



ORIGINAL RESEARCH PAPER

Pharmacology

PATTERN OF PRESCRIPTION AND UTILIZATION OF OFF-LABEL AND UNLICENSED DRUGS AMONG PEDIATRIC PATIENTS ATTENDING OUTPATIENTS DEPARTMENT OF TERTIARY CARE TEACHING HOSPITAL OF GUJARAT STATE

KEY WORDS: off-label drug, unlicensed drug, pediatric, outpatient

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ABSTRACT

Objectives: To determine the pattern of prescription and utilization of off-label and unlicensed drugs among pediatric patients attending outpatients department of tertiary care teaching hospital of Gujarat state. **Methods:** A prospective study was conducted for 6 months among 140 pediatric patients attending outpatient department of Gujarat Medical Education and Research Society Medical College, Dharpur, Patan. The demographic details and complete prescription were noted in predesigned form. The off-label drugs were categorized by using National Formulary of India. Off-label drugs were classified by using Anatomical Therapeutic Chemical classification. **Results:** Out of 481 drugs prescribed, the pattern of distribution of off-label and unlicensed drugs were 215(44.7%) and 3(0.6%) respectively. Majority (n=151, 70.2%) of off-label drugs prescribed among 1-12 years age group. Most of off-label drugs were prescribed for indication of respiratory system (68%). **Conclusion:** The findings of this study showed a high incidence of off-label prescribing mainly antibiotics for respiratory disease.

INTRODUCTION

The prescription of off-label and unlicensed medicines use among pediatric group present deep ethical and moral challenges. Children often receive several prescription, non-prescription (over-the-counter) and/or herbal medicines when they become ill. Most of these medicines have not been properly tested in controlled clinical trials for their age group.¹ This has led to only a few drugs being currently labelled for pediatric use and to a widespread off-label drug use, i.e. use of drugs outside the term of the Summary of Product Characteristics (SPC).² Drugs were classified as unlicensed either if the drugs are unregistered, an unlicensed formulation of a registered drug or the use of a non-pharmacological substance as a medicine.³ 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.⁴

A few studies on utilization of off-label or unlicensed drug in pediatric outpatients has been reported.⁵⁻⁹ Through extensive literature review it was found that there is a paucity of such studies in India, particularly outpatient of pediatric department. Hence these prospective study was planned to determine the utilization of off-label and unlicensed drugs among pediatric patients attending outpatients department of tertiary care teaching hospital of Gujarat state. Also to correlate with National Formulary of India¹⁰ for identification of such use and to assess the impact of such prescribing on drug therapy in pediatric outpatient department of a tertiary care teaching hospital.

METHODS

The present prospective study was carried out in pediatric outpatients a tertiary care teaching hospital in Gujarat Medical Education and Research Society (GMERS) medical college Dharpur, Patan. The permission to conduct the study was sought from Institutional Ethics Committee of GMERS Dharpur medical college. The informed consent was obtained from patient's parents/guardians.

The study was conducted for period of 6 months. All pediatric patients attending the outpatient department during the

study period were enrolled in the study.

Inclusion criteria:

Patients whose parents/guardians gave their consent for participation in the study, were enrolled in the study. Children up to the age of 12 years are considered pediatric patients who receiving at least one drug.

Exclusion criteria:

Pediatric patients on nutritional supplements, vaccines, drugs administered other than oral route e.g. ear, eye, nasal drops and topical preparation were excluded from this study.

Demographic details, complete medical history and complete prescription details were recorded in preformed proforma. The prescription details like prescribed drug, dosage of drug, frequency and duration of the treatment were recorded. National Formulary of India (NFI)¹⁰ was used as a reference source to identify off-label and unlicensed prescriptions off-label drugs were classified in regards to their indications by using Anatomical Therapeutic Chemical (ATC) Classification.-2011.¹¹

Statistical Analysis:

The data were presented as proportions. Chi square test was applied to compare the proportions. P value (P<0.05) was considered as statistically significant. The data were analyzed using Statistical Package for Social Science (SPSS-IBM) version 23.

