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Off-label and Unlicensed Drug Use in Paediatric Outpatient Department – A Prospective Study at a Tertiary Care Teaching Hospital

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ABSTRACT

Objective: To assess prevalence and pattern of off-label and unlicensed use of drugs in paediatric outpatient department. **Methods:** In this prospective study, children attending paediatric outpatient department of a tertiary care teaching hospital were enrolled. Demographic data, clinical history and completeprescription given to the patient were noted. Prescriptions were analysed for off-label and unlicensed drug use with the help ofrecent British National Formulary for Children (BNFC) and National Formulary of India (NFI). **Results:** Total of 170 patient's data was collected over 2 months with mean age 4.19 ± 3.66 years. Out of total of 405 drugs prescribed, 41 (10.1%)-BNFC and 32 (7.9%)-NFI were used in off-label manner. Number of children who received at least one off-label drug as per BNFC and NFI was 22.4% and 17.1%, respectively. Most common off-label drug was amoxicillin being 48.8%-BNFC and 34.4%-NFI of all drugs prescribed in this manner. Most common category for off-label prescription was inappropriate dose. Only one case was noted for unlicensed drug use. Off-label drug prescribing significantly correlated with age of the patient and number of drugs per prescription. **Conclusion:** Off-label drug use is prevalent in paediatric outpatient department, amoxicillin being the commonest drug.

Key words: Drug utilization, Off-label, Outdoor patients, Paediatric, Unlicensed.

INTRODUCTION

The FDA approved label is the official description of a drug product which includes indication (what the drug is used for); who should take it; adverse events (side effects); instructions for uses in pregnancy, children, and other populations; and safety information for the patient.[1] Drug authority approves a drug for use in population with a marketing label after thorough clinical studies have been conducted.

Paediatricians can prescribe drugs either adhering to these marketing label (i.e. label prescribing) or prescribing outside the marketing label (i.e. off-label prescribing) in the best interest of the patients. According to Turner *et al*, the category of off-label use includes use of a drug in situations not covered by the product licence: administration of a greater or lesser licensed dose, administration for indications which are not described in the license, administration to children outside approved age range,

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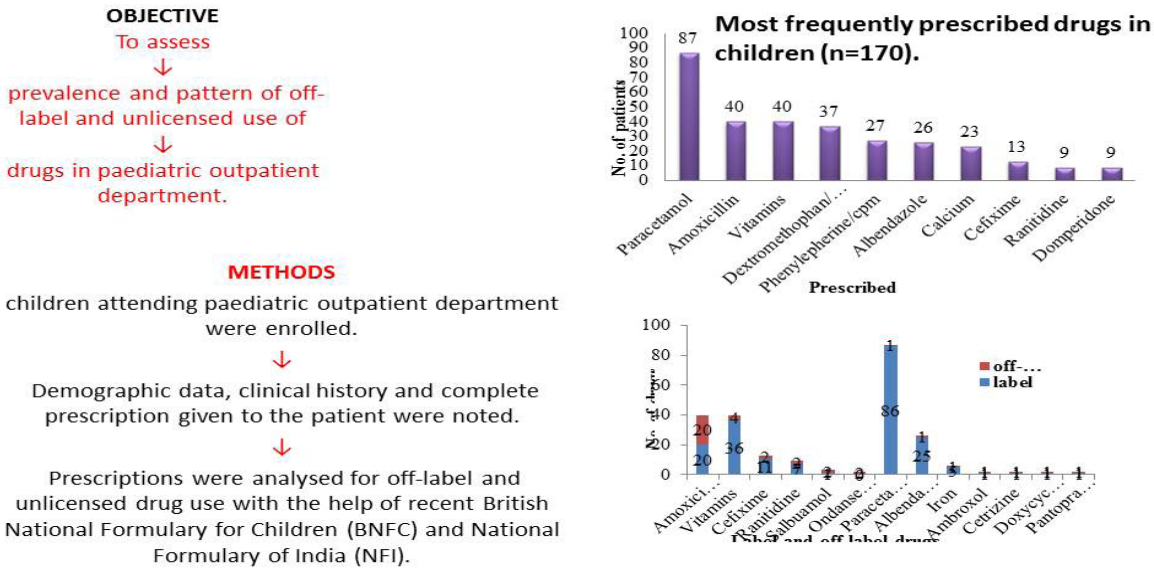

