Potential Drug–Drug Interactions in Infant, Child, and Adolescent Patients in Children's Hospitals

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abstract

BACKGROUND AND OBJECTIVES: Hospitalized infants, children, and adolescents are typically exposed to numerous distinct medications during inpatient admissions, increasing their risk of potential drug–drug interactions (PDDIs). We assessed the prevalence and characteristics of PDDI exposure of pediatric patients treated in children's hospitals.

METHODS: This retrospective cohort study included patients <21 years old hospitalized in children's hospitals throughout the United States. PDDIs were identified by using the MicroMedex DRUG-REAX system. We calculated the patients exposed to PDDIs, stratified according to the seriousness of the interaction; daily and cumulative counts of PDDI exposures; and characterization of the cited potential adverse effects.

RESULTS: Of 498 956 hospitalizations in 2011, 49% were associated with ≥1 PDDI, with a "contraindicated" PDDI occurring in 5% of all hospitalizations, a "major" PDDI present in 41%, a "moderate" PDDI in 28%, and a "minor" PDDI in 11%. Opioids were involved in 25% of all PDDIs, followed by antiinfective agents (17%), neurologic agents (15%), gastrointestinal agents (13%), and cardiovascular agents (13%). One-half of all PDDI exposures were due to specific drug pairs occurring in ≤3% of patients per hospital day. The most common potential adverse drug events included additive respiratory depression (in 21% of PDDIs), bleeding risk (5%), QT interval prolongation (4%), reduced iron absorption/availability (4%), central nervous system depression (4%), hyperkalemia (3%), and altered diuretic effectiveness (3%).

CONCLUSIONS: Exposure to PDDIs is common among hospitalized children. Empirical data are needed to determine the probability and magnitude of the actual harm for each specific PDDI, particularly for less common drug pairs.

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Dr Feinstein participated in the concept and design of the study, performed the statistical analyses and initial interpretation of data, drafted the initial manuscript, and critically revised the manuscript; Dr Dai conceptualized and designed the study, performed the statistical analyses and initial interpretation of data, and critically revised the manuscript; Dr Zhong and Dr Freedman participated in the concept and design, interpretation of the data, and critical revision of the manuscript; Dr Feudtner conceptualized and designed the study, performed the statistical analyses and interpretation of data, and critically revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Hospitalized pediatric patients are often exposed to many medications during an inpatient admission. Drug–drug interactions may increase the risk of developing medication-related adverse drug events, leading to serious clinical morbidity and mortality.

WHAT THIS STUDY ADDS: Exposure to "major" potential drug–drug interactions occurs in 41% of pediatric hospitalizations in children's hospitals. One-half of all these exposures were due to less common specific drug pairs (≤3% of patients exposed per hospital day) and thus may be less clinically familiar.

Hospitalized pediatric patients are often exposed to an extensive array of distinct medications, with counts exceeding 25 unique medications for children with longer stays or rare conditions.[1] Polypharmacy, defined as the concurrent use of multiple medications, has been implicated as a significant risk factor in the pediatric population for developing medication-related adverse drug events (ADEs),[2] likely as a consequence of exposure to drug–drug interactions. In addition, hospitalized pediatric patients are vulnerable to medication-related issues because of off-label prescribing of drugs,[3] lack of therapeutic profiles for rarer drugs, and weight-based dosing schemes.[4]

The Institute of Medicine has identified medication safety in children, including the recognition and prevention of ADEs, as an important priority for the delivery of effective health care.[5] With computerized physician order entry systems, standardized prescribing and checking of potential drug–drug interactions (PDDIs) at the time of order have become more prevalent.[4] The epidemiology of pediatric PDDIs, however, is largely unknown: we lack estimates of the prevalence of pediatric PDDIs, reliable knowledge regarding the risk posed by specific PDDIs (especially important given the countervailing risks posed by the condition under treatment), or an adequate understanding about pathways by which PDDIs may lead to harmful ADEs in pediatric patients (eg, as a direct physiologic effect on an organ system or through modulation of another medication's effect).[6–8] Each of these critical pieces of information is integral to developing and studying strategies to mitigate clinically important ADEs associated with specific PDDIs.

In the present study, our goal was to advance this research and quality improvement agenda by assessing the prevalence and characteristics of PDDI exposure of pediatric patients treated in children's hospitals. To do so, we performed a retrospective cohort study of hospitalized pediatric patients by using a large administrative database, including comprehensive clinical and pharmacy information. We then used a well-established compendium of PDDIs to perform a high-volume analysis of all PDDI exposures for each patient in the cohort on each day of their hospitalization.

METHODS

Human Subjects Protection

The institutional review board at The Children's Hospital of Philadelphia determined that this study of de-identified data did not constitute human subjects research.

