NEW DRUGS

Mirvasco for Rosacea

Brimonidine topical gel 0.33% (Mirvasco, Galderma) has been approved for the topical treatment of the facial erythema of rosacea in adults 18 years of age and older. Applied once daily, the medication reduces redness of the face and lasts up to 12 hours.

An alpha2-adrenergic agonist, brimonidine appears to constrict the dilated facial blood vessels, which reduces the redness of rosacea. A pea-sized amount of gel is applied to the forehead, chin, nose, and each cheek.

The drug’s approval was based on data collected from two phase 3 studies in which reductions in facial redness were greater with brimonidine than with the vehicle gel. In controlled clinical trials, adverse reactions included erythema, flushing, a burning sensation, and contact dermatitis.

Clinicians should use caution when prescribing this gel in patients with depression, cerebral or coronary insufficiency, Raynaud’s phenomenon, orthostatic hypotension, thromboangiitis obliterans, scleroderma, Sjögren’s syndrome, or uncontrolled cardiovascular disease. The drug’s approval was based on data collected from two phase 3 studies in which reductions in facial redness were greater with brimonidine than with the vehicle gel. In controlled clinical trials, adverse reactions included erythema, flushing, a burning sensation, and contact dermatitis.

Pylera for H. pylori Infection

Aptalis Pharma US, Inc., has announced the launch of Pylera 10 Day Therapy Pak in the U.S. The capsules contain bismuth subsalicylate potassium, metronidazole, and tetracycline HCl, in combination with omeprazole, for patients with Helicobacter pylori infection and duodenal ulcer disease.

Pylera is the only brand-name treatment option that does not contain clarithromycin, a macrolide antibiotic. The use of macrolides is believed to contribute to the growing rate of clarithromycin-resistant H. pylori.

The American College of Gastroenterology recommends that clinicians ask patients whether they have ever used a macrolide for any reason. The likelihood of clarithromycin-resistant H. pylori infection increases with multiple macrolide antibiotic courses prescribed before a diagnosis of H. pylori was made. The eradication of H. pylori reduces the risk of duodenal ulcers.

Pylera is contraindicated in patients with renal impairment and in those with known hypersensitivity to the product’s components.

Source: Aptalis, September 3, 2013

Generic Approvals

Divalproex for Seizures and Migraine

Dr. Reddy’s Laboratories has launched divalproex sodium extended-release tablets (ER), USP (250 mg and 500 mg), which are therapeutically equivalent to AbbVie’s Depakote ER tablets. Divalproex sodium is an oral anticonvulsant and anti-epileptic agent.

Sources: Dr. Reddy’s Laboratories and GlobalData, August 23, 2013

Rifampin for TB And Neisseria Infections

Lupin Pharmaceuticals has received the FDA’s final approval for its rifampin capsules USP (150 mg and 300 mg). The capsules are the AB-rated generic equivalent of Sanofi’s Rifadin capsules at the same strengths. Rifampin is indicated for patients with all forms of tuberculosis and for asymptomatic carriers of Neisseria meningitidis to eliminate meningococci from the nasopharynx.

Sources: Lupin, August 1, 2013; GlobalData, August 26, 2013

Preservative-Free-Ondansetron For Antiemesis

BD Rx, Inc., a subsidiary of Becton, Dickinson, has announced the FDA’s approval of a ready-to-administer prefilled generic injectable version of ondansetron. This 5-HT, (serotonin) receptor antagonist is used to prevent postoperative nausea and vomiting. It can also be used with initial and subsequent courses of cancer chemotherapy.

Ondansetron is the generic form of Zofran, made by GlaxoSmithKline, and it is currently on the drug shortage list.

BD Simplist prefilled injectables are designed to decrease the number of steps in the traditional vial-and-syringe injection sequence, reducing the potential risk of medication errors. Up to 20 steps are required in a traditional vial-and-syringe injection sequence; with BD Simplist prefilled injectables, the sequence is reduced to approximately 12 steps.

Ondansetron injection will be available as a 4-mg/2-mL strength in a 2-mL prefilled single-use syringe in a 24-count carton. The ready-to-use syringes are barcode for easy identification.


Capécitabine for Two Cancers

Teva’s version of the oral metastatic colorectal cancer drug capécitabine (Xeloda, Roche) has been approved. The generic version, also approved for the treatment of metastatic breast cancer, will be sold in strengths of 150 mg and 500 mg.

Capécitabine is packaged with a boxed warning stating that patients should avoid concomitant treatment with blood thinners, which may cause serious adverse events.

Source: FDA, September 16, 2013

Lansoprazole for Ulcers and GERD

Sun Pharmaceutical Industries Ltd. has announced the FDA’s final approval for its Abbreviated New Drug Application (ANDA) for lansoprazole delayed-release capsules in strengths of 15 mg and 30 mg. This product is the therapeutically equivalent of Takeda’s Prevacid
delayed-released capsules.

Lansoprazole is indicated as a short-term therapy (for 4 weeks) for healing and symptom relief of active duodenal ulcers and gastroesophageal reflux disease.

Source: Sun, September 14, 2013

**Morphine Sulfate ER Capsules**

Upsher-Smith’s morphine sulfate extended-release (ER) capsules, a Schedule II controlled substance, are now available. The capsules are indicated to relieve moderate-to-severe acute and chronic pain when the use of an opioid analgesic is appropriate. In general, opioid analgesics act primarily at the mu-receptors. Higher dosages, however, may result in activity at the other receptor subtypes.

Historically, the availability of morphine sulfate generic versions has been limited. The company’s version will be the first generic entrant for the 10-mg ER capsule dosage strength.¹ The capsules are sold in dosage strengths of 10, 20, 30, 50, 60, 80, and 100 mg.


**Oxymorphone HCl ER Tablets**

Actavis, Inc., has launched oxymorphone HCl extended-release (ER) tablets, 5 mg, 10 mg, 20 mg, 30 mg and 40 mg. This product is the generic equivalent of Endo’s Opana ER, an opioid agonist used to relieve moderate-to-severe pain in patients needing continuous, around-the-clock opioid treatment for an extended period of time.

