Current scenario and future prospects of adverse drug reactions (ADRs) monitoring and reporting mechanisms in the rural areas of the India

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Abstract

Pharmacovigilance (PV) deals with the detection, collection, assessment, understanding and prevention of adverse effects associated with the drugs. The objective of PV is to ensure safety of the medicines and patients by monitoring and reporting of all adverse drug reactions (ADRs) associated with prescribed medicine usage. Findings have indicated that about 0.2-24% of hospitalization cases are due to ADRs out of which 3.7% of patients have lethal ADRs. The reasons includes number of prescribing drugs, increased new drugs in the market, and inadequate PV system for ADRs monitoring, lack of awareness and knowledge about ADRs reporting. Serious ADRs leads to enhanced hospital stay, increased treatment cost, risk of death, and many medical and economic consequences. Therefore, ADR reporting at its first instance is important to avoid further harmful effects of the prescribed drugs. In India, the rate of ADR reporting is less than 1% whereas worldwide it is 5% due to lack of awareness about PV and ADR monitoring among healthcare providers and patients. Spontaneous reporting is the most commonly used PV method to report ADRs in both urban and rural areas of India. Evidences revealed that there is not any effective ADR reporting mechanisms developed in rural areas causing underreporting of ADR thus increasing threat to the rural population. Hence, PV and ADR reporting awareness among healthcare professionals and patients, telecommunication, telemedicine, use of social media and electronic medical records, and artificial intelligence are the potential approaches for prevention, monitoring and reporting of ADR in rural areas.

Keywords: Adverse Drug Reactions (ADRs); Drug Safety; Pharmacovigilance; Pharmacovigilance Methods; Rural Areas.

Key Points:

- It described about historical development of PV system in India.
- It demonstrated the comparison of ADR reporting mechanisms employed in urban and rural areas.
- It discussed various possible approaches to improve the ADR reporting especially in rural areas of India.

1. Introduction

According to WHO, pharmacovigilance (also known as drug safety) is a science which involves in the activities pertaining to detection, assessment, understanding, reporting and prevention of adverse reactions and any other problems associated with the drugs [2]. It is scattered over all therapeutic areas like general medicine, respiratory, oncology etc. It becomes an integral part of pharmaceutical industries and is ultimately associated with patient safety. Drug safety is important criteria to assess today, therefore pharmacovigilance programmes are must to prevent the ADRs in the present scenario. This is because various adverse effects of the drug have come into light even after the drug has passed phase 4 of clinical trials. It is necessary for a physician to understand all the adverse effects associated with medicine very well to assess the benefit-risk (B-R) balance of the drug when prescribing medicine to their patients [4]. Nowadays, medicines usages have become so common because of increase in various diseases due to change in lifestyles, cimate change, pollution etc. this had led to the increase in the adverse drug reactions (ADRs) associated with these medicines too. ADRs may be defined as ‘noxious and unintended or unwanted responses produced by medicine at doses normally used in individuals. Adverse drug events (ADEs) can be defined as ‘any unanticipated medical incident that may arise during treatment with a medicine, but which is not necessarily having a causal relationship with the treatment. The basic point here is that the event does not have the causal relationship with drugs or the treatment [5].

Studies showed that there was 0.2-24% of hospital admissions due to the ADRs out of which 3.7% of patients have lethal ADRs [6]. ADRs give rise to the prolongation of hospital stay; enhance the cost of treatment, risk of death, several medical and economic issues. Therefore, it becomes very necessary to report ADRs for the safety of the patient at its first instance [7]. Due to increase in drug safety concern and withdrawal of the high-profile drugs from the market, most of the major pharmaceutical companies are adapting the post-marketing surveillance to identify the risk associated with the medicinal product throughout its life cycle. Both, the pharmaceutical companies, and regulatory agencies are becoming more concerned for early signal detection from both the clinical trial and post-marketing surveillance, and managing the risk associated with the drugs by applying risk management plans [8].

In 1968, WHO started an International Programme for Drug Monitoring in coordination with Uppsala Monitoring Center, Sweden, with oversight by an International Board [9]. Currently, the pharmacovigilance (PV) programme has been adopted by 86 participating countries. In India, pharmacovigilance is still not very much developed compared to the Western countries counterpart. India needs to develop more understanding of pharmacovigilance, its importance and implementation as number of clinical trials and research activities are

increasing significantly in India. In India, the rate of ADR reporting is less than 1% whereas worldwide it is 5%, and the reason is lack of awareness about pharmacovigilance and ADR monitoring among healthcare service providers [10]. Therefore, it is utmost important to develop a proper and effective mechanism of ADRs reporting both in urban and rural areas of India. Various sources of information revealed that there are not any proper and effective ADRs reporting channels or mechanisms developed in rural areas which is posing threat to the health of rural population [3].

There are plenty of reasons for the continuous increase in ADRs including the number of prescribing drugs, increased new medicines in the market, inadequacy of the formal system for ADRs monitoring, lack of knowledge and awareness about ADRs monitoring and reporting. Unfortunately, principles and practices of pharmacovigilance are more often discussed in academic rather than applied sense. The physicians who are directly dealing with the patients or prescribing drugs are less indulged in ADRs monitoring. However, the pharmacists or pharmacologists who are not directly involved in patient care, more often involved in pharmacovigilance practices [11]. In this review, we have been discussing the basic mechanism of the ADRs reporting in the urban and rural areas, comparison of pharmacovigilance practices between urban and rural areas, present scenario and future prospects of pharmacovigilance, and the new strategies which can be adopted to improve the ADR monitoring and reporting mechanisms especially in rural areas of India.

