Findings Highlight Depression, MI Connections

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Depression strikes one in five patients hospitalized for myocardial infarction, with severe consequences, including a threefold increased risk of cardiac mortality and significantly elevated mortality from all causes, a comprehensive evidence review has concluded.

The review, conducted by the federal Agency for Healthcare Research and Quality at the behest of the American Academy of Family Physicians, is destined to become the framework for evidence-based clinical practice guidelines, according to the AAFP.

Highlights of the review coordinated by the Johns Hopkins Evidence-Based Practice Center in Baltimore include:

▶ Evidence from 25 trials pointing to a prevalence of depression in one in five patients hospitalized for an MI.

▶ Data from three studies that depression during the initial MI hospitalization persists from 1-4 months in 60%-70% of patients.

▶ "Strikingly consistent" evidence that post-MI depression puts patients at an increased risk for death by cardiac causes (a threefold increased risk) and other causes.

▶ Conclusions from three studies showing that depressed post-MI patients are less likely than are others to take their prescribed medications or to comply with lifestyle modification.

▶ Findings that suggest psychosocial intervention and selective serotonin reuptake inhibitors (SSRIs) improve depression in post-MI patients, but not necessarily other outcomes.

The lengthy analysis pointed out a number of important gaps in scientific knowledge about depression and MI, such as the best way to measure depression in hospitalized MI patients and the true impact of interventions.

For example, SSRIs were found to improve some surrogate markers of cardiac risk, "but no studies of sufficient power address the question of whether this treatment improves survival," the analysis said.

The Johns Hopkins team, led by Dr. David E. Bush and Dr. Roy C. Ziegelstein, included clinicians and researchers from cardiology, psychiatry, general internal medicine, and cardiac rehabilitation, as well as representatives from the AAFP, the nursing community, and private and government payers.

Evidence is 'strikingly consistent' that post-myocardial infarction depression puts patients at an increased risk of death by cardiac causes.

Six key questions were compiled, several with important subcategories. A literature review was conducted electronically and by hand of 16 specific journals and the electronic databases Medline, Cochrane Central Register of Controlled Trials, the Cochrane Database of Methodology Reviews, the Cumulative Index to Nursing and Allied Health Literature, the Psychological Abstracts, and Embase.

The intensive review unveiled the magnitude of evidence pointing to depression as an important impedance to a full recovery and a return to productive life in many MI patients.

Its conclusions suggest a pivotal role for family physicians, who may be in the best position to oversee "the whole patient" as he or she embarks on the long course of recovery, Dr. Lee A. Green, the AAFP representative to the review panel and a member of the family medicine faculty at the University of Michigan in Ann Arbor, said in a telephone interview.

Patients can survive heart attacks and their hearts can be fine, but they can be disabled by their depression, he said.

The severity of an MI may overshadow less evident aspects of health that should be identified early and managed with the best tools available.

Although the literature review shows that more research is needed to illuminate the best approaches to post-MI depression, it provides ample evidence of the worth of such research.

In the immediate future, the stark findings about the importance of depression following MI may lead to more communication among specialists, including psychiatrists, family physicians, and cardiologists, Dr. Green said. ■

References: **1.** Weisler RH, Kalali AH, Ketter TA, and the SPD417 Study Group. A multicenter, randomized, double-blind, placebo-controlled trial of extended-release carbamazepine capsules as monotherapy for bipolar disorder patients with manic or mixed episodes. *J Clin Psychiatry.* 2004;65:478-484. **2.** Weisler RH, Keck PE Jr, Swann AC, Cutler AJ, Ketter TA, Kalali AH, for the SPD417 Study Group. Extended-release carbamazepine capsules as monotherapy for acute mania in bipolar disorder: a multicenter, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry.* 2005;66:323-330. **3.** Data on file [301/304], Shire US Inc.

EQUETRO™ (carbamazepine) extended-release capsules **Rx only**
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 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 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 **DOSAGE 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.
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 a human daily dosage of 1200 mg on a mg/kg basis or 1.5-4 times the human daily dosage on a mg/m^2 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.
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 threat to life.
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.
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-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.
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 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 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 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.
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.
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 Highly Bound to Plasma Protein: Carbamazepine is not highly bound to plasma proteins; therefore, administration of EQUETRO™ to a patient taking another drug that is highly protein bound should not cause increased free concentrations of the other drug.
Agents that Inhibit Cytochrome P450 Isoenzymes and/or Epoxide Hydrolase: Carbamazepine is metabolized mainly by cytochrome P450 (CYP) 3A4 to the active carbamazepine 10,11-epoxide, which is further metabolized to the trans-diol by epoxide hydrolase. Therefore, the potential exists for interaction between carbamazepine and any agent that inhibits CYP3A4 and/or epoxide hydrolase. CYP3A4 inhibitors have been found, or are expected, to increase plasma levels of EQUETRO™. Commonly used agents that inhibit CYP3A4 are: azole antifungals (such as ketoconazole and itraconazole, calcium channel blockers (such as diltazem and verapamil), macrolide antibiotics (such as erythromycin, clarithromycin, and troleandomycin), grapefruit juice, and other drugs. Please see full prescribing information.
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 Decreased Levels in the Presence of Carbamazepine due to Induction of Cytochrome P450 Enzymes
Carbamazepine is known to induce CYP1A2 and CYP3A4. 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.
Warfarin's anticoagulant effect can be reduced in the presence 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 increase for the concomitant agent may be necessary.
Agents with Increased Levels in the Presence of Carbamazepine: EQUETRO™ increases the plasma levels of clomipramine 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 the treatment with EQUETRO™, it is reasonable to expect that a dose decrease for the concomitant agent may be necessary.
Phenytoin has been reported to decrease or increase in the presence of carbamazepine. Careful monitoring 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 dose approximately 0.2 times the human daily dose of 1200 mg on a mg/m^2 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).
Labor and Delivery
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. 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
The safety and 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 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 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 the 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[1], accidental injury, anxiety, depression[2], manic depressive reaction, chest pain, back pain, constipation, ataxia, and pruritus.
[1]Amnesia includes poor memory, forgetful and memory disturbance
[2]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 (fungal, viral, bacterial), pharyngitis, rhinitis, sinusitis, bronchitis, urinary tract infection, leukopenia and lymphadenopathy liver function tests abnormal, edema, peripheral edema, allergic reaction, photosensitivity reaction, alopecia, diplopia and ear pain.
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.

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