Second Edition

Manual of Prescription Writing *with* Case Scenarios

As per the latest CBME Guidelines | Competency Based Undergraduate Curriculum for the Indian Medical Graduate

Saroj Kothari
Ashok Kumar Jain

CBSPD *Dedicated to Education*
CBS Publishers & Distributors Pvt Ltd

Chapter

9

Off Label Prescribing

Background

Prescription of a licensed medicine for a use that is not approved by a regulatory agency and not included in the drug label or in the product information is off label prescribing. The practice is common and legal in many countries. The regulatory bodies do not have the legal authority to regulate the practice of the medicine, and the physician may prescribe a drug off label for standard care to the patients.

Off label prescribing includes the use of an approved drug for the following unlabeled conditions:

- *Indication*, e.g. anticancer drug mitomycin is indicated for the treatment of gastric and pancreatic carcinoma also used for the treatment of lung, bladder, breast, cervical, and other carcinomas not approved by the US FDA.
- *Age group:* Lack of paediatric indications on drug labels often lead to off label prescribing, hence many drugs indicated for adults are also prescribed off label in the paediatric population.
- *Dose strength:* When a drug is approved at a dose of 500 mg but prescriber advises other than approved dose.
- *Route of administration*, e.g. drugs approved by IV route and given by intrathecal route e.g. pentazocine, gentamicin.
- *Dosage form:* When a medication is approved as a tablet or capsule and is used topically or when tablets are given as suspension to children.

Medicine Areas with Frequency of Off Label Prescribing

Due to the fact that certain populations like the elderly, children and pregnant women and certain health conditions like mental health disorders, malignancy and patients in intensive care units are not always included in clinical trials, off label prescribing is frequently seen based on the latest evidence. Furthermore in mental disorders in addition, the similarity of symptoms between disease states also contributes to off label prescribing.

Pros and Cons of Off Label Prescribing

Physicians practice medicine based on their professional judgment keeping in mind both the safety and efficacy of the medication not limited to official, approved

indications. Many new therapies and evidence have emerged out of off label prescribing, however, for pharmaceutical companies to get approval for new uses of old drugs by clinical testing is time-consuming and costly. Some such off label uses are scientifically valid giving treatment benefits to patients. Paclitaxel initially approved for treating ovarian cancer, was found to be effective for treating breast cancer when used off label. After the publication of reports showing its effectiveness in breast cancer, it was later approved by regulatory bodies. Gabapentin an antiepileptic drug is used for bipolar disorder, fibromyalgia, headache, hot flashes, and restless leg syndrome as off label.

On the other hand, inappropriate use of off label drugs is a cause of concern when it is used without risk-benefit analysis. The safety with off label use has attracted much attention when caused serious adverse effects. For example "Fen-phen" an unapproved combination of fenfluramine and phentermine used for weight loss resulted in heart valve disease.

Though off label drug use is very common throughout the world, most often this is done without adequate scientific data. To date, there is no uniform regulatory framework available to help clinicians to assess the appropriateness of off label prescribing.

Proposed Points of Consideration for Appropriateness of Off Label Prescribing

Off label prescribing is not considered legal in India even when it does not violate ethical guidelines or other safety regulations. There is a need of universal guidelines to maximize the benefits and to minimize the harm from off label prescribing. We propose the following points:

- Make certain that it would better serve the patient's needs than a licensed alternative.
- Take patient's or their representative's consent for their treatment being done by the unlicensed drug. Explain the reasons why medicines are not licensed for their proposed use and make him/her understand this newer implication.
- Check clinical suitability and cost effectiveness of off label use of the drug. The decision must not be based on potentially biased information or commercial gain.
- Collect sufficient evidence to demonstrate the medication's safety and efficacy for that particular patient.
- Document the clinical management plan clearly in terms of which drug is chosen and the reason for choosing it, continuous monitoring of the treatment and progress of the treatment in detail.

Circumstances Motivating Off Label Prescribing

Physicians prescribe drugs off label for a variety of situations all aiming at better patient care:

1. Nonavailability of a suitable licensed medicine that will treat the patient's disease. For example, metformin in polycystic ovarian syndrome a hormonal disorder common in women of reproductive age.
2. In children when licensed medicine fails to treat a condition or symptom but a medicine licensed for the same condition or symptom in adults found effective.
3. The dosage specified for a licensed medicine when not found to correct the disease.

