

Off-label Drug Use in Hospitalized Children

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Objectives: To describe the magnitude of off-label drug use, to identify drugs most commonly used off-label, and to identify factors associated with off-label drug use in children hospitalized in the United States.

Design: Retrospective cohort study.

Setting: Administrative database containing inpatient resource utilization data from January 1 to December 31, 2004, from 31 tertiary care pediatric hospitals in the United States.

Participants: Hospitalized patients 18 years or younger.

Main Exposures: Institution and patient characteristics.

Main Outcome Measures: Off-label drug use was defined as use of a specific drug in a patient younger than the Food and Drug Administration–approved age range for any indication of that drug.

Results: At least 1 drug was used off-label in 297 592 (78.7%) of 355 409 patients discharged during the

study. Off-label use accounted for \$270 275 849 (40.5%) of the total dollars spent on these medications. Medications classified as central or autonomic nervous system agents or as fluids or nutrients, or gastrointestinal tract agents were most commonly used off-label, whereas antineoplastic agents were rarely used off-label. Factors associated with off-label use in multivariate analysis were as follows: undergoing a surgical procedure, age older than 28 days, greater severity of illness, and all-cause in-hospital mortality.

Conclusions: Most patients hospitalized at tertiary care pediatric institutions receive at least 1 medication outside the terms of the Food and Drug Administration product license. Substantial variation in the frequency of off-label use was observed across diagnostic categories and drug classes. Despite the frequent off-label use of drugs, using an administrative database, we cannot determine which of these treatments are unsafe or ineffective and which treatments result in substantial benefit to the patient.

Arch Pediatr Adolesc Med. 2007;161:282-290

MANY MEDICATIONS PRESCRIBED for children have not been formally studied in this population and most are not labeled for use in children.¹ This scarcity of pediatric data can lead to the withholding of potentially beneficial treatments or to administration of potentially harmful treatments. Despite evidence that recent legislation in the United States has resulted in improved pediatric drug labeling,² there is still little information about the extent of off-label drug use in hospitalized children, the types of drugs used most often off-label, and the characteristics of hospitalized patients receiving drugs off-label.

Current studies of off-label drug use in hospitalized children are limited by the few patients studied,³⁻¹¹ the focus on patients

receiving subspecialty care,^{4,5,7,10} and the inclusion of patients treated in both the hospital and ambulatory settings.^{4,5} All of these studies have been conducted outside of the United States.³⁻¹² Inasmuch as the requirement for hospitalization may differ depending on culture, health system, and national resources, findings of studies conducted in other countries may not be generalizable to the United States. This study was designed to describe the magnitude of off-label drug use, to identify drugs most commonly used off-label, and to identify factors associated with off-label drug use in children hospitalized in the United States. Because most drugs are not labeled for use in children,¹³ we chose to focus on those drugs that were either administered frequently or recommended for further study in children by the Food and Drug Administration (FDA).

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METHODS

DATA SOURCE

Data for this study were obtained from the Pediatric Health Information System (PHIS), an administrative database that contains inpatient data from 36 not-for-profit tertiary care pediatric hospitals in the United States. These hospitals are affiliated with the Child Health Corporation of America (Shawnee Mission, Kan), a business alliance of children's hospitals. Data quality and reliability are assured through a joint effort between the Child Health Corporation of America and participating hospitals. The data warehouse function for the PHIS database is managed by Solucent LLC (Evanston, Ill). For the purposes of external benchmarking, participating hospitals provide discharge data including demographic characteristics, diagnoses, and procedures. Thirty-one of these hospitals also submit resource utilization data (eg, pharmaceutical agents, radiologic imaging, and laboratory studies). Data are deidentified at the time of data submission and before data extraction and analysis and are subjected to a number of reliability and validity checks before being processed into data quality reports. Data are accepted into the database when classified errors occur less frequently than a criterion threshold of 2% of a hospital's quarterly data. If a hospital's quarterly data are unacceptable according to these limits, all of their quarterly data are rejected; however, these data can be resubmitted and reevaluated before inclusion in the database. During the study, 100% of drug use data from all 31 hospitals that submit resource utilization data was included in the data set.

ELIGIBILITY

Patients 18 years or younger at the time of hospital discharge from any of the 31 hospitals submitting resource utilization data to PHIS between January 1, 2004, and December 31, 2004, were eligible for inclusion. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

DEPENDENT VARIABLE

Drug use, the dependent variable, was categorized as either appropriate for age or off-label. The term "off-label drug use" indicated the use of a specific drug in a patient who at the time of hospital discharge was younger than the FDA-approved age range for any indication of that drug. Drug use was considered appropriate for age if the patient met the age criteria approved by the FDA regardless of indication. While we did not attempt to determine the specific indication for which a drug was prescribed, major diagnostic categories were used to classify off-label drug use according to each patient's principal diagnosis. The major diagnostic categories form a broad classification system of related diseases and disorders that divide principal diagnoses into mutually exclusive categories. The major diagnostic categories encompass each of the all-patient refined diagnosis-related groups codeveloped by the National Association of Children's Hospitals and Related Institutions (Alexandria, Va) and 3M Health Information Systems (Murray, Utah).¹⁴ Each major diagnostic category corresponds to a single organ system rather than to an etiologic diagnosis.

Drugs specifically examined for off-label use were either used commonly (defined here as being administered in more than 2.99% of all hospital patients discharged during the study period) or included on the FDA list of medications that were recommended for further study in pediatric patients.¹⁵⁻¹⁷ This list was mandated under the FDA Modernization Act and comprised recommendations from the American Academy of Pediatrics, the Pharmaceutical Research Manufacturers Association,

the National Institutes of Health, the Pediatric Pharmacology Research Units Network, the National Pharmaceutical Alliance, the Generic Pharmaceutical Industry Association, the National Association of Pharmaceutical Manufacturers, and the *United States Pharmacopeia*.¹⁸ This resulted in a list of 90 drugs included in this study.

