

## Original Research Article

# Pharmacoepidemiological assessment of off-label drug use in pediatric ambulatory departments at four tertiary care hospitals in Pakistan

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### Abstract

**Purpose:** To assess the frequency and possible predictors of off-label drug use in ambulatory pediatric units of four tertiary healthcare institutions in a Pakistani city.

**Methods:** A prospective study was conducted at the pediatric ambulatory department of four tertiary care hospitals of Peshawar, Pakistan. A total 1589 patients were included in the study which to evaluate their prescriptions for off-label drug use with the aid of Thomson Healthcare Micromedex DRUGDEX database.

**Results:** A total of 79 different drugs were prescribed 5668 times to pediatric patients. A high rate of off-label drug use (71.8 %) was observed in this study. Compared to corresponding reference categories, infants (OR 4.134, 95 % CI 2.076-8.235) and children (OR 1.857, 95 % CI 0.967-3.568) were more likely to receive off-label prescriptions. However, pediatric patients receiving less than four drugs (OR 0.414, 95 % CI 0.312-0.548) were less likely to receive off-label prescriptions.

**Conclusion:** A high incidence of off-label drug use has been observed in the ambulatory pediatric population studied, especially in infants. More research is needed to identify and evaluate the contributory factors to off-label use of drugs in ambulatory pediatric population in developing countries to achieve optimal drug therapy for pediatrics.

**Keywords:** Pediatric population, Ambulatory, Off-label drug use

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## INTRODUCTION

Rational Pediatric pharmacotherapy is a challenging endeavour to clinicians. Most of the drugs prescribed to pediatrics do not have established safety and efficacy data because of lack of sufficient clinical drug trials in this

population to date [1]. Many factors contribute to the absence of clinical trial based data e.g. patient recruitment, consent problems, lack of previous knowledge about the long term toxic effects of a drug, different pharmacokinetic and pharmacodynamic profile of children [2]. Due to these reasons, data from adult studies is

extrapolated for drugs to use in children that may be inappropriate. This lack of clinical knowledge of drugs for children has elicited the off-label drug use which contribute to the overall increase in the risk of harm to this particular age group [3].

Off label prescribing is an extensive global practice in pediatric pharmacotherapy. About 80 % of approved drugs are not labeled for use in children in United States [4]. According to Food and Drug Administration off label drug use is the use of a drug at a dose, medical condition, age or method of administration which is not in accordance with information labeled on product license of the drug.

Many drugs have been found to be used in off label manner that lead to inappropriate drug therapy such as salbutamol and cetirizine used in dose higher than recommended doses, montelukast used to treat perennial allergic rhinitis which is not a labeled indication. The use of promethazine under 2 years of children may cause respiratory depression and death [5].

Most of the studies addressing the use of off label drugs in pediatric population were hospital based though this setting does represent pediatrics with small proportion of risk of adverse drug reactions [6]. A very few studies have been reported in ambulatory pediatric department and most of the work related to dose, safety and efficacy have been insufficiently documented. Therefore, careful evaluation of pediatric pharmacotherapy in terms of proper drug selection, its proper dosage, age appropriateness and right formulation is a need of the day [7].

Currently no studies have been undertaken on prevalence of off label use of drugs in ambulatory pediatric population in our county. This inceptive study will facilitate to scrutinize the extent and frequency of off label use of drugs in ambulatory pediatric population in association to their predictors.

## METHODS

A prospective, cross-sectional study was conducted at two public [Hayatabad Medical Complex (HMC) and Khyber Teaching Hospital (KTH)] and two private [Northwest General Hospital and Research Center (NWGHRC) and Rehman Medical Institute (RMI)] hospitals located at Peshawar city, Khyber Pakhtunkhwa, Pakistan. These four hospitals are leading hospitals of province and have been offering comprehensive range of health care services to individuals with aim to raise long term health

status of the community. The study was undertaken at pediatric ambulatory departments over a period of January 2017 to December 2017. Sample size was determined by the formula for known populations [8]. In order to collect data simple random sampling technique was employed. Data of 1589 patients were obtained from all hospitals. In order to get access to the patient data of each hospital, approval was granted from their ethical committees. Confidentiality of patient prescription data was strictly maintained. The study was in compliance with the International Conference Harmonization Good Clinical Practice guidelines [9].

