurrence of original symptoms including a spiking fever. The mech development of the S aureus bacteremia is unclear. The authors ruled out the possibility of staphylococc

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 TEGRETOL(R)-XR extende tablets, 2007) (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(Australian Drug Evaluation Committee, 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. Ac should be consulted for further details.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

3) Crosses Placenta: Yes

4) Clinical Management

a) Retrospective reviews suggest that teratogenic effects are associated with the use of anticonvulsants in c therapy. If therapy is to be continued, monotherapy is preferred for pregnant women (Prod Info TEGRETOL(R release oral tablets, 2007). Carbamazepine can cause fetal harm when administered to a pregnant woman. W childbearing potential should be counseled to weigh the benefits of therapy against the risks. Antiepileptic dru discontinued abruptly in patients taking the drug to prevent major seizures due to the strong possibility of pre epilepticus with the danger of hypoxia and threat to life. Standard prenatal care of childbearing women taking should include currently accepted tests including a fetal echocardiograph during the first trimester to detect p defects (Diav-Citrin et al, 2001).

5) Literature Reports

a) Reports indicate an increased risk of neural-tube defects, cardiovascular defects, and urinary tract defects hypoplasia of the nose, anal atresia, meningomyelocele, ambiguous genitalia, congenital heart disease, hype hypoplasia of the nails, congenital hip dislocation, spina bifida, and inguinal hernia have also been reported (A possible risk of birth defects with the folic acid antagonist, carbamazepine, has been found when used duri trimester of pregnancy (Hernandez-Diaz et al, 2000). A negative relationship between serum folate and serum concentrations has been found, suggesting that folate deficiency may play a role in carbamazepine teratogen 1998).

b) If phenytoin or carbamazepine (or any prodrugs) are used in pregnant women, there is a substantially incr teratogenicity with many combinations of other anticonvulsants. The teratogenicity of these drugs is largely o the levels of the reactive epoxide metabolites (Finnell et al, 1992g; Van Dyke et al, 1991g; Buehler et al, 199 epoxide/parent drug ratio is generally increased when phenytoin or carbamazepine is combined with each otl other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrola valproic acid, progabide, and lamotrigine. Such combinations increase the risk of major birth defects 3- to 4-f monotherapy and about 10-fold over background rates.(Spina et al, 1996f; Ramsay et al, 1990g; Bianchetti e

c) In a large retrospective cohort study (n=1411), an increased risk of major congenital abnormalities was ob offspring of women treated with carbamazepine (relative risk (RR) 2.6) or valproate (RR 4.1) monotherapy du trimester of pregnancy. Risk was unaffected by the type of seizure disorder, but in the case of valproate and was dependent upon the dose used. The risk for phenobarbital was significantly increased when other antiep or caffeine were added (RR 2.5) or when all were combined (RR 5.1). Significant associations were observed tube defects and valproate alone (RR 4.0, p=0.03) and when combined with other antiepileptic medications (I specifically with carbamazepine (RR 8.1, p=0.01). In addition, the risk of hypospadia was higher with valproat p=0.05) or combined with other antiepileptic drugs (RR 4.8, p=0.03) (Samren et al, 1999).

d) The results of a prospective study involving 210 pregnant women suggest that carbamazepine treatment the risk of major congenital abnormalities when used in the first trimester of pregnancy. The data was gathere Teratogen Information Service between January 1989 and March 1999. The 210 carbamazepine-exposed pr compared with 629 controls. Sixty-eight percent of the women in the carbamazepine group were treated throu The relative risk (RR) of major congenital anomalies was 2.24 for women in the carbamazepine group (p= 0.0 birth weights were also noted (mean 3046 grams versus 3277 grams; p= 0.000). The prevalence of congenita was 2.9% in the treatment group, compared with 0.7% in the control group. As a result, the investigators reco echocardiography in women treated with carbamazepine in the first trimester (Diav-Citrin et al, 2001).

e) A case of radial microbrain form of microencephaly in a 35-week-old premature infant exposed to carbam was reported. The mother had a history of seizures for which she was receiving carbamazepine 600 mg/day pregnancy. The last carbamazepine level, measured 18 months prior to delivery, was within the therapeutic r mcg/mL). No other levels were obtained and no seizures were recorded during the pregnancy. At birth, facial were observed in the infant. An echocardiogram showed normal cardiac structure, but reduced contractility. C revealed a grossly undersized but histologically normal brain. Due to an extremely poor prognosis, life suppo The absence of trauma, infection, or vascular disease suggests that the disorder was related to impaired neu

Although causality cannot be definitively determined, the occurrence of multiple birth defects associated with raises the possibility that carbamazepine exposure may have contributed to the pathogenesis in this infant (H 1999).

f) A pregnant, 44-year-old woman ingested 24 carbamazepine 200 mg tablets and developed mild clinical to 28.5 mcg/mL). Last menstrual period, pelvic exam and sonography indicated she was 3 to 4 weeks postconc of ingestion, which correlated with the time period of the neural tube closure. Maternal alpha-fetoprotein level 16 weeks gestation and sonography at 20 weeks suggested spina bifida. The pregnancy was electively termi showed a fetus with a large open myeloschisis from T 11 to L 5 and a hypoplastic left cerebral hemisphere (L

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) The World Health Organization considers carbamazepine compatible with breast-feeding, but recommenc infant for jaundice, drowsiness, poor suckling, vomiting, and poor weight gain (Anon, 2002). Carbamazepine for use during the breast-feeding period (Froescher et al, 1984).

5) Literature Reports

a) Carbamazepine and the epoxide metabolite transfers to breast milk. The concentration ratio of breast milk plasma is nearly 0.4 for carbamazepine and 0.5 for the epoxide. Estimated doses transferred to the newborn feeding range from 2 to 5 mg/day for carbamazepine and 1 to 2 mg/day for the epoxide. Due to the potential adverse reactions in nursing infants from carbamazepine, a decision should be made regarding discontinuing discontinuing the medication, taking into account the importance for the use of the medication for the mother TEGRETOL(R)-XR extended-release oral tablets, 2007).

b) A lower milk:maternal plasma ratio was reported in women treated with multiple, unspecified anticonvulsa 1979). Carbamazepine levels in milk were equal to 39.4% of maternal serum concentration (milk equal to 1.9 equal to 4.3 mcg/mL; n= 3). These amounts were considered pharmacologically insignificant. No adverse effe the nursing infants in any of these reports (Kaneko et al, 1979; Niebyl et al, 1979; Pynnonen et al, 1977; Pynı 1975); however, such effects were not systematically sought.

c) In four women treated with carbamazepine and phenytoin the approximate milk to serum ratio of carbama (Wilson et al, 1980; Pynnonen et al, 1977; Pynnonen & Sillanpaa, 1975). The metabolite 10,11-epoxy carban measured. Milk levels of the epoxide were approximately equal to serum levels, but the epoxide was not dete nursing infants' serum for undetermined reasons. Maternal plasma concentrations assayed at 0.5 to 3.2 mcg/ lower than the therapeutic range of 6 to 8 mcg/mL (Gilman et al, 1980).

d) One case of cholestatic hepatitis in a breast-fed infant has been reported in association with maternal use carbamazepine. Symptoms resolved following cessation of breast-feeding (Anon, 2001; Frey et al, 1990; Cha nursing infant is expected to ingest between 2% to 7.2% of the lowest weight-adjusted therapeutic dose (Iqba another report, breast-fed newborns developed serum carbamazepine levels between 15% to 65% of matern Perel, 1998) Breast milk concentrations are reported to be approximately 24% to 69% of that found in matern usual infant serum levels of 0.4 mcg/mL (Pynnonen et al, 1977).

6) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.24-0.69 (Kok et al, 1982; Nau et al, 1982; Neibly et al, 1979; Pynnonen & Sillanpaa, 1975; Pyn

3.5 Drug Interactions

Drug-Drug Combinations

Drug-Food Combinations

Drug-Lab Modifications

3.5.1 Drug-Drug Combinations

Acetaminophen

Acetylcysteine

Activated Charcoal

Adenosine

Alprazolam

Amitriptyline

Amoxapine

Amprenavir

Anisindione

Aprepitant

Aripiprazole

Armodafinil

Atracurium

Azithromycin

Betamethasone

Bortezomib

Bromperidol

Buprenorphine

Bupropion

Caspofungin

Cimetidine

Cisatracurium

Cisplatin

Clarithromycin

Clobazam

Clomipramine

Clonazepam

Clorgyline

Clozapine

Cortisone

Cyclosporine

Dalfopristin

Danazol

Darunavir

Dasatinib

Dehydroepiandrosterone

Delavirdine

Desipramine

Dexamethasone

Dicumarol

Diltiazem

Dothiepin

Doxacurium

Doxepin

Doxorubicin Hydrochloride

Doxorubicin Hydrochloride Liposome

Doxycycline

Efavirenz

Ergocalciferol

Erlotinib

Erythromycin

Estazolam

Ethinyl Estradiol

Ethosuximide

Etonogestrel

Etravirine

Etretinate

Evening Primrose

Everolimus

Felbamate

Felodipine

Fentanyl

Fluconazole

Flunarizine

Fluoxetine

Fluvoxamine

Fosamprenavir

Fosaprepitant

Fosphenytoin

Ginkgo

Haloperidol

Hydrochlorothiazide

Hydrocortisone

Imatinib

Imipramine

Indinavir

Influenza Virus Vaccine

Iproniazid

Irinotecan

Isocarboxazid

Isoniazid

Itraconazole

Ixabepilone

Ketoconazole

Lamotrigine

Lapatinib

Levetiracetam

Levonorgestrel

Levothyroxine

Lithium

L-Methylfolate

Lopinavir

Loxapine

Maraviroc

Mebendazole

Mefloquine

Mestranol

Methadone

Methylphenidate

Methylprednisolone

Metronidazole

Mianserin

Midazolam

Mifepristone

Milnacipran

Miokamycin

Moclobemide

Modafinil

Nafimidone

Nefazodone

Nelfinavir

Nevirapine

Niacinamide

Nialamide

Nifedipine

Nilotinib

Nimodipine

Norelgestromin

Norethindrone

Norgestrel

Nortriptyline

Olanzapine

Omeprazole

Oxcarbazepine

Paliperidone

Pancuronium

Pargyline

Pentobarbital

Phenelzine

Phenobarbital

Phenprocoumon

Phenytoin

Pipecuronium

Praziquantel

Prednisolone

Prednisone

Primidone

Procarbazine

Propoxyphene

Protriptyline

Psyllium

Quetiapine

Quinupristin

Ranolazine

Rapacuronium

Remacemide

Repaglinide

Rifampin

Rifapentine

Risperidone

Ritonavir

Rocuronium

Rufinamide

Sabeluzole

Saquinavir

Selegiline

Sertraline

Simvastatin

Sirolimus

Sorafenib

St John's Wort

Sunitinib

Tacrolimus

Tadalafil

Telithromycin

Temsirolimus

Terfenadine

Theophylline

Tiagabine

Ticlopidine

Tipranavir

Toloxatone

Topiramate

Tramadol

Tranylcypromine

Trazodone

Trimipramine

Troleandomycin

Valnoctamide

Valproic Acid

Vecuronium

Verapamil

Vigabatrin

Viloxazine

Voriconazole

Warfarin

Yohimbine

Zaleplon

Ziprasidone

Zotepine

3.5.1.A Acetaminophen

1) Interaction Effect: an increased risk of acetaminophen hepatotoxicity

2) Summary: The hepatotoxicity of acetaminophen may be related to the formation of toxic metabolites in the carbamazepine, an enzyme inducer, is given concurrently with high and frequent doses of acetaminophen, th metabolism of acetaminophen may result in an increased level of hepatotoxic metabolites. In support of this t observed that patients who receive enzyme-inducing agents do not recover as well from an acetaminophen o patients who are not taking enzyme-inducing drugs. The significance of this interaction at therapeutic doses o administered intermittently appears low. In addition, acetaminophen has been shown to have lower bioavailal patients receiving enzyme-inducing agents (Perucca & Richens, 1979).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: At usual therapeutic oral doses of acetaminophen and carbamazepine, no special r required.

7) Probable Mechanism: increased metabolism of acetaminophen resulting in abnormally high levels of hepa metabolites

8) Literature Reports

a) A 17-year-old female with a history of anorexia nervosa and who was receiving carbamazepine 300 r stabilization ingested acetaminophen 7800 mg in a suicide attempt. Upon admission to the hospital, her were significantly elevated and her serum acetaminophen level was 15 mcg/mL. Treatment with acetylcy initiated and her acetaminophen level decreased in the expected manner. However, eight days later, she

transplant because of fulminant hepatic failure that was believed to be due to a combination of low body malnutrition, and carbamazepine therapy. A small portion of acetaminophen is metabolized by the cytoch system to toxic metabolites which are then detoxified by glutathione. Carbamazepine is known to induce P450 system, and her malnutrition status depleted her glutathione concentrations. These two factors res concentration of acetaminophen toxic metabolites, resulting in liver failure (Young & Mazure, 1998).

3.5.1.B Acetylcysteine

1) Interaction Effect: subtherapeutic carbamazepine levels
2) Summary: One woman experienced decreased carbamazepine trough levels three days after starting N-a therapy, which led to three consecutive tonic-clonic seizures. It was proposed that high doses of N-acetylcyst the clearance of carbamazepine and its metabolites to inactive derivatives, leaving the patient at an increase activity (Simonart et al, 1998a). Closely monitor carbamazepine levels in patients also receiving N-acetylcyste
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing N-acetylcysteine to patients who take carbamazepine of N-acetylcysteine and carbamazepine may cause decreased carbamazepine plasma concentrations resulti risk of seizures. Closely monitor carbamazepine levels in patients also receiving N-acetylcysteine.
7) Probable Mechanism: increased clearance of carbamazepine
8) Literature Reports
a) A 59-year-old female being treated for two years with carbamazepine 800 mg daily had serum trough mcg/mL. Lamotrigine was added to her therapeutic regimen to allow a slow withdrawal of carbamazepine lamotrigine increased to 75 mg daily, the patient developed fever, lymphadenopathy, conjunctivitis, and r eruptions on the face and upper torso. Carbamazepine trough level at this time was 11.1 mcg/mL. The p diagnosed with lamotrigine-induced hypersensitivity, and N-acetylcysteine 2 g every six hours was initiat clinical improvement. However, on the third day of N-acetylcysteine therapy, the patient had three tonic-c within five hours. Although her carbamazepine dose had not changed, the trough level was 8.1 mcg/mL. that the high doses of N-acetylcysteine increased the clearance of carbamazepine and its metabolites to derivatives, leaving the patient at an increased risk for seizure activity (Simonart et al, 1998).

3.5.1.C Activated Charcoal

1) Interaction Effect: decreased carbamazepine exposure
2) Summary: In a cross-over study involving six healthy volunteers, activated charcoal 8 g administered imm carbamazepine 400 mg resulted in a decrease in the carbamazepine absorption by 90%. Maximum concentr decreased from 2.7 mg/L to 0.28 mg/L, and the area under the concentration-time curve (AUC) of carbamaze mg/L/h to 11 mg/L/h (Neuvonen et al, 1988). This drug interaction may make activated charcoal useful in cas carbamazepine overdose, but should be kept in mind when using activated charcoal in therapy concurrently v carbamazepine.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Since activated charcoal binds carbamazepine in the gastrointestinal tract, administ two hours before or four to six hours after activated charcoal. If this is not possible, separate administration ti possible. During concurrent therapy, monitor carbamazepine serum levels closely and observe the patient for response to carbamazepine.
7) Probable Mechanism: reduced carbamazepine absorption

3.5.1.D Adenosine

1) Interaction Effect: a higher degree of heart block
2) Summary: Carbamazepine has been reported to increase the degree of heart block that may be produced Adenosine exerts its effect by decreasing conduction through the AV node, and may cause a short-lasting firs third-degree block. Therefore, higher degrees of heart block induced by adenosine may occur in the presence carbamazepine (Prod Info Adenocard(R), 2002).
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: If possible, carbamazepine should be withheld for at least five half-lives (approxima prior to the use of adenosine.
7) Probable Mechanism: additive effects

3.5.1.E Alprazolam

1) Interaction Effect: decreased alprazolam effectiveness
2) Summary: The addition of carbamazepine 600 mg daily to a patient stabilized on alprazolam resulted in a decrease in alprazolam concentration (43 ng/mL vs 20 ng/mL) (Arana et al, 1988a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of benzodiazepine clinical effectiveness. Concurrent use of carbar

alprazolam may require higher doses of alprazolam. The dose of alprazolam should be decreased if carbama discontinued.
7) Probable Mechanism: increased hepatic metabolism
8) Literature Reports
a) Combined therapy with alprazolam and carbamazepine was reported to result in significant reduction plasma levels, corresponding with clinical deterioration, in a 32-year-old male with atypical bipolar disord attacks (Arana et al, 1988). The patient was receiving oral lithium carbonate 1200 mg daily with oral alpr daily prior to the initiation of carbamazepine. Carbamazepine 300 to 600 mg daily orally was used to con impulsivity and psychosis; the lithium was discontinued. It is speculated that carbamazepine reduced alp levels by induction of hepatic microsomal enzymes. More studies are required to evaluate this interactior mechanisms.

3.5.1.F Amitriptyline
1) Interaction Effect: decreased amitriptyline effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991h; Brown et al, 1988b).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the amitriptyline therapy and for any signs of toxicity c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased amitriptyline metabolism
8) Literature Reports
a) A study examined the effect of carbamazepine on amitriptyline levels in 8 psychiatric inpatients treate amitriptyline dosage of 137.5 mg daily. All patients were treated for a minimum of 7 days prior to measur antidepressant concentrations. Carbamazepine was added in a mean dose of 593 mg continued over a patients receiving combination therapy, serum amitriptyline and nortriptyline concentrations were signific and 40% respectively) than in patients receiving amitriptyline alone, although the ratio of amitriptyline to remained relatively unchanged (Leinonen et al, 1991g).

3.5.1.G Amoxapine
1) Interaction Effect: decreased amoxapine concentration
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991e; Brown et al, 1990c). Although not reported for amoxapine, a similar interaction
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the amoxapine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased amoxapine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977a). Although not reported specifically for amoxapine, be potential for a similar interaction exists. Patients on chronic Carbamazepine therapy may require increas tricyclic antidepressants.

3.5.1.H Amprenavir
1) Interaction Effect: reduced amprenavir efficacy due to reduced amprenavir serum concentrations
2) Summary: Coadministration of carbamazepine and amprenavir may result in reduced amprenavir serum c Dose adjustments of amprenavir may be necessary to maintain antiviral efficacy of amprenavir (Prod Info Ag
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Clinicians may want to consider using alternative medication to carbamazepine in p amprenavir therapy. However, if it becomes necessary to give these agents concurrently, upward adjustment dosing may be needed to maintain antiviral effectiveness.
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated amprenavir metabolism

3.5.1.I Anisindione
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983a; Cohen & Arms Koch-Weser & Koch-Weser, 1975a; Kendall & Boivin, 1981a; Hansen et al, 1971b). A similar effect may occu
3) Severity: moderate

4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep reassessed periodically during concurrent therapy. Adjustments of the anisindione dose may be necessary in the desired level of anticoagulation.
7) Probable Mechanism: increased anisindione metabolism

3.5.1.J Aprepitant
1) Interaction Effect: reduced plasma aprepitant concentrations and decreased aprepitant efficacy
2) Summary: Coadministration of aprepitant with drugs that strongly induce cytochrome P450 3A4 activity, s carbamazepine, may result in reduced plasma concentrations of aprepitant and decreased efficacy of aprepit EMEND(R) oral capsules, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant administration of aprepitant and carbamazepine may result in reducec concentrations of aprepitant and may decrease the efficacy of aprepitant (Prod Info EMEND(R) oral capsules
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of aprepitant by carbamaz

3.5.1.K Aripiprazole
1) Interaction Effect: decreased aripiprazole concentrations
2) Summary: Coadministration of carbamazepine 200 milligrams (mg) twice daily with aripiprazole 30 mg on the maximum concentration (Cmax) and the area under the concentration-time curve (AUC) values of both a active metabolite, dehydro-aripiprazole, by approximately 70%. Aripiprazole is partly metabolized by cytochro (CYP3A4) enzymes. Coadministration with carbamazepine, a potent CYP3A4 inducer, could increase aripipr causing decreased blood concentrations. The dose of aripiprazole should be doubled when it is administered carbamazepine. If therapy with carbamazepine is discontinued, the dose of aripiprazole should then be decre ABILIFY(R) oral tablets, oral solution, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Coadministration of aripiprazole and carbamazepine has resulted in decreased arip concentrations. The dose of aripiprazole should be doubled when it is administered concurrently with carbam with carbamazepine is discontinued, the dose of aripiprazole should then be decreased.
7) Probable Mechanism: induction of CYP3A4-mediated aripiprazole metabolism

3.5.1.L Armodafinil
1) Interaction Effect: decreased armodafinil exposure or plasma levels
2) Summary: Armodafinil is partially metabolized by the CYP3A enzyme system. Use caution with the coadm armodafinil with other drugs that are potent inducers of CYP3A4, such as carbamazepine, as this could resul exposure or plasma levels of armodafinil (Prod Info NUVIGIL(TM) oral tablets, 2007). Also, monitor patient's armodafinil if these 2 agents are used concurrently.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution with the coadministration of armodafinil and carbamazepine as this ma decreased armodafinil exposure or levels (Prod Info NUVIGIL(TM) oral tablets, 2007). Monitor patient respon these 2 agents are used concurrently.
7) Probable Mechanism: induction of CYP3A-mediated armodafinil metabolism

3.5.1.M Atracurium
1) Interaction Effect: decreased atracurium duration of action
2) Summary: The effects of carbamazepine on the neuromuscular blocking effects of atracurium have been well-controlled studies. The effect of atracurium was significantly shortened in patients taking carbamazepine phenytoin or valproic acid, compared to patients not taking anticonvulsants (Tempelhoff et al, 1990a). Other reported that carbamazepine had no effect on the onset time or duration of atracurium (Spacek et al, 1997a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of atracurium may be needed in patients receiving carbamazepine.
7) Probable Mechanism: increased atracurium metabolism
8) Literature Reports
a) Researchers studied the effect of carbamazepine on the onset and duration of neuromuscular blocka atracurium. Three groups of patients were studied; 21 nonepileptic patients, 14 epileptic patients treated carbamazepine alone, and 18 epileptic patients receiving carbamazepine and either phenytoin or valproi receiving carbamazepine had been maintained for many years. All patients were treated with atracurium

intravenously following standard induction of anesthesia. The time to onset of neuromuscular blockade w different for the three groups of patients. However, time to recovery of baseline and train-of-four respons shorter for the two groups receiving carbamazepine (Tempelhoff et al, 1990).

b) Carbamazepine had no effect on the neuromuscular blockade induced by atracurium in one study. Af induction of anesthesia, 0.5 mg/kg of atracurium was administered in two groups of patients, with eight p carbamazepine and ten patients not receiving carbamazepine. The average duration of carbamazepine t weeks. There was no significant difference between the two groups in lag time, onset time, or time to rec neuromuscular blockade induced by atracurium (Spacek et al, 1997).

3.5.1.N Azithromycin

1) Interaction Effect: increased serum carbamazepine levels

2) Summary: Although some macrolide antibiotics interfere with hepatic metabolism of carbamazepine, azith the semisynthetic macrolides that does not inactivate cytochrome P450, and, therefore, does not interact with (Periti et al, 1992a; Hopkins, 1991a). It is suggested, however, that elevations of serum carbamazepine level the concomitant use of azithromycin, and that careful monitoring of patients is advised by the manufacturer (P Zithromax(R), 2001).

3) Severity: minor

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Until further data are available regarding drug interactions with azithromycin and ca careful monitoring of patients is advised.

7) Probable Mechanism: unknown

8) Literature Reports

a) Although quite variable in their ability to produce enzyme inhibition, the macrolide antibiotics have be significant drug interactions. They can be classified into three groups: 1) erythromycins and troleandomy nitrosoalkanes leading to inactive cytochrome P450- metabolite complexes, 2) clarithromycin, flurithromy midecamycin, miocamycin, and roxithromycin form complexes to a smaller degree and seldom cause dr and 3) azithromycin, dirithromycin, rokitamycin, and spiramycin do not affect cytochrome P450 and, ther produce drug interactions (Periti et al, 1992).

b) In a toleration and safety profile of azithromycin assessing 3995 patients, no pharmacokinetic interac observed with carbamazepine, cimetidine, methylprednisolone, theophylline, or warfarin (Hopkins, 1991)

3.5.1.O Betamethasone

1) Interaction Effect: decreased betamethasone effectiveness

2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982b). Although not specifically reported for betamethasone, a similar interaction could be expected.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor therapeutic efficacy of betamethasone. An increase in the steroid dosage m after three to five days of concurrent carbamazepine therapy.

7) Probable Mechanism: increased betamethasone metabolism

3.5.1.P Bortezomib

1) Interaction Effect: reduced efficacy of bortezomib

2) Summary: Carbamazepine may induce the metabolism of bortezomib. Monitor patients closely for reduce CYP3A4 inducers (ie, carbamazepine) are coadministered with bortezomib (Prod Info VELCADE(R) injection

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: The concomitant use of bortezomib and CYP3A4 inducers (ie, carbamazepine) may bortezomib efficacy. Monitor patients if bortezomib and carbamazepine are coadministered (Prod Info VELCA 2008).

7) Probable Mechanism: induction of CYP3A4-mediated bortezomib metabolism by carbamazepine

3.5.1.Q Bromperidol

1) Interaction Effect: decreased bromperidol efficacy

2) Summary: Concurrent administration of carbamazepine and bromperidol may decrease plasma concentra bromperidol and its reduced metabolite by inducing their metabolism. However, when carbamazepine and br coadministered in schizophrenic patients, clinical improvement was seen. This indicates that these two agent some pharmacodynamic synergism (Otani et al, 1997a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: established

6) Clinical Management: Monitor patients for bromperidol efficacy. When given concomitantly with carbamaz bromperidol may need to be increased.

7) Probable Mechanism: induction of bromperidol metabolism by carbamazepine

8) Literature Reports

a) In one study, 13 schizophrenic patients were given bromperidol 12 mg to 24 mg daily for 1 to 20 weel addition of carbamazepine 400 mg daily for 4 weeks. Carbamazepine reduced plasma concentrations of and reduced bromperidol by 37% and 23%, respectively, at four weeks. It appeared that the induction by was fastest during the first week of cotherapy, but maximal effects were seen at four weeks. The authors cytochrome P450 3A4 isoenzymes may be involved in this process, since carbamazepine is known to in CYP 3A4. Although carbamazepine and bromperidol coadministration resulted in decreased plasma con bromperidol, the Clinical Global Impression scores were decreased significantly, indicating that some ph synergism exists between carbamazepine and bromperidol which results in clinical improvement (Otani e

3.5.1.R Buprenorphine

1) Interaction Effect: decreased buprenorphine plasma concentrations
2) Summary: Buprenorphine is primarily metabolized by the CYP3A4 isoenzyme system. Coadministration o inducer, such as carbamazepine, may result in increased clearance and reduced plasma concentrations of b concomitant use of buprenorphine and carbamazepine is warranted, dosage adjustment may be necessary (buprenorphine hcl injection, 2004) along with increased monitoring for buprenorphine withdrawal signs and s et al, 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing buprenorphine to patients who take carbamazepine. of buprenorphine and carbamazepine may cause reduced buprenorphine plasma concentrations. If concurre dosage adjustments should be considered (Prod Info buprenorphine hcl injection, 2004). Increased monitorin signs and symptoms is also recommended when buprenorphine is coadministered with carbamazepine (Brid
7) Probable Mechanism: induction of CYP3A4-mediated buprenorphine metabolism by carbamazepine

3.5.1.S Bupropion

1) Interaction Effect: decreased bupropion effectiveness
2) Summary: Since bupropion is extensively metabolized by the cytochrome P450 enzyme system, the coad bupropion with other drugs that are inducers of the CYP450 system may affect its clinical activity. Carbamaze the metabolism of bupropion, resulting in decreased efficacy of bupropion (Prod Info Wellbutrin XL(TM), 2003
3) Severity: minor
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Care should be taken when administering bupropion with carbamazepine. Monitor t bupropion efficacy.
7) Probable Mechanism: induction of bupropion metabolism by carbamazepine

3.5.1.T Caspofungin

1) Interaction Effect: reduced caspofungin plasma levels
2) Summary: Enhanced clearance of caspofungin may occur during concomitant therapy with carbamazepin drug clearance. Patients may require an increase in dose to 70 mg caspofungin daily (Prod Info CANCIDAS(2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When caspofungin is coadministered with inducers of drug clearance, such as carb consider using a daily dose of 70 mg of caspofungin (Prod Info CANCIDAS(R) IV infusion, 2008).
7) Probable Mechanism: enzyme induction by carbamazepine
8) Literature Reports

a) Combined use of carbamazepine and caspofungin, an inducer of drug clearance, may result in a sign caspofungin plasma levels. This is based on regression analyses of pharmacokinetic data. It is not know clearance mechanism involved in caspofungin disposition may be inducible (Prod Info CANCIDAS(R) IV

3.5.1.U Cimetidine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The effects of cimetidine on carbamazepine plasma concentration may be temporary. Possible limitation of carbamazepine auto-induction may occur (Macphee et al, 1984; Dalton et al, 1985a; Dalton et al, 1985a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Consider obtaining plasma carbamazepine levels two to four days after starting or c cimetidine. Usual therapeutic levels are 6 mg/L to 12 mg/L; however, the relationship between plasma levels variable. Patients should also be cautioned that transient signs of carbamazepine toxicity may occur during th cimetidine therapy. An alternative H-2 blocker that has not been reported to cause this interaction, such as ra famotidine, might be considered.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) In a single dose study, cimetidine pretreatment increased the carbamazepine area under the curve by elimination half-life by 18% (Dalton et al, 1985). It is possible that this is due to decreased metabolism se inhibition of hepatic microsomal enzymes by cimetidine (Telerman-Toppet et al, 1981); however, others l significant alterations in steady-state plasma concentrations of carbamazepine or its metabolite with con administration of cimetidine (Sonne et al, 1983; Levine et al, 1985).
b) Cimetidine 400 mg three times daily significantly increased steady-state carbamazepine plasma level days. However, carbamazepine levels decreased to pretreatment levels by the seventh day of cimetidine Carbamazepine side effects appeared in most patients within 24 hours following cimetidine initiation, but next 48 to 72 hours. The investigators concluded that dosage adjustments appear unnecessary, but that warned of the appearance of carbamazepine side effects for the first 3 to 5 days after beginning cimetidi 1986).
c) A case of carbamazepine toxicity was reported in an elderly man receiving carbamazepine 200 mg th isoniazid 300 mg daily, and cimetidine 400 mg twice daily. Two days after initiating this drug combinatior developed nausea, vomiting, dizziness, and epigastric pain. Carbamazepine serum concentrations were receiving this combination of therapy should have close monitoring of carbamazepine concentrations (Ga

3.5.1.V Cisatracurium

1) Interaction Effect: resistance to neuromuscular blocking action
2) Summary: Some medications, including carbamazepine, may enhance resistance to the neuromuscular b nondepolarizing agents such as cisatracurium (Prod Info Nimbex(R), 1999). Dose adjustments of cisatracuriu when these agents are being used concurrently.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The dose of cisatracurium may need to be adjusted upward in patients receiving co carbamazepine.
7) Probable Mechanism: unknown

3.5.1.W Cisplatin

1) Interaction Effect: decreased carbamazepine plasma concentrations
2) Summary: A 36-year old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin subtherapeutic carbamazepine and valproic acid concentrations which resulted in tonic-clonic seizures. Altho mechanism is unknown, possible causes include decreased absorption or accelerated elimination of carbama Voogd-van der Straaten, 1988c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.
7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine
8) Literature Reports
a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988b).

3.5.1.X Clarithromycin

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Clarithromycin has been reported to elevate the serum levels of carbamazepine (Prod Info Biax resulting in the clinical symptoms of lethargy, fatigue, blurred vision, nausea, confusion, and ataxia (Tatum & Albani et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Decreasing the carbamazepine dose by approximately 25% is advised at the initiati clarithromycin therapy with further modification according to clinical symptoms and serum carbamazepine tro concentrations. Consider monitoring carbamazepine plasma levels.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Carbamazepine toxicity with an increase in serum level associated with the addition of clarithromycin 35-year-old female diagnosed with complex partial seizures (Tatum & Gonzalez, 1994). She was mainta carbamazepine 200 mg three times daily with an approximate steady-state level of 8.3 mcg/mL. With dev

upper respiratory infection, clarithromycin 500 mg two times daily was initiated. Symptoms of lethargy, fa vision, nausea, "muddled thoughts", and ataxia occurred within a few hours of the first dose. A carbamaz of 15.5 mcg/mL was obtained 26 hours after the first clarithromycin dose. The symptoms of toxicity resol level returned to baseline within 36 hours of discontinuing carbamazepine and clarithromycin.

b) A 29 year-old male was diagnosed with simple partial seizures since the age of 11 years and was ma carbamazepine 400 mg two times daily with an approximate steady-state level of 8 mcg/mL (Albani et al addition of clarithromycin increased the serum level to 12.7 mcg/mL, measured at the end of the clarithro despite decreasing carbamazepine (300 mg two times daily); yet, he did not notice any adverse symptor elevated serum level. Upon completion of the therapy, he was placed on the previous carbamazepine do the level returned to baseline.

c) Clarithromycin 500 mg was given concurrently with either oral carbamazepine 400 mg or placebo twi healthy volunteers in a randomized, double-blind study. The mean area under the concentration-time cu carbamazepine was increased and the formation of the 10,11-epoxide metabolite was significantly reduc significant change in carbamazepine pharmacokinetics (Sturgill & Rapp, 1992). Whether this would lead significant effect is unknown.

d) Macrolide antibiotics have been implicated in severe drug interactions, but there are differences amo not all are responsible for drug interactions. They can be classified into 3 groups: 1) erythromycins and t form nitrosoalkanes leading to inactive cytochrome P450-metabolite complexes, 2) clarithromycin, flurith josamycin, midecamycin, miocamycin, and roxithromycin form complexes to a smaller degree and are le drug interactions, and 3) azithromycin, dirithromycin, rokitamycin, and spiramycin do not affect cytochron therefore, would not be expected to interfere with drugs metabolized by this enzyme system (Periti et al,

3.5.1.Y Clobazam

1) Interaction Effect: decreased carbamazepine parent drug and/or increased active metabolite concentratio

2) Summary: Studies that investigated the effect of clobazam on carbamazepine have shown variable effects and active metabolite concentrations, including increases in carbamazepine levels (Franceschi et al, 1983), c et al, 1986a), and no significant change (Sennoune et al, 1992; Munoz et al, 1990a). Carbamazepine effects been shown to include decreased plasma levels and area under the concentration-time curve (AUC) of cloba levels and AUC of norclobazam (the active metabolite) (Bun et al, 1990; Jawad et al, 1984; Levy et al, 1983; 1992).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor carbamazepine serum concentrations and seizure control.

7) Probable Mechanism: increased hepatic metabolism

8) Literature Reports

a) Concomitant administration of clobazam and carbamazepine has been reported to result in a 14% re parent drug carbamazepine plasma concentrations; changes to active metabolites were not noted (Schm

b) Metabolite/parent drug plasma ratios were studied in 15 patients with seizure disorders on carbamaz and five patients receiving both clobazam and carbamazepine. Carbamazepine plasma concentrations w groups, but clobazam-treated patients demonstrated higher concentrations of metabolites, particularly th metabolite. This suggested induction of carbamazepine metabolism, probably by induction of cytochrom resulting increases in carbamazepine epoxidation (Munoz et al, 1990).

3.5.1.Z Clomipramine

1) Interaction Effect: decreased clomipramine effectiveness

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease ar levels (Leinonen et al, 1991f; Brown et al, 1990d). Although not reported for clomipramine, a similar interactic

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor for clinical efficacy of the clomipramine therapy and for any signs of toxicity carbamazepine. Serum levels of both agents should be considered when either agent is added or discontinue appropriate dosage adjustments made accordingly.

7) Probable Mechanism: increased clomipramine metabolism

8) Literature Reports

a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disord reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine enhances the hepatic microsomal metabolism of imipramine and other tricyclic antidepr inducing hepatic enzymes (Moody et al, 1977b). Although not reported specifically for clomipramine, be a potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increase tricyclic antidepressants.

3.5.1.AA Clonazepam

1) Interaction Effect: reduced plasma levels of clonazepam

2) Summary: Clonazepam and carbamazepine cotherapy has resulted in decreased clonazepam serum con may be a result of carbamazepine enzyme induction (Sunaoshi et al, 1988a; Lai et al, 1978a). One study invo administration to epileptic patients maintained on carbamazepine either alone or in combination with other an

determined that clonazepam administration did not influence serum concentrations of carbamazepine (Johan 1977a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clonazepam levels should be monitored whenever carbamazepine is added or with therapy, or when the carbamazepine dose is changed. Also monitor the patient for seizure control.
7) Probable Mechanism: induction of clonazepam hepatic metabolism
8) Literature Reports
a) The effect of carbamazepine on clonazepam plasma levels during chronic administration were evalua healthy volunteers (Lai et al, 1978). Subjects were given clonazepam 1 mg once daily for 29 consecutive carbamazepine 200 mg was coadministered on days 8 to 29. Clonazepam plasma levels reached a stea to the initiation of carbamazepine therapy. After the addition of carbamazepine, plasma clonazepam leve 5 to 15 days to a level 19% to 37% less than their prior steady-state concentrations. Carbamazepine alsc clonazepam half-life. The proposed mechanism for this drug interaction is enzyme induction caused by c
b) The effects of clonazepam on serum levels of phenytoin, phenobarbital, and carbamazepine were stu epileptic patients who were receiving one or two of these drugs (Johannessen et al, 1977). Clonazepam was added to their therapeutic regimens and anticonvulsant levels were determined weekly for at least s nine patients receiving carbamazepine either as monotherapy or combined with another anticonvulsant, plasma concentrations averaged 8.1 mcg/mL prior to clonazepam and 8.3 mcg/mL after clonazepam the concluded that clonazepam has an insignificant effect on plasma concentrations of carbamazepine.
c) Concurrently administered clonazepam and carbamazepine were investigated in epileptic children (S 1988). The steady-state plasma concentration of clonazepam was determined in 66 epileptic children wh both carbamazepine and clonazepam. These levels were compared to the plasma levels of clonazepam children who were receiving clonazepam as monotherapy. In another group of 12 children, some of whor the previous groups, carbamazepine was added to their pre-existing regimen of clonazepam. Another gr was maintained on clonazepam and carbamazepine, and their therapeutic regimen was changed to clon plasma levels were determined four or more weeks after maintaining the same dose and regimen. When plasma levels of clonazepam, children who received clonazepam monotherapy had a mean level of 30.9 children who were receiving therapy with clonazepam and carbamazepine had a mean level of 26.2 ng/r carbamazepine was added to clonazepam monotherapy, steady-state plasma concentrations of clonaze from 47.5 ng/mL to 35.1 ng/mL. Conversely, when children who were receiving clonazepam and carbam switched to clonazepam monotherapy, plasma levels of clonazepam increased from 28.6 ng/mL to 34.4

3.5.1.AB Clorgyline

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998e; Thweatt, 1986e). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995k; Barker & Ecclestor controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to mu therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995j). In addition to their regular carbamazepine anc four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcy maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984j).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985e). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992e). Four other patie

phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.AC Clozapine

1) Interaction Effect: an increased risk of bone marrow suppression, asterixis, or decreased serum clozapine
2) Summary: Clozapine and carbamazepine both have the potential to cause bone marrow suppression, incl agranulocytosis (Prod Info Clozaril(R), 2002). Asterixis (flapping tremor) has also been reported in patients u concurrent therapy with carbamazepine and clozapine (Rittmannsberger, 1996c). In addition, a therapeutic d study revealed significantly lower clozapine concentrations when carbamazepine was added to therapy (Jerli The mechanism may be due to carbamazepine induction of clozapine metabolism through cytochrome P450 studies are needed to further evaluate the pharmacokinetic and clinical effects of combining these agents.
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concurrent use; an alternative anticonvulsant agent should be considered. If these agents is necessary, monitor patients for decreased response to clozapine and agranulocytosis. Lower clozapine or carbamazepine may be required.
7) Probable Mechanism: additive bone marrow-suppressive effects and neurotoxicity; induction of clozapine
8) Literature Reports

a) One agranulocytosis fatality has been reported in association with the use of a multi-drug regimen wh clozapine, carbamazepine, clonazepam, benztropine, and lithium (Gerson & Lieberman JA Friedenberg, exhibited pancytopenia which is not characteristic of clozapine-induced agranulocytosis.

b) Over a three-year period, some drug combinations caused a greater risk of asterixis (flapping tremor) regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996b). With regard to the agents c clozapine, and lithium, incidence of asterixis was greatest in those patients that were on at least two of t Out of ten patients developing asterixis, five patients received carbamazepine and clozapine as part of m and in two cases carbamazepine and clozapine were the sole psychopharmacologic agents. In all cases the drugs were within normal therapeutic ranges, suggesting an additive effect of combination therapy ra of a single agent.

c) Therapeutic drug monitoring data showed a 50% lower clozapine concentration/dose (C/D) ratio whe carbamazepine was taken compared to clozapine alone. The clozapine C/D ratio was inversely correlate carbamazepine. An additional analysis of eight patients confirmed that upon addition of carbamazepine t regimen, clozapine concentrations decreased significantly. The mean C/D ratio during monotherapy was cotherapy with carbamazepine fell to 0.30. The change in clozapine metabolism was suggested to be du carbamazepine induction of cytochrome P450 3A4 (Jerling et al, 1994).

