Magellan Rx MANAGEMENT

Clinical Alert

JULY 2015

CDC Updates STD Treatment Guidelines

The Center for Disease Control and Prevention (CDC) has updated its 2010 guidelines for the prevention and treatment of sexually transmitted diseases (STDs). It is estimated that 20 million STD infections occur per year in the United States (U.S.). The CDC continues to advise that prevention of STDs is based on accurate assessment of people at risk; counseling on changes in sexual behaviors and use of prevention services; use of pre-exposure vaccines for STDs, such as human papillomavirus (HPV), hepatitis A virus (HAV), and hepatitis B virus (HBV); identification of asymptomatic and symptomatic patients with STDs; and effective treatment and counseling of infected persons and their sexual partners. Updates to the guidelines are discussed below.

The CDC has identified an increasing resistance of *Neisseria gonorrhoeae* to cefixime and tetracyclines in the U.S. As a result, they no longer recommend cefixime as first-line treatment of gonorrhea, and instead recommend dual therapy with ceftriaxone and azithromycin.

For the treatment of chlamydia or gonorrhea, the CDC supports the practice of expedited partner therapy (EPT), which allows for sexual partners of infected persons to be treated without evaluation by a healthcare provider (HCP). Affected individuals are treated and given medications or prescriptions to provide to their partner. It is important to note that the legal status of EPT varies by state; providers can obtain current information on their state at: http://www.cdc.gov/std/ept.

Although, hepatitis C virus (HCV) is not effectively transmitted through sexual contact, the CDC has revised its recommendation for HCV screening from a routine basis to at least annually for patients with HIV.

HPV Infections are usually asymptomatic and self-limiting, but can lead to certain cancers (cervical) and genital warts. The use of HPV vaccines (Cervarix®, Gardasil®) continues to be recommended for males ages 11 to 21 years and nonpregnant females ages 11 to 26 years. The CDC has added the recommendation for vaccination through age 26 years for previously unvaccinated or immunocompromised persons and men who have sex with men (MSM). In the U.S., HPV vaccines are approved as a three-dose regimen; however, they are not approved for use in men or women over 26 years of age.

The CDC has also added a section discussing the management of STDs in transgender patients. Transgender patients should be assessed for STD- and HIV-related risks based on their current anatomy and sexual behavior.

For further details, please visit the complete guidelines available at: http://cdc.gov.

FDA Safety Alert: Daytrana® and Skin Color Changes

The Food and Drug Administration (FDA) has alerted the public that permanent loss of skin color, also known as chemical leukoderma, may occur with the use of methylphenidate transdermal patch (Daytrana®), a central nervous system (CNS) stimulant used to treat Attention Deficit Hyperactivity Disorder (ADHD) in children and adolescents. The alert is based on 51 cases of leukoderma reported to the FDA Adverse Events Reporting System (FAERS) between April 2006 and December 2014 and one additional case that was not reported to the FAERS. In most cases, loss of skin discoloration was limited to areas

Drug Information Highlights

- The results of the third study evaluating the impact of DPP-4 inhibitors on cardiovascular (CV) risk have been published. The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) randomized 14,671 patients with type 2 diabetes and CV disease to sitagliptin (Januvia®) or placebo plus their existing antidiabetic therapy. After a median of three years, sitagliptin did not result in an increased risk of CV events, including hospitalization for heart failure, as measured by the primary outcome of composite of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or hospitalization for unstable angina. Based on the results of the EXAMINE and SAVOR-TIMI-53 trials, the FDA advisory panel recently determined that alogliptin (Nesina®) was associated with an acceptable CV risk profile, but recommended label revisions to reflect an increased risk of first hospitalization due to heart failure and a potential increased risk of all-cause mortality with saxagliptin (Onglyza®) use.
- On June 30, 2015, the FDAs new Pregnancy and Lactation Labeling Rule became effective. Use of Pregnancy Categories A, B, C, D and X will be phased out. Instead, labels for all new drugs and biologicals will now include a new section on Females and Males Reproduction Potential and new subsections to provide detailed information of potential risks and benefits for the mother, fetus, and breastfeeding child to aid in prescribing and counseling decisions. Use of the new format will be phased in for existing products.
- The FDA announced that there is currently a shortage of Factive® (gemifloxacin) 320 mg tablets by LG Life Sciences due to a legal dispute regarding the license to manufacture and distribute the drug. Gemifloxacin is a third generation fluoroquinolone antibiotic indicated to treat adults with bronchitis or pneumonia caused by susceptible bacteria. No resolution date for the shortage as been provided; however, the FDA recently approved the first-time AB rated generic for Factive.
- Merck has reported to the FDA that all Liptruzet™ (ezetimibe/atorvastatin), used to treat hyperlipidemia, has been discontinued. In January 2014, Merck voluntarily recalled all lots of Liptruzet due to a packaging defect. Merck expected that the supply would be depleted and decided not to resupply the product.

