NEW DRUGS

Menkinist and Tafinlar For Melanoma
Two drugs made by GlaxoSmithKline—dabrafenib (Tafinlar) and trametinib (Menkinist)—have been approved for patients with metastatic or inoperable melanoma. The FDA also approved a companion diagnostic test (THxID, bioMerieux) for both agents to detect certain mutations in the BRAF gene that render melanoma cells susceptible to treatment with the drugs.

The two drugs were approved separately as monotherapies, although compared with dabrafenib alone, they work better when they are used together.

The approval of dabrafenib was based primarily on a trial comparing dacarbazine (DTIC-Dome, Bayer). The pivotal trial for trametinib also involved a chemotherapy regimen as the comparator.

Sources: FDA and MedPage Today, May 29, 2013

Four-Strain Flu Vaccine
The FDA has approved Fluzone Quadrivalent vaccine (Sanofi Pasteur). The four-strain influenza vaccine is licensed for use in children (6 months of age and older), adolescents, and adults.

The 2013–2014 influenza season will be the first in which quadrivalent influenza vaccines will be available in the U.S. Until this year, seasonal influenza vaccines included only one B strain. The quadrivalent vaccine includes two A strains and two B strains.

Influenza B is a common cause of influenza-related morbidity and mortality in children and has been linked to pneumonia and other respiratory illnesses, nervous system disease, muscle pain and inflammation, and other complications.

Each winter the strains for the seasonal influenza vaccines are selected from the influenza strains anticipated to circulate in the Northern Hemisphere during the approaching influenza season. Seasonal influenza vaccines in the U.S. contained only two strains (one strain of type A and one strain of type B) until 1978, when a second type A influenza strain was incorporated to protect against both A strains that were co-circulating.

The vaccine will be available in the U.S. in prefilled syringes and single-dose vials for intramuscular administration.

Source: Sanofi Pasteur, June 10, 2013

Generic Approvals
Candesartan for Cardiac Disease
Sandoz has received the FDA’s approval to sell candesartan cilexetil tablets, the first generic version of AstraZeneca’s Atacand. Candesartan is indicated for the treatment of heart failure in adults with left ventricular systolic dysfunction and for hypertension in adults and children 1 to 17 years of age. The tablets will be available in the same strengths as for Atacand—4 mg, 8 mg, 16 mg, and 32 mg.

Source: Sandoz, May 22, 2013

Trosplium for Overactive Bladder
Perrigo’s generic version of Sanctura XR (Allergan) has been approved. Trosplium chloride extended-release capsules 60 mg are taken once daily for treating symptoms of urge urinary incontinence, urgency, and urinary frequency.


Flunisolide for Allergic Rhinitis
Rising Pharmaceuticals, Inc., a subsidiary of Aceto Corp., has launched the 0.025% strength of flunisolide nasal solution USP, a generic version of Nasalide (Dura/Ivax Res).

Flunisolide is an anti-inflammatory intranasal steroid indicated for the treatment of congestion, sneezing, and runny nose caused by seasonal or perennial allergies in children as young as 6 years of age.

Source: Reuters, June 5, 2013

Levofloxacin for Infections
Claris Lifesciences Ltd., based in India, has announced that the FDA approved levofloxacin injection to treat adults with pneumonia, acute bacterial sinusitis, or complicated urinary tract infections. Levofloxacin is the generic form of Levaquin (PriCara/Janssen).

Source: Reuters, June 7, 2013

Sildenafil for Pulmonary Hypertension
Teva Pharmaceuticals has launched sildenafil tablets, an AB-rated generic bioequivalent to Pfizer’s Revatio Tablets. A phosphodiesterase type-5 (PDE5) inhibitor, Revatio is used to improve exercise ability and delay clinical worsening in patients with pulmonary arterial hypertension. The drugs brings about relaxation of smooth muscle in the pulmonary vasculature. The tablets will be available in a 20-mg strength in 90-count bottles.


NEW INDICATIONS

Revlimid for Mantle-Cell Lymphoma
Celgene’s lenalidomide (Revlimid) is now approved for the treatment of mantle-cell lymphoma that has relapsed or progressed following two regimens. One of the regimens must have included bortezomib (Velcade, Millennium/Takeda). Mantle-cell lymphoma accounts for 6% to 7% of non-Hodgkin’s lymphoma cases.

As the first oral therapy for mantle-cell lymphoma, lenalidomide was previously approved to treat multiple myeloma and myelodysplastic syndromes.

Source: Reuters, June 5, 2013
Xgeva for Giant-Cell Bone Tumors

The FDA has expanded the approved use of denosumab (Xgeva, Amgen) to treat adults and some adolescents with giant-cell tumor of the bone. This tumor does not usually spread to other parts of the body, but normal bone is destroyed as the tumor grows. In rare instances, giant-cell tumors can become cancerous and spread to the lungs.

Denosumab was approved in 2010 to prevent fractures when cancer has spread to the bones.

Source: FDA, June 13, 2013

NEW FORMULATIONS

A Higher Lipase Dose for Creon

Pancrelipase (Creon, AbbVie) delayed-release capsules are now available in a 36,000 lipase-unit dose. This drug is used to treat patients with exocrine pancreatic insufficiency caused by cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions. This new strength is the highest dose of pancreatic enzyme replacement therapy currently available.

Pancrelipase therapy may increase the risk of fibrosing colonopathy, a rare bowel disorder. The capsules should always be taken with food and enough liquid so that they can be swallowed completely.

This product and other pancreatic enzymes are made from the pancreas of pigs, which may carry viruses.