After obtaining Ethical approval from hospitals the patient information was retrieved from prescriptions which includes patient demographics (age, gender, identification number, diagnosis and date of visit), detail of the medication prescribed (dosage form, dose, frequency, route of administration and duration of therapy). Generic of the drugs were obtained from Drug Manual and Pharmaguide 20th edition of Pakistan as prescription by trade name of drug was observed during collection of data. Off label drug use were evaluated for age, dose, indication and administration form by using Thomson Healthcare Micromedex DRUGDEX database [10]. The study included patients of either gender with age under 18 years attending pediatric outpatient department. Herbal drugs and topical preparations were excluded from study. The International Classification of Diseases 11 was used to classify the diseases of patients [11]. The prescribed drugs were classified using Anatomical Therapeutic Chemical Classification System [12].

## Data analysis

For analyzing data IBM SPSS Statistics for windows, version 20 (Armonk, NY: IBM corp.) was used. Demographic data of patients including age, gender and diagnosis were presented as frequencies, mean and standard deviation. Univariate and multivariate binary logistic regression was used to calculate the odd ratio with 95 % confidence interval (CI) for the predictors of off label use of drug.

## RESULTS

From both government & private tertiary care hospital sample of 1589 patients were included. Male population was predominant over female (59.9 %). Age groups were categorized according to WHO (World Health Organization) guidelines [13]. The median age of the population was 36 months while median of

number of prescribed drugs was 3. The patient characteristics are given in Table 1.

Most ubiquitous diagnosis found were pharyngitis (29.8 %), bronchitis (22.5 %), protozoal intestinal disease unspecified (12.8 %), tonsillitis (8.1 %), allergic rhinitis (7.3 %), asthma (4.2 %), oesophagitis (3.5 %), nasopharyngitis (2.8 %), sinusitis (1.6 %), Protein-energy malnutrition of moderate and mild degree (1.3 %). The patient morbidities are given in Table 1.

Anti-bacterial for systemic use (21.7 %), anti-histamines for systemic use (15.6 %), drugs for obstructive airway diseases (15.3 %), anti-inflammatory and anti-rheumatic drugs (10.4 %), analgesic drugs (10.1 %), anti-protozoal drugs (5 %), vitamins (4.4 %), miscellaneous (4.1 %), cough and cold drugs (3.6 %) and anti-anemic (3.0 %) were the most prevalent therapeutic drug classes. Most commonly prescribed drugs to the patients were paracetamol (9.9 %), ibuprofen (8.7 %), cefixime (6.1 %), amoxicillin/clavulanic acid (5.4 %), chlorpheniramine (4.3 %), montelukast (4 %), multivitamins (4 %), cetirizine

(3.8 %), metronidazole (3.2 %) and albuterol (3.2 %). Drug used as off-label was 71.8 % in pediatric patients. Patients received at least one off label drug were 566 (35.6 %). In off label categories age (40.2 %) and dose (27.5 %) were most recurrent categories in all therapeutic classes. Other categories of off label were age-indication (20.7 %), dose-age (5.7 %), age-dose-indication (3.7 %), dosage form (1.1 %), age-dosage form (15 %) and dose-dosage form (0.1 %). Most frequently prescribed drugs as off-label and their off-label categories are given in Table 2. Pediatric age variable is compared with reference to frequently prescribed off label drugs in Figure 1.

