NEW DRUG APPROVALS

Entresto for Heart Failure

The FDA has approved valsartan/sacubitril (Entresto, Novartis) to treat heart failure with reduced ejection fraction. The drug will be indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in patients whose condition is classified as New York Heart Association class II, III, or IV. It is usually administered with other HF therapies in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin-receptor blockers.

Valsartan/sacubitril is a first-in-class medication (an angiotensin receptor/ nephrilysin inhibitor) that reduces the strain on the failing heart. Available as a twice-daily tablet, it enhances the protective neurohormonal systems of the heart while suppressing the harmful renin–angiotensin–aldosterone system. Valsartan/sacubitril was evaluated under the FDA’s priority review program and received a fast-track designation.

The FDA decision was based on the PARADIGM-HF study, which included 8,442 HF patients. Compared with the ACE inhibitor enalapril, valsartan/sacubitril reduced the risk of death from cardiovascular causes by 20%; reduced HF hospitalizations by 21%; and reduced the risk of all-cause mortality by 16%. Overall, there was a 20% risk reduction on the primary endpoint, a composite measure of cardiovascular death or the time to first HF hospitalization.

Fewer patients treated with valsartan/sacubitril than with enalapril discontinued the study medication because of an adverse event. The valsartan/sacubitril group had more hypotension and nonserious angioedema but less renal impairment, hyperkalemia, and cough compared with the enalapril group.

Sources: FDA and Novartis, July 7, 2015

Rexulti for Schizophrenia, MDD

Brexpiprazole (Rexulti, Otsuka/Lundbeck) has received FDA approval as a treatment for adults’ schizophrenia and as an adjunctive therapy for adults’ major depressive disorder (MDD).

Although brexpiprazole’s mechanism of action is unknown, its efficacy may be mediated through a combination of partial agonist activity at serotonin 5-HT_{1A} and dopamine D_{2} receptors, and antagonist activity at serotonin 5-HT_{2A} receptors.

Brexpiprazole’s efficacy in adults with schizophrenia was established in two six-week, phase 3, randomized, placebo-controlled studies that compared fixed doses of brexpiprazole with placebo. In one study, the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score for brexpiprazole at 2 mg per day and 4 mg per day (−20.73 points and −19.65 points) was superior to placebo (−12.01 points); in the other study, the change from baseline in the PANSS total score for brexpiprazole at 4 mg per day was superior to placebo (−20.00 points versus −13.53 points, respectively), but the change from baseline in the PANSS total score with brexpiprazole 2 mg per day was not superior. The most common adverse events (AEs) associated with brexpiprazole versus placebo included weight gain and somnolence.

As adjunctive therapy for MDD, brexpiprazole’s efficacy was evaluated in two six-week, placebo-controlled studies of adults, with or without symptoms of anxiety, who had failed to achieve an adequate response during one to three treatment attempts with antidepressant therapy (ADT), and who had also failed to achieve an adequate response in a single-blind ADT phase for eight weeks. With brexpiprazole (2 mg or 3 mg) plus ADT, the mean baseline Montgomery–Åsberg Depression Rating Scale (MADRS) score decreased by 8.36 (2 mg) and 8.29 (3 mg) points from 27.0 points at randomization compared with reductions of 5.15 and 6.33 points with placebo plus ADT in the respective studies. The discontinuation rate due to AEs was 3% for brexpiprazole plus ADT compared with 1% for placebo plus ADT. The most common AEs for the combination of brexpiprazole and ADT included akathisia and weight increase.

Source: Lundbeck, July 13, 2015

Kengreal, an Antiplatelet Drug

The FDA has approved cangrelor (Kengreal, The Medicines Company), an intravenous antiplatelet drug that prevents the formation of blood clots in the coronary arteries, for use in adults undergoing percutaneous coronary intervention.

By preventing platelets from accumulating, cangrelor reduces the risk of serious clotting complications related to the procedure, including heart attack and stent thrombosis. As with other FDA-approved antiplatelet drugs, bleeding (sometimes life-threatening) is the most serious risk associated with cangrelor.

In the pivotal Champion-Phoenix trial, which compared cangrelor with clopidogrel (Plavix, Bristol-Myers Squibb) in more than 10,000 participants, cangrelor significantly reduced the occurrence of heart attack, the need for further procedures to open the artery, and stent thrombosis. The overall occurrence of serious bleeding was low but more common with cangrelor than with clopidogrel. Approximately one in every 170 cangrelor patients experienced a serious bleed, compared with approximately one in every 275 clopidogrel patients.

The FDA rejected cangrelor in April 2014 after its reviewers took issue with the way the Champion-Phoenix study was conducted, and asked The Medicines Company to re-analyze its data. Champion-Phoenix followed two failed studies; the company tweaked the design of the third study to differentiate heart attacks associated with its drug from those that...
may have resulted from the angioplasty.

Cangrelor takes effect rapidly and leaves the system about one hour after being administered. Other antiplatelet drugs keep working for five days or more, significantly increasing the risk of serious bleeding if a patient needs emergency or urgent follow-up procedures. Cangrelor would also benefit patients who are unable to swallow pills, analysts said.

Sources: FDA, June 22, 2015, and Reuters, April 13, 2015

Orkambi for Cystic Fibrosis

The FDA has approved the first drug for cystic fibrosis (CF) that seeks to treat the cause of the disease in people who have two copies of a specific mutation.