3.5.1.AD Cortisone

1) Interaction Effect: decreased cortisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982a). Although not specifically reported for cortisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased cortisone metabolism

3.5.1.AE Cyclosporine

1) Interaction Effect: reduced cyclosporine serum levels and potentially increased risk for organ rejection
2) Summary: In a number of case reports, the concomitant use of cyclosporine and carbamazepine resulted cyclosporine levels (Soto Alvarez et al, 1991; Yee & McGuire, 1990a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Within the first two to three weeks of initiating or discontinuing carbamazepine thera cyclosporine levels and adjust cyclosporine dosage as necessary; therapeutic trough levels range from 150 transplant, to 50 to 100 mcg/L thereafter; also monitor for signs of organ rejection.
7) Probable Mechanism: increased cyclosporine metabolism

3.5.1.AF Dalfopristin

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Quinupristin/dalfopristin is a potent inhibitor of cytochrome P450 3A4 enzymes and may cause carbamazepine concentrations when administered concurrently. Because carbamazepine possesses a narro window, carbamazepine concentrations should be closely monitored during therapy with quinupristin/dalfopri carbamazepine should be adjusted accordingly (Prod Info Synercid(R) I.V., 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable

6) Clinical Management: Monitor the trough carbamazepine concentrations when therapy with quinupristin/d administered concurrently. Dose reductions of carbamazepine may be required. Also monitor the patient for e carbamazepine toxicity.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated carbamazepine metabolism

3.5.1.AG Danazol
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concomitant use of danazol and carbamazepine has led to significant increases in carbamaze resulted in toxicity (Kramer et al, 1986a; Zielinski et al, 1987; Hayden & Buchanan, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for symptoms of carbamazepine toxicity when danazol is added to therapy. carbamazepine levels should also be considered with the addition or discontinuation of danazol and dosage a accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) In a case report of a patient on carbamazepine 600 mg daily, the concurrent use of danazol 600 mg c carbamazepine level 60%, the area under the concentration-time curve (AUC) 148%, half-life 120%, and clearance approximately 60% within a month. Evaluation of the interaction by stable isotope technique re danazol inhibits carbamazepine metabolism, specifically the epoxide-trans-diol pathway (Kramer et al, 19

3.5.1.AH Darunavir
1) Interaction Effect: increased carbamazepine plasma concentrations and potential toxicity
2) Summary: Coadministration of carbamazepine with darunavir/ritonavir, an inhibitor of CYP450 enzymes, r inhibition of CYP3A-mediated carbamazepine metabolism, resulting in significantly increased carbamazepine concentrations and potential toxicity. In a pharmacokinetic drug interaction study, concurrent administration o and darunavir/ritonavir significantly increased plasma concentrations of carbamazepine. No significant chang pharmacokinetic parameters were noted. If coadministration of carbamazepine and darunavir/ritonavir is nec monitoring of carbamazepine concentrations and dose titration is recommended to attain the desired clinical initiating coadministration of darunavir/ritonavir and carbamazepine, no dose adjustment of either darunavir/ri carbamazepine is required (Prod Info PREZISTA(R) film coated oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Coadministration of carbamazepine and darunavir/ritonavir may result in significant carbamazepine plasma concentrations due to inhibition of CYP3A-mediated carbamazepine metabolism by c coadministration of carbamazepine and darunavir/ritonavir is necessary, clinical monitoring of carbamazepine and dose titration is recommended to attain the desired clinical response. When initiating coadministration of and carbamazepine, no dose adjustment of either darunavir/ritonavir or carbamazepine is required (Prod Info film coated oral tablets, 2008).
7) Probable Mechanism: inhibition of CYP3A-mediated carbamazepine metabolism
8) Literature Reports
a) In a pharmacokinetic drug interaction study, concurrent administration of carbamazepine and darunav significantly increased plasma concentrations of carbamazepine. Subjects (n=16) were administered car mg twice daily concurrently with darunavir 600 mg/ritonavir 100 mg twice daily. Carbamazepine Cmax w (Least squares (LS) mean ratio 1.43; 90% confidence interval (CI), 1.34 to 1.53), AUC was increased 45 1.45; 90% CI, 1.35 to 1.57), and Cmin was increased 54% (LS mean ratio 1.54; 90% CI, 1.41 to 1.68). N changes in darunavir pharmacokinetic parameters were noted (Prod Info PREZISTA(R) film coated oral

3.5.1.AI Dasatinib
1) Interaction Effect: decreased dasatinib plasma concentrations
2) Summary: Dasatinib is a CYP3A4 substrate. Coadministration of a strong CYP3A4 inducer, such as carba dasatinib should be avoided as this may result in decreased dasatinib plasma concentrations leading to subth dasatinib levels. Consider using alternative therapeutic agents with low enzyme induction potential for coadm dasatinib. If concomitant use of dasatinib and carbamazepine is clinically warranted, a dasatinib dose increas considered and the patient should be monitored carefully for signs/symptoms of dasatinib toxicity (myelosupp retention, diarrhea, hemorrhage, or skin rash) (Prod Info SPRYCEL(R) oral tablets, 2008).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant administration of carbamazepine, a strong CYP3A4 inducer, and CYP3A4 substrate, as this may result in decreased dasatinib plasma concentrations and consequently, subth Consider using alternative therapeutic agents with low enzyme induction potential for coadministration with d if concomitant use with carbamazepine is clinically warranted, consider increasing the dasatinib dose and mo closely for dasatinib toxicity (myelosuppression, fluid retention, diarrhea, hemorrhage, or skin rash) (Prod Info oral tablets, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated dasatinib metabolism

3.5.1.AJ Dehydroepiandrosterone

1) Interaction Effect: reduced effectiveness of carbamazepine

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, 1992a). Pati 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 carbamazepine is being used for manic symptoms, concomitant use of dehydroep (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 bel 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).

b) A 13-year-old male decompensated with a subsequent two-year period of emotional problems accom use of LSD, hashish, barbiturates, and alcohol. His mental status included bizarre, disorganized, delusio auditory and visual hallucinations, paranoia, lack of attention to personal hygiene, agitation, and combati diagnosed with chronic paranoid schizophrenia; schizophrenia, chronic undifferentiated type, and schizo excited type. He was resistant to daily doses of trifluoperazine 40 mg, chlorpromazine 400 mg, and imipr was also resistant to combination therapy with chlorpromazine 400 mg with thiothixene 80 mg, thioridazi perphenazine 48 mg with lithium carbonate 1200 mg, clonazepam 4 mg, and carbamazepine 1200 mg d DHEA level exceeded 900 mcg/dL. A seven-day suppression test with dexamethasone 1 mg orally at be normal DHEA level of 200 mcg/dL. By day 5, psychosis improved and the patient was well-oriented, con was making good eye contact. Once dexamethasone was discontinued, rapid decompensation and floric despite "substantial amounts of psychotropic medications." DHEA increased to 536 mcg/dL. The author elevated DHEA levels were associated with florid psychosis resistant to conventional antipsychotic thera 1992).

3.5.1.AK Delavirdine

1) Interaction Effect: decreased trough plasma delavirdine concentrations

2) Summary: Pharmacokinetic data on eight patients suggested that coadministration of phenytoin, phenoba carbamazepine with delavirdine results in substantial reductions in trough plasma delavirdine concentrations 90%). Coadministration of delavirdine with any of these drugs is not recommended (Prod Info RESCRIPTOR 2006).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Coadministration of delavirdine and carbamazepine is not recommended, due to th reduction in plasma delavirdine concentrations seen with concurrent use.

7) Probable Mechanism: induction of delavirdine metabolism

3.5.1.AL Desipramine

1) Interaction Effect: increased carbamazepine toxicity, decreased desipramine effectiveness

2) Summary: The concomitant use of carbamazepine and desipramine has been reported to increase carbar concentrations and decrease desipramine concentrations (Lesser, 1984; Brown et al, 1990a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the desipramine therapy and for any signs of toxicity c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.

7) Probable Mechanism: increased desipramine metabolism, decreased carbamazepine metabolism

3.5.1.AM Dexamethasone

1) Interaction Effect: decreased dexamethasone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, Carbamazepine does interfere with the dexamethasone suppression test (Privitera et al, 1982c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased dexamethasone metabolism

3.5.1.AN Dicumarol
1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983c; Cohen & Arms Koch-Weser & Koch-Weser, 1975c; Kendall & Boivin, 1981c; Hansen et al, 1971e). A similar effect may occu
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in c the desired level of anticoagulation.
7) Probable Mechanism: increased dicumarol metabolism

3.5.1.AO Diltiazem
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concomitant administration of carbamazepine and diltiazem may increase carbamazepine leve 72%, resulting in toxicity (Prod Info Tiazac(TM), 1996; Shaughnessy & Mosley, 1992a; Brodie & Macphee, 19 al, 1986; Eimer & Carter, 1987a; Bahls et al, 1991).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine serum levels and clinical signs of carbamazepine toxicity. U levels are 6-12 mg/L; adjust dose accordingly. Nifedipine does not appear to interact with carbamazepine and considered as an alternative to diltiazem.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Concomitant carbamazepine and diltiazem administration may produce elevated serum carbamazepi in neurotoxicity (Brodie & Macphee, 1986; Eimer & Carter, 1987; Ahmad, 1990; Shaughnessy & Mosley, case report, diltiazem 60 mg three times daily elevated the carbamazepine level by 40% higher than bas clinical signs of carbamazepine toxicity. Nifedipine 20 mg three times daily did not produce any adverse Macphee, 1986). In another case report, a patient with a stable carbamazepine dose (800 mg daily) and concentration (8.5 to 10.1 mg/L) was started on diltiazem 30 mg three times a day for atrial fibrillation. Ap weeks later, the patient was admitted to the hospital with mental slowing and speech difficulties. The ser level the next day was 15.5 mg/L. Carbamazepine was consequently reduced to 300 mg daily, which pro level of 8.3 mg/L and resolution of the mental disturbances (Eimer & Carter, 1987). Competitive inhibitior system by diltiazem may be the most likely cause of the elevated carbamazepine serum concentrations.

3.5.1.AP Dothiepin
1) Interaction Effect: decreased dothiepin effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease se antidepressant levels (Leinonen et al, 1991l; Brown et al, 1990i). Although not reported for dothiepin, a simila occur.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the dothiepin therapy and for any signs of toxicity of c Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased dothiepin metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977d). Although not reported specifically for dothiepin, be av potential for a similar interaction exits. Patients on chronic carbamazepine therapy may require increased antidepressants.

3.5.1.AQ Doxacurium

1) Interaction Effect: decreased doxacurium duration of action

2) Summary: It has been demonstrated that in patients taking carbamazepine for at least one month prior to neuromuscular blockers, the recovery time after being given neuromuscular blockers was about 65% faster w control patients (Ornstein et al, 1991a; Prod Info Nuromax(R), 1994).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of doxacurium may be needed in patients receiving carbamazepine.

7) Probable Mechanism: unknown

8) Literature Reports

a) Twenty-seven adult neurosurgical patients participated in a study to determine the effects of doxacuri neuromuscular blockade. Patients were divided into three equal groups, with nine patients having been c therapy for at least one week, nine patients having been on carbamazepine therapy for at least one weel patients serving as controls. All subjects received a bolus intravenous dose of doxacurium 60 mcg/kg du with nitrous oxide, fentanyl, and droperidol. The onset of paralysis was prolonged by 49% in the phenyto not altered in the carbamazepine group. Recovery times were significantly shortened in both anticonvuls recovering approximately twice as fast as the controls. Times from doxacurium administration to 75% rec follows: control group, 203 minutes; phenytoin group, 97 minutes; carbamazepine group, 80 minutes. Sir recovery times were seen for 5%, 25%, 50%, and 90% recovery. Once the recovery from paralysis starte more quickly in the anticonvulsant groups. The 25% to 75% recovery index was increased by 67% in the group and 53% in the phenytoin group when compared to controls (Ornstein et al, 1991).

3.5.1.AR Doxepin

1) Interaction Effect: decreased doxepin effectiveness and possibly increased carbamazepine toxicity (diplop dizziness, tremor)

2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease do (Leinonen et al, 1991d).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the doxepin therapy and for any signs of toxicity of ca Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.

7) Probable Mechanism: increased doxepin metabolism

8) Literature Reports

a) The effect of carbamazepine on doxepin levels were examined in 17 psychiatric inpatients who were minimum of 7 days prior to measurement of baseline antidepressant concentrations. The average daily d was 201.5 mg. Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week perio concentrations were decreased to 46% in patients receiving combination therapy compared to patients r alone (Leinonen et al, 1991c).

3.5.1.AS Doxorubicin Hydrochloride

1) Interaction Effect: decreased carbamazepine plasma concentrations

2) Summary: A 36-year old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin subtherapeutic carbamazepine, phenytoin, and valproic acid concentrations which resulted in tonic-clonic sei the exact mechanism is unknown, possible causes include decreased absorption or accelerated elimination o (Neef & de Voogd-van der Straaten, 1988e).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.

7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine

8) Literature Reports

a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988d).

3.5.1.AT Doxorubicin Hydrochloride Liposome

1) Interaction Effect: decreased carbamazepine plasma concentrations

2) Summary: Although no formal drug interaction studies have been done with doxorubicin hydrochloride lipo may interact with drugs known to interact with the conventional formulation of doxorubicin (Prod Info Doxil(R) old epileptic female undergoing antineoplastic therapy with doxorubicin and cisplatin experienced subtherape carbamazepine, phenytoin, and valproic acid concentrations which resulted in tonic-clonic seizures. Although mechanism is unknown, possible causes include decreased absorption or accelerated elimination of carbama Voogd-van der Straaten, 1988a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Anticonvulsant levels should be closely monitored in patients receiving antineoplast doxorubicin or cisplatin. Doses of carbamazepine may need to be increased.
7) Probable Mechanism: decreased absorption or accelerated elimination of carbamazepine
8) Literature Reports
a) A 36-year old female epileptic patient requiring cisplatin and doxorubicin therapy for papillary adenoc experienced tonic-clonic seizures after two days of antineoplastic treatment. Plasma concentrations of ca valproic acid, and phenytoin were all determined to be subtherapeutic (0.5 mg/L, 24.3 mg/L, and 0.3 mg/ One month later, she was controlled on phenytoin 450 mg daily, carbamazepine 1200 mg daily, and valp daily. During her second course of cisplatin and doxorubicin, she again suffered a tonic-clonic seizure. P concentrations of her anticonvulsants were phenytoin 0.2 mg/L, carbamazepine 3.5 mg/L, and valproic a Three days following her chemotherapy, plasma concentrations of the anticonvulsants had returned to th values. During her sixth and final chemotherapy course, carbamazepine levels remained low (1.4 mg/L) all 15 days of the course (Neef & de Voogd-van der Straaten, 1988).

3.5.1.AU Doxycycline

1) Interaction Effect: decreased doxycycline effectiveness
2) Summary: Chronic carbamazepine therapy may decrease the half-life of doxycycline by 50% (Neuvonen e et al, 1974).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor clinical effectiveness of doxycycline therapy in patients concurrently receivi increased doxycycline dosage might be considered.
7) Probable Mechanism: may increase metabolism doxycycline

3.5.1.AV Efavirenz

1) Interaction Effect: decreased efavirenz plasma concentrations and/or carbamazepine plasma concentratio
2) Summary: Coadministration of carbamazepine and efavirenz resulted in lowered exposures and plasma c both carbamazepine and efavirenz. However, as no dosing recommendations can be made, use of an alterna anticonvulsant should be considered in patients receiving efavirenz (Prod Info SUSTIVA(R) oral capsules, tab
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: The concomitant use of carbamazepine and efavirenz has resulted in reduced plas of carbamazepine and efavirenz. An alternative anticonvulsant should be considered in patients receiving efa adjusted dosing recommendations are available for carbamazepine (Prod Info SUSTIVA(R) oral capsules, tal
7) Probable Mechanism: unknown
8) Literature Reports
a) Coadministration of carbamazepine and efavirenz resulted in decreased exposure and plasma conce carbamazepine in pharmacokinetic studies. In 12 subjects, efavirenz (600 mg orally daily for 14 days) de plasma Cmax, AUC, and Cmin of carbamazepine (200 mg/day for 3 days, 200 mg twice daily for 3 days, for 29 days) by an average of 20% (90% confidence interval (CI), 15 to 24%), 27% (90% CI, 20 to 33%), 24 to 44%), respectively. In 14 subjects, carbamazepine (200 mg/day for 3 days, 200 mg twice daily for 3 mg/day for 15 days) decreased the plasma Cmax, AUC, and Cmin of efavirenz (600 mg orally daily for 3 average of 21% (90% confidence interval (CI), 15 to 26%), 36% (90% CI, 32 to 40%), and 47% (90% CI, respectively. (Prod Info SUSTIVA(R) oral capsules, tablets, 2008).

3.5.1.AW Ergocalciferol

1) Interaction Effect: decreased systemic ergocalciferol (vitamin D) exposure
2) Summary: Coadministration of carbamazepine and vitamin D may reduce exposure to vitamin D and may events related to vitamin D deficiency, including hypocalcemia and secondary hyperparathyroidism. If carban vitamin D are used concomitantly, additional vitamin D supplementation may be necessary (Prod Info FOSAM oral tablets, 2008). Monitoring the patient for signs and symptoms of vitamin D deficiency (ie, hypocalcemia a hyperparathyroidism) may be warranted.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of carbamazepine and vitamin D may reduce exposure to increased ergocalciferol clearance. Consider additional vitamin D supplementation if these agents are used

(Prod Info FOSAMAX PLUS D(TM) oral tablets, 2008). Monitor the patient for adverse events related to vitam including signs and symptoms of hypocalcemia and secondary hyperparathyroidism.
7) Probable Mechanism: increased catabolism of vitamin D

3.5.1.AX Erlotinib
1) Interaction Effect: increased erlotinib clearance and reduced erlotinib exposure
2) Summary: Erlotinib is primarily metabolized by the CYP3A4 isozyme. Coadministration of erlotinib and rifa inducer, decreased the erlotinib AUC by approximately 67% to 80%, which is equivalent to an erlotinib dose c mg in non-small cell lung cancer patients; it also significantly increased erlotinib clearance. Although not direc concomitant use of erlotinib and carbamazepine, also a CYP3A4 inducer, could result in a similar interaction therefore be avoided. If concomitant use is clinically warranted, an increase in erlotinib dose as tolerated at 2 should be considered, while monitoring patient safety. If the erlotinib dose is increased, the dose should be re immediately to the indicated starting dose upon discontinuation of carbamazepine (Prod Info TARCEVA(R) o
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of erlotinib and carbamazepine as this may result in decreas exposure and efficacy. However, if concomitant use is clinically warranted, consider an increase in erlotinib d 2 week intervals and monitor patient's safety. If the erlotinib dose is increased, reduce it immediately to the in dose upon discontinuation of carbamazepine (Prod Info TARCEVA(R) oral tablets, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated erlotinib metabolism by carbamazepine

3.5.1.AY Erythromycin
1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Erythromycin decreases the hepatic clearance of carbamazepine causing elevated carbamaze concentrations and possible toxicity (Hendrick et al, 1983a; MacNab et al, 1987a; Miles & Tennison, 1989a; V 1987a; Wroblewski et al, 1986).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The combination of carbamazepine and macrolide antibiotics should be avoided an given to an alternative antibiotic. If the combination is necessary, carbamazepine levels should be obtained w adding or discontinuing erythromycin and dosage adjustments made accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Toxicity following concomitant administration of carbamazepine and erythromycin was reported in six (Goulden et al, 1986). Toxicity occurred in less than two days with erythromycin therapy in five patients; the interaction was not observed until the eighth day of erythromycin therapy when the dose was double mg/kg/day. Carbamazepine serum concentrations decreased to baseline levels within 8 to 12 hours of di erythromycin, suggesting that normalization of carbamazepine metabolism occurs rapidly.
b) It is suggested that erythromycin inhibits the metabolism of carbamazepine in liver (cytochrome P450 al, 1983). Concomitant administration of erythromycin and carbamazepine in healthy volunteers resulted increases in carbamazepine half-life and 24-hour postdose serum concentrations, as well as decreases i oral clearance (Miles & Tennison, 1989). Decreases in maximum carbamazepine-10,11-epoxide serum c area under concentration-time curve (AUC), and the carbamazepine-10,11-epoxide to carbamazepine ra observed during combined therapy. In this study, carbamazepine was given in daily doses of 300 mg to 4 17 consecutive days; subjects were given placebo erythromycin every six hours on days 12, 13 and 14, t base 250 mg every six hours for the final three days. It is suggested that erythromycin significantly inhibi metabolic pathway required for transformation of carbamazepine to carbamazepine-10,11-epoxide. Wide variability was seen in this study; individual changes in oral clearance ranged from plus 23% to minus 41 unpredictability of this interaction. Close patient monitoring is advised when these two agents are given c when one agent is discontinued.
c) Increases in carbamazepine serum concentrations were observed in four children during concurrent e carbamazepine therapy. All children developed signs of toxicity (nausea, vomiting, ataxia, dizziness) with initiation of erythromycin therapy, which subsided after erythromycin was discontinued and was associat in carbamazepine serum concentrations. The authors suggest that erythromycin inhibits the metabolism The onset of the interaction generally occurred three to four days after addition of erythromycin to the ca regimen (Hendrick et al, 1983).
d) Concomitant carbamazepine and erythromycin stearate therapy was reported to result in carbamazep SIADH in a 41-year-old epileptic woman (Carranco et al, 1985).
e) A further report of the interaction between erythromycin ethylsuccinate and carbamazepine was desc old girl with tonic-clonic seizures (Zitelli et al, 1987). The patient had been maintained on carbamazepine (serum level 12 mcg/mL) and developed symptoms of carbamazepine toxicity (vomiting, lethargy, ataxia, cogwheeling movements) after five days of erythromycin ethylsuccinate therapy (250 mg four times daily increases in carbamazepine serum levels to 26 mcg/mL. Following withdrawal of erythromycin, serum co carbamazepine returned to normal levels, with resolution of symptoms. This article also provides a brief r clinically-relevant erythromycin drug interactions.
f) Two cases describing the interaction of carbamazepine and erythromycin in children resulting in carba

were reported by (Woody et al, 1987). The authors suggest that parents should be advised of the interac medications are frequently prescribed independently by pediatrician and neurologist.

g) Concomitant administration of erythromycin and carbamazepine was reported to result in sinus arrest 10-year-old boy secondary to carbamazepine toxicity (MacNab et al, 1987). The patient recovered follow therapy and the EKG normalized when carbamazepine serum levels returned to the therapeutic range. T preexisting cardiac symptoms.

3.5.1.AZ Estazolam

1) Interaction Effect: decreased estazolam plasma concentrations and reduced effectiveness

2) Summary: Carbamazepine is a potent inducer of cytochrome P450-3A4 and estazolam metabolism is cata coadministration of carbamazepine and estazolam would therefore be expected to reduce estazolam plasma levels (Prod Info ProSom(TM), 2004).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Monitor for signs of benzodiazepine clinical ineffectiveness. Concurrent use of carb estazolam may require higher doses of estazolam. The dose of estazolam should be decreased if carbamaze discontinued.

7) Probable Mechanism: carbamazepine induction of CYP3A-isoform mediated estazolam metabolism

3.5.1.BA Ethinyl Estradiol

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consid breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestran (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sw dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.BB Ethosuximide

1) Interaction Effect: decreased ethosuximide serum concentrations

2) Summary: Two studies have documented that ethosuximide disposition is altered during carbamazepine t decreased steady-state plasma concentrations, decreased half-life, and increased clearance of ethosuximide 1996a; Warren et al, 1980a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Patients receiving concurrent therapy with carbamazepine and ethosuximide may a serum ethosuximide concentrations compared to patients not taking carbamazepine, leading to a decreased If these two agents are used together, careful evaluation of clinical response and serum drug level monitoring

7) Probable Mechanism: carbamazepine induction of cytochrome P450 enzymes

8) Literature Reports

a) In a study of 22 volunteers, the effects of chronic epileptic medication on the pharmacokinetics of eth

evaluated. The study consisted of 10 epileptic patients undergoing chronic treatment with carbamazepin phenobarbital, and 12 healthy control subjects taking no chronic medications. Each subject received a si dose of ethosuximide after an overnight fast. Patients on chronic epileptic therapy had a decreased mea half-life of 29.0 +/- 7.8 hours compared to 53.7 +/- 14.3 hours for control subjects. Patients on chronic ep had higher oral clearance values and slightly decreased apparent volume of distribution values compare patients. The authors postulate that the mechanism of action was due to antiepileptic medication inductic CYP3A (Giaccone et al, 1996).

b) The disposition of ethosuximide was demonstrated to be altered by carbamazepine therapy (Warren Concomitant therapy with carbamazepine 200 mg daily and ethosuximide 250 mg twice daily resulted in ethosuximide steady-state plasma concentrations. The clearance of ethosuximide was shown to increas concomitant decrease in serum half-life. Thus carbamazepine induced the metabolism of ethosuximide a adjustments may be required during concomitant therapy.

3.5.1.BC Etonogestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.BD Etravirine

1) Interaction Effect: decreased etravirine plasma concentrations

2) Summary: Carbamazepine and etravirine should not be coadministered. The combination of carbamazepi may result in significant decreases in etravirine plasma concentrations due to CYP3A4-mediated induction of carbamazepine (Prod Info INTELENCE(TM) oral tablets, 2008).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Carbamazepine and etravirine should not be coadministered. Concomitant use of c etravirine may result in decreased etravirine plasma concentrations and loss of therapeutic effect of etravirine CYP3A4-mediated induction of etravirine by carbamazepine (Prod Info INTELENCE(TM) oral tablets, 2008).

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of etravirine by carbamazepine

3.5.1.BE Etretinate

1) Interaction Effect: decreased etretinate effectiveness

2) Summary: A case report described a possible interaction between carbamazepine and etretinate (Moham Concurrent use resulted in the lack of etretinate efficacy; withdrawal of carbamazepine was followed by the e response to etretinate.

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor for therapeutic efficacy of etretinate. If no clinical response is seen, and etr necessary, consideration might be given to changing to an alternative anticonvulsant regimen.
7) Probable Mechanism: induction of etretinate metabolism
8) Literature Reports
a) A 15-year-old girl with epilepsy and pityriasis rubra pilaris was being treated with carbamazepine 200 acid 100 mg/d when etretinate 30 mg/d was added to her therapy. After 2 months of therapy no clinical i seen, and none of the usual cutaneous side effects of etretinate were noted. Etretinate was discontinued was gradually withdrawn and the valproic acid dose increased to 350 mg/d. Etretinate 30 mg/d was resta weeks a good clinical response and dry lips and mouth, a common side effect, were seen. No etretinate concentrations were reported, and rechallenge was not attempted (Mohammed, 1992).

3.5.1.BF 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.BG Everolimus

1) Interaction Effect: loss of everolimus efficacy
2) Summary: Drugs such as carbamazepine, which is a cytochrome CYP3A4 inducer, may increase the met everolimus, causing decreased everolimus plasma concentrations. Caution should be used when these two a concomitantly. Dosage increase of everolimus is recommended (Prod Info AFINITOR(R) oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Monitor the patient closely or perform additional tests to determine effectiveness of Dosage increase of everolimus is recommended (Prod Info AFINITOR(R) oral tablets, 2009).
7) Probable Mechanism: induction of cytochrome CYP3A4-mediated everolimus metabolism

3.5.1.BH Felbamate

1) Interaction Effect: decreased carbamazepine or felbamate effectiveness
2) Summary: Felbamate reduces carbamazepine levels (Albani et al, 1991a; Graves et al, 1989a; Wilensky e carbamazepine decreases felbamate levels (Prod Info Felbatol(R), 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Consider monitoring carbamazepine levels following the addition of felbamate thera carbamazepine concentrations may be reduced, there is an increase in the active metabolite (carbamazepine concentration, such that the overall effectiveness of carbamazepine may not change.
7) Probable Mechanism: increased carbamazepine or felbamate metabolism
8) Literature Reports
a) The manufacturer reports that a 50% increase in felbamate clearance and a 40% decrease in felbam trough concentration occurs when carbamazepine is added to felbamate therapy. Additionally, felbamate decrease in the steady-state plasma concentrations of carbamazepine and an increase in the steady-sta epoxide plasma concentration (Prod Info Felbatol(R), 2000).
b) Four patients who were receiving carbamazepine, phenytoin, and felbamate have been described. Fo discontinuation of phenytoin, felbamate clearance decreased 21%. Carbamazepine dosage was reduced additional felbamate clearance of 16.5% (Wagner et al, 1991).
c) Felbamate has been reported to increase carbamazepine metabolism. The effect of felbamate 3000 r carbamazepine levels in four patients on monotherapy was studied. Carbamazepine levels had previous at 4 to 12 mcg/mL with dosages of 800 to 1800 mg carbamazepine daily. Carbamazepine levels were re of 25% with concurrent use; this effect was evident within one week of initiation of felbamate and plateau weeks. Felbamate appeared to reduce carbamazepine concentrations and increase carbamazepine-epo concentrations without affecting free fraction (Albani et al, 1991). Similar results were reported in anothe al, 1989).
d) 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, 1990d; Van Dyke et al, 1991d; 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, 1987d; Ramsay et al, 1990d; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.BI Felodipine

1) Interaction Effect: decreased felodipine effectiveness

2) Summary: Several studies have shown that concurrent use carbamazepine with some but not all calcium (nimodipine, felodipine) has resulted in decreased levels of the calcium channel blocker (Capewell et al, 1987 1988a; Woodcock et al, 1991; Tartara et al, 1991a).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clinical response to felodipine with dose adjustments as needed to achieve cardiovascular response. Nifedipine does not appear to interact with carbamazepine and may be considered to felodipine.

7) Probable Mechanism: increased felodipine metabolism

8) Literature Reports

a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 was comprised of healthy 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 first-pass metabolism. The nimodipine AUCs were increased by 50% in the valproate-treated group.

b) Maximum plasma concentrations of felodipine were considerably lower in 10 epileptic patients (1.6 nr anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital) than in 12 healthy volunteers (8.7 nm administration of oral felodipine 5 mg twice daily for four days to both groups (Capewell et al, 1987). The the felodipine plasma concentration-time curve at 12 hours postdose was reduced from 33 nmol/L/hr in t nmol/L/hr in epileptics on anticonvulsant medications (Saltiel et al, 1988).

3.5.1.BJ Fentanyl

1) Interaction Effect: decreased plasma concentrations of fentanyl

2) Summary: Induction of fentanyl metabolism by carbamazepine, a cytochrome P450 inducer, may cause ir of fentanyl (Prod Info Duragesic(R), 2001).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Caution is advised when administering fentanyl to patients receiving carbamazepin adjustments should be considered if necessary.

7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of fentanyl

3.5.1.BK Fluconazole

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)

2) Summary: Several cases of carbamazepine toxicity attributed to the coadministration of fluconazole have (Finch et al, 2002a; Nair & Morris, 1999a; Ulivelli et al, 2004). Fluconazole inhibits cytochrome P450 3A4 enz for carbamazepine metabolism. A similar interaction has also been reported between fluconazole and phenyt

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Consider monitoring carbamazepine levels and symptoms of carbamazepine toxicit addition of fluconazole.

7) Probable Mechanism: fluconazole inhibition of cytochrome P450 3A4-mediated carbamazepine metabolis

8) Literature Reports

a) A 33-year-old male with mental retardation and a history of seizures had been taking carbamazepine times daily for more than five years. His last carbamazepine concentration before the initiation of flucona 11.1 mcg/mL, which was consistent with his past levels. Fluconazole 150 mg daily, ciprofloxacin 250 mg oral steroid taper were prescribed for a skin eruption which was thought to be candidiasis. Ciprofloxacin after two days since no clinical improvement was noted. By the end of the third day of fluconazole therap lethargic and unarousable to painful stimuli. A carbamazepine concentration was measured at 24.5 mcg/ was discontinued and carbamazepine was held for 24 hours. By the next day, the carbamazepine conce mcg/mL and his symptoms had resolved. He was restarted on his prior dose of carbamazepine and four level of 11.7 mcg/mL (Nair & Morris, 1999).

b) Fluconazole, an inhibitor of the cytochrome P450 enzyme system (CYP450), inhibits the metabolism but undergoes metabolism itself via the CYP3A4 isoenzyme. A 38-year-old mentally retarded male was hospital because of coffee ground emesis. His medications included lansoprazole, ranitidine, carbamaze three times a day and 400 mg at bedtime), cisapride, clonazepam, docusate, lactulose, dantrolene, and tablet. The serum carbamazepine level on admission was 6 mcg/mL. The patient seized and when seizu carbamazepine dose increased to 1000 mg/day with no further seizure activity. On hospital day 24, fluco initiated at 200 mg/day for severe tinea cruris. Three days later fluconazole was increased to 400 mg/da culture was positive for candida albicans. After 10 days of fluconazole therapy the carbamazepine level The patient showed no signs of toxicity. Carbamazepine was decreased to 200 mg four times daily whic therapeutic carbamazepine levels. He was discharged on day 45 of hospitalization. This case report sug elevations in carbamazepine serum concentrations can occur with concomitant fluconazole therapy (Finc

c) Addition of fluconazole to a stable drug regimen containing carbamazepine resulted in an increased c plasma level with associated symptoms of carbamazepine toxicity (ataxia, nystagmus, diplopia, nausea, year-old female with a history of partial epilepsy had been taking carbamazepine 1600 mg/day, lamotrigi and barbexaclone 100 mg/day for many years without incident. The carbamazepine plasma level drawn to initiation of fluconazole was approximately 7.5 mcg/mL. Fluconazole was initiated at 150 mg/day for tr corporis. On the first day of fluconazole administration the patient noted episodes of blurred vision and d head movements. After 11 days of fluconazole therapy the patient complained of severe diplopia, oscillo vomiting and gait instability. Lamotrigine and barbexaclone plasma levels remained mostly unchanged, b carbamazepine plasma level increased to approximately 18.5 mcg/mL. Neurological exam revealed a ga nystagmus and smooth pursuit impairment. Twenty four hours after fluconazole withdrawal, carbamazep decreased to approximately 8 mcg/mL and neurological symptoms improved (Ulivelli et al, 2004).

3.5.1.BL Flunarizine

1) Interaction Effect: increased carbamazepine serum levels and possible toxicity (ataxia, nystagmus, diplop vomiting, apnea, seizures, coma)
2) Summary: Among patients comedicated with flunarizine and carbamazepine, a mean increase of 0.22 mc carbamazepine serum levels was noted (Pledger et al, 1994a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Continue routine monitoring of carbamazepine serum levels. Some dose adjustmer both clinical symptoms and laboratory findings suggest carbamazepine toxicity.
7) Probable Mechanism: unknown
8) Literature Reports

a) During a 24-week trial of adjunctive flunarizine added to regimens consisting of either carbamazepine both, only patients in the group receiving carbamazepine-flunarizine showed a modest increase in mean serum levels of 0.22 mcg/mL compared to baseline. A parallel placebo-carbamazepine group showed a 0.57 mcg/mL (Pledger et al, 1994).

3.5.1.BM Fluoxetine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: The addition of fluoxetine to carbamazepine therapy has increased carbamazepine concentrati effects, including diplopia, blurred vision, dizziness, and tremors in some reports (Grimsley et al, 1991a; Gerr Pearson, 1990b). Conversely, no changes in steady state carbamazepine levels have been reported with the fluoxetine (Spina et al, 1993c). Symptoms of serotonin syndrome (hypertension, hyperthermia, myoclonus, m changes) have also been reported with this combination (Dursun et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore carbamazepine toxicity when fluoxetine is added to therapy. Carbamazepine levels should be considered wit weeks of adding or discontinuing fluoxetine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) An interaction between fluoxetine and carbamazepine was reported in six normal volunteers (Grimsle Carbamazepine was given for 28 days, and fluoxetine was added to the regimen on day 7. The addition daily to carbamazepine 400 mg daily resulted in an increase in the area under the concentration-time cu carbamazepine and carbamazepine-epoxide and a decrease in clearance of carbamazepine. No signific observed in absorption, volume of distribution or elimination rate constant, indicating that fluoxetine inhib of carbamazepine.

b) The effect of fluoxetine 20 mg daily was studied for three weeks in eight epileptic patients who were s carbamazepine therapy (Spina et al, 1993b). Steady-state plasma levels of carbamazepine and its epoxi were not significantly changed with concurrent use of fluoxetine. These results differ from previous repor speculate that chronic carbamazepine administration may have resulted in enzyme induction that caused of fluoxetine, thereby lowering the chances of a metabolic interaction. Unfortunately fluoxetine levels wer

c) An interaction between fluoxetine and carbamazepine was reported in two patients receiving chronic dosages of 600 mg and 1000 mg daily respectively. Within 7 to 10 days of initiation of fluoxetine 20 mg c developed symptoms of carbamazepine toxicity. Symptoms disappeared within two weeks in one patient carbamazepine dosage reduction by 200 mg daily; in the other patient, fluoxetine was discontinued with resolution within two weeks (Pearson, 1990a).

d) Two cases of parkinsonism were reported after fluoxetine was added to an existing carbamazepine r patient, a 74-year old man, developed symptoms three days after fluoxetine 20 mg per day was added t month regimen of carbamazepine 200 mg twice daily. The patient developed cogwheel rigidity, a mask-li parkinsonian gait. After discontinuation of fluoxetine and treatment with dexetimide, the patient showed c hypertonia of the arms 17 days later. The other patient, a 53-year old woman, developed parkinsonian s fluoxetine 20 mg per day was added to an existing regimen of carbamazepine 200 mg twice daily. The p been taking thioridazine 275 mg per day which was stopped when fluoxetine was added. The patient dev rigidity and a mask-like face nine days after initiation of fluoxetine therapy (Gernaat et al, 1991).

e) A female patient experienced a drug interaction 14 days after she had fluoxetine 20 mg added to a re carbamazepine 200 mg daily. The patient presented with symptoms of serotonin syndrome, such as unc shivering, agitation, incoordination, myoclonus, hyperreflexia, and diaphoresis. The patient also had leuk thrombocytopenia. After discontinuation of fluoxetine, all symptoms of serotonin syndrome and hematolo resolved over the next 72 hours (Dursun et al, 1993).

3.5.1.BN Fluvoxamine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Several cases have been reported in which fluvoxamine appeared to cause increased carbama symptoms of carbamazepine toxicity (Martinelli et al, 1993; Fritze et al, 1991b). However, one study of eight e found no such increase in carbamazepine levels with three weeks of concurrent use (Spina et al, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential to increase carbamazepine levels, patients should be monitore carbamazepine toxicity when fluvoxamine is added to therapy. Carbamazepine levels should be considered v discontinuing fluvoxamine, with dosage adjustments made as indicated.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) The addition of fluvoxamine to a constant dosage of carbamazepine in three patients caused an incre carbamazepine levels resulting in symptoms of toxicity (Fritze et al, 1991a). The authors concluded that inhibition of carbamazepine metabolism. However, (Spina et al, 1993) found no increase in carbamazepi epileptic patients who were given fluvoxamine 100 mg daily or fluoxetine 20 mg daily with carbamazepin

3.5.1.BO Fosamprenavir

1) Interaction Effect: reduced effectiveness of fosamprenavir due to reduced serum concentrations
2) Summary: Fosamprenavir is a prodrug of amprenavir and is susceptible to amprenavir-associated drug in Coadministration of carbamazepine and fosamprenavir may result in reduced amprenavir serum concentratio LEXIVA(R) oral solution, oral tablets, 2009).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when prescribing carbamazepine to patients who take fosamprenavir. of carbamazepine and fosamprenavir may cause reduced amprenavir plasma concentrations (Prod Info LEX solution, oral tablets, 2009).
7) Probable Mechanism: induction of CYP3A4-mediated amprenavir metabolism

3.5.1.BP Fosaprepitant

1) Interaction Effect: decreased plasma concentrations and efficacy of aprepitant
2) Summary: Fosaprepitant is a prodrug of aprepitant, which is a CYP3A4 substrate. Coadministration of wit inducer, such as carbamazepine, should be approached with caution as this may lead to decreased aprepita concentrations and efficacy (Prod Info EMEND(R) IV injection, 2008).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution if carbamazepine and fosaprepitant are coadministered as this may lea aprepitant levels and decreased efficacy (Prod Info EMEND(R) IV injection, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated aprepitant metabolism

3.5.1.BQ Fosphenytoin

1) Interaction Effect: decreased/increased phenytoin concentrations, decreased carbamazepine concentratio
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). Concurrent use of phenytoin and carbamazepine may carbamazepine levels (Zielinski & Haidukewych, 1987b; Randall & Tett, 1993a). The addition of carbamazepi therapy may decrease (Hansen et al, 1971d) or increase (Browne et al, 1988a) phenytoin levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Serum levels of both phenytoin and carbamazepine should be measured after initia discontinuation of either agent, with appropriate dosage adjustment made accordingly. Serum levels should a following dosage adjustments and periodically thereafter.
7) Probable Mechanism: altered metabolism
8) Literature Reports

a) Twenty-four epileptic patients who were stabilized on phenytoin (PHT) and had carbamazepine (CBZ drug regimen were studied (Zielinski et al, 1985). The mean phenytoin level increased from 13.89 +/- 4.6 (35.9% increase). The effect of carbamazepine on phenytoin in an individual is unpredictable; 12 of the s change in phenytoin levels while the other 12 patients showed an average increase of 81.3% in phenyto Five of the patients with increased levels had symptoms of acute phenytoin toxicity.

b) Concomitant administration of carbamazepine and phenytoin has been reported to result in a dual int simultaneous effects of inhibition of phenytoin metabolism by carbamazepine and induction of carbamaz by phenytoin. The result is potential phenytoin intoxication and significant reductions of carbamazepine p concentrations to subtherapeutic levels. These dual effects appear to be especially significant when phe levels approach a change from linear to saturation kinetics. It is suggested that the interaction may be av minimized by adjusting phenytoin plasma levels to approximately 13 mcg/mL prior to the addition of carb regimen or increasing carbamazepine doses (Zielinski & Haidukewych, 1987).
c) Factors influencing simultaneous plasma concentrations of carbamazepine and its epoxide metabolite (McKauge et al, 1981) and it was found that plasma carbamazepine concentrations were significantly lov taking carbamazepine and phenytoin than those taking carbamazepine alone. In contrast to another stuc epoxide levels were unaltered (Pynnonen et al, 1980). Other researchers studied carbamazepine plasma four groups of epileptic patients on a variety of anticonvulsants (Christiansen & Dam, 1973). Their results administration of phenytoin or phenobarbital to patients receiving carbamazepine results in a significant carbamazepine plasma concentration when compared to patients receiving carbamazepine alone. It sho however, that some subjects in the trial were treated with carbamazepine for only one week prior to the i phenytoin. Carbamazepine has been shown to induce its own metabolism for up to 30 days after the initi thus lowering carbamazepine plasma concentration (Pynnonen et al, 1980). This may account for some carbamazepine plasma concentration in subjects also receiving phenytoin.
d) A prospective controlled study of the effects of reduction and discontinuation of phenytoin and carbar levels of concomitant antiepileptic drugs was conducted (Duncan et al, 1991). Phenytoin discontinuation 48% increase in total carbamazepine concentration and a 30% increase in free carbamazepine concentr change in carbamazepine epoxide concentrations. The authors suggest that phenytoin is a strong induce enzymes metabolizing carbamazepine to carbamazepine epoxide, but has less of an effect on the epoxi enzyme. This results in elevations in carbamazepine-epoxide/carbamazepine ratios in patients on conco Conversely, when carbamazepine was discontinued, phenytoin concentrations decreased by a mean of change in free fraction. The authors propose that this may result from inhibition of phenytoin metabolism carbamazepine. There appeared to be no impact on protein binding of either drug. Similar results were r researchers in 49 patients on concomitant phenytoin and carbamazepine therapy (Ramsay et al, 1990a)
e) 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, 1990f; Van Dyke et al, 1991f; Finr 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, 1987f; Ramsay et al, 1990f; Spina et al, 1996e combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.BR 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 wh 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-r 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
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.BS Haloperidol

1) Interaction Effect: decreased haloperidol effectiveness

2) Summary: In a case report, the addition of carbamazepine to patients stabilized with haloperidol resulted i
of haloperidol levels by 60%. Two other case reports and a clinical study supported this finding, while a third
(Kahn et al, 1990a; Arana et al, 1986a; Fast et al, 1986; Klein et al, 1984; Hesslinger et al, 1999a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for the therapeutic efficacy of haloperidol following the addition of carbama
haloperidol dosage may be required in some clinical situations.

7) Probable Mechanism: increased cytochrome P450 2D6 and 3A4-mediated haloperidol metabolism

8) Literature Reports

a) Serum haloperidol levels of 14 schizophrenic patients dropped an average of 50% when carbamazep
their therapy. Haloperidol doses ranged from 2 mg to 20 mg daily and the carbamazepine dose was adju
of 8 to 12 mcg/mL. The drop in haloperidol levels resulted in the worsening of one patient's condition. Tw
significant symptom reduction while on carbamazepine, despite the decrease in the haloperidol levels. T
may have been due to direct effects of the carbamazepine, or as a secondary effect due to the lowering
levels. The authors recommend monitoring serum medication levels when administering haloperidol in c
carbamazepine (Kahn et al, 1990).

b) Serum haloperidol levels of seven patients treated for psychosis fell when carbamazepine was addec
Haloperidol doses ranged from 10 mg to 40 mg daily and carbamazepine doses ranged from 400 mg to
After carbamazepine was added, haloperidol levels decreased by 19% to 100%. The two patients whose
undetectable levels had a marked worsening of symptoms. Careful monitoring should take place if carba
to haloperidol therapy (Arana et al, 1986).

c) Concomitant administration of haloperidol and carbamazepine as reported to result in neurotoxicity (c
speech, concentration difficulties) in a 37-year-old woman with cerebral palsy and dipolar disorder (Brayl
1987). Withdrawal of carbamazepine resulted in subsidence of symptoms on this second occasion. It is s
interaction occurred at the level of the CNS, as opposed to toxic effects of either drug alone, as carbama
levels were subtherapeutic during the toxic episodes and due to the fact that carbamazepine is reported
haloperidol metabolism. In addition, the patient received higher doses of carbamazepine following withdr
without the occurrence of toxic effects. Cerebral palsy may have been a predisposing factor to the intera

d) Twenty-seven schizophrenic patients enrolled in a study to determine the effects of carbamazepine a
the plasma levels of haloperidol and the psychopathologic outcome. Following a four-day washout perioc
assigned to receive treatment for four weeks with haloperidol monotherapy, haloperidol with carbamazep
with valproic acid. Doses of haloperidol remained stable throughout the study, and the doses of carbama
valproic acid were titrated to a plasma level of 6 to 12 mg/L and 50 to 100 mg/L, respectively. When adm
carbamazepine, haloperidol plasma levels decreased by 45% (from 7.6 ng/mL to 4.6 ng/mL) over the 28
Decreases in the rating scores on the Positive subscale of the Positive and Negative Syndrome Scale (p
significant during the carbamazepine phase of the study, indicating that the coadministration of carbama
haloperidol may worsen the clinical outcome compared to haloperidol monotherapy (Hesslinger et al, 19

3.5.1.BT Hydrochlorothiazide

1) Interaction Effect: hyponatremia

2) Summary: Concomitant administration of carbamazepine and diuretics (hydrochlorothiazide or furosemide
reported to result in symptomatic hyponatremia in epileptic patients (Yassa et al, 1987). It is felt that a synerg
diuretics and carbamazepine is responsible for occurrence of the hyponatremia, and that epileptic patients m
to developing this complication than are patients with affective disorders, due to the higher doses of carbama
in epilepsy.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor electrolytes during concurrent therapy. Consider discontinuing the diuretic
alternative anticonvulsant if appropriate.

