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## Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature

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### Abstract

**Content:** Clinician prescribing of off-label medications is common due to a lack of pediatric-specific data regarding the dosing, efficacy and safety of medications regularly prescribed to children.

**Objective:** This systematic review summarizes the published incidence of off-label medication use in children from the past 10 years. We also performed a retrospective chart review to determine the incidence of off-label prescriptions for children seen in the OU Physicians clinics.

**Data Sources:** We conducted a literature search of PubMed and OVID Medline from 2007 to 2017. Search terms included off-label use of medications and all child. For the local review, the outpatient electronic medical record (EMR) was queried.

**Study Selection:** Studies were eligible for inclusion if the study included children < 18 years of age, defined off-label use in the paper, and included the incidence of off-label drug use.

**Data Extraction:** Each review author extracted the study data from their assigned studies. For the retrospective chart review, the EMR was queried for patients <21 years of age who had a clinic visit and received a new prescription during 2017.

**Results:** We identified 31 studies, with off-label prescription rates from 3.2 % to 95%. The local retrospective chart review included 1,323 prescriptions; 504 were off-label (38.1%) and 819 were

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Conflicts of Interest and Disclosures

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approved. The frequency of off-label prescriptions does not differ significantly between the meta-analysis from the systematic review and the local retrospective chart review (30.9% vs 38.1%).

**Conclusions:** The use of off-label medications in children remains a common practice for pediatric providers.

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## Introduction

In comparison to adults, there is limited data pertaining to the dosing, efficacy, and safety of medications in children. This relative lack of data can be attributed to many causes, including unfamiliarity with age-related developmental pharmacology in pediatric patients, ethical considerations with conducting pediatric research, and a lack of financial incentive for the pharmaceutical industry. As a result, over the years there have been many significant therapeutic misadventures with off-label use of medications involving children with thalidomide and chloramphenicol being prominent examples. This lack of knowledge regarding pediatric specific drug use is an on-going area of concern in need of significant research. To address these concerns, Congress approved several pieces of legislation over the last 30 years. Table 1 provides an overview of the actions created by each bill,[1] which were designed to stimulate research related to drug pharmacology in pediatric populations. Following introduction of these bills in the United States over the last 15 years, 1200 studies have been submitted to the Food and Drug Administration (FDA), resulting in changes to over 700 medication labels[2]. Other countries have also adopted similar legislation. The European Medicines Agency created the European Pediatric regulation in 2007 in an effort to facilitate the development and availability of medicines for children while Canada created the Pediatric Expert Advisory Committee in 2009 in order to promote the development and licensing of drugs for children.

Despite the passage of these bills and subsequent research, there is still a significant lack of both pediatric-specific drug information and governmental approvals for on-label pediatric prescribing. Until further research and applications occur, many clinicians are forced to prescribe medications off-label. In response to this practice gap, The American Academy of Pediatrics adopted a policy statement on the use of off-label medications in children; they defined off-label use as “use of a drug that is not included in the package insert (FDA-approved labeling) [and] does not imply improper, illegal contraindicated or investigational use”[3]. This statement also emphasizes that off-label use does not necessarily require prescribers to obtain informed consent if the decision to use the medication is supported by scientific or anecdotal evidence and is not investigational in nature. For example, enalapril has an FDA-approved indication for hypertension, heart failure, and asymptomatic left ventricular dysfunction in adults but only has a FDA-labeled indication for hypertension in children.[4] Despite this, enalapril is commonly used to treat heart failure in pediatric patients and informed consent is not required in these situations. It is important to recognize that designation of off-label use can refer not only to the clinical indication for which a drug is prescribed but also includes administration of a medication by any route or dosing scheme that is not included in the package labeling approved by the FDA. For example, dexmedetomidine, a commonly used sedative is labeled for administration via the IV route

only in adults but is used off-label when delivered via the inhaled route in adults and children.

