NEW DRUG NEWS

NEW INDICATIONS
Two Drugs Approved for Social Phobia

Two drugs that are commonly used to treat depression and generalized anxiety, venlafaxine HCl (Effexor® XR, Wyeth) and sertraline HCl (Zoloft®, Pfizer), have now been approved by the Food and Drug Administration (FDA) for the treatment of Social Anxiety Disorder, sometimes called “social phobia.”

Social Anxiety Disorder affects 13% of Americans and is marked by overwhelming and disabling fear of scrutiny, embarrassment, or humiliation in social situations, which the person often avoids or endures with dread. It is the third most common psychiatric disorder in the U.S. Adults with this mood disorder usually recognize that their fear is excessive. Patients have a 40% to 50% lifetime prevalence of coexisting major depressive disorder.

Venlafaxine works by increasing the levels of two different chemicals in the brain that are thought to be deficient in depressed or anxious patients, according to the manufacturer. In two 12-week studies, the drug significantly reduced symptoms associated with Social Anxiety Disorder, compared with placebo, within only four to six weeks, with continued improvement seen up to week 12.

Patients receiving the drug in short-term depression trials reported several adverse drug events, including nausea, dizziness, somnolence, delayed ejaculation, dry mouth, and sweating; patients in short-term Generalized Anxiety Disorder trials reported nausea, dry mouth, abnormal ejaculation, constipation, and sweating.

Venlafaxine is contraindicated in patients taking monoamine oxidase (MAO) inhibitors. Because of sustained increases in blood pressure in patients taking this drug, regular monitoring is necessary.

In two double-blind, placebo-controlled trials of more than 600 patients, sertraline was found to be more effective than placebo in reducing anxiety, fear, and avoidance behaviors experienced by those with Social Anxiety Disorder. The drug was found to be effective for long-term treatment of social phobia.

Although side effects of sertraline can include upset stomach, difficulty in sleeping, diarrhea, dry mouth, fatigue, tremor, indigestion, agitation, and decreased appetite, few patients in clinical studies were bothered enough to stop taking the medication.

(Source: Pfizer news release, February 10, 2003; Wyeth Pharmaceuticals news release, February 11, 2003.)

Can Progesterone Prevent Premature Births?

Researchers have found that the hormone progesterone, commonly used to treat infertile and menopausal women, might be able to help prevent prematurity in a surprisingly high number of high-risk pregnancies. The results were so dramatic that the research was stopped early. Findings were presented at the annual meeting of the Society for Maternal-Fetal Medicine.

Babies who are born prematurely are at risk for neurological, hearing, and behavioral problems. In 50% of cases of prematurity, the cause is unknown.

Progesterone is naturally produced by the ovaries, and it softens the uterine lining to hold the fertilized egg. The study found that weekly injections of the hormone reduced the chance of premature births by 34% in 306 high-risk women. An additional 153 women received placebo injections. All of the women had previously given birth prematurely, the single largest indication of risk.

The study was carried out at the 19 centers that comprise the Maternal-Fetal Medicine Units Network under the National Institutes of Health. In the 1960s and 1970s, progesterone had shown some promise for reducing premature births, but no serious study had been completed.


DRUG NEWS
Fentanyl Patches and Opioid Toxicity

As a transdermal patch, fentanyl (Durasgesic®, Janssen) provides up to 72 hours of analgesia at predictable concentrations. The package insert, however, warns that fever, hot tubs, and saunas can increase the rate of drug delivery, putting patients at risk for opioid toxicity.

One patient with a cervical carcinoma was given a heating pad. The pad was placed on her abdomen away from the patch, but at some point it shifted and covered the patch. Two hours later, she had pinpoint pupils and her breathing was shallow. After naloxone HCl was administered, she improved rapidly; after 24 hours, the fentanyl patch was applied again with no problems.

In another instance, a patient who had been wearing a transdermal fentanyl patch for three days was given a warming blanket during surgery for a stress fracture. Her breathing decreased steadily, and both pupils were pinpoint. The patch was removed, and the patient was given naloxone HCl; within 20 minutes, she began to improve. She recovered uneventfully, with no further need for naloxone.

