RESEARCH ARTICLE

# Off-label Medication Prescribing Patterns in Pediatrics: An Update

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ABSTRACT

**OBJECTIVES:** To describe the frequency of off-label drug use in 2014 as defined by the Food and Drug Administration (FDA)–approved age ranges in patients ≤18 years of age, to determine the rate of off-label drug use in 2014 by drug classification, and to compare current off-label medication usage rates with historical rates.

**METHODS:** This is a retrospective cohort study of an administrative database containing inpatient resource use data from January 1, 2014, to December 31, 2014. Patients ≤18 years of age receiving 1 of 76 selected commonly prescribed medications are included. Off-label drug use is defined as use in a patient younger than the lower limit of the FDA-approved age range for any indication or dosage form of that drug.

**RESULTS:** At least 1 drug was prescribed off label in 779 270 of 2 773 770 (28.1%) patient visits during the study period. Younger age, longer hospital stays, and mortality were associated with higher rates of off-label medication prescription. Off-label usage of certain medications differed between care settings. Rates of off-label medication use were higher in observational (45.5%), inpatient (53.9%), and ambulatory (54.2%) settings.

**CONCLUSIONS:** Although off-label drug use at major US pediatric hospitals is declining, 1 out of every 4 medications is not in accordance with FDA label indications for patient age. There exists substantial variation in off-label drug use among drug categories and encounter types. Although many commonly prescribed medications are FDA-approved for use in subpopulations of pediatric patients, studies of their safety, efficacy, pharmacokinetics, and optimal dosing are ongoing.

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The US Food and Drug Administration (FDA) requires that medications be tested for safety and efficacy at a specific dosage (and for a specific time period) before approval for clinical use in a particular population.[1] Use of medications outside of these parameters is considered "off-label" drug use. Children present challenges in clinical trials owing to scientific, clinical, ethical, and logistic concerns, which have previously limited and even discouraged the testing of medications in children.[1] Consequently, the majority of medications used in the care of children has historically been used off label without an adequate understanding of appropriate dosage, safety, or efficacy.[1]

Numerous legislative measures have been enacted to address the barriers in pediatric drug testing.[1,2] In 2002, the Best Pharmaceuticals for Children Act (BPCA) directed the implementation of methods for pediatric drug development, including identifying and prioritizing drugs needing pediatric study.[1] The BPCA priority list, first generated in 2004, is annually updated and identifies medications that are deemed critical to the treatment of children and adolescents and to the needs for pediatric therapeutics.[1] Passed in 2003, the Pediatric Research Equity Act (PREA) allowed the FDA to require pediatric studies of any product that was likely to be used in a substantial number of pediatric patients or that had meaningful benefits for children over existing treatments.[2] In 2012, the US Congress passed the FDA Safety and Innovation Act, aiming to ensure that pediatric evaluations are conducted earlier in the drug development process.[3] This act created accountability for the completion of pediatric studies under the BPCA and PREA. After the enactment of the BPCA and PREA, >500 pediatric-specific drug-labeling changes have been made.[3]

In 2007, Shah et al[4] published a retrospective cohort study in which they analyzed inpatient off-label drug use from January 1, 2004, to December 31, 2004, at 31 tertiary care pediatric hospitals in the United States. Results revealed that at least 1 drug was used off label in 78.7% of patients and that 40% of the total dollars spent on these medications was for off-label use.[4] Authors of recent studies have analyzed the off-label use of certain medication classes in subspecialty populations of children with similar findings.[5–7]

To our knowledge, no recent studies have been published to describe the frequency of off-label drug use in pediatric patients across the inpatient, observational, ambulatory, and emergency department settings. Our aim was to analyze current rates of off-label medication use in children in light of ongoing efforts to incentivize and promote projects that improve pediatric drug labeling.

## METHODS

### Data Source

In this retrospective cohort study, we used the Pediatric Health Information System (PHIS) data set from 2014 (accessed in November 2016). PHIS is a comparative pediatric database and includes clinical and resource use data for inpatient, ambulatory surgery, emergency department, and observation unit patient encounters for >45 children's hospitals in the United States. Blinded patient data are collected from >6 million patient encounters and include information about diagnoses, procedures, demographics, length of stay, and discharge dispositions of patients. Data are de-identified at the time of submission and before data extraction and analysis. Additionally, resource use data are subjected to a number of reliability and validity checks before data quality reports are generated.