Data Sources

The study used the Pediatric Health Information System (PHIS) database (Children's Hospital Association [CHA], Kansas City, KS), composed of 43 freestanding children's hospitals at the time of the study.[9] The PHIS database includes patient demographic characteristics, diagnosis, and procedures as well as detailed pharmacy information, including *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes and Clinical Transaction Classification (CTC) codes for each procedure, generic drug entity dispensed, and clinical services for each day of hospital stay of each patient. Data quality and reliability are assured through a joint effort between CHA and the participating hospitals. Every participating hospital performs coding audits monthly, and CHA performs data quality checks to assure that classified errors occur in <2% of a hospital's data.[1,10,11] Before distribution to end-users, CHA deletes all patient identifiers. One hospital without detailed pharmacy information was excluded from the present study.

Identification and Classification of Study Population

We included all hospitalized patients <21 years of age admitted to participating hospitals between January 1, 2011, and December 31, 2011. Complex chronic conditions (CCC) were defined as medical conditions that can be reasonably expected to last at least 12 months and that involve either several different organ systems or 1 organ system severely enough to require specialty pediatric care and probably some period of hospitalization in a tertiary care center. To identify whether an individual was diagnosed with a CCC, we used our previously published classification scheme based on *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes.[12]

Data Management

Drugs and therapeutic agents were recorded by using CTC codes and drug descriptions. We converted CTC codes into National Drug Codes (NDCs) by using a CTC–NDC crosswalk table provided by CHA.[13] We compared a subset of CTC codes for the most frequently used drugs versus their corresponding NDC codes and found that they correctly specified the same generic drugs. A standardized dictionary of 1227 generic drug entities was implemented. These generic drugs were grouped into 27 major categories, principally by using the American Hospital Formulary System Pharmacologic Therapeutic Classification hierarchy of drug and therapeutic agent classes and prevalent subclasses.[1]

Potential Drug–Drug Interactions

PDDIs were identified by using the DRUG-REAX system (Thomson Micromedex, Truven Health Analytics Inc., Greenwood Village, CO). The software has been previously validated and described in detail.[14–16] The software classifies the drug interactions into 5 levels of seriousness: contraindicated, major, moderate, minor, and unknown. The seriousness category represents the seriousness of the PDDI if it occurs

and does not assess the likelihood that the interaction may occur. "Contraindicated" drug pairs should not be used concurrently. "Major" interactions may be life-threatening or require medical intervention to minimize or prevent ADEs. "Moderate" interactions may result in exacerbation of the patient's condition or require an alteration in therapy. "Minor" interactions have limited clinical effect that may include an increase in the frequency or severity of the adverse effects but generally would not require a major alteration in therapy. The scientific documentation status of the PDDI is classified as excellent, good, fair, poor, or unlikely; we did not consider PDDIs in either the poor or unlikely categories. "Excellent" indicates controlled studies have clearly established the existence of the drug interaction; "good" means the documentation strongly suggests that a drug interaction exists, but well-controlled studies are lacking; and "fair" indicates that although the available documentation is scarce, pharmacologic consideration may lead clinicians to suspect the existence of a drug interaction.

Potential ADEs of PDDIs

For each PDDI combination, we determined the organ systems affected by the PDDI, as well as the specific physiologic end-effects or alterations of other pharmacologic agents.[7] We made these classifications by directly parsing the text in the drug–drug interaction compendium provided by Truven Health Analytics for each PDDI observed. For example, text containing "respiratory depression" was mapped to the respiratory system or "acute renal failure" was mapped to the renal system. The general classification scheme is provided in Supplemental Appendix 1; the authors will provide the complete scheme and software upon request.

Statistical Analysis

The demographic and clinical characteristics of the patients in the study cohort are described by calculation of percentages. To describe the prevalence of PDDIs, the percentages of specific PDDIs were calculated according to patient and each hospital day; we then calculated the percentage/proportion of patients with PDDI exposure (subsequently referred to as "exposure percentage/proportion") with 95% confidence intervals by interaction level and by patient demographic and clinical characteristics. Patient-level percentiles were calculated of the following: (1) the number of exposures of distinct PDDI on each day of hospitalization; (2) the cumulative number of exposures of distinct PDDI on each successive day of hospitalization; and (3) the PDDI exposure percentage with 95% confidence intervals in each day up to 30 days' in-hospital stay. Trend analyses were performed by using the Cochran-Armitage test. The PDDI patterns are also described according to age groups. For each of the PDDIs, we next calculated counts and percentages of the implicated medication pairs, the severity of the interaction, and the level of evidence for the interaction. Finally, we calculated the percentage of all PDDIs associated with each of the different categories of potential ADEs, as described in the previous section. Each PDDI could be associated with $\geq$1 potential ADE.

All data management and statistical analyses were conducted by using SAS version 9.3 (SAS Institute, Inc, Cary, NC) and Stata version 13.1 (StataCorp, College Station, TX).

RESULTS

In 2011, a total of 498 956 pediatric hospitalizations occurred in the 43 member children's hospitals (Table 1). The majority of patients were aged <5 years (51%), male (54%), and without a CCC (53%). Hospitalizations were most frequently due to respiratory diagnoses (19%), <4 days in length (60%), funded by Medicaid (49%), and resulted in home discharge (93%).

