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Off-label promotion of prescription medicine: is it ever justifiable?

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ABSTRACT:

Off-label promotion has attracted intense scrutiny from regulators in recent decades resulting in many pharmaceutical companies paying hefty penalties for illegal marketing practices. At the same time, the pharmaceutical industry has accused governments of applying double standards by encouraging the use of cheaper off-label alternatives to registered treatments, and defended their 'right' to promote off-label drugs on freedom of speech grounds. However, the debate about off-label promotion and the prescribing that results has largely failed to address the issue that really matters – what impact does off-label promotion and prescribing have on patients and the health system? In this paper we explore the benefits and problems with off-label prescribing in order to determine whether off-label promotion is ever justified, and if so, under what conditions.

KEYWORDS: off-label; promotion; misbranding; regulation; pharmaceutical industry; prescribing

Off-label promotion of pharmaceuticals (i.e. promotion of pharmaceuticals for indications beyond those approved by regulators) has attracted intense scrutiny over the past decade. Governments in the United States and Europe have responded to instances of off-label promotion by taking legal action against pharmaceutical companies, resulting in substantial settlements. Notable recent examples include Eli Lilly for off label promotion of Zyprexa (US\$1.4 billion),¹ Pfizer for Bextra, Geodon and Lyrica (US\$2.3 billion),² GlaxoSmithKline for Paxil, Wellbutrin and Avandia (US\$3billion),³ and Johnson and Johnson for Risperdal, Invega and Natrecor (US\$2.2billion).⁴

These forceful responses to off label promotion stem from the view that off-label promotion is an attempt to circumvent the regulatory system in order to increase market share, arguably putting corporate interests before the public good (in terms of both patient safety and providing a just and efficient distribution of resources). There is also the view that off-label promotion represents an abuse of regulatory incentives, such as those given to companies to produce drugs for orphan diseases. In support of this contention, it has been noted that several drugs given orphan status have become blockbusters as a result of off-label use.⁵ Examples include Recombinant Factor VIIa (Novo Nordisk), registered for rare cases of hemophilia but used widely for major hemorrhage, and Epogen (Amgen), registered for the treatment of anemia that results from kidney disease or cancer treatment, but used more generally to manage anemia.

While companies generally deny that they engage in off-label promotion, there is documented evidence of practices such as providing kick-backs to doctors for using products off label, publishing “seeding” trials to establish a precedent for off-label uses, using advisory boards, consultant meetings and accredited continuing medical education events to deliver promotional messages, and selectively disseminating information about products in order to portray them in the best possible light to clinicians who might want to prescribe them outside of regulator-approved indications.^{6,7}

The pharmaceutical industry denies that it is attempting to circumvent regulation, and continues to defend its “right” to promote drugs off-label by arguing, particularly in the United States, that it is a form of speech that is protected under the freedom of speech amendments of the US constitution.⁸ Companies also claim that they are being treated unfairly by governments who are simply concerned about cutting healthcare costs. In a recent position paper developed by the European Federation of Pharmaceutical Industries and Associations,⁹ the pharmaceutical industry explicitly criticised governments of having double standards, by condemning off-label promotion on the one hand, yet actively promoting the use of off-label drugs in cases where they present a cheaper alternative to labelled therapies.

We suggest that these arguments for off-label promotion are hollow as they fail to address what should really matter to critics of off-label promotion, namely, the impact that the subsequent off-label *prescribing* has on patients and on the health system. In this paper we will examine the pros and cons of off-label prescribing, and then use this analysis in order to determine whether off-label promotion is ever justified.

Off label prescribing

Off label prescribing—defined here as using a drug outside of the indication, dose, frequency, or route of administration for which it is registered by regulatory bodies—is common. It has been estimated that patients are prescribed drugs off-label in over 20% of prescriptions,¹⁰ while in some specialties, such as pediatrics, geriatrics, obstetrics and oncology, off-label prescribing can account for over 50% of prescribing.^{11,12,13} For some drugs, such as recombinant activated factor VII it may account for almost all prescriptions.^{14,15} Furthermore, it has been shown that new uses are identified for most drugs within 5 years of being on the market, of which almost 60% are “discovered” by physicians through off-label use.¹⁶

Concerns about off-label prescribing

Limited evidence of safety and efficacy: Off-label prescribing raises a number of legitimate concerns for prescribers and policy makers. The benefits and harms of medicines prescribed off-label are less certain than they would be if they had been tested and registered with the particular use in mind as

there is no minimum standard for scrutinising the quality and safety of off-label uses^{10,17,18}. In some cases, the potential for harms are known. For instance, misoprostol is proposed for management of post-partum haemorrhage in the developing world but is known to cause uterine rupture in rare instances.¹⁹ In other cases drugs may be used off-label for many years before evidence of potential harms are verified, as occurred with recombinant FVIIa (used widely off-label for major haemorrhage and subsequently found to increase the risk of thrombosis)²⁰ and Fen-Phen (a combination of drugs used for obesity that was never approved for use and was found to increase risk of primary pulmonary hypertension and heart valve damage).²¹