Despite the adoption of the previous legislation and subsequent studies, many medications continue to be used off-label in children. The Department of Pediatrics at The University of Oklahoma Health Sciences Center (OUHSC) is in the process of joining an ongoing national study, entitled “Pharmacokinetics of Understudied Drugs Administered to Children Per Standard of Care” (POPS). This trial aims to provide more data regarding drug administration in children in an effort to decrease off-label use of medications and improve FDA-labeling of medications for pediatric patients. As the study enrolls patients and gathers medication-specific data, study medications change over time; currently POPS is studying 32 drugs, which are regularly prescribed in an off-label manner. The purpose of this systematic review is to determine the incidence of off-label medication use in children across varying health care settings over the previous 10 years. We also evaluated the off-label use of medications in the outpatient pediatric clinics as part of our center’s preparation for participation in the POPS study.

## Methods

First, we conducted a literature review inclusive of prospective and retrospective studies on off-label use of medications in pediatric patients in any healthcare setting using PubMed (National Center for Biotechnology Information, U.S. National Library of Medicine, Bethesda MD), and OVID Medline (National Library of Medicine, Bethesda MD) databases. The initial search was performed April 6, 2018, and a second search was performed June 12, 2018. Search terms included all child (0–18 years), off-label use of medications with publication dates of 2007 to 2017. The studies included were limited to those written in English with the full article available through the OUHSC Bird Library (Appendix 1). Literature reviews, letters to the editor, or opinion papers were excluded. Studies were eligible for final inclusion if the study population included children, defined off-label use in the paper, and included the incidence of off-label drug use. As our objective was to report the overall incidence of off-label use in varying health care settings, studies were included if they focused on multiple classes of medications in any health care setting and excluded if they reported the incidence of off-label use of only a single medication or medication class. Eligibility assessment was done by two authors (CA &SD); article titles and abstracts were reviewed in an unblinded, standardized manner. Disagreements between the primary reviewers were resolved by consensus opinion of four of the authors (CA, SD, PJ, & JM). Studies from all countries were included, and we relied on the individual authors’ interpretation of the local regulatory agency’s ruling to determine off-label use of medications in the country the article was published.

The included studies were then divided amongst five of the authors (CA, SD, HC, NA, & JL) for review and extraction of study variables. A data extraction tool was created and pilot tested on 5 randomly selected articles; no changes were made to the data extraction tool after the pilot testing. Each review author extracted the study data from their assigned included studies. A single author (CA) checked extracted data, and disagreements were presented to a third author (SD) for resolution. Study variables included year of publication, years of data

collection or duration of data collection, study design, age range of patient population included in the study, setting of the study (i.e. inpatient unit vs. outpatient clinic), geographic location of study, total number of prescriptions, the rate of off-label medication use, and study definition of off-label use. The reason (i.e. dose, indication, frequency or route) drugs were determined to be off-label, adverse drug reactions, and handling of parental consent for off-label drug use was also collected if clearly stated in the paper.

There was no separate assessment of bias in the systematic review as all studies were either retrospective or prospective observational. There is the inherent bias due to the nature of the study design of retrospective and prospective observational studies.

Next we conducted a retrospective chart review of our electronic medical record system (Centricity EMR, GE Healthcare) to determine the prevalence of off-label medication use in children at our institution. Data were collected for patients 0 to 20 years of age, as POPS is enrolling patients through age 20, who had at least one outpatient visit at our institution during 2017, and received a prescription with a start date in 2017 for one of the POPS current 32 drugs of interest listed in Table 2. Data collected included the generic name of the drug prescribed, date of prescription, zip code to determine rural/urban status, patient race, patient ethnicity, and determination of off-label or approved use of the drug; if the drug was used in an off-label manner, the reason was noted. IBM Micromedex (IBM Corporation) was used to determine the Food and Drug Administration approved age range, route, dose and indication for medications. Two authors (CA and SD) reviewed and discussed unclear cases until consensus reached. The local retrospective study was approved by the Institutional Review Board at OUHSC.

