

# What's new in clinical pharmacology and therapeutics

*Paramjith S. Chawla, MD; Mahendr S. Kochar, MD, MS*

## Abstract

New drugs are being constantly introduced to treat diseases more effectively or with less side effects. Advances in molecular biology and genetics have led to the development of several of these new agents. They tend to have names that are difficult to pronounce, but the trade names are easier to remember. We have described here newer drugs pertaining to several body systems.

## Introduction

Several new drugs have been approved by the US Food and Drug Administration (FDA) in the last few years and are now part of the therapeutic armamentarium; in this article we discuss those that are being used more often. Wherever information is available, we have indicated safety of the drugs in pregnancy. Category A indicates that controlled studies have shown no risk to the fetus. Category B indicates that there are some human or animal studies that demonstrate

no risk to the fetus. Category C indicates that human studies are not available and animal studies are either not available or indicate possible fetal risk. Category D indicates positive evidence of risk to the fetus. Category X indicates that the drug is contraindicated in pregnancy as risks clearly outweigh potential benefits. Only about 40% of drugs currently are assigned a pregnancy classification. Use in pregnancy should be limited to those in category A or B.

Prior to prescribing any of these drugs, physicians should review the package insert for the latest information on adverse actions, drug interactions, and recommended dose.

## Gastrointestinal System

**Aprepitant** (Emend) is the first in a new class of drugs, called "Substance P blockers." It is a new anti-emetic for chemotherapy-induced nausea and vomiting. Substance P is found primarily in the gastrointestinal (GI) and central nervous systems and plays a role in nausea, pain, and mood.<sup>1</sup> It exerts its effects by blocking the NK1 receptors in the brain. It is the only agent for acute (0-24 hours) and delayed (25-120 hours) nausea and vomiting caused by highly emetogenic chemotherapy. It should be combined with a 5-HT<sub>3</sub>-receptor antagonist such as ondansetron (Zofran) and a corticosteroid; it should not be used as monotherapy.

Dosage adjustment is not necessary in the elderly or those with renal impairment or with mild to moderate hepatic insufficiency. Adverse effects include fatigue, dizziness, gastrointestinal complaints, headache, and hiccups. Aprepitant interacts with several drugs because of its metabolism by CYP3A4 system. It can decrease the efficacy of warfarin and oral contraceptives and increase levels of corticosteroids, midazolam, and diltiazem.

**Tegaserod** (Zelnorm) is a new drug for constipation due to Irritable Bowel Syndrome (IBS).<sup>2</sup> It is a 5-HT<sub>4</sub> serotonin partial agonist, which stimulates bowel motility, induces intestinal fluid secretion, and inhibits visceral sensitivity, thereby reducing abdominal pain, bloating, and constipation. IBS is a functional disorder that greatly affects the quality of life, and treatment with tegaserod is mainly symptomatic. It is approved only for use in women as the data for its use in men is still insufficient. It should be taken before meals for 4 to 6 weeks. The most common adverse effects are headache and diarrhea. It should not be used in patients with severe renal insufficiency, moderate to severe hepatic impairment, symptomatic gall bladder disease, suspected sphincter of oddi dysfunction, or abdominal adhesions. It is a category B drug in pregnancy.

**Pantaprazole IV** (Protonix IV) is the first injectable proton-pump

---

Doctor Chawla is a hospitalist with St. Joseph's Regional Medical Center in Milwaukee, Wis. Doctor Kochar is professor of medicine and pharmacology and toxicology and senior associate dean of graduate medical education at the Medical College of Wisconsin. Please direct correspondence to: Mahendr S. Kochar, MD, Medical College of Wisconsin, 8701 Watertown Plank Rd, Milwaukee, WI 53226; phone 414.456.4575; fax 414.456.6528; e-mail kochar@mcw.edu.