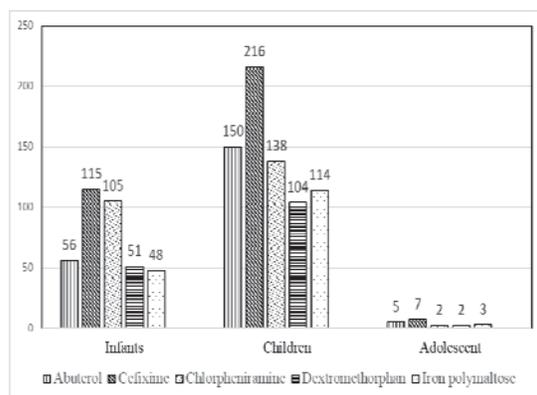
A significant association was found between type of hospitals and off label drug use ( $p < 0.0001$ ) by applying chi square test. In comparison between government & private hospitals drug use as off-label was more prevalent in private hospitals, i.e. in private healthcare setup NWGH it was 88.0 % and in RMI it was 78.5 % while in government hospitals HMC it was 56.3 % and in KTH it was 53.9 %.

**Table 1:** Patient characteristics and morbidities

Variable	Frequency NWGH (%)	Frequency RMI (%)	Frequency HMC (%)	Frequency KTH (%)	Total
<b>Age (months)</b>					
<i>Infant</i> $\geq 23$	165(10.4)	160(10.1)	98(6.2)	65(4.1)	488(30.7)
<i>Children</i> 24-143	228(14.3)	220(13.8)	296(18.6)	311(19.6)	1055(66.4)
<i>Adolescent</i> $\geq 144$	16(1.0)	6(0.4)	7(0.4)	17(1.1)	46(2.9)
<b>Total</b>	409(25.8)	386(24.3)	401(25.2)	393(24.7)	1589(100)
<b>Mean <math>\pm</math> SD</b>	41.5 $\pm$ (39.1)	37.5 $\pm$ (34.0)	45.6 $\pm$ (34.9)	60.4 $\pm$ (39.2)	46.3 $\pm$ (37.9)
<b>Range</b>	0.6-180	1-168	0.9-156	1-180	0.6-180
<b>Gender</b>					
<i>Male</i>	267(16.8)	262(16.5)	220(13.8)	203(12.8)	952(59.9)
<i>Female</i>	142(9.0)	124(7.8)	181(11.4)	190(11.9)	637(40.1)
<b>Total</b>	409(25.8)	386(24.3)	401(25.2)	393(24.7)	1589(100)
<b>Prescribed drugs</b>					
<i>1(1-3)</i>	176(11.1)	244(15.3)	319(20.1)	294(18.5)	1033(65.0)
<i>2(<math>\geq</math>3)</i>	233(14.7)	142(9.0)	82(5.1)	99(6.2)	556(35.0)
<b>Total</b>	409(25.8)	386(24.3)	401(25.2)	393(24.7)	1589(100)
<b>Mean <math>\pm</math> SD</b>	3.7 $\pm$ (1.0)	3.2 $\pm$ (0.9)	3.0 $\pm$ (0.6)	3.0 $\pm$ (0.7)	3.2 $\pm$ (0.9)
<b>Range</b>	2-7	2-6	2-5	2-5	2-7
<b>Diagnosis(ICD codes)</b>					
<i>Pharyngitis (J02)</i>	90(5.7)	122(7.7)	153(9.6)	108(6.8)	473(29.8)
<i>Bronchitis (J20)</i>	34(2.1)	25(1.6)	156(9.8)	142(8.9)	357(22.5)
<i>Protozoal intestinal disease unspecified (A07.9)</i>	57(3.6)	51(3.2)	53(3.3)	43(2.7)	204(12.8)
<i>Tonsillitis (J03)</i>	45(2.8)	22(1.4)	18(1.1)	43(2.7)	128(8.1)
<i>Allergic rhinitis (J30)</i>	46(2.9)	68(4.3)	1(0.1)	1(0.1)	116(7.3)
<i>Asthma (J45)</i>	19(1.2)	46(2.9)	1(0.1)	1(0.1)	67(4.2)
<i>Esophagitis (K20)</i>	31(2.0)	11(0.7)	4(0.2)	10(0.6)	56(3.5)
<i>Nasopharyngitis (J00)</i>	15(0.9)	25(1.6)	1(0.1)	3(0.2)	44(2.8)
<i>Sinusitis (J32)</i>	1(0.1)	1(0.1)	0(0)	23(1.4)	25(1.6)
<i>Protein-energy malnutrition of moderate and mild degree (E44)</i>	18(1.1)	1(0.1)	0(0)	1(0.1)	20(1.3)

