THE PEDIATRIC PERIODICAL

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In This Issue…

PPAG members at Fitness Fun and Games Event 2017

Welcome To Pediatric Periodical!

The Pediatric Pharmacy Advocacy Group (PPAG) at the University of Maryland School of Pharmacy was formed to expand awareness of unique characteristics of medication therapy in children and to foster and promote safe and effective medication use in pediatric population through communication, education and research. Members of PPAG are working towards that mission throughout our school and community by coordinating various events and outreach programs. Our members, also, have the opportunity to be part of various innovative research projects by networking with experienced pediatric pharmacists in the area.

Cardiovascular Updates

By YuJin Noh

2017 AAP Update on Screening and Management of Pediatric High Blood Pressure

Childhood and adolescence hypertension (HTN), or elevated blood pressure, contributes to the risk of adult HTN and early development of cardiovascular disease.[1, 2] With the increasing prevalence of childhood HTN, the American Academy of Pediatrics (AAP) published an updated clinical practice guideline for screening and management of HTN in pediatric patients. The definition of HTN and elevated blood pressure (BP) is determined based on normative distribution of BP in healthy children. Since 2004, this distribution was interpreted based on sex, age and height as described in the "Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents." However, the 2017 AAP guideline created a new normative distribution of BP table for normal weight children. The normal BP values for obese children (children with a body mass index (BMI) in the 85th percentile or greater) were excluded because of positive association between obesity and HTN. For BP screening, healthy children are recommended to have BP measured annually beginning at 3 years of age. Children with certain health issues such as obesity, renal disease or family history of renal disease, diabetes, solid organ transplant, malignancy, elevated intracranial pressure, congenital heart disease, or on those medications known to cause HTN (ex. oral contraceptives, epogen, corticosteroids, etc.) should have their BP measured at every doctor's visit. The new target BP goal in the 2017 AAP guideline is Systolic Blood Pressure (SBP)/Diastolic Blood Pressure (DBP) <90th percentile or <130/80mmHg.[1] In addition, the new guideline substituted the term "prehypertension" with "elevated blood pressure." Table 1 shows the simplified classification of HTN and elevated BP from the 2017 AAP guideline. Lifestyle modifications including increased physical activity, healthy diet, weight loss and stress reduction should be initiated in all pediatric patients with elevated BP and should have a follow up within 3-6 months if lifestyle modification was the only intervention for managing BP. Pharmacological treatment should be initiated in patients with symptomatic HTN; persistent stage 1 HTN after 4-6 months of lifestyle modification and stage 2 HTN; and any HTN patients with chronic kidney disease, diabetes and end-organ damage.[2]

ACEi, ARB, thiazide diuretics and CCB are listed as first line agents for pediatric HTN, and Table 2 summarizes the recommended dosing for pediatric patients.

Table 1. Definitions of BP Stages[1]	Children 1-3 years old	Children ≥ 13 years old
Normal BP	<90th percentile	<120/80 mmHg
Elevated BP	≥90th percentile to <95 percentile **OR** 120/80mmHg to <95th percentile (whichever is lower)	120/80mmHg
Stage 1 HTN	≥95th percentile to <95th percentile + 12mmHg **OR** 130/80mmHg to 139/89mmHg (whichever is lower)	130/80 to 139/89mmHg
Stage 2 HTN	≥95th percentile + 12mmHg **OR** ≥140/90mmHg (whichever is lower)	≥140/90 mmHg

Table 2. Recommended Dosing for First Line Agents[1]

ACE inhibitor	**Captopril**
	- infants:
	  - initial: 0.05mg/kg/dose once 1 to 4 times daily
	  - maximal: 6mg/kg/day
	- children:
	  - initial: 0.5mg/kg/dose 3 times daily
	  - maximal: 6mg/kg

	Lisinopril (children ≥6 years old) - initial: 0.07mg/kg/day up to 5mg once daily - maximal: 0.6mg/kg/day up to 40mg
ARB	**Losartan** (children ≥6 years old) - initial: 0.7mg/kg up to 50mg once daily - maximal: 1.4mg/kg up to 100mg
	Candesartan (1-5 years old) - initial: 0.02mg/kg/day up to 4mg/day 1 to 2 times daily - maximal: 0.4mg/kg/day up to 16mg/day
Thiazide diuretic	**Hydrochlorothiazide** (child) - initial: 1mg/kg/day 1-2 times daily - maximal: 2mg/kg/day up to 37.5mg/day