Descriptive statistics for the local data were calculated for demographic variables and outcome of interest, prescription off-label status (approved vs. off-label). Chi squares were calculated for categorical demographics (sex, rural/urban status, race, ethnicity), and log binomial regression was used for continuous predictors (age). A p value of < 0.05 was considered significant. Zip codes were used to determine rural/urban designation with rural urban commuting area (RUCA) codes, using the four category classification as defined by the Rural Health Research Center[5]. Comparisons of meta-analyses from the systematic review and local data were performed by observing proportions and confidence intervals of off-label prescriptions, and the frequencies of reasons for being off-label (age, dose, indication, and route), among off-label prescriptions. Meta-analyses were performed using MedCalc software's meta-analysis function for proportions for the systematic review. Analyses on local data were performed using SAS 9.4. Comparisons between Meta-analyses and local data were performed by observing estimated proportions of off-label prescriptions and their respective 95% confidence intervals.

## Results

During the literature review, 285 publications were initially identified. Eight duplicates were removed, leaving 277 studies for initial screening. 54 studies met initial screening criteria and were sent on for full review. From these, 23 studies were ultimately excluded; five studies were not available in full manuscript, eleven were specific for a single medication or

medication class, and seven published no incidence of off-label prescriptions (Diagram 1). Thirty-one studies were included in final analysis, including 16 retrospective studies and 15 prospective observational studies. Pediatric patients from infants to adolescents were included in 24 studies, while 7 studies included only neonates. A total of 19 of the studies were conducted in inpatient populations, 11 studies were outpatient and one study included both inpatient and outpatient locations at a single center. The majority of the studies were conducted in Europe (n=19), Asia (n=6) and Australia (n=3). The number of patients involved in each study varied between 81 and 1.9 million patients. The 31 studies in the systematic review had varied age ranges but overall included patients that were preterm infants to 19 years old

Off-label use was described in the included 31 studies. Use of the medication outside the package insert recommendations for indication, age, route, dose and frequency was the most common definition of off-label use. Four studies further defined off-label as “use of medications that had no pediatric indication or were contraindicated in children” [6–8]. The rate of off-label prescriptions varied widely in the 31 reviewed studies and was reported to be between 3.2% and 95%. Seven studies in our literature review specifically evaluated the use of off-label medications in the neonate population, with off-label drug use ranging from 26% to 95%. See Table 3 for individual article details.

Only two studies reported adverse drug reactions related to off-label use of medications. One study did not define or elaborate on the nature of the adverse drug reaction, however, the second study reported fever, diarrhea and rash as an adverse drug reaction secondary to off-label use of medications [9, 10]. No study commented on obtaining parental consent for the use of off-label medications.

In our local retrospective chart review 22 of the 32 POPS drugs of interest were prescribed as a new prescription in 2017, resulting in a total of 1,323 prescriptions for 1079 patients. Of the 1,323 prescriptions, 504 prescriptions were off-label (38.1%) and 819 prescriptions were on-label. Table 4 provides a list of the 22 included drugs and the off-label versus approved use prescription percentages. The reasons the prescriptions were classified as off-label are listed in Table 5, with patient age being the most common reason. Table 6 displays patient demographics and frequency of off-label prescriptions defined by demographic grouping. There was no significant difference in the frequency of off-label prescriptions between male and female patients (38.6%, 37.6%). Off-label prescription frequency did not significantly differ between urban and rural groups (37.7%, 39.1) or by ethnicity (Hispanic/Latino vs. Not Hispanic/Latino 41.4% v. 38.2%). Though ostensibly there is large range in off-label frequency between racial groups (27.8%–46.6%), this was not statistically significant. There is, however, a significant association between age (in years) and frequency of being prescribed an off-label drug ( $p < 0.001$ ). The probability of receiving an off-label prescription is reduced by 3% for every year increase in age, with the probability at less than a year old being 51.6% and the probability at 20 years old being 29.3%.