Undermining regulation and evidence-based medicine: Another major concern that critics have of off-label prescribing is that it does not satisfy the evidentiary standards of evidence based medicine, and that it undermines systems for regulation of drugs.^{22,23} Audits of off-label prescribing have shown clearly that it is often based on little evidence, with one study demonstrating that there was little or no scientific support for three quarters of off-label prescriptions in the outpatient setting.¹⁰ It has also been argued that off-label prescribing leads to a two-tiered regulatory system: one in which drugs are reviewed for both safety and efficacy, and another where drugs are only reviewed for safety.²⁴ In the latter case, health care professionals or other bodies are left to determine efficacy, and in some cases this may lead to drugs being used for indications for which they may never have been approved via normal regulatory process. Furthermore, evidence that a drug is safe in one population of patients does not mean it will be safe in another. Off-label prescribing can also undermine the research process underpinning drug assessment, as there is little incentive for patients to enrol in clinical trials if they have access to the same drugs off-label.²⁵

Pressure on health budgets: The circumventing of standard processes for the review of benefits, harms and cost-effectiveness of medicines is also of concern to governments and private insurers anxious about health budgets and reducing waste.²⁶ Since there is no agreed way of assessing the value of medicines prescribed off-label, it is likely that governments and patients are spending fortunes on drugs that provide little or no benefit relative to other, much cheaper, alternatives, and may even be harmful, adding not only to the burden borne by patients, but also to health care expenditure.²⁷ For instance, in Australia recombinant activated factor VII costs approximately \$10000 (US) per dose and it is used almost always off-label.²⁸ A study of 5 tertiary hospitals in Europe demonstrated that off-label uses of drugs did appear to provide benefits, but at a high cost and with some additional adverse effects.²⁹ As long as off-label drugs constitute a significant proportion of all prescribing, they will continue to be a major component of pharmaceutical spending, and the opportunity costs that arise are unclear but potentially significant.

Benefits of off-label prescribing

Despite the many concerns about off-label prescribing, the practice is legal, and there are reasons to believe that it performs important functions. There are several possible justifications for off-label prescribing, most notably that it fills gaps in the market and addresses unmet health needs; is consistent with the dynamics of innovation; and provides a mechanism that is more reflective of 'real-world' practice.

Filling gaps in drug development: While pharmaceutical companies play an important role in conducting basic biomedical research and developing new medicines, they are commercial entities, and so they need to focus their drug development processes on medications that are likely to be commercially viable, as well as fulfilling unmet healthcare needs. This unavoidably leads to gaps in drug development for conditions that affect only those in developing countries, for acute and self-limiting conditions (such as some infectious diseases), for rare diseases, or for medicines that are technically or ethically difficult to develop. . In some cases, drugs that are not likely to be

commercially successful are not developed at all. In other cases, they are developed but only tested for limited indications in limited populations, thus restricting the indications for which they can be approved by regulators. This leads to a situation where there exist many diseases for which there is a demand for treatment, but no mechanism to effectively meet that demand. For instance, in the United States alone more than 6800 “rare diseases” have been classified, which are estimated to collectively affect 10% of the population³⁰ while the European Organisation for Rare Diseases estimates rare diseases affect up to 8% of Europeans.³¹ The FDA has approved more than 340 treatments for rare diseases,³⁰ which, although significant, still falls short of what is needed. Furthermore, on average fewer than 30 new drugs being approved year of which only a third presented genuinely new drugs.³² This gap between patient needs and approved treatments will not be easily bridged in the short term. In this context, judicious off-label prescribing may be an important way of filling therapeutic gaps.

Recognising the limits of clinical research: While well designed and conducted clinical trials, followed by methodologically sound health technology assessments, are the most robust basis we have for guiding clinical practice, there are a number of logistical, financial and ethical reasons that not all pertinent clinical and public health questions can be answered in this way. First, clinical trials are expensive, and so academic researchers (unless funded by a pharmaceutical company) face similar challenges as drug companies about where best to direct limited resources. Second, ethical standards can make certain types of clinical trials impossible to conduct, as has been the case with children and women of ‘childbearing potential’ who have traditionally been excluded from research. Finally, in cases where off-label prescribing has become a well justified “standard of care” in an *ad hoc* manner, it may be difficult to meet the ethical requirement of equipoise (i.e. not knowingly giving a patient an inferior treatment) that is demanded by ethics committees.