### Aims and Hypothesis

We aimed to describe the frequency of off-label drug use in 2014 as defined by FDA-approved age ranges in patients ≤18 years of age and to determine the rate of off-label drug use in 2014 by drug classification and encounter type using PHIS. Additionally, we compared rates of off-label drug use in pediatric patients in 2014 with previous rates. We hypothesized that although the specific drugs used off label have changed over time, the frequency of off-label drug use has not changed.

### Eligibility

All patients ≤18 years of age at the time of presentation to any of the >45 hospitals submitting data to PHIS from January 1, 2014, to December 31, 2014 were eligible for inclusion. Those patients, prescribed 1 of 76 preselected medications on the basis of frequency, composed the study population (see below and Table 1). This study was

**TABLE 1** Percentage of Off-label Usage for 2014 BPCA Priority List Medications, Stratified by Encounter Type

| 2014 BPCA Priority List Medications | Off-label Usage, % | | | | | |
|---|---|---|---|---|---|---|
| | Total | Clinical | Emergency | Ambulatory | Observational | Inpatient |
| Albuterol | 29.5 | 17.8 | 28.5 | 27.6 | 29.1 | 33.0 |
| Ampicillin | 0 | 0 | 0 | 0 | 0 | 0 |
| Azithromycin | 7.1 | 0 | 3.3 | 4.5 | 8.9 | 8.9 |
| Clindamycin | 0 | 0 | 0 | 0 | 0 | 0 |
| Epinephrine | 0 | 0 | 0 | 0 | 0 | 0 |
| Furosemide | 0 | 0 | 0 | 0 | 0 | 0 |
| Heparin sodium | 0 | 0 | 0 | 0 | 0 | 0 |
| Hydrocortisone | 0 | 0 | 0 | 0 | 0 | 0 |
| Ketamine | 93.7 | 92.0 | 97.2 | 87.9 | 92.9 | 91.3 |
| Lorazepam | 65.0 | 42.6 | 45.2 | 46.9 | 60.4 | 67.2 |
| Metoclopramide | 0 | 0 | 0 | 0 | 0 | 0 |
| Midazolam | 0 | 0 | 0 | 0 | 0 | 0 |
| Morphine sulfate | 97.9 | 96.2 | 96.8 | 98.6 | 98.2 | 97.4 |
| Pantoprazole | 34.0 | 7.7 | 7.6 | 9.9 | 17.0 | 36.2 |
| Prednisone | 0 | 0 | 0 | 0 | 0 | 0 |
| Sulfamethoxazole and trimethoprim | 1.5 | 0 | 0.1 | 0.4 | 0.4 | 1.8 |

determined exempt by our institutional review board.

### Independent Variables

Demographic variables for each patient included age, sex, race, and insurance type. The specific encounter type (inpatient, observational, clinical, ambulatory, emergency, or other) and length of stay were recorded. Patient discharge disposition was determined and specifically defined as admitted, discharged from the hospital (to home, to court, or to law enforcement), transferred (to another hospital or health care institution), died, or other (hospice or left against medical advice).

### Dependent Variable

We categorized drug use, the dependent variable, as either appropriate for age or off label. We defined off-label drug use as use in a patient who was younger than the lower limit of the FDA-approved age range for any indication or dosage form of that drug. Drug use was considered appropriate if the patient was equal to or older than the lower limit of the FDA-approved age range of a drug regardless of indication or dosage form. Because of limitations of the PHIS database, we could not determine the specific indication for which a drug was prescribed.

The most commonly prescribed drugs were examined for off-label use, as represented by patient-level data within PHIS. The top 100 most commonly prescribed drugs were listed, from which 76 medications were ultimately examined. Twenty-four commonly prescribed agents were removed from the final list because they were determined to not be discrete therapeutic medications (see Supplemental Table 5).

The lower limit of the FDA-approved age range for each drug was determined on the basis of consensus definitions from 3 separate drug information resources: Micromedex, Lexicomp, and DailyMed. All but 13 of the 76 drugs that were analyzed achieved a consensus definition for the current lower limit of the FDA-approved age range in 2 of the 3 databases. When a consensus was not achieved, the lower limit of the FDA-approved age range was defined by a pharmacist at our institution (see Supplemental Tables 6). If a patient received a drug during 2014, regardless of the number of times the same drug was administered during the patient visit, it was counted as 1 prescription.