To estimate a combined proportion of off-label prescriptions from the systematic review for comparison with our own data, we performed a meta-analysis for proportions (Figure 1). The  $I^2$  statistic indicated that over 99% of the variation in proportions across studies was due

to heterogeneity, and thusly the estimated proportion derived from the random effects model used was 30.9%, (95% CI: 26.0–36.0) for the systematic review. Comparing the results of local data (38.1%, 95% CI: 35.5, 40.8) with the meta-analysis from the systematic review, the frequency of off-label prescription does not differ significantly (Table 7). When comparing the reasons for off-label prescription (among those studies that listed them), OU Physicians pediatric outpatient clinics showed a significantly larger proportion of off-label prescriptions due to age (74.5%, 25.6%), and a significantly smaller proportion due to dose (10.3%, 48.3%). There was no significant difference between proportions of off-label prescriptions due to indication (21.4%, 19.5%) or route (3.2%, 3.4%).

## Discussion

Our study and literature review demonstrate that off-label use of medications in pediatric patients is a common practice, with a significant number of children, inpatient and outpatient, receiving an off-label medication. With the exception of three of the reviewed studies [7, 11, 12], all studies demonstrate >12% of prescriptions are off-label. Though most of the articles reviewed were from European countries, all continents were represented. The historical practice of using off-label medications in children is a frequent worldwide occurrence and continues to be an issue despite the increased awareness and passed legislation. Eighteen of the reviewed studies were conducted in European countries and published after the European Union Pediatric Regulation was established in 2007, which proposed to stimulate pediatric specific research much like the United States regulations reviewed in the introduction. The single included United States study in children was published more than 10 years after FDAMA and Pediatric Rule, yet it continues to report a high incidence of off-label medication prescriptions (36%). [13] Our local study for new prescriptions in 2017 also demonstrated a high incidence of off-label use at 38.1%. Despite international government efforts to mandate further research for pediatric drug labeling, there continues to be a high rate of off-label use of medications.

The reason for off-label use varies among studies. Our local study had a significantly higher proportion of patients that were given a medication off-label due to age and fewer that were off-label due to dose when compared to the meta-analysis from the systematic review. As the majority of the studies included in the systematic review were outside of the United States, this may in part be due to different approved dosing regimens from the local regulatory entities in the various countries that the systematic review studies were conducted. In addition, we only included the 32 POPS drugs of interest in our local study, this may account for the disparity between age and dosage between our study and the meta-analysis.

The literature review demonstrates the incidence of off-label use is higher among younger populations, especially neonates as reflected in the neonate intensive care unit-specific articles with off-label prescription rates of at least 26%. While our local study was not focused primarily on the neonate population, we did find a significant number of off-label prescriptions were due to patient age and the risk of receiving an off-label prescription decreased as age increased.

Finally, none of the studies we reviewed addressed the issue of parental consent for off-label use despite two studies reporting an adverse drug reaction secondary to off-label medication use. This may in part be secondary to the above-referenced American Academy of Pediatrics adopted policy that specifically states providers do not need parental consent if the medication use is supported by current evidence in the literature or a practitioners experience with the medication. Additionally, there may be a lack of knowledge among prescribers about the on label indications for commonly used pediatric medications. Practitioners should be aware of the off-label medications they commonly use in children and be mindful of known potential adverse reactions and side effects but also be wary of possible new unreported drug reactions or side effects.

The real answer to this prescribing dilemma is more research in the pediatric population. Hopefully, the POPS study will generate pediatric safety data and result in FDA approval for many of the commonly prescribed medications currently used off-label, thereby eliminating the conflict providers may feel in the current prescribing environment.

Our literature review was limited to the previous ten years and excluded studies evaluating off-label use of a single specific drug or a specific class of drugs. Non-English language articles were not included in the final analysis. Exclusion of these types of studies may have limited the scope of our review. The systematic review included studies from multiple countries, a broad age range and settings such as inpatient and outpatient, which we felt would give us a current global perspective on off-label medication use but perhaps introduced bias as each setting and country defined off-label based on their local regulatory board. The studies included in the systematic review were also either retrospective or prospective observational studies, which have inherent increased risk of bias compared to randomized trials.

