IJPSR (2019), Volume 10, Issue 6 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 01 October 2018; received in revised form, 17 December 2018; accepted, 29 January 2019; published 01 June 2019

ASSESSMENT OF OFF-LABEL DRUG USE IN A TERTIARY CARE HOSPITAL

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Keywords:

Off-label drugs, Drug safety, FDA labeling, ADR

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ABSTRACT: Off-label use is defined as the use of pharmaceutical drugs for an unapproved indication or unapproved age group, dose, dosage or route of administration. An off-label use provides the best intervention for the patient when medical evidence justifies its use, but this can also be harmful due to the increased risk of adverse drug reactions when lacking a solid evidentiary basis. Hence, the aim was to assess the use of off-label drugs, observe and document the ADRs, and to find the medical evidence for the same. An observational study was conducted in PSG hospitals from January 2017- September 2017 which included patients prescribed with at least one drug for their medical condition. Patient's information was collected from the medical records and was referenced against the FDA label. Of the total 1646 prescriptions, 54.7% of prescriptions were off-label. Of the total of 10430 medications, 10.40% were off-label. The most common type of off-label drug use was an unapproved indication (74%) followed by unapproved drug (24%). Around 80% of the off-label drugs had high evidence. The number of off-label drugs increases with an increase in disease conditions of the patient. 10% adverse drug reactions were reported for off-label drugs whose incidence was higher with a decrease in evidence. The use of off-label drugs is found to be high in the tertiary care hospital, the primary reason being the lack of an on-label alternative. There is an increased risk of ADRs related to off-label drug use, hence continuous monitoring of off-label drugs is essential.

INTRODUCTION: The licensing of drugs ensures the use of safe, effective and high-quality medication. Before a drug can be approved for sale in a given market, governmental authorities in each country have to assess its safety, efficacy, and quality. At the end of this process, pharmaceutical companies are granted market authorization, and the drug is licensed for marketing in that country.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.10(6).3045-52

The article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.10(6).3045-52

The drug also has a label (*i.e.*, drug monograph), specifying the details for drug use (*e.g.*, target population, dose, indication, specific use). When the drug use deviates from the labeling considerations; it becomes an off-label indicated drug.

Off-label prescribing is an integral part of contemporary medicine and may provide the best available intervention for a patient, as well as the standard of care for a particular health problem [5, 6, 7]. When scientific and medical evidence justifies off-label uses, physicians promote patients' interests by prescribing off-label drugs. In recent years, there has been a manifold increase in the usage of off-label medications [6, 9].

The incidence of off-label prescriptions has been thought to be higher in pediatric and geriatric populations [37, 38]. This is because clinical trials do not include special populations. Hence, the lack of safety and efficacy profiles could be a major factor influencing off-label prescriptions [10, 11, 12].

On the other hand, off-label prescribing can also cause harm to the patients, thereby increasing the risk of adverse drug reactions. The potential for harm is greatest when an off-label use lacks a solid evidentiary basis [36].

Off-label prescribing of drugs has also been identified as a potentially important contributor to ADRs in both pediatrics and geriatrics [7, 8, 9, 10, 11]. The Institute of Medicine and Drug Regulatory Agencies have envisioned a post-marketing surveillance system in which patterns of drug use, indications for the use and associated ADRs could be tracked. However, an explicit link between prescribed drugs and their indication is rarely documented, making it challenging to measure off-label use and its effect [12, 13].

In the physicians' aspect of prescribing off-label drugs, an absence of sound knowledge about off-label medication usage among some of the prescribers and general practitioners resulted in higher incidence of off-label drug use [14-21].

The increase in the usage of off-label medications, increase in the incidence of ADRs associated with off-label use, fluctuating presence of knowledge among the physicians has prompted us to conduct a study on the usage and assessment of off-label medications. The objectives of the study were to understanding the usage of off-label drug use, observing and documenting the ADRs associated with off-label use, understanding the link between the off-label drugs and its prescribed indication. A questionnaire was also prepared to assess the decision-making process of the physician in prescribing off-label prescriptions.

