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Advances in Pediatric Pharmacology, Therapeutics, and Toxicology

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Abstract

In the United States, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act continue to promote clinical trials in pediatric populations across all age ranges. In 2014 and 2015, over 70 changes were made to drug labels with updates on information regarding pediatric populations. Additionally, multiple new therapies have received first-approvals for the treatment of pediatric indications ranging from rare genetic metabolic diseases to oncology. In the European Union, there have been more than 30 new authorizations for medicines used in children and 130 approved pediatric investigation plans. Despite the progress that has been made over the last two years, much work remains to further the development of safe and effective therapies for pediatric patients.

Keywords

Pediatrics; Pharmacology; Pharmacokinetics; Toxicology

INTRODUCTION

Over the last two years there have been numerous advancements in drug development for pediatric patients. In 2014 and 2015 the Food and Drug Administration (FDA) approved more than 70 product label changes related to pediatric populations (Table 1), resulting in greater than 530 overall since the enactment of the Best Pharmaceuticals for Children Act (BPCA) in 2002 and the Pediatric Research Equity Act (PREA) in 2003 [1]. There were

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over 10 approvals of new drugs specifically for the treatment of pediatric indications in the last 2 years, including several for rare or ultra-rare diseases, which reflects the major advancements that have occurred for drug development for these populations. In the European Union, there have been more than 30 new authorizations by the European Medicines Agency (EMA) for medications for use in pediatric populations. Additionally, the Pediatric Committee of the EMA has approved over 135 new pediatric investigation plans (PIPs) for new studies [2, 3]. The greatest numbers of PIPs are in the areas of endocrinology and infectious disease with 20 and 19, respectively, followed by oncology and gastroenterology. Furthermore, there have been many contributions by investigator-initiated studies that have led to a greater understanding of the use and effects of medications prescribed to children. Even though it has been recognized that there is a major need for drug development for neonates, there is still a lack of information on the safety and efficacy of drugs that are being used in this population [4].

Given the numerous advancements over the last two years, the goal of this article is to highlight specific developments in pediatric pharmacology, toxicology, and therapeutics from January 2014 through October 2015. The updates were extracted from the FDA Pediatric Labeling Information Database, EMA Public Assessment Report database, EMA Opinions and Decisions on Paediatric Investigation Plans database, clinicaltrials.gov, PubMed, and Embase. Articles were selected to identify important developments within various therapeutic areas.

ANESTHESIA

Sedation

Dexmedetomidine is a selective alpha-2 agonist that acts centrally in the brainstem to inhibit norepinephrine release, which results in sedative and anesthetic effects without causing respiratory depression [5]. It is currently FDA approved for use in adult patients for up to 24 hours while intubated and on mechanical ventilation in the intensive care setting, but has been used off-label in pediatric patients as an adjunct to sedation regimens and is increasingly being utilized as a primary sedative agent [6].

Given the lack of data surrounding dexmedetomidine usage in neonates, a phase II/III, open-label study was performed with the goal of characterizing the safety, efficacy, and pharmacokinetic (PK) properties of dexmedetomidine in preterm and term neonates between 28–44 weeks of gestational age [7]. The neonates were divided into two groups, with group 1 including preterm neonates born at 28–35 weeks gestational age and group 2 including term neonates born at 36–44 weeks. The investigators found that 90% of patients did not require midazolam for added sedation while receiving dexmedetomidine infusion. In regards to PK parameters, the neonates born between 28–35 weeks appeared to have a lower weight-adjusted plasma clearance (0.3 vs. 0.9 L/h/kg) and a prolonged terminal elimination half-life ($t_{1/2}$) (7.6 vs. 3.2 hours) compared to neonates born between 36–44 weeks. There were no serious adverse events related to dexmedetomidine usage and none that led to discontinuation of sedation. Fifty-six adverse events were reported in 26 patients (26/42, 62%), with 11 (11/18, 61%) in group 1 and 15 (15/24, 63%) in group 2. Three patients (3/42, 7%) reported 4 adverse events related to dexmedetomidine including hypertension,

hypotension, and agitation. Overall, the investigators concluded that the PK of dexmedetomidine is different in neonates compared to older children and adults indicating lower doses may be required for the same level of sedation and to limit potential adverse effects [7].

The majority of pediatric data for dexmedetomidine comes from studies examining usage for less than 72 hours [8]. As such, the safety of dexmedetomidine during long-term use was studied in a group of 98 patients under 21 years of age who received 0.2 to 0.7 µg/kg/hr for greater than 72 hours. The median (range) age of the cohort was 3.8 years (0.04–17) and duration of dexmedetomidine use was 141 hours (72–2472). There was a statistically significant reduction in both heart rate and systolic blood pressure from baseline after initiation of sedation and a decreased need for opioids and benzodiazepines. However, after cessation of the infusion there was a significant increase in heart rate and both systolic and diastolic blood pressure. Twenty-one percent of patients required either a new antihypertensive agent or the addition of clonidine for the treatment of rebound tachycardia and hypertension. Other withdrawal effects included agitation tremors, and decreased sleep [8]. Overall, the investigators concluded that longer-term dexmedetomidine administration in the intensive care setting is safe and effective. However, prominent withdrawal symptoms may occur and patients should be monitored for tachycardia and hypertension upon discontinuation of the medication.

Pain Management

In August of 2015, the FDA approved controlled release oxycodone hydrochloride (Oxycontin) for use in patients 11 years and older with pain and are opioid-tolerant and receiving a minimum daily dose of 20 mg of oxycodone. This approval was based on an open-label clinical trial of 155 opioid-tolerant pediatric patients with moderate to severe chronic pain. Mean (range) duration of therapy was 20.7 days (1–43) and daily dose was 33.30 mg/day (20–140) [9]. More than 50% of patients experienced any adverse event, with the most frequently reported being vomiting, nausea, headache, fever, and constipation. Pain was assessed using a revised FACES Pain Rating Scale, which was scored by the patient during screening, after the first dose, and twice daily (morning and evening) at the time of each dose. The mean (standard deviation) score at baseline was 4.44 (3.250) compared to the morning 3.13 (2.569) and evening 3.42 (2.974) of the 4th week. As such, the trial concluded that controlled release oxycodone is safe and effective at controlling pain in this opioid-tolerant pediatric population.

