NEW DRUGS

Olanzapine/Fluoxetine Combination for Bipolar Depression

The U.S. Food and Drug Administration (FDA) has approved Symbyax™ (Eli Lilly) for the treatment of depressive episodes associated with bipolar disorder. Symbyax™, a combination of olanzapine, the active ingredient in Zyprexa®, and fluoxetine, the active ingredient in Prozac®, is the first FDA-approved medication for bipolar depression, a notoriously difficult-to-treat condition that afflicts millions of Americans.

Patients with bipolar disorder experience debilitating mood swings, ranging from episodes of deep depression marked by feelings of extreme guilt; sadness; anxiety; and, at times, suicidal thoughts to episodes of mania (abnormal euphoria, elation, and irritability), interspersed with periods of normal mood. The depressive phase is associated with higher rates of morbidity and mortality.

During an eight-week clinical trial, Symbyax™ alleviated the symptoms of bipolar depression more effectively and at a significantly faster rate than placebo did. Improvement of symptoms was sustained throughout the duration of the study.

The most common adverse event in patients taking the drug was drowsiness; other common side effects included weight gain, increased appetite, weakness, swelling, tremor, sore throat, and difficulty concentrating.

All patients taking the atypical agents should be monitored for symptoms of hyperglycemia. Patients with diabetes should be monitored regularly for worsening of glucose control. If symptoms of hyperglycemia develop during treatment, patients should undergo fasting blood glucose testing.

Strokes or mini-strokes, including fatalities, have been reported in elderly patients with dementia-related psychosis who were participating in clinical trials for olanzapine. The drug may induce orthostatic hypotension or fainting, especially during initial therapy.

Patients should not take Symbyax™ until at least two weeks have passed since stopping monoamine oxidase inhibitors.

(Sources: Arch Gen Psychiatry 2003; 60(1):1079–1088; Eli Lilly, December 29, 2003; Wall Street Journal, December 30, 2004; http://symbyax.com)

NEW INDICATIONS

Lamotrigine: A New Option for Partial Seizures

The FDA has approved lamotrigine (Lamictal® Tablets, GlaxoSmithKline) as monotherapy for treatment of partial seizures in patients 16 years and above who are switching from the older antiepileptic drug valproate (valproic acid [Depakene®, Abbott] and divalproex sodium [Depakote®, Abbott]). According to the Epilepsy Foundation, epilepsy affects 2.3 million Americans of all ages.

The expanded indication and dosing recommendations are based on the findings of an 18-week study. Seventy-seven patients with epilepsy were switched from valproate to lamotrigine monotherapy over the course of the study, during which time blood concentrations of the drugs were closely monitored. A four-step dosing algorithm was used to achieve successful conversion, with patients maintaining consistent blood concentrations of lamotrigine.

The most common adverse events considered to be associated with study medication were dizziness (in 23% of patients), nausea (in 16%), headache (in 14%), tremor (in 13%), and asthenia (in 12%). Of the 77 patients enrolled in the study, 21% withdrew because of adverse events.

Serious rash requiring hospitalization and discontinuation of treatment have been reported in association with the use of lamotrigine.

Rare cases of toxic epidermal necrolysis with or without rash-related deaths have been reported. The drug should be discontinued at the first sign of rash unless the rash is not drug-related.


Oxaliplatin Approved for Metastatic Colorectal Cancer

Oxaliplatin for injection (Eloxatin™, Sanofi-Synthélabo/Debiopharm SA), in combination with 5-fluorouracil/leucovorin (5-FU/LV), has been approved by the FDA for the first-line treatment of advanced colorectal cancer. Eloxatin™ was approved in 2002 for the second-line treatment of patients with metastatic carcinoma of the colon or rectum.

