Adverse Drug Events in Pediatric Outpatients

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Objective.—To determine rates and types of adverse drug events (ADEs) in the pediatric ambulatory setting.

Methods.—A prospective cohort study at 6 office practices in the greater Boston area was conducted over 2-month periods. Duplicate prescription review, telephone surveys 10 days and 2 months after visit, and chart reviews were done. A 2-physician panel classified the severity, preventability, and ability to ameliorate (ie, if the severity or duration of the side effect could have been mitigated by improved communication) ADEs.

Results.—We identified 57 preventable ADEs (rate 3%; 95% confidence intervals [CI], 3%–4%) and 226 nonpreventable ADEs (rate 13%; 95% CI, 11%–15%) in the medical care of 1788 patients. Of the ADEs, 152 (54%) were able to be ameliorated. None of the preventable ADEs were life threatening, although 8 (14%) were serious. Forty (70%) of the preventable ADEs were related to parent drug administration. Improved communication between health care providers and parents and improved communication between pharmacists and parents, whether in the office or in the pharmacy, were judged to be the prevention strategies with greatest potential.

Conclusions.—Patient harm from medication use was common in the pediatric ambulatory setting. Errors in home medication administration resulted in the majority of preventable ADEs. Approximately one fifth of ADEs were potentially preventable and many more were potentially able to be ameliorated. Rates of ADEs due to errors are comparable in children and adults despite less medication utilization in children.

KEY WORDS: medication errors; patient safety

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Patient safety has emerged as an important medical issue in the last several years, and medication use has been identified as a major cause of iatrogenic injury.[1–4] Early studies demonstrated high rates of adverse drug events (ADEs) in adult inpatients, and a later study documented threefold higher rates of potentially harmful medication errors in pediatric inpatients.[5,6] Relatively less is known about the ambulatory setting, although one adult study documented 3 preventable ADEs and 24 nonpreventable ADEs per 100 ambulatory adult patients.[7]

The majority of medication use in children occurs in ambulatory clinics, yet few studies have assessed mediation errors and ADE rates in this setting. The medication process in the pediatric ambulatory setting has multiple steps, including medication ordering, transmitting the order to the pharmacy, dispensing, administering, and monitoring. Factors contributing to errors include weight-based dosing, the often-required dilution of stock medications, recompounding of pills and powders as liquid preparations, and multiple formulations of pediatric medications. Other factors include decreased communication abilities of young children, inability to self-administer medications, and the vulnerability of young children to injury from some medications. In addition, many drugs are used off label in pediatrics due to limited testing of drugs in children. These factors highlight the need for a study of medication use in ambulatory pediatric patients.[8,9]

We undertook this study to assess the rates and types of ADEs in pediatric outpatients at 6 office practices.

METHODS

We performed a prospective cohort study of patients under age 21 from 6 office practices. Data collection methodologies included duplicate prescription review, 2 surveys, and chart review. All data were reviewed for medication errors, including those with the potential for harm (near misses) and those that actually caused harm (preventable ADEs). In addition, data were reviewed for harm from medications that were not associated with an error (nonpreventable ADEs). All ADEs were further characterized according to types and potential prevention strategies.

Definitions

Medication errors were defined as errors in drug ordering, transcribing, dispensing, administering, or monitoring.

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An example of a preventable ADE is an amoxicillin-associated rash in a patient who was inadvertently prescribed amoxicillin despite a known allergy. In contrast, a nonpreventable ADE is an amoxicillin-associated rash in a patient with no known drug allergies. In accordance with the Institute of Medicine definitions, ADEs could result from the failure to administer a prescribed drug, such as a parent not administering an antibiotic for pneumonia because of financial constraints, with worsening of symptoms.[1] The term parent is used throughout this manuscript to refer to parents, guardians, and other home caregivers.

Again, in accordance with previous studies, ADEs were rated in 3 categories according to the severity of injury: life threatening, serious, or significant.[5–7] For example, anaphylaxis was classified as life threatening, hives as serious, and rashes as significant.[10] ADEs were rated on preventability (ie, preventable and nonpreventable) and further classified as able to be ameliorated if the severity or duration of the side effect could have been mitigated by any means.

