KNOWLEDGE AND AWARENESS OF ADVERSE DRUG REACTIONS

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ABSTRACT: The safe use of medicines is a critical issue for all health care professionals, including physicians, pharmacists and nurses as well as public. Adverse drug reactions (ADRs) are unwanted effects that are the major cause of morbidity and mortality in whole world also has prolongation of hospital stay and increase visiting of emergency department. The present review dealt to assess the knowledge, attitude and practices of Pharmacovigilance. Pharmacovigilance is applicable to persuade the safety of medicine and protect consumers from their harmful effects. Pharmacovigilance helps in early detection of ADRs and identification of risk factors. This is a questionnaire based study involving awareness of ADRs, knowledge of Pharmacovigilance system, availability of ADRs reporting system, patient counseling about ADRs and reporting of ADRs. Implementing good Pharmacovigilance practice in hospital settings can lead to proper reporting of ADRs. To monitor the ADRs in India Pharmacovigilance program of India (PvPI) is in an infancy period and as according to PvPI other branches like Haemovigilance, Biovigilance and Herbal Pharmacovigilance are also starts.

INTRODUCTION: The world health organization (WHO) defines adverse drug reactions (ADRs) as ‘a reaction which is noxious and unintended occurs at doses normally used in humans for prevention, diagnosis or therapy of disease, or for the modification of physiological functions’. ADRs are a major cause of morbidity and mortality around the world. Any substance which is having a therapeutic effect can also produce low as well as high risk of unwanted effects or ADRs. Out of the several methods of detecting ADRs, spontaneous reporting is one that has contributed significantly to improve levels of Pharmacovigilance in many countries, which is mostly used socio-economic surveillance system and basis of safety monitoring of new drugs. Pharmacovigilance is a part of patient care and patient safety that ensures the best use of medicines for the better treatment or prevention of adverse ADRs. According to WHO Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The serious cause of lack of awareness among health care professionals and patients is of ADRs. ADR monitoring and reporting system started in developing countries mainly in the wake of the Thalidomide tragedy. In order to improve reporting system in India a contribution to Uppsala Monitoring Database, which is very little responsible for international Monitoring Database. Pharmacovigilance is useful in early detection as same as identification of both risk factors and the mechanism underlying the ADRs. The terms adverse drug reaction and adverse effects are indistinguishable except that an adverse effect is seen from the point of view of drug while an adverse reaction seen from the point of patient. The

Keywords: Adverse drug reaction, Pharmacovigilance, Adverse event, Haemovigilance, WHO, PvPI.
term adverse effect is preferable to other terms such as side or toxic effect. Side effect is an “unintended effect occurring at normal dose related to the pharmacological properties” whereas as a toxic effect “is an exaggeration of the desired therapeutic, which is usually not common at normal doses”. Still the Adverse effects and adverse reaction are different from adverse events. Adverse events are medical occurrence temporally associated with the use of medicinal product, but not necessarily causality related.  

Serious adverse effects and reactions are untoward medical occurrence that at any dose:

- Results in death
- Requires inpatient hospitalization and prolongation of existing hospitalization
- Results in persistent and hospital disability
- Is it life threatening?

Classification of ADRs:

Type A (Augmented):
These are predictable, common and pharmacological action of drug.

- Toxicity of overdose (e.g.: hepatic failure with high dose of paracetamol),
- Side Effects (e.g.: sedation with Antihistamines),
- Secondary effects (e.g.: development of diarrhea with antibiotic therapy due to altered gastrointestinal bacterial flora),
- Drug Interaction (e.g.: Theophylline toxicity in the presence of erythromycin therapy).

Type B (Bizarre Effects):
These are unpredictable, uncommon, usually not related to the pharmacological action of the drug.

- Intolerance (e.g.: tinnitus with use of aspirin)
- Hypersensitivity: immunological reaction (e.g.: anaphylaxis with penicillin administration)
- Pseudoallergic: non-immunological reaction (e.g.: radio contrast dye reaction)

- Idiosyncratic Reaction (e.g.: development of Anemia with the use of antioxidant drugs in the presence of glucose 6-phosphate dehydrogenase deficiency).