CARDIOLOGY

Pulmonary Hypertension

Sildenafil is a phosphodiesterase type-5 inhibitor that lowers pulmonary vascular resistance and is used in patients with single ventricle heart defects [10]. Since children with single ventricle heart defects have altered hepatic physiology that might influence drug metabolism, a study was conducted to determine the effect of elevated hepatic pressure on the pharmacokinetics (PK) of sildenafil in this population [11]. A population PK model was developed for 20 children with a median (range) age of 3.2 years (0.8–5.3) receiving single

dose intravenous sildenafil during cardiac catheterization. The analysis showed that increased hepatic pressure affected the clearance of des-methyl-sildenafil, the active metabolite, but not of sildenafil. An increase of hepatic pressure from 4 to 18 mmHg was predicted to decrease des-methyl-sildenafil clearance by approximately 7-fold. Additionally, predicted drug exposure increased in subjects with hepatic pressures ≥ 10 mmHg compared to <10 mmHg by approximately 1.5 fold (median area under the concentration versus time curve, 533 vs. 792 ug·h/L). As such, the investigators concluded that hepatic pressure should be considered when prescribing sildenafil for children with single ventricular defects [11].

The randomized, double blind, placebo-controlled trial Sildenafil in Treatment-Naïve Children Aged 1 to 17 years with Pulmonary Arterial Hypertension (STARTS-1) was designed to evaluate the safety and efficacy of sildenafil citrate in children and adolescents. The study found that exercise capacity and hemodynamics improved in patients receiving medium and high doses of sildenafil and preliminary data published for STARTS-2, a trial examining long term >2 year treatment, showed increased mortality at higher doses [12]. This resulted in statements issued by both the FDA and EMA in 2012 that warned against off-label use of the medication [13, 14]. The FDA released an updated safety communication in 2014 advising against the chronic use of sildenafil in children [15]. Data from STARTS-2 was fully published in 2014 and showed that even though children randomized to higher doses of sildenafil had an unexplained increase in mortality, all dosage groups showed favorable survival for children with PAH [16]. Estimated Kaplan-Meier survival rates were 94%, 93%, and 88% for low, medium, and high dose groups, respectively. Within the study groups, 87%, 89%, and 80% were shown to be alive after 3 years from the start of treatment. Hazard ratios for mortality were 3.95 (95% CI, 1.46–10.65) for high vs. low dose groups and 1.92 (95% CI, 0.65–5.65) for medium vs. low dose groups. However, the investigators noted that multiple analyses raised uncertainty regarding the survival and dose relationship.

Hypertension

Losartan is an angiotensin II receptor blocker that is used as an antihypertensive therapy in adults and children over 6 years of age. Losartan has been shown to reduce blood pressure (BP) in a dose-dependent manner in children between the ages of 6 and 16 [17]. A 12-week randomized, open-label, dose-ranging study with a 2-year extension was conducted to assess safety and efficacy of losartan in a group of 101 children 6 months to 6 years of age with hypertension [18]. Patients were randomized to receive either 0.1 mg/kg per day (low dose), 0.3 mg/kg per day (medium dose), or 0.7 mg/kg per day (high dose). The dosage was titrated to the next dose level at 3, 6, and 9 weeks up to 1.4 mg/kg per day up to 100 mg/day if adequate BP control was not achieved. Over the course of the study, losartan was well tolerated and the incidence of adverse events was low and comparable between the groups. The investigators concluded that children between 6 months and 6 years of age taking losartan 0.1–0.7 mg/kg per day had significantly lower systolic and diastolic BP, though there was no dose-response relationship [18].

Lisinopril is a long-acting angiotensin converting enzyme inhibitor that prevents the conversion of angiotensin I to angiotensin II in the renin-angiotensin-aldosterone system to lower blood pressure. It is FDA approved for the treatment of essential hypertension in adult

and pediatric patients over 6 years of age. In adult kidney transplant patients, lisinopril has been shown to prolong allograft survival by affecting intraglomerular hemodynamics and reducing the activity of pro-fibrotic and inflammatory mediators [19]. In order to understand the effects of lisinopril on pediatric kidney transplant patients, a trial was conducted to determine the PK, pharmacodynamic, and safety profile of lisinopril in this population [20]. Twenty-two patients between the ages of 7 and 17 were divided into two groups based on prior lisinopril exposure (lisinopril naïve vs. lisinopril per standard of care). Patients in the lisinopril naïve group received a once daily dose of either 0.1 mg/kg (low), 0.2 mg/kg (medium) or 0.4 mg/kg (high) while the standard of care patients received doses of the medication as part of their ongoing care. Lisinopril was generally well tolerated and was associated with lowering of BP at approved pediatric dosages. The investigators found that the PK of lisinopril in patients with a kidney transplant was comparable to previous children who had not undergone a kidney transplant. Clearance was not affected by age after scaling allometrically for size across the age range studied. Additionally, clearance was proportional to dose and increased in proportion to estimated glomerular filtration rate (eGFR). As such, it is recommended that pediatric kidney transplant patients receive the currently approved pediatric dose with consideration for eGFR [20].

DERMATOLOGY

Atopic Dermatitis

In 2014, the American Academy of Pediatrics released updated recommendations regarding management and treatment of atopic dermatitis due to an increasing incidence nationwide. New data suggest that atopic dermatitis results from primary abnormalities of the skin-barrier which has placed a new focus on the importance of a skin-directed management approach [21]. These recommendations emphasize maintenance skin care such as the use of daily moisturizers in addition to the use of topical corticosteroids for active disease.

Topical calcineurin inhibitors including tacrolimus and pimecrolimus are FDA approved as second-line treatments for mild to severe atopic dermatitis in children over 2 years of age. Tacrolimus and pimecrolimus show comparable efficacy and safety and are a suitable and cost-effective alternative to topical corticosteroids, though the uncertain risk for malignancy should be considered [22–24]. Topical calcineurin inhibitors are also commonly prescribed off label to infants and young children since compliance to topical steroids can be poor due to parental concerns regarding side effects [25]. A 5-year phase 3 study in 2418 infants found that pimecrolimus had similar efficacy to topical corticosteroids [26]. Additionally, the data suggests that long term management of mild to moderate atopic dermatitis in infants with either pimecrolimus or topical corticosteroids was safe and without any effect on the immune system. As such, both are reasonable first-line treatment options.

GASTROENTEROLOGY

Inflammatory Bowel Disease: Ulcerative Colitis and Crohn's Disease

Pediatric inflammatory bowel disease is characterized by chronic, recurrent inflammation of the gastrointestinal tract and includes two subcategories, Crohn's disease and ulcerative

colitis. Patients with ulcerative colitis experience inflammation isolated to the mucosa that most commonly occurs in the colon and rectum. Pediatric patients with ulcerative colitis tend to experience a more severe form of the disease that evolves rapidly with a higher prevalence of pancolitis (70–90%) than in adults [27, 28].

