Off-label use of medicines: Medical research and medical practice

Off-label (unlabelled or unapproved) use of an approved product refers to the use of an approved product in a scenario that is not included or is disclaimed in the product information. Examples include use for a different indication, in a different patient age range-group, different dose or different route of administration to that which is approved by regulatory authorities. In India the regulatory authority for new drugs approval is the Drug Controller General of India. This has to be differentiated from use of a product that has neither been evaluated nor approved in India.

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 (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.[1] 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.[2] The off-label use is more common for diseases which occur less frequently or affect special patient populations where it is difficult to conduct clinical trials. This is true more often for our specialty of Ophthalmology. Widespread use of lignocaine 2% or 4% as a topical anesthetic agent is a classical example. Other well-known examples include peri-operative use of antibiotic eye drops, fortified antibiotic drops in the management of a hypopyon corneal ulcer, intravitreal antibiotics for endophthalmitis, subconjunctival injections of antibiotics for treatment of corneal ulcers or following surgery to prevent infection, use of steroids as a subconjunctival, peribulbar or intravitreal injection (such as dexamethasone, betamethasone, triamcinolone, methylprednisolone), mitomycin-c and 5-fluorouracil in management of glaucoma, retrobulbar injection of alcohol for painful blind eye. All the examples mentioned above and many more are described in standard textbooks following widespread publications in peer-reviewed journals.

The process of off-label use starts once the product is marketed. A large number of scientists and clinicians get access to the information and the product following its approval for the first indication. They start exploring the use of a new product to meet the requirement of the patients they manage or need to manage. This needs ingenuity, creativity and courage to do it for the first time. All such efforts are neither successful nor without safety concerns. The process may start as an anecdotal case report, a case series, a retrospective analysis or a controlled clinical trial. Use of bevacizumab for a variety of retinal diseases is one such example in recent times.[3]

Off-label use of a product by a medical professional is not illegal in any part of the world but it raises issues about its safety and efficacy. It also raises concern about ethical and moral responsibilities while providing quality care to our patients. In India, our professional conduct is controlled by Professional Conduct, Etiquette and Ethics Regulations, 2002 of the Indian Medical Council.[4] Accordingly, we are required not to evade legal restrictions like the Drugs and Cosmetics Act (Chapter 1. 9). We are also required not to violate human rights (Chapter 6. 4). Contravention of the Drugs and Cosmetics Act (Chapter 7. 8) for prescribing steroids and psychotropic drugs or violation of the Indian Council of Medical Research (ICMR) guidelines for research (Chapter 7. 22) is considered misconduct and is punishable. Drugs and cosmetics law of India and identical laws worldwide meant to control manufacturing and marketing of the products by a pharmaceutical company. Prescription by medical professionals are not covered barring a few exceptions like prescription of steroids, psychotropic and narcotic drugs.

The main concern against the off-label use is lack of adequate data in relation to the safety and efficacy of a product. The presence of high-quality evidence about safety and efficacy meets this requirement. It generally originates from controlled clinical trials with well-defined objectives, methods, including sample size. One of the best examples is the diabetic retinopathy study sponsored by the National Eye Institute to evaluate use of photocoagulation.[5,6] Once such evidence is generated it becomes the standard of care. The Indian Medical Council[4] requires that we follow this in our practice— "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"(Chapter 1. 2).

This leads to drawing a line between research and therapy and identifying the appropriate method for using it in our clinical practice and research. When a product is used in the treatment of a patient, it is a therapy and when it is used to conduct a clinical trial, it is research. However, anecdotal case reports find a place in almost all peer-reviewed journals.[7] It is necessary to follow ethical guidelines while conducting clinical trials.[8] This has to be in the form of approval from the institutional ethics committee and written informed consent from participating subjects.

The responsibility arising out of off-label use rests with users (medical professionals) and the manufacturer cannot be held responsible from liability arising out of it. The author is aware of an epidemic of endophthalmitis due to contaminated Ringer's lactate solution wherein manufacturers were not held responsible for poor quality (non-sterile) product since it was not the indication for which it was made and marketed.

Given the risk of the liability for using a product for an unapproved purpose, we should do so only when we are convinced that the unapproved status of the use is outweighed by the potential benefit to the patient. Often this is obvious, for example as in endophthalmitis.

In India, devices are not controlled by the Drugs and Cosmetics Act and the question of off-label use does not arise. A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopedic pins and other orthopedic accessories.[8]

In conclusion we must use a drug for an indication for which there is a high level of evidence for its safety and efficacy irrespective of its label claim. We may use it off-label when benefits outweigh risk in a given circumstance. Off-label use is also worthwhile in pursuing clinical research for advancing patient care.

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Achievements

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