REVIEW ARTICLE ISSN: 2349-2678

Contents lists available at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive

Index Copernicus Value 2017: 71.80

Volume 5 Issue 4; July-August; 2017; Page No.23-29

Off Label use of Medicines

Dr. Pravinkumar Ashok Wahane

Assistant Professor Dept. of Pharmacology

ABSTRACT

The term 'off label use' was first mentioned by Higgins et al. in 1988.[1] Off-label (unlabelled or unapproved) drug use (OLDU) refers to prescribing a registered medicine for a use that is not included or is disclaimed in the product information.[2] The term off-label drug use (OLDU) is used extensively in the medical literature, continuing medical education (CME) exercises and the media. It is a polarizing term because it can be associated with great benefit or harm to patients. [3] Examples include use of a drug for a different indication, patient age group, dose and route other than which is approved by regulatory authorities. Both prescription drugs and over the counter (OTC) drugs can be used in off label ways. An unlicensed or unregistered medicine is a medicine or dosage form of a medicine that has not been evaluated nor approved for a particular clinical condition by the regulatory authorities.

Keywords: off-label drug use, continuing medical education, Investigational New Drugs, expanded access programs

INTRODUCTION

Label is defined as the specific document which summarizes evidences concerning safety and effectiveness of product regarding specified clinical condition including dosing, duration of administration and drug interaction. It also gives information regarding the use of drugs in paediatric and geriatric population and specific warning or contraindication. In general 'label' is the result of negotiations between regulatory authorities and product manufacturers over a specific document.

The term 'off label use' was first mentioned by Higgins et al. in 1988.[1] Off-label (unlabelled or unapproved) drug use (OLDU) refers to prescribing a registered medicine for a use that is not included or is disclaimed in the product information.[2] The term off-label drug use (OLDU) is used extensively in the medical literature, continuing medical education (CME) exercises and the media. It is a polarizing term because it can be associated with great benefit or harm to patients. [3] Examples include use of a drug for a different indication, patient age group, dose and route other than which is approved by regulatory authorities. Both prescription drugs and over the counter (OTC) drugs can be used in off label ways. An unlicensed or unregistered medicine is a medicine or dosage form of a medicine that has not been evaluated nor approved for a particular clinical condition by the regulatory authorities.

In India the regulatory authority for new drug approval is Drug Controller General of India (DCGI). Use of a product that has neither been evaluated nor approved in India is not included in the jurisdiction of Drug Controller General of India (DCGI). Table 1 summarizes the definition list of various drug categories.[4]

Table No. 1:

Off-label use:	Practice of prescribing a drug outside the terms of its official labelling.
Unlicensed drugs:	Drugs that have not been subjected to the scrutiny provided by the licensing process.
Investigational Drugs:	Drugs that are being scientifically tested, but which are not yet been approved by the regulatory agencies.

**Corresponding author: Dr. Pravinkumar Ashok Wahane |*

Compassionate use:	Employment of a new unapproved agent through expanded access programs (EAPs) or single patient access, when no other treatments are available.

This review focuses on the use of off-label drugs in clinical practice and its pros and cons.

Drug Approval Process in India

In India, the process of approval of Investigational New Drugs (IND) of already existing drug for a new indication is governed by DCGI in accordance with the directions given by Drug and Cosmetic Act and Rules 1940 amendments 2013 chapter IV. Usual process of approval of Investigational New Drug (IND) involves sponsors/drug manufacturers submitting detailed information about trials of that drug done for specific indications in specific populations. The process can involve regulatory authorities submitting extensive databases of studies in animals, toxicological evaluations, and clinical trials to evaluate safety and effectiveness of that drug and determine whether the probability and magnitude of potential benefits are sufficient to justify a product's risks.[5] When DCGI approves a product, they approve a specific label for that product, too.