inhibitor. It is indicated for short-term treatment of gastroesophageal reflux disease (GERD) and Zollinger-Ellison syndrome in patients who cannot take oral drugs. It binds to the H<sup>+</sup>/K<sup>+</sup> ATPase on the surface of gastric parietal cells, thus inhibiting the last step in gastric acid synthesis, and suppresses acid production for 24 hours.<sup>3</sup> Oral and intravenous formulations of pantaprazole have been shown to be equivalent; no dose adjustment is required when switching between oral and IV forms. It is metabolized in the liver mainly by CYP2C19, 80% is excreted in the urine, and the remainder in feces via biliary secretion. There is no need to adjust the dose in patients with renal insufficiency or in those with mild to moderate liver impairment. The most common adverse effects are abdominal pain, chest discomfort, rash and itching, and injection site reactions. No clinically relevant drug interactions have been reported, but it can decrease the bioavailability of drugs that depend on gastric acidity for absorption, such as ketoconazole and ampicillin. Pantaprazole IV is being used for a variety of purposes, including the treatment of ulcers, post-surgical patients, unconscious patients, the prevention of stress ulcers in intensive care units and for the treatment of upper gastrointestinal bleeding, even though it has not yet been approved by the FDA for these indications. By and large, acid suppressive drugs are overused in hospitalized patients; they should be stopped in patients who no longer need them. The IV form should be switched to oral as soon as the patient is able to tolerate it.

**Adefovir** (Hepsera) is a nucleoside analog originally studied for HIV, but the high doses necessary proved to be nephrotoxic and it was not approved for this indica-

tion. The lower dose used for hepatitis B makes it more tolerable and has been approved for oral treatment of chronic active infection with hepatitis B virus (HBV).<sup>4</sup> Until recently, the mainstays of HBV infection treatment were interferon and lamivudine. Interferon therapy is associated with many adverse effects including flu-like symptoms, leucopenia, and depression, and has to be given subcutaneously. Lamivudine is well tolerated, but the main concern is the development of lamivudine-resistant mutants with continued treatment. Adefovir blocks HBV DNA polymerase, which is involved in the replication of the virus in the body. It is given once daily, with or without meals. The optimal duration of treatment is unknown. It is excreted mainly in urine, so dose should be modified in patients with impaired renal function and those on hemodialysis. Adefovir is active against lamivudine-resistant HBV strains. The main concern with adefovir use is the potential for nephrotoxicity in higher doses; hence it should be used cautiously when it is concomitantly administered with other nephrotoxic drugs. Adefovir has no known drug interactions. Prior to initiating therapy with adefovir, all patients should be offered HIV testing since the use of adefovir in HIV-infected patients may promote emergence of HIV resistance. Lactic acidosis and severe hepatomegaly with steatosis can occur in patients taking adefovir, necessitating its discontinuation.

#### Cardiovascular System

**Nesiritide** (Natrecor) is the first drug in a new class. It is a recombinant form of human B-type natriuretic peptide (BNP), a neurohormone secreted from the cardiac ventricles in response to symptomatic congestive heart failure.

Nesiritide has both arterial and venodilator effects and a diuretic effect by enhancing sodium excretion via suppression of the renin-angiotensin-aldosterone system. It also suppresses sympathetic nervous system. It is indicated for patients with acutely decompensated congestive heart failure (CHF) who have dyspnea at rest or with minimal activity.<sup>5</sup> It is better tolerated than nitroglycerin and causes less tachycardia and arrhythmias than dobutamine<sup>6</sup> but can cause prolonged hypotension, especially in patients receiving ACE inhibitors. Other adverse effects include headache and dizziness. It may cause azotemia in patients with severe CHF whose renal function is dependent on the renin-angiotensin-aldosterone system. It also increases serum creatinine if higher-than-recommended doses are used.

**Eplerenone** (Inspra) is a selective aldosterone receptor antagonist approved for treatment of hypertension<sup>7</sup> and is being studied for use in congestive heart failure. Aldosterone increases blood pressure by inducing sodium and water reabsorption and eplerenone opposes this. It has lower affinity for progesterone and androgen receptors than spironolactone. Eplerenone is metabolized in the liver mainly by CYP3A4 and excreted as inactive metabolites mostly in urine and partly in stool. A major risk associated with eplerenone use is hyperkalemia. Other adverse effects include gynecomastia, impotence, and menstrual disturbances, which are less common than with spironolactone. Drugs that inhibit CYP3A4, such as ketoconazole, erythromycin, or verapamil may increase serum concentration of eplerenone. Patients taking concomitant ACE inhibitors, angiotensin receptor blockers, or nonsteroidal anti-inflammatory drugs are at risk of de-

veloping hyperkalemia and should be monitored closely for it.