Namenda Extended Release

Memantine HCl (Namenda XR, Forest), a once-daily formulation, is now available in the U.S. The new dose, 28 mg, represents an extended-release formulation of immediate-release memantine. Memantine is approved to treat moderate-to-severe dementia of the Alzheimer’s type.


DRUG NEWS

Court: Natural Human Genes Cannot Be Patented

In June, the U.S. Supreme Court voted 9–0 that genes isolated from the human body (naturally occurring genes) are not patentable, whereas synthetically created genes are patentable. The justices ruled that parts of Myriad Genetics’ patents on genes linked to breast and ovarian cancer improperly covered natural phenomena. Other parts, the Court said, involve enough human intervention to be eligible for legal protection. The Court held that Myriad may patent a type of synthesized DNA that goes beyond extracting the genes from the body.

The company had claimed that isolated DNA has a different physical structure and chemistry than genes within the body. The justices generally agreed that Myriad deserved credit for its process of isolating the gene and its use—but not for the gene itself.

The decision represents a victory for those awaiting more individualized, gene-based approaches. With this ruling, patients should have better access to genetic testing, scientists can engage in research without fear of being sued, and the cost of testing may be less expensive.

Myriad Genetics, based in Utah, stated that its tests are still protected by 24 different patents and that the ruling ensures strong intellectual property protection for its BRACAnalysis test in the future.

The U.S. Patent and Trademark Office has been awarding gene patents since 1982.

Sources: NIH, Bloomberg Business Week, USA Today, June 13, 2013

Orphan Drug Designation Granted for Isavuconazole

The FDA has granted an orphan drug designation to isavuconazole (BAL8557), made by Basilea, for the treatment of invasive aspergillosis, caused by Aspergil-lus molds. This life-threatening infection typically affects patients with impaired or weakened immune systems and is associated with high mortality rates. Invasive aspergillosis occurs in 5% to 13% of bone-marrow transplant recipients, in 5% to 25% of heart/lung transplant recipients, and in 10% to 20% of patients receiving chemotherapy for leukemia.

Isavuconazole (isavuconazonium sulfate) is both an intravenous (IV) and an oral investigational broad-spectrum antifungal agent. The IV formulation is water-soluble and does not contain solubilizers, which can damage the kidneys.

Source: Basilea, May 28, 2013

Relaxing Restrictions on Avandia

An FDA advisory panel has voted to modify safety restrictions on the controversial diabetes drug rosiglitazone (Avandia, GlaxoSmithKline).

Researchers first raised concerns about links to heart attacks in 2007. In 2010, the FDA limited access to the drug and regulators in Europe banned it. Rosiglitazone is dispensed only by specialty pharmacies, and patients understand the drug’s risks before they can get a prescription.

Thirteen of the panel’s 26 members voted to modify the safety restrictions, seven voted to remove them, and five voted to keep them without any changes. One panelist voted to withdraw rosiglitazone from the market entirely.

The panel reassessed the RECORD trial (Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes), released in 2009. The panel’s vote is only a recommendation.

Sources: Reuters and Associated Press, June 6, 2013

Drug Shortages

Isoniazid for Tuberculosis

An unexpected shortage of the tuber-
The isoniazid shortage has already lasted months longer than predicted. In a survey, 69% of TB-control programs were trying to change suppliers; 72% were distributing isoniazid only to high-risk patients; 68% were delaying treatment of latent disease; and 88% reported using alternatives.

TB is usually treated with four drugs over a 6- to 9-month period: isoniazid, rifampin (Rifadin, Sanofi), pyrazinamide, and ethambutol (Myambutol, Stat-Trade/Pantheon). However, isoniazid is also recommended for preventing active TB in people with a latent infection.

Teva, VersaPharm, and Sandoz have been supplying isoniazid in the U.S. In January, VersaPharm said it would not be producing isoniazid until 2014. The companies reported a shortage of the 300-mg tablets in November 2012. The supply of 100-mg tablets, which the CDC had suggested as a work-around, also became limited. The CDC also noted a shortage of two combination formulations of isoniazid and rifampin, VersaPharm’s IsonaRif and Sanofi’s Rifamate. Shortages of other drugs have also hampered control of multidrug-resistant TB.


Importing TPN Drugs

The FDA plans to permit injectable drugs used in total parenteral nutrition (TPN) to be imported into the U.S.

TPN contains several drugs that have been in short supply, including trace elements, potassium phosphate, and sodium phosphate. Hospitals rely on TPN, an IV solution used primarily to nourish premature infants, cancer patients, and individuals undergoing gastrointestinal surgery.

The FDA is allowing Fresenius Kabi USA, LLC, based in Lake Zurich, Ill., to import trace elements and phosphate injection from its Norway plant.

The shortages are largely the result of a decision made by American Regent/Luitpold to temporarily shut down at the end of 2012. The company ceased operations in order to address quality problems, including particulate matter in its injectable products. The FDA is working with the company to prioritize the most critical drugs in shortage as it restarts production.

The decision to import the drugs is temporary and applies only to this critical shortage. Other manufacturers of TPN components, including Hospira, Inc., are also working to increase supplies of these essential drugs.

Since 2010, the FDA has exercised its regulatory discretion to import 14 drugs. With the addition of these injectables, the total will be 17.

Source: FDA, May 29, 2013

Restricting Doxycycline

Because of a continuing shortage of doxycycline, this drug should be used only when there is no alternative treatment, the Centers for Disease Control and Prevention (CDC) advises. Manufacturing problems and an increased demand have resulted in drug shortages of some formulations of doxycycline, including doxycycline hyclate capsules (e.g., Doxyx, Warner Chilcott) and doxycycline monohydrate capsules (Adoxa, Pharmab-Derm/Fougera), since January 18. The drug is available from most companies, but clinicians may need to find new contacts to order supplies.

