Off-label use of medicine: Perspective of physicians, patients, pharmaceutical companies and regulatory authorities

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ABSTRACT

Off-label prescribing of medicines is prevalent worldwide because it gives freedom to physicians to apply new therapeutic options based on the latest evidence. Although physicians may lawfully prescribe approved drugs for any use consistent with available scientific data and proper medical practice, but unfortunately, usually this is done without adequate scientific data. Often, when the best available therapeutic option fails, patients demand new approach or new treatment which ultimately leads to off-label uses. Major concerns about efficacy and safety have been raised by inappropriate use of off-label drugs because it leads to drug being used without risk-benefit analysis by the regulatory agency. Although the regulatory approval process requires ample proof of efficacy and safety for granting approval for specific indications of prescription drugs but unfortunately, more clarity is required about regulations governing off-label use of medicine. Above all because of the financial aspects involved it is highly impractical to expect that pharmaceutical companies will restrict or stop off-label promotion. Off-label use might be compared to double-edged sword which might be very useful for some patients while it can also expose them to unrestricted experimentation, unknown health risks, or ineffective medicine. Hence, there is an urgent need for guidance to encourage proper off-label use of medicine by the distribution of scientifically valid and authentic information from the pharmaceutical companies. In fact, few countries such as the USA and France have taken an initiative and have come up with the regulations about off-label use of medicine.

Key words: Clinical trial, key opinion leaders, off-label use, orphan disease, risk-benefit analysis, regulatory approval

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INTRODUCTION

"Labeled" uses of a prescription drug are approved by regulatory bodies after confirming its efficacy and safety based on its preclinical and clinical data, but medicines are prescribed off-label without undergoing the rigorous regulatory approval process mandatory for getting marketing approval.[1] Prescribing drugs off-label is extremely common worldwide, but unfortunately usually this is done without adequate

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scientific data.[2,3] It has been reported that only about 30% of off-label prescribing was supported by adequate scientific data.[4] In addition, major concerns about safety have been raised by inappropriate use of off-label drugs because it might lead to drugs being used without risk-benefit analysis by the regulatory agency.[3]

Off-label use of medicine not only involves physicians and pharmaceutical companies, but regulatory agencies and patients as well. Let's try to analyze the need for off-label prescribing and find out the pros and cons of it from the perspective of physicians, patients, pharmaceutical companies, and regulatory authorities.

PHYSICIANS PERSPECTIVE

In most of the countries, prescribing information and promotional materials by pharmaceutical companies are not permitted to promote non-approved indication, but physicians have a liberty to prescribe any approved drug for any indication, irrespective of the fact that the indication is not approved by regulatory bodies.[4] Off-label use by physicians is more common, if standard treatment regimens are non-existent or standard treatment regimens fails.[5] Although, it gives freedom to physicians to apply new therapeutic options based on the latest evidence but there is no guarantee of its scientific validity due to lack of evaluation of safety and efficacy. Therefore, while prescribing drugs for off-label use the physician must be aware about its scientific validity and medical evidence.[2,6]

If the reasons behind the off-label prescribing by the physicians are analyzed, it is usually found that there is no relation between prescribing information approved by regulatory authorities and the up-to-date medical practice. For example, paclitaxel was initially approved for treating ovarian cancer, but after published reports on breast cancer showed its effectiveness, it was employed for treating breast cancer years before this indication was approved by regulatory bodies.[5]

There is delay in granting a regulatory approval of a new indication of a medicine even after it has gone through clinical trial and proved to be effective and safe. While a drug is passing through the regulatory approval process, the opinion provided by recognized authorities or key opinion leaders (KOLs), sometimes suggests the use of the drug for a new indication. Usually, peer-reviewed journal already publishes about a new use of the drug even before a regulatory authority grants approval to those. It has been seen that other beneficial uses of approved drugs are discovered even after the regulatory approval and some time off-label use of a medicine is gradually recognized as a standard therapy.[6,7] For instance, even though the US Food and Drug Administration (FDA) initially approved propranolol for the treatment of cardiac arrhythmia in 1968, but propranolol was approved for the treatment of hypertension and angina pectoris in 1978, its very significant uses. Even more unexpectedly, when propranolol was given to patients with arrhythmias or angina who also had migraines, it was discovered to avert migraine attack. After many years of off-label use for migraine, it was finally approved for this use in 1979.[5]