INDEPENDENT VARIABLES

Variables for each institution included geographic location, average daily census, number of staffed beds, number of personnel, percentage of managed care penetration, and population served. Demographic variables for each patient discharged included age, sex, race (non-Hispanic white, non-Hispanic black, Hispanic, Asian, and other), and primary payer (private insurance, government insurance, or other). The category "Other insurance" included patients who were self-insured. Patient discharge disposition was also included, that is, discharged to home, died, or other (discharged to home with home health services, transferred to another facility, or left against medical advice). Resource use data included length of hospital stay (LOS) and case mix index (CMI), a widely used severity of illness and risk of mortality adjustment. The CMI of a patient population is an average of the patients' LOS weights. The LOS weight for each category in the *All-Patient Refined–Diagnosis-Related Group Classification System*, version 20, and severity level combination is computed as the ratio of the average LOS for patients in this group to the average LOS for all other patients.

DATA ANALYSIS

Categorical variables were summarized using frequencies and percentages for all patients included in the study, patients receiving any of the included drugs off-label, and subpopulations receiving any drug within the drug categories off-label. For continuous variables such as CMI and LOS, we summarized the data using mean (\pm SD) values. Comparisons of the demographic characteristics between the patients receiving a drug within a category off-label and those not receiving a drug within a category off-label were made using generalized estimating equations to control for hospital clustering. To understand factors associated with receiving any drug under consideration off-label, we also created multivariate generalized estimating equation models adjusting for hospital clustering and potential confounders. From these models, we provide odds ratios with associated binomial exact 95% confidence intervals to evaluate the precision of the effect. All statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC), and $P < .001$ was considered statistically significant because of large sample sizes.

RESULTS

At least 1 of 90 drugs was used off-label in 297 592 (78.7%) of 355 409 patients discharged during the study. The total charges for the 90 drugs in this study (**Table 1**) were \$666 544 241, which represents 5.7% of total inpatient charges. Off-label use accounted for \$270 275 849, or 40.5%, of the total dollars spent on these medications. This off-label expenditure represents 14.4% of all dollars spent on pharmaceutical agents and 2.3% of total inpatient charges. There was substantial variation in the frequency of off-label drug use, even within a drug category (Table 1). While some commonly used medications in a particular drug category were rarely used off-label (eg, acetaminophen), other

Table 1. Drug Classification, Frequency of Administration, and Frequency of Off-label Use in 355 409 Patients Discharged in 2004

| Medication | PHIS Patients Discharged Receiving Drug* | Patients Who Received Drug Off-Label |
|---|--|--------------------------------------|
| Central and autonomic nervous system drugs, % | | |
| Acetaminophen | 40.4 | 0 |
| Morphine | 27.8 | 96.7 |
| Fentanyl | 23.2 | 89.0 |
| Midazolam | 19.6 | 95.6 |
| Propofol | 16.3 | 29.5 |
| Narcotic-analgesic combinations | 15.8 | 93.3 |
| Ibuprofen | 15.2 | 8.2 |
| Ketorolac tromethamine | 10.2 | 46.4 |
| Neostigmine | 9.0 | 94.1 |
| Lorazepam† | 8.5 | 71.8 |
| Rocuronium bromide | 8.4 | 14.1 |
| Vecuronium bromide | 6.9 | 18.1 |
| Bupivacaine | 6.2 | 70.6 |
| Sevoflurane | 4.5 | 0 |
| Ketamine† | 2.6 | 0 |
| Meperidine | 1.6 | 0 |
| Isoflurane† | 1.6 | 0 |
| Methadone† | 1.1 | 95.6 |
| Baclofen† | 1.1 | 60.0 |
| Bupropion† | 0.3 | 90.0 |
| Lithium† | 0.2 | 29.4 |
| Anti-infective agents, % | | |
| Cefazolin | 16.4 | 7.8 |
| Ampicillin† | 11.4 | 0 |
| Gentamicin | 11.1 | 0 |
| Cefotaxime | 9.3 | 0 |
| Ceftriaxone | 9.3 | 0 |
| Vancomycin | 9.0 | 0 |
| Clindamycin | 8.1 | 0 |
| Nystatin | 6.7 | 98.2 |
| Bacitracin | 6.5 | 97.2 |
| Trimethoprim-sulfamethoxazole | 6.0 | 0 |
| Ceftazidime | 3.8 | 0 |
| Azithromycin† | 3.6 | 86.9 |
| Cefuroxime | 3.4 | 7.7 |
| Acyclovir† | 2.6 | 0 |
| Meropenem† | 1.6 | 28.0 |
| Rifampin† | 0.5 | 18.9 |
| Hydroxychloroquine† | 0.2 | 83.3 |
| Griseofulvin | 0.1 | 87.5 |
| Ethambutol† | 0.1 | 71.4 |
| Piperacillin-tazobactam† | 0 | 50.0 |
| Lindane† | 0 | 0 |
| Ivermectin† | 0 | ND |
| Cardiac adrenergic drugs, % | | |
| Lidocaine | 15.6 | 0 |
| Epinephrine | 7.9 | 82.6 |
| Atropine sulfate | 6.4 | 31.5 |
| Dopamine† | 4.2 | 98.8 |
| Nitroprusside† | 1.3 | 95.2 |
| Clonidine† | 1.2 | 60.5 |
| Dobutamine† | 1.2 | 0 |
| Diazoxide† | 0.1 | 0 |
| Flecainide† | 0 | 0 |

(continued)