Recognising the limits of regulation and clinical policymaking: Off-label prescribing may also be seen to address the limits of existing systems of medicines regulation and clinical guideline production. Regulatory processes can be slow, regulators in different jurisdictions often disagree with each other, and clinical guidelines, policies and drug labels are often inconsistent with each other, quickly outdated and not aligned to current best evidence. The increased ability for academics, physicians and other expert groups to access, synthesis and analyse evidence using, for example, electronic health records and clinical administrative and research databases makes the challenge to the currency of drug labels all the more pertinent. Off-label prescribing, therefore, may provide a more dynamic, more flexible, and more anticipatory guide to clinical practice. Examples of off-label prescribing that may be considered “routine” include once daily dosing of gentamicin, valproate for migraine, morphine for dyspnoea in palliative care and rituximab for rheumatoid arthritis.³³

Respecting the role and responsibility of clinicians and personalised care: Finally, since clinical trials can take years to complete, health care providers also have to decide whether it is justified to deprive patients of potential immediate benefits while waiting for definitive research results. Physicians are obliged to act in the best interests of their patients, and must respond to their needs after a judicious evaluation of all relevant factors that include evidence, expert knowledge, and the needs and preferences of the patient. A physician who limits his or her decision making to what is on the drug label might fail their duty of care to patients as espoused by the Declaration of Geneva of the WMA and the Code of Medical Ethics. However, there has also been persistent concern about legal liability associated with the off-label use of drugs, whether real or imagined, that could influence the decisions physicians make in practice.³⁴

In this regard it is important to bear in mind that off-label prescribing may be both logical and reasonable. Physicians may rationally conclude that a drug that works for one should work for

another related condition – even if there is no definitive scientific investigation of this proposition. They may also use a drug for its verified side effects rather than its approved indication, or because it is deemed to be safe and therefore the downsides are minimal. And they may make a judgement on the balance of evidence – since off-label drugs have already been tested for safety in a particular population, evidence of efficacy from phase II trials might provide sufficient justification to use it off-label. In this way physicians can proactively respond to patient needs in a judicious manner.

Striking a balance

Given these complexities, it is not surprising that there is an ongoing debate between those who argue that regulators need to take a more stringent stance to protect the public from the negative effects of off-label drug promotion (and therefore prescribing), and those who argue that regulation should be softened. On the one hand, it is arguable that if off-label prescribing can improve access to much needed treatments then off-label promotion could help to enhance care by raising awareness of different therapeutic options. On the other hand, as formal mechanisms to evaluate the appropriateness and cost-effectiveness of off-label prescribing is lacking, it is also possible that promotional activities could lead to increased prescribing of drugs that have little or no benefit, or may even be harmful, and ultimately waste limited health care resources. The question is, therefore, whether it is possible to move beyond the current arrangement—where there is no scope for off-label promotion at all—without compromising patient care, systems of rational prescribing and the sustainability of health care systems more generally.

Mackey and Liang have proposed a regulatory framework that would support targeted off-label promotion so that vulnerable patient populations could have better access to drugs via increased awareness of treatment options, while simultaneously instituting disincentives to discourage drug sponsors from inappropriate off-label promotion.²³ This framework requires pre-approval of promotional materials by an advisory committee, a commitment from drug sponsors to monitor and report usage and outcomes, and the specification of a prescribing threshold, which once passed, would require a new drug application to be made via usual processes. For those who breach permitted promotional activities, Mackey and Liang suggest that in addition to being penalized, drug companies should be barred from engaging in any future off-label marketing activities.

Like Mackey and Liang, we believe that off label promotion should NOT be allowed routinely but that companies might be able to make special applications to regulators to promote their medicines off label if they meet a number of strict criteria. These would include:

1. Explaining why clinical trials or routes to formal registration are unwarranted or impossible;
2. Explaining why they believe the promotion will be of benefit to patients and to the health system despite the inevitable risks and increased costs, supported by a summary of currently available evidence on safety and efficacy;
3. Establishing clear mechanisms for monitoring of use before any promotion begins and publishing a data management and reporting protocol;
4. “Registering” the off-label use;
5. Making explicit what the marketing strategy will be and having all relevant materials pre-approved by the regulator;
6. Repeating the above justification every 6 or 12 months to ensure that the emerging data reflects the predictions that have been made; and
7. Demonstrating the capacity and commitment to fund all of the above.

This approach might seem onerous but, in our view, given the many dangers to patients and the health system of uncontrolled off-label prescribing, it seems to be a fair compromise between improving access to new therapeutic options for those who need it, and maintaining high standards of public health and safety.

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