PDDIs and Exposure Proportions

Among these hospitalizations, we identified a total of 4 497 448 PDDI exposures, comprising 5292 distinct PDDIs. The level of evidence supporting PDDIs was excellent for 7% of all identified PDDIs, good for 55%, and fair for 38%. Overall, 49% of all hospitalized pediatric patients were exposed to a PDDI (Table 1). A contraindicated PDDI exposure occurred in 5% of all hospitalizations, a major PDDI exposure in 41%, moderate in 28%, and minor in 11%. The likelihood of PDDI exposure increased for patients who were older, had longer hospital stays, or had CCC. The presence of a CCC increased the likelihood of any PDDI exposure, with a 2.5-fold increase in children with >3 CCC compared with those without (85% vs 34%).

Most Frequent Specific PDDIs by Severity Level

Certain classes of drugs were commonly implicated in PDDIs, including opioids, antiinfective agents, neurologic agents, gastrointestinal agents, and cardiovascular agents (Table 2). Among contraindicated pairs, exposure to ibuprofen and ketorolac (with the potential for enhanced adverse gastrointestinal effects) occurred in 1.8% of hospitalizations, followed by fluconazole and ondansetron (0.9%) and calcium chloride and ceftriaxone (0.7%). Among pairs with major interactions, fentanyl and morphine (with the potential for additive respiratory depression) occurred in 13.2% of hospitalizations, followed by fentanyl and midazolam (11.2%), midazoloam and morphine (9.2%), and bupivacaine and propofol (5.8%). The pairs with moderate reactions included dexamethasone and rocuronium (3.3%), heparin and vitamin A (2.1%), and propofol and succinylcholine (2.0%). Opioids were

TABLE 1 Characteristics of Hospitalized Patients and Prevalence of PDDI in US Children's Hospitals

Characteristic	No. (%)[a]	Unique PDDIs Median (IQR)[b]	Prevalence of PDDI (%)				
			Contraindicated	Major	Moderate	Minor	Overall
Age, y							
All ages	498 956 (100.00)	0 (0–3)	4.65	40.85	28.06	10.53	49.23
<1	130 458 (26.15)	0 (0–2)	1.70	29.11	21.65	13.24	37.40
1–4	124 048 (24.86)	0 (0–2)	4.17	35.15	23.85	6.46	42.47
5–9	83 708 (16.78)	1 (0–3)	5.18	43.62	28.21	7.95	52.01
10–14	85 793 (17.19)	1 (0–5)	6.32	51.04	34.13	11.12	60.09
15–20	74 949 (15.02)	2 (0–6)	8.11	55.97	39.05	14.78	65.46
Gender							
Male	269 528 (54.02)	0 (0–3)	4.24	40.64	28.05	10.17	48.98
Female	229 364 (45.97)	0 (0–3)	5.14	41.09	28.07	10.95	49.52
Race							
White	247 393 (49.58)	0 (0–3)	4.77	43.41	29.39	11.55	51.77
Hispanic	91 419 (18.32)	0 (0–3)	4.51	40.46	28.48	9.72	48.73
Black	97 930 (19.63)	0 (0–2)	4.94	36.18	25.39	9.02	45.11
Other	53 076 (10.64)	0 (0–3)	4.08	38.71	27.24	9.95	46.46
CCC types							
Neurologic and neuromuscular	56 868 (11.40)	2 (0–7)	6.63	58.21	47.26	20.69	70.00
Cardiovascular	46 554 (9.33)	4 (1–12)	10.09	66.33	61.88	23.05	75.83
Respiratory	24 708 (4.95)	3 (0–8)	6.88	59.41	55.42	29.88	73.24
Renal and urologic	25 969 (5.20)	3 (1–9)	9.15	69.01	52.69	26.37	78.82
Gastrointestinal	55 506 (11.12)	3 (0–7)	7.03	60.63	52.28	25.72	73.71
Hematologic or immunologic	32 904 (6.59)	1 (0–5)	14.57	54.34	39.80	15.04	65.17
Metabolic	20 689 (4.15)	3 (0–9)	10.73	57.75	52.20	24.31	68.68
Other congenital or genetic defect	38 736 (7.76)	3 (0–8)	6.02	62.15	45.99	20.39	71.02
Malignancy	44 253 (8.87)	2 (0–5)	9.89	59.59	48.13	10.97	72.28
Premature and Neonatal	14 001 (2.81)	2 (0–7)	3.19	55.67	47.91	31.70	68.42
No. of CCCs							
0	272 928 (54.70)	0 (0–1)	2.51	27.60	13.95	4.50	33.53
1	139 255 (27.91)	1 (0–5)	5.92	51.99	38.26	13.34	63.21
2	53 813 (10.79)	3 (0–7)	7.98	62.00	51.69	21.22	73.46
3	22 095 (4.43)	4 (1–10)	10.27	66.30	59.68	27.47	78.20
>3	10 865 (2.18)	6 (2–15)	14.47	74.38	70.19	38.63	85.46
Length of stay, d							
1	114 012 (22.85)	0 (0–1)	1.50	28.94	15.76	2.80	34.80
2–3	187 669 (37.61)	0 (0–2)	2.89	31.08	19.95	5.49	39.42
4–7	113 301 (22.71)	1 (0–4)	6.05	48.58	33.12	11.35	58.53
8–14	44 965 (9.01)	3 (0–7)	8.18	61.61	48.24	21.82	72.68
15–30	23 321 (4.67)	5 (1–12)	12.14	72.41	59.80	33.48	81.27
>30	15 688 (3.14)	10 (3–24)	17.29	81.98	72.79	54.67	89.55
Disposition							
Home	461 801 (92.55)	0 (0–3)	4.37	39.55	26.57	9.45	47.82
Short–term hospital	4317 (0.87)	1 (0–6)	5.35	52.30	40.42	25.09	61.57
Home health care	19 135 (3.84)	2 (0–7)	8.06	58.50	46.46	22.68	69.78
Other transfer	6958 (1.39)	1 (0–7)	6.97	49.77	43.27	22.28	59.13
Died in hospital	4108 (0.82)	7 (2–18)	15.38	82.35	69.38	41.14	87.27

