IJBPAS, July, 2021, 10(7): 2227-2249

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

CURRENT STATUS AND FUTURE PROSPECTS OF PHARMACOVIGILANCE IN INDIA

MISHRA R AND CHAUDHARY K*

Institute of Pharmaceutical Research, GLA University, Mathura, U.P., India (281406)

***Corresponding Author: Kajal Chaudhary: E Mail: raghav.mishra92@gmail.com; Phone No.: +91-9808632494**

Received 17th Aug. 2020; Revised 16th Sept. 2020; Accepted 7th Oct. 2020; Available online 1st July 2021

https://doi.org/10.31032/IJBPAS/2021/10.7.5535

ABSTRACT

Pharmacovigilance is the medical pharmacology engaged in the identification, interpretation and mitigation of adverse effects, in particular long-term and short-term adverse reactions to medicinal products. Countries worldwide are focusing on establishment of comprehensive systems for pharmacovigilance. There are currently no approved COVID-19 therapies based on broad clinical trials evidence and therefore infection prevention, control measures and supportive care are involved in its management. While most developing countries have well-organized pharmacovigilance systems in place, there is still a lack of basic infrastructure in developing countries to implement them. As a major center of clinical research, the Indian pharmacovigilance framework is of considerable importance for healthcare and pharmaceutical sectors. This study is an attempt to emphasis on different pharmacovigilance facets including its need, present status and ensuing prospects in India.

Keywords: Adverse Drug Reactions, Clinical Trial, COVID-19, Pharmacovigilance

INTRODUCTION

In recent years, pharmacovigilance has grown significantly and recognized worldwide in the health care system.

In most of the countries, after the thalidomide tragedy in the 1960s, Pharmacovigilance programs evolved as thousands of children were born with Phocomelia as a side effect of drug thalidomide, leading to shortening or lack of limbs and this raised several concerns regarding medicine health **[1]**.

The widely recognized Vioxx-Recall was initially hoped to be more safe than previous analgesic drugs, a non-steroidal anti-inflammatory medication, because of its low risk of gastrointestinal bleeding. They were reported to be involved in fatal heart attacks **[2]**.

Pharmacovigilance is an ongoing process for tracking drug safety and providing new research and updates on Adverse Drug Reactions (ADRs) **[3]**.

There are many cases of product restriction and withdrawal on the grounds of safety concern. Rosiglitazone is the most recent medicine withdrawn from the European market **[4]**. Previously, very well-known medicines for example Terfenadine, Cisapride, Refocoxib, Cerivastatin, Phenylpropanolamine have been withdrawn for safety reasons.

Patient Centering is described as "Health care, which creates relationships between providers, patients and their families to ensure that the decision should respect the wishes, needs and desires of patients, and also ensure that patients are well informed and encouraged in decision making for their own care" **[5]**.

Pharmacovigilance is an essential part of clinical research **[6]**. Pharmacovigilance has different roles, including identifying, quantifying and documenting drug-related problems that are responsible for medication-related wounds **[7-8]**.

The critical and inseparable part of clinical research is Pharmacovigilance Security of both clinical trials and Post-Marketing Pharmacovigilance (Post marketing studies or Phase IV clinical trials) that are critical for the entire life of the product **[9]**.

The Indian Pharmaceutical Industry is the third largest in the world in terms of the volume and thirteen largest in terms of value. India was also a centre of drug development and clinical research. Indian Pharmaceutical industry needs a global Pharmacovigilance and standardization program to improve drug safety assessment **[10]**.

History of Pharmacovigilance

Medicine health has not been at the forefront of drug history. The 1960 thalidomide disaster had given drug regulators and other experts an eye for

finding ways of ensuring drug safety **[11-12]**.

The United States Federal, Food and Drug Act (USFDA) was first adopted in 1906 but was amended to combat ingredient mis-branding and falsified publicity claims after sulphanilamide elixir deaths **[11]**.

The diethylene glycol used as a solvent for sulphanilamide elixir resulted in 107 fatalities. The thalidomide tragedy was first reported in 1961, by William McBride, an Australian obstetrician. In the children, he mentioned the thalidomide associated "seal limbs". The tragedy has made the World more worried about the safety of drugs because the efficacy of drugs was only the parameter.

Immediately following the accident, the FDA Act was amended to mandate that efficacy and safety data should be submitted before the market in 1962.

The UK Medicines Act was enacted in 1968, but security control was introduced in 1964 via the "yellow card schemes". It was not until 1986 that a standardized monitoring system for ADR was introduced in India, consisting of twelve regional centres serving 50 million people each **[13]**. Three ADR surveillance centres, mostly in educational clinics, have been identified. A Pharmacovigilance centre located in the nation is in the Department of Pharmacology, All India Institute of Medical Science (AIIMS), New Delhi and two World Health Organization (WHO) specialised centres located in Mumbai (King Edward Memorial Hospital) and Aligarh (Jawahar Lal Nehru Medical College and Hospital). Such centres registered ADRs to the Indian drug regulators. ADRs of medicines that are marketed in India were the main role of these centres **[9]**.

By 2002, over 65 countries had their own centres for Pharmacovigilance. The WHO Membership is coordinated by the WHO International Drugs Monitoring Centre, known as the Uppsala Monitoring Centre (UMC). Pharmacovigilance today is based on strong science and integral for effective clinical practice. Disciplines must further grow to meet public standards and modern public health requirements **[14]**.

Pilot Research Project for International Drug Monitoring, this included creation of an international system for the identification of adverse effects of pharmaceutical products that were previously unknown or poorly understood **[15]**.

Adverse Drug Reaction

WHO describes the ADR as any negative or unintended reactions to a medication that may take place at doses used for prevention, diagnosis and treatment. Overall, the high prevalence of ADRs in both hospital and community populations increased morbidity and mortality. ADR is

recognised as one of the World's most important causes of patient injury. ADRs are among the leading causes of death and disease in numerous countries **[16]**.

The main clinical risk is ADR. In some countries, hospitalization due to ADRs is about 10% or more. However, 10-20% of the patient population is estimated to suffer from ADRs. Spontaneous reporting system (SRS), considering under-reports as a significant limiting factor, is the first and most widely used tool to monitor ADRs. It can detect new, rare and severe ADR at an early stage. The signal is produced on the basis of those reported cases. Signal is the new possible causal relationship that is previously unknown or incompletely recorded between a suspected ADR and a drug. The underreports of ADRs are very severe; only six percent of ADRs are registered. The expertise and attitudes of health professionals are closely linked in terms of ADR coverage **[3]**.