The approval process of a new drug involves clinical trial which costs time and money. In this context it is practically not possible to identify all potential uses of a particular product while it is under process of approval for an indication. This makes it impossible for a product getting approval for all indications, dosage forms, routes of administration and covering all age groups (such as children, pregnant and lactating mothers). This makes off label prescribing as an integral part of contemporary medicine. Many patients benefit when they receive drugs or devices under circumstances not specified on the label approved by the Regulatory Authorities. 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 and is more common for diseases which occur less frequently or affect special population where is difficult to conduct clinical trials. When scientific and medical evidence justify off-label uses, many physicians promote patients' interests by prescribing products off label. Off-label prescribing can be harmful to patients at times when it lacks a solid evidentiary basis.

Present Scenario

There are few studies available about the off label use of medicines in India. A 2006 nationwide study examining prescribing practices for 160 commonly prescribed drugs in USA by Radley et al found that 21% of overall medicines were prescribed off label. In certain subpopulations of patients, this rate was even higher - 83% for gabapentin.[3] It was observed that 73% of these medicines overall, were prescribed off-label with little or no scientific support. A study conducted by Shah et al found that 78.9% of children discharged from paediatric hospitals were taking at least 1 off-label medication.[6] In addition, in a paediatric emergency department, the rate of off label drug use was estimated to be 26.2%.[7] In an intensive care unit, Lat et al reported that 36.2% of medication orders were for an off-label use.[8] Off-label use of antidepressant, anticonvulsant, antipsychotic, antimicrobial and anticancer medications is high and is more prevalent with increasing patient age.[9] Off label prescription of anticancer drugs in European countries ranges from 9% to 46.2%.[10]

With regard to medical devices, the patterns of off-label use are quite variable, with a range from single digit to up to 80% of use, depending on the novelty and availability of the device in the market. Devices are often introduced for a single use, with other uses identified by health care providers once the product is widely available. Companies often then evaluate the unapproved uses for on-label indications.[10]

It has been estimated worldwide about 20% of the commonly prescribed medications are off-label, and the percentage increases in specific patient populations, such as children, pregnant women and cancer patients.[11] Table no. 2 & 3 describe the commonly prescribed off label medicines in adults and children's.

TABLE 2. Examples of Common Off-label Uses of Drugs in adults. [12]

Category and drug	**Off-label use(s)**
Psychiatry	
Fluoxetine	Diabetic neuropathy, borderline personality disorder, hot flashes, fibromyalgia, premature ejaculation [13]
Atypical antipsychotics (e.g., olanzapine, risperidone,)	Obsessive-compulsive disorder, anxiety, dementia, personality disorders, eating disorders, , posttraumatic stress disorder, substance abuse [14]
Citalopram	Alcoholism, fibromyalgia, obsessive-compulsive disorder, stuttering [8]
β Blockers	Performance anxiety, public speaking , social phobia,
Neurology	
Gabapentin	Neuropathic pain symptoms, restless leg syndrome , bipolar disorder, diabetes, fibromyalgia, headache, hot flashes, [13]
Atenolol, metoprolol, propranolol	Migraine prophylaxis [15]
Tricyclic antidepressants	Insomnia, Bulemia, neuropathic pain symptoms [8,13]
Donepezil	Frontotemporal dementia [16]
Lidocaine	Postherpetic neuralgia [13]
Paediatrics	
Morphine	Pain in children [6]
Atenolol	Hypertension in children [8]
Intranasal desmopressin	Nocturnal enuresis [17]
Amoxicillin (high dose)	Otitis media in children [8]
Sildenafil	Pulmonary hypertension in children [8]
Allergy	
Diphenhydramine	Chemotherapy-related emesis, insomnia.[8]
Cardiology	
Atorvastatin, simvastatin	Extended-interval dosing for hyperlipidemia.[8]
Aspirin	Antithrombotic in atrial fibrillation, Kawasaki disease. [8]
Indomethacin	Pharmacologic closure of patent ductus arteriosus. [18]
Dermatology	
Biologic agents (eg, etanercept, infliximab, intravenous immunoglobulin, rituximab.	Atopic dermatitis, pemphigoid, , pityriasis, alopecia areata, vasculitis, behçet disease, dermatomyositis, hidradenitis suppurati. [19]
Haematology/oncology	
Doxorubicin	Refractory multiple myeloma. [8]
Rituximab	Idiopathic thrombocytopenic purpura, Waldenström macroglobulinemia [8]
Alendronate	Hypercalcemia of malignancy. [8]
Dabigatran	Venous thromboembolism prophylaxis after orthopedic surgery [20]
Respiratory	
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Status asthmaticus [21]
Nephrology	
Erythropoietin	Anaemia of chronic disease [8]
Acetylcysteine	Prevention of contrast nephrotoxicity [8]
Albuterol	Hyperkalemia [22]

