NEW DRUGS

Trospium for Overactive Bladder

The U.S. Food and Drug Administration (FDA) has approved trospium chloride tablets (Sanctura™, Pliva) for the treatment of overactive bladder. Symptoms include urge urinary incontinence, urgency, and urinary frequency.

As a quaternary ammonium compound, this agent belongs to a class of anticholinergic compounds known as muscarinic receptor antagonists. These compounds relax smooth muscle tissue found in the bladder, thus decreasing bladder contractions. Overactive or unstable detrusor muscle function is believed to be the cause of overactive bladder. Sanctura™ is currently marketed as a prescription drug in Europe.

Patients with urinary or gastric retention, uncontrolled narrow-angle glaucoma, or hypersensitivity to the product should not use it.

Sanctura™ is scheduled to be available for sale in the U.S. in late 2004.


Combo Tablet for Cholesterol

The FDA has approved Vytorin™, a combination tablet of ezetimibe (Zetia®, Schering-Plough), and simvastatin (Zocor®, Merck). The medication combines a cholesterol blocker with a popular statin. It inhibits the production of cholesterol in the liver and blocks the absorption of cholesterol in the intestine, including cholesterol from food.

In a 12-week study, the drug reduced low-density lipoprotein cholesterol by 52% at the recommended starting dose (10/20 mg) and by 60% at the maximum dose (10/80 mg).

The new goals are expected to lead doctors to increase the use of drugs to reduce cholesterol levels when diet and exercise do not achieve the lower numbers. At least 36 million patients are candidates for statins.

Only 50% of patients are still taking cholesterol drugs a year after beginning the regimen, doctors say. A combination tablet might make it easier for patients to remember to take their medications.

A single product would also carry one co-payment and could be less expensive, but whether Vytorin™ will be economical will depend on its price.

For more information about Vytorin™, see the Pharmaceutical-Approval Update on page 507 of this issue of P&T.


SCOPE and Cardiovascular Risk

A post hoc analysis of data from the Study on Cognition and Prognosis in the Elderly (SCOPE) suggests that candesartan cilexetil (Atacand®, AstraZeneca), an angiotensin receptor blocker, significantly reduces major cardiovascular events in the elderly, the cardiovascular mortality rate, and the total mortality rate.

At the annual meeting of the European Society of Hypertension, the researchers said that their reanalysis reflected the original intent of the study—which was to compare candesartan and placebo; for ethical reasons, however, candesartan and other antihypertensive treatments were also compared.

Patients in the three-step trial first received 8 mg of candesartan or placebo. In the second step, they received 16 mg of candesartan or placebo. In the third step, another drug could be added, including open-label antihypertensive treatment.

The researchers compared outcomes among the 1,253 candesartan and 845 placebo patients who did not receive add-on therapy. The final difference in blood pressure reduction was 4.7 mm Hg in the treatment group and 2.6 mm Hg in the placebo group. The relative risk of a major cardiovascular event was 0.68; of cardiovascular mortality, 0.71; and of total mortality, 0.73.

(Source: Heartwire, www.theheart.org.)

Inappropriate antibiotic prescribing for acute respiratory tract infections (ARTIs) has declined in recent years, but some work still needs to be done, particularly in emergency departments (EDs), say researchers from the University of North Carolina. Even though fewer antibiotics were prescribed between 1995 and 2000, the researchers noted that too many were still being prescribed.

Of more than 50 million visits to EDs for ARTIs, 62% of these resulted in a prescription for an antibiotic. There were fewer prescriptions for ARTIs for which antibiotic therapy is nearly always inappropriate, such as nasopharyngitis and acute bronchitis (from 57% to 44%), but the downward trend was observed mostly in urban hospitals. Prescribing patterns remained virtually unchanged in the more rural areas.

