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Off-label Medication Use in an Academic Hospital Pediatric Critical Care Unit

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ABSTRACT

Objective: The objective of this study was to analyze medication use in a medium-sized academic hospital pediatric intensive care unit over a 1-year period and identify medications, medication classes, and age categories that would benefit most from pediatric drug trials.

Methods: The patient population included all pediatric patients <18 years of age (n=677) admitted to the pediatric intensive care unit from January 1, 2005 to December 31, 2005. The main outcomes assessed were medications and classes of medications most prevalent in each age category in comparison to currently available prescribing guidelines based on Food and drug Administration (FDA) approval as shown in the *PDR* and research as shown by *Lexi-Comp.*

Results: The 5 medications with highest exposure rates were acetaminophen (70.2%), ranitidine (51.7%), morphine (46.1%), fentanyl (39.3%), and propofol (39.1%). The medication classes with highest exposure rates were analgesics (42%), anesthetics (39%), and antiemetics (33.8%). Of the top 5 medications, only acetaminophen had FDA-approved prescribing guidelines in all age categories. FDA-approved prescribing guidelines were available for less than 35% of commonly prescribed medications in all age categories.

Conclusion: Pediatric off-label medication use continues to be prevalent. In the pediatric critical care population, most medications are not properly tested for pediatric use. The federal government passed the Best Pharmaceuticals for Children Act (BPCA) in 2002 to encourage pediatric drug studies. However, the medication classes specified for further testing do not reflect the critical care population. Further studies are necessary to delineate the medications and medication classes that need study the most.

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INTRODUCTION

For many pediatricians, prescribing off-label medications is a fact of life. Concerns about cost, small market populations, and ethical complexities have often led pharmaceutical companies to decide against conducting drug studies in the pediatric population.[1-2] Up to two-thirds of medications prescribed for children have not been officially studied under Food and Drug Administration (FDA) guidelines, and >70% of all medications listed in the *Physicians' Desk Reference (PDR)* have no FDA-approved guidelines for pediatric patients.[3-4] Nevertheless, pediatricians continue to prescribe off-label (outside the terms of the label) or off-license (not licensed for the pediatric population) medications. Even a 2002 American Academy of Pediatrics (AAP) policy statement noted "the practice of medicine may require a practitioner to use drugs 'off-label' to provide the most appropriate treatment for a patient."[2]

This problem of inadequate pediatric-specific, FDA-approved guidelines has become such a concern in recent years that the United States government has started to use legislative action to encourage pediatric studies,[5] the most recent being the Best Pharmaceuticals for Children Act (BPCA), enacted in 2002 and renewed in 2007. The BPCA mandated continued drug exclusivity for 6 months in exchange for medical trials in the pediatric population, thus offering a financial incentive for pediatric trials.[6] Although BPCA has caused numerous labeling changes and altered prescribing guidelines, the high prevalence of off-label use in pediatric populations continues.[7]

In order to identify medications needing pediatric trials, the BPCA directed the National Institutes of Health (NIH), the FDA, and pediatric experts to

Table 1. Comparison of Generic to *Physicians' Desk Reference (PDR)* Brand Name

Generic Name	PDR Brand Name
Acetaminophen	Tylenol
Albumin, Human	Buminate
Albuterol Sulfate	Accuneb
Alteplase, Recombinant	Activase
Cefazolin Sodium	Ancef
Ceftriaxone Sodium	Rocephin
Cefuroxime Sodium	Zinacef
Cisatracurium Besylate	Nimbex
Dexamethasone Sodium Phosphate	Decadron
Diphenhydramine Hydrochloride	Tylenol Cold/Allergy
Docusate Sodium	Colace
Dolasetron Mesylate	Anzemet
Epinephrine	EpiPen
Fentanyl Citrate	Actiq
Furosemide	Furosemide
Gentamicin Sulfate	Garamycin
Glycerin Colace	Glycerin
Hydromorphone Hydrochloride	Dilaudid
Ibuprofen	Motrin
Morphine Sulfate	Kadian
Pantoprazole Sodium	Protonix
Propofol	Diprivan
Ranitidine Hydrochloride	Zantac
Remifentanil Hydrochloride	Flumatidine
Ropivacaine Hydrochloride	Naropin
Thrombin	Thrombin
Vancomycin Hydrochloride	Vancocin