Opana ER was voluntarily withdrawn from sale in 2012. Actavis previously received approval for, and is currently marketing, oxymorphone HCl ER tablets in strengths of 7.5 and 15 mg. Actavis is currently a defendant in a lawsuit filed by Endo alleging that Actavis’ product infringes on certain Endo patents.

Source: Actavis, September 12, 2013

**NEW INDICATIONS**

**Abraxane for Pancreatic Cancer**

The FDA has expanded the indication for protein-bound particles of injectable paclitaxel suspension (Abraxane, Celgene) to include its use in combination with gemcitabine (Gemzar, Eli Lilly) for the treatment of late-stage pancreatic cancer. This version of paclitaxel is already approved for the treatment of breast cancer and as part of first-line combination therapy for non–small-cell lung cancer.

In MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial), an open-label, randomized, phase 3 international study of 861 patients, those receiving Abraxane plus gemcitabine versus gemcitabine alone lived about 1.8 months longer and had longer progression-free survival.

The new indication for Abraxane was approved under an expedited review. The drug was also granted an orphan product designation for pancreatic cancer.

Sources: FDA and Celgene, September 6, 2013

**Botox Cosmetic for ‘Crow’s Feet’**

The FDA has approved a new use for onabotulinumtoxinA (Botox Cosmetic, Allergan) for the temporary improvement in the appearance of moderate-to-severe lateral canthal lines (“crow’s feet”) in adults. This is the only FDA-approved drug treatment option for this condition.

Botox Cosmetic was approved in 2002 for the temporary improvement of glabellar lines (frown lines between the eyebrows). The drug works by keeping muscles from tightening so that wrinkles are less prominent. The product is administered via intramuscular injections. Treatment for both frown lines and crow’s feet can be given at the same time.

Botox Cosmetic’s safety and effectiveness for treating lateral canthal lines were established in two clinical efficacy and safety studies. The most common adverse reaction was eyelid edema.

OnabotulinumtoxinA is also sold as Botox, which is indicated for the treatment of chronic migraine headaches, severe underarm sweating, blepharospasm, and strabismus.

A boxed warning for both Botox and Botox Cosmetic states that the effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism (e.g., swallowing and breathing difficulties), which can be life-threatening. There has not been a confirmed serious case of toxin spread when either product was used at the recommended dose for the approved indications.

Source: FDA, September 11, 2013

**NEW FORMULATIONS**

**Trokendi XR for Epilepsy**

Supernus Pharmaceuticals, Inc., has received final approval from the FDA to sell Trokendi XR, a once-daily, extended-release (ER) formulation of topiramate for the treatment of epilepsy.

Trokendi ER is indicated for initial monotherapy in patients 10 years of age and older with partial-onset or primary generalized tonic–clonic seizures; as adjunctive therapy in patients 6 years of age and older with partial-onset or primary generalized tonic–clonic seizures; and as adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox–Gastaut syndrome.

The capsules will be available in strengths of 25, 50, 100, and 200 mg. Trokendi XR is discussed in the Pharmaceutical Approval Update column on page 604.

Source: Supernus, August 19, 2013

**Valchlor Gel for Lymphoma**

Mechloretamine (Valchlor, Ceptaris), commonly known as nitrogen mustard, has been approved for the treatment of the most common form of cutaneous
T-cell lymphoma (CTCL). This once-daily gel can be used for stage IA and IB mycosis fungoides-type CTCL in patients who have received previous skin-directed therapy. It is the first FDA-approved topical formulation of mechlorethamine.

Mechlorethamine was previously approved for the intravenous (IV) treatment of mycosis fungoides. Before the FDA’s approval of this topical form, only non-standardized, pharmacy-compounded petroleum ointment or aqueous-based topical preparations were available. The National Comprehensive Cancer Network is currently recommending topical mechlorethamine preparations for patients with early-stage CTCL.

Sources: Ceptaris and Fierce Biotech, August 26, 2013

**Bendamustine Liquid Injection**

Bendamustine HCl injection (Treanda, Cephalon/Teva) has been approved as a liquid formulation. The medication is indicated for patients with indolent B-cell non–Hodgkin’s lymphoma that has progressed during or within 6 months of treatment with rituximab (Rituxan, Genentech) or a rituximab-containing regimen, and for patients with chronic lymphocytic leukemia.

With the new liquid formulation, there is no need to reconstitute lyophilized powder with sterile water, thereby making dose preparation fast and convenient for the clinician.

Source: Teva, September 17, 2013

**DRUG NEWS**

**Orphan Drug Designations**

**EPZ-5676 for Epilepsy**

Epizyme’s EPZ-5676 is a small-molecule inhibitor of DOT1L (an oncogene-driver gene). It is used to treat acute leukemias in which the MLL (myeloid/lymphoid, or mixed-lineage, leukemia) gene is rearranged because of a chromosomal translocation (MLL-r). DOT1L causes inappropriate methylation, which results in the increased expression of genes that cause leukemia.

In September 2012, Epizyme initiated a phase 1 clinical trial. As of August 2013, this program was in the dose-escalation phase. An expansion phase is scheduled to enroll MLL-r patients exclusively beginning in the second half of 2013.

Epizyme retains all rights to EPZ-5676 in the U.S. and has granted Celgene an exclusive license to sell EPZ-5676 outside the U.S. The company is also working with Abbott to develop a companion diagnostic to identify patients with the MLL-r translocation.

Source: Epizyme, August 16, 2013

**ALN-AT3 for Hemophilia**

ALN-AT3 (Alnylam Pharmaceuticals) is a subcutaneously administered RNA interference (RNAi) agent that targets antithrombin for the treatment of hemophilia A, hemophilia B, hemophilia A or B with inhibitors, and other rare bleeding disorders. This anticoagulant normalizes thrombin generation, improves hemostasis in hemophilic mice, and corrects thrombin generation in a non-human primate hemophilia-inhibitor model.