Graphical Abstract

use of alternative route of administration, and use when the product is contraindicated. Category of unlicensed use includes: modifications of licensed dosage form, drugs that are licensed but the particular formulation is manufactured under a special license (such as when an adult preparation is not suitable for use in children and a smaller dose must be formulated), new drugs available under a special manufacturing license, use of those drugs have often been used for many years but have never undergone formal clinical trials or been subject to the licensing regulations and therefore have no product licence (such as caffeine injections for apnoea of prematurity), use of chemicals as drugs, drugs used before a license has been granted, and imported drugs.[2]

The licensing procedure of new drugs aims at ensuring their safety, efficacy, quality and positive benefit-risk balance. Such an assessment is based on sequential clinical trials, which in thepast were almost exclusively performed in adults. Many drugs pass through the licensing process without being evaluated in children. As a result, many drugs are neither tested nor authorized to be prescribed in children. This debt in the clinical trials in children is a grey area in licensing drugs for paediatric age group.[3,4] Therefore product license often contains statements such as "not recommended for use in children", or "no evidence for use in children". This usually reflects an absence of data in children ratherthan a specific reason for the drug not to be used.[5] Consequently, off-label or unlicensed drugs prescribing is higher in the paediatric age-group as compared to adult population.[3,4] Off-label or unlicensed drugs prescribing is reported to increase chances of under-prescribing, over-prescribing and cost of therapy[6] and potentially increases risk of adverse drug events.[3,7]

It has been reported that the vast majority of paediatric patients in hospital care are at risk of receiving at least one drugused off-label or unlicensed. Off-label prescribing is highly prevalent in neonates (up to 100%), in children (up to 80%), in over all paediatric age group (two-thirds), whereas the proportion of prescriptions for unlicensed drugs varies between 3 and 48%. In outpatient care, the proportions of off-label and unlicensed drug prescriptions varies between 11 and 31% and between 0.3 and 17%, respectively.[8]

Several studies both in outpatient and inpatient settings related to off-label and unlicensed use of drug in children have been reported worldwide.[9-12] However there is a paucity of such studies from India. Hence these prospective study was planned to estimate the off-label and unlicensed use of drug and to correlate between the British National Formulary for Children (BNFC)-2012[13] and National Formulary of India (NFI)-2011[14] for identification of such use and to assess the impact of such prescribing on direct cost of drug therapy in paediatric outpatient departmentof a tertiary care teaching hospital.

Table 1: Demographic and clinical characteristics of paediatric patients (n=170)

Variables		No of Patients (%)	No of Off-label BNFC (%)	No of Off-label NFI (%)
Gender	Male	102(60%)	22(12.9%)	15(8.8%)
	Female	68(40%)	16(9.4%)	14(8.2%)
Age Group	Less than 1 year	53(31.2%)	7(4.1%)	4(2.4%)
(in years)	1-5 years	59(34.7%)	17(10%)	11(6.5%)
	5-12 years	58(34.1%)	14(8.2%)	14(8.2%)
Symptom	Cough-cold	118(69.4%)	27(15.9%)	20(11.8%)
	Fever	99(58.2%)	26(15.3%)	18(10.6%)
	Vomiting	16(9.4%)	7(4.1%)	6(3.5%)
	Abdominal pain	14(8.2%)	2(1.2%)	2(1.2%)
Morbidity	Malaria	65(38.2%)	12(7.1%)	11(6.5%)
	URTI	60(35.3%)	14(8.2%)	12(7.1%)
	Diarrhoea	18(10.6%)	4(2.4%)	3(1.8%)