### Data Analysis

Descriptive statistics were obtained and stratified by off-label status to summarize the study population. All study medications were classified into 1 of 7 categories: central nervous system (CNS); respiratory and/or ear, nose, and throat (ENT); cardiac; endocrine; fluid, electrolyte, nutrition, and gastroenterology; hematology and/or oncology; and infectious disease (ID). The frequencies and proportions of visits in which patients received an off-label drug prescription were generated for each medication under these categories. The percent of off-label usage was also summarized for the 2014 BPCA priority list medications, which were also on the study medication list and stratified by encounter type.

## RESULTS

There were 2 773 770 patient visits (≤18 years of age) recorded in PHIS in 2014, during which 1 of the 76 selected drugs was prescribed. Of these visits, 779 270 (28.1%) included the prescription of at least 1 off-label drug. Characteristics of patients who were prescribed medications off label are listed in Table 2. Rates of off-label medication use were higher in the inpatient, observational, and ambulatory settings (53.9% [95% confidence interval (CI): 53.8%–54.0%]; 45.5% [95% CI: 45.3%–45.7%]; and 54.2% [95% CI: 54.0%–54.3%], respectively) compared with the emergency setting (10.3% [95% CI: 10.3%–10.4%]).

Rates of off-label medication prescription were similar despite patient sex, race, and insurance type. Younger patients had higher off-label rates when compared with their older counterparts. Specifically, prescriptions to neonates <28 days of age were off label 51% of the time (95% CI: 50.6%–51.3%). Infants 29 days to 1 year old received off-label prescriptions at a rate of 44.8% (95% CI: 44.7%–44.9%). Older patients, however, experienced lower rates of off-label medication prescription (21.5% [95% CI: 21.4%–21.6%] for children ages 13–18 years).

Longer patient stays (>1 day) were associated with higher rates of off-label medication usage (55.3% [95% CI: 55.1%–55.4%]) compared with visits of ≤1 day (22.8% [95% CI: 22.7%–22.8%] of visits). Regarding discharge disposition, patients who ultimately died had the highest off-label prescription rates (86.9% [95% CI: 85.9%–87.8%]), whereas patients who were discharged or transferred received off-label prescriptions at much lower rates (28% [95% CI: 27.9%–28.0%] and 38.1% [95% CI: 37.7%–38.6%], respectively).

There was substantial variation in off-label medication prescription by drug category (Table 3). CNS medications and respiratory and/or ENT medications had the highest rates of off-label use at 30.4% (95% CI: 30.3%–30.5%) and 24.9% (95% CI: 24.8%–25%), respectively. Medications in the ID category, by comparison, were prescribed off label at a rate of only 1.7% (95% CI: 1.7%–1.8%). Several medications were noted to have lower usage rates but nearly universal off-label prescribing. This was most notable within the CNS category. Dexmedetomidine, hydromorphone, and ketamine had overall usage rates of 2.5%, 2.3%, and 2%, with off-label usage rates of 98.7%, 95%, and 93.7%, respectively. Similarly, morphine was used in 12.2% of patients and was used off label 97.9% of the time. In contrast, ibuprofen was used in a relatively high percentage (23.5%) of patients and was used off label <1% of the time (Table 3).

Commonly prescribed 2014 BPCA priority list medications are further analyzed by prescription setting in Table 1. Although a number of these medications were used on label in all patients, variation in off-label usage was demonstrated for other medications on the basis of encounter setting. Albuterol had higher rates of off-label prescription in the emergency (28.5% [95% CI: 28.3%–28.7%]), observational (29% [95% CI: 28.5%–29.6%]), and inpatient settings (33% [95% CI: 32.7%–33.3%]) compared with in the clinical setting (17.8%