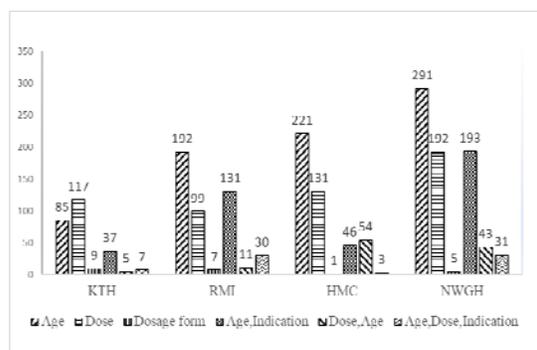
**Table 2:** Most frequently prescribed off-label drugs with their off-label categories

Generic	Age	Dose	Dosage form	Age, indication	Age, dose	Age, dosage form	Dose, dosage form	Age, dose, indication	Total
Cefixime	13	90	0	121	4	0	0	2	230
Chlorpheniramine	154	3	0	0	58	0	0	0	215
Iron polymaltose	0	1	0	135	0	0	0	29	165
Dextromethrophan	90	56	0	0	0	0	0	0	146
Albuterol	79	0	7	0	0	17	0	0	103
Levocetirizine	54	42	0	0	0	0	0	0	96
Domperidone	0	92	0	0	0	0	2	0	94
Tripolidine	57	3	0	0	22	0	0	0	82
Pseudoephedrine	59	1	13	0	0	2	0	0	75
Ipratropium bromide	0	0	0	70	0	0	0	0	70



**Figure 1:** Comparison of age groups with respect to most prevalent off label drugs

There was significant association between the age groups & off label drug ( $p < 0.0001$ ). Off-label use of drugs was prevalent more in children 44.2 % (702/1589) and infants 25.9 % (413/1589).



**Figure 2:** Comparison of hospitals with regard to frequency of off-label drug categories

While according to univariate and multivariate logistic regression insignificant association were found between gender & drug use on off label basis. We consider gender as an insignificant predictor of off-label use of drug because

multivariate logistic regression is more precise and accurate tool than chi square test.

Univariate logistic regression analysis shows that pediatric patients of age 0-23 months (OR 4.236, 95 % CI 2.250-7.975) were significantly more likely to receive off label drugs than adolescent. Similarly, patients receiving less than 4 drugs (OR 0.333, 95 % CI 0.256-0.434) were significantly less likely to receive off-label drugs as compared to patients receiving 4 or more drugs. NWGH (OR 0.268, 95 % CI 0.186-0.386), RMI (OR 0.159, 95 % CI 0.111-0.228) and HMC (OR 0.497, 95 % CI 0.338-0.730) were significantly less likely to receive off label drugs as compared to KTH.

Multivariate logistic regression analysis shows that pediatric patients of age 0-23 months (OR 4.134, 95 % CI 2.076-8.235) and of age 24-143 months (OR 1.857, 95 % CI 0.967-3.568) were significantly more likely to receive off label drugs than adolescent. Similarly, patients receiving less than 4 drugs (OR 0.414, 95 % CI 0.312-0.548) were significantly less likely to receive off-label drugs as compared to patients receiving 4 or more than 4 drugs. Hospitals such as NWGH (OR 0.388, 95 % CI 0.265-0.569), RMI (OR 0.231, 95 % CI 0.159-0.336) and HMC (OR 0.550, 95 % CI 0.370-0.818) were significantly less likely to receive off-label drugs as compared to KTH. Off-label use of drugs according to univariate and multivariate logistic regression are given in Table 3.