Table 1. Drug Classification, Frequency of Administration, and Frequency of Off-label Use in 355 409 Patients Discharged in 2004 (cont)

| Medication | PHIS Patients Discharged Receiving Drug* | Patients Who Received Drug Off-Label |
|---|--|--------------------------------------|
| Fluids and nutrients, and gastrointestinal tract drugs, % | | |
| Ondansetron | 24.8 | 61.3 |
| Ranitidine | 17.7 | 11.4 |
| Potassium chloride | 16.0 | 99.3 |
| Glycopyrrolate | 10.2 | 94.0 |
| Metoclopramide† | 8.0 | 95.1 |
| Sodium bicarbonate | 7.5 | 0 |
| Fat emulsions | 5.9 | 97.8 |
| Polyethylene glycol-electrolyte solution | 5.7 | 92.3 |
| Docusate | 4.9 | 89.3 |
| Lansoprazole | 4.9 | 0 |
| Calcium gluconate | 4.4 | 0 |
| Magnesium sulfate | 4.1 | 0 |
| Calcium chloride | 3.4 | 96.1 |
| Phytonadione | 3.3 | 0 |
| Endocrine and metabolic agents, % | | |
| Dexamethasone | 10.9 | 0 |
| Prednisolone | 6.9 | 0 |
| Methylprednisolone | 6.7 | 95.5 |
| Prednisone | 5.0 | 0 |
| Fluticasone propionate | 4.7 | 39.8 |
| Budesonide | 4.0 | 7.8 |
| Hydrocortisone | 3.7 | 0 |
| Hematologic, biological, and immunologic drugs, % | | |
| Heparin† | 44.3 | 0 |
| Human albumin | 5.6 | 97.3 |
| Thrombin | 3.4 | 94.7 |
| Cyclosporine† | 0.7 | 94.2 |
| Antineoplastic and diagnostic drugs, % | | |
| Vincristine† | 1.8 | 0 |
| Dactinomycin† | 0.2 | 4.2 |
| Respiratory tract and eye, ear, nose, and throat drugs, % | | |
| Albuterol | 16.8 | 42.0 |
| Diphenhydramine | 14.9 | 94.6 |
| Ipratropium bromide | 6.5 | 85.6 |
| Promethazine† | 4.2 | 7.1 |
| Other drugs, % | | |
| Furosemide† | 9.4 | 0 |
| Povidine-iodine | 3.7 | 95.4 |
| Spironolactone† | 1.4 | 95.8 |
| Metolazone† | 0.5 | 95.7 |
| Bumetanide† | 0.3 | 91.2 |
| Hydrochlorothiazide† | 0.2 | 0 |
| Sevelamer† | 0.1 | 84.6 |

Abbreviations: FDA, Food and Drug Administration; ND, not determined; PHIS, Pediatric Health Information System.

*Drugs used in less than 2.99% of all patients discharged are included because of their inclusion on the FDA list of medications recommended for further study in pediatrics. Drugs administered less frequently than in 0.05% of patients discharged are listed as being administered in 0% of patients discharged.

†Included on the FDA list of drugs for which pediatric studies are needed.

commonly used medications in that category were almost always used off-label. For example, morphine was used in 27.8% of patients discharged; its use was considered off-

Table 2. Demographic Characteristics of Patients in the PHIS Database*

| Characteristic | PHIS No. | Drug Classification | | | | | | | | | |
|------------------------|----------|-------------------------|---------------------------------------|----------------|------------------------|-----------------------------------|-------------------------|--|-------------------------------|--|-------------|
| | | All Categories Combined | Central and Autonomic Nervous Systems | Anti-Infective | Cardiac and Adrenergic | Fluids and Nutrients and GI Tract | Endocrine and Metabolic | Hematologic, Biological, and Immunologic | Antineoplastic and Diagnostic | Respiratory Tract and Eye, Ear, Nose, and Throat | Other |
| Age, % | | | | | | | | | | | |
| ≤28 d | 37 763 | 65.5 | 46.6 | 24.6 | 23.3 | 47.1 | 5.1 | 13.0 | 0 | 8.8 | 8.8 |
| 29 d to 1 y | 99 614 | 83.0 | 59.3 | 18.1 | 19.6 | 43.2 | 13.9 | 8.0 | 0.2 | 30.4 | 6.1 |
| 2-5 y | 66 829 | 84.9 | 63.4 | 16.2 | 12.7 | 51.7 | 18.4 | 6.8 | 0.5 | 36.8 | 4.4 |
| 6-12 y | 78 954 | 85.8 | 68.2 | 15.7 | 10.7 | 59.9 | 14.1 | 6.9 | 0.3 | 36.4 | 4.5 |
| 13-17 y | 60 934 | 82.0 | 67.7 | 13.6 | 9.7 | 62.6 | 11.2 | 8.1 | 0.2 | 37.8 | 4.5 |
| Race/ethnicity, % | | | | | | | | | | | |
| Non-Hispanic white | 172 118 | 78.1 | 68.6 | 32.9 | 14.9 | 57.2 | 12.3 | 9.2 | 0.3 | 31.3 | 5.8 |
| Non-Hispanic black | 76 051 | 79.3 | 62.5 | 27.9 | 15.1 | 48.0 | 17.5 | 6.4 | 0.2 | 40.8 | 4.0 |
| Hispanic | 56 698 | 79.5 | 65.1 | 32.6 | 13.3 | 52.9 | 13.6 | 7.9 | 0.2 | 28.2 | 6.7 |
| Asian | 6207 | 78.5 | 65.6 | 34.4 | 14.2 | 52.4 | 12.9 | 10.1 | 0.3 | 30.9 | 7.4 |
| Other | 24 372 | 77.8 | 65.4 | 34.6 | 16.7 | 51.7 | 12.0 | 9.5 | 0.2 | 30.0 | 6.1 |
| Sex, % | | | | | | | | | | | |
| Male | 194 917 | 79.4 | 66.3 | 32.0 | 15.7 | 53.0 | 14.2 | 8.3 | 0.2 | 33.0 | 5.6 |
| Female | 160 484 | 77.8 | 66.8 | 31.7 | 13.7 | 54.0 | 12.7 | 8.1 | 0.3 | 32.1 | 5.3 |
| Payer, % | | | | | | | | | | | |
| Government | 151 459 | 80.0 | 65.6 | 31.8 | 14.7 | 51.8 | 14.7 | 8.3 | 0.1 | 34.1 | 6.2 |
| Private | 122 020 | 76.4 | 65.8 | 31.5 | 14.0 | 54.2 | 11.9 | 8.3 | 0.3 | 29.9 | 5.1 |
| Other | 81 692 | 79.5 | 69.2 | 32.6 | 16.0 | 55.2 | 13.7 | 8.0 | 0.4 | 33.9 | 4.7 |
| Disposition, % | | | | | | | | | | | |
| Discharged to home | 336 090 | 78.5 | 66.0 | 31.4 | 13.6 | 52.3 | 13.2 | 7.3 | 0.3 | 32.4 | 5.1 |
| Died | 3824 | 93.5 | 89.5 | 48.1 | 80.9 | 84.6 | 26.0 | 54.9 | 0.1 | 39.7 | 24.3 |
| Other† | 15 283 | 78.5 | 71.1 | 38.3 | 24.1 | 70.3 | 17.0 | 16.8 | 0.2 | 33.8 | 8.4 |
| Census region, % | | | | | | | | | | | |
| North central | 102 772 | 78.6 | 68.8 | 28.7 | 12.9 | 49.4 | 12.6 | 7.5 | 0.2 | 33.1 | 4.8 |
| Northeast | 43 079 | 69.8 | 52.1 | 32.1 | 22.3 | 52.8 | 14.8 | 7.7 | 0.3 | 30.2 | 2.1 |
| South | 143 963 | 80.3 | 67.8 | 30.6 | 14.4 | 55.1 | 14.6 | 8.7 | 0.3 | 33.3 | 5.5 |
| West | 65 595 | 80.9 | 69.3 | 39.4 | 13.6 | 56.4 | 11.7 | 8.8 | 0.2 | 31.7 | 8.6 |
| Diagnostic category, % | | | | | | | | | | | |
| Medical | 264 216 | 73.1 | 55.6 | 19.3 | 9.6 | 42.7 | 14.1 | 2.9 | 0.3 | 33.1 | 2.9 |
| Procedural | 91 193 | 94.9 | 98.1 | 68.3 | 29.7 | 84.4 | 11.8 | 23.8 | 0.2 | 31.1 | 13.0 |