Obstetrics	
Magnesium sulfate	Premature labor [8]
Volatile anesthetics (eg, enflurane, isoflurane, halothane)	Intraoperative uterine contraction
Urology	
Sildenafil	Sexual dysfunction symptoms in women [20]
Anesthesiology	
Propofol,	Intracranial hypertension,
Meperidine	Postanesthetic shivering
Dexamethasone,	Postoperative nausea

Table 3: Examples of Off label use of Medicines in children.[23]

Reason for off-label use	
• **Indication**	Azithromycin used for anti-inflammatory effect in cystic fibrosis Quinolone antimicrobials used to treat bacterial gut infections or severe neonatal infections in the developing world
• **Dose**	Once daily dosing of gentamicin in children Use of adult formulations (e.g. tablets) in fractions (e.g. ¼ or 1/8th tablet) leading to dosing outside the approved paediatric dose in mg/kg
• **Age**	Valaciclovir used in children under 12 years Intravenous paracetamol use in neonates
• **Route**	Diazepam injection administered rectally for treatment of status epilepticus

Regulation of off label use

Off label use of a product is not illegal in most of the countries. Main concerns about such use of a drug is related to safety and efficacy of drug and ethical and moral responsibilities of the physician while providing quality care to patients. In USA, regulation of off label use is governed by USFDA.

In India, professional conduct of physicians is controlled by Professional Conduct, Etiquette and Ethics Regulation act 2002 of Indian Medical Council .[24] Accordingly physicians are required not to evade legal restrictions like the Drug and Cosmetic Act (Chapter 1.9) (applicable for both drugs and medical device). Doctors are also directed not to violate human rights (chapter 6.4). Contravention of the Drugs and Cosmetic Act (Chapter 7.8) for prescribing steroids and psychotropic drugs or violation of the Indian Council guidelines for research (Chapter 7.22) is considered misconduct and is punishable. Drugs and Cosmetic law in India and identical laws in other part of world are meant to control manufacturing and marketing of the conducts by a pharmaceutical company with regards to both drugs and medical device.[25]

Pros and cons of off label use of medicines

Arguments favouring off label use of medicines.

Key benefit of allowing manufacturer to distribute off-label drugs is that it allows more data to be readily available to physicians, enabling them to make better treatment decisions. It is extremely difficult for a physician to independently keep current by reading all of the medical journals and compendia available. This challenge creates a high risk that an important study which might significantly impact treatment practices might be missed. Relaxing restrictions on the distribution of off-label drugs enables clinicians practicing in some of the most challenging areas of medicine—oncology, psychiatry, and paediatrics to become more knowledgeable about treatment alternatives.[26] Timely dissemination of information through advertising or promotion plays a key role particularly in updating physician treatment decisions because this knowledge can be vital in keeping up with rapidly changing prescribing practices.[27] Allowing the distribution of off label drugs supports innovation in clinical practice, which is particularly important when approved treatments have failed in case of 'orphan diseases'.