ADR is commonly referred to as type A and type B. The pharmacological activities of the drug are consistent with and predictable for the type A reaction whereas the reaction of type B has not been correlated with and is not consistent with medicinal action. It is also called a rare reaction. The reaction of type A is more prevalent than the reaction of type B **[17]**.

***Classification of ADRs*: [18]**

1. **Type A Effects (Augmented)**

- ✓ Due to effects on pharmacology.
- ✓ It is linked to dosage: Doses that are important to the individual patient can often be avoided.
- ✓ For example: After H2 antihistamines, hypnotic effect is shown.

2. **Type B Effects ("Bizzard", Idiosyncratic Reactions)**

- ✓ Rarity and unpredictability in general.
- ✓ This occurs in patients predisposed to intolerance. Rare genetic polymorphism, allergic reactions could be clarified.
- ✓ For example: Allergies of Penicillin.

3. **Type C Effects ("Continuous")**

- ✓ Long-term treatment results in adverse reactions.
- ✓ Sometimes, there are no clear time relations and it can be difficult to prove the relation. The use of a pharmaceutical product increases the rate of 'spontaneous' illness.
- ✓ For example: Carcinogenicity.

4. **Type D Effects ("Delayed")**

- ✓ Adverse effect can occur years after a medication has been taken.
- ✓ For example: Vagina cancer in daughter after her mother received Diethylstilbestrol.

5. **Type E Effects ("Ending")**

- ✓ Absence of drug following withdrawal-Impact rebound.
- ✓ For example: Asthma treatment *via* corticosteroids.

Need of Pharmacovigilance

The pharmacovigilance methodology was recently expanded to herbal medicinal products, traditional medicinal products, organics, vaccines, medical instruments and blood products **[10]**.

A number of experiments and clinical trials were performed on animals and human subjects for the purpose of determining the medication's safety in relation to a specific disease and understanding the exact adverse effects. Although much of it remains undetected, certain ADRs are found in the post-marketing monitoring.

A considerable number of ADRs are estimated to decrease life quality, increase hospitalization, and increase mortality. A major study of the Lazarou reported in 1998 estimated that 3-7 percent of all hospital admissions were caused by ADRs as these were fourth to sixth leading death causes in the USA **[19]**.

The reaction of type A is more prominent and accounts for more than 80% than of type B reactions. [18] Signified morbidity and mortality are correlated with ADRs. Recent estimates indicate that ADRs are the fourth to sixth largest causes of death in the USA **[20]**.

ADRs are an important cause of admission to hospitals. [21] However, 10-20% of the hospital patients are expected to suffer from ADRs and this is the reason why ADRs are the growing clinical problem.

a. Pharmacovigilance in Health Regulations [18]

The foundation for a national ethos on medical safety and public confidence in medicines is established through robust regulatory provisions. For drug regulator authorities to be efficient, they must go beyond the authorisation of new medicinal products to include a wider range of medical safety issues, namely:

- Clinical trials;
- Protection of complementary and conventional pharmaceutical products.

b. Pharmacovigilance and Clinical Practices

Health control of widely used pharmaceutical items may form an integral part of clinical practice. This ensures that the daily flow and exchange of information is the ideal place to find differences in our understanding of medicinal diseases through National Pharmacovigilance Programs.

c. Public health monitoring systems for Pharmacovigilance

The monitoring of medical safety has been described as an issue of concern in countries without the implementation of regulatory or security monitoring systems in remote

areas with or without a medical monitoring or infrastructure. For example: for Treating tropical illnesses including malaria, leishmaniasis, and schistosomiasis; and for HIV /AIDS treatment and tuberculosis therapy. For every country with a public health surveillance system, pharmacovigilance should be a priority.

d. **Pharmacovigilance in Herbal pharmaceuticals**

Both national health authorities and the general public are particularly concerned about the safety of herbal medicines. Herbs are still widely used in traditional medicines throughout the World.

e. **Significance of ADR reporting in Patients**

Different, unexpected and unusual ADRs are often found in drugs used in a broader population or in a different population than those tested in early clinical studies in a limited number and particularly short-term patients in a controlled system. In this information, under reporting was a major drawback. The patient/ consumer reporting will therefore be an additional source of information that can help to reduce the limitation in reporting **[22-25]**.

Methods in Pharmacovigilance

Several researchers have developed various methods for evaluating the causality of ADRs by using different criteria such as the sequential relationship between drug administration and ADR incidence, screening of non-drug related factors and proof of *in vivo* or *in vitro* reaction, and precedents of homogeneous knowledge assigned to the clinical class of a suspected drug, ADRs in various categories to be identified **[26]**. No universally accepted approach is currently available for determining the causality of ADRs **[27]**.

There are currently several algorithmic causality assessment approaches, but the Gold Standard is not recognized because of their flaws and inconsistencies **[28]**.

a. **Australian Method:** Australian approach includes proof that leads to the inference, such as timing and recording of laboratory information and the test purposely omits a prior knowledge of the suspected drug profile **[29]**.

b. **Roussel Uclaf causality assessment Method:** For conditions like the liver and dermatological disorders, this approach is used. A retrospective evaluation of this method's reproducibility by four experts showed a concordance rate of 37-99% **[26]**.

c. **Loupi *et al.* Method:** In this way, the teratogenic potential of the drug was

assessed. The first parts of the algorithm allow for the drug to be skipped unless the abnormality was triggered. Additionally, bibliographical data are measured **[30]**.

d. **Ciba- Geigy Method:** The Ciba-Geigy approach was developed by expert consensus meetings. Experts used their professional judgements to determine and attribute Visual Analog Scale (VAS) causality to adverse drug events. This method uses a checklist of 23 questions, divided into three sections:
   a. Evidence of current adverse events,
   b. the history of patient reactions from the past, and
   c. Knowledge of the monitoring physician. Compared to evaluator tests, this revised methodology was found to have a high level of agreement (62 percent) **[31]**.

e. **Balanced assessment Method:** This method assesses a case report on several VAS models that meet specific requirements. It has an additional benefit that the alternative trigger factor is considered a possibility and not just a separate factor. Every case is evaluated by various assessors independently and the assessment depends on the expertise of the assessor **[32]**.

f. **Naranjo *et al.* Method (Naranjo scale):** It is used to test causes in different clinical circumstances using definite, likely, probable and questionable categories and concepts. There are 10 questions answered as Yes, No and Unknown. The incident is allocated to a category of probability based on the total score. A total of 9 is definite, 5-8 is probable, 1-4 is conceivable and 2 is uncertain. The measure is higher if the adverse event is linked to only one prescription, but if several drugs are involved or if drug interactions occur, the offending agent is not identified **[33]**.

g. **Kramer *et al.* Method:** This form refers to the administration of the offensive drug and there's been a single unfavourable drug case. Every adverse event is separately reviewed and analysed. The clarity of the algorithm is one of the advantages. Moreover, it takes certain levels of experience, knowledge and time to effectively use this tool **[34]**.

h. **Dangaumou's French Method:** The French Government department has been using this law since 1977. The way things are done distinguishes an inherent imputability (possible case of drug consumed and occurrence of dispassion) than extrinsically imputable (Data from bibliography) by

seven parameters in two different tables (three connected and four semiological).