Another classic example is thalidomide. The benefit of thalidomide in the treatment of cutaneous manifestations of erythema nodosum leprosum was initially reported in 1965. But this use was endorsed by the World Health Organization (WHO) in 1988 and eventually approved by the US FDA in September 1997.[6] Unfortunately, many medically accepted off-label uses sometimes do not become regulatory-approved indications leading to off-label prescribing by physicians.[6,7] For instance take the example of bevacizumab for age-related macular degeneration (AMD).[7]

AMD is the common reason for irreversible visual impairment in elderly people in the developed countries. The neovascular (wet or exudative) form is liable for about 90% of serious visual impairment emanating from AMD.[8] The recent approach for treating neovascular AMD is anti-angiogenic therapy such as antivascular endothelial growth factors (anti-VEGF) which intends to avert further neovascularization and not only extinguish it. Presently, the most often used VEGF antagonists are ranibizumab (Lucentis, Genentech Inc, south San Francisco, CA) and bevacizumab (Avastin; Genentech Inc, south San Francisco, CA). Ranibizumab, has been permitted for the neovascular AMD by the US FDA and by the European Medicines Agency (EMEA) since 2006 and 2007, respectively. But therapy with ranibizumab is very costly.[8]

After Lucentis (ranibizumab) was granted regulatory permission to treat age-related wet macular degeneration, doctors promptly replaced it with Avastin (bevacizumab), a related, low-priced drug approved for cancer treatment. Avastin was being preferred over the approved drug Lucentis by doctors for wet AMD due to a significant difference in cost.[9,10] In comparison to ranibizumab, bevacizumab was approved for the treatment of specific cancers such as metastatic colorectal cancer. It was not developed for the treatment of AMD and has no regulatory approval for this use.[8]

In 2005, the first paper of intravitreal bevacizumab administration for neovascular AMD was published. After this primary report, many papers supporting the efficacy and safety of bevacizumab were published. The price of intravitreal bevacizumab is much less than ranibizumab. This cost difference has important economic implications if we consider the huge number of patients treated for neovascular AMD every year. Apparently the low price and the encouraging results on visual acuity have led to extensive off-label use of bevacizumab for neovascular AMD.[8] Recently, bevacizumab

has been added to the latest WHO model list of Essential Medicines (April, 2013). This is an example of a drug being included in the list for an off-label use. Ranibizumab approved for this indication has not been included in this list.[11]

PATIENTS PERSPECTIVE

Therapeutic options might get restricted without off-label prescribing in some patient population.[1,4] Off-label uses can be useful to patients with an orphan disease where sometimes it can be the only available treatment.[2] Many cancer drugs which have originally been approved for treating one type of cancer have been tried in treating another type of cancer. For instance, mitomycin is indicated for the treatment of gastric and pancreatic carcinomas. In addition, it complies with the well-acknowledged benchmark of care in the treatment of lung, bladder, breast, cervical, and other carcinomas, although these uses are not approved by the US FDA.[5] Lack of pediatric indications on drug labels often lead to off-label prescribing, hence many drugs indicated for adults only are also prescribed off-label in pediatric patient population. Off-label prescribing is also common in psychiatry.[4,5,12]

Often, when the best available therapeutic option fails, patient demands new approach or new treatment which ultimately leads to off-label uses.[5] Moreover, the earlier access to potentially valuable medications to patients is provided by off-label use. Some off-label uses are scientifically valid and give tremendous benefits to patients. For example, aspirin has a multiple number of off-label usages. Recently it has been endorsed for prevention of a first myocardial infarction in individuals at moderate or greater risk of coronary heart disease. Researchers have also investigated the use of aspirin in the prevention of colon cancer, esophageal cancer, and other diseases.[13]

