Review Article

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Regulating off-label drug use in India: The arena for concern

Abstract

Off-label use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence. Off-label use of medicine not only involves physicians and pharmaceutical companies, but regulatory agencies and patients as well. Therapeutic options might get restricted without off-label prescribing in some patient population. Off-label uses can be useful to patients with an orphan disease where sometimes it can be the only available treatment. Permitting the promotion of drugs for off-label uses may be appropriate in instances in which a drug can improve the quality (e.g., same or better outcomes at lower cost). Although many controversies exist, experts generally agree that further efforts are needed to increase access to suitable off-label drugs for patients with rare and other diseases. However, they also concur that potential inappropriate promotion, as well as possibly dangerous prescribing practices for these drugs, should be prevented. Proponents argue that the key benefit of allowing manufacturers to distribute off-label information is that it allows more data to be readily available to physicians, enabling them to make better treatment decisions.

Key words: Off-label use, pharmaceutical companies, physicians, regulating agencies

INTRODUCTION

Off-label drug use refers to the use of drugs outside the conditions of the product license in terms of dose, patient age, route of administration, indications and contra-indications.[1] Off-label use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence.[2] Off-label use of medicine not only involves physicians and pharmaceutical companies, but regulatory agencies and patients as well.[3] Off-label use is subject to the contradictory expectations of various stakeholders, including health care payers, the pharmaceutical industry, physicians, and consumers.

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Off-label uses have not been subject to the testing and review that is a precondition for marketing approval. The scientific review of the evidence of effectiveness and safety that regulators weigh prior to approval for a labeled indication protects the patient. With off-label use, this protection often does not exist.[4] Several controversies and debates exist regarding the off-label use of drugs as this involves the use of drugs beyond their conventional indications and dosage.

Marketing authorization for drugs is granted on the basis of their safety for specific indications as ensured by a positive benefit-risk ratio in clinical studies.[2] It is practically impossible to identify all potential uses of the 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.[5] 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.[6]

In a review by Bavdekar and Gogtay across Germany, United kingdom, Ireland, Germany, Israel, Australia and some of the European countries, the off-label use of drug varied from 10.8 to 66.0%, the magnitude of such use varied amongst others, according to the level of health care available, subspecialty concerned and certain patient characteristics.[7] The prevalence of off-label and unlicensed drug use is higher in neonates and infants and in premature and low birth-weight babies.[7] The off-label use of drugs in oncology has been estimated to reach 50%, or even more. In pediatrics, the off-label issue is particularly widespread, all the more in pediatric oncology.[8]

Nevertheless, some licensed medicines may be prescribed for indications outside their marketing authorization in order to treat health problems for which there are currently no other approved medications – for instance, in the case of rare diseases or specific subgroups of patients.[2] The spectrum of off-label use includes guideline-recommended practice (aspirin in diabetes for prophylaxis against cardiovascular disease), last-resort therapy (Tacrolimus Prograf for autoimmune diseases, in addition to transplantation), and first-line therapy (gabapentin neurontin for painful diabetic neuropathy, in addition to its use in herpes zoster).[9]

Off-label prescription of a drug is generally legal, but 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.[4] Off-label uses have not been formally evaluated, and evidence provided for one clinical situation may not apply to others. As an area of controversy, off-label use is subject to the contradictory expectations of various stakeholders, including health care payers, the pharmaceutical industry, physicians, and consumers.[9]

Physicians' freedom to prescribe drugs off-label carries important advantages. It permits innovation in clinical practice, particularly when approved treatments have failed. It offers patients and physicians earlier access to potentially valuable medications and allows physicians to adopt new practices based on emerging evidence. And, it can provide the only available treatment option for the so-called "orphan" conditions in which no proven drug is effective.[5] Some off-label prescribing should be permitted to allow physicians to take good care of patients and offer them some therapeutic options, but such prescriptions must remain the exception to the rule and should be scrutinized and controlled by regulatory agencies using well-defined frameworks.[2]

RISKS AND BENEFITS FOR PATIENTS

The purpose of off-label use is to benefit an individual patient. It is important to note that the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use.[10] 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 for which, there is no relief from the standard drugs which are primarily indicated for its management. In oncology, pediatrics, geriatrics, obstetrics, and other practice areas, patient care may be difficult without some amount of off-label prescribing.[11-13] When scientific and medical evidence justify off-label uses, physicians help the patients by prescribing products off-label.