The requirements shall be:

a. The Threat for Drugs
b. Unchallenged and
c. The overall score of four different categories must challenge.

The semiological parameters are**:**

a. Semiological (clinical signs) either suggestive or otherwise
b. Part Favourable
c. None or probable of the unspecified associated non-drug,
d. Laboratory tests reveal three possible results (positive, negative or no event pair tests) **[35]**.

Pharmacovigilance in India

Such pharmacovigilance principles are negligible or nearly obsolete in mainly developing countries like India, with a population of millions, a poor literacy and a high rate of disease **[36]**.

It is therefore very clear that the total care burden for physicians, the main focus of which is disease control, is thus reduced to secondary ADR coverage, which is obviously the main source of 90% of the cases under investigation, consequently, the clinical data management of the pharmacovigilance system cannot contribute as much as is expected to or is necessary **[37]**.

Pharmacovigilance Programme of India (PvPI) is one of the most important parts of a safety program, identifying the potential risks associated with the medications, blood products, or medical devices, and enabling corrective and preventative actions to be taken. It also utilizes ADR data by drug distributors and producers, as well as education purposes, to produce signal and to improve, track and control medicines.

In 1998, India was included in the management of the UMC in Sweden. In 2010, Ministry of Health and Family Welfare (MOHFW) started a national PvPI with AIIMS as the National Coordination Centre (NCC) with 22 regional ADRs Monitoring Centres (AMCs) for drug adverse reactions across the country. Ghaziabad is the zonal centre in the north; Kolkata is in the east; Chennai is in the south, and Mumbai is in the west. Under MOHFW, the Indian Pharmacopoeia Commission (IPC) was created as NCC for PvPI since 2011, an autonomous body in Ghaziabad **[38]**. 250 AMCs are currently in operation in India and many others are introduced annually **[39]**.

The AMC's main function is to compile and upload ADR files in the Vigiflow app. The ADR reports are documented in suspected ADR form, comprising 4 areas, i.e. information of the patient, suspected adverse reactions, suspected drug(s) and reporter information submitted to each

AMC. PvPI's contribution to WHO-UMC up to 2016 is only 4.2% relative to the US, which is 49.4% **[40]**.

To enhance the exchange of information about drug safety and to safeguard the health of many communities of about 1.27 billion of people and 77.58% of the population using mobile telephones, for example ADR coverage, PvPI released a mobile app in 2015 **[41]**.

As mentioned in **Figure 1**, PvPI has also created a 1800-180-3024 toll-free helpline for continuous support. It even makes direct consumer reporting easier with the consumer's id pvpi.compat@gmail.com. PvPI decided in May 2017 to introduce drug monitoring into the drug supply chain in order to ensure quality. The first intensive drug monitoring program in 2017 was launched to monitor inhibitors, pioglitazone and sofosbuvir of sodium glucose co-transporters-2 (SGLT2) in India **[42]**. Proactive form of safety monitoring for bedaquiline (new drug for treating multidrug resistance tuberculosis) was initiated with active pharmacovigilance. Six AMCs operated on intensive bedaquiline surveillance **[43]**.

PvPI also holds a range of workshops for pharmaceutical establishments, regional Pharmacovigilance system training, pharmaceutical business buildings and build capacity, pharmacovigilance training program as included in **Figure 2**.

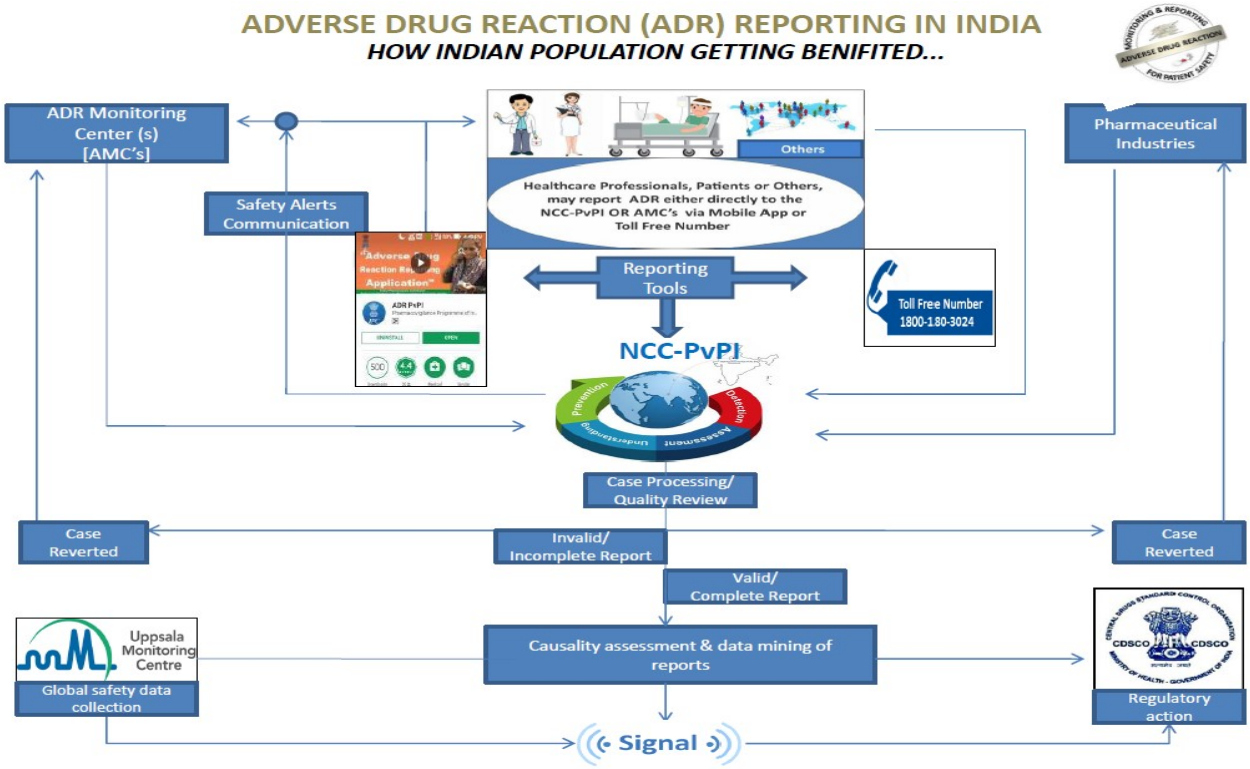

Figure 1: Pharmacovigilance System in India [36]

Figure 2: A Better Pharmacovigilance System in India

The PvPi also include drug safety alerts. In India, there are various types of PvPI:

(i) ***Materiovigilance programme of India (MvPI)***

On 6 July 2015 at the IPC, Ghaziabad, MvPI was launched by the Drug Controller General of India (DCGI). After an 8-minute power cut in the dialysis facility, in Puducherry, India, there has been an outcome of death **[44-45]**.