TABLE 1: REVIEW OF LITERATURE

S. no.	Author And Title	Year and Journal	Place	Conclusion
1	Randall S. Stafford, M.D., Ph.D. Regulating Off-Label Drug Use - Rethinking the Role of FDA	2008, Journal of England Medicine	England	FDA might consider undertaking a range of new activities in regulating off-label use, including systematically collecting post-marketing data, synthesizing evidence regarding off-label uses and disseminating its reports, increasing the use of active drugs as comparators in post-marketing clinical trials; and requiring information about anticipated off-label uses to be presented at the time of a drug's review for initial approval
2	Conroy S, Choonara I, Impicciatore P, *et al*., Survey of Unlicensed and Off-Label Drug Use in Paediatric Wards in European Countries	2000, British Journal of Medicine	Uk, Sweden, Italy, Netherlands, Germany	Off-label drug use in these hospitals was widespread, so it requires the action of the European Union
3	Surabhi S. Jain, S. B. Bavdekar Off-Label Drug use in Children	2008, The Indian Journal of Paediatrics	Mumbai	Off-label drug use was highly prevalent in the general pediatric ward of a tertiary care hospital in India

METHODOLOGY:

Study Setting and Criteria: The study was an observational study conducted at a tertiary care hospital in India, which included the patients admitted in the hospital and were prescribed at least one drug for their indication. The study did not have any special exclusion criteria. The duration of this study was 8 months (from January 2017 to September 2017).

For each patient, demographic information, such as the patient's age and gender were collected. From the patients' medical record, prescription medication data including the dose, frequency, route of administration was obtained from the date of admission to the date of discharge, with recording and monitoring of any newly prescribed medications during the hospital stay. The patients were continuously monitored until the day of

discharge for any adverse event. The FDA official website was used as the standard reference to identify off-label drugs. Each off-label drug event was categorized into different groups: unapproved Indication (which includes unlicensed drug and utilization of contraindicated drug), unapproved dose, unapproved dosing frequency, unapproved route of administration and unapproved age group.

The level of evidence for off-label use was classified into High: randomized controlled trials and systematic reviews, Moderate: prospective phase II trials, prospective case series, and retrospective controlled studies and Low: retrospective case series or case reports. The evidence was collected from books, journals, and articles.

Statistical Analysis: Statistical Package for Social Sciences (SPSS) Version 19.0 for windows was used for analysis. The following statistical analysis has been done: Pearson correlation, Curve estimation, ANOVA.

RESULTS AND DISCUSSION: A total of 1646 prescriptions were analyzed, which contained 10340 drugs. Of the total 1646 prescriptions, 901 (54.7%) were found to be off-label prescriptions. Of the 10340 drugs, 1083 (11%) of drugs were off-label. A study was conducted in a tertiary care hospital in Mumbai by Surabhi S. Jain *et al.*, to assess the extent of off-label drug use among pediatric patients across all departments. The analysis of 2000 prescriptions, revealed that the use of off-label prescriptions was 50% [22]. This result was fairly similar to this study.

Another study conducted in Canada by Nancy E. Winslade *et al*., in a primary care setting reported that only 12% of the total prescriptions were off-label [23]. This variation could be due to the reason that the definition of off-label used by them was conservative (only un-approved indication was considered), since it did not include dosage, frequency, route of administration, duration of treatment and patient's age range. Another study conducted by Kwon JH, *et al*., regarding the use of off-label medications in a palliative care unit, reported having 35% off-label prescriptions [24].

Although very few studies have been done with the emphasis on off-label drug use in a tertiary care hospital involving the patients across all age groups and all departments, the off-label usage was found to be fairly high. The most common type of off-label use for prescriptions, was found to occur when the drug was prescribed for an unapproved indication (74%) followed by unapproved drug (23%), unapproved dose (0.8%), unapproved age group (4%), unapproved dosing frequency and route of administration (0.30%) and utilization of contraindicated drug (0.30%). This was similar to a study conducted in the USA, where the off-label drug with an unapproved indication was the highest at 45% [24]. Another study conducted in Canada across various primary care setting also revealed that the off-label drug with unapproved indication was the highest at 52%, followed by the unapproved drug at 18%, unapproved age group at 2% and unapproved dose at 0.5% [20].

