WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 1, 1424-1438. Research Article ISSN 2277– 7105

OFF-LABEL USE OF DRUGS AMONG CHILDREN AND ITS IMPLICATIONS IN A TERTIARY CARE HOSPITAL IN NORTH INDIA

Dr. Puja*[1], Dr. D.C. Dhasmana[2], Dr. Saurabh Kohli[3] and Dr. Vipin Chander[4]

[1,2,3]Department of Pharmacology, Himalayan Institute of Medical Sciences, Dehradun.

[4]Department of Paediatrics, Himalayan Institute of Medical Sciences, Dehradun.

Article Received on
01 Nov. 2019,

Revised on 22 Nov. 2019,
Accepted on 12 Dec. 2019

DOI: 10.20959/wjpr20201-16479

***Corresponding Author**
Dr. Puja
Department of Pharmacology, Himalayan Institute of Medical Sciences, Dehradun.

ABSRACT

Background: Children are routinely prescribed medicine and most of them are lacking safety and efficacy data. This study was envisaged to find the prescribing pattern in pediatric general ward and extent of off-label use of medicines and its implications. **Methods and materials:** This was an observational cross-sectional study. Prescription of 120 patients were analysed and off-label use was determined on the basis of Summary Of Product Characteristics/Product Label and National Formulary Of India, 2015 for each drug. **Result:** In a cohort of 120 patients atleast one off-label drug was prescribed to 72(60%). 48(40%) received 2 or more than 2 drugs off-label. Out of the total number of drugs 128(16%) were prescribed off-label based on the US FDA criteria which classifies off-label use on the basis of age if the drug is used in the age group for which it is not approved or not recommended for use, dose if used at a higher or lower dose than approved, on the basis of route if any other route of administration is employed than approved or if used at a higher or lower frequency than approved. Dose (46%) was the most common reason for off-label use of drugs and followed by age(40.6%). **Conclusion:** off-label use of drugs is common in children and carries a risk of increased adverse drug reactions but this study could not establish a association between off-label use and increased risk of adverse drug reactions necessiating need for such more studies.

KEYWORDS: Off-label, hospitalised children, adverse drug reactions.

INTRODUCTION

Rapid therapeutic advances in adult medicine have been witnessed in the past few decades and have revolutionized the practice of medicine. Paediatric medicine evidently has not kept the same pace lagging far behind the therapeutic and diagnostic research as in adults.[1]

Children constitute about one-third of the total population in developing countries. They suffer from various disease conditions which may be similar to adults like gastroenteritis or remarkably different like cystic fibrosis akin only to the pediatric population.[2] On an average a child is prescribed 0.8-3.5 medicines per year on outdoor visits to clinicians inspite of the lack of information on pediatric dosing for most of the drugs.[3]

More than 100 years ago Dr. Abraham Jacob, the father of American pediatrics, had aptly quoted "Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but. Has its own independent range and horizon".[4] There are many differences between children and adults that simultaneously vary according to age and developmental stage which include physical, psychological and continuing changes in physiologic development for example, changes in the integrity of the skin, maturation of metabolic functions, changes in skeletal structure and composition, alteration in protein binding and displacement. But unfortunately most of the drugs do not receive, adequate study in infants and children even at present. Reasons being the ethical issues related to the inclusion of children in trials, lack of incentives and the profit driven industry by nature is reluctant to invest in pediatric studies. As a result, a barrier has been created in making proper drugs available for the pediatric patients. Thus, it is difficult to comment on the safety and efficacy of most drugs in children and many drugs are used outside the product license which is termed "off-label".

Off-label drug use does not necessarily mean that safety and efficacy have not been investigated at all but scientific evidence falls short of what the drug manufacturers are required to provide to receive approval from regulatory authorities for that indication.[7] Considerable problem may be associated with the off-label use in pediatric patients like increased risk of adverse drug reactions and inefficacy of drug treatment in children. Paediatric age group is specially vulnerable to adverse effects, so eternal vigilance is required as it is often dependent on unrelated adult data. To improve pediatric drug therapy, new legislation was introduced both in the United States (Pediatric Research Equity Act, 2003) and in the European Union (Pediatric Regulation, 2006).[1] These new legislations help the

pharmaceutical industry in terms of economic incentives to develop and make available safe and effective medicines for children.

