Adverse Drug Event-Related Emergency Department Visits Associated With Complex Chronic Conditions

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KEY WORDS

adverse drug events, emergency department, complex chronic conditions, special needs, drug safety

ABBREVIATIONS

ADE—adverse drug event
CCC—complex chronic condition
ED—emergency department
E-code—external cause of injury code
HCUP—Healthcare Cost and Utilization Project
ICD-9-CM—*International Classification of Diseases, Ninth Revision, Clinical Modification*
NEDS—National Emergency Department Sample

Dr Feinstein conceptualized and designed the study, performed the statistical analyses and initial interpretation of data, and drafted the initial manuscript; Drs Feudtner and Kempe participated in the concept and design, analysis and interpretation of data, and revision of the manuscript; and all authors approved the manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Children who experience outpatient adverse drug events represent 0.5% of pediatric emergency department visits. The subset of children with complex chronic conditions often take multiple medications, but the incidence and severity of adverse drug events in these children is unknown.

WHAT THIS STUDY ADDS: Children with complex chronic conditions have a higher risk of emergency department visits related to adverse drug events, compared with other children. The implicated drugs with the highest rates include psychotropic agents, antimicrobial agents, anticonvulsants, hormones/steroids, and analgesics.

abstract

BACKGROUND AND OBJECTIVES: Outpatient adverse drug events (ADEs) can result in serious outcomes requiring emergency department (ED) visits and hospitalizations. The incidence and severity of ADEs in children with complex chronic conditions (CCCs), who often take multiple medications, is unknown. We sought to describe the characteristics of ADE-related ED visits, including association with CCC status; determine the implicated medications; and determine if CCC status increased the risk of ADE-related admission.

METHODS: Retrospective cohort study of ED visits by patients aged 0 to 18 years using a national sample. ADEs were identified by external cause of injury codes; cases with overdose, wrongful administration, self-harm, or diagnosis of malignancy were excluded. Multivariable logistic regression was used to test outcomes of having an ADE-related ED visit and of subsequent admission. All statistics accounted for the complex survey design.

RESULTS: Of 144 million ED visits, 0.5% were associated with ADEs. Adjusting for age, gender, insurance type, day of week, and location of hospital, ADEs were associated with the presence of a CCC (odds ratio 4.76; 95% confidence interval: 4.45–5.10). The implicated medications differed significantly by CCC status. Adjusting for the same variables, ADEs were associated with subsequent inpatient admission (odds ratio 2.18; 95% confidence interval: 2.04–2.32) for all children; an interaction between ADE and CCC status was not significant.

CONCLUSIONS: ED visits associated with ADEs were more likely to occur for children with CCCs, and the implicated drugs differed, but ADE-related admissions were not differentially affected by CCC status. *Pediatrics* 2014;133:e1575–e1585

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Children in the United States have been increasingly exposed to medications, especially psychoactive drugs such as antipsychotics and stimulants.[1,2] Hospitalized children may encounter ≥25 medication exposures over an inpatient admission, with higher cumulative counts for children with complex chronic conditions (CCCs).[3] Little is known about the negative consequences of increased medication use among the pediatric population. In 2005, the Institute of Medicine publication *Preventing Medication Errors* identified a number of areas for improvement in pediatric medication prescribing practices.[4] In particular, the authors reinforced the need for accurate monitoring of adverse drug events (ADEs). ADEs have been described as "injuries resulting from a drug taken for medical intervention."[4] Previous pediatric studies have demonstrated that ADEs are responsible for 0.3% of all outpatient pediatric visits and 0.5% of all pediatric emergency department (ED) visits,[5,6] but less is known about the specific characteristics of pediatric patients who experience ADEs, the most common responsible drugs, and whether certain groups of patients are particularly vulnerable to experiencing ADEs.