Abbreviations: GI, gastrointestinal; PHIS, Pediatric Health Information System.

*The percentage of patients in a given demographic class (rows) who received at least 1 of the drugs in the category (columns) off-label are given. Bolded values highlight significant differences ($P < .001$) among the percentage of patients receiving a drug in a particular category off-label within a demographic category.

†Refers to children who were transferred to another facility or whose families removed them from the hospital against medical advice.

label in 96.7% of these patients (Table 1) because there is no FDA indication for its administration in the pediatric population. The use of more recently approved medications such as azithromycin was also considered off-label in most instances.

Demographic characteristics of patients receiving drugs off-label are given in **Table 2**. For purposes of comparison, specific drugs were classified by therapeutic category. Male patients represented 54.8% of the population. The racial distribution included 51.3% non-Hispanic white patients, 21.4% non-Hispanic black patients, and 16.0% Hispanic patients. For patients of all ages and in all drug categories except antineoplastic drugs, there was a significant difference between the percentage of patients discharged who received off-label drugs and those who did not. Racial differences in the receipt of drugs off-label were noted in the endocrine and respiratory tract drug categories. Male patients were more likely than female patients to receive a drug off-label in the cardiac, endocrine, and respiratory tract categories.

The overall mortality rate in patients discharged in 2004 was 1.07%. Most patients, regardless of whether they died or survived to hospital discharge, received at least 1 drug off-label (Table 2).

Substantial variation in the frequency of off-label use was observed across diagnostic categories and drug classes (**Table 3**). In every medical diagnostic category, at least 1 drug was used off-label in more than 50% of patients; off-label drug use occurred disproportionately in patients receiving central and autonomic nervous system agents. In all procedural or surgical categories, at least 1 drug was used off-label in more than 90% of patients; in each procedural category, off-label drug use occurred disproportionately with drugs in the central and autonomic nervous systems and in the fluids or nutrients, or gastrointestinal tract drug categories. There was a higher degree of illness among patients receiving a drug off-label (CMI, 1.83 ± 2.88) compared with those not receiving a drug off-label (CMI, 0.98 ± 0.97 ; $P < .001$). The mean CMI was significantly higher for patients who received

Table 3. Percentage of Patients in Each Major Diagnostic Category of the PHIS Database Who Received at Least 1 Drug in a Particular Category Off-label*

