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REVIEW ARTICLE

PHARMACOLOGY

CURRENT PROBLEMS AND FUTURE ASPECTS OF PHARMACOVIGILANCE IN INDIA

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ABSTRACT

Pharmacovigilance is related to the protection of public health and adverse drug reaction. While major advancements of the discipline of pharmacovigilance have taken place in the West, not much has been achieved in India. However, with more clinical trials and clinical research activity being conducted in India, there is an immense need to understand and implement pharmacovigilance. Now in India, pharmacovigilance has progressed from the situation as it was in past, but for different types of problems and limitations progress is yet not very rapid. So awareness is required for improvement of pharmacovigilance as well as public health. This review is aimed to offer an analytical study of current problems and future aspects of pharmacovigilance in India. The necessity of implementation of appropriate pharmacovigilance, its requirements, problems, limitation and the process how it can be more improved have been emphasized.

KEYWORDS

Pharmacovigilance, adverse drug reactions, public health programme, drug safety, polypharmacy, paradoxical reaction

INTRODUCTION

A very broad definition of a drug would include "all chemicals other than food that affect living processes." If the affect helps the body, the drug is a medicine. However, if a drug causes a harmful effect on the body, the drug is a poison. The same chemical can be a medicine and a poison depending on conditions of use, dose and the person using it. A person with drug toxicity has accumulated too much of a medication in the bloodstream [1, 2]. Adverse drug reactions, or ADRs, which are officially described as: "A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function."[3, 4]. ADRs also might be results of polypharmacy [5], iatrogenesis [6], pradoxical reaction [7] and other serious adverse events [8]. The word pharmacovigilance has derived from the Greek word pharmacon means 'drug' and the Latin word vigilare means 'to keep awake or alert, to keep watch.' Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines [9,10]. Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. Many other issues are also related to pharmacovigilance. These include counterfeit medicines. Generally speaking, pharmacovigilance is the science of collecting, monitoring, researching, assessing and evaluating information from healthcare providers and patients on the adverse effects of medications, biological products, herbalism and traditional medicines with a view to identifying new information about hazards associated with medicines and preventing harm to patients [11, 12]. Therefore pharmacovigilance deals with not only adverse effect of drug but also it deals with polypharmacy, iatrogenesis, paradoxical reaction and serious adverse event of a drug. Substandard medicines, medication errors, lack of efficacy, use of medicines for indication that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, assessment of medicine related mortality abuse and misuse of medicines, and adverse interaction of medicines with chemicals, other medicines and foods and drinks [13,14].

Recently pharmacovigilance is gaining importance for doctors and scientists as the number of stories in the mass media of drug recalls increases. Because clinical trials involve several thousand patients at most; less common side effects and ADRs are often unknown at the time a drug enters the market. Even very severe ADRs, such as liver damage, are often undetected because study populations are small. Postmarketing pharmacovigilance uses tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and postmarketing pharmacovigilance are critical throughout the product life cycle. With a number of recent high-profile drug withdrawals, the pharmaceutical industry and regulatory

agencies have raised the bar. Early detection of signals from both clinical trials and postmarketing surveillance studies have now been adapted by major pharmaceutical companies in order to identify the risks associated with the medicinal product and effectively managing the risks by applying robust risk management plans throughout the life cycle of the product. Signal detection and risk management has added a new dimension to the field of pharmacovigilance and as an evolving discipline, it requires ongoing refinement in order to increase its applicability and value to public health. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. Drug safety concerns are increasing in recent years with some high profile drug withdrawals by the regulatory authorities [15, 16].

Therefore I am taking an opportunity to write a review on "Current Problems in Pharmacovigilance and Future Aspects of Pharmacovigilance in India". The review will give insight on this important issue to the decision maker for marketing of new drug in India i.e. postmarketing surveillance studies and proper precautions for that, and as well as it might be used for the educational material to the teacher and student who would like to know details about this important topic.

Adverse drug reaction

An **adverse drug reaction** (abbreviated **ADR**) is an expression that describes harm associated with the use of given medications at a normal dose [3]. The meaning of this expression differs from the meaning of "side effect", as this last expression might also imply that the effects can be beneficial [4] .Adverse effects may be local [17], due to abnormal pharmacokinetics such as Comorbid disease states [18], Genetic factors [19,20], Phase I reactions [21, 22, 23], Phase II reactions [24, 25]. Interactions with other drugs are increased with polypharmacy [5], Protein binding 26 and Cytochrome P450 [21].