Office Practices and Physicians

We enrolled 6 office practices serving patients of diverse socioeconomic backgrounds—2 were at teaching hospitals, 2 were urban neighborhood health centers, and 2 were more affluent suburban practices. One hundred thirty-two pediatric health care providers prescribed at these office practices during the study period. All pediatric providers handwrote medication prescriptions because electronic ordering systems were not available. Data were collected in a consecutive 2-month block at each practice, from July 2002 to April 2003.

Patients

Patients were given an opportunity to opt out of the study, both through a mail-in postcard and at the time of the telephone survey. All children under age 21 who had an office visit in which they received at least 1 prescription during the study period were eligible for inclusion. Exclusion criteria included second visits by patients, siblings already included in the study, requests by prescribing physicians to exclude specific patients, prescriptions for oral contraceptives or potential treatment of sexually transmitted diseases, and prescriptions for equipment. We also excluded patients who did not have a working phone or did not primarily speak English, Spanish, or Cambodian.

Data Collection

Data were collected by 3 methods: prescription review through the use of duplicate prescription pads, telephone surveys, and chart review.[10] A research nurse reviewed all duplicate prescriptions, not including phone or faxed prescriptions, to document medication errors by using methodology previously developed and defined by the investigators.[5–7,11,12]

On the day of the visit, the patient was given written information about the study, including information regarding opting out of the study. The day after the visit, an informational sheet and an opt-out card were mailed to each parent. A trained research assistant telephoned parents who did not opt out within 10 days of the index visit for the initial survey, utilizing a structured survey instrument with scripted questions and close-end answers. We also surveyed patients over age 16 directly, since by this age they tend to self-administer medications. A minimum of 3 phone calls was attempted.

During the initial survey, we reviewed dispensed medications by having parents read the medication label. We then asked questions about potential side effects, method of medication administration, communication regarding the medication with the pharmacist and the health care provider, and demographic information. Research assistants underwent several weeks of training to ensure a standardized approach to surveys. If the parent completed the initial survey, we attempted a second survey 2 months after the index visit to capture persistent symptoms. Surveys were translated and back translated into Spanish and Cambodian and conducted by fluent bilingual interviewers. Surveys were pretested and revised based on 2 focus groups of parents representing a broad array of socioeconomic backgrounds. A nurse data collector reviewed office charts for evidence of ADEs and errors at 3 months after the index visit and collected additional data, including comorbidities, additional diagnoses, and other chart-based information.

Demographic Data

Demographic data including age, gender, and insurance were collected from computerized administrative databases at the office practices for all patients. At 4 office practices, race and ethnicity data were collected from this same computerized administrative database, but 2 office practices did not record these data. Therefore, a research assistant queried all parents visiting these 2 offices for a 2-week period about their race and ethnicity by using a standard 2-question format. We extrapolated from these data to impute race and ethnicity for all patients at these 2 office practices over the study period.

ADE Classification

The research nurse presented all suspected ADEs to 2 physician reviewers, who independently classified them as ADEs, near misses, medication errors, or exclusions. This rating and classification methodology has been used and validated in several previous studies.[5–7] The physicians rated ADEs according to the severity, preventability, and ability to be ameliorated.

The physician reviewers also assigned potential prevention strategies to preventable ADEs. We conducted a review of the literature to develop a comprehensive list of prevention strategies that had been cited in other reports, including: 1) basic computerized physician order entry (CPOE); 2) CPOE with clinical decision support systems, including checks such as drug dose, drug interactions, and patient factors; 3) clinical pharmacist availability; 4) enhanced communication, such as between health care providers