Lumacaftor 200 mg/ivacaftor 125 mg (Orkambi, Vertex Pharmaceuticals) is indicated for the treatment of CF in patients 12 years of age and older who have the F508del mutation, which causes the production of an abnormal protein that disrupts water and chloride transport in the body.

Lumacaftor/ivacaftor received FDA breakthrough therapy and orphan drug designations and was evaluated under the priority review program. A year’s treatment will cost an estimated $259,000.

CF affects approximately 30,000 U.S. residents. People who have two copies of the F508del mutation (one inherited from each parent) account for approximately half of the CF population in the U.S.

The safety and efficacy of lumacaftor/ivacaftor were studied in two double-blind, placebo-controlled trials involving 1,108 participants with CF who were 12 years of age or older with the F508del mutation. In both studies, the participants treated with lumacaftor/ivacaftor (two pills every 12 hours) demonstrated improved lung function compared with those who received placebo.

The drug’s efficacy and safety have not been established in CF patients other than those with the F508del mutation. If a patient’s genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

The most common adverse effects associated with lumacaftor/ivacaftor include shortness of breath, upper respiratory tract infection, nausea, diarrhea, and rash. Women treated with the drug had an increased incidence of menstrual abnormalities, such as increased bleeding.

Sources: FDA, July 2, 2015, and BioSpace, July 6, 2015

Generic Approvals, Launches

The first generic version of Zetia (Ezetimibe) has won FDA approval, but a 2010 settlement of patent litigation means Glenmark Pharmaceuticals Ltd. won’t be selling its 10-mg ezetimibe tablets just yet.

Under an agreement between Merck and Glenmark, the Indian pharmaceutical company will be able to launch its product on December 12, 2016, “or earlier under certain circumstances,” which were not specified. Merck’s patent on Zetia does not expire until April 25, 2017. According to Global Data, Zetia’s U.S. sales were almost $1.5 billion in 2014.

Ezetimibe inhibits absorption of intestinal cholesterol and related phytosterol. Its indications include reducing elevated total cholesterol, low-density lipoprotein-cholesterol, apolipoprotein B, and non-high-density lipoprotein-cholesterol in patients with primary hyperlipidemia (alone or in combination with a statin) or mixed hyperlipidemia (in combination with fenofibrate) as an adjunct to diet.

Sources: FDA, June 26, 2015; Glenmark, May 11, 2010; Global Data; and Zetia prescribing information

Desvenlafaxine Succinate ER

Four companies have received FDA approval to market desvenlafaxine succinate extended-release tablets—the first generic formulations of Pristiq (Pfizer, Inc.). Alerbic Pharmaceuticals Ltd., Lupin Pharmaceuticals Inc., Sandoz Inc., and Mylan Pharmaceuticals Inc. can sell 50-mg and 100-mg tablets.

Pristiq is a serotonin and norepinephrine reuptake inhibitor indicated for the treatment of major depressive disorder. According to Pfizer, its U.S. sales accounted for $553 million in 2014, up 2% from 2013.

Sources: FDA, June 29, 2015; Pfizer, Inc., January 27, 2015; and Pristiq prescribing information

Glatopa (Glatiramer) Launched

Sandoz has launched Glatopa, the first generic version of Teva’s Copaxone (glatiramer acetate injection) 20-mg/mL once-daily therapy for multiple sclerosis (MS). Glatopa is indicated for the treatment of patients with relapsing forms of MS, including those who have experienced a first clinical episode and have magnetic resonance imaging features consistent with MS.

Glatopa was developed under a collaboration agreement between Sandoz and Momenta Pharmaceuticals, Inc., which announced its launch immediately after the U.S. Court of Appeals in Washington, D.C., again invalidated a long-disputed Teva patent related to glatiramer acetate’s manufacturing.

Sources: Sandoz and Momenta Pharmaceuticals, June 18, 2015

Linezolid for Oral Suspension

Roxane Laboratories Inc. has secured FDA approval to market linezolid for oral suspension, 100 mg/5 mL. This is the first generic version of this formulation of Zyvox (Pfizer, Inc.), an oxazolidinone-class antibacterial indicated in adults and
children for the treatment of specific infections caused by susceptible gram-positive bacteria. Altogether, formulations of Zyvox had U.S. sales of $680 million in 2014, according to Pfizer.

Sources: FDA, June 3, 2015; Pfizer, Inc., January 27, 2015; and Zyvox prescribing information

Zolpidem Tartrate Sublingual Tablets

The FDA has approved the marketing of zolpidem tartrate sublingual tablets, 1.75 mg and 3.5 mg, by Novel Laboratories, Inc.—the first generic version of Intermezzo sublingual tablets (Purdue Pharma). Intermezzo is a GABAA agonist indicated for use as needed for the treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep.

Sources: FDA, June 3, 2015, and Intermezzo prescribing information

Clindamycin Phosphate/Tretinoin Gel

Actavis Mid Atlantic LLC has received FDA permission to sell clindamycin phosphate/tretinoin gel, 1.2%/0.025%. This is the first generic version of Ziana Topical Gel (Medicis), a lincosamide antibiotic and retinoid combination product indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

Sources: FDA, June 12, 2015, and Ziana prescribing information

Clindamycin Phosphate/Benzoyl Peroxide

Actavis Laboratories UT, Inc., now has FDA approval to market clindamycin phosphate/benzoyl peroxide gel, 1.2%/2.5%—the first generic formulation of Acanya Gel (Dow Pharmaceuticals), a lincosamide antibiotic and bacteriocidal/keratolytic combination product indicated for the topical treatment of acne vulgaris in patients 12 years of age or older.