Arguments against off label use of medicines

Most crucial point that goes against off label use of drugs is that permitting this activity could expose the practice of medicine to vulnerabilities that exist in the published literature [28] as peer review alone does not ensure that off-label information will be of a high quality. The risk involved in relying on such information includes:

- Pharmaceutical sponsors may solely publish positive trial results.
- Suppression of data on safety risks.
- Portrayal of misleading interpretation and results of studies with small sample size.
- Insufficient peer review.

Another point against off label drug use is insurance and reimbursement hurdles.[29] It may be difficult for physicians to sort out reimbursement for off-label drugs. Lastly, despite benefits of off-label drug use, patients may still have to pay high treatment costs for drugs and devices that physicians has been encouraged to use outside of labelling.[30]

Difference between off label and orphan drugs

Orphan drugs are medications that are developed and used for rare or orphan diseases. Due to drug's limited clinical use for an orphan indication, it has limited or no profit for the drug sponsor to seek regulatory approval for the limited (narrow) indication. Due to this, physicians are often forced to use medications in an off label manner to treat orphan diseases. Hence, sometimes orphan drugs can be considered as subtype of off label drugs. But after implementation of orphan drug act by USFDA which offers incentives to pharmaceutical manufacturers to develop new drugs in the form of tax benefits, exclusive marketing rights and reduced drug application fees has led to increased development of new, USFDA approved i.e. "On label" drugs for orphan disease.[28] Examples of off-label uses of medications for orphan disease include aspirin for Kawasaki disease and rituximab for Behcet's disease. [31]

Role of informed consent

US-FDA argues that, "Given the documented lack of scientific support, off-label drug use should be considered experimental or investigational; the use supports a theoretical assumption on the physician's part. If off-label use were classified as experimental, physicians would be required to obtain explicit consent from patients, most commonly in the form of written consent". [32] DCGI has not issued any guidelines regarding informed consent for off label use of drugs.

Two arguments that are often raised regarding informed consent of "off label use" are that disclosure may unduly frighten patients and the extensive burden placed on physicians to constantly review and communicate medication risk and benefit information and may divert attention away from other more important patient care issues.

From a physician's perspective, doctors are legally bound to inform patients of risks. The fact the there is a lack of research for off-label use should be considered a risk to the patient. Hence, physicians should follow legal standards that require them "to obtain informed consent from a person before performing a test or stating a treatment—particularly a treatment that involves some uncertainty". [33] It is important that patients be informed about the off-label use of a drug.

Ethical considerations

Off-label prescribing raises ethical issues. Appropriate off label prescribing depends whether the use is new or old, urgency of patient's situation and availability of alternative treatment approaches. Further, novel off label use of both newly approved and older products typically presents uncertainty about effectiveness. An example is thalidomide which is being used increasingly as an antitumor agent, originally developed as an agent to treat complications of leprosy developed in 1988.[34]

In addition, off label prescribing can have different objectives – they can be the only treatment option for seriously ill patients. So it can be said, off label prescribing can be ethically justified provided it has clear therapeutic goals, evidentiary basis and no safety and effectiveness concerns.[35]

Monitoring promotion of off label drug use

Self-regulatory initiatives may be taken by the pharmaceutical industry in the form of employment of compliance officers to focus on the transparency in clinical trials and improving disclosure to manage potential conflicts of interest in medical research. Such activities should be undertaken by the industry itself to curb inappropriate off label promotion.[36] Self-monitoring on part of the physicians may also needed for their prescribing practices in order to avoid inappropriate off label drug use by taking into consideration the clinical data available on drug, influence of promotional information from pharmaceutical companies, any reimbursement issues before deciding to prescribe a medication for off label use.[37]

Compulsory participation in continuing education should also be made as a condition for license renewal which will be an aid to limit off label promotion.[37, 38]

Medical journal editors have increased responsibility to carefully evaluate data and results of clinical trials involving off label use of product(s) to avoid poor quality of data from being published. These plays a key role for quality clinical data being made available to physicians influencing their prescribing practices.[39]

Conclusion

Because many problems, such as patient safety, reimbursement, legal risk, and the lack of regulation and information, are associated with off-label drug use, physicians should prescribe these drugs in accordance with existing national laws only when the potential toxic effects are outweighed by the potential benefit.