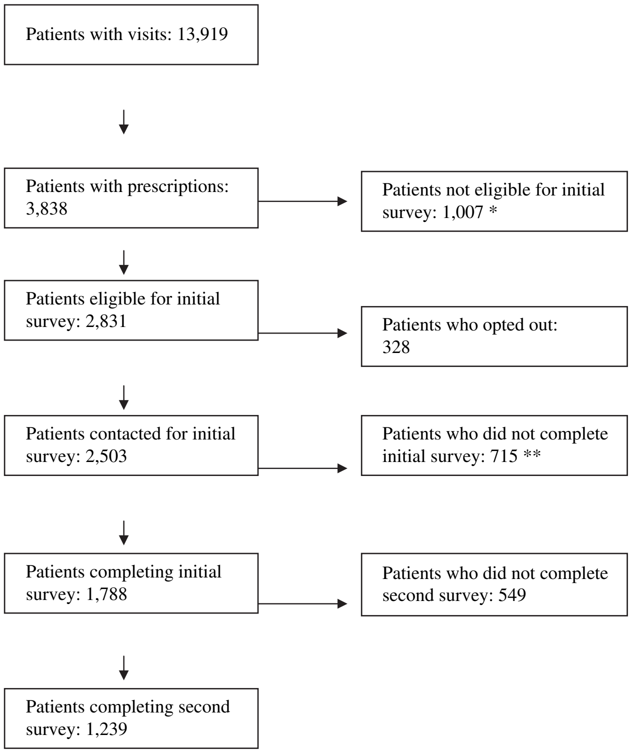

Figure 1. *Patient flow chart. *Noneligibility reasons included type of prescription (eg, for oral contraceptive pill or equipment), language (ie, parents do not speak English, Spanish, or Cambodian), lack of an accurate phone number (eg, moved, phone disconnected, or wrong number), and patients whose home health care providers had already been surveyed for siblings. **Phone calls were made to these parents, but they did not complete the survey for a variety of reasons, including parent or guardian was not available or the answering machine picked up the phone call.*

and parents or pharmacists and parents; 5) electronic transmission of prescriptions to the pharmacy; 6) improvements in training of health care providers; 7) changes in staffing of health care providers; and 8) changes in work hours for health care providers. Multiple prevention strategies could be assigned to each error.

The κ statistics for inter-rater reliability were 0.89 for classification of ADE, 0.75 for severity of ADE, and 0.95 for preventability of ADE.

All preventable ADEs were categorized according to the stages (ie, drug ordering, transmitting, pharmacy dispensing, administering, or monitoring) at which the error occurred, the body system involved, and the medication category.

Statistical Analysis

We report rates of ADEs per 100 patients for the patients who completed the initial survey regardless of whether or not they completed the second survey. We do not report rates for those patients who did not complete the initial survey, as parent report is a critical method of detection for ADEs.

We assumed overdispersion relative to a Poisson distribution of ADEs and calculated 95% confidence intervals (CIs) around the rates of ADEs. These adjusted CIs account for any clustering of counts at the level of physicians. No adjustment for potential clustering within practices was made because there were not a sufficient number of practices to provide a reliable estimate of variability. The SAS statistical package (Windows 8.2, SAS Institute Inc, Cary, NC) was used. Error prevention strategies were analyzed according to the proportion of total preventable ADEs that might have been prevented.

Institutional review boards at Brigham and Women's Hospital and Children's Hospital, Boston approved the study.

RESULTS

Rates of Prescriptions and Survey Responses

During the study period, 21 209 visits were made by 13 919 patients, of whom 3838 (28%) received a prescription (Figure 1). Of these, 1007 (26%) patients were excluded. Of the remaining 2831 patients, 328 (12%) opted out of the study and 1788 (63%) completed the initial survey, with office practice response rates ranging from 58% to 78%. The second survey was completed by 1239 (69%) of these 1788 patients.

Parents most commonly were the survey respondents (1715 [96%]), followed by legal guardians (23 [1%]) and grandparents (22 [1%]). Respondents and nonrespondents were comparable, except that the children of respondents were slightly younger, less likely to be on Medicaid, and less likely to be Hispanic (Table 1).

Of the prescriptions, 2186 were written for the 1788 patients who completed the initial survey (1.2 prescriptions per patient).

In total, 132 pediatric providers, including 53 (40%) staff physicians, 66 (50%) residents, and 13 (10%) nurse practitioners, participated in the study; 89 (67%) of the pediatric providers were women (Table 2). Their mean age was 39.8, and the staff physicians and nurse

Table 1. Demographics of Patients Eligible for Initial Survey*

	Nonrespondents of Initial Survey (n = 1056)	Respondents of Initial Survey (n = 1788)	*P* Value
Gender			
Female	534 (51%)	899 (50%)	.88
Age			
Neonates	23 (2%)	49 (3%)	.01
Infants	246 (23%)	469 (26%)	
Toddlers	346 (33%)	544 (30%)	
School age	330 (31%)	594 (33%)	
Adolescents	111 (11%)	132 (7%)	
Race/ethnicity:			
White	520 (49%)	874 (49%)	.007
Black	174 (17%)	279 (16%)	
Hispanic	246 (23%)	363 (20%)	
Other	113 (11%)	267 (15%)	
Missing	3 (<1%)	5 (<1%)	
Insurance			
Medicaid	145 (14%)	222 (12%)	.03
Non-Medicaid	911 (86%)	1566 (88%)	

*Due to rounding, some categories may not total 100%.

