

## Unlicensed and off-label utilization of drugs in pediatric department at tertiary care teaching hospital: A prospective study

Meeta D. Vadher<sup>1,\*</sup>, Kamlesh Patel<sup>2</sup>, D.K. Vadher<sup>3</sup>, Sujal Parkar<sup>4</sup>

<sup>1,3,4</sup>Assistant Professor, <sup>2</sup>Associate Professor, <sup>1,2</sup>Dept. of Pharmacology, <sup>3</sup>Dept. of Pediatric, <sup>4</sup>Dept. of Public Health Dentistry, <sup>1,4</sup>Siddhpur Dental College & Hospital, Siddhpur, Patan, Gujarat, <sup>2</sup>Smt. NHL Municipal Medical College & Hospital, Ahmedabad, <sup>3</sup>C.U.Shah Medical College & Hospital, Surendranagar, Gujarat

**\*Corresponding author:**

Email: meeta1180sdch@gmail.com

### Abstract

**Background:** The treatment of pediatric patients with drugs in hospitals is being impeded by a shortage in the availability of licensed drugs in an appropriate formulation. Aim of this study is to assess the extent of use of drugs that are not licensed (unlicensed) and drugs that are used outside the terms of the product license (off-label).

**Material and Methods:** A prospective study was conducted among 210 pediatric patients attending outpatient and inpatients (ward and pediatric intensive care unit) at tertiary care teaching hospital. Demographic data and complete prescription were noted in the predesigned case record form (CRF). Drugs were classified off-label and unlicensed by using National Formulary of India (NFI). Off-label drugs were classified in regards to their indications by using Anatomical Therapeutic Chemical (ATC) Classification. The proportion was compared using chi-square test for statistical analysis.

**Results:** Out of 1053 drugs, prescribed (42.5%) were off-label drugs and (13.7%) were unlicensed drugs respectively. There was no significant result difference ( $p>0.05$ ) when the proportion of drug prescribed for outpatients and inpatients. The highest proportion of off-label and unlicensed drugs were prescribed among 0-2 years. Respiratory drug (58.7%) and anti-infective (57.1%) had higher off-label use. The most common reason for off-label use of drugs was dosage of drugs.

**Conclusion:** This study shows high level of prevalence of prescribing off-label and unlicensed drugs outpatients and among 0-2 years hence it is recommended to generate more quality data on the safety and efficacy of off-label and unlicensed drugs to rationalize paediatric pharmacotherapy.

**Keywords:** Unlicensed drug, Off-label drug, Prescription, Pediatric patient

### Introduction

Before a drug is launched in the market, the favourable balance between benefit and harmful effects has to be demonstrated. The purpose of licensing is to ensure that medicines are marketed only after safety, efficacy, and quality approval. When a drug is prescribed outside these parameters, this support is lacking and the off-label or unlicensed prescribing may occur.<sup>(1)</sup> Off-label drugs usage is that in which drugs are prescribed outside their license indications with respect to dosage, age, indications or route and unlicensed drugs that are prepared as extemporaneous preparations, which are imported or used before a license is granted or that are chemical used for therapeutic purpose.<sup>(2)</sup>

Off-label prescription is not illegal; it is not necessarily incorrect and is present in several pediatric protocols. The quality of drug therapy is not necessarily related to the licensing status of the drug. However, there are several clinical, ethical, and safety factors that should be considered and there are no guidelines to assist off-label prescription. The decision on this type of prescription should be assessed according to clinical indication, treatment options, and risk-benefit analysis.<sup>(3)</sup>

Several studies both in outpatient and inpatient setting related to off-label and unlicensed use of drug in children have been reported worldwide.<sup>(4-7)</sup> Particularly

in India, previous study on pediatric inpatient and outpatients which reported 50.6 to 81% off-label drug used.<sup>(8-11)</sup> One study in outpatients by Bhadiyadara et al<sup>(12)</sup> reported 22.4% and 17.1% use in off-label manner according to BNFC and NFI respectively. Currently there are no studies conducted in India, all hospital setup with outpatients and inpatients (ward and pediatric intensive care unit) facilities available together at one place. Hence, this prospective study was planned to assess the extent of utilization of off-label and unlicensed drugs in pediatric department of different setting (outpatient and inpatients) of a tertiary care teaching hospital.