Sources: FDA, June 19, 2015, and Acanya Gel prescribing information

Gemifloxacin Mesylate

The FDA has approved the first generic version of gemifloxacin mesylate tablets (Factive, LG Life Sciences). Orchid Healthcare will market the 320-mg tablets, a synthetic broad-spectrum antibacterial agent for oral administration.

Sources: FDA, June 15, 2015, and Factive prescribing information

NEW INDICATIONS
Iressa for Lung Cancer

The FDA has approved gefitinib (Iressa, AstraZeneca) for first-line treatment of patients with metastatic non–small-cell lung cancer (NSCLC) whose tumors harbor specific epidermal growth factor receptor (EGFR) gene mutations, as detected by an FDA-approved test.

Gefitinib, a kinase inhibitor, blocks proteins that promote the development of cancerous cells with specific EGFR mutations. It is intended to treat patients whose tumors express the most common EGFR mutations in NSCLC (exon 19 deletions or exon 21 L858R substitution gene mutations). The therascreen EGFR RGQ PCR Kit (Qiagen Manchester Ltd.) was approved as a companion diagnostic test to identify patients with tumors appropriate for gefitinib treatment.

The efficacy and safety of gefitinib were demonstrated in a single-arm trial of 106 patients with previously untreated, EGFR mutation-positive, metastatic NSCLC who received 250 mg once daily. The study’s primary endpoint was the objective response rate. Tumors shrank in approximately 50% of the patients after treatment, and this effect lasted an average of six months. The response rates were similar for tumors with exon 19 deletions and exon 21 L858R substitution mutations.

These results were supported by a retrospective analysis of another clinical trial, which identified a subgroup of 186 patients with EGFR mutation-positive metastatic NSCLC who were receiving first-line treatment. These patients were randomly assigned to receive gefitinib or up to six cycles of carboplatin/paclitaxel. The results from this subgroup analysis suggested an improvement in progression-free survival with gefitinib compared with carboplatin/paclitaxel.

Gefitinib may cause serious adverse effects, including interstitial lung disease, liver damage, gastrointestinal perforation, severe diarrhea, and ocular disorders. The most common adverse effects were diarrhea and skin reactions.

Gefitinib received accelerated approval in 2003 for the treatment of patients with advanced NSCLC after progression on platinum doublet chemotherapy and docetaxel. Gefitinib was voluntarily withdrawn from the market after subsequent confirmatory trials failed to verify a clinical benefit. The new approval is for a different patient population (EGFR mutation-positive and previously untreated) than the 2003 approval.

Source: FDA, July 14, 2015

Fycompa for Tonic-Clonic Seizures

The FDA has expanded the indications for the antiepileptic drug perampanel hydrate (Fycompa, Eisai) to include adjunctive treatment of primary generalized tonic-clonic (PGTC) seizures in patients 12 years of age and older with epilepsy.

The agency’s decision was based on a phase 3, placebo-controlled trial of perampanel in 164 patients 12 years of age and older with PGTC seizures. A statistically significant reduction in the frequency of PGTC seizures was observed with perampanel compared with placebo (−76.5% versus −38.4%, respectively). In addition, the responder rate for perampanel was 64.2%, compared with 39.5% for placebo, and during the 13-week maintenance period, the proportion of patients free of PGTC seizures was 30.9% with perampanel versus 12.3% with placebo.

The most common adverse events with
perampanel included dizziness, fatigue, headache, somnolence, and irritability.

Perampanel is a selective, noncompetitive alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist that reduces the neuronal hyperexcitation associated with seizures by targeting glutamate activity at postsynaptic AMPA receptors. The FDA approved it as an adjunctive treatment for partial-onset seizures (with or without secondarily generalized seizures) in patients 12 years of age and older with epilepsy in October 2012.

Source: Eisai, June 22, 2015

**Zomig for Pediatric Migraine**

The FDA has approved zolmitriptan nasal spray (Zomig, Impax Pharmaceuticals) for the acute treatment of migraine with or without aura in patients 12 years of age and older. The product was first approved in September 2003 for the acute treatment of this condition in adults.

Zolmitriptan is the first nasal-delivered prescription medication approved for the treatment of children’s acute migraine attacks. It is a serotonin 5-HT1B/1D receptor agonist (triptan).

The FDA reviewed safety and efficacy data from pivotal clinical trials that demonstrated zolmitriptan nasal spray 5 mg was significantly more effective than placebo in providing no headache pain, the relief of headache, and other associated symptoms of migraine when treating migraine in pediatric patients. The medication had a safety profile similar to that shown with adults.

The recommended starting dose of zolmitriptan nasal spray in patients 12 years of age and older is 2.5 mg. The dose should be adjusted on an individual basis, with a maximum recommended single dose of 5 mg. Patients should not use more than 10 mg in any 24-hour period.

Sources: Impax Laboratories, June 16, 2015, and Zomig prescribing information

**DRUG NEWS**

**Breakthrough Therapy**

**DX-2930 for Hereditary Angioedema**

DX-2930 (Dynax Corp.) has received the FDA’s breakthrough therapy designation for hereditary angioedema (HAE).