The IV formulation of doxycycline hyclate and the oral suspension doxycycline calcium have not been affected by the shortage. The CDC recommended that health care professionals limit use of the short-supply drugs to the treatment of rickettsial infections, Lyme disease prophylaxis following a tick bite, and prophylaxis and treatment of malaria.

Alternative treatments exist for sexually transmitted diseases and Lyme disease and providers should use their judgment in deciding which agent to use.

In rickettsial infections, such as Rocky Mountain spotted fever and anaplasmosis, patients of all ages should receive doxycycline to prevent severe illness and death. Chloramphenicol should be used as an alternative only if a patient has a specific, life-threatening contraindication to doxycycline.

Although no other drugs are effective in preventing Lyme disease, alternatives may include amoxicillin (e.g., Amoxil, GlaxoSmithKline) and cefuroxime axetil (Ceftin, GlaxoSmithKline).

Several drugs that are effective prophylactics can be found on the CDC’s Web site.

Health care professionals should ensure that they have access to doxycycline for the listed indications, and planning is essential to ensure that treatment is not delayed.

Sources: MedPage Today, June 14, 2013; www.cdc.gov

Recalls

Injectable Methotrexate

In May, Sandoz voluntarily recalled two lots of its methotrexate sodium injectable product following the discovery of particulate matter in the vials. Parenteral injection of the drug from the affected lots (25 mg/mL in 40-mL vials) has the potential to lead to microembolization in areas where the particles lodge. It was considered unlikely that symptoms would
arise from these microemboli. Sandoz had not received any reports of related adverse events.

The recalled lot numbers, which were sold to hospitals in the U.S. and Poland, are CL0996 (expiration date, December 2013) and CJ4948 (expiration date, May 2013).


Fast-Track Status for Antibiotic In Gram-Negative Infections

On May 7, 2013, the FDA granted a fast-track designation to Cubist’s phase 3 antibiotic CXA-201 (cefotolozane/tazobactam) for patients with hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and complicated urinary tract infections caused by gram-negative bacteria. An effective broad-spectrum therapeutic for drug-resistant gram-negative bacterial infections remains a critical unmet need.

This development represents a victory for the controversial Generating Antibiotics Incentives Now (GAIN) Act, which has been criticized for not providing enough financial incentives to entice well-established drug developers back into research and development of antibiotics. Prior to this FDA designation, beneficiaries of the GAIN Act included mostly smaller biotech companies that lack marketed products, such as omadacycline (Paratek), dalbavancin (Durata), and TR-701 (Trius).

The current standard of care for gram-negative infections includes broad-spectrum beta-lactams and carbapenems (which have low barriers to resistance) and polymyxin E (Colistin), which promotes nephrotoxicity.

With CXA-201, Cubist hopes to circumvent resistance and concerns about toxicity with a fixed-dose, combination therapy approach.

Source: GlobalData, May 21, 2013

Another Infection Outbreak Tied to Compounding Pharmacy

After receiving corticosteroid injections from a Tennessee compounding pharmacy, seven patients fell ill. The FDA said it was working with the Centers for Disease Control and Prevention (CDC) and authorities in Tennessee to investigate the adverse events, linked to methylprednisolone acetate compounded by Main Street Family Pharmacy in Newbern.

At least one of the infections appeared to be fungal in nature.

As a precaution, the FDA recommended that any products labeled as sterile from Main Street be quarantined until further guidance could be provided.


Deaths Linked to Long-Acting Zyprexa Relprevv

Two patients died 3 to 4 days after receiving injections of long-acting olanzapine pamoate (Zyprexa Relprevv, Eli Lilly). The FDA has not determined whether the drug caused the fatalities.

Both patients received intramuscular injections of the drug at appropriate doses, but tests showed very high olanzapine blood levels after death. High doses are known to induce delirium, cardiopulmonary arrest, cardiac arrhythmias, and impaired consciousness ranging from sedation to coma.

The long-acting form of olanzapine was approved with a Risk Evaluation and Mitigation Strategy (REMS) that requires patients to remain in the clinic for a 3-hour monitoring period and to be escorted home afterward. The requirement was added because some patients in clinical trials became delirious or lost consciousness shortly after receiving injections.

Post-injection delirium-sedation syndrome was traced to an unexpectedly rapid release of olanzapine into circulation, leading to very high blood levels of the drug. However, all those cases occurred within hours of injection, not days, and no deaths were attributed to the syndrome, the FDA said.

Olanzapine pamoate is approved for injection every 2 to 4 weeks for treating patients with schizophrenia. It is one of several long-acting formulations of the second-generation antipsychotic drugs

With CXA-201, Cubist hopes to circumvent resistance and concerns about toxicity with a fixed-dose, combination therapy approach.

Source: GlobalData, May 21, 2013

Label Change: Limiting Magnesium in Preterm Labor

The FDA has advised clinicians not to give pregnant women magnesium sulfate to prevent preterm labor for more than 5 to 7 days because it may harm developing bones in the fetus. Longer off-label administration of magnesium for tocolysis, which is approved only for the prevention of seizures in pre-eclampsia, can lead to low calcium levels and osteopenia or fractures in the offspring.

A warning is being added to the drug’s labeling, and the teratogenicity category is being changed from Pregnancy Category A to D. The labeling will state that injectable magnesium sulfate is not indicated to prevent preterm labor and that it should be given only by trained clinicians in well-equipped hospitals.

currently available. The syndrome has not been seen with those other products.