### Material and method

After approval from Institutional Ethics Committee (IEC), a prospective study was conducted among 210 pediatric patients, out of which 105 were pediatric outpatients (OPD) and 105 were inpatients (ward and pediatric intensive care unit) to assess the extent and use of off-label and unlicensed drugs for the period of 6 months at a tertiary care teaching hospital in GMERS medical college, Dharpur, Patan, Gujarat.

### Inclusion criteria

- All the pediatric patients aged 0-12 years who were admitted or attended as an outpatient and inpatient were enrolled after obtaining informed consent of patient's guardian.

- Pediatric patients had received at least one medicine prescription were included.
- Patients staying for more than 24 hrs in the hospital were considered as inpatients.

#### Exclusion criteria:

- Standard IV replacement solution flushes of sodium chloride 0.9%, heparin and blood products, drugs given via ear, eye, nasal drops, oxygen therapy and topical preparation were excluded.
- Children whose medical records not available or whose diagnosing was indicated in their medical records were excluded.

The following details like demographic parameter of patient (age, gender, and weight), diagnosis, and details of drugs prescribed (name, dose, frequency, route of administration, indication) and for inpatients duration of stay was recorded in case record form. All the details were retrieved from patient's medical file.

Information in National Formulary of India<sup>(13)</sup> (NFI) version 2016 was used to ascertain if the drugs were unlicensed and off-label use. The category of unlicensed use included those drugs which were only imported or used before a licensed is granted for therapeutic purpose. The category of off-label use was based on outside conditions specified in their information leaflets with respect to dosage, age of patients, indication and route of administration. Off-label and unlicensed drugs were classified in regards to their indications by using Anatomical Therapeutic Chemical (ATC) Classification.<sup>(14)</sup>

**Statistical Analysis:** Data were organized in Microsoft Office Excel 2007 spreadsheet and analyzed using the SPSS 19.0 software. Descriptive statistics with absolute frequencies (mean and standard deviation) was used. The frequency was measured in terms of percentage. The Pearson Chi-square test was used to determine whether the proportion of patients receiving licensed,

unlicensed and off-label drugs differed significantly between outpatient and inpatients. A similar analysis was used to compare proportions of drugs prescribed between the settings. 'P' value ( $P < 0.05$ ) was considered as statistically significant.

#### Result

Demographic data were collected from a total of 210 patients from outpatients and inpatients admission. Of them, 132 were male (62.9%) and 78 were female (37.1%). The mean age of patients was  $4.59 \pm 3.83$  having age range between 13 days to 12 years. The mean weight was  $13.8 \pm 8.56$  Kg having which mean weight ranging from 1.60 to 48.89 Kg. The mean of hospital stay was  $5.53 \pm 4.63$  days which ranged between 1 to 20 days for inpatients.

Of the 210 patients included in the study, 188 (90%) patients received at least one off-label medication. A total of 1053 drugs were prescribed to 210 patients. Of the 1053 prescription, 461 (43.8%) were licensed drugs, 448 (42.5%) were off-label drugs and 144 (13.7%) were unlicensed drugs. The number of drugs prescribed in each setting (outpatients and inpatients) is shown in **Table 1**. More drugs were prescribed for inpatients (712, 68%) than outpatients (341, 32%). A total 341 drug prescription was prescribed to 105 out patients. Of the 341 prescriptions, 168 (49%) were off-label and 49 (14%) unlicensed drug. For inpatients (n= 105), of the 712 prescription, 280 (39%) were off-label drugs and 95 (13%) unlicensed drugs. There was no significant result difference ( $p > 0.05$ ) when the proportion of drug prescribed for outpatients and inpatients were analyzed. In the age range of 0-2 years, most of the drugs prescribed were in off-label (45%) and unlicensed (14.6%) manner respectively as compared to other age groups.