In a study sponsored by the National Cancer Institute and coordinated by the North Central Cancer Treatment Group (NCCTG), patients treated first with Eloxatin™, combined with infusional 5-FU/LV (the FOLFOX regimen), experienced an overall median survival time of 19.4 months after starting therapy. Patients taking a standard combination of irinotecan (Camptosar®, Pharmacia & Upjohn) plus 5-FU/LV (the IFL regimen) had a median survival time of 14.6 months; therefore, the median survival advantage for the FOLFOX patients was 4.8 months (a 35% improvement). The FOLFOX group reported less severe, more manageable, and more reversible side effects than the IFL group did.

(Sources: FDA, January 9, 2004; www.fda.gov; Sanofi-Synthélabo, January 12, 2004)

DRUG NEWS

Aspirin with Ibuprofen: Safe After Heart Attack

Concerns about the safety of discharging patients with both aspirin and ibuprofen an...
ibuprofen after a myocardial infarction (MI) might be unfounded, according to researchers from Yale University and Denver Health Medical Center. A retrospective study of 70,316 patients found that patients who took both drugs had a risk of death that was comparable to that of patients taking aspirin alone.

Of the 66,739 patients who were prescribed aspirin alone, 11,546 (17.5%) died. Of the 844 who were taking aspirin and ibuprofen, 118 (14%) died, as did 432 (15.8%) of the 2,733 patients who were taking aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).

Earlier reports that post-MI patients taking aspirin and ibuprofen were at increased risk resulted in recommendations against prescribing the two drugs together. However, the study had included only 187 patients receiving the two drugs and was not adjusted to determine the severity of cardiovascular disease. In contrast, the current retrospective study included four times as many patients, with adjustments made to measure the severity of shock, ejection fraction, and heart failure.

(Source: BMJ 2003;327:1322–1323.)

**A Happy “Medium” for Aspirin After Surgery**

The urge to prescribe low-dose aspirin after surgical procedures is strong, but it might not be the best course of action. In light of a recent study, researchers from Papworth Hospital in Cambridge, England, found that increasing the dose sometimes yielded better results.

The researchers reviewed studies comparing low-dose and medium-dose aspirin after coronary surgery. It has already been established that 75 to 325 mg of aspirin is equal to or better than high-dose (500 to 1,500 mg) aspirin in preventing vein-graft occlusion.

The researchers concluded that the “limited evidence” supports a medium-dose regimen, which lowered the relative risk of graft occlusion by about 45%; the low-dose regimen reduced the risk by 26%.

Until the optimal dosage is determined, 325 mg appears to be the best choice in the first year because of its proven safety profile, the absence of increased costs, and a lack of any proportional increase in major hemorrhage.

(Source: BMJ.com.)

**Vasopressin Saves Lives After Heart Attacks**

The survival rate for patients with asystole, the most lethal form of cardiac arrest, has been found to be greatly improved if patients receive an injection of vasopressin (e.g., Pitressin®, King), according to a new study from Europe. A naturally occurring hormone in the human body, vasopressin is a common therapy for frequent urination because of its effect on the kidneys.

In the study, vasopressin was superior to epinephrine in patients whose heart had stopped beating. Patients with asystole cardiac arrest had triple the survival rate when they were given an injection of vasopressin rather than epinephrine, the most common form of treatment in these cases.

Only four of the 262 patients (1.5%) who received epinephrine were eventually able to leave the hospital, whereas 12% of 258 patients (4.7%) who received vasopressin were discharged. Because the long-term survival of patients in cardiac arrest is very poor, the gain from 1.5% to 4.7% is considered significant.

The patients who received vasopressin were also 40% more likely to reach the hospital alive than those who received epinephrine. The American Heart Association estimates that more than 95% of cardiac arrest patients die before reaching the hospital.

The effects of vasopressin were similar to those of epinephrine in the management of ventricular fibrillation and pulseless electrical activity; however, vasopressin was superior in patients with asystole. The researchers suggested that vasopressin followed by epinephrine might be more effective than epinephrine alone in cases of refractory cardiac arrest. The results have been so impressive that meetings are scheduled to be held to determine whether resuscitation guidelines should be quickly revised to include the use of vasopressin.


