New Guidelines for Long-Term Management of Restless Legs Syndrome

The International Restless Legs Syndrome (RLS) Study Group has issued new RLS guidelines using evidence and clinical consensus. The report discusses consensus-based strategies for the prevention and treatment of drug-related complications, such as augmentation, loss of efficacy, excessive daytime sleepiness, and impulse control disorders, that may develop during long-term pharmacologic treatment of RLS, also known as Willis-Ekbom disease (WED). While there is currently no cure for RLS, there is effective treatment. One major finding of the report is the recommended expansion of the first-line treatment of RLS for most patients. For long-term management of RLS, the guidelines recommend dopamine-receptor agonists and calcium-channel ligands as first-line treatment. A summary of the key guideline recommendations is as follows: pramipexole (Mirapex®, Mirapex® ER) Level A, rotigotine (Neupro®) Level A, and ropinirole (Requip®, Requip® XL™) Level A are effective for the treatment of RLS for up to six months. Pramipexole is also probably effective for one year (Level B) and possibly effective for up to 10 years in 10 to 40 percent of patients who tolerate therapy and do not experience augmentation or loss of efficacy. Pregabalin (Lyrica®) is effective (Level A) for one year; gabapentin enacarbil (Horizant®) is probably effective (Level B) for one year; levodopa is probably effective for up to two years in 24 to 40 percent of patients who tolerate therapy and who do not develop augmentation or loss of efficacy. Pergolide and cabergoline should no longer be used in the treatment of RLS, except for patients whose symptoms are refractory to all other treatments, in whom the benefits outweigh the risks, and the evidence is insufficient to make a recommendation on the use of gabapentin (Neurontin®), tramadol, methadone, intrathecal morphine, or any single opioid in the long-term treatment of RLS. The new recommendations are published in the July issue of Sleep Medicine.

Olmesartan Medoxomil and Sprue-like Enteropathy

The Food and Drug Administration (FDA) has issued a new safety warning that the angiotensin II receptor blocker (ARB), olmesartan medoxomil, can cause intestinal problems known as sprue-like enteropathy. Symptoms include severe, chronic diarrhea with substantial weight loss. The enteropathy may develop months to years after initiating olmesartan, and sometimes require hospitalization. If patients taking olmesartan develop these symptoms and they are not attributable to other causes, olmesartan should be discontinued, and therapy with another antihypertensive should be started. The discontinuation of olmesartan has resulted in clinical improvement of sprue-like enteropathy symptoms in all patients. Patients should contact their physician if any of these symptoms occur while taking olmesartan-containing products (Azor®, Benicar®, Benicar HCT®, Tribenzor®, generics). Sprue-like enteropathy has not been detected with other ARBs.

Medtronic Issues Voluntary Recall Associated with Paradigm Insulin Infusion Pump

Medtronic, the makers of Medtronic Paradigm Infusion Pumps, has issued a Class I user-level recall of Paradigm MiniMed Insulin Infusion Sets used with Paradigm insulin pumps, due to the increased risk of leaking. Medtronic alerted the public that errors in insulin dosages can occur if insulin or other fluids are exposed to the inside of the Medtronic Paradigm tubing connectors. Vents that allow the pump to properly prime can be temporarily blocked, resulting in too much or too little insulin being delivered, and in turn potentially severe hypoglycemia or hyperglycemia. Medtronic has received a small number of reports of patients being hospitalized for diabetic ketoacidosis (DKA), which may be a result of insulin under-delivery due to the reservoir leaking. Medtronic has corrected this problem and is contacting patients for replacements. If patients notice anything unusual during the infusion set prime process, they should not insert the infusion set and should immediately contact Medtronic for assistance.

Ketoconazole Safety

A new FDA safety communication notes that ketoconazole tablets can cause severe liver injuries, adrenal gland problems, and lead to harmful drug interactions with other medications. A contraindication has been added against use in patients with active or chronic liver disease. A boxed warning provides new recommendations for assessing and monitoring patients for liver toxicity. As a result, ketoconazole oral tablets should not be a first-line treatment for any fungal infection. Oral ketoconazole for Candida and dermatophyte infections is no longer indicated. Ketoconazole should be used for the treatment of endemic mycoses, only when alternative antifungal therapies are not available or tolerated. Topical formulations of ketoconazole (Nizoral®) have not been associated with these serious adverse effects.