(ii) ***Hemovigilance programme of India (HvPI)***

In 2012 it was launched under PvPI in collaboration with MOHFW National Institute of Biologics, Noida, Uttar Pradesh to monitor blood and blood products related ADRs, thus improving patient safety **[46]**.

(iii)*Adverse event following immunization (AEFI)*

The AEFI is a medical event which is not inherently related to use of the vaccine following an immunization. Some adverse or unwanted signals, laboratory irregular findings, symptoms or conditions can be a traumatic event. As Medical Representatives (MRs) have a position in contact with Healthcare Professionals, PvPI has also extended its scope for private practitioners by educating MRs on Pharmacovigilance **[47]**.

Hurdles in Drug monitoring

Other reasons responsible for the failure were the lack of knowledge and understanding of PvPI, lack of time, workload and lack of training **[48]**. Often ADRs, which ultimately lead to increased morbidity and mortality, are not easily diagnosed by the physician and affect a

large stratum of public health. In addition, pharmacovigilance in undergraduate and postgraduate pharmacology should be included in the curriculum. The time spent on pharmacovigilance in undergraduate and postgraduate studies is small. Effective communication is a must to enhance the pharmacovigilance cycle and other aspects.

Pharmacovigilance Status in Other Countries

The term post-marketing monitoring in the United States refers to the monitoring of the safety, efficacy and quality of marketed drugs, and the term "post-marketing activities" within the European Union (EU) refers to regulators having more powers over more factors. Pharmacovigilance practices went beyond EU efforts and were greatly improved by the FDA's 2007 modernisation Act and by the recommendations of the FDA. These rules require the FDA to perform high-speed screening of the adverse event database and to publish new security information or potential signals of serious risk publicly every quarter. The UK Medicines and Health Products Regulatory Agency guidelines state that pharmacovigilance must not only include control of drug which is used to identify adverse effects, but also risk assessments for medicinal products **[49]**.

Pharmaceutical quality involves both attempts that is pre-licensure and post-licensure. The FDA has been working towards identifying the core data for pharmaceutical surveillance activities in the 21st century **[50]**. Due to the limited supplies among producers engaged in poor-quality production, many of the main medications used for treating leukaemia, lymphoma and testicular cancer have reported shortages in 2011, leading the FDA to engage in pharmacovigilance activity in an enhanced way **[51-52]**.

In 2014 the Pharmaceutical Quality Office was opened by the FDA to track the health, effectiveness and quality of pharmaceuticals **[53]**. Social media is becoming an important source of potentially important knowledge on pharmacovigilance Social media campaigns have revolutionized security concerns for rare diseases (for example, myelodysplastic syndrome) and reported ADR (for example, impairment associated with fluoroquinolone) in a number of key and observable circumstances **[54]**.

Regarding the safety and surveillance of cancer drugs, frequent and innovative risk management plans and careful effort are required. The use of a pharmacovigilance database to collect data for documented outcomes and identify new effects can boost pharmacovigilance efforts **[55]**.

Pharmacovigilance specialists contribute experience in evaluating key control records affecting clinical trial participants

including informed consent forms for clinical studies, reports of the institutional board of review, and meetings of the data management committee. The relevant documents include the compilation and recording of safety information by the clinical trial guidelines. Pharmacovigilance practitioners are rarely directly interested in first-in-human research and those studies do not typically belong in their work **[56]**.

Nonetheless, as these observations illustrate, they can play an ideal role in seeing the entire picture and keeping all key stake holders updated about the developments.

In October 2016 the EMA began proactively publishing clinical trials data submitted to its regulatory authorities by pharmaceutical companies, once the review process is completed **[57]**.

The Risk Management Plan includes:

1) Specification of safety (important identified threats, major potentials and lack of information)
2) Pharmacovigilance program (activities to measure and identify new adverse events of clinic relevance);
3) Risk minimization program (implementation of steps for risk minimization) **[58]**

It is also necessary, in certain circumstances, to need post-authorization safety and post-approval efficacy studies (clinical therapeutic issue) **[59]**.

It involves two terms:

(i) Dechallenge (Removal of the drug suspected): Positive dechallenge is the improvement / resolution of ADR when the suspected medicine is removed in a powerful, though not definitive indication of medicine induced reaction **[60-61]**.

(ii) Rechallenge (The suspicious drug was reintroduced after dechallenge): Rechallenge can only be justified if the advantage of the re-introduction of the suspected drug in the patient exceeds the possibility of an unusual repeat of the reaction **[62]**.

Considering Pharmacovigilance in Saudi Arabia, the Ministry of healthcare provides health services to the public through its diverse organizational structures, which include 244 hospitals, 2037 healthcare centres, referral clinics, health protection institutes and medical service and so in the kingdom's healthcare services, the growth area is extremely responsive and needs continuous improvement **[63]**.

Therefore, as shown by the WHO ranking of the Saudi health system in 26 of 190 countries worldwide, health services are a priority for the Saudi Government. In recent times, more attention is being paid to ADR coverage by pharmacovigilance. The effects of ADRs are harmful, but can be avoided if detected in due course of time. Therefore, their identification and

minimisation are critical that all health professionals, including physicians, pharmacists and nursing staff, have to make collective efforts **[64]**.

During recent days, the role of pharmacists in the health care system is becoming more visible as they are more concerned with patient care **[65-66]**.

ADR reports are provided by the subscribing countries and the number of the reports have reached 12 million since its formation in 1978. National Pharmacovigilance Centre (NPC) helps to address all suspicious signs in Saudi Arabia **[67]**.

Certain benefits include an international meeting to discuss how pharmaceutical surveillance practices can be strengthened in the participating countries.

Uppsala organizes several conferences and meetings annually around the globe, primarily seeking to promote awareness on pharmacovigilance and its aspects. These awareness conferences or meetings provide more pharmaceutical protection for the people in the community.

