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Evidence for Off Label Drug Use - Assessment of Benefits and Harms in an Indian Tertiary Care Hospital

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ABSTRACT

Background: Off-label drug usage has a big concern about safety and efficacy in clinical practice; the solid evidence for the use of off-label drugs brings enough confidence to use in required situations. The level of evidence for the drug was classified as High: randomized controlled trials and systematic reviews, Moderate: prospective phase II trials, prospective case series and retrospective controlled studies, and Weak: retrospective case series or case reports. **Aim:** Our study aims at providing evidence for the type of off-label drug use, assessing the benefits by analyzing the response to the drug and harms. **Methodology:** An observational study was conducted in a tertiary hospital in Coimbatore, Tamil Nadu which included patients who were admitted and treated for their medical condition. The patient's information was collected from medical records and was referenced against the FDA label. **Results:** From 1500 prescriptions, evidence was analyzed for each prescribed off label drug used. About 74% of drugs contributed to high-level evidence of off label use. While assessing the benefit, 99.13% had a complete response, and the risk was seen only in 2.06% of the patient population. **Conclusion:** Regardless of the levels of evidence for the use of Off-label drugs, benefits were found to outweigh the risk. Controlled clinical trials have to be conducted to ensure that patients are not exposed to unnecessary risk and to determine the most appropriate indications for a particular drug.

INTRODUCTION:

Marketing authorization is obligatory before advertising and marketing medicine, thus making sure the safety, quality, and efficacy of the drug. For a drug to be approved, manufacturers have to submit all information regarding animal studies and scientific trials to regulatory authorities to compare the safety and effectiveness of their meant use. [1] But, there is no clear-cut guideline on off-label use of the drug. [2]

Off-label drug use is described as the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dose, dosage, or route of administration (WHO).[3]Physicians prescribe medicines beyond manufacturer guidelines provided within the package insert.[4] In recent years, there is an increasing trend for the usage of off-label drugs from 30.2% to 39.1% from 1993 to 2008 and 54% in 2017.[5]The largest conducted analysis of outpatient prescribing patterns found 21% of medications used as Off-label and 73% lacked scientific evidence.[6]

Evidence-based practice is important because it aims to provide the most effective care that is available, intending to improve patient outcomes. [18] A cornerstone is a hierarchical system of classifying evidence. The level of evidence for the drug was classified as High: randomized controlled trials and systematic reviews, Moderate: prospective phase II trials, prospective case series and retrospective controlled studies, and Weak: retrospective case series or case reports. [16] For example, the drug was classified as high evidence if there was good evidence to support its use as an off-label drug for a specific condition. RCTs are given the highest level because they are designed to be unbiased and have less risk of systematic errors. [16] A case series or expert opinion is often biased by the author's experience or opinions and there is no control of confounding factors.[16] Observational studies are designed with specific data collection methods, it has the advantage of being tailored to collect specific exposure data and maybe more complete.[19] Usually cheaper than RCTs, can be used to investigate rare outcomes, to detect unusual side effects, and that some designs are easily and quickly performed. Although the evidence level of observational studies appears to be lower than that of RCTs, it is clear that this kind of investigation is crucial for elucidating many scientific questions. [20]

Many patients benefit when they receive drugs under circumstances no longer distinct on a label approved by way of the regulatory authority.[7] First, it gives innovation in medical

practice, especially while approved treatments have failed as well as allows physicians to undertake new practices primarily based on emerging evidence.[8] Next, it is important in the field of pediatrics where only a few medicines are examined, and finally, it avoids the lengthy and costly technique of modifying the FDA labeling of a medication.[6] An off-label drug use affords a great intervention for the patient whilst medical proof justifies its use.

Off-label use of drugs can cause adverse effects and the risk might also outweigh the potential benefits. It undercuts expectations that drug protection and efficacy had been completely evaluated. For example, sleeping pills, approved for use for a short period when used on a long-term basis can cause tolerance.[9] When medicines are used in an off-label manner, clinicians must be aware of the risk of developing ADR irrespective of the level of evidence to support its use. [4,10]

The use of the off-label drug in clinical practice needs to be safe and effective for usage and to show beneficial proof it should have an expert opinion, evidence-based literature reviews, and results of descriptive studies. [10, 11]

The objectives of our study are finding evidence for the type of off-label drug use, assessing the benefits and risks of off-label drug use in patients by seeing the response to the drug.