**Successful Trial of Anticancer Drug Ends Early**

The first new treatment in more than a decade for patients with multiple myeloma, a cancer of the blood, has proved so effective that the manufacturer, Millennium, has halted the control arm of the trial to give patients receiving dexamethasone the option of immediately switching to bortezomib (Velcade™ for Injection, Millennium). The first of a new class of medications called proteasome inhibitors, bortezomib was compared with high-dose dexamethasone in a phase III trial of nearly 700 patients. An interim analysis found a statistically significant improvement in the time to disease progression.


**Tacrolimus and HIV Drugs**

Now that patients with human immunodeficiency virus (HIV) infection have become better able to tolerate immunosuppression, they are more suitable candidates for solid-organ trans-
plantation when it is needed. However, physicians must still be very careful when they mix the drugs that help the transplant “take” with antiretroviral agents that are needed for keeping acquired immunodeficiency syndrome (AIDS) at bay, say researchers from University of Pittsburgh Medical Center.

A 48-year-old man who was receiving tacrolimus (Progra®, Fujisawa) 5 mg/day as immunosuppression therapy for liver transplantation began highly active antiretroviral therapy (HAART) with lopinavir/ritonavir (Kaletra®, Abbott). Within three days, tacrolimus concentrations had climbed to toxic levels—an eightfold increase. Even when tacrolimus was subsequently withheld, its half-life was five days, or 10 times the usual half-life in liver-transplant recipients. Because lopinavir/ritonavir was continued while the tacrolimus was withheld, inhibition of cytochrome P3A4 (CYP3A4) was prolonged, which extended the time needed for tacrolimus concentrations to return to normal.

The interaction between the drugs was confirmed when the patient stopped taking the HIV drugs and his tacrolimus concentration dropped to below the therapeutic target range. When lopinavir/ritonavir was restarted, the tacrolimus levels began to rise again. Ultimately, the patient was stabilized with a dose of 0.5 mg once weekly, an amount 140-fold lower than the usual dose.

Tacrolimus, an immunomodulator, is metabolized in the liver via CYP3A4, which is known to be blocked by protease inhibitors. Although other cases of interactions between tacrolimus and protease inhibitors have been reported, the researchers had seen no published reports about tacrolimus and lopinavir/ritonavir. Moreover, the dramatic peaking in this case was particularly remarkable.

Tacrolimus has a narrow therapeutic window. Dosages must be titrated to avoid organ rejection from underdosing or toxicity (especially in the kidneys or nerves) from underdosing. It is important for clinicians to recognize the magnitude of the potential interactions with anti-HIV drugs and the importance of adjusting tacrolimus to very low doses within 72 hours after the interacting medication is started. Daily monitoring is essential to prevent toxicity, to maintaining adequate concentrations, and to prevent organ rejection.

(Source: Ann Pharmacother 2003;37: 1793–1796.)

**Propofol for Emergency Sedation**

The ideal sedative for patients who are undergoing cardioversion in the emergency department (ED) might be propofol (Diprivan®, AstraZeneca), according to an experience reported from Hospital Clinic in Barcelona, Spain. The drug offers a fast onset, minimal cardiopulmonary depression, and a rapid recovery.

When researchers compared propofol and etomidate (Ben Venue Laboratories) and midazolam (Versed®, Roche), with or without flumazenil (e.g., Mazine®, Roche), propofol yielded superior results. Although all four regimens were uniformly effective, patients receiving propofol experienced the shortest recoveries and the fewest adverse effects.

The midazolam/flumazenil combination was found to be problematic when all patients, except one, became sedated again after flumazenil was discontinued.

Although etomidate offered hemodynamic stability, rapid sedation, and rapid recovery, it had adverse effects such as myoclonus, which can interfere with the interpretation of the electrocardiogram.


**Diabetic Foot Infections Respond to Linezolid**

A clinical trial involving 371 patients in eight countries has shown that the antibiotic linezolid (Zyvox™, Pharmacia) is at least as effective as two older therapies for treating foot infections in diabetic patients. This is important news for patients with infections that are increasingly caused by bacteria resistant to standard antibiotics and for those who, in severe cases, require amputation. The study, led by a Department of Veterans Affairs (VA) physician, was conducted at 30 U.S. and 15 European sites.