RESULTS

Demographic characteristic

A total 140 outpatients were enrolled in the study having age ranges from 0 to 12 years with a mean age of 4.74±4 years. The mean weight of patients was 13.5±12.2 kgs. A total of 481 drugs were prescribed with the mean number of prescriptions was 3.4±3 per patient.

Table 1 shows, all patients were classified into three age groups according to the classification by Indian Academy of Pediatrics (IAP). Out of 140 outpatients; 8, 24 and 108 were neonates, infants and children respectively.

Tables 2 shows, outpatients received 481 numbers of drugs, out of which male and female patients were prescribed 291(60.5%) and 190(39.5%) number of drugs respectively. Out of 481 drugs prescribed in outpatients, the pattern of distribution of off-label drugs and unlicensed drugs were 215(44.7%) and 3(0.6%) respectively. Gender wise

distribution for shows out of 215 prescribed off label drugs total 128 males and 87 females patients received off-label drugs. Similarly out of three prescribed unlicensed drugs two males and one female patient received unlicensed drugs. This was not significant statistically (P=0.71).

Table 1:- Age wise distribution of drug prescription

Age groups (years)	No. of outpatient s (n=140)	No. of off-label drug (n=215)	No. of unlicensed drug (n=3)	No. of total drug (n=481)
Neonates (0-27 days)	8(5.7%)	3(1.4%)	00	10(2.1%)
Infants (28 day-1 year)	24(17.1%)	61(28.4%)	00	107 (22.2%)
Children (1-12 years)	108(77.2 %)	151(70.2%)	03(100%)	364 (75.7%)

Table 2:- Gender-wise distribution of Label, Off-label and Unlicensed drugs prescribed in outpatient

Different setup	Gender	No (%) Label Drugs	No (%) Off-label Drugs	No (%) Unlicensed Drugs	P value
Outpatients n=481	Male (n=291)	161 (55.3%)	128 (44%)	02 (0.7%)	0.71
	Female (n=190)	102 (53.7%)	87 (45.8%)	1 (0.5%)	

P>0.05 Not significant

Disease Characteristic

The morbidity pattern found in descending order of disease was respiratory system (upper respiratory tract infection, tonsillitis, whooping cough) having 68% followed by GIT infection (diarrhoea, abdominal pain, constipation) having 22%, Infectious disease (malaria, viral fever) having 2% and others (8%) which includes worm infestation, fever and nephrotic syndrome.

Characteristic of off-label drug prescribing

The five most off-label drug prescribed were Azithromycin 65(30.2%), Dextromethorphan 62(18.9%), Paracetamol 15(7%), Chlorpheniramine maleate 11(5.1%) and Cefixime 10(4.7%) **Table-3** shows, according to the Anatomical Therapeutic Chemical (ATC) classification, off-label drugs belonged mainly to Anti-infective for systemic use 91(42%), Respiratory system 80(37%), Alimentary tract and metabolism 27(12.6%) and Nervous system 16(7.4%).

Table-3:- Licensed, Off-label and Unlicensed drug use according to ATC classification

WHO-ATC system	Total drug (n=481)	Licensed (n=263)	Off-label drug (n=215)	Unlicensed drug (n=3)
Anti-infective for systemic use	120 (25%)	26(9.9%)	91(42%)	03(100 %)
Nervous system	95(19.8%)	79(30%)	16(7.4%)	00
Alimentary tract and metabolism	115(24%)	88(33.5 %)	27(12.6%)	00
Respiratory system	113(23.5 %)	33(12.5 %)	80(37%)	00
Cardiovascular system	1(0.2%)	1(0.4%)	00	00
Hormonal preparation	02(0.4%)	2(0.8%)	00	00
Blood and blood forming agents	21(4.3%)	21(8%)	00	00
Antiparasitic products, insecticides and repellent	14(3%)	13(5%)	01(0.5%)	00

DISCUSSION

Our study aimed to determine the pattern of prescription and utilization of off-label and unlicensed drugs based on NFI and to find out the impact of such prescribing in pediatric outpatient department. Mean age of patients in our study was higher as compared with earlier Indian outpatient studies reporting 4.19±3.66.⁹ This difference might be due to variation in geographical location. In our study males were higher but there are no statistically significant different between gender and off-label drug prescribing similar like previous study.^{9,12} Our study shows most common diagnosis was upper respiratory tract infection, while Olsson et al¹³ study in Swedish outpatient reported systemic infectious disease and Bhadiyadara et al⁹ study reported malaria followed by upper respiratory tract infection. This might be due to differences in prevalence of diseases across different countries. Antibiotics are the most commonly prescribed off-label drug group followed by antitussive drug for upper respiratory tract infection, previous study reported similar finding in UK,¹⁴ but other study shows different antibiotics⁹ used may be seasonal variation in the type of disease.