Antibiotics were 57% less likely to be prescribed for adult ARTIs of unspecified or multiple sites and 80% less likely for nasopharyngitis, compared with ED visits for bronchitis. Nationally, the likelihood of antibiotic prescribing for children with ARTIs during emergency visits was approximately twice as high when the health providers were staff physicians or nonphysicians with hospital privileges than during visits in which residents or intern physicians were included.

When children with ARTIs arrived in the ED after 10 P.M., antibiotics were 30% more likely to be prescribed.

(Source: Ann Pharmacother 2004;38:928–935.)
MI Risk and Arthritis

At the European Congress of Rheumatology meeting, held June 9–12, 2004, a Stanford University investigator suggested that the cardiovascular risks attributable to rheumatoid arthritis (RA) have been underrecognized. More patients with RA are having heart attacks that necessitate hospital treatment, and in the past 10 years, hospital mortality rates following acute myocardial infarction (AMI) in those patients have not improved at all.

The researchers examined all hospitalized patients with a primary diagnosis of AMI and a secondary diagnosis of RA or diabetes. In 1991, nearly 11% of all patients with diabetes who were admitted for an AMI died. By 2001, the number was 7.7%—a 30% drop. In contrast, the case-fatality rate among patients with RA declined by just 0.03% per year.

The researchers suggest that the marked difference is attributable to the aggressive preventive and therapeutic treatment that diabetic patients now receive. Dealing with RA requires the same emphasis on modifying cardiovascular risk factors, such as improved routine screening for coronary disease. The investigators emphasized that only one third of RA patients were taking low-dose aspirin, despite the evidence that it reduces cardiovascular risk.

Other researchers at the meeting considered disease-modifying antirheumatic drugs (DMARDs) to be the best method of preventing cardiovascular disease in patients with RA. At McGill University in Montreal, one study found a 20% reduction in the risk of AMI. Current use of selective cyclooxygenase (COX-2) inhibitors, however, was associated with a 70% increase in risk.


Lidocaine and Diabetic Neuropathy

For patients with painful diabetic polyneuropathy, treatment is often inadequate and is limited by systemic effects. But the 5% lidocaine patch has been found to significantly improve pain and quality-of-life outcomes, with minimal adverse drug events (ADEs) and no systemic accumulation of the drug.

Researchers from the University of Rochester School of Medicine and Dentistry in Rochester, New York, and from Southern Drug Research in Birmingham, Alabama, tested the lidocaine patch in 56 patients who had painful diabetic neuropathy for at least three months. A patch (or multiple patches—sometimes as many as four per day) was applied daily to the area of worst pain for three weeks for 18 hours at a time. The patches could be cut, and patients decided on the manner of application. No new analgesics or increased doses of prior analgesics were allowed. At one of the three study sites, the patients were treated for an additional five weeks. During this time, the concomitant analgesic therapy was tapered while adequate pain control was maintained.

At the third week, 37 (70%) of 53 patients reported at least 30% less pain; 23 reported a more than 50% reduction, whether or not they had allodynia (pain resulting from a non-noxious source). Sleep quality and other aspects of pain-influenced quality of life also improved.

Among the 28 patients treated for five additional weeks, seven patients tapered their concomitant pain medications, three patients discontinued them, and four patients maintained a reduced dosage.

(Source: Arch Neurol 2004;61:914–918.)

More Risks from HRT

It appears that hormone replacement therapy might be more dangerous than thought for older women with diabetes. Doctors studied 423 postmenopausal women who had atherosclerosis. The women who had abnormal glucose tolerance (diabetes or prediabetes) and who took hormones showed changes in their blood that suggested a higher risk of heart disease. The study was based on an analysis of the results of the Women’s Health Initiative.

In another report from Yale University, doctors said younger women just entering menopause might be at risk for developing heart disease from the treatment.


Escitalopram Not for Children with Depression

The manufacturer of escitalopram (Lexapro™, Forest) has announced that its antidepressant does not help children or adolescents. The announcement came amid the growing controversy over clinical drug tests.

