NEW DRUGS
Colorectal Cancer Chemotherapy

Colorectal cancer is the second leading cause of malignancy-related death in the U.S. It accounts for more than 10% to 15% of all cancer deaths. Every year about 150,000 new cases in the U.S. and about one million cases worldwide are diagnosed.

After a 46-day priority review, the Food and Drug Administration (FDA) approved oxaliplatin (Eloxatin, Sanofi-Synthelabo) as an injection to treat patients with colorectal cancer that has recurred or progressed following six months of completion of first-line therapy with bolus infusional 5-fluorouracil (5-FU) and leucovorin (LV) plus irinotecan (Campsosar, Pharmacia). Oxaliplatin will be administered in combination with 5-FU/LV. Approval was based on response rate and interim analysis showing improved time to radiographic progression.

At this time, no results have demonstrated a clinical benefit, such as improvement of disease-related symptoms or increased survival. (Source: http://www1.internetwire.com/iwire/iwprj?id=45372 &cat=me)

CASE STUDY
Miconazole and Warfarin Don’t Mix

Physicians should be cautious when prescribing topical miconazole for patients taking warfarin, advise clinicians from Eastbourne District Hospital in England. They report on a case of an 80-year-old man who had been applying the broad-spectrum antifungal to the right groin area for two weeks. Although he had been taking warfarin for a long time for atrial fibrillation and had an International Normalized Ratio (INR) ranging between 2.2 and 3.1 on a dose of 6 mg daily, at a routine visit his INR was measured at 21.4. He had had no evidence of bruising or bleeding and had continued with his usual daily drugs (atenolol, isosorbide mononitrate, and diltiazem).

Upon hospital admission, both warfarin and miconazole were withdrawn. The patient’s INR returned to 3.2, and warfarin was reinstated. His INR has remained stable.

The clinicians assume that miconazole was the culprit. They note that it might increase the anticoagulant effect of warfarin by inhibiting hepatic microsomal cytochrome P-450 enzymes. Trace amounts of miconazole have been detected in the system after topical administration, they say, and interactions have also been reported with oral gel and pessary formulations.

They recommend avoiding prescribing miconazole for patients taking warfarin. When that isn’t possible, keeping a close eye on anticoagulation control is essential.

DRUG NEWS
Hypertension Drugs and Diabetes

Atenolol might impair insulin sensitivity, making it more likely for patients who take it to develop diabetes, say researchers from the LIFE (Losartan Intervention for Endpoint Reduction in Hypertension) trial. Comparing atenolol (a beta blocker) with losartan (an angiotensin II antagonist), they found that losartan had a neutral effect on insulin sensitivity, whereas atenolol seemed to have an outright negative effect.

Of 7,998 patients who did not have diabetes at baseline values, 562 developed diabetes over the course of the study. However, patients who took losartan in addition to other antihypertensive therapy had a 25% lower risk of developing diabetes than those taking atenolol. Of 4,019 patients taking losartan, 242 developed diabetes, compared with 320 of 3,979 taking atenolol.

Losartan also nearly reduced by half the risk of dying among patients with diabetes. Of the 9,193 patients enrolled in the four-year trial, 1,195 had diabetes. The group assigned to losartan saw an impressive 24% reduction in risk of cardiovascular mortality, stroke, and myocardial infarction and a 39% reduced risk in all-cause mortality. The benefit of losartan over atenolol was especially marked in the small group of diabetic patients (20%) who had not been treated for hypertension before the study, the researchers say.

The researchers stress, though, that losartan’s benefits are lost without a diuretic. Also, the vast majority of patients in the diabetes subgroup were taking hydrochlorothiazide and nearly 40% were also taking a calcium channel blocker. (Source: www.theheart.org/documents/page.cfm?from=590001200&doc_id=30898)

New Use for GHB in Cataplexy

Xyrem, manufactured by Orphan Medical, has been approved for treating patients with narcolepsy who have episodes of cataplexy, a sudden loss of muscular control and weakness, usually triggered by emotions. The drug’s active ingredient is sodium oxybate, also known as gamma hydroxybutyrate (GHB).

Because of the abuse of GHB—it is used recreationally and in date rapes—distribution will be tightly controlled under Schedule III of the Controlled Substances Act. For the 20,000 to 50,000 people in the U.S. who suffer from narcoleptic cataplexy, however, the news will be welcome, regardless of the restrictions. Cataplexy can cause a person with narcolepsy to collapse when the legs buckle. In clinical studies with 448 patients, the use of Xyrem, compared with placebo, reduced the number of cataplectic attacks.