Mesalamine is a 5-aminosalicylate that is used for the management of ulcerative colitis in both adults and pediatric populations [29, 30]. Two pediatric label changes were made for mesalamine in the last two years [1]. Delayed-release oral mesalamine capsule (Delzicol) is now approved for the treatment of mild to moderate ulcerative colitis in pediatric patients 5 years of age and older, which was based on data from studies in 82 patients 5 to 17 years of age [31]. The second label change was for another mesalamine delayed-release formulation (Asacol), which was originally approved for the treatment of mild to moderate ulcerative colitis in patients 5 years and older in 2012 based on a 6-week trial period. The label change includes the statement that efficacy was not demonstrated for the maintenance of remission of mild to moderate ulcerative colitis in this same age group [32]. This was based on a 26-week trial of two dosage levels in 39 patients age 5–17.

Crohn's disease is another form of inflammatory bowel disease that is characterized by transmural inflammation of the gastrointestinal mucosa leading to the formation skip lesions. Similar to ulcerative colitis, studies have shown that the onset of Crohn's disease is typically more severe in younger patients [27]. Adalimumab (Humira) is an anti-TNF antibody that functions as an immunosuppressing agent and is approved for the induction and maintenance of clinical remission of moderate to severe Crohn's disease in adults. In 2014, the FDA expanded the age range for use in pediatric patients 6 years and older as a treatment option when other treatments, including infliximab, have failed. The approval for pediatric use was based on the results of the IMaGINE-1 trial in 192 patients which showed that adalimumab was able to induce and maintain remission in patients 6–17 years of age with a comparable safety profile to that of adult patients [33].

Constipation

Functional constipation is associated with infrequent or painful defecation, fecal incontinence, and abdominal pain and is a common problem in childhood that often starts during the first year of life [34]. The European Society and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN and NASPGHAN, respectively) released updated consensus guidelines in 2014 for the evaluation and treatment of functional constipation in infants and children [35]. The updated guidelines recommend polyethylene glycol (PEG) with or without electrolytes orally 1 to 1.5 g/kg per day for 3 to 6 days as first line treatment for children presenting with fecal impaction. PEG is further recommended as a maintenance treatment at a starting dosage of 0.4 g/kg per day, which should be adjusted with clinical response. Lactulose is recommended if PEG is not available, though recent studies have shown that lactulose is not as effective as PEG in the treatment of chronic constipation in children 1 to 3 years of age [36]. Maintenance treatment should continue for up to two months or until all symptoms have resolved for 1 month. The updates do not recommend the routine use of lubiprostone, linacoltide, or prucalopride since there have been no randomized trials published establishing their safety and efficacy in children.

However, lubiprostone was evaluated in an open-label study in 109 patients between the ages of 3 and 17 and was found to be efficacious and well tolerated. Patients on lubiprostone experienced a significant increase in the number of spontaneous bowel movements per week compared to the group receiving placebo (3.1 vs. 1.5, $P<0.0001$). The most common adverse events included nausea, vomiting, diarrhea, abdominal pain, and headache [37].

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is characterized by the regurgitation of gastric acid into the esophagus. GERD in infancy is generally self-limiting and improves with age while older children who develop GERD along with other medical co-morbidities tend to experience a more prolonged disease course [38, 39]. Rabeprazole (Achipex), a proton pump inhibitor (PPI), was approved for the treatment of GERD in adolescents 12–17 years of age in 2008 [1]. The age range for rabeprazole was expanded to include children 1 year of age and older in 2013 [40]. A follow-up study was conducted to evaluate the maintenance of efficacy and safety in children between the ages of 1–11 years who had received 12 weeks of treatment and were maintained on the same dose for an additional 24 weeks. Subjects were originally randomized into 2 groups during the treatment phase to receive either 0.5 or 1.0 mg/kg of rabeprazole. Children who weighed 6 to 14.9 kg received up to 5 to 10 mg/day and children ≥ 15 kg received 10 to 20 mg/day. The primary study outcome was evaluated with esophagogastroduodenoscopy (EGD) and histology. Sixty-four patients who achieved healing during the 12-week treatment phase were enrolled in the 24-week maintenance phase. The overall healing rate was 90%, with 100% of children in the low-weight group reporting maintained healing compared to 89% (10 mg) and 85% (20mg) in the high-weight group [41].

GENETIC AND METABOLIC DISEASES

Significant advancements have been made in the treatment of rare genetic and metabolic diseases. A milestone for pediatric rare disease drug legislation occurred in 2012 with passage of the Creating Hope Act (CHA) as part of Food and Drug Administration Safety and Innovation Act. The CHA focuses on the use of priority review vouchers (PRV) as a market incentive for companies to develop drugs for rare pediatric diseases. Since the enactment of the CHA, 4 PRVs were issued with the approval of new entities for rare or ultra rare pediatric diseases. Additionally, as part of a requirement under a provision of FDASIA, a public meeting was held in 2014 to discuss ways to encourage and accelerate the development of new therapies for children with rare diseases. This culminated in the release of a new strategic plan on accelerating the development of therapies for pediatric rare diseases by the FDA [42].

In February 2014, elosulfase alfa (Vimizim) became the first FDA-approved treatment for Morquio A syndrome for patients 5 years and older [43]. Mucopolysaccharidosis Type IV A, also known as Morquio A syndrome, is a rare autosomal recessive lysosomal storage disorder caused by a deficiency in N-acetylgalactosamine-6-sulfate sulfatase (GALNS); leading to the accumulation of keratan sulfate and chondroitin-6-sulfate. Morquio A syndrome is clinically characterized by severe skeletal deformities as well a constellation of

other developmental abnormalities including corneal opacities, hepatosplenomegaly, and structural heart disease. Second, in March 2015, cholic acid (Cholbam) was approved for the treatment of patients with bile acid synthesis disorders as well as patients with Zellweger spectrum peroxisomal disorders [44]. These disorders are characterized by reduced bile flow, steatorrhea, and malabsorption of fatty acids and fat-soluble vitamins leading to liver disease and growth abnormalities over time. For patients with bile acid synthesis disorders, a single-arm trial following more than 50 patients over 18 years showed improvements in baseline liver function and weight gain over time [45]. Lastly, Uridine triacetate (Xuriden) was approved by the FDA in September 2015 for the treatment of hereditary orotic aciduria, an extremely rare autosomal recessive metabolic disorder which is thought to affect fewer than 20 people worldwide [46, 47].

