



Quarter Watch

Monitoring FDA MedWatch Reports

January 16, 2014 — Special Report on Children

ADVERSE DRUG EVENTS IN CHILDREN UNDER AGE 18

Psychiatric side effects prominent in 10 of 15 most frequently reported drugs
Ibuprofen associated with severe hypersensitivity
Few reports for antibiotics and albuterol

Executive Summary

This report analyzes 15 drugs that accounted for 41% of recent serious adverse events in children reported to the U.S. Food and Drug Administration (FDA) over the five years 2008-2012. In addition, we examine reporting trends from the same period for all domestic reports to the agency that identified adverse events in children under age 18.

QuarterWatch[™] is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. We analyze computer excerpts from the FDA Adverse Event Reporting System (FAERS). These reports (best known as MedWatch reports) are a cornerstone of the nation's system for monitoring the safety of therapeutic drugs after FDA marketing approval. This special report focuses on children; new quarterly data are not included because the FDA has not yet released new quarterly excerpts for 2013 due to technical problems.

Our study identified 45,610 adverse drug events reported in children less than 18 years of age. Of these, 64% (29,298) indicated a serious injury. Reports in children grew substantially over time--from 6,320 in 2008 to 11,401 in 2012, increasing at the same rate as for adult patients. Examined by year of age in children, the reports formed a U-shaped curve. The number was greatest in the first year of life, then declined and leveled off until adolescence, when cases again rose rapidly. There were insufficient data to evaluate 70% of the 741 drugs with reported serious adverse events in children because of fewer than 2 reports per year.

15 Most Frequently Reported Drugs

To identify signals of potential safety problems in children we focused on a subset of adverse event reports that were serious, had no known factors artificially increasing reporting, and resulted from normal or expected medical use. These criteria resulted in a list of 15 drugs that accounted for 41% of all reports in this category during the five-year period. The list included three medications for Attention Deficit Hyperactivity Disorder (ADHD), three antipsychotic drugs, and two biological products that block Tumor Necrosis Factor (anti-TNF agents), used for conditions such as rheumatoid arthritis and inflammatory bowel disease. The signals spanned a wide spectrum of child exposure to drugs ranging from a widely used pain medication to a skeletal muscle relaxant used in rare neurological disorders.

Among serious adverse drug events (ADEs), psychiatric side effects were prominent for 10 of the 15 drugs, including suicidal behaviors, hallucinations, aggression, and mood change. The drug signals are shown in Table 1.

Table 1. Most frequent suspect drugs in serious adverse drug events reported in normal medical use, 2008-2012

| Rank | Drug name | Brand name* | Cases | Medical use* | Psych** | Most freq ADE | 2d most freq ADE |
|------|------------------|-------------|-------|--------------------|---------|---------------------|----------------------|
| 1 | Infliximab | REMICADE | 1772 | Crohn's Disease | N | Crohn's disease | Ulcerative colitis |
| 2 | Montelukast | SINGULAIR | 944 | Asthma | Y | Suicidal ideation | Aggression |
| 3 | Somatropin | NUTROPIN | 606 | GH deficiency | N | Headache | Convulsion |
| 4 | Baclofen | LIORESAL | 579 | Muscle spasticity | N | Hypertonia | Drug ineffective |
| 5 | Isotretinoin | CLARAVIS | 447 | Acne | Y | Suicidal ideation | Depression |
| 6 | Methylphenidate | CONCERTA | 418 | ADHD | Y | Sudden death | Aggression |
| 7 | Lamotrigine | LAMICTAL | 335 | Epilepsy | Y | Convulsion | Stevens-Johnson synd |
| 8 | Lisdexamfetamine | VYVANSE | 314 | ADHD | Y | Suicidal ideation | Aggression |
| 9 | Aripiprazole | ABILIFY | 297 | Bipolar disorder | Y | Weight increased | Dystonia |
| 10 | Ibuprofen | MOTRIN | 242 | Pyrexia | N | Hypersensitivity | Renal failure acute |
| 11 | Etanercept | ENBREL | 231 | Juvenile arthritis | N | Injection site pain | Vomiting |
| 12 | Atomoxetine | STRATTERA | 227 | ADHD | Y | Suicidal ideation | Chest pain |
| 13 | Quetiapine | SEROQUEL | 210 | Bipolar disorder | Y | Weight increased | Tardive dyskinesia |
| 14 | Levetiracetam | KEPPRA | 206 | Epilepsy | Y | Convulsions | Drug ineffective |
| 15 | Risperidone | RISPERDAL | 195 | Bipolar disorder | Y | Aggression | Weight increased |

* Most frequently cited in case reports. **Psychiatric side effects > 25% of reports.