Pharmacovigilance and COVID- 19

Patient safety is a priority for pharmacovigilance activities, particularly adverse event reporting irrespective of clinical trials or clinical practice. Good safety control, accuracy in adverse effect reports and timely assessments are important because of the exposure to new drugs with insufficient knowledge to risks and benefits. The Central Indian regulators have promptly announced the accelerated monitoring and approval process for all COVID 19 drug and vaccine clinical trial applications to address the unmet medical need **[68]**.

Severe new and old medicines are being used, reviewed for clinical treatment and study, ranging from antimalarial to antiviral and immunomodulators with potential effects on existing coronavirus. Most pandemic studies are designed mainly to identify therapeutic advantages and outcomes and pay little attention to adverse effects and safety aspects. In comparison, the design of a true drug safety issue is not an effective gold standard analysis **[69]**.

Therefore, the compilation of drug safety data for timely analysis, causal assessment and real-time signal identification is a collective effort. While pharmacovigilance experts, clinicians and regulators may cooperate with this, evaluating suspected reports of adverse events, in particular causality assessments, will be a difficult task. The pharmacovigilance causality evaluation is a complex and time-consuming task. It would be even more difficult considering the current ban on physical touch, travel and free movement, isolation and quarantine during pandemics. Details of all incidents cannot be collected,

impacting the completeness and accuracy of security reports **[70]**.

The medicinal adverse effects can range from mild to life-threatening or serious medical incidents and can be uncommon or normal, Considering the enormous clinical workload and absence of formal pandemic monitoring, the data can be obtained only by a team of diligent practitioners who strictly follow the care protocols. The public outcry for COVID 19 treatment by using hydroxychloroquine is the finest example **[71-72]**.

Specific drug-induced reaction (Stevens-Johnson syndrome or acute dystonia) is also known as phenomenological reaction; thus, it is necessary to search for possible reasons to understand the causal links **[73]**.

In the Global Solidarity trial conducted by the WHO, the use of experimental drugs like Remdesivir and 'reusing' drugs such as Lopinavir/ Hydroxycholoroquine are being tested for the efficacy in COVID 19 patients **[74]**.

New vaccines of various types are being produced and initial doses were obtained from the first participants in the clinical trials **[75]**.

The convergence of drug monitoring with clinical practice is a crucial area of concern to many International Society of Pharmacovigilance (ISoP) members, who have also been addressed in our section and Special Interest Groups (SIGs) and at international meetings. It will be necessary to communicate and collaborate both within and outside pharmacovigilance culture. The ISoP executive council contacted individual ISoP leaders around the world during the outbreak of the COVID 19 pandemic **[76]**.

A research of 191 COVID 19 patients showed that 48% of patients had comorbidity, and 19% had diabetes **[77]**. As it is known, long term diabetes had a detrimental effect on various organs including eyes, kidney, heart, even causing diabetic nephropathy and hypertension. The first line treatment given in these conditions mainly work on Renin Angiotensin Aldosterone System (RAAS), drugs such as Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin II Receptor Blockers (ARBs) are the ones recommended now a days **[78-79]**.

ACE-2 which is a membrane bound receptor involved in RAAS, it is the host cell for the NOVEL SARS COV-2. The use of ACE-1, ARB, thiazolidinediones and ibuprofen contributes to an improved expression of ACE-2 which is responsible for the patients of diabetes and hypertension to be more prone to COVID 19 and increasing their chance of pulmonary oedema which is adverse effect of these drugs **[80-81]**.

In survey by Pharmacovigilance centres of French in COVID 19 patients, chloroquine

and particularly its analog hydroxychloroquine were suggested based on their experimental properties **[82]**.

Macrolide antibiotic azithromycin often correlated with suspected synergistic properties. [83] For this context, the Lopinavir as anti-HIV protease inhibitor with Ritonavir as a booster was also used. These four medicines have been used worldwide for clinical and observational research of all kinds **[84-87]**. Nonetheless, its protection, due to its tendency to extend the QT interval, remains challenging **[88]**.

120 cardiac adverse drug reaction reports were reported in one month, 103 of which are correlated with hydroxych loroquine (86%) or azithromycin (60%).

Given significant lack of coverage, the reported accidents range from 0.77% to 1.54% of all patients. With 17 records (14%), Lopinavir- Ritonavir came at third position and with 3 reports (2.5%), Hydroxychloroquine at fourth. There are eight sudden, unexplained or aborted deaths (7%), eight ventricular arrythmias (7%), 90 QTc reports (75%), most of which have been "significant" (64%), 48 of which have proved greater than to be 500 ms, 20 reports of extreme behavioural disorders (17%) and five reports of other cardiac causes (4%). Six automation-derived reports. Six records have been obtained from self-medication **[89]**.

Future Aspects of Pharmacovigilance

Pharmacovigilance systems capable of detecting new ADRs and taking regulatory steps to protect public health are important with the improved future prospects. The compilation and dissemination of knowledge on medication active monitoring safety is an essential Pharmacovigilance goal **[90]**.

When designing new approaches to closely track post marketing, it should be remembered that it is important to collect complete and accurate information for every serious event reported. The useful method for producing signals is spontaneous reporting, but the comparatively small number of reports for a certain group makes the established patient characters and risk factors less useful. Pharmacovigilance approaches must also identify which patients are at risk of an adverse drug effect.

The pharmacovigilance strategy as an information source is compliant with the increasing patient interest in drug safety **[91]**.

In evaluating individual risks for some ADRs, the Pharmacovigilance may play a role. In the upcoming time, Pharmacovigilance will concentrate on patients as a source of information among the more conventional groups, such as the health practitioners.

Now, the DCGI will move rapidly to refine enhance Pharmacovigilance in order to

implement Good Pharmacovigilance Practices (GPP) into the regulatory enforcement processes and procedures, as well as it will strengthen clinical safety and post marketing monitoring. Healthcare practitioners, regulators, drug makers and customers will be benefited.

It supports pharma companies in the surveillance of their risk medicines. Post-marketing Pharmacovigilance is a difficult and demanding process, at present not only in industry but for regulatory agencies also **[92]**.

The purpose of the Pharmacovigilance is to obtain online information, work documentation and expertise while prioritizing new and relevant security issues.

GlaxoSmithKline has established a powerful Pharmacovigilance approach that integrates traditional, case-basic Pharmacovigilance methods with disproportionality and data viewing tools **[93]**.

The tools reside within a program context that promotes ongoing analysis, monitoring and management of security issues.

This highly innovative instrument and processes will help improve Pharmacovigilance efficiency and offer new analytical capabilities. The pharmaceutical companies will use a similar method to rapidly identify and analyse ADRs. Openness and communication will improve consumer reporting, which are positive steps towards growing customer engagement in the Pharmacovigilance system **[94]**.

