CHAPTER: TWO

LITERATURE REVIEW

2.1 ADVERSE DRUG REACTIONS

Significant morbidity and mortality is being found to be associated with adverse drug reactions (ADRs) [49]. There is an increasing trend for reporting adverse drug reactions around the world to drug regulatory authorities. Another important term under pharmacovigilance is an adverse drug event (AE) which has been defined by the WHO as ‘any untoward medical occurrence that may arise during the treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.’ Similarly, another definition given by Edward and Aronson is stated as: ‘An appreciable harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regime or withdrawal of the product’ [14].

2.2 NEED FOR CONSUMER PHARMACOVIGILANCE

Spontaneous reporting has been the main method of recording ADRs since the 1960s [50]. Traditionally, physicians report many ADRs. However, pharmacists and nurses are also involved in ADR reporting in some countries. The aim of spontaneous reporting is detecting new signals for ADRs. A signal is the possible causal relationship between the adverse event and drug, which is not properly and previously recorded and documented incompletely. Signals can be further confirmed by bringing all the experiences from the other countries together for making it strong [51].
Underreporting is a very common and universal problem seen with voluntary reporting of ADRs by HCPs. Consumers can be an important additional source of information. Consumer pharmacovigilance is for the benefit of patients. Consumer reporting enables patients to obtain information on the medicines they use for treating their disease/s provided they are coupled well with their educational levels. Reports from consumers can cover all their personal experiences after using their medicines.

2.3 CONSUMER PHARMACOVIGILANCE

Consumer pharmacovigilance is still a new concept in Nepal. There is no provision for reporting of ADRs by consumers and the lay public in the pharmacovigilance program till date in Nepal. Consumers can directly report ADRs to a pharmacovigilance centre either by filling in a paper form through telephone or online in many developed countries. They can also submit ADRs indirectly through consumer organizations in some developed countries. We can also follow this system for ADR reporting by designing a separate form for consumers. Involving consumers can help to overcome the problem of underreporting of ADRs and reports can be obtained from all age groups of patients.

2.4 HISTORY OF CONSUMER PHARMACOVIGILANCE

The history of consumer pharmacovigilance is recent worldwide. The Australia was the first country to start consumer pharmacovigilance in the 1964 followed by in the USA involving maximum patients. In Sweden, it was started in 1978. In countries like Denmark and Canada consumer pharmacovigilance was started in the year 2003, followed by the Netherlands in 2004 and subsequently in the UK in the year 2005 [52, 53]. Consumers are involved in ADR reporting and can directly report ADRs through different consumer organizations. Consumers use a variety of ways to report ADRs like, telephone and paper based reports. Countries like the Netherlands and the UK have shown positive results from consumer reporting. The Yellow card scheme in the UK has collected many ADR reports by consumers.
Consumer reports were considered as a good source of information in the Netherlands [53].

2.5. BENEFITS OF INCORPORATING CONSUMERS IN ADR REPORTING PROGRAMS

As discussed previously in this chapter, incorporation of consumers in ADR monitoring programs can strengthen the program. Some of the associated benefits are listed below [54].

2.5.1 Contribution to knowledge – Patients can contribute significantly to ADR reports and add to the information provided by healthcare professionals.

2.5.2 Directness – These reports come directly from the persons who are using the medicines and who have experienced the adverse effects and do not have any intermediary in between them and the reports.

2.5.3 More detailed report – As an active reporter, patients can provide more details about the ADRs that have occurred to them using non-technical language. Patients can be considered as a direct reporter because they are the ones to consume medicines after the medicine has been prescribed. Hence, these direct reporters can report in greater detail about possible adverse drug reactions.

2.5.4 Alternate and new source of information – Patients can report new information about ADRs that have occurred to them and these may even be reactions which have not yet been reported. Thus, it could benefit the regulatory authorities and also be an important source of information in clinical practice. Reports by patients accounted for 19% of total reports in Denmark in 2008 [55].