GH = Growth hormone. ADHD = Attention deficit hyperactivity disorder. Additional note in Methods Summary

Highlights of the List

Three ADHD drugs: Psychiatric side effects predominated for methylphenidate (CONCERTA, RITALIN), lisdexamfetamine (VYVANSE), and atomoxetine (STRATTERA). Notable were suicidal behaviors, aggression, and hallucinations or other manifestations of psychosis. Cardiac arrest was associated with methylphenidate, and weight loss or arrested growth was also reported for all three drugs.

Three antipsychotic drugs: Reports of movement disorders, tics, weight gain and sexual organ side effects were seen for aripiprazole (ABILIFY), quetiapine (SEROQUEL), and risperidone (RISPERDAL). The reports frequently occurred in children being treated for depression or bipolar disorder.

Analgesics: Among the OTC and prescription analgesics used in children, ibuprofen (MOTRIN, ADVIL) produced unexpectedly large numbers of cases of the most severe hypersensitivity and skin reactions, notably Stevens-Johnson syndrome and toxic epidermal necrolysis. These skin reactions were seldom reported for acetaminophen and naproxen. Severe skin reactions were even more numerous for another top-15 drug, the anti-convulsant lamotrigine (LAMICTAL).

Asthma medications: Although approximately 10% of children are treated for asthma, only montelukast (SINGULAIR) produced a high number of serious adverse event reports – predominantly of psychiatric side effects including suicidal behaviors, aggression, and depression. Montelukast was also used to treat allergies. Reports surged in 2008, and then tapered off substantially.

Anti-TNF agents: Reports for two biological products showed that adverse events occurred in two different populations. Infliximab (REMICADE) events primarily affected the GI tract and occurred in patients treated for GI tract disorders including Crohn's disease, ulcerative colitis, and inflammatory bowel disease. The largest group of adverse events suggested treatment failure, which the company attributed to disease flares. Etanercept (ENBREL) adverse events were reported in patients treated for juvenile arthritis and psoriasis and were frequently related to infusion site reactions.

Where Cases Were Few

Three of the most widely used drugs in children accounted for few reported serious injuries in our primary analysis. For example, amoxicillin and azithromycin were the most widely prescribed drugs in children in 2010, with 28 million patients in a juvenile population of 74 million. Azithromycin accounted for only 51 cases over 5 years, and amoxicillin for 41 reports. Albuterol was prescribed for about 7% of all children, but accounted for only 56 serious adverse events in our primary analysis group. The low volume of reports may not only attest to the safety of these widely used drugs but also reflect a very low reporting rate as well as short term or intermittent use.

Other Adverse Events

Five groups of adverse events were excluded from our primary analysis. These included non-serious adverse events (n = 16,316), reports of product quality problems (n = 3,695), medication errors (n = 6,097), drugs with special reporting issues (n = 5,277), and events before the first birthday (n = 5,550). A case report could meet one or more of the exclusion criteria.

Estrogen products were one group of drugs excluded because of special reporting issues, mainly involving product identification and classification. However, adverse events identifying various types of contraceptives were prominently reported in teenage girls. The adverse events included gallstones and other biliary tree disorders, blood clots, and various problems with method used to deliver estrogen products.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FDA's Adverse Event Reporting System (FAERS) data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency's MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. More complete disclaimers and descriptions of our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

Psychiatric adverse drug events, notably suicidal behaviors, represent the major adverse effects reported in children under age 18. Dechallenge—or careful, tapered discontinuation—is often a viable strategy for testing whether a drug is responsible for changes in behavior or mood. For the ADHD drugs, the FDA has already required warnings for hallucinations and other psychotic symptoms, and it should investigate the need for warnings about the more frequent reports of suicidal behaviors.