BNFC-British National Formulary for Children; NFI-National Formulary of India

MATERIAL AND METHODS

A prospective, cross-sectional study was carried out in paediatric outpatient department of a tertiary care teaching hospital at VS Hospital, Ahmedabad over a period of 2 months–July 2012 to August 2012. Institutional ethics committee approval was obtained along with permission from hospital superintendent and head of pediatrics. All the patients attending the paediatric outpatient department during this period were enrolled in the study after obtaining informed consent of patient's guardian. Children up to the age of 12 years are considered paediatric patients. Demographic data, complete clinical history and complete prescription details were recorded in case record form. The prescription given to the patient including the drug prescribed, dose, frequency and duration of the treatment was noted.

BNFC and NFI were used as a reference source to identify off-label and unlicensed prescriptions. Direct cost of drug treatment calculated using patient's hospital and pharmacy bills. In case of missing bills, cost of drugs was obtained from commercial publications like Indian Drug Review 2012[15] and CIMS online.[16]

Statistical Analysis

All data were recorded in Microsoft excel 2010 spread sheet® and analysed using SPSS version 21.0®. Pearson correlation coefficient was used to determine the association of off-label prescribing with age, number of drugs and cost of pharmacotherapy. P value less than 0.05 was considered as significant.

RESULTS

Demographic and Morbidity pattern

Total 170 children were included with mean age of 4.19 ± 3.66 years (Range 15 days-12 years). Male patient's comprised-102 (60%). Most of the patients presented with cough-cold-118 (69.4%) and fever-99 (58.2%). The most common diagnosis was malaria-65 (38.2%) followed by upper respiratory tract infection-60 (35.2%). (Table 1)

A total of 405 drugs were prescribed with mean number of drugs prescribed per patient 2.3 ± 0.91. Paracetamol-87 (21.5%) was the most frequently prescribed drug followed by amoxicillin-40 (9.9%). (Figure 1)

Off-label drug use

Out of 405 drugs, 41 (10.1%) and 32 (7.9%) were used in off-label manner according to BNFC and NFI respectively. Number of children who received at least one off-label drug as per BNFC and NFI was 38 (22.4%) and 29 (17.1%) respectively. Number of children who received more than one off-label drugs as per BNFC and NFI was 3 (1.8%). The drug most frequently prescribed in off-label manner was amoxicillin-20 (48.8%) and 11 (34.4%) as per BNFC and NFI respectively. The frequency for amoxicillin off-label use was significantly higher than other drugs ($p< 0.0001$). (Figure 2A, 2B) Most common category for off-label prescription was inappropriate dose. (Table 2) Only one case was noted for unlicensed drug use; in category of inappropriate age.

BNFC and NFI correlation

As far as identification of off-label prescribing is concerned BNFC and NFI showed strong correlation ($r=0.879$, $p< 0.0001$).

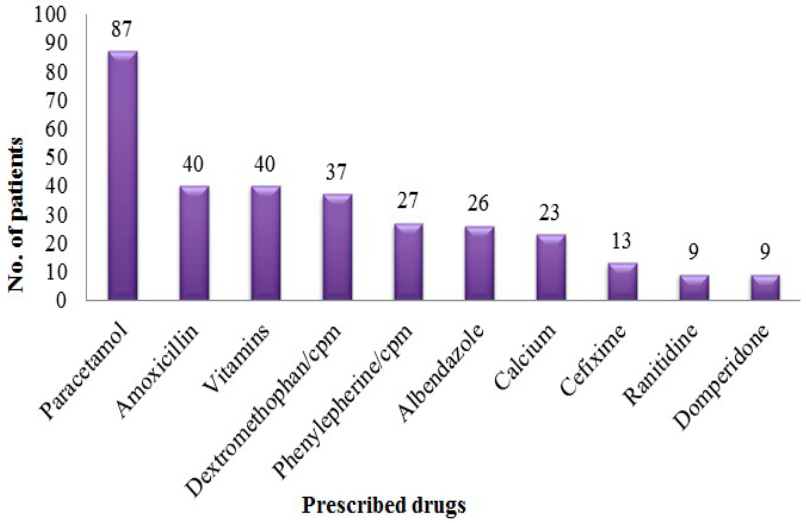

Figure 1: Most frequently prescribed drugs in children (n=170)