2.5.5 Overcoming the problem of underreporting
Underreporting is a global problem and reports from patients can be a good solution to overcome this problem. Consumer involvement in national pharmacovigilance programs will enable them to report ADRs which can contribute to the generation of signals for any potential threats due to the use of medicines. This will increase the number of ADR reports and reduce the problem of underreporting of ADRs. This will also promote the generation of new signals. A signal is a report on a possible causal relationship between an ADE and a medicine. There should be many reports for generating a signal. Signal generation also requires a review or action and has to be combined with other similar types of experiences from other countries on the same drug. This way, consumers experiences can be brought together to generate a new and unreported type of ADRs.

An example for the increased number of ADR reports is seen in the US where consumer reporting started in the 1950s, and by the end of the year 2008, patients contributed about 227,000 ADR reports [55].

2.6 PATIENTS AS AN IMPORTANT STAKEHOLDER IN THE PHARMACOVIGILANCE FRAMEWORK

Consumers are an important stakeholder in the pharmacovigilance system. They can report ADRs along with other health care professionals like doctors, nurses, pharmacists and other allied professionals.
Figure 2.1 The Pharmacovigilance Framework [56]

2.7 REVIEW OF LITERATURE WITH REGARD TO DIRECT PATIENT REPORTING OF ADVERSE DRUG REACTIONS IN VARIOUS COUNTRIES [55]

2.7.1 The Netherlands

Patients have been an active reporter in the Netherlands since 2003. From April 2004 onwards, the Dutch pharmacovigilance centre LAREB, started accepting reports from patients and consumers in a similar manner to that reported by health care professionals. A three year analysis of the reported ADRs was compared with the reports made by physicians. It was found that the seriousness of the ADRs was not different from the reports made by health care professionals and in fact, patients provided more detailed reports on life threatening and disabling events than the reports provided by the HCPs.
2.7.2 Denmark

In Denmark, the law allows patients and consumers to report ADRs from June 2003. This country was the first EU member state to introduce a direct patient reporting system. Patients can report ADRs by using telephone, post or through the official website of the Danish Medicine Centre.

2.7.3 Italy

Patients can report ADRs using a special form designed by AIFA (Italian Drug Regulatory Agency) and available on their website. This system came into effect from the year 2007. Patients can use this form for providing the details of ADRs and return the completed form to the local health district’s pharmacovigilance centre. Altraconsumo is a consumer organization in Italy which invites ADR reports from consumers for reporting their experiences with medicines. This system showed that consumers’ reports can be an important tool for collecting data about ADRs, and also to determine when medicines are used appropriately.

2.7.4 Sweden

A non-profit organization in Sweden known as KILEN (Consumers Association for Medicines and Health) is working on consumer reporting of ADRs in Sweden. This organization helps in informing and educating common people who have experienced an ADR after using medicines. Consumer reports are considered as a valuable contribution towards pharmacovigilance activities.

2.7.5 Belgium

Test-Achats is a national consumer organization in Belgium which established a direct patient reporting system in association with the Belgian Agency of Medicines (FAGG) in November 2006. The Test-Achats expert team (pharmacists and medical doctors) sends reports to the pharmacovigilance department of the medicines agency. This organization is run by a pharmacist.
who has been trained at FHAMP (Federal Agency for Medicines and Health Products). Consumers can download a report form in French from the website of this organization and these reports are analysed in the same way as reports from professionals. The ADR reporting form is also available in the Flemish language.

2.7.6 United Kingdom
The Medicines and Healthcare products Regulatory Agency (MHRA) started a pilot study on consumer ADR reporting in 2003. Consumers have been allowed to report ADRs to the British Yellow Card scheme. This card scheme is a system for collecting information on ADRs in the UK. This scheme has been developed for monitoring safety of medicines and vaccines. Since January 2005, consumers can submit the report form manually, or use electronic reports. In 2009, about 100 reports were received every month from patients [55].