While amoxicillin and azithromycin produced small numbers of adverse event reports, particularly in light of their extensive use, we hope the long-term trend continues toward reduced use of antibiotics in children. Lamotrigine was suspect in more reports of severe and life threatening cutaneous reactions in children than any other drug over the five-year period. Its use in children should be reassessed.

For 70% of the suspect drugs, too few adverse event reports were voluntarily submitted by consumers and health professionals to permit an assessment of their risks in children, and in particular to identify adverse effects that might differ in children compared to adults. We agree with a previous FDA study that concluded that either this form of passive surveillance needs to be strengthened, or other approaches adapted to improve our understanding of drug risks in children.

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Results

An Expectation of Safety

After the first year of life, the health status of children in the United States is so robust that the overall survival rate may exceed that of any other living creatures. Among 100,000 children reaching 12 months of age, 99,826 will reach age 10, and just 8 will die during the 10th year.[1] As a result, the expectation should be that drugs administered to children should be of exceptionally low risk and address substantial health issues. The reported adverse event data for children suggest lower risks than for other age groups, and drug utilization is declining in children.[2]

Exposure

Children up to 18 years of age account for 24% of the total population [3] and 19% of all doctors' office visits, [4] but only 7.3% of all dispensed outpatient prescriptions in 2010.[2] In 2010, systemic antibiotics were the drugs most frequently dispensed for children, accounting for 25% of all prescriptions. In another study, 15% of children were dispensed an asthma medication.[5] Psychotropic medication was prescribed for 6.7% of children in the United States in year 2000 data.[6] Other frequently prescribed medications included topical corticosteroid preparations and cough suppressants.

Treatment of Adverse Drug Events

Adverse drug events in children were treated in an annual mean of 586,000 visits to doctors' offices or outpatient departments, [4] or approximately 1 in 100 childhood doctor visits per year. The adverse events in this setting were mostly mild, primarily involving rashes or gastrointestinal (GI) distress. More severe adverse events accounted for an additional 160,000 emergency room visits per year [7] with unintentional overdose and allergic reactions accounting for 80% of the cases. Hospital admissions of children for adverse drug events could not be estimated. While these estimates were taken from different years and sources, published data suggest that from 1 to 2 per 100 children per year experience an adverse drug event requiring medical treatment.

An FDA study showed few of the adverse events occurring were reported to the agency. For the five years 2003 to 2007, the FDA reported receiving 36,241 reports of adverse drug events in children under age 18, of which 62% were serious. [8] The authors of the FDA study expressed concern for the small number of reports and called for measures to improve spontaneous reporting and steps to implement new methods of active surveillance.

The Five-Year Results Overview

The FDA received 45,610 domestic reports of adverse events in children less than 18 years of age from 2008 through 2012 (Table 2). Reports per year increased 80% from 6,320 in 2008 to 11,401 in 2012. This was a marked change from the FDA's report about the previous five years, when report volume decreased slightly. The five-year totals included 2,935 deaths (6%) and 16,316 (35.8%) events that were not serious.

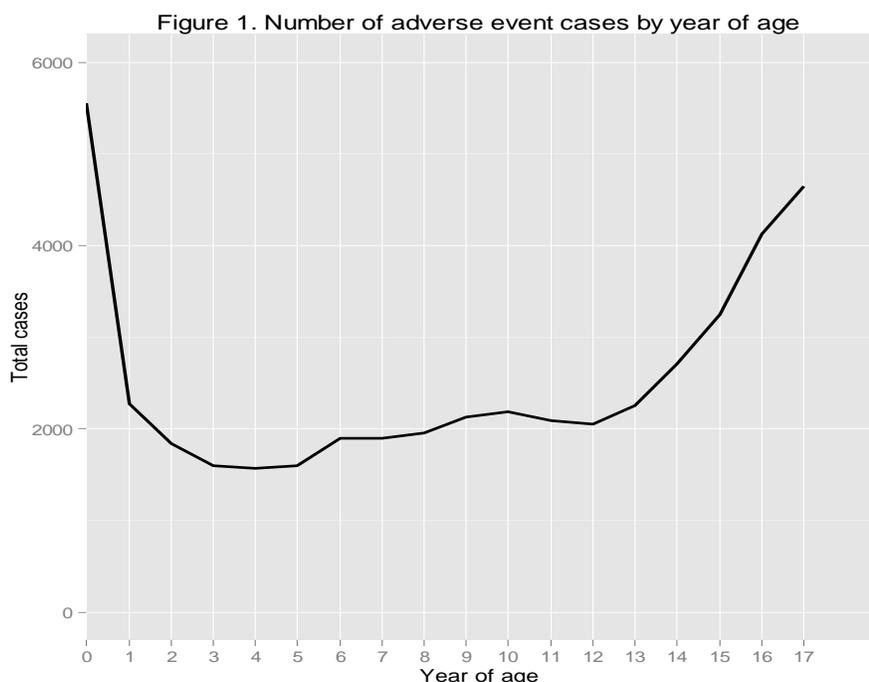
The reports in children showed several differences from the 883,364 reports that involved adults in the same period. (Cases with missing age values were excluded). In children, the events were more likely to occur in males (51% vs 34% for adults), to be submitted by health professionals rather than consumers (56% vs 44%), and to be