Examples of adverse effects associated with specific medications

1. Abortion, miscarriage or uterine hemorrhage associated with misoprostol (Cytotec), a labor-inducing drug (this is a case where the adverse effect has been used legally and illegally for performing abortions)
2. Addiction with many sedatives and analgesics such as diazepam, morphine, etc.
3. Birth defects associated with Thalidomide and Accutane.
4. Bleeding of the intestine associated with aspirin therapy.
5. Cardiovascular disease associated with COX-2 inhibitors (i.e. Vioxx).
6. Deafness and kidney failure associated with gentamicin (an antibiotic).
7. Death, following sedation in children using propofol (Diprivan)
8. Dementia associated with heart bypass surgery.
9. Depression or hepatic injury caused by interferon.
10. Diabetes caused by atypical antipsychotic medications (neuroleptic psychiatric drugs)
11. Diarrhea caused by the use of orlistat (Xenical).
12. Erectile dysfunction associated with many drugs, such as antidepressants.
13. Fever associated with vaccination (in the past, imperfectly manufactured vaccines, such as BCG and poliomyelitis, have caused the very disease they intended to fight).
14. Glaucoma associated with corticosteroid-based eye drops.
15. Hair loss and anemia may be caused by chemotherapy against cancer, leukemia, etc.
16. Headache following spinal anesthesia.
17. Hypertension in ephedrine users, which prompted FDA to remove the status of dietary supplement of ephedra extracts.
18. Insomnia caused by stimulants, Ritalin, Adderall, etc.

19. Lactic acidosis associated with the use of stavudine (Zerit, for anti-HIV therapy) or metformin (for diabetes).
20. Liver damage from paracetamol.
21. Melasma and thrombosis associated with use of estrogen-containing hormonal contraception such as the combined oral contraceptive pill.
22. Irreversible Peripheral neuropathy associated with the use of fluoroquinolone medications [27, 28, 29].
23. Rhabdomyolysis associated with statins (anti-cholesterol drugs).
24. Seizures caused by withdrawal from benzodiazepine.
25. Drowsiness or increase in appetite due to antihistamine use. Some antihistamines are used in sleep aids explicitly because they cause drowsiness.
26. Stroke or heart attack associated with sildenafil (Viagra) when used with nitroglycerine.
27. Suicide, increased tendency associated to the use of fluoxetine and other SSRI antidepressants.
28. Tardive dyskinesia associated with long-term use of metoclopramide and many antipsychotic medications.
29. Spontaneous Tendon rupture associated with fluoroquinolone drugs [30] even occurring as late as 6 months after treatment had been terminated [31] .

Polypharmacy

The term polypharmacy generally refers to the use of multiple medications by a patient. The term is used when too many forms of medication are used by a patient, when more drugs are prescribed than is clinically warranted [5] or even when all prescribed medications are clinically indicated but there are too many pills to take (pill burden). Furthermore, a portion of the treatments may not be evidence-based. The most common results of polypharmacy are increased adverse drug reactions, drug-drug interactions and higher costs [32]. Polypharmacy is most common in the elderly but is also widespread in the general population [33]. Pill burden is a term that refers to the number of tablets, capsules or other dosage forms that a patient takes on a regular basis. Patients at greatest risk of polypharmacy consequences include the elderly, psychiatric patients, patients taking five or more drugs concurrently, those with multiple physicians and pharmacies, recently hospitalized patients, individuals with concurrent comorbidities [34], low educational level [35], and those with impaired vision or dexterity. A patient with a complex or even an ostensibly straightforward illness whose personal pharmacopoeia reads like a drug store pharmacy is not necessarily receiving poor treatment. A carefully followed patient with whom a physician is using additive drug choice and dosage range on a trial and error basis may lead to a treatment program that, for a real example, includes two antidepressants, three antihypertensives, a beta blocker, a calcium channel blocker, a bone saving bisphosphonate, an antiepileptic, a stomach saving H2 blocker, aspirin, prostaglandin blocker, lactoferrin, a calcium-magnesium supplement and herbal preparations. Two generally true circumstances underlie the theory of thoughtful, therapeutic polypharmacy: (1) Drugs given for a single somatic locale act on biochemical mechanisms present throughout the body such that their nonlinear interactions can produce an (unknown except empirically) global physiological state of health [36]. (2) The more independent variables, "handles", to manipulate, the greater the likelihood of finding and stabilizing a small available parametric space of healthy function while minimizing unwanted effects [37]. Zarowitz *et al.*[38] studied clinical pharmacists performing drug therapy reviews and the teaching of physicians and their patients about drug safety and polypharmacy, as well as collaborating with

physicians and patients to correct polypharmacy problems. This led to a marked improvement in interactions and cost. Similar programs are likely to reduce the potentially deleterious consequences of polypharmacy. Such programs hinge upon patients and doctors informing pharmacists of other medications being prescribed, as well as herbal, over-the-counter substances and supplements that occasionally interfere with prescription-only medication.