2. Aims and objectives of pharmacovigilance

In broad sense, safety of the prescribed medicines and patients are the main aim and objective of the healthcare system at all levels of the society/community. However, it is not always true especially in rural areas of developing countries like India. The specific aims of the pharmacovigilance system of any country are [9]:

- To improve patient care and safety in terms of treatment and medicines usage.
- To help in the assessment of risk-benefit ratio thus effectiveness of medicines.
- To encourage the rational, safe, and effective use of medicines.
- To promote PV by providing education and training of PV and its effective dissemination among common people.

3. Historical development of pharmacovigilance system

Pharmacovigilance system in India is at its nascent stage and growing slowly for improving of drug safety. The history of ADR occurrence and its reporting to the regulatorybodies started since 1888 and till now, there are developments have been taken place in India (Table 1).

4. Current scenario of PV in India

India is a very big country and there are many drug brands with more than 6000 licensed drug manufacturers and over 60,000 branded formulations [3]. India ranks fourth in the production of pharmaceuticals in the world as well as a hub for clinical trials. Many newer drugs are introduced in the country, so it becomes very important to strengthen the pharmacovigilance system to protect the Indian patients from possible adverse effects caused by some new drugs [3]. Earlier, Indian regulatory agencies and drug manufacturing companies safety assessments were based on the results obtained from long-term drug use in the Western markets and there was no need felt by the government to establish a well built pharmacovigilance system of its own.

In current years, the time period between when a drug is marketed and its availability in India has decreased greatly and consequently the important long-term safety data is not available. Additionally, Indian drug manufacturing industries have improved their ability to launch and develop new drugs through their own research efforts and increased importance of pharmacovigilance to detect adverse drug events [3]. There is a need of effective strategic plan and focused vision for developing PV systems, in addition the funding, mainly in the Drug Controller General of India (DCGI) office, is lacking. In the past years pharmacovigilance Programme was not implemented in pharmaceutical companies of India, as well as multinational companies (MNC), the renowned people in this area are few who can advise the DCGI on this matter. PV is a very complex system with regulations and guidelines. Hence, there is a need for a completely independent adviser who has considerable and practical knowledge on PV.

Till now, data collected in the zonal centers from peripheral centers is not sufficient and not well examined. There is a lack of research on ADRs in India therefore the specific incidence adverse drug reactions are not known. The reporting forms used by people involved in various pharmacovigilance practices are different from the reporting forms used by the National Pharmacovigilance Program hence it becomes difficult to transfer data to the national database. There is a lack of motivation, importance and understanding of pharmacovigilance systems by healthcare professionals (HCPs) both in rural areas and urban cities and hospitals. No efforts are made by the department of health to provide training and to create awareness for better ADR reporting [3].

In India, several self-help groups are there who encourage the patients for ADRs reporting as and when occurred to them. However, there is no information for patients on ADRs reporting mechanisms directly to the regulatory authorities. Clinical research activities including clinical trials are increasing in India, therefore it is a great need to understand the importance of PV and how it can affect the life cycle of the product. The DCGI should act quickly to improve pharmacovigilance and to integrate Good Pharmacovigilance Practice into the regulatory procedures to improve the regulatory compliance and ensure the safety of clinical trials and post marketing surveillance [3].

5. ADRs reporting methods

Currently, there are mainly two methods through which ADRs are collected and processed further after due scrutiny of a particular ADR. These are passive and active surveillance methods. The brief descriptions about these methods with subcategories are discussed below:

5.1 Passive surveillance

5.1.1 Spontaneous reporting

Spontaneous reporting method is a voluntary reporting of suspected ADRs by the healthcare professionals or an individual to the ADR monitoring centre, company, regulatory authority or other organization. It plays a significant role in the identification of safety signals after the launch of medicines in the market. Various methods are used to detect signals in spontaneous reporting including proportional reporting ratio, Bayesian and data mining techniques. It is also helpful in detection of rare adverse events which was not noticed earlier during clinical trials. Moreover, it also gathers information on risk factors, vulnerable groups, and clinical manifestations of known serious ADRs. More information about patient safety problems can be collected in the early phase at minimum cost but disadvantages such as poor and under reporting, difficulty in ADRs rate and frequency estimation are also associated with it. Therefore, there is a need to develop other methods for better monitoring of medicine safety, to identify and characterize ADRs associated with particular medicines in a specific group of populations [40].

5.1.2 Cohort Event Monitoring (CEM)

It is complementing to the spontaneous reporting method which is known as prospective, observational, cohort study of ADEs associated with single medicine or group of medicines. This method observes ADEs at the early post-marketing phase of new drugs as well as old medicines during routine clinical practices. It applies the principles of the New Zealand Intensive Medicines Monitoring Programme and the UK Prescription Event

Monitoring except few countries. It is an interview-based method where patients are interviewed before and after the treatment procedure thus providing early warning signs of the medicines used in the clinical setting. It collects information regarding medicines such as medication errors, spurious medicines, problems due to poor storage conditions as well as drug-drug interactions. Steps followed in CEM includes establishment of patients cohort with medicine of interest, collection of ADRs by interviewing the patients and lastly, recording of the details of the patients, medicines and ADRs are reported based on questionnaires prepared [41].