Source: MedPage Today, June 18, 2013

**Disparities in Adherence**

Compared with Caucasian men, women and African-American patients with cardiovascular disease have higher mortality rates and are less likely to undergo cardiovascular procedures such as cardiac catheterization after acute myocardial infarction (MI). Perhaps not coincidentally, they also have very different patterns of adherence. African-Americans are 67% more likely to stop statin therapy, and women have a 10% lower odds of adhering to antihypertensive and lipid-lowering therapy.

Even though these differences are probably significant, little attention has been paid to the problem, say researchers from Brigham and Women’s Hospital and Harvard Medical School, Columbia University, and University of Toronto. The teams reviewed 53 studies involving nearly 3 million patients, focusing on the relationship between race, sex, and statin adherence.

Follow-up evaluation ranged from 3 months to more than 5 years. Average adherence in all studies was 48%. Crude rates of nonadherence were higher among women (53%) than among men (50%). When the rates were pooled for all studies, women were 10% more likely to be nonadherent. The risk persisted even with adjustments for race and socioeconomic status.

Non-Caucasians had crude rates of nonadherence of 50% compared with 45% among Caucasians. When the rates were pooled across studies, non-Caucasians were 53% more likely to be nonadherent. This held true in the five studies that adjusted for socioeconomic status, insurance status, and copayment amounts. Yet non-Caucasians were 67% less adherent than Caucasians in studies published before 2008, compared with a rate of 22% in studies published later.

The fact that the differences persisted despite the level of insurance and income is an argument against the idea that the lower-quality care received by women and non-Caucasian patients is a reflection of their socioeconomic status. The researchers suggested that women and ethnic minorities might be more likely to experience adverse effects from statins. The misconception that women have a lower risk for cardiovascular disease means that clinicians and the women themselves do not put the same priority on prevention. Finally, women are often caregivers, who as a group often have lower rates of adherence.

The reasons behind the low adherence rates for non-Caucasians are more complex. These patients are less likely to have a consistent relationship with a primary care provider and may be more likely to receive care from health care facilities that provide lower-quality care. Those factors may affect patients’ attitudes toward adherence, such as mistrust of health care systems.

Patient education, medication reminders, and reinforcement can help patients follow their regimens. Increasing diversity in clinical training may also boost the chances of a cultural match between patients and their health care team.

Source: Am Heart J 2013;165:665, e1–678.e1

**Namenda Plus Aricept Improves Cognition**

Combining memantine (Namenda, Forest) with the cholinesterase inhibitor (CI) donepezil (Aricept, Eisai/Pfizer) appears to improve cognition, function, behavior, and global outcomes better than the CI alone for patients with moderate-to-severe Alzheimer’s disease (AD). These benefits also appear to accumulate over time.

Researchers from Canada and Spain reviewed studies comparing memantine with donepezil, rivastigmine (Exelon, Novartis), or galantamine (Reminyl, Janssen). Their research supports the theory that more persistent drug exposure to symptomatic drugs for AD is associated with a slower rate of decline. When treatments are combined, the positive effects of memantine and a CI appeared to be sustained and even increased over time in patients with later-stage disease. It was not clear whether those findings were a result of a disease-modifying effect or a variation in sustained symptomatic effects.

Detailed post hoc analyses have helped to define the benefits that combination treatment offers, such as promoting independence through positive effects on language, memory, and activities of daily living; delaying the emergence of agitation and aggression; and reducing overall care dependency. The positive effects might also mean delayed admissions to nursing homes.

The therapy was well tolerated. Based on the data, therefore, the authors recommend that patients with mild AD should start treatment with CIs, adding memantine upon entering the moderate stage, or later, when the response to CIs declines. The authors suggest that combination therapy can be initiated when patients are first seen with moderate-stage AD, although one of the treatments should be started and the dose titrated first. The choice of treatment should depend on the personal and clinical characteristics of each patient.

Source: Alzheimer Dementia 2013;9:326–331

**Lyrica Lessens Neuropathic Pain**

Pregabalin (Lyrica, Pfizer) relieves pain and improves function and quality of life for patients with chronic pain caused by diabetic peripheral neuropathy (DPN)
or postherpetic neuralgia (PHN), yet few studies have looked at why pain relief and better quality of life go together. It might be that pregabalin has a direct independent effect on patient function and quality of life, or the improvements might be an indirect consequence of pain relief.

Researchers from Eastern Virginia Medical School in Norfolk reviewed data from 11 randomized, double-blind studies of pregabalin in 2,656 patients. The primary efficacy measure in each study was the mean pain score on an 11-point numeric scale, derived from patient pain diaries. Each study also used the 36-item Short Form Health Survey (SF-36), which covers general health, vitality, and social functioning; the Patient Global Impression of Change (PGI–C); and the Daily Sleep Interference Scale (DSIS).

Pregabalin had beneficial effects on patient quality of life, social functioning, emotional status, mental health, bodily pain, vitality, and general health. PGI–C scores also showed quality of life much or very much improved, compared with placebo. Patients in all pregabalin arms also reported improved sleep and less pain, often marked by a decrease in pain of 30% or more from baseline scores.

Pregabalin patients who achieved at least moderate pain relief had higher scores in the SF-36 domains; for all SF-36 domains, scores increased as mean pain scores decreased. Patients who felt less pain with pregabalin also had higher PGI–C scores. Patients who obtained the most pain relief reported the greatest improvement in SF-36 domain scores, which were often comparable to those of the general population.