The local retrospective study was limited to the 32 drugs of interest in the POPs study that are frequently prescribed off-label to children. The local prevalence of off-label use could be significantly different in our patient population if inpatient prescriptions or all prescriptions were included in analysis.

## Conclusions

Off-label medication use is common in the pediatric population, especially in neonates and younger age groups. More age-specific research is needed to provide adequate drug safety and effectiveness for children. Until more data is provided, clinical decision making should be guided by the best available evidence.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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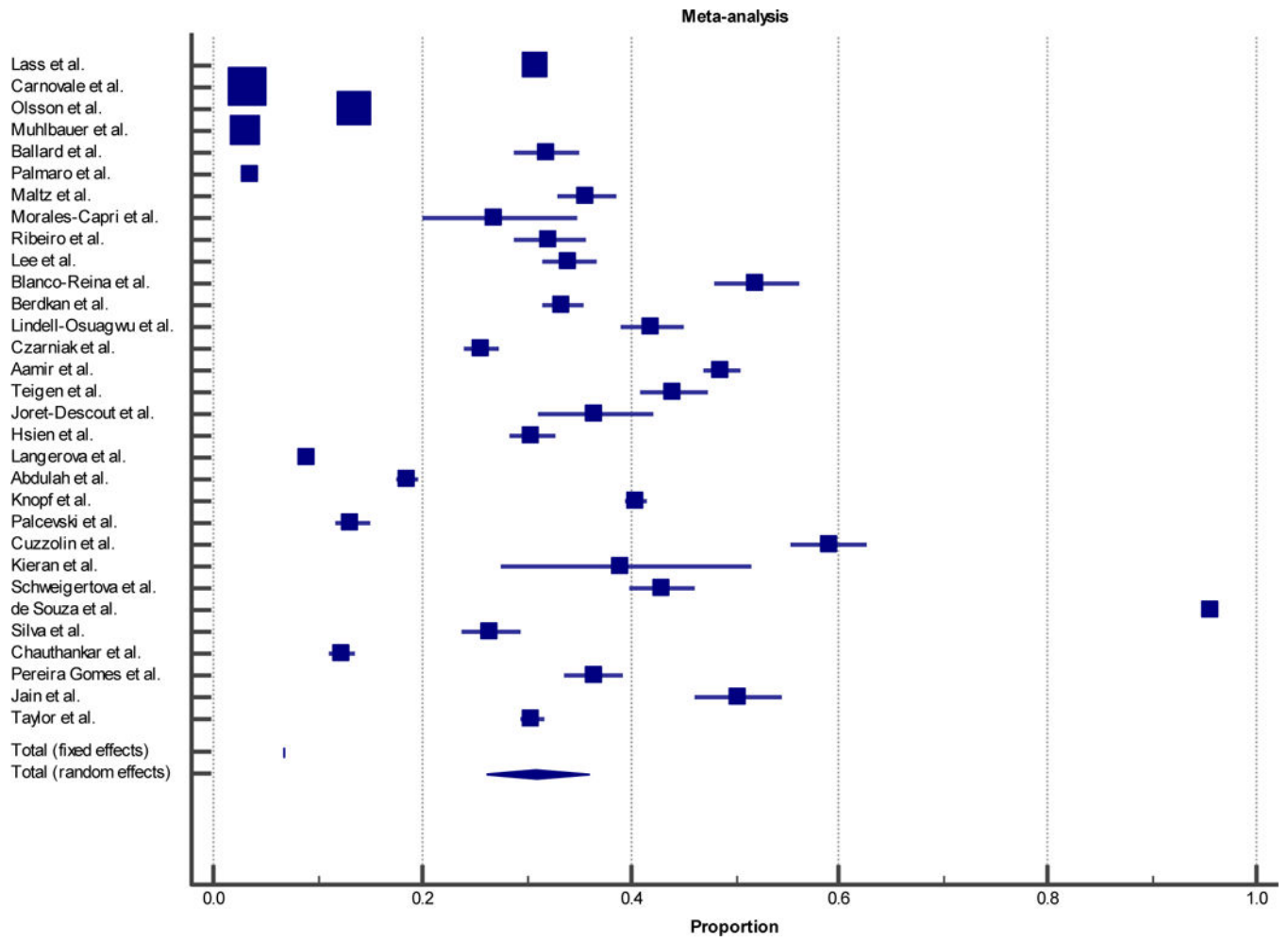
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**Figure 1:**  
Meta-analysis Forest Plot