Foot infections are among the most serious complications in diabetes and are the leading cause of diabetes-related hospitalizations.

In the study, patients with diabetic foot infections were randomly assigned to take either linezolid or one of two standard combination treatments, consisting of an amino-penicillin and a beta-lactamase inhibitor, a drug that blocks an enzyme that inactivates penicillin. Vancomycin could be added to the regimen for patients in the non-linezolid group if their infections were caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Linezolid produced a clinical cure in 81% of patients; the comparator combination was effective in 71% of patients. Although the overall statistical results for the two groups were almost equivalent, linezolid outperformed amino-penicillin in the largest subgroup, the patients with infected ulcers.

Linezolid is among the first new therapies since the introduction of vancomycin in the 1950s for treating MRSA infections. On the basis of the results of the new trial, the FDA has now extended the use of linezolid to treat most diabetic foot infections. Linezolid can be given orally and intravenously.

(Source: Clin Infect Dis 2004;38:17–24; VA Research Communications Ser-
vice, Seattle, WA; Infectious Diseases Society of America annual meeting, October 2002.)

**Doxazosin and Finasteride: A Powerful Team Against Prostate Enlargement**

Doxazosin mesylate (Cardura®, Pfizer), an α₁-receptor blocker, and finasteride (e.g., Proscar®, Merck), a 5α-reductase inhibitor, seem to work better together than they do alone in men with benign prostatic hyperplasia (BPH), say researchers for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. Their study of 3,047 men found a reduced overall risk of BPH progression by 66% compared with placebo.

The study measured the effects of the drugs with each other and with placebo on the clinical progression of BPH. The combination therapy not only reduced the risk of overall clinical progression of BPH more than either drug alone but also improved American Urological Association (AUA) symptom scores and maximal urinary flow rate better than did either drug alone.

The four-year incidence of overall clinical progression was only 5% in the patients receiving combination therapy, compared with 10% in both monotherapy groups, and 17% in the placebo group. Combination therapy reduced the risk of overall clinical progression by 66%, compared with 39% with doxazosin, and 34% with finasteride.

At four years, serum levels of prostate-specific antigen (PSA) had increased by a median of 15% in the placebo patients and by 13% in the doxazosin patients. Surprisingly, serum PSA levels had dropped by 50% in both the finasteride and combination-treatment patients. Similarly, prostate volume in the 1,148 men who were receiving placebo or doxazosin increased by a median of 24%, whereas volume among the 427 men receiving finasteride or combination therapy was decreased by a median of 19%.


**An Update of the Beers Criteria**

Studies published in the late 1990s about polypharmacy, inappropriate medication use, and adverse drug events in older people had a salutary effect—or, some might say, a chilling effect—on drug prescribing. Finding out just how differently the “usual” drugs worked in older patients had some clinicians second-guessing their own prescribing habits. Now a consensus panel of experts has further updated one of the most famous studies: the widely used Beers criteria, published in 1997. Forty-four medications have been added to the list of drugs to watch, and 15 medications or drug classes have been dropped or modified.

The update also includes information on several old and new medications, including selective serotonin reuptake inhibitors and amiodarone (Cordarone®, Wyeth).

The criteria are meant to apply to the general population of patients 65 and older. Thus, some drugs that are not appropriate for “old-old” or more frail patients do not appear on the list.

The panel also cautions that “defining inappropriate medications by specific lists of medications rather than other mechanisms may miss some problems such as the underuse and interactions of drugs in older people.”

(Source: *Arch Intern Med* 2003;163:2716–2724.)

**Pre-filled Syringes of Peginterferon alfa-2a for Hepatitis C**

The FDA has approved pre-filled syringes of peginterferon alfa-2a (Pegasys®, Roche) to treat chronic hepatitis C virus (HCV) infection, a blood-borne disease of the liver. HCV infection is the leading cause of cirrhosis and liver cancer and is the primary reason for liver transplants in the U.S. An estimated 2.7 million Americans have chronic hepatitis C infection.