7) Probable Mechanism: additive hyponatremic effects

3.5.1.BU Hydrocortisone

1) Interaction Effect: decreased hydrocortisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982). Although not specifically reported for hydrocortisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased hydrocortisone metabolism

3.5.1.BV Imatinib

1) Interaction Effect: decreased plasma levels of imatinib
2) Summary: Concurrent administration of imatinib and carbamazepine may result in a significant decrease i imatinib due to induction of CYP3A4-mediated imatinib metabolism. Caution is advised when these two agen coadministered. Alternatives to carbamazepine, with less enzyme induction potential, should be considered. ' used concurrently with carbamazepine, consider an increase in imatinib dose by at least 50% to maintain the and monitor clinical response closely (Prod Info GLEEVEC(R) oral tablets, 2005).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of imatinib and carbamazepine, a CYP3A4 inducer, may result in reduction in exposure to imatinib. Caution is advised when these two agents are coadministered. Consider us carbamazepine with less enzyme induction potential. However, if imatinib is used concurrently with carbamaz increase in imatinib dose by at least 50% to maintain therapeutic efficacy and monitor clinical response close
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of imatinib by carbamaze

3.5.1.BW Imipramine

1) Interaction Effect: decreased imipramine effectiveness
2) Summary: In a retrospective study of 36 children suffering from hyperactivity secondary to attention deficit antidepressant levels (imipramine and its metabolite desipramine) were decreased by 50% in children receivi compared to levels obtained with imipramine alone (Brown et al, 1990h).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for clinical efficacy of the imipramine therapy and for any signs of toxicity of Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased imipramine metabolism
8) Literature Reports
a) In a retrospective study, of 36 children with attention deficit hyperactivity disorder, the average plasm imipramine was significantly lower in patients treated with carbamazepine concurrently. The average dos was 1.3 mg/kg in patients receiving imipramine alone, compared to an imipramine dose of 1.8 mg/kg in p both imipramine and carbamazepine. The plasma level of imipramine, desipramine, and total tricyclic ant plasma levels were significantly lower in patients treated with carbamazepine concurrently. The dose of i need to be increased if carbamazepine is added to therapy and the dose of imipramine may need to be carbamazepine is stopped (Brown et al, 1990g).
b) Combination therapy with carbamazepine decreases steady-state total serum concentrations of imipr concentrations of desipramine. Thirteen patients were treated with imipramine 2 mg/kg/day for 3 weeks, carbamazepine 400 mg/day was added. The ratios of total concentrations of imipramine to desipramine and two weeks after carbamazepine intake (0.7 +/- 0.41 versus 0.63 +/- 0.36; p greater than 0.05). Free imipramine and desipramine were elevated after the addition of carbamazepine. Despite lowever imiprar desipramine total concentrations, the combination treatment with carbamazepine in depressed patients i tolerated. Dosage increase of imipramine does not appear to be necessary in the depressed patients inc (Szymura-Oleksiak et al, 2001).

3.5.1.BX Indinavir

1) Interaction Effect: decreased indinavir plasma concentrations and an increased risk of antiretroviral therap
2) Summary: Inducers of cytochrome P450 3A4 enzymes, including carbamazepine, may decrease the plasi of indinavir during concurrent therapy. Decreased plasma concentrations of indinavir may cause antiretrovira Caution should be observed when these two drugs are given together. If alternative therapy is not possible, c adjustments, therapeutic drug monitoring, and close clinical observation should be utilized to reduce adverse consequences (Prod Info Crixivan(R), 2004; Hugen et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent treatment with indinavir and carbamazepine should be undertaken caut patient for an adequate response to indinavir therapy. Alternatives to carbamazepine therapy should be cons

7) Probable Mechanism: induction of cytochrome P450 3A4-mediated indinavir metabolism
8) Literature Reports
a) A 48-year-old HIV-positive male was started on triple therapy consisting of indinavir 800 mg every eig lamivudine 150 mg twice daily, and zidovudine 200 mg three times daily with a resulting undetectable HI later. Because of the development of postherpetic neuralgia, carbamazepine 200 mg daily was initiated a approximately 10 weeks. His indinavir concentrations drawn during carbamazepine therapy were 25% ar population values, whereas before carbamazepine was started, they were slightly below the lower limit o population curve. Two weeks following the discontinuation of carbamazepine, the HIV-RNA was detectal to lamivudine therapy was observed in a blood sample. A further increase in HIV-RNA prompted his anti to be switched to nevirapine, didanosine, and zidovudine. Carbamazepine is an inducer of the cytochrom enzyme system, while indinavir is a substrate of this pathway. Decreased indinavir concentrations cause between indinavir and carbamazepine is the most likely explanation for the increased HIV-RNA and the d lamivudine resistance in this patient (Hugen et al, 2000).

3.5.1.BY Influenza Virus Vaccine

1) Interaction Effect: increased carbamazepine serum concentrations
2) Summary: Influenza vaccine has been reported to cause a decrease in the elimination and an increase in carbamazepine, resulting in an increase in the carbamazepine plasma concentration (Jann & Fidone, 1986a; 1990). It has been proposed that the immune response after influenza vaccination may cause a depression o P450 isoenzymes responsible for oxidation of carbamazepine (Robertson, 2002a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: The majority of patients might experience only a transient and slight increase in car levels. No routine monitoring appears necessary.
7) Probable Mechanism: decreased cytochrome P450-mediated metabolism of carbamazepine
8) Literature Reports
a) In a study conducted on mentally retarded residents who were receiving single-drug anticonvulsant th vaccine resulted in increased levels of phenytoin, phenobarbital, and carbamazepine. Prior to vaccinatio carbamazepine concentration was 6.17 mcg/mL. Serum carbamazepine concentrations were measured to vaccination (day 0), and on days 7, 14, and 28. On day 7, the mean carbamazepine concentration hac 6.89 mcg/mL. By day 14 and 28, concentrations had increased and decreased to 9.04 mcg/mL and 8.65 respectively. Similar increases in plasma concentrations were observed in patients receiving phenobarbi The proposed mechanism for the increased carbamazepine concentration is that influenza vaccine decre of hepatic enzymes which are responsible for carbamazepine metabolism (Jann & Fidone, 1986).
b) Influenza vaccination may significantly increase carbamazepine blood levels. A report describes a ca carbamazepine toxicity that developed 13 days after administration of the influenza vaccine. A female 14 old complained of ataxia and increased lethargy. Her drug regimen included carbamazepine for partial c and gabapentin. Thirteen days prior to her complaints the patient received the inactivated influenza vacc manufactured by Aventis Pasteur, Inc (Swiftwater, PA). Thirteen days later the child complained of naus subsequently vomited. She was dizzy, had slurred speech, became lethargic and poorly responsive. In th department her CBZ level was 27.5 mcg/mL and a urine drug screen was positive for TCAs and cocaine intubated, received IV fluids and activated charcoal. Four days after admission her CBZ level was 9.1 mc recovered and remains seizure free on her former dose of CBZ (400 mg am and 600 mg pm) and gabap TID). The author concludes that the patients immune response after influenza vaccination caused a depr isoenzymes responsible for oxidation of CBZ. This resulted in a rise in CBZ levels and observed CBZ tox instances of CBZ toxicity may be secondary to inhibition of hepatic clearance by interferon production (R

3.5.1.BZ Iproniazid

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998b; Thweatt, 1986b). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995e; Barker & Eccleston controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proven refractory to mu therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc

carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995d).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984d).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru presented (Joffe et al, 1985b). Conversely, five patients on tranylcypromine were reported to need a mea carbamazepine 1040 mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patient phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 et al, 1992b).

3.5.1.CA Irinotecan

1) Interaction Effect: substantially decreased exposure to irinotecan and its active metabolite SN-38 and may irinotecan efficacy

2) Summary: Concomitant use of carbamazepine and irinotecan has resulted in a substantially decreased ex irinotecan and its active metabolite SN-38 in both adult and pediatric patients. This decreased exposure is du carbamazepine induction of CYP3A4-mediated metabolism of irinotecan and may decrease the efficacy of iri An alternative non-enzyme inducing anticonvulsant should be considered. Substitution should be implemente weeks prior to initiation of irinotecan therapy (Prod Info Camptosar(R) Injection, 2004).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Consider a non-enzyme inducing anticonvulsant alternative for those patients requi therapy. Begin substitution at least 2 weeks prior to initiation of irinotecan therapy. The appropriate starting d for patients on CYP3A4 inducing anticonvulsants has not yet been established.

7) Probable Mechanism: induction of CYP3A4-mediated irinotecan metabolism

3.5.1.CB Isocarboxazid

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Info Marplan(R), 1998). Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure ac Parnate(R), 1995h; Prod Info Tegretol(R), 1998i; Thweatt, 1986i). However, there is preliminary evidence tha of carbamazepine and an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 19 Eccleston, 1984s). Further controlled studies are needed.

3) Severity: contraindicated

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression who had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995r).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984r).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985i). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992i). Four other patier phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.CC Isoniazid

1) Interaction Effect: elevated carbamazepine levels and toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: Concomitant carbamazepine and isoniazid therapy has been reported to produce increases in serum concentrations and toxicity at isoniazid doses of 200 mg daily or more (Block, 1982a; Wright et al, 198 changes were noted in 10 of 13 epileptics following the addition of isoniazid 200 mg daily to their maintenanc therapy (Valsalan & Cooper, 1982). Carbamazepine may increase isoniazid liver toxicity (Wright et al, 1982a)

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Watch for signs of carbamazepine toxicity such as nausea, vomiting, drowsiness ar consider monitoring serum carbamazepine levels following the addition of isoniazid; lower carbamazepine do required. Conversely, if isoniazid is discontinued or the dosage reduced, carbamazepine levels should be mo dose adjusted accordingly. Usual anticonvulsant levels are 6-12 mg/L.

7) Probable Mechanism: decreased carbamazepine metabolism

8) Literature Reports

a) Five days after concurrent use of carbamazepine with isoniazid 300 mg daily, a patient presented wit headache, vomiting, drowsiness, and confusion. Carbamazepine serum levels had increased from 5 mcg mcg/mL. The patient was also receiving phenytoin, with levels increasing from 13 to 18 mcg/mL; this was in the therapeutic range and not related to an interaction with carbamazepine. Upon withdrawal of the iso carbamazepine level decreased to 6 mcg/mL within seven days, and the phenytoin level remained at 18 patient's symptoms disappeared at day 2. However, it is difficult to rule out the effects of phenytoin as a p toxicity, since some patients may present with toxic symptoms at these serum concentrations (Block, 198

b) Administration of isoniazid to a patient receiving chronic carbamazepine therapy resulted in significar carbamazepine clearance as well as delayed isoniazid-induced hepatotoxicity. This was presumably rela carbamazepine's microsomal enzyme metabolism by isoniazid and increased metabolism of isoniazid to metabolite (acetylhydrazine) by carbamazepine (Wright et al, 1982).

c) One study reported a case of carbamazepine toxicity following the addition of antituberculosis medica anticonvulsant medication. Carbamazepine levels had previously been 8.5 to 9.5 mcg/mL without eviden Isoniazid 300 mg daily was well tolerated for three days prior to the introduction of rifampin 600 mg daily. of initiation of rifampin, the patient developed nausea, ataxia, confusion and drowsiness. The carbamaze noted to be 16.9 mcg/mL. The authors suggest that rifampin may have augmented the enzyme inhibiting isoniazid, resulting in carbamazepine toxicity (Fleenor et al, 1991).

3.5.1.CD Itraconazole

1) Interaction Effect: loss of itraconazole efficacy

2) Summary: Concomitant administration of itraconazole and carbamazepine has resulted in subtherapeutic concentrations and therapeutic failure (Hay et al, 1988; Tucker et al, 1992a). Itraconazole is a known inhibito P450 3A4 enzyme system, which is the major isoform responsible for the metabolism of carbamazepine. Bas metabolic pathways, it seems possible that itraconazole could inhibit the metabolism of carbamazepine, resu plasma concentrations of carbamazepine (Prod Info Sporonox(R), 2002; Prod Info Tegretol(R), 1997). Howev not been reported to date.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Monitor antifungal therapy for clinical efficacy; larger itraconazole doses may be rec situations.

7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated itraconazole metab

8) Literature Reports

a) Interactions between azole antifungals and rifampin, phenytoin, and carbamazepine have been descr 1992). Twelve patients receiving a combination of these agents for systemic mycoses experienced drug resulted in substantial decreases in the azole serum concentrations. All four of the patients who received concurrent phenytoin or carbamazepine failed to respond to the antifungal therapy or suffered a relapse These four patients had undetectable or substantially lower serum concentrations of the azole compared measured during therapy with the azole alone.

3.5.1.CE Ixabepilone

1) Interaction Effect: decreased ixabepilone plasma concentrations

2) Summary: Ixabepilone is a CYP3A4 substrate. Coadministration of a strong CYP3A4 inducer, such as car ixabepilone may result in decreased ixabepilone plasma concentrations leading to subtherapeutic ixabepilone using alternative therapeutic agents with low enzyme induction potential for coadministration with ixabepilone IXEMPRA(TM) IV injection, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of carbamazepine, a strong CYP3A4 inducer, and ixabe substrate, may result in decreased ixabepilone plasma concentrations and consequently, subtherapeutic leve

alternative therapeutic agents with low enzyme induction potential for coadministration with ixabepilone (Proc (TM) IV injection, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated ixabepilone metabolism

3.5.1.CF Ketoconazole
1) Interaction Effect: increased carbamazepine serum levels
2) Summary: Ketoconazole, a CYP 3A4 enzyme system inhibitor, can inhibit the metabolism of carbamazepi plasma carbamazepine levels would be expected (Prod Info Tegretol(R), 2002).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If carbamazepine and ketoconazole are administered together, carefully monitor se carbamazepine levels and monitor the patient for signs and symptoms of toxicity.
7) Probable Mechanism: inhibition of CYP 3A4 mediated metabolism of carbamazepine

3.5.1.CG Lamotrigine
1) Interaction Effect: reduced lamotrigine efficacy, loss of seizure control, and a potential risk of neurotoxicity nystagmus, ataxia)
2) Summary: The clearance of lamotrigine may double during concomitant therapy with carbamazepine (Goa Rambeck & Wolf, 1993; Ramsay et al, 1991a; Mikati et al, 1989a; Jawad et al, 1987a). In addition, increased concentrations of carbamazepine-10,11-epoxide (an active metabolite of carbamazepine) and neurotoxicity h during concomitant administration of carbamazepine and lamotrigine (Wolf, 1992; Warner et al, 1992). Other found that lamotrigine had no effect on either carbamazepine or its metabolite (Schapel et al, 1991; Pisani et & Boreus, 1997a). While lamotrigine has no appreciable effect on the steady-state carbamazepine concentra carbamazepine decreases the lamotrigine steady-state level by 40% (Prod Info Lamictal(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor seizure control and follow patients for signs of neurotoxicity (nausea, vertig ataxia). Anticipate a possible need to increase lamotrigine doses and/or reduce carbamazepine doses. It may to monitor the serum concentration of both carbamazepine and its metabolite, carbamazepine-10,11-epoxide effects have been associated with carbamazepine-10,11- epoxide serum levels above 9 micromoles/liter. Wh combination with an enzyme-inducing antiepileptic agent, the manufacturer recommends an initial lamotrigine once daily for the first two weeks for adult patients, followed by 50 mg twice daily for the third and fourth weel 100 mg daily every two weeks to a total daily dose of 300 mg to 500 mg administered in two divided doses.
7) Probable Mechanism: hepatic induction by carbamazepine of lamotrigine metabolism; possible alteration elimination by lamotrigine
8) Literature Reports
a) While lamotrigine alone has a steady-state elimination half-life of between 25 to 37 hours, coadminist carbamazepine reduces the half-life to approximately 14 or 15 hours (Binnie et al, 1986; Jawad et al, 198 Lamotrigine clearance ranged from 0.021 to 0.035 L/h/kg (0.35 to 0.59 mL/min/kg) in healthy volunteers alone (Cohen et al, 1987; Posner et al, 1989; Posner et al, 1991). Comparable values during combinatio from 0.044 to 0.084 L/h/kg (0.73 to 1.4 mL/min/kg) (Jawad et al, 1987; Mikati et al, 1989; Ramsay et al, Carbamazepine was found to decrease incrementally the half-life of lamotrigine by 1.7 hours for every 1 carbamazepine within the dosing range of 800 to 1600 mg daily (Jawad et al, 1987).
b) 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, 1990g; Van Dyke et al, 1991g; 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, 1987g; Ramsay et al, 1990g; Spina et al, 1996 combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ov rates.
c) No pharmacokinetic interaction between carbamazepine and lamotrigine was found in children. Three eleven children with intractable generalized epilepsy who had been treated with carbamazepine for longe started lamotrigine 1 mg/kg/day divided into two daily dosages. The lamotrigine dose was increased by 1 other week until clinical response or side effects occurred. The mean carbamazepine levels did not chan from baseline when lamotrigine was coadministered (29.9 mmol/L vs. 28.8 mmol/L). In addition, the plas of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide, significantly decreased from 6 mmol/L with lamotrigine therapy (Eriksson & Boreus, 1997).
d) Carbamazepine reduces the plasma levels of lamotrigine. A 65-year-old male suffering from complex for 40 years was receiving carbamazepine (400 mg three times daily) and lamotrigine (200 mg three time occurred at least twice a week. Steroids, ipratropium bromide and a beta-agonist were used for an obstru disease. A current pneumonia was being treated with an oral amoxicillin preparation. A trough lamotrigin mcmol/mL and a trough carbamazepine was 11 mcmol/mL. The patient continued to suffer from seizures was gradually replaced by levitiracetam (1500 mg twice daily) within 4 weeks. After 4 weeks of levitiracet patient's carbamazepine plasma levels were 1.3 mcmol/mL and lamotrigine plasma levels were 12.1 mc Lamotrigine levels increased rapidly after reductions in the carbamazepine dose. Levetiracetam and lam

combination was well tolerated and seizures stopped completely after 4 weeks. A drug interaction should when carbamazepine and lamotrigine result in ineffective antiepileptic therapy (Koch et al, 2003).

3.5.1.CH Lapatinib

1) Interaction Effect: decreased lapatinib exposure or plasma concentrations

2) Summary: In healthy participants, concurrent administration of lapatinib with carbamazepine, a CYP3A4-i 100 mg twice daily for 3 days and 200 mg twice daily for 17 days led to a 72% decrease in lapatinib AUC. Th recommended that concurrent use of carbamazepine with lapatinib be avoided. However, if these agents mu concurrently, then depending on tolerability, a gradual titration of lapatinib dose from 1250 mg/day up to 450 considered. This adjustment is recommended based on pharmacokinetic data and would be expected to adju the therapeutic ranges achieved without CYP3A4 inducers. However, no clinical data is currently available wi adjustments. If carbamazepine is discontinued, the increased lapatinib dose should be reduced to the indicat TYKERB(R) oral tablets, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Coadministration of lapatinib with carbamazepine, a CYP3A4-inducer, resulted in si decreased lapatinib AUC and should be avoided. However, if concurrent use is warranted, then consider titra lapatinib gradually from 1250 mg/day up to 4500 mg/day, depending on tolerability. Once carbamazepine is d reduce the increased lapatinib dose to the indicated dose (Prod Info TYKERB(R) oral tablets, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated lapatinib metabolism

3.5.1.CI Levetiracetam

1) Interaction Effect: symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double vision)

2) Summary: In pharmacokinetic and clinical studies, concurrent administration of carbamazepine and levetir affect serum levels of either drug (Prod Info KEPPRA(R) oral solution, tablets, 2006). However, in post-marke coadministration of these agents resulted in symptoms consistent with carbamazepine toxicity in 4 individuals refractory epilepsy. While the exact mechanism for this interaction is unknown, it is postulated to be pharmac pharmacokinetic, in origin. Caution is advised when these agents are prescribed together. Patients may neec closely for symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double vision). Reduction of c dosage may be necessary to resolve the symptoms (Sisodiya et al, 2002).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Although in pharmacokinetic and clinical studies, coadministration of carbamazepin levetiracetam did not significantly affect serum levels of either drug (Prod Info KEPPRA(R) oral solution, table marketing experience, coadministration of these agents resulted in symptoms consistent with carbamazepine individuals with severe refractory epilepsy. Therefore, use caution when these agents are prescribed togethe need to be monitored closely for symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double v of carbamazepine dosage may be necessary to resolve the symptoms (Sisodiya et al, 2002).

7) Probable Mechanism: unknown

8) Literature Reports

a) Symptoms of carbamazepine toxicity occurred with coadministration of carbamazepine and levetirace severe refractory epilepsy. The patients, aged 31 to 57 years old, received levetiracetam as add-on thera anti-epileptic drug (AED) therapy, which included monotherapy with carbamazepine 600 mg twice daily i polytherapy in the other 3 cases, with medications including carbamazepine 600 to 1600 mg/day (regula release), sodium valproate, lamotrigine, primidone, or phenobarbital. Levetiracetam was initiated at 500 daily and slowly titrated up to either 500 mg twice daily (in 2 cases), 1000 mg twice daily (in 1 case), or 1 case). Following introduction of levetiracetam, serum blood levels in 3 of the cases were within the norm ranges for all the AEDs. However, in all 4 cases, upward titration of levetiracetam led to symptoms consi carbamazepine toxicity, which included unsteadiness of gait, nystagmus, double vision, dizziness, nause 1 patient, symptoms worsened upon further increase in levetiracetam dose from 500 mg twice daily to 25 Symptoms resolved with a reduction in carbamazepine dosage from 600 mg once daily or twice daily to twice daily, respectively (in 2 cases), and from 800 mg twice daily to 600 mg twice daily (in 1 case). One discontinued levetiracetam on her own accord following symptom onset and data are not available with r symptom resolution. While the exact mechanism for this interaction is unknown, based on serum levels, interactions or altered compliance were ruled out. It was postulated that this interaction may be pharmac (Sisodiya et al, 2002).

3.5.1.CJ Levonorgestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports
a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.
b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1
c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.CK Levothyroxine

1) Interaction Effect: decreased levothyroxine effectiveness
2) Summary: Concomitant use of carbamazepine and levothyroxine may decrease levothyroxine efficacy by metabolism potentially resulting in hypothyroidism. Carbamazepine may also reduce serum protein binding o total- and free- T4 by 20% to 40%. If concurrent use of carbamazepine and levothyroxine is required, an incre levothyroxine dose may be necessary (Prod Info SYNTHROID(R) oral tablets, 2008; Prod Info LEVOTHYRO oral tablet, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbamazepine and levothyroxine may result in reduced levoth As a result, an increase in the levothyroxine dose may be required (Prod Info SYNTHROID(R) oral tablets, 2(LEVOTHYROXINE SODIUM(R) oral tablet, 2007). Consider monitoring TSH levels and/or other measures of when carbamazepine is initiated or discontinued during levothyroxine treatment.
7) Probable Mechanism: increased hepatic metabolism of levothyroxine

3.5.1.CL Lithium

1) Interaction Effect: additive neurotoxicity (weakness, tremor, nystagmus, asterixis)
2) Summary: Case reports have described the development of neurotoxicity during concurrent administratior carbamazepine despite normal therapeutic levels of either drug (Rittmannsberger, 1996a; Chaudhry & Water & Richens, 1980).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor for signs of neurotoxicity with concomitant therapy; serum levels have not b predicting this adverse effect. If neurotoxicity occurs, one or both of the agents may need to be discontinued.
7) Probable Mechanism: unknown
8) Literature Reports
a) A potential interaction between lithium and carbamazepine has been reported (Chaudhry & Waters, 1 a 22-year-old woman with bipolar affective disorder, developed neurotoxicity despite therapeutic plasma drugs. Previous reports of neurotoxicity due to either of these agents have occurred when recommendec were exceeded. Toxicity due to carbamazepine was not observed in this case when the plasma level wa (therapeutic: 8 to 12 mcg/mL). Similarly, no neurotoxicity occurred with plasma lithium levels of 0.9 mEq/ to 1.4 Eq/L). However, when the drugs were administered concurrently, neurotoxicity, characterized by u truncal tremors, ataxia, horizontal nystagmus, hyperflexia of all four limbs, and occasional muscle fascicu within three days. Plasma levels of lithium and carbamazepine were 0.9 mEq/L and 7.6 mcg/mL, respect discontinuation of carbamazepine, neurologic symptoms subsided within three days. Therapeutic plasma two drugs administered concomitantly may lead to acute neurotoxicity.
b) Neurotoxic syndromes developed in five manic patients treated with a combination of lithium and carb although all five had therapeutic plasma levels of both drugs (Shukla et al, 1984). The clinical picture of t consisted of symptoms of confusion, drowsiness, generalized weakness, lethargy, coarse tremor, hyperr cerebellar signs. Patients with previous lithium-induced neurotoxicity and those with underlying CNS dise disease appeared to be at greater risk for developing the neurotoxicity when the combination of the two

c) The laboratory effects of adding lithium to carbamazepine were examined in 23 patients with affective (Kramlinger & Post, 1990). The combination produced additive antithyroid effects, particularly on T4 and addition of lithium resulted in prompt reversal of carbamazepine-induced leukopenia.
d) An analysis of the data from other researchers (Chaudhry & Waters, 1983; Shukla et al, 1984) was p (McGinness et al, 1990). The analysis demonstrated no synergistic toxicity between the two drugs, but n hypothetical plot of blood levels of both drugs that lithium appears to contribute more significantly to the t The authors further concluded that usually used therapeutic ranges cannot be used in monitoring for toxi drugs are used together and a two-dimensional plot of serum levels may be of assistance in ascertaining serum levels with combinations of drugs.
e) Over a three-year period, some drug combinations were observed to cause a greater risk of asterixis in patients on a regimen of multiple psychopharmacologic agents (Rittmannsberger, 1996). With regard t clozapine, and lithium, the incidence of asterixis was greatest in those patients that were on at least two agents. Serum levels of all three drugs were within normal therapeutic ranges, suggesting an additive eff therapy rather than the effect of a single agent.
f) Lithium intoxication occurred in a patient following carbamazepine-induced renal failure. A 33-year-old with bipolar manic-depressive disorder was treated with lithium for the last 18 months. Carbamazepine 6 to his drug regimen. Serum lithium levels were 1.08 mEq/L and serum carbamazepine concentration was weeks later. Upon admission he was stuporous but arousable. His serum creatinine was 6.5 mg/dL, and carbamazepine concentration was 11mcg/mL and serum lithium concentration was 3.5 mEq/L. After 2 L was administered, this patient developed pulmonary edema. After one session of hemodialysis, serum lit concentrations decreased to 1.3 mEq/d, and serum creatinine decreased to 3.5 mg/dL. Three weeks late was 1.0 mg/dL and lithium concentrations were within the therapeutic range. Renal failure was most likel carbamazepine induced interstitial nephritis. Patients who are treated with lithium and carbamazepine sh carefully to prevent carbamazepine-induced interstitial nephritis. The presence of fever, eosinophiluria, u casts, and the patients improvement after withdrawal of carbamazepine support the diagnosis of interstit Patients who are treated with lithium and carbamazepine should be followed carefully to prevent carbam interstitial nephritis (Mayan et al, 2001).

3.5.1.CM L-Methylfolate

1) Interaction Effect: decreased carbamazepine serum levels
2) Summary: Concomitant administration of first-generation anticonvulsants, including carbamazepine, with l folate may lead to decreased serum levels of the anticonvulsant, thereby decreasing carbamazepine efficacy risk of seizures. Although there have been no such reports with the use of carbamazepine and l-methylfolate, if these agents are used concomitantly (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tab Monitor patients for loss of carbamazepine efficacy.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if l-methylfolate is prescribed to patients receiving carbamazepir folate may theoretically result in decreased serum carbamazepine levels, thereby reducing carbamazepine e increasing the frequency of seizures (Prod Info DEPLIN(R) oral tablets, 2006; Prod Info Zervalx(R) oral tablet agents are used concomitantly, monitor patients for loss of carbamazepine efficacy.
7) Probable Mechanism: unknown

3.5.1.CN Lopinavir

1) Interaction Effect: decreased lopinavir exposure; increased serum carbamazepine levels and toxicity
2) Summary: Coadministration of carbamazepine and lopinavir/ritonavir may result in reduced lopinavir seru resulting from carbamazepine induction of CYP3A metabolism. The effectiveness of lopinavir/ritonavir is likely in patients receiving concurrent carbamazepine therapy due to reduced lopinavir bioavailability. The once dai for lopinavir/ritonavir should not be used when a patient is also taking carbamazepine (Prod Info KALETRA(F solution, 2005). Carbamazepine toxicity has been reported in an HIV-positive patient upon concomitant treatr lopinavir/ritonavir, as part of a highly active antiretroviral regimen. This may be a result of inhibition of CYP3A carbamazepine metabolism by the protease inhibitors. If used concurrently with lopinavir/ritonavir, consider re carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine levels, 3 to 5 day lopinavir/ritonavir (Bates & Herman, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution with the coadministration of carbamazepine and lopinavir/ritonavir due lopinavir metabolism. Do not use a once daily dosing regimen of lopinavir/ritonavir concurrently with carbama Additionally, coadministration of carbamazepine with a lopinavir/ritonavir-containing highly active antiretrovira resulted in increased serum carbamazepine levels and toxicity. If used concurrently with lopinavir/ritonavir, co the carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine levels, 3 to 5 initiating the protease inhibitor.
7) Probable Mechanism: carbamazepine induction of CYP3A-mediated lopinavir metabolism; inhibition of CY carbamazepine metabolism by lopinavir/ritonavir
8) Literature Reports
a) Symptoms of carbamazepine toxicity developed in a 50-year-old HIV-positive male upon addition of l

his highly active antiretroviral therapy (HAART). The patient had been stabilized on carbamazepine 400 for 7 months, with a serum concentration within reference range (10.3 mg/L) 1 week prior to starting the tenofovir 300 mg daily; lamivudine 150 mg twice daily; and lopinavir 133 mg/ritonavir 33 mg, 3 capsules 9 of the new HAART regimen, the patient experienced excessive drowsiness, and the carbamazepine se increased by 46% to 15 mg/L. Decreasing the carbamazepine dose to 400 mg twice daily improved drow repeat serum level on day 11 was 7.4 mg/L. On day 12, the patient developed fatigue, difficulty swallowi hemorrhagic lesions over the extremities. The HAART regimen was stopped and carbamazepine dose w 400 mg 3 times daily. The patient was hospitalized 10 days later for evaluation of the rash. Blood tests a marrow toxicity. Subsequently, a neurology consult resulted in tapering of carbamazepine (over 2 to 4 we topiramate 25 mg twice daily and titrating to a target dose of 200 mg twice daily. On day 17 of hospitaliza regimen was re-initiated, replacing lopinavir/ritonavir with nelfinavir 1250 mg twice daily. On day 20, the p feeling tired and unsteady on his feet and the carbamazepine serum level had increased to 15 mg/L. Dec carbamazepine dose as before prompted resolution of symptoms within 24 hours. This interaction betwe as probable by the Naranjo probability scale and inhibition of CYP3A4-mediated carbamazepine metabo lopinavir/ritonavir or nelfinavir was postulated as the probable mechanism (Bates & Herman, 2006).

3.5.1.CO Loxapine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: The concurrent use of carbamazepine and loxapine has resulted in neurotoxicity in one case re 1993a). Also, the use of carbamazepine in pregnant women has been reported to increase the risk of birth de al, 1990j; Van Dyke et al, 1991j; Finnell et al, 1992j).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: For patients receiving concurrent carbamazepine and loxapine therapy, monitor for carbamazepine toxicity and adjust doses accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) A patient experienced neurotoxicity (visual disturbances, lethargy, ataxia, and falling) 10 days after ca mg three times a day was added to a regimen including loxapine 350 mg daily (Collins et al, 1993). His s with a reduction of carbamazepine to 100 mg twice daily. Subsequently loxapine was discontinued, and l carbamazepine epoxide (an active metabolite) to carbamazepine decreased from 0.76 to 0.18. A retrosp four other cases in which carbamazepine and loxapine had been coadministered showed a greater than carbamazepine epoxide to carbamazepine ratio. Loxapine appeared to interact with carbamazepine to ir carbamazepine epoxide plasma concentrations. The mode of action may be induction of carbamazepine epoxide metabolite and/or inhibition of carbamazepine epoxide metabolism to an inactive metabolite.

b) 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, 1990i; Van Dyke et al, 1991i; Finn 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, 1987i; Ramsay et al, 1990i; Spina et al, 1996h combinations increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold ove rates.

3.5.1.CP Maraviroc

1) Interaction Effect: decreased maraviroc concentrations

2) Summary: Maraviroc is a substrate of CYP3A4. Concomitant administration of a CYP3A4 isoenzyme indu carbamazepine, may increase maraviroc metabolism, leading to loss of virologic response, and possible resis maraviroc. Use caution if maraviroc and carbamazepine are used concomitantly (without a strong CYP3A inh increase the dose of maraviroc to 600 mg twice daily (Prod Info SELZENTRY(R) oral tablets, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when carbamazepine is co-administered with maraviroc as the combin loss of virologic response and possible resistance to maraviroc. If maraviroc and carbamazepine are used co (without a strong CYP3A inhibitor), monitor carefully for maraviroc effectiveness and increase the dose of ma twice daily (Prod Info SELZENTRY(R) oral tablets, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated maraviroc metabolism

3.5.1.CQ Mebendazole

1) Interaction Effect: decreased mebendazole effectiveness

2) Summary: In patients with prior or current use of carbamazepine or phenytoin, the use of mebendazole fo resulted in therapeutic failure. This is thought to be due to the lower concentration of mebendazole in the pati anticonvulsants. For treatment of whipworms or hookworms, this interaction is not significant (Luder et al, 198 1986).

3) Severity: moderate

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of mebendazole. Depending on the reason for use of m higher doses may be required for some therapeutic uses.
7) Probable Mechanism: increased mebendazole metabolism

3.5.1.CR Mefloquine
1) Interaction Effect: loss of seizure control
2) Summary: In patients taking an anticonvulsant, such as carbamazepine, the concomitant use of mefloquir seizure control by lowering the anticonvulsant plasma levels (Prod Info Lariam(R), 2003).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If mefloquine and carbamazepine must be administered concurrently, monitor the le carbamazepine. Adjustments of the carbamazepine dose may be required. Also monitor the patient for seizu
7) Probable Mechanism: unknown

3.5.1.CS Mestranol
1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness
2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 19
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports
a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.
b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1
c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.CT Methadone
1) Interaction Effect: decreased methadone effectiveness
2) Summary: The concurrent use of anticonvulsants and methadone resulted in lower methadone levels (eg, ng/mL) (Bell et al, 1988; Ketter et al, 1991).
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Higher methadone doses may be required in patients taking enzyme-inducing medi carbamazepine.
7) Probable Mechanism: increased hepatic metabolism

3.5.1.CU Methylphenidate
1) Interaction Effect: loss of methylphenidate efficacy
2) Summary: Two case reports describe the loss of methylphenidate efficacy after carbamazepine therapy w Carbamazepine is an inducer of cytochrome P450 enzymes, a pathway involved in methylphenidate metabol methylphenidate plasma concentrations are not routinely measured, they may be helpful in patients receiving who are showing no benefits or side effects from methylphenidate (Behar et al, 1998a; Schaller & Behar, 199

3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Clinicians should monitor patient response to methylphenidate therapy when carba initiated. Monitoring of plasma methylphenidate levels may also be helpful. Doses of methylphenidate may ne increased to maintain efficacy.
7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated methylphenidate m
8) Literature Reports
a) A 7-year-old male with severe mental retardation and attention deficit disorder was failing to respond methylphenidate 20 mg every four hours and thiothixene 10 mg daily. Other drug therapy included carba mg daily to control grand mal epilepsy. After five days of confirmed medication compliance, plasma level methylphenidate were measured two hours after the morning dose. No trace of either psychotropic agen metabolites could be found. Doses were increased to methylphenidate 30 mg every four hours and thioth with no evidence of efficacy or side effects. Both agents were then discontinued (Behar et al, 1998).
b) Attention deficit/hyperactivity disorder (ADHD) was being treated with methylphenidate 20 mg three ti year-old female. Because of mood lability and significant impulsivity, carbamazepine was introduced at 2 strict two-hour peak methylphenidate and ritalinic acid serum level was 5.3 ng/mL (normal range 5 to 20 time. ADHD symptoms began to worsen as the carbamazepine dose was increased to 800 mg daily. Six start of combination therapy, the patient's methylphenidate and ritalinic acid strict two-hour peak blood le to 4.2 ng/mL. A month later, the carbamazepine dose was increased to 1000 mg daily with a steady-stat 11.2 mcg/mL. Despite an increase in her methylphenidate dose to 35 mg three times daily, her methylph ritalinic acid peak level had further decreased to 2.4 ng/mL. After another two months, her carbamazepir mg daily with a steady-state blood level of 11.5 mcg/mL, and methylphenidate was increased to 60 mg th regain the benefit from the drug that she had experienced before the initiation of carbamazepine (Schalle

3.5.1.CV Methylprednisolone

1) Interaction Effect: decreased methylprednisolone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982e), possibly by inducing the cytochrome P450 3A4 enzymes which are responsible for methylpredniso (Feldweg & Leddy, 1999a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased cytochrome P450 3A4-mediated methylprednisolone metabolism
8) Literature Reports
a) A 54-year-old male who developed progressive distal sensory and motor impairment during a four we diagnosed with Churg-Strauss vasculitis. He was treated with methylprednisolone 40 mg intravenously tw rapidly resolved his eosinophilia. Because of nocturnal neuropathic pain, carbamazepine was initiated at Within 24 hours of starting carbamazepine, new motor weakness developed in the patient's fingers, and eosinophils increased from a baseline of 160/mcgL to 1330/mcgL. Carbamazepine therapy was stopped methylprednisolone was replaced with dexamethasone. Intravenous immunoglobulin therapy was also in eosinophils disappeared within 48 hours. The patient was subsequently maintained on oral cyclophosph prednisone, with substantial recovery of motor and sensory function (Feldweg & Leddy, 1999).

3.5.1.CW Metronidazole

1) Interaction Effect: increased carbamazepine serum concentrations and potential carbamazepine toxicity
2) Summary: Significantly increased carbamazepine serum concentrations and CNS toxicity have been repo receiving concurrent metronidazole (Patterson, 1994a). The mechanism was thought to be inhibition by metro cytochrome P450 aromatic oxidative metabolism of carbamazepine. Further study is needed to validate this i
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When metronidazole and carbamazepine are coadministered, monitor carbamazep concentrations and observe patients for signs and symptoms of carbamazepine toxicity (nausea, dizziness, d effects). Doses of carbamazepine may need to be adjusted when metronidazole is added to or withdrawn fro
7) Probable Mechanism: unknown but may involve inhibition of carbamazepine metabolism by metronidazole
8) Literature Reports
a) A 49-year-old woman was seen in the ER with left quadrant pain thought to be caused by diverticulitis carbamazepine 1000 mg daily for bipolar disorder. Her other medications included conjugated estrogens Her carbamazepine serum concentration at 12 hours was 9 mcg/mL. She was then started on metronida times a day and trimethoprim/sulfamethoxazole double strength twice a day. Two days later she was adr worsening symptoms. Her metronidazole was increased to 500 mg intravenously every eight hours. Cefa and trimethoprim/sulfamethoxazole withdrawn. Two days later she reported nausea, dizziness, and diplo her 10-hour carbamazepine serum concentration was 14.3 mcg/mL, a 60% increase over the previous 9 mechanism of this interaction was thought to be inhibition of the hepatic cytochrome P-450 enzyme syste metronidazole (Patterson, 1994).

3.5.1.CX Mianserin

1) Interaction Effect: decreased mianserin serum concentrations

2) Summary: Serum mianserin levels were reported to be decreased in patients treated with carbamazepine (Leinonen et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Serum levels and clinical response to mianserin should be carefully monitored if ca added to therapy or discontinued.

7) Probable Mechanism: increased metabolism of mianserin

8) Literature Reports

a) The effect of carbamazepine on mianserin levels was examined in 4 psychiatric inpatients stabilized f days prior to measurement of baseline antidepressant concentrations. The average daily mianserin dos Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. Serum mian concentrations were decreased an average of 46% in patients receiving combination therapy compared with mianserin alone (Leinonen et al, 1991).

3.5.1.CY Midazolam

1) Interaction Effect: decreased efficacy of midazolam

2) Summary: Carbamazepine and phenytoin have been shown to greatly reduce the bioavailability of a sing midazolam. Carbamazepine is known to induce the cytochrome P450 3A enzymes, the same pathway that m midazolam during its first-pass and elimination phases. Patients receiving both carbamazepine and midazola have a hypnotic response to midazolam due to the induction of its metabolism caused by carbamazepine (Ba 1996a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In a patient receiving carbamazepine therapy, larger doses of midazolam may be re a hypnotic response. Because of patient intervariability, a hypnotic other than midazolam may be preferable.

7) Probable Mechanism: induction of cytochrome P450 3A enzymes by carbamazepine

8) Literature Reports

a) Six patients with epilepsy and seven healthy control subjects were studied to determine the effects of and phenytoin on an oral dose of midazolam. Epileptic patients had been receiving either carbamazepin mg to 900 mg daily), phenytoin (dose range 150 mg to 300 mg daily), or both drugs twice daily for at leas control subjects were not receiving any enzyme-inducing agents. All study participants were administere dose of midazolam 15 mg. In the patient group, the mean area under the concentration-time curve of mi 5.7% (0.60 mcg/min/mL vs. 10.5 mcg/min/mL) and the maximum concentration was 7.4% (5.2 ng/mL vs. the control values. In one patient, only traces of midazolam (less than 0.1 ng/mL) were detectable in the elimination half-life of midazolam was reduced to 1.3 hours in the patient group compared to 3.1 hours in There was no difference in the time to maximum concentration (1 hour) between the two groups. As exp reduced serum concentrations of midazolam, the majority of the patient group did not report any sedatio subjects from the control group experienced sedative effects which lasted from two to four hours. The lo plasma concentrations, decreased elimination half-life, and lack of sedative effects are most likely the re P450 3A enzyme induction by carbamazepine and phenytoin, since midazolam is extensively metabolize enzymes during first-pass and elimination phases (Backman et al, 1996).

3.5.1.CZ Mifepristone

1) Interaction Effect: decreased serum levels of mifepristone and potentially decreased efficacy

2) Summary: Although formal interaction studies have not been conducted, carbamazepine may induce the metabolism of mifepristone, thereby decreasing serum levels of mifepristone (Prod Info MIFEPREX(R) oral ta

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Clinicians should be aware that carbamazepine may induce mifepristone metabolis resulting in decreased mifepristone efficacy.

7) Probable Mechanism: induction of CYP3A4-mediated metabolism of mifepristone by carbamazepine

3.5.1.DA Milnacipran

1) Interaction Effect: slight reductions in milnacipran plasma levels

2) Summary: In a multiple-dose study involving healthy subjects (provided by the manufacturer), a moderate milnacipran plasma levels (20%) was observed when the drug was given in combination with carbamazepine accompanied by an increase in plasma levels of the N-dealkylated metabolite of milnacipran (inactive). Carba active metabolite were unaffected (Puozzo & Leonard, 1996). The reduced concentration of milnacipran is of significance, and dose adjustment is not indicated during initiation of combined therapy. However, baseline a therapy plasma levels of milnacipran are suggested if prolonged treatment is expected (where assays are av

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Dose adjustment is not indicated during initiation of combined therapy with carbama milnacipran. However, baseline and combination-therapy plasma levels of milnacipran are suggested if prolo expected.
7) Probable Mechanism: hepatic enzyme induction by carbamazepine

3.5.1.DB Miokamycin
1) Interaction Effect: an increase in carbamazepine plasma levels
2) Summary: Miokamycin has been reported to increase half-life and area under the concentration-time curv decrease the clearance of carbamazepine in 14 healthy volunteers (Couet et al, 1990a; Prod Info Miokacin(R
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised when using miokamycin in combination with carbamazepine. Mo carbamazepine plasma concentrations and adjust the carbamazepine dose as necessary.
7) Probable Mechanism: inhibition of carbamazepine metabolism
8) Literature Reports
a) The effect of miokamycin 800 mg twice daily for 12 days on the pharmacokinetics of carbamazepine single oral dose of 200 mg was assessed in a crossover study involving 14 healthy volunteers. The study statistically significant increase (13%) in half-life and area under the concentration-time curve (AUC) of c decrease in its clearance. The authors also demonstrated that the maximum concentration (Cmax) and A epoxycarbamazepine, a major active metabolite of carbamazepine, were significantly decreased during t miokamycin (Couet et al, 1990; Prod Info Miokacin(R), 1996).