DX-2930, a fully human monoclonal antibody inhibitor of plasma kallikrein (pKal), is being investigated as a subcutaneous injection for prevention of HAE attacks. Uncontrolled pKal activity leads to excessive generation of bradykinin, a vasodilator thought to be responsible for the localized swelling, inflammation, and paincharacteristically associated with HAE.

The designation is supported by interim results from a phase 1b clinical trial of DX-2930 that met all objectives in assessing the safety, tolerability, and pharmacokinetics of multiple subcutaneous administrations of DX-2930. In a prespecified proof-of-concept efficacy analysis, DX-2930 demonstrated statistically significant reductions in the HAE attack rate compared with placebo.

Source: Dynax Corp., July 7, 2015

**Priority Review**

**MM-398 for Pancreatic Cancer**

The FDA will give priority review to the newly accepted application for MM-398 (irinotecan liposome injection, Merrimack Pharmaceuticals, Inc./Baxalta Incorporated) for the treatment of patients with metastatic adenocarcinoma of the pancreas who have previously been treated with gemcitabine-based therapy. The agency’s goal date for action is October 24, 2015.

The application is based on the phase 3 NAPOLI-1 study, conducted in patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy. MM-398 in combination with fluorouracil and leucovorin significantly improved overall survival, progression-free survival, and overall response rate compared to a combination of fluorouracil and leucovorin. The most common grade 3 or higher adverse events in patients receiving MM-398, fluorouracil, and leucovorin were neutropenia, fatigue, and gastrointestinal effects.

The FDA previously granted MM-398 fast-track and orphan drug designations. MM-398, also known as “nal-IRI,” is a novel encapsulation of irinotecan in a long-circulating liposomal formulation. The activated form of irinotecan is SN-38, which inhibits topoisomerase I (an essential enzyme involved in DNA transcription and replication).

Sources: Merrimack Pharmaceuticals, Inc./Baxalta Incorporated, June 25, 2015

**Fast-Track Status**

**Aerucin for Hospital-Acquired Pneumonia**

Aerucin (Aridis Pharmaceuticals, Inc.) has received the FDA’s fast-track designation for the treatment of hospital-acquired and ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*.

Aerucin is a broadly reactive fully human immunoglobulin G monoclonal antibody targeting *P. aeruginosa* that exhibits broad binding to more than 90% of clinical isolates of that bacterium. A phase 1 clinical trial is evaluating the product’s safety and pharmacokinetics in healthy adults.

Source: Aridis Pharmaceuticals, Inc., June 30, 2015

**Orphan Drug Designations**

**Volanesorsen for Familial Chylomicronemia Syndrome**

The FDA has given an orphan drug designation to volanesorsen (ISIS-APO-CIIIIRx, Akcea Therapeutics) for the treatment of patients with familial chylomicronemia syndrome (FCS), a rare genetic disease characterized by extremely high triglyceride levels and risk of pancreatitis.

In a phase 2 study, patients with FCS treated with volanesorsen, an antisense drug, achieved substantial reductions in
apilipoprotein CIII (apoC-III), triglycerides, chylomicrons, and apoC-III-associated very-low-density lipoprotein-cholesterol particles. Akcea is conducting an international, multicenter, randomized, double-blind, placebo-controlled phase 3 study in FCS patients.

Source: Akcea Therapeutics, July 6, 2015

Gedeptin for Oral/Pharyngeal Cancers
PNP Therapeutics Inc. has received an FDA orphan drug designation for Gedeptin (adenoviral vector expressing *Escherichia coli* purine nucleoside phosphorylase gene) for the intratumoral treatment of anatomically accessible oral and pharyngeal cancers, including cancers of the lip, tongue, gum, floor of the mouth, salivary gland, and other oral cavities.

PNP Therapeutics recently completed a phase 1 clinical trial to examine the safety and efficacy of Gedeptin in the treatment of head and neck cancer. Significant tumor responses were seen in patients treated with the highest doses, with no major toxicities associated with use of the product. Gedeptin has been shown to work with a variety of well-characterized nucleoside prodrugs, generating active metabolites with high levels of antitumor activity.

Source: PNP Therapeutics Inc., June 16, 2015

Daytrana May Discolor Skin
Permanent skin-color loss may occur with use of the methylphenidate transdermal system (Daytrana, Noven Pharmaceuticals) for attention-deficit/hyperactivity disorder (ADHD), the FDA says. A new warning has been added to the drug label to describe this condition, chemical leukoderma, in which the skin loses color after repeated exposure to specific chemical compounds.

The areas of skin-color loss seen with the Daytrana patch ranged up to 8 inches in diameter. While not physically harmful, the condition is disfiguring and apparently irreversible, which may cause emotional distress.

The FDA recommends that patients or their caregivers watch for new areas of lighter skin, especially under the Daytrana patch. They should immediately report these changes to their health care professionals. Patients should not stop using the patch without talking to their caregivers. Health care professionals should consider alternative treatments for patients who experience these skin-color changes.

Daytrana treats ADHD by working to increase attention and decrease restlessness in children and adolescents who are overactive, cannot concentrate for very long, or are easily distracted and impulsive.

Source: FDA, June 24, 2015

Potiga Study Ordered
The FDA is requiring GlaxoSmithKline to conduct a long-term observational study of its antiseizure drug ezogabine (Potiga) to explore any potential lasting consequences of pigment changes to the retina and skin seen in some patients. However, the agency has concluded that potential risks with ezogabine can be managed adequately by following recommendations in the current labeling.

An FDA review of safety reports does not indicate that the pigment changes affect vision. Skin discoloration associated with the use of the medication appears to be a cosmetic effect not associated with more serious adverse effects.