IQR, interquartile range.

[a] Percentages in groups do not add to 100% due to small numbers of missing values.

[b] Data are reported as median (interquantile range); small number of patients with missing characteristics are omitted from the gender, race, and disposition strata.

involved in nearly 25% of all PDDIs, followed by antiinfective agents (17%), neurologic agents (15%), gastrointestinal agents (13%), and cardiovascular agents (13%). Of all 4 497 448 PDDIs, morphine was involved in 10%, followed by fentanyl (8%), midazolam (8%), furosemide (6%), and aspirin (6%). Complete lists of all distinct PDDIs, along with lists of most commonly involved specific generic drug pairs and individual drugs, are provided in Supplemental Appendix 2 and 3.

PDDI Exposure Proportions Over the Course of Hospitalization

Although the likelihood of exposure to PDDIs increased over the course of hospitalizations, the patterns varied according to patient age (Fig 1). For infants, 21.8% of patients were exposed to a PDDI on hospital day 1; by hospital day 30, 32.0% had been exposed (trend test, $P < .05$). Infants at the 90th percentile of PDDI exposure had 2 unique PDDIs on hospital day 1, and 3 by hospital day 30; cumulatively, this finding corresponded to 2 PDDIs on hospital

TABLE 2 Top 10 Most Frequent Specific PDDIs Stratified According to PDDI Seriousness

Drug–Drug Combination	Potential ADE	Total No. of Exposures	No. of Patients Exposed	Exposure %	95% Confidence Interval	
Contraindicated						
Ibuprofen and ketorolac	Enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding and/or perforation)	9968	9011	1.81	1.77	1.84
Fluconazole and ondansetron	An increased risk of QT interval prolongation	17 935	4272	0.86	0.83	0.88
Calcium chloride and ceftriaxone	Formation of ceftriaxone-calcium precipitates and contraindicated in neonates	4661	3364	0.67	0.65	0.70
Aspirin and ketorolac	Enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding, and/or perforation)	3095	1639	0.33	0.31	0.34
Glycopyrrolate and potassium chloride	Risk of gastrointestinal lesions	2583	778	0.16	0.15	0.17
Calcium gluconate and ceftriaxone	Formation of ceftriaxone-calcium precipitates and contraindicated in neonates	1325	629	0.13	0.12	0.14
Metoclopramide and promethazine	Increased risk of extrapyramidal effects	1557	596	0.12	0.11	0.13
Ketorolac and naproxen	Enhanced gastrointestinal adverse effects (peptic ulcers, gastrointestinal bleeding, and/or perforation)	586	524	0.10	0.09	0.11
Epinephrine and linezolid	Increased hypertensive effects	1010	443	0.09	0.08	0.10
Atropine and potassium chloride	Risk of gastrointestinal lesions	682	427	0.09	0.08	0.09
Major						
Fentanyl and morphine	Additive respiratory depression	89 009	65 730	13.17	13.07	13.27
Fentanyl and midazolam	Additive respiratory depression	114 538	55 824	11.19	11.09	11.28
Midazolam and morphine	Additive respiratory depression	95 871	45 915	9.20	9.11	9.28
Bupivacaine and propofol	An increased hypnotic effect of propofol	29 859	28 827	5.78	5.71	5.84
Lidocaine and propofol	An increased hypnotic effect of propofol	28 293	25 922	5.19	5.13	5.26
Hydrocodone and morphine	Additive respiratory depression	38 259	25 185	5.04	4.98	5.11
Morphine and oxycodone	Additive respiratory depression	28 223	18 131	3.63	3.58	3.68
Lorazepam and morphine	Additive respiratory depression	72 743	16 907	3.39	3.34	3.44
Fentanyl and lorazepam	Additive respiratory depression	45 469	14 652	2.94	2.89	2.98
Fentanyl and hydromorphone	Additive respiratory depression	17 911	13 803	2.77	2.72	2.81
Moderate						
Dexamethasone and rocurorium	Decreased rocurorium effectiveness; prolonged muscle weakness and myopathy	17 822	16 394	3.28	3.23	3.36
Heparin and vitamin A	Increased risk of bleeding	85 366	10 531	2.11	2.07	2.15
Propofol and Succinylcholine Chloride	Bradycardia	10 544	10 032	2.01	1.97	2.05
Midazolan and ranitidine	Increased midazolam bioavailability	21 604	9625	1.93	1.89	1.97
Midazolam and sevoflurane	Potential of anesthetic effects of sevoflurane	10 067	9212	1.85	1.81	1.88
Rocuronium and sevoflurane	Enhanced action of rocuronium	8333	7849	1.57	1.53	1.61
Furosemide and vecuronium	Increased or decreased neuromuscular blockade	20 871	6940	1.39	1.38	1.42
Dexamethasone and vecuronium	Decreased rocurorium effectiveness; prolonged muscle weakness and myopathy	8117	6698	1.34	1.31	1.37
Aspirin and furosemide	Decreased diuretic and antihypertensive efficacy	52 952	6633	1.32	1.29	1.36
Cyclophosphamide and ondansetron	Decreased cyclophosphamide systemic exposure	12 174	6402	1.28	1.25	1.31

