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# What Can Consumer Adverse Drug Reaction Reporting Add to Existing Health Professional-Based Systems?

## Focus on the Developing World

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## Abstract

The current system of pharmacovigilance encourages reporting of adverse drug reactions (ADRs) mainly from healthcare professionals. Underreporting is a major problem, more so in the developing world than in the developed world. Less than 3% of reports added to the WHO database in the year 2000 originated from developed countries, although around 80% of the global population lives in the developing world. Also a considerable time lag still exists in recognition of serious ADRs. Hence, there is a need for a different approach to pharmacovigilance.

We present an overview of possible reasons for underreporting by healthcare professionals with particular emphasis on the developing world, and the potential benefits of encouraging consumer reporting. Only a few countries accept consumer reports. We suggest an independent consumer reporting system for hypothesis generation to complement the present health professional-based system. We also highlight the low priority given by multinational pharmaceutical companies to the developing countries regarding new safety information.

The important questions are whether the resources available would be sufficiently robust to sustain such a system in the developing world, and whether it will be sufficiently robust and sensitive for the early detection of signals.

Proper interpretation of scientific information depends upon exact description of the rules and conventions under which the information was collected. Hence, in the field of pharmacovigilance, health professionals, mainly doctors (who after all were the ones with the most scientific training) were considered the right choice for observation and interpretation of an adverse drug reaction (ADR). However, at the first International Conference on Consumer Reports on Medicine held in Sigtuna, Sweden in 2000 and attended by the medical profession, pharmaceutical industry, consumer associations and patients who had experienced drug-induced injury, it was clearly evident that the consumers of drugs were looking for a monitoring system that heard the voice of the consumer and not for an instrument which made scientific decisions on cause.[1] This focussed the attention of those in the field of pharmacovigilance on the role of the consumer in drug safety and whether consumer reporting on medicines should be encouraged in the new millennium to supple-

ment the existing health professional-based system. This article focuses on a few case studies, discusses the limitations of the present health professional based reporting system and presents our views on 'consumer ADR reporting' in particular from a view point of the developing world.

Undoubtedly, the discipline of pharmacovigilance has developed and improved over the years since the thalidomide disaster of 1961.[2] Despite this, very few diseases come close to drug injury as a cause of morbidity. In a study done in 1998, it was estimated that ADRs to prescription only, and over-the-counter drugs result in the deaths of more than 100 000 Americans and seriously injure an additional 2.2 million each year.[3] The problem has been further compounded by recent data that a staggering 19.5 million American patients were estimated to have been exposed to five new chemical entities (NCEs) that were removed from the market for causing serious ADRs.[4] The existing evidence does not support the hypothesis that the recent number of market withdrawals is related to the improved speed of the FDA review and approval.[4] But, that postmarketing surveillance systems would have to become more active and essential in ensuring drug safety in the coming decade, with the manufacturer, regulator, prescriber and consumer all playing a responsible and active role.

## 1. Limitations of the Existing System

### 1.1 Underreporting of Adverse Drug Reactions (ADRs)

Successful implementation of the existing pharmacovigilance system depends heavily upon the firm commitment of health professionals. The main sources of information on the safety of drugs are the spontaneous reports and published case reports from doctors. Reporting rates have undoubtedly increased over the years, but many recent publications attest to the high rate of underreporting in both day-to-day clinical practice[3,5-8] and clinical trials,[9] and that less than 10% of even serious ADRs and about 2–4% of non-serious ADRs are reported.[7] Furthermore, there is a large discrepancy in the reporting rates between the developed and developing world. In 2000, the WHO database was updated with a new record number of reports; 549 140.[10] But the top 11 reporting countries were the US, UK, France, Australia, Spain, Germany, New Zealand, Canada, the Netherlands, Japan and Sweden. Only 14 463 came from all other countries, which includes the developing world and which accounts for over 80% of the world population.

A basic requirement for the generation of a report is that the doctor suspects that the signs and/or symptoms of his/her patient may be caused by a drug. Hence, recognition of an ADR would depend on an ill-defined threshold of suspicion that is personal to the doctor and subject to modification in the light of his reading and experience with the drug. Other recognised reasons for underreporting include: concern as to whether the incident is the result of the physician's action with the possibility of litigation; lack of time; the features of the ADR are already well known; the physician is uncertain of causality; the signs and/or symptoms simulate a common spontaneously occurring disease; or the suspected ADR has never been previously reported. Even, if a doctor observes an ADR, he/she would still have to report it in a predesigned form for it to be documented. In some developing countries such a form may not exist and even if a report is made, there is no designated official to receive them.[11] In most developing countries, drug regulatory authorities are often a department in the Ministry of Health with few material resources and even fewer human resources. Developing countries are unlikely to give priority to pharmacovigilance over pressing and visible issues such as drug registration.

