Magellan Rx MANAGEMENT

Clinical Alert

March 2017

Hypertension in the Older Adult: Guidelines by the American College of Physicians (ACP) and American Academy of Family Physicians (AAFP)

The ACP and AAFP published evidence-based recommendations on the benefits and harms of higher (< 150 mmHg) versus lower (< 140 mmHg) systolic blood pressure (SBP) targets in the treatment of hypertensive adults, age 60 years and older. The ACP and AAFP recommend initiating antihypertensive therapy in adults 60 years and older with SBP ≥ 150 mmHg with a target SBP < 150 mmHg to reduce the risk of mortality, stroke, and cardiac events (strong recommendation, high-quality evidence). A stricter goal of SBP < 140 mmHg may be considered in older adults with a history of stroke or transient ischemic attack to reduce the risk for recurrent stroke (weak recommendation, moderate-quality evidence). A stricter goal, SBP < 140 mmHg, may also be considered in older adults at high cardiovascular (CV) risk to reduce the risk of stroke or cardiac events (weak recommendation, moderate-quality evidence). The clinician and patient should discuss the risk versus benefit when determining the most appropriate blood pressure goal. The ACP and AAFP also state that providers should consider treatment with nonpharmacologic options (e.g., weight loss, diet, exercise), as well as pharmacologic therapy. Given the potential for other comorbid conditions, treatment burden (e.g., total number of drugs prescribed, drug interactions, adverse effects) should also be taken into consideration when treating hypertensive older adults. If pharmacologic therapy is chosen, the guidelines recommend generic formulations to reduce cost and improve treatment adherence.

The guidelines may be accessed at http://annals.org.

Cystic Fibrosis (CF) Diagnosis Guidelines

In 2010, universal newborn screening (NBS) for CF was implemented in the United States. The majority of patients with a positive NBS have a diagnosis of CF confirmed by a high sweat chloride concentration (≥ 60 mmol/L) using sweat chloride testing. However, diagnosis of CF is not always clear. In addition, diagnosing those born before 2010 can be problematic since age of onset and symptom severity can vary based on the level of CF transmembrane conductance regulator (CFTR) dysfunction. To address these challenges, the Cystic Fibrosis Foundation (CFF) published international consensus guidelines regarding the diagnosis of CF and other conditions associated with mutations in the CFTR gene (e.g., CFTR-related metabolic syndrome [CRMS] or CF screen positive, inconclusive diagnosis [CFSPID], and CFTR-related disorders).

A diagnosis of CF is made when both a clinical presentation of the disease and evidence of CFTR dysfunction are present. The CFF provides an algorithm outlining the hierarchy of diagnostic testing. They recommend testing in those with clinical presentation of CF (NSB+, signs/symptoms of CF, or family history) in the following order: sweat chloride test, CFTR genetic analysis (for sweat chloride 30 to 59 mmol/L), then CFTR physiologic testing (if CFTR genotype is undefined). If a CF diagnosis is still inconclusive, then CRMS/CFSPID or CFTR-related disorder should be considered.

The full guidance, which provides 27 detailed recommendations for diagnosing CF, is available at www.cff.org.

Drug Information Highlights

- 2016-2017 Flu Season Update: During the week of February 12-18, 2017, influenza activity decreased slightly, but remained elevated in the U.S. The most frequently reported subtype continued to be influenza A (H3). The proportion of outpatient visits for influenza-like illness (4.8%) exceeded the national baseline (2.2%). Twenty-seven states reported high influenza-like activity; New York City and 5 states experienced moderate activity. The remaining states and Puerto Rico experienced low or minimal activity, while data were insufficient in the District of Columbia. Overall, the 2016-2017 influenza vaccine has been 48% effective in preventing influenza-related medical visits across all age groups. There are adequate supplies of the antiviral agents to treat influenza, oseltamivir (Tamiflu®) and zanamivir (Relenza®).
- In an analysis of the Trial Evaluating CV Outcomes with Sitagliptin (TECOS) published in *Diabetes Care*, sitagliptin (Januvia®) was found to have a neutral effect on CV risk in older patients (≥ 75 years) with well-controlled type 2 diabetes mellitus (T2DM) and CV disease. Of the 14,351 participants with age data within the trial, 2,004 were 75 years or older. During the mean 2.9 year follow up, older participants had a higher rate of the composite outcome (CV death, nonfatal stroke, nonfatal myocardial infarction [MI], or unstable angina [UA] hospitalization) compared to younger patients (hazard ratio [HR], 1.72; 95% confidence interval [CI], 1.52 to 1.94). This older group was also at higher risk for death, severe hypoglycemia, and fractures. However, use of sitagliptin did not significantly impact the primary composite outcome (HR, 1.1; 95% CI, 0.89 to 1.36). Likewise, no significant impact of sitagliptin was found in death, heart failure hospitalization, severe hypoglycemia, acute pancreatitis, pancreatic cancer, or serious adverse events.
- Boehringer-Ingelheim's tiotropium bromide inhalation spray (Spiriva® Respimat®) received an expanded indication for use in patients as young as 6 years for the long-term treatment of asthma. It was previously approved for asthma in patients ≥ 12 years old and for chronic obstructive pulmonary disease (COPD) in adults. Dosage for asthma in those 6 to 11 years of age is 1.25 mcg/actuation, 2 puffs once-daily. Tiotropium bromide inhalation powder (Spiriva® Handihaler®) is only approved for adults with COPD.