## DISCUSSION

Drug use as off label was widely observed in pediatric ambulatory population. This study underlines high rate of off label use of drugs (71.8 %) as compared to report published in France (29 %) [14]. A French study revealed 42 % off label use of drugs in pediatric ambulatory department [15]. Other studies performed in

**Table 3:** Predictors of off-label drug use

Variable	Univariate analysis		Multivariate analysis	
	OR(95% CI)	Significance	OR(95% CI)	Significance
Gender				
<i>Female</i>	1.33(1.068-1.663)	0.11	1.147(0.904-1.457)	0.259
<i>Male</i>	Reference		Reference	
Age				
<i>Infant</i>	4.236(2.250-7.975)	0.000***	4.134(2.076-8.235)	0.000***
<i>Children</i>	1.530(0.842-2.778)	0.16	1.857(0.967-3.568)	0.063*
<i>Adolescent</i>	Reference		Reference	
Prescribed drugs				
1(< 4)	0.333(0.256-0.434)	0.000***	0.414(0.312-0.548)	0.000***
2(≥4)	Reference		Reference	
Hospitals				
<i>NWGHRC</i>	0.268(0.186-0.386)	0.000***	0.388(0.265-0.569)	0.000***
<i>RMI</i>	0.159(0.111-0.228)	0.000***	0.231(0.159-0.336)	0.000***
<i>HMC</i>	0.497(0.338-0.730)	0.000***	0.550(0.370-0.818)	0.003**
<i>KTH</i>	Reference		Reference	

OR odd ratio, CI confidence interval, \*\*significant at  $p < 0.05$ ; \*\*\* significant at  $p < 0.01$

Germany from 2003-2006 showed 40.2 % of off-label use of drugs [16]. While studies performed in United States, Estonia and Sweden also reported a high rate of off label use of drug from 13.5 to 62 % [1,5,14]. This variability in rate of off label use of drugs may be on account of different drug authorization status for pediatric use in different region as well as lack of data on dose and indication for specific age group of children in essential drug lists of respective region. In the study drug use as off label was less prevalent in government than private healthcare setups. This difference is due to variation in morbidities and different prescribing practice in hospitals. In this study 35.6 % patients received at least one off-label drug which was much lower when compared to the Swedish study (64 %) [1]. This variability is probably due to different types of off label drug categories considered in the different studies.

We have analyzed off label use of drug in relation to age of pediatrics and found high prevalence of off label drug use in children and infants. Reports from studies performed in France also revealed similar high proportion of off labeling in children 23.1 %, infant 18.8 % and adolescent 16.8 % [14]. There was significant relationship found between infant and children age group and off label use of drugs. Other studies performed in USA, Malta and Spain also showed high percentage of off label use of drugs in children and infants [5,17,18].

In this study age and dose were the common were the common reason for off label drug use, study conducted in USA in an outpatient sitting reported the same reason [5]. In contrast to other studies slightly different reasons have been found. A Spanish study conducted in pediatric gastroenterology outpatient had revealed that

indication (82 %) and dose (17.3 %) were the main causes for the drug use as off label [18]. Alike study in France reported indication and dose as most prevalent off label drug use categories [15]. An Irish study has showed dose 63.3 % as most prevalent off label drug use category followed by age 34.3 % [19]. Many studies revealed dose as most common off label category in outpatient setting [20,21]. Another study has also reported dose as the major cause for drug use as off label followed by indication. When compared to other researches, dose was common among all off label drug categories. The reason could be lack of clinical trials in children for their dose estimation which have not been covered by summary of product characteristics and for same reason not reported in Micromedex DRUGDEX database.