Calcium channel blocker	**Amlodipine**
	- 1-5 years old
	  - initial: 0.1mg/kg daily
	  - maximal: 0.6mg/kg up to 5mg/day
	- ≥ 6 years old
	  - initial: 2.5mg/day
	  - maximal: 10mg/day

	Felodipine (≥6 years old) - initial: 2.5mg daily - maximal: 10mg daily

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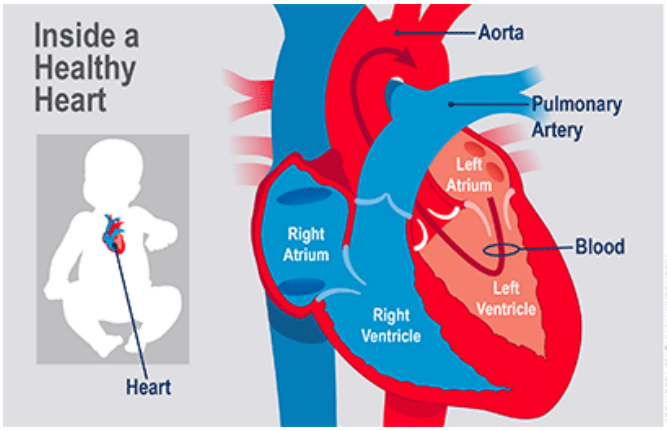
Use of Acetaminophen for Patients with Patent Ductus Arteriosus (PDA)

PDA is a congenital heart defect caused by failure to close the ductus arteriosus (DA) in preterm neonates. The DA connects the pulmonary artery to the aorta and allows the blood to bypass the non- functioning lung of the fetus.[4] Failure to close the DA can lead to complications such as pulmonary edema and intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, renal impairment and decreased perfusion and oxygen delivery to end organs contributing to greater mortality rate in preterm neonates.[1,2,3] NSAIDs (ibuprofen and indomethacin) are used as first line agents to close the DA with closure rate of about 70%.[1] Their ability to inhibit prostaglandin production reduces vasodilation surrounding the DA and helps close the PDA.[6]



However, the use of NSAIDs is associated with adverse effects such as gastrointestinal and renal impairment, peripheral vasoconstriction, and risk of bleeding due to decreased platelet aggregation.[1] Thus, there has been an increase in the use of acetaminophen for the patients with contraindications to NSAIDs.

Preterm neonates born with extremely low birth weight can possibly have contraindications or treatment failure experiences with NSAIDs therapy.[2] To minimize the need for surgical ligation, the use of acetaminophen in those PDA patients was studied as an alternative therapy for NSAIDs. Like NSAIDs, acetaminophen inhibits prostaglandin synthesis, but it acts on a different site of prostaglandin synthetase called the peroxidase region.[6] According to a systematic review, oral administration of acetaminophen in PDA patients was as effective as that of the NSAIDs.[5] Usual dosing for acetaminophen in preterm neonates is acetaminophen 15mg/kg every 6 hours for 7 days.[2] The major concern when using acetaminophen is its hepatotoxic adverse effects, but only transient increases in hepatic enzymes without any long term complications or signs of hepatotoxicity have been reported.[2,5]

According to the studies and a systematic review, acetaminophen can be considered an alternative therapy for preterm neonates for whom NSAIDs are contraindicated. However, there is a need for randomized control trials to verify the validity of the existing studies.[2,4]

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Disease Updates

By Danielle Reeves

Kawasaki Disease

Kawasaki disease (KD; also called mucocutaneous lymph node syndrome) is an acute vasculitis of unknown etiology that generally occurs in infancy and childhood. Children with KD are at risk for serious cardiovascular sequelae, particularly coronary artery abnormalities (CAAs), which can lead to myocardial ischemia, infarction, and sudden death. The risk of developing CAAs is highest among children with KD who are not treated early in the disease with high-dose intravenous immune globulin (IVIG).[1]

