Review Article

Off-Label Prescribing: A Curse or A Boon

Gitashree Dutta[1], Tarun Kumar[2], Siddhartha Dutta[2*], Ritesh Kumar[3], Ravi Prakash Sharma[4], Sudeshna Banerjee[5]

[1]Senior Resident, Department of Community Medicine, NEIGRIHMS, Shillong, India.
[2]Senior resident, Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, India.
[3]Senior Resident, Department of Pharmacology, RIMS, Imphal, India.
[4]Junior resident, Department of Pharmacology, All India Institute of Medical Sciences, Jodhpur, India.
[5]Senior Lecturer, Medical surgical nursing, RSVM Nursing college, Jodhpur, India.
***Corresponding author's E-mail:** siddhartha.dutta87@gmail.com

Received: 05-07-2020; **Revised:** 25-09-2020; **Accepted:** 03-10-2020; **Published on:** 20-10-2020.

ABSTRACT

The use of Off-label drugs is quite a common phenomenon around the whole world as it provides an autonomy to physicians to explore new therapeutic options based on the latest evidence. Approved drugs can be prescribed lawfully by the physicians that must be supported with adequate scientific data but unfortunately, this is done without the acceptable scientific data. Limited available options in some rare and terminal illnesses lead to the inappropriate use of off-label drugs. But in these cases, the prescribing is solely intending to benefit the patient. With the inappropriate use of off-label drugs, concerns of efficacy and safety have been raised because of drugs being used without a documented risk-benefit analysis or clinical trial in its favor. Though the regulatory approval is completely based on evidence of efficacy and safety for approving specific indications of prescription drugs, still more precision is required about regulations governing off-label usage of the medicine. Off-label use might be compared to a two-edged sword which might be very useful for some patients while it can also expose them to unrestricted experimentation, mysterious health risks, or futile medicine. To some, using a drug off-label is a matter of personal choice and is solely based on the clinical experience gained by him all through his years of practice. Above all because of the financial aspects and limited options involved, it is highly impractical to expect that doctors will restrict or stop off-label prescriptions for the treatment of diseases with no approved drugs.

Keywords: Off-label, Safety, Prescription, Drugs.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2020.v64i02.020

DOI link: http://dx.doi.org/10.47583/ijpsrr.2020.v64i02.020

INTRODUCTION

In therapeutics, medicines or drugs play a crucial role in healing disease and maintaining health. Drugs, before they come to the market undergo rigorous preclinical and clinical trials to prove its safety, efficacy, and importance in a particular disease condition following which they are subjected to get market approval if found propitious. The drugs which come to the market are approved for disease condition/s as specified in the product license are called labeled indications.[1] Off-label use of drugs refers to the usage outside the indications prescribed in the product license in terms of indications, dose, patient age, route of administration, and contra-indications.[2,3] To simplify, off label use is any usage of drugs outside the approved indication. It is also important to note that the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use.[4]

Off-label usage of drugs is not a rare phenomenon but is very common worldwide.[5] According to previous research, this practice can be as high as 90% in the pediatric population or 40% in adults.[6] In a recently conducted survey in the USA, the off-label use for 160 commonly prescribed medicines was found to be 21% overall and as high as above 80% for some of them.[7] It has been found that the prevalence of off-label and unlicensed drug use is higher in neonates and infants and premature and low birth-weight babies. The off-label use of drugs in oncology has been estimated to reach 50%, or even more.[8]

When off-label use is scientifically and medically justified, physicians, promote patients' interests by prescribing off label drugs. As off label prescribing is done without adequate scientific data and safety of the drug in the particular condition is supposed to be the main concern.[9,10] It has been reported that only about 30% of off-label prescribing was supported by adequate scientific data. Off-label use of medicine involves physicians, pharmaceutical companies, regulatory agencies, and patients.[10] This article tries to discuss the need for off-label prescribing and find out the pros and cons associated with it.

Off Label Prescribing Scenario

In most of the countries including India, prescribing information and promotional drug literature by pharmaceutical companies are not allowed to promote for non-approved indication, but physicians have the autonomy to prescribe any approved drug for any indication, disregarding of the fact that the indication is not

approved by regulatory bodies in emergency conditions, absence of approved medication for the disease or in the belief that the drug would benefit the patient supported by previous evidence or experience.[10] Off-label prescription of a drug is generally legal, but the promotion of off-label uses by a drug manufacturer is considered to be illegal as the manufacturer does not completely understand the effects of these medicines.[11] Off-label use by general physicians is quite often if standard treatment regimens are non-existent or standard treatment regimens fail to treat the condition.[12]