2.7.7 United States
Med Watch is the US FDA’s Safety Information and Adverse Event Reporting Program, which provides scope for patients to directly report ADRs. Patients were allowed to report ADRs by downloading the form for reporting ADRs, or by telephone. FDA has received about 227,000 ADR reports from consumers in 2008. Assessment of the reports from consumers is done by trained and qualified clinical pharmacists and physicians. ADR reports from consumers are analysed in the same way as those received from healthcare professionals [55].

2.7.8 Australia
Consumer reporting started in early 1964 in Australia. The Australian Incident Monitoring System (AIMS) is monitored and run by the Australian Patient Safety Foundation. A total of 10,000 reports per year are received by the national reporting system, Adverse Drug Reactions Advisory Committee (ADRAC) which includes all appropriately documented patient reports.
Countries like Australia, New Zealand and Canada allowed patient involvement in ADR reporting from the 1960s as shown in figure 1 below. Later in 2000s, many other countries like Brazil, Croatia, Czech Republic, Italy, Morocco, Nigeria, and Switzerland implemented patient ADR reporting system [47].

Fig. 2.2 World map showing the starting date of the direct patient adverse drug reporting in the 50 countries of the study [47]
Fig. 2.3 World map showing the means of adverse drug reaction reporting proposed to patients (online, paper form, others) in the 50 countries of the study [47]
Fig. 2.4 World map showing the number of adverse drug reaction reports per year per million of inhabitants in the 50 countries of the study [47]
Fig. 2.5 World map showing the percentage of patient reports versus those of healthcare professional in the 50 countries of the study [47]
2.9.1 LITERATURE ABOUT CONSUMER PHARMACOVIGILANCE

A systematic review published in 2007 by Blenkinsopp et al. examined adverse drug reaction reporting by patients and consumers. The review describes the different advantages of consumer reporting in different countries of the world [57]. There have been very few published studies with reference to consumer reporting of ADRs. A study done by Medawar and Herxheimer, in 2002 examined the quality of the reports made by patients. They concluded that the reports were quite comparable to those made by healthcare professionals. Another study conducted by the Sri Lankan authors Fernandopulle and Weerasuriya in 2003 has confirmed underreporting of ADRs as a limitation for the existing system of pharmacovigilance in developing countries and consumer reporting would strengthen the existing system of ADR reporting [58]. Van Grootheest et al. in 2004 studied the role of consumers in ADR reporting and stressed the importance of patient’s role towards consumer pharmacovigilance [59].

2.9.2 LITERATURE REGARDING PERCEPTION OF PATIENTS AND CONSUMERS TOWARDS ADVERSE DRUG REACTIONS

A study done among consumers by Hughes et al. in 2002 in Italy has described that the patients were counselled properly about medicines before taking them. Authors also assured that the patients were well informed about proper use of over the counter medicines before the purchase [60].

Similarly, Saul et al. in 2004 conducted a study among hospitalized patients and found many adverse events in reports from consumers or patients which were not identified by medical personnel [61]. Another study done in Thailand claims the increased interest of consumers towards adverse drug reactions and identification of the medicine use errors may ensure better safety of patients [62]. A study from Sri Lanka has emphasized the patient’s awareness about the medicines Authors have highlighted that patients show an improved compliance for drugs used in treating their diseases, if they are well informed [63]. It was found that that even in the patients with a good level of education, there was low awareness about the negative and harmful reactions caused due
to the drugs. Lack of information and knowledge can affect the usage of medicines and may increase the incidences of ADRs [64]. A study done by Researchers have stated the importance of adequate information for the management of negative effects caused due to the drugs and their long term use [65]. The literature survey has thus shown that there is a need for healthcare professionals to understand and respect patients’ choices for achieving maximal safe and rational patient care. Nepal should also support consumer pharmacovigilance as there is high prevalence of self-medication and many events caused due to ADRs would have gone unnoticed.