The third patient was wearing a transdermal fentanyl patch for neuropathy related to human immunodeficiency virus (HIV) infection. While he was at camp, swimming, hiking, and playing ball, he became tired and soon was unresponsive to stimuli. In the emergency de-
Antioxidants for the Critically Ill: Better Sooner Than Later

Giving critically ill patients supplemental antioxidants before they appear to need them can help keep organs from failing, say researchers from Harborview Medical Center in Seattle, Washington.

Of 595 patients, 310 were randomly assigned to receive alpha-tocopherol and ascorbate and 294 were assigned to standard care. By day 28, 152 (18%) standard-care patients had developed acute respiratory distress syndrome (ARDS), versus 47 (16%) of the patients receiving antioxidants. In the same time period, 53 (18%) standard-care patients had developed acute respiratory distress syndrome (ARDS), versus 47 (16%) of the antioxidant group. Seven (2.3%) of the patients in the group receiving antioxidants died.

Overall, only 26 (4%) patients had multiple organ failure, but the antioxidant group had a 57% lower incidence. The patients receiving antioxidants also had, on average, one less day of mechanical ventilation, more ventilator-free days, shorter stays in the intensive-care unit (by 1.2 days), and shorter hospital stays (by 0.4 day).

The researchers suggest that antioxidants might reduce both the amount of oxidative tissue injury and the early inflammatory response, possibly because of their effects on gene activation.

(Source: Ann Surg 2002;236:814–822.)

Pneumonitis after Methotrexate Plus Infliximab

Methotrexate, the treatment of choice for rheumatoid arthritis, is known to cause pneumonitis in approximately 1% of patients. Researchers from St. Barnabas Medical Center in Livingston, NJ, suggest that when the drug is combined with infliximab (Remicade®, Centocor), the risk of pneumonitis might be higher.

Over five years, the investigators observed 362 patients with rheumatoid arthritis who were taking methotrexate and noted no cases of methotrexate pneumonitis. When infliximab was added to methotrexate, however, they observed pulmonary toxicity in three of 50 patients over 13 months. In each case, the patient experienced life-threatening pulmonary symptoms shortly after the third infusion of infliximab.

In the first patient, fever, prostration, and night sweats occurred within one week of her third infliximab infusion. Two weeks later, she was hospitalized with severe dyspnea, bilateral interstitial pulmonary infiltrates, and extreme hypoxemia. The other two patients had similar symptoms.

The authors note that two cases of infliximab-related pneumonitis have been reported to date: one in a patient with Crohn’s disease and another in a patient treated for ankylosing spondylitis.

(Source: Arthritis Rheum 2002;47:670–671.)

High-Risk Patients and High-Dose Intravenous Immune Globulin

Caution is imperative when high doses of intravenous immune globulin (IVIg) treatment are given to obese patients and to patients with risk factors for thrombosis, say researchers who reported on two cases of thrombotic complications.

One patient, with idiopathic thrombocytopenic purpura, received 1 g/kg of IVIg per day as a five-hour infusion daily for two days. During the second infusion, she experienced expressive aphasia, right facial droop, and right hemiparesis. The infusion was stopped, and she was given platelets for a presumed intracranial hemorrhage. Magnetic resonance imaging showed acute nonhemorrhagic infarcts in the brain, but a transthoracic echocardiogram and carotid ultrasonography showed nothing significant. On day six, the patient felt pain in her left lower leg, which ultrasound examination revealed to be thrombosis. Enoxaparin sodium (Lovenox® Injection, Aventis) therapy was initiated, and her speech and the hemiparesis improved over the next few days.

The second patient, who had Evans’ syndrome, had received several courses of IVIg over the eight years since her diagnosis. On hospital admission, she had pain and swelling in the left lower leg. One week earlier, she had been treated for hemolytic anemia with high-dose IVIg, 400 mg/kg per day, infused over five hours for five days. Ultrasonography showed a thrombosis of the popliteal vein extending into the calf, with several deep muscular vein thromboses around the knee. Heparin and warfarin therapy was initiated, and she was readmitted because of hemolytic anemia and myalgia. Again, she was given high-dose
IVIg. Discharged on day five, she returned six hours after the last IVIg infusion, dizzy and short of breath. She died in the emergency room. An autopsy revealed bilateral diffuse thromboemboli in the pulmonary arteries.