3.5.1.DC Moclobemide
1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998d; Thweatt, 1986d). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995i; Barker & Eccleston controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995h). In addition to their regular carbamazepine an four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylc maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984h).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985d). Conversely, five patients on tranylcypromine needed a mean daily dose of carb mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992d). Four other patie phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

3.5.1.DD Modafinil
1) Interaction Effect: decreased modafinil efficacy
2) Summary: Coadministration of modafinil with other drugs that are potent inducers of CYP3A4, such as ca could result in decreased efficacy of modafinil which is partially metabolized by the CYP3A4 isoenzyme (Proc modafinil, 2004).
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Clinicians should monitor patient response to modafinil therapy when carbamazepir
7) Probable Mechanism: induction by carbamazepine of cytochrome P450 3A4-mediated modafinil metaboli

3.5.1.DE Nafimidone

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concurrent use of nafimidone in 6 patients with intractable seizures taking carbamazepine and in a reduction in carbamazepine elimination by 76 to 87% and a reduction in phenytoin elimination by 38 to 7 showed symptoms characteristic of carbamazepine toxicity by the second day of nafimidone treatment. Effec were apparent within 24 hours of initiation of nafimidone and began to decline within 12 hours of discontinuat Ben-Menachem, 1987a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine concentrations closely when adding or discontinuing nafimi adjust carbamazepine dose accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) Addition of nafimidone to the anticonvulsant regimens of 6 patients with intractable seizures taking ca phenytoin resulted in a reduction in carbamazepine elimination by 76% to 87% and a reduction in phenyt 38% to 77%. This effect was apparent within 24 hours of initiation of nafimidone and began to decline wi nafimidone discontinuation. The effect on carbamazepine elimination persisted over the course of 1 year elected to continue therapy beyond the trial period. Two patients showed symptoms characteristic of carl toxicity by the second day of nafimidone treatment. The degree of toxicity was greatly reduced for 4 addi reducing both the phenytoin and carbamazepine doses during the titration of nafimidone. Although the p of this interaction is unknown, the authors postulate that nafimidone may inhibit the cytochrome P-450-m function oxidase system (Treiman & Ben-Menachem, 1987).

3.5.1.DF Nefazodone

1) Interaction Effect: reduced plasma concentrations and efficacy of nefazodone and its active metabolite, ar risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma)
2) Summary: Coadministration of nefazodone and carbamazepine is contraindicated. Concomitant use may reduce plasma concentrations of nefazodone and its active metabolite, resulting in reduced therapeutic effica (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspension, 2007; Prod Info SERZONE(R) oral a study conducted on 12 healthy volunteers, the coadministration of nefazodone with carbamazepine at steac a reduction in the mean AUC of nefazodone and hydroxynefazodone by 93% and 94%, respectively. Additior increase in carbamazepine plasma levels and a 21% decrease in carbamazepine-10,11 epoxide levels were findings suggest that nefazodone inhibits carbamazepine metabolism through the CYP3A4 system, and carb induces nefazodone metabolism through the same pathway (Laroudie et al, 2000a). Two other cases of nefa carbamazepine toxicity have been reported in the literature (Ashton & Wolin, 1996).
3) Severity: contraindicated
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of carbamazepine and nefazodone is contraindicated due to redu nefazodone and its active metabolite (Prod Info TEGRETOL(R) chewable oral tablets, oral tablets, suspensio SERZONE(R) oral tablets, 2005). In addition, concomitant use may also result in increased toxicity of carbam Wolin, 1996).
7) Probable Mechanism: induction of CYP3A4-mediated nefazodone metabolism; inhibition of CYP3A4-med carbamazepine metabolism
8) Literature Reports
a) Twelve healthy male volunteers participated in an open-label multiple-dose study to explore the poter interaction between carbamazepine and nefazodone. Each subject received nefazodone 200 mg twice d through 5. A four-day washout period followed. On days 10 to 12, carbamazepine 200 mg daily was give was increased to 200 mg twice daily from days 14 to 39. From days 40 to 44, nefazodone 200 mg twice carbamazepine 200 mg twice daily were coadministered. Carbamazepine mean steady-state area under time curve (AUC) increased from 60.77 mcg/hr/mL to 74.98 mcg/hr/mL in the presence of nefazodone, w the metabolite carbamazepine-10,11-epoxide decreased from 7.1 mcg/hr/mL to 5.71 mcg/hr/mL. The ma concentration (Cmax) of carbamazepine increased from 5794 mg/L to 7133.2 mg/L and the Cmax for ca 10,11-epoxide decreased from 680.5 mg/L to 535.2 mg/L. Nefazodone mean steady-state AUC was dec ng/hr/mL to 542 ng/hr/mL in the presence of carbamazepine, although the clinical significance of carbam on nefazodone metabolism has not yet been studied (Laroudie et al, 2000).
b) A 35-year-old female with bipolar disorder developed carbamazepine toxicity following the addition of to 150 mg twice daily) to an existing drug regimen of carbamazepine (1000 mg daily) and risperidone (3 Prior to nefazodone therapy, her carbamazepine serum concentrations ranged from 7.0 mcg/mL to 8.3 m days after her nefazodone dose was increased to 300 mg daily, she presented with lightheadedness and carbamazepine serum concentration was 10.8 mcg/mL (Ashton & Wolin, 1996a).
c) In a second case, a 39-year-old female with bipolar disorder developed carbamazepine toxicity after r 150 mg twice daily) was added to an existing regimen of carbamazepine (1000 mg daily). During concon serum carbamazepine levels increased to 15.1 mcg/mL from a previous range of 5.2 mcg/mL to 6.2 mcg

carbamazepine alone (Ashton & Wolin, 1996a).

3.5.1.DG Nelfinavir

1) Interaction Effect: decreased nelfinavir plasma concentrations; increased serum carbamazepine levels an
2) Summary: The concurrent use of carbamazepine and nelfinavir may result in decreased nelfinavir plasma potentially reducing the efficacy of nelfinavir (Prod Info Viracept(R), 1999). Carbamazepine toxicity has been HIV-positive patient upon concomitant treatment with nelfinavir, as part of a highly active antiretroviral regime result of inhibition of CYP3A4-mediated carbamazepine metabolism by nelfinavir. If used concurrently with ne reducing the carbamazepine dose by 25 to 50%. Additionally, monitor patients for serum carbamazepine leve after initiating nelfinavir (Bates & Herman, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for signs of reduced efficacy of nelfinavir. Dosing adjustments of ne necessary. Additionally, coadministration of carbamazepine with a nelfinavir, as part of a highly active antiretr has resulted in increased serum carbamazepine levels and toxicity. If used concurrently with nelfinavir, consi carbamazepine dose by 25 to 50% and monitor patients for serum carbamazepine levels, 3 to 5 days after in
7) Probable Mechanism: induction of cytochrome P450 3A-mediated metabolism of nelfinavir; inhibition of C carbamazepine metabolism by nelfinavir
8) Literature Reports
a) Symptoms of carbamazepine toxicity developed in a 50-year-old HIV-positive male upon addition of l his highly active antiretroviral therapy (HAART). The patient had been stabilized on carbamazepine 400 for 7 months, with a serum concentration within reference range (10.3 mg/L) 1 week prior to starting the tenofovir 300 mg daily; lamivudine 150 mg twice daily; and lopinavir 133 mg/ritonavir 33 mg, 3 capsules 9 of the new HAART regimen, the patient experienced excessive drowsiness, and the carbamazepine se increased by 46% to 15 mg/L. Decreasing the carbamazepine dose to 400 mg twice daily improved drow repeat serum level on day 11 was 7.4 mg/L. On day 12, the patient developed fatigue, difficulty swallowi hemorrhagic lesions over the extremities. The HAART regimen was stopped and carbamazepine dose w 400 mg 3 times daily. The patient was hospitalized 10 days later for evaluation of the rash. Blood tests a marrow toxicity. Subsequently, a neurology consult resulted in tapering of carbamazepine (over 2 to 4 we topiramate 25 mg twice daily and titrating to a target dose of 200 mg twice daily. On day 17 of hospitaliza regimen was re-initiated, replacing lopinavir/ritonavir with nelfinavir 1250 mg twice daily. On day 20, the p feeling tired and unsteady on his feet and the carbamazepine serum level had increased to 15 mg/L. Dec carbamazepine dose as before prompted resolution of symptoms within 24 hours. This interaction betwe as probable by the Naranjo probability scale and inhibition of CYP3A4-mediated carbamazepine metabo lopinavir/ritonavir or nelfinavir was postulated as the probable mechanism (Bates & Herman, 2006).

3.5.1.DH Nevirapine

1) Interaction Effect: decreased plasma concentrations of carbamazepine
2) Summary: Nevirapine is an inducer of cytochrome P450 3A4 enzymes, which are also involved in the met carbamazepine. Although studies involving nevirapine and carbamazepine have not been conducted, nevirap shown to induce the metabolism of carbamazepine, significantly decreasing carbamazepine bioavailability (P (R), 2004).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Dose adjustment of carbamazepine may be needed due to possible decrease in cli
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of carbamazepine by nevi

3.5.1.DI Niacinamide

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Two case reports describe a decrease in carbamazepine clearance when niacinamide was ad decrease seen in the carbamazepine clearance correlated highly with increasing niacinamide doses (Bourge
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine plasma levels in patients receiving niacinamide concomitar carbamazepine doses accordingly.
7) Probable Mechanism: inhibition of cytochrome P450 enzymes by niacinamide
8) Literature Reports
a) Carbamazepine concentration increased in two epileptic patients after the addition of niacinamide. Bo also receiving primidone therapy, and niacinamide was added to decrease the conversion of primidone t Patient 1, a 23-month old male receiving carbamazepine 72.7 mg/kg/day, had a carbamazepine clearan prior to niacinamide treatment, and the carbamazepine clearance decreased to 2.16 L/kg/day by the time dose had been titrated up to 178 mg/kg/day. In patient 2, a 10-year old male, the carbamazepine clearar from 8.0 L/kg/day before niacinamide therapy to 3.37 L/kg/day when the niacinamide dose was 60 mg/kg suspected that niacinamide inhibited the cytochrome P450 metabolism of carbamazepine (Bourgeois et

3.5.1.DJ Nialamide

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(
Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(
Info Tegretol(R), 1998f; Thweatt, 1986f). However, there is preliminary evidence that the combination of carb
MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995m; Barker & Eccleston,
controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors
contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of
if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m
therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca
benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four
phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir
daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc
carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were
different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and
discharged (Ketter et al, 1995l).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was
intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v
illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few
improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili
placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc
and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p
approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine
two months of follow up at the time of publication (Barker & Eccleston, 1984l).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru
(Joffe et al, 1985f). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep
achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only
daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992f).

3.5.1.DK Nifedipine

1) Interaction Effect: decreased nifedipine exposure and may decrease nifedipine efficacy

2) Summary: Concurrent administration of nifedipine and carbamazepine may induce CYP3A4-mediated nife
and decrease exposure to nifedipine, which may increase the risk of hypertension or angina (Prod Info Adala
Release Tablets, 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: Concomitant administration of nifedipine and carbamazepine may decrease exposu
Monitor patient for loss of calcium channel blocker effects, including clinical signs or symptoms of hypertensio
Consider a dose adjustment of nifedipine.

7) Probable Mechanism: induction of CYP3A4-mediated nifedipine metabolism

3.5.1.DL Nilotinib

1) Interaction Effect: decreased nilotinib plasma concentrations

2) Summary: Nilotinib is a CYP3A4 substrate. Coadministration of rifampin, a strong CYP3A4 inducer, at a d
for 12 days decreased nilotinib AUC by approximately 80% in healthy subjects. Although not studied with car
a strong CYP3A4 inducer, a similar interaction would be expected. Concomitant use of carbamazepine and n
therefore be avoided. However, if concomitant use is required, nilotinib dose may need to be increased depe
tolerability. Upon discontinuation of carbamazepine, reduce the nilotinib dose to the indicated dose (Prod Info
capsules, 2007).

3) Severity: major

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Avoid concomitant administration of carbamazepine, a strong CYP3A4 inducer, and
CYP3A4 substrate, as this may result in decreased nilotinib plasma concentrations and consequently, subthe
concomitant administration is warranted, consider increasing nilotinib dose depending on patient tolerability.
discontinuation of the strong CYP3A4 inducer, reduce the nilotinib dose to the indicated dose (Prod Info TAS
capsules, 2007).

7) Probable Mechanism: induction of CYP3A4-mediated nilotinib metabolism

3.5.1.DM Nimodipine

1) Interaction Effect: decreased nimodipine effectiveness

2) Summary: A single study has shown that concurrent use of enzyme inducing antiepileptic agents (phenyto and carbamazepine) with nimodipine has resulted in decreased nimodipine levels (Tartara et al, 1991b).

3) Severity: minor

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor clinical response to nimodipine, with dose adjustments as needed to achiev cardiovascular response.

7) Probable Mechanism: increased nimodipine metabolism

8) Literature Reports

a) Three groups of eight subjects were studied (Tartara et al, 1991). Group 1 was comprised of healthy 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.DN Norelgestromin

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consid breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.DO Norethindrone

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 198

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended

estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

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3.5.1.DP Norgestrel

1) Interaction Effect: a decrease in plasma concentrations of estrogens and in estrogen effectiveness

2) Summary: Breakthrough bleeding, spotting, and pregnancy have been reported in women on anticonvulsa contraceptives (Prod Info Ortho Evra(TM), 2001; Mattson et al, 1986a; Crawford et al, 1986; Haukkamaa, 19

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: In some women the use of higher estrogen content in the contraceptive may be suf use of alternate methods of birth control may be necessary.

7) Probable Mechanism: increased metabolism of contraceptive steroids

8) Literature Reports

a) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, prima phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contr et al, 1986). The benzodiazepines and valproic acid have not been associated with increased failure rate receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may als of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; howev pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be consic breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestrar (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be disc rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Sv dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women moderate or high-dose contraceptives.

b) Carbamazepine reduced the area under the plasma concentration time curve (AUC) of ethinyl estrad 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norges also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding ca most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol (Crawford et al, 1

c) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus 400 mg daily (Haukkamaa, 1986). The plasma concentration of levonorgestrel in this patient was very lo pg/mL) when compared to controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma le concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel relied upon as the sole means of contraception in patients on anticonvulsant therapy.

3.5.1.DQ Nortriptyline

1) Interaction Effect: decreased nortriptyline effectiveness

2) Summary: One case has been reported in which nortriptyline levels dropped by more than half after carba added (Brosen & Kragh-Sorensen, 1993b). Similar effects have been observed with other tricyclic antidepres al, 1991k; Brown et al, 1988c; Moody et al, 1977c).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical efficacy of the nortriptyline therapy and for any signs of toxicity o Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.

7) Probable Mechanism: increased nortriptyline metabolism

3.5.1.DR Olanzapine

1) Interaction Effect: reduced olanzapine efficacy

2) Summary: Carbamazepine induces CYP1A2 mediated oxidation. Concomitant administration of olanzapir carbamazepine 200 mg twice daily increased the clearance of olanzapine by 50% (Prod Info Zyprexa(R), 19

doses of carbamazepine may cause an even greater effect on olanzapine clearance. In a study of 11 healthy concurrent administration of olanzapine and carbamazepine resulted in a 46% increase in olanzapine clearar 1998). Because patients respond to a relatively wide range of olanzapine serum concentrations, close clinica symptom patterns and changes is necessary whenever carbamazepine is added to or withdrawn from olanza need for olanzapine dose adjustments will most likely be highly patient specific (Licht et al, 2000a).

3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor patients for olanzapine efficacy. Doses of olanzapine may need to be adjus concomitantly with carbamazepine.
7) Probable Mechanism: induction of cytochrome P450 1A2-mediated olanzapine metabolism
8) Literature Reports

a) A 23-year-old paranoid schizophrenic female was admitted to the hospital for treatment of hallucinatic Her only medication on admission was perphenazine 12 mg daily, but carbamazepine 600 mg daily was aggressive outbursts. Perphenazine was replaced by risperidone 6 mg daily due to akathisia, rigidity, an risperidone was also discontinued due to extrapyramidal side effects. Olanzapine 15 mg daily was starte psychiatric symptoms improved over the next three weeks. Because her aggressive outbursts were still carbamazepine was discontinued due to lack of efficacy. She had received cotherapy with olanzapine 15 carbamazepine 600 mg daily for three consecutive weeks. The day prior to carbamazepine discontinuati olanzapine serum concentration was measured at 21 ng/mL. Over the next few weeks, her olanzapine c increased by 114% to 45 ng/mL. The dose of olanzapine was decreased to 10 mg daily and a correspon olanzapine level occurred. This case report suggests that carbamazepine induces the metabolism of ola likely through the cytochrome P450 1A2 enzyme system (Licht et al, 2000).

3.5.1.DS Omeprazole

1) Interaction Effect: an increased risk of carbamazepine toxicity
2) Summary: Omeprazole has been reported to increase the elimination half-life, increase the area under the time curve (AUC), and decrease the clearance of a single-dose of carbamazepine (Dammann, 1996a). Conv Getz, 1995a) described a patient who had no alteration in the carbamazepine plasma level during concurrent omeprazole for helicobacter pylori gastritis. One of the reasons for the conflicting results may be that carbam own metabolism, thereby possibly causing different interactions between single-dose and multiple-dose thera carbamazepine.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent carbamazepine and omeprazole therapy for s carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma). Also moni serum levels. Doses of carbamazepine may need to be reduced.
7) Probable Mechanism: inhibition of carbamazepine metabolism
8) Literature Reports

a) The administration of a single dose of carbamazepine to nine patients receiving omeprazole therapy prolongation of the carbamazepine half-life (17.2 hours vs. 37.3 hours) and an increase in the AUC from 668 mcg/hr/mL. The clearance of carbamazepine decreased from 20.7 mL/hr/kg to 12.5 mL/hr/kg. These any adjuvant therapy of omeprazole has the potential to interact with carbamazepine concentrations, and administered with close monitoring of the carbamazepine serum levels (Dammann, 1996).

b) An epileptic patient stabilized on carbamazepine (900 mg daily) therapy, had a serum level of 7.5 mg the addition of clarithromycin (500 mg three times daily) and omeprazole (20 mg twice daily), the carbam risen to 14 mg/L. Despite carbamazepine dose reductions of 200 mg daily, the plasma level reached 20. clarithromycin was then discontinued, and metronidazole and bismuth subsalicylate were substituted. Th carbamazepine returned to normal, even though therapy with omeprazole was continued. Omeprazole is hepatic microsomal cytochrome P450 2C enzymes, whereas carbamazepine is metabolized by and indu different metabolic pathways between omeprazole and carbamazepine suggest that in this patient, claritl solely responsible for the increased carbamazepine serum levels and no drug interaction exists between carbamazepine (Metz & Getz, 1995).

3.5.1.DT Oxcarbazepine

1) Interaction Effect: decreased plasma concentration of the active 10-monohydroxy metabolite of oxcarbaze
2) Summary: Concurrent administration of oxcarbazepine and carbamazepine (CBZ) has resulted in a 40% plasma concentration of the active 10-monohydroxy derivative (MHD) of oxcarbazepine (Prod Info TRILEPTA oral suspension, 2005). Although the exact mechanism for this decrease is unknown, it is believed to be parti potential induction of oxcarbazepine's metabolism by CBZ, which is strong inducer of cytochrome P450 enzy 1994). Although, the clinical significance of this interaction is unknown, decreased plasma MHD concentratio potential loss of oxcarbazepine efficacy. If oxcarbazepine and carbamazepine are administered concurrently, to oxcarbazepine may need to be monitored.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Coadministration of oxcarbazepine and carbamazepine may result in a decreased

the active 10-monohydroxy metabolite of oxcarbazepine. Monitor patients for clinical response to oxcarbazep
7) Probable Mechanism: potential induction of cytochrome P450-mediated oxcarbazepine metabolism
8) Literature Reports
a) In a randomized, double-blind, placebo-controlled trial in adults, coadministration of carbamazepine (
oxcarbazepine resulted in decreased levels of the pharmacologically active 10-monohydroxy derivative (
oxcarbazepine. Patients (n=12) being treated with a mean CBZ dose of 1025 milligrams (mg) (range 40
administered a single 600 mg oral dose of oxcarbazepine and were randomized, a week later, to receive
oxcarbazepine three times daily or matched placebo for 3 weeks. Active controls (n=7) were untreated p
received the single 600 mg oxcarbazepine dose and 3 weeks active treatment. Study results showed tha
the concentration-time curve (AUC) for MHD at steady state was reduced by 40% (90% confidence inter
57% decrease) in the CBZ-treated group compared to the active controls (p less than 0.05) while AUC fo
significantly. Although the exact mechanism for this decrease is unknown, it was partially attributed to a p
of oxcarbazepine metabolism by carbamazepine, a strong inducer of cytochrome P450 enzymes (McKee
Info TRILEPTAL(R) oral tablets, oral suspension, 2005).

3.5.1.DU Paliperidone
1) Interaction Effect: decreased paliperidone concentration
2) Summary: Concomitant use of paliperidone and carbamazepine decreased the maximum concentration (C
area under the concentration-time curve (AUC) values of paliperidone by 37%. Coadministration with carbam
CYP3A4 inducer, could increase paliperidone renal clearance by 35%. The dose of paliperidone should be ev
administered concurrently with carbamazepine. If therapy with carbamazepine is discontinued, the dose of pa
be decreased if necessary (Prod Info INVEGA(TM) extended-release oral tablets, 2007).
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of paliperidone and carbamazepine resulted in decreased paliperi
concentrations. Dosing of paliperidone should be evaluated when it is administered concurrently with carbam
with carbamazepine is discontinued, the dose of paliperidone should be decreased if necessary(Prod Info IN
extended-release oral tablets, 2007).
7) Probable Mechanism: induction of paliperidone metabolism
8) Literature Reports
a) Coadministration of paliperidone 6 mg daily and carbamazepine 200 mg twice daily decreased the pa
steady-state maximum concentration (Cmax) and area under the concentration-time curve (AUC) by app
This decrease is caused by a 35% increase in renal clearance of paliperidone. There is little effect on the
bioavailability of paliperidone when coadministered with carbamazepine. Carefully evaluate paliperidone
initiation or discontinuation of carbamazepine (Prod Info INVEGA(TM) extended-release oral tablets, 200

3.5.1.DV Pancuronium
1) Interaction Effect: decreased pancuronium duration of action
2) Summary: It has been demonstrated that, in patients taking carbamazepine for at least one month prior to
pancuronium, the recovery time after being given pancuronium was about 65% faster when compared to con
& Ebrahim, 1987a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker.
intervals or higher doses of pancuronium may be needed in patients receiving carbamazepine.
7) Probable Mechanism: unknown
8) Literature Reports
a) Nine patients on chronic carbamazepine therapy undergoing craniotomy for tumors or cerebrovascula
pancuronium 0.1 mg/kg intravenously to facilitate endotracheal intubation. As compared with controls, th
from neuromuscular blockade was significantly (65%) reduced. Times to percent recovery of baseline tw
controls and the carbamazepine group are as follows: 25%, 85 vs 30 minutes; 50%, 106 vs 39 minutes;
minutes; 90%, 149 vs 57 minutes. Carbamazepine and pancuronium may compete for binding sites at th
junction or carbamazepine may increase the rate of pancuronium metabolism (Roth & Ebrahim, 1987).

3.5.1.DW Pargyline
1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures
2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(
Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(
Info Tegretol(R), 1998j; Thweatt, 1986j). However, there is preliminary evidence that the combination of carba
MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995u; Barker & Eccleston, 1
controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors
contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of

if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995t).
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984t).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985j). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992j).

3.5.1.DX Pentobarbital
1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control
2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) has been sugg primidone concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentrat al, 1983e). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & F with the barbiturate decreasing the level of carbamazepine while increasing the level of 10, 11-epoxide metab carbamazepine (McKauge et al, 1981c; Eichelbaum et al, 1985b). Evidence from these studies indicates that effects may be more pronounced in children.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: With combined carbamazepine-pentobarbital therapy, monitor patients for seizure a pediatric patients, and adjust doses accordingly.
7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug
8) Literature Reports
a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15 year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10, 11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987d).
b) A study of primidone levels and metabolism related to age and coadministration of other anticonvulsa children metabolize primidone more extensively than older persons and that coadministration of carbama primidone causes lower primidone to dose ratios and higher derived phenobarbital to primidone levels co primidone monotherapy (Battino et al, 1983d).
c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa difference was not statistically significant. It was unknown how long patients were on primidone therapy i before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) One study prospectively examined carbamazepine in patients already on other anticonvulsants. Eigh studied. Four patients were on phenytoin and phenobarbital, and four were on phenytoin, phenobarbital Although the authors concluded that serum phenobarbital and primidone levels appeared to actually incr patients after nine days of carbamazepine therapy, numerical data were not given. The increased levels and primidone could reflect only the incremental changes typical of rises to steady state levels (Cereghir
e) One study examined 14 patients on concomitant carbamazepine and phenobarbital therapy. A mean carbamazepine levels was noted with an increase in levels of carbamazepine epoxide and free carbama The carbamazepine epoxide to carbamazepine ratio was also increased in these patients. No effect on p phenobarbital metabolite levels was observed (Ramsay et al, 1990h). Similarly, a prospective, controlled carbamazepine reduction and discontinuation produced no change in phenobarbital levels in patients on therapy (Duncan et al, 1991c).
f) If phenytoin or carbamazepine (or any prodrugs) is used in pregnant women, there is a substantially ir 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, 1990h; Van Dyke et al, 1991h; 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) (barbiturates, felbamate), or drugs epoxide hydrolase, such as valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987h; Ramsay et et al, 1996g). Such combinations increase the risk of major birth defects 3- to 4-fold over monotherapy a over background rates.

3.5.1.DY Phenelzine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998a; Thweatt, 1986a). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995c; Barker & Ecclestor controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: Avoid concurrent administration of carbamazepine and monoamine oxidase inhibitc monoamine oxidase inhibitors 14 days or longer before starting carbamazepine therapy. Successful concomi reported; monitor carbamazepine levels and adjust doses accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995b).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984b).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985a). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0 to 11.1 mcg/mL. Four other patients receiving phenelzine on daily dose of carbamazepine 450 mg to attain a blood level of 8.7 to 10.9 mcg/mL (Barklage et al, 1992a

3.5.1.DZ Phenobarbital

1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control

2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) has been sugg primidone concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentrat al, 1983a). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & F with the barbiturate decreasing the level of carbamazepine while increasing the level of carbamazepine meta al, 1981a; Eichelbaum et al, 1985). Evidence from these studies indicates that the metabolic effects may be r in children.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: theoretical

6) Clinical Management: With combined carbamazepine-phenobarbital therapy, monitor patients for seizure pediatric patients, and adjust doses accordingly.

7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug

8) Literature Reports

a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15 year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10, 11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987).

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c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa

difference was not statistically significant. It was unknown how long patients were on primidone therapy i
before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) A study prospectively examined carbamazepine in patients already on other anticonvulsants. Eight pa
studied. Four patients were on phenytoin and phenobarbital, and four were on phenytoin, phenobarbital
Although the authors concluded that serum phenobarbital and primidone levels appeared to actually incr
patients after nine days of carbamazepine therapy, numerical data were not given. The increased levels
and primidone could reflect only the incremental changes typical of rises to steady-state levels (Cereghir
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carbamazepine levels was noted with an increase in levels of carbamazepine epoxide and free carbama
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other drugs that induce cytochrome P450 enzymes (3A4, 2C9, 2C19) (barbiturates, felbamate), or drugs
epoxide hydrolase, such as valproic acid, progabide, and lamotrigine (Bianchetti et al, 1987b; Ramsay et
et al, 1996b). Such combinations increase the risk of major birth defects 3- to 4-fold over monotherapy a
over background rates.

3.5.1.EA Phenprocoumon

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a
effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983b; Cohen & Arms
Koch-Weser & Koch-Weser, 1975b; Kendall & Boivin, 1981b; Hansen et al, 1971c).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR (i
normalized ratio) should be closely monitored with the addition and withdrawal of treatment with carbamazep
reassessed periodically during concurrent therapy. Adjustments of the phenprocoumon dose may be necessa
maintain the desired level of anticoagulation.
7) Probable Mechanism: increased phenprocoumon metabolism

3.5.1.EB Phenytoin

1) Interaction Effect: increased phenytoin concentrations and decreased carbamazepine concentrations
2) Summary: Concurrent use of phenytoin and carbamazepine may decrease carbamazepine levels (Zielinsk
1987a; Randall & Tett, 1993). The addition of carbamazepine to phenytoin therapy may decrease (Hansen et
increase (Browne et al, 1988) phenytoin levels.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Serum levels of both phenytoin and carbamazepine should be measured after initia
discontinuation of either agent, with appropriate dosage adjustment made accordingly. Serum levels should a
following dosage adjustments and periodically thereafter.
7) Probable Mechanism: inhibition of cytochrome P450 2C19-mediated metabolism of phenytoin by carbama
8) Literature Reports
a) Twenty-four epileptic patients who were stabilized on phenytoin (PHT) and had carbamazepine (CBZ
drug regimen were studied. The mean phenytoin level increased from 13.89 +/- 4.68 to 19 +/- 4.75 (35.9
effect of carbamazepine on phenytoin in an individual is unpredictable; 12 of the subjects showed no cha
levels while the other 12 patients showed an average increase of 81.3% in phenytoin concentration. Five
with increased levels had symptoms of acute phenytoin toxicity (Zielinski et al, 1985).
b) Concomitant administration of carbamazepine and phenytoin has been reported to result in a dual int
simultaneous effects of inhibition of phenytoin metabolism by carbamazepine and induction of carbamaz
by phenytoin. The result is potential phenytoin intoxication and significant reductions of carbamazepine p
concentrations to subtherapeutic levels. These dual effects appear to be especially significant when phe
levels approach a change from linear to saturation kinetics. It is suggested that the interaction may be av
minimized by adjusting phenytoin plasma levels to approximately 13 mcg/mL prior to the addition of carb
regimen or increasing carbamazepine doses (Zielinski & Haidukewych, 1987).
c) Factors influencing simultaneous plasma concentrations of carbamazepine and its epoxide metabolite
(McKauge et al, 1981) and it was found that plasma carbamazepine concentrations were significantly lov
taking carbamazepine and phenytoin than those taking carbamazepine alone. In contrast to another stud
epoxide levels were unaltered (Pynnonen et al, 1980). Other researchers studied carbamazepine plasma
four groups of epileptic patients on a variety of anticonvulsants (Christiansen & Dam, 1973). Their results
administration of phenytoin or phenobarbital to patients receiving carbamazepine results in a significant
carbamazepine plasma concentration when compared to patients receiving carbamazepine alone. It sho

however, that some subjects in the trial were treated with carbamazepine for only one week prior to the i phenytoin. Carbamazepine has been shown to induce its own metabolism for up to 30 days after the initi thus lowering carbamazepine plasma concentration (Pynnonen et al, 1980). This may account for some carbamazepine plasma concentration in subjects also receiving phenytoin.

d) A prospective controlled study of the effects of reduction and discontinuation of phenytoin and carbar levels of concomitant antiepileptic drugs was conducted (Duncan et al, 1991). Phenytoin discontinuation 48% increase in total carbamazepine concentration and a 30% increase in free carbamazepine concentr change in carbamazepine epoxide concentrations. The authors suggest that phenytoin is a strong induce enzymes metabolizing carbamazepine to carbamazepine epoxide, but has less of an effect on the epoxi enzyme. This results in elevations in carbamazepine-epoxide/carbamazepine ratios in patients on conco Conversely, when carbamazepine was discontinued, phenytoin concentrations decreased by a mean of change in free fraction. The authors propose that this may result from inhibition of phenytoin metabolism carbamazepine. There appeared to be no impact on protein binding of either drug. Similar results were n researchers in 49 patients on concomitant phenytoin and carbamazepine therapy (Ramsay et al, 1990a)

e) If phenytoin or carbamazepine is used in pregnant women, there is a substantially increased risk of te many combinations of other anticonvulsants. The teratogenicity of these drugs is largely or wholly relatec the reactive epoxide metabolites (Buehler et al, 1990a; Van Dyke et al, 1991a; Finnell et al, 1992a). The drug ratio is generally increased when phenytoin or carbamazepine is combined with each other, any oth induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, such as progabide and lamotrigine (Bianchetti et al, 1987a; Ramsay et al, 1990a). Such combinations increase th birth defects three- to four-fold over monotherapy and about 10-fold over background rates.

3.5.1.EC Pipecuronium

1) Interaction Effect: resistance to neuromuscular blockade

2) Summary: Phenytoin and carbamazepine have been reported to cause some resistance to neuromuscula patients treated with pipecuronium. A prolonged onset time of action was observed in patients with therapeut levels, but the accelerated recovery from paralysis was seen in all patients treated with anticonvulsants, rega plasma level (Hans et al, 1995a; Jellish et al, 1993a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: In patients on chronic carbamazepine therapy, higher doses of pipecuronium may b the depth of neuromuscular blockade and adjust the dose of pipecuronium accordingly.

7) Probable Mechanism: unknown

8) Literature Reports

a) Twenty adults scheduled for neurosurgery were enrolled in a study. The patients were then divided in group 1 (n=10) was not on anticonvulsant therapy, and group 2 (n=10) was being treated with either phe carbamazepine (n=5). All patients achieved muscle relaxation by a single intravenous dose of pipecuron The onset time was prolonged in patients receiving anticonvulsants when compared to controls (230.5 s seconds). Of the patients who had therapeutic anticonvulsant levels (n=6), the onset time was more prol seconds) than the patients (n=4) who had subtherapeutic levels (181.8 seconds). The recovery index wa shortened in patients who were receiving anticonvulsant therapy when compared to controls (35 min vs. plasma anticonvulsant level was not a discriminant factor for recovery from the neuromuscular blockade

b) An accelerated recovery rate from pipecuronium-induced neuromuscular blockade in patients receivi alone and in combination with other anticonvulsants was observed. Nineteen adult patients were divided six healthy patients who had never received any anticonvulsant medications, and 13 epileptic patients wi seizures who had been treated for years with anticonvulsants. Of these 13 epileptic patients, they were f a group who received carbamazepine as monotherapy (n=6) and a group who was treated with carbama phenytoin or valproic acid (n=7). Anesthesia was induced with thiopental sodium and fentanyl prior to a s bolus dose of pipecuronium 0.08 mg/kg. No statistical significance was reached when comparing the tim (T-1 25%), T-1 50%, and T-1 75%, although there was a trend suggesting that patients on carbamazepir the effects of pipecuronium more quickly than controls. However, the train-of-four recovery times were si shortened in the carbamazepine monotherapy group and the multiple anticonvulsant group when compa Results were as follows when comparing controls with the carbamazepine monotherapy and carbamaze anticonvulsant groups: train-of-four recovery to 10% (TR 10%), 142 vs. 101 vs. 78 minutes; TR 20%, 16 minutes; and TR 25%, 172 vs. 130 vs. 101 minutes (Jellish et al, 1993).

3.5.1.ED Praziquantel

1) Interaction Effect: decreased praziquantel effectiveness

2) Summary: A controlled study demonstrated that carbamazepine reduced the AUC of praziquantel by 90% plasma level by 92% (Bittencourt et al, 1992). Phenytoin also significantly reduced praziquantel AUC and pea concentration in the same study. Because seizure disorders commonly accompany neurocysticercosis, comb these agents may frequently be necessary. Cimetidine (an enzyme inhibitor) has been successfully employed counteract the enzyme induction caused by phenytoin and phenobarbital, however these results have not be controlled prospective study (Dachman et al, 1994).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: If concomitant use is necessary, an increased dose of praziquantel may be required effective.
7) Probable Mechanism: increased praziquantel metabolism

3.5.1.EE Prednisolone
1) Interaction Effect: decreased prednisolone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of prednisolone (Privitera Olivesi, 1986f).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of prednisolone. An increase in prednisolone dosage m after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased prednisolone metabolism

3.5.1.EF Prednisone
1) Interaction Effect: decreased prednisone effectiveness
2) Summary: Carbamazepine has been demonstrated to increase the metabolism of corticosteroids (Olivesi, al, 1982d). Although not specifically reported for prednisone, a similar interaction could be expected.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor therapeutic efficacy of the corticosteroid. An increase in the steroid dosage after three to five days of concurrent carbamazepine therapy.
7) Probable Mechanism: increased prednisone metabolism

3.5.1.EG Primidone
1) Interaction Effect: decreased carbamazepine effectiveness with loss of seizure control
2) Summary: Concomitant use of carbamazepine and primidone (a prodrug of phenobarbital) may lower the concentration/dose ratio, while increasing the phenobarbital concentration to primidone concentration ratio (E 1983c). Concurrent therapy has also been reported to lower carbamazepine concentrations (Benetello & Furl the barbiturate decreasing the level of carbamazepine while increasing the level of carbamazepine metabolite 1981b; Eichelbaum et al, 1985a). Evidence from these studies indicates that the metabolic effects may be mo children.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: With combined carbamazepine-primidone therapy, monitor patients for seizure activ pediatric patients, and adjust doses accordingly.
7) Probable Mechanism: microsomal enzyme induction with altered metabolism of either drug
8) Literature Reports
a) Concomitant administration of primidone and carbamazepine has been reported to result in lack of se low levels of carbamazepine in a 15-year-old male with partial complex seizures. Withdrawal of the primi significant increases in carbamazepine serum levels with decreases in carbamazepine-10,11-epoxide le reduction (60%) in carbamazepine clearance (Benetello & Furlanut, 1987b).
b) A study of primidone plasma levels and metabolism related to age and coadministration of other antic done. This study found that children metabolize primidone more extensively than older persons and that of carbamazepine with primidone causes lower primidone to dose ratios and higher derived phenobarbita levels compared with primidone monotherapy (Battino et al, 1983b).
c) Decreased levels of primidone, which is converted to phenobarbital and PEMA in vivo, have been rep taking carbamazepine. A retrospective study statistically analyzed routine determinations of serum conce anticonvulsant medications in patients on combination regimens. A phenobarbital-carbamazepine interac specifically examined. A lowering of primidone levels during combination therapy with carbamazepine wa difference was not statistically significant. It was unknown how long patients were on primidone therapy i before the levels were taken, so auto-induction of primidone could not be ruled out (Windofer & Saver, 1
d) One study analyzed 14 patients on concomitant carbamazepine and phenobarbital therapy. A mean c carbamazepine levels were noted with an increase in levels of carbamazepine epoxide and free carbama No effect on phenobarbital or phenobarbital metabolite levels was observed (Ramsay et al, 1990c). Simi prospective, controlled study of carbamazepine reduction and discontinuation produced no change in ph in patients on concomitant therapy (Duncan et al, 1991b).
e) If phenytoin or carbamazepine is used in pregnant women, there is a substantially increased risk of te many combinations of other anticonvulsants. The teratogenicity of these drugs is largely or wholly related the reactive epoxide metabolites (Buehler et al, 1990c; Van Dyke et al, 1991c; Finnell et al, 1992c). The drug ratio is generally increased when phenytoin or carbamazepine is combined with each other, any oth induce cytochrome P450 enzymes (3A4, 2C9, 2C19), or drugs which inhibit epoxide hydrolase, such as progabide and lamotrigine (Bianchetti et al, 1987c; Ramsay et al, 1990c). Such combinations increase th birth defects three- to four-fold over monotherapy and about 10-fold over background rates.

3.5.1.EH Procarbazine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(
Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(
Info Tegretol(R), 1998g; Thweatt, 1986g). However, there is preliminary evidence that the combination of car
an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995o; Barker & Eccleston
controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors
contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of
if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m
therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca
benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four
phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir
daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc
carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were
different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and
discharged (Ketter et al, 1995n).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was
intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v
illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few
improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili
placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc
and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p
approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine
two months of follow up at the time of publication (Barker & Eccleston, 1984n).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru
(Joffe et al, 1985g). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep
achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only
daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992g).

3.5.1.EI Propoxyphene

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo
seizures, coma)

2) Summary: Concurrent propoxyphene therapy significantly increases carbamazepine concentrations and n
moderate to severe neurotoxicity (Allen, 1994a; Oles et al, 1989; Yu et al, 1986a; Kubacka & Ferrante, 1983;
1997a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Concurrent use of propoxyphene and carbamazepine should be avoided. Use of ar
analgesic, such as a codeine or hydrocodone, should be considered. If concomitant therapy with propoxyphe
carbamazepine is required, closely monitor carbamazepine serum concentrations. Dosage reductions are like
necessary.

7) Probable Mechanism: decreased hepatic metabolism

8) Literature Reports

a) In an observational study of elderly patients, carbamazepine serum concentrations were significantly
carbamazepine side effects were significantly more common when propoxyphene was taken concomitar
used both carbamazepine and propoxyphene were compared to patients who took either carbamazepine
and to patients who took neither of these drugs. The patients were matched for gender, age, and concor
In patients who took propoxyphene and carbamazepine the average dose of carbamazepine was lower (
compared to 378.6 mg) and the average serum level of carbamazepine was higher (28.2 mcmol/L compa
mcmol/L), than in those that took carbamazepine, but not propoxyphene; serum concentrations of carba
metabolites were also higher. In addition, side effects related to carbamazepine occurred significantly mo
patients taking both carbamazepine and propoxyphene, including depression, sedation, sleep disturbanc
restlessness (Bergendal et al, 1997).

b) Seven outpatients (6 with epilepsy and 1 with trigeminal neuralgia) were receiving carbamazepine alo
combination with phenobarbital, clonazepam, or ethosuximide (Dam & Christiansen, 1977). Study subjec
coadministered propoxyphene 65 mg 3 times a day. In 5 patients, carbamazepine clearance decreased
carbamazepine plasma levels increased 44% to 77%. The other 2 patients discontinued the propoxyphe
due to severe side effects.

c) Six epileptic patients who had taken carbamazepine (600 to 800 mg/day) for more than 6 months we

dextropropoxyphene 65 mg 3 times/day (Hansen et al, 1980). A 66% mean increase in carbamazepine s concentrations was observed 6 days after initiation of propoxyphene dosing.

d) Three elderly patients were administered carbamazepine 200 mg 3 times a day (one patient only rec a day) and dextropropoxyphene 32 mg every 4 hours or 64 mg every 6 hours (Yu et al, 1986). All 3 deve carbamazepine toxicity and 2 became comatose.

e) A 24-year-old epileptic man on maintenance carbamazepine therapy was given dextropropoxyphene ear infection (Allen, 1994). He experienced acute onset ataxia, marked intention tremor, slurred speech, multidirectional nystagmus. On presentation, he was hardly able to stand. During the preceding 24 hours coproxaml tablets (propoxyphene 32.5 mg, acetaminophen 325 mg). A fourfold increase in his carbamaz concentration was found. Carbamazepine was withheld for 48 hours, by which time his serum concentra normal. His symptoms rapidly resolved.

3.5.1.EJ Protriptyline

1) Interaction Effect: decreased protriptyline plasma concentrations and increased carbamazepine plasma c possible toxicity (ataxia, nystagmus, apnea, seizures, coma)

2) Summary: The concomitant use of carbamazepine and tricyclic antidepressants has been reported to dec antidepressant plasma concentrations and raise carbamazepine levels (Leinonen et al, 1991j; Brown et al, 19 Kragh-Sorensen, 1993a). Although not reported specifically for protriptyline, a similar interaction would be ex Carbamazepine is known to induce enzyme action. Tricyclic antidepressants can lower the seizure threshold stabilized on anticonvulsants.

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for antidepressant efficacy and carbamazepine toxicity (nausea, vo tremor, blurred vision) with concurrent use. Doses of protriptyline may need to be increased and carbamazep reduced. Serum carbamazepine levels might be considered when a tricyclic antidepressant is added to or dis therapy.

7) Probable Mechanism: alterations in hepatic metabolism

8) Literature Reports

a) The effect of carbamazepine on doxepin levels was studied in 17 psychiatric inpatients stabilized for a days prior to measurement of baseline antidepressant concentrations. The average daily doxepin dosag Carbamazepine was added in a mean dose of 593 mg and continued over a 4-week period. In patients r combination therapy, serum doxepin concentrations were decreased an average of 46% (Leinonen et al,

b) Concomitant administration of imipramine and carbamazepine to children with attention deficit disord reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E

c) One case was reported in which nortriptyline levels dropped by more than half after carbamazepine w & Kragh-Sorensen, 1993).