5.1.3 Targeted Spontaneous Reporting (TSR)

The targeted spontaneous reporting methodology proposed by WHO in 2010 that builds on the principles of spontaneous reporting system [42]. Health professionals manage a well-defined group of patients in this methodology system. TSR may be born either to report all types of suspected reactions in the population or to focus only on one specific reaction of a particular target. The WHO also aimed to introduce TSR in the treatment of TB programmes. It is feasible and sustainable with limited financial and human resources, and helpful in promoting PV to improve the safety. It targeted those adverse events which are responsible for poor adherence toward treatment, for example nausea, thus increasing ADRs reporting rate. The main aim of TSR is increase reporting rate by targeting, training and mentoring the ADRs reporters especially nurses, pharmacists, and patients as well. TSR is also playing a vital role in linking public health programmes with PV to promote ADRs reporting. Monitoring for suspected drug-related problems during normal investigation, record of suspected ADRs in patients history, and involvement of healthcare professionals in ADRs monitoring are the steps required to achieve the objectives of TSR [42].

5.1.4 Stimulated reporting

The aim of a stimulated reporting system is to inspire and accelerate the healthcare professionals to report ADRs in specific circumstances. It encourages on-line reporting of and methodical motivation of ADRs reporting according to the pre-designed method. It is helpful in generating and preparing spontaneous reports of adverse drug events identified at an early stage of post-marketing phase. Thus, it is considered as a procedure of spontaneous reporting to enhance the reporting rate however it is unable to provide precise information about ADRs incidence rate [43].

5.1.5 Case series

It is a theoretical methodology which provides a relationship between a medicine and an adverse drug related event. It is profoundly valuable in developing theories without providing strong evidence about post-marketing medicine exposure and its result [40].

5.2 Active surveillance method

It is a more achievable method in comparison to passive surveillance because in this surveillance a wide range of data is generated on the basis of discrete adverse event manner. Active surveillance methods may be classified as sentinel sites, drug event monitoring, registries, case control study, cohort study and targeted clinical investigations. It uses pre-organized process and follows up a patient thereby complete list of adverse events are extracted. It is more feasible to get comprehensive and exclusive data on individual AE reports.

5.2.1 Sentinel sites

In this active surveillance method an observation is done to get data of ADR from medical records patients and practitioners. This method gives specific data from specific groups and subgroups of patient, drug abuse etc. which is in passive surveillance a little bit difficult. It is carried out at institutions, nursing homes and hospitals etc. for patients who are taking orphan drugs. This method is useful for observation of adverse drug events [3, 40].

5.2.2 Drug Event Monitoring

It is the procedure of active surveillance where electronic prescription data or health insurance claims are used to identify the patients. Further, demographic information of the patients, treatment details such as indication for treatment, duration of treatment, dosage, clinical manifestations, and reasons of discontinuation, if any, are collected through questionnaires sent to both physicians and patients at specified intervals [40].

5.2.3 Registries

It is a comprehensive list of patients exhibiting with the same characteristics. For example; disease registries, drug registries, pregnancy registries etc. and have differences among them depending on patients type [40].

5.2.4 Cohort study

In cohort study, patients are monitored over the time to record the occurrence of the disease or event in a population who are at risk for the disease or event. Information on exposure status of medicine is accessible during the follow-up for each patient and each time span. At the same time the population exposure of medicine during follow-up is acknowledged and incidence rates can be calculated. A cohort of interest (special population) is selected on the basis of concerning medicine exposure and monitored over time, in many cohort studies. These studies are useful when it is required to know the prevalence rates of adverse events with relative risks and many ADRs can also be examined utilizing the same data source under the study [40].

5.2.5 Case control study

This identifies disease cases where controls or patients without the disease or event of interest are selected from the source population. Exposure status of the two groups is compared using the odds ratio which calculates the risk of disease. This study is useful when a comprehensive relationship is present between drug and adverse drug events or risk factors [40].

6. ADRs reporting mechanisms in urban areas

In India, the monitoring of adverse drug reactions was introduced in 1982 [11]. With the aim to start a monitoring program in the whole country, the Drug Controller of India has established 5 centers. It contains three phases of ADRs monitoring: (i) at institutional level (ii) in CGHS, and (iii) in general practitioners. In 1987, Indian Council of Medical Research (ICMR) conducted a multi-institutional level pilot study with 58194 cases [11]. Its nodal centre (National Pharmacovigilance Centre) is located at the Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India. It is affiliated with WHO collaborating centre for ADR monitoring, Uppsala, Sweden. The other special centers located at different institutes of the country are PGI (Chandigarh), JIPMER (Pondicherry), KGMU (Lucknow) and Seth GS medical College (Mumbai) [11].

It was thought to be the collaborative activity of both clinicians and pharmacologists but it was done by pharmacologists with or without the involvement of clinicians in India. However, the physicians play an important role in the entire monitoring process because they help in patient data accessibility and subsequent suspected ADRs reports analysis. In many other countries, this work is performed by pharmacists or nurses. Clinicians and pharmacologists are involved in the reviewing, explanation of the collected data or hypothesis testing on the basis of reports. In India, half of the reported ADRs are associated with the use of non-narcotic analgesics and antibiotics and these ADRs varies from country to country [11].

Spontaneous reporting is the most widely preferred ADR reporting form by HCPs where healthcare professionals or patients are able to link an adverse reaction to the use of a particular drug thus reporting to an adverse drug reaction (ADR) monitoring centre (AMU). Further, Individual case safety reports (ICSRs) are sent to the International Drug Monitoring Centre, (Uppsala Monitoring Centre) for processing, identification and assessment of new signals for ADRs associated with the use of a particular drug [44].