### 1.2 Generation of Signals

Spontaneous reports by doctors have played an important role in postmarketing drug regulation.[12] Spontaneous reports have been of less use in the following situations: the early detection of ADRs with a relatively high background frequency; ADRs without a suggestive temporal rela-

tionship; and for ADRs unique for the developing world or when the ADR has arisen due to the way a drug is used in the community due to social circumstances in the developing world. An example of the latter would be misoprostol being used for abortions in Brazil and causing fetal malformations.[13]

Whilst, it is true that serious ADRs that appear to new drugs usually elicit regulatory action in due course, a considerable time lag still exists in recognition of serious ADRs as illustrated by the recent drug withdrawals in US. However, it takes even longer to detect non-serious symptomatic ADRs that affect the consumers' quality of life. For example, it took almost a decade for dependence to benzodiazepines to be recognised and two decades to appreciate that the risk of hip fractures in the elderly was significantly increased by ≥50% with the use of benzodiazepines in doses of ≥3 mg/day in diazepam equivalents.[14] The most recent worldwide withdrawal of cerivastatin is yet another example. Cerivastatin was approved for use in the UK in 1997 and subsequently in 16 other countries. In 1999 a signal was issued concerning an association between cerivastatin, myopathy and rhabdomyolysis. However, it was only in August 2001 that it was voluntarily withdrawn by the manufacturer.[15]

## 2. Should 'Consumer Reports on ADRs' Complement the Existing System?

It is clear that there are several recognised limitations in the present health professional-based system. We in the field of pharmacovigilance should acknowledge these limitations to the public and strive hard to achieve the goal of limiting drug-induced injury with their cooperation. The basic requisite for enhanced effectiveness of the existing system is an increased flow of information in both quantitative and qualitative terms. As we are academics from the developing world, we would like to discuss methods of increasing information quantitatively, with relevance to the developing world as a whole, by encouraging consumer reports.

### 2.1 Lack of Time

One of the cited reasons for underreporting is the doctor's lack of time. This would be most relevant to the developing world. In Sri Lanka the number of doctors per 100 000 population could be as low as less than ten in some areas, the average for the country is approximately 34.6 per 10 000.[16] In India it is estimated that the average consultation time per given patient is 3 minutes.[11] Given these figures, would ADR reporting be a physicians priority? Presently, in Sri Lanka, the ADR Monitoring Unit receives under 50 reports per year from the health professionals and an occasional report or two from the industry despite frequent reminders.

To support the argument that consumers could be a useful source of reporting we quote an example from two developing countries, Sri Lanka and the Philippines. It is reported from the Philippines[17] that, on the basis of a consumer report on gastrointestinal bleeding caused by mefenamic acid, regulatory action was initiated and misleading product advertising and information rectified. In Sri Lanka too, consumer and prescriber reports on muscle necrosis after intramuscular diclofenac, led to education of the prescriber on administering diclofenac sodium to the outer upper quadrant of the buttock only.[18] However, it should be stressed that underreporting is not peculiar to developing countries, as illustrated by a recent report form Australia, a country that has one of the highest reporting rates in the present system. An example is a case report of a patient who died suddenly within hours of obtaining his first prescription for sildenafil.[19] The doctor had not mentioned sildenafil on the death certificate nor reported it to the monitoring centre. The patient's wife reported it after hearing a TV programme on sildenafil. Australia is one of the few countries that accept consumer reports although they do not actively encourage them.

### 2.2 'Doctor Shopping'

Another well-known phenomenon in developing countries is 'Doctor Shopping'. Unlike in the industrialised world where there is a well-organised family practitioner system, in developing countries patients either alone or with the help of a health professional seek treatment from any doctor or specialist of their choice. If a problem arises they may go to another doctor and not disclose information on any previous medication. In this scenario even if the consumer felt that the problem they are presenting with could be drug-induced they may have some apprehension in telling a health professional and would feel more confident to report to an independent authority. 'Doctor shopping' may be seen in developed countries too but there it is more organised and the records follow the patient.