Pantoprazole (22.8%) for NSAIDs induced ulcer prophylaxis, folic acid and its derivatives (9.69%) for Prophylaxis of Iron Deficiency Anemia in Pregnancy, Enoxaparin (7.75%) for cerebrovascular accident, Propranolol (4%) for Portal hypertension, Isosorbide mononitrate (3.2%) for esophageal varices and hypertension including diastolic dysfunction prophylaxis, sertraline (2.4%) for Myocardial Infarction-Depression and delirium due to CVA or alcohol withdrawal and Trimetazidine (3.21%) were the commonly prescribed off-label medications. Pantoprazole was the most commonly prescribed off-label drug. A study conducted in Croatia and USA in a tertiary care setting revealed similar results where pantoprazole was found to be the highest used off-label drug [25, 26, 38]. Another multicenter study conducted in Spain revealed that rituximab and omalizumab were the commonly used off-label drugs [28]. A study conducted in a tertiary care hospital across all departments involving pediatric patients revealed that Diclofenac and morphine were the commonly used off-label drugs [28]. The commonly used off-label drugs vary concerning the hospitals, study area, and study participants.

Evidence available for each prescribed off-label medication was evaluated. Around 83% of the off-label medications were found to have high evidence, followed by 9.9% medications having moderate evidence and 8.5% of the drugs having low evidence.

A similar trend was found in a study conducted in U.S.A by Maher H.R, *et al*., where an off-label drug with high evidence was 70%, with moderate evidence was 19% and with low evidence was 11% [29]. Another study conducted by Verhagen *et al*., in the Netherlands in a palliative care setting also revealed that off-label use with high evidence was 70% which was similar to our study [30]. The numbers of off-label drugs which can be replaced with on-label drugs were analyzed. The availability of on-label alternatives was found to be 17.9% of the off-label medications. Around 80% of the drugs had no replacement which was similar to a study conducted in the US by Jung Hye Kwon *et al.,* [24, 31]. Various other studies conducted at other parts of the world revealed that most of the off-label drugs did not have an on-label alternative [24-31].

For the off-label drugs, the number of adverse reactions **Table 2** was also checked. Of the total of 1083 off-label drugs, 108 (10%) cases of ADRs were reported. Adverse drug reactions were associated with 31 off-label, with Inj. Enoxaparin induced Hematuria in 14 patients, T. Isosorbide mononitrate induced Postural Hypotension in 11 patients, Inj. Ofloxacin induced infusion reactions in 9 patients, T. Clobazam induced excessive daytime sleep in 8 patients being the top four drugs having repeated adverse drug reactions. This result was found to be similar to a study conducted by Turner. S of Liverpool in pediatric populations which states that 11% of their patient receiving off-label was presented with an ADR [32].

Another study conducted by Buckeridge *et al*., of U.S in an adult population, revealed that of the total 17478 were off-label drugs 12% of the drugs were presented with ADRs [33]. Their incidence of adverse events increases with an increase in off-label drug use (P<0.001). This result was found to be in similarity with a study conducted in India by Saiyed *et al.* and Eugale in U.SA which reported that off-label status is a risk factor for ADR [33]. A study conducted in U.S.A by Tewodroset al stated that off-label drugs with low evidence had a higher chance of adverse events [24, 33].

Similarly, we have established that drugs having high evidence presented the least ADRs and the drugs with low evidence had a high incidence of ADRs (P<0.001). Additionally, we have also correlated the adverse drug reactions of off-label drugs with different age groups. Pediatrics and geriatrics were more susceptible to an ADR with off-label usage (P<0.001).