Table 2. Characteristics of Office Practices and Health Care Providers

Office Practice	Total Pediatric Providers	No. of Staff Physicians (%)	No. of Residents (%)	No. of NPs* (%)	No. of Women (%)	Mean Years After Training	Mean Age
A	7	6 (86%)	0 (0%)	1 (14%)	5 (71%)	10.25	40
B	11	6 (55%)	5 (45%)	0 (0 %)	10 (91%)	9.5	36.6
C	88	22 (25%)	58 (66%)	8 (9%)	60 (68%)	10.1	34.2
D	9	6 (67%)	3 (33%)	0 (0 %)	3 (33%)	14.6	36.7
E	11	8 (73%)	0 (0%)	3 (27%)	8 (73%)	15.4	46.5
F	6	5 (83%)	0 (0%)	1 (17%)	3 (50%)	10.5	45
Totals	132	53 (40%)	66 (50%)	13 (10%)	89 (67%)	11.7	39.8

*NPs indicates nurse practitioners.

practitioners were an average of 11.7 years post-training. All physicians were trained in pediatrics.

Rates of ADEs

In 1788 patients, we identified 57 preventable ADEs (rate 3%; 95% CI, 3–4) and 226 nonpreventable ADEs (rate 13%; 95% CI, 11–15; Table 3). Of the 283 ADEs, 152 (54%) were potentially able to be ameliorated. The 57 preventable ADEs occurred in the care of 56 individual patients. Most ADEs had low severity ratings, with the majority rated as significant. Table 4 lists examples of ADEs of varying severity levels.

Types of ADEs

Among the preventable ADEs, 70% occurred due to errors at the stage of drug administering, predominantly by parents, and 26% at the stage of pediatric provider ordering (Figure 2). Three (5%) of the preventable ADEs were due to insurance issues, primarily because of delays in obtaining a medicine.

The most common organ system involved in preventable ADEs was skin (Table 3), followed by the gastrointestinal tract and respiratory tract. Forty percent of the nonpreventable ADEs were antibiotic-related gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Another 9% of the nonpreventable ADEs were gastrointestinal symptoms related to other medications and 31% were cutaneous reactions.

Table 3. Rates, Severity, and Types of ADEs*

	Preventable ADEs (n = 57)	Nonpreventable ADEs (n = 226)
Rate per 100 patients (95% CI†)	3 (3–4)	13 (11–15)
Severity, No. (%)		
Fatal or life threatening	0 (0%)	1 (0.4%)
Serious	8 (14%)	26 (11%)
Significant	49 (86%)	199 (88%)
System involved, No. (%)		
Skin	17 (30%)	69 (31%)
Gastrointestinal	11 (19%)	111 (49%)
Respiratory	7 (12%)	0
Central nervous system	6 (11%)	34 (15%)
Eyes	4 (7%)	0
Ears	3 (5%)	0
Nose	3 (5%)	1 (0.4%)
Throat	2 (4%)	3 (1%)

*ADE indicates adverse drug event.
†CI indicates confidence interval.

Since office practice C (Table 2) was significantly larger and had a greater proportion of resident trainees, we compared the results of this practice to the other 5. Per 100 patients, the rates of preventable ADEs and ADEs that were judged able to be ameliorated were similar between the groups.

Drugs Associated With ADEs

Evaluation of the ADEs (Table 5) showed that preventable ADEs were most frequently caused by penicillin or a derivative followed by inhaled steroids. Nonpreventable ADEs were also most commonly caused by penicillin or a derivative followed by cephalosporins and inhaled bronchodilators.

Amelioration of ADEs

Of the 152 ADEs that were potentially able to be ameliorated, 82 (54%) involved parents not notifying the pediatric provider of side effects or an allergic reaction to the medication, and 22 (14%) involved parental delay in such notification. Parents did not notify the pediatric provider that they gave the prescribed medication differently then

Table 4. Examples of ADEs*

Serious ADE, preventable
A 9-year-old with streptococcal pharyngitis was prescribed amoxicillin, and the parent did not complete the course of medicine. The patient returned with persistent streptococcal pharyngitis.

Significant ADE, preventable
A 4-year-old with ringworm was prescribed clotrimazole. The prescription was not filled, and the patient returned with persistent symptoms.