**Table 1: Age distribution showing the number of licensed, off-label and unlicensed drug prescribed in each setting**

Patients Setting and age (in year)	Total drug used (n=1053)	Drugs prescribed			P
		Licensed drug (n=461,43.8%)	Off-label drug (n=448,42.5%)	Unlicensed drug (n=144,13.7%)	
All setting (outpatients and inpatients) (n=210)					
0-2	453(n=79)	180 (40%)	207 (45%)	66 (14.6%)	0.06
2-6	359(n=73)	157 (44%)	153 (42%)	49 (13.6%)	
6-12	241(n=58)	124 (52%)	88 (36%)	29 (12%)	
Outpatients (n=341)					
0-2	129 (n=39)	41 (32%)	72 (56%)	17 (33%)	0.24
2-6	100 (n=33)	35 (35%)	48 (48%)	17 (35%)	
6-12	112 (n=33)	49 (44%)	48 (43%)	15 (31%)	

Inpatients (n=712)					0.06
0-2	324 (n=40)	139 (43%)	135 (42%)	49 (15%)	
2-6	259 (n=40)	122 (47%)	105 (41%)	32 (12%)	
6-12	129 (n=25)	75 (58%)	40 (31%)	14 (11%)	

p>0.05= not significant

**Table 2** shows off-label prescriptions. Following types and frequencies were seen: off-label dose, 303 (52%); followed by indication, 126 (22%); and age, 122 (21%). The most ten common off-label prescription were for dextromethorphan 70(33%), azithromycin 62(29.5%), ondansetron 45 (21.4%), dicyclomine 22 (10.5%), amoxy-clav 18 (8.6%), paracetamol 16 (7.6%), pantoprazole 13 (6.2%), ranitidine 16 (7.6%), magnesium sulphate 19 (9%) and ceftriaxone 12(5.7%)

**Table 2: Reasons for off-label prescribing**

Reasons for off-label prescribing category	Frequency (n=448)
Dose	303 (52%)
Age	122 (21%)
Indication	126 (22%)
Route of drug administration	19 (3%)
Absence of pediatric information	16 (3%)

**Table 3** shows main therapeutic classes of drugs used. These belong to alimentary tract and metabolism (28.1%), anti-infective for systemic use (26.11%) and nervous system (17.5%). When all 1053 drugs were classified into their specific ATC classification categories, the highest percentage of off-label prescribing was for drugs of respiratory system 58.7%, anti-infective 57.1% and alimentary tract 52.7%. In ATC classification categories, the highest percentage of unlicensed prescribing was for anti-infective drugs 26.2% and alimentary tract 20.3%. Frequency of licensed, off-label and unlicensed drugs prescribed in each Anatomical Therapeutic Chemical classification (ATC) category for respiratory system, nervous system and for anti-infective shows significant result. Drugs classified as off-label for respiratory system included dextromethorphan and phenylephrine and anti-infective drugs such as azithromycin and ceftriaxone and for alimentary tract were ondansetron, pantoprazole and ranitidine.

**Table 3: Frequency (percentage) of licensed, off-label and unlicensed drugs prescribed in each Anatomical Therapeutic Chemical classification (ATC) category**

WHO – ATC system	Licensed drugs	Off-label Drug	Unlicensed drugs	p-value
Alimentary tract and metabolism (n=296) (28.1%)	76 (25.6)	155 (52.7)	60 (20.3)	Reference
Blood and blood forming organs (n=64) (6.1%)	62 (96)	2 (3.1)	00 (0.0)	<0.001**
Cardiovascular system (n=9) (0.9%)	1 (11.1)	3 (33.3)	5 (55.5)	0.04*
Systemic hormonal preparations excluding sex hormones (n=9) (0.9%)	5 (55.5)	4 (44.4)	00 (0.0)	0.09
Anti-infectives for systemic use (n=275) (26.1%)	45 (16.4)	157 (57.1)	72 (26.2)	0.01*
Nervous system (n=184) (17.5%)	157 (85.3)	27 (14.7)	5 (2.7)	<0.001**
Antiparasitic products, insecticides and repellent (n=43) (4.1%)	35 (81.4)	7 (16.2)	0 (0.0)	<0.001**
Respiratory system (n=155) (14.7%)	62 (40)	91 (58.7)	2 (1.3)	<0.001**

p<0.05\*=significant, p<0.001\*\*=highly significant

The p-values in the last column compare the proportion of licensed drugs within each ATC class against the proportion in the alimentary tract ATC group (the largest group of drugs).

The respiratory disease group was one of the most common reasons for hospitalization in 51% followed by gastrointestinal disease 15%. Most of the drugs prescribing in respiratory infection were antibiotics and cough syrup.