Therapeutic options might get restricted without off-label prescribing in some patient population.[4,14] Off-label uses can be useful to patients with an orphan disease where sometimes it can be the only available treatment.[9] Off-label use is sometimes unavoidable; three-quarters of marketed prescription drugs have no labeling indications for children, a population only recently included in clinical trials.[15] Off-label prescribing is also common in psychiatry.[6] Cancer patients have benefited significantly from this process and the overall cure rate of more than 70% in paediatric malignancies would not have been achieved without the use of the off-label use of cytostatic drugs which were developed and provided by the pharmaceutical industry.[16]

The off-label drug use also carries some risks for the patients in case inappropriately utilized. 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.[14-16] Off-label use of drugs has been associated with serious adverse effects. The appetite suppressant pondimin (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.[17,18] In children, off-label use of drugs is associated with an increased number and severity of adverse effects.[5]

Prescribing medicines "off-label" is clearly widespread in pediatrics, not illegal, and in some cases represents best practice. However, it does bypass the safeguards of the drug regulatory process and places a greater onus of responsibility on the individual prescriber to assess the benefits and risks of such use for an individual patient. While this may be acceptable as an exception, it is clearly unacceptable when

it becomes the norm.[19] The main advantage does not deny children the potential to benefit from new medicines. Such use may be clinically appropriate (e.g., exceptional use in an appropriately informed patient with serious disease, when there are no alternatives, and potential benefits outweigh potential risks).[5] However, it may also be associated with a number of potential risks, some of which appear to be less well-recognized or appreciated by health professionals and parents/carers.[20]

Particular risk-benefit ratios presented by the unproven therapies must be carefully considered and disclosed, and standard of care practices should be reviewed. When use of the drug is truly investigational, drug use should be performed in conjunction with a well-designed clinical trial whenever possible. This is especially true when the physician proposes to treat a group of patients rather than a single individual.[10]

ROLE OF REGULATING AGENCIES

Although physicians are free to prescribe off-label, the federal regulatory system imposes constraints that affect off-label use. A major challenge for regulatory agencies is balancing the need for rapid access to drugs for new indications against the limited information on their benefit – risk ratio for those uses.[21] Several approaches to regulating off-label prescribing have been proposed.[22]

Off-label use is not uniformly regulated across the globe. It could be as liberal as in Japan where a new drug application permits the approval of off-label usages without even some preliminary clinical evidence of their effectiveness.[23] In some countries, such as France, drug agencies that regulate marketing prohibit dissemination of information on off-label use. The European medicines agency is more receptive to the off-label practice by proactively supporting clinical trials of off-patent drugs for off-label indications, especially in children. For example, they promote specific clinical trials which fall within the priority list that is prepared from a public health perspective for studies into off-patent pediatric drugs.[24] These studies would be funded by the European Union through the framework programme for health-research community program and although not obligatory, are likely to contribute to the development of pediatric use marketing authorization.[25,26] Moreover, the European Society of Medical Oncology has suggested a search for new regulatory mechanisms that could permit the extension of drug labels beyond the initiative of the manufacturers.[27] The Food and Drug Administration (FDA) also encourages studies in the pediatric population, providing the sponsor with an additional 6 months of marketing exclusivity.[28] This incentive has led to enhanced understanding of the pharmacology of drugs in children.

In India, the drug controller general of India (DCGI) is the regulatory authority for granting approval for new drugs but, unfortunately, there are no clear-cut guideline on the off-label use of drugs.[2] Indian law does not currently allow drugs to be prescribed for indications for which they have not been approved. Amendments to the Indian medical council act 2 years ago made off-label prescribing illegal.[29] Off-label marketing by pharmaceutical companies are regarded as a violation of law in India, and it is an offence under the drug and magic remedies (objectionable advertisements) act, 1954.[30,31]

Despite the IMA's positive opinion about off-label prescribing, any rule about the off-label prescribing is yet to come in India. Many are of the opinion that authorizing off-label prescribing will set a bad example because of ignorance of patients and domination of pharmaceutical companies on prescribing patterns in India.[3] In a policy statement submitted to the health ministry, the association said doctors in India should be allowed to prescribe drugs for unapproved indications when there is scientific evidence and medical opinion to justify such "off-label" treatment.

