

# Alzheimer's Cognition Falls as Depression Spikes

BY MITCHEL L. ZOLER  
Philadelphia Bureau

PHILADELPHIA — Patients with mild to moderate Alzheimer's disease have a faster rate of cognitive decline as they accumulate more symptoms of depression, Ann Marie Hake, M.D., reported in a poster at the Ninth International Conference on Alzheimer's Disease and Related Disorders.

This relationship held regardless of the

patient's gender or the treatment received, said Dr. Hake, a neurologist at the Indiana University Center for Aging Research, Indianapolis.

The patients Dr. Hake and her associates studied were enrolled in a trial with the primary aim of testing the efficacy of transdermal selegiline. Cognition of all patients was assessed at baseline and after 48 weeks of treatment using the Alzheimer's Disease Assessment Scale—cognitive subscale (ADAS-cog). The study failed to show a sig-

nificant treatment effect of selegiline on cognition among the 265 patients who completed 48 weeks of treatment.

All patients were also assessed for depression at baseline using the Hamilton Depression Scale. Symptoms of depression were assessed during the study and at week 48 using the Cornell Scale for Depression.

When average changes in the ADAS-cog scores over the 48 weeks were correlated with changes in the Cornell depression

scores, the researchers found a highly significant, positive association: As the Cornell total score increased from baseline through week 48, the patients' decline in cognition became greater, Dr. Hake reported at the conference, which was presented by the Alzheimer's Association.

The degree of depression at baseline did not predict the extent of deterioration in cognition over the following 48 weeks.

Results from several prior studies have shown a link between depression and dementia, but this study provides additional information about the nature of this relationship. Depression affects 20%-30% of people older than 65 years; more than 60% of elderly people with depression do not receive treatment.

Among people with dementia, up to 20% have major depression and up to 30% have dysthymia, she said.

## Diabetes Drug Appears to Slow Cognitive Decline

PHILADELPHIA — The diabetes drug rosiglitazone appears to preserve cognitive function in patients with mild cognitive impairment and Alzheimer's disease, G. Stenris Watson, Ph.D., reported at the Ninth International Conference on Alzheimer's Disease and Related Disorders.

The finding, from a small randomized clinical trial funded by GlaxoSmithKline, suggests that "there may be a therapeutic window ... a novel approach to treating cognitive dysfunction," study coauthor Dr. Suzanne Craft said at a press briefing.

Twenty subjects with either mild cognitive impairment or Alzheimer's disease were randomized to receive 4 mg/day of rosiglitazone for 24 weeks, while another 10 subjects with similar degrees of cognitive impairment were randomized to receive placebo. Tests of cognition were performed at 2, 4, and 6 months, said Dr. Watson of the University of Washington, Seattle.

On the eight-word delayed recall part of the Buschke Selective Reminding Test, subjects who received rosiglitazone remembered significantly more words than did the placebo subjects at 4 months (5.7 vs. 5.4) and 6 months (5.4 vs. 4.9), after adjustment for baseline performance. Similarly, the rosiglitazone group made fewer errors on the Stroop Color-Word Interference test, which measures selective attention. At 6 months, the rosiglitazone subjects made an average of 1.9 errors, compared with the expected 3.2 in the placebo group.

The effects are likely due to the drug's insulin-sensitizing and anti-inflammatory properties, and perhaps also to the amyloid-processing modulation action of rosiglitazone and other agents of the same class, Dr. Watson said at the conference, presented by the Alzheimer's Association.

A larger trial aimed at replicating these findings is underway in Europe, he noted.

—Miriam E. Tucker

**EQUETRO™ (carbamazepine) extended-release capsules**  
100 mg, 200 mg and 300 mg

### Brief Summary Prescribing Information

**WARNING: APLASTIC ANEMIA AND AGRANULOCYTOSIS** HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE. DATA FROM A POPULATION-BASED CASE-CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA. ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF CARBAMAZEPINE, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITION OF APLASTIC ANEMIA OR AGRANULOCYTOSIS. BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON CARBAMAZEPINE ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IN PATIENTS WITH LOW BLOOD CELL COUNTS, MONITORING WITH PERIODIC BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing EQUETRO™, the physician should be thoroughly familiar with the details of the full prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

### INDICATIONS AND USAGE

EQUETRO™ is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder. The efficacy of EQUETRO™ in acute mania was established in 2 placebo-controlled, double-blind, 3-week studies in patients meeting DSM-IV criteria for Bipolar I Disorder who currently displayed an acute manic or mixed episode.