Alnylam plans to file an Investigational New Drug (IND) application for ALN-AT3 in the fourth quarter of 2013 and to begin a phase 1 clinical trial in early 2014.

Source: Alnylam, August 20, 2013

**SGX94 for Radiation Syndrome**

SGX94 is being investigated for the treatment of acute radiation syndrome. Made by Soligenix, Inc., SGX94 is an innate defense regulator. This is a new class of short, synthetic peptides that accelerate the resolution of tissue damage following exposure to bacterial pathogens, trauma, radiation, and chemotherapy. In preclinical models, SGX94 showed the potential to lessen damage to the skin and gastrointestinal tract and to eradicate infection as a result of damage to the hematopoietic system.

Source: Soligenix, September 16, 2013

**Nerve Growth Factor For Retinitis Pigmentosa**

An investigational drug, discovered by Nobel Laureate Professor Rita Levi Montalcini, has been granted an orphan drug designation by the FDA for the treatment of retinitis pigmentosa. Recombinant human nerve growth factor (rhNGF) was developed by the Dompé group. Currently, there is no cure for this disease.

The FDA’s designation comes just a few months after an orphan drug designation was granted by the European Medicine Agency. The drug is already in late-stage clinical development for the treatment of neurotrophic keratitis, a severe corneal disease.

rhNGF is produced by transferring human genetic material into a bacterium, which then becomes capable of producing NGF. The product is the same type of protein as the one naturally produced by the human body. It promotes the development and survival of nerve cells, including retinal cells. NGF inhibited retinal degeneration in animals with retinitis pigmentosa. RhNGF may be able to improve the survival of retinal cells, slow down disease progression, and help preserve vision.

Source: GlobalData, September 11, 2013

**Bimagrumab for Muscle Wasting**

Bimagrumab (BYM338, Novartis) is being used to treat patients with sporadic inclusion-body myositis, a rare but potentially life-threatening muscle-wasting condition. The new breakthrough therapy designation is granted only after preliminary clinical evidence indicates substantial improvement over currently available
therapy. The designation for bimagrumab was based on results of a phase 2 proof-of-concept study.

A fully human monoclonal antibody, bimagrumab stimulates muscle growth by blocking signaling from inhibitory molecules. It was granted an orphan drug designation for muscle wasting in 2012. No other medications have been approved for sporadic inclusion-body myositis.

Source: Novartis, August 20, 2013

**Entinostat for Advanced Breast Cancer**

Entinostat, manufactured by Syndax, is being tested for the treatment of locally recurrent or metastatic estrogen receptor–positive (ER+) breast cancer when added to exemestane (Aromasin, Pfizer) in postmenopausal women whose disease has progressed after therapy with a nonsteroidal aromatase inhibitor.

Entinostat is an investigational oral inhibitor of class I histone deacetylases, which are key enzymes that alter the structure of chromatin to control gene expression. Entinostat is designed to target the HDAC isoforms that are most relevant to the biology of tumors, thereby normalizing dysregulated gene expression in cancer cells and restoring the cells’ sensitivity to targeted therapy. The new designation for entinostat is based on promising data from the completed phase 2 ENCORE 301 study.

Source: Syndax, September 11, 2013

**Volasertib for Leukemia**

Volasertib, an investigational inhibitor of polo-like kinase (Plk), is being assessed in patients 65 years of age or older with previously untreated acute myeloid leukemia (AML) who are ineligible for intensive remission-induction therapy.

A phase 2 study enrolled patients with newly diagnosed AML who were considered to be ineligible for intensive remission-induction therapy. Rates of objective response and event-free survival were higher in patients receiving volasertib in combination with low-dose cytarabine (LDAC) compared with patients receiving LDAC alone. The results were presented at the 54th American Society of Hematology (ASH) meeting in December 2012.

These results led to the initiation of a phase 3 trial, POLO-AML-2, in January 2013. This study is designed to assess the efficacy and safety of volasertib plus LDAC, compared with placebo in combination with LDAC, in patients 65 years of age and older.

Volasertib is designed to inhibit the activity of Plk1, an enzyme in the Plk family that regulates cell mitosis. This inhibition is intended to result in prolonged cell-cycle arrest, ultimately leading to apoptosis.

Volasertib can be taken either orally or via IV infusion. After circulating in the bloodstream, it is distributed throughout the body.

Source: Boehringer Ingelheim, September 17, 2013

**Fast-Track Designation Ganetespib for Lung Cancer**

Ganetespib (Synta) is an investigational heat-shock protein (Hsp) 90 inhibitor that improved overall survival when given with docetaxel (Taxotere, Sanofi) for patients with metastatic non–small-cell lung adenocarcinoma that has progressed after one previous chemotherapy regimen. The drug is being evaluated in the Ganetespib Assessment in Lung cancer with docetaxel (GALAXY) trials.

Hsp90 is a molecular “chaperone” that controls the folding and activation of client proteins that drive tumor development and progression. In preclinical models, inhibition of Hsp90 by ganetespib resulted in the inactivation, destabilization, and eventual degradation of these cancer-promoting proteins.

Ganetespib is also being used in trials of breast cancer and other tumor types.

Source: Synta, September 12, 2013

**Recalls**

**Cubicin Injection**

Cubicin voluntarily recalled four lots of daptomycin for injection 500 mg (Cubicin) after glass particulate matter was found in some 10-mL, single-use vials. The product was shipped from May 2011 to March 2013. Lots 950453F, 090203F, 201703F, and 201653F are affected by the recall.

Daptomycin for injection is used to treat skin and bloodstream infections.

The administration of glass particulate, if present in an intravenous drug, can lead to the formation of granulomas, thromboembolism sequela, and pulmonary emboli.

Customers with an existing inventory of these lots should quarantine and discontinue distributing them.

Source: FDA, August 29, 2013

**Risperdal Consta 25 mg**

One lot of Risperdal Consta was voluntarily recalled after mold was discovered during a routine testing process. This long-acting injectable form of Johnson & Johnson’s risperidone antipsychotic medication is used to treat patients with bipolar disorder and schizophrenia. Basic risperidone is sold as a tablet.