Expanded Black Box Warning for Promethazine-Codeine Antitussive Combination Products

The Black Box Warning for promethazine/codeine phosphate combination oral solutions has been expanded to include the following statement: Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism. The Black Box Warning had already noted a contraindication in pediatric patients younger than six years of age, and post-marketing cases of respiratory depression, including fatalities, reported with use of promethazine hydrochloride in patients younger than two years of age.

Drug Information Highlights

- Sunovion Pharmaceuticals’ lurasidone (Latuda®) is now approved as monotherapy and adjunctive therapy with lithium or valproate for the treatment of adult patients with major depressive episodes associated with Bipolar I Disorder. Latuda is also indicated for the treatment of patients with schizophrenia.
- The FDA has approved Rixubis®, recombinant coagulation factor IX, for the management of hemophilia B in patients 16 years of age and older. It is intended for routine prophylaxis, control and prevention of bleeding episodes, and perioperative management.
- Novartis’ rivastigmine (Exelon®) transdermal patch has received an expanded indication to include the treatment of severe Alzheimer’s disease. Exelon patches are already indicated for the treatment of mild to moderate dementia associated with Alzheimer’s disease or Parkinson’s disease.
- Pylera™ in a 10-Day Therapy Pak™ (bismuth subcitrate potassium, metronidazole, and tetracycline hydrochloride capsules) became available on July 29, 2013. AptaIIS will no longer supply Pylera in a 120 count bottle in the U.S. The new packaging contains 10 blister cards, each having 4 dosing sections with 3 capsules, each designed to encourage compliance.
- Fenofibric acid 45 mg and 135 mg delayed-release capsules, generic for Trilipix®, are now available. Trilipix is indicated in the treatment of hypertriglyceridemia, hypercholesterolemia, and to increase high-density lipoprotein cholesterol levels.
- There has been an ongoing shortage of clonidine transdermal patch (Catapres® TTS) due to production delays. The Boehringer-Ingelheim product shortage is improving as Catapres TTS is available but on allocation with an expected August release date.
- FluMist® Quadrivalent, a live, intranasal vaccine to protect against four influenza strains (two influenza A and two influenza B strains), is the first and only nasal spray quadrivalent flu vaccine. It is now available by MedImmune for the 2013–2014 flu season for the active immunization of persons 2–49 years of age.