Management of patients with KD and CAAs is aimed at preventing and treating coronary artery thrombosis. The management approach for CAAs was updated to be generally consistent with the 2017 guidelines of the American Heart Association.[1]

When the diagnosis of KD is considered, an echocardiograph should be performed to conduct a luminal dimension assessment, normalized as Z-scores adjusted for body surface (Table 1). For uncomplicated patients, this should be repeated within 1-2 weeks and 4-6 weeks after treatment. For patients with CAAs detected acutely, more frequent echocardiographs are required until luminal dimensions have stopped progressing to determine risk and presence of thrombosis.[2]

Table 1. Z-Score Classification

Classification	Z-Score
No involvement	Always <2
Dilation only	2 to <2.5 **OR** if initially <2, a decrease in Z score during follow up ≥1
Small aneurysm	≥2.5 to <5
Medium aneurysm	≥5 to <10, **AND** absolute dimension <8mm
Large aneurysm	≥10, **OR** absolute dimension ≥8mm

For the prevention of coronary thrombosis, patients with KD in the acute phase are generally treated with aspirin at antipyretic doses (30-100 mg/kg/day). To reduce coronary thrombosis risk, low dose aspirin (3-5 mg/kg per day) is continued for a minimum of 4-6 weeks after acute phase treatment. If CAAs have not developed at this time or if there is just dilation, aspirin can be discontinued. No further therapy or long term follow up is indicated unless dilation persists, and at that point, the pediatric cardiologist can follow the patient in 12 months and then every 2-5 years.[1]

If CAAs have developed, additional treatment depends on the size and persistence of the CAAs. For small aneurysms, low dose aspirin or an antiplatelet agent (e.g. clopidogrel) if intolerance to aspirin is suggested until regression to normal size or dilation only. For medium aneurysms, continue low dose aspirin even if there is regression. In select high risk patients with persistent medium sized aneurysms, dual antiplatelet therapy (e.g. aspirin and clopidogrel) may be considered. For large aneurysms, systemic anticoagulation is warranted with low molecular weight heparin (LMWH) or warfarin (INR target 2.0-3.0) in addition to low dose aspirin. If there is regression to a small or medium size, systemic anticoagulation can be discontinued but dual antiplatelet therapy is reasonable if the remodeling of the large aneurysm results in a medium aneurysm. Patients with large aneurysms are at a higher risk for myocardial infarction, hence ongoing monitoring is recommended with the most intense monitoring during the first few months after the initial illness.[1]

In patients with clinical signs of coronary ischemia, coronary artery revascularization either by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) procedure is recommended. The goals of coronary revascularization are to relieve symptoms of angina and to reduce the risk of myocardial infarction or sudden death. The 2017 AHA guidelines recommend CABG in older children with KD with left main coronary artery disease (CAD), multivessel CAD with reduced left ventricle (LV) function, and multivessel CAD with lesions not amenable to PCI. PCI is preferred in patients with single-vessel or focal multivessel disease amenable to PCI. Multivessel PCI may be considered for patients who are acceptable CABG candidates but prefer to avoid CABG. Stand-alone balloon angioplasty should not be used for PCI in KD patients with coronary obstructions.[1]

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Septic Shock

Sepsis is a clinical syndrome complicating severe infection that is characterized by systemic inflammation, immune dysregulation, microcirculatory derangements, and end-organ dysfunction. Sepsis severity lies on a continuum from sepsis to severe sepsis and then to septic shock, a high morbidity and mortality state. Septic shock refers to sepsis with persistent cardiovascular dysfunction and the dysfunction of ≥ 2 organ systems. Goal-targeted therapy for children with septic shock, after rapid recognition, refers to an aggressive systematic approach to resuscitation aimed at improving physiologic indicators of perfusion and vital organ function within the first 6 hours of care.[3]

The recently updated approach for pediatric and neonatal septic shock is largely consistent with rapid, goal-targeted therapy.[3] New knowledge was added regarding hemodynamic management and the timely use of antimicrobials.[4] Specifically, administering the first appropriate antimicrobial agent within 60 minutes of recognition (however, if given before 3 hours of recognition, there were no signs of decreased mortality[4]), starting appropriate fluid resuscitation within 30 minutes of recognition, and appropriately initiating inotropes for fluid refractory shock or fluid overload within 60 minutes of recognition.[3] These changes focusing on early recognition and action were shown in studies to decrease mortality rates. The changes were made in large part due to the Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study, which was a global epidemiologic study that revealed the demographics, therapeutic interventions and prognostic outcomes for pediatric sepsis.[4] The SPROUT study demonstrated the prevalence of severe sepsis among pediatric populations and the association of substantial morbidity and mortality. This warranted the use of more well-designed trials targeting both mortality and morbidity outcomes which led to these updated guideline changes.