In 2013, the FDA approved ezogabine label changes underscoring risks of abnormalities to the retina in the eye, potential vision loss, and skin discoloration. The revised label added a boxed warning and advised that ezogabine be reserved for patients who have not responded adequately to several alternative therapies. The FDA recommended that patients have eye exams by an ophthalmic professional before starting ezogabine and every six months during treatment.

If retinal pigment abnormalities or vision changes are detected, ezogabine should be stopped unless no other suitable seizure treatment options are available and the benefits of treatment outweigh the potential risk of vision loss. Ezogabine is available under a risk evaluation and mitigation strategy.

Sources: FDA, June 16, 2015, and October 31, 2013

Meningococcal Group B Vaccine
The Advisory Committee on Immunization Practices (ACIP) has approved a Category B recommendation for meningococcal group B vaccination. Health care professionals will decide who to vaccinate based on risk assessments of individual patients ages 16 to 23 years (with a preferred age of 16 to 18 years).

The ACIP recommendation will become final upon future publication in the Centers for Disease Control and Prevention *Morbidity and Mortality Weekly Report (MMWR)*. Meningococcal group B vaccines include Bexsero (Glaxo-SmithKline), given as a two-dose series, and Trumenba (Wyeth Pharmaceuticals, Inc.), given as a three-dose series.

The ACIP recommends meningococcal group B vaccines for people at increased risk for meningococcal disease: persons with persistent complement component deficiencies; persons with anatomic or functional asplenia; microbiologists routinely exposed to isolates of *Neisseria meningitides*; and persons at increased risk because of a serogroup B meningococcal disease outbreak. Meningococcal group B accounted for 32% of reported U.S. cases in all age groups in 2013.

Sources: GlaxoSmithKline, June 24, 2015, and *MMWR*, June 12, 2015
FDA Eyes Pediatric Codeine Use

The FDA is investigating the possible risks of using codeine-containing medicines to treat coughs and colds in children younger than 18 years of age because of the potential for serious side effects, including slowed or difficult breathing. The agency will convene an expert advisory committee to discuss the issue.

Health care professionals should continue to follow the recommendations in product drug labels and use caution when prescribing or recommending codeine-containing cough-and-cold medicines to children.

In April 2015, the European Medicines Agency announced that codeine must not be used to treat coughs and cold in children younger than 12 years of age and that codeine is not recommended in children and adolescents between 12 and 18 years of age who have breathing problems, including those with asthma and other chronic breathing problems.

Source: FDA, July 1, 2015

FDA: Avoid ScienceLab.com Drugs

The FDA has advised health care providers, researchers, and patients not to purchase or use drugs labeled or marketed as sterile by ScienceLab.com due to the possibility of product contamination. FDA investigators inspected the headquarters of ScienceLab.com in Houston, Texas, and observed conditions that could result in a lack of sterility of purportedly sterile drug products. The agency is not aware of reports of illness associated with the use of these products.

Source: FDA, June 15, 2015

RESEARCH BRIEFS
ED Visits for Tramadol Up

Emergency department (ED) visits involving the opioid tramadol have risen sharply, according to the Substance Abuse and Mental Health Services Administration (SAMHSA). The report cites two studies. One found ED visits related to adverse reactions to the drug increased 145% between 2005 and 2009. The other found visits related to misuse or abuse of the drug rose 250% between 2005 and 2011.

In both cases, the increases were highest among women, who accounted for 75% of all visits in 2005 and remained in the majority through 2011. Although all adult age groups showed notable increases, the greatest was among patients ages 55 years and older—a 481% increase, from 892 visits in 2005 to 5,181 visits in 2011.

The increases probably reflect the fact that tramadol prescriptions are also rising: up 88% from 23.3 million in 2008 to 43.8 million in 2013. Older patients are receiving tramadol more often because it does not have the side effects of gastrointestinal bleeding and kidney dysfunction associated with nonsteroidal anti-inflammatory drugs. However, tramadol puts patients at risk for other serious consequences, such as seizures and dangerous sedative effects.

The SAMHSA report notes that the studies found a significant difference between the disposition of visits involving adverse reactions and those involving misuse or abuse. Although patients were treated and released in the majority of visits in both cases, twice as many ED visits involving misuse required hospitalization or transfer to another health facility (38% versus 17%).

Source: SAMHSA, May 14, 2015

Switching to Quetiapine Helpful

Up to half of patients using antipsychotics must switch because the drugs are not effective or not tolerable, say researchers from Hokkaido University and the University of California. Little is known about optimal clinical strategies for switching, but it seems rational to choose a drug with a different receptor binding profile, they say, and quetiapine is a “strong candidate.” They cite its relatively high affinity for the 5-HT2A receptor and relatively low affinity for the D2 receptor, which would make quetiapine appropriate if the first drug was, for example, risperidone or another drug with high affinities for dopamine receptors.

Citing studies that compared quetiapine favorably with risperidone in long-term effectiveness, the researchers noted there were no data on the long-term neurocognitive effects in patients who had not responded well to prior antipsychotics. They conducted a one-year open-label study to examine the long-term efficacy and tolerability of quetiapine in 29 patients with schizophrenia who switched from risperidone, haloperidol, olanzapine, aripiprazole, or blonanserin. Patients were assessed at three, six, and 12 months. Three patients dropped out because their psychotic symptoms worsened, two because of somnolence, and one because of alopecia. One patient was lost to follow-up.