When all the prescriptions were assessed by using BNFC or NFI, the group which received at least one off-label or unlicensed drug had higher mean age and greater number of drugs which was statistically significant. There was positive and significant correlation between off-label prescribing and age of the patient (Pearson correlation coefficient r=0.198, p=0.010 for BNFC, r=0.287, p<0.0001 for NFI) and number of drugs (Pearson correlation coefficient r=0.239, p=0.002 for BNFC, r=0.205, p=0.008 for NFI). There was no correlation between off-label drug prescribing and cost of pharmacotherapy. (p=0.469 for BNFC, p=0.314 NFI).

DISCUSSION

Our study aimed to analyze the proportion of off-label and unlicensed drug use based on BNFC and NFI andto correlate between the BNFC and NFI and to find out the impact of such prescribing on direct cost of drug therapy in paediatric outpatient department.

Mean age of patients in our study was higher as compared with earlier two Indian inpatient studies reporting 3.70 ± 3.57 years and 3.96 ± 3.48 years, respectively.[17,18] This difference might be due to variation in geographical location. In our study males were higher as seen as in previous Indian inpatient study.[18] In our study most common diagnosis was malaria followed by upper respiratory tract infection while in previous Brazilian inpatient study pneumonia was the most common diagnosis.[9] While in the Swedish outpatient study systemic infectious diseases was the most common diagnosis followed by respiratory tract infection.[11] This might be due to differences in prevalence of diseases across different countries. Mean number of drugs prescribed per

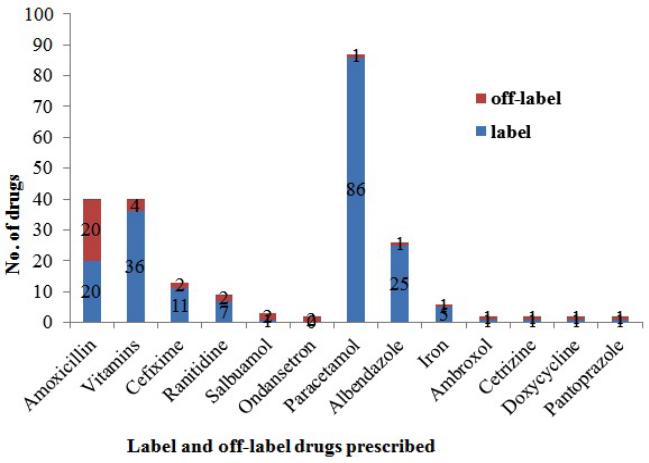

Figure 2(A): Off-label prescribing as per British National Formulary for Children (BNFC) -2012