Our study also found that the maximum off-label prescribing was found in children (1-12 years), up to 70.2%, and the reason may be in other categories there are low level of patients and hence larger sample would be necessary to provide more confidence in these estimate.

The proportion of off-label and unlicensed prescribing in our study was 44.7% and 0.6% respectively which was higher than previous Indian study reported by Bhadiyadara et al⁹ 22.4% and 17.1% use of drugs in off-label manner according to BNFC and NFI respectively. The proportion of prescribing off-label and unlicensed drug was also high as compared to the previous studies conducted by Lengerova et al⁷ (9.01% off-label and 1.26% unlicensed drug), Horen et al⁸ (18.9% were off label). 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.

There were few limitation of our study; we included prescription from only in outpatient of pediatric department so result may not accurately reflect practise in other setting. Study duration was short hence a study needs to be conducted for longer duration involving larger sample size.

CONCLUSION

The pattern of prescribing off-label drugs was very high among pediatric outpatient practice. Antibiotics are the most commonly prescribed off-label drug group followed by antitussive drug for upper respiratory tract infection. There is need to raise awareness among pediatricians and encourage evidence based off-label drug used by the pharmacologist.

REFERENCES

- Nahata MC. Licensing of medicines for children in USA. *Paediatric and Perinatal Drug Therapy* 1997; 1:50-51.
- Bonati M, Choonara I, Hoppu K, Pons G, Seyberth H. Closing the gap in drug therapy. *Lancet* 1999;353:1625
- Czarniak P, Bint L, Favié L, Parsons R, Hughes, Sunderland. Clinical Setting Influences Off-Label and Unlicensed Prescribing in a Pediatric Teaching Hospital. *J PLoS ONE* 2015; 10(3):e0120630. doi:10.1371/ journal.pone.0120630
- Oberoi SS. Regulating off-label drug use in India: the arena for concern. *Perspect Clin Res* 2015;6: 129-133
- McIntyre J, Conroy S, Avery A, Corns H, Choonaral. Unlicensed and off label prescribing of drugs in general practice. *Arch Dis Child* 2000; 83:498-501.
- Chalumeau M, Treluyer JM, Salanave B, et al. Off label and unlicensed drug use among French office based paediatricians. *Arch Dis Child* 2000; 83:502-505.
- Langerová P, Vrtal J, Urbánek K. Incidence of unlicensed and off-label prescription in children. *Ital J Pediatr*. 2014; 40:12.
- Horen B, Montastruc JL. Adverse drug reactions and off-label drug use in paediatric outpatients. *Br J Clin Pharmacol* 2002; 54:665-70.
- 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.
- National Formulary of India, 5th edition, 2016
- WHO Collaborating Centre for Drug Statistics Methodology, Guidelines for

ATC Classification and DDD Assignment, Norwegian Institute of Public Health, Oslo, Norway, 14th edition, 2011.

12. Santos D, Clavenna A, Bonati M, Coelho H Off-label and unlicensed drug utilization in hospitalized children in Fortaleza, Brazil. *Eur J Clin Pharmacol* 2008;64 (11):1111-18
13. Olsson J, Kimland E, Pettersson S, Odling V. Paediatric drug use with focus on off-label prescriptions in Swedish outpatient care—a nationwide study. *Acta Paediatrica*. 2011;100(9):1651-2227
14. J McIntyre, S Conroy, A Avery, H Corns, I Choonara. Unlicensed and off-label prescribing of drugs in general practice. *Arch Dis Child*. 2000;83(6):498-501.