Risperdal Consta is administered to patients by health care professionals only.

Patients were being advised to continue their prescribed treatment.

The injectable drug is manufactured by Alkermes PLC and is marketed by J&J’s Janssen division in the U.S. The recall applies only to doctors who still have the affected batches.

Janssen stated that if the patient is taking oral risperidone (Risperdal) or is receiving any other dose of Risperdal Consta besides 25 mg, this recall does not apply.
A patient in Europe with possible multiple sclerosis (MS) developed a rare and serious brain infection after taking fingolimod (Gilenya, Novartis), leading the FDA to issue a warning to the public. This is the first case of progressive multifocal leukoencephalopathy (PML) reported following the administration of fingolimod to a patient who had not previously received natalizumab (Tysabri, Biogen Idec). When used for MS, natalizumab was associated with a higher risk of PML. Fingolimod is used to treat relapsing forms of MS.

PML is caused by the John Cunningham (JC) virus, which damages myelin, and it usually results in death or severe disability and generally affects those with weakened immune systems.

Patients should not stop taking fingolimod without first consulting their health care professional. Novartis did not believe fingolimod was responsible for PML in this case, as the patient was taking other drugs in addition to fingolimod.

Sources: FDA and MedPage Today, August 29, 2013

**Delaying Antibiotics For Urinary Tract Infections**

In a study of 176 women with urinary tract infections (UTIs), more than 70% of those who chose to delay treatment experienced fewer symptoms within a week. In a study conducted at the University of Amsterdam, patients who were experiencing painful or frequent urination for no more than 7 days were recruited from 20 general practices nearby. The general practitioners were to ask all patients if they were willing to delay treatment. After 7 days, the patients reported whether their symptoms had improved and whether they had used any antibiotics.

Of the 137 women who were asked to delay treatment, 51 (37%) agreed. After 1 week, 28 women (55%) had not used antibiotics; of these, 20 (71%) reported clinical improvement or cure.

The results of the baseline cultures were not known until after the follow-up week. The culture was positive for 26 (51%) of the 51 delaying women and 58 (67%) of 86 women who did not delay. Of the 20 women who reported improvement or cure, 7 (35%) had a positive culture.

None of the subjects developed pyelonephritis. Although the researchers say that placebo arms of randomized trials suggest that cystitis seldom progresses to pyelonephritis, they acknowledge that clinicians sometimes consider the risk of pyelonephritis as a reason to treat all women with a suspected UTI.

The researchers say that this is the first study to describe women who are willing to delay antibiotic therapy for symptoms of a UTI. Qualitative research already suggests that women may actually prefer not to take antibiotics. Still, clinicians in one practice did not ask any of their 25 patients to delay antibiotic treatment because they disagreed in principle with the approach. The researchers suggest that clinicians might have a misperception that patients want antibiotics when in fact they do not.

Interestingly, patients who were excluded from the study by their health care professional did not have worse baseline characteristics than those who were included. On the contrary, women who reported at least considerable pain or who thought they had a UTI were more likely to be included. This suggests that the clinician’s decisions about asking women to delay antibiotic treatment were based more on their personal attitude toward antibiotic prescribing than on patient characteristics. The clinicians could also have been influenced by patients’ attitudes or previous health experiences, such as a problematic history of UTIs.

Placebo arms of randomized trials have shown that 25% to 50% of women presenting with UTI symptoms recover in a week without using antibiotics. In another trial, delaying antibiotics reduced antibiotic use by 20% while yielding the same symptom control as immediate antibiotic treatment.

New research is under way that might lead to a change in initial treatment—not with antibiotics but with pain medication.
Drug Shortages: Quality Control Problems Persist

Fewer medications are on the drug shortage list this year, but those already on the list show few signs of moving off. The University of Utah tracked only 86 new shortages through July 31, down from 204 in all of last year, 267 in 2011, and 211 in 2010. However, the number of active shortages as of the end of July was 302 (similar to figures since the third quarter of 2012).

Existing drug shortages continue to be a problem, because it is taking a long time for drug companies to fix their quality problems. Antimicrobials, chemotherapy agents, and electrolyte and parenteral nutrition products continue to be in short supply. Although the FDA prevented 282 shortages last year, present shortages are likely to persist until the factories are updated.

Quality control is a major cause of these shortages, particularly with generic products. Glass particles or particulates found in products have caused several manufacturers of sterile injectables to shut down.

A July 23 decision by the District of Columbia Circuit Court of Appeals could hurt the FDA’s efforts to alleviate shortages. The three-judge panel permanently disallowed the FDA to import versions of thiopental (which is used in executions) into interstate commerce.

Shortages of the cancer drug thiopenta (e.g., Tepadina, Adienne), ethiodized oil (Ethiodol, Lipiodol, Guerbet, formerly Nycomed/Savage), and trace element products rely on imported drugs when the supply of the FDA-approved versions is not enough to meet demand.

Sources: University of Utah and MedPage Today, August 23, 2013

Fluoroquinolones May Carry A Risk of Kidney Damage

Physicians aren’t usually thinking of kidney injury when they prescribe fluoroquinolones, even though reports of acute kidney injury have been published and the product label includes renal failure as a rare but possible adverse reaction. Yet oral fluoroquinolones more than double the risk of acute kidney injury that can be severe enough to require hospital admission in adult men.

Researchers from the University of Florida, the University of British Columbia, McGill University, Royal Victoria Hospital, the University of Washington, and the Department of Health and Human Services evaluated data for 1,292 men (40 to 85 years of age) who were admitted to the hospital with acute kidney injury and 12,651 matched controls admitted for other diagnoses. The study focused on outpatient-dispensed preparations: ciprofloxacin, gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, and norfloxacin. They also selected two common oral antibiotics—amoxicillin and azithromycin—as control drugs. Ciprofloxacin and levofloxacin were the most commonly used fluoroquinolones and were used most often to treat respiratory or genitourinary infections.

The researchers found an increased risk of acute kidney injury with current use of oral fluoroquinolones. There was no change in risk with either recent or past use. No association was observed between amoxicillin or azithromycin use and acute kidney injury.