Source: Clin Ther 2013;35:612–623

**Avodart and BPH Prevention**

Although the 5α-reductase inhibitor dutasteride (Avodart, GlaxoSmithKline) reduces urinary tract symptoms in men with benign prostatic hyperplasia (BPH), it is not clear whether men with minimal symptoms should take this drug as a preventive treatment.

Researchers from University of Toronto conducted the first study to explore the benefits of dutasteride in this group. Their post hoc analysis of the 4-year double-blind Reduction by Dutasteride of Prostate Cancer Events (REDUCE) study examined data from 792 men taking dutasteride and 825 taking placebo.

BPH progressed in 167 patients (21%) taking dutasteride and in 297 (36%) receiving placebo. Dutasteride therapy significantly reduced clinical progression of BPH over a period of 4 years, with a relative risk reduction of more than 50%.

Treating asymptomatic patients is not an uncommon approach in medicine, and preventing urinary symptoms can have a dramatic effect. Although acute urinary retention is not as serious as cardiovascular disease (which is treated preventively), its 10-year cumulative risk is estimated to be twice that of stroke or myocardial infarction (MI). Acute urinary retention also has a substantial impact on quality of life.

The tradeoffs, however, include adverse effects. In this study, adverse effects were erectile dysfunction (9% with dutasteride vs. 5% for placebo) and lower or absent libido (7% vs. 2% for placebo). Acknowledging that some men might not be receptive to preventive treatment, the authors say that the magnitude of risk reduction seen in their study nonetheless warrants further evaluation of patient preferences for choosing optimal management.

Source: BMJ 2013;346

**Forteo Protects Against Drug-Induced Osteoporosis**

Studies of medication-induced osteoporosis in men have been limited. In a study from Germany, teriparatide injection (Forteo, Eli Lilly) significantly increased lumbar spine bone mineral density (BMD), compared with risendronate (Actonel, Warner Chilcott), in men with osteoporosis who received excessive amounts of glucocorticoids. These steroid hormones are used to treat inflammatory, autoimmune, and allergic disorders.

Conventional computed tomography (CT) and high-resolution quantitative CT were used to measure BMD. According to Eli Lilly, quantitative CT is superior to conventional dual X-ray absorptiometry (DXA) in discriminating between patients with or without prevalent vertebral fractures and in identifying patients with glucocorticoid-induced osteoporosis who are at highest risk for fracture.

Secondary outcomes with teriparatide included better vertebral strength, higher bone volume, and fewer clinical fractures.

Sources: J Bone Mineral Res 2013; (6):1355–1368; Eli Lilly; May 29, 2013

**NSAIDs May Raise Heart Risk In Patients With Arthritis**

Patients with rheumatoid arthritis (RA) and other inflammatory musculoskeletal diseases are often treated with nonsteroidal anti-inflammatory drugs (NSAIDs).

A study presented in June at a meeting of the European League Against Rheumatism (EULAR) in Madrid, Spain, involved 108 patients in Dublin who received NSAIDs during a 2-month period in 2012; 16% received these drugs for RA or other inflammatory arthropathies, even though patients with arthritis are already at an elevated risk for cardiovascular disease.

Some discussants said it would be preferable to use disease-modifying anti-inflammatory drugs before prescribing NSAIDs. Although these agents are often prescribed in primary care to treat inflammation and pain, their long-term use has been found to be unsafe. The short-term use of NSAIDs has been considered safer for the heart.
New Drugs

However, a Danish study found that the use of diclofenac (e.g., Cataflam, Voltaren, Novartis) was associated with an increased risk of death or recurrent myocardial infarction (MI) in patients with a previous MI within only 1 week of treatment, and ibuprofen was linked to an increased risk after 1 week.

Of the 108 patients who received NSAIDs over the 2-month study period (age range, 50–87 years), 36% of them had documented ischemic heart disease or risk factors such as diabetes or hypertension.

Diclofenac was prescribed for more than 1 month in 56% of the patients and for 1 year or longer in 15%.

In 25% of the patients, the drugs were given for non-inflammatory conditions such as postoperative pain and fibromyalgia, when an alternative, such as acetaminophen, could have been prescribed.

For patients with inflammatory arthropathies such as RA, another reason for avoiding NSAIDs is that these drugs should not be used with methotrexate, which is often prescribed for this disease.

For some patients with inflammatory arthropathies who are not at particular risk for ischemic heart disease, NSAIDs might be safe.

The researchers recommended that emphasis should be on controlling inflammation, which underlies both RA and heart disease and that even the short-term use of NSAIDs should be elaborated. Diclofenac should also be avoided as the NSAID of choice.

Sources: European League Against Rheumatism, 2013; Abstract OP203-PC; MedPage Today, June 15, 2013

Botulinum Toxin Helps Control Blepharospasm

Patients with blepharospasm, an involuntary closure of the eyelid caused by spasms of the ocular muscles, have been able to obtain relief with injections of botulinum toxin. When blepharospasm was secondary to Parkinson’s disease (PD) patients appeared to achieve greater relief with the product than patients with primary blepharospasm.

Findings from Tel Aviv University were reported at the International Conference of Parkinson’s Disease and Movement Disorders.

The blink rate decreased from 30 to 21.86, largely driven by a reduction in blink rate among those with PD who did not undergo deep brain stimulation. Most of the patients appeared to have improved in their condition on the Clinician Global Impression of Change outcome measure.

The researchers acknowledge that larger studies will be needed to assess the effect of botulinum toxin A on PD patients compared with other patients with blepharospasm.