**Table 1:**

Overview of Federal Legislation to Promote Pediatric Studies (Data from U.S. Drug and Food Administration<sup>1</sup>)

Legislation [Year Enacted]	Implications of Legislation
Food and Drug Modernization Act (FDAMA) [1997]	<ul style="list-style-type: none"> <li>• Encouraged pharmaceutical manufacturers to perform pediatric studies</li> <li>• Offered 6 months patent exclusivity as financial incentive</li> </ul>
Pediatric Rule [1998]	<ul style="list-style-type: none"> <li>• Required efficacy &amp; safety testing for NDAs if medication could be used in children</li> <li>• Studies under Pediatric Rule were eligible for 6 month patent extension under FDAMA</li> <li>• Federal court overturned in 2002 because FDA did not have authority</li> </ul>
Best Pharmaceuticals Act for Children (BCPA) [2002]	<ul style="list-style-type: none"> <li>• Authorized FDA to request pediatric studies with NDAs (including orphan drugs) for new indications</li> <li>• Extended 6 month patent exclusivity through 2007</li> <li>• Required NIH to publish list of needs for future study in children</li> </ul>
Pediatric Research Equality Act (PREA) [2003]	<ul style="list-style-type: none"> <li>• Required pediatric assessment &amp; development of PSP with NDAs (expanded version of Pediatric Rule) for certain drugs (NOT orphan drugs)</li> <li>• Allowed for modifications to existing indications</li> <li>• Pediatric plan must be developed before approval in adults</li> </ul>
Food and Drug Administration Amendments Act (FDAAA) [2007]	<ul style="list-style-type: none"> <li>• Reauthorized PREA &amp; BPCA × 5 years</li> <li>• Expanded the BCPA so FDA could issue request for &gt; 1 indication (i.e., “on” &amp; “off-label” use)</li> <li>• Introduced Pediatric Medical Device Safety &amp; Improvement Act</li> </ul>
Food and Drug Administration Safety and Administration Act (FDASIA) [2012]	<ul style="list-style-type: none"> <li>• Made BPCA &amp; PREA permanent</li> </ul>

**Table 2:**

## List of 32 POPS drugs of interest

- 
1. Alfentanil
  2. Amikacin
  3. Atropine
  4. Cefepime
  5. Ceftazidime
  6. Cidofovir
  7. Ciprofloxacin
  8. Clozapine
  9. Dexmedetomidine
  10. Diazepam
  11. Etomidate
  12. Fosphenytoin
  13. Haloperidol
  14. Low Molecular Weight Heparin
  15. Hydromorphone
  16. Lidocaine
  17. Lurasidone
  18. Meropenem
  19. Methadone
  20. Methylprednisolone
  21. Midazolam
  22. Molindone
  23. Nafticillin
  24. Pentobarbital
  25. Piperacillin
  26. Timolol
  27. Tobramycin
  28. Valproic Acid
  29. Vancomycin
  30. Vecuronium

- 
- 31. Warfarin
  - 32. Ziprasidone

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Table 3:

List of studies included in the literature review.