Iatrogenesis

The terms **iatrogenesis** and **iatrogenic artifact** refer to inadvertent adverse effects or complications caused by or resulting from medical treatment or advice. Causes of iatrogenesis include chance, medical error, negligence, social control and the adverse effects or interactions of prescription drugs. In the United States, from 120,000 to 225,000 deaths per year may be attributed in some part to iatrogenesis [6]. Examples of iatrogenesis are medical error, wrong prescription illegible handwriting, negligence, faulty procedures, techniques, information, or methods, failure in life support instruments, prescription drug interaction, adverse effects of prescription drugs, over-use of drugs leading to antibiotic resistance in bacteria, nosocomial infection, blood transfusion and harmful emotional distress from the ascription of mental pathology nomenclature for transient personal problems Nosocomial infection is A related term is *nosocomial*, which refers to an iatrogenic illness due to or acquired during hospital care, such as an infection [39]. In psychology, iatrogenesis can occur due to misdiagnosis (including diagnosis with a false condition as was the case of hystero-epilepsy [40]. Conditions hypothesized to be partially or completely iatrogenic include bipolar disorder [41], dissociative identity disorder [40, 42] fibromyalgia 43 somatoform disorder and chronic fatigue syndrome [44] posttraumatic stress disorder [45] substance abuse [46] antisocial youths [47] and others [48] though research is equivocal for each condition. Medical treatment does not only have an effect on the mind and body of patients but also on their wallet. Meessen et al. used the term “Iatrogenic poverty” to describe impoverishment induced by medical care [49]. Impoverishment is described for households exposed to catastrophic health expenditure [50] or to hardship financing [51]. Every year, worldwide, over 100,000 households fall into poverty due to health care expenses. Especially in countries in economic transition, the willingness to pay for health care is increasing and the supply side does not stay behind and develops very fast. But, the regulatory and protective capacity in those countries is often lagging behind. Patients easily fall in a vicious circle of illness, ineffective therapies, consumption of savings, indebtedness, sale of productive assets and eventually poverty. Iatrogenesis is a major phenomenon, and a severe risk to patients. A study carried out in 1981 more than one-third of illnesses of patients in a university hospital were iatrogenic, nearly one in ten were considered major, and in 2% of the patients, the iatrogenic disorder ended in death. Complications were most strongly associated with exposure to drugs and medications [52]. In another study, the main factors leading to problems were inadequate patient evaluation, lack of monitoring and follow-up, and failure to perform necessary tests [53].

Paradoxical reaction

A **paradoxical reaction** or **paradoxical effect** is when medical treatment, usually a drug, has an opposite effect to an effect normally expected. An example of a paradoxical reaction is when a pain relief medication causes an increase in pain. Some sedatives prescribed for adults actually cause hyperactivity in children. For example, there are serious complications occurring in conjunction with the use of sedatives creating a series of effects in some people, that create the total opposite