The researchers stratified patients by type of blepharospasm, identifying 10 participants with primary disease; six with blepharospasm secondary to PD; six with PD who had received deep brain stimulation, and six with other types of blepharospasm. The patients had been living with blepharospasm for an average of 7.7 years before undergoing treatment at the clinic.

Blepharospasm occurs frequently in older individuals and in patients with PD and in those with dystonia. The disorder can arise from both the disease and from therapies for the disease.

Sources: Movement Disorders Society, 2013; MedPage Today, June 17, 2013

Stopping Breast Cancer With Bazedoxifene

A drug approved in Europe to treat osteoporosis has been shown to stop the growth of breast cancer cells, even in cancers that have become resistant to targeted therapies. Findings from a study from the Duke Cancer Institute in Durham, North Carolina, were presented at the annual Endocrine Society meeting in San Francisco in June.

Bazedoxifene not only prevents estrogen from fueling breast cancer cell growth; it also flags the estrogen receptor for destruction. It is already approved in Europe under the trade name Conbriza.

In animal and cell-culture studies, the drug inhibited growth both in estrogen-dependent breast cancer cells and in cells that had developed resistance to the antiestrogen drug tamoxifen and to the aromatase inhibitors, two widely used classes of drugs to prevent and treat estrogen-dependent breast cancer. If breast cancer cells develop resistance to these agents, patients must usually be treated with toxic chemotherapy agents that have significant side effects.

Bazedoxifene, like tamoxifen, is a specific estrogen receptor modulator (SERM). Drugs in this class have estrogenic effects in some tissues, such as bone, while blocking estrogen action in other tissues. Unlike tamoxifen, bazedoxifene has some properties of a newer group of drugs, known as selective estrogen receptor degraders (SERDs).

In December 2012, Pfizer and Ligand announced that the FDA accepted for review their New Drug Application (NDA) for bazedoxifene/conjugated estrogens for treating vasomotor symptoms and vulvar and vaginal atrophy associated with menopause, as well as for preventing postmenopausal osteoporosis in women who have not had a hysterectomy. The combination was studied in a phase 3 clinical development program called Selective estrogens, Menopause And Response to Therapy [SMART].

Because bazedoxifene has already undergone safety and efficacy studies as a therapy for osteoporosis, it may be a viable option for patients with advanced breast cancer whose tumors have become resistant to other treatments.

In clinical trials, the most commonly continued on page 385
Statins Found Effective in Children With Type-1 Diabetes

In a small randomized study, statin therapy has been found to be effective and safe in children and teenagers with type-1 diabetes and high levels of low-density lipoprotein-cholesterol (LDL-C).

The study took place at Nemours Children’s Clinic in Jacksonville, Fla., and findings were reported at the Endocrine Society’s June meeting in San Francisco.

Average non–high-density lipoprotein-cholesterol (non–HDL-C) levels dropped from about 250 to 180 mg/L after 6 months of treatment with atorvastatin (Lipitor, Pfizer) but increased slightly in the patients receiving placebo. The medication also helped to reduce levels of various atherogenic lipoprotein subparticles.

Treatment was well tolerated. Rates of adverse events were similar in the two groups, and few musculoskeletal problems were reported.

Cardiovascular disease can begin to develop during childhood in patients with type-1 diabetes, and it becomes clinically evident earlier in life compared with the general population. Despite improved survival and fewer long-term complications in these patients, rates of cardiovascular disease are growing.

The American Diabetes Association recommends screening for dyslipidemia in children with diabetes starting at age 10 if there is no family history of cardiovascular disease and at age 2 if there is a history.

Diet and lifestyle interventions are the first options for lowering cholesterol levels. Drug treatment can be considered if LDL-C levels remain above 160 mg/dL (or above 130 mg/dL in patients with at least one cardiovascular risk factor). These recommendations are based on expert consensus and are not supported by evidence from randomized trials.

The current trial examined the efficacy and safety of statins in patients 10 to 18 years of age (mean age, 15). The patients had type-1 diabetes more than a year before enrolling in the study. Glycosylated hemoglobin (HbA1c) levels were below 10%, and the children were on stable insulin therapy with no other medications.

Body mass index was below the 95th percentile, and LDL-C levels exceeded 100 mg/dL.

Initially, 89 patients were enrolled. All patients received a nutritional intervention for 3 months that was aimed at lowering the consumption of dietary cholesterol and saturated fat. After 3 months, 42 patients with LDL-C levels greater than 100 mg/dL were randomly assigned to receive atorvastatin or placebo.

Although most characteristics were well matched at baseline, patients in the placebo group had a significantly higher HbA1c (9.1% vs. 7.9%, respectively) and a lower insulin sensitivity score (7.2 vs. 8.8, respectively).

Within the first 3 months of treatment, HbA1c values increased in the atorvastatin group, but by 6 months, there was no difference between the two groups.

Treatment with atorvastatin significantly decreased levels of lipoproteins, including small and medium very-low-density-lipoprotein-cholesterol (VLDL-C), LDL-L1, and apo-lipoprotein B. The concentrations of the various lipoproteins measured were not correlated with glycemic variables.

There were 39 adverse events in the placebo group and 23 in the atorvastatin group. Only one serious adverse event occurred and was unrelated to treatment.

Sources: Endocrine Society meeting, Abstract OR11-2; MedPage Today, June 17, 2013

New Hypertension Guidelines Published

Several significant changes to hypertension treatment are being recommended by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC). The 2013 guidelines were announced June 14 at the ESH congress in Milan, Italy.

