NEW DRUGS

Fetzima for Major Depression

The FDA has approved levomilnacipran extended-release capsules (Fetzima, Forest/Pierre Fabre), a serotonin-norepinephrine reuptake inhibitor (SNRI), for adults with major depressive disorder (MDD).

Forest and Cypress also manufacture milnacipran (Savella), which is indicated for the relief of fibromyalgia. Milnacipran is not indicated for depression, and levomilnacipran is not indicated for fibromyalgia.

For more information about levomilnacipran, please see the Pharmaceutical Approval Update column on page 523 in this month’s issue of P&T.

Source: Forest Laboratories, July 26, 2013

Injectafer For Iron-Deficiency Anemia

Ferric carboxymaltose injection (Injectafer, Luitpold/American Regent) has been approved for the treatment of iron-deficiency anemia in adults who cannot tolerate or have not responded well to oral iron as well as in adults with non–dialysis-dependent chronic kidney disease.

This is the first high-dose, non-dextran IV iron indicated for a broad patient population.

Approximately 7.5 million people in the U.S. have iron-deficiency anemia. Current therapies are limited to treating the condition in patients with chronic kidney disease, those who require infusions over the course of several hours, or those who need multiple dosing sessions.

A single dose of up to 750 mg of ferric carboxymaltose can be administered undiluted as an IV push injection at a rate of 100 mg/minute, or it may be given as an IV infusion in up to 250 mL of 0.9% sodium chloride injection over the course of at least 15 minutes.

Source: Luitpold, July 25, 2013

Tivicay for Resistant HIV Infection

A long-awaited new drug for HIV infection, Tivicay (dolutegravir, ViiV/GlaxoSmithKline), has been approved for adults and, in some cases, children. The drug is a welcome addition for patients who have developed resistance to two or more classes of antiretroviral drugs.

This integrase inhibitor is indicated for use in combination with other antiretroviral agents. Integrase inhibitors block HIV replication at a crucial stage by preventing the viral DNA from integrating into the genetic material of T cells.

The approval was based on data from four pivotal phase 3 clinical trials involving 2,557 adults and children 12 years of age and older. Participants were randomly assigned to receive dolutegravir or raltegravir (Isentress, Merck), each in combination with other antiretroviral drugs, or Atripla (Bristol-Myers Squibb/Gilead), a fixed-dose combination of efavirenz, emtricitabine and tenofovir.

The regimens containing dolutegravir reduced viral loads. In SPRING-2, a study evaluating the once-daily study drug and twice-daily raltegravir in 822 HIV-infected, treatment-naive patients, 88% of dolutegravir-treated patients achieved virological suppression (HIV-1 RNA below 50 c/mL) by week 48, compared with 86% of raltegravir-treated patients. And in SINGLE, a study evaluating once-daily dolutegravir plus abacavir/lamivudine versus once-daily Atripla in 833 treatment-naive patients, the proportion of patients who achieved virological suppression at 48 weeks were 88% for dolutegravir and 81% for Atripla, a statistically significant difference.

In a third study, SAILING, dolutegravir was compared with twice-daily raltegravir in 719 patients whose current therapy was not working but who had not been treated with an integrase inhibitor. Both groups were on regimens that contained up to two agents, including at least one fully active agent. At week 24, 79% of the patients receiving dolutegravir achieved virological suppression compared with 70% of those receiving the regimen containing raltegravir—again, a statistically significant difference.

In VIKING-3, twice-daily dolutegravir was added to the regimen for 183 adults with HIV resistance to multiple classes of HIV drugs, including the integrase inhibitors raltegravir, elvitegravir, or both. After 7 days of treatment, mean HIV/RNA levels declined by 1.4 log10 c/mL. At week 24, 63% of patients achieved virological suppression, although integrase strand transfer inhibitor resistance impeded virological response in some patients.

A 24-week multicenter trial established the pharmacokinetics, safety, and activity of dolutegravir for children age 12 and older, weighing at least 88 pounds, who had not previously taken integrase inhibitors.

Dolutegravir can be taken with or without food, at any time of day. It has been hailed as a “clean” drug, with a low side-effect profile and few drug–drug interactions. Tolerability was similar to that of raltegravir and better than that of Atripla. When used in first-line therapy, it compared favorably to efavirenz (Sustiva, Bristol-Myers Squibb), with fewer discontinuations due to adverse effects. Commonly reported adverse events were insomnia and headache. Serious side effects included hypersensitivity reactions and abnormal liver function in patients co-infected with hepatitis B and/or C.

This is the second FDA-approved integrase strand transfer inhibitor. Raltegravir (Isentress) was approved in 2007. Elvitegravir is used only in combination with three other drugs (cobicistat, emtricitabine, and tenofovir disoproxil fumarate) as Strivil (Gilead).

Sources: FDA and GlaxoSmithKline/ViiV, August 13, 2013
Generic Approvals
Lamotrigine Orally Disintegrating Tablets

Actavis, Inc., has received approval from the FDA for its Abbreviated New Drug Application (ANDA) for lamotrigine orally disintegrating tablets (ODT), 25 mg, 50 mg, 100 mg, and 200 mg. This generic product is equivalent to GlaxoSmithKline’s Lamictal ODT. Lamotrigine is indicated for the treatment of epilepsy and bipolar disorder.

Source: Actavis, July 15, 2013

 Donepezil Tablets, 23 mg

Dr. Reddy's Laboratories has launched donepezil HCl tablets, 23 mg, in the U.S. This generic product is equivalent to Aricept (Eisai/Pfizer) 23 mg. Donepezil is used as a therapy for Alzheimer’s disease. The Dr. Reddy product is available in bottle count sizes of 30 and 90.