Lexapro™ contains essentially the same active ingredient as another Forest antidepressant, Celexa®, which is widely prescribed for use in children. The company released a second statement to address how it had handled its disclosure of results from two trials of Celexa® in depressed children.

Pharmaceutical companies have been facing growing pressure on the issue of disclosure of drug test results. The American Medical Association has called on the government to create a database in which trials can be tracked from start to finish.

Forest said that it had issued a safety report to the FDA indicating that Lexapro™ did not cause an increase in the test patients’ suicidal thinking. The company is not permitted to promote either Lexapro™ or Celexa® as a treatment for
Depression in young people.

Because Celexa’s patent is about to expire, Forest has been marketing Lexapro™ to treat adult depression. The company intends to discuss with federal regulators its plan to start more pediatric tests of Lexapro™ in hopes of eventually winning approval for such uses.


**Lower Numbers for Pre-Diabetes . . .**

“Pre-diabetes”—a condition that raises a person’s risk for the development of type-2 (non-insulin-dependent) diabetes, heart disease, and stroke—is far more common in the U.S. than previously believed. Approximately 40% of American adults aged 40 to 74 (41 million people) have above-normal blood glucose levels. Pre-diabetes often evolves into type-2 diabetes within 10 years.

The new estimate is based on a more accurate definition of the illness from the American Diabetes Association (ADA).

Pre-diabetes is sometimes called “impaired fasting glucose” (IFG) or “impaired glucose tolerance” (IGT), depending on the test used to diagnose it. Some people have both conditions.

In patients with IFG, blood glucose levels are high (100 to 125 mg/dl) after an overnight fast but not high enough to be classified as diabetes. (IFG was formerly defined as 110 to 125 mg/dl).

In patients with IGT, levels are high (140 to 199 mg/dl) after a two-hour oral glucose tolerance test but are not high enough to be classified as diabetes. (The ADA did not change the definition of IGT.)

Type-2 diabetes is associated with being overweight and with obesity. Losing 5% to 7% of body weight through diet and increased physical activity may help to prevent or delay the progression of pre-diabetes to type-2 diabetes.

Overall, about 18.2 million Americans have diabetes, and about 1.3 million new cases are diagnosed each year. Most of these individuals have type-2 diabetes.

(Sources: Diabetes Care, November 2003; U.S. Department of Health and Human Services, April 30, 2004; www.cdc.gov.)

**. . . And for Cholesterol**

People who have recently had a heart attack are encouraged to reduce their low-density lipoprotein (“bad”) cholesterol (LDL-C) to even lower levels than previously recommended, according to new guidelines.

A target goal of 70 mg/dl is urged for patients who have just had a heart attack or those who already have cardiovascular disease plus diabetes; who are persistent smokers; or who have high blood pressure or other multiple risk factors.

Heart patients in need of drastic measures can use statin drugs in higher doses, or they can combine statins, which block the formation of cholesterol, with drugs that block cholesterol’s uptake by the body. Studies have shown that lives can be saved with a drastic lowering of LDL levels in people who have had recent heart attacks.

- For very-high-risk patients, the new goal is a level of 70 mg/dl; the previous target was 100 mg/dl.
- For almost all high-risk patients with LDL levels over 100 mg/dl, the new guidelines call for drug therapy.
- For moderately high-risk patients with multiple risk factors and a 10% to 20% chance of heart attack or cardiac death within 10 years, drug therapy is indicated if LDL levels are 130 mg/dl or higher, and it is an optional consideration if LDL levels are between 100 and 129 mg/dl.
- For patients at lower to moderate risk, the guidelines are the same; low-risk patients should maintain a level of 160 mg/dl or lower, and moderate-risk patients should stay at 130 mg/dl or lower.

The new recommendations pose a significant challenge for physicians and patients. Most patients will probably not achieve levels below 70 mg/dl with standard doses of statins. The average LDL level in the U.S. is 127 mg/dl.

Although statins are generally considered safe, higher doses can increase the risks of liver problems and muscle pain.