identify a list of medications most in need of study each year.[8] Part of this process was to examine published studies on the frequency of use in various settings. However, the paucity of research specific to the US population and the inconsistency of past research distorted this analysis. This study clarifies medication use over a 1-year period in a pediatric intensive care unit (PICU) of a medium-sized academic children's hospital and identifies medications, medication classes, and age categories that would benefit most from pediatric drug trials.

METHODS

Data were obtained from an internal hospital pharmacy database covering all patient stays in a medium-sized academic hospital PICU between January 1, 2005 and December 31, 2005. Data points included a unique patient identifier, medication name, age, weight, and sex of the patient at the time of the dose. Institutional Review Board approval was obtained prior to the study.

The only exclusion criterion of the patient population was being >18 years old. Age-group differentiation of the sample was based on FDA Guidance for Industry, E11 Clinical Investigation of Medicinal Products in December 2000.[9] We categorized the study population as newborn (0-27 days), infants/toddlers (28 days-24 months), children (2-11 years), and adolescents (≥12 years).

Off-label use was defined as having no FDA-approved indications. Medications were identified as "commonly used" when the percentage of exposure exceeded 10% of an age category. Medications commonly used were analyzed using 2 sources: the *PDR* 2006 Edition and the *Lexi-Comp Pediatric Dosage Handbook*, 13th Edition 2006-2007. The *PDR* was used as a proxy for FDA-approved prescribing guidelines. Listings in the *PDR* were organized by brand name (Table 1). Data analysis was conducted using Microsoft Excel.

RESULTS

A total of 685 unique patient stays occurred in the pediatric critical care unit between January 1, 2005 and December 31, 2005. Eight patient stays were excluded, including a patient >18 years old resulting in final population size of 677. Of this population, 5.65% of patients were newborns, 35.92% were infants and toddlers, 34.81% were children, and 23.62% were adolescents. Male-to-female ratios and age comparisons within each age category were well matched, with sex distributions ranging from 44.6% to 55.4% respectively (Table 2).

All Age Categories

Thirty-three medications were given to >10% of the PICU population. Acetaminophen (70.2%) and ranitidine (50.7%) were given to more than 50% of the population (Table 3). The average number of medications per patient by age category ranged from 10.9 to 16.2, with the highest number belonging to the newborn population.

Of the 33 commonly used medications, only 3 (acetaminophen, ceftriaxone, albumin) had FDA-approved, age-specific dosing guidelines. Fifteen (45%) had no product listing in the *PDR*, although 7 of these 15 were replacements and non-pharmaceuticals, such as electrolytes, water, or dextrose solutions. The other 8 included midazolam, lorazepam, vecuronium, atropine, epinephrine, methylprednisolone, bacitracin, thrombin, and gelatin (Table 3).

A summary of the prescribing guidelines for commonly used medications in all age categories shows that the newborn category is most lacking in FDA-approved guidelines. This trend also emerges when looking at available research in *Lexi-Comp* (Table 3). Furthermore, when broken down by classes, these medications dem-

Table 2. Age Definitions with Breakdown by Age and Sex

			Male		Female	
Age Category	**Definition**	**No. Patients**	**n**	**Average Age**	**n**	**Average Age**
Preterm	Before Term	NA	NA	NA	NA	NA
Newborn	0 - 27 Days	25 (5.65%)	13 (53.7%)	12.4 Days	12 (46.3%)	9.8 Days
Infants/Toddlers	28 Days - 24 Months	185 (35.9%)	86 (44.6%)	11.4 Months	99 (55.4%)	9.9 Months
Childen	2 - 11 Years	266 (34.8%)	136 (49.6%)	6.8 Years	130 (50.4%)	6.5 Years
Adolescent	12+ Years	201 (23.6%)	103 (47.5%)	15.5 Years	98 (52.5%)	15.3 Years
Total		677	338 (47.5%)	7.7 Years	339 (52.5%)	7.2 Years