**Ezetimibe** (Zetia) is a cholesterol absorption inhibitor. It acts at the brush border of the gut wall to prevent cholesterol absorption through the intestinal villi. It can be used as monotherapy or in combination with a statin. In combination with a statin, it lowers LDL an additional 25%, triglycerides about 10% and slightly increases HDL level.<sup>8,9</sup> It can be taken with or without food and at the same time as the statin. It is safe in patients with mild hepatic impairment, renal insufficiency, and for the elderly. It can cause GI-upset, fatigue, pharyngitis, sinusitis, arthralgia, back pain, and cough. When used with a statin, it causes slightly higher incidence of increase in liver transaminases that are usually asymptomatic and return to baseline with continued therapy or discontinuation of therapy. In pregnancy, it is a category C drug.

### Infectious Diseases

**Drotrecogin alfa** (Xigris) is a recombinant form of human activated protein C. It is the first FDA approved biologic treatment of critically ill adults with severe sepsis that has been shown to improve survival. Until now, the main treatment for severe sepsis was antibiotics. In patients with severe sepsis there is excessive inflammatory response to infection as well as inappropriate coagulation and impaired fibrinolysis.<sup>10</sup> Activated protein C has anti-inflammatory and anticoagulant effects. It also increases fibrinolysis, and in vitro inhibits synthesis of cytokine, tumor necrosis factor (TNF), which has also been implicated in the sepsis syndrome.<sup>11</sup> In patients with severe sepsis, it should be started within 48 hours of organ dysfunction and given as a 96-hour infusion. No dose adjustment is required in the

presence of hepatic or renal impairment. It increases the risk of serious bleeding secondary to its anticoagulant effect. Gastrointestinal and intra-abdominal bleeding is more common and occurs during the infusion; intracranial hemorrhage has also been reported. It is contraindicated in patients with conditions in which bleeding could be associated with a high mortality, such as active internal bleeding, trauma, or recent hemorrhagic stroke. It should be used cautiously in patients with other risk factors for bleeding.

**Cefditoren** (Spectracef) is a new oral third-generation cephalosporin. It inhibits cell wall synthesis and is bactericidal against many gram-positive and gram-negative organisms, including *Streptococcus pyogenes*, *Streptococcus pneumoniae* (penicillin-susceptible strains only), and methicillin-susceptible *Staphylococcus aureus*. It is also active against *Hemophilus influenzae*, *Moraxella catarrhalis*, *Neisseria gonorrhoeae*, and many gram-negative bacilli. It has no activity against methicillin-resistant *Staphylococcus aureus* and *Streptococcus epidermidis*, *Pseudomonas aeruginosa*, enterococcus and many anaerobes or organisms causing atypical pneumonia including legionella, mycoplasma, and chlamydia. It is indicated for acute bacterial exacerbations of chronic bronchitis, pharyngitis, tonsillitis and uncomplicated skin and soft-tissue infections in adults and children 12 years or older. It has not been studied for the prevention of rheumatic fever following *Streptococcus pyogenes* pharyngitis/tonsillitis. It should be taken with meals to enhance absorption. It is well absorbed when taken orally and mainly excreted by the kidneys. One of its metabolites increases the renal excretion of the amino acid carnitine, and therefore can lead to carnitine deficiency, which is mani-

festated as muscle weakness, hypoglycemia, confusion, and fatigue. This may occur only in patients with disorders of fatty acid metabolism associated with carnitine deficiency. Cefditoren is generally well tolerated for short-term use. The most common adverse effects include diarrhea, nausea, and vaginal candidiasis. These are mild and are self-limiting. Cefditoren contains sodium caseinate, a milk protein, hence it should not be given to patients with milk-protein hypersensitivity (not lactose intolerance). Antacids containing magnesium or aluminum or H<sub>2</sub>-receptor antagonists such as ranitidine decrease absorption of cefditoren. Cefditoren has a similar clinical spectrum as other oral cephalosporins such as cefdinir (Omnicef) or cefpodoxime (Vantin).