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Psychological Updates

By Chloe Kim and Jiye Lee

The Effect of Long Term Use of Acetaminophen During Pregnancy on Diagnosis of Attention Deficit Hyperactivity Disorder in Children

Acetaminophen, often used to treat pain and fever, has been the focus of several epidemiologic studies for safety of use in pregnant women. A previous study showed a correlation between the prenatal exposure of acetaminophen and attention deficit hyperactivity disorder (ADHD) in children. However, there were several limitations in the study, leading to ambiguous conclusions.

A recent study conducted by the Norwegian Institute of Public Health based on data collected from the Norwegian Mother and Child Cohort Study (MoBa) examined weather a correlation between utero acetaminophen exposure and development of ADHD exists. The study took into consideration of maternal use of acetaminophen during pregnancy as well as paternal use before pregnancy. Although the researchers were not able to confirm, they hypothesized that paternal use of acetaminophen can cause male germline epigenetic effects.[2]

Although it cannot yet be definitively stated, the study showed that prenatal acetaminophen exposure for greater than 29 days increased the risk of ADHD, while exposure for less than eight days showed no correlation.[1]
This positive association between the use of acetaminophen for more than 29 days and diagnosis of ADHD was observed regardless of the indications of acetaminophen use. Even though the use of acetaminophen for less than 8 days was negatively associated with ADHD, pregnant women should still be counseled on excessive use of acetaminophen, as there may be potential risk of maternal mortality if the daily dose of acetaminophen exceeds the maximum recommended daily dose of 3 grams/day.

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Latuda Receives FDA Approval in the Treatment of Bipolar Depression in Pediatric Patients

Latuda (lurasidone), originally used in the U.S. for the treatment of bipolar depression in adults and schizophrenia in adults and adolescents, received FDA approval on March 6, 2018 for use in the treatment of bipolar depression in pediatric patients ages 10 to 17.[1] Robert Findling, M.D., M.B.A., Vice President of Psychiatric Services and Research at the Kennedy Krieger Institute, Director, Child & Adolescent Psychiatry at the Johns Hopkins University of School of Medicine stated that the approval of Latuda in the treatment of bipolar depression in pediatric patients is important because "it is the first single-agent formulation to receive regulatory approval for" bipolar depression in pediatrics.[1] During phase 3 clinical study of individuals ages 10 to 17 with bipolar depression, Latuda demonstrated statistical and clinical significance compared to placebo with meaningful improvement in bipolar depression symptoms and was considered to be well tolerated.[1]

Latuda	
Approved age	10-17
Indication	Mono therapy for bipolar disorder (depressed phase)
Dosing	20mg by mouth once daily with food (≥350 calories) Maximum daily dosing: 80mg
Side effects	**Common:** dyslipidemia, increased glucose level, weight increase, diarrhea, nausea, vomiting, akathisia, extrapyramidal disease **Serious:** orthostatic hypotension, syncope, cerebrovascular accident, seizure, suicidal ideation, neuroleptic malignant syndrome

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NEW FDA INDICATIONS FOR KALYDECO

By Jiye Lee

KALYDECO (Ivacaftor), first approved in January 2012 for the treatment of cystic fibrosis (CF), recently expanded its indications. First, it was indicated for patients 6 years and older with at least one copy of the G551D mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which accounted for 4% of the CF patients.[1] In February 2014, eight more mutations were added to the FDA approved label. The medication was approved for children 2 years of age and older in March 2015.[2] In May 2017, the FDA approved the medication for additional mutations, increasing the total number of mutations indicated to 33.[3]