Table 9.1: Examples of some off label uses

Drug	*On label*	*Off label*
Propranolol	Hypertension, thyrotoxicosis	Anxiety
Amitriptyline	Depression	Neuropathic pain, prophylaxis migraine
Prazocin	Hypertension	Nightmares
Gabapentin	Epilepsy	Hot flushes, restless leg syndrome
Metformin	Diabetes mellitus	PCOD
Divalproex	Antiepileptic	SSRI-induced headache
Escitalopram	Depression	Bipolar disorder
Bupropion	Depression	Bipolar disorder
Sertalazine	Depression	Bipolar disorder
Venlafaxine	Depression	Bipolar disorder
Duloxetine	Depression	Anxiety
Trazodone	Depression	Sleep disturbances

4. The patient asks for a formulation of a drug that is not specified in an applicable license.
5. Due to a temporary shortage in supply of a suitable licensed medicine, other suitable approved drug which is not indicated for this condition is used to treat the patient.
6. The prescribing forms part of a properly approved research project.
7. In case of emergency when there is an urgent need for a new drug or indication, and there is a report of nonefficacy of labeled drug in certain demographics.
8. In cases when label drug is costly for the patient and physician prescribes another drug which is cost effective though not having a label for that particular use. For example, bevacizumab a low-priced drug approved for the treatment of metastatic colorectal cancer is used off label for age-related macular degeneration in place of approved drug ranibizumab which is very costly.

When Off Label use is Illegal or Problematic?

1. Violation of ethical guidelines or other safety regulations.
2. Nonavailability of adequate data regarding drug safety and effectiveness for the off label use.
3. Physician promoting off label uses through mass media such as the television and internet.
4. Drug's manufacturer promoting a drug for an indication which has not received marketing authorization from the government agency, even if significant scientific evidence exists for that unapproved indication.

Bibliography

1. Ackermann E, Litt J and Morgan M. Prescribing Drugs of Dependence in General Practice, Part C1: Opioids (2017).
2. Aronson JK, Henderson G, Webb DJ and Rawlins MD. A Prescription for Better Prescribing (2006).
3. Bennet PN, Brown MJ, Sharma P. Clinical Pharmacology, 11th edn, 2012, Charchill Livingstone, Edinburg.
4. Buxton ILO. Principles of prescription order writing and patient compliance. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th edn, 2011, McGraw-Hill, New York.
5. Cash JC and Glass CA (Eds.). Family Practice Guidelines, 2017, Springer Publishing Company.
6. De Vries TPG, Henning RH, Hogerzeil HV, Fresle DA, Policy M, and World Health Organization. (1994). Guide to Good Prescribing: a practical manual (No. WHO/DAP/94.11).
7. Guidelines of Programmatic Management of Drug Resistant Tuberculosis In India 2019 by Revised National Tuberculosis Control Programme, Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare, Nirman Bhawan, New Delhi.
8. Hitchings A, Lonsdale D, Burrage D and Baker E. The top 100 drugs: Clinical Pharmacology and Practical Prescribing (2018). Elsevier Health Sciences.
9. Hogerzeil HV (editor), et al. Teacher's Guide To Good Prescribing (No. WHO/EDM/PAR/2001.2).
10. International Ethical Guidelines For Health Related Research Involving Humans by CIOMS in collaboration with WHO 2016.
11. Jameson LJ, Fauci A, Kasper D, Hauser S, Longo D & Loscalzo J. Harrison's Principles of Internal Medicine, 20 th edn, 2018 (Vol.1 & Vol.2), McGraw-Hill Education.
12. Katzung BG, Masteres SB, Trevor AJ (Eds): Basic and Clinical Pharmacology, 14th edn, 2018, New Delhi, McGraw-Hill, Education (India).
13. Kennan K, Mathiharan K (editors). A Textbook of Medical Jurisprudence and Toxicology, 25th edn, 2016 Lexis Nexis, Reed Elsevier, Gurgaon, Haryana, India.
14. National Formulary of India (NFI 2016). Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare, Directorate General of Health Services, New Delhi, 2015.
15. National List of Essential Medicines (NLEM 2015) Govt of India, Ministry of Health and Family Welfare, Directorate General of Health Services, New Delhi, 2015.
16. Papadakis MA, McPhee SJ and Rabow MW. Current Medical Diagnosis and Treatment, 2020, Lange McGraw-Hill, New York.
17. Proposed guidelines for prescription writing and handling for drugs having misuse or abuse potential, proposed by FDA, Goa at the stakeholders meeting held on 23rd September, 2009.
18. Rang HP, Ritter JM, Flower RJ, Handerson G. Rang and Dale's Pharmacology, 8th edn, 2020, Elsevier, Churchill Livingstone Edinburgh.

19. Teichman PG and Caffee AE. Prescription writing to maximize patient safety. Family Practice Management, vol 9 no. (7), 2002.
20. VenkateshS, Chauhan LS, Gadpayle AK, Jain TS, Ghafur A and Wattal C. National treatment guidelines for antimicrobial use in infectious diseases. India: National Centre for Disease Control, MOHFW, Government of India, (2011). 1–64.
21. WHO. How to Investigate Drug Use in Health Facilities: Selected Drug Use Indicators: EDM Research Series No. 007. 1993. [Last accessed on 2015 May 05]. Available from: http://www.apps.who.int/medicinedocs/en/d/Js2289e/
22. Woodfield G, Phillips BL, Taylor V, Hawkins A and Stanton A. Essential Practical Prescribing. (2016). John Wiley & Sons.