In the adult literature, geriatric patients are at risk for experiencing ADEs because of their medical complexity, fragility, and common exposure to polypharmacy.[7–10] Many of these characteristics are shared by the pediatric population comprising children with CCCs, who have a chronic or life span–shortening disease process, require lifelong medical care, and often rely on supportive technology (such as tracheostomy, ventilator, or gastrostomy tube) and multiple prescription medications.[11] Children with CCCs may be exposed to multiple concurrent medications in the inpatient[3] and ambulatory settings, potentially increasing their risk of developing ADEs. Although children with CCCs represent a small fraction of the population, they disproportionately use medical resources; children with CCCs account for >30% of pediatric inpatient hospital charges and are frequently readmitted.[12,13] Given their exposure to medications, their potential vulnerability for developing medication-related problems, and the conceivable impacts on resource utilization, assessing the scope of ADEs in pediatric patients with CCCs is important, especially in the home and ambulatory settings, where they spend most of their time.[14,15]

Do children with CCCs, in fact, experience more ambulatory ADEs and, if so, what types of medications are most commonly implicated? Previous studies using the National Ambulatory Medical Care Survey and the National Hospital and Ambulatory Medical Care Survey were unable to examine smaller subgroups, such as children with CCCs, because of limited sample sizes.[5,6] We conducted a study using the National Emergency Department Sample (NEDS), which is a sufficiently large sample containing numerous visits by children with CCCs. We aimed to (1) describe the characteristics of ADE-related ED visits and examine the association with the presence of a CCC, (2) determine the types of medications implicated in ADE-related visits, and (3) test whether the presence of an ADE is associated with an increased likelihood of inpatient admission in children with CCCs compared with children without CCCs.

METHODS

Data Source

Annual data on pediatric patient visits to the ED were obtained from the 2006–2010 NEDS, which are abstracted from billing records as part of the Healthcare Cost and Utilization Project (HCUP).[16] The NEDS is the largest publically available all-payer ED database in the United States, and it approximates a 20% stratified sample of US hospital-based ED visits; weights are provided to calculate national estimates. As per the American Hospital Association, the NEDS represents "all non-Federal, short-term, general, and other specialty hospitals." Each year contains >6 million ED records for pediatric visits, and a record includes up to 15 *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnoses codes, up to 4 ICD-9-CM external cause of injury codes (E-codes), patient demographics, payment sources, and hospital characteristics.

Study Design, Setting, and Population

We performed a retrospective cohort analysis of all US hospital-based ED visits by all pediatric patients aged 0 to 18 years. Visits associated with ADEs were classified by ICD-9-CM E-codes corresponding to "drugs, medicinal and biological substances causing adverse effects in therapeutic use" (E930–E949) or ICD-9-CM codes corresponding to unclassified drug reactions (292, 3576, 7794, or 9952; Appendix 1). E-codes can specify the suspected pharmaceutical agent, and the use of E-codes to identify ADEs has been previously reported.[16–19] Up to 4 drugs could be associated with an ADE based on E-codes. Only 7% of those with ADEs had ≥2 drugs listed, and the majority of additional drugs were classified as "not elsewhere classified"; we considered only the first listed implicated drug for analysis. We classified visits associated with CCCs using a previously published taxonomy of ICD-9 codes that divide cases into CCC subcategories.[20] Because each observation is not linked to other encounters, we attempted to remove potential subsequent visits by the same patient

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by matching on 6 variables (month, age, insurance, household location, hospital identifier, and the E-code specifying the ADE; Fig 1). We excluded cases associated with wrong substance administration, poisoning (E9500–E9505), intentional self-harm, or use of illicit substances (E850–E858, 9600–9899). Children with a CCC corresponding to "malignancy" were excluded because (1) chemotherapy's antitumor activity so commonly causes concomitant neutropenia, and this anticipated "double" effect of most chemotherapy agents is qualitatively different than most other medication side effects or ADEs and (2) these children overrepresented ADEs among children with CCCs (and would have accounted for ~25% of CCC-related ADEs).

Statistical Analysis

All analyses accounted for the NEDS's complex sampling design. We calculated national estimates of ED visits associated with ADEs and descriptive statistics regarding visit characteristics. We classified medications into classes according to groupings of E-codes (Appendix 1).

To examine the relationship between patient and visit characteristics associated with ADE visits, we used multivariable logistic regression. Univariate methods, including χ^2 and simple logistic regression, were used to identify patient and visit characteristics associated with ADEs. We considered variables for inclusion in the multivariable model with a univariate relationship with the outcome ($P < .05$) or that had been previously associated with ED use including patient age, gender, insurance type, and CCC status.[21] We used forward stepwise regression to generate preliminary regression models and also tested for an interaction between age and CCC status. The final regression model was selected based on comparison of Akaike information criteria fit statistics, which penalizes for additional variables that do not significantly improve model fit; the unequal sampling probabilities inherent in a complex weighted survey limit the applicability of traditional model comparison methods for nested models.[22,23]

To compare the types of drugs responsible for ADEs between patients with and without CCCs, we generated estimates of ADEs for each drug class per 100 000 visits. To aid comparison, we calculated odds ratios comparing the likelihood of ADEs for each drug class in CCC to non-CCC visits, adjusting for age.