INFECTIOUS DISEASE

Pharmacokinetics

Several advancements have been made in characterizing the PK properties of anti-infective agents in pediatric populations (Table 2).

Pneumonia

Community-acquired pneumonia is a major cause of hospitalization of children in the United States [48]. It is most commonly caused by *Streptococcus pneumonia* but due to uncertainty of the causative organism and susceptibility patterns in the clinical setting, patients are frequently prescribed broad-spectrum antibiotics as empirical therapy [49]. The Pediatric Infectious Disease Society and the Infectious Diseases of Society of America published guidelines in 2011 for the treatment of uncomplicated community acquired pneumonia in pediatric patients and recommended the empiric use of narrow-spectrum coverage with agents such as ampicillin or penicillin G [50]. A multicenter retrospective cohort study was conducted to compare the effectiveness of empiric treatment with narrow-spectrum vs. broad-spectrum therapy [51]. Children between the ages of 2 months to 18 years (n=492) who had been discharged with a diagnosis of community-acquired pneumonia and received either narrow or broad-spectrum therapy in the first two days of hospitalization were included in the study. Narrow coverage was defined as amoxicillin, ampicillin, penicillin, or amoxicillin/clavulonic acid and broad coverage was defined as a second or third generation cephalosporin or fluoroquinolones. The study found that patients on narrow spectrum therapy had a 10-hour shorter length of hospitalization (P=0.4) with no other significant differences in outcomes. As such, the investigators concluded that both narrow and broad-spectrum coverage are associated with similar outcomes [51]. Similarly, a prospective, randomized study in 58 children between 3 months and 15 years of age found that penicillin G was as safe and effective as cefuroxime for the treatment of community acquired pneumonia [52].

Hepatitis B

Entecavir (Baraclude) is a reverse transcriptase inhibitor that was approved for the treatment of chronic hepatitis B in adult patients in 2004. In 2014, the FDA expanded the indication age range to include pediatric patients 2 years of age and older. This was based on 2 clinical

trials in pediatric patients between 2–18 years with hepatitis B envelope antigen (HBeAg)-positive chronic hepatitis B infection and compensated liver disease [53].

HIV

Significant progress has been made over the last decade in decreasing the incidence of HIV in pediatric populations. In 2014, Joint United Nations Programme on HIV/AIDS reported a 60% reduction in the number of new infections in children under 15 years of age between 2001 and 2013, from 500,000 to approximately 200,000 cases. Pediatric HIV/AIDS is currently estimated to affect 3.2 million children worldwide, which is approximately 9% of the global HIV/AIDS population [54]. In the last two years, there have been multiple FDA labeling changes for HIV drugs for use in pediatric populations. Atazanavir (Reyataz), which was previously available as a capsule for patients 6 years and older, became available in a new dosage form as an oral powder for patients greater than 3 months of age and weighing at least 5 kg. Abacavir (Ziagen) and lamivudine (Epivir) both underwent label revisions to provide new information on once-daily dosing for pediatric patients 3 months and older. A label change for combined lopinavir-ritonavir (Kaletra) recommended that the drug should be administered twice daily and not once daily in pediatric patients. Combination lamivudine-raltegravir tablets (Dutrebis) were approved for the treatment of HIV infection in adult and pediatric patients over 6 years of age and weighing at least 30 kg [55]. The indication for rilpivirine (Edurant) and the combination medication abacavir sulfate-lamivudine (Epzicom) was expanded from adults to include pediatric patients.

During the initiation of antiretroviral therapy (ART), both CD4 percentage (CD4%) and age are important factors [56, 57]. Investigators of the Pediatric AIDS Clinical Trials 390/ Paediatric European Network for Treatment of AIDS 9 (PENPACT-1) quantified the impacts of ART initiation at different ages and CD4% on CD4% recovery after 4 years in pediatric patients 0–17 years of age [58]. Overall, 72% of 162 vertically infected, immunosuppressed children recovered to normal CD4% within 4 years of ART initiation. Those who had mild or advanced immunosuppression as defined by World Health Organization criteria were more likely to recover to normal CD4% compared to those who were considered severely immunosuppressed at baseline. Additionally, for each 5-year increase in baseline age, the proportion of children achieving recovery declined by 19%. The study concluded that combining baseline CD4% and age effects resulted in >90% recovery after 4 years when ART was initiated with mild immunosuppression at any age or with advanced immunosuppression <3 years of age [58].

Congenital Cytomegalovirus

Congenital cytomegalovirus (CMV) infection is a leading cause of sensorineural hearing loss in infants and children [59]. Approximately 10–15% of infants with congenital CMV infection will be symptomatic at birth, and up to 20% of all infected children will develop long-term sequelae including cognitive impairment and sensorineural hearing loss [60]. Neonates with symptomatic congenital CMV involving the central nervous system can be treated with 6 weeks of intravenous ganciclovir, or oral valganciclovir, which has been shown to improve outcomes at 6 months of life [61]. A randomized, placebo-controlled trial

of valganciclovir therapy in neonates with symptomatic congenital CMV was conducted to compare 6 months vs 6 weeks of therapy [62]. Ninety-six neonates with gestational age 32 weeks, postnatal age 30 days, and weighed at least 1800 g were randomized to receive oral valganciclovir at a dose of 16 mg/kg twice daily for either 6 weeks (followed by 4.5 months of placebo) or 6 months. Brain-stem auditory evoked response was assessed at baseline and performed in combination with visual-reinforcement audiometry to assess hearing at 6, 12, and 24 months. Additionally, the Bayley-III scale to assess infant and toddler development was administered at 12 and 24 months. The results of the 6-month hearing assessment were similar between the two groups. However, hearing was more likely to be improved or to remain the same at 12 months in the 6-month group compared to the 6-week group (73% vs 57%, $P=0.01$). The benefit in the 6-month group was maintained at 24 months (77% vs 64%, $P=0.04$). Additionally, patients in the 6-month group had better neurodevelopmental scores on the Bayley-III. Overall, the investigators concluded that treating neonates with symptomatic CMV for 6 months did not improve hearing in the short term but was associated with improved outcomes in the long term [62].