India is home to the world's largest child population and children suffer with a variety of diseases which may sometimes self-limiting but often requiring medications.[4] In developing country like India there is paucity of systematic data on the prescription pattern in children and studies related to off-label use of drugs in children. Only two studies to our knowledge being reported on off-label use. Hence this study was undertaken to assess the prescription pattern of medicines in hospitalized children and to assess the extent of off-label use of medicine and its association if any with the increased adverse drug reactions in children. More such studies are envisaged to bring into light the highly unfortunate situation in which the progress of medical care is directed to the most vulnerable amongst us.

MATERIALS AND METHODS

The study was carried out in Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun, in the Department of Pharmacology and the Department of Pediatrics over a period of twelve months after obtaining institutional ethical clearance. Newly admitted patients in the pediatric ward on being prescribed drug treatment, were followed up until discharge and prescription auditing was done, as per the pro forma attached, after obtaining a written informed consent from parent/legal guardian.

Study Design: Observasational cross sectional study.

Selection of Subjects

Inclusion criteria: Consecutive newly admitted patients in one pediatric unit upto the age of 18 years, receiving drug prescription were followed up until discharge. Repeat admission of the same patient was counted as two admissions when separated by a period of one month.

Exclusion criteria

a. Patients with incomplete demographic or prescription details.
b. Oncological patients and those with HIV infection.
c. Patients admitted in pediatric or neonatal intensive care.

Study Tool

Patient details (age, weight, anthropometric measurements), prescription drug details (indication, dose, frequency) and other relevant information were recorded as per the pro forma.

Off–label status of the drug will be determined on the basis of National Formulary of India year NFI(2015)/Product literature. The drug was classified off-label on the basis of age if there was lack of information regarding dosing in children or if contraindicated in that particular age. The drug was classified off-label on the basis of dose if the dose was higher or lower than the dose recommended in the NFI with a 10% margin. The drug was categorized as off-label if it was used for an indication different than that mentioned in the NFI or product license, or at a different frequency or by a different route of administration. A drug was classified off-label only in one category. Age was the first criteria for defining off-label category followed by indication, dose, frequency and route of administration.

Study Protocol

Auditing of prescriptions was done to assess the safety and efficacy of the drugs and to determine the extent off-label drug use.

- Diagnosis was classified according to the International- Classification of Diseases (ICD).
- Patients were classified into different age groups: 1-12 months, 1-2 years, 2-6 years, 6-12 years and 12-18 years.
- Drugs were classified as per the World Health Organisation-Anatomical Therapeutic classification(WHO-ATC) (AnnexureIV).
- Drugs were classified according to the licensed status into on-label, off-label or unlicensed.
- Each off-label prescription was categorized in relation to age, indication, dose and route of administration.
- Adverse drug reaction monitoring was done according to the Central Drugs Standard Control Organisation (CDSCO) guidelines.
- World Health Organisation core drug use indicators were used to investigate the rationality of drug use (Annexure V).

Data Management and Statistical Analysis

Descriptive statistics were used to present the data i.e. percentage, proportions, frequency, mean and standard deviation using Microsoft excel worksheet.

RESULTS

120 patients consecutively admitted in one unit of the pediatric general ward were included as per the inclusion criteria and their prescription were analysed according to the WHO core drug use indicators. The average duration of stay in the hospital was 8.5 ± 3.24 days and they were prescribed drugs varying in number from 2 to 14 (table 1).

Table 1: Demographic Profile of The Patients Admitted In One Unit of Pediatric Ward.

Mean number of drugs prescribed during stay	6.6±2.68
Mean duration of stay in hospital in days	8.5+3.24
Male : Female ratio of the patients	2.42

The most common cause of admission was infectious and parasitic disease(A00-B99) followed by disease of the nervous system(G00-G99)(Fig: 1). The most common diseases were Scrub Typhus, Bronchopneumonia and Seizure disorder. Maximum number of the patients were between 2 years-6 years of age (Fig:2).