Finally, to examine the relationship between the ADEs and subsequent hospital admission, we used the same multivariable logistic approach described earlier. The main predictor of interest was an interaction term between presence of an ADE and CCC status and the outcome was inpatient admission. In addition to the selection of covariates as mentioned earlier, we adjusted for the number of acute conditions coded on the chart as a proxy for the severity level of the visit.

All estimates and 95% confidence intervals were calculated by using survey procedures in SAS 9.3 (SAS Institute, Cary, NC), as recommended by HCUP to compute accurate standard errors.[24] Per HCUP policies, no statistics were reported for cells where the unweighted number of observations was ≤10. We considered an α of <.05 statistically significant. This study was exempted by the Colorado Multiple Institutional Review Board.

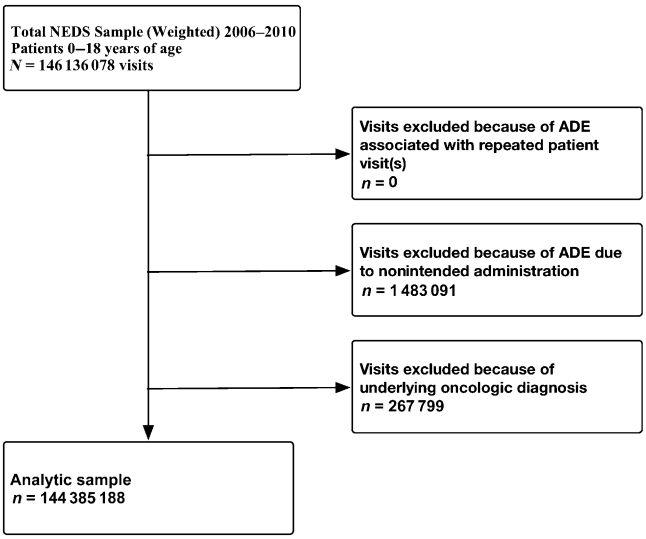

FIGURE 1
Construction of analytic sample from the NEDS.

RESULTS

Characteristics of the Study Population

Between 2006 and 2010, there were 31 895 341 unweighted observations, resulting in an estimated 146 136 078 million total ED visits by pediatric patients. After applying the exclusion criteria, 144 385 188 remaining visits comprised the analytic sample (Fig 1). Among these visits, patients were most frequently 10 to 18 years old (40%), male gender (52%), with private insurance (54%), and without a CCC (98%) (Table 1). The treating EDs were located in the South (38%), Midwest (24%), West (19%), and Northeast

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(19%), and visits primarily occurred on weekdays (69%). Significantly more children with CCCs were treated in teaching EDs and/or level 1/2 designated trauma centers when compared with those without. Overall, 716 664 visits (0.5%) were associated with an ADE. Further stratification by the presence of a CCC demonstrated that 2.2% of CCC-related visits were associated with an ADE compared with 0.5% of non-CCC-related visits.

Independent Risk Factors Associated With ADEs

Increasing age, female gender, private insurance, weekend timing of the visit, regional location of the hospital, and the presence of a CCC were independently associated with increased risk of an ADE-related visit (Table 2). Among children with a CCC and an ADE, the neuromuscular CCC class accounted for the majority of visits (56%), cardiovascular (17%), hematologic/immunologic (11%), and metabolic (10%) classes; multiple CCCs were present in 20% of these visits. Adjusting for age, gender, insurance status, weekday of visit, and regional location of the hospital, the presence of a CCC remained strongly associated with the likelihood of any ADE (odds ratio 4.76; 95% confidence interval 4.45–5.10). An interaction between CCC and age was not significant ($P = .11$).