Table 2. Reported adverse drug events in children 0-17 years, 2008-2012

| | Number, pct | |
|---|-------------|--------|
| Total | 45610 | |
| Male gender* | 22522 | (51.0) |
| Outcome | | |
| Death | 2935 | (6.4) |
| Disability | 816 | (1.8) |
| Life-threatening | 1430 | (3.1) |
| Required intervention | 774 | (1.7) |
| Hospitalization | 10032 | (22.0) |
| Other serious | 13311 | (29.2) |
| Not serious | 16312 | (35.8) |
| Report Group** | | |
| Primary analysis | 16992 | (37.3) |
| Medication error | 6097 | (13.4) |
| Product quality | 4066 | (8.9) |
| Reporting issues | 5277 | (11.6) |
| * Percent excludes missing values | | |
| ** Cases may be in multiple categories or be excluded | | |

submitted directly to the FDA rather than through drug manufacturers (14% vs 11%). Reports in children were less likely to indicate a death outcome (6% vs 9%).

Reports in children examined by year of age demonstrated a U-shaped curve with the largest number occurring in the first year of life, then declining sharply, and then rising again after adolescence. The number of reports by age is shown in Figure 1.



The Primary Analysis Group

To identify the drugs with the highest reported risks to children, we focused on cases that were serious and occurred in normal medical use rather than from medication error, intentional overdose, or because of product quality complaints. (See the Methods Summary for additional detail.) These more restrictive criteria captured 16,992 reports (37.3% of the total) over the five-year period, and 73% were originated by health professionals (and submitted either through manufacturers or directly to the FDA). A key finding was that 2% or 15/741 of identifiable primary suspect drugs accounted for 41% of reported cases. The pattern of a small number of drugs accounting for a large share of reported events has been observed in many different patient populations and time periods.

Psychiatric Side Effects Predominate

Of all the systems that might be adversely affected in drug therapy, psychiatric side effects were prominent in the cases of serious injury reported to the FDA, both in the number of cases and the number of suspect drugs frequently implicated. The most frequent specific psychiatric side effects reported were suicidal ideation (n = 714), aggression (n = 686) and abnormal behavior (n = 580). Suicidal behaviors were by no means limited to thoughts of suicide, but also included 274 completed suicides, 159 suicide attempts, and 100 cases labeled “self-injurious behavior.” Also reported were various forms of psychosis including hallucination (n = 276), psychotic disorder (n = 124), and paranoia (n = 74).

Suspect Drugs

Psychiatric disorders were reported for 25% or more of all adverse events for 10 of the 15 drugs on the *QuarterWatch* ranking of the most frequent suspects. The total included two drugs without intended psychotropic effects, montelukast (SINGULAIR for asthma and allergies) and isotretinoin (CLARAVIS for acne). One of the anti-epileptic drugs, lamotrigine (LAMICTAL), is approved for treating bipolar disorder, while another antiepileptic, levetiracetam (KEPPRA) is not. The results for the 10 drugs are shown in Table 3. The category “Suicidal and self-injurious behavior” includes the most common psychiatric term, suicidal ideation.