During the follow-up period, the maximum quetiapine dose was 750 mg per day. Patients could continue using psychotropics and drugs for parkinsonism, but these were tapered off if possible.

The researchers used a battery of tests, including the Brief Assessment of Cognition in Schizophrenia. Patients who switched to quetiapine improved in all test areas. Notably, their verbal memory test results improved significantly. The researchers say that improvement continued through the year. However, they say this result should be viewed with caution because the study wasn’t designed to compare cognitive remediation effects.

Switching to quetiapine reduced prolactin levels, improved extrapyramidal symptoms, and lessened the use of anticholinergics. No weight gain or glucose intolerance were observed. Somnolence and worsening of psychotic symptoms...
were noticeable adverse effects, but the sedative effect improved patients’ insomnia.

Source: *Annals of General Psychiatry*, January 22, 2015

**Cancer Death Rates Fall**

Cancer-related mortality continues to decrease, according to the National Cancer Institute’s *Annual Report to the Nation on the Status of Cancer*. Between 2002 and 2011, mortality rates dropped by about 1.8% per year among men, 1.4% among women, and roughly 2% among children.

Mortality rates among men went down for 10 of the 17 most common cancers and among women for 13 of the top cancers.

Age-adjusted incidence rates for all cancers and both sexes combined declined 0.5%. The largest declines in incidence for men were in cancers of the colon and rectum (3.0%), lung and bronchus (2.4%), and prostate (2.1%). Among women, incidence rates of colorectal cancer (2.7%), cervical cancer (2.4%), and lung and bronchus cancer (1.0%) had the biggest drops. The decrease in lung cancer cases reflects the falling smoking rate.

Not all of the news is positive. Among men and women, the incidence rose for thyroid cancer (5.3% and 5.8%, respectively) and kidney cancer (2.0% and 1.6%, respectively), although no increase in mortality has been noted. Liver cancer cases (up 3.6% for men, 2.9% for women) and deaths (up 2.6% for men, 1.9% for women) are also increasing; this may reflect, in part, higher rates of hepatitis C and/or behavioral risk factors, such as alcohol abuse, the report says.

Oral/oropharyngeal cancers are increasing among white men, perhaps associated with higher incidence of human papillomavirus, the researchers suggest. The incidence and mortality rates are increasing as well for uterine cancer among white, African-American, and Asian Pacific Islander women, with the largest increase seen in African-American women. The cause of the increases is unknown.

Source: *National Cancer Institute*, March 30, 2015

**Statins and Sepsis Patients**

Mortality was lower among patients with sepsis and septic shock who received atorvastatin than it was among patients who received simvastatin, according to a study by researchers from Henry Ford Hospital in Detroit. However, statins as a class were not associated with improved mortality.

Of 1,661 patients with sepsis, 359 had received statins prior to hospitalization; 1,302 had not. The two groups’ mortality rates were roughly similar (27% versus 30%). But of 92 patients who received atorvastatin prior to hospitalization, 17 died, significantly fewer than the 76 of 258 patients who received simvastatin (19% versus 30%). And patients who received atorvastatin prior to hospitalization and continued on statins in the hospital had a mortality rate half that of patients who never received statins.

Individual statins have unique biological properties, varying considerably in first-pass metabolism, half-life, and bioavailability. They have also been shown *in vitro* to have different antibacterial properties.

The researchers caution that statins’ potential benefits are offset by potent adverse effects in intensive care patients. Statins are metabolized by the cytochrome P450 system in the liver, and liver disease—common in the critically ill—affects the metabolism of statins and raises the risk of muscle disease. Statin bioavailability is affected by food intake, which could be important for patients who cannot receive oral nutrition. And statins are highly protein-bound, also important in the critically ill.


**Benzodiazepines and Opioids**

In 2010, 30% of overdose deaths related to opioid analgesics involved benzodiazepines, according to researchers from Brown University, Boston University, and the University of Michigan. To investigate related prescribing patterns, the researchers looked at data on 422,786 veterans, 112,069 of whom received both opioid analgesics and benzodiazepines between 2004 and 2009.

During the study period, 2,400 veterans died of a drug overdose while on opioid analgesics. About half of those (1,185) were being prescribed benzodiazepines and opioids concurrently when they died.

The relationship between benzodiazepines and death from drug overdose was dose-dependent. The risk of death from drug overdose increased with a history of benzodiazepine prescription and as the daily dose of benzodiazepine increased.

Benzodiazepines were more likely to be prescribed to patients with substance misuse and other psychiatric disorders—which also carry a risk for overdose death, the researchers note. However, they adjusted for those factors. The degree to which benzodiazepines contributed to the actual cause of death from overdose is unclear. Half of the deaths occurred during periods when benzodiazepines were not prescribed.

Notably, the researchers found no association between as-needed dosing and the risk of death from overdose compared with regularly scheduled dosing.

The researchers say their findings indicate a need for clinicians to be aware of the higher risk among patients receiving both benzodiazepines and opioids, especially those on higher doses of either or both drugs.

Source: *BMJ*, June 2015

**Preventing Falls Saves Money**

It costs just $500 per person, but a fall-prevention program developed by the U.S.
Information Often Lacking After Colorectal Surgery

After surgery for colorectal cancer, patients are often sent home with pain, nausea, and fatigue—which can make it hard to absorb the discharge information they receive. But they may not be getting enough discharge information, researchers from Lund University in Sweden say.

