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PHARMACOVIGILANCE AND ITS INDIAN PERSPECTIVE

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ABSTRACT:

With massive expansion of healthcare as well as drug research and development activity in a populous developing nation, pharmacovigilance is the code word for quality and safety of the endeavors. A review of basic understanding and executionery tasks is attempted, drawing upon the contemporary national scenario. In the past, India's regulatory agencies and Drug Company based their safety assessments on experiences derived from long term drug use in the western market and there was no urgency for the government to establish a strong Pharmacovigilance system of its own. But in recent years(after 2005) DCGI office significantly involve in set up of ADR monitoring centers throughout the country with help of Ministry of Health & Family Welfare Govt.of India and World health organization (WHO) Uppsala.

Keywords: ADR, Drug research, Pharmacovigilance, Pharmacoepidemiology, Therapeutics.

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INTRODUCTION

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[1,2]. Recently, the concerns of pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biologicals, medical devices and vaccines. 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[3, 4].

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[5,6].

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. Post marketing 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. Early detection of signals from both clinical trials and post marketing 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. Drug safety concerns are increasing in recent years with some high profile drug withdrawals by the regulatory authorities[7, 8].

ADVERSE DRUG REACTION

As per WHO following is the definition of adverse drug reaction (ADR).

"A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function". This definition is a well accepted definition for the marketed product.

Consequences of adverse drug reaction direct or indirect:

1. Adverse effect on patient quality of life.
2. Admission to hospitals or attendance in primary health center.
3. Length of hospital stay gets increased (prolongation of inpatient hospitalization).
4. Cost of patient care gets increased.
5. Adverse reaction may mimic disease and result in unnecessary investigations and/or delay in treatment procedures.
6. Adverse reaction may lead to death/permanent disability/congenital anomaly or birth defects.

PHARMACOLOGICAL CLASSIFICATION OF ADR

Type A (Augmented): This is the commonest type (up to 70%) of ADR which is predictable by the pharmacological mechanisms, e.g., hypoglycaemia caused by insulin or oral hypoglycaemics.

Type B (Bizarre): This type of ADR is not expected from the known pharmacological mechanism e.g., hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol. Such ADR$_s$ are unrelated to dose.

Type C (Continuous drug use): This type of ADR is occurs as a result of continuous drug use. Such type of ADR may be irreversible, unexpected, unpredictable, e.g., tardive dyskinesias by antipsychotics, dementia by anticholinergics medications.

Type D (Delayed): This type of ADR characterized by delayed occurrence even after the cession of treatment e.g. corneal opacities after thioridazine, ophthalmopathy after chloroquine.

Type E (End of Dose): This type of ADR is usually characterized by withdrawal reactions. Such ADR occurs typically with the depressant drugs, e.g. hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal, first dose hypotension caused by alpha blocker (Prazosin).

Type F (Failure of therapy): This type of ADR results from the infective treatment, e.g., accelerated hypertension because of inefficient control. This may be called as lack of efficacy[9].

Polypharmacy: The term polypharmacy generally refers to the use of more than one medication by a patient. Furthermore, a portion of the treatments may not be evidence-based. 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[10], low educational level[11], and those with impaired vision or dexterity. 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 combination treatment program.

Iatrogenesis The terms **iatrogenesis** refers to inadvertent adverse effects or complications caused by or resulting from medical treatment or advice. 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. A related term is *nosocomial*, which refers to an iatrogenic illness due to or acquired during hospital care, such as an infection[12]. Patients easily fall in a vicious circle of illness, ineffective therapies, consumption of savings, indebtedness, sale of productive assets and eventually poverty. 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. The main factors leading to problems are inadequate patient

evaluation, lack of monitoring and follow-up, and failure to perform necessary tests[13].

Paradoxical reaction: A **paradoxical reaction** or **paradoxical effect of** medication refers to an opposite effect rather than a 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. Paradoxical effects of benzodiazepines appear to be dose related, that is, likelier to occur with higher doses[14]. Environmental or social stresses such as difficulty coping with a crying baby combined with the effects of tranquilizers may precipitate a child abuse event[14]. 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[15]. 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[16].