Antibacterial for systemic use (21.7 %) and Anti histamine for systemic use were the most frequently prescribed therapeutic drug class in accordance with Swedish and Irish studies conducted on ambulatory pediatric clinics [1,19]. Another study conducted in US also observed concurrent findings[5]. An Italian study showed anti-bacterial for systemic use and drugs for alimentary tract as most common prescribed drug classes [22]. Similarly, evidence from other studies, report anti-bacterial for systemic use and anti-histamine for systemic use as most prevalent therapeutic drug class [19]. A pharmacovigilance survey in France on 1419 patients also report anti-bacterial for systemic use as most commonly prescribed drug class.[15]. A high prevalence of anti-bacterial and anti-histamine in pediatric population might be due to exposure to microbial infections and most of drugs under these therapeutic drug classes were not labeled for pediatrics.

In our study the most commonly drugs prescribed were ibuprofen and acetaminophen in concordance with other studies [14,20]. Similarly, Lifshitz *et al* conducted a study at Israel which revealed amoxicillin in addition to acetaminophen as most prevalent prescribed drugs to pediatrics [19]. Kazouini *et al* analyzed prescribing of acetaminophen in Scottish children and found it typically prescribed as an off label drug [16]. Acetaminophen is not licensed for children under 2 months of age in British National Formulary [23] and according to Micromedex DRUGDEX database in children having age under 2 years the use of acetaminophen is not suggested.

In this study, there was positive and significant relationship between off label drug use and age. Patients in younger age groups (infants and children) were significant predictor for the use of drug as off label as demonstrated by other studies [20,21,24]. Another significant positive predictor for the use of drug as off label in the current study was patients receiving 3 or less than 3 drugs. A similar finding has been reported by many other studies [5,15,21]. There was no significant correlation between gender and off label drug use like many other studies [15,24]. The reason behind this may be that no consideration is given to the gender during drug development processes.

The adverse effects of drug also increasing due to prescribing drugs in off label manner. It is noted that because of off label drug use 17 % adverse drug reaction occurs [18]. Therefore, certain measures have been taken to improve pediatric pharmacotherapy. An example is the launching of pediatric regulations for the purpose of improving the health of the children [7]. Many legislations including the Pediatric Research Equity Act of 2003, the best Pharmaceuticals for children Act of 2002, the pediatric exclusivity component of the Food and Drug Modernization Act of 1997, the Food and Drug Administration Amendments Act and European Union regulations 2007 are appreciable but more incentives and funds are required to conduct clinical drug trials on pediatrics to achieve unmet therapeutic requirements of children. Still more than 400 products have not been formally analyzed in children [7].

The high level of off label use of drug in children suggested that further clinical researches are required to find out the reasons for the use of drug in off label manner. Gazarian *et al* described that many prescribers believed that off label use of drugs is legal where benefits outweigh risks. However, it should not be recommended since adequate knowledge of true

balance between risk and benefit is unknown that may lead to adverse effects. [21]. Clinical trials should not be done only for new drugs but also for already available drugs in the market currently used as off label. It is also recommended that upon new information on literature of the product should be made available and updated time to time by the regulatory in order to ensure children are not exposed to unnecessary risks and provide them with approved evidenced based therapy.

This current study analyzed off-label use of drug only in pediatric ambulatory population in tertiary care system, off label drug use should also be monitored in other ambulatory departments. In addition, it should be extended to primary health care system.

### Limitations of the study

The study was specifically conducted in pediatrics ambulatory departments of tertiary care hospitals, it does not reflect the trends of off-label use of drugs in other departments of hospitals in Pakistan. The results of study need to be generalized with caution in population. Electronic medical records were not available that's why study took time.

### CONCLUSION

This study has reported a higher rate of off label use of drug in ambulatory pediatrics. To the best of our knowledge, no such study has recognized this problem in ambulatory pediatric in our country. In order to avoid pediatrics from exposing to unnecessary risk researchers should target those unstudied drugs that accounts for off label prescribing. It is important that new ways and strategies should be established by national and international authorities to ensure safe and effective evidence-based pediatric pharmacotherapy.

### DECLARATIONS

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#### Conflict of interest

No conflict of interest is associated with this work.

### Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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