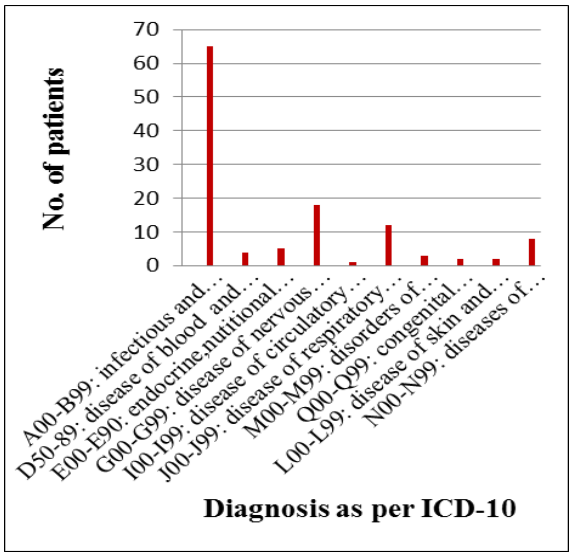


Fig 1: Distribution of 120 Patients Include in the Study According to Diagnosis(ICD-10).

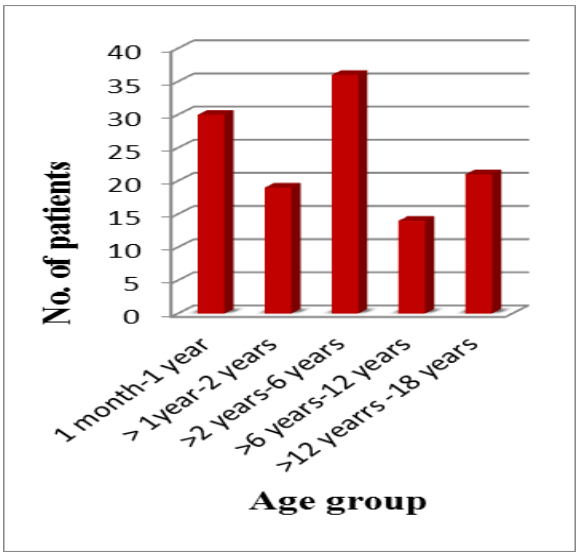


Fig 2: Agewise distribution of patients.

Prescription analysis as per WHO indicators for drug use

The most commonly prescribed class of drugs were antimicrobials, followed by drugs acting on the alimentary system and those acting on the nervous system (Fig:3). 100 out of 120

(83%) patients were prescribed atleast one antibiotic during their stay in the hospital. Out of the 100 patients receiving antibiotic, 91 received antibiotic by parenteral route and remaining 9 patients received antibiotic by oral route. The most commonly prescribed antibiotics were Ceftriaxone, Amikacin, Cefotaxime, Doxycycline and Ampicllin+Clavulanic acid combination in decreasing order. Among the drugs acting on the central nervous system the most commonly prescribed drugs were Lorazepam, Phenytoin, Valproic acid, and Promethazine in decreasing order. Among the drugs acting on the alimentary tract Ranitdine was the most common drug followed by Ondansetron, Domperidone and Aluminium Hydroxide gel in decreasing order. Among the Nonsteroidal Anti-inflammatory Drugs Paracetamol was the most frequently prescribed followed by combination of Paracetamol+Ibuprofen.

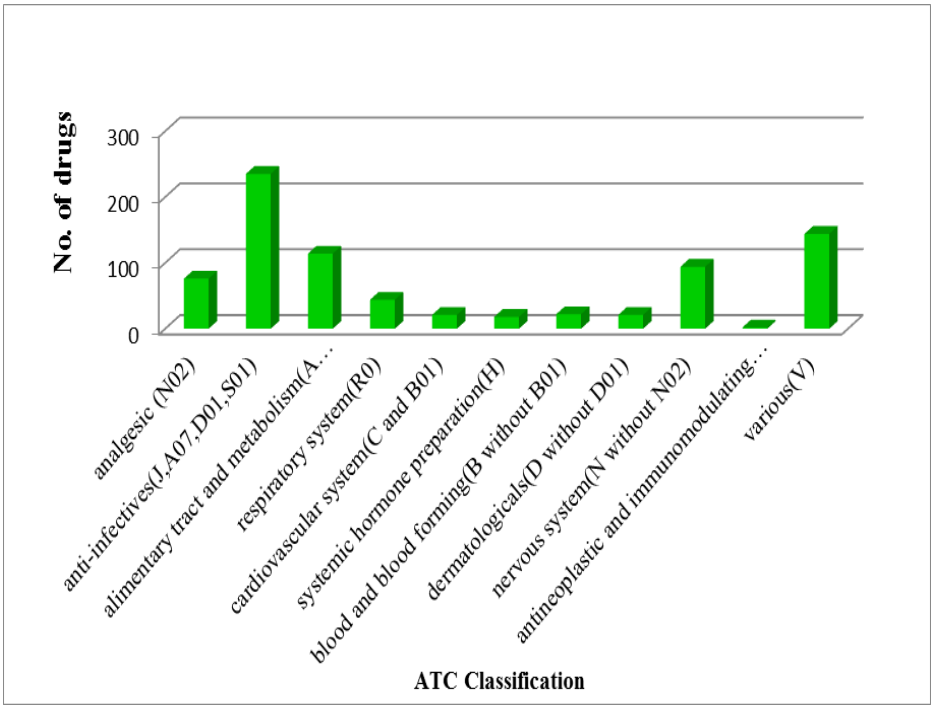


Fig. 3: ATC classification of the drugs prescribed.

