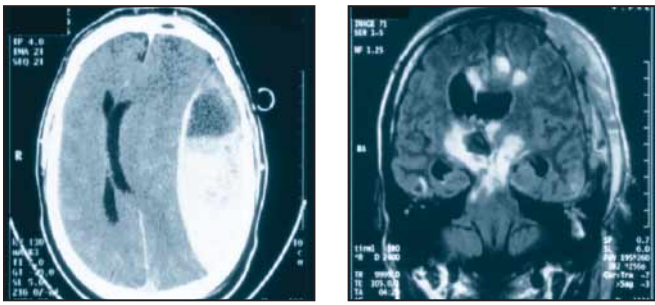


# Brain Stem Lesions Worsen Head Injury Outcomes



CT shows large extradural hematoma (left). MRI of midline shows traumatic lesion; tissue extends into brain stem (right).

BY SHERRY BOSCHERT  
San Francisco Bureau

SAN FRANCISCO — The largest series of head injury patients to undergo magnetic resonance imaging found brain stem injuries in 60% of 200 patients, a much higher rate than the 10% usually quoted in the literature, Dr. Raimund P. Firsching reported at the annual meeting of

the American Association of Neurological Surgeons.

Fewer than 1 in 10 brain stem lesions were visible on CT scans, he said.

Investigators performed CT and MRI scans on patients within a week of head injury; all patients were in a coma for at least 1 day.

Functional and mortality outcomes 3 months after injury

were associated with the location of brain injury on MRI, with much worse prognoses in patients who had brain stem lesions, said Dr. Firsching, of the department of neurosurgery at Otto-von-Guericke University, Magdeburg, Germany, who conducted the study with Dr. Dieter Woischneck, also of the university.

The results challenge the commonly held notion that when CT shows no lesions after brain trauma, a patient's failure to improve must be a result of diffuse brain injury, Dr. Firsching said.

Among patients who emerged from coma after 1 day, 63% had brain stem lesions seen on MRI.

The longer the coma lasted, the greater the likelihood of brain stem lesion: Of patients who were in a coma for 1 week, 96% had brain stem lesions. "This is really in sharp contrast to the literature," he noted.

The imaging could not differentiate between primary and secondary lesions, he acknowledged.

Commenting on the study at the meeting, Dr. M. Ross Bullock said that it was limited by not identifying postherniation changes in the brain, by not reporting how many patients had lesions removed, and by not discussing the implications of high intracranial pressure with the MRI findings.

"If these data represent simply a very high, unusual incidence of herniation, that's not a major contribution to our knowledge base," said Dr. Bullock, the Reynolds Professor of neurosurgery at Virginia Commonwealth University, Richmond, Va.

At his institution, MRIs on 13 patients with trauma found brain stem lesions in 10%, he noted.

Among all patients in Dr. Firsching's study, 37% had supratentorial lesions confined to the hemispheres or the corpus callosum; two-thirds of this group had a good outcome, and 10% died, Dr. Firsching reported. A lesion in a unilateral region of the brain stem, seen in 20% of patients, was associated with a slight or moderate functional handicap after 3 months, and 21% of these patients died. Severe disability was likely in the 22% of patients with bilateral mesencephalic lesions, and 21% died. Among the 21% of patients with a bilateral pontine lesion, 92% died.

Lesions on the corpus callosum did not predict the likelihood of death or the length of coma, he added. Pontine and midbrain lesions, which CT failed to detect, are most important for prognosis, he emphasized.

In nearly 10 years of doing MRIs on brain trauma patients, "we have yet to see a patient who was in a vegetative state who did not exhibit a bilateral pontine lesion," Dr. Firsching said.

The investigators began the series of MRIs on head trauma patients after a man in a bus accident failed to emerge from his coma. The patient's brother, a neuroradiologist, insisted on getting an MRI, which showed lesions that were invisible on CT. MRI is indicated in the evaluation of some head trauma patients who don't improve over time, according to Dr. Bullock. ■

Reference: 1. Kwan P, Brodie MJ. Clinical trials of antiepileptic medications in newly diagnosed patients with epilepsy. *Neurology*. 2003;60(suppl 4):S2-S12.

## CARBATROL®

(carbamazepine extended-release capsules)  
100 mg • 200 mg • 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 VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS. BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST 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. 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.

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

### INDICATIONS AND USAGE

#### Epilepsy

Carbatrol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvements than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by carbamazepine (see PRECAUTIONS, General).

#### Trigeminal Neuralgia

Carbatrol is indicated in the treatment of the pain associated with true trigeminal neuralgia. Beneficial results have also been reported in glossopharyngeal neuralgia. This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

#### 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, nortriptyline 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 Carbatrol contains carbamazepine and should not be used in combination with any other medications containing carbamazepine.