When the investigators stratified their analysis by product, ciprofloxacin posed the largest relative risk, followed by moxifloxacin and levofloxacin. There were also drug interactions with the combined use of fluoroquinolones and renin–angiotensin–system (RAS) blockers, amounting to a more than four-fold increase in the relative risk for acute kidney injury with active use of both drugs. A similar increased risk was noted for the dual use of fluoroquinolones and either angiotensin-converting-enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs).

Previous evidence of acute kidney injury with fluoroquinolones came from case reports, most of them describing an allergic or a hypersensitivity reaction (acute interstitial nephritis). They current researchers wrote that fluoroquinolones have also been implicated in cases of granulomatous interstitial nephritis, crystalluria, and acute tubular necrosis. Most published case reports involve ciprofloxacin, but this could be an artifact of its high use.

Although the study enrolled adult men, there is no reason to suppose that the increased risk is limited to this population. The researchers advised caution and recommended further study in other patient groups.

Source: Can Med Assoc J, July 9, 2013

Lithium: A Standby With Unexpected Benefits?

Patients with mood disorders are at high risk for suicide, and the risk is as much as 30 times higher than that of the general population, say researchers from the University of Verona and the University of Oxford. Medication plays a relatively minor role in most suicide-prevention strategies, they add, but that role might have been underestimated. Having previously reported in 2005 on the benefits of long-term lithium in reducing the risk of suicide in mood disorders, they decided to update their meta-analysis. They found that there is still a place for long-term lithium therapy and that its anti-suicidal effect may be greater than its effect on mood episodes.

The team looked at 48 studies, including eight that contributed new data. Nearly half of the studies compared lithium with placebo. Lithium was also compared

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with 14 other medications, including amitriptyline, carbamazepine, valproate, and fluoxetine. Follow-up ranged from 4 to 48 months. A total of 6,674 patients were assigned to receive one of the active agents or placebo.

Lithium was associated with a reduced risk of death and suicide by more than 60% compared with placebo. The consistency of results in the studies could indicate that lithium’s life-preserving effect is independent of the comparator drug. However, there was no clear benefit for lithium over placebo in preventing deliberate self-harm.

In patients with unipolar depression, lithium was associated with a reduced risk of suicide and fewer deaths compared with placebo. When lithium was compared with other drugs, a statistically significant difference was found only with carbamazepine for deliberate self-harm, but lithium tended to be more effective than the other active comparators.

A new finding was that lithium reduced the risk of suicide and of total deaths in patients with both unipolar and bipolar depressive disorder. The reduced risk of all-cause mortality mainly reflected a reduction in suicide. The researchers suggested that lithium reduced the relapse of the mood disorder; however, because the drug is not as potent in the acute phase of therapy as other antidepressants (which do not seem to have similar anti-suicidal effects), something else could be at work, particularly since the anti-suicidal effect in their analysis was larger than the effect on mood episodes. One explanation might be that lithium reduces aggression and possibly impulsivity, both of which are associated with a higher risk of suicide.

Lithium’s adverse effects, which are probably dose-related, are a concern for both patients and clinicians. The oral dose and plasma concentrations need to be monitored to ensure optimal efficacy and adequate tolerability. Despite those drawbacks, clinicians might consider the fact that lithium can reduce deliberate self-harm in people with bipolar disorder and recurrent unipolar depression.

Source: *BMJ* 2013;346:f3646, June 27, 2013

### Lucentis Appears Superior to Laser for Diabetic Eye Condition

Patients with diabetic macular edema (DME) who received ranibizumab (Lucentis, Genentech) reported more improvement in eyesight than those who received laser treatments alone. As the first approved drug for the treatment of age-related neovascular (wet) macular degeneration, ranibizumab is a monoclonal antibody fragment that inhibits the biologic activity of human vascular endothelial growth factor A (VEGF-A), which promotes the growth of blood vessels in the eye.

In a study from the University of Sydney, after 12 months, almost 50% of patients receiving the drug alone reported at least a 5-point improvement in a visual questionnaire compared with 43% of patients treated with the drug plus laser and with 31% of patients treated with laser alone.

The FDA approved ranibizumab for patients with DME in 2012. Patients typically receive once-monthly injections, but the cost (as much as $2,000 per dose) has proved controversial. A 2012 National Eye Institute-sponsored trial that compared ranibizumab to a similar VEGF-A-binding drug, bevacizumab (Avastin, Genentech), found the two drugs to be equally effective for patients with age-related macular degeneration (AMD). However, adverse events were slightly more common with bevacizumab, which costs about $50 per dose.

Patients with better baseline visual acuity or lower central retinal thickness showed the greatest improvements after receiving ranibizumab compared with laser treatment in composite and some subscale scores.

The researchers cautioned that long-term follow-up data from the RESTORE study (Ranibizumab Monotherapy or Combined With Laser vs. Laser Monotherapy for Diabetic Macular Edema) would be needed to determine whether the 12-month benefits of ranibizumab are sustained during the 3-year period of the trial.

In addition to bevacizumab, another VEGF-targeting drug, aflibercept (Eylea, Regeneron), had beneficial results in two phase 3 trials of DME. Patients who received aflibercept experienced greater visual improvements compared with patients treated with laser alone.

A phase 3 clinical trial has been initiated to compare ranibizumab, aflibercept, and bevacizumab in patients with DME.


### Zonegran Relieves Sleep Apnea

In a pilot trial, zonisamide (Zonegran, Eisai, formerly Elan), a seizure drug, modestly eased obstructive sleep apnea in overweight and obese adults. Apnea–Hypopnea Index (API) scores fell by 22% among patients who randomly received zonisamide over a period of 4 weeks, compared with a slight increase in scores in those receiving placebo.

The study was conducted at the University of Gothenburg in Sweden, and the findings were reported at the European Respiratory Society (ERS) meeting in September.