2.9.3 HEALTHCARE PROFESSIONALS PERCEPTIONS ABOUT ADR AND ADR REPORTING

There is a paucity of literature from developing countries in this area. In the context of Nepal, there are very few studies which have been carried out. Literature highlights healthcare professionals have poor knowledge about reporting ADRs. A study done by Subish et. al., in 2008 found that many healthcare professionals like medical doctors, nurses, pharmacists and others related to healthcare service delivery lacked awareness about pharmacovigilance [66]. Similarly, another study done by Santosh et.al., in 2013 revealed that healthcare professionals have poor understanding of the ADR reporting process [35]. Likewise, a study done by Alshakka et.al, in 2013 studied the perception of healthcare professionals in Malaysia. The authors found lack of adequate knowledge and awareness about pharmacovigilance and consumer pharmacovigilance in Malaysia [67]. Consumer pharmacovigilance is a new concept in a developing country like Nepal. A study evaluating the need for consumer pharmacovigilance in Nepal mentioned the concept is very new and challenging. However there are a number of benefits of consumer pharmacovigilance which have been mentioned by Nisha et. al., in 2014 and Alshakka [13, 48].

This situation is not true in the case of developed countries like the UK. Green et. al., in 2001 studied attitudes of UK hospital pharmacists and their understanding of ADR reporting. The study found hospital pharmacists do
have knowledge about ADRs and ADR reporting and were in favour of the Yellow Card spontaneous ADR reporting scheme. The same study also highlights the importance of educational intervention and trainings for pharmacists to encourage ADR reporting by them [68]. Another study done by Backstrom et al. in 2000 from Sweden revealed that the clinicians had good knowledge about the spontaneous ADR reporting process [69].

2.9.4 AWARENESS OF COMMUNITY PHARMACISTS ABOUT CONSUMER PHARMACOVIGILANCE

The researchers Toklu and Uysal in 2008 from Istanbul examined the knowledge and awareness of community pharmacists about pharmacovigilance. The results showed that pharmacists had little knowledge about pharmacovigilance [70].

Looking into the literature from Nepal, Subish et al in 2007 found that pharmacists along with other healthcare professionals lack the proper knowledge about spontaneous reporting of ADRs. [66] Similarly, another study done by Bhuwan et. al in 2013 has also emphasized that there is a lack of awareness among pharmacists about pharmacovigilance, and also highlighted the roles and responsibilities of pharmacists towards drug safety in community settings [42]. Similar findings were noted in a study done by Santosh et al. in 2013 among Nepali healthcare professionals [35].

A study done by Vessel et al. in 2008 described knowledge, attitude and practice of Iranian pharmacists. Again a poor level of knowledge for ADR reporting was seen and there was less awareness regarding the reasons for and benefits of the ADR reporting system [63]. A study done by Aziz et al. in 2007 in Malaysia found underreporting of ADRs. This study highlighted that though maximum number of doctors came across ADRs, all of them did not report ADRs and 40% of the study participants did not even know about the existence of an ADR reporting mechanism at the national level [71].
2.9.5 STRATEGIES FOR IMPROVING REPORTING OF ADRs