Currently, India has been planning to estimate the pharmacoeconomic data of ADRs; such as hospital admission, prolonged hospital stay, total cost incurred in ADR management by hospitals and government, ADRs

related morbidity and mortality rate. Later, systematic analysis is done to obtain data and circulate to the health agencies, regulatory authorities, pharmaceutical companies, and healthcare professionals including physicians, pharmacists, nurses, dentists and paramedical staff. Ministry of Health and Family Welfare, Government of India initiated a pharmacovigilance program of India (PvPI) for ensuring drug safety in all states of the country under Central Drug Standard Control Organisation (CDSCO), New Delhi. The Government of India also maintains an international pharmacovigilance regulatory authority and reviews periodic safety unit reports (PSUR) of pharmaceutical analysis [45].

The PvPI programme is coordinated by the Indian Pharmacopoeia Commission (IPC) situated in Ghaziabad. IPC also involves in publishing official policy documents, ensuring safety and efficacy of medicines by modifying the existing monographs of the Indian Pharmacopoeia. Clinical Pharmacists are involved in the patients care and performs activities such as drug interaction monitoring, adverse drug monitoring and reporting, prescription analysis/auditing and patient counseling for better therapeutic outcome thus to ensure safety of the patients. Healthcare professionals or patients can directly report ADRs to the regional monitoring centre which later collected by IPC [45]. NCC-PvPI collaborates with WHO-UMC to participate in the drug international monitoring programme. Software such as Vigiflow, Vigibase, Vigimine, Vigimed, Vigisearch, Vigilyze are provided by WHO-UMC to achieve the objective of PvPI in a more efficient way. India became the first country to report over 1 lakh ICSR to Vigiflow. Today, India is the seventh largest contributor to the UMC international drug safety database (Vigibase). PvPI conducted a comparative study related to the risk of serious ADRs to the patient associated with the use of medicines and has taken several steps to improve the safety of medication [45]. Healthcare professionals (physicians, dentists, nurses, pharmacists) working in this field to deliver the safe health care to the patients by reporting the suspected ADRs through the letter, phone call, fax, e-mail, or the personal contact to any of the five ADR monitoring centers located in the country [11] (Fig. 1).

Knowledge, attitude and practice (KAP) are the key points to evaluate safety and ADR of existing and new drugs in the whole world including India. Pharmacists, doctors and ADR monitoring workers are the backbone supporters to maintain the Pharmacovigilance data and provide a good safety practice regarding the ADR. Many private and government sectors are working to provide a good practice for reporting ADR to prevent fatal cases. In this connection, a questionnaire based study was conducted in urban Odisha to check out the KAP among doctors. There were about 124 doctors included in this study from Cuttack and Bhubaneswar, out of which only 54 were given positive responses towards this study. For this study 12 and 9 questions were designated to evaluate ADR

reporting knowledge regarding PVPI and conducted from May 2013 to August 2013 (4 months). Among these 33 doctors were dependent on past knowledge whereas 21 followed the relevant literature. The findings from this study demonstrated that there is very little knowledge about ADR reporting such as to whom, how and where to report the ADRs [46].

Another ADR monitoring study was conducted in Tertiary Care Teaching Hospital, Nagpur, Maharashtra, to know KAP level, to reduce underreporting and to enhance the knowledge towards ADR reporting. This study was based on 84 questionnaires, from which only 93.33% responded. Among these study a ratio was generated regarding to the ADR reporting, this says that, 64.28% subjects were aware to the Pharmacovigilance, 52.38% of subjects were aware to the ADR reporting mechanism, 83.33% subjects were suggested that only serious ADR should be reported, 35.72% subjects opined that ADR should be reported only for new marketed drugs. Among all of these 67.85% subjects observed the ADR and only 25% were reported. Only 44.04 % subjects were well aware regarding the whole process of the ADR reporting mechanism. This study was also concluded to increase the awareness of reporting ADR [47].

Moreover, a KAP study was conducted from July to August 2014 at tertiary care hospital, (SSG Hospital) combined with Govt. Medical College, Vadodara, Gujarat, India. This study was based on 22 questionnaires in respect to KAP aspects and conducted on postgraduates belonging to different clinical departments. For this study 101 sample sizes (students from 1st, 2nd and 3rd year students) were taken, out of 101, male and female were 76 and 25 respectively. This study concluded that from 1st, 2nd and 3rd year students only average 28.33%, 34.17% and 35.38% students had right knowledge about Pharmacovigilance and ADR reporting, out of them only 25.74% students heard about “Yellow Card” and ADR reporting mechanism, and only 14.85% students were well known about whole process of ADR reporting system [48].

7. ADRs reporting mechanisms in rural areas

Establishing a pharmacovigilance centre in urban areas is successful to some extent whereas there is still much difficulty to establish PV programmes in rural areas. There are some countries which are trying to improve the patient safety through ADRs monitoring in rural areas also. Countries such as South Africa have studied the effect of training and monitoring of health care workers, visits for supervision and the availability of telecommunication and transport facilities in implementing pharmacovigilance program in rural district of Mozambique [49].

A study was done in the Ghanian region of Africa to investigate the under- reporting of ADRs. Africa took a step of reporting by the patient itself to avoid chronic under reporting. However, there is very little knowledge about ADRs among people as well as how to identify and report these ADRs. The steps taken to improve reporting mainly focused on Health Care Workers (HCWs) and rarely on patients. The survey was done by randomly selecting the patients; they found that less educated people (as mostly found in rural areas) fail in recognizing the ADRs. Most of them were in a view whether they could report an ADR to an HCW or not. Further, most of them were unwilling to report directly to the Ghana FDA patient reporting system. This was probably due to their incomplete knowledge about ADRs, and its necessity to report. Additionally, they were unsure about the mechanisms of ADR reporting [50].