Life threatening ADE, nonpreventable
A 2-year-old female was treated with a cough and cold medicine, resulting in hives involving the entire body, including the lips and eyes. She was taken to the emergency department and required epinephrine, diphenhydramine, and steroids.

Serious ADE, nonpreventable
A 9-year-old with juvenile rheumatoid arthritis was prescribed oral methotrexate and developed nausea, vomiting, hair loss, and mouth sores. The medicine was changed 2 mo later.

Significant ADE, nonpreventable
A 4-year-old male prescribed oral prednisolone and albuterol developed hyperactivity a day after beginning the medications.

Nonpreventable ADE, able to be ameliorated
A 1-year-old female was prescribed amoxicillin-clavulanate for an otitis media. The patient developed 7 days of diarrhea and diaper rash. The parents did not adjust the diet, treat the rash, or notify the provider.

*ADE indicates adverse drug event.

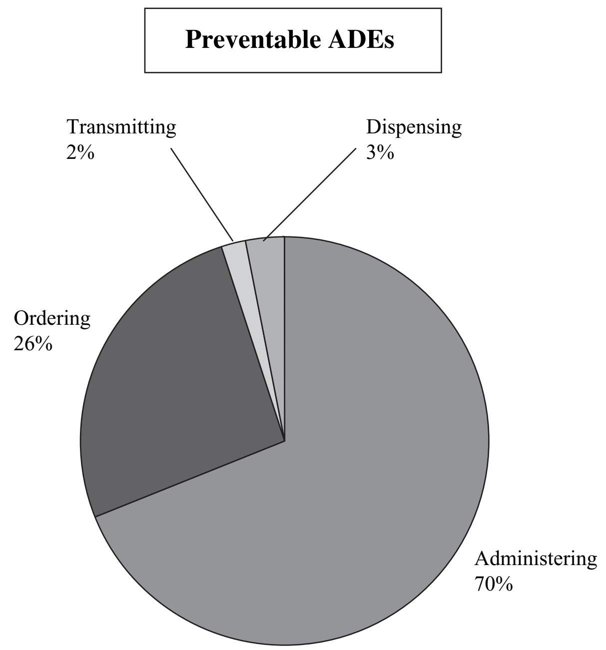

Figure 2. *Stages of preventable adverse drug events (ADEs).*

intended in 16% of cases and did not notify the pediatric provider that they did not give the prescribed medication at all in 5% of cases. In total, parents were responsible for 136 (89%) of ADEs that were able to be ameliorated.

Strategies to Prevent Errors That Result in Preventable ADEs

The clinicians who reviewed preventable ADEs concluded that 72% could have been potentially prevented by improved communication between the prescribing pediatric provider and the parent, whereas 21% could have been prevented by CPOE with clinical decision support systems (Table 6). The types of decision support elements that appeared to be potentially most effective were drug allergy, drug frequency, and drug weight/dose checks.

DISCUSSION

We found that ADEs were common in the pediatric ambulatory setting, occurring in about 16% of children treated. This result is particularly surprising given the simpler medication regimens in pediatric outpatients compared with pediatric inpatients and adult outpatients. Of the ADEs, 1 in 5 were judged to be preventable, and just over half were able to be ameliorated. Most were of relatively low severity. Of note, errors resulting in ADEs occurred most commonly at the stage of drug administration by parents. This is in contrast to earlier work with pediatric inpatients that has demonstrated the majority of errors occur at the drug ordering, not the drug administration, stage.[6] Similarly, parents could have ameliorated many ADEs by notifying health care providers of side effects.

Detected rates of errors and ADEs are dependent on the type of methodology used. In this study, we used 3 major methods of data collection: prescription review, survey, and chart review. An adult study using similar methodology found the same rate of preventable ADEs in adults (3%). However, this study documented higher rates of nonpreventable ADEs in adults (24%) than our pediatric rate of 13%.[7] This higher adult rate of nonpreventable ADEs may be due to the more complex typical medication regimen of the adult patient. Nevertheless, the higher adult rate of nonpreventable ADEs makes the finding of similar adult and