### 2.3 Lack of Health Professionals

One way of over coming underreporting by doctors is to train other health professionals such as pharmacists in ADR reporting as happens in some developed countries. However, the bigger problem faced by developing countries including ours is the inadequacy of trained pharmacists. Drugs that cannot be sold in developed nations or that are available only with a prescription can be freely bought over-the-counter in poorer nations. In such situations ADRs would go undetected as no doctor has been actively involved in the therapy.

### 2.4 Concept of Self Interest

The last, but not the least, advantage of encouraging consumer reporting will be the interest in one's own medication. In everyday life situations the consumer is considered the best evaluator of the product he or she purchases. Furthermore, when it comes to pharmaceuticals the consumer is the living laboratory for the medical profession to study the effects of the drugs for efficacy and safety. Doctors listen very enthusiastically to the positive aspects of drug efficacy but very often tend to dismiss negative aspects such as ADRs very hastily.[20] In our limited experience on ADR monitoring it is note worthy to mention that most inquiries as to whether a certain illness could be drug related, originate from doctors and other health professions when they become patients, which highlights the concept of self interest.

### 2.5 Generation of Signals

Would consumer reports add anything new to the existing system or only delay finding the needle by increasing the haystack of reports? Yes and no would be the answer. The present system has been fine tuned and is effectively recognising new serious ADRs to NCE, even though there is some time lag. Hence, consumer reporting may not add anything new which is serious in nature. However, the findings of Egbert et al.,[21] Mitchell et al.,[22,23] and Alvarez et al.[24] suggest that patients could contribute to earlier detection of ADRs and that patients are a valuable and better source of detection of symptomatic reactions to new drugs.

It is our experience and that of others,[24] that doctors tend to report ADRs that are serious rather than those which interfere with the patient's day-to-day life and ADRs which on causality assessment would be probable or certain rather than those which are possible. By this process they will be systematically weeding out important ADRs which initially would be categorised as possible, and thereby delay early recognition. Consumer reports on adverse events may help to bridge this vacuum. Charles Medowar in his article 'The antidepressant web',[25] shows evidence for consumer reporting on antidepressants in the developed world, to be a more sensitive tool than that of the health professionals in detecting dependence to the newer antidepressants. He also shows evidence for a similar scenario with benzodiazepines 20 years ago, when public concern on dependence caught the medical profession unaware.

It is also known that the rate of reporting by doctors declines with time after the drug is introduced into the market, hence common delayed ADRs especially the ones causing morbidity rather

than mortality may come to light with consumer reports.

## 3. Future Concerns

### 3.1 Global Registration of Drugs

With reference to our country, in the past it took some years to register a NCE following registration in a reference regulatory agency such as the US, UK or Australia, with the exception of a NCE that was a significant therapeutic advance. Thus, patients in Sri Lanka benefited from the experiences and reports of the ADR systems in the developed world. It is interesting to note that in the past US citizens too were spared from ADRs as it took longer to get a drug approved by the FDA than in UK, Germany and Italy.[4] Now this situation is fast changing with multinational companies attempting a 'global' registration, and the latter scenarios are less likely. At least in the developed countries where effective postmarketing surveillance systems are in place, regulatory action though somewhat late will eventually take place. Examples of drugs withdrawn by the manufacturer in developed countries but still sold in our country include cisapride, terfenadine and astemizole. The manufacturers have not informed the regulatory authority about the withdrawals in other countries or communicated any of the safety concerns to the prescribers. Although the availability of both trademarked products and generics in developing countries such as ours complicates the situation, it is not an excuse for differential treatment by multinational companies. This situation may not be peculiar to the developing world as cisapride is still available in some European countries. It is possible that those authorities have decided that there is a case for cisapride remaining rather than the company not withdrawing the product.

Litigation is distinctly uncommon in our part of the world and therefore pharmaceutical companies can and do keep products that would normally be taken off the market in more litigious environment. We are unable to make regulatory decisions, as we are unaware of the magnitude of the problem in our population. On the other hand, developing countries will also have to consider whether the much more expensive newer drug that will replace some of these will be affordable and free of ADRs. In such situations would consumer reports have helped?