American College of Physicians (ACP) Guidance for Chronic Low Back Pain

The ACP updated their 2007 guidelines on noninvasive treatment for chronic low back pain based on a systematic review of randomized controlled trials and other literature published through November 2016. The ACP notes that acute or subacute low back pain tends to improve over time regardless of treatment. Nonpharmacological therapy (e.g., heat, massage, acupuncture, spinal manipulation) should be considered as initial therapy. Non-steroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants may also be used (moderate quality evidence). Acetaminophen and systemic corticosteroids are not recommended due to lack of benefit. For chronic pain (lasting > 12 weeks), first-line treatment with non-drug therapy is recommended. Examples with moderate-quality evidence include exercise, multi-approach rehabilitation, acupuncture, and stress reduction; those with low-quality evidence include tai chi, yoga, spinal manipulation, and low-level laser therapy. If needed, NSAIDs, followed by tramadol or duloxetine, be may be added. Opioids may be considered for chronic pain only if prior therapy fails and potential benefits outweigh potential risks. Furthermore, head-to-head trials revealed few differences between recommended therapies. Clinicians should base treatment decisions on patient preference that also minimize harm and cost.

The full guidance may be viewed at http://annals.org.

Pediatric Endocrine Society (PES) Guidelines for Growth Hormone Deficiency (GHD)

The PES updated their 2003 guidelines for growth hormone (GH) and insulin-like growth factor-I (IGF-I) treatment in children and adolescents. Distinction between GHD, primary IGF-I deficiency (PIGFD), and idiopathic short stature (ISS) are often unclear; therefore, the PES focuses on recommendations for diagnosing and managing these conditions.

The PES advises against using GH provocative test results as the only diagnostic tool to determine GHD. They require inadequate response to 2 different provocative tests for GHD diagnosis; however, provocative testing is not required in select patients meeting certain criteria, as outlined in the guidelines.

GH therapy is recommended to normalize adult height and avoid extreme shortness in children and adolescents with GHD. In children, dosing is based on weight or body surface area (BSA) with an initial recommended dose of 0.16 to 0.24 mg/kg/week (subsequently individualized). GH doses should not routinely be increased to 0.7 mg/kg/week during puberty. The PES suggests measuring serum IGF-I levels to assess adherence and response to treatment. GH therapy should not continue at pediatric doses after a growth velocity below 2 to 2.5 cm/year is achieved. During the transitional period from late puberty to attainment of adult muscle and bone composition, the PES recommends serum IGF-I levels and GH provocative tests be evaluated after a 1-month trial of GH therapy interruption. Therapy may be offered if GHD persists, but there are little data to identify patients who will benefit or the optimal dosage during this period.

In 2003, the Food and Drug Administration (FDA) expanded the approved use of GH therapy to include ISS; however, ISS continues to be a debated indication for GH therapy. ISS is defined as height standard deviation score ≤ -2.25 with a predicted adult height less than the normal range (63 inches in men; 59 inches in women). The PES recommends against routine use of GH in children with height standard deviation ≤ -2.25 since response to therapy varies. Treatment decision should be based on physical and psychological effects and risks versus benefits. The initial GH dose for ISS is 0.24 mg/kg/week, but some patients may require up to 0.47 mg/kg/week. Treatment benefit, based on height standard deviation improvement and psychosocial impact, should be reassessed after 12 months of optimally-dosed therapy.