Table 5. Medications Associated with ADEs*

	Preventable ADEs			Nonpreventable ADEs		
Medication Category	No.	Per ADEs* (%)†	Per RXs‡ (%)§	No.	Per ADEs* (%)	Per RXs‡ (%)
Penicillin or derivative	15	26	2	123	54	18
Steroids, inhaled	6	11	7	6	3	7
Antifungal, topical	4	7	1	1	0.4	1
Antihistamine	4	7	5	2	1	3
Histamine H2 receptor antagonist	3	5	14			
Bronchodilators, inhaled	3	5	2	16	7	9
Cephalosporins	3	5	5	18	8	31
Macrolides	3	5	3	13	6	12
Steroids, oral	2	4	3	6	3	10
Ophthalmic preparations	1	2	1			
Stimulants	1	2	6	8	4	44
Ibuprofen	1	2	1	2	1	2
Steroids, topical						
Acetaminophen				1	0.4	2
Antiviral				2	4	50
Scabicides	1	0.4	29	2	4	14
Laxative	3	1	5	1	2	14
Antifungal, oral	1	0.4	3	1	2	8

*ADE indicates adverse drug event.

†Proportion of ADEs (eg, preventable ADEs) attributable to a given drug category. For example, penicillins or derivatives caused 26% of the preventable ADEs.

‡RX indicates prescription.

§Proportion of prescriptions for a given drug category that resulted in a specific type of ADE. For example, 2% of penicillin or derivative prescriptions resulted in a preventable ADE.

Table 6. Prevention Strategies for ADEs*

Prevention Strategy	Preventable ADEs No. (%)
Changes in communication between physicians and patients	41 (72)
Clinical pharmacist in office setting discussing drug administration with parent	16 (28)
Changes in communication between pharmacists in pharmacy and patients	14 (25)
CPOE	
Basic CPOE†	3 (5)
Advanced CPOE with CDSS‡	12 (21)
Changes in communication between nurses and patients	9 (16)
Clinical pharmacist in office setting discussing drug ordering with pediatric provider	6 (11)
Clinical pharmacist in office setting monitoring drug dispensing	4 (7)
Electronic transmission of prescription	1 (2)

*ADE indicates adverse drug event.
†CPOE indicates computerized physician order entry.
‡CDSS indicates clinical decision support systems.

pediatric rates of preventable ADEs even more striking. The ideal comparison would be rates of ADEs per 100 prescriptions rather than per 100 patients, but these data are not available in prior published studies.

There are relatively few previous pediatric studies regarding medication errors and ADEs in the ambulatory setting. One study examined pharmacy data from 3 health maintenance organizations and concluded that potential dosing errors occur frequently in outpatient pediatrics.[13]

The majority of errors leading to preventable ADEs occurred at the stage of drug administration. This finding strongly suggests that communication with parents must be improved. Both preventable ADEs and ADEs that are able to be ameliorated were frequently caused by inconsistent drug administration, at times due to incomplete knowledge of measuring devices. Several studies have documented parental confusion regarding the correct use of teaspoons, tablespoons, and dose cups.[14,15]

Rigorous qualitative research will be required to understand further the etiology and potential solutions to these communication problems. Potential solutions will need to address improved parental access to information about side effects and need for medical attention, to office practices, and to information at appropriate levels of health literacy in languages in which parents are proficient.[16–18] Accurate internet-based information on drugs or personalized Web pages might be helpful. Allowing parents to routinely review their child's medication records may improve communication and further drive down errors.[19]

This study has several limitations. Although we undertook many efforts to improve the response rate, the final response rate may have led to biased results in several ways. For example, parents who primarily spoke a language other than English may have been more reluctant to answer the phone. In addition, the children of parents who primarily spoke a language other than English may be more prone to errors due to greater difficulties in understanding medication administration instructions. Another concern is the generalizability of our results. We studied only 6 office practices; however, we intentionally studied office practices serving diverse socioeconomic, racial, and ethnic populations. We relied on parent reports of ADEs, but we did have 2 independent physician reviewers clinically interpret each report. Using 2 independent physicians rather than the patient's physician may have decreased bias, and our physician reviewers had high levels of agreement.

In summary, this study demonstrates that ADEs were surprisingly common in ambulatory pediatrics despite relatively simple pediatric medication regimens. Fortunately, most of the ADEs were of low severity, but given their frequency they result in substantial morbidity. The epidemiology of preventable ADEs appears distinct from other settings because they occurred most frequently at the drug administration stage. Improved communication between pediatric providers and parents appears to have particularly strong potential as prevention strategies.

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