In addition to drug therapy, patients are also encouraged to follow a diet low in saturated fat and cholesterol, to exercise, and to keep their weight under control.

Created by the National Cholesterol Education Program, the guidelines are endorsed by the American Heart Association, the American College of Cardiology, and the National Heart, Lung, and Blood Institute.

Although the guidelines omitted mention of the panelists’ links to some of the drug companies that manufacture the statins, cardiologists expressed no doubts about the quality of research leading to the updated guidelines.


**Expensive, New Blood Thinner No Better Than Heparin?**

A newer blood thinner might not be an improvement over an old standby—heparin—at treating patients having heart attacks or chest pain. Although the newer drug, enoxaparin (Lovenox®, Aventis), is more convenient to use than heparin, it also caused modest increases in bleeding.

Heparin has been used for several decades to treat blood clots in heart patients.
The FDA approved enoxaparin in the late 1990s for use in patients with cardiac disease. It is one of several newer, more potent heparin varieties with a lower molecular weight. Although it costs about $100 a day, several times more than heparin, enoxaparin supporters say that it is ultimately the same in cost or cheaper because it is easier to administer; it can be delivered by injection rather than a continuous intravenous drip, and no blood tests are required to monitor its efficacy.

Investigators at Duke Clinical Research Institute in Durham, North Carolina, and at other institutions conducted two major studies involving nearly 14,000 patients. One study was funded by Aventis. Earlier, smaller studies had favored enoxaparin over heparin. Approximately 30% of heart patients receive enoxaparin.

The larger study, which involved approximately 10,000 patients, found that 14% of those who received enoxaparin died or experienced repeated heart attacks in the 30 days afterward; 14.5% of those who received heparin died or experienced repeated heart attacks. However, patients receiving enoxaparin had more bleeding—usually at the catheter site in the groin—but rarely enough to cause complications.

The smaller study involved almost 4,000 patients who received other drugs commonly given to heart patients. No difference in effectiveness was observed between enoxaparin and heparin.

A third study, also funded by Aventis, analyzed results from six studies, including the two new ones and found that enoxaparin was more effective than heparin. However, other physicians questioned the findings because the analysis included older data from a time when treatment practices were different.


### Following NSAIDs with GI Treatment

Many patients who receive long-term therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) do not receive treatment to prevent the gastrointestinal (GI) side effects of the drugs, say investigators from the PHARMO Institute for Drug Outcomes Studies in Utrecht, The Netherlands.

In their retrospective study of 10,121 patients who used NSAIDs for at least 100 days, the researchers found that only 4,340 (43%) were given gastroprotective treatment. Of the patients who were given such drugs, more than one third (36%) were treated inadequately.

The more risk factors the patients had, the more likely they were to receive preventive treatment—from 24% of patients with no additional risk factors to nearly 80% of those with four or more risk factors. The percentage of patients following a preventive strategy also rose with increasing doses of NSAIDs.

Similarly, the percentage of patients who received adequate GI therapy increased with the number of risk factors. However, more than 50% of all patients with one or more risk factors and nearly 40% of those with four or more risk factors did not receive adequate treatment. Even among patients who had previously been admitted for ulcers, 46% received inadequate preventive treatment or no treatment at all.

(Source: Neurology 2004;62:1552–1557.)

### Alprostadil for Erectile Dysfunction

Sildenafil citrate (Viagra®, Pfizer) is still the front-line treatment for men with erectile dysfunction (ED), but for men who do not respond to it, intraurethral alprostadil (Caverject®, Pfizer) might be a good next choice.

Researchers observed 44 men for up to 15 months. In 10 patients, ED was a result of radical retropubic prostatectomy. Nine patients also had hypertension, seven had diabetes, and eight had both conditions. Six men had drug-induced ED. In all, 13 patients (30%) responded well to intraurethral alprostadil.

Because the study was small, no statistically significant conclusions were able to be drawn. However, five of the 10 men who had undergone earlier radical retropubic prostatectomy reported improved erectile function: two who had received 500 mcg and three who had received 1,000 mcg.