Contact

Dona Jones
Executive Assistant
djjones@magellanhealth.com

under the patch; however a small number of reports included loss of color in areas where the patch was never applied. Affected areas could be as large as 8 inches in diameter. Leukoderma was reported 2 months to 4 years after starting therapy with the patch.

The FDA is requiring label revisions for the patch to include a warning describing leukoderma. If patients or caregivers notice areas of lighter skin, particularly under the drug patch, they should contact their HCP immediately. Patients are advised not to stop using the patch without talking to their HCP. The FDA recommends alternative treatments be considered for patients who report skin discoloration.

FDA Approves Two Agents for Irritable Bowel Syndrome

Irritable bowel syndrome with diarrhea (IBS-D) affects up to 15 million people in the U.S. It is a functional bowel disorder characterized by chronic, sometimes debilitating, abdominal pain and frequent diarrhea. The FDA has approved two oral agents for the treatment of IBS-D, eluxadoline (Viberzi™; Actavis) and rifaximin (Xifaxan®; Salix) for use in adult men and women with IBS-D.

The first-in-class agent, eluxadoline, is a mu and kappa receptor agonist and a delta receptor antagonist, which reduces bowel contractions. In clinical trials, eluxadoline was superior to placebo in improving both abdominal pain and diarrhea on the same day and for at least 50% of trial days. The recommended dosage is 75 to 100 mg taken twice daily with food. Adverse effects include constipation and nausea. Eluxadoline should not be used in patients with a history of bile duct obstruction, pancreatitis, severe liver impairment, severe constipation, and in those who drink more than three alcoholic beverages per day. Market launch is expected in early 2016, after the Drug Enforcement Administration (DEA) has assigned a controlled substance schedule designation.

Rifaximin is a nonsystemic rifamycin antibiotic that acts locally in the gut. In two clinical trials, significantly more patients given rifaximin reported relief of abdominal pain and diarrhea than those given placebo during the month following 14 days of treatment ($p<0.05$). In a third trial, patients with symptom recurrence were treated for two additional 14-day courses. More patients retreated with rifaximin reported improvements in abdominal pain and diarrhea compared to those treated with placebo. The recommended dose of rifaximin for IBS-D is 550 mg orally three times daily for 14 days; therapy may be repeated for up to two courses, if recurrence of symptoms occurs. Rifaximin is already indicated for the management of hepatic encephalopathy and for the treatment of travelers' diarrhea due to noninvasive *Escherichia coli.*

Alosetron (Lotronex®; Prometheus), an oral selective serotonin 5-HT3 antagonist, is also FDA approved for use in women with IBS-D who have failed conventional therapy. HCP who wish to prescribe alosetron must be enrolled in the Prescribing Program for Alosetron (PPA). Other agents recommended for the management of IBS-D by the American College of Gastroenterology include antispasmodics, tricyclic antidepressants, and selective serotonin reuptake inhibitors.

- As an update to the previous warning in October 2013, the FDA has determined that the current labeling for ezogabine (Potiga®) is appropriate to manage the risk of retinal abnormalities (pigment changes), potential vision loss, and skin discoloration. The FDA is requiring GSK to conduct a long-term observational study to further examine consequences of pigment changes. Ezogabine is indicated for use with other antiseizure drugs to treat refractory partial-onset seizures in adults.

Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **July 5, 2015:** Orkambi™; lumacaftor/ivacaftor; oral cystic fibrosis transmembrane conductance regulator (CFTR) corrector/CFTR potentiator; CF with two copies of F508del mutation; Vertex.
- **July 11, 2015:** brexpiprazole; oral atypical antipsychotic; schizophrenia, MDD, PTSD; inhibition of cognitive decline; ADHD; H. Lundbeck A-S/Otsuka.
- **July 24, 2015:** Praluent®; alirocumab; subcutaneous anti-PCSK9 antibody; hyperlipidemia; Sanofi/Regeneron.
- **July 26, 2015:** Kyprolis®; carfilzomib; intravenous proteasome inhibitor; relapsed multiple myeloma; Amgen/Onyx.
- **August 27, 2015:** Repatha; evolocumab; subcutaneous anti-PCSK9 antibody; hyperlipidemia; Amgen.
- **3rd Quarter 2015:** Brilinta®; ticagrelor; oral platelet aggregation inhibitor; prevention of atherothrombotic events in patients post MI; AstraZeneca.
- **3rd Quarter 2015:** Durlaza™; acetylsalicylic acid; oral NSAID; secondary prevention of stroke and acute cardiac events; New Haven.
- **3rd Quarter 2015:** Iressa™; gefitinib; oral EGFR inhibitor; EGFRm positive non-small cell lung cancer; AstraZeneca.

IMPROVE-IT: The Addition of Ezetimibe to Simvastatin on Cardiovascular Risk

The placebo-controlled Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) evaluated the cardiovascular (CV) effect of adding ezetimibe (Zetia®) to moderate doses of simvastatin (Zocor®). The study enrolled 18,144 stable patients who had been hospitalized for an acute coronary syndrome (ACS) within the previous 10 days and had a low-density lipoprotein cholesterol (LDL-C) level of 50 to 100 mg/dL. Primary outcome measure was the composite of CV death, major coronary event, or nonfatal stroke. The addition of ezetimibe was associated with a reduction of LDL-C by approximately 23% (53.7 versus 69.5 mg/dL; $p<0.001$) and resulted in a significant reduction in CV events at seven years (32.7% versus 34.7%; HR 0.936; $p<0.016$). A significant reduction in MI and ischemic stroke and a nonsignificant increase in risk of hemorrhagic stroke were also reported with combination therapy. Safety outcomes were similar.

The CV impact per unit of LDL-C reduction with the addition of ezetimibe reported in the IMPROVE-IT trial is similar to that with statin monotherapy reported in the large Cholesterol Treatment Trialists' (CTT) meta-analysis. Study investigators argue that IMPROVE-IT provides further evidence that a relationship between lipid lowing and improved CV outcomes exist; however, the study cannot discount that other lipoproteins and C-reactive protein may also play a role.

Current guidance from the American Heart Association (AHA) and the American College of Cardiology (ACC) recommend statin therapy as the preferred treatment option for patients with established CV disease or hyperlipidemia. In contrast to the results of IMPROVE-IT, the AHA and ACC no longer support the use of specific LDL-C targets to manage drug therapy, as they state that clinical trial data do not define an appropriate target and the expected magnitude of additional atherosclerotic CV disease risk reduction with one target lower than another is unknown.

Smoking and Schizophrenia: A Swedish Prospective Study

There is a strong association between smoking and schizophrenia; however, the causal relationship is unknown. A Swedish study reviewed two prospective cohort trials in an attempt to understand the link between smoking and the subsequent development of schizophrenia and nonaffective psychoses. The study included over 1.4 million women and 230,000 men from the Swedish Birth Register and Military Conscription Register, respectively. Smoking was evaluated during prenatal care for the women, with a mean follow-up of over 18 years; for the men, mean follow-up was nearly eight years. Mean age at the start of the trial was 27 years for the women and 18 years for the men.

In both the female and male samples, risk for schizophrenia was more strongly associated with heavy smoking (> 10 cigarettes/day) compared with light smoking (< 10 cigarettes/day). In addition, when confounders, such as socioeconomic status and drug abuse were controlled for, hazard ratios declined only modestly in both groups.

A plausible explanation for the association of smoking and schizophrenia is that smoking initiation is part of the schizophrenia prodrome. To evaluate this, a buffer period of 1, 3, and 5 years between smoking assessment and schizophrenia onset was included. Researchers found that the association did not decline with longer buffer periods and, therefore, the association was not due to smoking onset during a schizophrenic prodrome.