Pharmacological treatment might be an option for about half of the patients who are unable or unwilling to use continuous positive airway pressure (CPAP). Zonisamide may relieve sleep apnea in two ways: it leads to weight loss, and it increases breathing. Like the anti-
convulsant topiramate (Topamax, Janssen), zonisamide is a carbonic anhydrase inhibitor. Blocking the action of these enzymes, which help convert carbon dioxide and water to bicarbonate for pH balance in the body, the patient becomes a bit more “acidified,” which increases breathing in most situations.

The study included 47 patients 18 to 75 years of age with a body mass index between 27 and 35 kg/m² (mean, 31.2 kg/m²) and an API score of at least 15 events per hour (mean, 41.5) with daytime sleepiness. They received zonisamide 300 mg, CPAP, or placebo. Although weight loss was expected, based on earlier studies with zonisamide, patients did not receive counseling on dietary or lifestyle changes.

API scores dropped from 41.6 per hour at baseline to 32.9 per hour at week 4 with zonisamide, representing a significant mean reduction. By contrast, the placebo group experienced an insignificant increase in hypoxic events.

By 24 weeks, the zonisamide group had lost an average of 6 pounds compared with a gain of 5.1 pounds in the CPAP group. However, CPAP provided more relief, and most of the zonisamide-treated patients reported adverse events (87% vs. 11%) with CPAP.

More research is needed to show whether the drug reduces the risk of obstructive sleep apnea–related adverse events.

Sources: ERS 2013, Abstract P4036; MedPage Today, September 11, 2013

**CDC: Drug-Resistant ‘Superbugs’ Pose Urgent Threat**

Every year, more than 2 million people in the U.S. acquire infections that are resistant to antibiotics, and at least 23,000 people die as a result, according to a new report issued by the Centers for Disease Control and Prevention (CDC).

The report, titled *Antibiotic Resistance Threats in the United States 2013*, presents the first snapshot of the burden posed by antibiotic-resistant organisms that have the greatest effect on human health. The threats are ranked as urgent, serious, and concerning.

Infections classified as urgent threats include carbapenem-resistant Enterobacteriaceae (CRE), drug-resistant gonorrhea, and *Clostridium difficile*, a serious diarrheal infection usually associated with antibiotic use. *C. difficile* causes about 250,000 hospitalizations and at least 14,000 deaths every year in the U.S. According to the CDC, the use of antibiotics is the single most important factor leading to antibiotic resistance. Up to 50% of all the antibiotics prescribed today are not needed or are not prescribed appropriately.

The CDC has identified four actions needed to halt resistance:

- Preventing infection. Avoiding infections reduces the amount of antibiotics that have to be used and decreases the likelihood that resistance will develop. Drug-resistant infections can be prevented by immunization, by actions taken in health care settings, by safe food preparation and handling, and by general handwashing.

- Tracking: The CDC gathers data on antibiotic-resistant infections, on causes of infections, and on any particular risk factors that lead to resistant infection. With that information, experts can develop strategies to prevent those infections and to prevent the resistant bacteria from spreading.

- Improving Antibiotic Stewardship: Up to 50% of antibiotic use in humans and much of antibiotic use in animals is unnecessary. These drugs should be used only when they are needed to treat disease, and they must be chosen and given in the right way each time in a practice known as “antibiotic stewardship.”

- Developing drugs and diagnostic tests: Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not completely stopped. Therefore, new antibiotics will always be needed to keep up with resistant bacteria, as will new tests to track the development of resistance.

Source: CDC, September 16, 2013

**AMG 145 Successful In Treating Hyperlipidemia**

Lipoprotein(a), or Lp(a), is regarded as a risk factor for cardiovascular disease. Researchers sought to evaluate the impact of Amgen’s AMG 145 as a therapy for hyperlipidemia.

As part of the LAPLACE–TIMI 5 trial, 631 patients with hypercholesterolemia who were receiving statins were randomly assigned to receive AMG 145 at one of three different doses every 2 weeks or one of three different doses every 4 weeks compared with placebo. Lp(a) and other lipid parameters were measured at baseline and at week 12.

Compared with placebo, AMG 145 70 mg, 105 mg, and 140 mg every 2 weeks reduced Lp(a) levels at 12 weeks by 18%, 32%, and 32%, respectively. At doses of 280 mg, 350 mg, and 420 mg every 4 weeks, the medication reduced Lp(a) levels by 18%, 23%, and 23% respectively. The reduction in Lp(a) correlated with the reduction in low-density lipoprotein-cholesterol (LDL-C).

The effect of AMG 145 on Lp(a) levels was consistent regardless of patients’ age, sex, race, history of diabetes, and previous statin regimen. Patients with higher levels of Lp(a) at baseline had larger absolute reductions but comparatively smaller percentage reductions in Lp(a) with AMG 145 compared with patients who had lower baseline Lp(a) values.

AMG 145 significantly reduced Lp(a) by up to 32% in subjects with high cholesterol who were receiving a statin.
Sources: Circulation 2013;128:962–969 (August 28); ClinicalTrials.gov; Amgen

**Faster Spontaneous Clearance Of Hepatitis C in Women**

A study of patients infected with acute hepatitis C virus (HCV) infection found that women had higher rates of spontaneous viral clearance—undetectable viral levels without drug therapy. The gene **IL28B** (rs12979860) and HCV genotype 1 were also independent predictors of spontaneous HCV clearance.

In 2011, 1,229 cases of acute HCV were reported to the Centers for Disease Control and Prevention (CDC); this represents a 44% increase over 2010. Medical evidence indicates that acute HCV is spontaneously cleared in about 25% of individuals. Previous prospective studies link female sex, immune responses, neutralizing antibodies, and genetics to viral clearance.

Lead author Dr. Jason Grebely, from The Kirby Institute at the University of New South Wales in Australia, explained that our knowledge of acute HCV clearance is limited. Patients are typically asymptomatic during the initial stages of infection, and at-risk populations, such as people who inject drugs, are often marginalized. The study was conducted to learn more about predictors of HCV clearance in order to improve early therapeutic intervention options.