**Ertapenem** (Invanz), meropenem (Merrem) and imipenem (Primaxin) are new carbapenems. Ertapenem has a more narrow spectrum of activity compared to the other two drugs in the same class, but it differs in dosing and indications. It acts by inhibiting cell wall synthesis. It is indicated for complicated intra-abdominal, urinary tract, skin, soft-tissue and acute pelvic infection, and community-acquired pneumonia. Unlike other carbapenems, it is not indicated for nosocomial infections caused by *Pseudomonas aeruginosa* and acinetobacter. It has little activity against methicillin-resistant staphylococci, enterococcus species, highly-penicillin resistant streptococci, or organisms causing atypical pneumonia. It is excreted mainly by the kidneys; hence dose should be decreased by 50% in patients with a creatinine clearance of less than 30 ml/min. Adverse effects include diarrhea, nausea, vomiting, and infusion-site complications such as phlebitis. Seizures have occurred in 0.5% of patients. Seizure

risk is increased in patients with CNS disorders (brain lesions or history of seizures) and compromised renal function. It was found to have similar efficacy when compared to ceftriaxone in the treatment of community-acquired pneumonia<sup>12</sup> and complicated urinary tract infection including pyelonephritis. There are no clinical studies to demonstrate that ertapenem has activity against penicillin resistant strains of *Streptococcus pneumoniae* and beta lactamase producing *H. influenzae*. For treatment of intra-abdominal, skin and soft-tissue, and pelvic infections, ertapenem has equal efficacy to piperacillin,<sup>13</sup> which is also effective against piperacillin-susceptible *Pseudomonas aeruginosa* and enterococci, an advantage over ertapenem. Ertapenem is unlikely to replace ceftriaxone or piperacillin because of the broader indications of these two drugs. Ertapenem offers better anaerobic coverage than ceftriaxone and requires fewer doses per day than piperacillin and other drugs used to treat infections involving anaerobes. It may be a desirable antibiotic to use in the home treatment of some infections. It offers no advantage over ceftriaxone for treatment of community-acquired pneumonia.

**Enfuvirtide** (Fuzeon) is the first of a new class of medications called "fusion inhibitors." It binds to a portion of transmembrane glycoprotein of HIV that is required for fusion between the viral and cellular membranes and thus prevents entry of HIV-1 into CD4 cells. Other anti-HIV drugs block viral replication after the virus has already entered the cell. Enfuvirtide is approved for use in combination with other anti-HIV agents in patients with advanced disease who continue to have viral replication despite use of antiretroviral therapy.<sup>14</sup> It is given twice daily subcu-

taneously into the upper arm, anterior thigh, or abdomen. It can also be used in children between 6 and 16 years of age. The most significant adverse effects associated with enfuvirtide are injection site reactions and hypersensitivity reactions. Other adverse effects are diarrhea, nausea, and fatigue. It is a pregnancy category B drug. Mothers taking enfuvirtide should not breast-feed their infants since there is a risk for HIV transmission and it is not known whether enfuvirtide is excreted in human milk. Enfuvirtide costs about \$20,000 per year, which may limit its use.

### Rheumatology

**Adalimumab** (Humira) is a TNF-alpha inhibitor similar to infliximab and etanercept. In rheumatoid arthritis patients, elevated levels of TNF are found in the synovial fluid and play an important role in both the pathologic inflammation and joint destruction that are hallmarks of rheumatoid arthritis.<sup>15</sup> Adalimumab is a recombinant human IgG1 monoclonal antibody approved for treatment of moderate to severe rheumatoid arthritis in adults who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs). It can be used alone, or in combination with methotrexate or other DMARDs.<sup>16</sup> It is given every other week subcutaneously by the patient. If the patient is not receiving methotrexate, increasing the frequency to weekly dosing derives additional benefit. The most common adverse reaction with adalimumab is injection site reactions, which are mild. Upper respiratory tract infections, flu-like symptoms, and rash may also occur soon after the injection. The incidence of serious infections has been higher with adalimumab than with placebo. Cases of tuberculosis, frequently disseminated or extrapulmonary,

have occurred, probably as a result of reactivation of latent tuberculosis. Patients should be evaluated for latent tuberculosis with a tuberculin skin test and, if necessary, treated prior to therapy with adalimumab. Invasive fungal infections have also occurred. An increased incidence of lymphoma has been associated with each of the 3 TNF-alfa inhibitors—etanercept, infliximab, and adalimumab. Drug-induced lupus-like syndrome has rarely been reported with adalimumab, and is reversible when the drug is stopped. Live vaccines should not be given concurrently with adalimumab. It is a category B drug in pregnancy.