TABLE 1 Demographic and Clinical Characteristics of the Study Population, 2006–2010

	All Visits, % (N = 144 385 188)	Visits Without CCC, %[a] (n = 141 554 531)	Visits With CCC, %[a] (n = 2 830 657)
Demographic factors			
Age			
<1	12.1	12.1	13.4
1–4	29.0	29.2	22.6
5-9	18.5	18.5	17.4
10-18	40.4	40.2	46.6
Gender[b]			
Male	51.8	51.8	53.1
Female	48.2	48.2	46.9
Insurance			
Public	46.4	46.2	53.7
Private	53.6	53.8	46.3
Time of visit[c]			
Weekday	69.0	68.9	72.6
Weekend	31.0	31.1	27.4
Location of ED			
Northeast	18.6	18.6	16.7
Midwest	23.6	23.6	22.4
South	38.3	38.3	37.7
West	19.5	19.5	23.2
Teaching status of ED			
No	59.4	59.9	38.1
Yes	40.6	40.1	61.9
Level 1 or 2 trauma center			
No	75.9	76.2	62.1
Yes	24.1	23.8	37.9
Clinical factors			
CCC			
None	98.0	100.0	0
Any	2.0	0	100.0
ADE			
No	99.5	99.5	97.8
Yes	0.5	0.5	2.2
No. of acute diagnoses[d]			
1	54.3	54.7	34.4
2–3	38.6	38.7	36.0
4–5	5.6	5.4	15.4
>5	1.5	1.2	14.2
Hospital admission			
No	94.8	95.5	61.8
Yes	5.2	4.5	38.2

[a] All group comparisons between visits with and without CCC significant at $P < .01$.
[b] There were 63 336 weighted observations with missing data.
[c] There were 24 076 weighted observations with missing data.
[d] E-codes not included.

Medications Associated With ADEs

Among CCC-related ADE visits, psychotropic medications were the suspected cause in 18% of cases, followed by unclassified medications (13%), antimicrobial agents (12%), and anticonvulsants (11%). Among non-CCC-related ADE visits, unclassified medications were the suspected cause in 39% of cases, followed by antimicrobial agents (29%), analgesics (5%), and vaccines (4%). ADEs associated with CCC-related visits had higher rates of occurrence for all classes of medications, compared with non-CCC-related visits, even after adjusting for age (Table 3). Differences existed between specific implicated medications for CCC and non-CCC-related ADE visits (Table 3). For example, among psychotropic ADEs, antipsychotics accounted for 41% of ADEs in CCC visits versus 26% in non-CCC visits, tranquilizers (28% CCC vs 14% non-CCC), psychostimulants (8% CCC vs 30% non-CCC), and antidepressants (8% CCC vs 18% non-CCC).

Association of CCC Status and Presence of ADE on Inpatient Admission

Younger age, male gender, presence of a CCC, number of acute diagnoses, and presence of an ADE were independently associated with hospital admission (Table 4). Insurance status, time of week, and regional location of hospital were associated with hospital admission. The final multivariable model

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TABLE 2 Independent Risk Factors Associated With Any ADE, 2006–2010

Predictor Variables	No ADE, %[a]	Any ADE, %[b]	Unadjusted OR (95% CI)[c]	Adjusted OR (95% CI)[d]
Demographic factors				
Age				
<1	12.1	10.5	1.00 (ref)	1.00 (ref)
1–4	29.0	25.2	0.99 (0.97–1.03)	1.02 (0.99–1.05)
5–9	18.5	17.8	1.10 (1.07–1.14)	1.12 (1.08–1.15)
10–18	40.4	46.5	1.32 (1.28–1.36)	1.32 (1.28–1.36)
Gender				
Male	51.8	49.6	0.92 (0.90–0.93)	0.93 (0.91–0.94)
Female	48.2	50.4	1.00 (ref)	1.00 (ref)
Insurance				
Public	46.4	45.5	1.00 (ref)	1.00 (ref)
Private	53.6	54.5	1.04 (1.00–1.07)	1.04 (1.02–1.07)
Time of visit				
Weekday	69.0	68.0	1.00 (ref)	1.00 (ref)
Weekend	31.0	32.0	1.04 (1.03–1.06)	1.07 (1.06–1.08)
Region				
Northeast	18.6	15.8	1.00 (ref)	1.00 (ref)
Midwest	23.6	23.2	1.16 (1.03–1.31)	1.17 (1.04–1.31)
South	38.3	39.4	1.21 (1.07–1.37)	1.23 (1.08–1.39)
West	19.5	21.6	1.30 (1.16–1.46)	1.31 (1.17–1.47)
Clinical factors				
CCC				
No	98.1	91.3	1.00 (ref)	1.00 (ref)
Yes	1.9	8.7	4.83 (4.52–5.16)	4.76 (4.45–5.10)

OR, odds ratio; CI, confidence interval.