CONCLUSION

The increasingly growing diversity and effectiveness of drugs, along with their eventual and sometimes uncertain damage capacity, continue to have a vital function to be addressed by pharmacovigilance. When harmful effects and toxicity arise, in particular if previously unnoticed, these are documented, evaluated and accurately reported to the public with the ability to understand the results. Due to their accessibility to the public and the public health staff, the adverse incidents recorded by the Pharmacovigilance program are likely to help the society with respect to language and awareness of the lifestyles and habits of the patients, and also provide easy access to reporters. Newer and successful pharmaceutical drugs lead significantly to people's safety and well-being. Considering all the aspects, one can be optimistic that Pharmacovigilance will remain committed to track pharmaceutical products to improve patient safety around the world despite all these problems this year. Pharmacovigilance has become a significant public health concern in India, with a range of challenges confronted by authorities, product manufacturers, consumers and healthcare professionals.

The Pharmacovigilance is continuing to develop, evolve and improve in India. However, in order to boost the contribution to public health, there is a need to develop pharmacovigilance programs to track and take action more efficiently on the safety issues linked with medicines. Pharmacovigilance is indeed a collective responsibility of industry, drug authorities and professionals and all health care professionals for health protection to support patients and treat them optimally or appropriately.

ACKNOWLEDGMENTS

Sincere gratitude to Institute of Pharmaceutical Research, GLA University for providing literature survey facility to carry out the work.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

Involvement of Human Participants and/or Animals: Formal consent is not required for this type of study.

SOURCE OF FUNDING

For this work, the author has received no specific funding.

REFERENCES

[1] Kim J. H., Scialli A. R., Thalidomide: The tragedy of birth defects and the effective treatment of disease, **Toxicol. Sci**, 122(1), 2011, 1-6.

[2] Najafi S., Importance of pharmacovigilance and the role of healthcare professionals, **J. Pharmacovigil**, 6(1), 2018, 1-2.

[3] Santosh K. C., Tragulpiankit P., Pharmacovigilance: An overview, **Mahidol Univ. J. Pharm. Sci**, 38, 2011, 1-2.

[4] Avandia (withdrawn from market - October 2010), Available at https://www.netdoctor.co.uk/medicines/diabetic/a8230/avandia-withdrawn-from-market-october-2010/.

[5] Saleh H. A., Fourrier-Réglat A., Diogène E., Patient-centered pharmacovigilance: A review, **Trop. J. Pharm. Res**, 17(1), 2018, 179-188.

[6] World Health Organization, Pharmacovigilance: Ensuring the safe use of medicines. Available at https://apps.who.int/iris/handle/10665/68782.

[7] Skalli S., Bencheikh R. S., Safety monitoring of herb-drug interactions: A component of pharmacovigilance, **Drug Saf**, 35(10), 2012, 785-791.

[8] Arnott J., Hesselgreaves H., Nunn A. J., Peak M., Pirmohamed M., Smyth R. L., Turner M. A., Young B., What can we learn from parents about enhancing participation in pharmacovigilance? **Br. J. Clin. Pharmacol**, 75(4), 2013, 1109-1117.

[9] Nandha R., Pharmacovigilance: Indian Perspective, **Int. J. Drug Form. Res**, 5(4), 2014, 1-8.

[10] Wal P., Mehra R., Rizvi S., Vajpayee R., Pharmacovigilance: Need for Indian Pharma industry, **Int. Res. J. Pharm**, 6(11), 2015, 740-743.

[11] Routledge P., 150 years of Pharmacovigilance, **Lancet**, 351(9110), 1998, 1200-1201.

[12] Lawson D. H., Pharmacovigilance in the 1990s, **Br. J. Clin. Pharmacol**, 44(2), 1997, 109-110.

[13] Kulkarni R. D., Reporting system for rare side effects of non-narcotic analgesics in India: Problems and opportunities, **Med. Toxicol**, 1, 1986, 110-113.

[14] Jeetu G., Anusha G., Pharmacovigilance: A worldwide master key for drug safety monitoring, **J. Young Pharm**, 2(3), 2010, 315-320.

[15] Van Grootheest K., Olsson S., Couper M., de Jong-van den Berg L., Pharmacists' role in reporting adverse drug reactions in an international perspective, **Pharmacoepidemiol. Drug Saf**, 13(7), 2004, 457-464.

[16] World Health Organization, The Importance of Pharmacovigilance- Safety Monitoring of Medicinal Products. Available at https://apps.who.int/iris/handle/10665/42493.

[17] Pirmohamed M., Breckenridge A. M., Kitteringham N. R., Park B. K., Adverse drug reactions, **BMJ,** 316(7140), 1998, 1295-1298.

[18] Chauhan A. and Goyal M.: Pharmacovigilance: An Overview, **Curr. Res. Pharm. Sci**, 1(1), 2011, 15-19.

[19] Rajgopal J. K., Shilpi K. and Srivastav A. K.: Pharmacovigilance: A Review Article, **Innovare J. Med. Sci**, 4(4), 2016, 6-7.

[20] Lazarou J., Pomeranz B. H. and Corey P. N.: Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies, **JAMA**, 279(15) ,1998, 1200-1205.

[21] World Health Organization, Safety of medicines: A guide to detecting and reporting adverse drug reactions. Available at https://apps.who.int/iris/handle/10665/67378.

[22] Nebeker J. R., Barach P., Samore M. H., Clarifying adverse drug events: A clinician's guide to terminology, documentation, and reporting, **Ann. Intern. Med**, 140(10), 2004, 795-801.

[23] World Health Organization, Safety monitoring of medicinal products: Reporting system for the general public. Available at https://www.who.int/medicines/areas/quality_safety/safetyefficacy/ConsumerReporting.pdf?ua=1.

[24] Ahmed A. M., Izham I. M., Subish P.: Importance of consumer pharmacovigilance system in developing countries: A case of Malaysia, **J. Clin. Diagn. Res**, 4(4), 2010, 2929-2935.

[25] Reporting adverse events. Available at https://www.tga.gov.au/node/4581.

[26] Danan G., Benichou C., Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries, **J. Clin. Epidemiol**, 46(11), 1993, 1323-1330.

[27] Agbabiaka T. B., Savovic J., Ernst E., Methods for causality assessment of adverse drug reactions: A systematic review, **Drug Saf**, 31(1), 2008, 21-37.

[28] Macedo A. F., Marques F. B., Ribeiro C. F., Texeira F., Causality assessment of adverse drug reactions: Comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, **Pharmacoepidemiol. Drug Saf**, 14(12), 2005, 885-890.

[29] Mashford M. L., The Australian method of drug-event assessment. Special workshop-regulatory, **Drug Inf. J**, 18(3-4), 1984, 271-273.