Xyrem can have serious side effects, including confusion, depression, difficulty breathing while sleeping, loss of consciousness, and abnormal thinking. Abuse of the drug can lead to dependence. For these reasons, and in light of the drug’s history, the FDA and the manufacturer have designed a comprehensive risk management program (the Xyrem Success Program). For instance,
prescribers and patients will be able to get the drug only through a single centralized pharmacy. (Source: [www.fda.gov/cder/drug/infopage/xyrem/xyrem_qa.htm](http://www.fda.gov/cder/drug/infopage/xyrem/xyrem_qa.htm))

**HAART Safe for Patients with HIV and Hepatitis C**

Hepatitis C has no effect on the outcomes of patients with human immunodeficiency virus (HIV) who are treated with highly active antiretroviral therapy (HAART), according to researchers from Johns Hopkins University. The researchers said that the liver infection does not decrease the response to anti-AIDS drugs or speed progression of the illness.

The researchers followed 1,955 HIV-infected patients for at least two years. Nearly half of the patients had been exposed to hepatitis C. Patients who had both an HIV infection and hepatitis C seropositivity were less likely to have been prescribed antiretroviral therapy. The researchers explained that physicians were less likely to prescribe antiretroviral therapy to these patients, whom they believed were more likely to experience liver complications from such medications.

This study was presented at the 14th International AIDS Conference. (Source: [www.nih.gov/news/pr/jul2002/nida-06.htm](http://www.nih.gov/news/pr/jul2002/nida-06.htm); [www.reutershealth.com/archive/2002/07/08/eline/links/20020708elin019.html](http://www.reutershealth.com/archive/2002/07/08/eline/links/20020708elin019.html))

**Drug Combination for Bipolar Depression**

Olanzapine alone improves symptoms in bipolar depression, but adding fluoxetine is even better, say researchers in a trial supported by Eli Lilly and Company. The combination of olanzapine and fluoxetine produced a “robust” response, compared with olanzapine alone and with placebo. The researchers, reporting at the annual meeting of the American Psychiatric Association, say the response showed no evidence of the drug-induced switch to mania, which has been the limitation in the use of other antidepressants for treating patients with bipolar depression. There are no FDA-approved treatments for bipolar depression.

In the eight-week double-blind trial, the researchers randomly assigned 270 patients to olanzapine 5 to 20 mg/day, 377 to placebo, and 80 to a combination of olanzapine 6 or 12 mg/day plus fluoxetine 25 or 50 mg/day. Mean change in symptoms at eight weeks was significantly greater for olanzapine and the combination group than for placebo patients. Adverse events (<10%) included somnolence, weight gain, increased appetite, and drymouth. (Source: [www-peerviewpress.com/news/content.nsf/PeerViewPress/8525697700573E1885256BC6006094AC](http://www-peerviewpress.com/news/content.nsf/PeerViewPress/8525697700573E1885256BC6006094AC))

**Patient-Friendly OTC Labels**

As of May 16, 2002, most over-the-counter (OTC) drug manufacturers have begun using “consumer-friendly” labeling.

The new Drug Facts label—patterned after the Nutrition Facts food label—features simpler language and an easier-to-read format. In addition to a larger type size and other changes to enhance readability, the label must include the drug’s information in the following order:

- the product’s active ingredients, including the amount in each dosage unit
- purpose of the drug
- uses of the drug
- specific warnings, including when the product should not be used under any circumstances
- when, how, and how often to take the drug
- inactive ingredients (important for those who have allergies)

The new simplified labels have also eliminated some of the more technical jargon. For instance, the word “uses” replaces “indications” and words like “precautions” and “contraindications” have been eliminated. Products with the old labels will still be distributed until their inventories are exhausted. (Source: [www.fda.gov/fdac/features/2002/402_otc.html](http://www.fda.gov/fdac/features/2002/402_otc.html))

**Cancer Symptoms Still Undertreated**

A symposium on cancer treatment has revealed that cancer-related pain, depression, and fatigue are still undertreated despite effective strategies to manage them.