The combination of Pegasys®, a pegylated alpha interferon, and ribavirin (Copegus®, Roche) was approved by the FDA in December 2002 to treat adults with chronic HCV infection who had compensated liver disease and who had not previously received interferon alpha.

The new syringes should be available in pharmacies by February 2004 and will be sold as packages of four per box. Until now, the product has been sold in vials as a pre-mixed solution.

Pegasys® is administered as a subcutaneous injection (180 mcg) taken once a week. Copegus® is available as a 200-mg tablet and is taken orally two times a day as a split dose.

(Source: Roche, January 12, 2004; www.rocheusa.com.)

**NEW MEDICAL DEVICES**

By Marvin M. Goldenberg, PhD, RPh, MS


**Name:** Uni-Gold™ Recombigen® HIV

**Manufacturer:** Trinity Biotech, Wicklow, Ireland

**Approval Date:** December 30, 2003

**Use Classification:** This single-use rapid test helps detect human immunodeficiency virus (HIV-1) antibodies in plasma, serum, and whole blood (by venipuncture) in point-of-care settings.

**Description:** The test employs genetically engineered recombinant proteins that represent the immunodominant
regions of the envelope proteins of HIV-1. The recombinant proteins are immobilized at the test region of the nitrocellulose strip. These proteins are also linked to colloidal gold and are impregnated below the test region of the device. A narrow band of nitrocellulose membrane is also sensitized as a control region.

If antibodies to HIV-1 are in the sample, they combine with the HIV-1 antigen/colloidal gold reagent; this complex then binds to the immobilized antigens in the test region of the device. A positive result is manifested by a pink-red band in the test region of the device; in a negative sample, no band is visible.

**Purpose:** This product is reportedly the first device to be approved for detecting HIV in serum, plasma, and whole blood. Only one step is required, and a result is produced within 10 minutes. (In contrast, results from conventional HIV tests typically take hours or even days.)

**Precautions:** The test is restricted to use by clinical laboratory professionals in facilities with adequate quality-assurance programs and is not approved for home use or for screening blood, plasma, cell, or tissue donors.

Staff personnel should observe Standard Precautions when using the kit and should wash their hands thoroughly afterward. Employees should wear protective clothing (e.g., a laboratory coat and disposable gloves) when handling specimens and assay reagents. If a wash buffer comes into contact with the eyes, the eyes should be rinsed immediately with plenty of water and medical advice should be sought. Personnel should not eat, smoke, drink, apply cosmetics, or touch contact lenses in areas where specimens are being handled.

**Name:** Tigris® Direct Tube Sampling (DTS™) System

**Manufacturer:** Gen-Probe, San Diego, CA

**Approval Date:** December 30, 2003

**Use Classification:** The system is used in the diagnostic testing of sexually transmitted diseases.

**Description:** The device runs the APTIMA® Combo 2 assay, an FDA-approved test for the simultaneous detection of Chlamydia trachomatis and Neisseria gonorrhoeae organisms. The assay is a second-generation, nucleic acid-amplification test that uses target capture for *in vitro* differentiating recombinant RNA from *C. trachomatis* and *N. gonorrhoeae*. The assay uses a family of Gen-Probe’s known technologies, which are also used to screen the blood supply in the U.S. It is not necessary to prepare a sample manually in order to initiate a run or to generate test results.

**Transcription-mediated amplification** provides a new standard in reliability by targeting RNA or DNA sequences and by regenerating the sequences a billion-fold in 15 to 30 minutes. The *hybridization protection assay* uses a specific DNA probe that enables a chemiluminescent signal to be emitted for ease of detection and differentiation. The *dual kinetic assay* is an exclusive feature that allows for two analytes in a single specimen to be detected and differentiated.