MATERIALS AND METHODS:

Study design, setting, and criteria

This was an observational study conducted in PSG Hospitals, Coimbatore, Tamil Nadu; included patients who were admitted and treated for their medical condition from February 2019 to September 2019. A sample size of 1500 was selected using Rao software based upon the number of inpatient admissions in the hospital. Patients admitted to the hospital for their condition are included in the study and no exclusion criteria.

Data collection

Patient details and adverse events were collected from the patient medical record and confirmed to a physician.

Determination of the type of off-label use and level of evidence

The above-collected drug list and its indication were cross-referenced with the FDA approved

label. Each off-label drug is identified and categorized as an unapproved indication, unapproved dose, unapproved dosing frequency and route of administration, unapproved age group, utilization of the contraindicated drug, unapproved drug**.** Using guidelines from Oxford Centre for evidence-based medicine; evidence for each prescribed off-label drug was classified into high, moderate, low evidence. A review of published evidence for every drug use in each clinical indication was performed searching for information on the PubMed database, articles in Google scholar engine, and level of evidence was classified individually.

Determination of benefit and harm assessment.

The clinical responses to off-label use of drugs were classified as complete response (CR), partial response (PR) taking into account different parameters of efficacy for each disease. Drug categories like anti-seizure drugs, anti-hypertensives were set with specific efficacy endpoints like reduction in the frequency of seizures and decrease in blood pressure as an endpoint. Similarly, for other drugs, specific endpoints were set and patient analysis was done and documented. Adverse drug reactions occurring due to off-label drug use were classified according to the WHO-UMC causality assessment scale.

Statistical Analysis

Pearson correlation was done for analyzing the correlation between evidence and adverse reactions with the level of significance 0.01 and done using Statistical Package for the Social Sciences version 20.0.

RESULTS AND DISCUSSION:

RESULTS:

Out of 1500 prescriptions, 69.8% prescriptions had off label which contained 215 varieties of off-label drugs which were classified according to off-label use; provided with evidence as high, moderate, and low evidence. Evaluated benefits by setting endpoints for assessable drugs as well as harms by observing adverse drug reactions to off-label drug use.

Table 1: Summary showing Total off-label drug prescriptions, drugs, assessable drugs, response, and adverse events to the drug

During stay	Count (%)
Total number of off-label prescriptions	1047 (69.80%)
Total number of off-label drugs	1799 (17%)
Actual off-label drugs	215
Drugs not assessable	190
Assessable drugs	25
Complete response	115(99.13%)
Partial response	1(0.86%)
Total Adverse reactions	31
Adverse events from assessable drugs	1

- Drugs, not assessable – 190 off-label drugs were not assessed for benefit outcomes. Specific efficacy endpoints were unable to set to determine the outcome. For example, drug categories like Neuro protectant(citicoline), liver protectants(N-acetylcysteine)

- Assessable drugs – 25 drugs from the study were completely assessed for the benefit, harm, and evidence**.**

I. ASSESSMENT OF EVIDENCE FOR TOTAL OFF-LABEL DRUG USE

About 74.4% of off-label drugs were found to have high evidence followed by 21.2% medications having moderate evidence and 4.4% of drugs having low evidence.

Evidence was analysed for the actual number of drugs used (n= 215).

Drugs such as pantoprazole used for the treatment of ulcer prophylaxis, ondansetron for vomiting prophylaxis, lorazepam for sedation are common as off-label drugs for the above said indications and found to have high evidence. In the same way, oseltamivir used for the treatment of flu prophylaxis, bisoprolol for hypertension, carvedilol for portal hypertension is found to have moderate evidence. Similarly, drugs like pre-pro used as probiotic, lorazepam for the treatment of seizure, calcium gluconate for rickets are found to have low evidence.

Evidence for the type of off-label use:

The evidence for off-label drug use was categorized based on the type of off-label use. The off-label drug in the category of unapproved age group has a high level of evidence followed by unapproved drug whereas utilization of contraindicated drug has a low level of evidence followed by unapproved dose.