### 3.2 Complementary Medicines and Direct-to-Consumer Advertising

Self-medication with complementary and alternative medicines has exploded globally. It is reported that one in three Americans use some form of alternative medicine without informing their primary care allopathic physician.[26] Even in a developing country like ours pharmacologically active substances are available in the market as dietary supplements. Examples are dehydroepiandrosterone (DHEA), and glucosamine, which were not registered as drugs by the regulatory authority. DHEA is not registered as a drug as it is not effective in any illness where a positive outcome can be shown; this however leads to DHEA being imported as a general substance which also means the usual controls on a drug cannot be imposed. The advertisements then mention that it is registered in the US (though not mentioning that it is a food supplement) and make health claims. A part of the problem in this case is the huge and poorly regulated food supplement market in the US whereas the other is inadequate legislation in Sri Lanka on health claims.

It is also becoming increasingly clear that direct-to-consumer advertising encourages the use of newer drugs[27] and better health benefits due to this have yet to be demonstrated. However, it will be certain that this wider use of newer drugs will bring about a much more rapid exposure to drugs whose safety profile has yet to be defined.

Certainly in developed countries, the development of internet is a contributing factor to the increased use of direct-to-consumer advertising. If that be the case, could not the internet be made use of to develop a system of direct-from-consumer reporting of ADRs?

At a time when many consumers are bypassing the traditional medical model it is about time for us to seriously review the traditional approach to ADR reporting. Novel ADRs either due to self medication or interactions of allopathic and complimentary medications may otherwise go unreported.

## 4. Foreseeable Problems on Consumer Reporting

We suggest an independent consumer reporting system. The objective of which will be for hypothesis generation particularly of non-serious ADRs, which affect the consumer's quality of life. The present health professional based system should be fine-tuned for hypothesis generation of ADRs to NCEs and serious ADRs and hypothesis strengthening.

The obstacles in the way of direct reporting would be the huge number of reports that would very likely arise, the quality of such reports, duplication of reports, how effectively they could be integrated into the existing system and if reporting rates would be consistent over time.

### 4.1 Quality of Consumer Reports

Although there is very little information on this, in their study Mitchell et al.[23] found that consumers reported adverse drug events (using the WHO definition) in a reliable and valid manner, but were less skilled than health professionals in attributing causality to the event. But even in the present system in the US, the FDA accepts adverse events reports from consumers and their experience could be utilised in handling these reports. It is also possible that consumer reports may not be easily or effectively integrated into the present system, as the terminology would differ. But education of the patient is not a daunting task. In a feedback survey of the patient's page in *JAMA*,[28] the physician focus groups felt that the reading level of the page was too high for patients. On the other hand, the patient focus groups felt that the page was readable and understandable and did not need simplification. Patients also preferred medical terms to be used but requested them to be followed by definitions in order for them to understand what the physicians discussed with them. Hence, it may not be impossible to educate consumers on ADR terminology.

### 4.2 Quantity

Regarding actual numbers, extrapolating from the experiences of US where such a system already exists, both the health professionals and consumers together contribute approximately 6% (around 16 000) of reports annually.[29] Reports from the industry (90%) and other sources account for the rest. Their current systems are designed to focus primarily on rare unexpected adverse events; nontheless, it represents a significant undertaking and resource commitment even for the FDA. Would this lead to bankruptcy of the already meagerly financed monitoring centres of the developing world or would the scale be adjusted for the consumer/patient reticence all too frequently seen in the developing world and the reports be manageable?

## 5. Conclusion

ADR are manifold and heterogenous and many situations still interfere with their early detection. Consumer reporting ensures that the accumulated data would not only rely on the inquiring mind of a few doctors from certain parts of the globe but also on observations volunteered by a set of people of different levels of competence, cultural backgrounds and ethnicity who think their experiences worthy of reporting.

If we trace back the evolution of pharmacovigilance since 1937, it has been a series of landmark incidents that have led to the introduction of new concepts or rethinking of old concepts within the discipline.[2] Hence, from the evidence provided, would the rethinking of the old concept of a totally health professional-based system to a broader based system involving the consumer, be a valuable landmark in the history of pharmacovigilance for the new millennium? For the developing world already exposed to the globalised pharmaceutical industry, pharmacovigilance is moving into centre

stage and consumers and patients can play an important role in it. It remains to be seen whether healthcare professionals are willing to concede some of their 'sovereignty' and whether consumers and patients are willing to accept that responsibility.

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