Definitions of age are determined by the Food and Drug Administration Guidance for Industry, E11 Clinical Investigation of Medicinal Products, December 2000. Preterm age category was not used for this paper.

onstrate exposure rates highest in the analgesic (42.1%), anesthetic (39.1%), and antiemetic (33.8%) classes (Table 4).

A summary of the prescribing recommendations by age category further shows that the age category most in need of research is the newborn class, for which only 8% of medications prescribed had a detailed *PDR* listing. In general, the younger age classes have a higher exposure risk and fewer FDA-approved guidelines (Table 5).

Newborn Age Category

Thirty-six medications were given to >10% of this PICU age group. Midazolam (80.0%), ranitidine (64.0%), fentanyl (60.0%), acetaminophen (52.0%), and vecuronium (52.0%) were given to more than 50% of the population. Compared to the overall population, new medications include ampicillin, gantamicin, cefazolin, milrinone, dopamine, epinephrine, methadone, alteplase, heparin, metoclopramide, and cisatracurium (in addition to 2 electrolyte replacements). This population was the most divergent in types and prevalence of medications used in comparison to the overall population.

Infants/Toddlers Age Category

Thirty-one medications were given to >10% of this PICU age group. Acetaminophen (74.6%) alone was given to more than 50% of the population. Compared to the overall population, new medications include metoclopramide in addition to 1 standard IV solution (dextrose/sodium chloride.) This population most closely matched the overall population.

Children Age Category

Thirty-two medications were given to >10% of this PICU age group. Acetaminophen (70.3%) and ranitidine (50.4%) were given to more than 50% of this population. Compared to the overall population, new medications include remifentanil in addition to 1 standard IV solution (dextrose/sodium chloride.) This population also closely matched the overall population.

Adolescent Age Category

Twenty-nine medications were given to >10% of this PICU age group. Acetaminophen (68.2%), ranitidine (58.2%), and fentanyl (52.2%) were given to more than 50% of this population. Compared to the overall population, new medications include docusate, remifentanil, and ropivicane (in addition to 2 electrolyte replacements).

DISCUSSION

Off-label and off-license prescribing for children continues to occur. Review articles, drawing primarily from an international population, have characterized off-label and off-license use at rates ranging from 11% to 80% across centers and pediatric settings, including non-intensive care wards and outpatient clinics.[10] Compared to outpatient practice, inpatient services, especially those with higher acuity, require more frequent off-label use of medications. Higher rates correlated with patients in neonatal intensive care units, PICUs, and oncology wards at highest risk. In many cases, the care in these settings necessitates the extrapolation of medications used in the adult literature into the pediatric world. In 1 study, 93% of extremely low birthweight infants received unlicensed or off-label medications,[11] whereas an outpatient study found only 13.2% of medications to be off-label.[12] However, the preponderance of international studies compared to US studies has been a common concern with these reviews. A recent paper examining 52 studies conducted from 1990 to 2006 found only 1 based in the United States.[13] A review of more recent literature found 1 additional study examining off-label use and 2 looking at drug utilization based in the United States.[14-16] Thus, there remains a significant gap in our knowledge regarding the prevalence of off-label prescribing and the subsequent

Table 3. Prescribing Guidelines for Medications with >10% Exposure for All Patients