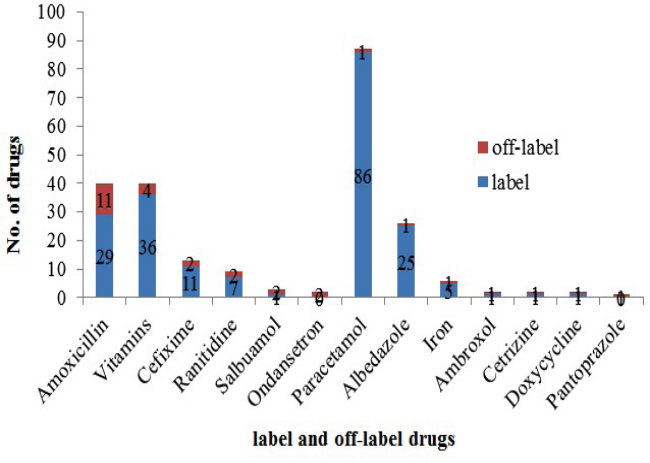

Figure 2(B): Off-label prescribing as per National Formulary of India-2011

Table 2: Drugs prescribed in off-label manner as per BNFC and NFI

Drug	ATC code	Reason for off-label	Frequency as per BNFC N=41	Frequency as per NFI N=32
Amoxicillin	J01CA04	Inappropriate dose	20 Higher dose-17 Lower dose-3	11 Higher dose-10 Lower dose-1
Vitamins	A11AA03	Indication and Inappropriate dose	4 Not indicated-2 Lower dose-2	4 Not indicated-2 Lower dose-2
Ondansetron	A04AA01	Indication	3 Not indicated-3	3 Not indicated-3
Cefixime	J01DD08	Inappropriate dose	2 Higher dose-1 Lower dose-1	2 Higher dose-1 Lower dose-1
Ranitidine	A02BA02	Inappropriate dose	2 Higher dose-1 Lower dose-1	2 Higher dose-1 Lower dose-1
Salbutamol	R03AC02	Inappropriate dose	2 Higher dose-2	2 Higher dose-2
Pantoprazole	A02BC02	Inappropriate dose	2 Higher dose-2	2 Higher dose-2
Paracetamol	N02BE01	Inappropriate dose	1 Higher dose-1	1 Higher dose-1
Albendazole	P02CA03	Inappropriate dose	1 Higher dose-1	1 Higher dose-1
Iron	B03AA07	Inappropriate dose	1 Lower dose-1	1 Lower dose-1
Ambroxol	R05CB06	Inappropriate dose	1 Higher dose-1	1 Higher dose-1
Cetrizine	R06AE07	Inappropriate dose	1 Higher dose-1	1 Higher dose-1
Doxycycline	J01AA02	Inappropriate dose	1 Lower dose-1	1 Lower dose-1

ATC=Anatomical Therapeutic Chemical classification; BNFC= British National Formulary for Children (BNFC)-2012; NFI= National Formulary of India (NFI)-2011.

patient was 2.3 ± 0.91 which are comparable to previous outpatient studies from UK.[19,20] In our study antipyretics and antibiotics were most commonly prescribed drug groups which is in accordance with previous inpatient studies from UK and Ireland.[20,21] but Swedish outpatient study showed antibiotics and drugs for respiratory system were the most frequently prescribed drug groups.[11] This difference might be due to variation in morbidity pattern in different countries. Paracetamol was the most frequently prescribed drug followed by amoxicillin which was similar to a previous outpatient study from UK.[20] This result is expected as most common presenting complaint was fever in both the studies.

In our study, out of 405 drugs, 41 (10.1%) and 32 (7.9%) drugs were used in off-label manner according to BNFC and NFI respectively which was comparable to a previous outpatient study reported a decade back from UK which showed 10.5% off-label prescription of drugs according to BNFC.[20] However it was lower as compared to previous outpatient studies from Brazil, Swedish, Estonia; the possible reason of this difference might be due to variation in prescribing pattern across different countries.[10-12] Number of children who received at least one off-label drug as per BNFC and NFI was 38 (22.4%) and 29 (17.1%) respectively which was lower as compared to earlier Swedish outpatient study (64%),[11] which suggests possibly greater awareness among paediatricians related to issue of off-label prescribing. In our study antibiotics, vitamins followed by anti-emetics were the most common off-label drugs. While in previous outpatient studies from Sweden and US, topical dermatological agents, antidepressant, hypnotics, NSAIDs, cardiovascular-renal, pain, gastrointestinal and pulmonary medications were the most frequently prescribed off-label drugs.[11,12] However our results are comparable to previous inpatient study from Ireland.[21] The drug most frequently prescribed in off-label manner was amoxicillin being 20 (48.8%) and 11 (34.4%) as per BNFC and NFI, respectively. The frequency for amoxicillin off-label use was significantly higher than other off-label drugs similar to previous outpatient study in UK,[20] it might be due to greater number of prescriptions of this drug in the study population. The dose of amoxicillin should be calculated on body weight bases in paediatric patients. When calculated in

this way both higher and lower than recommended doses were identified which could lead to adverse effect, failure of therapy or emergence of resistance.

