DRUG Watch

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FDA WARNS OF SUICIDALITY WITH ANTIEPILEPTICS

- An FDA alert issued after a lengthy metaanalysis indicates that antiepileptic drugs have been associated with suicidal ideation and behavior.
- Nurses should assess for symptoms of suicidality, and the patient and family should be instructed to notify the health care provider of any unusual or sudden changes in the patient's mood or behavior.

The Food and Drug Administration (FDA) has issued an alert indicating that antiepileptic drugs have been associated with suicidal ideation and behavior (suicidality). Besides preventing epileptic seizure, the drugs can also treat psychiatric disorders (such as bipolar disorder, depression, and anxiety) and certain other conditions, such as migraine and neuropathic pain syndrome. The alert follows a lengthy metaanalysis of 199 placebo-controlled clinical trials involving 11 drugs (see box, below) and 43,892 patients ages five and older: 27,863 received drug therapy and 16,029 received placebo. Four patients who took an antiepileptic medication committed suicide, and no patient who took a placebo did. Although the risk appears to be extremely slight, suicidal ideation or behavior occurred in 0.43% of patients treated with antiepileptics, compared with 0.22% of patients who received a placebo. This nearly twice greater risk was statistically significant. Suicidality was noted as soon as one week after drug therapy began and continued for as long as 24 weeks, the maximum duration of therapy in most of the trials. No conclusion can be drawn about the presence of the risk after 24 weeks. The relative risk of suicidality was found to be greater in patients taking the medication to treat epilepsy.

The FDA expects that the adverse effect will be found to pertain to all drugs in the class, so that pertinent information would be added broadly to the product labeling of antiepileptic medications.

Nurses should assess all patients who take antiepileptics, watching for new-onset or worsening depression, anxiety, agitation, hostility, mania, or hypomania; any of these could portend suicidality. Nurses should also inform patients and their families that antiepileptics shouldn't be discontinued without consulting a health care professional because of possible complications of rapid withdrawal (such as seizure in patients with epilepsy). The patient and family should bear in mind the risk of suicidal ideation or behavior and remain vigilant for unusual, possibly sudden, changes in the patient's behavior or mood, of which they should promptly inform the prescriber.

Center for Drug Evaluation and Research. *FDA alert: Information for healthcare professionals. Suicidality and antiepileptic drugs.* Rockville, MD: U.S. Food and Drug Administration; 2008 Jan 31. http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm.

Eleven Antiep ilep tic Drugs That Have Been Associated with Suicidality

- carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol-XR)
- felbamate (Felbatol)
- gabapentin (Neurontin)
- lamotrigine (Lamictal)
- levetiracetam (Keppra)
- oxcarbazepine (Trileptal)
- pregabalin (Lyrica)
- tiagabine (Gabitril)
- topiramate (Topamax)
- valproate (Depakote, Depakote ER, Depakene, Depacon)
- zonisamide (Zonegran)

For information on each, visit www.accessdata.fda.gov/scripts/cder/drugsatfda/ and perform a search for the drug of interest.

LIVER RISK FROM MULTIPLE SCLEROSIS AND CROHN'S DISEASE DRUG

- The labeling of natalizumab (Tysabri), the monoclonal antibody used to treat relapsing forms of multiple sclerosis and Crohn's disease, has been revised to include a warning that the drug can cause significant liver injury.
- Nurses should carefully monitor patients' laboratory work for evidence of liver injury, which has been reported as soon as six days after the first dose.

A warning has been added to the labeling of natalizumab (Tysabri), the monoclonal antibody used in treating relapsing forms of multiple sclerosis and moderate-to-severe Crohn's disease. Signs of clinically significant liver injury (including markedly higher serum hepatic enzyme levels and higher total

Understanding Pharmacokinetics:

Part 2: Drug Distribution

In the second in a four-part series, the coordinator of Drug Watch *provides an overview.*

The four phases of pharmacokinetics (the processing of drugs in the body) are absorption, distribution, metabolism, and elimination. In the May *Drug Watch,* alterations in absorption that can affect a drug's effectiveness were discussed. This month's column describes alterations in distribution (the movement of drug molecules throughout the body from the point of absorption), one of which might be overlooked by nurses during drug administration. To watch an animated video demonstrating the processes of drug distribution in the body, go to http://links.lww.com/A431.

A drug's effectiveness depends upon its distribution, which involves the drug's ability to exit the blood circulation and its ability to enter nearby tissue. Generally, nurses understand that narrowed, stiff, or occluded blood vessels—or other pathophysiologic changes in the vascular system—impair the distribution of drug molecules (as I explain in my textbook, *Drug Therapy in Nursing*) and that this can prevent attainment of full therapeutic effect. It is also commonly understood that certain conditions are difficult to treat when a drug can't be well distributed into certain areas of the body. For example, the blood–brain barrier prevents large molecules, including those of drugs and other foreign substances, from entering the brain. Normally, that mechanism promotes health by protecting the brain from toxins, but occasionally it impedes pharmacologic treatment, such as when antibiotics are administered for life-threatening infections such as bacterial meningitis. Gentamicin, for example, is distributed widely throughout the body to treat serious infections, but IV administration of it isn't useful in treating meningitis because it doesn't cross the blood–brain barrier effectively, necessitating intrathecal administration.