735(93%) drugs were prescribed from the National Essential medicine list 2011(Fig:4). Oral route(48%) was the most common route of drug administration followed by intravenous route(43%)(Fig: 5). The number of drugs prescribed by generic name was 239(30.2%) while those prescribed by brand name was 552(69.8%) (Fig: 6).

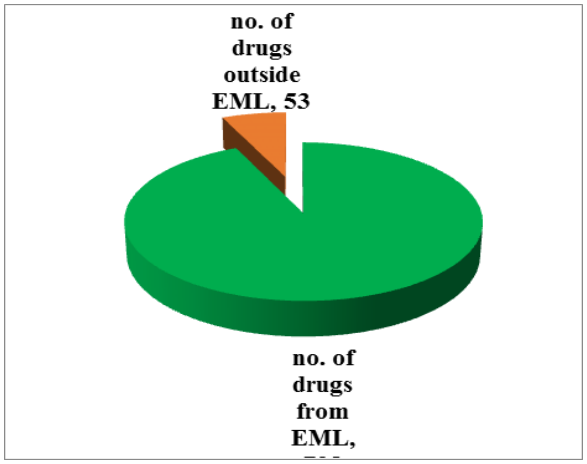


Fig 4: Distribution of 791 drugs prescribed in the study from the NELM 2015 and those outside NLEM 2015.

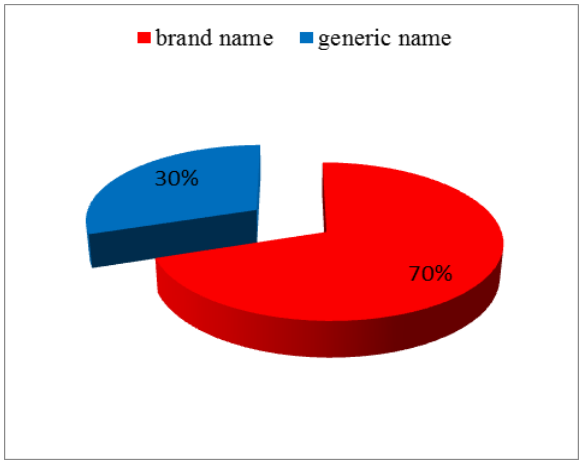


Fig 5: Distribution of the 791 drugs prescribed in one unit of pediatric ward according to those prescribed by brand name and generic name.

Off-label use of drugs: In a cohort of 120 patients atleast one off-label drug was prescribed to 72(60%) 48(40%) received 2 or more than 2 drugs off-label. Out of the total number of drugs 128(16%) were prescribed off-label based on the US FDA criteria which classifies off-label use on the basis of age if the drug is used in the age group for which it is not approved or not recommended for use, dose if used at a higher or lower dose than approved, on the basis of route if any other route of administration is employed than approved or if used at a higher or lower frequency than approved. Dose (46%) was the most common reason for off-label use of drugs and followed by age(40.6%) (Table:2).

Table 2: Distribution of off-label drugs according to category (n=128).

Age	Dose	Indication	Frequency	Route
52(40.6%)	59(46%)	6(4%)	8(6%)	3(2%)

Out of the 128 drugs used off-label 49(38%) were antimicrobials, 32(25%) were drugs acting on gastrointestinal system and 16(12.5%) were drugs acting on respiratory system(Table 3).

Table 3: Off-label use of drugs according to ATC.