ADR reporting should be done on a regular basis by all healthcare professionals. This issue should be handled seriously by the regulatory authorities. Various studies have shown that strategies like educational interventions are helpful in improving ADR reporting rates. For regular reporting of ADRs, adequate information should be shared among the reporters. Till now, only healthcare professionals are involved in the ADR reporting process in a voluntary capacity. A study done in India by Radhakrishnan R et. al in 2011 showed improvement in ADR reporting by healthcare professionals. In this interventional study, healthcare professionals involved were clinicians, pharmacists and nurses. This study also highlighted the importance of educational intervention in developing the culture of ADR reporting among healthcare professionals [72]. The study done by Molokhia et. al., in 2009 has described the importance of educational intervention for preventing ADRs in many countries. This study has also suggested that the educational intervention proved to be effective but has not measured the retention of the information shared during the educational intervention to the healthcare professionals [73]. Another study done by Tabali et.al., in 2009 has shown the possible benefits for physicians after conducting an educational intervention for reporting of ADRs [74]. The retention effects were not sustained in this study. In the Nepalese context, a study done by Jha et. al., in 2014 has revealed that an educational intervention was effective in improving knowledge, and attitude scores for adverse reactions and pharmacovigilance among healthcare professionals [34]. Another study done by Santosh KC et. al., in 2013 and Subish et. al., in 2011 evaluated the awareness of and attitude towards ADR reporting of healthcare professionals, but no intervention was carried out [35, 75]. To the best of our knowledge, the study done by Jha et.al., in 2014 is the first study done to measure the effectiveness of an educational intervention among healthcare professionals with regard to ADRs and pharmacovigilance in Nepal.

Pharmacists are an important part of the healthcare team. They have multiple responsibilities like monitoring drug safety, advocating rational use of medicines, educating other members of the healthcare team to reduce the risk
of ADRs and providing pharmaceutical care to patients. Similarly, nurses are an integral part of the healthcare team. They are the most important member of the team to take care of their patient’s illness. A study done by Subish et. al, in 2011 suggested that nurses were also having poor KAP similar to the other healthcare professionals and a need for educational and managerial intervention was noted regarding the importance of ADR reporting [75].

Educational intervention as a strategy to educate pharmacists and nurses would be a noble initiative towards pharmacovigilance and ADR reporting process. A study done by Riberio, Vaz et.al., in 2009 in Portugal showed that educational intervention was effective in increasing ADR reporting among the Portuguese pharmacists [76].

Having examined the global scenario of pharmacovigilance and consumer pharmacovigilance, now the study will be focused on the Nepalese context. An article about the need for involving consumers in Nepal’s pharmacovigilance system explores the possible benefits and challenges for ADR reporting. There is no advocacy for pharmacovigilance and consumer pharmacovigilance in documents or policies of Nepal’s health institutes, organizations for doctors, nor in any public health programs. Pharmacovigilance has been recently incorporated in the national medicine policy. The article highlights the importance of involving consumers in the existing pharmacovigilance program. One of the important reasons for emphasizing consumer pharmacovigilance in Nepal is the difference in Nepali people’s genetics, way of using medicines, and use of complementary and traditional medicines. Consumers should be involved in the ADR reporting process as self-medication is a very common problem in Nepal. There is an important role for community pharmacists also as most of the time, they are the first point of contact for patients for obtaining medicines and information related to medicines. A study done by Bhuwan et. al., in Nepal in 2013 identified less awareness about ADRs and reporting of ADRs in the community setting [42].

More studies have to be conducted in the community setting for understanding this scenario in Nepal. Studies have identified various reasons for underreporting in Nepal [42, 75]. Involving consumers and patients in the

*Initiating Consumers Pharmacovigilance in Lalitpur District*
existing program will be a welcome approach towards strengthening pharmacovigilance in Nepal.

2.9.6 A CONCEPTUAL FRAMEWORK
Consumers can be an important source of information for adverse drug reactions of common drugs available without a prescription also known as over the counter medicines. The Nepalese population uses a variety of traditional medicines. The incidence of self-medication is very common in the Nepalese context. Consumers can be a primary source of information for negative and adverse reactions caused due to the use of certain drugs. They can give detailed report about bad or unpleasant experiences with the use of medicine.