Pneumococcal Disease

Premature infants, particularly those <32 weeks gestational age, are at increased risk for invasive pneumococcal disease due to factors such as an reduced maternal-fetal transfer of pneumococcal antibodies and immature immune system [63, 64]. Despite this increased risk for infection, vaccination of preterm infants is often delayed [65]. A clinical trial was conducted to evaluate the immune response and safety profile of the 13-valent pneumococcal conjugate vaccine (PCV13) in preterm compared to term infants on the same vaccination schedule [66]. Two hundred healthy infants (preterm, $n=100$, term, $n=100$) between 42 and 98 days postnatal age were enrolled in a phase 4, open label, multicenter parallel-group study. Infants received PCV13 at 2, 3, 4 (infant series) and 12 months of age (toddler dose), along with other routine vaccinations. The primary study objective was to evaluate the immune response 1 month after administration of the infant series and 1 month after the toddler dose. The secondary objective was to measure the safety profile based on incidence of local reactions, systemic events, and adverse events. Most subjects in the study achieved an immunoglobulin G (IgG) concentration 0.35 ug/mL for all serotypes with >85% after completing the infant series and >97% after the toddler dose. Preterm infants were found to have an overall lower IgG geometric mean concentration compared to term infants. However, the geometric mean increased similar amounts for both groups after the toddler dose at 12 months and the difference in IgG response between the two groups almost disappeared. The vaccination was tolerated well regardless of gestational age. The investigators concluded that majority of subjects in both groups were able to exceed the World Health Organization threshold of protection and functional antibody response after the infant series [66].

NEUROLOGY

Migraines

Triptans are vascular serotonin 5-HT₁ receptor agonists that cause vasoconstriction and are an option for migraine treatment and prophylaxis in adult and pediatric populations. Prior to

2014, only two triptans were FDA approved for use in pediatric populations: almotriptan for use in adolescents (12–17 years) and rizatriptan (6 years and older) [1]. Over the last two years, two additional triptans have been approved for the acute treatment of migraines in adolescent patients 12 to 17 years of age. The first is zolmitriptan (Zomig), which was approved in 2014 based on a randomized, double blind, placebo-controlled trial of 310 patients with an established diagnosis of migraine for at least 1 year with a typical untreated migraine attack lasting 3 hours or more. Two hours following the initiation of treatment, 30% of patients who had received 5 mg of zolmitriptan reported no more headache pain compared to 17% in the placebo group [67]. Sumatriptan in combination with naproxen (Treximet) was also approved in 2014. In terms of efficacy, 3 different doses of sumatriptan/naproxen were found to be superior to placebo at reducing headache severity from moderate or severe pain to no pain at 2 hours' postdose (10/60 mg, 30/180 mg, and 85/500 mg vs placebo, 29%, 27%, 24% vs 10%, $P<.01$) [68].

Topiramate (Topamax) is an antiepileptic medication that is also used for migraine treatment and prophylaxis. In pediatric populations, it is approved for the treatment of partial onset or primary generalized tonic-clonic seizures both as a monotherapy or adjunctive treatment. In 2014, topiramate was also approved for migraine prophylaxis in adolescent patients 12–17 years of age [69].

Seizures

Benzodiazepines are considered a first-line therapy for the treatment of status epilepticus (SE) in pediatric patients [70]. Diazepam is currently FDA approved for the treatment of SE in pediatric patients while lorazepam is not. However, previous studies have suggested that lorazepam may have potential advantages compared to diazepam, such as improved effectiveness in terminating convulsions, a longer duration of action, and a lower incidence of respiratory depression [71, 72]. A study was conducted to determine if lorazepam has better efficacy and safety than diazepam for the treatment of pediatric SE [73]. Two hundred seventy-three patients between 3 months and 18 years of age presenting with convulsive SE to 11 US academic pediatric emergency departments were enrolled and randomized to receive 0.1 mg/kg of lorazepam or 0.2 mg/kg of diazepam. The primary efficacy outcome was cessation of convulsions by 10 minutes without additional recurrence within 30 minutes, which occurred in 72.1% of patients in the diazepam group and 72.9% of patients in the lorazepam group with an absolute efficacy difference of 0.8% (95% CI, -11.4 to 9.8%). For the primary safety outcome, 16.0% of patients in the diazepam group and 17.6% of patients in the lorazepam group required mechanical ventilation, resulting in an absolute efficacy difference of 1.6% (95% CI, -9.9% to 6.8%). There were no statistically significant differences in secondary outcomes between the two groups. As such, the investigators concluded that lorazepam for the treatment of SE in pediatric patients did not have improved efficacy or safety over diazepam [73].

ONCOLOGY

Two label changes were made for oncology drugs in the last two years [1]. For erlotinib (Tarceva), which is used in the treatment of refractory or recurrent ependymoma, the label

change includes a statement that safety and effectiveness have not been established in pediatric patients. This is based on a phase 2 study in 25 pediatric patients which was terminated prematurely for lack of efficacy [74]. For bortezomib (Velcade), a drug used in the treatment of relapsed acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma, the label change states that the effectiveness in pediatric patients with relapsed pre-B ALL has not been established.

Dinutuximab (Unituxin) became the third novel agent approved for the treatment of a pediatric cancer in the last 25 years [75]. Dinutuximab is a monoclonal antibody targeting GD2, a glycolipid that promotes cell growth in neuroblastoma. It is approved for the treatment of high-risk neuroblastoma in combination with isotretinoin (RA), IL2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients who have shown some response to first line therapy but require further treatment. The approval was based on a phase 3 study in 226 patients who had already completed multi-drug chemotherapy, surgery, radiation therapy, and stem cell transplant [76].

PULMONARY AND ALLERGY

Asthma

There were multiple label changes for anti-asthmatic therapies in 2014 and 2015. Mometasone furoate (Asmanex HFA) and fluticasone furoate (Arnuity Ellipta), which are used as maintenance treatment and prophylactic therapy, have both been approved for use in patients 12 years and older. For levalbuterol (Xopenex inhalation solution) used to treat reactive airway disease or asthma, the first label change stated that efficacy was not established in pediatric patients from 0 to 5 years of age. This was later updated to state that levalbuterol was not indicated for pediatric patients less than 4 years of age. A placebo-controlled clinical trial found no statistical difference in the primary efficacy endpoint and an increased incidence of adverse events in the study group compared to the placebo group [77].

Terbutaline is a beta-2 receptor agonist that is administered intravenously to patients who do not improve on initial treatments for severe acute asthma. A retrospective chart review of 120 subjects admitted to the pediatric intensive care unit for severe asthma and receiving treatment with terbutaline was conducted to determine if earlier terbutaline administration was associated with improved outcomes [78]. Of the patients who had received terbutaline for a significantly shorter amount of time (0.69 ± 1.38 vs. 2.91 ± 2.47 hours, $P < 0.001$), 60% of patients required mechanical ventilation compared to 27% of patients who had received terbutaline sooner. The study suggests that earlier administration of terbutaline may be beneficial in patients with severe acute asthma and decrease the incidence of respiratory failure [78].