Table 2: Percentage of evidence for the category of off-label drug use

Category	High evidence	Moderate evidence	Low evidence
Unapproved age group	11(100%)	0	0
Unapproved drug	44(80%)	1(1.81%)	10(18.18%)
Unapproved Indication	123(74%)	10(6.06%)	32(19.39%)
Unapproved dosing frequency	5(55%)	0	4(45%)
Unapproved dose	6(46.15%)	0	7(53.8%)
Utilization of contraindicated drug	2(18.18%)	1(9.09%)	8(72.2%)

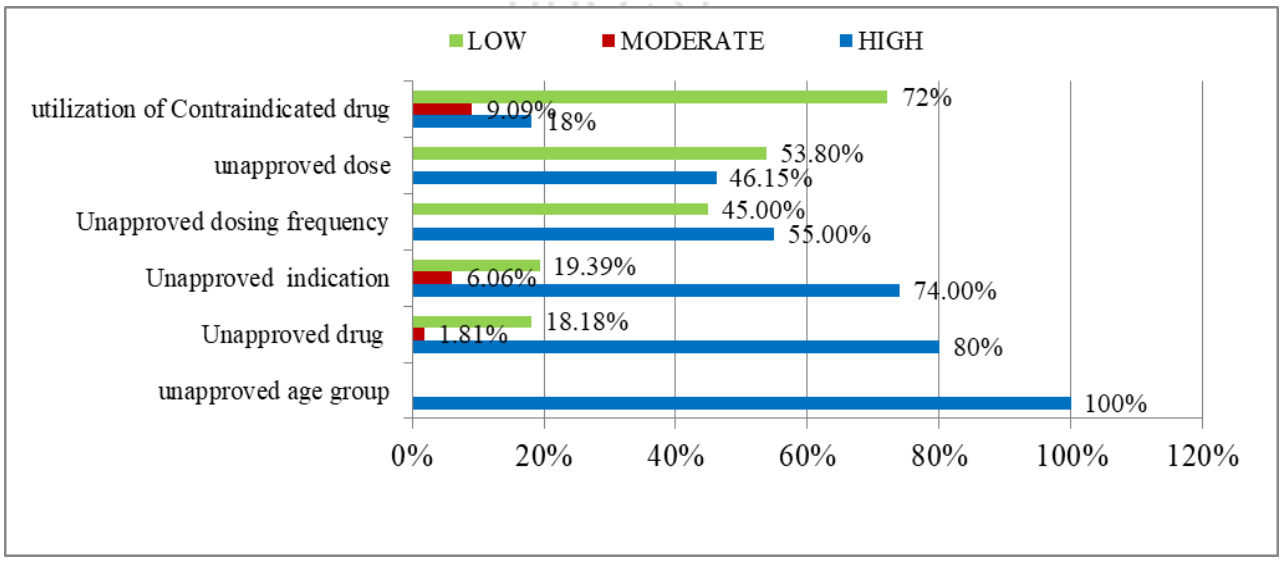

Figure 1: Percentage of evidence for the type of off-label drug use

II. ASSESSMENT OF BENEFITS FOR OFF-LABEL DRUG USE

The majority of drugs for which response was assessable are pain killers followed by antihypertensive drugs. Patients were observed from hospital admission to check their improvement up to discharge and assess the response at the end of off-label treatment.

Table 3: Assessment of response for off-label drug use

S.no	Assessable drugs	Indication	Evidence	Efficacy Endpoint	Complete / partial Response	Adverse reaction
1	T.Aceclofenac	Pain	High	Relief of pain	Complete	-
2	T.Amitriptyline	Pain	High	Relief of pain	Complete	Headache
		Pain	High	Relief of pain	Complete	-
		Headache	Low	Complete relief of headache	Complete	-
3	T.Azathioprine	Bullous pemphigoid	High	Decrease in blister formation, pain, and pruritis	Complete	-
4	T.Bethanecol	Urinary retention	Low	Improvement in micturition and bladder emptying	Complete	-
5	T.clinidipine	Hypertension	High	Maintenance of blood pressure	Complete	-
6	T.Clonazepam	Tremor	Low	Reduction in tremor	Complete	-
7	T.Chymoral forte	Pain	High	Relief of pain, swelling	Complete	-
8	T.Disencher	Pain	High	Relief of pain	Complete	-
9	T.Doxyphyline	Bronchodilator	High	Reduction in asthma symptoms	Complete	-