Pulmonary medications such as salbutamol, ambroxol and cetirizine were used in off-label manner for a common reason i.e. use of higher than recommended doses which was similar to previous Swedish and US outpatient studies.[11,12] This practice of giving higher doses of drugs can result into adverse events.

Vitamins were used in off-label manner without their indication and use in lower doses than required according to age. This finding was also seen in previous neonatal inpatient study reported in UK.[22] This might be due to vitamins being prescribed frequently because of parenteral anxiety. Three malarial patients received ondansetron to suppress vomiting. This use was in off-label manner because ondansetron is only indicated to suppress the post operative and chemotherapy induced vomiting.[23] However there is certain evidence that the use of oral ondansetron is effective in paediatric age group.[24] There were two prescriptions for pantoprazole and both were off-label due to administration of higher than recommended doseswhich was similar to previous US outpatient study.[12]

Most common category for off-label prescription was inappropriate dose (85% of total off-label prescribing) which was similar to previous UK outpatient studies (89% and 73% of total off-label drug prescribing).[20,22] Lack of pharmacokinetic data and clinical trials in children leads to larger discrepancies in dose estimation, leading paediatricians to use doses based on extrapolation from adult parameters.[22]

Only one incidence of unlicensed prescribing (0.25%) was seen comparable to Estonian outpatient study (0.05%).[10] Paracetamol being prescribed to a fifteen days old child suffering from fever amounts to an unlicensed use according to BNFC and NFI. Paracetamol is not licensed for use in less than 2 months old child according to BNFC. NFI recommends use of paracetamol only for post immunization pyrexia.[14] Such use can lead to severe hepatotoxicity to the neonate.[13,14]

There was good correlation between BNFC and NFI, but we found out that the drug information in BNFC which is specific for children is greater in depth as compared to NFI which is meant for all age groups including children. There were a few limitations of our study; we included prescription from tertiary care teaching hospital so result may not accurately reflect practice in other settings. Study period wasshort but adequate considering prospective design.

There is a need to raise awareness of off-label prescribing problem among paediatricians so as to improve the prescribing of drugs. Clinicians can prescribe off-label or unlicensed drugs provided they are aware about the benefits of such prescribing in certain special conditions.[25,26] To ensure that children are not exposed to unnecessary risks, controlled paediatric clinical trials are required for drugs to determine the most appropriate dose in children of different age groups.[27]

CONCLUSION

Off-label drug prescribing is prevalent in paediatrics outpatient practice. Antibiotics are the most commonly prescribed off-label drug group, among them amoxicillin being the most common followed by vitamins, anti-emetics and antacids. There is a need to raise awareness among paediatricians and encourage evidence based off-label drug used by the pharmacologists. Moreover use of various drug formularies also can improve the prescribing for children.

CONFLICTS OF INTEREST

Authors declared there is no conflict of interest.

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Highlights of Paper

- Number of children who received at least one off-label drug as per BNFC and NFI was 22.4% and 17.1%, respectively.
- Most common category for off-label prescription was inappropriate dose.
- Only one case was noted for unlicensed drug use.
- Off-label drug prescribing significantly correlated with age of the patient and number of drugs per prescription.
- Off-label drug use is prevalent in paediatric outpatient department, amoxicillin being the commonest drug.

Author Profile

- Dr. Devang Rana, is a Lecturer at the Department of Pharmacology, NHL Municipal Medical college, Ahmedabad. His interest is in the area of Clinical trials and clinical research. At NHLMMC additionally, he is also done DNB Clinical Pharmacology and won SC Verma National Award at Indian Pharmacological Society, Ahmedabad Conference.

- Dr. Sunil is a 3rd year PG student at the Department of Pharmacology, NHL Municipal Medical college, Ahmedabad. His interest is in the area of Clinical trials and clinical research. At NHLMMC additionally, he is also done many research paprs and presentations.

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