[a] n = 143 668 524.

[b] n = 716 664.

[c] Overall type 3 effect for each variable in relation to the outcome was $P < .01$.

[d] Final model adjusted for age, gender, CCC status, insurance type, weekday, and regional location of ED.

included each of these variables. The presence of an ADE increased the likelihood of inpatient hospital admission (odds ratio 2.18; 95% confidence interval 2.04–2.32), but not differentially for children with and without CCCs (odds ratio 0.93; 95% confidence interval 0.84–1.03).

DISCUSSION

Our estimates of ADE-related ED visits using NEDS data are consistent with previously reported yearly estimates using NAMCS and NHAMCS data (average of 143 333 visits per year in our study vs 131 142 and 158 520, respectively).[5] That increasing age is associated with increased ADEs is also consistent with previous reports and not clinically surprising.[5] Public insurance status, weekend timing of visit, and regional location of the hospital outside the Northeast were associated with higher rates of ADE visits; this may reflect different patterns of ambulatory resource utilization. Although children with CCCs may be expected to have a higher risk of outpatient ADEs due to their greater exposure to medications, our study quantifies and examines aspects of this risk. The true frequency of ADE visits is likely higher, given that ADEs are likely to be undercoded,[19,25] which could occur because of provider uncertainty about an ADE diagnosis or because of delayed recognition of an ADE until further diagnostic information is available after an ED visit (such as the development of characteristic symptoms, additional patient history, or laboratory results).

The implicated drugs differed between children with and without CCCs, even after exclusion of children with malignancies, who frequently experience expected chemotherapy side effects. Psychotropics, antimicrobial agents, anticonvulsants, hormones/steroids, and analgesics were responsible for the majority of CCC-related ADEs, and antibiotics ranked highest among children without CCCs. Within those classes, certain specific categories showed differences between children with and without CCCs, which may guide more targeted investigations based on problematic medications rather than classes of medications. The observed differences in implicated drugs are consistent with those most frequently prescribed in the ambulatory setting to these different populations of children. Despite the variety of rare diagnoses comprising CCCs, this group of children frequently share a common set of underlying issues.[26] Broadly, these are categorized as neurologic issues (seizures, pain control, behavior/mood disorders), pulmonary issues (asthma, chronic lung disease, aspiration), gastrointestinal issues (gastrostomy tube, reflux, constipation), endocrine disturbances (adrenal insufficiency), and infectious issues (central line, catheter, or shunt infections). The likelihood of ADE visits related to vaccines was not significantly different between groups; this supports validity of our findings because most children should receive standard childhood vaccinations, which pose a low risk of ADEs.

Contrary to our expectations that children with CCCs would be more severely affected by ADEs because of their underlying conditions, we did not observe significant differences in risk of hospitalization associated with an ADE between children with and without CCCs. Conceivably, ADEs may not be more severe in children with CCCs. Another possibility is that for children with CCCs who are frequently admitted, ED providers may focus on and code the multiple non-ADE issues relating to an admission (29% of CCC visits had >4 acute diagnoses coded, compared with 6% in non-CCC visits), biasing the effect toward the null.

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TABLE 3 Drug Classes and E-codes Associated With ADEs by CCC Status, 2006–2010