India is also not well versed in establishing pharmacovigilance systems, especially when it comes to rural areas; the lack of knowledge makes the reporting system of little importance. A questionnaire-based study was conducted at Gangtok and Sikkim based ADR Monitoring Centre (AMC) [51, 52]. Knowledge, perception, attitude and awareness of healthcare professionals are indicators of ADRs reporting practices. The questionnaire based study aimed at evaluating these indicators in the hospital attached to a medical institute, and also to find out measures to improve existing ADRs reporting practices. The result indicates that ADRs reporting was necessary, discouragement from ADR reporting due to difficulty in causality assessment of an ADR, unawareness about the affiliation of an AMC to the hospital. Hence, the study showed that respondents have an average knowledge and positive attitude towards ADRs reporting. More efforts are required to increase awareness and attitude towards pharmacovigilance. We can conclude from this study that it is the knowledge which is lacking. Adequate education about ADRs and their effects are crucial among patients as well as HCWs [51, 52].

Since 2004, voluntary web based adverse event reporting has been initiated with a special target on small rural and critical access hospitals (CAHs). Adverse Drug Events rates in the passive surveillance system were substantially lower, that were reported in research findings. Major problem of passive surveillance is under-reporting. It was believed that systematic feedback would improve reporting rates. A web based medical error reporting system (Occurrence Report Management System) was provided free of cost to the hospitals. The hospitals selected were from states acute care hospitals in rural areas and some critical access hospitals (CAHs), this system achieved sustained reporting at consistent rates from most participating facilities [53].

Pharmacovigilance development is questionable now in many areas of India probably because of lack of knowledge and awareness. Due to this there are many surveys done to assess the impact of education in enhancing

pharmacovigilance knowledge, attitude, and practice (KAP) among rural doctors. A suitable KAP survey questionnaire was designed, validated and used to conduct face to face interviews of randomly selected doctors in rural areas of Thane and Raigad districts of Maharashtra, India [54]. About 8 to 10 weeks of pharmacovigilance education programme was set up for all the participants in the survey, pre KAP survey and post KAP survey after the educational programme showed differences in their knowledge. This study demonstrated that providing proper education and training improved the awareness of pharmacovigilance practices among rural doctors of those districts. Hence, we can conclude from this study that creating education and awareness is utmost important to implement pharmacovigilance programmes effectively in rural areas to report ADRs [54].

An observational cross sectional study based on ADR reporting was done in Pravara rural hospital, Loni in 2018 [55]. All the suspected ADRs reported during that year were recorded for the following criterion; Age, Sex, department from which ADR was found, the drugs suspected, severity of ADR and causality assessment of the ADR. The causality assessment was done using WHO-Uppsala Monitoring Center causality scale with the departmental causality assessment committee. It was found that all the ADRs were reported by doctors and there was no report submitted by nurses. This was observed even after the nurses were sensitized for reporting ADRs. The reasons for this could be due to inattention or low confidence or fear of making possible mistakes that could occur during filling ADR form. Further, only 40 cases were reported in this study [55]. This study explained that ADR reporting is a crucial topic that should be taught along with practice of filling ADR form, internships, and training programs in the institute. Undergraduate and postgraduate students should be made aware of Pharmacovigilance. India comprises many rural and unprivileged sections where largely quacks are practicing the medicines which is the major cause of ADRs in rural areas. According to a study, there are around 1.5 million quacks in India if it is presumed that one quack causes ADR of one patient in one year due to wrong diagnosis and treatment, nearly 1.5 million ADRs take place across the country [56]. These ADRs go unaddressed even though they experience the ADR they don’t see its reporting as a major issue thus there is reduced ADR reporting in India. Hence educating rural health care providers about ADR reporting is a major area to look upon today [57].

Furthermore, the rural people mainly depend on community pharmacies for their medicines so the community pharmacists can also play a significant role in ADR reporting. The patients directly consult them about any adverse reactions happening so it is necessary that community pharmacists should know about pharmacovigilance and ADR reporting. They should learn to report it directly to NCC- PVPI. Various studies were held wherein educational workshops were kept for the community pharmacists. One such study was done where

training was provided to the community pharmacists in pharmacovigilance and ADRs monitoring and reporting programmes. Continuing pharmacy education (CPE) programs about ADRs monitoring and reporting were conducted timely to the community pharmacists both in the study centre and respective pharmacies. They were provided education regarding the issues on pharmacovigilance and need for ADR reporting in the community setting. The materials were delivered through instructive lectures, explanations, and interactive discussions conducted timely to the community pharmacists. The questionnaire which was filled by the community pharmacists Pre-CPE and post-CPE showed totally different results demonstrating that the knowledge about ADR reporting of the pharmacist increased substantially. In the post-CPE survey, most of the respondents agreed that reporting ADRs is necessary and the majority of respondents strongly agreed that ADRs reporting should be a part of a professional role [58].

The era coming in some years will be a digital era. Many people from rural areas have started using androids (though not much till now) therefore the ADR reporting has been tried to be digitalized so that the patients can themselves fill the ADR reporting form which will directly reach the NCC-PVPI. This will also overcome the problems of under reporting. The ADR-PVPI App made by the IPC, offers direct reporting by the patients as well. The studies done so far showed that the pharmacovigilance practice has not developed in rural areas due to their illiteracy and fear to report ADRs. From the various studies it is observed that it is the knowledge which is lacking. Adequate education about ADRs and their effects are crucial among patinets as well as HCWs [51, 52]. They did not find it much important earlier but after proper knowledge through various awareness programmes, training and workshops, they become aware about ADRs reporting, its process and importance. Thus, it can encourage the patients to report the ADR directly to safeguard their health.