Allergic Rhinitis

Drug-label changes were made for 4 drugs indicated for the treatment of allergic rhinitis. The indication for omalizumab (Xolair), originally approved in 2003 for asthma, was expanded to include the treatment of chronic idiopathic urticarial (CIU) in patients 12 years

and older. The approved age range for ciclesonide (Zetonna) for the treatment of perennial allergic rhinitis was expanded from 12 years and older to include patients 6–11 years of age. Use of beclomethasone dipropionate (QNASL) for the treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis was expanded to include patients 4 years and older. Finally, the age category for azelastine indicated for the treatment of seasonal allergic rhinitis was expanded to include patients as young as 6 months of age. Two new approvals were made for the treatment of allergic rhinitis associated with grass pollen allergies. The first was a combination allergen extract of Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens (Oralair), which was the first approved sublingual alternative to allergy shots [79]. The approval was based on studies conducted in the United States and Europe in 2,500 patients between the ages of 10 through 65 years. Patients taking the extract experienced a 16 to 30% reduction in symptoms compared to those who received the placebo [80]. The second approval was for another allergen extract of Timothy Grass pollen (Grastek) in patients 5 to 65 years of age, which showed a similar reduction in symptoms in a trial in 1501 patients [81].

Intranasal corticosteroids are frequently prescribed for the control of symptoms associated with allergic rhinitis. Triamcinolone acetonide aqueous nasal spray (Nasacort) has been approved in the United States for over a decade for treating symptoms related to perennial and seasonal allergic rhinitis in both adults and children 2 years and older [1]. Previous studies have yielded varying results regarding the potential systemic effects of intranasal corticosteroid such as growth retardation. The first randomized controlled trial based on FDA guidelines to assess the long-term effect of intranasal triamcinolone acetonide examined the difference in the growth velocity of children between 3 and 9 years of age who were treated for 12 months [82]. The randomized, double blind, placebo-controlled, parallel-group multicenter study was composed of a 4–6 month screening period followed by a 12 month treatment phase and a 2 month post-treatment follow-up. After screening and baseline visits, the patients were stratified by age group (3–5 years vs. 6–9 years) and gender and were randomized to receive either 110 µg of intranasal triamcinolone acetonide or placebo for 12 months. The investigators found that triamcinolone acetonide had a small, statistically significant effect on growth velocity (−0.45 cm/year, 95% CI: −.78—0.11, $P=0.01$). However, during the follow-up period, the growth velocity in the triamcinolone acetonide increased to approach the baseline growth velocity [82].

Cystic Fibrosis

Ivacaftor, which was originally approved for the treatment of patients with the *G551D* cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation, in children 6 years and older has been approved by the FDA for use in children over 2 years of age [1]. Additionally, the combination lumacaftor-ivacaftor was approved for the treatment of patients 12 years and older who are homozygous for the *F508del* mutation based on 2 phase 3 randomized trials (TRAFFIC and TRANSPORT) totaling 1108 patients [83]. The groups receiving different daily doses of lumacaftor-ivacaftor for 24 weeks showed improvement in predicted forced expiratory volume in 1 second (FEV₁). The mean (95% confidence interval) absolute improvement in percentage of predicted FEV₁ for 600mg/day lumacaftor-ivacaftor was 2.6% (1.2–4.1) and 400mg every 12 hours was 3.0% (1.6–4.4) over the

placebo group ($P < 0.001$). Additionally, patients experienced an increase in body mass index and a reduced frequency of pulmonary exacerbations [83]. Lumacaftor-ivacaftir combination treatment was well tolerated with the incidence of adverse events similar between the groups.

PSYCHIATRY

Five label changes were made for psychiatric drugs between 2014 and 2015 [1]. First, asenapine (Saphris) is now approved for the treatment of acute manic or mixed episodes associated with bipolar 1 disorder in patients between 10 and 17 years of age. Safety and efficacy were established in a phase 1 study in 403 patients. Asenapine was not shown to be effective in the treatment of schizophrenia in adolescents age 12–17 years [84]. Second, a 24-week open-label safety study for escitalopram oxalate (Lexapro) did not identify any new safety concerns in 118 children 7 to 11 years of age with major depressive disorder (MDD). The label change states that escitalopram oxalate is safe and well tolerated in this population even though efficacy was not established. Third, selegiline (Emsam) also used for the treatment of MDD failed to demonstrate efficacy in adolescents 12 to 17 years of age based on a phase 4 study in 306 patients. Additionally, selegiline is contraindicated in children under 12 years of age due to increased risk of hypertensive crisis compared to adults and adolescents. Fourth, safety and efficacy for lamotrigine (Lamictal) used in the maintenance of bipolar disorder was not established for patients 10 to 17 years of age. Lastly, a study of duloxetine hydrochloride (Cymbalta) in 272 patients for the treatment of generalized anxiety disorder established safety and efficacy in children 7 to 17 years.

Advances in pharmacotherapies for attention deficit hyperactivity disorder (ADHD) are covered in the chapter by Leung and Hon.

RHEUMATOLOGY

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood and is composed of several subgroups of autoimmune diseases depending on onset and disease course [85]. Polyarticular JIA is characterized by the involvement of ≥ 5 joints within 6 months of the onset of illness. Adalimumab is an anti-TNF antibody that is approved for the treatment of moderate to severe polyarticular JIA in patients ≥ 4 years of age [1]. A phase 3 open-label, multicenter trial was conducted to determine the safety, efficacy, and PK profile of adalimumab in children between the ages of 2–4 years with moderate to severe polyarticular JIA [86]. Each patient received 24 mg/m² of adalimumab subcutaneously every other week for a minimum of 24 weeks and were allowed to continue concomitant treatments including methotrexate, NSAIDs, or low dose steroids. The study followed 32 patients with a mean (standard deviation) age of 3.0(0.72) years and duration of polyarticular JIA of 12(9.3) months. Patients received a mean duration (standard deviation) of 515(245) days of adalimumab exposure. 90.6% of patients reported at least one adverse event with infections and worsening of JIA being the most frequent. Adalimumab was associated with sustained improvement of core JIA disease parameters as defined by the American College of Rheumatology pediatric score for up to 96 weeks. Mean steady-state

concentrations were within the range observed in older populations of children between ages 14–17 [87]. Overall, the investigators concluded that adalimumab therapy with or without concomitant methotrexate was well tolerated and effective for the treatment of moderate to severe polyarticular JIA in this population [86].