Table 3. Psychiatric side effects for frequently reported drugs

| Rank | Drug | Suicidal behavior* | | Any psychiatric disorder** | | All Events |
|------|------------------|--------------------|--------|----------------------------|--------|------------|
| | | Number | pct | Number | pct | |
| 1 | Montelukast | 438 | (46.4) | 831 | (88.0) | 944 |
| 2 | Lisdexamfetamine | 83 | (26.4) | 192 | (61.1) | 314 |
| 3 | Risperidone | 36 | (18.5) | 100 | (51.3) | 195 |
| 4 | Isotretinoin | 149 | (33.3) | 191 | (42.7) | 447 |
| 5 | Methylphenidate | 58 | (13.9) | 171 | (40.9) | 418 |
| 6 | Atomoxetine | 41 | (18.1) | 84 | (37.0) | 227 |
| 7 | Quetiapine | 52 | (24.8) | 71 | (33.8) | 210 |
| 8 | Aripiprazole | 31 | (10.4) | 94 | (31.6) | 297 |
| 9 | Lamotrigine | 23 | (6.9) | 96 | (28.7) | 335 |
| 10 | Levetiracetam | 14 | (6.8) | 52 | (25.2) | 206 |

* Suicidal and self-injurious behavior High Level Term, cases/percent of all events.

**Psychiatric disorder System Organ Class, cases/percent of all events

ADHD Drugs

The three drugs for ADHD include two stimulants, lisdexamfetamine (VYVANSE) and methylphenidate (CONCERTA), as well as the antidepressant-like atomoxetine (STRATTERA). Suicidal behaviors were the most frequently reported psychiatric side effect for all three ADHD drugs, although within that category suicidal ideation was the most frequent specific symptom reported. Atomoxetine shares a suicidal behavior warning with other antidepressants, but lisdexamfetamine and methylphenidate do not carry a warning about suicidal behaviors, even though in these data suicidal behaviors were reported in 26.4% and 13.9% of all cases, respectively. All three ADHD drugs have warnings for psychosis and hallucinations, and such cases were reported for all three drugs in these data. The FDA studied the incidence of hallucinations and other forms of psychosis in the stimulants [9] and required a warning. It should assess the need for a warning for the more frequently reported suicidal thoughts and behaviors.

The three ADHD drugs also had noted non-psychiatric adverse effects. The most frequently reported adverse event for methylphenidate was 37 cases of sudden death; the prescribing information [10] currently contains a warning, but the literature is mixed.[11] [12] Cardiac adverse effects were reported for atomoxetine, including chest pain (n = 16), syncope (n=11) and electrocardiogram QT interval prolonged (n = 10). Movement disorders were reported for lisdexamfetamine, including dyskinesia (n = 17), tics (n = 16) and tremor (n = 9). Antipsychotic Drugs

The full spectrum of antipsychotic drug adverse effects occurring in adults was also reported in this population of children for aripiprazole (ABILIFY), quetiapine (SEROQUEL), and risperidone (RISPERDAL). Suicidal behaviors were reported for all three drugs, accounting for 24.8% of quetiapine cases, 18.5% of risperidone cases, and 10.4% for aripiprazole.

Dyskinesias—which are disfiguring and typically irreversible movement disorders—were reported for aripiprazole (n = 44), quetiapine (n = 27), and risperidone (n = 22). In a clinical trial of risperidone and haloperidol (HALDOL) given for the first time to young adults, from 8 -12% treated for one year developed tardive dyskinesia. [13]

Other adverse events reported for the antipsychotic drugs included neuroleptic malignant syndrome, dystonia, lactation disorders, gynecomastia, weight increase, diabetes, and convulsions.

Despite these high risks, the reports indicated that antipsychotic drugs were given to children for a wide range of disorders, including depression, ADHD, aggression, and sleep disorders.