Familial and genetic factors may play a role in the smoking-schizophrenia association. In close relatives discordant for smoking, the smoking member was at a significantly greater risk for future nonaffective psychosis; however, environmental factors that increase the risk for both smoking and nonaffective psychosis could not be ruled out.

The causes of the smoking-schizophrenia association are complex. While the impact of schizophrenia as a cause of smoking cannot be ruled out as a factor, the findings of this study strongly suggest that tobacco smoking is an independent risk factor for developing schizophrenia and nonaffective psychoses, with a dose-response association.

Antipsychotic Drug Use During Pregnancy

Antipsychotic drug use during pregnancy is on the rise; however, data concerning the effects of the newer atypical antipsychotics on maternal and perinatal health outcomes are lacking. A recent study examined possible links between second generation antipsychotics and medical conditions that often develop during pregnancy.

A population-based cohort study using health administrative data in Ontario, Canada, between 2003 and 2012 was the basis for the study design. The study compared 1,021 pregnant women who took antipsychotics during pregnancy with an equal number of pregnant women with similar demographics who did not take antipsychotics. The study enrolled women who delivered an infant and had at least two consecutive prescriptions for an antipsychotic medication during pregnancy, of which at least one was filled in the first or second trimester. About 90% of matched users were exclusively prescribed an atypical antipsychotic medication; quetiapine, olanzapine, and risperidone were the most frequently prescribed.

Researchers found that, compared with non-users, women who were prescribed an antipsychotic during pregnancy were not seen to be at higher risk for gestational diabetes (rate ratio 1.10 [95% CI 0.77 to 1.57]), hypertensive disorders (1.12 [0.70 to 1.78]), or venous thromboembolism (0.95 [0.40 to 2.27]). In addition, antipsychotic drug use did not impact the rate of preterm birth (defined as < 37 weeks) and birth weight <3rd or >97th percentile. The only exceptions were a slightly higher risk of labor induction and vaginal delivery among exposed pregnancies.

Although women requiring antipsychotic medications may be at higher absolute risk for certain adverse maternal and perinatal outcomes compared with the general population, this study demonstrates that antipsychotic medications do not appear to have a negative effect on important measures of maternal and perinatal health. As always, careful assessment is imperative for a woman being prescribed an antipsychotic during pregnancy and careful monitoring is prudent.

A Review of Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia (OIH) has been reported in the literature with growing frequency and there are very few evidence-based recommendations to assist clinicians with its management. OIH is the over-sensitization to pain due to opioid exposure. There are at least three types of OIH. The first type occurs in patients on methadone as part of a maintenance program to manage opiate dependence; the second type occurs post- or peri-operatively; and the third type occurs during opiate detoxification or sudden opioid withdrawal.

The development of OIH is likely the result of complex and overlapping mechanisms. The most common pathways thought to play a role are: spinal descending pathway modulation, increased concentrations of dynorphin-dependent excitatory neurotransmitters, increased sensitivity of dorsal horn neurons to excitatory neurotransmitters, inflammatory processes mediated by cyclooxygenase (COX) pathways, neuronal cell apoptosis, and suppression of endogenous opioid activity. OIH is almost always a diagnosis of exclusion; opioid tolerance must be ruled out before a diagnosis can be considered. A key distinguishing feature is that a patient with opioid tolerance will be relieved with increasing doses of opioids, while a patient with OIH will experience worsening pain with dose increases. Pain due to OIH is usually a different quality than the pain of the original injury or pain site. In addition, patient factors and drug interactions may slow the metabolism of an opioid to its active form causing a reduced analgesic effect which may be misinterpreted as OIH.