Two patients with ED secondary to nonoperative factors improved with the lowest dose (250 mcg), but none who had undergone radical retropubic prostatectomy responded satisfactorily.

Intraurethral alprostadil acts directly to promote the inflow and retention of blood within the corpora; it does not rely on sexual stimulation or intact penile...
innervation. Because sildenafil and intrarethral alprostadil work differently, they may be complementary treatments for patients who have not responded to one or the other. The researchers cite a study in which 90% of 65 patients experienced satisfactory results with combination therapy after monotherapy had failed.

One drawback of the study is that patients tried sildenafil only five times before the treatment was considered unsuccessful (mainly because of cost). Other reports suggest that at least eight attempts should be made.

(Source: Urology 2004;63:951-954.)

Generic AIDS Drug Patented in Africa

Cipla, Ltd., of India has patented a three-in-one combination tablet, Triomune, to treat acquired immunodeficiency syndrome (AIDS) in South Africa.

Triomune contains copies of three drugs: lamivudine (Epivir®, GlaxoSmithKline), stavudine (Zerit®, Bristol-Myers Squibb), and nevirapine (Viramune®, Boehringer Ingelheim). These agents themselves are still under patent protection. The tablet needs to be taken only twice a day.


South Africa Rejects AIDS Drug for Women

The South African government has rejected a common treatment used to reduce the transmission of the AIDS virus by pregnant women to their babies. Instead, it has recommended a 28-week regimen that combines nevirapine (Viramune®, Boehringer Ingelheim) and zidovudine (Retrovir® AZT, GlaxoSmithKline), a more complex schedule that might reach fewer women.

The researchers cite a study in which 90% of 65 patients experienced satisfactory results with combination therapy after monotherapy had failed.

One drawback of the study is that patients tried sildenafil only five times before the treatment was considered unsuccessful (mainly because of cost). Other reports suggest that at least eight attempts should be made.

(Source: Urology 2004;63:951-954.)

FDA Urged to Bar Psoriasis Drug

A federal panel of dermatologists has asked the FDA to avoid approving Tazoral (Allergan), a medication for treating moderate-to-severe psoriasis because of concerns about birth defects and weakened bones.

The drug's active ingredient, tazarotene, is available as a gel and a cream. The FDA will be considering the panel's vote when it decides whether to allow the tablet form of the drug in the U.S.

(Sources: The Wall Street Journal, July 13, 2004; www.reuters.com.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Powerheart® G3 Fully Automatic Public Access Defibrillator

Manufacturer: Cardiac Science, Inc., Irvine CA

Approval Date: July 2, 2004

Use Classification: This fully automated external defibrillator (AED) is designed for public places, corporate settings, and in-home use by consumers.

Description: A rescuer listens to voice instructions that explain how to attach the device to the heart attack patient. There are no buttons to push, and no additional action is needed. The instrument analyzes the patient’s condition to detect any life-threatening heart rhythms. If warranted, the AED delivers potentially life-saving defibrillation shocks to restore a normal sinus rhythm.

Purpose: The AED is designed for sophisticated users of lifesaving equipment such as hospital personnel, medical professionals, paramedic firefighters, and emergency medical technicians. The device provides health care and rescue professionals with uninterrupted cardiac monitoring ability and decision-making opportunities during the emergency treatment of people experiencing sudden cardiac arrest.

Benefit: The AED can quickly provide a life-saving defibrillation shock to restore normal heart rhythm to patients in cardiac arrest.

Sources: pharmacyonesource.com; www.cardiaccscience.com.

Name: Mammmomat Novation DR

Manufacturer: Siemens Medical Solutions, Erlangen, Germany

Approval Date: July 1, 2004
Use Classification: This system offers digital screening of the breast along with diagnostics and biopsy capabilities.

Description: Digital screening, diagnosis, and stereotactic biopsy capabilities are provided in one system. A flat-panel detector enables a direct conversion of x-ray data to digital information. The detector can provide higher spatial resolution and improved clinical detail.