Montelukast (SINGULAIR) and Isotretinoin (CLARAVIS)

Montelukast (SINGULAIR) for asthma and allergies, and isotretinoin for acne are notable examples of drugs with numerous reported psychiatric effects but no intended psychotropic action. Montelukast ranks among the most widely used drugs in children, prescribed for 2.9 million children in 2010,[2] including 4.5% of all children aged 2-11. Although a leukotriene inhibitor, 831 cases (88%) indicated psychiatric symptoms, including 438 (46.4%) indicating suicidal behavior. Other psychiatric symptoms reported included aggression (n=292), depression (n = 208), crying (n = 125), and mood swings (n = 101). Montelukast, previously examined in *QuarterWatch* in 2009, [14] also provides a cautionary tale about interpreting the number of adverse events, especially over a short period of time. In early 2008 Merck, the manufacturer of brand name montelukast (Singulair), reported to the FDA a handful of cases of suicide and suicidal behavior over several preceding years. The FDA responded in March of 2008 by posting a public Drug Safety Communication indicating that the agency was investigating the reported psychiatric side effects. What followed was a massive surge in adverse event reports of psychiatric side effects that peaked with 397 cases in 2008 and then steadily declined to 84 cases in 2012, a period in which prescription volume remained mostly unchanged. However, when we examined the much smaller numbers of 2011 and 2012 reports, the same pattern of psychiatric side effects remained, just in smaller numbers. We attribute the change in number of reports to variability in reporting rates but note that the association with drug treatment remained convincing.

For isotretinoin, suicidal behaviors number among four prominent side effects warranting careful consideration prior to use of this medication for severe and resistant acne. In women, isotretinoin has extremely high risk of birth defects should pregnancy occur. Reported cases included 42 unintended pregnancies. Other major reported side effects included depressed mood (n=101) and colitis (n=20). ACCUTANE, the original brand name drug manufactured by Roche, was discontinued in 2009 after thousands of lawsuits were filed and generics were approved. The birth defect risks of isotretinoin spawned one of the FDA's most aggressive risk management programs (called iPledge), which includes requirements that prescribing doctors be trained and registered, that females of child-bearing age have two negative pregnancy tests and agree to use two different forms of birth control or abstain from sexual intercourse, visit the doctor monthly for progress visits, and sign a written informed consent form. (https://www.ipledgeprogram.com/FAQ_Public.aspx)

Severe Skin Reactions

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are feared, life-threatening hypersensitivity reactions associated with some drugs widely used in children. Cases begin with fever and flu-like symptoms occurring 1-3 weeks after starting drug treatment. [15] In a few more days, blisters develop in mucous membranes of eyes, mouth, and genitalia. As the more severe cases progress, massive skin lesions and blisters appear and become so pervasive that large areas of skin may become denuded, leading to extreme pain, bleeding, infection, and hypothermia. Patients are often treated in burn units with treatments intended to mitigate the effects of massive compromise of the skin. Drugs with five or more cases over 5 years reported in children are shown in Table 4. All the drugs were associated with SJS/TEN in a landmark study [16] or in the case of lamotrigine in the prescribing information.[17]

Table 4. Drugs with reports of severe skin reactions

| Drug | SJS/TEN* | All Cases** |
|--------------------------------|----------|-------------|
| Lamotrigine | 66 | 335 |
| Ibuprofen | 32 | 242 |
| Sulfamethoxazole; trimethoprim | 16 | 70 |
| Phenytoin | 7 | 37 |
| Carbamazepine | 7 | 43 |
| Amoxicillin | 5 | 41 |

* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN).

** Primary analysis group.

This is the second instance in which *QuarterWatch* has observed a disproportionate signal for lamotrigine and severe skin reactions. In the 2011 annual survey of patients of all ages, lamotrigine also led all other drugs in reports of severe cutaneous events. The FDA's required Boxed Warning notes that the rates of SJS/TEN appear to be higher in children than in adults, and less severe rashes may appear in 10% of treated patients. [17] Its first line use as adjunctive therapy for seizures should be reevaluated, and its approved use for maintenance in bipolar disorder reconsidered.

Reports of SJS/TEN associated with ibuprofen (MOTRIN, ADVIL) were instrumental in pushing the reported serious adverse event totals for ibuprofen (n=242) higher than other mostly over-the-counter (OTC) pain medications used in children, acetaminophen (TYLENOL, n = 137) and naproxen (ALEVE, n = 61). Also notable for ibuprofen were 34 cases of renal failure and impairment. Acetaminophen, on the other hand, had 32 reports of liver disorders, including 10 cases of liver failure, consistent with its known risks of liver damage.