	Exposure		*Physicians' Desk Reference (PDR)*, 2006				*Lexi-Comp* 13th Edition, 2006-2007			
Medication	**n**	**%**	**Adolesc**	**Children**	**Infants**	**Newborns**	**Adolesc**	**Children**	**Infants**	**Newborn**
Acetaminophen	475	70.2	●	●	●	●	●	●	●	●
Ranitidine Hydrochloride	350	51.7	●	●	●	O	●	●	●	●
Morphine Sulfate	312	46.1	O	O	O	O	●	●	●	●
Fentanyl Citrate	266	39.3	◗	O	O	O	●	●	●	●
Propofol	265	39.1	●	●	◗	O	●	●	◗	O
Midazolam Hydrochloride	250	36.9					●	●	●	●
Dolasetron Mesylate	229	33.8	●	●	O	O	●	●	◗	O
Vecuronium Bromide	194	28.7					●	●	●	●
Bacitracin	150	22.2					●	●	●	O
Furosemide	132	19.5	●	●	●	O	●	●	●	●
Thrombin	132	19.5	O	O	O	O	●	●	●	●
Cefuroxime Sodium	109	16.1	●	●	◗	O	●	●	●	●
Diphenhydramine Hydrochloride	105	15.5	●	●	◗	O	●	●	O	O
Dexamethasone Na Phosphate	98	14.5	O	O	O	O	●	●	●	●
Albuterol Sulfate	98	14.5		●	O	O	●	●	◗	O
Ceftriaxone Sodium	94	13.9	●	●	●	●	●	●	●	●
Albumin, Human	90	13.3	●	●	●	●	●	●	●	●
Atropine Sulfate	89	13.1					●	●	●	●
Hydromorphone Hydrochloride	88	13.0	O	O	O	O	●	●	◗	O
Lorazepam	79	11.7					●	●	◗	◗
Pantoprazole Sodium	77	11.4	O	O	O	O	●	●	◗	O
Vancomycin Hydrochloride	71	10.5	O	O	O	O	●	●	●	●
Epinephrine Racemic	70	10.3					●	●	●	●
Methylprednisolone Na Succinate	69	10.2					●	●	◗	O

● Complete Prescribing Guidelines; ◗ Partial Prescribing Guidelines; O No Prescribing Guidelines; Those blank had no prescribing guidelines for any age groups including adults.
Medication list does not include the following widely used supplements/non-pharmaceuticals: Sodium Cl, Dextrose, Magnesium Sulfate, Potassium Cl, Gelatin Sponge, Calcium Gluconate, Sterile Water, Potassium Phosphate, and Glycerin.
The *PDR* denotes Food and Drug Administration-approved prescribing guidelines whereas *Lexi-Comp* combines available evidence including multi-center trials, published studies, and case reports.

impact on quality of care. This paper aims to address the first step, framing the scope of the issue by identifying medications and medication classes with the highest prevalence of off-label prescribing in the pediatric critical care setting.

One BPCA mandate is to identify the medication and medication classes most in need of study. With the paucity of research in the US population, characterizing the medications and medication classes in greatest need of analysis becomes difficult. Although the physiology and pharmacology involved in pediatric dosing does not change based on the country, the definition of what is considered off-label and off-license does. The FDA has long been known to possess a more stringent approval process compared to other international bodies. Moreover, practice standards and the standard of care in prescribing a medication also varies among countries. Overall, these concerns alter the exposure rates as determined by international studies, when compared to US studies.

Since 2005, the focus of BPCA has been based on a "therapeutic class" approach instead of a "drug-specific" approach. This has led to identifying the following as key areas of research: infectious diseases (with a focus on methicillin-resistant *staphylococcus aureus* [MRSA] infections), pediatric cancer (specifically neuroblastoma), neonatal pain, asthma, pediatric hypertension, sickle cell anemia, and attention deficit hyperactivity disorder.[8]

Our study demonstrates that the therapeutic classes identified by BPCA do not correlate with the PICU population. Classes that would benefit the most based on the highest exposure rates include analgesia, anesthetics, and antiemetics agents. In addition, this study shows the age-based discrepancy of commonly used medications. An overall population assessment of off-label exposure in the pediatric critical care setting would drive research that primarily benefits children and infants/toddlers. This analysis would not represent the medications used in the newborn population, which

has the highest number of medications prescribed per patient and the highest number of commonly used medications, yet was the most divergent age category from the overall population.