TABLE 2: ADVERSE REACTIONS DUE TO OFF-LABEL DRUG USE

Drug	Adverse Reactions	No of Patients
T. Amitriptyline	Dry Mouth, Drowsiness	2, 1
T. Sertraline	Sedation	5
T. Cyclopam	Dry Mouth, Sedation	1,1
T. Azathioprine	Nausea, Vomiting	2
T. Tadalafil	A headache	1
Inj. Octreotide	Abdominal Pain	2
T. Haloperidol	Mild EPS	1
T. Lorazepam	Day Time Sleep	3
T. Propranolol	Hypotension	2
T. Isosorbide Mononitrate	Giddiness	11
T. Carvedilol	Giddiness	5
T. Olanzapine	Drowsiness	6
C. Fluconazole	Headache	6
T. Sulfamethoxazole/ Trimethoprim	Leucopenia	1
Inj. Linezolid	Decreased Platelet Count	1
Inj. Enoxaparin	Hematuria	14
T. Quetiapine	Drowsiness, Daytime Sleepiness	5
T. Prednisolone	Steroid-Induced Diabetes	1
C. Indomethacin	Abdomen Pain	1
T. Sertraline	Sedation	1
T. Clobazam	Day Time Sleepiness	8
T. Albendazole	Abdomen Pain	5
Divalproate Sodium	Decrease In Platelet	2
Inj. Human Mixtard	Hypokalemia	1
T. Nifedipine	Headache	1
Inj. Lorazepam	Severe Day Time Sleepiness	1
T. Clonazepam	Sleepiness	1
T. Haloperidol	Disorientation	1
C/Inj. Clindamycin	Headache	4
Inj. Ofloxacin / Ornidazole	Infusion Reactions	9
T. Moxonidine	Insomnia	1

The first and the foremost reason for off-label use were found to be the lack of an on-label alternative medication. Studies conducted all over the world also revealed that the lack of an on-label alternative was the main reason for off-label prescribing [22-33].

Apart from the lack of an on-label alternative, the age of the patient and multiple disease conditions [13] were found to influence the total number of off-label drugs prescribed to the patient. Similarly, in our study, we found that an increase in the number of disease conditions leads to an increase in the number of off-label drugs prescribed to the patient (P<0.001).

Additionally, we have correlated the use of off-label drugs with different age groups. The usage of off-label drugs was higher in pediatric and geriatric populations when compared to the normal adult population which could be due to the limited numbers of trials done on these two populations during the process of approval (P<0.001). To understand the trends of off-label drug use across the hospital, the off-label usage across individual departments was also studied **Table 3** and **4**. The percentage of off-label prescriptions were found to be the highest in the orthopedics department (86.7%) followed by neurology (58%) and lowest in dermatology (22.50%). The percentage of off-label drugs was found to the highest in OG department (19.60%), followed by nephrology department (19.30%) and lowest in gastroenterology department (5.50%). The type of off-label use as unapproved indication was high in dermatology department 100% and low in cardiology department (48%), as the unapproved drug was high in cardiology (52%) and low in dermatology, as unapproved age group was high in pediatrics department (45.5%) and low in dermatology department. The presence of high evidence for the off-label drugs was high (100%) in dermatology, followed by (97.67%) in CTVS and low (67%) in the orthopedics department. The percentage of drugs having low evidence was found to be high in the orthopedics department (31%), followed by (20.12%) in neurology. In the surgery department, about 40% of the off-label drugs had an on-label alternative which was the highest across all departments.