| Diagnostic Category | PHIS No. | Drug Classification | | | | | | | | | |
|--|----------|-------------------------|---------------------------------------|----------------|------------------------|-----------------------------------|-------------------------|--|-------------------------------|--|-------|
| | | All Categories Combined | Central and Autonomic Nervous Systems | Anti-Infective | Cardiac and Adrenergic | Fluids and Nutrients and GI Tract | Endocrine and Metabolic | Hematologic, Biological, and Immunologic | Antineoplastic and Diagnostic | Respiratory Tract and Eye, Ear, Nose, and Throat | Other |
| Medical,% | | | | | | | | | | | |
| Alcohol or drug use | 255 | 54.1 | 54.1 | 8.6 | 9.4 | 24.7 | 2.4 | 0.8 | 0 | 20.0 | 0.4 |
| Burns | 1469 | 95.3 | 95.3 | 38.5 | 7.4 | 46.2 | 1.3 | 7.1 | 0 | 35.9 | 1.6 |
| Site of disease or disorder | | | | | | | | | | | |
| Blood or blood-forming organs and immunologic system | 14 103 | 80.9 | 79.7 | 25.5 | 3.7 | 53.5 | 9.0 | 3.8 | 0 | 51.1 | 1.6 |
| Circulatory system | 7781 | 69.4 | 62.4 | 25.8 | 14.7 | 53.4 | 12.3 | 9.3 | 0.1 | 28.1 | 10.4 |
| Digestive system | 27 543 | 71.5 | 52.2 | 10.4 | 3.8 | 59.4 | 10.2 | 1.8 | 0 | 17.7 | 2.0 |
| Ear, nose, mouth, and throat, and craniofacial | 10 144 | 74.2 | 58.5 | 16.1 | 16.4 | 29.8 | 11.6 | 1.2 | 0.2 | 23.8 | 1.6 |
| Endocrine, nutritional, and metabolic systems | 14 345 | 65.8 | 38.9 | 12.6 | 3.7 | 53.0 | 5.0 | 2.0 | 0 | 14.2 | 1.9 |
| Eye | 1504 | 67.0 | 58.2 | 20.5 | 9.0 | 24.9 | 12.5 | 0.6 | 0.1 | 16.3 | 2.5 |
| Female reproductive system | 858 | 77.4 | 77.4 | 17.7 | 3.0 | 42.5 | 3.8 | 1.3 | 0.1 | 23.8 | 2.6 |
| Hepatobiliary system and pancreas | 3115 | 71.5 | 65.3 | 18.8 | 5.9 | 58.3 | 11.5 | 8.0 | 0 | 28.4 | 6.2 |
| Kidney and urinary tract | 9774 | 74.0 | 66.3 | 17.8 | 4.8 | 37.4 | 8.1 | 8.5 | 0.2 | 15.3 | 6.6 |
| Male reproductive system | 284 | 75.7 | 75.7 | 35.6 | 3.9 | 29.9 | 3.5 | 2.1 | 1.1 | 28.2 | 2.8 |
| Mental | 9865 | 61.0 | 49.0 | 4.8 | 7.4 | 12.1 | 2.8 | 0.4 | 0 | 38.3 | 0.4 |
| Musculoskeletal system and connective tissue | 8683 | 81.3 | 80.1 | 22.8 | 8.1 | 43.5 | 13.0 | 2.7 | 0.2 | 26.1 | 3.0 |
| Nervous system | 27 464 | 65.3 | 63.0 | 9.0 | 6.2 | 35.5 | 6.2 | 1.5 | 0 | 14.9 | 1.9 |
| Respiratory system | 58 774 | 84.5 | 47.1 | 30.4 | 17.3 | 34.0 | 38.7 | 2.0 | 0 | 68.2 | 2.5 |
| Skin and subcutaneous tissue, and breast | 11 288 | 71.7 | 70.0 | 28.9 | 4.1 | 24.4 | 5.1 | 1.1 | 0 | 20.9 | 2.7 |
| HIV infection | 271 | 74.9 | 74.9 | 53.9 | 11.4 | 53.1 | 26.6 | 9.2 | 0 | 52.4 | 4.8 |
| Infectious and parasitic diseases, systemic or unspecified sites | 13 795 | 71.6 | 60.8 | 22.5 | 6.7 | 33.0 | 6.1 | 5.0 | 0 | 20.2 | 3.7 |
| Malignancies, and chemotherapy and radiotherapy | 14 084 | 93.4 | 64.6 | 21.2 | 7.5 | 93.4 | 4.8 | 2.9 | 4.5 | 52.0 | 2.9 |
| Multiple significant trauma | 592 | 94.6 | 89.5 | 38.2 | 20.1 | 67.6 | 4.4 | 6.3 | 0 | 27.0 | 2.2 |
| Neonatal conditions originating in the perinatal period | 20 368 | 54.1 | 33.2 | 10.4 | 14.3 | 41.5 | 1.6 | 4.2 | 0 | 4.3 | 4.4 |
| Poisonings, and toxic effects and other complications of treatment | 4622 | 52.7 | 40.8 | 9.2 | 10.7 | 37.6 | 7.5 | 2.7 | 0 | 18.3 | 1.2 |
| Pregnancy, childbirth, and the puerperium | 30 | 80.0 | 80.0 | 13.3 | 3.3 | 56.7 | 3.3 | 3.3 | 0 | 30.0 | 6.7 |
| Rehabilitation or aftercare | 2776 | 53.5 | 45.4 | 17.4 | 5.3 | 37.7 | 5.8 | 3.4 | 0.1 | 15.5 | 3.4 |
| Ungroupable | 429 | 65.5 | 51.3 | 28.4 | 18.4 | 45.9 | 11.0 | 6.8 | 0.5 | 25.2 | 2.1 |

(continued)

an off-label drug compared with those who did not receive an off-label drug in every category except the antineoplastic or diagnostic drug category; the mean CMI in the diagnostic drug category was 1.40 for patients receiving drugs off-label compared with 1.67 ($P=.34$) for those not receiving drugs off-label. For patients receiving a drug off-label, the mean CMI ranged from 1.40 (antineoplastic drugs) to 4.73 (hematologic, biological, or immunologic agents). For patients who did not receive a drug off-label, the mean CMI ranged from 1.06 (fluids and nutrients, or gastrointestinal tract drugs) to 1.67 (antineoplastic drugs). The mean LOS was also longer for patients receiving a drug off-label compared with those not receiving a drug off-label (6.68 vs 2.79 days; $P<.001$). This difference was significant in every drug category except antineoplastic or diagnostic agents, with mean LOS of 5.60 days for those receiving antineoplastic drugs off-label compared with 5.95 days ($P=.87$) for those not receiving the drugs off-label. The longest LOS was for pa-

tients receiving other category drugs (19.58 days); hematologic, biological, or immunologic drugs (18.91 days); cardiac or adrenergic drugs (17.64 days); and anti-infective drugs (13.89 days) off-label.