Researchers used data from the InC3 Study—a collaboration of nine prospective studies from Australia, Canada, the Netherlands, and the U.S. Participants with HCV and human immunodeficiency virus (HIV) were recruited between 1985 and 2010. The present study included 632 individuals with acute HCV; 35% of the patients were women, and 82% were Caucasian. Roughly 96% of the participants had injected drugs, 47% were infected with HCV genotype 1, and 5% were co-infected with HIV.

The results showed that the virus was spontaneously cleared in 173 of the 632 participants during the follow-up period. At 1 year post infection, 25% experienced HCV clearance.

The authors called for further research to understand the effect of sex in controlling HCV infection.

Sources: Hepatology, August 2, 2013 (online); Wiley Science, September 12, 2013

**Experimental Vaccine May Clear AIDS Virus**

A vaccine for the treatment of HIV/AIDS infection, developed by researchers at Oregon Health & Science University, appears to have the ability to completely clear an AIDS-causing virus from the body. The promising vaccine candidate is being tested through the use of a non-human primate form of HIV, called simian immunodeficiency virus (SIV), which causes AIDS in monkeys. Following further development, it is hoped that an HIV form of the vaccine candidate can be used in humans.

So far, HIV infection has been cured in a only a few unusual clinical cases in which HIV-infected patients were treated with antiviral medications very early after the onset of infection, or they received a stem-cell transplant to fight cancer. The new research suggests that certain immune responses elicited by a new vaccine may also be able to completely remove the virus from the body.

In the laboratory, researchers used cytomegalovirus (CMV), a common virus already carried by many people. The team discovered that a modified version of CMV, engineered to express SIV proteins, generates and maintains “effector memory” T cells that can search out and destroy SIV-infected cells.

About 50% of monkeys that received highly pathogenic SIV after being inoculated with the investigational vaccine became infected with SIV. Over time, however, all traces of SIV were eliminated from the body.

Through this method, the researchers explained, they were able to teach the monkey’s body to better prepare its defenses to combat the disease. Their vaccine mobilized a T-cell response that overtook the SIV invaders in 50% of the cases treated. In those monkeys with a positive response, the study suggested that SIV was eliminated from the host. The investigators anticipate that pairing their modified CMV vector with HIV will lead to a similar result in humans.

Source: Nature, September 11, 2013 (online)

**Teflaro, an Antibiotic, Shows Promise for MRSA Pneumonia**

Ceftaroline fosamil (Teflaro, Forest), which was approved by the FDA two years ago for the treatment of bacterial infections, such as community-acquired pneumonia, may prove beneficial for patients with potentially fatal methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia.

Researchers at Henry Ford Hospital found that patients who were treated with the antibiotic had a lower mortality rate after 28 days compared with patients who received vancomycin, the most common drug therapy for MRSA pneumonia.

In the retrospective study, 33 of 38 patients responded well to treatments of ceftaroline and were discharged from the hospital after the infection cleared. Of the five patients who died, three of the deaths were attributed to other serious medical conditions.

The mortality rate for patients treated with vancomycin has been reported to be as high as 32% after 28 days. In the new study, the mortality rate for the ceftaroline-treated patients was 13%.

**DEVICES IN THE NEWS**

**Zimmer Shoulder Implant**

Zimmer’s Patient Specific Instruments (PSI) shoulder system has been approved by the FDA for use in reverse implant procedures. Three-dimensional (3-D) visualization, together with the company’s Trabecular Metal Reverse Shoulder implant, is used to ease placement of the device. With the 3-D view, the surgeon can plan the size and position of the implant according to each patient’s shoulder structure.

The trabecular metal technology is a porous bone implant that supports biologic ingrowth and promotes high friction and stability in the joints. The shoulder system has been available in Europe since May, and the Trabecular implant has been on the market for 2 years.

Source: FierceMedical Devices, August 26, 2013

**UroLift Implant for BPH**

The UroLift system (NeoTract) is the first permanent implant that relieves low or blocked urine flow in men 50 years of age and older with benign prostatic hypertrophy (BPH).

The system relieves urine flow by pulling back prostate tissue that is pressing on the urethra. More than 50% of all men in their 60s and as many as 90% of men in their 70s and 80s have some symptoms of BPH, such as more frequent urination with hesitant, interrupted, or weak stream and urgency and leaking.

Current treatment options to relieve symptoms associated with BPH include drug therapy or surgical procedures, including removal of the enlarged part of the prostate. The UroLift is less invasive than surgery and may be an option for men who cannot tolerate available drug therapies.

The FDA’s review of the UroLift system included data from two clinical studies of men with BPH implanted with two or more UroLift sutures. The first study included 64 men between the ages of 53 and 83, and the second study included 210 men between the ages of 49 and 86. In both studies, physicians successfully inserted the device in 98% of participants.

The studies also measured urine flow and the ability to empty the bladder. Throughout the study period, there was a 30% increase in urine flow and a steady amount of residual urine in the bladder. Study participants reported a decrease in symptoms and an increase in quality of life in the 2 years following treatment.

Minor adverse events included pain or burning during urination, blood in the urine, a frequent or an urgent need to urinate, incomplete emptying of the bladder, and decreased urine flow. No serious device-related adverse events were reported.

The FDA reviewed the UroLift system through its de novo classification process, a regulatory pathway for some novel low-to-moderate risk medical devices that are not substantially equivalent to an already legally marketed device.

Source: FDA, September 13, 2013

**NEW MEDICAL DEVICES**

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

**Name:** Nit-Occlud PDA

**Manufacturer:** PFM Medical, Carlsbad, Calif./Cologne, Germany

**Approval Date:** August 16, 2013

**Purpose:** The Nit-Occlud PDA serves as a plug to close an abnormal opening between the pulmonary artery and the aorta in patients with a patent ductus arteriosus (PDA), a congenital heart defect. The device is permanently implanted during a catheter-based procedure and is intended to be used in nonsurgical closure of the defect.

**Description:** The occluder (plug) is made of a self-expanding coil spiral consisting of an inner (core) wire tightly wrapped by an outer coil wire. After the device is in place, tissue grows over it and the ability to empty the bladder. Throughout the study period, there was a 30% increase in urine flow and a steady amount of residual urine in the bladder. Study participants reported a decrease in symptoms and an increase in quality of life in the 2 years following treatment.