**TABLE 2** Characteristics of the Study Population, Stratified by Off-label Status

| | Overall ($N$ = 2 773 770) | Off-label Usage ($n$ = 779 270), $n$ (%) | No Off-label Usage ($n$ = 1 994 500), $n$ (%) |
|---|---|---|---|
| Age | | | |
| ≤28 d | 87 324 | 44 506 (51.0) | 42 818 (49.0) |
| 29 d–1 y | 639 652 | 286 666 (44.8) | 352 986 (55.2) |
| 2–5 y | 759 503 | 160 836 (21.1) | 598 667 (78.8) |
| 6–12 y | 776 361 | 177 579 (22.9) | 598 782 (77.1) |
| 13+ y | 510 930 | 109 683 (21.5) | 401 247 (78.5) |
| Sex | | | |
| Boys | 1 505 561 | 451 678 (30.0) | 1 053 883 (70.0) |
| Girls | 1 267 900 | 327 466 (25.8) | 940 434 (74.2) |
| Race | | | |
| White | 1 510 569 | 460 818 (30.5) | 1 049 751 (69.5) |
| African American | 641 279 | 151 186 (23.6) | 490 093 (76.4) |
| Other | 505 786 | 137 089 (27.1) | 368 697 (72.9) |
| Insurance type | | | |
| Public | 1 602 570 | 423 162 (26.4) | 1 179 408 (73.6) |
| Private | 988 218 | 310 822 (31.5) | 677 396 (68.6) |
| Other | 171 856 | 42 588 (24.8) | 129 268 (75.2) |
| Encounter type | | | |
| Inpatient | 532 850 | 287 153 (53.9) | 245 697 (46.1) |
| Observational | 189 874 | 86 351 (45.5) | 103 523 (54.5) |
| Ambulatory | 442 818 | 239 915 (54.2) | 202 903 (45.8) |
| Emergency department | 1 451 426 | 149 969 (10.3) | 1 301 457 (89.7) |
| Clinic visit | 87 342 | 7543 (8.6) | 79 799 (91.4) |
| Other | 69 438 | 8337 (12.0) | 61 101 (88.0) |
| Length of stay | | | |
| ≤1 d | 2 320 730 | 528 843 (22.8) | 1 791 887 (77.2) |
| >1 d | 453 040 | 250 427 (55.3) | 202 613 (44.7) |
| Discharge disposition | | | |
| Discharged | 2 647 285 | 739 921 (28.0) | 1 907 364 (72.0) |
| Transferred | 37 161 | 14 175 (38.1) | 22 986 (61.9) |
| Died | 4851 | 4215 (86.9) | 636 (13.1) |
| Other | 9971 | 1103 (11.1) | 8868 (88.9) |

[95% CI: 16.5%–19.1%]). Lorazepam was used off label at rates of 60.4% (95% CI: 58.6%–62.1%) and 67.2% (95% CI: 66.8%–67.6%) in the observational and inpatient settings, respectively, compared with 42.6% (95% CI: 38.8%–46.4%) in the clinical setting and 45.2% (95% CI: 43.6%–46.8%) in the emergency setting. Similar findings were noted for azithromycin, pantoprazole, and sulfamethoxazole and trimethoprim.

## DISCUSSION

Our analysis of off-label drug use in children's hospitals during 2014 reveals that the majority of patient encounters included prescriptions for drugs in accordance with FDA label indications for patient age. Higher rates of off-label medication use in pediatric patients were associated with younger patient age, longer hospital stays, and encounters categorized as inpatient, observational, or ambulatory. Patients who died had notably higher rates of off-label medication prescription compared with patients who were discharged or transferred. Although we are unable to directly correlate off-label drug use with illness severity, with these results, it is suggested that children with more severe diseases are more likely to receive medications outside of FDA labeling indications.

These findings differ from those of previous studies in which off-label medication use was analyzed in pediatric patients.[4–10] In their study, Shah et al[4] similarly measured off-label drug use in a broad cohort of pediatric patients who were hospitalized as reported through PHIS in 2004. Shah et al[4] concluded that 78.7% of patients received at least 1 of the most frequently prescribed drugs off label. In contrast, with our multicenter study, we were able to capture not only children who were hospitalized but also clinical, emergency, ambulatory, and observational patient encounters. The inclusion of outpatient visits in the current study could, in part, explain the overall lower rates of off-label drug use when compared with those in the 2007 study. However, at 53.9% (Table 2), our inpatient off-label prescription rates were nearly 25% less than those described by Shah et al[4]. Furthermore, rates in the clinical setting were 8.6%, >50% lower than rates cited in a 2009 study by Bazzano et al,[9] in which outpatient data from the 2001–2004 National Ambulatory Medical Care Surveys were used to analyze off-label drug use in pediatric clinic patients. Although direct comparisons with previous studies are affected by differing definitions of off-label drug usage and medications analyzed, these comparisons reveal that drug labeling for children has increased while reinforcing the need for further pediatric-specific research.