The effectiveness of EQUETRO™ for longer-term use and for prophylactic use in mania has not been systematically evaluated in controlled clinical trials. Therefore, physicians who elect to use EQUETRO™ for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSE AND ADMINISTRATION**).

### CONTRAINDICATIONS

Carbamazepine should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of carbamazepine, MAO inhibitors should be discontinued for a minimum of 14 days, or longer if the clinical situation permits.

### WARNINGS

Patients should be made aware that EQUETRO™ contains carbamazepine and should not be used in combination with any other medications containing carbamazepine.

Carbamazepine can cause fetal harm when administered to a pregnant woman.

Epidemiologic data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. If this drug is used during pregnancy, or if the patient becomes pregnant while on this drug, the patient should be apprised of the potential hazard to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy.

In humans, transplacental passage of carbamazepine is rapid (30-60 minutes), and the drug is accumulated in the fetal tissues, with higher levels found in liver and kidney than in brain and lung.

Carbamazepine has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the human daily dosage of 1200 mg on a mg/kg basis or 1.5-4 times the human daily dosage on a mg/m<sup>2</sup> basis. In rat teratology studies, 2 of 135 offspring showed knicked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

Tests to detect defects using current accepted procedures should be considered a part of routine prenatal care in childbearing women receiving carbamazepine.

**General**  
Patients with a history of adverse hematologic reaction to any drug may be particularly at risk. Severe dermatologic reactions, including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with carbamazepine. These reactions have been extremely rare. However, a few fatalities have been reported.

In patients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong possibility of precipitating status epilepticus with attendant hypoxia and other complications. However, a few fatalities have been reported.

Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of carbamazepine to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

Co-administration of carbamazepine and delavirdine may lead to loss of virologic response and possible resistance to the class of non-nucleoside reverse transcriptase inhibitors.

### PRECAUTIONS

**General**  
Before initiating therapy, a detailed history and physical examination should be made. Therapy should be prescribed only after critical benefit-risk appraisal in patients with a history of cardiac, hepatic, or renal damage; adverse hematologic reaction to other drugs; or interrupted courses of therapy with carbamazepine.

**Suicide:** The possibility of suicide attempt is inherent in Bipolar Disorder and close supervision of high risk patients should accompany drug therapy. Prescriptions for EQUETRO™ should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

### Information for Patients

Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, rash, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any of these signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

If necessary, the EQUETRO™ capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. EQUETRO™ capsules or their contents should not be crushed or chewed. EQUETRO™ may interact with some drugs. Therefore, patients should be advised to report to their doctors the use of any other prescription or non-prescription medication or herbal products.

### Laboratory Tests

Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic complete blood counts, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic complete blood counts, including platelets and serum iron, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of the potential for renal dysfunction. Increases in total cholesterol, LDL and HDL have been observed in some patients taking anticonvulsants. Therefore, periodic evaluation of these parameters is also recommended.

Monitoring of blood levels (please see full prescribing information) may be useful for verification of drug compliance, assessing safety and determining the cause of toxicity including when more than one medication is being used. Thyroid function tests have been reported to show decreased values with carbamazepine administered alone.

Hypohydratemia has been reported in association with carbamazepine use, either alone or in combination with other drugs. Interference with some pregnancy tests has been reported.

### Drug Interactions

Clinically meaningful drug interactions have occurred with concomitant medications and include, but are not limited to the following:

### Rx only

Thus, if a patient has been titrated to a stable dosage of EQUETRO™, and then begins a course of treatment with one of these CYP3A4 or epoxide hydrolase inhibitors, it is reasonable to expect that a dose reduction for EQUETRO™ may be necessary.

**Agents that Induce Cytochrome P450 Isoenzymes:** Carbamazepine is metabolized by CYP3A4. Therefore, the potential exists for interaction between carbamazepine and any agent that induces CYP3A4. CYP3A4 inducers have been found, or are expected, to decrease plasma levels of EQUETRO™. Commonly used agents that induce CYP3A4 are phenytoin, primidone, theophylline, anticancer agents and other drugs. Please see full prescribing information. Thus, if a patient has been titrated to a stable dosage on EQUETRO™, and then begins a course of treatment with one of these CYP3A4 inducers, it is reasonable to expect that a dose increase for EQUETRO™ may be necessary.

**Agents with Increased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes:** Carbamazepine is known to induce CYP1A2 and CYP2A6. Therefore, the potential exists for interaction between carbamazepine and any agent metabolized by one (or more) of these enzymes. These agents have been found, or are expected, to have decreased plasma levels in the presence of EQUETRO™ due to induction of CYP enzymes. Commonly used agents that induce CYP enzymes are: acetaminophen, benzodiazepines (such as alprazolam, diazepam, lorazepam, midazolam, and triazolam), protease inhibitors, oral contraceptives, antidepressants (tricyclics and SSRIs), phenytoin, and other drugs. Please see full prescribing information. Break through bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

**Agents with Increased Levels in the Presence of Carbamazepine:** EQUETRO™ increases the plasma levels of cimetidine, HCl and primidone.