But 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] The disputes related with the diet drug fen-phen show the hazards of off-label prescribing. "Fen-phen" was a combo of two drugs, fenfluramine (or the closely linked dexfenfluramine) and phentermine, employed to help weight loss. The US FDA permitted phentermine, fenfluramine, and dexfenfluramine in 1959, 1973, and 1996, respectively as appetite suppressants to be used for a brief duration. They never attained much popularity because they were not very effective. In the 1990s it was reported that the combination "fen-phen" led to significant reduction in weight. The finding resulted in a substantial upsurge in the number of "fen-phen" prescriptions. Even though fenfluramine, dexfenfluramine, and phentermine were all US FDA approved drugs, the combination "fen-phen" was never separately approved by the US FDA and hence its prescription was termed off-label. Subsequently, in July 1997 it was reported that 24 women taking fen-phen developed heart valve disease. Additional small studies revealed that heart-valve disease was quite prevalent in women taking fen-phen. Fenfluramine and dexfenfluramine were discontinued in September 1997 because further scrutiny of the data affirmed an association of heart valve disease with fenfluramine and dexfenfluramine. Critics of off-label prescribing argued that the combination of fenfluramine and phentermine was never given regulatory permission, thus was being prescribed off-label which led to health hazards.[5]

PERSPECTIVE OF THE PHARMACEUTICAL COMPANIES

During the drug development process, the drug may be found to be effective in many indications but pharmaceutical companies must select limited indications to pursue further research. Cost is one of the major factors which decide the number of indications applied for. The patients and duration required to complete the trials both increase if there are many indications. Because new drug development is a costly and time-consuming process, the pharmaceutical companies are reluctant to include new indications which might further escalate the cost and time. Moreover, any delay in getting regulatory approval will shorten the period of marketing for a drug during drug's patent life.[1,6]

Gabapentin (Neurontin) was allegedly promoted for various off-label uses for treating a multiple number of neurological conditions. Amusingly, regardless of the very fact that the gabapentin was initially approved by US FDA in 1994 as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy, its nominal market these days are epilepsy and seizures. A variety of off-label or unapproved uses of gabapentin have been reported, encompassing treatment of neuropathic pain, diabetic neuropathy, complex regional pain syndrome, bipolar disease, attention deficit disorder, migraine, restless legs syndrome, periodic limb movement disorders of sleep, etc., All these purported off-label uses have culminated in drug sells worth many billion dollars resulting in huge revenue.[13]

Another aspect to off-label use of medicine from perspective of pharmaceutical companies is to get regulatory approval for new uses of old drug which is also a costly and time-consuming process. A supplemental new drug application is required to add a new indication to the drugs label and indications which are not well-supported by clinical trials usually do not get approval from regulatory bodies. The regulatory agencies have to strike a balance between the need for rapid approval for new indications of drugs and very less

information on their safety and efficacy.[3] From a business point of view, to seek supplemental approval for new uses late in a drug's patent life is not very enticing for pharmaceutical companies. The developmental cost of new uses of old drug might exceed the benefit of regulatory approval.[5] There might be a lack of funding in case of generic drug and in case of innovator drugs conducting expensive clinical trials that could produce non-supportive evidence is a risk nobody wants to take especially when innovator drug is commonly used off-label.[2] Further, off-label use might discourage evidence based practice by discouraging the manufacturer to conduct well-controlled clinical studies.[2]

PERSPECTIVE OF REGULATORY AGENCIES

Most of the countries do not have any clear-cut guidance about off-label uses of medicine and there is no consistency about off-label regulations in different countries.[17] This has led to off-label promotion based primarily on covert marketing techniques ultimately leading to many controversies. For example, in the USA before 1997, marketing of off-label uses by pharmaceutical companies was illegal. This legal constraint was the ground for a benchmark lawsuit in 1996. A lawsuit was filed in 1996 under the False Claims Act that debated that the pharmaceutical company Warner-Lambert, a subsidiary of Pfizer, endorsed the drug Neurontin (gabapentin) for various off-label uses. The case resulted in huge fines for a pharmaceutical company.[18] Thereafter, the need for guidance was felt to encourage proper off-label use of medicine by the distribution of scientifically valid and authentic information from the pharmaceutical companies.[3,19]