In a smaller study published in 2010, Czaja et al[5] analyzed a cohort of PICU patients and found that 85% received at least 1 medication off label. Patients requiring intensive care often experience longer inpatient stays and may have a higher likelihood of mortality. Although not specifically analyzing PICU patients, we found that inpatient encounters, hospital stays >1 day, and patient mortality correlated with higher rates of off-label drug prescription (Table 2). In a 2010 single-center study, Phan et al[10] analyzed the frequency of off-label and unlicensed medication use in a pediatric emergency department, concluding that 26.2% of

medication orders in 2191 patients were off label. In our study, rates of off-label medication prescription in emergency settings were 10.3%; however, this number accounts only for those patients seen in the emergency department and not subsequently admitted. In 2012, Lee et al[7] found that antidepressant prescription in children and adolescents was on label only 9.2% of the time. In our study, we did not capture psychiatric prescriptions because they did not occur in high frequency. In contrast to our study, these investigations are limited by their smaller sample size and are focused on subspecialty care.

Off-label drug prescription rates continue to vary by patient age. In our study, neonates ≤28 days of age had the highest rates of off-label medication prescription. Similarly, in their study, Hsu and Brazelton[11] concluded that patients ≤27 days of age are the most lacking in FDA-approved medication guidelines.[12–27] These results contrast with findings in the study by Shah et al,[4] in which patient age >28 days was associated with higher rates of off-label drug use. Bazzano et al[9] found that children <2 years of age were more likely to receive medications off label. This finding is reiterated in the current study, indicating that drug safety and efficacy research in young children should remain a priority.

Our study reveals that there continues to be substantial variation in off-label drug use by drug categories, which is consistent with a previous study.[4] Medications that affect the CNS were used off label >30% of the time in the current study, whereas use of off-label anti-infective agents occurred <2% of the time, and steroid use was nearly always on label. This suggests that further investment in the research of analgesics, anesthetics, and sedatives in the pediatric population is warranted over other drug categories.

Off-label drug prescription of a number of medications was influenced by clinical setting in our study, as demonstrated in Table 1. Medications such as azithromycin, lorazepam, pantoprazole, and sulfamethoxazole and trimethoprim were used off label at notably higher rates in the observational and inpatient settings compared with in the clinical, emergency,

**TABLE 3** Drug Classification, Frequency, and Proportion of Study Patients Prescribed Drug and Percent of Off-label Prescription

| Commonly Prescribed Medications by Drug Classification | Patients in PHIS Prescribed Drug, *n* (%) | Patients in PHIS Prescribed Drug Off Label, *n* (%) |
|---|---|---|
| CNS | 1 821 645 (65.7) | 553 655 (30.4) |
| Acetaminophen | 735 724 (26.5) | 0 (0) |
| Bupivacaine | 117 041 (4.2) | 83 061 (71.0) |
| Dexmedetomidine | 68 493 (2.5) | 67 576 (98.7) |
| Diazepam | 38 958 (1.4) | 266 (0.7) |
| Fentanyl | 449 284 (16.2) | 97 361 (21.7) |
| Hydromorphone | 62 330 (2.3) | 59 206 (95.0) |
| Ibuprofen | 652 754 (23.5) | 4354 (0.7) |
| Ketamine | 55 547 (2.0) | 52 023 (93.7) |
| Ketorolac | 220 696 (8.0) | 19 785 (9.0) |
| Levetiracetam | 40 676 (1.5) | 987 (2.4) |
| Lorazepam | 60 647 (2.2) | 39 429 (65.0) |
| Meperidine | 40 769 (1.5) | 0 (0) |
| Midazolam | 339 571 (12.2) | 0 (0) |
| Morphine sulfate | 338 584 (12.2) | 331 332 (97.9) |
| Neostigmine | 101 920 (3.7) | 0 (0) |
| Oxycodone | 94 012 (3.4) | 53 417 (56.8) |
| Propofol | 415 430 (15.0) | 9239 (2.2) |
| Rocuronium | 111 341 (4.0) | 11 301 (10.2) |
| Sevoflurane | 58 020 (2.1) | 0 (0) |
| Succinylcholine | 27 970 (1.0) | 0 (0) |
| Vecuronium | 32 106 (1.2) | 4724 (14.7) |
| Respiratory and/or ENT | 652 987 (23.5) | 162 447 (24.9) |
| Albuterol | 336 152 (12.1) | 99 264 (29.5) |
| Chlorhexidine | 61 226 (2.2) | 0 (0) |
| Diphenhydramine | 189 414 (6.8) | 27 016 (14.3) |
| Fluticasone | 48 573 (1.8) | 381 (0.8) |
| Ipratropium bromide | 126 516 (4.6) | 0 (0) |
| Oxymetazoline | 69 288 (2.5) | 40 967 (59.1) |
| Phenylephrine | 37 692 (1.4) | 0 (0) |
| Cardiac | 665 259 (24.0) | 64 154 (9.6) |
| Atropine | 28 843 (1.0) | 0 (0) |
| Bupivacaine and epinephrine | 70 588 (2.5) | 49 299 (69.8) |
| Epinephrine | 87 471 (3.2) | 0 (0) |
| Lidocaine | 463 803 (16.7) | 0 (0) |
| Lidocaine and epinephrine | 80 844 (2.9) | 0 (0) |
| Lidocaine and prilocaine | 31 431 (1.1) | 0 (0) |
| Ropivacaine | 25 954 (0.9) | 15 520 (59.8) |
| Endocrine | 652 823 (23.5) | 0 (0) |
| Dexamethasone | 453 142 (16.3) | 0 (0) |
| Hydrocortisone | 36 121 (1.3) | 0 (0) |
| Methylprednisolone | 58 120 (2.1) | 0 (0) |
| Prednisolone | 127 383 (4.6) | 0 (0) |
| Prednisone | 38 340 (1.4) | 0 (0) |