**Anakinra** (Kineret) is the first in a new class of drugs—an interleukin-1 (IL-1) receptor blocker. It is indicated for patients 18 years or older with moderate to severe rheumatoid arthritis who have not responded to at least one DMARD, such as methotrexate.<sup>17</sup> IL-1 mediates inflammatory and immunological responses and can also affect cartilage degradation. IL-1Ra is an endogenous antagonist which binds to IL-1 receptors and inhibits the pro-inflammatory effects of IL-1. Anakinra is a recombinant form of human IL-1 Ra. It is given by subcutaneous injection once a day. It is mainly excreted in the urine. The most common adverse effect is injection site reactions such as pruritis, rash, erythema, and pain, whereas the most serious adverse reactions are neutropenia and severe infections. It can be used as monotherapy or with another DMARD. It may increase the risk of infection when combined with TNF-blocking drugs. It has been found to be superior when compared with placebo. When added to methotrexate, response rate is improved.<sup>18</sup> It is classified as pregnancy category B drug.

**Teriparatide** (Forteo) is the first

bone-forming drug to be approved for osteoporosis, whereas others like bisphosphonates, raloxifene, and calcitonin prevent bone resorption. It is a recombinant human parathyroid hormone indicated for the treatment of osteoporosis in postmenopausal women<sup>19</sup> and in men with primary or hypogonadal osteoporosis who are at high risk of fracture. When given once daily, it has osteoblastic activity, whereas continuous infusion could lead to osteoclastic activity. It increases bone mineral density of hip and lumbar spine in both men and women.<sup>20</sup> A reduction of fracture risk has been demonstrated in women. The effects of teriparatide on fracture risk in men have not been studied. It is given subcutaneously (SC) once daily for 2 years. Adverse effects are usually mild and include nausea, dizziness, leg cramps, and headaches. Orthostatic hypotension can occur with the first few doses, but resolve within a few hours. Teriparatide can cause mild hypercalcemia and predispose patients to digitalis toxicity. Calcium and vitamin D supplements can be taken at the same time as teriparatide. Animal studies suggest it might increase the risk of osteosarcoma; hence it should not be given to patients who are at an increased risk of osteosarcoma, such as those with Paget's disease of bone, unexplained elevation of serum alkaline phosphatase, prior skeletal radiation, or to children or young adults with open epiphyses. It is not recommended for use in combination with anti-resorptive agents such as calcitonin, alendronate, estrogen, and calcitriol since there have not been sufficient studies on the safety of such combinations.

#### Endocrinology

**Insulin Glargine** (Lantus) is a new long-acting human insulin analog differing from human insulin by 3

amino acids. Unlike neutral protamine Hagedorn (NPH) insulin and ultralente insulin, which cause peaking of insulin levels leading to hypoglycemia, insulin glargine has a peakless action because of formation of microprecipitates in the subcutaneous tissue after injection, which results in its slow absorption providing relatively constant levels for 24 hours.<sup>21</sup> It has been approved for treatment of both type 1 and type 2 diabetes to be administered SC at bedtime for adults and children 6 years of age and older. When switching patients from once-daily NPH or ultralente insulin, the same dose of insulin glargine is used. For patients using twice-daily NPH insulin, the dose of insulin glargine is reduced by 20% and is adjusted based on the patient's response. The starting dose for patients with type 2 diabetes on oral hypoglycemic is 10 units daily adjusted based on the blood glucose level. As is the case with other insulin formulations, hypoglycemia is the most common adverse effect. Injection site pain is more common with insulin glargine than NPH insulin due to its acidic pH, but it is usually mild. Localized lipodystrophy may also occur, but can be minimized by rotation of the injection site. It should not be mixed with any other insulin. To prevent medication administration errors, patients should be counseled that insulin glargine is a "clear" solution, unlike other long-acting insulins such as NPH insulin and ultralente insulin, which are "cloudy." Insulin glargine is an improvement over previously available long-acting insulins since it produces less variable effect on fasting glucose levels, has a peakless action profile, causes less nighttime hypoglycemia, and is conveniently dosed once a day. A combination of basal insulin glargine at bedtime and rapidly acting lispro

insulin (Humalog) with each meal mimics normal physiologic insulin in patients with diabetes.