Systemic JIA is another subgroup of childhood arthritis with onset of disease that is characterized by high fever, rash, hepatosplenomegaly, lymphadenopathy, anemia, and occasionally macrophage activation syndrome [88]. Patients may also experience poor long-term outcomes such as growth failure, musculoskeletal deformities, and osteoporosis [89]. Rilonacept is an inhibitor of interleukin-1, which is a mediator in the inflammatory cascade that contributes to the pathogenesis of systemic JIA. It is currently only FDA approved for the treatment of Cryopyrin-Associated Periodic Syndromes in adults and children 12 years and older [90]. The Randomized Placebo Phase Study of Rilonacept in the Treatment of Juvenile Idiopathic Arthritis (RAPPORT) trial was conducted to determine the safety and efficacy of rilonacept in the treatment of systemic JIA [91]. Seventy-one children between the ages of 18 months and 19 years were randomized to receive either 24 weeks of rilonacept treatment or 4 weeks of placebo followed by 20 weeks of treatment. At week 4, 57% of the patients receiving rilonacept had a response compared to 27% of patients receiving the placebo ($P=0.016$). The most common adverse events were the exacerbation of systemic JIA and elevated transaminase levels. A pharmacokinetic analysis conducted as part of this study found that rilonacept clearance increased with increasing body weight and age and decreased with increasing serum albumin levels. Overall, it was observed that the range of exposure after a loading dose of 4.4 mg/kg followed by 2.2 mg/kg weekly maintenance doses used in the RAPPORT trial were comparable to values observed in adult populations [92].

SYMPTOMATIC CARE

Clonidine is an alpha-2 adrenergic agonist that is used in conjunction with morphine for the treatment of withdrawal in neonatal abstinence syndrome (NAS). To determine whether single-agent clonidine treatment is as effective as morphine in the treatment of NAS, a pilot randomized double-blind single center study was conducted [93]. A total of 31 infants 35 weeks' gestational age were enrolled in the study and randomized to receive morphine (0.4 mg/kg per day) or clonidine (5 ug/kg per day) divided into 8 doses. Neurobehavioral performance was assessed using the NICU Network Neurobehavioral Scale (NNNS) 1 week and 2 to 4 weeks after start of treatment. The Bayley Scales III and Preschool Language Scale IV were administered at 1-year adjusted age. The study found that duration of treatment for infants on morphine ($n=15$) was significantly longer when compared to clonidine ($n=16$). Additionally, NNNS scores improved with clonidine but not morphine and one-year motor, cognitive, and language scores did not differ between the two groups. The investigators concluded that clonidine single agent therapy is as effective as morphine used for the treatment of NAS [93]. Since this was a small pilot study, a large randomized multicenter trial is necessary.

SUMMARY

There has been major progress in the development of drugs for pediatric patients over the last two years. The top areas under investigation included infectious disease, particularly antivirals, and anti-allergy and anti-asthma medications. Other areas of progress included anti-inflammatory medications used in the treatment of gastrointestinal disease and anti-epileptics for pediatric seizures. Additionally, there has been a recent surge in the development of medications for the treatment of rare diseases that affect pediatric populations, specifically inherited metabolic disorders.

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Key points

- Pediatric research continues to expand in both the United States and in Europe as a result of ongoing efforts to promote pediatric drug development and labeling.
- Despite the progress that has been made over the last two years, much work remains including gathering more data on medications that are currently available and developing new, safe, and effective therapies for pediatric patients.

Table 1

Select drug-label changes made by US Food and Drug Administration in 2014 and 2015.

Generic Name	Trade Name	Indication Studied	Summary of label change(s)
Abacavir sulfate and lamivudine	Epzicom	HIV-1 infection	Expanded indication from adults to pediatric patients weighing at least 25 kg
Acyclovir/hydrocortisone	Xerese	Treatment of recurrent herpes labialis	Expanded indication to include pediatric patients 6 y of age
Amphetamine	Dyanavel XR	Attention Deficit Hyperactivity Disorder	Safety and efficacy established in patients 6–17 years of age
Aripiprazole	Abilify	Maintenance treatment of irritability associated with autistic disorder	Effectiveness was not established in a 12 week clinical trial in 85 pediatric patients 6 – 17 y of age
Aprepitant	Emend	Prevention of nausea and vomiting associated with highly and moderately emetogenic cancer chemotherapy	Indicated for patients 12 y of age and older and patients less than 12y who weigh at least 30 kg
Asenapine	Saphris	Treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder	Safety and effectiveness established in by placebo-controlled, double-blind trial of 403 patients 10 – 17 y of age
Atazanavir	Reyataz	Treatment of HIV-1 infection	Oral powder approved for use in pediatric patients at least 3 mo and weighing between 10 to 25kg, and was then expanded to patients 3 mo and older weighing 5 to <10kg and to those weighing >25kg
Beclomethasone dipropionate	QNASL	Treatment of nasal symptoms associated with seasonal allergic rhinitis and perennial allergic rhinitis	Expanded indication to pediatric patients 4 y
Bortezomib	Velcade	Relapsed Acute Lymphoblastic Leukemia and Lymphoblastic Lymphoma	Effectiveness in pediatric patients with relapsed pre-B ALL has not been established
Calcipotriene/betamethasone dipropionate	Taclonex	Treatment of psoriasis vulgaris	Expanded indication to patients 12 – 17 y of age
Cysteamine bitartrate	Procysbi	Treatment of nephropathic cystinosis	Expanded indication to pediatric patients down to 2 years
Darbepoetin alfa	Aranesp	Initial treatment of anemia in pediatric patients with chronic kidney disease (CKD)	Indication expanded to include patients from 1 – 18 y of age
Duloxetine hydrochloride	Cymbalta	Treatment of generalized anxiety disorder	Safety and effectiveness established in 10-week, placebo-controlled trial of 272 patients with GAD 7 – 17 y of age
Entecavir	Baraclude	Treatment of chronic hepatitis B virus (HBV) infection	Approved for use in pediatric patients 2 y
Erlotinib	Tarceva	Treatment of recurrent or refractory ependymoma	Safety and effectiveness not established in pediatric