3.5.1.EK Psyllium

1) Interaction Effect: decreased absorption and effectiveness of carbamazepine

2) Summary: In healthy volunteers, carbamazepine bioavailability was reduced when psyllium was administe (Etman, 1995a). If patients are treated with carbamazepine and psyllium, their administration times of should far as possible, and plasma levels of carbamazepine should be monitored (Etman, 1995a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: If patients are treated with carbamazepine and psyllium, their administration times s separated as far as possible, and plasma levels of carbamazepine should be monitored.

7) Probable Mechanism: reduced dissolution rate and slowed diffusion of carbamazepine

8) Literature Reports

a) Decreased absorption, a decreased maximum concentration, and reduced area under the curve (AU carbamazepine were noted after administration with a psyllium product to 4 healthy volunteers. Voluntee other medications one week prior to and during the study. Carbamazepine 200 mg orally was administer husk (psyllium) suspended in 200 milliliters (mL) of water. Cmax with carbamazepine alone was 2.33 mi (mcg/hour), which was reduced to 1.11 mcg/hour when psyllium was added. AUC with carbamazepine a micrograms/milliliter/hour (mcg/mL/hour), when psyllium was added AUC was reduced to 25.03 mcg/mL increased from 5.52 hours to 24.14 hours with psyllium cotreatment. Bioavailability was reduced to 55% carbamazepine alone. Statistical significance values were not provided. The mechanism of interaction w due to a decrease in the amount of biological fluid available in the gastrointestinal tract as a result of wat psyllium, which would reduce the dissolution rate of the drug from the tablet. Diffusion of the drug may b result of gel formation by psyllium. Administration times of carbamazepine and psyllium should be separ possible, and plasma levels of carbamazepine should be monitored (Etman, 1995).

3.5.1.EL Quetiapine

1) Interaction Effect: decreased serum quetiapine concentrations

2) Summary: Increased doses of quetiapine may be required to maintain control of symptoms of schizophrer receiving carbamazepine, a hepatic enzyme inducer (Prod Info Seroquel(R), 2001).

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is indicated when quetiapine is administered with carbamazepine or other i cytochrome P450 3A. Increased doses of quetiapine may be required to maintain control of psychotic sympto receiving quetiapine and carbamazepine.
7) Probable Mechanism: unknown

3.5.1.EM Quinupristin
1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Quinupristin/dalfopristin is a potent inhibitor of cytochrome P450 3A4 enzymes and may cause carbamazepine concentrations when administered concurrently. Because carbamazepine possesses a narro window, carbamazepine concentrations should be closely monitored during therapy with quinupristin/dalfopris carbamazepine should be adjusted accordingly (Prod Info Synercid(R) I.V., 1999).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the trough carbamazepine concentrations when therapy with quinupristin/d administered concurrently. Dose reductions of carbamazepine may be required. Also monitor the patient for e carbamazepine toxicity.
7) Probable Mechanism: inhibition of cytochrome P450 3A4-mediated carbamazepine metabolism

3.5.1.EN Ranolazine
1) Interaction Effect: decreased ranolazine plasma concentrations
2) Summary: The concomitant use of carbamazepine and ranolazine is contraindicated. Ranolazine is a sub glycoprotein and is primarily metabolized by CYP3A. In pharmacokinetic studies, coadministration of 600 mg CYP3A and P-glycoprotein inducer) with ranolazine 1000 mg twice daily resulted in a 95% decrease in ranol concentration. Although not evaluated, concomitant use of ranolazine and other CYP3A and P-glycoprotein i carbamazepine, could result in a similar interaction (Prod Info RANEXA(R) extended-release oral tablets, 200
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of ranolazine and CYP3A inducers, such as carbamazepine, i (Prod Info RANEXA(R) extended-release oral tablets, 2008).
7) Probable Mechanism: induction of P-glycoprotein- and CYP3A-mediated ranolazine metabolism

3.5.1.EO Rapacuronium
1) Interaction Effect: resistance to neuromuscular blocking action
2) Summary: Some medications, including carbamazepine, may enhance resistance to the neuromuscular b nondepolarizing agents such as rapacuronium (Prod Info Raplon(TM), 1999). Dose adjustments of rapacuror needed when these agents are being used concurrently.
3) Severity: minor
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The dose of rapacuronium may need to be adjusted upward in patients receiving cc carbamazepine.
7) Probable Mechanism: receptor up-regulation

3.5.1.EP Remacemide
1) Interaction Effect: reduced remacemide exposure and increased carbamazepine exposure
2) Summary: Coadministration of carbamazepine with remacemide may significantly decrease serum levels and its active metabolite. A remacemide-induced increase in serum levels of carbamazepine may also occur 1991; Walker & Patsalos, 1995a; Bialer, 1993a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor the patient for reduced remacemide effectiveness. Higher doses of remace necessary during concomitant therapy with carbamazepine. However, until target therapeutic serum levels/op remacemide are known (as well as its potential for interaction with other anticonvulsants), it will be difficult to with this agent in refractory epilepsy. In addition, because carbamazepine serum concentrations may be mod during concomitant therapy, monitor the patient for signs and symptoms of carbamazepine toxicity.
7) Probable Mechanism: induction by carbamazepine of remacemide metabolism
8) Literature Reports
a) Preliminary studies in epileptic patients receiving either carbamazepine or phenytoin (monotherapy) h significantly lower steady-state serum concentrations of both remacemide and its desglycinated (active) compared to values achieved in healthy volunteers receiving remacemide alone (Muir & Palmer, 1991; W 1995; Bialer, 1993). Serum level reductions of both parent compound and active metabolite have been 5

many patients (Bialer, 1993).
b) In addition, serum concentrations of both carbamazepine and phenytoin have been increased by up t combined remacemide therapy (Walker & Patsalos, 1995). Interaction data for remacemide and other ar unavailable.

3.5.1.EQ Repaglinide
1) Interaction Effect: decreased repaglinide plasma concentrations
2) Summary: Repaglinide is metabolized by the CYP2C8 and CYP3A4 enzyme systems. Coadministration w carbamazepine, an inducer of CYP2C8 and CYP3A4 enzyme systems, may result in decreased repaglinide p concentrations. Use caution if carbamazepine and repaglinide are coadministered (Prod Info PRANDIN(R) or Dosage adjustments to repaglinide may be necessary and blood glucose concentrations should be carefully m
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if carbamazepine and repaglinide are coadministered as this ma induction of repaglinide metabolism, thereby decreasing repaglinide plasma concentrations (Prod Info PRANI 2006). Dosage adjustments to repaglinide may be necessary and blood glucose concentrations should be ca
7) Probable Mechanism: induction of CYP2C8- and CYP3A4-mediated repaglinide metabolism

3.5.1.ER Rifampin
1) Interaction Effect: elevated carbamazepine levels and toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)
2) Summary: Carbamazepine toxicity following the addition of antituberculosis medication to chronic anticonv has been reported (Fleenor et al, 1991a). Carbamazepine levels had previously been 8.5 to 9.5 mcg/mL with toxicity. Isoniazid 300 mg daily was well tolerated for three days prior to the introduction of rifampin 600 mg d hours of initiation of rifampin, the patient developed nausea, ataxia, confusion and drowsiness. The carbama noted to be 16.9 mcg/mL. The authors suggest that rifampin may have augmented the enzyme inhibiting effe
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor the patient for signs of carbamazepine toxicity, including ataxia, nystagmus headache, vomiting, apnea, seizures, and coma. A carbamazepine plasma concentration may be helpful in d carbamazepine toxicity.
7) Probable Mechanism: inhibition of carbamazepine metabolism

3.5.1.ES Rifapentine
1) Interaction Effect: decreased anticonvulsant effectiveness
2) Summary: The efficacy of anticonvulsants may be impaired with concomitant use of rifapentine. Rifapentin 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.ET Risperidone
1) Interaction Effect: increased risperidone clearance
2) Summary: The manufacturer reports that carbamazepine may increase risperidone clearance with chronic Patients should be closely monitored. Patients may be placed on a lower dose of risperidone between 2 to 4 planned discontinuation of carbamazepine therapy to adjust for the expected increase in plasma concentratio plus 9-hydroxyrisperidone. Eleven subjects received risperidone titrated to 6 mg/day orally for 3 weeks, follow coadministration of carbamazepine for an additional 3 weeks. Plasma concentrations of risperidone and 9-hy were decreased by 50%. The plasma concentrations of carbamazepine were unaffected (Prod Info Risperdal 2003a). One published case report describes a patient who had risperidone levels which were less than expe carbamazepine therapy, along with decreased risperidone efficacy. The risperidone level dramatically increas carbamazepine was discontinued (de Leon & Bork, 1997a). Carbamazepine is an inducer of cytochrome P45 enzymes, while risperidone is primarily metabolized by CYP2D6. Whether carbamazepine is also inducing C risperidone may be partly metabolized by CYP3A is uncertain (Lane & Chang, 1998; de Leon & Bork, 1998). decrease in risperidone levels caused by carbamazepine may result in decreased therapeutic efficacy. When used in combination with carbamazepine larger doses of risperidone may be required to achieve or maintain antipsychotic effect (Spina et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor therapeutic efficacy of risperidone following the addition of carbamazepine weeks of therapy; higher risperidone doses may be needed. Patients may be placed on a lower dose of rispe to 4 weeks before the discontinuation of carbamazepine therapy to adjust for the expected increase in plasm

risperidone plus 9-hydroxyrisperidone.
7) Probable Mechanism: induction of cytochrome P450-mediated metabolism of risperidone by carbamazepi
8) Literature Reports
a) Carbamazepine was reported to induce the metabolism of risperidone in a 22-year-old male with chro resulting in low risperidone levels and lack of effectiveness. The patient was started on carbamazepine 6 risperidone 4 mg daily. The plasma concentration of 9-hydroxyrisperidone was less than half the expecte when the dose of risperidone was doubled to 8 mg daily. After achieving a therapeutic plasma concentra hydroxyrisperidone (19 mcg/L), the dose of carbamazepine was tapered and stopped. Plasma levels of 9 hydroxyrisperidone increased to 49 mcg/L, necessitating a decrease in the dose of risperidone (de Leon
b) Plasma concentrations of risperidone and 9-OH risperidone decreased when carbamazepine was ad when it was discontinued. One study evaluated the pharmacokinetic interactions between risperidone an Thirty-four patients with a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorde the study. All patients were stabilized on risperidone alone or in combination with carbamazepine for at le Steady-state plasma concentrations of risperidone and 9-hydroxyrisperidone (9-OH risperidone) were co treated with risperidone alone and patients comedicated with carbamazepine. The plasma concentration risperidone and the sum of risperidone and 9-OH risperidone (active moiety) differed significantly among patients evaluated with and without comedication, the plasma concentrations of risperidone and 9-OH ris decreased when carbamazepine was added or increased when it was discontinued. The results demons patients receiving risperidone alone, the concentration of the active moiety (risperidone plus its active me risperidone) was reduced by approximately 70% when carbamazepine was given concomitantly (Spina e
c) The concomitant use of carbamazepine and risperidone leads to a marked decrease in the steady-sta concentrations of risperidone and 9-hydroxyrisperidone through stimulation of an inducible cytochrome a influence of the cytochrome P450 2D6 genotype. A 50-year-old male with chronic schizophrenia and def activity was given carbamazepine with his existing risperidone therapy. Carbamazepine 800 mg/day for 5 to his medication regimens as a mood stabilizer. After 4 weeks of carbamazepine treatment, the patient symptoms including hallucinations, paranoid delusions, ideas of reference, and mild excitement. Plasma risperidone and its active metabolite 9-hydroxyrisperidone, had decreased from 22 and 30 ng/mL, respec Carbamazepine concentration was 8.2 mcg/mL. The risperidone dose was increased to 9 mg/day, carba discontinued, and lorazepam 5 mg/day was added. Psychotic symptoms improved over the following 3 w concentrations of risperidone and 9-hydroxyrisperidone increased to 40 and 57 ng/mL, respectively. A re in the plasma concentrations of risperidone and 9-hydroxyrisperidone suggest that the CYP2D6 genotyp susceptibility to a clinically important interaction with risperidone and carbamazepine (Spina et al, 2001).
d) Eleven schizophrenic patients in a drug interaction study received oral risperidone titrated to 6 mg/da followed by concurrent administration of carbamazepine for an additional 3 weeks. The plasma concentr risperidone and its pharmacologically active metabolite, 9-hydroxyrisperidone, were decreased by about initiation of therapy with carbamazepine, patients should be closely monitored during the first 4-8 weeks, risperidone may need to be adjusted. A dose increase or additional risperidone may need to be consider carbamazepine is discontinued, the dosage of risperidone should be re-evaluated and, if necessary, dec dose of risperidone may be required between 2 to 4 weeks before the planned discontinuation of carbam adjust for the expected increase in plasma concentrations of risperidone plus 9-hydroxyrisperidone (Proc Consta(TM), 2003).

3.5.1.EU Ritonavir
1) Interaction Effect: increased carbamazepine serum concentrations and potential toxicity
2) Summary: Coadministered ritonavir may significantly increase serum concentrations of carbamazepine du inhibition of cytochrome P450 3A enzymes, resulting in carbamazepine toxicity (Prod Info NORVIR(R), 2005; 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor carbamazepine serum levels and follow patients for signs and symptoms of toxicity (nausea, drowsiness, dizziness, weakness, headache). Reduce doses of carbamazepine as required
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports
a) A 36-year-old HIV-positive patient maintained on carbamazepine and phenytoin to control seizures ex dizziness and progressive gait disorder after the addition of ritonavir to his antiretroviral treatment. The p managed for over a year when his antiretroviral therapy, consisting of lamivudine, didanosine and saquir augmented with ritonavir 600mg twice a day. At that time, serum phenytoin and carbamazepine levels w 16.5mcg/mL and 6.5mcg/mL, respectively. Approximately two months later, the patient presented with di impaired gait. Carbamazepine serum levels were measured at 18mcg/mL while phenytoin levels remaine (14.7mcg/mL). Carbamazepine was discontinued and replaced with primidone, resulting in resolution of t and continued seizure control. Viral load remained undetectable (Garcia et al, 2000).
b) A case report demonstrates a severe interaction between ritonavir and carbamazepine resulting in ca toxicity. A 36-year-old AIDS patient with a history of alcoholism, intravenous drug use, hepatitis B and C tuberculosis, and seizures developed elevated plasma carbamazepine levels leading to CNS disorders w concomitant treatment with ritonavir. His anticonvulsant medication regimen consisted of carbamazepine times daily, phenytoin 200 mg in the morning and 100 mg at night. Two days after initiation of the new ar schedule (after 4 ritonavir doses), he presented with diplopia, disorientation, drowsiness, vertigo, and se

Carbamazepine plasma levels were increased by 99.4% to 16.6 mg/L (4-12), and his phenytoin concentı by 32.7% to 7 mg/L (10-20). Carbamazepine concentration returned to the therapeutic range two days a dosage was reduced to 200 mg three times daily, ritonavir was discontinued and nelfinavir 1000 mg twic initiated. Symptoms of toxicity disappeared as well. The author concludes that blood concentrations of a be monitored during the first 24-48 hours when ritonavir is added to carbamazepine and phenytoin treatr Reduction of the carbamazepine dose may prevent toxicity (Mateu-de Antonio et al, 2001).

3.5.1.EV Rocuronium

1) Interaction Effect: decreased duration of rocuronium-induced neuromuscular blockade

2) Summary: One case report has described a resistance to rocuronium in a patient maintained on chronic c therapy. This resistance is similar to that seen during therapy with other neuromuscular blockers and carbam precise mechanism of this interaction is not known, but may involve both pharmacodynamic and pharmacoki (Baraka & Idriss, 1996a). A study involving 22 healthy individuals undergoing neurosurgical procedures also duration of the rocuronium-induced neuromuscular block is significantly shortened by chronic carbamazepine et al, 1999a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: probable

6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of rocuronium may be needed in patients receiving carbamazepine.

7) Probable Mechanism: induction of rocuronium metabolism via cytochrome P450 enzyme system

8) Literature Reports

a) A 61-year old epileptic male who had been maintained on oral carbamazepine 200 mg three times da underwent cataract surgery. Anesthesia was induced with thiopental and fentanyl prior to the administrat intravenous bolus dose of rocuronium 0.6 mg/kg. This dose of rocuronium is twice the 95% effective dos Rocuronium caused a partial neuromuscular block and was followed by rapid recovery to T1 to 25% of th within five minutes. This response suggests that long-term therapy with carbamazepine causes a resista nondepolarizing neuromuscular blocking effects of rocuronium (Baraka & Idriss, 1996).

b) Twenty-two healthy individuals scheduled for neurosurgical procedures were studied to determine the carbamazepine therapy on the duration of rocuronium-induced neuromuscular blockade. Eleven patients treated with carbamazepine for a minimum of four weeks prior to surgery, while the other eleven patients controls. All patients received oral diazepam one hour prior to surgery, and anesthesia was induced with thiopental. A single bolus dose of rocuronium 0.6 mg/kg, which is two times the ED95, was given intrave the two groups, the lag time and the onset time did not differ significantly. However, when comparing the carbamazepine groups, the time to 10% recovery was 29.2 min vs. 19.8 min, 25% recovery was 36.1 mi 50% recovery was 43.5 min vs. 30.4 min, and 75% recovery was 57.0 min vs. 36.5 min, respectively. Th calculated as the time required for the response to the first stimulus to recover from 25% to 75% of base decreased from 20.8 min in the control group to 10.9 min in the carbamazepine group (Spacek et al, 199

3.5.1.EW Rufinamide

1) Interaction Effect: decreased carbamazepine and rufinamide plasma concentrations

2) Summary: Concomitant administration of carbamazepine and rufinamide may result in rufinamide concen of 19% to 26% (dependent on the carbamazepine dose) and carbamazepine concentration decreases of 7% Carbamazepine decreases are dependent on the concentration of rufinamide, so maximum changes will mos children and other patients who achieve significantly higher levels of rufinamide (Prod Info BANZEL(TM) oral

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Caution is advised if carbamazepine and rufinamide are coadministered as this ma decreased carbamazepine or rufinamide plasma concentrations. Risk of carbamazepine concentration reduc children and in other patients who achieve significantly higher levels of rufinamide (Prod Info BANZEL(TM) o

7) Probable Mechanism: induction of carboxylesterase-mediated rufinamide metabolism by carbamazepine

3.5.1.EX Sabeluzole

1) Interaction Effect: reduced sabeluzole efficacy

2) Summary: In epileptic patients receiving a variety of anticonvulsants (primarily carbamazepine or phenyto combinations), sabeluzole plasma concentrations have been reduced compared to data from healthy subject al, 1995a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Higher doses of sabeluzole may be required during combined therapy with carbam therapeutic plasma levels of sabeluzole are unknown, dose titration is necessarily empirical.

7) Probable Mechanism: induction by carbamazepine of sabeluzole metabolism

8) Literature Reports

a) In one study, a target minimal trough sabeluzole concentration of 50 ng/mL was not achieved in most receiving anticonvulsants (primarily carbamazepine and/or phenytoin) and sabeluzole in doses of up to 6 (Aldenkamp et al, 1995). In contrast, prior sabeluzole pharmacokinetic studies have consistently demons

levels of 40 to 50 ng/mL with 10-mg twice daily doses (De Deyn et al, 1992). Unpublished data from the (Janssen) also provide evidence of enhanced elimination of sabeluzole when combined with antiepileptic levels of anticonvulsants were unaffected by sabeluzole (Aldenkamp et al, 1995). However, these data n preliminary and are based predominantly on indirect observations; a formal kinetic study in epileptic patie ascertain the magnitude of the interaction with specific anticonvulsants.

3.5.1.EY Saquinavir

1) Interaction Effect: reduced saquinavir effectiveness
2) Summary: Coadministration of carbamazepine and saquinavir may result in reduced saquinavir serum cor Info Invirase(R), 2003). The mechanism of action is thought to be induction by carbamazepine of the cytochro isoenzyme, the enzyme primarily responsible for saquinavir metabolism. The effectiveness of saquinavir is lik decreased in patients receiving carbamazepine-saquinavir therapy due to reduced saquinavir bioavailability.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Clinicians may want to consider using alternative medication to carbamazepine in p saquinavir therapy. However, if it becomes necessary to give these agents concurrently, upward adjustments dosing may be needed to maintain antiviral effectiveness.
7) Probable Mechanism: P450 induction of saquinavir metabolism

3.5.1.EZ Selegiline

1) Interaction Effect: an increase in selegiline concentrations
2) Summary: Concomitant administration of carbamazepine and MAO inhibitors, such as selegiline, is contra Info EMSAM(R) transdermal patch, 2006; Prod Info Tegretol(R), 1998). Simultaneous use may theoretically r hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(R), 1995; Prod Info Tegretol(R), 1998; Thwe minimum of 14 days should elapse after discontinuing selegiline before initiating therapy with carbamazepine EMSAM(R) transdermal patch, 2006). However, there is preliminary evidence that the combination of carbam MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995a; Barker & Eccleston, 1 controlled studies are needed.
3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated. Selegiline should be discontinued for a minimum of 14 days, or longer if the clinical situation carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics) (Ketter et al, 1995). In addition to their regular carbamazepine and four patients received phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylc maximum dose 55 mg daily) for a mean duration combination therapy of 52.2 days. During MAOI coadm concentrations of carbamazepine and lithium did not change significantly from baseline values. Self-rate not substantially different. Four patients (three on phenelzine and one on tranylcypromine) responded to were subsequently discharged.

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru case (Joffe et al, 1985). Conversely, five patients on tranylcypromine needed a mean daily dose of carba mg to achieve a carbamazepine blood level of 8.0-11.1 mcg/mL (Barklage et al, 1992). Four other patien phenelzine only required a mean daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9

d) In subjects who had received carbamazepine (400 mg/day) for 14 days, slightly increased levels of s metabolites were seen after a single application of selegiline transdermal patch, Emsam (R), 6 mg/24 ho the selegiline plasma levels were nearly 2 fold and variable across the subject population (Prod Info EMS transdermal patch, 2006).

3.5.1.FA Sertraline

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vo seizures, coma)
2) Summary: Coadministration of sertraline and carbamazepine may cause reduced carbamazepine clearan carbamazepine toxicity manifesting in blurred vision, dizziness, tremor, and possibly blood dyscrasias (Joblin Similar interactions have been reported between carbamazepine and two other selective serotonin reuptake i

fluoxetine and fluvoxamine (Pearson, 1990; Fritze et al, 1991). However, in two separate in vivo studies, coad sertraline and carbamazepine under steady-state conditions did not increase the plasma concentrations of ca (Prod Info Zoloft(R), 2002). Two case reports of coadministration of carbamazepine and sertraline resulted in expected levels as well as lack of efficacy of sertraline (Khan et al, 2000).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Due to the potential for elevated carbamazepine levels, patients should be closely f evidence of carbamazepine toxicity when sertraline is added to therapy. Consider measuring carbamazepine concentrations within two to three weeks of adding or discontinuing sertraline, with dosage adjustments as ne cytochrome P450 3A4-mediated metabolism of sertraline, sertraline levels may be lower than expected, whic lack of efficacy of sertraline when carbamazepine is coadministered.

7) Probable Mechanism: inhibition of carbamazepine metabolism, increase in sertraline CYP3A4-mediated n

8) Literature Reports

a) A 24-year-old woman received maintenance carbamazepine 600 mg daily and flecainide 100 mg dail beginning sertraline 100 mg daily, her carbamazepine trough level increased from 4.7 to 8.5 mg/L (norm mg/L), and her blood counts were normal. Two months later, in routine testing before elective surgery, he platelet, and red and white blood cell counts were abnormally low. Postoperatively her blood counts rem blood transfusions, and on day 3 her trough carbamazepine was 11.9 mg/L, although she had missed or On bone marrow examination, erythroid hyperplasia with megaloblastic characteristics and reduced meg numbers were observed. Her hematologic counts began to improve five days after withdrawal of sertralir carbamazepine; she was not rechallenged. Suggested mechanisms of action were reduced carbamazep due to inhibition of cytochrome P450 isoenzymes and carbamazepine protein binding displacement (Job 1994).

b) Sertraline is suspected of inhibiting cytochrome P450IIIA4 (CYP3A4) enzyme activity (DeVane, 1994 carbamazepine is known to be a CYP3A4 substrate, carbamazepine might have a potentially significant sertraline. Conversely, carbamazepine is also a known potent inducer of CYP3A4 and may stimulate the sertraline, resulting in decreased sertraline concentrations (Spina et al, 1996).

c) Two cases have been reported in which concomitant use of sertraline and carbamazepine resulted in efficacy. The first such case describes a 33-year-old female with schizoaffective disorder who had been treated with haloperidol and carbamazepine for 3 years. After a depressive episode, sertraline had been titrated slowly to 300 mg/day. A plasma level for carbamazepine and sertraline was obtained after sertral Sertraline was undetectable with levels below 10 ng/ml. Another case describes a 25-year-old male diag posttraumatic stress disorder who had been successfully treated with carbamazepine for 13 years. Sertr after the patient developed major depressive disorder. Plasma levels were obtained for sertraline and ca during therapy. Sertraline levels were undetectable with carbamazepine doses of 400 mg/day and sertra mg/day (Kahn et al, 2000).

3.5.1.FB Simvastatin

1) Interaction Effect: reduced simvastatin exposure

2) Summary: Concurrent administration of carbamazepine with simvastatin significantly reduced maximum s concentration, serum half-life, and area under the concentration-time curve for both simvastatin and its active simvastatin acid (Ucar et al, 2004).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor cholesterol levels in patients receiving concomitant therapy with carbamaze simvastatin. Simvastatin dose may need to be adjusted.

7) Probable Mechanism: induction of CYP3A4-mediated first-pass metabolism of simvastatin by carbamazep

8) Literature Reports

a) Concurrent administration of carbamazepine with simvastatin significantly reduced simvastatin expos randomized, crossover study with a 2-week wash out period, healthy subjects (n=12) received either no carbamazepine 200 milligrams (mg) once daily for 2 days, after which the active drug group received car mg twice daily for the next 12 days. On day 15 (12 hours after the last carbamazepine dose), subjects fa prior to receiving a single dose of simvastatin 80 mg. Serial blood samples were obtained immediately pr hours after simvastatin administration. Carbamazepine co-administration significantly reduced the mean concentration for both simvastatin and its active metabolite simvastatin acid (from 18.7 nanograms/millili ng/mL and from 3.5 ng/mL to 1.1 ng/mL, respectively; p less than 0.01, both values). Simvastatin and sir mean areas under the concentration-time curves (AUC, 0-infinity) declined from 88.8 ng/mL x hour to 22 and from 33.5 ng/mL x hour to 6.8 ng/mL x hour, respectively (p less than 0.001, both values). Concurre with carbamazepine also significantly reduced simvastatin acid serum mean half-life (from 5.9 hours to 3 than 0.01) (Ucar et al, 2004).

3.5.1.FC Sirolimus

1) Interaction Effect: decreased plasma sirolimus concentration

2) Summary: Sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) enzymes in the gut w such as carbamazepine, which are cytochrome P450 3A4 inducers, may increase the metabolism of sirolimu decreased sirolimus plasma concentrations. Caution should be used when these two agents are used concor

Rapamune(R), 2005).
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Monitor sirolimus levels and adjust sirolimus dosage accordingly. Monitor the patier perform additional tests to determine effectiveness of sirolimus.
7) Probable Mechanism: induction of cytochrome P450-mediated sirolimus metabolism

3.5.1.FD Sorafenib
1) Interaction Effect: decreased sorafenib concentrations
2) Summary: Sorafenib is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) enzymes in the live carbamazepine, which are inducers of CYP3A4, may increase the metabolism of sorafenib, thus decreasing concentrations. Although no drug studies have been conducted between carbamazepine and sorafenib, cauti when these two agents are coadministered (Prod Info NEXAVAR(R) oral tablets, 2005).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Coadministration of carbamazepine and sorafenib may result in decreased sorafeni due to induction of cytochrome P450-mediated sorafenib metabolism by carbamazepine. Use caution if carba sorafenib are administered concurrently. Monitor patients for clinical response to sorafenib.
7) Probable Mechanism: induction of cytochrome P450-mediated sorafenib metabolism

3.5.1.FE St John's Wort
1) Interaction Effect: altered carbamazepine blood concentrations
2) Summary: An open trial involving 8 healthy volunteers taking St. John's Wort (300 milligrams (mg) three ti carbamazepine (400 mg once daily) concomitantly for 14 days demonstrated no alterations of mean carbama (Burstein et al, 2000a). This trial found some individual variability in carbamazepine clearance, indicating that have differing sensitivity to enzyme induction, which may be clinically significant. It is unknown if longer thera days as used in this trial) with St. John's Wort may affect carbamazepine levels due to a more slowly accumu which may induce cytochrome P450 enzymes. Carbamazepine is metabolized by the cytochrome P450 syste CYP3A4, and is capable of autoinduction of its own metabolism by these enzymes. St. John's Wort has been CYP3A4 in human subjects (Durr et al, 2000a; Moore et al, 2000a; Roby et al, 2000a), which suggests that a between St. John's Wort and drugs metabolized by CYP3A4 such as carbamazepine is possible. St. John's W significantly alter the cytochrome P450 system once it has already been induced by carbamazepine, which m of effect in this trial (Burstein et al, 2000a). Carbamazepine may also be capable of inducing the clearance of and its metabolites, specifically hyperforin which has been found to induce CYP3A4 transcription and expres activation of pregnane X receptors (Burstein et al, 2000a; Moore et al, 2000a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised if St. John's Wort and carbamazepine are taken concomitantly. a consistent dose of St. John's Wort with a reputable product containing a consistent amount of active ingred Wort. Carbamazepine concentrations should be monitored if patients report the loss of seizure control or new taking St. John's Wort concomitantly. When patients discontinue St. John's Wort, carbamazepine levels and carbamazepine toxicity (e.g. drowsiness, ataxia, slurred speech, nystagmus, dystonic reactions, hallucination should be monitored.
7) Probable Mechanism: induction of cytochrome P450 3A4 by St. John's Wort
8) Literature Reports
a) St. John's Wort had no effect on steady state carbamazepine and carbamazepine-10,11-epoxide pha Eight volunteers participated in an unblinded study in which subjects received immediate release carbam days. A dose titration upward from carbamazepine 200 mg daily to carbamazepine 400 mg daily occurre therapy. From days 22 through 35 subjects received 1 tablet of St. John's Wort (300 mg reagent grade ta hypericin) 3 times daily with food concomitantly with the once daily dose of carbamazepine 400 mg. No c carbamazepine or the carbamazepine-10,11-epoxide concentration-time profiles before and after St. Joh noted. None of the pharmacokinetic parameters for carbamazepine and carbamazepine-10,11-epoxide w concomitant administration of St. John's Wort. The data in this study suggest that the potential for a phar interaction is minimal and that the two agents can be given safely in combination. However, interindividu enzyme induction may be clinically important. Carbamazepine concentrations should be monitored if pat loss of seizure control or new side effects while taking St. John's Wort concomitantly (Burstein et al, 200
b) In 8 healthy male volunteers, St. John's Wort significantly induced intestinal P-glycoprotein/MDR1 an cytochrome P450 3A4. Subjects were nonsmokers, aged 23-35 years, and abstained from caffeine, alco and medications for 5 days prior to and during the study. Biopsy specimens of the duodenal intestinal mu obtained to determine P-gycoprotein/MDR1, CYP3A4 expression, and villin content at baseline and on d Erythromycin breath test was performed on days 2, 15 and 16 to determine effect on CYP3A4 function. D milligrams (mg) was given orally on day 2 for pharmacokinetic analysis. St. John's Wort extract (LI 160, L AG, Berlin) was given as 300 mg three times daily for 14 days, digoxin 0.5 mg was given again on day 1 bioavailability was increased by 18% after St. John's Wort administration. Mean intestinal P-glycoprotein increased 1.37 +/- 0.31 times following St. John's Wort (p = 0.025). One subject demonstrated a decreas

glycoprotein/villin ratio, indicating that interindividual variability is possible. Mean CYP3A4/villin ratios inc
0.17 times following St. John's Wort (p = 0.012). Induction of CYP3A4 was further evidenced by increase
erythromycin, 1.44 +/- 0.28 times over baseline, by the erythromycin breath test (Durr et al, 2000).
c) St. John's Wort has been reported to induce cytochrome P450 isoenzyme 3A4 as measured by urina
hydroxycortisol to cortisol ratios in a study of 13 healthy volunteers treated with St. John's Wort for 2 wee
baseline, mean urinary 6-beta hydroxycortisol to cortisol ratios increased from 7.1 to 13.0 (p=0.003). One
experienced an unexplained 25% decrease in urinary 6-beta hydroxycortisol to cortisol ratio. The results
recommended doses of St. John's Wort induce CYP3A4 activity (Roby et al, 2000).
d) Hyperforin was shown to activate the pregnane X receptor (PXR), which regulates expression of CYP
human hepatocytes. Levels of hyperforin in humans taking standard doses of St. John's Wort (300 mg th
are well above those required for hyperforin to activate PXR. All three St. John's Wort extracts tested act
extent comparable to that of rifampicin, which is a known activator of PXR and CYP3A4 expression (Moo

3.5.1.FF Sunitinib

1) Interaction Effect: decreased plasma concentrations of sunitinib and its active metabolite
2) Summary: Sunitinib is primarily metabolized by the cytochrome P450 3A4 (CYP3A4) enzyme to its active
is also further metabolized by CYP3A4. Coadministration of sunitinib with a CYP3A4 inducer, such as carban
result in decreased plasma concentrations of sunitinib and its active metabolite. Selection of an alternative to
with no or minimal enzyme induction potential is advised. However, if carbamazepine is used concurrently, a
sunitinib is recommended. The dose may be increased in 12.5 milligrams (mg) increments, depending on ind
tolerability, to a maximum daily dose of 87.5 mg (Prod Info SUTENT(R) oral capsules, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to induction of the cytochrome P450-mediated sunitinib metabolism, concomita
of sunitinib and carbamazepine may result in decreased plasma concentrations of sunitinib and its active met
of an alternative to carbamazepine, with no or minimal enzyme induction potential is advised. However, if car
used concurrently, consider increasing sunitinib dose in increments of 12.5 milligrams (mg), based on individ
tolerability, to a maximum daily dose of 87.5 mg.
7) Probable Mechanism: induction of cytochrome P450-mediated sunitinib metabolism

3.5.1.FG Tacrolimus

1) Interaction Effect: decreased tacrolimus efficacy
2) Summary: Tacrolimus, an immunosuppressant agent, is principally metabolized by the CYP3A hepatic en
Coadministered drugs known to induce this enzyme system could be expected to reduce plasma concentrati
Carbamazepine is one of the agents known to induce the cytochrome P-450 system. Patients receiving carba
concomitantly with tacrolimus may exhibit decreased plasma and whole blood levels of tacrolimus. When the
concurrently, monitor patients for reduced tacrolimus plasma concentrations and reduced tacrolimus efficacy.
tacrolimus doses may need to be increased (Prod Info PROGRAF(R) oral capsules, IV injection, 2006).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If carbamazepine and tacrolimus are used concurrently, monitor patient for reduced
plasma concentrations and reduced tacrolimus efficacy. Additionally, tacrolimus doses may need to be increa
7) Probable Mechanism: increased CYP3A-mediated tacrolimus metabolism

3.5.1.FH Tadalafil

1) Interaction Effect: decreased tadalafil plasma concentrations
2) Summary: Although the carbamazepine/tadalafil interaction has not been studied, concomitant use of rifar
CYP3A4 inducer) 600 mg/day, and tadalafil (a CYP3A4 substrate) as a 10-mg single dose resulted in decrea
Cmax and AUC by 88% and 46% compared with tadalafil 10 mg alone. Therefore, tadalafil use should be avo
chronically treated with potent inducers of CYP3A4, such as carbamazepine (Prod Info ADCIRCA (TM) oral t
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbamazepine, a CYP3A4 inducer, and tadalafil, a CYP3A4 su
resulted in significantly decreased tadalafil bioavailability. Therefore, tadalafil use should be avoided in patier
chronic treatment with a potent CYP3A4 inducer, such as carbamazepine (Prod Info ADCIRCA (TM) oral tabl
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of tadalafil by carbamazepine

3.5.1.FI Telithromycin

1) Interaction Effect: subtherapeutic telithromycin concentrations and/or elevated serum levels of carbamaze
2) Summary: Concomitant administration of carbamazepine, a cytochrome P450 3A4 inducer, is likely to res
subtherapeutic levels of telithromycin and loss of effect. Elevation of serum levels of drugs metabolized by th
P450 system, such as carbamazepine, may be observed when coadministered with telithromycin, a cytochro
inhibitor. As a result, increases or prolongation of the therapeutic and/or adverse effects of carbamazepine m
(Prod Info Ketek(TM), 2004).
3) Severity: moderate

4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant treatment of telithromycin and carbamazepine is not recommended. W and carbamazepine are coadministered, monitor carbamazepine concentrations and monitor for telithromycin
7) Probable Mechanism: induction of cytochrome P450 3A4-mediated metabolism of telithromycin by carban of cytochrome P450-mediated phenytoin metabolism by telithromycin

3.5.1.FJ Temsirolimus

1) Interaction Effect: decreased maximum concentration of sirolimus, the active metabolite of temsirolimus
2) Summary: Temsirolimus is primarily metabolized by the CYP3A4 isozyme into 5 metabolites, of which sirc principal active metabolite. Sirolimus is also primarily metabolized by CYP3A4 (Prod Info RAPAMUNE(R) ora tablets, 2007). Although not studied with carbamazepine, coadministration of rifampin, a potent CYP3A4 indu intravenous temsirolimus decreased the Cmax and AUC of sirolimus by 65% and 56%, respectively, compare alone. Therefore, avoid using carbamazepine and temsirolimus concurrently. If concurrent use of temsirolimu CYP3A4 inducer is clinically warranted, the temsirolimus dose may be increased from 25 mg/week up to 50 r discontinuation of the inducer, the temsirolimus dose should be returned to its original dose used prior to initia (Prod Info TORISEL(TM) KIT IV injection, 2007).
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Avoid using carbamazepine and temsirolimus concurrently as coadministration may substantially decreased exposure and maximum concentration of sirolimus (active metabolite of temsirolimus of temsirolimus with a strong CYP3A4 inducer, such as carbamazepine, is clinically warranted, consider increa temsirolimus dose from 25 mg/week up to 50 mg/week. Upon discontinuation of the inducer, reduce the tems to its original dose used prior to initiation of the inducer (Prod Info TORISEL(TM) KIT IV injection, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of sirolimus (active metabolite of temsir

3.5.1.FK Terfenadine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: A case report indicates that terfenadine may displace carbamazepine from protein binding sites free carbamazepine levels and toxicity when terfenadine is added to carbamazepine therapy (Hirschfeld & Ja
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Monitor serum concentrations of carbamazepine when terfenadine is added or disc therapy. Patients should be followed for any symptoms of carbamazepine toxicity.
7) Probable Mechanism: carbamazepine displacement from protein binding sites by terfenadine
8) Literature Reports
a) An 18-year-old female displayed confusion, disorientation, visual hallucinations, nausea, and ataxia. began shortly after terfenadine 60 mg twice daily was added to her regular regimen of carbamazepine (d unspecified) which resulted in an excess of free (unbound) carbamazepine (6 mg/L). The free carbamaz returned to 2.1 mg/L (normal, 1.6 to 2.2 mg/L) and the symptoms resolved after terfenadine was disconti may have displaced carbamazepine from protein binding sites, leading to the high free carbamazepine le Jarosinski, 1993).

3.5.1.FL Theophylline

1) Interaction Effect: decreased theophylline effectiveness
2) Summary: The concurrent use of theophylline and carbamazepine could lead to decreased theophylline le et al, 1983a). Carbamazepine induces hepatic cytochrome P450 activity and would be expected to affect theo metabolized in the liver (Prod Info Tegretol(R) carbamazepine chewable tablets, 2002). An increase in theopl be necessary with concomitant use. One report of decreased carbamazepine levels and efficacy suggests tha both drugs is necessary (Mitchell et al, 1986a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Carbamazepine and theophylline serum concentrations should be closely monitored carbamazepine is added, discontinued, or when dosing changes of either drug occur. Dosing adjustments of be necessary.
7) Probable Mechanism: increased theophylline metabolism
8) Literature Reports
a) A single case was reported in which a short course of theophylline appeared to cause a mild reductio of carbamazepine in close temporal relationship to a brief generalized tonic-clonic seizure. During hospit trough serum carbamazepine levels were reduced by about 50% after six doses of theophylline every 6 l seizure occurred shortly after the seventh dose (Mitchell et al, 1986).
b) An asthmatic child was receiving theophylline 10 mg/kg/day and phenobarbital. The phenobarbital wa carbamazepine, resulting in subtherapeutic theophylline levels and markedly decreased half-life after 3 w concurrent use. Within 3 weeks of changing carbamazepine to ethotoin, the half-life of theophylline had i asthma controlled (Rosenberry et al, 1983).

3.5.1.FM Tiagabine

1) Interaction Effect: decreased tiagabine efficacy

2) Summary: Concurrent use of tiagabine and carbamazepine had no effect on the steady-state plasma conc carbamazepine or its epoxide metabolite in epileptic patients. However, it has been shown in population phar studies that tiagabine clearance is 60% greater in patients taking carbamazepine than in patients not receivin inducing agents. Tiagabine is metabolized primarily by the cytochrome P450 3A isoform subfamily of enzyme is known to induce these enzymes, therefore causing an increase in the metabolism of tiagabine (Prod Info G

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for tiagabine efficacy. It may be useful to obtain tiagabine plasma l after the addition or withdrawal of carbamazepine.

7) Probable Mechanism: induction of tiagabine metabolism by carbamazepine

3.5.1.FN Ticlopidine

1) Interaction Effect: an increased risk of carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vor seizures, coma)

2) Summary: Carbamazepine toxicity developed in a patient one week after ticlopidine therapy was initiated. carbamazepine is mediated through the cytochrome P450 3A4 enzyme system, and ticlopidine appears to be pathway (Brown & Cooper, 1997a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor patients for signs of carbamazepine toxicity if ticlopidine is added to their th A carbamazepine plasma level may be useful if toxicity is suspected and downward dosing adjustments may carbamazepine dose may need to be increased when ticlopidine is discontinued.

7) Probable Mechanism: inhibition of cytochrome P450-mediated carbamazepine metabolism by ticlopidine

8) Literature Reports

a) A 67-year-old male scheduled to undergo elective coronary stenting was started on ticlopidine 250 m week prior to the procedure. Other medications included aspirin , diltiazem 180 mg daily, a nitroglycerin p carbamazepine 600 mg twice daily. Shortly after ticlopidine therapy was initiated, the patient experienced ataxia that resulted in his inability to walk. These symptoms would resolve five to six hours after his ticlop Although the patient's carbamazepine level had been 43 mol/L (therapeutic range 25 to 50 mol/L) five we carbamazepine was 75 mol/L on admission to the hospital. The carbamazepine dose was decreased to and his symptoms resolved. One week after the dose decrease, the carbamazepine level was 53 mol/L. the discontinuation of ticlopidine, the carbamazepine level had fallen to 42 mol/L (Brown & Cooper, 1997

3.5.1.FO Tipranavir

1) Interaction Effect: decreased tipranavir concentrations

2) Summary: Tipranavir is a CYP3A substrate. Concomitant use of tipranavir and carbamazepine, a CYP3A cause decreased tipranavir plasma concentrations (Prod Info APTIVUS(R) oral capsules, solution, 2008).

3) Severity: moderate

4) Onset: unspecified

5) Substantiation: theoretical

6) Clinical Management: Use caution when prescribing carbamazepine to patients who are taking tipranavir decreased tipranavir plasma concentrations (Prod Info APTIVUS(R) oral capsules, solution, 2008).

7) Probable Mechanism: induction of CYP3A-mediated tipranavir metabolism

3.5.1.FP Toloxatone

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant MAO inhibitor and carbamazepine therapy is contraindicated (Prod Info Tegretol(Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998h; Thweatt, 1986h). However, there is preliminary evidence that the combination of car an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995q; Barker & Ecclestor controlled studies are needed.

3) Severity: contraindicated

4) Onset: rapid

5) Substantiation: theoretical

6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.