Tumor Necrosis Factor Blockers

Two biological products that inhibit Tumor Necrosis Factor (anti-TNF agents) ranked among the 15 most frequently reported drugs, with infliximab (REMICADE) ranked first with 1,772 reports and etanercept (ENBREL) ranked 11th with 231 reports. Although the two drugs share a similar mechanism of action, the events occurred in children with different medical disorders.

More than 80% of the adverse events identifying infliximab as suspect occurred in patients with gastrointestinal disorders, notably Crohn's disease, inflammatory bowel disease, and ulcerative colitis. In addition, approximately 1 out of 3 cases indicated a complaint of treatment failure including colitis (n = 651), diarrhea (n = 35), and drug ineffective (n = 35). We asked the manufacturer, Johnson & Johnson, for more information about the large number of treatment failure reports. The company attributed the results to two factors. It noted some patients with ulcerative colitis and Crohn's disease may continue to experience worsening of disease or disease flares, despite an overall benefit of treatment. The number of reports may also have been increased by the company's pediatric registry.

The reports for etanercept were far fewer, and primarily reported in patients treated for juvenile arthritis and psoriasis. The most numerous adverse events included infection and injection site reactions.

The immunosuppressant properties of both agents have led to Boxed Warnings about the risk of serious infections and cancer, notably lymphoma in children and adolescents. The five-year data for these two drugs include 63 cases of malignant cancers for infliximab and 15 for etanercept. Infections were reported in 391 cases for infliximab and 74 for etanercept. Hypersensitivity was reported with 185 cases for infliximab as suspect, and 34 with etanercept.

Because of differences in the juvenile patient populations and likely differences in exposure (infliximab has more indications for treatment in children), the seven-fold higher reported serious adverse events do not

necessarily imply higher relative risks for infliximab compared to etanercept. However, the results in both children and adults continue to show that anti-TNF agents are high-risk treatments requiring vigilance in their use.

Where Reports Were Few

A study of dispensed prescriptions [2] reported that dispensed outpatient prescription for children declined 7% from 2002 to 2010, led by a 14% decrease in systemic antibiotics. Nevertheless, in 2010 amoxicillin and azithromycin accounted for 28 million prescriptions in a juvenile population of 74 million, indicating extensive exposure. Despite such widespread use, adverse event reports for the two antibiotics were few. In 2010 we identified 7 reports of serious injury in our primary analysis group for amoxicillin, and 13 for azithromycin. For the five-year period reports totaled 51 for amoxicillin and 41 for azithromycin. In the adverse event reports the drugs were prescribed for ear aches, sinus infections, and strep throats.

Exposure was extensive and reports were few for albuterol, primary treatment for asthma attacks. In one study albuterol was dispensed for 7.2% of all children enrolled in a group of health plans.[5] Over the five-year period we identified 56 serious adverse event cases in our primary analysis group.

While this small number of reports provides an assurance of safety, we believe that the reporting rates for adverse events are lowest for generic drugs that have been on the market for decades.

Other Adverse Event Types

Nearly two thirds of all the reports of adverse drug events in children were excluded from our primary analysis of serious drug risks. Product quality complaints (serious and non-serious) were prominently reported over the five-year period and accounted for 4,066 reports, or 6% of all cases. The case totals were led by 1,509 complaints about defective DAYTRANA brand name methylphenidate patches and complaints associated with Johnson & Johnson's massive 2009 OTC withdrawal that included products for adults, infants, and children. *QuarterWatch* previously reviewed the Daytrana patch in January of 2013, [18] and the Johnson & Johnson product recall in June 2010. [19] The category of reported medication errors for this report totaled 6,097 cases and were dominated errors applying or removing Daytrana methylphenidate patch (n = 1,450).

Also excluded from the primary analysis were 5,277 cases we categorized as having special issues involving how adverse events are reported or classified. In some cases through marketing policies or FDA requirements, drug manufacturers maintain extensive contact with most or all customers and learn of death, hospitalization, or other events whether or not a drug role is suspected. Examples include Dianeal solution for kidney dialysis at home, where Baxter delivers the product, and natalizumab (TYSABRI), a multiple sclerosis drug where the company monitors all patients using the drug for serious viral brain infections. Both products generate substantial numbers of reports despite being used in small patient populations.