#### Hematology

**Fondaparinux** (Arixtra) is the first in a new class of synthetic antithrombotic agents. It selectively binds to antithrombin molecules and increases factor Xa inhibition without neutralizing thrombin. It has no effect on platelet function. Heparin and low-molecular weight heparins (LMWHs) bind to antithrombin, which results in inhibition of both thrombin and factor Xa. Fondaparinux has been approved for prophylaxis of deep vein thrombosis (DVT) after hip fracture surgery or knee or hip replacement.<sup>22</sup> It should be given once daily as a subcutaneous injection starting 6 to 8 hours after surgery for a duration of 9 to 11 days. It does not affect prothrombin time, activated partial thromboplastin time, bleeding time, or platelet function, hence PT and PTT are insensitive measures of its activity and are not recommended. The most common adverse effect is bleeding, and the incidence of major bleeding is similar to the incidence with enoxaparin. The risk of major bleeding is greater in elderly patients and in those with severe renal impairment (creatinine clearance <30 ml/min) or in patients weighing <50 kg. Other adverse effects are thrombocytopenia, local injection site reactions, and elevations of serum aminotransferases (AST and ALT). It should not be used in patients with active major bleeding, bacterial endocarditis, thrombocytopenia associated with a positive in vitro test for antiplatelet antibody in the presence of fondaparinux, or in patients with known hypersensitivity to fondaparinux. When compared to enoxaparin, incidence of DVT is less with fondaparinux in patients having surgery for hip fracture. In patients

having major knee surgery, DVT occurred less in patients receiving fondaparinux than enoxaparin, but major non-fatal bleeding was more common with fondaparinux.

### Oncology

**Imatinib** (STI-571; GLEEVEC) is the first of a new class of drugs that specifically targets cancer cells. It is an oral tyrosine kinase inhibitor approved for treatment of all phases of chronic myeloid leukemia (CML).<sup>23</sup> In CML patients, translocation of chromosomes 9 and 22 occurs, which creates a tyrosine kinase fusion gene called Bcr-Abl. This phosphorylates effector proteins and causes cell proliferation. Imatinib inhibits tyrosine kinase and blocks the rapid growth of white blood cells. It is well absorbed after oral administration and highly bound to plasma proteins. It is metabolized in the liver, primarily by CYP3A4 and eliminated mainly in feces. Side effects include nausea, vomiting, diarrhea, edema, muscle cramps, skin rash, and headache. Nausea is less common when the drug is taken with meals and a glass of water. Neutropenia and thrombocytopenia have also been reported, sometimes requiring discontinuation of treatment. Imatinib increases the serum concentration of drugs such as warfarin that are metabolized by CYP3A4. Plasma level of imatinib is increased by drugs that inhibit CYP3A4, such as itraconazole or erythromycin. Phenytoin, which induces this enzyme system, decreases imatinib serum level. In clinical trials, imatinib has been shown to have better response in patients who had previous interferon treatment. Imatinib is also effective in treatment of a rare, gastrointestinal stromal sarcoma (GIST).

### Respiratory System

**Omalizumab** (Xolair) is the first

biologic treatment for moderate-to-severe persistent allergy-related asthma.<sup>24</sup> It is a monoclonal antibody that blocks IgE antibodies that trigger allergic reactions and airway inflammation. It is indicated to treat patients 12 years and older with allergy-related asthma who have inadequate response to inhaled steroids. It decreases the number of asthma exacerbations.<sup>25</sup> It is given subcutaneously every 2 to 4 weeks. In clinical trials, it showed better response rate than placebo in patients with persistent symptoms despite the use of inhaled corticosteroids. The adverse effects include severe allergic reactions and anaphylaxis and also development of a new or recurrent cancer.