Drug Class	CCC Visits (n = 2 830 657)		Non-CCC Visits (n = 141 554 531)		Likelihood of ADE in CCC vs non-CCC Visits
	Weighted Frequency of ADEs[a]	Estimated ADEs per 100 000 Visits (95% CI)	Weighted Frequency of ADEs[a]	Estimated ADEs per 100 000 Visits (95% CI)	OR[b] (95% CI)
Total ADEs, *n*	62 118	2194 (1884–2505)	654 546	462 (435–490)	4.8 (4.4–5.1)
Psychotropics, *n*	11 433	404 (371–437)	22 326	16 (15–17)	23.6 (21.9–25.4)
Antipsychotics (E9393)	41%		26%		
Psychostimulants (E9397)	8%		30%		
Antidepressants (E9390)	8%		18%		
Phenothiazines (E9391)	17%		5%		
Benzodiazepines (E9394)	11%		9%		
Other	15%		12%		
Misc/not elsewhere classified[c]	8071	285 (256–437)	254 278	180 (163–196)	1.6 (1.5–1.7)
Antimicrobials	7396	261 (213–310)	187 296	132 (125–140)	2.0 (1.8–2.2)
Penicillins (E9300)	16%		46%		
Cephalosporins (E9305)	15%		12%		
Antibiotics NEC/NOS (E9308-9)	46%		18%		
Sulfonamides (E9310)	7%		10%		
Erythromycin (E9303)	3%		7%		
Other	13%		7%		
Anticonvulsants	6766	239 (204–274)	7231	5 (5–6)	45.1 (40.9–49.9)
Anticonvulsants NEC (E9363)	75%		79%		
Hydantoin derivatives (E9361)	24%		19%		
Other	1%		2%		
Hormones/steroids	5295	187 (146–228)	18 424	13 (12–14)	13.7 (12.1–15.7)
Corticosteroids (E9320)	92%		71%		
Insulin/Anti-diabetics (E9323)	3%		17%		
Ovarian hormones (E9322)	2%		10%		
Other	5%		2%		
Analgesics	4210	149 (120–178)	35 479	25 (24–27)	5.5 (4.8–6.2)
Opiates (E9352)	66%		40%		
Antirheumatics (E9356)	7%		26%		
Aromatic analgesics (E9354)	5%		16%		
Analgesics NEC/NOS (E9358-9)	15%		11%		
Salicylates (E9353)	4%		5%		
Other	3%		2%		
Chemotherapy[c,d]	3981	141 (81–201)	1436	1 (1–1)	138.7 (105.2–182.8)
Non–E-code[c]	2946	104 (87–121)	52 749	37 (34–41)	2.6 (2.2–2.9)
Sedatives/hypnotics/anesthetics[c]	2763	98 (78–117)	8270	6 (5–6)	16.2 (14.4–18.2)
Gastrointestinal agents	1867	66 (57–75)	8308	6 (5–6)	10.8 (9.6–12.2)
Antiemetics/allergics (E9330)	83%		75%		
Antacids (E9430)	4%		8%		
Other	13%		17%		
Respiratory agents	1806	64 (40–88)	11 353	8 (6–10)	8.2 (6.1–11.0)
Antiasthmatics (E9457)	92%		77%		
Antitussives (E9454)	6%		15%		
Other	2%		8%		

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TABLE 3 Continued

Drug Class	CCC Visits (n = 2 830 657)		Non-CCC Visits (n = 141 554 531)		Likelihood of ADE in CCC vs non-CCC Visits
	Weighted Frequency of ADEs[a]	Estimated ADEs per 100 000 Visits (95% CI)	Weighted Frequency of ADEs[a]	Estimated ADEs per 100 000 Visits (95% CI)	OR[b] (95% CI)
Hematologic agents	1668	59 (42–76)	4459	3 (1–6)	18.4 (8.7–39.1)
Anticoagulants (E9342)	28%		74%		
γ globulin (E9346)	23%		16%		
Blood products (E9347)	38%		2%		
Iron and compounds (E9340)	3%		5%		
Other	8%		3%		
Electrolytes/minerals/vitamins[c]	1042	37 (26–48)	1238	1 (1–1)	40.7 (32.5–51.1)
Autonomic agents	861	30 (25–36)	4144	3 (3–3)	9.9 (8.3–11.8)
Sympathomimetics (E9412)	35%		53%		
Parasympathomimetics (E9411)	31%		21%		
Other	34%		26%		
Cardiovascular agents	916	32 (26–39)	2254	2 (1–2)	19.4 (15.4–24.4)
Antihypertensives (E9426)	39%		37%		
Cardiotonics (E9421)	17%		11%		
Rhythm regulators (E9420)	15%		5%		
Other	29%		47%		
Musculoskeletal/topical agents[c]	584	21 (16–26)	11 115	8 (7–9)	2.6 (2.0–3.2)
Vaccines[b]	513	18 (13–23)	24 186	17 (12–16)	1.1 (0.9–1.4)

OR, odds ratio; CI, confidence interval.