The 2013 guidelines, which replace the 2007 edition, illustrate how much the hypertension landscape has changed. Lifestyle changes are primary in preventing hypertension, such as reducing sodium intake to about half the present levels, moderating alcohol consumption, maintaining a healthy weight, exercising regularly, ensuring an adequate intake of fruits and vegetables, and eliminating smoking.

The guidelines highlight the lack of awareness of the potential problems of hypertension among patients, with poor long-term adherence to treatment. The “inertia” of doctors is also problematic when they don’t take appropriate action when confronted with patients with uncontrolled blood pressure.

Despite the evidence that hypertension is a major cardiovascular risk, studies show that many are still unaware of the condition and blood pressure levels goals are seldom achieved.

A major development is the decision to recommend a single systolic blood pressure target of 140 mm Hg for almost all patients. This is in contrast with the 2007 version of the guidelines, which recommended a 140/90 mm Hg target for moderate-risk to low-risk patients and a 130/80 mm Hg target for high-risk patients.

Other changes include an increasing role for home blood pressure monitoring with ambulatory blood pressure monitoring; more emphasis on assessing a person’s risk factors for cardiovascular and other diseases (e.g., organ damage,
Diet May Affect Brain Proteins In Alzheimer’s Disease

In a small trial of 47 participants, a low-fat, low-carbohydrate dietary intake altered levels of lipid-depleted beta-amyloid peptides, suggesting a biochemical explanation for risk factors related to Alzheimer’s disease (AD). The Mediterranean diet, for instance, is associated with a lower incidence of the disorder.

The study was conducted at Wake Forest University.

Participants assigned to a low-fat, low-carbohydrate diet for 4 weeks showed a 0.34-log decline in lipid-depleted, 42-mer beta-amyloid (AB42) in the cerebrospinal fluid (CSF). Those eating foods high in fat and with a high glycemic index had a 0.5-log increase. The decreases in lipid-depleted beta-amyloid levels in participants on the low-fat, low-carbohydrate diet were associated with healthy increased levels of insulin in the CSF. Insulin resistance and diabetes are risk factors for AD.

In the current study, 20 cognitively normal older individuals and 27 participants with mild cognitive impairment were enrolled (mean ages, 69 and 67 years, respectively.) The diets were designed to provide equal total caloric content and adequate overall macronutrient amounts.

CSF samples were taken at baseline and after the 4-week intervention. Levels of total and lipid-depleted apolipoprotein E (apoE) and AB40 and AB42 peptides, as well as insulin, were measured.

The study did not address whether the biochemical changes would lead to decreased plaque burden, less brain atrophy, or improved cognition. Nevertheless, dietary changes can affect amyloid chemistry in the brain, possibly a step toward solving the causes of AD.

Limitations to the study included its small size and short duration. It was also unclear whether fat or carbohydrate was primarily responsible for the effects seen.

Source: JAMA Neurol, June 2013 (online); MedPage Today, June 17, 2013

Insulin Resistance May Increase When Breakfast Is Skipped

In a study reported from the University of Colorado at Aurora, on days when women did not eat breakfast, there were greater spikes in insulin and glucose levels after lunch compared with levels noted on the days when the women had only water in the morning. Findings were reported at the Endocrine Society’s meeting in June.

Not eating breakfast was also associated with higher levels of free fatty acids before lunch because lipolysis was occurring. The researchers suggested that insulin resistance over time may predispose to further metabolic derangements and, possibly, progression to type-2 diabetes. Longitudinal studies have identified a relationship between skipping breakfast and increased weight gain and a risk of type-2 diabetes.

Many people eat only one or two meals a day and then snack. Sometimes people do that in a effort to eat less, but they end up with a dysfunctional use of fuel that causes them to gain more weight and develop more insulin resistance.

From 10% to 20% of the population skips breakfast. This practice is associated with increased body mass index (BMI) in both adolescents and adults.

Some short-term studies have looked at the metabolic effects of skipping breakfast and have noted impaired insulin sensitivity, no change or an increase in energy intake, increased hunger, decreased satiety, and worse lipid profiles.

The current crossover study enrolled 10 women, ages 25 to 40 (mean 29), who had a BMI of 27 to 35 kg/m² (mean 31.4). Eight of the women regularly ate breakfast, and two regularly skipped the meal.

The study took place on two separate days, 1 month apart, during the follicular phase of the women’s menstrual cycles. The women were told to not exercise the day before each assessment. The night before each study day, the women were given a standardized dinner of 15% protein, 30% fat, and 55% carbohydrates providing 35% of the total daily energy requirements.

On the morning of the first study day, the women were assigned to either eat a standardized breakfast or to drink only a glass of water. On the second study day, the women did the opposite.

Four hours after eating breakfast or drinking the water, the participants were given a standardized lunch providing 35% of daily energy requirements.

Pre-lunch insulin levels were similar in both the breakfast and no-breakfast groups, but insulin levels were elevated after lunch in women who did not eat breakfast that day.

One potential limitation of the study was the use of a healthy breakfast with a mix of protein, fat, and carbohydrates. This does not reflect a typical American breakfast, which often consists of mostly carbohydrates.

Sources: Endocrine Society meeting, Abstract OR09-2; MedPage Today, June 17, 2013
radiofrequency identification (RFID) technology to enhance blood safety by preventing the release of unsuitable blood components in blood banks.

A small memory-storage chip is placed on the item being tracked. The iTrace application is designed to augment existing blood bank systems and to work with bar-code identification and labeling processes already in place.

Source: FDA, May 28, 2013

**New Silicone Gel-Filled Breast Implant**

The MemoryShape Breast Implant has been approved for use in women at least 22 years of age who wish to augment breast size and in women of any age who wish to undergo breast reconstruction. The implants are made by Mentor Worldwide LLC.