Source: Business Wire, July 28, 2013

Fluticasone Propionate Solution
Perrigo Co. has received final approval for its ANDA for fluticasone propionate lotion, 0.05%, the generic equivalent of Cutivate Lotion 0.05%. This medication is indicated for the relief of inflammation and pruritus associated with atopic dermatitis in patients 1 year of age or older.

Sources: Perrigo and RTT News.com, July 31, 2013

Zoledronic Acid Injection
The FDA has approved Sagent Pharmaceuticals’ zoledronic acid injection 4 mg/dL. This is the generic form of the bisphosphonate Zometa (Novartis). The product is in a ready-to-use premix IV bag, designed to reduce medication errors. This medication is a complement to a vial product that Sagent launched in March.

In conjunction with standard antineoplastic therapy, zoledronic acid is indicated for patients with hypercalcemia of malignancy, multiple myeloma, and bone metastases and for men with prostate cancer that has progressed after at least one hormonal therapy has been tried.

Source: Sagent, August 5, 2013

Acamprosate Delayed-Release Tablets
Glenmark has received the FDA’s approval to sell a generic version of Campral Delayed-Release Tablets (Forest) in the U.S. This medication is used for alcohol abstinence.

Source: Silobreaker, August 12, 2013

Temozolomide Capsules
Sandoz, a subsidiary of Novartis, has launched temozolomide capsules in the U.S. in strengths of 5 mg, 20 mg, 100 mg, 140 mg, and 180 mg. This alkylating agent is used to treat glioblastoma multiforme and refractory anaplastic astrocytoma. Temodar (Merck/Schering) is a brand name for temozolomide.

Source: Sandoz, August 13, 2013

NEW INDICATIONS
Vaccines for Younger Patients
Menveo for Protection Against Meningococcal Disease

Novartis has announced the FDA’s approval of meningococcal group A, C, W-135, and Y conjugate vaccine (Menveo) for the prevention of meningococcal disease caused by four strains of the bacterium Neisseria meningitidis in infants and toddlers from 2 months of age.

This quadrivalent conjugate vaccine has been available for use in adolescents and adults (11 to 55 years of age) since February 2010 and in children (2 to 10 years of age) since January 2011.

Source: Novartis, August 1, 2013

FluLaval Quadrivalent
GlaxoSmithKline’s FluLaval Quadrivalent is now approved for the active immunization of individuals 3 years of age and older to help prevent disease caused by seasonal influenza (flu) virus subtypes A and B contained in the vaccine. This is the company’s second FDA-approved intramuscular quadrivalent influenza vaccine. Fluarix Quadrivalent was the first intramuscular influenza vaccine approved by the FDA in December 2012, and it is now being shipped to customers.

FluLaval was originally approved for individuals 18 years of age and older.

Source: PharmaLive and GlaxoSmithKline, August 16, 2013

NEW FORMULATIONS
Astagraf XL for Prevention of Kidney Rejection

Tacrolimus extended-release (ER) capsules (Astagraf XL, Astellas) have been approved to prevent organ rejection in patients receiving a kidney transplant with mycophenolate mofetil (CellCept, Genentech) and corticosteroids, with or without the induction of basiliximab (Simulect, Novartis).

This is the first once-daily oral formula-
tion of tacrolimus available in the U.S. for these patients. Tacrolimus ER capsules have been approved in 73 countries.

This product should not be used with cyclosporine (Neoral and Sandimmune, Novartis; Gengraf, AbbVie). It is not known whether tacrolimus is safe to use with sirolimus (Rapamune, Pfizer) in kidney transplant recipients or in children younger than 16 years of age who have had kidney transplants.

Previously known as fujimycin, tacrolimus is an immunosuppressant that was first approved by the FDA in 1994 for use in liver transplantation.

Source: Astellas, July 19, 2013

Simponi Aria Infusion for Rheumatoid Arthritis

Golimumab (Simponi Aria, Janssen) has been approved as an intravenous (IV) infusion in combination with methotrexate for adults with moderately to severely active rheumatoid arthritis (RA). The approval was supported by findings from a phase 3 trial, GO-FURTHER (Golimumab, an Anti-TNF-alpha Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy).

Golimumab, as Simponi, was previously approved as a subcutaneous injection for RA, psoriatic arthritis, and ankylosing spondylitis. In May 2013, golimumab received a new indication for ulcerative colitis. Simponi Aria is discussed in the Pharmaceutical Approval Update column on page 522.

Sources: Janssen, July 18, 2013; Drugs.com

Liquid Enalapril (Epaned) For Hypertension In Children and Adults

Enalapril maleate powder for oral solution (Epaned, Silvergate) has been approved to treat hypertension in adults and in children as young as 1 month old.

Enalapril is an angiotensin-converting enzyme (ACE) inhibitor.

Before this approval, children had to rely on an adjusted adult dose. Patients with swallowing difficulties may respond well to the liquid formulation.

Children with high blood pressure tend to have other medical problems, such as obesity, high lipid levels, and/or diabetes mellitus.

Source: PipelineReview.com, August 14, 2013

DRUG NEWS

Label Changes

New Limits for Oral Ketoconazole

Oral ketoconazole (Nizoral, PriCara/Janssen) should never be used as first-line therapy for fungal infections because of the risk of liver toxicity, adrenal gland insufficiency, and adverse interactions with other drugs. The label and a new medication guide are being revised to emphasize the risks. The restrictions do not apply to topical versions.

The indications for dermatophyte and Candida infections have been removed, and the indications for blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidiomycosis are retained only if patients have not tolerated or responded to other antifungal agents.