**TABLE 3** Continued

| Commonly Prescribed Medications by Drug Classification | Patients in PHIS Prescribed Drug, *n* (%) | Patients in PHIS Prescribed Drug Off Label, *n* (%) |
|---|---|---|
| Fluid, electrolyte, nutrition, and gastroenterology | 1 398 749 (50.4) | 164 517 (11.8) |
| Calcium gluconate | 24 408 (0.9) | 0 (0) |
| Docusate | 41 216 (1.5) | 5322 (12.9) |
| Famotidine | 29 236 (1.1) | 0 (0) |
| Furosemide | 49 828 (1.8) | 0 (0) |
| Glycerin | 34 832 (1.3) | 23 630 (67.8) |
| Glycopyrrolate | 143 812 (5.2) | 3479 (2.4) |
| Lansoprazole | 42 270 (1.5) | 10 536 (24.9) |
| Magnesium sulfate | 40 016 (1.4) | 0 (0) |
| Metoclopramide | 29 910 (1.1) | 0 (0) |
| Ondansetron | 817 265 (29.5) | 7583 (0.9) |
| Pantoprazole | 27 668 (1.0) | 9400 (34.0) |
| Phytonadione (vitamin $K_1$) | 48 495 (1.8) | 0 (0) |
| Polyethylene glycol-electrolyte solution | 99 461 (3.6) | 1720 (1.7) |
| Potassium chloride | 71 281 (2.6) | 69 832 (98.0) |
| Ranitidine | 101 162 (3.7) | 6498 (6.4) |
| Sodium bicarbonate | 38 159 (1.4) | 0 (0) |
| Sodium chloride | 727 576 (26.2) | 83 220 (11.4) |
| Sodium phosphate and sodium biphosphate | 28 916 (1.0) | 2570 (8.9) |
| Hematology and/or oncology | 178 098 (6.4) | 2099 (1.2) |
| Heparin | 167 190 (6.0) | 0 (0) |
| Thrombin | 22 571 (0.8) | 2099 (9.3) |
| ID | 678 333 (24.5) | 11 705 (1.7) |
| Amoxicillin | 63 138 (2.3) | 0 (0) |
| Amoxicillin and clavulanate | 22 924 (0.8) | 0 (0) |
| Ampicillin | 61 330 (2.2) | 0 (0) |
| Azithromycin | 33 722 (1.2) | 2382 (7.1) |
| Bacitracin | 90 389 (3.3) | 0 (0) |
| Cefazolin | 186 461 (6.7) | 6942 (3.7) |
| Cefotaxime | 30 116 (1.1) | 0 (0) |
| Ceftriaxone | 119 479 (4.3) | 0 (0) |
| Clindamycin | 85 267 (3.1) | 0 (0) |
| Erythromycin | 49 823 (1.8) | 0 (0) |
| Gentamicin | 46 660 (1.7) | 0 (0) |
| Nystatin | 32 951 (1.2) | 0 (0) |
| Ofloxacin | 34 498 (1.2) | 577 (1.7) |
| Piperacillin and tazobactam | 35 007 (1.3) | 2750 (7.9) |
| Sulfamethoxazole and trimethoprim | 37 494 (1.4) | 552 (1.5) |
| Vancomycin | 58 677 (2.1) | 0 (0) |

and ambulatory settings. This may be driven by patient-level factors, such as severity of illness, that influence location of presentation and need for admission and provider-level factors, such as subspecialty training and familiarity with therapeutic alternatives.