8. Comparative analysis of ADR reporting in urban and rural areas

In India, there are so many studies conducted on knowledge and attitude of HCPs toward PV, role of HCPs in PV, awareness and mechanisms of ADR reporting among HCPs and patients, impact of educational interventions in improving ADR reporting, etc. in both urban and rural areas. Studies have concluded that there is a need to solve the under-reporting problem by encouraging the HCPs and patients to understand the importance of PV and ADR reporting, by organizing awareness programmes on PV and its significance, by providing necessary infrastructure and facilities for smooth ADR reporting etc (Table 2). Multiple studies have demonstrated that there are major differences in ADR monitoring and reporting mechanisms in the urban and rural areas of India (Table 3). The urban

areas have their pharmacovigilance system more developed as compared to rural areas and efforts are made to introduce it in rural areas as well. Various studies done on rural areas showed that pharmacovigilance can be brought into rural areas through educating people about ADR, why it is important to report, to whom they need to report, ways of ADR reporting from remote locations etc.

9. Future prospects of Pharmacovigilance and ADRs reporting mechanisms in rural areas

There is a need of a properly working pharmacovigilance system for detecting, identifying, reporting and assessment of adverse drug events. India is the 4th medical hub in the world. However, there is not a well developed pharmacovigilance system in India to benefit all stakeholders including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. In India, a well structured pharmacovigilance system will help the pharmaceutical companies to maintain the safety of medicines thus it will be beneficial for pharmaceutical marketing and consumers as well. It advises and implements effective risk management plans ensure the safety of their marketed medicines and the patients at the end of therapy.

The 21st century will come up with new ways through which drugs and pharmaceuticals will be developed, sold, and consumed. Thus, as the market becomes more and more difficult to control, pharmacovigilance may have to play an increasingly central role. In a report from 2002, the World Health Organization (WHO) wrote: “Within the last decade, there has been a growing awareness that the scope of pharmacovigilance should be extended beyond the strict confines of detecting new signals of safety concerns. Globalization, consumerism, the explosion in free trade and communication across borders, and increasing use of the Internet have resulted in a change in access to all medicinal products and information on them. These changes have given rise to new kinds of safety concerns [9].”

Herbal medicines will be a major demand in the future. These herbal medicines classified as ‘dietary supplements’, are not controlled to the same standards as pharmaceutical drugs. The rural areas depend largely on herbal medicines and believe in it for their illness. But, it is not that herbal medicines are entirely safe. The herbal medicines also carry side effects which are sometimes fatal. Reports of side effects and interactions are seen with some drugs. However, due to the ease with which many herbal medicines are made and consumed, it is very difficult to regulate their entry into the market. Hence pharmacovigilance would be the best option in assuring the safety of drugs in a world of increasing herbal medicines. Therefore, an increasing awareness about ADR detection and reporting directly among rural people will provide their safety and also the growth of pharmacovigilance systems in rural areas [86].

The AMCs together with NCC are giving attention in promoting PvPI in rural areas. In order to make the people aware about the importance and advantages of PvPI especially in rural areas, the concept and importance of ADRs reporting is displayed in regional newspapers and also communicated through radio. IPC is also taking help of Doordarshan to expand the message of pharmacovigilance which will lead to education of the public particularly in rural areas. There are possible ways through which we can improve the progress of pharmacovigilance programmes and ADRs reporting thus providing safeguard to the people of rural areas. These include awareness of ADRs and its reporting system, use of social media in ADRs reporting, use of electronic medical records, telecommunication, telemedicine, artificial intelligence etc.

10. Tools to improve the ADRs reporting mechanisms in rural areas

PV systems should be more capable of detecting the new ADRs. It should generate more accurate information which would be helpful for the health professionals and patients in decision making. Involvement of the patients as a source of information in addition to more traditional sources of information, such as healthcare professionals could be an approach to Pharmacovigilance in rural areas. The people are moving towards a digital era. People from rural areas have started using androids (though not much till now) therefore the ADR reporting has been tried to be digitalized so that the patients can themselves fill the ADR reporting form which will directly reach the NCC-PVPI. This will also overcome the problems of under reporting. The ADR-PVPI App made by the IPC, now offers direct reporting by the patients as well.

For the improvement of the PV in future, DCGI needs to take action for the integration of Good Pharmacovigilance Practice (GPP) into the processes and procedures to ensure regulatory compliance. DCGI should establish an independent and well structured entity as the National Pharmacovigilance Center to ensure the safe use of drugs. Major priority needed to serious events rather than non-serious events but important health changes should be screened routinely in present time [87]. There are few suggestions for improving PV system in India (See box below).

BOX

There should be an expansion of PvPI reaching out to the district and rural level hospitals.

There should be self sustainability of the PvPI programme. Either DCGI should establish an independent and well-structured entity as the National Pharmacovigilance Center to ensure the safe use of drugs or Indian Pharmacopeia Commission (IPC) should try to become a Centre of Excellence in Pharmacovigilance.

The DCGI may invite the well trained and experienced persons from industries and academia to help, train and set-up the pharmacovigilance system to overcome the problems of lack of experienced and trained people [1].

The Health Ministry of India needs to bring a law pertaining to PV and to make a pharmacovigilance reporting system mandatory for every hospital as well as pharmaceutical companies.