Minor adverse events included pain or burning during urination, blood in the urine, a frequent or an urgent need to urinate, incomplete emptying of the bladder, and decreased urine flow. No serious device-related adverse events were reported.

The FDA reviewed the UroLift system through its de novo classification process, a regulatory pathway for some novel low-to-moderate risk medical devices that are not substantially equivalent to an already legally marketed device.

Source: FDA, September 13, 2013

**Hand-Hand Test May Predict Osteoporotic Fractures**

A portable device that can diagnose the early signs of osteoporosis could be available for use within 5 years.

The technology is being tested at the University of Southampton in the United Kingdom with support from the Engineering and Physical Sciences Research Council (EPSRC). The original concept was developed at the University of California at Santa Barbara.

Unlike current methods of evaluating bone strength, which is measured by x-rays, the device is designed to measure the ability of bone tissue to prevent small cracks from growing into full-blown fractures. A microscopic needle is pressed a tiny distance into the top layer of bone. Measured electronically, the amount of penetration indicates how fragile the bone tissue is and, therefore, the risk of a person’s experiencing an osteoporotic fracture later in life.

In a normal reading, the needle might sink into the bone by around 20 micrometers (0.02 mm); a reading of 40 micrometers might indicate a significant risk of fracture.

As people age and life expectancy increases, the cost of treating osteoporotic fractures will increase. One in three women older than 50 years of age is predicted to experience an osteoporotic fracture in her lifetime. Globally, the costs of treatment costs are projected to exceed $130 billion by 2050.

The project leaders hope that improvements in assessing osteoporosis and future fracture risk offered by this new technology might lead to a reduction in the burden of broken bones for individuals, health care systems, and the economy.

Source: EPSRC, September 17, 2013
and the device becomes part of the pulmonary artery. A delivery tube (catheter) containing the occluder is threaded into a vein in the groin and through the pulmonary artery. The catheter is then advanced through the defect. When the catheter is in the correct position, the coil is advanced through the catheter into the aorta. The coil wire is released so that the last loop is on the pulmonary side of the defect.

**Benefit:** This device prevents blood from passing through the PDA. Large openings may cause fatigue, difficult or rapid breathing, growth failure, or chronic respiratory infections, such as colds and pneumonia, and may lead to heart failure and death. The device is implanted without the need for open-heart surgery.

A phase 2 clinical study was conducted with 378 subjects enrolled in 15 study centers throughout the U.S. under an Investigational Device Exemption. Favorable results meeting all criteria were the basis for the FDA’s premarket approval decision.

**Precautions:** The device should not be used in patients who weigh less than 11 pounds, in patients with blood clots at the defect site or in the vessels leading to the defect, or in those with endocarditis or pulmonary hypertension.

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

**Name:** BioFlo Port with Endexo Technology

**Manufacturer:** AngioDynamics/Navilyst Medical, Inc.

**Approval Date:** August 20, 2013

**Purpose:** This device is used to reduce the accumulation of catheter-related thrombus on and within the port catheter.

**Description:** Ports are implanted under the skin to facilitate the long-term delivery of medication and to access the patient’s vascular system for repeated intravenous (IV) chemotherapy, blood withdrawal, or total parenteral nutrition. Thrombi resulting from ports cost the health care system an estimated $1 billion annually, and more than 50,000 deaths per year are caused by thromboembolism. Cancer patients are among those most susceptible to thrombosis.

**Benefit:** The BioFlo technology shows promise in decreasing the accumulation of catheter-related thrombus without the use of heparin, antibiotics, or antimicrobials, or other materials typically associated with coated or impregnated technologies. In vitro blood-loop model test results show that, on average, the BioFlo port catheter was associated with 96% less thrombus accumulation on its surface compared with non-coated conventional port catheters.

**Sources:** www.angiodynamics.com

**Name:** Intella Tip MiFi Ablation Catheter; Zurpaz 8.5 French Steerable Sheath

**Manufacturer:** Boston Scientific, Natick, Mass.

**Approval Date:** August 21, 2013

**Purpose:** The ablation catheter and steerable sheath are used to treat cardiac arrhythmias. Catheter ablation, a procedure in which localized electrical energy is delivered into the heart tissue, has become a first-line treatment approach for patients with specific types of irregular heartbeats.

**Description:** The high-resolution catheter provides data to aid electrophysiologists in pinpointing sites for ablation. Mini-electrodes on the catheter tip help clinicians assess the lesion’s maturation and differentiate viable from nonviable tissue. The sheath is used to gain access to the heart and facilitates the placement of catheters in patients with atrial flutter, atrial fibrillation, or ventricular tachycardia.

**Benefit:** Atrial flutter affects nearly 1 million people in the U.S. With enhanced features, including a soft distal tip, advanced shaft construction, and an ergonomic handle, the sheath is designed to help clinicians deliver catheters consistently and safely during electrophysiology procedures.

The catheter and the sheath are next-generation electrophysiology tools designed to redefine ablation technology. The catheter is compatible with the Rhythmia Mapping System, which the FDA approved in July.

**Sources:** www.pharmalive.com; www.drugs.com

**Device Recall**

Covidien has voluntarily recalled 14 lots of its Monoject Prefill Flush Syringes. The syringes are used to reduce blood clots in veins and to remove medication left at catheter sites.

Some syringes, which are designed to inject saline or heparin drug, had the wrong tip cap, labeling, volume, and wrapper. In addition, the syringes were filled with water but were not subjected to the autoclave sterilization process. Water that is not sterilized can cause life-threatening bloodstream infections.

If the clinician uses the heparin lock flush syringe containing only water on peripheral or venous catheters, the patency of the intravascular device might not be maintained and clotting may occur. This could result in nonfunctional IV access, and the device would have to be replaced.

These syringes were sold in the U.S. and Bermuda.

**Sources:** FDA, August 20, 2013; Reuters, August 19, 2013