7) Probable Mechanism: unknown

8) Literature Reports

a) A double-blind study was conducted in ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir

daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995p).

b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimelidine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984p).

c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985h). Conversely, five patients on tranylcypromine need a mean daily dose of carbamazep achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992h).

3.5.1.FQ Topiramate

1) Interaction Effect: decreased topiramate concentrations

2) Summary: In controlled, clinical pharmacokinetic studies, patients with epilepsy showed a 40% decrease i concentrations when carbamazepine was added to topiramate therapy (Prod Info TOPAMAX(R) oral tablets, capsules, 2008). Topiramate oral and nonrenal clearance is twofold to threefold higher during concurrent carl therapy. The renal clearance of topiramate, however, is not affected by concomitant carbamazepine therapy. changes in carbamazepine pharmacokinetic parameters were evident upon coadministration with topiramate 1996a). In another study, addition of topiramate to existing carbamazepine regimens in epileptic patients resu significant pharmacokinetic changes in either drug (Wilensky et al, 1989a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Upon the addition of carbamazepine to a drug regimen involving topiramate, the do may need to be increased to accommodate for the decreased concentration of topiramate that occurs with co (Prod Info TOPAMAX(R) oral tablets, oral sprinkle capsules, 2008).

7) Probable Mechanism: unknown

8) Literature Reports

a) Twelve patients with partial epilepsy receiving chronic stable doses of carbamazepine were enrolled i determine the steady-state pharmacokinetic profile of topiramate and the effects of comedication with ca subjects were receiving carbamazepine in doses of 300 mg to 800 mg every eight hours. Topiramate wa doses were increased at approximately two week intervals until the highest tolerated dose was reached. was then tapered off over the next four weeks, and topiramate was maintained as monotherapy for two r Results showed that the mean topiramate area under the concentration-time curve (AUC), Cmax, Cmin, were all approximately 40% lower during carbamazepine treatment as compared to topiramate monother suggest that the metabolic clearance of topiramate increases when carbamazepine is coadministered. T significant changes in the carbamazepine pharmacokinetic profile during topiramate administration (Sach

b) The interaction between carbamazepine and topiramate was assessed in eight epileptic patients. Pha profiles were evaluated after a single dose of topiramate, after two weeks at three different doses of topir each subject had taken topiramate at its highest tolerated dose for two months. No significant changes ir carbamazepine, or carbamazepine metabolite pharmacokinetics were observed at any dose level (Wilen

3.5.1.FR Tramadol

1) Interaction Effect: decreased tramadol efficacy and increased seizure risk

2) Summary: Chronic carbamazepine therapy increases the metabolism of tramadol by the cytochrome P45(which may significantly reduce the analgesic effect of tramadol. Due to the seizure risk involved with tramadc administration of tramadol and carbamazepine is not recommended (Prod Info ULTRAM(R)ER extended-rele 2005).

3) Severity: major

4) Onset: unspecified

5) Substantiation: probable

6) Clinical Management: Concomitant administration of carbamazepine and tramadol is not recommended, a may reduce tramadol efficacy and tramadol may increase the risk of seizure.

7) Probable Mechanism: induction of CYP3A4 metabolism of tramadol by carbamazepine

3.5.1.FS Tranylcypromine

1) Interaction Effect: hypertensive urgency, hyperpyrexia, and seizures

2) Summary: Concomitant tranylcypromine and carbamazepine therapy is contraindicated (Prod Info Tegretc Simultaneous use may theoretically result in hyperpyrexia, excitation, and seizure activity (Prod Info Parnate(Info Tegretol(R), 1998c; Thweatt, 1986c). However, there is preliminary evidence that the combination of carl an MAOI may be safe and efficacious, even in some refractory cases (Ketter et al, 1995g; Barker & Eccleston controlled studies are needed.

3) Severity: contraindicated
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of carbamazepine and monoamine oxidase inhibitors contraindicated by the manufacturer. Monoamine oxidase inhibitors should be discontinued for a minimum of if the clinical situation permits, before carbamazepine therapy is initiated.
7) Probable Mechanism: unknown
8) Literature Reports
a) A double-blind study was conducted on ten inpatients with depression that had proved refractory to m therapies (electroconvulsive therapy, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, ca benzodiazepines, and antipsychotics). In addition to their regular carbamazepine and lithium doses, four phenelzine (mean maximum dose 67.5 mg daily) and six patients received tranylcypromine (mean maxir daily) for a mean duration combination therapy of 52.2 days. During MAOI coadministration, serum conc carbamazepine and lithium did not change significantly from baseline values. Self-rated side effects were different. Four patients (three on phenelzine and one on tranylcypromine) responded to this therapy and discharged (Ketter et al, 1995f).
b) A 60-year-old woman who had an atypical endogenous, depressive illness of psychotic intensity was intermittently with cyclic antidepressants and intermittent electroconvulsive therapy. Following an acute v illness, she was treated successfully with a combination of phenelzine and L-tryptophan. Following a few improvement, her situation worsened and she was subsequently treated with zimeldine and lithium. Faili placed on a regimen of tranylcypromine with doses increasing progressively up to 30 mg daily in conjunc and tryptophan. Subsequently, carbamazepine was added in small doses with increments to achieve a p approximately 5 mg/L. This regimen proved successful, and she was discharged home and had remaine two months of follow up at the time of publication (Barker & Eccleston, 1984f).
c) Addition of tranylcypromine to carbamazepine therapy did not significantly affect carbamazepine seru (Joffe et al, 1985c). Conversely, five patients on tranylcypromine needed a mean daily dose of carbamaz achieve a carbamazepine blood level of 8.0-11.1 mcg/mL. Four other patients receiving phenelzine only daily dose of carbamazepine 450 mg to attain a blood level of 8.7-10.9 mcg/mL (Barklage et al, 1992c).

3.5.1.FT Trazodone

1) Interaction Effect: decreased trazodone plasma concentrations
2) Summary: An increase in carbamazepine concentration/dose ratio was reported when trazodone was add although the patient did not exhibit any signs of carbamazepine toxicity (Romero et al, 1999a). Trazodone se have been decreased during coadministration with carbamazepine. Patients should be closely monitored to s need for an increased dose of trazodone when taking both drugs (Prod Info Desyrel(R), 2003).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When given concurrently with carbamazepine, trazodone serum concentrations sho monitored and trazodone dose adjustments made as needed.
7) Probable Mechanism: induction of trazodone CYP3A4-mediated metabolism
8) Literature Reports
a) A 53-year-old male diagnosed with generalized partial epilepsy was receiving carbamazepine 700 mg corresponding serum concentration of 7.9 mg/L. The concentration/dose ratio, calculated by dividing the concentration (mg/L) by the dose (mg/kg), was 0.89. Trazodone therapy was initiated for depression, and the carbamazepine serum concentration had increased to 10.0 mg/L with a corresponding concentration The serum concentration of the main pharmacologically active metabolite of carbamazepine, carbamaze epoxide, was not measured. Although this patient did not show any signs or symptoms of carbamazepin interaction may be clinically significant in patients stabilized at a higher carbamazepine steady-state con et al, 1999).

3.5.1.FU Trimipramine

1) Interaction Effect: decreased trimipramine effectiveness
2) Summary: The concomitant use of carbamazepine and antidepressants has been reported to decrease se antidepressant levels (Leinonen et al, 1991b; Brown et al, 1990). Although not reported for trimipramine, a sir could occur.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor for clinical efficacy of the trimipramine therapy and for any signs of toxicity Serum levels of both agents should be considered when either agent is added or discontinued, with appropria adjustments made accordingly.
7) Probable Mechanism: increased trimipramine metabolism
8) Literature Reports
a) Concomitant administration of imipramine and carbamazepine to children with attention deficit disorde reported to result in a 50% decrease in the total plasma concentration of imipramine plus desipramine (E Carbamazepine probably enhances the hepatic microsomal metabolism of imipramine and other tricyclic by inducing hepatic enzymes (Moody et al, 1977). Although not reported specifically for trimipramine, be

potential for a similar interaction exists. Patients on chronic carbamazepine therapy may require increase tricyclic antidepressants.

3.5.1.FV Troleandomycin

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Concurrent administration of carbamazepine and troleandomycin has resulted in increased pla carbamazepine levels and signs of toxicity (Dravet et al, 1977; Mesdjian et al, 1980a).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: The combination of carbamazepine and macrolide antibiotics should be avoided an given to an alternative antibiotic. If the combination is necessary, carbamazepine levels should be obtained w adding or discontinuing troleandomycin and dosage adjustments made accordingly.
7) Probable Mechanism: decreased carbamazepine metabolism
8) Literature Reports

a) Seventeen epileptic patients receiving troleandomycin concurrently with carbamazepine alone or in c other anticonvulsants experienced symptoms of acute intoxication (dizziness, drowsiness, nausea, vomi Troleandomycin was given a second time to 3 patients who experienced similar symptoms. Six patients increase in carbamazepine plasma levels after administration of troleandomycin; when the antibiotic was carbamazepine levels returned to normal (Mesdjian et al, 1980).

3.5.1.FW Valnoctamide

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: One study in six epileptic patients demonstrated that concurrent administration of valnoctamide carbamazepine (CBZ) resulted in a significant increase in carbamazepine epoxide serum concentrations. Fou experienced clinical symptoms of carbamazepine intoxication. Carbamazepine epoxide serum levels returned discontinuation of valnoctamide, and all signs of toxicity abated (Pisani et al, 1993).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of carbamazepine and valnoctamide is best avoided; however, if th necessary, careful monitoring for signs of carbamazepine toxicity is needed with dosage adjustments made a
7) Probable Mechanism: inhibition of carbamazepine metabolism
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, 1990e; Van Dyke et al, 1991e; 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, 1987e; Ramsay et al, 1990e; 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.FX Valproic Acid

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, 1985a; 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,
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drov 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 1985; Flachs et al, 1979; Adams et al, 1978). In an in vitro study of protein binding, valproic acid compet 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 c 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 c 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, 1985; Mahaly et al, 1979). Infrequent reports have indicated symptoms c 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, 1994).

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, 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, 1996a). Such c increase the risk of major birth defects 3- to 4-fold over monotherapy and about 10-fold over background

3.5.1.FY Vecuronium

1) Interaction Effect: decreased vecuronium duration of action

2) Summary: Patients on carbamazepine maintenance therapy required significantly higher doses of vecuron similar neuromuscular blocking effects as controls (Whalley & Ebrahim, 1994a; Norman, 1993a). This may be pharmacokinetic interaction between carbamazepine and vecuronium, although a pharmacodynamic interact ruled out (Alloul et al, 1996a).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: Monitor patients for an appropriate clinical response to the neuromuscular blocker. intervals or higher doses of vecuronium may be needed in patients receiving carbamazepine.

7) Probable Mechanism: increased clearance of vecuronium

8) Literature Reports

a) Twenty-four surgical patients were evaluated, of which eight were receiving carbamazepine (along wi other drugs) and 16 were using several different drugs but not carbamazepine (Whalley & Ebrahim, 199 vecuronium required for 50%, 90%, and 95% depression of first twitch were 29, 52, and 64 mcg/kg, resp carbamazepine group, compared with 21, 36, and 44 mcg/kg, respectively, for the non-carbamazepine g 40% higher dose of vecuronium was required in study subjects using carbamazepine.

b) A case report describes a 19-year old epileptic female who underwent a sigmoid colectomy (Norman, patient had been maintained on carbamazepine 700 mg daily. The first bolus dose of vecuronium 6 mg p for only 18 minutes. A continuous infusion of vecuronium at an average of 6.67 mg/hr was needed to sus neuromuscular block. This is higher than the average of vecuronium 4 mg/hr that is needed to produce b patients not treated with carbamazepine.

c) The pharmacokinetic and pharmacodynamic effects of a bolus intravenous dose of vecuronium were carbamazepine-treated subjects and in ten control subjects (Alloul et al, 1996). No changes in onset time distribution at steady-state were observed. However, the carbamazepine group had a shorter mean reco (T1 25%) compared to controls (28.1 minutes vs. 47.3 minutes). The T1 25% to T1 75% recovery index v the carbamazepine group compared to 21.9 minutes in controls. Clearance of vecuronium was 9.0 mL/kg carbamazepine group and only 3.8 mL/kg/min in the control group. This two-fold increase in the clearanc provides evidence of a pharmacokinetic origin to the interaction with carbamazepine, although the possib concurrent pharmacodynamic interaction cannot be ruled out.

d) Long-term phenytoin or carbamazepine therapy accelerates recovery from vecuronium-induced paral The patients were assigned to one of 3 groups: control (n=10; no history of epilepsy and not receiving ch affecting neurotransmission), children receiving phenytoin (n=10) or carbamazepine (n=10). The eliminat significantly shorter for the phenytoin and carbamazepine groups compared with control. A statistically si in clearance of vecuronium occurred in the carbamazepine groups compared with control. Increased clea vecuronium in the phenytoin group also occurred but was not statistically significant. The recovery indice vecuronium-induced block for the children on antiepileptic drugs were significantly faster than those for th The author concludes that resistance to vecuronium in children on chronic anticonvulsant therapy is part increased metabolism. The contribution of altered pharmacodynamics to the resistance to vecuronium co determined in this study (Soriano et al, 2001).

3.5.1.FZ Verapamil

1) Interaction Effect: increased carbamazepine plasma concentrations and risk of toxicity (ataxia, nystagmus headache, vomiting, apnea, seizures, coma)

2) Summary: Concomitant administration of carbamazepine and verapamil has resulted in increased carbam increasing the risk of toxicity (Summers et al, 2004; Prod Info Covera HS(R), 2003; Brodie & Macphee, 1986l 1986a; Eimer & Carter, 1987b; Bahls et al, 1991a).

3) Severity: moderate

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: Monitor for clinical signs of carbamazepine toxicity along with carbamazepine serur dose accordingly. Nifedipine does not appear to interact with carbamazepine and may be considered as an a verapamil.

7) Probable Mechanism: decreased carbamazepine metabolism and inhibition of p-glycoprotein-mediated ef

8) Literature Reports

a) Concomitant administration of verapamil 120 mg orally 3 times a day in patients receiving carbamaze partial epilepsy was reported to result in carbamazepine neurotoxicity in all of 6 patients treated (MacPhe Increase in free and total carbamazepine levels were observed in 5 patients (mean increases of 33 and associated with a concurrent decrease by 36% in the ratio of carbamazepine-10,11 epoxide to carbamaz resolved after several days following withdrawal of verapamil in all patients. Rechallenge in 2 patients re neurotoxic symptoms. These data suggest that verapamil inhibits carbamazepine metabolism. Reductior carbamazepine may be required when verapamil is administered, and increased when verapamil is witho exacerbation of epileptic seizures. Seizure aggravation occurred in one patient in this series following ab verapamil.

b) The concurrent use of verapamil with carbamazepine was effective in suppressing p-glycoprotein-me carbamazepine transport and clearance in a 24-year-old woman with intractable epilepsy. The patient's c seizures had been refractory to multiple anticonvulsants, partial temporal lobectomy, and vagal nerve sti resulted in intermittent hospitalization a mean of every 55 days for management of complex partial status Verapamil 180 milligrams (mg)/day was added to an anticonvulsant regimen comprising carbamazepine in addition to levetiracetam, topiramate, and clonazepam. Baseline carbamazepine plasma concentratior low end of the therapeutic range (4.2 mg/milliliter (mL). At 1-month follow up, carbamazepine plasma cor mg/L, and the patient reported subjective improvement in seizure control. Verapamil dose was titrated in 480 mg daily, resulting in an increase in carbamazepine plasma concentration to 13.3 mg/L, without repo effects, and with an extension of between-hospitalization time to approximately 4 months between admis et al, 2004).

3.5.1.GA Vigabatrin

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

2) Summary: In a study of sixty-six epileptic patients, when vigabatrin was added to carbamazepine therapy carbamazepine serum concentrations increased 24.2%. A strong negative correlation between the value of th the initial level of carbamazepine concentration after vigabatrin addition also was revealed in this study (Jedrz 2000a).

3) Severity: major

4) Onset: delayed

5) Substantiation: probable

6) Clinical Management: When vigabatrin is added to carbamazepine therapy, concentration of carbamazepi monitored and the dose of carbamazepine should be adjusted accordingly.

7) Probable Mechanism: decreased carbamazepine metabolism

8) Literature Reports

a) Sixty-six epileptic patients were evaluated for the changes in carbamazepine concentration following All patients had simple or complex partial seizures, and all were drug-resistant. Vigabatrin was added as after long-term (at least 3 months) carbamazepine monotherapy and was administered in increasing dos Carbamazepine concentrations prior to vigabatrin addition was 9.41 mcg/ml (range 4.33 to 13.05 mcg/m vigabatrin the mean carbamazepine concentration increased to 11.31 mcg/ml (range 6.88 to 18.57 mcg/ increase in carbamazepine concentration was 24.2%. An increase in carbamazepine concentration by at occurred in 46 out of 66 patients, i.e. 69.7%, after vigabatrin therapy. Twenty-four patients (36.4%) respo carbamazepine level of at least 12 mcg/ml. Carbamazepine concentration in this group ranged from 11.9 whereas the carbamazepine concentration before vigabatrin therapy was 10.57 mcg/ml (range 6.59 to 1 significant relationship was found between vigabatrin dosage and the percentile change in carbamazepir after the addition of vigabatrin. There was a strong negative correlation between the percentile increase concentration and initial carbamazepine concentration (Jedrzejczak et al, 2000).

b) Vigabatrin produces a statistically significant increase in the plasma clearance of carbamazepine (CE drugs are given simultaneously. Fifteen patients with refractory partial epilepsy and receiving vigabatrin a were studied. Treatment 1 consisted of an initial period with CBZ monotherapy. Treatment 2 consisted o combination with vigabatrin. CBZ monotherapy was given for 3-12 months with monitoring of CBZ plasm After an initial period, patients received open add-on treatment with vigabatrin 1500 mg/day in two divide 1500 mg daily dose of vigabatrin was increased up to a maximum of 4000 mg. The final daily dose of vig 2150+/-900 mg, with a range of 1500-4000 mg. The steady-state trough plasma concentration of CBZ w the presence of vigabatrin, with a mean value of 7.9+/-1.4 vs 6.5+/-2.0 mcg/mL (p less than 0.03), respe

ratio of CBZ was significantly decreased from 0.59 +/- 0.20 in monotherapy to 0.45+/-0.15 in combinatior less than 0.05). CBZ plasma clearances in monotherapy ranged from 40 to 128 mL/h/kg, with a mean va mL/h/kg. When CBZ was combined with vigabatrin there was a marked increase in the plasma clearance mL/h/kg) with a mean value of 105.8 +/- 38.9 mL/h/kg (P less than 0.01). The plasma clearance of CBZ i 35% in the presence of vigabatrin. Dosing of CBZ and vigabatrin in combination is best adjusted by indiv drug monitoring (Sanchez-Alcaraz et al, 2002).

3.5.1.GB Viloxazine

1) Interaction Effect: carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizur
2) Summary: Viloxazine administered concurrently with carbamazepine increased carbamazepine steady-sta significantly (Pisani et al, 1984a; Pisani et al, 1986aa). These increased serum levels were associated with sy carbamazepine toxicity (dizziness, ataxia, fatigue, drowsiness) in five of seven patients and four of seven pat aformentioned studies, respectively. The concentration of the active metabolite, carbamazepine-10,11-epoxic increased (Pisani et al, 1986aa). In another study by (Pisani et al, 1986ba), viloxazine pharmacokinetics were the administration of carbamazepine.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Downward adjustment of carbamazepine dosage may be necessary when adding v therapy. Monitor serum carbamazepine concentrations closely.
7) Probable Mechanism: inhibition of carbamazepine hepatic metabolism by viloxazine
8) Literature Reports

a) The possibility of a drug interaction between viloxazine and carbamazepine was studied in seven epil stabilized on carbamazepine therapy. Viloxazine 100 mg three times daily was added to drug therapy for significantly increased steady-state carbamazepine serum levels from an average of 8.1 mcg/mL before to an average of 12.1 mcg/mL during the second and third weeks of viloxazine therapy (p less than 0.005 increased levels were associated with mild symptoms of carbamazepine toxicity (dizziness, ataxia, fatigu five patients. Serum carbamazepine levels returned to normal and symptoms abated after discontinuing et al, 1984).

b) Significant increases in serum carbamazepine and carbamazepine-10,11-epoxide levels during viloxa investigated. The study was performed in six epileptic patients stabilized on carbamazepine. After three viloxazine administration, steady-state plasma carbamazepine levels increased by 55% (p less than 0.00 carbamazepine-10,11-epoxide levels increased by 16% (p less than 0.001). Three of the six patients suf symptoms of carbamazepine intoxication. In a seventh patient, viloxazine had to be discontinued after tw severe carbamazepine intoxication (Pisani et al, 1986a).

c) The pharmacokinetics of viloxazine and whether chronic anticonvulsant therapy has any affect on vilo pharmacokinetics were studied in six epileptic patients taking one or two anticonvulsants (carbamazepin or phenytoin) and six drug-free control subjects. One oral viloxazine 200 mg dose followed by a single in of viloxazine 200 mg at least one week later were administered to each patient and control subject. Term not affected by anticonvulsant therapy (4.3 +/- 1.5 hours for the patients and 4.3 +/- 1.8 hours for the cor Absolute oral availability was 85% +/- 14%. Clearance and volume of distribution calculated from the intr the patients were 124 +/- 11 mL/kg/hr and 0.73 +/-0.28 L/kg, respectively. The authors concluded that vil pharmacokinetics did not appear to be significantly altered by carbamazepine, phenobarbital, or phenyto 1986b).

3.5.1.GC Voriconazole

1) Interaction Effect: reduced systemic exposure to voriconazole
2) Summary: Although not studied clinically, plasma voriconazole concentrations may be significantly reduce administration of carbamazepine (Prod Info VFEND(R) IV injection, oral tablets, suspension, 2008).
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of voriconazole and carbamazepine is contraindicated (Prod Info injection, oral tablets, suspension, 2008).
7) Probable Mechanism: induction by carbamazepine of cytochrome P450-mediated voriconazole metabolis

3.5.1.GD Warfarin

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant carbamazepine and warfarin therapy has been reported to result in a decreased a effect, secondary to the induction of hepatic metabolism of the anticoagulant (Massey, 1983; Cohen & Armstr Weser & Koch-Weser, 1975; Kendall & Boivin, 1981; Hansen et al, 1971).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When carbamazepine is added or deleted from oral anticoagulant therapy with warf coumarin anticoagulant, intensified monitoring of the prothrombin time ratio or international normalized ratio (undertaken. It is often necessary to increase the dose of warfarin with the addition of carbamazepine, while a warfarin dose is frequently required upon the discontinuation of carbamazepine. Stabilization of the warfarin d

anticoagulant effect may require four to six weeks after the addition or deletion of carbamazepine.
7) Probable Mechanism: increased warfarin metabolism
8) Literature Reports
a) A patient taking carbamazepine 300 mg to 600 mg daily and warfarin 6 mg daily was stable at 2 to 3 i experienced a PT increase to 5 times the control value within four weeks of discontinuation of carbamaz dosage was reduced to 4 mg daily. Carbamazepine was reinstituted, and five weeks were required for re steady-state warfarin level at a dose of 5.5 mg daily (Ross & Beeley, 1980).

3.5.1.GE Yohimbine
1) Interaction Effect: increased risk of manic episodes in patients taking carbamazepine for bipolar disorder
2) Summary: Yohimbine may exacerbate bipolar disorder by precipitating manic episodes. This effect has be reports, generally within one to two hours of yohimbine administration. The authors concluded that patients w diathesis are predisposed to the psychogenic effect of yohimbine (Price et al, 1984a). Yohimbine appears to alpha2-adrenergic receptors on sympathetic nerve endings, increasing noradrenergic output through negative Alpha2-adrenoceptors may be involved in the pathogenesis of psychiatric disorders (Price et al, 1984a). Theo taking carbamazepine for bipolar disorder may experience a return of manic symptoms if they take yohimbine
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid yohimbine use in patients taking carbamazepine for treatment of bipolar diso
7) Probable Mechanism: increased norepinephrine release by yohimbine
8) Literature Reports
a) Yohimbine challenges were administered to 55 patients with major depression, 39 patients with agora disorder, and 20 normal control subjects. Three patients developed manic-like symptoms, 2 of which hac bipolar disorder and one with manic symptoms which developed on withdrawal of desipramine. Normal s experienced either mild anxiety or no effect after yohimbine. Yohimbine increases anxiety in patients with disorder (Price et al, 1984).
b) A 41-year-old male with a 3 year history of bipolar disorder presented with depressive symptoms of 1 unresponsive to a 6 month trial of desipramine 250 mg/day and lithium 2100 mg/day. Lithium was discor given a 10 mg yohimbine challenge upon hospital admission. One hour after receiving yohimbine, the pa tremulousness, restlessness, giddiness, pressured speech, and feelings of increased energy and euphor after receiving yohimbine, he began to return to his baseline state. He continued to experienced increase decreased hopelessness, and decreased depression 4 hours after the yohimbine challenge. His full depr returned by the next morning. Following a 4 week period during which desipramine was discontinued and given, the patient's depression resolved. A second challenge of yohimbine 10 mg led to chills within 60 m 90 minutes he reported feeling euphoric. After 2 hours he returned to his baseline state (Price et al, 1984
c) A 20-year-old female with melancholic major depression with mood-congruent psychosis during her s was treated with desipramine 250 mg and perphenazine 40 mg daily with partial response. Perphenazine 6 weeks postpartum and desipramine was tapered off and discontinued 5 days prior to hospital admissio placebo washout period, she reported hearing voices telling her to kill herself. She was given a 20 mg yo challenge. Within one hour she experienced tremor, lacrimation, rhinorrhea, and became talkative. In the her affect brightened, her speech became increasingly clear and loud, and her hallucinations stopped. D symptoms gradually returned over the next several hours. Bupropion was initiated at doses up to 600 mg depression and intermittent hallucinations continued. A second challenge of yohimbine 20 mg led to mild tremulousness within 30 minutes, which resolved over an hour. Her affect improved and remained bright after which she returned to her baseline state (Price et al, 1984).
d) A 43-year-old woman with a 26-year history of bipolar disorder was discontinued from all medications admission (thioridazine, lithium, l-triiodothyronine, methylphenidate, and lorazepam) with the exception o was tapered off over 5 days following admission. One hour after receiving yohimbine 20 mg orally, she b voluble, and expansive. She experienced diaphoresis, palpitations, and tremors. Her elation progressed loud hysterical, inappropriate laughter. The intense manic symptoms persisted for 40 minutes. Her affect for the remainder of the day (Price et al, 1984).

3.5.1.GF Zaleplon
1) Interaction Effect: reduced zaleplon plasma concentrations
2) Summary: Zaleplon is partially metabolized by the CYP3A4 isozyme. Concomitant use of rifampin, a poter inducer, and zaleplon reduced zaleplon exposure and plasma concentrations by approximately 80%. Althoug carbamazepine, also a potent CYP3A4 inducer, a similar interaction can be expected. An alternative hypnotic substrate of CYP3A4 should be considered in patients receiving rifampin (Prod Info SONATA(R) oral capsule
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of carbamazepine, a potent CYP3A4 inducer, and zaleplon may r zaleplon levels and efficacy. Consider using an alternative hypnotic agent that is not a substrate of CYP3A4 i receiving rifampin (Prod Info SONATA(R) oral capsules, 2007).
7) Probable Mechanism: induction of CYP3A4-mediated zaleplon metabolism by carbamazepine

3.5.1.GG Ziprasidone

1) Interaction Effect: decreased ziprasidone plasma concentrations
2) Summary: Ziprasidone is metabolized primarily by CYP3A4. The concomitant use of carbamazepine (a C
200 mg twice daily for 21 days decreased the ziprasidone AUC by approximately 35%. Therefore, caution sh
carbamazepine and ziprasidone are coadministered due to the potential for reduced ziprasidone plasma con
Info GEODON(R) oral capsules, IM injection, 2008).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Use caution when prescribing carbamazepine to a patient who takes ziprasidone. C
carbamazepine and ziprasidone has resulted in decreased ziprasidone plasma concentrations (Prod Info GE
capsules, IM injection, 2008).
7) Probable Mechanism: induction of CYP3A4-mediated ziprasidone metabolism by carbamazepine

3.5.1.GH Zotepine

1) Interaction Effect: decreased zotepine plasma concentrations
2) Summary: Carbamazepine enhances the metabolism of zotepine by induction of the hepatic microsomal e
This may result in lower plasma levels of zotepine (Prod Info Nipolept(R), 1994).
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor the patient carefully and increase the dose of zotepine if necessary.
7) Probable Mechanism: hepatic microsomal enzyme induction

3.5.2 Drug-Food Combinations

3.5.2.A Grapefruit Juice

1) Interaction Effect: increased carbamazepine bioavailability
2) Summary: Grapefruit juice increased the peak concentration, trough concentration, and area under the co
curve of carbamazepine by 40.4%, 39.2%, and 40.8%, respectively, during a randomized crossover study. C
metabolized in the liver to the active metabolite 10,11-epoxide by cytochrome P450 3A4 enzymes. Grapefruit
metabolic pathway, causing an increase in the bioavailability of carbamazepine. Because of the narrow thera
carbamazepine, patients should be advised to avoid the consumption of grapefruit juice (Garg et al, 1998a).
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Patients receiving carbamazepine therapy should be instructed to avoid grapefruit j
7) Probable Mechanism: inhibition by grapefruit juice of cytochrome P450 3A-mediated carbamazepine meta
8) Literature Reports
a) Ten hospitalized epileptic patients who had been receiving carbamazepine 200 mg three times daily f
three to four weeks received 300 mL of grapefruit juice or water with their morning dose of carbamazepir
maximum concentration (Cmax) and minimum concentration (Cmin) values of carbamazepine increased
to 9.2 mcg/mL and from 4.51 mcg/mL to 6.28 mcg/mL, respectively, in the presence of grapefruit juice. T
concentration-time curve (AUC) from 0 to 8 hours also increased from 43.99 mcg/h/mL to 61.95 mcg/h/m
indicate that grapefruit juice does inhibit the metabolism of carbamazepine in epileptic patients (Garg et a

3.5.3 Drug-Lab Modifications

Perphenazine measurement

Tricyclic antidepressant measurement

3.5.3.A Perphenazine measurement

1) Interaction Effect: false increases in perphenazine levels
2) Summary: Carbamazepine was reported to cause false increases in perphenazine levels when measured
Beckman Ultrasphere ODS 3 mcm particle, 4.6 x 75 mm column using the method of Larson (with modificatic
patient (Spigset et al, 1994). Retention times were indistinguishable for the two drugs, resulting in a greater th
overestimation of the perphenazine concentration. Serendipitous changing of the column to a Nucelosil C18 5
x 150 mm column adequately resolved the two peaks. All HPLC perphenazine assay methods should be eva
carbamazepine interference.
3) Severity: minor
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: All HPLC perphenazine assay methods should be evaluated for carbamazepine int
7) Probable Mechanism: perphenazine assay interference

3.5.3.B Tricyclic antidepressant measurement

1) Interaction Effect: false positive tricyclic antidepressant assay results with serum fluorescence-polarized ir

2) Summary: Because carbamazepine is structurally similar to tricyclic antidepressants (TCAs), it can interfe fluorescence-polarized immunoassays for TCAs, causing falsely positive results. Carbamazepine does not in enzyme-linked immunoassays for TCAs, as they are much less sensitive than the serum assays. In the event assay with no history of TCA use, gas chromatography/mass spectrometry (GC/MS) should be considered to TCA toxicity (Saidinejad et al, 2007).

3) Severity: moderate

4) Onset: rapid

5) Substantiation: established

6) Clinical Management: The molecular structural similarity of carbamazepine to tricyclic antidepressants (TC falsely positive results with the serum fluorescence-polarized immunoassay but not the less sensitive urine en immunoassay. When an assay is positive for TCAs and there is no history of TCA use, gas chromatography/m (GC/MS) should be considered, as they are specific enough to differentiate between TCAs and structurally si (Saidinejad et al, 2007).

7) Probable Mechanism: molecular structural similarity of carbamazepine to the tricyclic antidepressant class

8) Literature Reports

a) A cross-sectional study of pediatric patients (n=52) taking carbamazepine or oxcarbazepine showed carbamazepine significantly interferes with the serum fluorescence-polarized immunoassay for tricyclic a (TCAs), but does not interfere with the urine enzyme-linked immunoassay for TCAs. Patients aged 3 to 1 been prescribed carbamazepine or oxcarbazepine and needed routine laboratory testing were enrolled in were also excluded if they had used TCAs or a structurally similar compound other than the medications week prior to the study. The investigators used the TCA screening serum and urine assays, measured s carbamazepine or oxcarbazepine metabolite levels, and then performed gas chromatography/mass spec to confirm or rule out the presence of TCAs in the serum. Thirteen of 33 patients on carbamazepine had the serum assay, which had a positive cutoff of 50 micrograms per liter (mcg/L). All of the patients had a level within therapeutic range (4 to 12 mcg/L), but 12 of the 13 patients with carbamazepine levels of 8 m positive serum assay results. Linear regression showed a significant dose-dependent relationship betwe carbamazepine levels and the quantity of TCAs detected (p less than 0.0001). The investigators estimate mcg/L of carbamazepine present in the serum, the assay detected 4.2 mcg/L of TCAs. Urine assays had 150 mcg/L, as recommended by the manufacturer, and there were no positive results in patients taking e carbamazepine or oxcarbazepine.(Saidinejad et al, 2007).

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) Laboratory Parameters

a) Monitor blood concentrations of carbamazepine is recommended to optimize therapeutic effect and reduc (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR ext tablets, 2007).

b) The usual adult therapeutic levels are between 4 and 12 micrograms/milliliter (Warner et al, 1998; Yukawa

c) Levels drawn during the first few weeks of therapy should be cautiously interpreted, due to induction of en

d) Routine monitoring of the epoxide metabolite may also be required during carbamazepine therapy, as ser carbamazepine levels alone may not be adequate to detect toxicity in some patients. Total serum carbamaze epoxide serum levels above 9 micromol/L are associated with greater side effects than lower levels (Patsalos

e) Therapeutic levels for therapy of neuralgias have been reported to be 2 to 7 micrograms/milliliter (HPLC) (1993).

2) Physical Findings

a) EPILEPSY

1) Monitor patients for reduction in seizure frequency.

b) NEUROLOGICAL PAIN SYNDROMES

1) Monitor patients for improvement in pain of trigeminal neuralgia and other neurological syndromes.

B) Toxic

1) Laboratory Parameters

a) High-resolution human leukocyte antigen-B*1502 (HLA-B*1502) typing in Asian patients including South A should be performed due to a strong correlation between the risk of developing serious and sometimes fatal c reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis) and the presence of HLA-B* Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007; US Food and Drug Administration, 2007).

1) Prevalence of HLA-B*1502 allele

a) Human leukocyte antigen-B*1502 (HLA-B*1502) allele is common in Asians including South Asia prevalence of HLA-B*1502 is not known for all regions of Asia. The following are known HLA-B*150 prevalence rates in some regions of Asia: greater than 15% in Hong Kong, Thailand, Malaysia, and Philippines; about 10% in Taiwan; 4% in North China; 2% to 4% in South Asians, including Indians b in some groups; and less than 1% in Japan and Korea. Individuals not of Asian origin (eg, Caucasia Americans, Hispanics, and Native Americans) generally are not HLA-B*1502 positive (Prod Info TE chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tab Food and Drug Administration, 2007).

b) Perform complete blood counts including platelets, and possibly reticulocytes and serum iron before thera periodically (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETO release oral tablets, 2007).

1) If significant bone marrow depression develops, the manufacturer recommends the following (Prod In oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tab

a) Stop drug

b) Perform daily CBC, platelet, and reticulocyte counts

c) Do bone marrow aspiration and trephine biopsy and repeat as necessary to monitor recovery

d) Other specific studies that might help include: white cell and platelet antibodies, (59)Fe-ferrokine peripheral blood cell typing, cytogenetic studies on marrow and peripheral blood, bone marrow cultu colony-forming units, hemoglobin electrophoresis for A(2) and F hemoglobin, and serum folic acid a

c) Hepatic function tests (AST, alkaline phosphatase) should be conducted prior to and periodically during th TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-rele 2007).

d) Baseline and periodic monitoring of renal function tests (complete urinalysis and BUN) is recommended d renal dysfunction (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGI extended-release oral tablets, 2007).

e) Monitor serum sodium due to the risk of hyponatremia (Prod Info TEGRETOL(R) oral chewable tablets, ta 2007).

f) Conduct periodic thyroid function tests at the physician's discretion during therapy as thyroid levels may be Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended tablets, 2007)

2) Physical Findings

a) Observe patients for hypersensitivity reactions who previously experienced this reaction to anticonvulsant phenytoin and phenobarbital (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Pro (R)-XR extended-release oral tablets, 2007).

b) Due to the potential of serious and sometimes fatal dermatologic reactions, carefully observe patients for symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis (Prod Info TEGRETOL(R) oral chew tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

c) Baseline and periodic eye examinations, including slit-lamp, funduscopy, and tonometry, are recommende phenothiazines and related drugs have been shown to cause eye changes (Prod Info TEGRETOL(R) oral ch tablets, suspension, 2007; Prod Info TEGRETOL(R)-XR extended-release oral tablets, 2007).

d) Monitor patients with a mixed seizure disorder, including atypical absence seizures, for the potential incre generalized convulsion (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007; Prod Info XR extended-release oral tablets, 2007).

e) Activation of latent psychosis is a possibility due to the relationship between carbamazepine and tricyclic c Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007).

f) Confusion or agitation in the elderly is a possibility due to the relationship between carbamazepine and tric (Prod Info TEGRETOL(R) oral chewable tablets, tablets, suspension, 2007).

g) 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 an AED and continued to at least 24 weeks. Patients treated for epilepsy, psychiatric disorders, or other conc an increased risk for suicidality compared to placebo. Closely monitor patients treated with AEDs for emerge 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) Carbamazepine (By mouth)

Carbamazepine

Treats different types of seizures. Also used to treat nerve pain and bipolar disorder, also known as manic-depres

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to carbamazepine or to certain medicines fo
as amitriptyline, desipramine, imipramine, protriptyline, and nortriptyline. You should not use this medicine if you h
bone marrow depression (low blood counts). Do not use this medicine if you are using nefazodone (Serzone®) or
MAO inhibitor (MAOI) such as selegiline (Eldepryl®), isocarboxazid (Marplan®), phenylzine (Nardil®), or tranylcyp
(Parnate®) within the past 14 days. Do not use this medicine if you are pregnant.

How to Use This Medicine:
Long Acting Capsule, Liquid, Tablet, Chewable Tablet, Long Acting Tablet
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.
It is best to take this medicine with food or milk.
Swallow the extended-release tablet or extended-release capsule whole. Do not crush, break, or chew it. Do
extended-release tablet that is cracked or chipped.
If you cannot swallow the extended-release capsule, you may open it and pour the medicine into a small amo
such as pudding, yogurt, or applesauce. Stir this mixture well and swallow it without chewing.
The chewable tablet must be chewed before you swallow it.
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 d
then to use the medicine and skip the missed dose. Do not use extra medicine to make up for a missed dose

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.
There are many other drugs that can interact with carbamazepine. Make sure your doctor knows about all oth
are using. Some medicines that can interact include heart medicines, blood pressure medicines, seizure mec
antidepressants, pain medicines, cancer medicines, steroids, and medicines to treat infections, including HIV
medicines. Also tell your doctor if you are using cimetidine (Tagamet®), haloperidol (Haldol®), levothyroxine
nicotinamide, praziquantel (Biltricide®), risperidone (Risperdal®), theophylline (Theo-Dur®), ziprasidone (Ge
thinner such as warfarin (Coumadin®).
Birth control pills, implants, or shots will not work while you are using this medicine. To keep from getting pre
form of birth control such as condoms or a diaphragm with contraceptive foam or jelly.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.
Tell your doctor if you are using any medicines that make you sleepy. These include sleeping pills, cold and a
narcotic pain relievers, and sedatives.
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 have glaucoma, liver disease, kidney disease
heart or heart rhythm problems, or if you have ever had a mental illness or an inherited disease such as porp
doctor if you have had an allergic reaction to any other medicines (especially seizure medicines).
Do not stop using this medicine suddenly without asking your doctor. You may need to slowly decrease your
stopping it completely.
Your doctor will need to check your blood or urine at regular visits while you are using this medicine. Be sure
appointments.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may a
certain medical tests.
This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that cou
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, d
trouble breathing.
Blistering, peeling, red skin rash.
Change in how much or how often you urinate.
Chest pain, fast or uneven heartbeat.

Dark-colored urine or pale stools.
Fever, sore throat, or sores in your mouth.
Lightheadedness or fainting.
Nausea, vomiting, loss of appetite, or pain in your upper stomach.
Problems with balance, walking, or speech.
Shortness of breath, cold sweat, and bluish-colored skin.
Swelling in your hands, ankles, or feet.
Unusual bleeding, bruising, or weakness.
Yellowing of your skin or the whites of your eyes.

If you notice these less serious side effects, talk with your doctor:
Anxiety, confusion, depression, restlessness, or agitation.
Diarrhea, constipation, or upset stomach.
Dizziness, drowsiness or unsteady on your feet.
Dry mouth.
Headache or back pain.
Vision changes.

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

4.3 Place In Therapy

A) Carbamazepine is considered the drug of first choice with the least toxicity for treating partial seizures with or witho generalization (Herman & Pedley, 1998). Carbamazepine should not be used for absence seizure since an exacerbati occur (Parker et al, 1998).
B) In comparison with phenobarbital, phenytoin, and primidone, carbamazepine appears to have the least effect on c and behavioral disturbances (Trimble, 1988).
C) Carbamazepine is the drug of choice for trigeminal neuralgia and is considered a drug of choice for bipolar disorde
D) Carbamazepine should be included on the hospital formulary.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION
1) SUMMARY
a) Carbamazepine is an anticonvulsant chemically related to imipramine; its mechanism of action in preventi remains unclear but may involve reduction of polysynaptic responses and blocking the post-tetanic potentiati models, carbamazepine reduces pain by stimulation of the infraorbital nerve. In addition, the drug may depre potential and bulbar and polysynaptic reflexes (Prod Info Tegretol(R), 2002a).
2) Carbamazepine is a dibenzoazepine iminostilbene derivative, which has shown to be an effective anticonvulsa patients not responding to other anticonvulsant therapy. Carbamazepine has been shown effective in <GENERAL CLONIC SEIZURES>, COMPLEX PARTIAL SEIZURES, and SIMPLE PARTIAL SEIZURES, as well as those rep secondary generalization (Troupin et al, 1974; Penovich & Morgan, 1976; Anon, 1975). True ABSENCE SEIZURE SPASMS have not responded well although atypical absence seizures have been more responsive (Troupin et al
3) Carbamazepine possesses psychotropic effects. Carbamazepine is less sedating than most anticonvulsants (1974). The drug elevates mood in some depressed patients with epilepsy and is considered a drug of choice for b
4) Although effective in psychiatric disorders, carbamazepine does not have a neurochemical profile resembling t antipsychotics. Data suggest, however, that carbamazepine may decrease dopamine turnover without directly blo receptors (Post et al, 1986).
B) REVIEW ARTICLES
1) The treatment of seizures have been reviewed; these include treatment of first seizure and status epilepticus (treatment of the elderly (Rowan, 1998), and management of epilepsy in adults (Feely, 1999; Mattson, 1998). Pedi management has also been reviewed (Wolf et al, 1998; Pellock, 1998).
2) With the addition of the newer antiepileptic drugs, polypharmacy in epilepsy is being revisited (Schneiderman, 1998).
3) Carbamazepine prophylaxis for bipolar disorder has been reviewed (Keck et al, 1998; Post et al, 1997).
4) A review of the metabolism of carbamazepine is presented (Eichelbaum et al, 1985c).
5) Reviews of the use of carbamazepine in children are available (Gilman, 1991; Seetharam & Pellock, 1991).
6) The treatment and prophylaxis of facial neuralgias has been reviewed (Diener et al, 1994).
7) Drug-interactions of antidepressants are reviewed in German language (Zapotoczky & Simhandl, 1995).