IGF-I therapy has been added to the guidelines and is recommended to increase height in patients with severe PIGFD. After exclusion of secondary causes, diagnosis of PIGFD is based on auxological measures, IGF-I concentration, and GH-binding protein level. As outlined in the guidelines, a trial of GH therapy is recommended prior to initiating IGF-I therapy for patients with unexplained IGF-I deficiency, unless hormone signaling defects known to be unresponsive to GH therapy are present. The suggested IGF-I dose is 80 to 120 mcg/kg twice daily.

The complete guidelines are available at www.pedsendo.org.

- Amgen announced preliminary results that evolocumab (Repatha®), a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, performed better than placebo in both the primary composite endpoint (CV death, MI, stroke, hospitalization for UA, or coronary revascularization) and a secondary composite endpoint (CV death, MI, or stroke). The results were reported in the FOURIER trial, a phase 3, double-blind, randomized, placebo-controlled study in patients with clinically evident atherosclerotic CV disease who were on optimized statin therapy. A substudy of FOURIER, the EBBINGHAUS trial, also demonstrated that evolocumab was non-inferior to placebo in its effects on cognitive function. Full results will be presented at the American College of Cardiology Scientific Sessions in March 2017.
- OTC Flonase® Sensimist™, a nasal corticosteroid spray approved to treat symptoms of seasonal and perennial allergic rhinitis in patients ≥ 2 years of age and for itchy, watery eyes in patients ≥ 12 years of age, became available on February 6, 2017. Previously available with a prescription as Veramyst®, the OTC product is available as a 27.5 mcg spray. Dosage is 2 sprays/nostril once daily in patients ≥ 12 years and 1 spray/nostril once daily in patients ages 2 to 11 years.
- Abbvie's oral fixed-dose direct-acting antiviral ombitasvir/paritaprevir/ritonavir (Technivie™) gained an expanded indication for use in patients with chronic hepatitis C virus genotype 4 infection with compensated cirrhosis. It was previously approved only for use in noncirrhotic patients. Technivie (2 tablets) once-daily plus weight-based ribavirin for 12 weeks is approved for patients with or without compensated cirrhosis. A sustained viral response rate of 97% was reported in patients with compensated cirrhosis treated with 12 weeks of therapy.

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

- **March 8, 2017:** Keytruda®; pembrolizumab; IV programmed cell death 1 (PD-1) inhibitor; microsatellite instability-high (MSI-H) cancer; Merck.
- **March 15, 2017:** Keytruda®; pembrolizumab; IV PD-1 inhibitor; refractory Hodgkin's lymphoma; Merck.
- **March 21, 2017:** Xadago; safinamide; oral alpha-aminoamide; Parkinson's disease; Meiji Seika/ Newron/ US Worldmeds/ Zambon.
- **March 23, 2017:** Symproic; naldemedine tosylate; oral peripheral opioid antagonist; opioid-induced constipation; Shionogi.
- **March 28, 2017:** Ocrevus; ocrelizumab; IV anti-CD20 antibody; primary progressive multiple sclerosis (MS), relapsing MS; Genentech/ Roche.
- **March 29, 2017:** Dupixent; dupilumab; subcutaneous (SC) interleukin 4 and 13 receptor antagonist; moderate to severe atopic dermatitis; Regeneron/ Sanofi.
- **March 30, 2017:** abaloparatide; SC parathyroid hormone/analog; postmenopausal osteoporosis; Radius Health.
- **April 3, 2017:** Austedo; deutetrabenazine; oral vesicular monoamine transporter 2 (VMT2) inhibitor; Huntington's disease associated chorea; Auspex/ Teva.
- **H1, 2017:** baricitinib; oral janus kinase inhibitor; rheumatoid arthritis, psoriasis; Eli Lilly/ Incyt.

Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
fluticasone propionate	ArmonAir™ Respiclick®	The FDA granted approval for the corticosteroid fluticasone (ArmonAir Respiclick) for the maintenance treatment of asthma in patients aged ≥ 12 years. It is not indicated for the relief of acute bronchospasms and should not be used to treat status asthmaticus or acute asthma episodes requiring intensive measures. ArmonAir Respiclick was approved as a dry inhalation powder containing 55 mcg, 113 mcg, or 232 mcg of fluticasone per actuation. The drug is administered as 1 oral inhalation twice daily; starting dose is based on asthma severity. Use with a spacer or volume holding chamber is not recommended. Contraindications include hypersensitivity to milk proteins. ArmonAir contains the same active ingredient as Flovent® (GlaxoSmithKline) which is approved for maintenance treatment of asthma in patients as young as 4 years. Dosages for Flovent are slightly less than ArmonAir; both are administered twice-daily.	Teva	FDA NDA approval 01/27/2017
fluticasone propionate; salmeterol xinafoate	AirDuo™ Respiclick®	AirDuo Respiclick is a fixed-dose combination of fluticasone propionate and salmeterol, a corticosteroid and long-acting beta-agonist (LABA), to treat asthma in patients aged ≥ 12 years. It is not indicated for the relief of acute bronchospasms and should not be used to treat status asthmaticus or acute asthma episodes requiring intensive measures. AirDuo Respiclick was approved as a dry inhalation powder containing fluticasone propionate 55 mcg, 113 mcg, or 232 mcg and salmeterol 14 mcg per actuation. The drug is administered as 1 inhalation twice daily and is not recommended for use with a spacer or volume holding chamber. Labeling carries a contraindication for milk protein hypersensitivity and a boxed warning for asthma-related death. AirDuo contains the same active ingredients as Advair® HFA and Advair Diskus® (GlaxoSmithKline), with similar indications and warnings; however, dosages vary between the products and Advair Diskus is approved for use in patients as young as 4 years. AirDuo is expected to be available in 2017.	Teva	FDA NDA approval 01/27/2017
nivolumab	Opdivo®	The human PD-1 blocking antibody, nivolumab (Opdivo), gained a new approved indication for locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy. Dosing for this indication is 240 mg every 2 weeks administered as a 60-minute IV infusion. Nivolumab is also indicated to treat advanced stages of melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, and squamous cell carcinoma.	Bristol-Myers Squibb	FDA sBLA approval 02/02/2017
etelcalcetide	Parsabiv™	The FDA approved etelcalcetide (Parsabiv), a calcium-sensing receptor antagonist, for secondary hyperparathyroidism (HPT) in adults with chronic kidney disease (CKD) on hemodialysis. Etelcalcetide has not been studied in adults with parathyroid carcinoma, primary HPT, or with CKD who are not on hemodialysis and is not recommended for use in these populations. Approved as a 5 mg/mL concentration in 0.5 mL, 1 mL, and 2 mL single-dose vials, initial dose is 5 mg IV bolus 3 times per week; maintenance dose is 2.5 mg to 10 mg 3 times per week. All doses are given at the end of hemodialysis treatment by a healthcare professional.	Amgen	FDA NDA approval 02/07/2017
deflazacort	Emflaza™	The oral corticosteroid, deflazacort (Emflaza), was FDA approved for the treatment of Duchenne muscular dystrophy (DMD) in patients ≥ 5 years of age. It is the first agent approved to treat all genetic forms of DMD and was granted orphan drug and rare pediatric disease product designations. Deflazacort is approved as 6 mg, 18 mg, 30 mg, and 36 mg oral tablets, as well as a 22.75 mg/mL oral suspension, to be taken once-daily at a dose of 0.9 mg/kg. If therapy is stopped, gradual discontinuation is recommended when used for more than a few days. Date of commercial launch is to be determined.	Marathon	FDA NDA priority approval 02/09/2017
brodalumab	Siliq™	The FDA has approved the human interleukin-17 receptor A (IL-17RA) antagonist brodalumab (Siliq) for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy and have failed to respond to or have lost response to other systemic therapies. It is approved as a single-dose prefilled syringe, containing 210 mg of brodalumab, to be self-injected as 210 mg SC at weeks 0, 1, and 2 and 210 mg every 2 weeks, thereafter. A boxed warning exists for suicidal ideation and behavior, including completed suicides. It is contraindicated in patients with Crohn's disease. Siliq is available only through a restricted Risk Evaluation and Mitigation Strategy (REMS) program. Launch is expected during the second half of 2017.	Valeant	FDA BLA approval 02/15/2017

ANDA = Abbreviated New Drug Application; BLA = Biologics License Application; NDA = New Drug Application; sBLA = Supplemental Biologics License Application; sNDA = Supplemental New Drug Application

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https://www1.magellanrx.com/magellan-rx/publications/pharmacy-clinical-alerts.aspx

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