This study validates the notion that pediatricians prescribe off-label drugs for their patients at extremely high rates. Examining medications with >10% exposure rates and comparing the guidelines of *PDR* and *Lexi-Comp* revealed a significant departure from FDA-approved guidelines and those supported by the clinical research documented in Lexi-Comp. Only 3 medications (acetaminophen, ceftriaxone, albumin) had FDA-approved guidelines for all age categories, whereas *Lexi-Comp* had complete guidelines in 15. This represented an alarming difference. Although practitioners may feel comfortable using *Lexi-Comp* guidelines given the scientific literature backing the recommendations, the US Government Accountability Office in 2007 found that since the start of BPCA, labeling changes were present for 87% of medications that were granted exclusivity and underwent clinical trials.[3] Changes were made based on newly discovered adverse events and ineffective medication or dosing.

This study had several weaknesses. The research only targeted the pediatric critical care population in 1 center, with attending and institutional specific practices. Furthermore, as a teaching institution, significant variability across trainee groups may exist. These groups included intensive care fellows, pediatric residents, and pharmacy students. The variability across staff and trainees was not controlled for by this analysis. This population was chosen to address the general population at greatest risk given the clinical instability of this group. However, to address the question of the greatest impact, the whole US pediatric population, regardless of clinical location, needs to be examined. As noted in this research, an essential component of any study addressing the area of greatest need must be based on a distribution by established age categories.

This study also failed to take into account dosing guidelines and solely examined whether or not guidelines existed based on age categories. In addition, the diagnostic criteria for medication use were not addressed. Given that there are significant discrepancies in prescribing guidelines of the pediatric population based on weights and diagnosis, this would have lent additional clarity about whether current guidelines are appropriate.

Finally, this study did not capture the outcomes of medication use. Categorizing adverse outcomes based on medication use, depending on whether approved guidelines were followed, would give more weight to the need for stringent testing of pediatric medications and would identify individual high risk drugs that could be targeted for trials. Previous international studies have demonstrated adverse drug reactions resulting from the off-label and off-license use of medication in pediatrics.[17-18] This analysis, if conducted in the United States, would further stress the need for pediatric trials.

Table 4. Medication Classes Based on *Lexi-Comp,* 2006-2007 on Medications with >10% Exposure for All Patients

Medication Class	Medications Within Class *n*	*n*	Possible	Exposure Rate (%)
Analgesic	4	1141	2708	42.10
Anesthetic	1	265	677	39.10
Anti-emetic	1	229	677	33.80
Gastrointestinal	2	427	1354	31.50
Paralytic	1	194	677	28.70
Sedative	2	329	1354	24.30
Nutritional	2	306	1354	22.60
Electrolytes	5	724	3385	21.40
Diuretic	1	132	677	19.50
Hemostasis	1	132	677	19.50
Anticoagulant	1	127	677	18.80
Antibiotic	4	424	2708	15.70
Antihistamine	1	105	677	15.50
Bronchodilator	1	98	677	14.50
Volume Expander	1	90	677	13.30
Anticholinergic	1	89	677	13.10
Steroid	2	167	1354	12.30
Laxative	1	70	677	10.30
Sympathominmetic	1	70	677	10.30

Medication within class denotes the number of distinct medications with >10% exposure that falls within each class. Possible exposure is equal to the number of medication in the class multiplied by total number of patients.

CONCLUSION

Off-label and off-license use of medications continue to plague pediatricians. In treating a population exhibiting varying pharmacophysiology based on age, it is vital that additional research be done to standardize pediatric prescribing guidelines with the same stringency currently applied to adults. This research showed that the current BPCA recommendations for research have not addressed the high-risk medication classes sometimes prescribed to the PICU population. Further research detailing the whole pediatric population, taking into account weight and diagnostic criteria, will clarify the medications putting pediatric patients at greatest risk. In the meantime, providing appropriate pediatric labeling should remain a primary focus for all pharmaceutical research and new drug discoveries.