The researchers conducted 31 interviews with 16 patients during their first seven weeks at home. Patients “expressed surprise” at the lack of discharge instructions; they felt healthier when they could take an active part in self-care, and information was a prerequisite. A theme emerged from the interviews: trying to regain control of life by using information, including how to manage symptoms and self-care.

Patients lacked information on how long recovery would take, how to improve physical fitness, what to eat and drink, how bowel function and weight would be affected, and how to remove the suture and care for the wound. Some patients were concerned about how to take medications and painkillers; some received incorrect prescriptions.

Patients wanted a role in planning. Some compared the discharge process unfavorably with preoperative preparation, which they described as calmer with easier-to-follow information. Patients also wanted straightforward information given in a meeting, which was important in part because they closely observed health care practitioners’ facial expressions and intonation to determine whether anything was being withheld.

Lack of information added to their worry about treatment and their future. One patient said, “...[W]hen you go home with news like this, you see the terminal station racing towards you like an express train ... so that’s why I want to have information, then I can process it.”

The researchers acknowledge that not all patients want information, or they may want it later in the process. But when they do seek information, they may choose untrustworthy sources. The onus is on health care professionals, the researchers say, to provide “person-centered” care with easily accessible information for all patients.

Source: BMC Nursing, June 2015

Elderly Do Well After ICU Stays

Octogenarians who make it through the first year after a stay in the intensive care unit (ICU) have long-term survival rates similar to those of the rest of their age group, according to researchers who retrospectively analyzed data on 395 patients admitted to the Haukeland University Hospital in Norway.

One-year survival was 42%. The majority of patients who did not survive the ICU died within two days, and most had limitations on life-sustaining treatment (withholding or withdrawal). High hospital mortality was predicted by an unplanned surgical admission. Patients who had undergone planned surgery had higher survival rates than those with unplanned surgery up to three years later. One-year mortality was predicted by respiratory failure and isolated head injury. After five years, 22% of all patients were still alive.

Health-related quality of life (HRQOL) did not differ, according to questionnaire responses from 58 survivors and 179 control subjects over a 13-year post-ICU follow-up.

Source: Annals of Intensive Care, June 2015

Cardiovascular Device Data Often Remain Unpublished

About half of clinical trials for high-risk cardiovascular devices remain unpublished more than two years after FDA approval, according to researchers from Massachusetts General Hospital, the University of California, and the University of Sydney. Moreover, high-risk devices are often approved based on a single study.

The researchers examined “selective reporting” for medical devices. FDA documents containing the evidence to support device approval are available but not easy to access, so the researchers compared clinical trial data in FDA summaries with information in corresponding peer-reviewed publications. They examined discrepancies between study characteristics, primary endpoints, and results.

They found summaries for 106 cardiovascular devices approved between 2000 and 2010. Of 177 studies (mean, 1.7
per device), 86 were published, corresponding to 60 distinct devices (mean, 1.4 published studies per device). The pivotal studies corresponded to the same 60 devices (mean, 1.1 published pivotal studies per device). The researchers contacted 23 manufacturers to request publication references; eight (35%) responded, confirming that the trials of interest had not been published. A subgroup analysis restricted to the pivotal studies showed that, of 112, there were 66 corresponding publications (59%).

The average time from FDA approval to publication was 6.5 months but took up to 7.5 years. For the 66 pivotal studies, the average time to publication was 7.9 months; 22 (33%) were published before FDA approval. All publications that specified a funding source were industry-funded.

The summaries and publications were “nearly identical” on clinical design features such as randomization, blinding, and number of centers. However, in one-quarter of the published studies, the number of patients enrolled in the study differed between the summary and the publication. Demographic information, such as age and gender, differed in 11% and 16%, respectively, of the studies.

Some summaries and published studies presented primary endpoints differently. Endpoints labeled as primary in summaries were sometimes secondary in studies. Nearly 10% were missing. Those alterations mean, the researchers say, that primary endpoints were “rebranded” to modify the emphasis of the findings in the literature. Less than half of the results for primary endpoints were identical in both summaries and published studies, and 11% were “substantially different,” the researchers say.

Although systematic reviews increasingly serve as a basis for evidence-based clinical practice guidelines, documents from regulatory agencies are seldom included, the researchers say. Thus, guidelines might not be based on complete and accurate information.

Source: BMJ, June 2015

**DEVICE NEWS**

**CoreValve Evolut R Approved**

The FDA has approved the CoreValve Evolut R system (Medtronic) for transcatheter aortic valve replacement in patients with severe aortic stenosis who are at high or extreme risk for surgery.

The new system consists of the CoreValve Evolut R transcatheter valve and the EnVeOR delivery system, which features an InLine sheath that reduces the profile to less than 1/5 inch. A smaller profile size provides a greater opportunity to treat an expanded patient population with smaller vessels (down to 5.0 mm) through the preferred transfemoral access route, which may minimize the risk of major vascular complications in some patients. An extended sealing skirt on the 26-mm and 29-mm valve sizes is intended to further promote valve sealing at the annulus.

In March, initial clinical outcomes for the CoreValve Evolut R system were presented at the scientific session of the American College of Cardiology. At 30 days, all recapture attempts were performed safely with no strokes. In addition, correct valve position with one device was achieved in 98.3% of patients, and there were no cases of valve dysfunction, procedural death, annular rupture, coronary occlusion, valve embolization, or conversion to surgery. The pacemaker rate was 11.7%.