[30] Loupi E., Ponchon A. C., Ventre J. J., Evreux J. C., Imputability of a teratogenic effect, **Therapie**, 41(3), 1986, 207-210.

[31] Venulet J., Ciucci A., Berneker G. C., Standardized assessment of drug-adverse reaction associations- Rationale and experience, **Int. J. Clin. Pharmacol. Ther. Toxicol**, 18(9), 1980, 381-388.

[32] Lagier G., Vincens M., Castot A., Imputability in drug monitoring. Principles of the balanced drug reaction assessment method and principal errors to avoid, **Therapie**, 38(3), 1983, 303-318.

[33] Naranjo C. A., Busto U., Sellers E. M., Sandor P., Ruiz I., Roberts E. A., Janecek E., Domecq C., Greenblatt D. J., A method for estimating the probability of adverse drug reactions, **Clin. Pharmacol. Ther**, 30(2), 1981, 239-245.

[34] Kramer M. S., Leventhal J. M., Hutchinson T. A., Feinstein A. R., An algorithm for the operational assessment of adverse drug reactions. I. Background, description, and instructions for use, **JAMA**, 242(7), 1979, 623-632.

[35] Dangoumau J., Evreux J. C., Jouglard J., Method for determination of undesirable effects of drugs, **Therapie**, 33(3), 1978, 373-381.

[36] Pharmacovigilance Programme of India, Available at https://www.pmda.go.jp/files/000225777.pdf.

[37] Khan M. A., Krishna P., Pharmacovigilance in India: A Need Indeed, **J. Pharmacovigil**, 2(126), 2014, 1-2.

[38] Gadhade J. B., Hiray R. S., Aherkar R. Y., Shah K. U., Pharmacovigilance programme of India: Revival of the renaissance, **Int. J. Basic Clin. Pharmacol**, 7(11), 2018, 2281-2285.

[39] Thota P., Thota A., Medhi B., Sidhu S., Kumar P., Selvan V. K., Singh G. N., Drug safety alerts of pharmacovigilance programme of India: A scope for targeted spontaneous reporting in India, **Perspect. Clin. Res**, 9(1), 2018, 51-55.

[40] Drug Safety Matters, Available at https://www.who-umc.org/global-pharmacovigilance/pharmacovigilance-communications/drug-safety-matters-podcast/

[41] Pharmacovigilance Programme of India, Available at www.ipc.gov.in/PvPI/newsletter/Newsletter%20Vol%205%20Issue%2012%202015%20PDF.pdf

[42] Singh K. N. M., Kanase H. R., Pharmacovigilance Programme of India: The beginning, current status and recent progress, **Adv. Pharmacoepidemiol. Drug Saf**, 6(4), 2017, 1-2.

[43] Pharmacovigilance Programme of India, Available at www.ipc.gov.in/PvPI/newsletter/Newsletter%20Vol%205%20Issue%2011%202015%20PDF.pdf

[44] Pharmacovigilance Programme of India. Available at http://www.ipc.gov.in/PvPI/adr.html.

[45] Power outage at Puducherry hospital kills three dialysis patients, Available at https://www.thehindu.com/news/cities/puducherry/power-outage-kills-three-patients/article17436721.ece.

[46] Haemovigilance Programme of India, Available at http://nib.gov.in/haemovigilance/dummy_HvPI/Newsletter/5th%20Newsletter%20of%20Haemovigilance%20Programme%20of%20India,%20Vol%20No.3%20%20%20,Issue%205,%20Jan-June%202015.pdf

[47] Pharmacovigilance Programme of India, Available at http://www.ipc.gov.in/PvPI/newsletter/Newsletter%20Vol%206%20Issue%2014%202016%20PDF.pdf

[48] Tandon V. R., Mahajan V., Khajuria V., Gillani Z., Under-reporting of adverse drug reactions: A challenge for pharmacovigilance in India, **Indian J. Pharmacol**, 47(1), 2015, 65-71.

[49] Pitts P. J., Le Louet H., Moride Y., Conti R. M., 21st century pharmacovigilance: Efforts, roles, and responsibilities, **Lancet Oncol**, 17(11), 2016, e486-92.

[50] Strategic Plan for Preventing and Mitigating Drug Shortages, Available at http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM372566.pdf.

[51] Emanuel E. J., Short changing Cancer Patients, Available at http://www.nytimes.com/2011/08/07/opinion/sunday/ezekiel-emanuel-cancer-patients.html?_r=0

[52] Fox E. R., Tyler L. S., Call to action: Finding solutions for the drug shortage crisis in the United States, **Clin. Pharmacol. Ther**, 93, 2013, 145-147.

[53] Office of Pharmaceutical Quality, Available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-pharmaceutical-quality.

[54] Kaur K., Fayad R., Saxena A., On behalf of the Southern Network on Adverse Reactions (SONAR) project. Fluoroquinolone-related neuropsychiatric and mitochondrial toxicity: A collaborative investigation by scientists and members of a social network, **J. Community Support Oncol**, 14, 2016, 54-65.

[55] Durrieu G., Mazau B., Jégu J., Lapeyre-Mestre M., Delord J. P., Montastruc J. L., Drugs and cancer: An analysis of the French Pharmacovigilance Database, **Therapie**, 68, 2013, 149-154.

[56] Beninger P., Pharmacovigilance: An overview, **Clin. Ther**, 40(12), 2018, 1991-2004.

[57] Clinical data publication, Available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/clinical-data-publication

[58] Guideline on good pharmacovigilance practices (GVP), Available at http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf.

[59] Risk-management plans, Available at https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management/risk-management-plans.

[60] Agrawal P., Drug Discovery and Development: An Insight into Pharmacovigilance, **J. Pharmacovigil**, 2(3), 2014, 1-2.

[61] Patil J. S., Pharmacovigilance in India, **J. Pharmacovigil**, 2(2), 2014, 1000e119.

[62] Amarendra K. E., Overview of Pharmacovigilance, **J. Pharm. Toxicol. Stud**, 4(3), 2016, 125-133.

[63] Alshammari T. M., Alshakka M., Aljadhey H., Pharmacovigilance system in Saudi Arabia, **Saudi Pharm. J**, 25(3), 2017, 299-305.

[64] Almalki M., Fitzgerald G., Clark M., Health care system in Saudi Arabia: An overview, **East Mediterr, Health J**, 17(10), 2011, 784-793.

[65] Chisholm-Burns M. A., Lee J. K., Spivey C. A., Slack M., Herrier R. N., Hall-Lipsy E., Graff Zivin J., Abraham I., Palmer J., Martin J. R., Kramer S. S., Wunz T., US pharmacists' effect as team members on patient care: Systematic review and meta-analyses. **Med. Care**, 48(10), 2010, 923-933.