Table 4 gives the unadjusted and adjusted results of a logistic regression model evaluating the odds of off-label drug use based on patient and hospital factors while adjusting for hospital clustering. Patient age greater than 28 days, severity of illness (as measured by the CMI), undergoing a surgical procedure, and all-cause in-hospital mortality were associated with off-label drug use. Differences in race, sex, payer, and hospital region were not associated with overall off-label drug use.

COMMENT

Our study of clinical prescribing practice in major children's hospitals in the United States demonstrates that

Table 3. Percentage of Patients in Each Major Diagnostic Category of the PHIS Database Who Received at Least 1 Drug in a Particular Category Off-label* (cont)

| Diagnostic Category | PHIS No. | Drug Classification | | | | | | | | | |
|---|----------|-------------------------|---------------------------------------|----------------|------------------------|-----------------------------------|-------------------------|--|-------------------------------|--|-------|
| | | All Categories Combined | Central and Autonomic Nervous Systems | Anti-Infective | Cardiac and Adrenergic | Fluids and Nutrients and GI Tract | Endocrine and Metabolic | Hematologic, Biological, and Immunologic | Antineoplastic and Diagnostic | Respiratory Tract and Eye, Ear, Nose, and Throat | Other |
| Procedural, % | | | | | | | | | | | |
| Alcohol or drug use | 3 | 100.0 | 100.0 | 66.7 | 3.3 | 66.7 | 33.3 | 33.3 | 0 | 100.0 | 33.3 |
| Burns | 359 | 100.0 | 100.0 | 73.0 | 68.5 | 89.4 | 1.1 | 63.5 | 0 | 72.1 | 17.5 |
| Site of disease or disorder | | | | | | | | | | | |
| Blood or blood-forming organs and immunologic system | 964 | 98.1 | 98.1 | 69.5 | 24.8 | 83.7 | 20.1 | 22.5 | 0 | 44.4 | 13.5 |
| Circulatory system | 9722 | 97.0 | 97.0 | 84.3 | 69.4 | 88.7 | 37.6 | 64.9 | 0 | 30.9 | 30.2 |
| Digestive system | 17 240 | 98.0 | 98.0 | 36.6 | 18.2 | 79.6 | 5.5 | 6.1 | 0 | 23.3 | 12.0 |
| Ear, nose, mouth, and throat, and craniofacial | 10 614 | 98.0 | 98.0 | 57.2 | 24.2 | 77.2 | 9.0 | 12.8 | 0 | 23.4 | 3.5 |
| Endocrine, nutritional, and metabolic systems | 1166 | 97.8 | 97.8 | 67.2 | 27.4 | 89.3 | 9.6 | 23.3 | 0 | 39.4 | 11.7 |
| Eye | 845 | 92.9 | 90.2 | 56.9 | 41.8 | 74.8 | 11.1 | 5.1 | 0.1 | 21.8 | 12.4 |
| Female reproductive system | 962 | 98.0 | 98.0 | 50.8 | 7.0 | 74.0 | 0.8 | 3.1 | 0 | 27.1 | 8.0 |
| Hepatobiliary system and pancreas | 1545 | 99.1 | 99.1 | 55.8 | 24.3 | 90.4 | 16.6 | 23.9 | 0.1 | 44.9 | 14.4 |
| Kidney and urinary tract | 5384 | 98.6 | 98.6 | 73.1 | 19.3 | 83.3 | 7.4 | 10.5 | 2.3 | 34.4 | 11.6 |
| Male reproductive system | 579 | 95.5 | 95.5 | 68.6 | 14.2 | 73.2 | 3.3 | 2.8 | 0.7 | 25.2 | 14.3 |
| Mental | 163 | 97.5 | 96.9 | 71.2 | 52.8 | 82.8 | 6.1 | 37.4 | 0 | 41.1 | 12.9 |
| Musculoskeletal system and connective tissue | 15 751 | 99.3 | 99.3 | 86.6 | 18.5 | 85.4 | 3.5 | 15.9 | 0.1 | 34.1 | 8.7 |
| Nervous system | 11 967 | 98.5 | 98.5 | 85.7 | 21.1 | 88.6 | 6.6 | 30.6 | 0 | 29.9 | 7.3 |
| Respiratory system | 3741 | 98.5 | 98.5 | 71.8 | 34.0 | 89.2 | 24.2 | 15.8 | 0 | 60.1 | 15.7 |
| Skin and subcutaneous tissue, and breast | 1358 | 97.3 | 97.3 | 65.6 | 15.8 | 71.1 | 3.3 | 9.1 | 0 | 26.1 | 8.3 |
| Infectious and parasitic diseases, systemic or unspecified sites | 651 | 95.5 | 95.5 | 68.7 | 35.6 | 87.3 | 12.6 | 31.2 | 0 | 49.8 | 18.6 |
| Malignancies, and chemotherapy and radiotherapy | 1027 | 98.3 | 98.3 | 68.8 | 31.5 | 95.1 | 33.1 | 43.9 | 0.6 | 75.2 | 20.1 |
| Multiple significant trauma | 504 | 99.0 | 98.8 | 84.7 | 44.6 | 95.8 | 7.1 | 33.5 | 0 | 50.0 | 9.9 |
| Neonatal conditions originating in the perinatal period | 5448 | 100.0 | 97.6 | 72.2 | 71.2 | 94.1 | 23.0 | 60.0 | 0 | 23.1 | 28.5 |
| Poisoning, and toxic effects and other complications of treatment | 814 | 94.8 | 94.8 | 54.2 | 20.1 | 78.5 | 8.4 | 12.5 | 0 | 28.3 | 7.2 |
| Pregnancy, childbirth, and the puerperium | 8 | 100.0 | 100.0 | 25.0 | 50.0 | 87.5 | 0 | 37.5 | 0 | 12.5 | 25.0 |
| Rehabilitation or aftercare | 378 | 96.0 | 95.0 | 57.9 | 29.1 | 83.3 | 12.7 | 17.2 | 0 | 34.7 | 16.9 |

Abbreviations: GI, gastrointestinal; HIV, human immunodeficiency virus; PHIS, Pediatric Health Information System.