To control the menace of covert marketing practices of pharmaceutical companies, the USA took an initiative and came up with the regulations about off-label use of medicine. As mentioned earlier, in USA before 1997, marketing of off-label uses by pharmaceutical companies was illegal. But in 1997, US Congress approved standards for off-label promotion in the Food and Drug Administration Modernization Act (FDAMA). This act permitted pharmaceutical companies to circulate scientifically valid information and to sponsor independent scientific educational activities. Some FDAMA requirements were to send a copy of the scientifically valid information to the US FDA in advance before distribution and to verify its plan in seeking approval of the off label use. FDAMA's limitation on off-label promotion expired on September 20, 2006.[4,20]

New guidance issued by US FDA in January 2009 about the promotion of off-label uses of drugs is known as "Good Reprint Practices". It describes provisions under which pharmaceutical companies may distribute reprints of journal articles describing drug indications that the regulatory agency has not approved. US FDA guideline recognizes that in certain circumstances the exchange and distribution of scientific information on off-label uses can be allowed. Selected provisions of this guideline are described in the following section.[21,22]

Furnishing scientific data

With some restrictions, pharmaceutical companies may give scientific data about new drugs or new uses of old drugs.

Unsought requests

Pharmaceutical companies may offer receptive, non-promotional, and valid scientific data in response to unsought request.

Medical journal articles and reference texts

In some conditions, pharmaceutical companies may offer certain types of medical journal articles and medical reference texts.

In Japan, as pointed out by Gota and Patial, a new drug application allows the approval of off-label usages without clinical trials. The EMEA too is sympathetic to off-label practice by actively endorsing clinical trials of off-patent drugs for off-label uses, notably in the pediatric population.[17] Recently, France came up with regulations for prescriptions of medicines for non-regulatory approved indications as well.[3]

In India, the Drug Controller General of India (DCGI) is the regulatory authority for granting approval for new drugs but unfortunately, there is no clear-cut guideline on the off-label use of drugs. 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.[17,23] Khamar (2007) emphasizes that off-label prescribing also raises apprehension about ethical and moral concerns. In India, professional conduct of doctors is guided Indian medical council act (professional conduct, etiquette, and ethics) regulations 2002. Therefore, doctors are expected not to avoid legal restrictions like the Drugs and Cosmetics Act and not to violate human rights as well.[23]

The issue of off-label use was debated up in India in 2003 when it was found that letrozole, an anti-breast cancer drug was being promoted for infertility. Subsequently, the Drug Controller-General of India (DCGI) authorized a probe into media reports that few pharmaceutical companies had endorsed letrozole for treating infertility in women, without the valid regulatory permission.[24] But the issue of letrozole had at least one good impact. Following this controversy, the DCGI asked the Indian Medical Association (IMA) to prepare an exhaustive report about the various attributes related to off-label use of drugs. 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. IMA has appealed for changes in the rule so that doctors in India can lawfully prescribe drugs for indications

other than those for which the drug was originally approved.[25] Despite the IMA's positive opinion about off-label prescribing, any rule about the off-label prescribing is yet to come in India.[17] 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.[25]

CONCLUSION

There have always been attempts from pharmaceutical companies to increase the use of their drug. Because of the financial aspects involved it is highly impractical to expect that pharmaceutical companies will restrict or stop off-label promotion. Whereas, the regulatory agencies would always try to balance the need for rapid access to drugs for new indications against the limited information on their benefit-risk ratio.

At the other end of this paradigm, off-label use gives freedom to physicians to apply new therapeutic options based on the latest evidence. In fact physicians may lawfully prescribe approved drugs for any use consistent with available scientific data and proper medical practice. Sometimes patients suffering from terminal illness demand new approach or new treatment and if their logical demands are rejected it will definitely not benefit other new patients. It has been recommended that the attempt should be to strike a balance in the best interest of the patient. Off-label use might be compared to double-edged sword which at the one end might be very useful for some patients while it can also expose them to unrestricted experimentation.

It has been recommended that proper off-label prescribing should only be encouraged by the distribution of truthful and non-misleading information. If off-label prescribing is disallowed, many new therapies and evidences would not come into the forefront because the incentive for pharmaceutical companies to get the regulatory approval for new uses of old drugs by clinical testing is very less.

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