The findings came from national experts in a National Institutes of Health (NIH) State-of-the-Science Conference on Management of Cancer Symptoms: Pain, De-
pression, and Fatigue. Panel members considered evidence from all studies published in English between 1966 and 2001 that assessed the prevalence of these debilitating symptoms in cancer patients. They found a perplexing variety of measurement tools, definitions, and results.

According to the research, at some point during their treatment, most patients experience pain that impairs quality of life and functionality. Calling the finding “disturbing,” the panel notes that the research reflects data from developed countries, where patients are often in tertiary care or in specialist consultative settings. Minority patients, women, and the elderly may be at greater risk for undertreatment of pain. Pain is generally not eliminated, the panel found, despite analgesic therapy administered, according to World Health Organization recommendations, and might continue to be a problem even after the cancer is gone. The number of patients enrolled in methodologically sound trials of cancer pain relief is a small fraction of those receiving care, the panel reported.

Major depression and depressive symptoms are common, although the reported data range widely in calculating incidence and prevalence, the report says. Prevalence rates in the studies varied from 10% to 25% for major depressive disorders; clinically significant depressive symptoms show a similar range. The panel estimates that the rates of major depression in cancer patients could be at least four times greater than the 2.2% estimated point prevalence in the general population.

The prevalence of fatigue, similarly, was difficult to pin down, although the studies showed a range of from 4% in breast cancer patients prior to chemotherapy to 91% in breast cancer patients after surgery and chemotherapy and before bone marrow transplantation. The panel noted that “of significant concern” were the prevalence rates of fatigue in cancer survivors: 26% in Hodgkin’s disease survivors, 35% to 56% in breast cancer survivors, and 48% in a cohort treated for various cancers.

When tracking the prevalence and incidence of symptoms, the panel found that the main problem involved the different criteria used to define the presence of the symptom and its severity. When measuring the prevalence of pain, for instance, the panel found that in 218 trials, 125 distinct tools were used. Similarly, they point out, a wide array of self-assessment instruments have been used to evaluate fatigue.

The panel noted that although a variety of interventions are supported by evidence, numerous obstacles to adequate symptom management include:

- incomplete effectiveness of some treatments
- lack of sufficient knowledge about effective treatment
- patient reluctance to report symptoms to caregivers
- a belief that the symptoms are simply a part of the process and must be tolerated
- inadequate coverage and reimbursement for some treatments

The panel also pointed out that interactions among the three symptoms might mean that a successful treatment for depression also alleviates fatigue but, conversely, adequate pain management might exacerbate fatigue.

The panel’s report concludes that much more research is needed on how to best define and manage cancer-related symptoms. In the meantime, however, the panelists urge clinicians to use brief assessment tools routinely to ask patients about pain, depression, and fatigue and to initiate evidence-based treatments. (Sources: www.nih.gov/news/pr/jul2002/d-17.htm; www.ahrq.gov/clinic/epcsums/csypsum.htm)

**Enalapril Effective for African-American Patients?**

Recent studies have suggested that angiotensin-converting enzyme (ACE) inhibitors do not work as well in African-American patients as in white patients. Researchers from the University of Texas and Loyola University, however, take issue with those findings.

Based on their own retrospective analysis of data from 403 African-American and 3,651 white participants in the Studies of Left Ventricular Dysfunction Prevention Trial, they say that ethnicity does not influence the effectiveness of at least one ACE inhibitor, enalapril.

The researchers were concerned that the publicity surrounding ACE inhibitors and race might dissuade clinicians from using a life-saving drug for their black patients. However, in their study, they found that enalapril worked equally well in both groups, both in reducing the need for medications for heart failure symptoms and reducing the risk of developing heart failure or dying from it.

That’s not to say that blacks are not still at higher risk for symptomatic heart failure than whites. Studies have shown that even after adjusting for differences in severity of symptoms, comorbidities, and socioeconomic factors, blacks have a substantially greater absolute risk for progression from asymptomatic LVD to symptomatic HF, the researchers note. And, despite the comparable relative reduction in risk associated with enalapril in both whites and blacks, the differences in the baseline magnitude of risk was such that blacks randomized to enalapril remained at higher risk than whites randomized to placebo. The differences between black and white patients in the risk of progression of ALVD persisted after the researchers adjusted for potential confounders such as ejection fraction, NYHA class, serum sodium, and etiology of LV dysfunction.

The researchers interpret their findings as suggesting either that residual confounding exists or that there are differences in the natural history of ALVD in blacks and whites.