The Evolut R system comes in 23-mm, 26-mm, and 29-mm sizes.

Source: Medtronic, June 23, 2015, and March 14, 2015

**Device Recalls**

**HeartWare Ventricular Assist System**

The HeartWare Ventricular Assist System (HVAS) was recalled after a series of problems led to 40 reported malfunctions with five injuries and three deaths.

An FDA recall notice cited three problems: 1) worn alignment guides can cause power supply connection pins to twist or bend, potentially interrupting electricity to the pump; 2) a battery that powers an alarm may fail, so the alarm will not alert the patient if power is disconnected; and 3) the connector for a driveline that provides power may be damaged if it is pulled too often with too much force.

The HVAS helps deliver blood from the heart to the body in patients at risk of death from end-stage left ventricular heart failure who are awaiting heart transplants. A controller governs the speed and function of a pump implanted in the pericardium. Loss of the two external power sources will stop the pump, with potentially fatal consequences.

The class I recall affects all 1,763 U.S. systems (products 1101 and 1103), which were distributed from January 2008 to March 2015. HeartWare described these and other issues in an urgent medical device correction on May 11, 2015. HeartWare reminded clinicians and patients to follow directions in the patient manual and to be aware of signs of wear.

Providers should see patients subject to this recall as soon as possible and inspect the HVAS power supply connectors for wear, twisting, or bending. Consider replacing the controller if necessary. HeartWare will replace all defective controllers by the end of June 2016. Health care providers with questions should contact their HeartWare representative or HeartWare’s 24-hour Clinical Support at 1-888-494-6365, or email FSCA@heartware.com.

Sources: FDA, June 16, 2015, and June 26, 2015, and HeartWare, June 8, 2015

**Maquet FLOW-i Anesthesia Systems**

The FLOW-i Anesthesia System (Maquet Critical Care AB) was recalled

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after 10 foreign reports that patient cassettes—the center of gas flow in the system—had come loose, potentially imperiling ventilation support or causing anesthesia to leak. The patient cassette locking device may accidentally release the cassette from its mount as users tend to the system.

The system administers anesthesia while providing ventilation to patients with no or limited breathing ability. The units were distributed from July 2011 to May 5, 2014. Maquet will contact users to arrange replacement of the cassette locking device. For questions about this class I recall, contact Maquet at 1-888-627-8383, Monday through Friday, 8 a.m. to 5 p.m. Eastern time.

Source: FDA, July 1, 2015

**Zimmer Hip Replacement Implants**

Zimmer, Inc., recalled 64 lots of hip replacement implants because a process-monitoring failure left unexpectedly high amounts of manufacturing residue that could cause allergic reactions, pain, infections, or death. Some implants may require replacement. The Zimmer M/L Taper with Kinectiv Technology Femoral Stems and Necks were distributed from March 31 through April 20, 2015. A list of products and lot numbers in this class I recall is available at http://tinyurl.com/ZimmerImplants. Customers with questions can contact Zimmer at 1-877-946-2761, 8 a.m. to 5 p.m. Eastern time.

Source: FDA, June 19, 2015

**Teleflex Hudson Resuscitator**

The Hudson RCI Lifesaver Single Patient Use Manual Resuscitator (Teleflex Medical) has been recalled because the oxygen intake port may be blocked, which could prevent the bag from filling and delivering breathing support. The disposable device provides temporary breathing support during acute ventilatory failure. The class I recall affects 2,405 devices in the U.S. made and distributed from June 2014 to April 2015. Customers with questions may contact Teleflex Customer Service at 1-866-246-6990, Monday through Friday, 8 a.m. to 7 p.m. Eastern time, or call their local sales representative.

Source: FDA, July 2, 2015

**DEVICE SPOTLIGHT**

**Kunj Gohil, PharmD, RPh**

**Name:** Theranos System  
**Manufacturer:** Theranos, Inc., Palo Alto, California  
**Approval Date:** July 2, 2015  
**Purpose:** The system is used to facilitate testing of herpes simplex 1 virus immunoglobulin G.

**Description:** The system is comprised of the new finger-stick and venous blood test. Using novel Theranos Nanotainer Tubes, samples can be collected through a few drops of blood from a simple finger prick.

**Benefit:** Theranos has created a system that is expected to mitigate the human error associated with the manual processing of samples. FDA approval was supported by data from 818 subjects, which showed that the test could be run accurately using the finger stick as well as a venous blood draw. This new technology is a cheap and simple alternative to current testing practices.

**Sources:** www.theranos.com, www.medscape.com

**Name:** Proteus Ingestible Sensor Technology  
**Manufacturer:** Proteus Digital Health Inc., Redwood Shores, California  
**Approval Date:** July 2, 2015  
**Purpose:** This sensor is designed to report specific metrics, mainly around medication adherence.

**Description:** The system is comprised of an ingestible sensor that can be used with a medication to record patient-specific metrics, such as steps, rest, heart rate, and most importantly intake time. This information is then communicated to an adhesive patch, the Proteus Patch, through the use of Bluetooth.

**Benefit:** Billions of dollars in avoidable health care costs are associated with the unnecessary escalation of treatment. As the first FDA-approved device with an indication for medication adherence, the Proteus Ingestible Sensor is an innovation that has the ability to improve real-world effectiveness of medicines. Additionally, this device will help investigators better understand patient adherence throughout clinical trials.

**Sources:** www.fda.gov, www.edwards.com