The silicone gel contains more cross-linking compared with the gel used in Mentor’s previously approved implant; the result is a firmer gel. The FDA’s approval was based on 6 years of data showing reasonable assurance of safety and effectiveness for this implant.

Women should understand that the implants might not be permanent and that they will need to undergo monitoring over the long term.

The company is required to conduct a series of post-approval studies.

With the new approval, there are now five FDA-approved silicone gel-filled breast implant products available in the U.S., manufactured by three companies: Allergan, Mentor, and Sientra.

Source: FDA, June 14, 2013

**NEW MEDICAL DEVICES**

**Marvin M. Goldenberg, PhD, RPh, MS**

**Name:** Sedasys Computer-Assisted Personalized Sedation System

**Manufacturer:** Ethicon Endo-Surgery, Inc., Cincinnati, Ohio

**Approval Date:** May 3, 2013

**Purpose:** The Sedasys system delivers propofol (Diprivan, AstraZeneca) via an intravenous (IV) infusion for patients 18 years of age and older who need minimal-to-moderate sedation during colonoscopy and upper endoscopy procedures.

**Description:** The four-piece system can detect signs associated with oversedation and can automatically modify or stop an infusion. A bedside monitoring unit is designed to stay with the patient before, during, and after the procedure.

A procedure room unit provides additional monitoring and contains the propofol infusion pump controller.

**Benefit:** Comprehensive patient monitoring is provided, and the depth of sedation can be adjusted. The device is restricted for use by specially trained staff.

In one study that included 1,000 patients, the system was associated with less hypoxia, shorter recovery times, and better physician and patient satisfaction compared with the current standard of care for sedation, which involves a benzodiazepine and an opioid.

**Precautions:** The system should not be used in patients with hypersensitivity to fentanyl or to 1% propofol injectable emulsion or its components; in those with allergies to egg or soy products; in pregnant or lactating women; or in individuals with a full stomach.

**Sources:** www.ethicon.com; www.fda.gov

**New Dahabia Intracardiac Defibrillators (ICDs)**

**Name:** Viva CRT-D and Evera CD

**Manufacturer:** Medtronic, Inc., Minneapolis, Minn.

**Approval Date:** May 6, 2013

**Purpose:** The two devices are used to improve heart rhythm in patients experiencing heart failure or arrhythmias.

**Description:** The Viva portfolio of cardiac resynchronization therapy with defibrillation (CRT-D) devices and the Evera portfolio of implantable cardioverter-defibrillators (ICDs) are designed to adapt to preserve normal heart rhythms. The AdaptivCRT algorithm can distinguish dangerous from harmless rhythmic abnormalities.

**Benefit:** The countour-shaped devices enhance patient comfort and reduce skin pressure by 30%. The battery is long-lasting and is equipped with shock-reduction technology. It is anticipated that insurance companies and hospitals will experience lower overall health care costs, compared with CRT-D devices with traditional programming.

**Sources:** www.medtronic.com; www.cxvascular.com

**Name:** Cobas Integra 800 Tina-Quant HbA1c Dx Assay

**Manufacturer:** Roche Laboratories, Basel, Switzerland

**Approval Date:** May 23, 2013

**Purpose:** The Tina-quant assay, a laboratory-based test, is used to diagnose diabetes and to monitor blood glucose control.

**Description:** This is the first assay to be marketed as a diagnostic tool for diabetes. Current tests for glycosylated hemoglobin (HbA1c) have been approved only for monitoring glucose control, not to diagnose the disease. The new test measures the percentage of HbA1c that is bound to glucose and reports a patient’s average glucose level over a 3-month period. Analyzing 141 blood samples, investigators found a difference of less than 6% in the accuracy of assay results compared with results from the standard reference for hemoglobin analysis.

**Benefit:** Approximately 25.8 million people in the U.S. have diabetes, including 7 million people who do not know that they have the disease. The Cobas assay should prove valuable for identifying undiagnosed cases of diabetes before problems (e.g., ocular problems, heart disease, stroke) develop.
Precaution: HbA\textsubscript{1c} tests, including the new assay, should not be used to diagnose diabetes during pregnancy or to monitor diabetes in patients with hemoglobinopathy; hereditary spherocytosis; malignancies; or severe, chronic hepatic or renal disease. The device should also not be used to diagnose or monitor diabetes in patients with the hemoglobin variant hemoglobin F.

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

Recall

Cook Medical’s Zilver PTX paclitaxel-eluting stent for peripheral artery disease (PAD) has been recalled because of a defect in the delivery system. Initiated in late April, the Class I recall covers all lots of the product distributed from December 13, 2012, to April 16, 2013.

An internal component of the delivery catheter caused a few devices to separate during implantation, affecting 0.043% of placements. One patient died, and another patient experienced an adverse event. The stent itself is safe, according to the company, and patients who have already received the implant are not affected by the recall.

The Zilver PTX became the first FDA-approved drug-eluting stent for treating PAD in the U.S. in December 2012. The early-stage recall will probably delay Cook’s plans to launch additional sizes of Zilver PTX.

In cases of breakage of the inner catheter, surgery might be needed to remove the catheter tip. Other adverse events may include vascular occlusion, thrombosis, amputation, cardiac arrest, and death.

Bare-metal stents are not included in the recall. Customers who bought the stent during the period covered by the recall should quarantine remaining inventory and return the devices to the company for credit.

Sources: www.medpagetoday.com; www.fda.gov; www.healio.com