In Europe, regulators recommended that oral ketoconazole be pulled from the markets entirely. Gynecomastia in men and menstrual irregularities in women have been observed with high doses.

Sources: FDA, July 26, 2013; Clinical Advisor, July 30, 2013

Acetaminophen and Serious Skin Reactions

Pain medications containing acetaminophen (e.g., Tylenol) have caused rare but potentially deadly rashes and blistering of the skin, the FDA has warned. Two of the conditions, Stevens–Johnson syndrome and toxic epidermal necrolysis (TEN), can be fatal. They typically begin with flu-like symptoms, followed by rash, blistering, and detachment of the upper skin surface.

Another condition, acute generalized exanthematous pustulosis, is not usually life-threatening. It is characterized by the sudden appearance of red skin containing dozens or hundreds of small blisters filled with white or yellow fluid.

Ibuprofen (e.g., Advil) and naproxen (e.g., Aleve) are also used to treat fever and pain and may cause serious skin conditions, but this risk is already described in the warning section of those drug labels.

The FDA is requiring companies that sell prescription and over-the-counter acetaminophen to add a warning about continued on page 510
the risk of rash to the prescribing information.

Sources: FDA and Reuters, August 1, 2013

Enhanced Warning: Nerve Damage From Fluoroquinolones

The FDA is requiring drug labels and medication guides for all fluoroquinolone antibacterial drugs to be updated to address the serious side effect of peripheral neuropathy. Nerve damage potentially caused by fluoroquinolones may occur soon after these drugs are taken, and the effects may be permanent. The problem appears to be unrelated to the duration of therapy or to the patient’s age.

The risk occurs only with oral or injected fluoroquinolones such as levofloxacin (Levaquin, PriCara/Janssen), ciprofloxacin (Cipro, Bayer), moxifloxacin (Avelox, Bayer/Merck), norfloxacin (Noroxin, Merck), ofloxacin (Floxin), and gemifloxacin (Factive, Cornerstone).

Topical formulations that are applied to the ears or eyes are not known to be associated with this risk.

The risk of neuropathy was added to the labels of systemic fluoroquinolone drugs in 2004 and was also mentioned in patient medication guides. The FDA has continued to receive reports of the problem even after the adverse reaction was added to the drug labels. The agency is strengthening the warning because the potential rapid onset and risk of permanence were not adequately described.

Peripheral neuropathy is a nerve disorder occurring in the arms or legs. Symptoms include pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain, or temperature, or in the sense of body position.

The adverse event can occur at any time during treatment with fluoroquinolones and can last for months to years after the drug is discontinued.

Source: FDA, August 15, 2013

Fast-Track Status
ELND005 in Alzheimer’s Disease

Transition Therapeutics Inc. has announced the FDA’s approval of a fast-track designation for ELND005. This oral medication is intended for the treatment of neuropsychiatric symptoms in patients with mild-to-moderate Alzheimer’s disease (AD). ELND005 is being evaluated in a 12-week clinical trial.

Sources: PharmaPhorum and Transition Therapeutics, July 18, 2013

AYX1, an Injectable for Pain

A fast-track designation has been granted to AYX1 Injection, made by Adnyxx, for the prevention of chronic pain. In September 2012, the company completed a dose-escalating study of AYX1 in 30 healthy volunteers. The medication was well tolerated at all dose levels, with no serious adverse events reported. No subjects withdrew from the study.

The company is currently enrolling 90 patients in a placebo-controlled phase 2 study to evaluate AYX1, given as a single administration before unilateral total knee arthroplasty to reduce or prevent postsurgical pain.

Source: Adnyxx, July 17, 2013

Orphan Drug Status
LJPC-0712 for Niemann–Pick Disease

La Jolla Pharmaceutical Company has received an orphan drug designation for LJPC-0712 (allo-pregnanolone), for use in patients with Niemann–Pick type C (NP-C) disease. This rare hereditary disease is caused by mutations in either the NPC1 gene (in 95% of cases) or the NPC2 gene. These mutations lead to the accumulation of cholesterol and glycosphingolipids in the brain and other tissues.

Disease onset is typically during childhood, but adults are increasingly being affected by late-onset neurological symptoms or psychiatric manifestations. In general, younger patients experience more rapid disease progression and do not live as long as those who acquire the condition later in life. The estimated median survival is less than 20 years.

Reduced levels of allo-pregnanolone, which is present in the blood and brain, may contribute to the neurological deterioration associated with this disease. Replacement therapy with this neurosteroid represents a potential treatment.


CGTG-102 for Sarcoma

The FDA has granted an orphan drug designation for CGTG-102 (Oncos Therapeutics, Ltd.), a granulocyte–macrophage colony stimulating factor-coding oncolytic adenovirus for the treatment of soft-tissue sarcoma. A phase 1 study is expected to be completed this year, and phase 2 studies are scheduled to start in 2014.

Source: GlobalData, July 31, 2013

Captisol-Enabled Topiramate Injection

Captisol-enabled topiramate injection (Ligand Pharmaceuticals) has been designated as an orphan drug for the treatment of partial-onset or primary generalized tonic–clonic seizures in hospitalized epilepsy patients who are unable to take oral topiramate.

Captisol is a chemically modified cycloextrin with a structure designed to optimize the solubility and stability of drugs. This technology has also enabled the introduction of carfilzomib (Kyprolis, Onyx) for multiple myeloma, injectable amiodarone (Nexeterone, Baxter), and voriconazole injection (Viend, Pfizer).

More than 30 Captisol-enabled products are in development.