#### Usage in Pregnancy

Carbamazepine can cause fetal harm when administered to a pregnant woman. Epidemiological 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 taking 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 maximum human daily dosage (MHDD) of 1200 mg on a mg/kg basis or 1.5-4 times the MHDD on a mg/m<sup>2</sup> basis. In rat teratology studies, 2 of 135 offspring showed kinked 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. Antiepileptic drugs should not be discontinued abruptly in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. 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. Carbamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy. Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be considered.

#### PRECAUTIONS

##### General

Before initiating therapy, a detailed history and physical examination should be made. Carbamazepine should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients carbamazepine has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE). Therapy should be prescribed only after critical benefit-to-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.

##### 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 such 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 Carbatrol capsules can be opened and the contents sprinkled over food, such as a teaspoon of applesauce or other similar food products. Carbatrol capsules or their contents should not be crushed or chewed.

##### 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 evaluations of liver function, 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 eye examinations, including slit-lamp, funduscopy, and tonometry, 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 observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used. Thyroid function tests have been reported to show decreased values with carbamazepine administered alone. Hyponatremia 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:

##### Agents that may affect carbamazepine plasma levels:

CYP 3A4 inhibitors inhibit carbamazepine metabolism and can thus increase plasma carbamazepine levels. Drugs that have been shown, or would be expected, to increase plasma carbamazepine levels include: cimetidine, danazol, diltiazem, macrolides, erythromycin, troleandomycin, clarithromycin, fluoxetine, lorazepam, terfenadine, isoniazid, niacinamide, nicotinamide, propoxyphene, ketocazole, itraconazole, verapamil, valproate.\* CYP 3A4 inducers can increase the rate of carbamazepine metabolism and can thus decrease plasma carbamazepine levels. Drugs that have been shown, or would be expected, to decrease plasma carbamazepine levels include: cisplatin, doxorubicin HCL, felbamate, rifampin\*, phenobarbital, phenytoin, primidone, theophylline.

##### Effect of carbamazepine on plasma levels of concomitant agents:

Carbatrol increases levels of clomipramine HCL, phenytoin and primidone. Carbatrol induces hepatic CYP activity. Carbatrol causes, or would be expected to cause decreased levels of the following:

acetaminophen, alprazolam, clonazepam, clozapine, dicumaryl, doxycycline, ethosuximide, haloperidol, methsuximide, oral contraceptives, phenisuximide, Phenytoin, theophylline, valproate, warfarin.

The doses of these drugs may therefore have to be increased when carbamazepine is added to the therapeutic regimen. Concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects. Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications. Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

##### 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 dose approximately 0.2 times the maximum 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.

##### Usage in Pregnancy

Pregnancy Category D (See WARNINGS)

The effect of carbamazepine on human labor and delivery is unknown.

##### Nursing Mothers

Carbamazepine and its epoxide metabolite are transferred to breast milk and during lactation. The concentrations of carbamazepine and its epoxide metabolite are approximately 50% of the maternal plasma concentration. Because of the potential for serious 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

Substantial evidence of carbamazepine effectiveness for use in the management of children with epilepsy (see INDICATIONS for specific seizure types) is derived from clinical investigations performed in adults and from studies in several *in vitro* systems which support the conclusion that (1) the pathogenic mechanisms underlying seizure propagation are essentially identical in adults and children, and (2) the mechanism of action of carbamazepine in treating seizures is essentially identical in adults and children. Taken as a whole, this information supports a conclusion that the generally acceptable therapeutic range of total carbamazepine in plasma (i.e., 4-12 µg/mL) is the same in children and adults. The evidence assembled was primarily obtained from short-term use of carbamazepine. The safety of carbamazepine in children has been systematically studied up to 6 months. No longer term data from clinical trials is available.

##### Geriatric Use

No systematic studies in geriatric patients have been conducted.

##### ADVERSE REACTIONS

**General:** If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive patient with epilepsy may lead to seizures or even status epilepticus with its life-threatening hazards. The most severe adverse reactions previously observed with carbamazepine were reported in the hemopoietic 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 following additional adverse reactions were previously reported with carbamazepine:

**Hemopoietic 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.

**Genitourinary System:** Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN, and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving carbamazepine orally from 4-52 weeks at dosage levels of 50-400 mg/kg/day. Additionally, rats receiving carbamazepine in the diet for 2 years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg/day and higher. Relevance of these findings to humans is unknown.

**Nervous System:** Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Isolated cases of neuroleptic malignant syndrome have been reported with concomitant use of psychotropic drugs.

**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 cortical 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, and leg cramps.

**Metabolism:** 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.

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 dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

\*increased levels of the active 10, 11-epoxide

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