[a] Percentages listed indicate the percent of the weighted frequency of ADEs for the particular drug class listed.

[b] Adjusted for age.

[c] Further subcategorization could not be reported because of inadequate sample size within each contained subcategory.

[d] Although malignancies were excluded, these cases either represent uncoded cases of malignancy or use of chemotherapy in the treatment of other conditions.

Our results must be interpreted in the context of several limitations. First, because of the nature of billing data, we cannot determine the true nature or severity of recorded ADEs. Although we examined proxy variables, such as number of acute diagnoses and hospitalization rates, these variables only indirectly suggest severity, and other potential severity indicators, such as whether a visit resulted from transfer from another facility, were not available in the NEDS. Second, because the data do not contain prescription data, we cannot verify whether a subject was actually taking the medication that was coded as the offending drug, nor can we determine whether a subject was taking other concomitant prescriptions. Third, although only 13% of ADEs were "unclassified" among children with CCCs, 39% of ADEs were unclassified in children without CCCs; the latter is consistent with previous studies.[5,6,27] If the identity of the suspected agents were known, specific comparisons between medication classes could change and thus limit our ability to calculate exact frequencies for the medications associated with ADEs (Tables 3 and 4). This highlights the importance and need for improved identification of potential ADEs. Despite this limitation, the overall finding that children with CCCs are at higher risk for ADE-related visits holds. Finally, there may be differential utilization of the ED by CCC and non-CCC subjects, for example, because of a patient's underlying true or perceived medical complexity. Future analyses should include additional ambulatory settings to determine whether a bias exists in patterns of place of care, although severe ADEs should result in ED-level care captured in our study. Each of these limitations could be solved with improved outpatient clinical and pharmacy data as it becomes available.

Considering our findings, reasons for the increased risk of ADE-related visits

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TABLE 4 Independent Risk Factors Associated With Inpatient Hospital Admission, 2006–2010

Predictor Variables	Discharge, %[a]	Admission, %[b]	Unadjusted OR (95% CI)[c]	Adjusted OR (95% CI)[d]
Demographic factors				
Age				
<1	11.6	21.6	1.00 (ref)	1.00 (ref)
1–4	29.3	23.6	0.43 (0.42–0.44)	0.43 (0.42–0.44)
5–9	18.7	14.4	0.53 (0.51–0.56)	0.46 (0.44–0.49)
10–18	40.4	40.4	0.41 (0.40–0.43)	0.41 (0.40–0.43)
Gender				
Male	51.7	54.4	1.11 (1.10–1.12)	1.14 (1.13–1.15)
Female	48.3	45.6	1.00 (ref)	1.00 (ref)
Insurance				
Public	46.2	48.7	1.00 (ref)	1.00 (ref)
Private	53.8	51.3	0.91 (0.86–0.96)	1.05 (0.99–1.11)
Time of visit				
Weekday	68.8	71.4	1.00 (ref)	1.00 (ref)
Weekend	31.1	28.6	0.88 (0.87–0.89)	0.89 (0.88–0.90)
Region				
Northeast	18.5	20.1	1.00 (ref)	1.00 (ref)
Midwest	23.6	22.6	0.90 (0.77–1.06)	0.78 (0.67–0.91)
South	38.6	33.8	0.80 (0.69–0.91)	0.61 (0.52–0.70)
West	19.3	23.5	1.10 (0.92–1.32)	0.99 (0.84–1.16)
Clinical factors				
CCC				
No	98.7	85.5	1.00 (ref)	1.00 (ref)
Yes	1.3	14.5	13.39 (12.60–14.21)	8.79 (8.05–9.60)
No. of additional acute diagnoses				
1	55.9	25.8	1.00 (ref)	1.00 (ref)
2–3	38.4	43.0	2.45 (2.35–2.55)	2.47 (2.36–2.58)
4–5	4.9	18.3	8.28 (7.56–9.07)	8.17 (7.45–8.97)
>5	0.8	12.9	35.6 (30.42–41.88)	30.19 (25.95–35.13)
ADE				
No	99.6	98.4	1.00 (ref)	1.00 (ref)
Yes	0.4	1.6	3.86 (3.53–4.23)	2.18 (2.04–2.32)

OR, odds ratio; CI, confidence interval.