[66] Kaboli P. J., Hoth A. B., McClimon B. J., Schnipper J. L., Clinical pharmacists and inpatient medical care: A systematic review, **Arch. Int. Med**, 166 (9), 2006, 955-964.

[67] The Uppsala Monitoring Center. Introduction to the WHO Programme for International Drug Monitoring. Available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/collab-centre-uppsala/en/#:~:text=The%20Uppsala%20Monitoring%20Centre%20(UMC,Monitoring%20was%20transferred%20to%20Sweden.

[68] The Central Drugs Standard Control Organization, Available at http://www.cyrilshroff.com/wp-content/uploads/2020/05/PharmaCDSCO-1105.pdf.

[69] Singh S., Loke Y. K., Drug safety assessment in clinical trials: Methodological challenges and opportunities, **Trials**, 13(138), 2012, 1-8.

[70] Descriptive analysis of COVID19-Descriptive analysis of COVID19-related spontaneous related spontaneous reports from VigiBase: Interim results, Available at https://www.who.int/medicines/regulation/medicines-safety/Descriptive_analysis_PV_REG7.pdf?ua=1.

[71] Rathi S., Ish P., Kalantri A. and Kalantri S.: Hydroxychloroquine prophylaxis for COVID 19 patients in India, **Lancet**

Infect. Dis, 2020. Available at https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930313-3.

[72] ICMR's Latest Clarification on Its Hydroxychloroquine Policy Is Just Baffling, Available at https://science.thewire.in/health/covid-19-hydroxychloroquine-policy-raman-gangakhedkar-icmr-observational-study/.

[73] Desai M. K., Pharmacovigilance and assessment of drug safety reports during COVID 19, **Perspect. Clin. Res**, 11(3), 2020, 128-131.

[74] "Solidarity" clinical trial for COVID-19 treatments, Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.

[75] Le T. T., Andreadakis Z., Kumar A., Roman R. G., Tollefsen S., Saville M., Mayhew S., The COVID-19 vaccine development landscape, **Nat. Rev. Drug Discov**, 19(5), 2020, 305-306.

[76] Chandler R. E., McCarthy D., Delumeau J. C., Harrison-Woolrych M., The Role of Pharmacovigilance and ISoP During the Global COVID-19 Pandemic, **Drug Saf**, 43(6), 2020, 511-512.

[77] Zhou F., Yu T., Du R., Fan G., Liu Y., Liu Z., Xiang J., Wang Y., Song B., Gu X., Guan L., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study, **Lancet**, 395(10229), 2020, 1054-1062.

[78] James P. A., Oparil S., Carter B. L., Cushman W. C., Dennison-Himmelfarb C., Handler J., Lackland D. T., LeFevre M. L., MacKenzie T. D., Ogedegbe O., Smith S. C., 2014 evidence-based guideline for the management of high blood pressure in adults: Report from the panel members appointed to the Eighth Joint National Committee (JNC 8), **JAMA**, 311(5), 2014, 507-520.

[79] American Diabetes Association.: Standards of medical care in diabetes-2020 abridged for primary care providers, **Clin. Diabetes**, 38(1), 2020, 10-38.

[80] Patel A. B., Verma A., COVID-19 and angiotensin- converting enzyme inhibitors and angiotensin receptor blockers: What is the evidence? **JAMA**, 323(18), 2020, 1769-1770.

[81] Stafford E. G., Riviere J. E., Xu X., Kawakami J., Wyckoff G. J., Jaberi-Douraki M, Pharmacovigilance in patients with diabetes: A data-driven analysis identifying specific RAS antagonists with adverse pulmonary safety profiles that have implications for COVID-19 morbidity and mortality, **J. Am. Pharm. Assoc.** in press

[82] Wang M., Cao R., Zhang L., Yang X., Liu J., Xu M., Shi Z., Hu Z., Zhong W., Xiao G., Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*, **Cell Res**, 30(3), 2020, 269-271.

[83] Dixon D. L., Van Tassell B. W., Vecchie A., Bonaventura A., Talasaz A., Kakavand H., D'Ascenzo F., Perciaccante A.,

Castagno D., Ammirati E., Biondi-Zoccai G., Cardiovascular considerations in treating patients with coronavirus (COVID-19), **J. Cardiovasc. Pharmacol**, 75(5), 2020, 359-367.

[84] Cao B., Wang Y., Wen D., Liu W., Wang J., Fan G., Ruan L., Song B., Cai Y., Wei M., Li X., A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19, **N. Engl. J. Med**, 382, 2020, 1787-1799.

[85] Cortegiani A., Ingoglia G., Ippolito M., Giarratano A., Einav S., A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19, **J. Crit. Care**, 57, 2020, 279-283.

[86] Dong L., Hu S., Gao J., Discovering drugs to treat coronavirus disease 2019 (COVID-19), **Drug Discov. Ther**, 14(1), 2020, 58-60.

[87] Kalil A. C., Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics, **JAMA**, 323(19), 2020, 1897-1898.

[88] Chorin E., Dai M., Shulman E., Wadhwani L., Bar-Cohen R., Barbhaiya C., Aizer A., Holmes D., Bernstein S., Spinelli M. and Park D. S.: The QT interval in patients with COVID-19 treated with hydroxychloroquine and azithromycin, **Nat. Med**, 2020, 26 808-809.

[89] Gérard A., Romani S., Fresse A., Viard D., Parassol N., Granvuillemin A., Chouchana L., Rocher F., Drici M. D., "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers, **Therapies**, 75(4), 2020, 371-379.

[90] Sawarkar A., Sharma R. K., Gautam V., Shramankar K., Dinodia N., Pharmacovigilance: Present status and future perspectives, **Pharma Innovation**, 8(8), 2019, 84-92.

[91] Flower D. R., Pharmacovigilance, drug repositioning and virtual screening, **J. Pharmacovigilance**, 1(1), 2013, 100-103.

[92] Ghewari P. S., Salunkhe S. S., Bhatia N. M., Killedar S. G., Chitranagari K., Strategies and current scenario of pharmacovigilance in India, **J. Adv. Drug Deliv**, 1(3), 2014, 122-134.

[93] Borja-Oliveira C. R., Alcohol-Medication interactions: The Acetaldehyde Syndrome, **J. Pharmacovigilance**, 2(5), 2014, 1-5.

[94] Kalaiselvan V., Prasad T., Bisht A., Singh S., Singh G. N., Adverse drug reactions reporting culture in pharmacovigilance programme of India, **Indian J. Med. Res**, 140(4), 2014, 563-564.