### References

1. Lieb K, Treffurth Y, Berger M, et al. Substance P and affective disorders: new treatment opportunities by neurokinin 1 receptor antagonists. *Neuropsychobiology*. 2002;45:52-56.
2. Baker DE. Tegaserod for the treatment of constipation predominant irritable bowel syndrome. *Rev Gastroenterol Disord*. 2001;1(4):187-198.
3. Avner DL. Clinical expression with pantoprazole in gastroesophageal disease. *Clin Ther*. 2000;22:1169-1185.
4. Marcellin P, Chang T-T, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348:808-816.
5. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343:246-253.
6. Silver MA, Horton DP, Ghali JK, Elkayam U. Effect of nesiritide versus dobutamine on short-term outcomes in the treatment of patients with acutely decompensated heart failure. *J Am Coll Cardiol*. 2002;39:798.
7. Flack JM, Oparil S, Pratt JH, et al. Efficacy and tolerability of eplerenone and losartan in hyper-

tensive black and white patients. *J Am Coll Cardiol*. 2003;41(7):1148-1155.

8. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol*. 2002;90:1092.
9. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous hypercholesterolemia. *Am J Cardiol*. 2002;90:1084.
10. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med*. 1999;340:207-214.
11. Bernard GR, Vincent JL, Laterec PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344:699-609.
12. Ortiz-Ruiz G, Cabellero-Lopez J, Friedland IR, et al. A study evaluating the efficacy, safety and tolerability of ertapenem versus ceftiraxone for the treatment of community-acquired pneumonia in adults. *Clin Infect Dis*. 2002;34:1076-1083.
13. Solonskin JS, Choe KA, Christou NV, et al. A prospective randomized, blinded study of ertapenem vs piperacillin/tazobactam for intraabdominal infection. *Surg Infect*. 2001;2(1):68.
14. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infections in North and South America. *N Engl J Med*. 2003;348:2175-2185.
15. Choy EHS, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 2001;344:907-916.
16. Weinblatt MF, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the AR-MADA trial. *Arthritis Rheum*. 2003;48(1):35-45.
17. Bresnihan B, Alvara-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recom-

- binant human IL-1 receptor antagonist. *Arthritis Rheum.* 1998;41:2196.
18. Cohen S, Hurd E, Cush J, et al. Treatment of rheumatoid arthritis with ankinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate. *Arthritis Rheum.* 2002;46(3):614-624.
  19. Delmas PD. Treatment of postmenopausal osteoporosis. *Lancet.* 2002;359:2018-2026.
  20. Neer RM, Arnaud CD, Zanchetta JR et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001;344:1434-1441.
  21. Gillies PS, Figgitt DP, Lamb HM. Insulin glargine. *Drugs.* 2000;59(2):253-260.
  22. Turpie AG, Bauer KA, Eriksson BI, Larsen MR. Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: a randomized double-blind trial. *Lancet.* 2002;359:1721.
  23. Druker BJ, Talpaz M, Resta DJ, et al. Efficacy and safety of a specific inhibition of the BCR-ABL tyrosine kinase in chronic myeloid leukemia. *N Engl J Med.* 2001;344:1031-1037.
  24. Boulet LP, Chapman KR, Cote J, et al. Inhibitory effects of anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med.* 1997;155:1835-1840.
  25. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces the incidence and frequency of exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J.* 2001;18:254-226.

# Wisconsin Medical Journal

The mission of the *Wisconsin Medical Journal* is to provide a vehicle for professional communication and continuing education of Wisconsin physicians.

The *Wisconsin Medical Journal* (ISSN 1098-1861) is the official publication of the Wisconsin Medical Society and is devoted to the interests of the medical profession and health care in Wisconsin. The managing editor is responsible for overseeing the production, business operation and contents of *Wisconsin Medical Journal*. The editorial board, chaired by the medical editor, solicits and peer reviews all scientific articles; it does not screen public health, socioeconomic or organizational articles. Although letters to the editor are reviewed by the medical editor, all signed expressions of opinion belong to the author(s) for which neither the *Wisconsin Medical Journal* nor the Society take responsibility. The *Wisconsin Medical Journal* is indexed in Index Medicus, Hospital Literature Index and Cambridge Scientific Abstracts.

For reprints of this article, contact the *Wisconsin Medical Journal* at 866.442.3800 or e-mail [wmj@wismed.org](mailto:wmj@wismed.org).

© 2004 Wisconsin Medical Society