TABLE 3: OFF- LABEL DRUG USE ACROSS VARIOUS DEPARTMENTS

Department	Number of off-label prescription	Number of off-label drugs	Commonly used off-label drugs	Type of off-label use	Evidence for off-label drugs	Availability of on-label alternative
Cardiology	86(46.50%)	108(7.80%)	T. Pantoprazole T. Trimetazidine T. Sertraline	1. Unapproved indication 47.30% 2. Unapproved drug 52.70%	1. High 81.55% 2. Moderate 17.47% 3. Low 5.82%	1.No 81.49% 2.Yes 18.51%
CTVS	31(51.66%)	43(6.50%)	Syp. Sucralfate T. Ranitidine T. Trimetazidine	1. Unapproved indication 60.40% 2. Unapproved drug 39.60%	1. High 97.67% 2. Moderate 2.32%	1.No 95.34% 2.Yes 4.65%
Dermatology	09(22.50%)	14(6.70%)	T. Azathioprine T. Tadalafil T. Mycophenolate mofetil	1. Unapproved indication 100%	1. High 100%	1.No 100%
Gastroenterology	51(28.80%)	67(5.50%)	T. Propranolol Inj. Octreotide T. ISMO	1.Unapproved indication 95.50% 2. Unapproved drug 4.50%	1. High 65.67% 2. Moderate 31.34% 3. Low 3%	1.No 86.56% 2.Yes 13.43%
Nephrology	75(53.20%)	93(7.30%)	T. Pantoprazole T. ISMO C. Fluconazole	1. Unapproved indication 84.75% 2. Unapproved drug 15.05	1. High 90.32% 2. Moderate 9.67%	1.No 81.73% 2.Yes 18.27%
Neurology	158(68.80%)	258(13.70 %)	Inj. Enoxaparin T. Pantoprazole T. Nuhenz	1. Unapproved indication 76% 2. Unapproved drug 24%	1. High 75.47% 2. Moderate 4.50% 3. Low 20.12%	1..No 91.47% 2.Yes 8.52%
Pediatrics	79(35.50%)	95(14.90%)	T. Clobazam Syp Ascazin T. Pantprazole	1. Unapproved indication 48.40% 2. Unapproved age group45.40% 3. Unapproved dose 4.20% 4. Unapproved drug 1%	1. High 76% 2. Moderate 3.15% 3. Low 20%	1.No 77.89% 2.Yes 22.10%

Obstetrics and Gynecology	103(65.20%)	154(19.60 %)	T. Autrin Folic acid T. Winofit	1. Unapproved indication 77.92% 2. Unapproved drug 19.40% 3. Unapproved dose 1.30% 4. Utilization in contraindicated condition 1.30%	1. High 75.32% 2. Moderate 9.33% Low 15.33%	1.No 74.67% 2.Yes 25.33%
Orthopedics	65(86.70%)	87(19.30%)	T. Pantoprazole T. Chymoralforte T. Sertraline	1. Unapproved indication 72.40% 2. Unapproved drug 27.60%	1. High 67.81% 2. Moderate 1.14% 3. Low31.03%	1.No 94.52% 2.Yes 5.74%
Psychiatry	40(30%)	45(7.30%)	T. Clonazepam T. Lorazepam T. Olanzapine	1. Unapproved indication 97.70% 2. Unapproved drug 2.30%	1. High 91.11% 2. Moderate 6.66% 3. Low 2.22%	1.No 82.22% 2.Yes 17.77%
Surgery	87(40.30%)	98(6.90%)	T. Pantoprazole Inj. Ofloxacin C. Clindamycin	1. Unapproved indication 92.50% 2. Unapproved drug 7.50%	1. High 63.50% 2. Moderate 30.61% 3. Low 4.08%	1.No 59.18% 2.Yes40.81 %