Author	Year Published	Type of Report (# Patients)	Age Range	Location	Country of Origin	% Off-Label Prescriptions
Lass et al [6]	2011	Retrospective (n=151,476)	< 19 years	Multi-center outpatient clinics	Estonia	31%
Carnovale et al. [7]	2013	Retrospective database search (n=1,708,755)	0-18 year	Single-center outpatient clinics	Italy	3.3%
Olsson et al. [8]	2011	Retrospective database search (n=1,911,417)	0-18 years	Multi-center outpatient clinics	Sweden	13.5%
Mühlbauer et al. [12]	2009	Retrospective database search (n=289,000)	0-16 years	Multi-center outpatient clinics	Germany	3.2%
Ballard et al. [9]	2013	Retrospective (n=300)	< 12 years	Single center general pediatric wards	Australia	32%
Palmaro et al. [10]	2015	Prospective (n=2,313)	0-16 years	Multi-center outpatient clinics	France	37.6%
Maltz et al. [13]	2013	Retrospective (n=82)	< 18 years	Single-center CVICU <sup>3</sup>	USA	36%
Morales-Capri et al. [14]	2010	Prospective observational (n=462)	< 14 years	Single center emergency department	Spain	27%
Ribeiro et al. [15]	2013	Retrospective (n=700)	< 18 years	Single-center emergency department	Portugal	32.2%
Lee et al. [16]	2013	Prospective observational (n=192)	Preterm to 18 years	Single-center PICUs	Malaysia	34.1%
Blanco-Reina et al. [17]	2014	Prospective observational (n=81)	Birth to 14 years	Single-center PICU and NICU <sup>4</sup>	Spain	52%
Berdkan et al. [18]	2016	Retrospective (n=500)	1 day to 16 years	Multi-center including multiple wards	Lebanon	30.2%
Lindell- Osiagwu et al. [19]	2014	Retrospective (n=123)	< 18 years	Single-center including multiple wards	Finland	42%
Asmir et al. [20]	2017	Prospective observational (n=895)	< 18 years	Multi-center Surgical wards	Pakistan	48.2%
Czarniak et al. [21]	2015	Retrospective (n=699)	All ages	Single Center inpatient and outpatient	Australia	25.7%
Tøigen et al. [22]	2017	Prospective (n=400)	0-17 years	Multi-center including multiple wards	Norway	44%
Joret-Descount et al. [23]	2015	Retrospective (n=120)	0-18 years	Single-center including multiple wards	France	36.5%
Taylor et al. [24]	2015	Retrospective (n=3343)	0-17 years	Multi-center outpatient	Australia	30.5%
Hsien et al. [25]	2008	Prospective observational (n=417)	All ages	Single-center including multiple wards	Germany	31%
Langerova et al. [11]	2014	Prospective (n=4,282)	0-15 years	Single-center outpatient clinics	Czech Republic	9.01%
Abdulah et al. [26]	2015	Retrospective (n=4,936)	0-5 years	Multi-center outpatient clinics	Indonesia	18.6%
Knopf et al. [27]	2013	Retrospective (n=17,450)	0-17 years	Single-center outpatient clinics	Germany	40.2%
Palcevski et al. [28]	2012	Prospective (n=691)	0-19 years	Single-center including multiple wards	Croatia	13.3%
Cuzzolin et al. [29]	2016	Prospective (n=220)	Preterm/neonates	Multi-center NICUs	Italy	59%
Kieran et al. [30]	2014	Prospective (n=110)	Neonates	Single-center NICU	Ireland	39%

Author	Year Published	Type of Report (# Patients)	Age Range	Location	Country of Origin	% Off-Label Prescriptions
Schweigtova et al.[31]	2016	Prospective (n=202)	< 29 days old	Multi-center NICUs	Slovakia	43%
Jain et al.[32]	2014	Prospective (n=156)	Neonates	Multi-center NICUs	India	26%
de Souza et al. [33]	2016	Retrospective (n=192)	< 28 days old	Single-center NICU	Brazil	95.6%
Silva et al. [34]	2015	Retrospective (n=218)	< 28 days old	Single-center NICU	Portugal	25.7%
Chauthankar et al.[35]	2017	Prospective observational (n=460)	Preterm/neonates	Single-center NICU	India	12.3%
Pereira Gomes et al. [36]	2015	Prospective observational (n=320)	2–18 years	Single-center inpatient ward	Brazil	57.2%