Importantly, in 2016, 16 of the 76 most commonly prescribed pediatric medications in 2014 remained on the BPCA priority list for the same year[1] (Table 4). Furthermore, 22 of the commonly prescribed medications are on the most recent BPCA priority list (published in 2017). In our study, the rate of off-label usage of BPCA priority list medications ranged from 0% to 98.7%, suggesting that although a number of medications may be FDA-approved for use in many members of the pediatric population, there remain ongoing questions regarding pharmacokinetics, optimal dosing, safety, and efficacy.

The current study has limitations that require acknowledgment. First, the PHIS database captures only a portion of pediatric care delivered in the United States because the majority of children receive their care outside of tertiary and quaternary children's hospitals. Thus, our study is only reflective of prescribing in these settings, and rates may be higher or lower than true pediatric population rates. In addition, we were unable to determine specific indications for which medications were prescribed and could not determine the dose, form, or route of the medication. These limitations likely led to an underestimation of off-label drug usage in pediatric patients. For example, although albuterol nebulization is approved for ages $\geq$2 years, the metered-dose inhaler is approved only for age $>$4 years. Thus, the metered-dose inhaler given to a 3-year-old patient was considered on label in the current study, although, by FDA definition, it was truly off label. Similarly, we were unable to capture any patient who received a higher than approved dose or a medication for any indication for which it was not labeled. In our study, we only analyzed the most commonly prescribed medications to children in 2014. Less common disease states, such as psychiatric or oncologic disease, were not captured in our study because the medications employed to manage these illnesses were less commonly prescribed. It is possible that such medications are used off label frequently because of smaller patient populations, less opportunities for study, and/or fewer on-label alternatives.

Although more than a quarter of patient visits in our study included the use of at least 1 commonly prescribed medication off label, we were unable to determine whether use led to adverse events or whether the drug was effective in managing the condition for which it was

**TABLE 4** BPCA Priority List by Year and Off-label Usage in 2014

| BPCA Priority List 2017 | BPCA Priority List 2014 | BPCA Priority List 2004 | Off-label Use in 2014, % |
|---|---|---|---|
| Albuterol | Albuterol | — | 29.5 |
| Ampicillin | Ampicillin | Ampicillin | 0 |
| Azithromycin | Azithromycin | Azithromycin | 7.0 |
| Clindamycin | Clindamycin | — | 0 |
| Dexmedetomidine | — | — | 98.7 |
| Diazepam | — | — | 0.7 |
| Epinephrine | Epinephrine | — | 0 |
| Furosemide | Furosemide | Furosemide | 0 |
| Heparin | Heparin | Heparin | 0 |
| Hydrocortisone | Hydrocortisone | — | 0 |
| Hydromorphone | — | — | 95.0 |
| Inhaled anesthetics (sevoflurane) | — | — | 0 |
| Ketamine | Ketamine | Ketamine | 93.7 |
| Levetiracetam | — | — | 2.4 |
| Lorazepam | Lorazepam | Lorazepam | 65.0 |
| Prokinetic drugs | Prokinetic drugs | Metoclopramide | 0 |
| Midazolam | Midazolam | — | 0 |
| Morphine | Morphine | — | 97.9 |
| Ondansetron | — | — | 0.9 |
| Pantoprazole | Pantoprazole | — | 34.0 |
| Prednisone | Prednisone | — | 0 |
| Sulfamethoxazole and trimethoprim | Sulfamethoxazole and trimethoprim | — | 1.5 |
| — | — | Piperacillin and tazobactam | 7.9 |

—, not applicable.

prescribed. It is possible that these medications were used off label because no reasonable on-label alternative exists, further highlighting the importance of addressing gaps in pediatric-specific drug knowledge.

## CONCLUSIONS

Our study reveals lower rates of off-label medication use in children compared with previous studies, suggesting the positive impact of FDA labeling initiatives. However, 1 out of every 4 patient visits were associated with off-label prescriptions, and variation in off-label medication use by drug class and clinical setting persists, highlighting the continued need for comprehensive drug development studies in which safety, efficacy, pharmacokinetics, and optimal dosing are evaluated in pediatric patients.


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