4.5 Therapeutic Uses

Aggressive behavior

Agitation - Brain injury

Agitation - Dementia

Alcohol withdrawal syndrome

Apraxia

Behavioral syndrome - Mental retardation

Benzodiazepine withdrawal

Bipolar I disorder, acute manic and mixed episodes

Chorea

Chronic paroxysmal hemicrania - Tic disorder

Cocaine dependence

Dementia

Depression

Diabetes insipidus

Diaphragmatic tic

Dystonia

Encephalitis due to human herpes simplex virus; Adjunct

Epilepsy, Partial, generalized, and mixed types

Erythrodermic psoriasis

Facial spasm

Glossopharyngeal neuralgia

Hiccoughs, Intractable

Huntington's disease

Migraine; Prophylaxis

Multiple sclerosis, Sensory symptoms

Myoclonus

Myokymia

Neuralgia

Neurogenic pain

Neuropathy, General

Obsessive-compulsive disorder

Obsessive compulsive personality disorder

Pain

Panic disorder

Phantom limb syndrome

Polyradiculoneuropathy

Postherpetic neuralgia

Posttraumatic stress disorder

Psychotic disorder

Restless legs syndrome

Schwartz-Jampel syndrome

Subacute sclerosing panencephalitis

Tabes dorsalis

Temporal lobectomy behavior syndrome

Tinnitus

Trigeminal neuralgia

Trigeminal trophic syndrome

Uremic neuropathy

4.5.A Aggressive behavior

1) 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

2) Summary:

Possibly effective for aggression (Coons, 1992; Yatham & McHale, 1988)

3) Adult:

a) Case reports of CARBAMAZEPINE 300 to 800 milligrams daily were reported effective in the treatment of BEHAVIOR (Coons, 1992; Yatham & McHale, 1988).

4.5.B Agitation - Brain injury

1) 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

2) Summary:

May be safe and effective for the treatment of post-traumatic agitation, but the response is inconsistent (

3) Adult:

a) Post-traumatic agitated behaviors, particularly irritability and disinhibition, were effectively treated with car patients severe CLOSED-HEAD INJURY. In this prospective, open trial, patients (mean age 34 years) receiv

200 milligrams (mg) per day, increased by 200 mg increments until 600 to 1200 mg/day was reached. Behav including the Neurobehavioral Rating Scale-revised (NRS-R) and the Agitated Behavior Scale (ABS) were pe baseline and every 2 weeks during treatment. Significant improvement in scores of both tools was observed a assessment (p=0.02 for both), but considerable interindividual variability was observed. Five patients demons than 50% improvement in NRS- R score, while 3 showed a 25% to 43% improvement, and 2 patients showed during the study period. Adverse effects consisted of drowsiness, for which the dose was reduced, and 1 cas allergic cutaneous reaction requiring drug withdrawal (Azouvi et al, 1999).

4.5.C Agitation - Dementia

1) Overview

FDA Approval: Adult, no; 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

2) Summary:

Effective in the treatment of hyperactivity, psychomotor restlessness, and agitation associated with deme

3) Adult:

a) In a 6-week, randomized, parallel-group study, carbamazepine was more effective than placebo in patient and aggression associated with dementia (Tariot et al, 1998); however following DRUG WITHDRAWAL, agita aggressive behavior returned to baseline levels (Tariot et al, 1999). At multiple nursing home sites, patients r carbamazepine (n=27) or placebo (n=24). The modal carbamazepine dose at 6 weeks was 300 milligrams/da serum level of 5.3 micrograms/milliliter was achieved. Mean total Brief Psychiatric Rating Scale decreased by carbamazepine group and 0.9 for the placebo group. The Clinical Global Impression ratings showed improve patients taking carbamazepine and 21% of those taking placebo. Staff perception of the extra time required t behavioral problems also significantly decreased in the carbamazepine group as compared to placebo. The s terminated after a planned interim analysis showed that carbamazepine provided more benefit than placebo (An additional open treatment period of 12 weeks was undertaken to examine long-term efficacy and safety a patterns of behavioral response. Behaviors were assessed at 6, 9, 15, and 21 weeks. Evaluations performed washout period demonstrated that scores for agitation and aggression were no different from untreated basel those assessing anxiety, depression, psychosis, and cognitive function were similar to those following 6 week carbamazepine treatment. Longer treatment with carbamazepine produced similar benefits regarding aggres behaviors, as well as improvements in other psychopathologic behaviors. Over the 21 weeks of study, 26 pat from participation for the following reasons: adverse effects (11), administrative reasons (12), lack of efficacy oral medications (1). Only 1 adverse effect, ataxia, was possibly related to carbamazepine treatment. Ongoin generally well tolerated (Tariot et al, 1999).

b) CARBAMAZEPINE 200 to 1000 milligrams daily was useful in the treatment of agitation in 6 of 9 patients disease (Gleason & Schneider, 1990). Corresponding serum concentrations ranged from 2.3 to 9.6 micrograi Overall improvement was greatest in agitation and hostility; some improvement was also seen in tension and uncooperativeness. Clinical improvement was generally seen within 2 to 4 weeks following the start of treatm

c) CARBAMAZEPINE was reported effective in the treatment of assaultive and aggressive behavior in patier DEMENTIA in a small study involving 8 ambulatory male patients (Patterson, 1987). The drug was given in d milligrams (mg) 3 times daily for 1 day, followed by 200 mg orally 4 times daily for the second day; subseque administered to achieve serum levels of 8 to 12 micrograms/milliliter. The number of assaults decreased sign CARBAMAZEPINE therapy (by more than 50%); assaultive behavior was also considered to be less intense duration.

4.5.D Alcohol withdrawal syndrome

1) 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

2) Summary:

May prove useful in the treatment of anxiety, dysphoria, somatization, and other signs of alcohol abstine (Flygenring et al, 1984; Agricola et al, 1982; Wilbur & Kulik, 1981).

See Drug Consult reference: DRUG THERAPY OF ETHANOL WITHDRAWAL

3) Adult:

a) In an open trial of approximately 100 patients, CARBAMAZEPINE was found to be effective in relieving ar associated with acute alcohol withdrawal syndromes (Poutanen, 1979).

4.5.E Apraxia

1) 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

2) Summary:

Apraxia may respond to carbamazepine therapy (Naqvi et al, 1998)

3) Pediatric:

a) In a case series, carbamazepine was useful in treating 3 patients with apraxia and new-onset partial seizu 1998). Seven children (2 to 12 years old) with either oral motor apraxia or ocular motor apraxia received carb milligrams/kilogram/day. Responders had interictal epileptiform discharges on EEG while non-responders (n= seizures and had non-epileptiform EEG findings.

4.5.F Behavioral syndrome - Mental retardation

1) 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

2) Summary:

Effective in the treatment of overactive, severely mentally handicapped patients (Reid et al, 1981)

3) Adult:

a) CARBAMAZEPINE was used for behavioral disorders including aggression, self-injurious behavior, hyper tantrums in 76 chronically institutionalized mentally retarded individuals previously unresponsive to other mec patients demonstrated nearly complete resolution of symptoms and 10 showed some improvement. Previous seizure disorders or underlying electroencephalogram abnormalities were noted in 27 of the 30 responders. T study is limited due to the lack of psychiatric diagnosis and the failure to distinguish among "behavior disorde 1989).

4.5.G Benzodiazepine withdrawal

1) 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

2) Summary:

Possibly useful in the treatment of benzodiazepine withdrawal (Ries et al, 1989; Klein et al, 1986)

3) Adult:

a) CARBAMAZEPINE in doses of 400 to 800 milligrams daily was reported effective in treating withdrawal fr benzodiazepines (CHLORDIAZEPOXIDE, ALPRAZOLAM, DIAZEPAM, CLONAZEPAM) in a small open stuc 1989; Klein et al, 1986). Controlled studies are required to confirm these findings.

4.5.H Bipolar I disorder, acute manic and mixed episodes

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes (Extended release formulation); 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

2) Summary:

Indicated for the treatment of acute manic and mixed episodes associated with bipolar I disorder (Prod In extended release capsules, 2004)
Effective in the acute and prophylactic treatment of bipolar affective disorder
Effective in bipolar patients who have shown no response to LITHIUM therapy
In combination with LITHIUM may be effective when either or both agents alone have failed

3) Adult:

a) Therapy with carbamazepine extended-release (ER) capsules was more effective than placebo in the trea manic and mixed episodes in patients with bipolar disorder. In two randomized, double-blind, multicenter, flex patients diagnosed with bipolar I disorder with manic or mixed episodes received carbamazepine ER (titrated of 400 to 1600 milligrams (mg)/day, given twice daily in divided doses) or placebo for 3 weeks. The mean car dose during the last week of treatment was 952 mg/day in the first study and 726 mg/day in the second study Young Mania Rating Scale scores from baseline to endpoint were significantly more reduced in carbamazepi patients as compared with those who received placebo (Prod Info Equetro(TM) extended release capsules, 2

b) In a double-blind study in 52 bipolar patients, lithium and carbamazepine had a roughly equal but less tha prophylactic efficacy in overall bipolar illness (Denicoff et al, 1997a). Patients were randomly assigned to 1 ye with lithium or carbamazepine, and then crossed over to the other drug in the second year. During a third yea received a combination of the 2 drugs. A marked or moderate improvement occurred in 33% of patients recei 31% of patients receiving carbamazepine and 55% of those receiving the combination. Lithium, however, wa prophylaxis of mania (no mania experienced by 11% on lithium, 4% on carbamazepine, and 33% on combina

less than 0.01). The combination of lithium and carbamazepine was better than monotherapy in rapid cyclers
c) The addition of LITHIUM CARBONATE (plasma levels, 0.7 to 1.2 milliequivalents/liter) to CARBAMAZEPI
to 1500 milligrams daily) was reported effective in improving MANIA in 6 of 7 patients previously refractory to
alone. These patients were also refractory to several weeks of CARBAMAZEPINE therapy (Kramlinger & Pos
data support previous studies suggesting that some manic patients may respond to a combination of LITHIU
CARBAMAZEPINE, but not to each agent alone (Woods, 1986).
d) CARBAMAZEPINE was effective as an adjunctive medication in the treatment of 11 of 13 patients with tre
affective disorders including LITHIUM nonresponders. CARBAMAZEPINE was used in combination with neu
as well as with LITHIUM CARBONATE. Four patients were judged to have had markedly effective responses
effective response and in 4 there was a slightly effective response. The mean daily dose varied from 300 to 1
(Kwamie et al, 1984).

4.5.I Chorea

1) 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 B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective in the treatment of chorea

3) Adult:

a) CARBAMAZEPINE 15 to 24 milligrams/kilogram/day orally (plasma levels, 6.5 to 8.8 micrograms/milliliter)
be effective in the treatment of NONHEREDITARY CHOREA in 5 patients (Roig et al, 1988). Chorea was cau
streptococcal infection in 2 patients and head injury in 1 other; the cause in the remaining 2 patients could no
Clinical improvement was observed within 4 to 15 days after initiation of CARBAMAZEPINE treatment. Side e
observed in 4 patients during 3 months to 36 months therapy. In one patient, withdrawal of the drug was requ
an allergic cutaneous reaction after 17 days. More studies are required to evaluate the efficacy of CARBAMA
b) CARBAMAZEPINE has been reported to be effective in the treatment of benign dominant hereditary chor
mother and daughter). Both showed decreased involuntary movements and functional improvement and felt s
quieter. Doses of CARBAMAZEPINE were 250 milligrams (mg) (3.5 mg/kilogram) daily in the child and 400 m
mother (Roulet & Deonna, 1989).

4) Pediatric:

a) Carbamazepine was found to be safe and effective in the treatment of choreic movements in 17 pediatric
female; 10.9 +/- 2.4 years-old) with SYDENHAM'S CHOREA in an open-label trial. The children received 15 m
kilogram per day of carbamazepine. Onset of clinical improvement was 7.4 +/- 8.2 days; time to complete rem
movements was 6.7 +/- 6.3 weeks; and the duration of treatment was 5.0 +/- 2.4 months. There was a recurr
and no adverse drug events were reported during the trial (Genel et al, 2002).
b) A prospective case series of 10 children with RHEUMATIC CHOREA found low-dose CARBAMAZEPINE
effective (Harel et al, 2000). Ages of the children ranged from 7 to 16 years; 9 children in the cohort had Syde
with concomitant carditis and 1 child had antiphospholipid antibody syndrome that evolved to systemic lupus
Dosing of carbamazepine was 4 to 10 milligrams/kilogram daily (associated plasma concentrations were 2.8
micrograms/milliliter). Initial improvement was observed within 2 to 14 days. Chorea disappeared in 7 childre
and in all patients within 12 weeks. Treatment duration was 1 to 15 months. Symptoms recurred in 3 patients
retreatment. One patient experienced a treatment-related side effect, a maculopapular rash that responded to

4.5.J Chronic paroxysmal hemicrania - Tic disorder

1) 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

2) Summary:

INDOMETHACIN and CARBAMAZEPINE may be beneficial for treatment of chronic paroxysmal hemicra
based on anecdotal evidence (Martinez-Salio et al, 2000)

3) Adult:

a) A 52-year-old man suffering from chronic paroxysmal hemicrania- tic syndrome (CPS-tic) was successfull
INDOMETHACIN and CARBAMAZEPINE . The patient initially presented with a 2-month history of headache
severe, sharp, or stabbing pain behind the right eye and temporal area, with attacks occurring 5 to 8 times a
to 15 minutes. During the attacks, he also experienced ipsilateral lacrimation, nasal congestion, and rhinorrhe
PAROXYSMAL HEMICRANIA (CPH) was diagnosed. Indomethacin 25 milligrams (mg) 3 times a day brough
complete relief. Some months later (indomethacin had been terminated after 6 months), he developed brief e
pains spreading from his right jaw to his right ear, that were triggered by talking, chewing, or touching the affe
shock-like pains were diagnosed as TRIGEMINAL NEURALGIA. Indomethacin was tried unsuccessfully. CA
200 mg 3 times a day brought complete relief in 24 hours. Two months later (with continuing use of carbama
type of headache (CPH) returned. Again indomethacin provided complete response. One month later, he suc
discontinued indomethacin, and carbamazepine was slowly tapered off. At 3-months follow-up, the patient wa

(Martinez-Salio et al, 2000).

4.5.K Cocaine dependence

1) 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

2) Summary:

Effective in reducing cocaine craving and assisting in maintaining cocaine abstinence

3) Adult:

a) In a 12-week, randomized, double-blind, placebo-controlled study, carbamazepine reduced the duration a craving episodes but had little impact on frequency of urges (Halikas et al, 1997). Patients (n=183) were ranc placebo, carbamazepine 400 milligrams (mg), or 800 mg daily (31% of patients randomized completed the st carbamazepine levels were associated with lower rates of positive cocaine urinalysis (p=0.004), fewer days c cocaine use (p=0.014), shorter craving duration (p less than 0.001), and greater overall therapeutic effect (p=

b) CARBAMAZEPINE 200 to 400 milligrams daily was reported to be effective in reducing COCAINE craving maintaining COCAINE abstinence in 1 small study (Halikas et al, 1989). Similar results were reported in place crossover studies for the treatment of crack cocaine use (Halikas et al, 1992; Halikas et al, 1991). CARBAMA more than 4 micrograms/milliliter were associated with greater improvement.

4.5.L Dementia

See Drug Consult reference: BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

4.5.M Depression

1) 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

2) Summary:

Carbamazepine was effective in unipolar depressed patients who had not previously been treated with a other psychotherapeutic treatments in a double-blind, randomized, placebo-controlled study (n=89) (Zha
Carbamazepine was effective in the prophylaxis of unipolar depression in an open-label study involving
(Stuppaeck et al, 1994)
Carbamazepine was effective in patients with depression resistant to other treatment, but the high rate o may limit its utility (Cullen et al, 1991)

3) Adult:

a) Carbamazepine was effective in unipolar depressed patients who had not previously been treated with an other psychotherapeutic treatments in a double-blind, randomized, placebo-controlled study (n=89). Patients with a history 2 or more episodes of major depression, no history of mania or hypomania, and currently exper episode of depression with a duration of at least 2 weeks, were randomized to immediate release carbamaze placebo (n=38) for 12 weeks. Carbamazepine was started at 300 milligrams/day (mg/day) in 2 divided doses (within 2 weeks) to a maximum of 800 mg/day based on patient response and tolerability. The mean final car was 461.6 +/- 87.7 mg/day. The primary efficacy analysis was based on a modified-intention-to-treat (MITT) p as all patients who completed at least one post baseline evaluation utilizing the last observation carried forwa method. Measures of primary efficacy included the Hamilton Rating Scale for Depression (HAMD), the Montg Depression Rating Scale (MADRS), and the Clinical Global Impression-Severity (CGI-S). Clinical response w greater than or equal to a 50% reduction in score on the HAMD from baseline to endpoint. Patients in both ar symptomatic improvements by week 8 (p less than 0.05 vs baseline), but significant separation in HAMD, MA results occurred between treatment groups (p less than 0.05). Mean HAMD score improved from 25 at baseli 8 in the carbamazepine arm compared with an improvement from 24 to 13.1 in the placebo arm (p less than (endpoint clinical response rate of carbamazepine-treated patients was 73.9% (34/46) compared to 45.9% (17 patients (p=0.018). The most frequently reported adverse event was benign leucopenia (30.4%) in the carbar Four carbamazepine patients discontinued treatment due to intolerable adverse events (3 rash, 1 blurred visi 2008).

b) Carbamazepine was effective in the prophylaxis of unipolar depression in an open-label study involving 15 study, patients received an initial dose of carbamazepine of 200 milligrams/day (mg/day), slowly increasing to final dose was adjusted to maintain a serum level in the lower end of the therapeutic range of 5 to 12 microgr Patients were followed for a period of 5 years. Carbamazepine was beneficial in 11 of 15 (73%) treated patie patients were completely free of depressive episodes (Stuppaeck et al, 1994).

c) Carbamazepine was effective in patients with depression resistant to other treatment, but the high rate of may limit its utility. In a retrospective study, 7 of 16 patients. demonstrated moderate to marked improvement included those with both psychotic and nonpsychotic depression as well as patients with organic brain diseas responders discontinued medication because of rash, hyponatremia, or hepatotoxicity (Cullen et al, 1991).

d) Relapse of depression was prevented with carbamazepine prophylaxis in a single patient. Recurrence of

appeared within 2 to 4 months of carbamazepine discontinuation. No significant side effects were noted durir (Kobayashi et al, 1988).

4.5.N Diabetes insipidus

1) 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

2) Summary:

Induces antidiuresis by releasing antidiuretic hormone

3) Adult:

a) Seven of 9 patients with diabetes insipidus (1 to 23 years' duration) were successfully treated with CARBA to 1200 milligrams daily in divided doses for 7 to 10 days in a controlled study. In 7 patients, there was satisfa urine output and fluid intake. Plasma osmolality significantly decreased after 7 days. Upon substituting placeb symptoms of diabetes insipidus recurred (Wales, 1975).

b) Carbamazepine therapy successfully treated a patient's NEPHROGENIC DIABETES INSIPIDUS induced drug was also effective in the treatment of the patient's affective psychosis (Brook & Lessin, 1983).

c) Successful use of CARBAMAZEPINE was described in a 19-year-old black pituitary dwarf with diabetes ir age of 6 (Dindar & Cooper, 1974). Doses of 100 milligrams (mg) twice daily to 200 mg three times daily resul urinary output from 3 to 4 liters/day (L/day) to 1.5 L/day. Upon discontinuing therapy, urinary volume increase successfully maintained at 100 mg twice daily. The patient had previously failed to respond to pituitary snuff, and CHLORPROPAMIDE.

d) One study investigating the mechanism of ANTIDIURETIC ACTION showed that CARBAMAZEPINE in dc milligrams orally increased plasma ADH from 0.4 micrograms/milliliter (mcg/mL) to 3.8 mcg/mL and increasec from 0.4 to 1.7. Water loading did not inhibit the effects of CARBAMAZEPINE (Kimura et al, 1974).

4.5.O Diaphragmatic tic

1) 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

2) Summary:

Successfully treated with carbamazepine in 3 patients (Vantrappen et al, 1992)

3) Adult:

a) High frequency diaphragmatic flutter characterized by esophageal belching, hiccups, and retching was tre CARBAMAZEPINE 200 to 400 milligrams 3 times daily in 3 patients with long-standing symptoms. All patient complete remission or significant improvement in symptoms and reductions in flutter as demonstrated by elec (Vantrappen et al, 1992).

4.5.P Dystonia

1) 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

2) Summary:

Limited data suggests efficacy of CARBAMAZEPINE in dystonia (Geller et al, 1976)

3) Adult:

a) Successful use of CARBAMAZEPINE in 8 of 8 patients with dystonic symptoms (hereditary torsion dyston dystonia, 4) has been reported. The drug was given in doses of 300 to 1200 milligrams daily for a period of 4 was noted that brief episodes of dystonia responded most dramatically and completely, but returned the soor discontinuation of the drug. More sustained tension in dystonia responded more slowly to CARBAMAZEPINE completely, and required higher doses than brief dystonic episodes. Effectiveness of the dystonias was maint for periods of 4 to 12 months. Although symptoms remained improved for some time after withdrawal in 2 pat eventually relapsed following discontinuation of therapy or when placebo was substituted (Geller et al, 1976).

4.5.Q Encephalitis due to human herpes simplex virus; Adjunct

1) 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

2) Summary:
Stabilized psychiatric sequelae of herpes simplex encephalitis (Vallini & Burns, 1987)
3) Adult:
a) In 1 case report, carbamazepine 200 milligrams 3 to 4 times daily was effective in stabilizing psychiatric se simplex ENCEPHALITIS in a 62-year-old male. It is unclear if beneficial effects observed were secondary to s mesial temporal seizure activity observed in this patient, or to mood-stabilizing effects of the drug (Vallini & B

4.5.R Epilepsy, Partial, generalized, and mixed types
FDA Labeled Indication
1) Overview
FDA Approval: Adult, yes; Pediatric, yes
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
2) Summary:
Indicated for the following seizure types (Prod Info Tegretol(R), 2002):
Partial seizures with complex symptomatology (psychomotor, temporal lobe)
Generalized tonic-clonic seizures (grand mal)
Mixed seizure patterns which include the above or other partial or generalized seizures
Not effective against absence seizures (petit mal)
3) Adult:
a) GENERAL INFORMATION
1) Carbamazepine is the drug of choice for the initial treatment of partial seizures with or without seconc (Herman & Pedley, 1998a). The drug is ineffective for absence seizures (may actually exacerbate these only minimally effective for atonic and myoclonic seizures (Parker et al, 1998a; Troupin et al, 1974a). CA as single-agent therapy has been effective in controlling seizures in over 75% of outpatients, reducing se more than 75% (Dodson, 1987; Andersen et al, 1983a). Other studies report that CARBAMAZEPINE is a PHENYTOIN as initial seizure therapy in adults with partial and generalized seizures (Mattson et al, 198 1983b). The sustained-release formulation of carbamazepine provides less peak-related adverse effects control, and greater compliance (Herman & Pedley, 1998a).
b) Following temporal lobectomy for treatment of medically intractable temporal lobe epilepsy, carbamazepir has been shown to be as effective as multidrug therapy (Kuzniecky et al, 1992). In this study, patients were r either carbamazepine or continued on their same multidrug antiepileptic regimen that they were on prior to su to monotherapy was achieved by discontinuing other antiepileptic drugs postoperatively. Carbamazepine ser maintained in the range of 6 to 10 micrograms/milliliter.
4) Pediatric:
a) CARBAMAZEPINE was effective in the treatment of grand mal seizures and psychomotor seizures, and w against absence seizures. Carbamazepine therapy was evaluated in 106 children and adolescents with vario disorders (Fischel & Heyer, 1970). Average doses of 15 to 20 milligrams/kilogram/day (mg/kg/d) (100 to 120(administered for an average of 45 months. In 40 patients with grand mal seizures alone, good to excellent re in 21 patients with no response in 14 patients and worsening of seizure control in 5. In 20 patients with psych alone, good to excellent results were obtained in 16 patients. The drug was not effective in absence seizures patients treated, 71 exhibited good to excellent results. Only 6 patients worsened during therapy with CARBA this group, 44 patients received other anticonvulsants concurrently with CARBAMAZEPINE. The main side e were initial fatigue, headache, and abdominal pains.
b) In 45 patients with chronic complex partial seizures or secondarily generalized tonic-clonic seizures, CAR monotherapy significantly improved complex-partial seizures regardless of the site of the EEG focus. In patie secondarily generalized seizures, seizures were better controlled in patients with a left-sided vs right-sided E et al, 1991).
c) Although CARBAMAZEPINE has generally been considered ineffective in absence seizures, one study re of CARBAMAZEPINE in a case of absence seizures unresponsive to ETHOSUXIMIDE or VALPROIC ACID (1988).
d) The successful use of a combination of benzodiazepines and CARBAMAZEPINE in controlling refractory myoclonic-astatic seizures in 24 children was reported (Tatzer et al, 1987). During the 5-year follow-up perioc infantile spasms and 4 children with myoclonic seizures became seizure-free; 6 additional children demonstra reduction in seizure frequency. Further controlled studies are required in this area.
e) In one study, carbamazepine controlled seizures in 22 of 58 children not adequately controlled on other m (Gamstorp, 1970). An additional 8 children experienced a 75% reduction in seizure frequency. After follow-up 19 of the 22 complete responders still remained seizure-free and 5 of the 8 patients maintained a 75% reduct frequency. Follow-up after 2 to 6.5 years revealed that 13 of 22 patients remained seizure-free, and in 3 of 22 carbamazepine was successfully withdrawn after 5 years.

4.5.S Erythrodermic psoriasis
1) 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

2) Summary:
Effective in one case of psoriatic erythroderma (Smith & Skelton, 1996)

3) Adult:
a) A 29-year-old HIV-1-positive man with a CD4+ T-cell count below 10 cells per cubic millimeter was succes carbamazepine for psoriatic erythroderma. This patient's skin disease had become progressively more difficu EXFOLIATIVE ERYTHRODERMA developed. He has continued to take carbamazepine for 1 year without re disease and with no changes in his laboratory values (Smith & Skelton, 1996). Other practitioners have been duplicate this response (Redondo & Vazquez-Doral, 1998).

4.5.T Facial spasm

1) 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

2) Summary:
Effective in the treatment of HEMIFACIAL SPASM in uncontrolled studies (Alexander & Moses, 1982)

3) Adult:
a) Efficacy of CARBAMAZEPINE in hemifacial spasm was reported in 3 patients receiving doses of 600 to 1 daily. These authors reviewed previous reports indicating the efficacy of the drug in over 50% of patients trea controlled trials are required to establish the efficacy of the drug as compared to surgical therapies or other m (Alexander & Moses, 1982).

4.5.U Glossopharyngeal neuralgia

FDA Labeled Indication

1) Overview
FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class IIa
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:
Indicated for glossopharyngeal neuralgia (Prod Info Tegretol(R), 1998)

3) Adult:
a) CARBAMAZEPINE 600 milligrams daily was effective in the treatment of paroxysms of pain and associate symptoms in an 83-year-old woman with glossopharyngeal neuralgia (Saviolo & Fiasconaro, 1987). It is sugg CARBAMAZEPINE may be an alternative to surgical resection of the glossopharyngeal nerve in these patien studies are required to fully evaluate the efficacy of CARBAMAZEPINE in glossopharyngeal neuralgia.
b) The efficacy of CARBAMAZEPINE 1200 milligrams daily in controlling paroxysmal pain associated with gl neuralgia in a 53-year-old man was reported (Johnston & Redding, 1990).

4.5.V Hiccoughs, Intractable

1) 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

2) Summary:
Effective in 1 patient with INTRACTABLE HICCUPS due to multiple sclerosis (McFarling & Susac, 1974)

4.5.W Huntington's disease

1) 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

2) Summary:
May alleviate micturitional disturbances in some patients with Huntington's disease (Cochen et al, 2000)

3) Adult:
a) CARBAMAZEPINE 200 milligrams (mg)/day resolved PRECIPITATE MICTURITIONS and DIURNAL or N INCONTINENCE in 3 male patients (aged 42 to 50 years) with genetically confirmed Huntington's disease (H patients with severe HD, dementia, and incontinence not characterized as precipitate micturition were not hel carbamazepine therapy. For those benefiting from carbamazepine, micturition difficulties ceased within 2 to 7

carbamazepine 200 mg/day. Two of these 3 patients failed on 100 mg/day, but were successful when the dos
to 200 mg/day. None of the patients who responded to carbamazepine had demonstrated seizures. The auth
that carbamazepine may have a direct action on the control center of micturition and defecation (Cochen et a

4.5.X Migraine; Prophylaxis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy; 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

2) Summary:

Carbamazepine has been used for migraine headache prophylaxis
Studies on the effectiveness of carbamazepine for migraine prophylaxis have produced mixed results

3) Adult:

a) Carbamazepine was moderately effective in the prophylactic treatment of 51 adult patients with symptoms
(Anthony et al, 1972). Carbamazepine 600 milligrams/day was effective in reducing the frequency of migraine
patients. Fifty-three percent of patients experienced side effects (giddiness, ataxia, drowsiness, nausea) and
discontinued in 24% of these patients.

b) CARBAMAZEPINE was more effective than placebo in a double-blind study of 48 patients with migraine h
CARBAMAZEPINE treatment resulted in improvement in 84.4% of patients as compared to 27.1% of patients
placebo. Doses of CARBAMAZEPINE were not specified (Rompel & Bauermeister, 1970).

4) Pediatric:

a) Carbamazepine 10 to 20 milligrams/kilogram/day divided into 2 doses has been used in children for migra
prophylaxis (Hamalainen, 1998). The dosage should be increased slowly and the patient monitored every 3 r
monitoring the usual lab values, height and body weight should also be monitored.

4.5.Y Multiple sclerosis, Sensory symptoms

1) 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

2) Summary:

Effective in a few patients with PAROXYSMAL DYSARTHRIA and ATAXIA associated with multiple scle

3) Adult:

a) CARBAMAZEPINE was effective 100 milligrams three times daily in a 41-year-old male with multiple scler
loss of control of right arm and leg with burning sensations around the left eye and dysarthria. These attacks
following administration of the drug and recurred when the drug was discontinued. Three other patients with r
(including 1 PHENYTOIN failure) experienced suppression of attacks when CARBAMAZEPINE was administ
Walker, 1967).

b) Two patients with multiple sclerosis and paroxysmal dysarthria and ataxia were treated with CARBAMAZE
milligrams twice daily (Miley & Forster, 1974). Paroxysmal episodes decreased in both patients within 2 days
patient, the drug was discontinued after 1 month of therapy with no recurrences seen at a 5 month follow-up.

c) CARBAMAZEPINE 400 milligrams daily was effective in alleviating both spontaneous and TONIC SPASM
hyperventilation and pain in a 31-year-old man with multiple sclerosis (Honig et al, 1991).

4.5.Z Myoclonus

1) 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

2) Summary:

ACTION MYOCLONUS secondary to acute hypoxia has responded to CARBAMAZEPINE therapy (Hiros

4.5.AA Myokymia

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Effective for the treatment of myokymia based on 1 case report (Kinnett & Keebler, 2001)

3) Pediatric:

a) Oral CARBAMAZEPINE successfully prevented painful cramping of the anterior thigh muscles in a 12-yea diagnosed with HEREDITARY MYOKYMIA. Her condition received medical attention when she declined to pa physical education classes due to recurrent cramping. The patient was started on carbamazepine 200 milligra daily. Compared with test results before carbamazepine, endurance time on a treadmill without cramping was after she began receiving carbamazepine. Strength testing showed improvement in only the hamstring muscl reports of sedation, the dose of carbamazepine was reduced to 100 mg twice a day and gradually increased twice a day. After 2 years, she was slowly weaned off of carbamazepine over 8 weeks, without symptom recu later, she was using prednisone for an exacerbation of asthma and the cramping returned. Reintroduction of brought relief. She received a 2-week course of carbamazepine 100 mg twice daily while being weaned off pr patient continued to do well without carbamazepine (Kinnett & Keebler, 2001).

4.5.AB Neuralgia

1) 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

2) Summary:

Effective in treating a variety of neuralgias

3) Adult:

a) Two patients with SUNCT SYNDROME (short-lasting, unilateral, neuralgi-form, headache attacks with cor and tearing) received relief with carbamazepine therapy (Raimondi & Gardella, 1997). The first patient was a whose moderately painful episodes in the medial right supraciliary area lasted between 15 and 20 seconds a times per day. Treatment with carbamazepine 600 milligrams (mg) provided a decrease in intervals between months. After 3 months the medication was discontinued with only 2 attacks per week. The second patient wa woman with 6 or 7 attacks of right orbitofrontal area pain which peaked in intensity after 30 seconds followed lesser pain for 35 to 120 minutes. She was treated with prednisolone 60 mg for 6 days and then 20 mg for 10 carbamazepine 800 mg/day for 11 weeks. She eventually received complete relief from this regimen.

b) CARBAMAZEPINE 200 milligrams (mg) at bedtime was effective in treating the pain associated with MOR NEURALGIA in a 79-year-old woman. Similarly, 200 mg 3 to 4 times daily effectively controlled pain in a 46-y (Guiloff, 1979).

4.5.AC Neurogenic pain

1) Overview

FDA Approval: Adult, no; 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

2) Summary:

Effective in some types of neurogenic pain

3) Adult:

a) Carbamazepine effectively reduced NEURITIC PAIN and OPIOID REQUIREMENTS in 12 patients recove GUILLAIN-BARRE SYNDROME. In a prospective, double-blind, crossover study, mechanically ventilated pat 54 years with moderate to severe body and back aches requiring increasing doses of opioids were randomize placebo or carbamazepine 100 milligrams via a nasogastric feeding tube every 8 hours for 3 days. Carbamaz associated with significantly reduced pain scores, meperidine requirements, and less sedation (p less than 0. groups). It is suggested that these effects may benefit patients with Guillain-Barre syndrome who are candida weaning (Tripathi & Kaushik, 2000).

b) CARBAMAZEPINE 400 milligrams (mg) to 1200 mg daily was effective in the treatment of intractable neu 7 patients (Rapeport et el, 1984). However, of 16 patients entering the study, 9 withdrew due to side effects o the 7 patients completing the protocol were used for efficacy evaluation. Controlled studies are required to de the drug in neurogenic pain.

c) CARBAMAZEPINE 200 milligrams 3 times daily was effectively used in combination with HYDROMORPH old patient with PANCOAST SYNDROME who had suffered severe, unrelieved pain for approximately 10 mo combination therapy, the patient was able to remain pain-free until the time of death (Tanelian & Cousins, 19

4.5.AD Neuropathy, General

1) 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

2) Summary:

Effective in some types of neuropathic pain

3) Adult:

a) Reduced pain was noted in patients (n=12) with THIAMINE-DEFICIENCY NEUROPATHY treated with PH milligrams (mg) at bedtime or CARBAMAZEPINE 200 mg at bedtime (Skelton & Skelton, 1991). Two patients were unable to tolerate the side effects of these medications. Of the remaining patients, similar effects were r treatment groups with significant reductions in pain noted in all patients. Two patients treated with PHENYTC treated with CARBAMAZEPINE reported complete relief.

4) Pediatric:

a) Two 14-year-old boys experienced relief of their painful neuropathy secondary to MERCURY POISONING carbamazepine 20 milligrams/kilogram/day (Karagol et al, 1997). Both had distal extremity pain with severe a along with, excessive sweating, weight loss, fatigue, photophobia and diarrhea. Urine mercury levels were 70 micrograms/liter (mcg/L) (normal 2 to 26 mcg/L). Both experience continued pain after 2 days of N-acetyl-D,L therapy. After 2 days of carbamazepine and pyridoxine therapy the pain subsided.

4.5.AE Obsessive-compulsive disorder

1) 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

2) Summary:

Mixed results have been obtained when assessing carbamazepine in the use of obsessive-compulsive d

3) Adult:

a) The addition of carbamazepine to clomipramine therapy was effective in the treatment of refractory obses disorder (OCD) in a 27-year-old woman. The patient had been unresponsive to clomipramine treatment since Coadministration of numerous medications (haloperidol, thioridazine, bromazepam, sulpiride, oxazepam, diaz risperidone) with clomipramine failed to improve her condition. After adding carbamazepine 500 milligrams (m (plasma level=6.1 mg/milliliter) to clomipramine 200 mg/day, her OCD symptoms dramatically improved withi improvement was sustained for at least 5 months (Iwata et al, 2000).

b) CARBAMAZEPINE in mean doses of 1088 mg daily was ineffective in the treatment of obsessive-compuls uncontrolled study involving 9 patients (Joffe & Swinson, 1987). No effects on mood or behavior were observ of treatment.

c) A small population of patients with obsessive-compulsive symptoms might respond to CARBAMAZEPINE anticonvulsant effects. The use of CARBAMAZEPINE 600 to 1000 milligrams daily in 7 patients meeting diag obsessive-compulsive disorder was reported (Khanna, 1988). Blood levels were maintained in the range of 8 micrograms/milliliter during the 12-week study. Only 2 patients reported a greater than 50% reduction in obse symptoms; in both cases, there was a history of a seizure disorder likely to respond to CARBAMAZEPINE.

4.5.AF Obsessive compulsive personality disorder

1) 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

2) Summary:

Improved symptoms in one case (Greve & Adams, 2002)

3) Adult:

a) Carbamazepine reduced irritable and agitated behavior of a 61- year-old man with Obsessive-Compulsive Disorder (OCPD). The man presented with mild cognitive impairment, including reduced attention, concentrat motivation, which had been worsening over the preceding 3 years. He had a life-long rigid, perfectionistic, an personality style and became easily irritated and agitated. He was diagnosed with OCPD with features of Obs Compulsive Disorder. One month after starting carbamazepine 100 milligrams (mg) twice daily, he reported f less prone to excessive reactions. The dosage was raised to 200 mg twice daily, and he developed a rash. T discontinued. Eight months later he reported some return of symptoms, including problems with self- regulatc & Adams, 2002).

4.5.AG Pain

1) 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

2) Summary:

Possibly effective for pain associated with depression (Kudoh et al, 1998)

3) Adult:

a) Carbamazepine demonstrated both analgesic and antidepressant effects in depressed patients who had f adequate pain relief with tricyclic or tetracyclic antidepressants or nonsteroidal analgesics. After a central me

a clinically significant organic disorder were ruled out, carbamazepine 450 milligrams/day was started. Doses every 2 weeks until satisfactory pain relief and then maintained for 3 weeks. Thereafter, placebo was adminis followed by an additional 3 weeks of carbamazepine at the same dose that previously produced satisfactory p of 15 patients completed the study, 3 patients were unable to tolerate the initial dose. On a visual analog scal significantly improved from 8.2 to 4.0 on the first round of carbamazepine therapy (p less than 0.05), increase during placebo, and decreased to 4.1 with the second carbamazepine trial (p less than 0.05). Hamilton depre improved from 27.4 to 20.2 with carbamazepine therapy (Kudoh et al, 1998).

4.5.AH Panic disorder

1) 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

2) Summary:
Results were mixed in the treatment of panic disorder (Uhde et al, 1988)

3) Adult:
a) Mixed results were obtained when 14 patients with panic disorder were treated with CARBAMAZEPINE 2(milligrams daily (median 800 milligrams) during a 3-week, placebo-controlled trial. Although a statistically sign overall anxiety was noted on several rating scales, only 1 patient demonstrated sustained clinical improveme panic attacks was noted in 40% of patients as compared with an increase in 50% of patients (Uhde et al, 198

4.5.AI Phantom limb syndrome

1) 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

2) Summary:
Total abatement of phantom limb pain has been achieved (Patterson, 1988)

3) Adult:
a) The successful use of CARBAMAZEPINE 200 milligrams four times a day in the treatment of phantom lim year-old male was reported. The drug was given in increasing doses to achieve serum levels of 8 to 12 micro resulted in total abatement of pain. Controlled studies are required to more fully evaluate the efficacy of CARI phantom limb pain (Patterson, 1988).

4.5.AJ Polyradiculoneuropathy

1) 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

2) Summary:
Effective in one case report (Winspur, 1970)

3) Adult:
a) A case of POLYRADICULONEUROPATHY with severe shooting pains in both legs was successfully treat CARBAMAZEPINE 400 milligrams (mg) at bedtime initially, followed by 200 mg three times daily in combinat PREDNISONE 60 mg daily. Further investigations are required to determine the efficacy of CARBAMAZEPIN polyradiculoneuropathy (Winspur, 1970).

4.5.AK Postherpetic neuralgia

1) 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

2) Summary:
Variable results in POSTHERPETIC NEURALGIA (Thompson & Bones, 1985)

3) Adult:
a) Limited response was seen with carbamazepine 400 to 1200 milligrams/day in 4 patients with intractable (associated with post-herpetic neuralgia. A favorable response (greater than 50% reduction in subjective pain attained in 1 patient. The response was limited by side effects, especially neurotoxicity (drowsiness, diplopia, ataxia), as only 7 of a total of 16 patients in the study were able to complete the entire 6-week protocol (Rape
b) Carbamazepine has been reported to be ineffective for preventing post-hepatic neuralgia. Forty otherwise

over 50 years of age with early, severe painful herpes zoster were randomly grouped to receive either predni daily for 10 days with gradual reduction over 3 weeks or carbamazepine 400 milligrams daily. Thirteen (65%) given carbamazepine developed post-herpetic neuralgia lasting up to 2 years whereas three (15%) of 20 pre patients had post-herpetic neuralgia lasting up to 5 months only (Keczkes & Basheer, 1980).

4.5.AL Posttraumatic stress disorder

1) 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

2) Summary:

Symptomatic improvement has been seen with the use of carbamazepine for posttraumatic stress disorc 1986)

3) Adult:

a) In a preliminary study of CARBAMAZEPINE in 10 patients with post-traumatic stress disorder, 7 patients marked to moderate improvement as measured by the Clinical Global Impression Scale. Symptomatic impro in reduced frequency and intensity of flashbacks, intrusive memories and nightmares. CARBAMAZEPINE do to maintain levels at 5 to 10 micrograms/milliliter (Lipper et al, 1986).

4.5.AM Psychotic disorder

1) 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

2) Summary:

May augment neuroleptic therapy in psychotic patients with aggression (Neppe et al, 1991)
In case reports, provides neuroleptic-augmentation of CANNABIS-INDUCED PSYCHOTIC DISORDER
In case reports, relieves sensory-induced psychotic symptoms

3) Adult:

a) Two patients with cannabis-induced psychotic symptoms benefited from adding carbamazepine to their n (Leweke & Emrich, 1999). These young patients (19 and 22 years old) developed a schizophrenia-like psych term cannabis use. They were both treated with perazine up to 400 milligrams. One patient had also failed h risperidone trials. Symptoms improved over the next 2 weeks as measured on the Brief Psychiatric Rating Sc

b) Eight women with violent episodic outbursts ranging from murder to serious assaults, with EEGs revealin were successfully treated with CARBAMAZEPINE 400 to 800 milligrams/day (mg/day). Patients were also re doses of neuroleptics (mean 2040 mg/day in CHLORPROMAZINE equivalents). CARBAMAZEPINE therapy 2 months to 11 years (mean 2.7 years). Violent behavior disappeared almost completely in all 8 patients and schizophrenic symptoms decreased markedly. By the end of the trial, the neuroleptic dosage had been reduc of 1310 mg/day in CHLORPROMAZINE equivalents. It appears that the combination of CARBAMAZEPINE a therapy successfully controls violent schizophrenia and allows reduced doses of the neuroleptics (Hakola & L

c) One study reported CARBAMAZEPINE efficacy in 9 schizophrenic patients with episodic hostility and agg suggested that the presence of these target features may be predictive of CARBAMAZEPINE responsivenes 1991).

d) The combination of CARBAMAZEPINE plus HALOPERIDOL was superior to haloperidol plus placebo in involving 43 patients with EXCITED PSYCHOSES. Combination therapy was reported superior to HALOPER clinical benefits being as apparent in excited SCHIZOPHRENIA as in mania (Klein et al, 1984a).

e) Carbamazepine therapy was effective for MUSICAL HALLUCINATIONS with temporal lobe abnormalities woman (Terao & Tani, 1998). The woman's musical hallucinations had lasted for at least 2 years. Alpha wave predominately in the occipital area were evident on electroencephalography (EEG). Carbamazepine 300 milli softened, slowed and decreased the duration of the music. The mild spike activity on EEG disappeared.

f) A 40-year-old man with PALINOPSIA (the recurrence of visual images after the stimulus is removed) was treated with carbamazepine. This man's diagnoses included DSM-IV diagnostic criteria for psychosis not othe anxiety disorder not otherwise specified, and some of the symptoms of post-traumatic stress disorder. He des abnormalities as unrelated to his combat experiences and as perseverations of images or objects he had pre He was treated with imipramine 200 milligrams (mg) and trifluoperazine 10 mg daily. This decreased his flash and insomnia; however, the palinopsia continued. Carbamazepine 400 mg/day was started and within 48 hou had decreased. After 6 days of carbamazepine 800 mg, his palinoptic experiences disappeared (Silva et al, 1

4.5.AN Restless legs syndrome

1) 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

2) Summary:

Short-term efficacy for restless legs syndrome

See Drug Consult reference: RESTLESS LEG SYNDROME - DRUGS OF CHOICE

3) Adult:

a) CARBAMAZEPINE in doses of 200 milligrams at bedtime initially, increasing to maximum doses of 200 m morning and 400 milligrams at bedtime, was effective in reducing the number of attacks of restless legs (EKE SYNDROME) in a placebo-controlled study (Lundvall et al, 1983).

b) An additional report of the efficacy of CARBAMAZEPINE in restless legs (Ekbom's syndrome) was reporte 1984). In this study, the placebo response was remarkable, although response to CARBAMAZEPINE was su daily dose was 236 milligrams CARBAMAZEPINE.