*Bolded values represent percentages higher than 75%.

most hospitalized children receive medications outside of the FDA product license. Substantial variation in the frequency of off-label drug use was observed across diagnostic categories and drug classes. Several factors, including age older than 28 days, greater severity of illness, undergoing a surgical procedure, and all-cause in-hospital mortality, were independently associated with off-label drug use. The licensing system is the main tool regulators have to protect public health by ensuring that only medications meeting strict criteria of quality, safety, and efficacy reach the market. However, despite several regulatory changes in the licensing process, we still have incomplete knowledge about the safety and efficacy of many medications commonly used to treat children across a range of drug classes and clinical diagnoses.

Our multicenter study of children hospitalized in the United States revealed a high frequency of off-label drug use during a sustained period. During 1 year, off-label use of 90 drugs at the 31 children's hospitals included in this study accounted for more than \$250 million. We

also identified specific drugs that were commonly used off-label that did not appear on the FDA list of medications requiring further study in children. Since we cannot know beforehand whether a drug administered in a particular situation will benefit or harm a patient, we believe that the frequency of administration should be considered when deciding which drugs warrant further study in children. Inasmuch as most drugs are not labeled for use in children, our results will assist in further prioritizing certain drugs for additional pediatric studies of safety and efficacy. To our knowledge, no previous studies of off-label drug use in hospitalized children have been performed in the United States. However, several smaller studies conducted in other countries have also reported a high frequency of off-label drug use in hospitalized children.³⁻¹² In patients followed up by subspecialty services, including pediatric oncologists,⁴ gastroenterologists,⁵ cardiologists,¹⁰ and pain management teams,⁹ off-label or unlicensed drug use ranged from 33% to 76%. Other single-center studies have included patients in gen-

Table 4. Characteristics Associated With Off-label Drug Use

| Characteristic | Unadjusted OR (95% CI) | P Value* | Adjusted OR (95% CI) | P Value* |
|---------------------|------------------------|----------|----------------------|----------|
| Age | | | | |
| ≤28 d | 1 [Reference] | <.001 | 1 [Reference] | <.001 |
| 29 d to 1 y | 2.47 (1.74-3.41) | | 4.62 (3.32-6.42) | |
| 2-5 y | 2.87 (2.04-4.04) | | 5.38 (3.82-7.58) | |
| 6-12 y | 3.10 (2.16-4.45) | | 5.11 (3.53-7.40) | |
| 13-17 y | 2.39 (1.64-3.47) | | 3.81 (2.57-5.64) | |
| Race/ethnicity | | | | |
| Non-Hispanic white | 1 [Reference] | .66 | 1 [Reference] | .27 |
| Non-Hispanic black | 0.95 (0.85-1.04) | | 1.07 (0.97-1.19) | |
| Hispanic | 0.97 (0.80-1.16) | | 0.93 (0.80-1.07) | |
| Asian | 0.93 (0.77-1.12) | | 0.93 (0.84-1.02) | |
| Other | 0.87 (0.68-1.12) | | 0.88 (0.75-1.03) | |
| Sex | | | | |
| Male | 1 [Reference] | <.001 | 1 [Reference] | <.001 |
| Female | 0.93 (0.90-0.96) | | 0.96 (0.93-0.99) | |
| Payer | | | | |
| Government | 1 [Reference] | .02 | 1 [Reference] | .01 |
| Private | 0.85 (0.75-0.95) | | 0.86 (0.78-0.95) | |
| Other | 1.10 (0.90-1.36) | | 1.08 (0.94-1.25) | |
| Disposition | | | | |
| Discharged to home | 1 [Reference] | <.001 | 1 [Reference] | <.001 |
| Died | 8.45 (4.89-14.57) | | 3.45 (2.47-4.82) | |
| Other | 1.22 (0.99-1.51) | | 1.04 (0.85-1.26) | |
| Census region | | | | |
| North central | 1 [Reference] | .31 | 1 [Reference] | .37 |
| Northeast | 0.60 (0.44-0.81) | | 0.55 (0.38-0.78) | |
| South | 1.02 (0.76-1.04) | | 1.02 (0.77-1.34) | |
| West | 1.12 (0.86-1.15) | | 1.06 (0.85-1.32) | |
| Diagnostic category | | | | |
| Medical | 1 [Reference] | <.001 | 1 [Reference] | <.001 |
| Procedural | 27.75 (11.73-65.62) | | 21.76 (9.39-50.40) | |
| Case mix index | 1.53 (1.33-1.76) | <.001 | 1.62 (1.43-1.84) | <.001 |

Abbreviations: CI, confidence interval; OR, odds ratio.

* $P < .001$ was considered statistically significant.

eral pediatric wards along with patients in either intensive care units^{6,7,11} or surgical wards¹⁹; in these studies, the off-label drug use ranged from 36% to 92%. Few multicenter studies of off-label drug use have been published. A multicenter study of children admitted to the general pediatrics wards of 9 hospitals in Italy found that 1182 (89%) of 1461 hospitalized children received at least 1 drug off-label.¹² In a multicenter study of general pediatric wards in the United Kingdom, Sweden, Germany, Italy, and the Netherlands, 421 (67%) of 624 children received a drug off-label during a 4-week period; off-label or unlicensed use occurred in 46% of all drug prescriptions.³ Direct comparison of off-label drug use in children hospitalized in other countries may be confounded by differences in hospitalization practices among those countries.