Source: Ligand, July 26, 2013

AGT-182 in MPS-II, a Brain Disease

One problem in targeting brain-based...
disorders (such as Alzheimer’s and Parkinson’s disease) is the blood–brain barrier. Only very small molecules can pass through this barrier, which protects the brain from infection. A biotechnology company, ArmaGen, has learned how to get large drugs like antibodies into the brain without damaging the sensitive barrier and without surgery.

AGT-182 targets mucopolysaccharidosis type-II (Hunter syndrome, MPS-II). This rare liposomal storage disease is caused by a deficient or absent enzyme, iduronate-2-sulfatase. This life-threatening disease can affect children as young as 2 years of age.

Clinical trials of AGT-182 are expected to begin within the next 2 years.

Source: Medical Daily, July 19, 2013

Defactinib for Mesothelioma

Verastem’s defactinib (VS-6063), a cancer stem-cell inhibitor, has received an orphan drug designation for mesothelioma, a rare, aggressive form of lung cancer with limited treatment options.

The company is conducting a double-blind, placebo-controlled trial, with an expected enrollment of approximately 350 to 400 patients at sites in 11 countries.

The FDA has granted an orphan drug designation to Eisai’s investigational compound (E7777) for cutaneous T-cell lymphoma (CTCL). E7777 is designed with an improved purity profile and manufacturing process. It is currently in a pivotal trial. CTCL is a rare type of cancer that begins in the white blood cells and attacks the skin.

Sources: GlobalData and ASCO Post, August 8, 2013

Vaccine for Anal Cancer

Advaxis, Inc., has received an orphan drug designation for ADXS-HPV for the treatment of human papillomavirus (HPV)–associated anal cancer. This IV product is under development for the treatment of HPV-induced cervical dysplasia, cervical cancer, cervical intraepithelial neoplasia, oropharyngeal carcinoma, anal cancer, and head and neck cancers.

Formerly known as Lovaxin C vaccine, this live attenuated vaccine is based on a platform that uses modified Listeria monocytogenes to deliver a tumor-specific antigen fusion protein.

Source: GlobalData, August 15, 2013

Compounding Company Recalls Products

Specialty Compounding, LLC, in Cedar Park, Texas, voluntarily recalled all products produced and distributed for sterile use after reports of bacterial bloodstream infections possibly caused by its calcium gluconate infusions.

Facilities, health care professionals, and patients who received the products since May 9, 2013, should immediately stop using them and should return them to the company.

The recall applies to all sterile drugs that have not reached their expiration dates, including all strengths and dosage forms. The affected products were distributed directly to patients in all states (except North Carolina) and to hospitals and physicians’ offices in Texas.

Two patients in Texas had received a 2-g infusion of the company’s calcium gluconate in sodium chloride 0.9% for injection. The patients had bacterial bloodstream infections caused by Rhodococcus equi, thought to be related to the infusions. Cultures from an intact sample of calcium gluconate, compounded by the company, showed the growth of bacteria consistent with Rhodococcus species.

Source: FDA, August 11, 2013; updated August 15, 2013

Improving Adherence to Blood Pressure Regimens

In a study reported from Canada, patients with mild hypertension improved blood pressure control when they were able to minimize their out-of-pocket drug costs and when they visited one health care provider.

When patients had a routine place of care and consulted with the same physician, their hypertension awareness, treatment, and BP control improved. It was suggested that routine brings familiarity and comfort, which can enhance communication between doctor and patient.

Patients who had insurance coverage had better awareness and BP control and better adherence to their antihypertensive regimen.


Avandia Now Seen as Safe?

In a post hoc analysis of data from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial (BARI 2D), the controversial diabetes drug rosiglitazone (Avandia, GlaxoSmithKline) was not associated with an increased risk of major cardiovascular events or mortality in diabetic patients with coronary artery disease. Patients taking rosiglitazone had an equal likelihood of dying over a period of 5 years as those who did not take any drug in the thiazolidinedione (TZD) class. Rosiglitazone also appeared to lower the risk of a composite of death, myocardial infarction (MI), and stroke. The study was conducted at Washington University in St. Louis, Missouri.

A few months ago, an FDA advisory panel had recommended that the agency loosen restrictions on prescribing rosiglitazone, which were set in place in 2010 after several studies noted an increased risk of MI with use of the drug.

A re-evaluation of GlaxoSmithKline’s
Cancer Linked to a Lower Risk Of Alzheimer’s Disease

Preliminary research suggests that patients with cancer might have lower rates of Alzheimer’s disease (AD); chemotherapy appears to lower the risk.

In an observational study of more than 80,000 veterans with AD observed for a mean period of 5.65 years, most types of cancer were associated with a reduced risk of AD.

AD was also less common in veterans with a history of cancer than in those without. The results were presented at the Alzheimer’s Association International Conference (AAIC) in Boston.

Researchers analyzed the health records of 3.5 million veterans, 65 years of age and older, who were seen in the Veterans Affairs health care system between 1996 and 2011. Participants did not have dementia at baseline.

Among veterans with a cancer history, chemotherapy (but not radiation) reduced the risk of AD by 20% to 45%. Liver cancer reduced the risk of AD by 51%, pancreatic cancer by 44%, esophageal cancer by 33%, myeloma by 26%, lung cancer by 25%, and leukemia by 23%.

Melanoma, prostate cancer, and colorectal cancer did not confer a reduced risk of AD; these diseases were associated with an increased risk.

The authors suggested that cancer and AD cells behave so similarly that some people have called AD a cancer of the brain. Cells in patients with AD try to divide, acting much like cancer cells, and chemotherapy may prevent them from dividing. More study is needed before any therapeutic implications can be drawn.