There is also a need for systematic identification of gaps in knowledge regarding off label use of medicines which in turn will lead to development of new knowledge influencing future treatment decisions. Finally, there is a need for policy reforms and enactment of new laws for better vigilance of drugs used off label. It provides a pathway to innovation in clinical practice but drug licencing is the gold standard.

References:

1. Higgins, LC. et al "Off-label Rx. Insurers starting to balk." Med World News, 1988; 22(26): 31-2.
2. Turner S. Unregistered and off-label drug use in paediatric inpatients. Aust J Hosp Pharm. 1999; 29: 265-268.
3. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006; 166(9): 1021-1026.
4. Rosa L, Pellegrino M, Michele A, Carla P, Alfredo T. Off-label use of anti-cancer drugs between clinical practice and research: the Italian experience. Eur J Clin Pharmacol. 2012; 68:505–512.
5. Kesselheim AS, Avorn J. Pharmaceutical Promotion to Physicians and First Amendment Rights. N Engl J Med. 2008; 358(16):1727–1732.
6. Shah SS, Hall M, Goodman DM, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med. 2007; 161(3):282-290.
7. Qureshi ZP, Liu Y, Sartor O, Chu YH, Bennett CL. Enforcement actions involving Medicaid fraud and abuse, 1996-2009. Arch Intern Med. 2011; 171(8):785-787.
8. Lat I, Micek S, Janzen J, Cohen H, Olsen K, Haas C. Off-label medication use in adult critical care patients. J Crit Care. 2011; 26(1):89-94.
9. Chen H, Reeves JH, Fincham JE, Kennedy WK, Dorfman JH, Martin BC. Off-label use of antidepressant, anticonvulsant, and antipsychotic medications among Georgia Medicaid enrolees in 2001. J Clin Psychiatry. 2006; 67(6):972-982.
10. Lerose R, Musto P, Aieta M, Papa M, Tartarone A. Off-label use of anti-cancer drugs between clinical practice and research: the Italian experience. Eur J Clin Pharmacol 2012; 68:505–512.
11. Nair MD. Off-label use of drugs: safety concerns. http:// www.pharmabiz.com/article /detnews.asp?articleid=24106& sectionid=46 (accessed on April 30, 2014.)
12. Christopher MW, Christopher MB, William LL. Ten Common Questions (and Their Answers) About Off-label Drug Use. Mayo Clin Proc. 2012; 87(10):982-990.
13. Dobecki DA, Schocket SM, Wallace MS. Update on pharmacotherapy guidelines for the treatment of neuropathic pain. Curr Pain Headache Rep. 2006; 10(3):185-190.
14. Liebowitz MR, Gorman JM, Fyer AJ, Klein DF. Social phobia: a review of a neglected anxiety disorder. Arch Gen Psychiatry. 1985; 42:729-736.
15. Lin H-W, Phan K, Lin S-J. Trends in off-label - blocker use: a secondary data analysis. Clin Ther. 2006; 28(10):1736-1746; discussion 1710-1731.
16. Kerchner GA, Tartaglia MC, Boxer A. Abhorring the vacuum: use of Alzheimer's disease medications in frontotemporal dementia. Expert Rev Neurother. 2011; 11(5):709-717.
17. Hoffmann F, Glaeske G, Steuber C. Did the removal of the indication of nocturnal enuresis for intranasal desmopressin change prescribing practice? Pharmacoepidemiol Drug Saf. 2011; 20(1):105-109.
18. Friedman WF, Hirschklau MJ, Printz MP, Pitlick PT, Kirkpatrick SE. Pharmacologic closure of patent ductus arteriosus in the premature infant. N Engl J Med. 1976; 295(10):526-529.
19. Kerns MJ, Graves JE, Smith DI, Heffernan MP. Off-label uses of biologic agents in dermatology: a 2006 update. Semin Cutan Med Surg. 2006; 25:226-240.
20. Feldhaus-Dahir M. Treatment options for female sexual arousal disorder: part II. Urol Nurs. 2010; 30(4):247-251.
21. Shankar V, Churchwell KB, Deshpande JK. Isoflurane therapy for severe refractory status asthmaticus in children. Intensive Care Med. 2006; 32(6):927-933.
22. Berthet S, Charpiat B, Mabrut JY. Erythromycin as a prokinetic agent: risk factors. J Visc Surg. 2010; 147(2):e13-e18.
23. Pandolfini C, Bonati M. A literature review on off-label drug use in children. Eur J Pediatr 2005; 164:552-8.
24. Code of Ethics Regulations, 2002, Medical Council of India, (Published in part III, Section 4 of the Gazette of India, dated 6th April 2002) 2002.Available online at