In our study, the lowest off-label drug use occurred with antineoplastic agents. However, there were no significant differences in the variables evaluated in this study between patients who did and those who did not receive an antineoplastic agent off-label. The routine enrollment of children receiving antineoplastic agents in clinical trials may more consistently result in pediatric age-inclusive FDA approval of commonly used antineoplastic agents. Furthermore, the frequent participation

of children receiving antineoplastic agents in clinical trials may minimize the differences between children receiving these agents off-label and those receiving these agents in accord with the FDA product label. Conroy et al⁴ examined inpatient and outpatient prescriptions in pediatric patients with cancer during a 4-week period; unlicensed or off-label use occurred in 45% of prescriptions. The different definitions of off-label drug use in our study compared with the study by Conroy and colleagues may explain the discrepant study results. In our study, drug use was considered off-label only if the patient was younger than the FDA-approved age range for any indication of that drug at the time of discharge. Many cases of off-label use identified by Conroy and colleagues were due to modifying cytotoxic preparations such as methotrexate and etoposide for oral administration. Such modifications were not identified as off-label use in our study.

Factors associated with off-label drug use are not well characterized. One previous study identified age younger than 6 months as a risk factor for off-label drug use at univariate analysis.⁶ However, the generalizability of that study is limited because patients in intensive care units accounted for more than 50% of the patient population.⁶ Turner et al⁸ did not find a significant difference in the frequency of off-label drug use in patients hospi-

talized in medical wards compared with those hospitalized in surgical wards; that study was limited to the experience of a single center during 13 weeks. In our multicenter study conducted during 1 year, off-label drug use was associated with patient age greater than 28 days, all-cause in-hospital mortality, procedural interventions, and greater severity of illness. Neonates were less likely to receive drugs off-label than were older children. In the case of neonates, we believe that a more conservative clinical approach is taken, in part because of the scarcity of reliable drug dosing information in this population, particularly in the context of clinically unstable children in the first few weeks of life and the known exaggerated differences in the metabolism of many other medications in neonates compared with older children. While we cannot determine causality in the association of greater severity of illness and off-label drug use, we suspect that in many cases drugs are prescribed off-label in children who are already critically ill because either they have failed approved therapy or there are few situation-specific FDA-approved options.

This study has several limitations. We defined off-label drug use based solely on age criteria. Use of these medications for reasons other than those stated on the product label also constitutes off-label use. Since the indications for prescribing a particular drug were not available and only 90 drugs were evaluated, the results of our study likely underestimate the magnitude of off-label drug use in children. Approximately 20% of tertiary care general children's hospitals participate in PHIS. Given the geographic heterogeneity of the participating hospitals and the racial and ethnic diversity of their patient populations, we believe these data can be generalized to other tertiary care children's hospitals. It is also possible that off-label drug use occurs more commonly in tertiary care hospitals than in community hospitals. Since this study included only tertiary care children's hospitals, the results may not accurately reflect practice in other settings. However, one study suggested that off-label drug use is greater in community settings than in academic settings.⁶ Therefore, it is unlikely that our data overstate the magnitude of off-label drug use in children.

Despite the frequent use of drugs off-label, using an administrative database, we cannot determine which of these treatments are unsafe or ineffective and which result in substantial benefit to the patient. Though off-label drug use also occurs in adults, the problem is substantially greater in children because many drugs have not been tested in any pediatric population for any indication. The use of medications inadequately studied in children has contributed to adverse outcomes,¹⁹⁻²¹ underscoring the importance of comprehensive evaluation of these medications in children. Continued off-label use of drugs is not an acceptable alternative to documenting the safety and effectiveness of drugs used to treat infants and children. By describing the volume of off-label drug use, the number of children affected by the use of particular drugs off-label, and the costs associated with off-label use, we have provided insight into the magnitude of the problem. With greater cooperation between industry, academia, and government, the necessary stud-

ies could be carried out to ensure that the pediatric patient does not remain a "therapeutic orphan."²²

Accepted for Publication: October 13, 2006.

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Author Contributions: Dr Hall had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Shah, Hall, Goodman, Feuer, Sharma, Fargason, Hyman, Jenkins, White, Levy, Levin, Bertoch, and Slonim. *Acquisition of data:* Hall and Bertoch. *Analysis and interpretation of data:* Shah, Hall, Goodman, Feuer, Hyman, Jenkins, White, Levy, Levin, and Slonim. *Drafting of the manuscript:* Shah, Hall, Feuer, Jenkins, White, Levy, Bertoch, and Slonim. *Critical revision of the manuscript for important intellectual content:* Shah, Hall, Goodman, Feuer, Sharma, Fargason, Hyman, White, Levy, Levin, Slonim. *Statistical analysis:* Shah, Hall, Goodman, Levin, and Slonim. *Administrative, technical, and material support:* Fargason, Bertoch, and Slonim. *Study supervision:* Shah, Sharma, Bertoch and Slonim.

Financial Disclosure: None reported.

Funding/Support: This study was supported in part by KO-8 HS14009-01 from the National Institutes of Health (Dr Slonim).

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Announcement

Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), *Archives of Pediatrics and Adolescent Medicine* will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as <http://ClinicalTrials.gov>). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorials by DeAngelis et al in the September 8, 2004 (2004;292:1363-1364) and June 15, 2005 (2005;293:2927-2929) issues of JAMA. Also see the Instructions to Authors on our Web site: www.archpediatrics.com.

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Correction

Error in Table 2. In the article titled "Off-label Drug Use in Hospitalized Children" by Shah et al, published in the March issue of the *Archives* (2007;161[3]:282-290), the value given in Table 2 (page 285) in the "Characteristic" column, "Age, %" subheading, "29 d to 1 y" row in the "PHIS No." column, should have been 99 614. Online versions of this article on the *Archives of Pediatrics & Adolescent Medicine* Web site were corrected on May 8, 2007.