Sources: Circulation, July 15, 2013; online; MedPage Today, July 22, 2013

ACE Inhibitors Might Delay Cognitive Decline

There could be an early cognitive benefit for dementia patients who begin taking angiotensin-converting enzyme (ACE) inhibitors for blood pressure (BP) control.

In an observational study conducted in Ireland, patients taking ACE inhibitors experienced slightly slower rates of cognitive decline compared with those not taking these drugs. Further, the brainpower of patients who were recently prescribed ACE inhibitors improved during the 6-month study, compared with those already taking these drugs and with those not taking them at all.

This is the first time that evidence has suggested that BP-lowering drugs not only might halt cognitive decline but might also improve brainpower. The improvement might be related to patients’ better adherence to their regimen or to a by-product of better BP control or better blood flow to the brain.

An earlier study also suggested that angiotensin receptor blockers (ARBs) might also have protective benefits against Alzheimer’s disease (AD).

For the newer study, conducted between 1999 and 2010, the average age of the 361 participants was 77 years. The patients were nearly equally divided between women and men. A total of 85 patients were already taking ACE inhibitors; the rest were not.

A strength of the study was the inclusion of different dementia types: AD, vascular, and mixed. However, limitations included the observational design, a lack of compliance data, and missing Standardized Mini-Mental State Examination scores for a considerable number of patients. The researchers also referred to evidence that ACE inhibitors might contribute to amyloid burden, which could accelerate dementia severity and cognitive decline.

Larger studies are needed to confirm the findings and to determine whether these effects can be sustained. The effect of ACE inhibition, while statistically significant, was very small and was unlikely to affect most patients at risk of dementia.

Sources: BMJ Open 2013;3:e002881 (online); MedPage Today, July 26, 2013

Medicare Spending Tops VA Outlay for Drugs

If the Centers for Medicare & Medicaid Services (CMS) spent money on drugs the way the Department of Veterans Affairs (VA) does, the agency could save millions of dollars without lowering the quality of patients’ medications.

In a multicenter study from Pittsburgh, Pennsylvania, researchers looked at the percentage of patients taking oral hypoglycemic agents, statins, and angiotensin-converting enzyme (ACE) inhibitors, or angiotensin-receptor blockers (ARBs) who filled brand-name drug prescriptions. The team also measured the percentage of patients filling prescriptions for long-acting analogue insulins.

Analyzing data on 1,061,095 Medicare...
Part D beneficiaries and 510,485 veterans, the researchers estimated that for the four medication groups studied, Part D spending would have been $1.4 billion—39% less—if Medicare’s use of generic drugs had mirrored the VA’s use during the study period. Conversely, if VA patients used brand-name drugs at the same rate as the Medicare patients during that period, spending would have increased by $108 million, or 57%.

Medicare patients were using double to triple the number of brand-name drugs: 35% versus 13% for oral hypoglycemic agents, 51% versus 18% for statins, 43% versus 21% for ACE inhibitors or ARBs, and 75% versus 27% for insulin analogues. Although the proportions of each cohort using oral hypoglycemic agents and long-acting insulins were nearly identical, Medicare patients were less likely than veterans to use statins and ACE inhibitors or ARBs.

One factor that might explain the difference between the systems is the VA’s practice of promoting therapeutic substitution (interchanging generic drugs in the same class as, but not identical to, single-source, brand-name drugs). For instance, the clinician might prescribe generic simvastatin instead of brand-name atorvastatin. This differs from generic substitution, such as using simvastatin instead of Merck’s Zocor.

Medicare Part D plans have tools for encouraging clinicians to use less costly drugs, but the agency has not applied these tools as extensively as the VA has. The researchers suggest that Part D plans may lack the incentives to apply the tools; for instance, private Part D plans could lose market share and rebates if they restricted the use of widely prescribed drugs. This is believed to be the first study demonstrating the magnitude of differences between brand-name and generic drug prescribing by Medicare and the VA.

Source: Ann Intern Med 2013;159:105–114 (July 16)

**Patients Give a Green Light To Placebos**

Patients are more open to the use of placebos than many clinicians might think, according to the National Institutes of Health. However, patients might not always want to know that they were given a placebo.

Debates flourish about the ethical considerations of using placebos, even though many clinicians use them regularly. The voices of patients in the U.S. have been largely missing from the discussion, although studies in other countries have included patients’ opinions.

Researchers surveyed 853 adult members of a large California health plan. Approximately 44% of the respondents were highly educated, had health insurance, and had seen a physician in the previous 6 months for a chronic condition. The researchers acknowledged that this sample might not have represented the U.S. population as a whole.

Respondents were asked about their beliefs regarding the connection between mind, body, and illness; placebos and the placebo effect; and the acceptability of doctors recommending placebo treatments. The researchers used both general questions and scenarios that varied the nature of the placebo treatment, the treatment indication, and the manner in which the physician described the treatment to the patient.

For instance, in one scenario, a 45-year-old man has been having stomach pains. The cause is not clear, but the condition is not serious. Two versions of this scenario differed according to whether the patient was aware that the doctor was recommending a placebo.

Nearly all respondents who watched the video on stomach pain believed that the mind can affect health; most said they would probably or definitely be willing to use the treatment even if they knew that it was intended to relieve pain through the mind–body self-healing process.

About two-thirds of respondents believed that placebos can produce physical changes in the body, but most also believed that placebo treatment can be effective only if patients don’t know they’re receiving a placebo and if they trust the physician. However, when they were shown a video about patients who were told a placebo could relieve pain through mind–body self-healing, 64% thought such a treatment might work even when the patient knew about it.