effects as those expected. The paradoxical reactions may consist of depression, with or without suicidal tendencies, phobias, aggressiveness, violent behavior and symptoms sometimes misdiagnosed as psychosis [7]. Benzodiazepines, a class of psychoactive drugs called the "minor" tranquilizers, have varying hypnotic, sedative, anxiolytic, anticonvulsant, and muscle relaxing properties, but they may create the exact opposite effects. Susceptible individuals may respond to benzodiazepine treatment with an increase in anxiety, aggressiveness, agitation, confusion, disinhibition, loss of impulse control, talkativeness, violent behavior, and even convulsions. Paradoxical adverse effects may even lead to criminal behaviour [54]. Severe behavioral changes resulting from benzodiazepines have been reported including mania, schizophrenia, anger, impulsivity, and hypomania [55]. Self aggression has been reported and also demonstrated in laboratory conditions in a clinical study. Diazepam was found to increase people's willingness to harm themselves [56]. Paradoxical effects of benzodiazepines appear to be dose related, that is, likelier to occur with higher doses [57]. In a letter to the *British Medical Journal*, it was reported that a high proportion of parents referred for actual or threatened child abuse were taking drugs at the time, often a combination of benzodiazepines and tricyclic antidepressants. Many mothers described that instead of feeling less anxious or depressed, they became more hostile and openly aggressive towards the child as well as to other family members while consuming tranquilizers. The author warned that environmental or social stresses such as difficulty coping with a crying baby combined with the effects of tranquilizers may precipitate a child abuse event [58] .Benzodiazepines can sometimes cause a paradoxical worsening of EEG readings in patients with seizure disorders [59]. Paradoxical rage reactions due to benzodiazepines occur as a result of an altered level of consciousness, which generates automatic behaviors, anterograde amnesia and uninhibited aggression. These aggressive reactions may be caused by a disinhibiting serotonergic mechanism [60]. Chlorpromazine, an antipsychotic and antiemetic drug, which is classed as a "major" tranquilizer may cause paradoxical effects such as agitation, excitement, insomnia, bizarre dreams, aggravation of psychotic symptoms and toxic confusional states [61]. Antidepressants can sometimes make users obsessive violent suicidal compulsions which are in contrast to what antidepressants are meant to do. This can be regarded as a paradoxical reaction [62]. Children and adolescents are particularly sensitive to paradoxical reactions of self harm and suicidal ideation whilst consuming antidepressants [63]. The paradoxical effect or Eagle phenomenon (named after J. Eagle who first described it) refers to an observation of an increase in survivors, seen when testing the activity of an antimicrobial agent. Initially, when an antibiotic is added to a culture media, the number of bacteria that survive drops, as you would expect. But after increasing the concentration beyond a certain point, the number of bacteria that survive, paradoxically, increases. One of the explanations could be that as the concentration is too high, the agent might be self-antagonising the receptor with which it binds. (Penicillin binding proteins, for example, in the case of penicillin) This self antagonism is only a possible explanation for the phenomenon [64].

Serious adverse event

A **serious adverse event** (SAE) in human drug trials are defined as any untoward medical occurrence that at any dose a) results in death, b) is life-threatening, c) requires inpatient hospitalization or prolongation of existing hospitalization, d) results in persistent or significant disability/incapacity, or e) is a congenital anomaly/birth defect [8] Investigators

in human clinical trials are obligated to report these events in clinical study reports [65]. Research suggests that these events are often inadequately reported in publicly available reports [66]. Because of the lack of these data and uncertainty about methods for synthesising them, individuals conducting systematic reviews and meta-analysis of therapeutic interventions often unknowingly overemphasise health benefit [67]. In order to balance the overemphasis on benefit, scholars have called for more complete reporting of harm from clinical trials [68].

Pharmacovigilance in India

India has more than half a million qualified Doctors and15, 000 hospitals having bed strength of 6, 24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our country. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs. Clearly aware of the enormity of task the Central Drugs Standard Control Organization (CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Programme. It is largely based on the recommendations made in the WHO document titled "Safety Monitoring of Medicinal Products – Guidelines for Setting up and Running a Pharmacovigilance Centre" [15].
The National Pharmacovigilance Programme was officially inaugurated by the Honorable Health Minister Dr. Anbumani Ramadoss on 23 November, 2004 at New Delhi [69].

The specific aims of the Pharmacovigilance Programmers are to:

- Contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
- Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to use of medicines.
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

The Programmer aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO-UMC.

Under the program 26 peripheral centers, 5 Regional Centers and 2 Zonal Centers were established. The Peripheral centers will record the Adverse Events (AE) and send to the Regional Centers. They in turn collate and scrutinize the data received from the Peripheral Centers and submit to the Zonal Centers. The Zonal Centers will analyze the data and submit consolidated information to the National Pharmacovigilance Centre. The Zonal Centre will also provide training, general support and coordinate the functioning of the Regional Centers. Pharmacovigilance is still in its infancy in India and there exists very limited knowledge about the discipline. While major advancements of the discipline of pharmacovigilance have taken place in the Western countries, not much has been achieved in India [15].

Next in 1997, India joined the World Health Organization (WHO) Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden. Three centres mainly based in teaching hospitals were identified for ADR monitoring a national Pharmacovigilance centre located in the Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), New Delhi and two special centers of WHO in Mumbai (KEM Hospital) and Aligarh (JLN) Hospital, Aligarh Muslim University) the major

role of these centre were to monitor ADRS to medicines marketed in India. But this attempt was unsuccessful and hence, again from the 1st January, 2009, the WHO sponsored and world's Bank funded National Pharmacovigilance Program (NPP) for India was made operational [69]. The objectives of NPP were to involve a large number of health care professionals in the process, inculcate the culture of reporting ADRS and to be a land mark for global drug monitoring [15, 69, 70, 71].