4.5.AO Schwartz-Jampel syndrome

1) Overview

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

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Possibly beneficial for Schwartz-Jampel syndrome (Topaloglu et al, 1993)

3) Pediatric:

a) Three cases of MYOTONIC CHONDRODYSTROPHY (Schwartz-Jampel syndrome) were reported to ber with carbamazepine. The three children were placed on carbamazepine 20 milligrams/kilogram/day. Symptor gradually improved over several months (Topaloglu et al, 1993).

4.5.AP Subacute sclerosing panencephalitis

1) 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

2) Summary:

Effective in 1 case report (Kertesz et al, 1970)

3) Adult:

a) CARBAMAZEPINE effectively reduced the number and intensity of akinetic attacks secondary to subacute PANENCEPHALITIS in 1 patient with doses of 200 milligrams three times daily. Symptoms were ameliorated initiation of therapy (Kertesz et al, 1970).

4.5.AQ Tabes dorsalis

1) 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

2) Summary:

Effective for lightning pains of tabes dorsalis (Ekbom, 1972; Alarcon-Segovia & Lazcano, 1968; Ekbom,

3) Adult:

a) Three uncontrolled studies have revealed the beneficial effects of carbamazepine in 10 of 10 patients with tabes dorsalis (Ekbom, 1972; Alarcon-Segovia & Lazcano, 1968; Ekbom, 1966). In all patients, pain symptom 1 to 3 days and attempts to withdraw medication led to reappearance of pain. During long-term therapy, mild sporadic pain was usually exacerbated by infections with fever or by consumption of ETHANOL. Also, during larger doses were required in some patients to maintain adequate analgesia.

4.5.AR Temporal lobectomy behavior syndrome

1) 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

2) Summary:

Effective in one case of posttraumatic Kluver-Bucy syndrome (Stewart, 1985)

3) Adult:

a) In one case, CARBAMAZEPINE blood levels of 8 to 11 micrograms/milliliter were effective in controlling ra affective blunting, hypersexuality, hyperorality and hypermetamorphosis in a 20-year-old man with post-traun

syndrome. His bulimia was unaffected by drug therapy (Stewart, 1985).

4.5.AS Tinnitus

1) 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

2) Summary:

Ineffective in the general treatment of tinnitus (Hulshof & Vermeij, 1985)
Effective in case reports of ear clicking and HYPERACUSIS

See Drug Consult reference: DRUG THERAPY OF TINNITUS

3) Adult:

a) Two women with hyperacusis due to Lyme disease benefited from carbamazepine therapy (Nields et al, 1 had other central nervous system effects which remitted after treatment with cefotaxime. After cefotaxime, bo remained so sensitive to sound that they wore ear plugs, rifle range headphones, or airport headphones to pr kindling-like phenomenon occurred in each woman where repeated subthreshold sound lowered their toleran hours or days. This led to a trial of carbamazepine titrated to a blood level of 4 to 6 micrograms/milliliter. Both experienced an increase in baseline sound tolerance. Symptoms again worsened in each patient after a trial

b) Although an early study (Rahko & Akkinen, 1979) demonstrated CARBAMAZEPINE to have considerable treatment of clicking tinnitus (clicks almost totally disappeared in 3 patients, with symptoms reappearing whe discontinued), a double-blind study involving 78 patients failed to show a statistically significant difference in t patient's tinnitus when taking CARBAMAZEPINE or placebo (Donaldson, 1981a).

c) In an anecdotal report, benefits were reported with CARBAMAZEPINE 200 milligrams orally three times a treatment of ear-clicking tinnitus. Withdrawal of CARBAMAZEPINE resulted in return of tinnitus and reinstituti again produced symptom resolution. In this case report, a caffeine-free diet was also reported helpful in allev when the patient was not receiving CARBAMAZEPINE. More studies are required to fully evaluate the efficac CARBAMAZEPINE in this form of tinnitus (Mardini, 1987).

4.5.AT Trigeminal neuralgia

FDA Labeled Indication

1) Overview

FDA Approval: Adult, yes; Pediatric, no
Efficacy: Adult, Effective
Recommendation: Adult, Class I
Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Indicated for pain associated with trigeminal neuralgia
Drug of choice

3) Adult:

a) CARBAMAZEPINE has been used effectively in patients with trigeminal neuralgia for many years and is n drug of choice (Voorhies & Patterson, 1981; Tomson et al, 1980; Daly & Sajor, 1973; Lewis, 1969; Killian, 19 Sachdev, 1969; Marotta, 1969; Sturman & O'Brien, 1969; Killian & Fromm, 1968a; Walsh & Smith, 1968). Eff these studies range from 100 to 800 milligrams daily resulting in blood levels of 6 to 12 micrograms/milliliter. can be used over long periods of time for the treatment of trigeminal neuralgia without loss of efficacy.

b) The results of 143 patients with trigeminal neuralgia who had received CARBAMAZEPINE over a 16-year reviewed (Taylor et al, 1981). Fifty-six males and 87 female patients received a starting dose of CARBAMAZ 200 milligrams (mg) 3 or 4 times daily. The dose was increased until the pain was controlled or side effects d then continued to receive the minimum dose needed to prevent pain and were instructed to stop the drug dur Forty-six (32%) of the patients were completely or well-controlled by CARBAMAZEPINE and 53 (37%) were p acceptably, controlled. Ten patients experienced mild side effects, but did not stop treatment. Of these 99 pa good initial response, 19 developed a late resistance in that pain recurred and did not respond to CARBAMA Resistance developed anywhere from 2 months to 10 years after treatment began. Sixty-three of the original required alternate treatment. Thirty-six of the patients failed to respond to CARBAMAZEPINE initially, eight p intolerant and 9 responded initially, but developed resistance.

c) A synergistic effect between BACLOFEN and CARBAMAZEPINE was shown in the treatment of trigemina 57-year-old patient. The patient had a history of paroxysmal jaw pain unresponsive to CARBAMAZEPINE alo eventually controlled with BACLOFEN 60 milligrams (mg) per day plus CARBAMAZEPINE 800 mg per day (E

4.5.AU Trigeminal trophic syndrome

1) 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

2) Summary:
Successfully treated a case of trigeminal trophic syndrome (Bhushan et al, 1999)
3) Adult:
a) Carbamazepine was effective in the treatment of trigeminal trophic syndrome in a 58-year-old male. This i
caused by damage to the trigeminal nerve and is associated with facial dysesthesias and ulceration. Carbam
milligrams twice daily effectively reduced the patient's sensory symptoms within 48 hours of initiation (Bhusha

4.5.AV Uremic neuropathy
1) 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
2) Summary:
Antidepressant actions may contribute to analgesic effectiveness
Further data is needed to evaluate this mode of therapy
3) Adult:
a) CARBAMAZEPINE was effective in relieving pain in 5 patients with severe UREMIC NEUROPATHY (Zar
1976). Doses of 100 milligrams (mg) twice daily were given initially, followed by maintenance doses of 200 to
daily for several weeks. In all patients, pain relief was noted within 1 to 2 weeks. However, motor weakness,
other symptoms remained unchanged in all patients.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Amitriptyline

Baclofen

Clonazepam

Haloperidol

Lamotrigine

Lithium

Lorazepam

Oxazepam

Oxcarbazepine

Phenobarbital

Phenytoin

Primidone

Progabide

Propranolol

Tiapride

Topiramate

Valproic Acid

Vigabatrin

Zonisamide

4.6.A Amitriptyline

4.6.A.1 Neurogenic pain

a) Carbamazepine 800 mg daily was compared with amitriptyline 75 mg daily in a 4-week, randomized, doub over trial in 15 patients with central post-stroke pain. Amitriptyline produced a statistically significant reductior weeks of the start of treatment. Five of the patients treated with carbamazepine obtained pain relief but it was significant as compared with placebo. Carbamazepine produced a greater number of side effects which requi reduction in 4 patients (Leijon & Boivie, 1989).

4.6.B Baclofen

4.6.B.1 Trigeminal neuralgia

a) Baclofen reduced the number of trigeminal neuralgic attacks in patients resistant to carbamazepine but ef significant when the drug was combined with carbamazepine. This was a double-blind trial (Parekh et al, 198

4.6.C Clonazepam

4.6.C.1 Psychomotor epilepsy

a) Clonazepam and carbamazepine were equally effective in the treatment of newly diagnosed and previous psychomotor epilepsy. In a double-blind, randomized study, 36 patients were maintained on either clonazepa or carbamazepine 900 milligrams/day for a period of 6 months. Plasma levels for each drug remained within t range throughout treatment. Both drugs were equally effective in controlling epilepsy. Side effects were simila (Mikkelsen et al, 1981).

4.6.D Haloperidol

4.6.D.1 Drug-induced psychosis, Inhalant

a) Carbamazepine demonstrated comparable efficacy to haloperidol in the treatment of inhalant-induced psy (Hernandez- Avila et al, 1998). Patients received either 1 capsule of carbamazepine 200 milligrams (mg) 3 tir 1 capsule of haloperidol 5 mg 3 times daily (n=20) for 5 weeks. Doses were increased at weekly intervals by patient failed to show a 25% decrease in the Brief Psychiatric Rating Scale (BPRS). At the end of the study, r were carbamazepine 920 mg (serum level of 10.8 micrograms/liter) and haloperidol 21.7 mg. Similar improve in both groups with 48.3% improvement in the carbamazepine group and 52.7% improvement in the haloperi

4.6.E Lamotrigine

4.6.E.1 Seizure

a) Carbamazepine and lamotrigine are equally effective as monotherapy in patients with newly diagnosed ep double-blind manner, patients were randomly assigned to a fixed dosage titration of either carbamazepine or four weeks, all patients were receiving either 150 milligrams/day (mg) of lamotrigine or 600 mg/day of carbam next 24 weeks, doses were adjusted according to efficacy, tolerance, and drug serum levels. The percentage were seizure-free for the last 6 months of the study were 39% and 38% for lamotrigine and carbamazepine g respectively. However, lamotrigine was better tolerated, and more patients were able to complete the study p treated with carbamazepine. Sleepiness was significantly more common with carbamazepine than lamotrigin 12%, respectively) (Brodie et al, 1995).

b) As initial monotherapy in elderly patients newly diagnosed with epilepsy, lamotrigine demonstrated a supe tolerability profile compared to carbamazepine. Subjects (n=150) were randomized in a double-blinded 2:1 ra 25 milligrams/day (mg/day) or carbamazepine 100 mg/day. Both medications were titrated slowly upward ove mg twice daily and 200 mg twice daily, respectively, with adjustments as needed over the 24-week study dura doses of lamotrigine and carbamazepine in study completers were 100 mg/day and 400 mg/day, respectively serum concentrations at week 24 were 2.3 mg/liter (L) and 6.9 mg/L, respectively. Somnolence (29% versus (25% versus 9%) occurred significantly more often in the carbamazepine versus lamotrigine groups, respecti corresponding withdrawal rates were 58% and 29%, with adverse events accounting for 42% and 18% of dis respectively. The hazard ratio for withdrawal with carbamazepine compared to lamotrigine was 2.4 (95% con 1.4 to 4). Efficacy measures were considered secondary endpoints in this trial. While no between-group differ respect to time to first seizure, significantly more lamotrigine recipients remained seizure-free over the last 16 study (39% versus 21%, p=0.03) (Brodie et al, 1999).

4.6.F Lithium

Bipolar disorder

Depression

Mania

4.6.F.1 Bipolar disorder

a) SUMMARY: Comparisons of prophylactic use of lithium and carbamazepine for bipolar disorder have proc results for superiority of one agent over the other, with both agents showing only modest efficacy rates.

b) In treatment-naive bipolar patients, lithium was superior to carbamazepine for preventing recurrence of m depressive episodes. Based upon analyses of 94 patients who had been randomized to blinded treatment eit blood levels 0.6 to 1.0 millimoles/liter) or carbamazepine (target blood levels 6 to 10 milligrams/liter), 27% an on lithium and carbamazepine, respectively, experienced relapse within the 2-year study period. Among relap almost all on lithium had initially experienced a hypomanic episode, and had recurrent episodes within the firs therapy. In contrast, patients relapsing during carbamazepine had episodes that were more evenly distributed entire study period. Notably, patients randomized during an acute episode showed different results from thos during the prophylactic treatment phase; the authors speculated that differences may be attributed to the dise which randomization occurred or to characteristics of bipolar disease. Post hoc analysis of subgroup characte to clarify these differences (Hartong et al, 2003).

c) In an open, randomized, controlled clinical trial, lithium was superior to carbamazepine for maintenance th with bipolar disorder. Patients received lithium (n=86) and carbamazepine (n=85) in average doses of 26.8 m per day (serum concentration 0.61 +/- 0.12 mmol/liter) and 635 milligrams per day (serum concentration 6.12 micrograms per milliliter), respectively, for 2.5 years. Outcomes measured included inter-episodic morbidity, a average severity of affective symptoms during outpatient treatment, as well as drop-out rate, and rate of reho Although rates of rehospitalization were similar for both treatment groups, more patients demonstrated a goo (low inter-episodic morbidity without rehospitalization or drop-out) with lithium than during carbamazepine tre versus 24%; p=0.03). This difference was largely due to a difference in drop-out rate in patients without rehos versus 42%). Drop-outs were primarily related to the development of adverse effects. Overall, inter-episodic r similar. However, in lithium-treated patients, average inter-episodic morbidity declined by about 50% during th months and remained at this level for the rest of the observation period, while in those treated with carbamaz was not observed (Kleindienst et al, 2002)

d) Lithium appeared superior to carbamazepine in the treatment of classic bipolar symptoms (Bipolar Type I) carbamazepine may have been more useful in patients with nonclassic symptoms (Greil et al, 1998). Patients depressive symptoms or schizoaffective disorder requiring prophylactic therapy were categorized as having e symptoms (bipolar type I) or nonclassic symptoms, and randomized to receive either lithium or carbamazepir during the 2.5-year study were lithium 26.8 millimoles (mmol)/day with a serum level of 0.61 mmol/liter (L) an 190 milligrams/day with a level of 6.12 micrograms/milliliter. Prevention of hospitalization was the primary out with classic symptoms (n=67), lithium use was associated with significantly fewer hospitalizations than carba (p=0.005). In the non- classic bipolar patients (n=104), there was a trend favoring carbamazepine (p=0.075). group, hospitalizations correlated significantly with the number of nonclassic features (p=0.035). In the carba negative association was found between hospitalization rate and number of nonclassic features (p=0.033). D in both groups with fewer occurrences in the lithium group (p=0.004).

e) In a retrospective chart review, younger patients with rapid cycling affective disorder had their manic symp controlled with carbamazepine while older-onset patients had their symptoms better controlled with lithium (F 1998). Early-onset cases were defined as affective disorder beginning at 25 years of age or younger (n=14) v disorder was defined as beginning after the age of 25 (n=21). Further controlled studies are needed.

f) In a double-blind study of 52 bipolar patients, lithium and carbamazepine had a roughly equal but less thar prophylactic efficacy in overall bipolar illness (Denicoff et al, 1997). Patients were randomly assigned to 1 yea lithium or carbamazepine, and then crossed over to the other drug in the second year. During a third year, pa combination of the 2 drugs. A marked or moderate improvement occurred in 33%, 31%, and 55% of patients carbamazepine, and the combination, respectively. Lithium, however, was superior in the prophylaxis of man experienced by 11% on lithium, 4% on carbamazepine, and 33% on combination therapy; p less than 0.01). lithium and carbamazepine was better than monotherapy in rapid cyclers (p less than 0.05).

4.6.F.2 Depression

a) In an controlled study, 15 depressed patients who did not respond to treatment with carbamazepine were Eight of the 15 patients responded to the addition of lithium therapy (0.8 +/= 0.2 mmol/L) within 4.1 +/- 2.4 da responders tended to be more rapid cyclers (ie, 6.9 +/- 4.1 affective episodes/year versus 3.4 +/- 2.4 year) (K 1989a). A controlled study comparing the two drugs in patients unresponsive to lithium may be useful in disce characteristics of patients most likely to respond to carbamazepine.

4.6.F.3 Mania

a) Lithium and carbamazepine were similarly effective in the treatment of manic patients in a controlled study 1987). However, results suggested that lithium is more effective than carbamazepine in a heterogenous popu patients. A more consistent beneficial effect was observed in lithium-treated patients with regard to Clinical G the Brief Psychiatric Rating Scale and the Beigel- Murphy Manic State Rating Scale. It is suggested that carb antimanic potential in specific types of bipolar patients whose characteristics must be defined in further clinica in this study suggested that carbamazepine may be useful in the "brittle" lithium non- responsive bipolar patie affective relapses.

b) The combination of lithium plus carbamazepine was more effective than lithium alone in reducing depress

episodes in patients with bipolar disorder. Lithium concentrations were maintained between 0.6 and 1 milliequ
those taking carbamazepine concurrently maintained carbamazepine concentrations 4.6 to 8.8 milligrams/mil
was limited in that there were only 8 patients per group (Di Costanzo & Schifano, 1991).
c) Efficacy of carbamazepine and lithium carbonate was compared in a randomized trial of 52 patients with r
previously failed other courses of treatment (Small et al, 1991). Following a two-week drug withdrawal period
assessments were performed for 8 weeks with long term follow-up in responders for up to 2 years. Dosages
titrated to obtain therapeutic plasma levels. One third of the patients showed a positive response with no stati
differences noted between the two treatment groups. Carbamazepine-treated patients demonstrated better c
during the first 3 weeks of therapy although the drop-out rate was higher in this group.

4.6.F.4 Adverse Effects

a) In a comparative efficacy trial for bipolar disorder, adverse effects occurred more often with lithium than w
despite therapeutic blood levels in the majority of each group. Effects that occurred more often with lithium in
vision, difficulties concentrating, feeling thirsty, decreased appetite, hand tremor, muscle weakness. Increase
occurred more often with carbamazepine, however (Hartong et al, 2003).

4.6.G Lorazepam

4.6.G.1 Alcohol withdrawal syndrome

a) Carbamazepine and lorazepam were equally efficacious for the treatment of symptoms associated with al
but carbamazepine was superior for preventing rebound withdrawal symptoms and for reducing post-treatme
especially in those patients with a history of multiple withdrawals. In a randomized, double-blind trial, 136 trea
patients with alcohol dependence were stratified according to number of previous withdrawal experiences (2
than 2) prior to randomization to treatment with carbamazepine on a 5-day fixed dose taper, starting with 600
(mg) on day 1 and tapering to 200 mg as a single dose on day 5, or lorazepam, 6 to 8 mg on day 1 and taper
mg dose on day 5. Prior research had determined the equivalency of the dosages of carbamazepine and lora
with 2 or more previous detoxifications had significantly higher scores on the CIWA-Ar (Clinical Institute Witho
Assessment for Alcohol-Revised) throughout treatment and during the post-treatment follow-up (days 7 to 12
with fewer than 2 previous detoxifications. The mean number of drinks per day during post-treatment was sim
carbamazepine-treated and lorazepam-treated patients who had 0 or 1 prior detoxifications, whereas, among
than 2 prior detoxifications, the average daily consumption was 5 drinks for the lorazepam group and 1 for the
group (p=0.004). The relative risk of having a first drink was 3 times higher for the lorazepam group than for t
group. Twenty percent of carbamazepine-treated patients and 1.3% of lorazepam-treated patients complaine
not with rash). Seven percent of the carbamazepine group and 23% of the lorazepam group showed signs of
incoordination, light-headedness, and drowiness, which they themselves did not recognize (Malcolm et al, 20

4.6.H Oxazepam

4.6.H.1 Alcohol withdrawal syndrome

a) Carbamazepine (CBZ) and oxazepam were equally effective in the treatment of alcohol withdrawal in a 7-
study in 60 inpatients (Stuppaeck et al, 1992). Oxazepam 120 milligrams (n=30) or CBZ 800 milligrams (n=30
days 1 to 3; on days 4 through 7, the doses were reduced to 90 milligrams and 600 milligrams, respectively; a
the 7-day trial, all patients received CBZ 200 milligrams twice a day on day 8 and 200 milligrams/d on day 9.
Institute Withdrawal Scale-Alcohol (CIWA-A), Clinical Global Impression Scale (CGI), and self-rating scores s
improvement of symptom severity throughout the trial. CBZ was superior to oxazepam on days 6 and 7 as m
A (p less than 0.05) and on day 7 as measured by CGI (p less than 0.05). Three patients from each group dr
of side effects, and 1 patient in each group withdrew consent and left treatment. The authors conclude that C
treatment in non-delirious patients with alcohol withdrawal syndrome.
b) Carbamazepine 200 milligrams orally 4 times daily was as effective as oxazepam 30 milligrams orally 4 ti
treatment of severe alcohol withdrawal during a 7-day, double-blind study involving 86 alcoholic men (Malcol
Both drugs were equally effective in reducing alcohol withdrawal symptoms, and adverse effects were also si
carbamazepine was more effective with regard to improving psychiatric symptoms and is therefore recomme
rehabilitation phase of alcoholism therapy.

4.6.I Oxcarbazepine

Epilepsy

Trigeminal neuralgia

4.6.I.1 Epilepsy

a) SUMMARY: Oxcarbazepine appears to be as effective as carbamazepine in the treatment of epilepsy; se
effects have occurred to a lesser degree with oxcarbazepine in some studies. Further studies are needed to i
enzyme-inducing effects, particularly at higher doses.
b) Oxcarbazepine is similar in efficacy to carbamazepine as monotherapy or add-on therapy in epileptic pati
1989; Reinikainen et al, 1987); (Bulau et al, 1987)(Houtkooper et al, 1987; Houtkooper et al, 1984; Dam, 199

1986; Anon, 1990; Jensen, 1990). There is some evidence of efficacy in patients unresponsive to carbamaze associated with therapeutic equivalency in some studies have been 200 mg carbamazepine and 300 to 400 r (Houtkooper et al, 1987), however the ratio has been closer to 1:1 in others (Bulau et al, 1987).

c) Oxcarbazepine is at least as effective as carbamazepine in patients receiving polytherapy, and oxcarbaze tolerated in some patients. The efficacy of oxcarbazepine and carbamazepine was compared in 48 epileptic i controlled on polytherapy, including carbamazepine, in a double- blind, crossover study (Houtkooper et al, 19 seizures were generalized (9 patients), partial (10 patients), or both generalized and partial (29 patients); all p least 2 seizures/week despite therapy with 2 to 4 antiepileptic agents. Patients were randomly allocated to ox mg/day or carbamazepine 200 mg/day. Following a titration period, where the dose of each was increased to seizure control, therapy was continued for 12 weeks (steady- state) in each trial period. As compared to carb therapy with oxcarbazepine reduced the total number of seizures by 9%; tonic-clonic and tonic seizures were 20% and 31%, respectively. In 5 patients, a shift from complex partial to simple partial seizures or atypical ab was observed during oxcarbazepine therapy. Other differences reported during oxcarbazepine therapy were alertness and greater ability to concentrate in 5 patients and remission of carbamazepine related allergic skin Serum levels of valproic acid and phenytoin were higher in oxcarbazepine treated patients, and serum sodiur were lower. Other adverse effects were similar with each agent.

d) In a double-blind study, the efficacy of oxcarbazepine and carbamazepine in 16 epileptic patients inadequ at least 1 anticonvulsant (other than carbamazepine) was evaluated (Bulau et al, 1987). Each patient had exp 1 tonic-clonic or complex partial seizure per month. Oxcarbazepine or carbamazepine were added sequentia fashion during a 1 month titration period; therapy was continued for an additional 3 months. Mean doses were mg daily for oxcarbazepine and carbamazepine, respectively. Concomitant anticonvulsants were continued th frequency was reduced by 90% during therapy with both agents, with 28% of all patients becoming seizure-fr effects were less in oxcarbazepine treated patients. Increases in serum levels of valproic acid, phenytoin, and observed in the oxcarbazepine group, presumably secondary to a lesser degree of enzyme induction as com carbamazepine.

4.6.I.2 Trigeminal neuralgia

a) Oxcarbazepine and its 10-hydroxy-metabolite (10-hydroxy-carbazepine; 10,11-dihydro-10-hydroxy carbar compared with carbamazepine in 24 patients with trigeminal neuralgia (Farago, 1987). All patients had either trigeminal neuralgia or other idiopathic facial neuralgias for at least 2 weeks. Fourteen patients had been trea carbamazepine. Oxcarbazepine was administered to 13 of the 24 patients for a mean of 11 months (mean m 1100 milligrams daily), resulting in an adequate clinical response in 10 and a moderate response in 3. Sympt however, was seen in 1 patient after 6 months of treatment. Eleven patients were treated with the 10-hydroxy oxcarbazepine (GP 47779) for a mean of 3.5 months (mean maximal dose, 1100 milligrams daily), with 7 ach of symptoms and 4 noticing definite improvement. However, recurrence of symptoms occurred in 2 patients a months of treatment, respectively. In the 14 patients treated previously with carbamazepine, therapy with eith or its metabolite was reported to be more effective than carbamazepine in 12; efficacy was considered equiva worse in another. These overall results suggest the potential superiority of oxcarbazepine over carbamazepir neuralgia. However, placebo-controlled trials are required to confirm these findings.

4.6.I.3 Efficacy

a) The primary difference between oxcarbazepine and carbamazepine is in regard to pharmacokinetic prope affect the propensity of these agents to elicit adverse effects. Following absorption, oxcarbazepine is rapidly converted via reduction to 10-hydroxy-carbazepine, the active metabolite, which is excreted in the urine as th conjugate. A portion of the 10-hydroxy-metabolite is hydroxylated to isomeric 10,11-diols, the trans-diol predo (Theisohn & Heimann, 1982; Schutz et al, 1986; Anon, 1989).

b) In contrast, carbamazepine is oxidized to the active carbamazepine-10,11-epoxide; a portion of this metal converted to the inactive 10,11-diol (Eichelbaum et al, 1985d; Anon, 1989; Anon, 1990). The 10,11-epoxide r carbamazepine is responsible for dose-dependent adverse effects (Anon, 1990; Anon, 1989). Because an ep produced during oxcarbazepine metabolism, this drug is expected to be better tolerated than carbamazepine

4.6.I.4 Adverse Effects

a) A trend toward a lower incidence of severe adverse effects has been observed with oxcarbazepine as cor carbamazepine in some studies (Bulau et al, 1987)(Dam, 1990; Houtkooper et al, 1987), which at times reach significance (Dam, 1990).

b) Oxcarbazepine appears less likely than carbamazepine to influence oxidative processes, as the metabolis oxcarbazepine is facilitated primarily by reduction. Studies have reported that oxcarbazepine lacks autoinduc unlike carbamazepine, a feature which may decrease the incidence of breakthrough seizures (Anon, 1989; B Anon, 1990).

c) In some studies, oxcarbazepine has not influenced antipyrine kinetics, suggesting an advantage with rega interactions (Anon, 1989). However, dose-dependent enzyme induction has been reported by other investiga doses producing effects similar to carbamazepine (Patsalos et al, 1990). As the optimal dose of oxcarbazepir undefined, further studies will be needed to determine if the drug will offer a significant advantage in regard to and autoinduction.

4.6.J Phenobarbital

Epilepsy

Epilepsy, Children

4.6.J.1 Epilepsy

a) Phenobarbital in doses of 4 to 5 mg/kg/day proved to be more effective than carbamazepine 20 mg/kg/da day doses) in the treatment of recurrent febrile convulsions in a double-blind study. Nine of 19 carbamazepin (47%) had recurrent seizures despite therapeutic blood levels, however only two of the phenobarbital treated had recurrent seizures (Antony & Hawke, 1983).

b) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy and if treatment failure occurred, patients were randomly switched to an alter There was no significant difference among the drugs in the treatment of tonic-clonic seizures. Conversely, ca significantly more effective in controlling simple partial and complex partial seizures than were any of the othe rather than seizure control appeared to be the greatest differentiating factor among the four study drugs with primidone manifesting the highest incidence of side effects early in therapy with no significant differences afte Patient tolerance of the drugs as measured by retention rates were significantly better among carbamazepine treated patients. In studies of behavioral toxicity, carbamazepine-treated patients showed the least deteriorat of patients were successfully managed for 1 year on monotherapy, regardless of the drug chosen. The autho based on anticonvulsant activity and side effect profile, carbamazepine may be the preferred drug for initiatio adults with either generalized tonic-clonic, simple partial or complex partial seizures (Smith et al, 1987).

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 (n=167) with at least two previously untreated tonic-clonic or partial seizures were eligible for participation in drugs were equally efficacious with 20% of the patients remaining seizure-free and 73% achieving a 1-year re years. However, randomization to phenobarbital was discontinued early in the study period due to unaccepta Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatme 9% of children treated with phenytoin.

4.6.K Phenytoin

Epilepsy

Epilepsy, Children

Impaired cognition

Myotonia

4.6.K.1 Epilepsy

a) Carbamazepine is as effective an anticonvulsant as phenytoin (Simonsen et al, 1975; Ramsay et al, 1983 1975).

b) In a controlled study, carbamazepine was reported as effective as phenytoin as initial seizure therapy in 7 with either simple seizures, complex seizures, partial evolving to generalized seizures and generalized convu (Ramsay et al, 1983). Thirty-five patients were treated with each drug. Complete control of seizures was achi patients in each treatment group. Mean serum levels during weeks 8 to 24 of treatment were 9.1 to 11 mcg/m and 4.7 to 6.5 mcg/mL for carbamazepine. The incidence of side effects was similar in both groups. Carbama recommended as a major anticonvulsant to be given initially as single agent therapy in the management of th

c) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy with doses titrated to produce blood levels in the therapeutic range. If treatme (inadequate seizure control with the initial drug or unacceptable toxicity from the initial drug), patients were ra to an alternate study drug. Combined results with all four drugs suggested that full seizure control was signifi patients with generalized tonic-clonic seizures than for those with partial seizure disorders (56% vs 39%). Th significant difference among the drugs in treatment of tonic- clonic seizures. Conversely, carbamazepine was effective in controlling simple partial and complex partial seizures than were any of the other drugs. Toxicity a greatest differentiating factor among the 4 study drugs. Patients taking primidone exhibited the highest incide early in therapy, although there were no significant differences with chronic therapy. Patient tolerance of the d by retention rates were significantly better among carbamazepine- and phenytoin-treated patients. In studies toxicity, carbamazepine-treated patients showed the least deterioration. Overall, 80% of patients were succes 1 year on monotherapy, regardless of the drug chosen. The authors concluded that based on anticonvulsant carbamazepine may be the preferred drug for initiation of therapy in adults with either generalized tonic-clonic complex partial seizures (Smith et al, 1987a).

d) One hundred eighty-one patients with previously untreated epilepsy were randomized to receive valproic a carbamazepine as monotherapy and followed for 14 to 24 months (Callaghan et al, 1985). The oral drug dose phenytoin 300 milligrams/day (mg/day) (adults) and 5 to 10 milligrams/kilogram/day (children), carbamazepin (adults) and 5 to 10 mg/kg/day (children), and valproic acid 600 mg/day (adults) and 5 to 10 mg/kg/day (child were highly effective in the control of generalized seizures but less effective for partial seizures. There was no difference between the overall incidence of side effects between the 3 drugs.

4.6.K.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 side Carbamazepine and sodium valproate were the best tolerated with only 4% of children discontinuing treatmen 9% of children treated with phenytoin.

4.6.K.3 Impaired cognition

a) Most studies have found phenytoin to cause more cognitive impairment than carbamazepine, but there wa didn't find any clinically significant differences in cognitive adverse effects between phenytoin and carbamaze similar kinds of neuropsychological evaluations (Meador et al, 1991).

b) A study was conducted to compare the cognitive effects of phenytoin and carbamazepine during monothe controlled withdrawal in two groups of chronic epileptic patients who were seizure-free for at least two years. (mean age 28.5 +/- 7 years) who took phenytoin for a mean duration of 32.08 +/- 17.8 months and 13 patient +/- 8.9 years) receiving carbamazepine for a mean duration of 28.07 +/- 16.1 months were compared with 26 age 23.57 +/- 8.3 years). Neuropsychological baseline assessment included tests of intelligence, vigilance, at and visuomotor performance. The effects of drug withdrawal were assessed by further neuropsychological re months after a fifty percent dosage reduction and three months and one year following complete withdrawal o carbamazepine. Results of neuropsychological testing at baseline showed that patients taking phenytoin suffe impairments in attention, visuomotor, and intellectual abilities as well as in global performance. Patients who carbamazepine performed markedly worse only on tasks requiring attention. After discontinuation of phenytoi markedly worse performances on verbal digits span, three months after a fifty percent dosage reduction and performances on verbal learning three months after discontinuation of phenytoin. Following discontinuation of patients suffered no further impairments on neuropsychological testing. One year after complete withdrawal o carbamazepine, both groups were no different than controls on the neuropsychological exam, thus demonstra reversibility of cognitive effects (Gallassi et al, 1988).

c) The cognitive effects of phenytoin and carbamazepine during monotherapy were compared in two groups referrals with epilepsy and with an untreated control group of epileptic patients. Twenty-one patients were in e seizure activity well-controlled in the majority of patients for 2 to 3.5 years. Patients in the phenytoin-treated g phenytoin plasma concentrations of 9.5 microgram/milliliter (mcg/mL) (range 1 to 21 mcg/mL) and had been t duration of 5.8 years. Patients in the carbamazepine-treated group had mean carbamazepine plasma concen mcg/mL (range 0.5 to 10.6 mcg/mL) and had been treated for a mean duration of 3.6 years. Assessments of included tests of memory scanning, word list learning, memory (immediate recall and with a one-hour delay), (three subtasks of graduated difficulty), and the tracking task. The phenytoin group performed significantly wo two groups on the most demanding subtest of short-term memory scanning (p less than 0.05). Performance o memory tasks were significantly worse in the phenytoin-treated group (p less than 0.05). The phenytoin-treat demonstrated greater impairment on the prose recall test than the carbamazepine-treated group. Patients tre carbamazepine showed a trend to learn more rapidly than the phenytoin-treated patients. After a one-hour de carbamazepine-treated patients forgot significantly more than the phenytoin-treated patients (p less than 0.05 next list-learning task, the carbamazepine group relearned significantly more than the phenytoin group (p less significant difference was observed between the two treatment groups for the decision-making task or trackin et al, 1986).

d) In another clinical trial, patients receiving carbamazepine performed better than those receiving phenytoin tasks. The phenytoin group performed significantly worse (p less than 0.05) on short-term memory scanning t short-term memory task became more complex, the phenytoin group made more errors as compared with the treated group (p less than 0.06). Patients on carbamazepine performed significantly better than the phenytoin the tracking task (p less than 0.05) (Andrewes et al, 1984).

e) A randomized, double-blind, 10-month study, in 56 adult patients with chronic epilepsy was conducted to c cognitive effects of phenytoin and carbamazepine. Following a two-month stabilization period, patients were r to continue phenytoin or begin carbamazepine and then continue treatment for four months. All patients were to receive treatment for an additional four months. Mean phenytoin plasma concentrations were 31.2 +/- 2.13 microgram/milliliter (mcg/mL) for the entire study population, and the mean dose of phenytoin administered w milligrams/kilogram (mg/kg). Mean carbamazepine plasma concentrations were reported to be 9.3 +/- 0.55 m patients on mean doses of carbamazepine of 18.4 mg/kg. Twenty patients from each treatment group were ra from 47 patients who completed the 10 month study. No significant differences were reported on Halstead's r battery or the Weschler adult intelligence scale regardless of treatment; however, even though patients solve the same number of problems when receiving either phenytoin or carbamazepine, fewer errors were made on high cognitive component while taking carbamazepine. Patients reported feeling more alert during carbamaze than while taking phenytoin (Troupin et al, 1977).

f) A double-blind, crossover study compared the cognitive effects of four month trials of phenytoin and carba adult patients with chronic epilepsy. No significant differences were reported between phenytoin or carbamaz the Halstead battery or the Weschsler intelligence scale. Other neuropsychological tests showed significant i patients taking phenytoin on tasks requiring concentration and mental manipulation such as receptive aphasi 0.05), constructional dyspraxia (p less than 0.01), Stroop attention tasks (p less than 0.05), and Wonderlic pr tasks (p less than 0.05). Differences in performances on tasks requiring greater mental manipulation were mo patients being treated with phenytoin. As the task increased in complexity, the cognitive impairment effects o became more apparent as compared to carbamazepine. The investigators suggested that the impact of phen abilities may not be readily detectable when testing performance on routine tasks, but may require testing tas complexity to detect subtle cognitive impairment. The patients in this study reported feeling more alert when t treatment with carbamazepine compared to phenytoin (Dodrill & Troupin, 1977).

4.6.K.4 Myotonia

a) One study reported that phenytoin in doses of 200 to 300 milligrams (mg) daily and carbamazepine 600 to were similarly effective in the treatment of myotonia (Sechi et al, 1983). Carbamazepine is indicated as the a myotonia and Steinert's disease by virtue of its lesser long-term side effects.

4.6.L Primidone

4.6.L.1 Seizure

a) The efficacy and toxicity of carbamazepine, phenobarbital, phenytoin and primidone were compared in 62 simple partial, complex partial and secondarily generalized seizures in a multicenter, randomized, double blin were treated with monotherapy with doses titrated to produce blood levels in the therapeutic range. If treatme (inadequate seizure control with the initial drug or unacceptable toxicity from the initial drug), patients were ra to an alternate study drug. Combined results with all four drugs suggested that full seizure control was signifi patients with generalized tonic-clonic seizures than for those with partial seizure disorders (56% vs 39%). The significant difference among the drugs in treatment of tonic-clonic seizures. Conversely, carbamazepine was effective in controlling simple partial and complex partial seizures than were any of the other drugs. Toxicity r control appeared to be the greatest differentiating factor among the four study drugs with patients taking prim the highest incidence of side effects early in therapy although there were no significant differences with chron tolerance of the drugs as measured by retention rates were significantly better among carbamazepine- and p patients . In studies of behavioral toxicity, carbamazepine-treated patients showed the least deterioration. Ov patients were successfully managed for 1 year on monotherapy, regardless of the drug chosen. The authors based on anticonvulsant activity and side effect profile, carbamazepine may be the preferred drug for initiatio adults with either generalized tonic-clonic, simple partial or complex partial seizures (Smith et al, 1987b).

4.6.M Progabide

4.6.M.1 Epilepsy

a) There are no direct comparisons of progabide with carbamazepine in the treatment of any form of epilepsy comparisons of clinical studies suggest that adjunctive therapy with progabide in therapy-resistant partial seiz effective as other primary anticonvulsants such as phenytoin, phenobarbital, primidone, or carbamazepine wh adjunctive therapy to patients who have failed previous therapy (Schmidt, 1984; Schmidt, 1982).

4.6.N Propranolol

4.6.N.1 Intermittent explosive disorder

a) One study (Mattes, 1990) compared the efficacy of propranolol and carbamazepine in a randomized trial i diagnosed with intermittent explosive disorder. An additional 29 patients with rage outbursts secondary to res deficit disorder, alcohol or drug abuse, antisocial personality disorder, unsocialized conduct disorder and bord disorder; 27 of these patients received carbamazepine. Mean daily dosages were 486 mg and 860 mg for pro carbamazepine respectively. Both medications were equally well tolerated and were effective in reducing targ However, the absence of a placebo-control group makes the efficacy of either drug difficult to evaluate. Two f predict a differential benefit between the two drugs; these were diagnosis of attention deficit disorder, residua more effective) and age of onset of symptoms (again, propranolol more effective). Carbamazepine appeared patients with intermittent explosive disorder.

4.6.O Tiapride

4.6.O.1 Alcohol withdrawal syndrome, acute

a) Tiapride was as effective as carbamazepine in the treatment of acute alcohol withdrawal. Sixty patients w receive either tiapride 200 milligrams (mg) 3 times daily (n=30) or carbamazepine 200 mg 3 times daily (n=30 Withdrawal symptoms improved significantly in both groups. Symptoms such as frequent awakening, nightma palpitations decreased more quickly in the carbamazepine group while aggression and gastrointestinal disco more quickly in the tiapride group. Carbamazepine was more effective against fear and hallucinations, while t vertigo. No seizures occurred and both drugs were well tolerated. Overall, tiapride and carbamazepine demo efficacy for the treatment of acute alcohol withdrawal (Agricola et al, 1982).

4.6.P Topiramate

4.6.P.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, 2003a).

4.6.Q Valproic Acid

Epilepsy

Epilepsy, Children

Rheumatic chorea

4.6.Q.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% mec 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, 2003).

4.6.Q.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, 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 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 treatme 9% of children treated with phenytoin.

4.6.Q.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.R Vigabatrin

4.6.R.1 Seizure

a) Time to withdrawal for lack of efficacy or adverse events did not differ in newly diagnosed epileptic patient carbamazepine (n=226) or vigabatrin (n=220) in a double-blind, randomized, monotherapy study (p=0.318) (However, patients treated with carbamazepine were more likely to withdraw sooner than vigabatrin patients, first 4 to 6 months of therapy. The total daily dose of vigabatrin was 1 gram (g) during the first 6 weeks after r Vigabatrin dose was increased to 2 g as an initial maintenance dose with a dose range from 1.5 g to 4 g daily dose of carbamazepine was 200 milligrams (mg) followed by an increase to 600 mg after 6 weeks. Maintena carbamazepine ranged from 400 mg to 1600 mg per day. No treatment differences between treatment groups throughout the study. After 12 months of double-blind therapy, 107 vigabatrin and 116 carbamazepine patien months of remission. The time to first seizure was significantly less for vigabatrin patients compared to carba (p=0.0003). Twenty-three vigabatrin and 9 carbamazepine patients withdrew from the study solely due to lac effect (p=0.0298). Drowsiness, fatigue, and headache were reported by more than 20% of patients with no di the two treatment groups observed.. Adverse events in the psychiatric system were reported significantly mo vigabatrin patients (25%) compared to carbamazepine patients (15%; p less than 0.05). Likewise, more patie vigabatrin experienced weight gain (11%) compared to those treated with carbamazepine (5%; p less than 0. Carbamazepine patients experienced significantly more adverse events in the skin and appendages system vigabatrin patients (14%; p less than 0.05). A decrease in white-cell counts, uric acid and bilirubin and an inc phosphatase were observed in carbamazepine patients.

b) Preliminary results from an open-label comparative trial (n=34) suggested the potential superiority of carb monotherapy over vigabatrin monotherapy in patients with newly diagnosed epilepsy (Grant & Heel, 1991). In patients treated with vigabatrin 50 milligrams/kilogram/day were considered non- responders; 1 of these patie failed to respond to carbamazepine. None of the patients treated with carbamazepine (plasma levels of 35 m considered non-responders. However, 3 carbamazepine-treated patients discontinued therapy due to hypers

c) Carbamazepine monotherapy was compared to vigabatrin monotherapy in patients with newly-diagnosed

generalized tonic-clonic seizures (Kalviainen et al, 1995). Sixty percent of patients (n=50) were considered su in both groups; however, significantly more patients were totally seizure free while receiving carbamazepine. resulted in fewer side effects that resulted in discontinuation of therapy. Vigabatrin monotherapy may be an a carbamazepine or other standard antiepileptic drugs in cases where patients are intolerant of toxic or cognitiv

4.6.S Zonisamide

4.6.S.1 Epilepsy

a) In a small study, zonisamide was as effective as carbamazepine in the treatment of refractory partial seizu week run-in period, 8 patient with a poor response to phenytoin (more than 4 seizures/month) received either zonisamide for 12 weeks, and then were switched to the other drug for an additional 12 weeks. Patients rece carbamazepine and zonisamide adjusted to maximal therapeutic response and minimal toxicity; phenytoin wa the 4 patients completing the study, 2 had the best response to carbamazepine, an intermediate response to poor response to phenytoin. Two patients responded best to zonisamide. Optimal seizure control and minima seen with serum zonisamide concentrations of 20 to 30 micrograms/milliliter (mcg/mL), and a high incidence were seen with serum levels exceeding 30 mcg/mL (Wilensky et al, 1985a).

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