Feelings were mixed about whether the physician should tell the patient about the placebo. Most respondents said it was acceptable for doctors to recommend placebo, but honesty and trust played a big part in the responses. Generally, respondents felt that physicians should tell the truth, when asked, but that they need not necessarily volunteer the information. The fact that so many respondents seemed receptive to the idea of placebo treatment led the researchers to suggest that physicians should consider engaging their patients to discuss the subject.

Source: BMJ 2013;346:f3757 (July 13)

**Less Costly Avastin Equal To Lucentis In Wet Macular Degeneration**

Bevacizumab (Avastin) appears to have efficacy similar to that of ranibizumab (Lucentis) (both made by Genentech) in treating neovascular (wet) age-related macular degeneration (AMD), a common cause of vision loss. A monthly regimen may offer some advantages over as-needed treatment.

In the Inhibit VEGF in Age-related Choroidal Neovascularization (IVAN) trial, bevacizumab did not meet the criteria for either non-inferiority or inferiority when compared with ranibizumab for...
best-corrected distance visual acuity at 2 years. Similarly, as-needed administration was neither non-inferior nor inferior to continuous monthly administration on that endpoint.

Safety was generally similar between the two vascular endothelial growth factor (VEGF) inhibitors. However, there was an increased risk of systemic serious adverse events with bevacizumab when the IVAN results were pooled with those from a parallel U.S. study. IVAN’s 2-year results show that sight was equally well preserved with either drug. Giving the treatment regularly every month resulted in slightly better sight.

In previous studies, ranibizumab and bevacizumab were considered similarly effective in AMD, but only ranibizumab is approved for that use. Bevacizumab, a cancer drug, has been used increasingly off-label, however, because it is less expensive.

Ranibizumab was associated with a lower likelihood of systemic serious adverse events, and continuous administration was associated with lower mortality rates. However, continuous treatment caused more thinning of the retina.

Sources: Lancet and Queen’s University Belfast, July 19, 2013; News Medical, July 20, 2013

**New Guidelines For Restless Legs Syndrome**

The International Restless Legs Syndrome Study Group has published a report on the long-term management of restless legs syndrome (RLS), also known as Willis–Ekbom disease. Sequelae, such as augmentation of symptoms, loss of efficacy, daytime sleepiness, and impulse-control disorders, may develop during long-term pharmacological treatment.

The group recommends expending first-line treatment for most patients with either a dopamine-receptor agonist or an alpha_2-delta calcium-channel ligand as well as including the use of pramipexole (Mirapex, Pfizer), Rotigotine (Neupro, UCB), and ropinirole (Requip, GlaxoSmithKline) for up to 6 months. Pregabaline (Lyrica, Pfizer) and gabapentin enacarbil (Horizon, XenoPort) may be used for 1 year.

Levodopa is effective for up to 2 years in 24% to 40% of patients who tolerate therapy and who do not experience augmentation or loss of efficacy.

Pergolide (Permax, Valeant) and cabergoline (Dostinex, Pfizer) should no longer be used for RLS unless symptoms do not respond to other treatments and only if the benefits outweigh the risks. There is not enough evidence to recommend tramadol (Ultram, PriCara/Janssen), methadone, intrathecal morphine, or any single opioid for long-term treatment.

Sources: Reuters; July 22, 2013; Sleep Med, July 2013

**One Dose of ADHD Drug May Prevent Falls**

A single dose of methylphenidate (e.g., Ritalin, Novartis; Concerta, McNeil), which is used to treat attention-deficit/hyperactivity disorder (ADHD) and narcolepsy, may improve balance control during walking and may reduce the risk of falls among elderly adults.

Researchers in Israel enrolled 30 healthy adults who were at least 70 years of age with the ability to walk 70 feet (20 meters) without a helper or an assistive device. The participants were given 10 mg of methylphenidate and were assessed during various motor and cognitive tasks.

In the study, patients receiving methylphenidate showed improved balance control when walking, especially when they were performing more than one task. The research team suggested that the drug might improve gait, not solely by enhancing attention but also by directly influencing areas of the brain that affect motor and balance control.

Sources: J Gerontology, July 10, 2013; Science Daily, retrieved July 25, 2013

**FDA Says Stop Selling Unapproved Diabetes Therapies**

The FDA has taken action to remove illegal products from the market, including some items labeled as dietary supplements, that claim to mitigate, treat, cure, or prevent diabetes and related complications. The agency warned 15 foreign and domestic companies that the sale of their illegally marketed diabetes products violates federal law.

The illegally sold products include “natural” treatments, supplements, Ayurvedic remedies, unapproved nonprescription and homeopathic drugs, and prescription drugs for diabetes sold by online pharmacies that do not require a prescription.

The FDA is advising consumers not to use these or similar products because they could contain harmful ingredients or might be improperly sold as over-the-counter products when they should be sold as prescription products. Using these products could cause consumers to delay seeking proper medical treatment. Some products might also contain undeclared active ingredients or might not have been manufactured according to FDA quality standards. The manufacturers were requested to state within 15 business days how they would correct the violations.

Source: FDA, July 23, 2013

**Opioid Overdoses Are Worse in Women**

Addiction to prescription opioid pain drugs appears to be spreading faster among women than men. The Centers for Disease Control and Prevention (CDC) reported a 41.5% increase in opioid-related deaths among women between 1999 and 2010 compared with a 26.5% increase among men.

Emergency department (ED) visits for
misuse and abuse of opioids more than doubled among women between 2004 and 2010. ED rates were highest among women 25 to 34 years of age. Nearly 50,000 ED visits resulted from opioids in 2010. The increase in deaths and ED visits among women correlates with increased prescribing of opioids. Of the 15,323 deaths among women that were attributed to drug overdoses in 2010, almost 6,700 deaths (71%) involved prescription opioids. This was a substantial increase from the 1,290 deaths related to opioids that occurred in 1999. The increase in death rates was highest among women 45 to 54 years of age.

