

Off-label Medicine Use in India: Need for linking Research with Policy and Practice

Running Title: Off-label Medicine Use in India

Dr. Kanchan Mukherjee,
Professor and Chairperson
Centre for Health Policy, Planning and Management,
TISS, Mumbai.
Email: kanch@tiss.edu

Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration.[1] Drug manufacturers are not legally permitted to encourage the use of regulated drugs for any indications that have not been formally approved by the country's government even if another country's drug agency has approved that indication. However, healthcare providers are not required to limit prescriptions or recommendations to the indications approved by their country's drug regulatory agency. Prescribing a drug for a condition or use that has not been formally approved by the country's drug regulatory agency is called off-label use. Both prescription drugs and over-the-counter drugs (OTCs) can be used in off-label ways and can contribute to polypharmacy.

Off-label use of medicines is relatively common in medical practice, even if it's often not supported by strong scientific evidence. The approval process for a new drug includes a clinical trial, which costs time and money. It is practically impossible to identify all potential uses of a product

while it is under process of approval initially. This makes it impossible for a product getting approved for all indications, dosage forms, routes of administration, and covering all age groups or specific groups (such as children, pregnant women and lactating mothers). This makes the practice of off-label use common all over the world. Its usage can be as high as 90% in the pediatric population or 40% in adults.[2] Often, when the best available therapeutic option fails, patients demand new approach or new treatment which ultimately leads to off-label uses.[3]

Some key concerns regarding off-label use of medicines include scientific evidence to support its use, benefit-harm ratio and coverage by health insurance.

In India, off label use of drug is very common. Review of studies in India show off-label prescription in the areas of neonatal care, pediatric age group, peri-operative indications and cancer.[4-9] Off-label medicine use in India is high among the pediatric and neonatal age groups in the form of altered dosage, different indications

and different route of administration. Common clinical conditions for off-label use of medicines in India include respiratory diseases and anti-infective's. The key agencies and acts related to regulation of medicines in India include the Drug Controller General of India (DCGI), Drugs and Magic Remedies (Objectionable advertisement) Act (1954) and the Central Drug Standard Control Organization (CDSCO) which prepares the National Formulary of India (NFI). The DCGI is the regulatory authority for granting approval for new medicines but, unfortunately, there are no clear-cut guidelines on the off-label use of new medicines. Indian law does not currently allow medicines to be prescribed for indications for which they have not been approved. Off-label marketing by pharmaceutical companies are regarded as a violation of law in India, and it is an offense under the Drugs and Magic remedies (objectionable advertisements) act, 1954.

However, neither the DCGI nor the CDSCO regulate the practice of medicine. The practice of medicine is regulated by the Professional conduct, etiquette and ethics regulations (2002) of the Indian Medical Council. This regulation states that, "Physicians should try continuously to improve medical knowledge and skills and should make available to their patients and colleagues the benefits of their professional attainments." Therefore, doctors are expected not to avoid legal restrictions but also try to do the best for their patients based on their experience. It is this ethical and moral obligation that opens up a window of opportunity for use of off-label medicines by a physician.

The issue of off-label use gained a lot of media attention in India in 2003 when it was found that letrozole, an anti-breast cancer drug was being promoted for infertility.

Subsequently, the DCGI authorized a probe into media reports that few pharmaceutical companies had endorsed letrozole for treating infertility in women, without the valid regulatory permission.[10] Following this controversy, the DCGI asked the Indian Medical Association (IMA) to prepare a report about the various attributes related to off-label use of medicines. The IMA submitted their report recommending that doctors in India should be allowed to prescribe off-label indications if there is scientific evidence and medical basis for the same. Despite the IMA's positive opinion about off-label prescribing, currently there is no rule regarding off-label prescription in India.[11]

While off-label use may be associated with a greater number of side effects, the benefits may outweigh the risks. Again, off-label practices based solely on intuition are unlikely to be effective as against off-label use supported by clinical evidence. Therefore, audits of off-label practices should include these metrics in the overall assessment of the utility of such practices. Off-label use of medicines has several advantages in cancer treatment, and therefore, the government in close association with the DCGI should look at ways and means to streamline the practice. Such measure would enlarge the armamentarium for the treatment of cancer. Although some off-label therapies can be beneficial and even lifesaving for some patients, in many cases, off-label use can be problematic, especially if there is inadequate data regarding drug safety and effectiveness for the off-label use. Ideally, the use of drugs in clinical practice should be based on rational scientific theory, expert medical opinion and well-controlled clinical trials (i.e., evidence-based) rather than the package insert.

Research initiatives are very limited and should be developed with the involvement of all key stake holders. There are many potential area of research in use of off-label medicines in India. These include evidence-based approach to improve rationality of pharmacotherapy (especially pediatrics and cancer treatment), developing dosage guidelines, pharmacovigilance for causality assessment of adverse events and risk benefit assessment and a potential role of Health Technology Assessment (HTA) for studying cost-effectiveness.

Off-label medicines regulation in India remains a grey area and the legal implications are unclear. The good reprint practices guidance of the Food and Drug Administration (FDA) in the USA can be a starting point and provides guidance on the dissemination of medical journal articles about off-label uses. Manufacturers should not be protected from state persecution when their promotional activities are fraudulent. Hence, off label prescription laws in India should focus not only on the health care provider but also the manufacturers promoting off label use without scientific evidence. In individual clinical practice, physicians can use the deprescribing process and algorithm used to address polypharmacy [12] to identify inappropriate or unnecessary medications and discontinue them. Off label use of medicine is an issue which invites research and intervention at both the micro and macro levels of the health system. To ensure healthy outcomes, the decision on off-label use of medicine requires a fine interplay between clinical autonomy, ethics and evidence based treatment guidelines and policies.

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