## Discussion

This present study, among 210 patients was conducted to investigate the extent of off-label prescribing in outpatient and inpatients population in a pediatric department, at a tertiary care teaching hospital. In our study,  $4.59 \pm 3.83$  mean age of patients was a little higher than as previous Indian studies which reported  $3.70 \pm 3.57$  years and  $3.96 \pm 3.48$  years and  $4.19 \pm 3.66$  years respectively.<sup>(9,10,12)</sup> In our study, there were more male pediatric patients which higher than that seen in previous study.<sup>(8, 12, 15)</sup>

In our study most common diagnosis was respiratory tract infection followed by gastrointestinal disease while in previous study in India<sup>(12)</sup> and Nigeria<sup>(15)</sup> common diagnosis reported was malaria followed by respiratory tract infection. In other study Brazil,<sup>(4)</sup> pneumonia was common diagnosis. This might be due to difference in prevalence of disease across different countries.

The proportion of off-label and unlicensed prescribing in our study was 42.5% and 13.7% respectively which was higher than reported in recent study in Netherland<sup>(16)</sup> 25.7% off-label and 2.6% unlicensed drugs and other study in Nigeria<sup>(15)</sup> 21.5% off-label and 20.4% unlicensed drugs were prescribed but lower than the Brazil<sup>(17)</sup> study in which reported 77.8% off-label and 20.9% unlicensed drugs were used respectively. In our study, inpatient received 39% off-label and 13% unlicensed drugs, which was comparatively lower than the previous Indian studies by Saiyed et al<sup>(8)</sup> reported 70%, Jain S et al<sup>(9)</sup> 50.6%, Bhavdekar S et al<sup>(10)</sup> 70.58% and Vohra F et al<sup>(11)</sup> 81% use of off-label drugs. In outpatients study, 49% and 14% were off-label and unlicensed drugs used respectively which was higher than previous study by Lengerova et al<sup>(3)</sup> who reported 9.01% off-label and 1.26% unlicensed drug used, Bhadiyadara et al<sup>(12)</sup> reported 22.4% and 17.1% use of drugs in off-label manner according to BNFC and NFI respectively. In our study, there was no significant result difference ( $p > 0.05$ ) when the proportion of drug prescribed for outpatients and inpatients were analyzed, but previous study reported a significant result.<sup>(16)</sup> So, present study shows outpatients pediatric population which is quite the opposite finding to that of our countries where the prevalence of prescribing off-label and unlicensed drugs was more in inpatients pediatric population.<sup>(8-12)</sup> The reason of this difference might be due to variation

in prescribing pattern by pediatricians, which suggest possible greater awareness among pediatricians related to issue of off-label and unlicensed prescribing.

Overall, the most common Anatomical Therapeutic Chemical (ATC) classification categories of off-label prescribing was respiratory system 58.7%, anti-infective 57.1% and alimentary tract 52.7% and unlicensed prescribing was anti-infective 26.2%, alimentary tract 20.3%. A study by Malta<sup>(18)</sup> observed off-label and unlicensed drug prescription for respiratory system and antibiotics. In our study, frequency of licensed, off-label and unlicensed drugs prescribed in each Anatomical Therapeutic Chemical classification (ATC) category for respiratory system and nervous system showed significant result for anti-infective drugs which was not in accordance with the previous study which reported non-significant result for anti-infective.<sup>(16)</sup>

10 most commonly prescribed drugs were dextromethorphan, azithromycin, ondansetron, dicyclomine, amoxy-clav, paracetamol, pantoprazole, ranitidine, magnesium sulphate and ceftriaxone, which is in accordance with the previous study.<sup>(12,15)</sup>

The most common category of off-label prescribing was dosage (52%) which is similar to that of previous study.<sup>(8,12,17,19)</sup> The reason for off-label drug use was lack of pharmacokinetic data and clinical trial in children which resulted in to larger discrepancies in terms of which dose estimation, lead pediatricians to use doses based on extrapolation from adult parameter. The extent of off-label and unlicensed prescribing were highest (45% and 14.6%) in age group 0-2 years. In previous studies also shows that age group of 0 to 2 years is the highest recipient of off-label prescriptions.<sup>(8)</sup> This is mainly due to absence of specific dosing guidelines and route administration in 0 to 2 year age group in NFI.