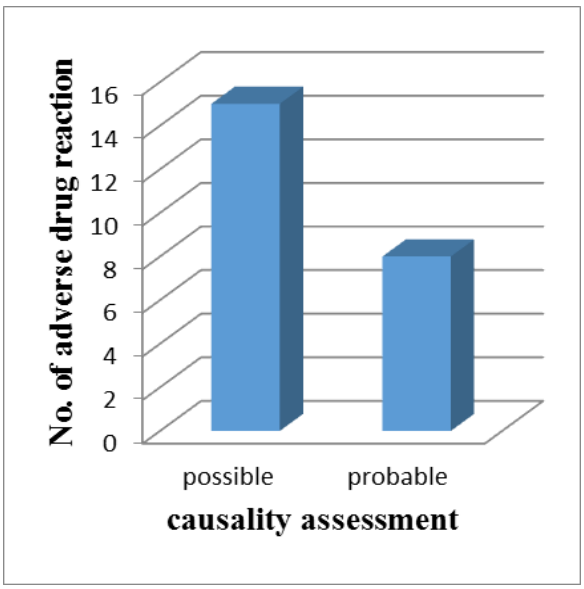
ATC of drugs	No. of off-label drugs(n=128)
Anti-infectives(J,A07,D01,S01)	49 (38%)
Alimentary tract and metabolism(A without A07)	32 (25%)
Respiratory system(R0)	16 (12.5%)
Nervous system(N without N02)	12 (9.4%)
Analgesic (N02)	7 (5%)
Cardiovascular system(C and B01)	6 (4.6%)
Systemic hormone preparation(H)	2 (1.5%)
Blood and blood forming(B without B01)	2 (1.5%)
Dermatologicals(D without D01)	2 (1.5%)

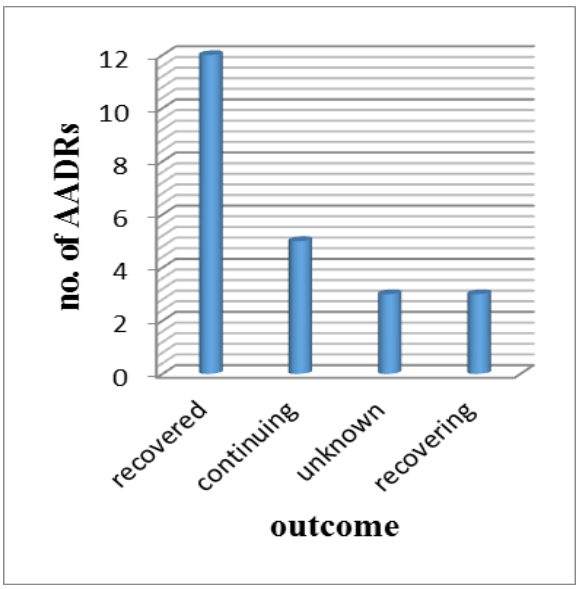
Out of the 72 patients receiving off-label drugs 15 received 2 off-label drug and 3 received 3 off –label drugs. Among the 128 drugs prescribed off-label, 44(34.4%) drugs were prescribed by generic name and 84(65.6%) drugs were prescribed by brand name. Out of the 128 drugs prescribed off-label, 23(18%) were not from the NLEM 2015 in comparison with 7% of all the drugs being prescribed outside the NLEM 2015.

Analysis of adverse event and their causality assessment:

Among the 120 patients there were 23 ADRs observed in 18 patients (15%).4 serious adverse event were observed which were cataract with Prednisolone, thrombocytopenia with Valproic acid, maculopapular rash with Valproic acid and erythrematous rash with Carbamazepine. Antiepileptic drugs and steroids were most commonly implicated in causing ADRs.

Causality assessment of the 23 ADRs was done according to the CDSCO guidelines, 8 were probable and 15 were possible (Fig:6). Outcome of the 23 adverse drug reaction was recovered for 12, continuinig for 5, unknown for 3 and recovering for 3(Fig: 7). Out of the 18 patients with ADR, in about 11 patients atleast one off-label drug was prescribed and 7 did not receive any off-label drug. Among the 4 serious adverse event observed 2 were due to drug which was used off-label on the basis of dose. As per causality assessment all were probable in serious adverse events.





DISCUSSION

In this study 791 drugs were administered to a total of 120 patients with a mean of 6.6+ 2.68 drugs per patient. The average number of drugs prescribed per patient was similar to 5.6 as

reported in study in indoor patients in a teaching hospital in north India[50] and 5.8 in another study from south India done on indoor patients in a tertiary care teaching hospital[51] but higher than 3.42 as reported from a study of central India on outdoor patients.[53] These findings suggest that polypharmacy is rampant in all studies on indoor patients. The dissimilarity in the number of drugs prescribed might be due to the difference in the disease profile of the patients in a particular geographical area.