The DCGI must appoint pharmacovigilance inspectors who will do inspections in the pharmaceutical companies as well as all hospitals.

There should be high levels of discussion with various stakeholders across a country i. e. Ministry of Health and Family Welfare (MHW), Indian Council of Medical Research (ICMR), Medical Council of India (MCI), Pharmacy Council of India (PCI), Nursing Council, Dental Council, Pharmaceutical Companies, Consumers Association, Non-governmental Organization (NGOs) regarding developing a pharmacovigilance system in India.

The adverse event reporting form should be present in all the hospitals including primary, secondary and tertiary healthcare hospitals and healthcare facilities of rural areas as well.

The training programme should be done frequently in both urban and rural areas too.

The DCGI should have to create a database for clinical trials and post-marketing data for signal detection, assessment of all data from various stakeholders. The data of drugs from various stakeholders should comply with the Consolidated Standards of Reporting Trials (CONSORT) guidelines including overall benefit-risk profile of the product. For drugs that are already present in the market, type and frequency of all adverse events (serious/non-serious) should be submitted in periodic safety update reports (PSURs) and also added to the summary of product characteristics.

A list of all new drugs with their indications should be developed by the Regulatory Authorities and Pharmaceutical companies in the database. Pharmaceutical companies should have meetings with the DCGI to outline their Risk Management Plans (RMP) for the safety issues.

Education and training of Medical, Pharmacy and Nursing students should be done in the areas of pharmacovigilance by the well trained and experienced person of pharmacovigilance system.

There should be integration of pharmacovigilance studies with pharmacoepidemiology.

The use of information technology should be done to develop Apps and Softwares for easy and smooth reporting of ADRs even from remote corners of the country [3].

Considering the issues and challenges, there are few prospective approaches/suggestions which may be useful for the development of a robust pharmacovigilance system in India especially in rural areas (Table 4).

The Government of India need to focus on providing complete training in all aspects of PV to the Physicians, Pharmacists, nurses and other healthcare professionals and make them more aware to report ADRs from rural areas as well. There are various possible ways which can be integrated with Pharmacovigilance system to develop a robust pharmacovigilance programme and ADRs reporting in the country and thus to safeguard the people of urban and rural areas. These include awareness of ADRs and its reporting system, use of social media in ADRs reporting, use of electronic medical records, telecommunication, telemedicine, artificial intelligence etc. The following is detailed description of some tools which might be beneficial to improve the ADRs reporting in rural areas.

10.1 Organization of awareness camps

Now, consumer adverse reactions reporting mechanisms have come as a new concept in pharmacovigilance where ADRs are directly reported from them. Currently, about 44 countries have adopted consumer ADRs reporting mechanism which contributes 9% of the total ADRs reports. It is necessary to make the consumers aware about ADRs reporting and its mechanism to collect ADRs directly from them. A 4 months study was conducted on in-patients at AIIMS, New Delhi, India to determine the level of consumer or patient awareness of ADRs reporting mechanisms in India. The findings of this study demonstrated that the patients should be fully aware about the existing pharmacovigilance system and ADRs reporting mechanism and possible ADRs reporting mode in India in future. Further, total 1000 patients were taken part but only 770 have recorded their responses. A majority (74%) of respondents were aware of ADRs and out them only 29.4% experienced ADRs in the past. Further, about 40.6% respondents admitted that ADRs reporting is important but only 8.9% of respondents thought of its reporting. One third respondents have considered the doctors as suitable person for reporting ADRs. Results demonstrated that there is little awareness about the existence of the National Pharmacovigilance Programme in India among consumers (4%). The findings of this study indicated that there is low awareness in patients. Hence, it should be improved by introducing an educational intervention programme on awareness of patients to report ADRs directly from patients and it will be a new mechanism in ADR reporting in near future [88].

10.2 Use of electronic medical records

Electronic medical records is one of the major source of information about a patient's health history. Presently, Governments are taking necessary steps to collect the patient's health history to conduct research and for future

preparedness in case of any disease outbreaks in the country. Medical literature states that many drugs have been approved whose complete safety profile is unknown [89]. Drugs which showed serious ADRs on the patients were recorded electronically and later withdrawn from the market. Electronic medical records (EMR) can be used to retrieve the details regarding the drug administration and to find out any serious adverse event (SAE) by employing the Bayesian classifier. It also analyses the various data mining techniques to find adverse events [89].

Recently, the Prime Minister of India has launched a National Digital Health Mission (NDHM) on August 15, 2020 with the objective to provide high-quality healthcare services to every citizen of India. It will be a digital health ecosystem integrating all digital health services by utilizing the existing health information systems of our country. It comprises four key components including Health ID, Personal health records, Digi Doctor and Health facility registry. Later, it will also have space for e-pharmacy and telemedicine services, and provision for framing regulatory guidelines. Importantly, Health ID cards are prepared for every Indian citizen where all health-related information will be stored. Health ID card will work on both mobile App and website, and it will have records of every aspect of treatment including patient's personal information, doctor's name, medical history, medicines prescribed, and other vital information related to the health of the person. Later on, ADRs associated with prescribed medicines can be recorded in Digital Health ID card to enable HCPs to gather information related to ADRs to ensure safety of the patients, thus it may be useful in enhancing ADR reporting digitally. Moreover, Digital Health ID will be useful to prevent medical errors and to increase the safety and quality of care in patients [90, 91].