2.9.7 CONCEPTUAL FRAMEWORK
Knowledge, attitude and practice are very important for using medicines properly. Two third of the terrain in Nepal is mountainous or hilly. Due to the country’s uneven geography, people find difficulty in accessing healthcare facilities in Nepal. This can be understood with reference to the figure 3 for healthcare delivery in Nepal. People’s knowledge about medicines is very important for proper use of medicines. The overall literacy rate of Nepal is 67%. Most people are aware about the adverse reactions caused by drugs but not very specifically. Also, they think that the English medicines are not very safe as compared to herbal and traditional medicines. Demographics of the people also plays a role in people’s knowledge about medicines. Consumers from remote areas of the country will have less idea about ADRs. Consumers from rural areas differ from those in urban areas in many ways. Differences may be observed in level of education, and facilities for healthcare delivery.

The main objective of this research is to evaluate knowledge, attitude and practice about ADR and ADR reporting. The definitions for these terms are given below:

**Knowledge:** It was defined as “the act or state of knowing; clear perception of fact, truth, or duty; certain apprehension; familiar cognizance; cognition. Knowledge, which is the highest degree of the speculative faculties, consists in the perception of the truth of affirmative or negative propositions” [77].

**Attitude:** It was defined as “an enduring, learned predisposition to behave in a consistent way toward a given class of objects, or a persistent mental and/or neural state of readiness to react to a certain class of objects, not as they are but as they are conceived to be” [77].

**Practice:** It was defined as “frequently repeated or customary action; habitual performance; a succession of acts of a similar kind; usage; habit; custom; as,
the practice of rising early; the practice of making regular entries of accounts; 
the practice of daily exercise” [77].

Positive attitude towards medicine use can be beneficial and advantageous 
whereas a negative attitude will focus more on the bad aspects associated with 
drug use. There are many people who still believe in traditional healers in 
Nepal known as ‘Dhamis’ and ‘Jhankris’. These people are actively involved 
in providing advice regarding use of medicines and treating diseases in remote 
areas. Practice of medicines can be influenced by a person’s previous existing 
belief and level of knowledge about medicines. Practice can be transferred 
from one individual to another and therefore to the entire community. 
Therefore, the overall KAP about medicines can be influenced to a significant 
extent by various strategies and interventions. The present research aims to 
measure the KAP about ADRs and consumers pharmacovigilance among three 
different groups of the general population in Imadol VDC of Lalitpur district 
of Nepal. The first group of population is healthcare professionals. Healthcare 
professionals in Nepal mean doctors, dentists, pharmacists, nurses, health 
assistants. The second population is that of community pharmacists and the 
third population is of consumers of medicines.

The term “Consumer reporting of ADRs” is used to refer to reporting of 
adverse drug reactions (ADRs) by the general public. Some countries use the 
term “patient reporting”, but consumer reporting is a broader term, as not all 
consumers of medicines are patients.

A patient can be a person obtaining any type of medical attention or treatment 
for any medical condition from a medical doctor or any other healthcare 
professionals. Similarly, a consumer can be any patient who buys a medicine 
with a valid prescription along with the physician’s advice, or any person who 
goes to buy an over the counter medicine without any advice from healthcare 
professionals [51].

ADR reports from consumers can be considered as a report of a suspected 
ADR towards any use of medicine, which was initiated by a consumer without
obtaining any help from healthcare professionals. The reports from consumers can be assessed using various methods, for example, carrying out the causality scaling of ADRs. Here, the Naranjo’s causality scale can be used for assessing the causal relationship of the reported ADR. Predictability and preventability scales can also be used for assessing ADR reports by consumers.

Consumers should live a quality life after using medicines for their disease. In Nepal, there is no provision of health insurance for patients who are using medicines. They have to pay out of their pocket for any treatment options. Hence, there should be some system for sharing their adverse reactions experiences for saving others from the possible sufferings. Consumers are more likely to report ADRs if they have paid for the treatment. Establishing the system for consumers to report ADRs will definitely help people to be in a safer side for any mishaps with the use of medicines. Starting consumer pharmacovigilance would be beneficial for consumers and patients to improve the quality of life for regular users of medicine.