The most common class of drugs prescribed was antimicrobials (29.7%) which is similar to 28% that observed in the study from south India.[52] 83% of patients were prescribed at least one antibiotic which is higher than 72% as reported in similar study from Israel on indoor patients[51] and lower than the reported 93% of the patients being prescribed antibiotic from a study in north India.[54] Among the antimicrobials most commonly prescribed class of antibiotic was Beta-lactams which is similar to findings from other study from south India.[52] Among the NSAIDs, Paracetamol (90%) was the most commonly prescribed followed by combination of Paracetamol and Ibuprofen. Similar study done in central India[53] and Nepal[56] also report Paracetamol as the most commonly prescribed NSAIDs by the paediatricians. Commonest indication for Paracetamol was fever. The use of somewhat irrational fixed dose combination of Paracetamol and Ibuprofen widely remains unexplained.[57]

As per the WHO prescribing indicators, 93% of the drugs were prescribed from the Essential medicine List 2015 which is higher than 86.45% as reported in the study from south India in 2013 in a tertiary care teaching hospital.[52] This is a healthy sign as very high number of drugs were prescribed from the Essential Medicine List 2015. About 30% of the drug were prescribed by generic name and 70% were prescribed by brand name. The finding is similar to 30.7% of drugs prescribed by generic name as reported in a study from Andhra Pradesh done in a tertiary care hospital[57] and lower than 60% of drugs prescribed by generic name in a similar study from south India.[52]

In this study 72 patients (60%) were prescribed atleast one off-label drug which is surprisingly similar to 56% as reported in earlier study from France done on indoor patients(13). 128 (16.18%) drugs out of 791 were off-label which is similar to 13% that reported in a study in indoor patients in Brazil[21] and less as compared to 25% in a study from Europe in 2000.[10] Most of the studies on off-label use of drug in hospitalized children have reported around 50% of the patient receiving off-label drug with 10-40% of the total

prescriptions being off-label drug. The prevalence of off-label drug use in this study is consistent with the available literature on off-label use of drugs. It seems that these figures on off-label use have remained static over throughout the world.

In this study the most common reason for off-label use of drugs was dose (46%) which is consistent with findings of other studies conducted on off-label use.[46] Age (40.6%) was the next most common reason for off-label use. Most of the drugs described off-label on the basis of age lacked information about safety and efficacy of that drug in pediatric age group. Off-label use on the basis of indication was 6% which is substantially less compared to other studies where the off-label use on the basis of indication have been found to be around 31% in studies done outside India.[23] Although reasons cannot be ascertained, this difference could be related to difference in the demographic profile of the hospitalized patients. In most of the studies highest percentage of cardiovascular drugs(60%) were prescribed off-label on the basis of indication.[22] In this study, very few patients were diagnosed with cardiovascular disease and this may be a reason behind the lesser number of off-label use on the basis of indication as disease pattern, epidemiology varies from region to region and from time to time. Ironically, Dopamine was prescribed off-label in terms of age as there is lack of its safety information in pediatric age group. It has been a life saving drug and though it has been used since long times it lacks safety information in the product license and most of the past studies on off-label drug have highlighted this point in their study.[19] Sildenafil was used for pulmonary hypertension and it lacks approval for this indication in pediatric age group.[46] Still there is lack of approved drug for this dreaded indication in children and the clinician is bound to prescribe because of the lack of alternate approved medicine. Off-label use thus may sometimes be a bare necessity because denial of treatment just because of lack of approved medication raises serious ethical concern.

Surprisingly in contrast to cardiovascular drugs, 36% of the total drugs affecting the respiratory system was used off-label and Salbutamol was most commonly prescribed off-label drug on the basis of age and also according to frequency. Salbutamol is widely used as a bronchodilator since long time and it is one of the most commonly prescribed off-label drug. Use of Salbutamol is not recommended in children less than 18 months of age as there are greater risk of rare adverse events like paroxysmal bronchospasm and clinical efficacy is uncertain in this age group as mentioned in the product license. More over uncertainity on increased mortality still exists with chronic use of beta agonists in children.[20] Salbutamol is

recommended for 6 hourly administration in the product license but is commonly used at 4 hourly interval and even 2 hourly. In this study 60% of Salbutamol prescription were off-label with 35% on the basis of frequency and 65% on the basis of age. Off-label use of commonly prescribed respiratory drugs was very common in this study which is consistent with the findings of a study in hospitalized chidren from Brazil.[21]

