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Labelling and 'Dear Doctor' Letters
Are They Noncommittal?

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Abstract

Over the past few years, a number of drugs have been withdrawn for safety reasons, either by drug approval authorities, or by the manufacturer. A recent example is the withdrawal of cerivastatin in connection with rhabdomyolysis. Several other drugs have also been taken off the market as a security measure, not because the nature of the risk involved was unknown but because the risk had proved apparently uncontainable. It seems that the inclusion of a warning or contraindication in the Summary of Product Characteristics (SPC) or sending a 'Dear Doctor' letter is insufficient to ensure compliant prescription behaviour. There appears to be a discrepancy between the careful use of evidence underpinning the SPC content and formal warnings and changes to the SPC and the effect they have on the prescription and dispensing of the drugs involved. This results in undue loss or damage for both the manufacturer and the patient.

There are no easy solutions to tackle this problem; the ineffectiveness of labelling and 'Dear Doctor' letters has ramifications for the whole regulatory/industrial/educational complex.

We discuss briefly four possible strategies for improving the current situation, with the emphasis on the place the prescriber has in this process.

The first strategy is education-based. Clinicians need to know about the comparative merits of the effectiveness and risk of drugs, as well as how they work pharmacologically, toxicologically, and what interactions they have with each other. The second strategy involves improving the information available for clinicians. Frequently, physicians do not consult the SPC for verification, leaving aside whether they have taken notice of the contents of the official SPC in the first place. It is recommended that the accessibility of SPCs is enhanced for doctors and pharmacists, drawing attention specifically to any changes. There needs to be a single body of information that covers every drug.

The third strategy involves communication. There is much to be done in this area both in terms of follow-up and understanding of health professional's behaviour and how to empower best practise.

The final strategy involves professional freedom. It goes without saying that doctors who issue off-label prescriptions may need to justify their actions. Deviating from the SPC should always be a considered decision and health professionals need to be aware of the additional responsibilities associated with such a decision. The dispensing pharmacist can play an important role in the implementation of warnings and contraindications.

Withdrawing a drug from the market is a drastic measure. Over the past few years a number of drugs have been withdrawn for safety reasons, either by drug approval authorities, or by the manufacturer. A recent example is the withdrawal of cerivastatin in connection with rhabdomyolysis, occurring especially when cerivastatin is prescribed in combination with gemfibrozil. What was remarkable in this case was the fact that the Summary of Product Characteristics (SPC) did include a warning for this interaction and also that the manufacturer had alerted the health professionals in 'Dear Doctor' letters about the complication.

Several other drugs have also been taken off the market as a security measure, not because the nature of the risk involved was unknown but because the risk had proved apparently uncontainable. It seems that including a warning or contraindication in the SPC or sending a 'Dear Doctor' letter is insufficient to ensure compliant prescription behaviour.

A number of studies have been published on the effects of adjustments of the SPC content and 'Dear Doctor' letters in connection with the incidence of arrhythmia associated with the use of cisapride.[1,2] Notwithstanding the fact that in the US four label changes and notifications had been issued, in 3.4% of the cases the concomitant use of at least one contraindicated drug had occurred.[1] It was not until the risks of cisapride had received more extensive media attention that the co-dispensing of drugs that should not be taken together with cisapride actually decreased.[2]

In March 2000, troglitazone was recalled from the market because of life-threatening acute liver failure. The risk was known and was referred to in the SPC. In the US the manufacturer had distributed four 'Dear Doctor' letters, which included the recommendation that liver function be tested more frequently. Although subsequently the number of patients tested increased 3-fold, a mere 5% of users were tested in the recommended frequency after 3 months on the drug.[3]

Recently, research results on the indications for which rofecoxib is prescribed were published in The Netherlands.[4] Rofecoxib was originally approved in The Netherlands for the indication 'symptomatic treatment of arthrosis'. However, promotional material directed at physicians particularly emphasised 'pain relief', even though costs are officially only reimbursed for the indication (osteo)arthrosis. An evaluation of the electronic data collected from the prescribing general practitioners showed that over 80% of the prescriptions involved a different diagnosis than that of 'arthrosis', thus constituting a deviation from the indication specified in the SPC. The researchers concluded that rofecoxib is prescribed for a wider range of indications than for that indication for which it was approved.

The content of the SPC is compiled with due consideration of the evidence available, including information from the clinical trials conducted prior to marketing authorisation. The definitive text is determined by the drug approval authorities and the SPC becomes part of the registration file. 'Dear Doctor' letters are drawn up in close co-operation with the manufacturer and the drug approval authorities. This also holds for any changes in the content of the SPC, such as alterations resulting from postmarketing research that have led to new insights into the safety aspects of the drug.

There appears to be a discrepancy between the careful use of evidence underpinning the SPC content and formal warnings and changes to the SPC and the effect they have on the prescription and dispensing of the drugs involved, as shown by the cases mentioned above. If and when physicians and pharmacists do not adhere to the SPC and their decisions lead to an increased safety risk, the decision to withdraw a particular drug from the market may be expedited. This results in undue loss or damage for both the manufacturer and the patient.[5] It may be argued, therefore, that physicians and pharmacists should adhere to the indications, warnings and contraindications as described in the SPC. Also, any alterations in the content of the SPC should be followed up in daily practice. The same applies for the information disseminated via 'Dear Doctor' letters.