<sup>1</sup> ND = Not defined in study;

<sup>2</sup> PICU = Pediatric Intensive Care Unit;

<sup>3</sup> CVICU = Cardiac Intensive Care Unit;

<sup>4</sup> NICU = Neonatal Intensive Care Unit

**Table 4:**

Summary of Prescription Off-label Status by Drug (N=1323 prescriptions)

Drug	Off-label N (%)	Approved N (%)
amikacin	1 (50.0)	1 (50.0)
atropine	4 (100)	-
cefepime	2 (66.7)	1 (33.3)
ceftazidime	-	1 (100)
ciprofloxacin	120 (66.7)	60 (33.3)
clozapine	3 (100)	-
diazepam	43 (22.3)	150 (77.7)
haloperidol	6 (54.6)	5 (45.4)
heparin	95 (100)	-
hydromorphone	6 (100)	-
lidocaine	9 (4.3)	201 (95.7)
lurasidone	18 (85.7)	3 (14.3)
methylprednisolone	-	285 (100)
midazolam	2 (66.7)	1 (33.3)
nafcillin	1 (100)	-
piperacillin	4 (100)	-
timolol	28 (100)	-
tobramycin	31 (31.3)	68 (68.7)
valproic acid	13 (61.9)	8 (38.1)
vancomycin	1 (4.3)	22 (95.7)
warfarin	89 (89.9)	10 (10.1)
ziprasidone	28 (90.3)	3 (9.7)



**Table 5:**

Summary of Off-label Status Frequency and Off-label Frequency by Reason

	n (%)
<b>Off-label Status</b>	
Approved	819 (61.9)
Off-label	504 (38.1)
<b>Reason for Off-label Status<sup>*</sup></b>	
Age	338 (74.5)
Dose	52 (10.3)
Indication	108 (21.4)
Route	16 (3.2)

\* Four “Off-label” missing reason. 14 prescriptions contributing to more than one reason

**Table 6:** Summary of Demographic characteristics by Prescription Off-label Status (N=1,323 prescriptions)

	Off-label N (%)	Approved N (%)	
Sex			p=0.71
Male	252 (38.6)	401 (61.4)	
Female	252 (37.6)	418 (62.4)	
RUCA *			p=0.63
Rural	144 (39.1)	224 (60.9)	
Urban	360 (37.7)	595 (62.3)	
Race			Ref=White
American Indian/ Alaska Native	27 (46.6)	31 (53.4)	p=0.21
Asian	5 (27.8)	13 (72.2)	p=0.27
Black/ African American	56 (36.1)	99 (63.9)	p=0.63
Native Hawaiian/ Pacific Islander	5 (45.4)	6 (54.6)	p=0.63
White	400 (38.1)	649 (61.9)	
Ethnicity			p=0.43
Hispanic or Latino	72 (41.4)	102 (58.6)	
Not Hispanic or Latino	421 (38.2)	680 (61.8)	
Age (years)			p<0.001 **
Mean (Standard Deviation)	10.2 (6.1)	11.8 (5.7)	
Median	12	13	
Min, Max (Interquartile Range)	<1 month, 19 (5,16)	<1 month, 20 (7,17)	

\* Rural Urban Commuting Area

\*\* Age in years: RR 0.97 (0.96–0.98)

**Table 7:**  
 Summary of Off-label Prescription Frequency and Off-label Prescription Frequency by Reason:  
 OUHSC Children's Hospital Outpatient compared to Meta-Analysis

	OU Physicians Percent Off-label (95% CI)	Meta-Analysis Percent Off-label (95% CI)
Off-label	38.1 (35.5, 40.8)	30.9 (26.0, 36.0)
Reason for Off-label		
Age	74.5 (70.2, 78.4)	25.6 (15.4, 37.3)
Dose	10.3 (7.8, 13.3)	48.3 (35.7, 61)
Indication	21.4 (17.9, 25.3)	19.5 (12.4, 27.8)
Route	3.2 (1.8, 5.1)	3.4 (0.6, 8.3)