Purpose: The device offers enhanced breast-imaging technology for women.

Benefit: At 25 x 29 cm, the detector enables imaging of a wider-than-usual range of breast sizes. The system features an acquisition workstation and a dedicated soft-copy reporting workstation that allows ultra-fast loading times. One case with eight images can be loaded in less than one second. The system enables physicians to achieve a utilization rate of nearly 100% in clinical practice.


Name: Leeches (Hirudo medicinalis)
Supplier: RicarimpeX SAS, France
Approval Date: June 28, 2004
Use Classification: Leeches have been used in medicine throughout the world as tools in skin grafts and in reattachment surgery. They help heal the graft by removing pooled blood under the graft, and they help restore blood circulation in blocked veins.

Description: These bloodsucking aquatic animals usually live in fresh water.

Purpose: Under the law, leeches are considered a “medical device,” defined by the FDA as an article intended to diagnose, cure, treat, prevent, or mitigate a disease or condition, or to affect a function or structure of the body, that does not achieve its primary effect through a chemical action and that is not metabolized.

Benefits: By removing pooled blood, leeches help heal skin grafts and restore blood circulation.

Sources: www.pharmacyonesource.com; www.fda.gov.

Name: Triage Profiler Shortness-of-Breath Panel
Manufacturer: Biosite, San Diego CA
Approval Date: June 30, 2004
Use Classification: The panel targets three of the most common causes of shortness of breath: congestive heart failure, pulmonary embolism, and heart attack or silent heart attack.

Description: The device simultaneously measures the concentrations of B-type natriuretic protein, D-dimer, myoglobin, creatine kinase-MB, and cardiac troponin. The breath panel is performed in one step from a whole blood sample using a small disposable diagnostic device and the Triage MeterPlus portable meter.

Purpose: The panel enables the rapid diagnosis and assessment of the severity of heart failure, suspected disseminated intravascular coagulation (including pulmonary embolism), and the risk stratification of patients with acute coronary syndromes in 15 minutes.

Benefit: This portable unit can be used in emergency departments and obviates the need to obtain multiple blood samples or to use one or more laboratory-based analyzers.


Recalled Devices

Paradigm® Quick-set® Plus Infusion Sets
Initial: May 18, 2004: Medtronic MiniMed’s Diabetes Division notified diabetic patients, health care professionals, and distributors that it is recalling these infusion sets because of problems leading to interruption of insulin flow. These problems have caused serious injuries, including hospitalizations. Medtronic recommends that patients monitor their blood glucose levels frequently and be prepared to treat any elevated glucose levels that may occur with injections.

Source: www.fda.gov/oc/po/firm recalls/medtronic05_04.html.

Final: July 8, 2004: Medtronic, Inc., recalled these insulin infusion sets because of problems that can result in an interruption of insulin flow, such as bent cannulas, occlusions in the tubing, leaking at the insertion site, and accidental dislodging of the set during removal of the insertion device. This recall covers all Paradigm® models (MMT-359S6, MMT-359S9, MMT-359L6, and MMT-359L9) and lot numbers. Patients are eligible to receive replacement sets.

Source: www.accessdata.fda.gov/psn/transcript.cfm?show=29#2.

Taxus (Paclitaxel-Eluting) Stents
Initial: July 2, 2004: Boston Scientific Corporation recalled 200 units of its Taxus coronary stent systems because of characteristics in the delivery catheters that have the potential to impede balloon deflation during coronary angioplasty.

Final: July 16, 2004: The company widened its recall to include 85,000 drug-coated stents and another 11,000 bare metal stents. The paclitaxel-eluting and bare metal stent systems share the same delivery catheter. The company received reports of one death and 18 serious injuries associated with the Taxus stents and two deaths and 25 serious injuries associated with the bare metal stents.

The FDA is reviewing the recall to see whether enough is being done to protect consumers.