Autism Increase Not a Result of Reclassification

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◆he apparent increase in autism disorders reflects an actual increase in prevalence, rather than a reclassification of other developmental disorders as autism, reported Craig Newschaffer, Ph.D., of Johns Hopkins University, Baltimore, and his colleagues.

Some researchers have suggested that children who would once have been classified in other categories—such as mental retardation or speech disorders—are now being diagnosed as autistic and that this "diagnostic shifting" accounts for the increase in autism. This is not the case, the investigators maintained, because although autism diagnoses have risen, there has been no corresponding decrease in other diagnostic categories (Pediatrics 2005;115:e277-82).

Dr. Newschaffer and his associates examined data from the U.S. Department of Education's office of special education programs for 1992-2001. These records reflect state counts of children who received free public education services. The children were classified into 13 primary disability categories defined under the Individuals with Disabilities Education Act.

The researchers calculated the prevalence of autism, traumatic brain injury, mental retardation, speech/language impairment, and other health impairments in children aged 6-17 years during each of

these years. They then superimposed those data onto birth cohorts extending as far back as 1975.

There were clear, significant increases in the prevalence of autism among younger birth cohorts, especially those born between 1987 and 1992. During those years, autism prevalence rose by about 50% every 2 years; the prevalence was 5.3/10,000 in 1984, 7.8/10,000 in 1986, 11.8/10,000 in 1988, and 18.3/10,000 in 1990.

There were no changes, however, in the prevalence of mental retardation, speech/language impairment, or traumatic brain injury, which suggests that the increase in autism is real and not the result

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of reclassification of diagnoses or acrossthe-board increases in special education classification.

The yearly increases seemed to begin leveling off after 1992. It's impossible to know if that observation represents a true decrease

in prevalence, however. Since 1997, federal law has allowed state and local education agencies to classify as "developmentally delayed" children as old as 9 years, Dr. Newschaffer and his associates noted.

"It is possible that increasing proportions of children in younger cohorts who would have been classified previously as having autism as they transitioned out of preschool special education retain developmental delay classifications," the investigators said. This may mean that children are now simply being diagnosed with autism at later ages.

Additionally, Thomas Burns, Psy.D., said in an interview, the numbers paint the spectrum of autism diagnoses with the broadest brush possible.

The Department of Education uses only one autism classification, which includes all students receiving services who have been diagnosed with any one of the autism spectrum disorders. Thus, the study's prevalence numbers included an array of children whose disabilities ranged from severe to mild, Dr. Burns said.

The study makes it a little hard to compare apples to apples," said Dr. Burns, director of neuropsychology at Children's Healthcare of Atlanta, because it included "kids who are severely mentally handicapped as well as kids with IQs of 130 who are delayed socially."

Upcoming studies by the Centers for Disease Control and Prevention, which use uniform diagnostic criteria, may further illuminate the issue. "Some of these other disorders are really objective and easy to identify. You either have traumatic brain injury or you don't. You either have a low IQ and mental retardation, or you don't. With autism and Asperger's, you can be dealing with very vague symptoms and diagnostic criteria that vary from physician to physician and from study to study," he 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, Cutter 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.

Brief Summary Prescribing Information

Information, particularly regarding use with other uses.

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 still patients meeting DSM-V cottenia for Bipolar O Ibsorder who currently displayed an acute mania or mixed episode. The effectiveness of EQUETRO® for longer-term use and for prophylactic use in mania has not been systemate evaluated in controlled clinical trials. Therefore, physicians who elect to use EQUETRO® for extended periods of periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE ANMINISTRATION).

CONTRAINDICATIONS

RAINDICATIONS

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

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 feath 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 matformations, including spina bilida. The prescribing physician will wish to weigh the benefits of therapy against the risks in treating or counseling women of childbearing potential. It 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 feture. 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/m² basis. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 40 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.

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

atients with seizure disorder, carbamazepine should not be discontinued abruptly because of the strong ibility of precipitating status epilepticus with attendant hypoxia and threat to life. lamazepine has shown mild anticholinergic activity; therefore, patients with increased intraocular sure should be closely observed during therapy. use of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent shoists and, in elderly patients, of confusion or agitation should be considered. diministration of carbamazepine and delavidine may lead to loss of virologic response and possible tance to the class of non-nucleoside reverse transcriptase inhibitors.

risk patients should accompany drug therapy. Prescriptions or 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

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pratory Tests

plete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be ined as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet this, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence (grificant bone marrow depression develops. Use of the production of the drug should be considered if any evidence (grificant bone marrow depression develops. It is a present of the production of the produ

ollowing: r Bound to Plasma Protein: Carbamazepine is not highly bound to plasma proteins; therefore, of EQUETRO** to a patient taking another drug that is highly protein bound should not cause concentrations of the other drug.

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 antitugals (such as ketoconazole and itraconazole, calcium channel blockers (such as dilazem and verapamil), macrolide antibiotics (such as erythromycin, clarithromycin, and troleandomycin), grapefruit juice, and other drugs. Please see full prescribing information, clarithromycin, and troleandomycin), grapefruit juice, and other drugs. Please see full prescribing information.

one of these CYP3A4 or peoxide 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, benzodazepines (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.

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Presence of the concomitant agent may be necessary.

Agents with Increased Levels in the Presence of Carbamazepine.

EQUETRO™ increases the plasma levels of clomignamine HCl and primidone.

drugs and alcohol.

Carcinagenesis, Mulagenesis, Impairment of Fertility
Administration of carbamazepine to Sprague-Daviley 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/m² 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-Daviley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these tindings relative to the use of carbamazepine in humans is, at present, unknown.

Usage in Pregnancy

Usage in Pregnancy
Pregnancy Category D (See WARNINGS).
Labor and Delivery
The effect of carbamazepine on human labor and delivery is unknown

ffect of carbamazepine on numer about and statement of the graph of th discontinue nursing or to discontinue the drug, taking into account the interpolation of the pediatric Use. The safety and effectiveness of EQUETRO** in pediatric and adolescent patients have not been established.

Gerlatric 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 hemopoletic 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, anasteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the lowest dosage recommended.

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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 10 lorder in the double-blind, placebo-controlled trais of 3 weeks duration are: dizziness, somnolence, nausea, Disorder in the double-blind, placebo-controlled trais of 3 weeks duration are: dizziness, somnolence, nausea, alternation of the common adverse events with an incidence of 5% or more are: headen, dizziness, rash, infection, pain, somnolence, distributed the service of the common adverse events with an incidence of 5% or more are: headen, dizziness, rash, infection, pain, somnolence, distributed the subject of the common adverse events with an incidence of 5% or more are: headen, dizziness, rash, infection, pain, somnolence, distributed the common adverse events with an incidence of 5% or more are: headen, dizzines, and promition of the common adverse events with a nicide suicide attempt, main reaction, insomnia, nervousness, depersonalization and extrapryamidal symptoms, infections (fungal, viral, bacterial), pharyngitis, rhinitis, sinusitis, bronchitis, urinary tract infection, leukopenia and ymphadenopathy liver function tests abnormal, dedma, peripheral edema, allegier reaction, phorosensitivity reaction, alopecia, diplopia and ear pain. The following additional adverse reactions were previously reported with carbanazepine:

Hemopoleite System: A plastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, ac

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