The CDC suggested that women are more likely to be prescribed opioids and to use them chronically. The most common forms of pain are also more prevalent, intense, and longer-lasting among women. Female patients often receive higher doses of these drugs, even though they are more likely to experience adverse events from higher doses.

A CDC spokesperson said that there was no clear indication for opioids other than for cancer pain and suggested that physical therapy, exercise, and cognitive therapies might also relieve chronic pain.

The data were obtained from the National Vital Statistics System (1999–2010) and the Drug Abuse Warning Network (2004–2010).


**HPV Vaccine Reduces Infection Rates in Teenage Girls**

A study that looked at the prevalence of human papillomavirus (HPV) infections, before and after the HPV vaccine was introduced in 2006, found that the rate of vaccine-type HPV decreased by 56% among females 14 to 19 years of age.

The vaccine was found to be effective, and the decline in HPV infections was higher than expected.

According to the CDC, each year in the U.S., about 19,000 cancers caused by HPV occur in women, and cervical cancer is the most common. About 8,000 cancers caused by HPV occur each year in men in the U.S., with oropharyngeal cancers the most common.

Sources: J Infect Dis 208(3):385–393 (July 1); CDC, July 2, 2013, www.cdc.gov/hpv

**DEVICE NEWS**

**Device Recalls Diabetes Test Strips**

Nova Diabetes Care has voluntarily recalled several lots of glucose test strips because of false and abnormally high readings. The company pulled back 21 lots of Nova Max Glucose test strips, which were distributed in the U.S. and internationally. Nova Max Plus glucose meter kits, which include test strips from the recalled lots, are also included in the recall. The error could prompt patients to take an excessive dose of insulin, which could lead to hypoglycemia and other serious health risks. Patients should stop using the strips immediately.

Sources: FDA, July 29, 2013

**Orthopedic Implant Component**

DePuy, a subsidiary of Johnson & Johnson, has recalled 16 lots of an orthopedic implant part prone to fracturing. Limb loss is listed as one of the risks. All lots were distributed between February 2007 and May 2013.

At issue in the Class I recall is the lower-extremity dovetail intercalary component, which helps reconstruct severe soft-tissue and bone defects in the knee caused by tumors, trauma, and infections. The part can replace portions of the femur or tibia; in the recall notice, however, there is a chance that the component might cause an implant fracture (possibly leading to the need for more surgery), pain, loss of mobility, loss of the limb, or neurovascular damage. Patients weighing more than 200 pounds and highly active individuals are at particular risk.

Source: FierceMedical Devices, August 2, 2013

**Device Approvals**

**Breath Test Detects H. pylori Bacteria**

Exalenz Bioscience has launched BreathID Hp, a noninvasive breath test for the detection of Helicobacter pylori. The compact system can fit on a small table or countertop and is compatible with electronic medical records. Results are delivered in 10 to 15 minutes. The system can also be used to test whether the H. pylori bacteria have been eradicated.

Source: Exalenz, July 15, 2013

**Updated PillCam SB 3 In Endoscopy**

Given Imaging’s next-generation PillCam SB 3 is used to detect and monitor small-bowel abnormalities associated with Crohn’s disease, occult gastrointestinal bleeding, and iron deficiency anemia.

The updated device can transmit between two and six images per second, and image resolution has been improved. The capsule is minimally invasive and weighs less than 4 g.

Initially approved by the FDA in 2001, PillCam SB 3 is indicated for patients 2 years of age and older. The new version will be available in the U.S. beginning in the fourth quarter of 2013.

Source: FierceMedical Devices, August 13, 2013

**HIV Diagnostic Test**

The Alere Determine HIV-1/2 Ag/Ab Combo test (Orgenics, Ltd.) simultaneously detects HIV-1 p24 antigen as well as antibodies to both HIV-1 and HIV-2 in human serum, plasma, and venous or fingerstick whole-blood specimens. The test is not indicated for screening blood donors.

Source: FDA, August 8, 2013
TB Test for Children

A new test that diagnoses tuberculosis (TB) in children detects roughly two-thirds of cases identified by the current culture test—but more quickly. In a study reported from South Africa, the Xpert MTB/RIF test also detected five times the number of cases identified by microscopy. Results are ready in 24 hours on average, compared with an average of more than 2 weeks for the culture test that was used in the study. Diagnosis is more difficult in children because they tend to have lower levels of the TB bacterium. The test can also identify children with drug-resistant TB. Among children who did not have TB, the test results were negative for TB with 99% accuracy. The study was supported by the National Institutes of Health.

Sources: NIH, July 24, 2013; FDA, July 25, 2013

Special MRI Lessens Need for Cervical Cancer Surgery

A new type of magnetic resonance imaging (MRI) scan might prevent the need for radical surgery in young women with early-stage cervical cancer. Specialist high-resolution MRI has the potential to limit the extent of surgery.

In the United Kingdom, the scan yielded information that affected doctors’ plans for surgical management in 39% of women who were scheduled to undergo a trachelectomy, a procedure that preserves fertility. Infants born to women who have undergone trachelectomy are delivered by cesarean section.

Researchers used the new MRI scan to evaluate 57 women with suspected stage 1A or stage 1B cervical cancer. The scan produced greater resolution and contrast between tumor tissue and normal tissue, giving more detailed information about the extent of cervical disease, compared with current diagnostic tests. Some of the women were able to undergo less radical surgery (e.g., extended cone biopsy). When more of the cervix can be preserved, the chances of a successful pregnancy are increased.