10.3 Use of Social media [92]

Nowadays the pharmaceutical industry is doing active contact with patients on social media to gather the adverse effects of data of drugs. Two types of data reporting can be distinguished namely solicited and unsolicited which can be further analyzed in terms of the context and purpose of data disclosure and the area where the data are captured.

Type 1: solicited reporting (social media as a reporting channel)

The new technology can be used for ADRs reporting directly by the patients using new methods and tools. In this connection, the WEB-RADR is new initiative which promotes the use of social media and other technologies for ADR reporting in a easy, quick and efficient way, also seeking to establish guidelines and a regulatory framework on the use of the technology for such ADRs reporting**.**

Type 2: unsolicited reporting (social media monitoring)

Social media data are increasingly recognized as a valid source of patient perspectives and data on adverse events. This information is a major source and is timely, relevant and often publicly available. Social media have thus the

potential to become a new-age tool for monitoring data regarding patient's experience with medications in real time, making and providing early indications of potential safety issues that require further investigation. A typical methodology (passive collection) is used for the detection of ADR (signal detection) using social media data and it involves several steps including collection of raw data, validation of drug names and description of associated symptom/events, identification of relevant informative posts, data cleaning (removal of duplicates and noise), removal of data related to personal details, addition of other data sources (e.g. product label, sales data) to expedite the review process and contextualize the results for interpretation.

10.4 Telecommunication

One of the major challenges for the pharmacovigilance system to develop is the need for communication. Safe and effective prescribing of drugs can take place only when the prescriber has sufficient current knowledge of the potential harms of a drug and its likely benefits. When a new drug enters the market the profile of its adverse effects is limited because it has been tested in small groups of people and also for a limited period of time. But serious and probably fatal adverse effects can come into light some years later. Hence, it becomes important to continue monitoring the safety of drugs post-marketing and also HCPs should have access to timely communication about the safety concerns of the drug. Telecommunication will play a major role in communication of adverse reactions among HCPs, pharmaceutical industries and the common people in the coming years. It will provide a rapid and effective system to report ADRs. The European countries have a well established telecommunication system in Pharmaceuticals. It provides a platform for the exchange of information between healthcare professionals and pharmaceutical industries. The telecommunication system used by them is called **EUDRANET.** It can also be used in rural India to collect and report the ADRs thus ensuring the safety of the people from adverse effects of the drugs used for the treatment of a particular ailment [93].

10.5 Telemedicine

Telemedicine is an application of information Technology (IT) which is associated with patient health care, treatment, monitoring of drugs and electronic reporting and recording of adverse drug reactions. Telemedicine is practiced by store and forward methods, interactive services, remote monitoring and the telepharmacy practice with the use of the internet. It was adapted even in remote areas and rural setups to save the lives, time and cost of suffering. In India, it is not developed but steps are taken to improve it. It would help to provide better health services with less expense and better quality [94].

10.6 Artificial Intelligence

Artificial Intelligence or AI has become one of the most important technologies of the healthcare industry. AI refers to the use of automated algorithms to perform tasks which traditionally were done by humans. However, the use of AI has not been so accepted on a much larger scale in the pharma industry. Though, its rapid rate of development exhibits that it will surely be established in the future. The healthcare sector mostly consists of complex communication between healthcare providers and patients. AI has the potential to improve the communication between the provider and the patient. There are chances that adverse drug reactions and drug interactions from a medication can be harmful. Hence to counter the problems of tracking drugs, machine learning algorithms are generated. They are capable of extracting information of specific drugs and their harmful adverse effects. This may lead to a good communication of adverse effects of medication even in rural areas [94].

11. Conclusion

Safety of the prescribed medicines and patients are the main aim and objective of the healthcare system at all levels of the society/community. Globally, the movement for the improvement of patient safety is gaining momentum thus the subject of drug safety has become even more prominent. So far, the PvPI has been quite successful in improving the Pharmacovigilance in urban areas through developing reporting facilities like toll free dial number, ADR App, message, E-mail and ADR form in vernacular languages. Still India is lacking behind as ADR reporting is less than 1% when compared with worldwide reporting of 5%. Unfortunately, still the principles and practices of pharmacovigilance are more often discussed in academics and conferences rather than applied sense. The implementation part has great lacking by health authorities. The various KAP studies showed that there is a great lacking or absence in knowledge, positive attitude and practice of pharmacovigilance in rural areas. The physicians who are directly dealing with the patients or prescribing drugs are less or not indulge in ADRs monitoring. Moreover in rural areas the healthcare is still in the hand of quacks, who are causing great harm to the health of rural population therefore, it is utmost important to report the ADRs at its first instance to avoid further harmful effects of the prescribed drugs and it is only possible by effective implementation of pharmacovigilance system with the help of healthcare professionals as well as patients. A well-developed Pharmacovigilance offers great opportunities for reducing harm to patients and costs to healthcare systems. The PHCs are the focal point of healthcare in rural areas. Most prominently at first instance government needs to focus on the awareness and enhancement of pharmacist's knowledge and empowering them with facilities to conduct PV activity. Every PHC and hospital should have the

special PV cell to monitor and report the ADRs. As digitalization is becoming more prominent and there is a great increase in the use of smart phones in rural areas the use of social media in awareness and ADRs reporting can be proved highly beneficial. Promoting the use of electronic medical records, telecommunication, telemedicine and use of artificial intelligence to identify ADRs could be the next move in developing a robust pharmacovigilance system. From small beginnings, with the right knowledge and skills, pharmacovigilance system can make a significant contribution to the health of the rural India.

13. Conflict of interests

There is no conflict of interests among authors.

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15. References