[a] n = 136 877 158.

[b] n = 7 508 030.

[c] Overall type 3 effect for each variable in relation to the outcome was $P < .01$.

[d] Final model adjusted for age–gender, insurance type, presence of ADE, number of acute diagnoses, weekday, and regional location of ED.

by children with CCCs must be further studied. Although clinicians may intuitively expect children with CCCs to have a higher risk of ADEs prompting medical attention, there are multiple underlying possible explanations as to why. Three important and potentially modifiable etiologies come directly from the geriatric literature on ADEs: increased exposure to medications with a greater risk of ADEs, increased exposure to multiple medications concurrently, and both of these exposures occurring in a medically fragile population.[9]

First, children with CCCs may have exposure to more and potentially riskier medications than patients without CCCs, which increases the risk of developing ADEs. Hospitalized children were observed to have exposure of up to 25 drugs in children's hospitals, with higher exposures among children with rare conditions.[3] Although this has not been replicated in the outpatient setting, similar patterns in drug exposure likely exist. Adult studies have demonstrated that higher cumulative medication exposures are associated with an increased frequency of ADEs.[7–9] Complicating the issue, because the underlying disease processes comprising CCCs are rare and heterogeneous, clinicians may use riskier medications without reliable information to identify, guide, and subsequently monitor drug therapies.[28] Even for routine medications frequently used in the treatment of children with CCCs, such as proton pump inhibitors or antihistamines, there is little evidence to guide best practice in children with CCCs.

Second, children with CCCs who take multiple concurrent medications may be at higher risk for drug-drug and drug-disease interactions. Geriatric literature describes polypharmacy as the concurrent use of multiple medications, usually ≥5. Outpatient pediatric polypharmacy has not been adequately described; in a study examining medication reconciliation for children with CCCs, subjects took, on average, 5 chronic medications.[29] Polypharmacy, whether necessary for successful treatment of a patient, has been

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associated with increased risk of drug-drug interactions or ADEs.[30] Complex medication regimens may also be difficult to manage for both caregivers and clinicians.[31–33]

Finally, both these phenomena may exist together in children with CCCs, exacerbated by their fragile medical conditions. Children with CCCs use a disproportionately high fraction of medical resources,[15] are frequently readmitted,[13] and, with each readmission, have a higher predicted risk of death.[34] In these children with an already elevated baseline risk of morbidity and mortality, ADEs due to either increased exposures or polypharmacy may pose a much greater risk than in healthy children. It will be important to understand how to separate and evaluate each type of risk in children with CCCs, because each type of risk will require different mitigation strategies.

CONCLUSIONS

Children with complex chronic conditions have a higher risk of ED visits related to ADEs, compared with other children. The implicated drugs are different, with the highest rates attributed to psychotropic agents, antimicrobial agents, anticonvulsants, hormones/steroids, and analgesics. To improve pharmaceutical safety and reduce ADEs over these children's lifetimes, it will be important to understand the reasons for the increased risk of ADEs among children with CCCs. This will allow for identification of certain risky drug exposures and dangerous drug-drug or drug-disease combinations, improvement in the management of and communication about complex drug regimens, and the development of enhanced monitoring strategies.

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Appendix 1 Classification Scheme for Medications Using E-Codes

Medication Class	ICD-9-CM Code(s)[a]
Antimicrobial	E930*
	E931*
Hormone/steroid	E932*
Hematologic	E934*
Analgesic	E935*
Anticonvulsant	E9360-E9364
Sedative/hypnotic/anesthesia	E937*
	E938*
Psychotropic (including psychostimulants)	E939*
Autonomic	E940*
	E941*
Cardiovascular	E942*
Respiratory	E9454-E9458
Gastrointestinal	E9330
	E9430–E9439
Electrolytes/minerals/vitamins	E9332–E9337
	E9440–E9447
Musculoskeletal/topical	E9450–E9453
	E9460–E9469
Chemotherapy	E9331
Vaccine	E9480–E9499
Miscellaneous, not elsewhere classified	E933
	E9338–E9339
	E947*
	292*
	3576
	7794
	9952*

[a] Asterisk denotes potential additional digit (1–9) that can further specify the diagnosis.

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