Estrogens in Teenage Females

Product identification issues create a third group of drugs usually excluded from analysis. For both insulin and estrogen products, numerous large and small variants are FDA approved, and product identification is often weak. However, estrogen products accounted for 1,160 reports of serious injury, almost all in girls 12-17 years age. The cases, however, identified more than 20 different products that included tablets, implants, injections, intrauterine devices, rings, and patches. The products with reports were used for contraception, acne, and menstrual problems. Reported events included pain and discomfort, gallstones, gallbladder disorders, and blood clot-related events, both pulmonary embolisms and deep vein thrombosis. In a pattern seen with other drugs, 309/1,160 (26.6%) cases reported a psychiatric side effect.

Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to the FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source. [20] A full description of our methodology is available on the *QuarterWatch* pages of the ISMP web site. (<http://www.ismp.org/QuarterWatch/detailedMethods.aspx>) The FDA normally releases data on a quarterly basis, but because of technical problems has not released any data for 2013. This special report on children focused on case reports initially released in the previous five years, from 2008-2012.

We selected all domestic reports that identified patients from birth through age 17. For comparisons with adults, we selected all other reports with an identifiable patient age. We excluded cases without an age indicated, those reported to have occurred in foreign countries, as part of clinical studies, or involving a legal claim or lawsuit.

The severity of the adverse event was classified as serious if the case indicated an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[21] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[22] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs, and System Organ Classes combine the terms into 26 categories. The *QuarterWatch* database was updated in November 2013 to MedDRA version 16.1.

The MedDRA terminology was used to create three additional report categories: product quality complaints and medication errors, both identified by HLGTs of that name. An event was classified as occurring in normal medical use if there were not an indication of either a medication error (including intentional overdoses) or product quality complaint indicated on the report.

Events in *QuarterWatch* are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[23] When cited in the text, tables, or charts, the brand name of a drug used is the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, *QuarterWatch* does not distinguish dose, route of administration, or extended release and other forms.

In this special report we created a primary analysis group of serious adverse drug events occurring in normal medical use. To create this group we excluded non-serious adverse events, product quality complaints, and cases indicating a medication error. Also were excluded were a group of drugs with special issues that affect identification or report rates. This includes drugs with restricted distribution schemes that result in reports of events where a possible drug causal role was not evaluated, drugs where product identification is weak, or products with direct-to-consumer marketing or contact. In addition, we excluded reports for the first year of life because of difficulties separating maternal from infant exposure, as well as the special health issues of premature babies.

Definitions of MedDRA terms used in this report: Psychiatric side effects means reports with a Preferred Term in the Psychiatric disorders System Organ Class. Suicidal behaviors means reports with a term in the Suicidal and self-injurious behavior HLT. Colitis was an HLT of that name. Hypersensitivity, malignant cancers, and dyskinesia were broad scope SMQs. Others were Preferred Terms. Additional note to Table 1: Some MedDRA terms do not describe an adverse event and were omitted from two drug rankings. "Off label use" was the second most frequent term for lisdexamfetamine and "Therapeutic response unexpected with drug" was the second most frequent MedDRA term for levetiracetam.

QuarterWatch Team and Funding Sources

QuarterWatch is published by the Institute for Safe Medication Practices as a public service. It has no regular income, foundation grant, or other dedicated financial support and is provided to the public and health professions without charge. We seek outside peer reviewers for each issue but their identities are not disclosed.

QuarterWatch's essential costs are funded from the general budget of ISMP, a non-profit organization dedicated solely to promoting the safe use of medication. ISMP, in turn, is supported by charitable donations, volunteer efforts, foundation grants, and subscription income from its four other medication safety newsletters, for pharmacists in the acute care and ambulatory care settings, for nurses, and for consumers.

Thomas J. Moore serves as a part-time project director for *QuarterWatch*. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. He is also a lecturer in the Department of Epidemiology and Biostatistics in The George Washington University School of Public Health and Health Services. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). He also worked as a consulting expert for plaintiffs in the civil litigation regarding Chantix. In 2011 Moore examined the completeness and accuracy of adverse drug event reports for biological products for Amgen. In 2013 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. He has also conducted confidential assessments for attorneys inquiring about the safety profiles of bisphosphonates, antipsychotic drugs, and proton pump inhibitors.

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