Type C (Chronic):
These reactions are associated with long term drug therapy (e.g: Benzodiazepine dependence and analgesic neuropathy).

Type D (Delayed):
These reactions refer to carcinogenic and teratogenic effects. These reactions are delayed on onset and is time related (e.g.: diethylstilbesterol taken by women can cause vaginal and other reproductive organ damage in female offspring).

Type E (Ending of Use):
This occurs when a drug was suddenly stopped a long term used drug, the patient suffers from a withdrawal reaction (e.g.: rebound hypertension following sudden cessation of clonidine).

Type F (Failure of treatment):
It is a common dose related and often results from ineffective treatment of drug.

Type G (Genotoxicity):
Many drugs can produce genetic damage in humans. Notably some are potential carcinogenic and genotoxic.

Type H (Hypersensitivity reaction):
These reactions are side effects caused by allergy or hypersensitivity, they are probably the most common adverse reaction after type A. They are not pharmacologically predictable and dose dependent. Accordingly dose reduction does not leads to amelioration of symptoms, so the drug must be stopped.

Type U (Unclassified):
Some ADRs have a mechanism that’s not understood and these must remain unclassified until more is known about them.

| TABLE 1. ADRS ARE ALSO CLASSIFIED IN TERMS OF SEVERITY, CAUSALITY AND PREVENTABILITY |
|-----------------|---------------------------------|
| Severity        | Definitions                     |
| Minor           | No antidote, therapy or prolongation of hospital required. |
Moderate | Change in drug therapy, specific treatment or an increase in hospitalization by at least one day.
Severe | Potentially life-threatening cause permanent damage or require intensive care.
Lethal | Directly or indirectly contributed to death of patient.

Causality:

- **Certain:** A clinical event or laboratory test abnormality with plausible time relationship to drug intake, which cannot be explained by disease or other drugs. The response to withdrawal of drug should be clinical plausible. The event must be definitive pharmacologically and phenomenologically using satisfactory rechallenge procedure if necessary.\(^5\)

- **Probable/likely:**
  A clinical event or laboratory test abnormality with, reasonable sequence to drug intake. Unlikely to be attributed to disease or other drugs or chemicals and which follows a clinically reasonable on withdrawal.\(^1\)

- **Possible:**
  A clinical event or laboratory test abnormality with, reasonable time relationship to drug intake, that makes a casual relationship in improbable and in which other drugs, chemicals. Information on drug withdrawal may be lacking or unclear.\(^29\)

- **Unlikely:**
  A clinical event or laboratory test abnormality with, a temporal relationship to drug intake that makes a casual relationship in improbable and in which other drugs, chemicals or underlying disease provide plausible explanation.\(^29\)

- **Conditional / Unclassified:**
  A clinical event or laboratory test abnormality, have been reported as an ADR, about more data for proper assessment is needed, or additional data under examination.\(^1\)

- **Unassessable / Unclassifiable:**
  A report suggesting an adverse drug reaction which cannot be judged because information is insufficient and contradictory and which cannot be supplemented or verified.\(^1\)

All the reportings were evaluated, after collecting adequate data from appropriate sources. After having assessed the casual relationship between the suspected drug and the adverse reaction, irrespective of their casual category, the reports were subjected to further analysis including their severity, predictability and preventability of adverse reactions.\(^15\)

**Causality assessment:** is a method by which the extent of relationship between a drug and suspected reaction is established.\(^1\)

The assessment of Pharmacovigilance is done by different type of scales like

- Karch & Lasagna scale
- Naranjo's scale
- WHO probability scale
- Spanish quantitative imputation scale
- Kramer's scale
- Jones scale
- European ABO system
- Bayesian system.

But among the above scales the Naranjo's scale and the WHO scale of assessment are the most commonly used scales.

