Off-label drug use in pediatric wards: a prospective study in a tertiary care hospital in Pune

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Aim and objectives
The aim of this study was to identify the most common off-label drug used in pediatric wards and to classify the age group in which off-label medications were prescribed.
Materials and methods
A 2-month prospective study was carried out in a tertiary care hospital in Pune. Seventy patient medication charts were reviewed. Two drug databases, the Micromedex drug database and Medscape drug reference, were the secondary sources of reference used and the National Formulary of India (NFI) was also used as the tertiary source of reference to assess and identify off-label drug use.
Results
Out of 70 patients enrolled in the study, 57 (81%) patients were prescribed off-label medications. The most common off-label prescription were for ipratropium bromide (12%), pantoprazole (12%), salbutamol (11%), and fosphenytoin (10%); it was found that safety and efficacy in the pediatric population were not established on most of the drugs that were prescribed off label, whereas some drugs were prescribed in an indication for which the drug was not approved by the Food and Drug Administration (FDA). The highest proportion of off-label drugs was prescribed in infants.
Conclusion
Off-label prescribing in the pediatric population was very high; the highest proportion of off-label drugs was prescribed in infants. Use of a drug database and the NFI can be useful in identifying off-label prescribing in pediatrics.

keywords:
medscape, micromedex, off-label

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Introduction

The term off-label drug use is a polarizing term because it can be associated with great benefit or harm to patients. The most common form of off-label drug use involves prescribing currently available and marketed medications, but for an indication (e.g. a disease or a symptom) that has never received Food and Drug Administration (FDA) approval. In the pediatric population, off-label drug use can also apply to the use of a marketed medication at a dose or dosage form that does not have FDA approval [1]. The administration of unlicensed and off-label medicines to children is highly prevalent. In the absence of clinical trials, neither efficacy nor safety has been established for the indications for which the medicines may be used [2]. The purpose of off-label use is to benefit an individual patient. 'Off-label' does not imply an improper, illegal, contraindicated, or investigational use. An off-label use may provide the best available intervention for a patient as well as the standard of care for a particular health problem for which there is no relief from the standard drugs that are primarily indicated for its management. Off-label use is sometimes unavoidable; three-quarters of marketed prescription drugs have no labeling indications for children [3]. The American Academy of Pediatrics states in their policy statements that Best Pharmaceuticals for Children Act and Pediatric Research Equity Act are two complementary federal laws that have considerably increased clinical evaluation and labeling of drugs in children both by the pharmaceutical industry and through government-sponsored trials. The PREA mandates that almost all new drugs and certain approved drugs must be studied in children for approved uses of the product if there is potential for use of that drug in children and that the applications for new drug approval include the results of adequate pediatric studies unless the studies are deferred or waived by the FDA. The BPCA allows sponsors to qualify for an additional 6 months of market exclusivity if the sponsor completes and

submits pediatric studies to the FDA [4]. Also, off-label use is not regulated uniformly worldwide. In countries such as France, drug agencies that regulate marketing prohibit dissemination of information on off-label use. The European Medicines Agency is more receptive to the off-label practice by proactively supporting clinical trials of off-patent drugs for off-label indications, especially in children [3].

Pandolfini and Bonati [5] performed a literature review of 30 studies from 1985 to 2004 to identify the off-label prescribing patterns across various settings; it was found that off-label/unlicensed prescriptions ranged from 16 to 62%. In France, a prospective one-day survey of all written prescriptions in pediatrics was carried out by Chalumeau *et al.* [6]; this study showed that 56% of pediatric patients received one or more off-label prescriptions. Neither efficacy nor safety has been established in most of the indications for which the medicines may be used in pediatrics. It is therefore necessary to identify indications for which medicines are actually used in pediatrics [2]. As a result, there is a need to generate more quality data on off-label use of medicines in the pediatric population to rationalize pediatric pharmacotherapy.

Materials and methods

This was a prospective study carried out in a 300-bed tertiary care hospital in Pune. The study was carried out over a 2-month period between August and September 2015; all inpatients admission in pediatric wards during this period were enrolled in the study. Patients from the pediatric ICU, the high-dependency unit, and the general ward were also included in the study. The aim of the study was to identify the most common off-label drug used in the pediatric wards and to identify the age group in which off-label medications were prescribed. Two drug databases, the Micromedex drug database and the Medscape drug reference, were the secondary sources of reference used and the National Formulary of India (NFI) was also used as a primary source of reference to assess and identify off-label drug use. Off-label use was categorized as follows: age (drug medicines may be used outside the approved age range), dose (dose higher than recommended), non-FDA indication/non-FDA approved in pediatrics, route of administration, drug administered by a route not approved by FDA, safety and efficacy not established, and safety and efficacy uncertain by the route in which it was administered. The percentages of off-label drug prescribed in various pediatric age groups were determined and presented as summary statistics.

Results

Seventy pediatric inpatient medication charts were reviewed during the study period of 2 months; of these 70 patients, 57 (81%) patients were prescribed off-label medications. In these 57 patients, 30 patients were admitted in the general ward, 15 patients were admitted in the high-dependency unit, and 12 patients were admitted in the pediatric ICU. The male–female ratio was found to be 2 : 1; 38 admitted patients were males and 19 patients were females. Patients across all the pediatric age groups were included in the study (Table 1).