In this study, the distribution of patients was somewhat skewed as most of the patients were hospitalized because of infectitious and parasitic diseases due to seasonal epidemic of scrub typhus fever which may be a reason for the high number of antimicrobials prescribed. Among the antibiotics, Tetracyclines(100%) were prescribed in an off-label manner on the basis of age as they are contraindicated in children below the age of 12 years. In this study, Doxycycline was prescribed to patients diagnosed with Scrub Typhus. Tetracyclines are contraindicated in children because they cause permanent discolouration of the growing enamel in children and affect bone growth. The reason for its use may be lack of other effective agents and increased incidence of scrub typhus with complications.

In this study a large number of patients with seizure disorders were present. Among the anti-epileptic agents Gabapentin was used off-label in terms of indication as it was prescribed in patients diagnosed with Guillian Barre syndrome for which it lacks approval. Gabapentin is an epileptic drug having complex actions in the central nervous system and there have been reports of increased behavioral side effects with Gabapentin in children with epilepsy.[15] In this study there was no such findings as the patients were followed up until their discharge and such effects may manifest after a long time interval, nevertheless off-label use for different indication should have been closely monitored. Clobazam and Lamotrigine was used off-label on the basis of age as they are not recommended for use in pediatric age group because of lack of safety and efficacy data in children but still used because those patients had adverse events with the other drugs like Phenytoin, Carbamazepine and Valproic acid. In this study out of the 128 drugs prescribed in off-label manner 23(18%) were outside the NLEM 2015 which is higher than 7% of the total drugs in the study. This denotes that many drugs which are prescribed off-label are not included in the essential medicine list.

In this study, 23 adverse events were observed in 18 patients out of 120 patients. There was low incidence of adverse event reported which may be due to lack of active reporting and difficulty in differentiating the symptoms from adverse drug reactions. Out of the 18 patients in whom adverse events were observed, 11(61%) patients received atleast one off-label drug

and 7(39%) did not receive any off-label drug. In this 60% of the total 120 patients had received atleast one off-label drug which is similar to the frequency of off-label use in patients with adverse drug reaction. An increased risk of adverse drug events could not be established on the basis of these findings from this study. Unexpectedly, this was in contrast to other studies where incidence of off-label drug was more among those patients who experienced an adverse drug reaction as reported in a study from Europe.[38] Among the serious adverse events 2 were associated with off-label use of drugs on the basis of dose and 2 were observed with onlabel drugs. This indicates that serious adverse events may be more common with off-label use of drugs as off-label drugs were prescribed in lesser number compared to onlabel drugs. The results from this study could not establish the association of adverse drug reaction nor could it disapprove the association. The reason could be small sample size of the study and difference in the demographic and diagnostic profile of the patients. In most of the studies which have shown a higher incidence of adverse drug reaction with off-label use had off-label use for a different indication while in our study the most common reason for off-label use was for a different dose and age.[39]

The limitation of this study was the small sample size of this observational study. The sample size was 120 which is small for an observational study. Also the patients included were from pediatric general ward where the diseases were common infectious disease like enteric fever, gastroenteritis and seizure. Also the patients from pediatric and neonatal intensive care were excluded in this study which is a major limitation of the study as those patients have a higher incidence of off-label use. Also patients in pediatric speciality like pediatric nephrology, cardiology, oncology have higher incidence of off-label use was excluded(). Most of the medicine are not approved for use in neonates and neonates were not included in this study which is a major drawback of the study. The long term adverse effects of the drugs could not be monitored as patients were followed up only throughout the stay in hospital. Doxycycline was used in about 12 patients and long term effect on the growing enamel could not be observed during the hospital stay.

CONCLUSION

This study on prescription pattern and off-label use of drugs in indoor paediatric patients setup creates caveat for further robust studies in this area that can be designed for the benefit of children. More such studies undertaken on a periodic basis with a greater number of a variety of patients and in varied circumstances shall definitely help in understanding the

practice of off-label/unlicensed use with their consequences. This may divert the attention of the regulatory authorities and drug industry to invest and explore the paediatric age group drug safety, efficacy and availability of appropriate formulations.

ACKNOWLEDGMENT

We are thankful to our constant force of motivation Mr Shambhu Shankar. We also thank the staff and patients for their help and support.

Funding: No funding

Conflict of interest: None.

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