day 1, increasing to 16 distinct PDDIs by day 30. For patients aged >1 year, 34.7% were exposed to a PDDI on hospital day 1, increasing to 66.3% by day 30 ($P < .05$). Patients aged >1 year at the 90th percentile of exposure to PDDIs had 3 unique PDDIs on hospital day 1, and 8 by hospital day 30; cumulatively, this finding corresponded to 3 PDDIs on hospital day 1, increasing to 30 distinct PDDI exposures by day 30.

Distribution of Distinct PDDI Exposures Among Patients

Several more common distinct PDDIs, such as those involving combinations of opiates and/or hypnotic agents), had exposure proportions exceeding 15% of patients. However, a large proportion of less common PDDI drug pairs were associated with contraindicated and major interactions. Examining the cumulative distribution of all PDDI exposures across the range of exposure proportions for distinct PDDIs (from rarer to more common), 50% of all major PDDI exposures were due to specific drug pairs occurring in ≤2.8% of patients per hospital day, and 10% were due to

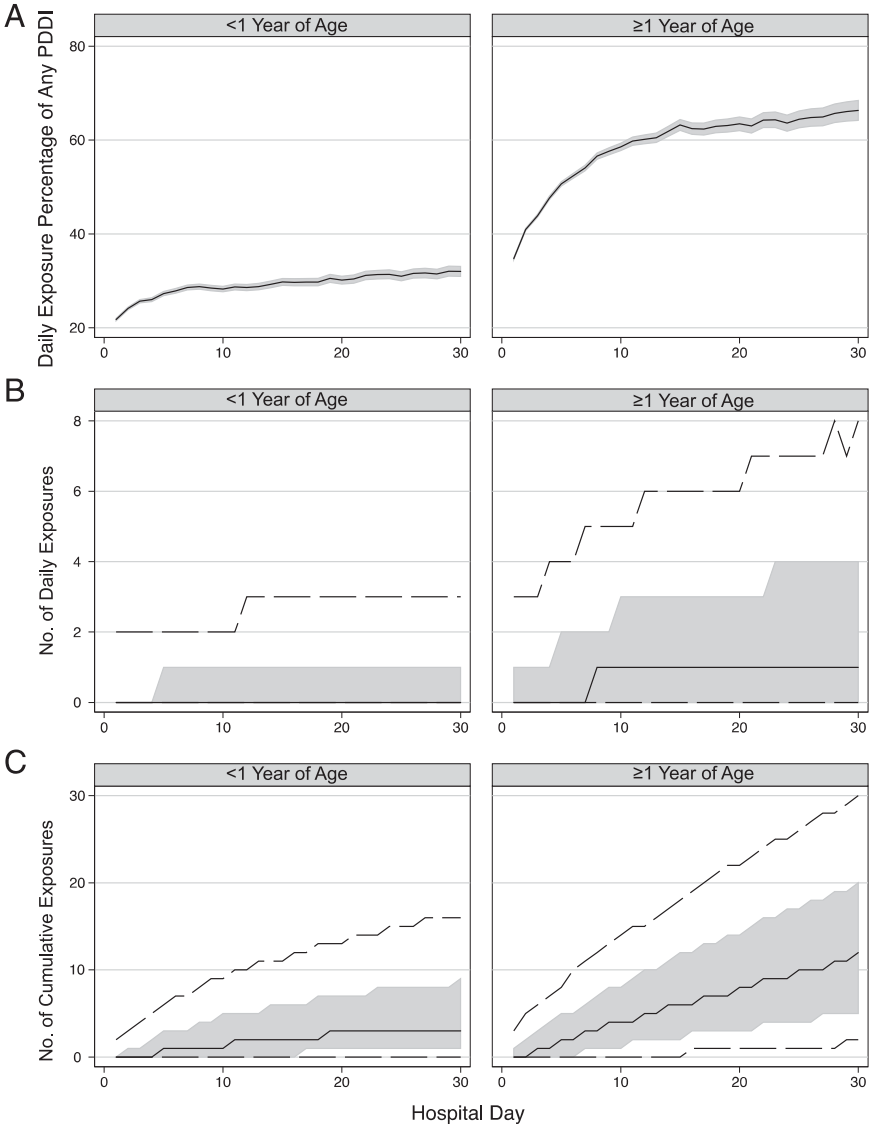

FIGURE 1

A, Daily exposure percentages; B, number of daily distinct exposures; and C, number of cumulative distinct exposures to distinct PDDIs by age and length of stay. Daily exposure shows the proportion of patients exposed to any PDDI for each hospital day, from day 1 up to day 30 of hospitalization, for patients who remained in hospital for those lengths of stay. The plotted solid black line shows the exposure proportions and the shaded zone is the 95% confidence intervals. The number of daily and cumulative distinct PDDI exposures show the levels of exposure to distinct PDDI for each hospital day, from day 1 up to day 30 of hospitalization, for patients who remained in hospital for those lengths of stay. For each hospital day, we determined the level of exposure for patients at various percentiles of exposure; the plotted solid black lines display the median, the plotted black dash lines display 10th and the 90th percentiles, and the shaded zone the interquartile range (IQR). Daily exposure proportions is defined as the number of patients exposed to any PDDI per 100 patients on that hospital day. Number of daily PDDI exposures is defined as the number of distinct PDDI that patients at each percentile were exposed to on that hospital day. Number of cumulative PDDI exposures is defined as the number of distinct PDDI that patients at each percentile were exposed to up to and including that hospital day.