Sources: Br J Cancer, July 12, 2013; Institute of Cancer Research, July 19, 2013

NEW MEDICAL DEVICES

Marvin M. Goldenberg PhD, RPh, MS

Name: Neuropsychiatric EEG-Based Assessment Aid (NEBA) System
Manufacturer: NEBA Health, Augusta, Ga.
Approval Date: July 15, 2013
Purpose: This is the first medical device based on brain function that aids in the diagnosis of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents 6 to 17 years of age.
Description: When used as part of a complete medical and psychological examination, the device can help clinicians confirm an ADHD diagnosis or can help them decide whether further diagnostic testing should focus on ADHD or other medical or behavioral conditions that produce symptoms similar to those of ADHD.

An electroencephalogram (EEG) is used, and the test takes 15 to 20 minutes. Sensors are attached to a child’s head and are hooked by wires to a computer to measure brain waves. The device traces different types of electrical impulses given off by nerve cells in the brain and records how many times the impulses are given off each second. The ratio of two standard brain-wave frequencies—theta and beta waves—is calculated. The theta/beta ratio is higher in children and adolescents with ADHD than in children without the disorder.

Benefit: The FDA reviewed the NEBA system through the de novo classification process. In a clinical study, the device aided in more accurate diagnoses compared with performing a clinical assessment alone.

According to the American Psychiatric Association, 9% of adolescents in the U.S. have ADHD. The NEBA system, along with other clinical information obtained, may help health care providers clarify whether ADHD is the cause of a behavioral problem.

Source: FDA, July 15, 2013

Name: SynGenX-1000
Manufacturer: SynGen, Inc., Sacramento, Calif.
Approval Date: July 15, 2013
Purpose: The device is indicated for patients with blood disorders such as leukemia, lymphoma, and genetic diseases.
Description: A programmable control module, docking station, and disposable cartridge are used for harvesting stem cells and progenitor cells from units of collected umbilical cord blood. The cells are used to reconstitute the hematopoietic system of patients with hematological malignancies. The SynGenX-Series platform separates specific cell populations from source material in an automated, sterile environment. Used with a table-top centrifuge, the device transfers stratified cell populations into red blood cells, white blood cells (including stem and progenitor cells), and plasma using infrared sensing technology. Firmware and software communicate with a host personal computer for clinical and medical record integration.

The disposable cartridge is a sterile, single-use injection-molded polycarbonate component. It contains a unit of cord blood during the buffy coat harvesting process and comprises the fluid path of the system. Cord blood (between 40 and 220 mL) is transferred into the disposable cartridge through a clot filter. The loaded cartridge is then snapped into the control module for placement in the centrifuge. The mechanism that pinches or releases the red blood cell and buffy coat transfer
tubing is integrated into the cartridge and is operated by the control module. During centrifugation, the blood is stratified into red blood cells, buffy coat, and plasma.

The CryoPRO-2 cryopreservation/storage disposable bag set simplifies the workflow for blood bank personnel and provides a medical record of the process. SynGen DataTrak software captures the data associated with processing each cord blood unit for the blood bank’s records.

**Benefit:** This new-generation system improves the recovery of stem and progenitor cells from cord blood units, which should increase the number of clinical grade units available for transplantation.

**Source:** SynGen Inc., www.syngeninc.com

**Name:** Visius iCT

**Manufacturer:** Imris, Inc., Winnipeg, Canada

**Approval Date:** July 22, 2013

**Purpose:** The ceiling-mounted intraoperative computed tomography (iCT) scanner represents the first device of its kind. The state-of-the-art surgical theater provides personalized dose management for patients and quality diagnostic imaging during surgical procedures to assist surgeons in critical decision-making.

**Description:** The 64-slice scanner moves effortlessly into and out of the operating room (OR) during surgery via ceiling-mounted rails to ease workflow. This capability enables configurations of multiple rooms to meet clinical requirements without compromising image quality or examination speed.

**Benefit:** This new technology may become an essential part of the hybrid OR of the future, especially for spinal and neurosurgical procedures. Surgeons are provided with on-demand CT imaging that guides and confirms implant placement. Patient transport and the need for floor-mounted rails used in other systems are eliminated. Valuable OR space is augmented, and surgical equipment is easily moved. Infection control is also simplified, and image quality is optimal. The system offers the longest scanner travel range available.

Software provides three-dimensional volume. The software allows physicians to visualize the dosage before scanning begins and to adjust settings based on the patient’s needs. Detailed dosage reports are produced after each scan.

**Source:** Imris, www.imris.com

**Recall**

GE Healthcare is urging customers to stop using more than 20 models of its nuclear imaging devices until the company can inspect each one and ensure that it is not prone to the same mishap that resulted in a patient’s death in a Veterans hospital.

In June, GE learned that a patient died during scanning after bolts came loose on an Infinia Hawkeye 4 device. The attached camera was dropped, and the patient was fatally injured.

In the weeks after the incident, GE warned customers to avoid using Infinia scanners until company inspectors could verify safety. GE then updated the recall to include all of its nuclear medicine systems, saying that design similarities between all of the devices could put patients at risk if they were left uninspected.

The FDA has assigned its most serious Class I to the recall.

GE recommended that all sites suspend use of the devices until it can ensure they are properly secured. Included in the warning are the Infinia, Varicam, and Millennium VG scanners, which are installed in hospitals and are used for oncology, cardiology, neurology, and other clinical diagnostics. These devices were distributed from October 1992 through June 2013.

**Sources:** FDA, July 29, 2013; GE Healthcare, July 3, 2013