Causes of failure of implementation of pharmacovigilance in India

A number of studies conducted throughout the world have demonstrated that ADRs significantly decrease the quality of life, increase hospitalizations, prolong hospital stay and increase mortality. A landmark study by Lazarou in 1998 described ADRs to be the 4 th - 6 th largest cause of death in the USA and ADRs are estimated to cause 3-7% of all hospital admissions [72]. More than half of these ADRs are not recognized by the physicians on admission and ADRs may be responsible for death of 15 of 1000 patient's admitted [73]. Furthermore, the financial cost of ADRs to the healthcare system is also huge. With more new medicines being approved for marketing more quickly without long-term safety studies by the regulatory authorities and switching of prescription-only medicines (POM) to over-the-counter (OTC) to be used more widely by patients for self-medication, the general public is at risk of exposing itself to ADRs. In the past, India's regulatory agencies and drug companies based their safety assessments on experiences derived from long-term drug use in the Western markets and there was no real urgency for the government to establish a strong pharmacovigilance system of its own. In recent years, however, the lag between when a drug is placed on the market and its subsequent availability in India has decreased considerably so that the much needed longer-term safety data is no longer available. In addition, India-based drug companies have increased their capacity to develop and launch new drugs through their own research efforts and this has heightened the importance of developing adequate internal pharmacovigilance standards to detect adverse drug events [71].

However, what needs to be more important along with the funding is a focused vision and effective strategy for developing the pharmacovigilance systems, especially in the DCGI Office, which is lacking. Traditionally, pharmacovigilance was never done in India in Pharmaceutical companies, be it Indian or MNCs, so there is an immense shortage of knowledgeable people who will be able to advice the DCGI on this matter, as pharmacovigilance is a very complex subject, intertwined with regulations and complex systems. The need is therefore to engage a completely independent adviser who has an extensive and practical knowledge on pharmacovigilance, who can act as a Pharmacovigilance Advisor to the Government of India to effectively implement the systems and policies on pharmaocvigilance. This will help the DCGI to spearhead the activities and implementation of pharmacovigilance. India is a vast country and there is a surfeit of drug brands-more than 6,000 licensed drug manufacturers and over 60,000 branded formulations. India is the fourth largest producer of pharmaceuticals in the world and is also emerging as a clinical trials hub. Many new drugs are being introduced in the country, so there is an immense need to improve the pharmacovigilance system to protect the Indian population from potential harm that may be caused by some of the new drugs. However, there are many issues and problems that have prevented building a robust pharmacovigilance system, which are described below [15].

1. Pharmacovigilance systems are not well-funded and organized for a vast country like India to serve patients and the public.

2. The information obtained to date in the zonal centers from various peripheral centers is often poor and not well-analyzed. There is insufficient research on ADRs in India, so the exact incidence of specific ADRs is unknown.
3. Understanding by healthcare professionals (both in rural areas and urban cities and hospitals) and knowledge and motivation for pharmacovigilance is almost negligible. There is hardly any encouragement from the department of health to provide more training and create more awareness amongst them for better reporting.
4. In India, there are several consumers' groups who encourage patients to report any adverse reactions encountered by them, although there is no information for patients to report ADRs directly to the regulatory authority.

Current problems in pharmacovigilance [74]

1. Topical tacrolimus (Protopic) and pimecrolimus (Elidel): potential cancer risk.
2. Duloxetine (Yentreve, Cymbalta): need for monitoring.
3. Tenofovir (Viread): interactions and renal adverse effects.
4. Linezolid (Zyvox): severe optic neuropathy.
5. CosmoFer and high risk of anaphylactoid reactions.
6. Drotrecogin alfa (activated) (Xigris): risk-benefi t in the management of sepsis.
7. Rosuvastatin (Crestor): introduction of 5 mg starting dose [75].
8. Osteonecrosis of the jaw with bisphosphonates.
9. High dose inhaled steroids: new advice on supply of steroid treatment cards [76, 77].
10. Local reactions associated with pre-school d/DTap-IPV boosters.
11. Salmeterol (Serevent) and formoterol (Oxis, Foradil) in asthma management [78, 79].
12. Risk of QT interval prolongation with methadone [80].
13. Tamsulosin (Flomax) and Intraoperative Floppy Iris Syndrome (IFIS) [81].
14. Cardiovascular safety of NSAIDs and selective COX-2 inhibitors.
15. Erythromycin and other macrolides: focus on interactions [82, 83].
16. Glucosamine adverse reactions and interactions [84].
17. Isotretinoin (Roaccutane): psychiatric adverse reactions.
18. Cardiac arrhythmias associated with antipsychotic drugs.
19. HRT and tibolone (Livial): update on the risk of endometrial cancer.
20. Hypoglycaemia unawareness on transferring insulins.
21. Withdrawal of co-proxamol [85].
22. Intravenous human normal immunoglobulin (IVIg) and thromboembolic adverse reactions.
23. NSAIDs and infertility.
24. Patients across the UK may report suspected adverse reactions.