Pain in patients with OIH is typically difficult to manage. Strategies developed to provide relief include reducing the opioid dose, changing to a different opioid, changing to or adding methadone, or adding an N-methyl-D-aspartate (NMDA) receptor antagonist (memantine), an alpha-2 receptor antagonist, or a COX inhibitor. Unfortunately, there is little quality data on the management of OIH. Further study and additional clinical experience may aid treatment decisions in the future.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
olodaterol/ tiotropium bromide	Stiolto™ Respimat®	The FDA approved the combination of a long-acting beta$_2$-adrenergic agonist, olodaterol and anticholinergic, tiotropium bromide (Stiolto Respimat) for maintenance treatment of chronic obstructive pulmonary disease (COPD). Stiolto Respimat is not indicated to treat asthma or acute deterioration of COPD and does not replace rescue inhaler use. The oral inhalation spray is dosed as 2 inhalations once daily. Each actuation delivers 3.124 mcg tiotropium bromide monohydrate and 2.736 mcg olodaterol HCl (equivalent to 2.5 mcg of tiotropium and 2.5 mcg olodaterol, respectively).	Boehringer Ingelheim	FDA NDA Approval 05/21/2015
insulin lispro recombinant	Humalog® KwikPen®	A new strength of the rapid-acting human insulin analog, insulin lispro (Humalog KwikPen) was FDA approved for the treatment of adults and pediatrics with diabetes mellitus. In addition to the U-100 (100 units/mL) 10 mL vial and 3 mL KwikPen and cartridge, Humalog is now available as a U-200 (200 units/mL) 3 mL KwikPen. Administer both strengths by subcutaneous (SC) injection within 15 minutes prior to or immediately after a meal. Do not administer insulin lispro U-200 via continuous SC infusion or by intravenous (IV) infusion and do not mix with any other insulin.	Eli Lilly	FDA NDA Approval 05/26/2015
sirolimus	Rapamune®	Oral sirolimus (Rapamune), an immunosuppressive agent, gained FDA approval for the treatment of lymphangioleiomyomatosis (LAM), a progressive lung disease. Sirolimus is available as 1 mg/mL oral solution and 0.5, 1, and 2 mg tablets. The initial dose for LAM is 2 mg/day; adjust to achieve a sirolimus trough level of 5 to 15 ng/mL. Oral sirolimus is also indicated for the prophylaxis of organ rejection in renal transplant patients.	Pfizer	FDA sNDA Approval 05/28/2015
eltrombopag	Promacta®	Eltrombopag (Promacta), a thrombopoietin receptor agonist, is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. It was granted approval for use in patients 6 years and older; previously, the drug was only approved for use in adults. Initial dosage for adults and pediatrics is 50 mg orally once daily; adjust dose to maintain a platelet count ≥ 50 X 10^9/L. Eltrombopag is available as 12.5, 25, 50, 75, and 100 mg oral tablets.	Novartis	FDA sNDA Approval 06/11/2015
zolmitriptan	Zomig®	The FDA expanded the indication for the triptan zolmitriptan (Zomig) nasal spray for the acute treatment of migraine, with or without aura, to include use in adolescents ages 12 to 17 years. The nasal spray is available as 2.5, and 5 mg single-use units. The recommended dose in adults and adolescents is 2.5 mg to start, which may be repeated after 2 hours, if needed. Do not exceed 10 mg in a 24-hour period. Zolmitriptan tablets and orally disintegrating tablets are indicated for use in adults only.	AstraZeneca	FDA sNDA Approval 06/12/2015
perampanel	Fycompa®	The second generation anticonvulsant perampanel (Fycompa) received approval as an adjunctive treatment for primary generalized tonic-clonic (PGTC) seizures in patients 12 years of age and older with epilepsy. The recommended dose for PGTC seizures is 8 mg once daily at bedtime; adjust dose based on patient response and tolerability. Perampanel is also indicated for the treatment of partial-onset seizures in patients at least 12 years of age. Perampanel is a Schedule III controlled substance and is available as 2, 4, 6, 8, 10, and 12 mg tablets.	Eisai	FDA sNDA Approval 06/19/2015
cangrelor	Kengreal™	Cangrelor (Kengreal) is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor. Prior to PCI, administer cangrelor 30 mcg/kg via IV bolus; followed immediately by 4 mcg/kg/min IV infusion for at least 2 hours or for the duration of the procedure, whichever is longer. Therapy with an oral $P2Y_{12}$ platelet inhibitor should follow cangrelor IV therapy as per the package insert. The product is available as a single-use 10 mL vial containing 50 mg cangrelor as lyophilized powder. Once reconstituted and diluted, it should only be given through a dedicated IV line. The most common adverse reaction is bleeding. Launch is expected in July 2015.	Medicines	FDA NDA Approval 06/22/2015

References
https://www.magellanmedicaid.com/news/clinicalalerts.asp http://mhc.cpnp.org www.fda.gov
www.cdc.gov www.pubmed.gov