Nurses might be unaware of protein binding as a process in drug distribution. Drug particles form reversible bonds with proteins in the blood, primarily albumin, which is a large molecule and does not readily pass through the capillary wall, thereby inhibiting the passage of medication to tissue. For that reason, drugs that bind most readily to albumin can't be distributed to the site of action to achieve the desired therapeutic effect. It is important to remember that drugs have varying affinities to protein molecules: those with "high" affinity are identified in the literature as "highly protein-bound." Phenytoin, for example, is between 90% and 95% protein-bound, but digoxin, with a "low" affinity to protein, is only about 30% protein-bound. (The chemical bond in protein binding is temporary, and each drug molecule eventually separates from the albumin molecule, binding to another or diffusing through the capillary wall).

When a patient has an albumin level lower than normal (hypoalbuminemia), the distribution of a highly protein-bound drug is altered.

Drug manufacturers calculate recommended dosages based on a drug's protein-binding characteristics and normal levels of proteins in the blood. But when a patient has an albumin level lower than normal (hypoalbuminemia), the distribution of a highly protein-bound drug is altered (see "Conditions That Can Produce Hypoalbuminemia," page 69). In that case, when protein is lacking in the blood, more

bilirubin levels) in patients taking natalizumab have been documented in postmarketing case reports as soon as six days after the first dose. This association was substantiated when some patients who had discontinued natalizumab therapy after showing such signs suffered them again upon resuming therapy. The natalizumab label already bears a black box warning that the drug increases the risk of progressive multifocal leukoencephalopathy, and its distribution is restricted (see *Drug Watch*, May). Patients with jaundice or other signs of liver injury should stop taking natalizumab, and nurses should carefully monitor laboratory work for evidence of such injury in patients taking the drug. Before beginning natalizumab therapy, patients should be informed that the drug can cause liver injury and instructed to contact the

Conditions That Can Produce Hypoalbuminemia

- malnutrition, cachexia, starvation
- protein malabsorption (such as tropical and nontropical sprue [both also known as celiac disease], pancreatic duct problems, Crohn's disease, cystic fibrosis, ulcerative colitis, complications of Whipple procedure)
- liver disease (cirrhosis, chronic alcoholism, for example)
- kidney disease (nephritic syndrome, glomerulonephritis, for example)
- autoimmune disease or disorder (systemic lupus erythematosus, rheumatoid arthritis, for example)
- severe burns, severe skin disease
- lymphoma (Hodgkin's disease, for example)
- hyperthyroidism
- heart failure
- acute inflammations (in tuberculosis, osteomyelitis, for example)
- pregnancy
- prolonged bed rest
- prolonged use of certain hospital diets (clear liquids; nothing by mouth and IV fluids of 5% dextrose in water, 5% dextrose in normal saline solution and 5% dextrose in lactated Ringer's solution)
- congenital analbuminemia (rare)

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drug molecules are unbound and can proceed to receptor sites, thereby producing greater therapeutic effect and possibly greater adverse effects. The nurse must carefully assess the serum protein levels in patients at risk for hypoalbuminemia. If a patient does have a low serum level of albumin, the nurse should check the manufacturer's prescribing information for all medications the patient takes. If the patient is taking a drug that is identified as highly protein-bound (protein binding of 90% or more), the nurse should closely monitor for adverse effects. The best way to prevent such effects is to replace albumin in patients with low serum levels of the protein. Nurses need not be as concerned with low serum levels of albumin in patients taking only drugs with a low affinity to protein (that aren't highly protein-bound), because the amount of such a drug that can enter cells doesn't change significantly according to the serum albumin level.

physician if they develop symptoms of hepatotoxicity (nausea, vomiting, abdominal pain, loss of appetite, diarrhea, fatigue, weakness, jaundice, and hepatomegaly). Nurses should also instruct patients to read the entire medication guide accompanying each prescription for natalizumab, because the information in such guides can change as new concerns arise.

Biogen Idec. Dear healthcare professional [letter]: Important safety information. New safety information regarding TYSABRI (natalizumab). Feb, 2008; Biogen Idec. *[Prescribing information]: Tysabri (natalizumab) injection for intravenous use.* 2008. http://www.fda.gov/medwatch/safety/2008/Tysabri_PI.pdf.

A TREATMENT FOR GERD IS NOW APPROVED FOR YOUNG CHILDREN

- Esomeprazole (Nexium), a proton pump inhibitor for the short-term treatment of gastroesophageal reflux disease, formerly indicated only in adults and patients ages 12 to 17 years, has been approved for use in children one to 11 years old.

Esomeprazole (Nexium), a proton pump inhibitor used to treat gastroesophageal reflux disease (GERD), is now approved for use in children one to 11 years old. (It was previously approved for children 12 through 17 years old and adults). This latest approval was based on safety and pharmacokinetics studies conducted in pediatric patients, as well as on the extrapolation of data from previous studies conducted in adults. These youngest patients should receive a lower dosage than that appropriate for older patients (10 to 20 mg daily for children one to 11 years old, compared with 20 to 40 mg daily for patients 12 years old and older). The most common adverse effects of esomeprazole in adults are headache, diarrhea, and abdominal pain. Patients 12 to 17 years old have most commonly experienced those adverse effects and nausea. The most common adverse effects among patients one to 11 years old are diarrhea, headache, and sleepiness.

FDA approves Nexium for use in children ages 1–11 years [press release]. *FDA news* 2008 Feb 28. http://www.fda.gov/bbs/topics/NEWS/2008/NEW01802.html; AstraZeneca Pharmaceuticals. *Prescribing information: Nexium (esomeprazole magnesium) delayed-release capsules and delayed-release oral suspension.* 2008. http://www1.astrazeneca-us.com/pi/Nexium.pdf. ▼

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