Thus, if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with EQUETRO™, it is reasonable to expect that a dose increase for the concomitant agent may be necessary.

**Agents with Increased Levels in the Presence of Carbamazepine:** EQUETRO™ increases the plasma levels of phenytoin plasma levels following co-medication with carbamazepine is advised.

### Pharmacological/Pharmacodynamic Interactions with Carbamazepine

Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Given the anticonvulsant properties of carbamazepine, EQUETRO™ may reduce the thyroid function as has been reported with other anticonvulsants. Additionally, anti-malarial drugs, such as chloroquine and mefloquine, may antagonize the activity of carbamazepine.

Thus if a patient has been titrated to a stable dosage on one of the agents in this category, and then begins a course of treatment with EQUETRO™, it is reasonable to expect that a dose adjustment may be necessary.

Because of its primary CNS effect, caution should be used when EQUETRO™ is taken with other centrally acting drugs and alcohol.

### Carcinogenesis, Mutagenesis, Impairment of Fertility

Administration of carbamazepine to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day (low, medium and approximately 0.2 times the human daily dose of 1200 mg on a mg/m<sup>2</sup> basis), resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

### Pregnancy

Pregnancy Category D (see **WARNINGS**).

### Laboratory and Delivery

Carbamazepine is contraindicated on human labor and delivery is unknown.

### Nursing Mothers

Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. Because of the potential for adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

The relative effectiveness of EQUETRO™ in pediatric and adolescent patients have not been established.

### Geriatric Use

No systematic studies in geriatric patients have been conducted.

### ADVERSE REACTIONS

**General:** The most severe adverse reactions previously observed with carbamazepine were reported in the hematologic system (see **BOX WARNING**), the skin, and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

The most commonly observed adverse experiences (5% and at least twice placebo) seen in association with the use of EQUETRO™ (400 to 1600 mg/day, dose adjusted in 200 mg daily increments in week 1 in Bipolar I Disorder) in the double-blind, placebo-controlled trials of 3 weeks' duration are: dizziness, somnolence, nausea, vomiting, ataxia, pruritus, dry mouth, amblyopia, and speech disorder.

EQUETRO™ and placebo-treated patients from two double-blind, placebo-controlled studies were enrolled in a 6-month open-label study. The most common adverse events with an incidence of 5% or more are: headache, dizziness, rash, infection, pain, somnolence, diarrhea, dyspepsia, nausea, asthenia, amnesia, accidental injury, anxiety, depression, manic depressive reaction, chest pain, back pain, constipation, ataxia, and pruritus.

Other adverse events reported in clinical trials include: depression, forgetful and memory disturbance (depression includes suicidal ideation).

Other significant adverse events seen in less than 5% of patients include: suicide attempt, manic reaction, insomnia, nervousness, depersonalization and extrapyramidal symptoms, infections (ungal, viral, bacterial), pharyngitis, rhinitis, sinusitis, bronchitis, urinary tract infections, lymphadenopathy, liver function tests abnormal, edema, peripheral edema, allergic reaction, photosensitivity reaction, alopecia, pitting and ear pain.

The following additional adverse reactions were previously reported with carbamazepine: **Hematologic System:** Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

**Skin:** Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see **WARNINGS**), Stevens-Johnson syndrome (see **WARNINGS**), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

**Cardiovascular System:** Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, thrombophlebitis, thromboembolism, and adenopathy or lymphadenopathy. Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

**Liver:** Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

**Respiratory System:** Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis, or pneumonia. A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenge, and the meningitis reappeared upon rechallenge with carbamazepine.

**Digestive System:** Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

**Eyes:** Scattered punctate corneal lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

**Musculoskeletal System:** Aching joints and muscles, red and leg cramps.

**Metabolic System:** Fever and chills, inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion have been reported in association with carbamazepine use (see **PRECAUTIONS**, Laboratory Tests). Decreased levels of plasma calcium have been reported.

**Other:** Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol, and triglycerides in patients taking anticonvulsants.

419 1207 001 (rev. 12/2004) Manufactured for: **Shire US Inc.**  
725 Chesterbrook Blvd., Wayne, PA 19087-5637  
1-800-829-2088. Made in U.S.A.  
©2005 Shire US Inc.

**Shire**