Off-label use of drugs gives freedom to physicians to apply new therapeutic options based on the newest evidence but there is no guarantee of its scientific validity due to deficiency of evaluation of safety and efficacy. Therefore, while prescribing drugs for off-label use the physician must be mindful of its scientific viability and medical confirmation.[5,13] For example, Sildenafil citrate, a drug used in angina, was also found to be useful in the treatment of pulmonary hypertension for which it was prescribed off-label.[14] Bevacizumab is a full-length, humanized monoclonal antibody focused against all the biologically active isoforms of vascular endothelial growth factor (VEGF-A). The antibody was primarily designed and studied as an anti-angiogenic strategy to treat a variety of solid tumors.[15] Unfortunately, many medically accepted off-label uses sometimes do not get adequate attention from the regulatory authorities for example- Bevacizumab for age-related macular degeneration(AMD).[16] Curative choices might curb without off-label prescribing in some patient populations.[10,11] Off label drugs can be useful to patients with an orphan disease where sometimes that is the sole existing treatment.[9] Off-label prescribing is also a common practice in psychiatric practices.[10,12] Numerous anticancer drugs which were originally been approved for treating a single type of cancer have been later found effective in treating another type of cancer.[12] Cancer patients have been benefited significantly from this off label prescribing and the overall cure rate of more than 70% in pediatric malignancies would not have been achieved without the use of the off-label cytotoxic drugs.[17]

Need for Off Label Use

Often, when the best available therapeutic option fails, the patient's situation demands a new approach or new treatment which ultimately ushers to off-label uses.[12] Moreover, the early access to potentially valuable medications to patients can be provided by off-label use. Some off-label uses are scientifically valid and do provide enormous advantages to the patient. For example, aspirin has numerous off-label usage which is usually endorsed for the prevention of myocardial infarction in individuals at moderate or greater risk of coronary artery disease (CAD). Researchers have also investigated the use of aspirin in the prevention of colon and esophageal cancer and other diseases.[18] So, in short, the benefits of off-label prescribing include speedy drug availability to patients as medical knowledge advances, reduced cost in new treatments. It may be useful when standard treatments fail and when patients are heterogeneous. It also allows for experimentation and serendipitous discovery.[19]

But when there is no surety about the scientific validity of off-label use, then it might expose the patient to unrestricted experimentation, unknown health risks, or ineffective medicine.[20,21,22] Off-label use of drugs has been associated with serious adverse effects. The appetite suppressant fenfluramine, approved for short-term use, was widely prescribed with phentermine, and used long-term. The off-label combination “fen-phen” caused valvular heart disease.[20,21] In children, off-label use of drugs is associated with an increased number and severity of adverse effects.[6] The summary of some commonly off label prescribed drugs are illustrated in Table-1.[23]

Table 1: Summary of Off-Label Drugs

S.No.	Drug name	Approved use	Off-label use	Reference
1	Sildenafil citrate	Angina, Erectile dysfunction	Pulmonary hypertension	9
2	Paclitaxel	Ovarian Cancer	Breast cancer	7
3	Propranolol	Cardiac Arrhythmia	Hypertension, Angina pectoris, Migraine	7
4	Thalidomide	Cutaneous manifestations of erythema nodosum leprosum	Aphthous stomatitis, Behçet's disease, lupus erythematosus, prurigo nodularis, sarcoidosis, actinic prurigo, graft-versus-host disease, Langerhans cell histiocytosis, erythema multiforme, lichen planus, Kaposi sarcoma, Jessner lymphocytic infiltrate	24
5	Bevacizumab	Metastatic colorectal cancer	Age-related macular degeneration (AMD)	10, 11
6	mitomycin	gastric and pancreatic carcinomas	lung, bladder, breast, cervical, and other carcinomas	7
7	Quetiapine	Schizophrenia	Bipolar, maintenance	18
8	Warfarin	Atrial fibrillation	Hypertensive heart disease	18
9	Escitalopram	Depression	Bipolar	18
10	Risperidone	Schizophrenia	Bipolar, maintenance	18

11	Montelukast	Asthma	COPD	18
12	Bupropion	Depression	Bipolar	18
13	Sertraline	Depression	Bipolar	18
14	Venlafaxine	Depression	Bipolar	18
15	Celecoxib	Joint sprain/ strain	Fibromatosis	18
16	Lisinopril	Hypertension	Chronic artery disease	18
17	Duloxetine	Depression	Anxiety	18
18	Trazodone	Depression	Sleep disturbance	18
19	Olanzapine	Schizophrenia	Depression	18
20	Epoetin-alfa	Chronic renal failure	Anemia of chronic disease	18