Some factors that affect causality assessment

- The temporal relationship (onset of time)
- The clinical
- Pathological characteristics of event
- Pharmacological plausibility
- Existing information and concomitant medication
- Underlying and concurrent illness
- Dechallenge and dose reduction
- Rechallenge and dose increase
- Patient's characteristics and previous medical history
- Drug interactions.\(^17, 29\)
TABLE 2: NARANJO’S CAUSALITY ASSESSMENT SCALE

<table>
<thead>
<tr>
<th>Naranjo’s Causality Assessment</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questions</td>
<td>Yes</td>
</tr>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
</tr>
<tr>
<td>2. Did the adverse even appear after the suspected drug was administered?</td>
<td>+2</td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
</tr>
<tr>
<td>4. Did the adverse reaction reappear when the drug was readministered?</td>
<td>+2</td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could solely have caused the reaction?</td>
<td>-1</td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?</td>
<td>+1</td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by objective evidence?</td>
<td>+1</td>
</tr>
</tbody>
</table>

Total Score

> 9 = definite ADR, 5-8 = probable ADR, 1-4 = possible ADR, 0 = doubtful ADR

Epidemiology of ADRs:
The epidemiology of ADRs in the Indian population is not known as very few studies have been reported. The prevalence of hospital admissions in several parts of the world is resulted from adverse reactions and many other problems is 4.2-6.0 % of admissions were due to serious adverse drug reactions, with a median of 5.8%. A much cited study from US demonstrated that the incidence of adverse drug reactions among hospitalized patients was 6.7% and in 0.3% the outcome was fatal. This makes ADRs the fifth leading cause of death in USA. In India it is reported that 5.9% of all visits to the medical emergency department are deemed to be drug related. Adverse drug reactions accounted for 45% of events.11

TABLE 3: EXAMPLES OF DRUGS HAVING HIGH TOXICITIES

<table>
<thead>
<tr>
<th>S.NO</th>
<th>Drugs</th>
<th>Year of withdrawn</th>
<th>Reason of withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Lysergic acid diethylamide (LSD)</td>
<td>1950</td>
<td>Marketed as Psychiatric cure all, withdrawn after it became widely used recreationally</td>
</tr>
<tr>
<td>2.</td>
<td>Thalidomide</td>
<td>1950</td>
<td>Withdrawn because of risk of teratogenecity, returned to market for leprosy and multiple myeloma under FDA orphan drug rules</td>
</tr>
<tr>
<td>3.</td>
<td>Phenytoin</td>
<td>1978</td>
<td>Withdrawn because of risk of lactic acidosis</td>
</tr>
<tr>
<td>4.</td>
<td>Methaqualone</td>
<td>1984</td>
<td>Withdrawn because of risk of addiction and overdose</td>
</tr>
<tr>
<td>5.</td>
<td>Astemizole</td>
<td>1999</td>
<td>Arrhythmias because of interaction with other drugs</td>
</tr>
<tr>
<td>6.</td>
<td>Cisapride</td>
<td>2000</td>
<td>Withdrawn in many countries because of risk of cardiac arrhythmias</td>
</tr>
<tr>
<td>7.</td>
<td>Rofecoxib</td>
<td>2004</td>
<td>Withdrawn because of risk of myocardial infraction</td>
</tr>
<tr>
<td>8.</td>
<td>Inhaled insulin</td>
<td>2007</td>
<td>Withdrawn in UK due to poor sales caused by national restrictions on prescribing, doubts over long term safety and too high in cost</td>
</tr>
<tr>
<td>9.</td>
<td>Lumiracoxib</td>
<td>2007-2008</td>
<td>Progressively withdrawn around the world because of serious side effects, manly liver damage</td>
</tr>
<tr>
<td>10.</td>
<td>Rosiglitazone</td>
<td>2010</td>
<td>Withdrawn in Europe because of increased risk of heart attacks and death. This drug continues to be available in U.S.</td>
</tr>
</tbody>
</table>