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. Research suggests that these events are often inadequately reported in publicly available reports[17]. Because of the lack of these data and uncertainty about methods for synthesizing them, individuals conducting systematic reviews and meta-analysis of therapeutic interventions often unknowingly overemphasize health benefit[18]. In order to balance the overemphasis on benefit, scholars have called for more complete reporting of harm from clinical trials[19].

WHO Definition of Pharmacovigilance: WHO define the Pharmacovigilance (PV) as the pharmacological science relating to the detection, evaluation, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines[20].

In General, pharmacovigilance is the knowledge of collecting, observing, examining, assessing and estimating evidence from health care workers and patients on the contrary effects of drugs, natural products, herbal and traditional medicines with a view to:

1. Finding new risks associated with remedies.
2. Prevention and control of infectious diseases in patients.
3. Reporting requirements in special situations. Pharmacovigilance is an important and integral part of clinical research. Both clinical trials safety and post marketing pharmacovigilance are critical throughout the product life Cycle[21].

Pharmacovigilance through Public Health Programmes: An important arm of patient carries pharmacovigilance. Prevention of unwanted disease by use of medicines is the main aim of the Pharmacovigilance. Good pharmacovigilance will identify the hazard aspects in the short period of time. Public Health Programmers (PHP) are intended to develop the health of target inhabitants by use of medicines, education, environmental modifications, nutrition involvement, behavioral changes and preventive actions such as immunization, hypertension and assessment for breast cancer are the important components of a PHP[22].

The systematized efforts of the public to care for and encourage people's health are known as Public health. Through mutual or community actions can be increase the health of all the people, this can be mainly done by the combination of sciences and skills.

Pharmacovigilance through Pharmacogenomics:

For the treatment of different type of disorders, different classes of medication are available. Due to difference in genetic pattern, patient may respond differently to medication and develop different adverse effects[23]. Difference in drug response and drug tolerability can be understood by use of Pharmacogenomics and Pharmacokinetics. Many types of assumed ADRs are complex and involve or depend upon several factors which cause disease for examples it include the metabolic syndrome, suicidality, hepatic dysfunction and cardiac abnormalities. Individual who are susceptible to ADRs and has a potential to reduce the personal and population costs of drug related morbidity can be helped by Pharmacogenetics. Although promising, the eventual impact of pharmacogenomics profiling for identification of ADR susceptibility among individuals would depend upon incidence of drug toxicity, prevalence of variants severity of consequence and also the availability of rapid, reliable and cost effective assays. Several researchers have proposed the integration of genomic information with the pharmacovigilance database.

Pharmacovigilance through Pharmacoenvironmentology: The drug may be metabolized to some amount and expelled into the surrounding areas (including through respired air) as main drug or its metabolites, or as a mixture of both. If these drugs arise from subjects subsequent to pharmacotherapy, it should be a specific field of pharmacology and not of environmental studies.

This domain may be referred as Pharmacoenvironmentology[24].

Pharmacoenvironmentology may be an enlargement of Pharmacovigilance which is allocating with the possessions related to the surrounding areas and ecosystem. Pharmacologists having this particular expertise (pharmacoenvironmentologist) may be is a compulsory component of the team assessing different aspects of drug safety.

Pharmacovigilance through Pharmacoepidemiology: Pharmacovigilance and pharmacoepidemiology are relatively new fields relevant to processes within pharmacovigilance. Epidemiologists, pharmacists and other people can also contribute to the development of the system[25].

Pharmacovigilance through academics: Good pharmacovigilance programmes are needed for every country. Teaching of PV should be problem-based, activity-based and linked to the rational use of medicines.

A major source for pharmacovigilance to get information about drug is spontaneous reporting. Pharmacovigilance must be linked to component on the rational use of medicines (RUM). Pharmacovigilance course for pharmacologists and other healthcare personnel has been suggested by Uppsala Monitoring Centre (UMC) and the international collaborating centre for ADR.