DISCUSSION

The use of a drug for a specific indication in a particular patient is generally based on the existing scientific evidence in the literature and the usual informed-consent conversations include informing the patients about the anticipated risks, benefits, and alternatives. If the off-label use is based on sound medical evidence, no additional informed-consent beyond that routinely used in therapeutic decision-making is needed. However, if the off-label use is experimental, then the patient (or parent) should be informed of its experimental status.[10]

While findings from many research studies and clinical trials support the rationale for off-label uses for drugs, a recent analysis of reports from 2001 National disease and therapeutic index (which tracks the epidemiological trends and treatment patterns among private practice physicians in the united states) found that 73% of the off-label use lacked evidence of clinical efficacy and only 27% were supported by the strong clinical evidence.[6] The greatest evidence for disparity was found between supported and unsupported off-label uses was found between prescriptions for psychiatric uses (4% strong support vs. 96% limited or no support) and allergies (11% strong support vs. 89% limited or no support).

Although many controversies exist, experts generally agree that further efforts are needed to increase access to suitable off-label drugs for patients with rare and other diseases. However, they also concur that potential inappropriate promotion, as well as possibly dangerous prescribing practices for these drugs, should be prevented.[15] Proponents argue that the key benefit of allowing manufacturers to distribute off-label information is that it allows more data to be readily available to physicians, enabling them to make better treatment decisions.[32,33]

There are two completely divergent views regarding the dissemination of off-label information by manufacturers: The belief that it provides transparency regarding treatment choices versus the opinion that it presents a significant risk to public health and well-being.[32] Various groups have assembled both in support of and against the new reprint policy.[21] Pharmaceutical companies and patient advocacy groups have expressed support, whereas consumer organizations and health insurers have voiced objections.[21]

If employed judiciously, the benefits of off-labeled use far outweigh the risks. Therefore, it calls for legislations to streamline this practice. Instead of totally banning promotion of drugs for off-label indications, the law should take a middle path and try to regulate it. While the DCGI does not regulate the practice of medicine, and thus cannot regulate off-label prescription of drugs by physicians, it can surely regulate the promotion of off-label use by pharmaceutical companies.[30]

Even the most reasonable guidance on promotion of off-label drug use should not protect the manufacturers from state persecution when their promotional activities are fraudulent. Such a legal backing would ensure that legislations made in public interests are not misused by groups with vested interest. Finally, the system could be further streamlined by directing the insurance companies to cover off-label uses as long as they are supported by sound scientific evidence. Identifying drugs compendia as shown by Centers for Medicare and Medicaid Services would encourage rational prescribing. Agencies like Indian Council for Medical Research has to take a lead in this direction.[30]

The good reprint practices guidance of FDA could be a good starting point. It imposes significant constraints on the dissemination of medical journal articles about off-label uses, but does not oppose it if done within the boundaries of the guidance. Fraudulent practices by the industry may still threaten this liberal stance, as in the case of Pfizer in 2009. The company was brought to book with a stringent penalty of $2.3 billion, the largest health care fraud settlement in the history of US Department of Justice.[34] Even the most reasonable guidance on promotion of off-label should not protect the manufacturers from state persecution when their promotional activities are fraudulent. Such a legal backing would ensure that legislations made in public interests are not misused by groups with vested interest.

The situation in the developing countries needs to be studied, as, barring a few, all the studies on this issue have been carried out in European countries, United States and Australia. This noteworthy absence of studies from developing countries could be indicative of lack of awareness or interest amongst health care professionals. Either way, this is a worrisome phenomenon. If doctors in the developing world are not aware of or are not sensitive to the issue of unlicensed and off-label drug use in children, they are likely to prescribe these drugs even when a proven, safe and effective option is available, thereby exposing children in these countries to unproven therapies.[7]

CONCLUSION

States and other jurisdictions have a duty to protect the health of the public. Allowing off-label promotion of drugs for untested, unproven benefits maximizes industry profits at the expense of public health. A risk – benefit ratio cannot be assessed without knowing whether benefits exist.[4] Where no benefits exist, no risk is acceptable. Off-label use of drugs has several advantages, and therefore, the government in close association with the DCGI should look at ways and means to streamline the practice.

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