**Purpose:** This is the first fully automated, high-throughput instrument in the molecular diagnostics marketplace. It is hoped that diagnostic laboratories, in which shortages of trained technicians have been an industry concern, will now be able to use this system to cut labor costs, minimize errors, and increase productivity and accuracy.

The system can process approximately 500 samples in an eight-hour shift and up to 1,000 samples in approximately 13 hours. Because one trained operator can run two or three Tigris® machines simultaneously, the productivity of a single technician using the new system might be as much as 10 times greater than that of a technician who is using current semiautomated systems.

**Precautions:** None listed.

**Name:** Restylane®

**Manufacturer:** Q-Med AB, Uppsala, Sweden

**Approval Date:** December 12, 2003

**Use Classification:** Anti-wrinkle gel

**Description:** Restylane® is a clear transparent, viscous, sterile gel consisting of non-animal, stabilized, hyaluronic acid at a concentration of 20 mg/ml. It is supplied in a disposable glass syringe. Each syringe contains 0.4 or 0.7 ml of gel.

**Purpose:** The product is used to fill in moderate to severe wrinkles around the nose and mouth. Most patients have needed one injection to obtain optimal correction; about one-third of patients need more than one injection for a satisfactory result. The effect lasts approximately six months.

In a clinical trial, the effectiveness of Restylane® was found to be equivalent to that of bovine dermal collagen (Zyplast®, Inamed). Restylane® adds volume to tissues, thereby restoring the skin contours to the desired level of correction.

**Precautions:** In a clinical trial comparing applications of Restylane® and Zyplast® to the side of patients’ faces, restylane treatment resulted in a lower incidence of severe redness (5.1% for Restylane® vs. 5.8% for Zyplast®) and an increased incidence of severe bruising (3.6% vs. 0.7%), severe swelling (3.6% vs. 1.4%), severe pain (3.6% vs. 1.4%), and severe tenderness (2.9% vs. 1.4%), respectively. The incidence of adverse effects was lower when follow-up injections of both products were administered.

The FDA has voiced concern about the potential for hypersensitivity reactions with Restylane®.

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Genes and Panic Disorder

A new finding, combined with evidence from animal studies, suggests that genes might increase the risk of panic disorder by coding for decreased expression of specific receptor molecules. This finding is the first in humans to show that a receptor, which is pivotal to the action of widely prescribed anti-anxiety medications, may be abnormal in patients with the disorder and may help to explain how genes might influence vulnerability.

Using positron emission tomography (PET), researchers discovered that three brain areas in patients with panic disorder lacked a key component of a chemical messenger system that regulates emotion. Brain scans revealed that a type of serotonin receptor was reduced by nearly one third in three structures straddling the center of the brain.

Researchers have long suspected a genetic component as a cause of the disorder. It is not yet clear whether the animal models will apply to the disorder in humans.

(Source: J Neurosci 2004;24:589–591.)

Can MRI Help Patients with Depression?

A study from McLean Hospital in Belmont, MA, has found that low-field magnetic stimulation of the brain might help to alleviate bipolar depression (also called manic depression).

Thirty of 40 patients underwent echo-planar magnetic spectroscopic resonance imaging (EP–MRSI) that used extremely weak magnetic fields to penetrate throughout the brain; 10 patients underwent a simpler brain scan used as a placebo. Of the 30 patients in the treated group, 77%, felt better after the scan; only three of the 10 patients in the placebo group reported improved well-being. The study did not examine how long the improved mood might last.

The McLean scan was originally designed as a tool to study brain function, not as a treatment. It is thought that the electromagnetic stimulation might alter the firing patterns of nerve cells. Research into magnetic stimulation of the brain as a treatment for mental disorders has been going on since the 1980s. More work is needed to determine the effects of MRI on memory.


Generic Bupropion for Depression

Under a supply agreement with GlaxoSmithKline (GSK), Watson Pharmaceuticals, Inc., has begun shipments of 100-mg-strength bupropion HCl sustained-release (SR) tablets. The product is the generic version of GlaxoSmithKline’s Wellbutrin SR®, which is indicated for the treatment of depression.