Doctors (general practitioners and specialists) are important in reporting ADRs to the pharmacovigilance programme. Training programmes for doctors should be problem-based, activity-based and carried out in small groups.

Pharmacovigilance of Herbal medicines: Herbal medicines are popular in general public but the safety of these remedies is major issue for population of nation and national health committee[26].

Pharmacovigilance in India: 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. 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". The National Pharmacovigilance Programme was officially inaugurated by the Honorable Health Minister Dr. Anbumani Ramadoss on 23 November, 2004 at New Delhi[27].

The specific aims of the Pharmacovigilance Programme: Contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.

1. Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions.
2. Improve public health and safety in relation to use of medicines.
3. Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

Problem of implementation of Pharmacovigilance in India: More than half of these ADRs are not recognized by the physicians. The financial cost of ADRs to the healthcare system is huge. With more new medicines being approved for marketing more quickly without long-term safety studies and switching of prescription-only medicines (POM) to over the counter (OTC) 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 the lag between drug introduction 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 this has heightened the importance of developing adequate internal pharmacovigilance standards to detect adverse drug events [28]. Besides funding, a focused vision and effective strategy for developing the pharmacovigilance systems, by DCGI Office, is desirable. Traditionally, pharmacovigilance was never done in India in Pharmaceutical companies, as pharmacovigilance is a very complex subject, intertwined with regulations and complex systems. The need is therefore for independent adviser who has an extensive and practical knowledge on pharmacovigilance, to the Government of India to effectively implement the systems and policies on pharmacovigilance. This will help the DCGI for implementation of pharmacovigilance.

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. More training and create more awareness amongst them for better reporting, is crucial need.

4. In India, there are several consumers' groups who encourage patients to report any adverse reactions encountered by them, but linkage to the regulatory authority is undeveloped.

PROMINENT PERSPECTIVES EMERGING OF PHARMACOVIGILANCE [29]

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-benefit in the management of sepsis.
7. Rosuvastatin (Crestor): introduction of 5 mg starting dose[30].
8. Osteonecrosis of the jaw with bisphosphonates.
9. High dose inhaled steroids: new advice on supply of steroid treatment cards[31, 32].
10. Local reactions associated with pre-school d/D Tap-IPV boosters.
11. Salmeterol (Serevent) and formoterol (Oxis, Foradil) in asthma management[33, 34].
12. Risk of QT interval prolongation with methadone[35].
13. Tamsulosin (Flummox) and Intraoperative Floppy Iris Syndrome (IFIS)[36].
14. Cardiovascular safety of NSAIDs and selective COX-2 inhibitors[37].
15. Erythromycin and other macrolides: focus on interactions[38, 39].
16. Glucosamine adverse reactions and interactions[40].
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.
22. Intravenous human normal immunoglobulin (IVIg) and thromboembolic adverse reactions.
23. NSAIDs and infertility.
24. Patients across the UK may report suspected adverse reactions[41].

FUTURE OF PHARMACOVIGILANCE IN INDIA

India is becoming a hub for clinical trial, clinical research and manufacturing of new drugs. Due recognition of pharmacovigilance and how it impacts the life cycle of the product a pharmacovigilance system is essential if medicines are to be used safely. It will benefit all, including healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It helps pharmaceutical companies to monitor their medicines for risk.

CONCLUSION

Pharmacovigilance is the only best tool to ensure the safety of drug product throughout the whole lifecycle. Its significance is very much crucial as the clinical trial have its own limitation to detect the rare and very rare ADR$_s$. The data and profile regarding safety of any drug products is very much important to take appropriate regulatory decision by drug regulatory authorities to safeguard public health. Spontaneous reporting system remains as a most widely used method to report ADR$_s$ and is able to generate signal of rare and very rare types of ADR$_s$. If all the healthcare professionals take ADR reporting as ethical obligations and their major responsibilities, we can make our country and world safer than what is today.

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