CONCLUSION

Once a drug has been approved for a particular condition, can be prescribed for treatment of other disorders too but with certain restrictions. New uses for old drugs are often discovered so a significant part of all prescriptions are for uses for which the drug has not been approved by licensing authorities like the US-FDA. The risk-benefit ratios presented by the unproven therapies must be carefully considered and disclosed, and standard of care practices should be reviewed. When the use of the drug is truly investigational, the drug is tested with a well-designed clinical trial. However, prescribing a drug outside its labeled condition can sometimes get the prescriber into trouble. The prevalence of 'off-label' prescribing has generated worry that prescribing is not scientifically sound or in the patient's interest. A better understanding and obligation of the off-label system should be brought by the regulatory authorities to benefit the patients with diseases where no approved drugs are available.

REFERENCES

1. Indications and Usage Section of Labeling for Human Prescription 2 Drug and Biological Products – Content and Format Guidance for Industry. Food and Drug Administration. Accessed on 06 Aug 2020. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM612697.pdf
2. Understanding Unapproved Use of Approved Drugs "Off Label" Food and Drug Administration. Accessed on 06 Aug 2020. Available from: https://www.fda.gov/forpatients/other/offlabel/default.htm
3. Conroy S. Unlicensed and off-label drug use: issues and recommendations. Paediatr Drugs. 4(6), 2002, 353-9.
4. Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, et al. Off-label use of drugs in children. Pediatrics. 133, 2014, 563–7.
5. Stafford RS. Regulating off-label drug use -- Rethinking the role of the FDA. N Engl J Med. 358, 2008, 1427–9.
6. Gazarian M, Kelly M, McPhee JR, Graudins LV, Ward RL, Campbell TJ. Off-label use of medicines: Consensus recommendations for evaluating appropriateness. Med J Aust. 185, 2006, 544–8.
7. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 166, 2006, 1021–6.
8. Bavdekar SB, Gogtay NJ. Unlicensed and off-label drug use in children. J Postgrad Med. 51, 2005, 249–52.
9. Emmerich J, Dumarcet N, Lorence A. France's New Framework for Regulating Off-Label Drug Use. N Engl J Med. 367, 2012, 1279–81.
10. Field RI. The FDA's new guidance for off-label promotion is only a start. P T. 33, 2008, 220–49.
11. Fugh-Berman A, Melnick D. Off-label promotion, on-target sales. PLoS Med. 5, 2008, e210.
12. Tabarrok AT. Assessing the FDA via the anomaly of off-label drug prescribing. Indep Rev. 5, 2000, 25–53.
13. Maddin S. Off-label (unlabeled) Use of Drugs.; Skin Therapy Letter.1998 4:1–6. Available from: http://www.skintherapyletter.com/download/stl_4_1.pdf . Accessed on 16th Aug 2020.
14. GAO. US general accounting office report: off-label drugs: initial results of a national survey. GAO/PEMD 91-14; 1991.
15. Grisanti S, Ziemssen F. Bevacizumab: off-label use in ophthalmology. Indian J Ophthalmol. 55(6), 2007, 417-20.
16. Klein DB, Tabarrok A. Do off-label drug practices argue against FDA efficacy requirements. A critical analysis of physicians' argumentation for initial efficacy requirements? Am J Econ Sociol. 67, 2008, 743–75.
17. Boos J. Off label use - label off use? Ann Oncol. 14, 2003, 1–5.
18. Sirven JI. New uses for older drugs: The tales of aspirin, thalidomide, and gabapentin. Mayo Clin Proc. 85, 2010, 508–11.

19. Gupta SK, Nayak RP. Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities. J Pharmacol Pharmacother. 5(2), 2014, 88–92.
20. Dresser R, Frader J. Off-label prescribing: A call for heightened professional and government to versight. J Law Med Ethics. 37, 2009, 476–86.
21. Kesselheim AS, Mello MM, Studdert DM. Strategies and practices in off-label marketing of pharmaceuticals: A retrospective analysis of whistleblower complaints. PLoS Med. 8, 2011, e1000431.
22. Hill P. Off license and off label prescribing in children: Litigation fears for physicians. Arch Dis Child. 90(Suppl 1), 2005, i17–8.
23. Stanford Report Dec 2008. Available at- https://news.stanford.edu/news/2008/december3/med-offlabel-120308.html. Last accessed on- 6 Aug 2020.
24. Chen M, Doherty SD, Hsu S. Innovative uses of thalidomide. Dermatol Clin. 28(3), 2010 Jul, 577-86.

Source of Support: None declared.

Conflict of Interest: None declared.