Even though the present study was conducted with the appropriate statistical methodology, the results should be interpreted with caution considering few limitations of the study. First limitation is that the present study was conducted only in one tertiary care hospital. Second, we did not assess the outcomes of medication use, so we cannot argue about the real risk versus benefits of their use.

## Conclusion

Our present study shows high level of prevalence of prescribing off-label and unlicensed drugs among outpatients; however, for inpatients it was low. The highest proportion of off-label and unlicensed drugs were prescribed among 0-2 years age groups. Hence, it is recommended to generate more quality data on the safety and efficacy of off-label and unlicensed drugs to rationalize pediatric pharmacotherapy.

## References

1. Narong N, Sitthiworanan C. A Survey of Off-label and Unlicensed Prescribing Drugs at a Community Hospital in Thailand Mahidol University Journal of Pharmaceutical Sciences 2007;34:13-16.
2. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Paediatr 2005;164(9):552-58.
3. Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. Ital J Pediatr. 2014;40:12.
4. Kimland E, Nydert P, Odlind V, Böttiger Y, Lindemalm S. Pediatric drug use with focus on off-label prescriptions at Swedish hospitals – a nationwide study. Acta Paediatrica. 2012;101(7):772–8.
5. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A et al. Survey of unlicensed and off label drug use in pediatric wards in European countries. BMJ 2000;320:79-82.
6. O'Donnell PF, Stone RJ, Morley CJ. Unlicensed and Off-Label Drug Use in an Australian Neonatal Intensive Care Unit, Pediatrics 2002;110(5):52.
7. Lass J, Irs A, Pisarev H, Leinemann T, Lutsar I. Off label use of prescription medicines in children in outpatient setting in Estonia is common. Pharmacoepidemiol Drug Saf. 2011;20(5):474-81.
8. Saiyed MM, Lalwani T, Rana D. Off-label medicine use in pediatric inpatients: a prospective observational study at a tertiary care hospital in India. Intern Jour of Paed 2014;1-6.
9. Jain SS, Bavdekar SB, Gogtay NJ, Sadawarte PA. Off-label drug use in children. Ind J Paedr 2008;75:1133-36.
10. Bavdekar SB, Sadawarte PA, Gogtay NJ, Jain SS, Jadhav S. Off-label drug use in a pediatric intensive care unit. Ind J Pediatr 2009; 76(11):1113-18.
11. Vohra F, Pawar S, Off-label drug use in pediatric wards: a prospective study in a tertiary care hospital in Pune. Egypt Pharmaceut J 15:70–73.
12. Bhadiyadara SN, Rana DA, Malhotra SD, Patel VJ. Off-label and unlicensed drug use in pediatric outpatient department—a prospective study at a tertiary care teaching hospital. Journal of Young Pharmacists 2015;7(3):164-70.
13. National Formulary of India, 5th edition, 2016.
14. WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for ATC Classification and DDD Assignment, Norwegian Institute of Public Health, Oslo, Norway, 14th edition, 2011.
15. Raymond C Okechukwu, Ochuwak E Aghomo, “prescription pattern of unlicensed and off-label medicines for children aged 0-5 years in a tertiary hospital and primary health care centre in Nigeria (2009) 2,62-66.
16. Czarniak P, Bint L, Favié L, Parsons R, Hughes J, Sunderland B (2015) Clinical Setting Influences Off-Label and Unlicensed Prescribing in a Pediatric Teaching Hospital. PLoS ONE 10(3): e0120630. doi:10.1371/journal.pone.0120630.
17. Gomes VP, Kedma Melo da Silva, Suely O Chagas, Igor Rafael dos Santos Magalhaes, “Off-label and unlicensed utilization of drugs in a Brazilian bpediatric hospital” Farm Hosp. 2015;39(3):176-180.
18. Ellul IC, Grench V, Montalto SA, “Pediatric off-label and unlicensed prescribing in primary care Malta: prospective observation drug utilization study”, international journal of risk and safety in medicine.(2015)22,123-34.
19. Goncalves MG, Heineck I, “Frequency of prescriptions of off-label drugs and drugs not approved for pediatric use in primary health care in a southern municipality of Brazil” (2016) 34(1), 11-17.