Generic Name	Trade Name	Indication Studied	Summary of label change(s)
			patients based on an open-label, multi-center trial with 25 patients (median age 14 y, range 3 – 20 y)
Finaxofacin	Xtoro	Treatment of acute otitis externa	Safety and effectiveness established in patients 1y by two randomized multicenter placebo-controlled trials of 1234 patients
Fluticasone furoate	Arnuity Ellipta	Maintenance treatment of asthma as prophylactic therapy	Approved for use in patients 12 y
Fluticasone propionate	Cutivate	Treatment of atopic dermatitis	Indication expanded to patients 3 mo of age
Lamivudine and raltegravir	Dutrebis	Treatment of HIV-1 infection	Indicated in pediatric patients 6 – 16 y of age weighing at least 30 kg
Lamotrigine	Lamictal	Maintenance treatment of bipolar disorder	Safety and effectiveness were not established for patients 10 – 17 y of age based on a double-blind placebo controlled trial in 301 patients
Levalbuterol	Xopenex inhalation solution	Treatment of asthma or reactive airway disease	Effectiveness was not established a trial in 291 patients from 2 – 5 y of age and another trial in 88 patients from birth to less than 2 y of age
Levetiracetam	Keppra	Treatment of partial onset seizures (POS), primary generalized tonic clonic seizures (PGTC), myoclonic seizures	Safety and effectiveness established for adjunctive treatment of POS in patients 1mo to 16 y, PGTC in patients 6 – 16 y, and myoclonic seizures in patients 12 – 16 y
Levetiracetam	Keppra XR	Adjunctive therapy in the treatment of partial onset seizures	Safety and effectiveness established in patients 12 y
Memantine hydrochloride	Namenda XR	Treatment of autism spectrum disorders	Safety and effectiveness not established in 2 12-week controlled trials of 578 patients 6 – 12 y of age
Meropenem	Merrem IV	Treatment of complicated intra-abdominal infections	Expanded indication to pediatric patients less than 3 mo of age
Mesalamine	Asacol	Maintenance of remission of mildly to moderately active ulcerative colitis	Safety and effectiveness have not been established in pediatric patients
Mesalamine	Delzicol	Treatment of mild to moderately active ulcerative colitis	Expanded indication to patients 5 years and older
Methylphenidate hydrochloride	Aptensio XR	Treatment of attention deficit hyperactivity disorder (ADHD)	Safety and effectiveness established in patients 6 – 17 y of age
Mometasone furoate	Asmanex HFA	Maintenance of asthma as prophylactic therapy	Approved for use in children 12 y
Naftifine hydrochloride	Naftin	Treatment of interdigital tinea pedis	Expanded indication to include pediatric patients 12 – 18 y

Generic Name	Trade Name	Indication Studied	Summary of label change(s)
Olopatadine hydrochloride	Pazeo	Treatment of ocular itching associated with allergic conjunctivitis	Safety and effectiveness established in patients 2 y
Omalizumab	Xolair	Treatment of chronic idiopathic urticarial (CIU)	Approved for treatment of CIU in children 12 y who remain symptomatic despite H1 antihistamine treatment
Oxycodone hydrochloride	Oxycontin extended release tablets	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment	Safety and efficacy established in patients 11–16 y of age
Palonosetron hydrochloride	Aloxi	Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) and postoperative nausea and vomiting (PONV)	Approved for use in pediatric patients 1 mo to 17 y
Perampanel	Fycompa	Treatment of primary generalized tonic clonic seizures	Safety and efficacy established in patients 12 y of age in a randomized, double-blind, placebo-controlled multicenter trial with 11 patients
Rifapentine	Priftin	Treatment of latent tuberculosis infection (LTBI) caused by Mycobacterium tuberculosis in combination with isoniazid	Safety and effectiveness established in pediatric patients 2 – 17 y of age
Riliprivine	Edurant	HIV-1 infection in treatment-naïve patients	Expanded indication from adults to pediatric patients 12–18 y of age
Rufinamide	Banzel	Adjunct treatment of seizures associated with Lennox Gastaut Syndrome	Indication expanded to patients 1 y of age
Sapropterin dihydrochloride	Kuvan	Treatment to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)- responsive phenylketonuria (PKU)	Expanded indication to include 1 mo to 4 y
Selegiline	Emsam	Treatment of major depressive disorder (MDD)	Effectiveness was not established in a multi-center randomized, double-blind, placebo-controlled, flexible-dose trial in 308 adolescents 12 – 17 y
Spinosad	Natroba	Treatment of head lice infestation	Indication expanded to patients 6 mo of age
Tiotropium bromide	Spiriva Respimat Inhalation Spray	Long-term maintenance treatment of asthma	Safety and efficacy established in patients 12–17 years of age
Topiramate	Topamax	Prophylaxis of migraine headache	Approved for use in children 12 y
Valganciclovir	Valcyte	Prevention of cytomegalovirus disease in heart transplant patients	Indication expanded to patients 1 – 4 mo of age
Zolmitriptan	Zomig Nasal Spray	Acute treatment of migraine with or without aura	Efficacy established in patients 12 – 17 y of age

Data from the FDA Pediatric Labeling Information Database. Available at: <http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. Accessed November 20th, 2015.

Table 2

Pediatric antimicrobial pharmacokinetic studies published in 2014 and 2015.

Drug Name	Patient Population	PK Analysis Approach	Dosing modifications recommended for studied population (yes/no)
Antimicrobials			
Ampicillin [94]	Neonates	Population	Yes
Azithromycin/chloroquine [95]	Children and adults	Population	Yes
Ciprofloxacin [96]	Neonates and infants	Population	Yes
Clindamycin [97]	Neonates, infants, children, adolescents	Population	Yes
Piperacillin/tazobactam [98]	Children	Population	Yes
Piperacillin/tazobactam [99]	Infants	Population	Yes
Teicoplanin [100]	Children	Population	No
Teicoplanin [101]	Children, adolescents	Population	Yes
Antifungals			
Fluconazole [102]	Children	Population	Yes
Micafungin [103]	Children, adolescents	Noncompartmental	No
Micafungin [104]	Children, adolescents	Population	Yes
Antivirals			
Acyclovir [105]	Infants	Population	Yes
Fosamprenivir/ritonavir [106]	Children, adolescents	Noncompartmental	No
Fosamprenivir/ritonavir [107]	Infants, children	Noncompartmental	No
Lopinavir/ritonavir [108]	Infants, children	Noncompartmental	No
Nevirapine [109]	Children, adolescents	Noncompartmental	No
Raltegravir [110]	Neonates	Noncompartmental	No
Raltegravir [111]	Children, adolescents	Noncompartmental	No
Raltegravir [112]	Infants, children, adolescents	Population	No
Vancomycin [113]	Infants, children, adolescents	Compartmental	No
Zidovudine [114]	Children	Noncompartmental	No
Antiparasitic			
Benznidazole [115]	Children	Population	Yes