specific drug pairs occurring in ≤0.2% of patients per hospital day. The patterns differed for infants compared with older patients, with a larger proportion of infant PDDI exposures being due to more common PDDIs (Fig 2). For example, in patients aged <1 year, 50% of major PDDI exposures were due to specific drug pairs occurring in ≤7.5% of patients per hospital day. In comparison, for patients ≥1 year of age, 50% of major PDDI exposures were due to specific drug pairs occurring in ≤1.6% of patients per hospital day.

Potential ADEs Associated With PDDIs

In the source compendium of PDDIs, each distinct PDDI was cited as having ≥1 specific harmful end-effect. Among all the PDDIs identified for this study's cohort of hospitalized patients, the most common physiologic end-effects or specific alterations of pharmacologic agents due to PDDIs (Table 3) were respiratory depression (21% of PDDIs), followed by bleeding risk (5%), QT interval prolongation (4%), iron absorption/availability (4%), central nervous system depression (4%), hyperkalemia (3%), and diuretic effectiveness (3%).

We classified all specific harmful end-effects regarding the organ system or systems likely to be harmed (Fig 3), which varied based on the exposure percentages for PDDIs. Significantly more contraindicated exposures occurred as the exposure percentage for a distinct PDDI decreased (exposure >5%: 0 contraindicated exposures; exposure 1%–5%: 27 903 contraindicated exposures; and exposure <1%: 34 981 contraindicated exposures.

DISCUSSION

Having identified all PDDIs for a large cohort of pediatric patients treated at 42 children's hospitals in the United States, we found that nearly one-half of patients were exposed to a PDDI during their admission. Contraindicated PDDIs occurred in 5% of hospitalizations and major PDDIs in 41% of hospitalizations. The likelihood of PDDI exposure increased for patients who were older, had longer hospital stays, or had CCC (all likely due to exposure to more drugs). Certain classes of drugs were commonly implicated in PDDIs,