http://www.mciindia.org / know/rules/ethics.htm. Assessed on 20 December 2014.
25. Khamar B, Off label use of medicines: Medical research and medical practice. Ind J Opth 2007; 55(6): 411-412.
26. Koroneos G. In defense of peer review: Waxman opponents argue for distribution of off-label info. Pharmaceutical Executive, Direct Marketing Edition, December 5, 2007. Available at: http:// pharm exec. findpharma.com /pharmexec/News+Analysis/In-Defenseof-Peer-Review-Waxman-Opponent s-Arguef/ArticleStandard/Article/detail/ 477262 ?contextCategoryId=39871. Accessed on 16 December 2014.
27. Calfee JE. The role of marketing in pharmaceutical research anddevelopment. Pharmacoeconomics 2002; 20(3):77–85.
28. Psaty BM, Ray W. FDA guidance on off-label promotion and the state of the literature from sponsors. JAMA 2008; 299(16):1949–1951.
29. Lavine G. Orphan Drug Act passes quarter-century milestone in fight against rare diseases. Am J Health-Syst Pharm. 2008; 65(13):1205-1210.
30. O'Reilly J, Dalal A. Off label or out of bounds? Prescriber and marketer liability for unapproved uses of FDA-approved drugs. Ann Health Law 2003; 12(2):295–324.
31. Drug Facts and Comparisons 4.0. http://online.factsandcomparisons.com/ index.aspx. Accessed December 20 2014.
32. Mithani Z. Informed Consent for Off-Label Use of Prescription Medications. American Medical Association Journal of Ethics 2012; 14 (7): 576-581.
33. Wilkes M, Johns M. Informed consent and shared decision-making: a requirement to disclose to patients off-label prescriptions. PLoS Med. 2008; 5(11):e223.
34. Kumar S, Witzig TE, Rajkumar SV. Thalidomide as an anticancer agent. J Cell Mol Med 2002. 6(2): 160-74
35. Gazarian M, et al. Off-Label Use of Medicines: Consensus Recommendation for Evaluating Appropriateness. Medical Journal of Australia 2006; 185 (10):544–548.
36. Ventola CL. Off-Label Drug Information Regulation, Distribution, Evaluation, and Related Controversies FDA Policy. Pharmacy and Therapeutics Aug 2009; 34(8): 429-49.
37. Fugh-Berman A, Melnick D. Off-label promotion, on-target sales. PLoS Med 2008; 5(10):e210.
38. Hampton T. Experts weigh in on promotion, prescription of off-label drugs. JAMA 2007; 297(7):683–684.
39. Mello M, Studdert DM, Brennan TA. Shifting terrain in the regulation of off-label promotion of pharmaceuticals. N Engl J Med 2009; 360(15):1557–1566.