Future aspect of pharmacovigilence in India:

With more and more clinical trials and other clinical research activities being conducted in India, there is an immense need to understand the importance of pharmacovigilance and how it impacts the life cycle of the product. Given this situation at present, the DCGI should act quickly to improve pharmacovigilance so as to integrate Good Pharmacovigilance Practice into the processes and procedures to help ensure regulatory compliance and enhance clinical trial safety and postmarketing surveillance. A properly working pharmacovigilance system is essential if medicines are to be used safely. It will benefit all parties including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk and to devise and implement effective risk management plans to save their

drugs in difficult circumstances [15].

Having considered the problems and challenges facing the development of a robust pharmacovigilance system for India, the following proposals[15] might be follows:

1. Building and maintaining a robust pharmacovigilance system.
2. Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections.
3. High-level discussions with various stakeholders.
4. Strengthen the DCGI office with trained scientific and medical assessors for pharmacovigilance.
5. Creating a single country-specific adverse event reporting form to be used by all.
6. Creating a clinical trial and post marketing database for SAEs / SUSARs and ADRs for signal detection and access to all relevant data from various stakeholders.
7. List all new drugs / indications by maintaining a standard database for every pharmaceutical company.
8. Education and training of medical students, pharmacists and nurses in the area of pharmacovigilance.
9. Collaborating with pharmacovigilance organizations in enhancing drug safety With advancements in information technology, there has been the emergence of new opportunities for national [86] and international [87] collaborations that can enhance postmarking surveillance programs and increase drug safety. The Uppsala Monitoring Center (UMC) is an example for an international collaboration to establish a harmonized post marketing surveillance database [87].
10. Building a network of pharmacovigilance and pharmacopeidemiologists in India.

CONCLUSION

India has more than half a million qualified Doctors and15,000 hospitals having bed strength of 6,24,000. It is the fourth largest producer of pharmaceuticals in the world. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in our country. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by some of these new drugs [15].The recent USFDA safety warning on rosiglitazoine, a drug approved to treat Type 2 diabetes. On 23 rd May, The New England Journal of Medicine rushed out an analysis by prominent cardiologist Steven Nissen, of data about patients taking Avandia (rosiglitazone manufactured by GSK). It suggests they have a 43% higher chance of suffering a heart attack [15].

We earlier had Vioxx, which created serious adverse events in patients taking this drug. This popular painkiller went on the market in 1999, the same year as Avandia. The same scientist, Nissen, raised some of the earliest concerns that tied Vioxx to higher rates of heart attack and stroke. After Merck finally pulled Vioxx off the market in 2004, an FDA whistle-blower testified that the agency had failed to heed ample warnings. These examples show that after FDA certifies new drugs as safe and effective based on clinical trials, adverse effects can show up when millions use them. Vioxx caused such problems. So, perhaps, has Avandia. This further testifies the urgent need of a pharmacovigilance program in India for even Generic drugs which are already marketed elsewhere in the world [15].

Pharmacovigilance has not picked up well in India and the subject is in its infancy. India rates below 1% in pharmacovigilance as against the world rate of 5%. This is due to ignorance of the subject and also lack of training. The office of the Drugs Controller General of India has attempted to implement a

pharmacovigilance program in India without much success. A regulation is required to implement the system of reporting adverse events of drugs introduced in the Indian market by pharmaceutical companies. The government has to play an important role in ensuring the availability of safe medicines to the public [16].

The mind set of all including the bureaucrats and politicians and healthcare professionals need to be changed. The politicians and bureaucrats need only to support with full powers to the DCGI and the professionals. Symogen deals with all aspects of pharmacovigilance and has also started functioning in India. With the help of all stakeholders, let us pledge to make this happen in India and build a world-class pharmacovigilance system and safe more life from new drug toxicity tragedy.

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