High-dose IVIg is generally regarded as safe, but thrombotic, embolic, and ischemic complications have been reported. The mechanism of thrombosis might be related to the increased blood viscosity, which is dose-related and can last for weeks, the authors say, noting that IVIg reportedly induces platelet activation and arterial vasospasm.

After ruling out such risk factors as the length of infusion, the type of preparation, and the patient’s condition, the authors speculated that the patient, rather than the infusion, holds the clue to the thrombosis. Both patients described in this article were significantly overweight as a result of steroid treatment for autoimmune disease (236 pounds and 230 pounds). Because IVIg dosage is determined by the patient’s weight rather than by intravascular volume, the two patients were exposed to high intravascular concentrations of IVIg and high serum viscosities. Close follow-up of high-risk patients is recommended for at least two weeks after treatment ends.

(Source: *Pharmacotherapy* 2002;22:1638–1641.)

**Fast Relief for Breakthrough Cancer Pain**

“Breakthrough” pain, a transitory exacerbation of pain that has been generally stable, can be unpredictable and can escalate rapidly in patients with cancer. Oral opioid agents are not always the answer because they may act too slowly.

A nasal morphine-chitosan solution might be a fast, reliable, convenient way to tame breakthrough pain, say British researchers who conducted a pilot study of the drug combination. The nose offers advantages to enhance drug absorption, because it is a large, highly vascularized surface area and the venous blood drains from the nose directly into the systemic circulation, thus avoiding hepatic first-pass metabolism.

Chitosan, a bioadhesive material that binds to mucous membranes, provides other benefits. Morphine, a hydrophilic drug, is poorly absorbed nasally. Chitosan delays clearance and gives the drug more time to work. Adding chitosan to morphine boosts its nasal bioavailability from 10% to 54%, with a time to maximum concentration of 15 minutes. In contrast, even “immediate-release” morphine can take 20 to 30 minutes to begin relieving pain, with peak analgesia reached after one hour or more.

In the study of 14 patients, the researchers observed 20 episodes of breakthrough pain. The patients were given 5 to 80 mg of nasal morphine-chitosan in addition to their regularly prescribed analgesics. Nearly all of the patients rated the treatment as “good” to “excellent”; two found it only “fair.” Morphine-chitosan acted rapidly, with pain relieved or reduced after only five minutes and with maximal improvement reached after 45 minutes.

Side effects were slight and transient. Four patients reported “severe” taste disturbance, which was apparently dose-related. The most common adverse effect was sedation, reported during 16 episodes.

The researchers suggest that the formulation allows morphine to be given more conveniently, which might benefit patients at home and those who are vomiting or unable to swallow.

(Source: *J Pain Symptom Manage* 2002; 24:598–602.)

**Limits Urged for Nasal Flu Vaccine**

An investigational nasal-spray influenza vaccine has been deemed to be safe and effective by the FDA for healthy people from five to 49 years of age, but there are still concerns. The pain-free vaccine has not yet proved safe for some groups with compromised immunity, including older adults, toddlers, and anyone with asthma or another chronic disease, the FDA emphasizes.

FluMist™ (Influenza Virus Vaccine Live, Intranasal, MedImmune) is delivered as a nasal mist and has the potential to offer a new approach to protect people against influenza. The Centers for Disease Control and Prevention (CDC) has estimated that approximately 114,000 people in the U.S. are hospitalized and about 20,000 people die each year because of the flu.

If FluMist™ is licensed by the FDA, it would be the first commercially available influenza vaccine delivered as a nasal mist in the U.S.

(Source: Associated Press, December 17, 2002; University of Michigan School of Public Health, December 18, 2002; www.sph.umich.edu/news_events/62press.html.)

**Coxibs Can Go It Alone**

Although cyclooxygenase 2 (COX-2) inhibitors, also called “coxibs,” can be easier on the gastrointestinal system than nonsteroidal anti-inflammatory drugs (NSAIDs) are, some physicians prefer to err on the side of caution by prescribing a gastroprotective agent
Canadian researchers analyzed data from 42,267 patients who were taking COX-2 inhibitors; 8,235 patients who were taking NSAIDs, and 19,716 patients who received acetaminophen. The researchers concluded that adding a GPA to a coxib constitutes an unnecessary financial burden, particularly if the GPA prescription is unwarranted.