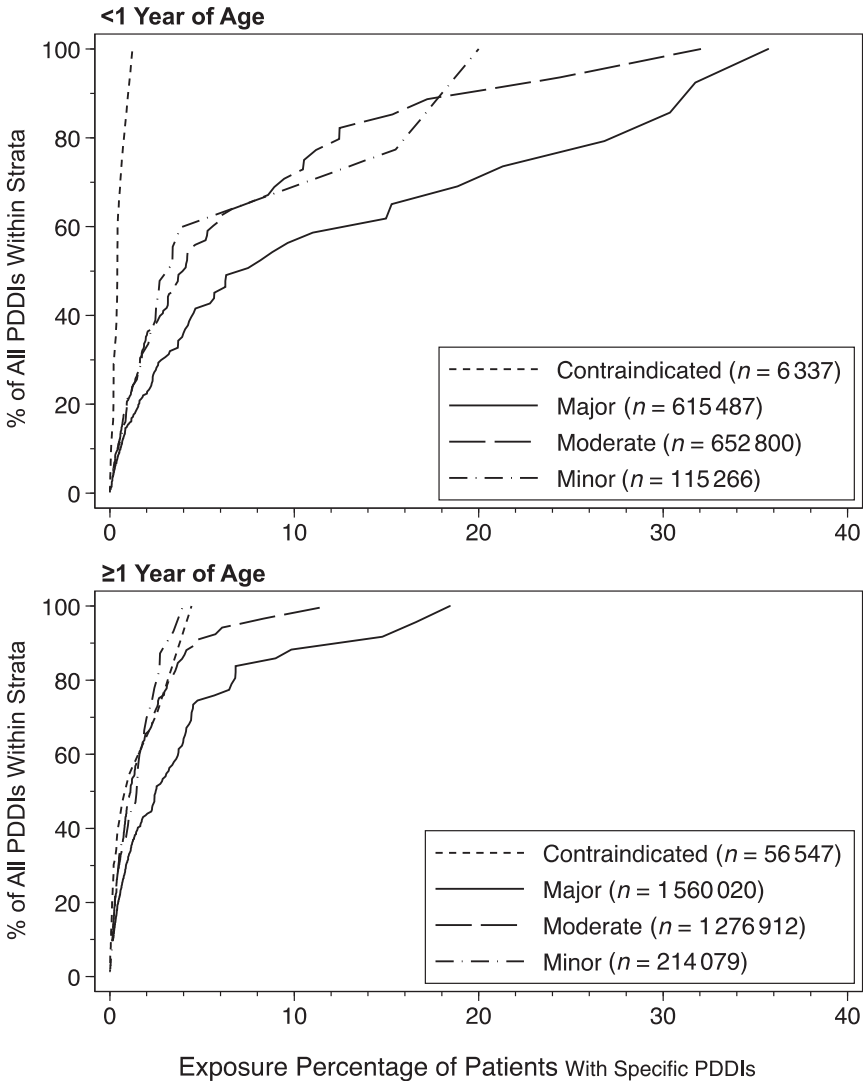

FIGURE 2

Cumulative distribution of unique PDDIs by exposure percentage. For each interaction severity level (contraindicated, major, moderate, or minor) and by age (<1 or ≥1 year of age), we plotted the cumulative proportion of all PDDIs within the specified strata (y-axis) against the percentage of patients exposed to a specific PDDI (x-axis). The short dash line represents contraindicated PDDIs, the solid line major PDDIs, the long dash line moderate PDDIs, and the dotted dash line minor PDDIs. For example, in the panel for <1 year of age, 50% of all major PDDI exposures (y-axis) occurred in ≤7.5% of patients (x-axis).

including opioids, anti-infective agents, neurologic agents, gastrointestinal agents, and cardiovascular agents, and were associated with a small subset of all potential PDDI consequences, such as additive respiratory depression or gastrointestinal disturbances, which may (due to the frequency with which they are encountered) be anticipated or recognized and appropriately managed. By contrast, a large proportion of less common PDDI drug pairs were associated with contraindicated and major interactions distributed across many diverse consequences, including physiologic end-effects, alterations of other drugs, and different body systems affected.

Our findings need to be interpreted keeping in mind that our data identify only potential drug–drug interactions: our study used an administrative database that is insufficient for detecting actual harm.[17] The high prevalence of observed PDDI exposures does not correspond with reported rates of ADEs, which either occur or are recognized far less frequently.[2,8,18,19] At the same time, ADEs can result in significant morbidity and mortality.[20–22] Our findings therefore point to a central problem or tradeoff of warning systems, encapsulated by the story of the boy who cried wolf: the current compendiums of PDDIs suffer from identifying so many PDDIs that the signal of true potential patient harm may get lost in the noise of too many alarms. This situation is analogous to the growing concern that an overabundance of bedside patient monitors and their separate alarms does not necessarily improve patient safety.[23]

Improving the system of PDDI identification and management, accordingly, requires responses in 3 complementary directions. First, we need to identify currently listed PDDIs that do not warrant a red flag. The prevalence of PDDI exposures resulting in clinically significant ADEs is likely substantially lower than the percentage of patients exposed to a PDDI that we observed.[19] Furthermore, the level of evidence for assignment of severity to a PDDI was good to excellent for only 62% of the PDDIs, indicating that the remaining PDDIs have a theoretical basis for inferring the possibility of an ADE, but that these inferences have not been empirically substantiated in clinical practice. Classifying drug interactions into various levels of seriousness (severity) is challenging. Thus, interpreting the results according to level of seriousness may be misleading. Even medication combinations labeled as contraindicated are not necessarily an absolute contraindication. Labels applied by various compendia to the same interactions have been shown to vary substantially and may contribute to clinician alert

TABLE 3 Most Common Potential Physiologic End-Effects or Specific Alterations of Pharmacologic Agents Involved in PDDIs

Physiologic End-Effect	Count	%
Respiratory depression	926 087	20.66
Bleeding	218 010	4.86
QT interval prolongation	198 185	4.42
CNS or respiratory depression	159 000	3.55
Hyperkalemia	128 098	2.86
Gastrointestinal bleeding	75 045	1.67
Postural hypotension	71 215	1.59
Cardiotoxicity	54 231	1.21
Hypokalemia	48 203	1.08
Nephrotoxicity	45 466	1.01
Alteration of pharmacologic agent		
Iron absorption/availability	164 566	3.67
Diuretic	115 721	2.58
Tacrolimus	92 896	2.07
Digoxin	73 340	1.64
Aminoglycoside	73 085	1.63
Antihypertensive	61 907	1.38
Lansoprazole	61 458	1.37
Propofol	58 152	1.30
Cyclosporine	57 589	1.28
Rocuronium	47 101	1.05