The most common off-label prescriptions were for ipratropium bromide (12%), pantoprazole (12%), salbutamol (11%), fosphenytoin (10%), piperacillin, and tazobactum (8%), followed by phenylephrine HCl, clobazam, valproate, and azithromycin. Figure 1 shows a list of off-label medications prescribed in the study.

On categorical classification, it was found that the safety and efficacy in the pediatric population was not established for most of the drugs that were prescribed as off-label as some drugs were prescribed in an indication for which the drug was not approved by FDA. Categorical classification of off-label use is shown in Table 2.

It was found that 59% of off-label medications were prescribed in infants, followed by young children (2–6 years), 19%, children in the age range of 6–12 years, 12%, and adolescents, 10%.

Discussion

After reviewing the inpatient medication charts in the pediatric ward of a tertiary care hospital, we found

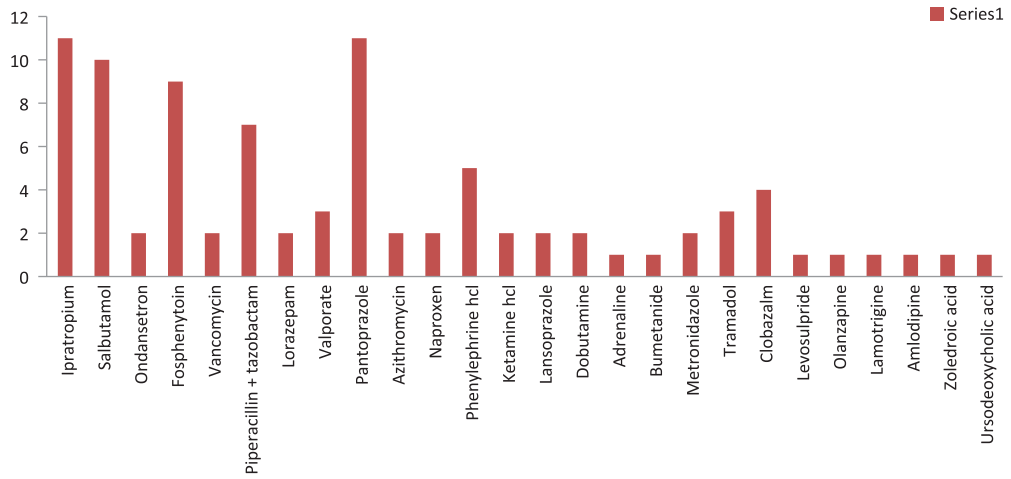
Table 1 Age distribution of patients

Age distribution of patients	Total number of patients
Infant (1 month to 2 years)	34
Young child (2–6 years)	10
Child (6–12 years)	10
Adolescent (12–18 years)	3

Table 2 Categorical classification of off-label use

Categorical classification of off-label use	
Safety and efficacy not established	49%
Non-FDA indication/non-FDA approved	21%
Safety and efficacy uncertain by the route in which it was administered	21%
Age (drug medicines may be used beyond the approved age range)	2%
Route of administration, drug administered by a route not approved by FDA	1%

Figure 1



Prescribed off-label medications.

that off-label drug prescribing in the pediatric wards was 81% compared with previous studies carried out in India by Jain *et al.* [7], which showed up to 50.6% off-label prescribing; this study was comparable with our study as it was a 2-month prospective study, but our 2-month study showed up to 30% higher rates of off-label prescribing. Saiyed *et al.* [8] carried out a 6-month study that reported up to 70% off-label prescribing; the off-label prescribing that we found during our 2-month study period was higher than their 6-month study. Schmiedl *et al.* [9] carried out a drug utilization and off-label prescribing study of respiratory drugs in children; the study showed that the highest absolute number of off-label prescriptions was found for inhaled salbutamol (42.0%). Our study was not limited to respiratory drugs; however, we found up to 11% off-label prescribing of salbutamol. The study by Jain and colleagues reported that the maximum rate of off-label drug use was noted in infants. 'Change in dosage' was by far the most common reason for off-label use, followed by 'age' and 'indication [7]; our study also found that the maximum off-label prescribing was found in infants, up to 59%, and the most common reason that we found was that most off the drugs fell into the category of safety and efficacy not being established for pediatric population. Our study was only limited to identifying the off-label drug prescribing in pediatric wards; adverse events because of off-label prescribing were not determined in this study. Some studies suggest that off-label medicines are more likely to be implicated in an ADR than authorized medicines and off-label drug use was significantly associated with adverse drug reactions [10,11].

Conclusion

The study concluded that the off-label prescribing in the pediatric population was very high; the most common off-label drugs were respiratory disease drugs, Proton pump inhibitors, and antiepileptic drugs. Safety and efficacy had not been established with most of the drugs and non-FDA-approved drugs were prescribed. The highest proportion of off-label drugs was prescribed in infants. The study also concluded that the use of drug databases and the NFI was useful as secondary and primary sources of references.

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Nil.

Conflicts of interest

None declared.

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