Legally, however, physicians can deviate from

the indications as described in the SPC. In some cases they have no other option, as occurs for instance in paediatric practice quite often because of lack of clinical trial information on children. In addition, warnings and contraindications can be ignored. There can be sound clinical reason in this. Clinical trial and epidemiological evidence can only provide a guide as to the normal group response to a drug or other therapy. It goes without saying that doctors who issue off-label prescriptions may be need to justify their actions. Deviating from the SPC should always be a considered decision and health professionals need to be aware of the additional responsibilities associated with such a decision.

We are aware that as we are discussing the ineffectiveness of labelling and 'Dear Doctor' letters, it has ramifications for the whole regulatory/industrial/educational complex. The complexity of this could easily hinder the necessary debate. We will briefly discuss four possible strategies. Given that clinicians must interpret evidence and not try to force patients into convenient algorithms, what can be done to prevent the SPC from being perceived as a prescriptive legal document and to be more empowering?

1. Education

Drug therapy is a complex business. New drugs become available all the time, as well as new information on old drugs. The clinician, in particular, has the role of the 'learned intermediary' to evaluate knowledge critically and to use and explain it in a given individual setting. To be a 'learned intermediary' health professionals must understand the drugs they use and it is important to acknowledge that undergraduate curricula are overloaded, and only the rudiments of clinical therapeutics can be taught. Clinicians need to know about the comparative merits in effectiveness and risk of drugs, as well as how they work pharmacologically, toxicologically, and how they interact with each other. Then the clinicians may make logical inferences for the therapy of the patients they treat.

2. Information

Frequently, physicians do not consult the SPC for verification, leaving aside whether they have taken notice of the contents of the official SPC in the first place. It is recommended that the accessibility of SPCs for doctors and pharmacists is enhanced, drawing attention specifically to any changes. All evidence-based findings, including information obtained in clinical trials performed during the pre-marketing stage (not just didactic statements), need to be made available. Greater awareness about adverse drug reactions, regarding their significance, recognition, management and prevention, needs to be established. In order to enhance the knowledge of the effects of drugs in the clinical practice it is vital that doctors and pharmacists report suspected adverse effects to their national pharmacovigilance centres. These centres need to find effective ways to disseminate the data they have collected to the various professional groups and should be involved in and contribute to the education of health professionals.

In short, there needs to be a body of information for every drug that is available from a single accessible source.

There are numerous publications and websites that provide useful information but they do not have regulatory approval. The Cochrane Foundation provides useful reviewed information, but does not go far enough in factoring in knowledge other than from controlled trials. As argued above, other material is essential to bridge the gap between information from an ideal therapeutic situation and the application of such knowledge in a difficult patient.

Publication in national Drug Bulletins and issuing notices on special websites should be considered. In this context the US FDA has recently published proposals regarding improvements of the SPC.[6]

Doctors must make decisions on the relative effectiveness and risks of the treatments they advise for their individual patients. There needs to be much more thought about how to support this essential function. The UK's National Institute for

Clinical Excellence (NICE) can be seen as a way forward in this respect, for the introduction of new therapies. NICE tackles the difficult issue of reconciling relative effectiveness and cost; and issues guidelines, not mandates. A recent review of its work so far was positive, although indicating that the magnitude of the tasks facing NICE are great. The main challenge was seen as providing comprehensive treatment guidelines into which context any new treatment must be fitted.[7] Similar initiatives have been developed in the US (Centers for Education and Research on Therapeutics) and The Netherlands ('standards' of The Netherlands Society of General Practitioners).

3. Communication

Communication is a two-way loop; one must ensure that information is received, understood and acted upon correctly before a communication can be said to have been successful.

There is much to be done in the area of communication, both in terms of follow-up and understanding of health professionals' behaviour and how to empower best practise. In the Erice Report on drug safety information it is stated that 'drug safety information must serve the health of the public'.[8] The Erice Declaration also commends the idea of actively communicating uncertainty. This is a difficult issue, but in the safety area it has a good deal to recommend it because of the tentative information about many even serious adverse drug reactions.

4. Professional Freedom and Professional Responsibility

Physicians and pharmacists have enjoyed great professional freedom. Given the experiences already described, one needs to ensure that information and systems support such freedom. This requires that more attention be given to the feedback parts of the communication loop mentioned in section 3. More stringent approaches need to be set in place to find out about deviations from SPCs. Off-label prescriptions need to be documented and any adverse effects should be reported. The impact of a change in the content of an SPC or a 'Dear Doctor letter' will be greater when these conditions are fulfilled, since they will reflect rather than force clinical practice.

The dispensing pharmacist can play an important role in the implementation of warnings and contraindications. Increasingly, pharmacists consider providing pharmaceutical care a part of their professional responsibilities.[9] As with prescription of drugs, dispensing drugs cannot be noncommittal. Pharmacies in developed countries have sophisticated computer tools that help them monitor drugs for known interactions, contraindications and other important information contained in the SPC. To be able to monitor the indication for which the drug is being prescribed, the pharmacist needs to be informed of the physician's indications for prescribing the drug. In practice this is as yet rarely the case and many health professionals object to providing this information. Jones et al.[1] conclude in their study that in 89% of the cases in which cisapride had been prescribed in conjunction with a contraindicated drug, both drugs had been dispensed by one and the same pharmacy. Pharmacists need to be given a pivotal role in the surveillance of the safe use of drugs.

Although careful attention is being paid to the contents of SPCs and 'Dear Doctor' letters it has become clear that this is not enough. There is a gap between the determination of an SPC and daily practice. Creative, not a legalistic ways need to be found that will fill that gap to the benefit of all concerned parties: professionals, registration authorities, pharmaceutical companies and above all: the patient involved.

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