CF is a rare, inherited disorder that can cause life-threatening damages to the lungs and other organs. This genetic disease is due to a mutation in the CFTR gene leading to the production of thick and sticky mucus. Build up of these secretions can lead to problems in the respiratory and/or digestive tract. CF is a critical disease that is affecting approximately 30,000 individuals in the United States.[3]

KALYDECO works by potentiating certain genes of the CFTR, improving lung functions and other complications of CF. However, only certain patients with at least one of the 33 following genes are indicated for the use of this drug. These genes include E56K, G178R, S549R, K1060T, G1244E, P67L, E193K, G551D, A1067T, S1251N, R74W, L206W, G551S, G1069R, S1255P, D110E, R347H, D579G, R1070Q, D1270N, D110H, R352Q, S945L, R1070W, G1349D, R117C, A455E, S977F, F1074L, R117H, S549N, F1052V, and D1152H.[5]

KALYDECO is available as oral tablets or granules. For pediatric patients between the ages of 2 and 6, a 50-75 mg (depending on the body weight) packet of granules is mixed with 5 mL of liquid and given orally every 12 hours. For patients 6 years and older, a 150 mg oral tablet is given every 12 hours.[5] Both formulations should be administered with fat-containing foods. There are gastrointestinal-related side effects associated with KALYDECO, as well as headache, dizziness, nasal congestion, nasopharyngitis, throat pain, and upper respiratory infections. KALYDECO can elevate liver enzymes.[5] There are drug-drug interactions with strong CYP3A inducers, such as St. John's Wort and rifampin, and should be avoided due to substantial decrease in the effectiveness of KALYDECO.[3] With the newly updated indications of KALYDECO, more pediatric patients will be able to receive treatment for CF.

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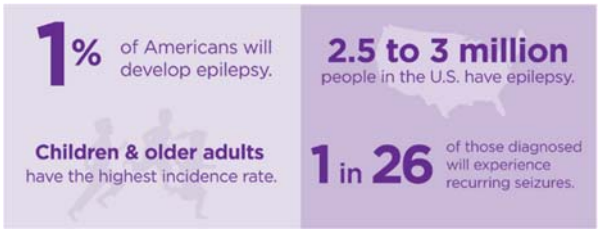
NEW FDA INDICATIONS FOR APTIOM

By Adele Fu

As of November 2017, the indication for Sunovion Pharmaceuticals' Aptiom (eslicarbazepine acetate) has been expanded and approved by the FDA to treat patients 4 years of age and older. Aptiom is an oral medication used to treat partial-onset seizures. Aptiom is the third-generation member of the dibenzazepine family of antiepileptic drugs, a family that also includes carbamazepine (CBZ) and oxcarbazepine (OXC).[3] CBZ is known to interact with many other medications, has a higher risk of skin reaction, and requires routine blood tests to monitor its pharmacodynamic characteristics.[5,6] For both CBZ and OXC, children are at an increased risk of developing a wider range of side effects.[7]



From 2010 to 2014, the CDC found that 0.7% of children and adolescents aged 6–17 years in the United States had at least one seizure during each preceding year.[8] Aptiom prevents seizures by blocking sodium ion channels, which then slows the nerve firing sequence that causes seizures.[5] Randomized, double-blind, placebo- and active-controlled 4-period crossover trials were conducted on adults for a total of five studies (n varied from ~80 to 215 people).[2] Aptiom was shown to reduce seizure frequency in adults when compared to the placebo. The median percent reduction from baseline in seizure frequency was also larger in the adult Aptiom arm when compared to the adult placebo arm.[2] A pharmacokinetic study of Aptiom's effect on partial-onset seizures was conducted in 29 pediatric patients. At 1 to 3 hours after receiving the dose, the peak plasma concentration

(Cmax) of Aptiom was observed.[2] It was also found that higher body weight significantly correlates with better clearance of Aptiom in pediatric patients. Thus, a weight- based dosing regimen is required in order to achieve similar results to those in adult patients.[2]

Once-daily Aptiom was shown to have similar effectiveness in epilepsy when compared to twice-daily carbamazepine and is noted to have potential ease of administration and dose titration compared to carbamazepine and oxcarbamazepine therapy.[9]

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