Table 5. Summary of Prescribing Recommendations by Age Category

	Number of Medications	*Physicians' Desk Reference*				*Lexi-Comp*			
Age Category	**Commonly Prescribed**	**Detailed**	**Partial**	**None**	**NA**	**Detailed**	**Partial**	**None**	**NA**
Newborn	36	3 (8%)	0	14 (39%)	19 (53%)	31 (86%)	1 (3%)	0	4 (11%)
Infants/Toddlers	31	5 (16%)	3 (10%)	8 (26%)	15 (48%)	23 (74%)	7 (23%)	0	1 (3%)
Children	32	10 (31%)	0	7 (22%)	15 (47%)	31 (97%)	0	0	1 (3%)
Adolescent	29	10 (34%)	1 (3%)	4 (14%)	14 (48%)	28 (97%)	0	0	1 (3%)

Abbreviations: None, no age specific dosing recommendations; NA, medications that were not listed.

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REFERENCES

1. Christensen ML, Helms RA, Chesney RW. Is pediatric labeling really necessary? *Pediatrics.*1999;104:593-597.
2. Committee on Drugs, American Academy of Pediatrics. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics.* 1995;95:286-294.
3. Crosse M. The Study and Labeling of Drugs for Pediatric Use Under the Best Pharmaceuticals for Children Act. Washington, DC. United States Government Accountability Office. May 22, 2007. GAO-07-898T.
4. Blumer JL. Off-label uses of drugs in children. *Pediatrics.* 1999;104:598-602.
5. McKinney RE. Congress, the FDA, and the fair development of new medications for children. *Pediatrics.* 2003;112:669-670.
6. Li JS, Eisenstein EL, Grabowski HG, et al. Economic return of clinical trials performed under that pediatric exclusivity program. *JAMA.* 2007;297:480-488.
7. Benjamin DK, Smith PB, Murphy MD, et al. Peer-reviewed publication of clinical trials completed for pediatric exclusivity. *JAMA.* 2006;296:1266-1273.
8. Food and Drug Administration. *List of Drugs for Which Pediatric Studies are Needed.* Federal Register Notice. 72FR14588-72FR14589. 2007.
9. Center for Biologics Evaluation and Research and Center for Drug Evaluation and Research, Food and Drug Adminstration, US Department of Health and Human Services. *Guidance for Industry: E11 Clinical Investigation of Medicinal Products in the Pediatric Population.* Washington, DC. December 2000.
10. Pandolfini C, Bonati M. A literature review on off-label drug use in children. *Eur J Pediatr.* 2005;164:552-558.
11. O'Donnell CP, Stone RJ, Morley CJ. Unlicensed and off-label drug use in an Australian neonatal intensive care unit. *Pediatrics.* 2002;110:e52.
12. Bucheler R, Meisner C, Kalchthaler B, et al. "Off-label" prescribing of drugs in the ambulatory care of children and adolescents. *Dtsch Med Wochenscher.* 2002;127(48):2551-2557.
13. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. *Expert Opinion Drug Saf.* 2006;5:703-718.
14. Shah SS, Hall M, Goodman DM. Off-label drug use in hospitalized children. *Arch Pediatr Adoles Med.* 2007;161:282-290.
15. Warrier I, Du W, Natarajan G, Salari V, Aranda J. Patterns of drug utilization in a neonatal intensive care unit. *J Clin Pharmacol.* 2006;46:449-455.
16. Zuppa AF, Adamson PC, Mondick JT, et al. Drug utilization in the pediatric intensive care unit: monitoring prescribing trends and establishing prioritization of pharmacotherapeutic evaluation of critically ill children. *J Clin Pharmacol.* 2005;45:1305-1312.
17. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse dug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol.* 2002;54:665-670.
18. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. *Acta Paediatr.* 1999;88:965-968.

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