10	T.Etoricoxib	Pain	High	Relief of pain	Complete	-
11	T.Flunarizine	Migraine	High	Reduction in frequency and severity of headache	Complete	-
12	T.Levetiracetam	Seizure	Low	Reduction in frequency and severity of seizures	Complete	-
13	T.Metoclopromide	Vomiting	High	Reduction in nausea and vomiting	Complete	-
14	T.Nefopam	Pain	High	Relief of pain	Complete	-
15	T.Ondansetron	Vomiting	High	Reduction in nausea and vomiting	Complete	-
	Inj.Ondansetron	Vomiting	High		Complete	-
16	T.Pregabalin	Neuropathic Pain	High	Decreased pain intensity	Complete	-
17	T.Prucalopride	Constipation	Low	Stool passed	Complete	-
18	T.Signoflam	Pain	High	Relief of pain	Complete	-
19	T.Piroxicam	Pain	High	Relief of pain	Complete	-
	Inj.Piroxicam	Pain	High		Complete	-
20	Inj.Labetalol	Hypertension	High	Normal range	Complete	-
21	Inj.Lorazepam	Seizure	High	Cessation of seizure	Complete	-
22	Inj.Levetiracetam	Seizure	Low	Reduction in frequency and severity of seizures	Complete	-
23	Inj.Pentazocine	Pain	High	Relief of pain	Complete	-

24	Inj.Sodium valproate	Tonic-clonic seizure	High	Reduction in frequency and severity of seizures	Complete	-
25	Syp.Ambroxol	Cough	High	Reduction in cough	Complete	-

III. ASSESSMENT OF HARMS FOR OFF-LABEL DRUG USE - ADVERSE REACTIONS

For the Off-label drugs, the number of adverse drug reactions **Table 3** was also checked. A total of 31(2.06%) patients experienced adverse drug reactions and they were classified according to the WHO-UMC causality assessment scale as Probable (8), possible (13), unlikely (1). 31 adverse drug reactions developed in response to 22 off-label drugs. Out of 14 patients prescribed with Lorazepam, 5 patients developed dizziness, and 3 out of 6 patients prescribed with Inj. enoxaparin presented with hematuria.

Table 4: Causality assessment of off-label adverse drug reactions

Drug	Adverse Reactions	Evidence	WHO -UMC Causality Assessment	Number Of prescriptions (n=214)	Number Of reactions (n=22)
T. Lorazepam	Dizziness	High	Possible	14	5(35.71%)
Inj.Enoxaparin	Hematuria	High	Probable	6	3(50%)
T. Azathioprine	Leukopenia	High	Probable	8	2(25%)
T. Cyclosporine	Nephrotoxicity	High	Probable	5	1(20%)
T. Olanzapine	Weight Gain	High	Possible	6	2(33.33%)
T. Clonidine	Dry Mouth	High	Possible	6	1(16.66%)
T. Carvedilol	Dizziness	Moderate	Possible	20	1(5%)
Inj.Octreotide	Abdominal Pain	High	Probable	18	1(5.55%)
T. Atorvastatin	Muscle Pain	High	Probable	9	1(11.11%)
Inj.Ofloxacin	Infusion Reactions	Moderate	Possible	10	2(20%)
T. Tranexamic Acid	Headache	Low	Possible	3	1(33.33%)

T. Chlorpheniramine	Sedation	Moderate	Possible	2	1(50%)
T. Livogen	Black Stools	High	Possible	39	1(2.56%)
T. Clobazam	Sedation	High	Possible	32	1(3.12%)
T. Acitrom	Gingival Bleeding	High	Probable	10	1(10%)
T. Sertraline	Insomnia	Low	Unlikely	2	1(50%)
T. Prednisolone	Hyperglycemia	Low	Probable	4	1(25%)
C.Tamsulosin	Headache	High	Possible	7	1(14.28%)
T.Mycophenolate	Musculoskeletal Pain	High	Possible	4	1(25%)
T. Amitriptyline	Headache	High	Possible	7	1(14.28%)
T. Cabergoline	Giddiness	High	Possible	1	1(100%)
T.Haloperidol	EPS	High	Probable	1	1(100%)

Overall, about 74.4% of off-label drugs used were found to have high evidence. The off-label drug in the category of unapproved age group has a high level of evidence followed by unapproved drug whereas utilization of contraindicated drug has a low level of evidence followed by unapproved dose. The majority of drugs showed benefits when used as an off-label drug disregarding the level of evidence. The risk from using off-label drugs showed minimal adverse reactions and when they were analyzed for correlation between the level of evidence and adverse drug reactions of the drug the results were statistically not significant.