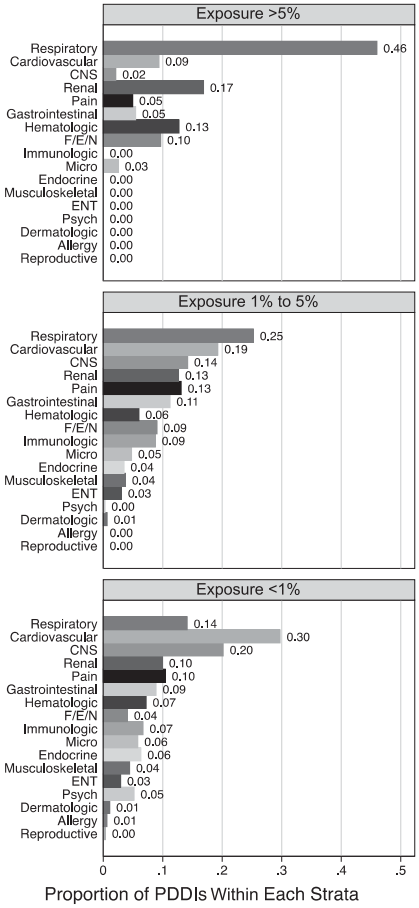

FIGURE 3
Affected end-organ systems or body category involved with PDDIs. By directly parsing the text in the on the drug–drug interaction compendium supplied by Truven Health Analytics, we identified the organ systems involved in each specific PDDI. Each panel of the graph displays the distribution of the affected organ systems based on the percentage of patients exposed to specific PDDIs, either >5% (more common PDDIs), 1% to 5% (common PDDIs), or <1% (less common PDDIs). For example, in the >5% panel, 46% of PDDIs affected the respiratory system (due to frequent specific PDDIs including commonly used pain medications and sedatives), whereas in the <1% panel, only 14% of the less common specific PDDIs affected the respiratory system. CNS, central nervous system; F/E/N, fluids/electrolytes/nutrition; ENT, ears, nose, and throat.

fatigue.[24–27] Clinicians may be oversaturated by computer-based warnings of PDDIs, which can result in a general disregard of these warnings in clinical practice. Even when prompted by computer-based alerts, clinicians disregard certain PDDIs and do not complete the recommended monitoring for subsequent ADEs.[28] In addition, if clinicians avoid the use of specific drugs due to unwarranted concerns for PDDIs, the effectiveness of therapy may be compromised. For these reasons, future research should continue to discern specific PDDIs that can be downgraded or altogether omitted from alerting systems regarding clinical decision support. Doing so will enable us to combat PDDI alert fatigue and enable clinicians to focus on a more limited set of PDDIs, which is important because their retention of PDDI knowledge declines without practical reinforcement of specific PDDIs.[29,30] Effort will also be required to address the medico-legal concerns or consequences from delisting a PDDI.[31]

Second, given that severe ADEs do occur secondary to PDDIs, we need to prioritize PDDIs based on the probability of occurrence and the magnitude of harm to patients, and subsequently develop remediation plans for specific high-priority PDDIs; therefore, the likelihood of hospitalized patients experiencing significant ADEs is reduced. The most common contraindicated and major PDDIs were due to more commonly used medications, such as opiates and antiinfective agents. For these types of common PDDIs, clinicians may understand clinical situations in which coadministration is acceptable, monitor for potential ADEs, and adjust medications regimens when ADEs do develop. For example, a combination of an opioid and a benzodiazepine is often used to provide analgesia/sedation for patients who are critically ill or are undergoing invasive procedures; the potential ADE of additive respiratory depression is well known, with a conscious assessment of the potential benefits and harms of administering this combination of drugs. We therefore hypothesize that the majority of unanticipated harm, in particular that from more severe interactions, may arise from pairs of less common medications, prescribed by clinicians with limited experience or insight into the potential adverse effects and the necessary monitoring for a wide range of adverse effects.

Finally, given the rarity of certain specific drug–drug combinations, we need to develop and use customized

strategies to identify potential harm in small samples of patients. Specifically, we should consider combining the information from large data sets (eg, PHIS) with more detailed information obtained either from other clinical data sources (eg, electronic medical records) or from research data sources (eg, pharmacologic studies or active adverse event surveillance studies) by using 2-stage sampling or other methods.[32]

CONCLUSIONS

Hospitalized patients are commonly exposed to PDDIs, but the subsequent probability of occurrence and magnitude of patient harm requires further empirical substantiation. Less common PDDIs represent the majority of all PDDI exposures, and these less common PDDIs may provide a high-yield target to improve patient safety.

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