Sources:
www.ashp.org
www.cdc.gov
www.fda.gov

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<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
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<tbody>
<tr>
<td>paroxetine mesylate</td>
<td>Brisdelle*</td>
<td>Brisdelle, a low-dose paroxetine mesylate product, is a selective serotonin reuptake inhibitor (SSRI), approved for the treatment of moderate to severe vasomotor symptoms (VMS), such as hot flashes and night sweats, associated with menopause. It is the first FDA-approved treatment for VMS that is not hormone therapy. It is available as a 7.5 mg capsule given once daily at bedtime.</td>
<td>Noven</td>
<td>FDA NDA Approval 06/28/2013</td>
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<tr>
<td>buprenorphine, naloxone</td>
<td>Zubsov®</td>
<td>The FDA approved a buprenorphine/naloxone sublingual (SL) partial opioid agonist combination, Zubsov, indicated for the maintenance treatment of opioid dependence. Zubsov has a REMS when dispensed as a maintenance treatment but not when dispensed to patients admitted to an opioid treatment program. It has a faster dissolve rate and bioavailability, and is a smaller tablet than currently available buprenorphine/naloxone formulations. The recommended maintenance dose is 11.4 mg/2.8 mg administered SL once daily. It should not be crushed or chewed. Available doses are 1.4 mg/0.36 mg and 5.7 mg/1.4 mg.</td>
<td>Orexo AB</td>
<td>FDA NDA Approval 07/03/2013</td>
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<tr>
<td>desvenlafaxine, extended-release</td>
<td>Khedezla®</td>
<td>Khedezla, an extended-release desvenlafaxine tablet, is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the treatment of major depressive disorder (MDD) in adults. It is available as 50 mg and 100 mg tablets with a recommended dose of 50 mg once daily with or without food. It is not therapeutically equivalent or substitutable to desvenlafaxine succinate (Pristiq®). Pristiq is the only desvenlafaxine ER tablet that is the succinate salt form. Pristiq’s patent expires on August 29, 2015.</td>
<td>Osmotica</td>
<td>FDA NDA Approval 07/10/2013</td>
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<tr>
<td>afatinib</td>
<td>Gilotrif®</td>
<td>Afatinib was approved as a once-daily kinase inhibitor for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) with common epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test. In clinical trials, there was no statistically significant difference in survival rate versus chemotherapy, but it demonstrated a 4.2-month delay in tumor progression. The recommended dose is 40 mg daily, 1 hour before or 2 hours after a meal, until disease progression or the drug is no longer tolerated by the patient. It will be available in 20 mg, 30 mg, and 40 mg tablets.</td>
<td>Boehringer Ingelheim</td>
<td>FDA NDA Approval 07/12/2013</td>
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<tr>
<td>golimumab</td>
<td>Simponi Aria®</td>
<td>Simponi Aria is an intravenous form of golimumab. It is a fully human monoclonal antibody anti-tumor necrosis factor (TNF) infusion therapy for the treatment of moderate to severe rheumatoid arthritis (RA) in combination with methotrexate. It is administered intravenously over 30 minutes at 2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter. It is available as a 50 mg/4 mL single dose vial, which must be further diluted, as directed, prior to administration.</td>
<td>Janssen Biotech</td>
<td>FDA BLA Approval 07/18/2013</td>
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<tr>
<td>tacrolimus, extended-release</td>
<td>Astagraf XL</td>
<td>A once-daily tacrolimus extended-release capsule, Astagraf XL, a calcineurin-inhibitor immunosuppressant for the prophylaxis of organ rejection, has been approved for use with mycophenolate mofetil (MMF) and corticosteroids, with or without basiliximab induction, in patients receiving a kidney transplant. It is not should not be used with cyclosporine. When initiating therapy and frequently thereafter, tacrolimus trough concentration monitoring is recommended. Daily oral dose with basiliximab induction is 0.15 mg/kg/day, without induction, pre-operative, 0.1 mg/kg/day, or post-operative, 0.2 mg/kg/day. It is available in 0.5 mg, 1 mg, and 5 mg capsules.</td>
<td>Astellas</td>
<td>FDA NDA Approval 07/19/2013</td>
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<tr>
<td>ferric carboxymaltose</td>
<td>Injectafer®</td>
<td>Ferric carboxymaltose is a high-dose non-dextran intravenous (IV) iron, approved for treatment in adults with iron deficiency anemia who are intolerant to oral iron or have had an insufficient response to oral iron, and for the treatment of non-dialysis dependent chronic kidney disease. Using less frequent administration than oral iron, a single dose of up to 750 mg of Injectafer can be administered undiluted as an IV push injection at a rate of 100 mg/minute, or as an IV infusion in up to 250 mL at 0.9 % Sodium Chloride Injection, USP, over at least 15 minutes. The initial dose is followed by a second dose 7 days later, for a total treatment of up to 1,500 mg of iron. The total dose is determined by body weight. Its available dosage form is 750 mg iron/15 mL in a single-use vial.</td>
<td>Luitpold</td>
<td>FDA NDA Approval 07/25/2013</td>
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<td>levomilnacipran</td>
<td>Fetzima®</td>
<td>Levomilnacipran, a serotonin and norepinephrine reuptake inhibitor (SNRI), is approved for the treatment of major depressive disorder (MDD) in adults. It is an active enantiomer of milnacipran (Savella®) but levomilnacipran is not FDA approved for fibromyalgia. The recommended dose is 40 mg to 120 mg once daily with or without food. The extended-release capsule is available in 20 mg, 40 mg, 80 mg, and 120 mg strengths. Launch is expected fourth quarter of 2013.</td>
<td>Forest</td>
<td>FDA NDA Approval 07/25/2013</td>
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