Physicians in the study were more likely to prescribe coxibs than NSAIDs for patients who were older or sicker or who had risk factors associated with gastropathy from NSAID use. They also tended to prescribe coxibs over acetaminophen for patients with musculoskeletal disorders and osteoarthritis, presumably because of the anti-inflammatory analgesia associated with coxibs. (At the time of the study, rofecoxib had not yet been indicated for rheumatoid arthritis.)

As coxibs gained popularity, it was expected that prescriptions for GPAs might decline along with the decrease in NSAID prescriptions, but that was not the case. GPAs in this study, however, were prescribed 47% less often for coxib users than for NSAID users. Studies have indicated that coxibs—although more expensive than NSAIDs—would be cost-effective in patients at high risk for gastrointestinal events with NSAIDs, the investigators noted.

Other studies have shown that the cost-effectiveness of rofecoxib, compared with that of the nonselective NSAIDs, for patients with osteoarthritis is “sensitive to the rate of prophylactic GPA use,” according to the authors.

When the researchers re-analyzed the data, keeping only the patients who did not have any previous gastrointestinal events, cancer, or any filled prescriptions for coxibs, NSAIDs, or acetaminophen, a GPA co-prescription was 61% less frequent with coxibs than with NSAIDs. A co-prescription of a GPA with coxibs was equivalent to one with acetaminophen—a striking finding, the researchers say, considering that physicians do not perceive acetaminophen as being toxic to the gastrointestinal tract.

(Source: Arthritis Rheum 2002;47: 595–602.)

New Tool for Hospital Pharmacies
The Formulary AdvisorTM is a new product that is expected to simplify the development and management of online formularies in hospitals. It allows prescribing clinicians to view, create, manage, and update a complete formulary on a desktop or laptop computer or on a personal digital assistant (PDA).

The device provides immediate access to current information and should benefit prescribing clinicians, pharmacists, and, eventually, patients. Hospital personnel will be able to access the information with a minimal disruption of workflow, thus saving time.

The Formulary AdvisorTM also displays prices for each medication in the formulary; posts documents, Web links, policies, or news needed by hospital staff; and prints hard copies of the entire formulary. It is expected that using the product will lead to a reduced number of drug-delivery delays, which are a primary cause of medication errors.

(Source: www.microdex.com; news release, December 3, 2002.)

Lower-Dose Muscle Relaxant Found Effective for Pain
Cyclobenzaprine (Flexeril®, Merck/Alza), a muscle relaxant, is now available in a lower-dose version that is less sedating for patients than the previous formulation. Until this year, the drug was available only as 10-mg tablets. The new lower dose of 5 mg should enable physicians to have greater flexibility in prescribing the drug for the initial treatment of sprains, strains, and other painful musculoskeletal conditions.

The approval of cyclobenzaprine 5 mg was based on results of two seven-day double-blind, placebo-controlled, randomized trials enrolling 1,405 patients with acute painful muscle spasm in the lower back or neck. Over one week of treatment, without taking other analgesics, psychotropic drugs, or sedating agents, the patients reported that the 5-mg dose provided greater relief of symptoms than placebo did.

(Source: McNeil Consumer & Specialty Pharmaceuticals, February 4, 2003.)

Autoimmune Disease Web Site
The Autoimmune Disease Research Foundation has announced the launch of its Web site, www.cureautoimmunity.org. This site describes and supports the hypothesis that many autoimmune diseases have a common cause and, possibly, a common cure.

The Foundation supports novel, high-impact research and clinical trials that might hasten a cure for many autoimmune diseases. Crohn’s disease, rheumatoid arthritis, scleroderma, Addison’s disease, and Graves’ disease are some of the 80 autoimmune diseases that strike 50 million Americans of all ages.

Autoimmune disease occurs when the body’s immune system perceives its own tissue as foreign and attacks it. In patients with type-1 diabetes, for example, the immune system destroys insulin-producing beta cells; in patients with lupus, the immune system destroys connective tissue; and in patients with multiple sclerosis, the nerve covering is destroyed. Autoimmune diseases typically run in families.

(Source: www.cureautoimmunity.org.)