DISCUSSION:

The use of off-label drugs is supported by providing evidence by categorizing into high, moderate, and low evidence using the oxford center for evidence-based medicine. About 74.4% of drugs had high evidence. In our study, Aceclofenac is used as off label for pain, the patient experienced complete response which is supported by randomized controlled trials justifying high evidence for its use. Evidence is quoted from this study An Open-label Randomized trial conducted regarding the safety and efficacy of Aceclofenac for lower pain demonstrated that aceclofenac has significant symptom relief, improvement in the quality of life, and functional score.[12] Similarly, bethanechol used for urinary retention had low evidence supported with a review article in which treatment with bethanechol helped subside

urinary retention within a few days.[13]

For assessment of benefit, drugs with specific efficacy points were included. The majority of patients experienced relief from illness after usage of the off label and thus patients benefited from therapy irrespective of the level of evidence. The benefit could only be assessed for a few drugs i.e., 25 drugs for which specific endpoints could be set. For the remaining drugs, it was not possible to determine endpoint like in the Neurology department, most of the patients with stroke were given with neuroprotectant for which response is not assessable. For some drugs, treatment endpoints would take time to determine which could not be assessed because of the shorter hospital stay of patients. Clinical response was observed in the majority of patients, 99.13% with complete clinical response and 0.86% had a partial response to Off label treatment. This approach was quoted from a prospective study conducted in Hospital Universitari Valld'Hebron, Spain by I. Danes et.al. to evaluate the outcomes of Off label use in the year 2011-2012 which were mostly biologicals and clinical response was observed in 72.6% of patients; 36.3% had a partial response,31.4% with a complete clinical response and 4.9% with stabilization and 26% had lack of response and 1% it was unknown. [8] For example in our study T. Azathioprine indicated for bullous pemphigoid; the complete response was observed by a decrease in blister formation, pain and pruritis supported by systemic review on evidence-based treatment for *pemphigus vulgaris*, bullous pemphigoid which demonstrated azathioprine is the most effective steroid-sparing agent beneficial for bullous pemphigoid.[17]

For harm assessment, the analysis was done using correlation which showed drugs have adverse event profile irrespective of the level of evidence for use as off label drug. Adverse reactions were documented for 22 off drugs which notably produced 31 adverse reactions. In our study, only 2.06% of patients experienced harm i.e. adverse reactions due to Off label use. The prominent adverse reaction due to Off label use is Lorazepam-induced Dizziness which occurred in 14 prescriptions and was classified as possible according to the WHO-UMC causality assessment scale. While the study conducted by Mathew et al during the year 2017 in an Indian tertiary care hospital reported 10% adverse events. [15] On the other hand, our study shows a decline in adverse events compared to a previous study from 10% to 2%. There was no significant association *P-value-0.095) found* between evidence of off-label drug use and adverse reactions.

CONCLUSION:

Off-label drugs being prescribed for a particular condition were mostly to alleviate symptoms, supported by the high level of evidence. When patients were observed for risks and benefits occurring due to off-label drug use, minimal risk, and complete response was observed in most of the patients. Irrespective of the levels of evidence for the use of off-label drugs, benefits were found to outweigh the risk.

There are only a few studies conducted on the outcomes of off-label drugs. It is necessary that audits have to be implemented to keep a check on off-label drug use and drug-associated issues that may arise from off-label use. Health experts are apprehensive regarding the lack of information about the use of off-label drugs in this population. For that reason; Clinical Pharmacists have to play their role in the hospital to analyze off-label drugs and evidence which serve as information for the physicians to provide better patient outcomes. To avoid unnecessary risk to the patient, phase 3 clinical trials need to be conducted for the off-label drug which has an excellent clinical positive response with the high level of evidence.

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Nil.

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