TABLE 4: USAGE OF OFF-LABEL DRUGS

Department	Commonly Used Off-label Drugs (In Hospital)	Indications for Off-Label Use	Category of Off-Label Use	Evidence	Alternative Available
Cardiology	1. Pantoprazole 2.Trimetazidine 3. Sertraline	1. NSAID Induced Ulcer Prophylaxis 2. CAD, Vasodialation 3. MI, Depression	1. Unapproved Indication 2. Unapproved Drug 3. Unapproved Indication	1. High 2. High 3. Moderate	1. No 2. No 3. No
CTVS	1. Syp. Sucralfate 2. T. Ranitidine 3. Trimetazidine	1. Stress Ulcer Prophylaxis 2. Drug Induced Ulcer 3. CAD, Vasodialation	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Drug	1. High 2. High 3. High	1. No 2. No 3. No
Dermatology	1. T. Azathioprine 2. T. Tadalafil 3. T. Mycophenolate Mofetil	1. Ectopic Dermatitis 2. Raynaud's Syndrome, Sclerosis 3. Systemic Sclerosis	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Indication	1. High 2. High 3. High	1. No 2. No 3. No
Gastroenterology	1. T. Propranolol 2. Inj. Octreotide 3. T. Isosorbide Mononitrate 4. T. Carvedilol	1. Portal HTN, Esophageal Bleed 2. Esophageal Varices 3. Esophageal Varices, Portal HTN 4. Portal HTN	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Indication 4. Unapproved Indication	1. High 2. High 3. High 4. Moderate	1. No 2. No 3. No 4. No
Nephrology	1. T. Pan 2. T. Isosorbide Mononitrate 3. C. Fluconazole	1. NSAID Induced Ulcers 2. Hypertension, Diastolic Dysfunction Prophylaxis 3. Candidia Pyelonephritis Prophylaxis	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Indication	1. High 2. High 3. Moderate To High	1. No 2. No 3. No
Neurology	1. Inj. Enoxaparin 2. T. Pantoprazole 3. T. Nuhenz 4. T. Quetiapine	1. CVA Accident 2. NSAID Induced Ulcer Prophylaxis 3. Neuroprotector 4. Alcohol Dependence, Delirium due to CVA Craniotomy Induced Depression	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Drug 4. Unapproved Indication	1. High 2. High 3. High 4. Low (Craniotomy)	1. No 2. No 3. No 4. No
Pediatrics	1. T. Clobazam 2. Syp Ascazin 3. T. Pantoprazole	1. Febrile Seizure 2. Nutrition Deficiency 3. Drug-induced Ulcer	1. Unapproved Age Group 2. Unapproved	1. High 2. High 3. High	1. No 2. No 3. No

		Prophylaxis	Indication 3. Unapproved Indication		
Obstetrics & Gynecology	T. Autrin Folic Acid T. Winofit	Prophylaxis Of Iron Deficiency Anemia	Unapproved Indication	High	No
Orthopedics	1. T. Pantoprazole 2. T. Chymoral Forte 3. T. Sertraline	1. Drug-Induced Ulcer Prophylaxis 2. Inflammation, Swelling. 3. Dysthymia and Prophylaxis	1. Unapproved Indication 2. Unapproved Drug 3. Unapproved Indication	1. High 2. High 3. Moderate	1. No 2. No 3. Yes
Psychiatry	1. T. Clonazepam 2. T. Olanzapine 3. T. Lorazepam	1. insomnia due to Psychotic Illness, Somatoform Disorder 2. ADHD,OCD, Emotionality 3. Agitation, Insomnia	1. Unapproved Indication 2. Unapproved Indication 3. Unapproved Indication	1. High 2. Moderate 3. High	1. No 2. Yes 3. No
Surgery	T. Pantoprazole Inj. Ofloxacin T. Inj. Metronidazole	1. Drug-Induced Ulcers 2. Surgical Prophylaxis	Unapproved Indication	1. High 2. Moderate 3. Moderate	1. No 2. Yes 3. Yes

CONCLUSION: The percentage of off-label prescriptions was around 54%. Of the total drugs administered, 11% were off-label. The most common type of off-label was an unapproved indication which was followed by the unapproved drug. Of the total off-label drugs used, 83% of the drugs had high evidence. A total of 10% adverse drug reactions were reported for the off-label drugs and the drugs with low evidence had a high incidence of ADR. The main reason for off-label prescribing was lack of an on-label alternative. Around 80% did not have an on-label alternative. Since, there is an increased risk of adverse reactions associated with off-label drugs, continuous monitoring and follow up is required for patients receiving off-label drugs.

There have been very few studies carried out regarding the use of off-label drugs. A constructive idea which can be implemented is to have a periodic audit of off-label use and the drug-related problems arising from the off-label use. A major problem remains with many drugs commonly used in pediatrics and geriatrics. Health professionals are concerned about the lack of information regarding the use of drugs in these populations which places them in a difficult situation. To ensure that nobody is exposed to unnecessary risk due to off-label drugs, controlled clinical trials are required to determine the most appropriate dose in different ages.

IHEC No: 17/086

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: The authors declare no conflict of interest.

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How to cite this article:
Mathew KT, Kishor S, Jess SE, Dutt VS and Sivakumar V: Assessment of off-label drug use in a tertiary care hospital. Int J Pharm Sci & Res 2019; 10(6): 3045-52. doi: 10.13040/IJPSR.0975-8232.10(6).3045-52.