Pharmacovigilance:
The term Pharmacovigilance first appeared in 1960s. It is a system used to collect information, which is helpful in the surveillance of medicinal products with particular reference to human beings and to evaluate such information scientifically.15 The history of Pharmacovigilance goes back more than 40 years. A chain of cluster of cases resulted
due to the use of some drugs (Thalidomide disaster, Sulfonamides disaster etc). Thalidomide was introduced in 1957 and widely prescribed for morning sickness and nausea. It was soon linked to a congenital abnormality, which caused severe birth defects in children of women who had prescribed this medicine during pregnancy. By 1965, Thalidomide had been removed from the market in most countries.\textsuperscript{16-18}

**Objectives of Pharmacovigilance:**
The objective of this study was to calculate the Knowledge, Attitude and Practice of ADR monitoring and reporting system among Health Care professionals.

**Functions of pharmacovigilance:**

Identification and analysis of new adverse drug reaction (ADR)

- Information exchange
- Publication of periodical newsletter
- Provision of WHO database as a reference source for signal strengthening
- Supply of tools for management of clinical information
- Provision of training and consultancy support to national centers.
- Designing of computer software for case report management

**Methods of Pharmacovigilance**

In safety study, signals can be generated via four different methods: Spontaneous Reporting Published Case Reports, Cohort Studies and Post Marketing Clinical Trials. Now the primary method is Spontaneous Reporting System.\textsuperscript{7}

- **Spontaneous reporting:** system whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufactures to the national regulatory authority.\textsuperscript{12}

- **Intensified ADR reporting:** To enhance ADR reporting of specific medicines in early post marketing phase.\textsuperscript{13}

- **Targeted spontaneous reporting:** To estimate the incidence of Known ADR to a specific medicine in a population or to learn more about the ADR profile of specific medicine.

- **Cohort event monitoring:** It is a prospective, observational study of events that occur during the use of medicines, for intensified follow up of selected medicinal product phase. Patients are monitored for the time they begin treatment, and for a defined period of time.
Data mining: A general term for computerized extraction of potentially interesting patterns from large data sets often based on statistical logarithms. In Pharmacovigilance the most commonest application of data mining is so called disproportionality analysis.\(^{13}\)

Purpose of Pharmacovigilance:
The ADR reporting done in two cases, when the reaction is serious or unusual. Pharmacovigilance involves monitoring and assessing the quality of drugs along with detection and prevention of any adverse effects of drugs. In the study conducted by Al-Hazmi, 53.25% of surveyed community pharmacists stated that ADR reporting purpose is to identify safe drugs, 29% agreed that it is useful for calculating the rate of incidence of ADE, 6% of the system served as a source of information about the characteristics of ADRs, 12% of community pharmacists considered the purpose of ADE reporting was to detect potential ADRs and whereas 6% of surveyed community the purpose of ADR reporting system to identify ADE within the same pharmaceutical class. The purpose of this is to present case for the importance of Pharmacovigilance, to record the growth and potential as a significant discipline within medical science, and to describe its impact on patient welfare and public health.

It highlights the need of critical examination of the strengths and weakness of Pharmacovigilance system in order to increase impact. It anticipates development to necessary to meet the challenges of next ten years Pharmacovigilance and all drug safety issues are relevant for surveys.\(^{26}\)

Pharmacovigilance reporting and monitoring:
Reporting of ADRs has become an important component of monitoring and evaluation activities performed in hospitals. Such reporting program encourage surveillance for ADRs, promote the reporting of ADRs and stimulate the education of health care professionals regarding potential ADRs.

MED WATCH program:
The MED WATCH program of food and drug administration (FDA) in USA collects reports from medical practitioners and health care professionals about the occurrence of adverse event as a voluntary report.\(^{32}\) Recently the USFDA has developed a MED WATCH program specially developed for the reporting of ADRs related to medical products, equipments and medication. The goal of an investigation by the FDA is to prevent the occurrence of further adverse drug reactions. Other advantage to report in MED WATCH is that this new group aims to ensure the new safety information is quickly communicated to health care professionals, thus reducing further incidents.\(^{33}\)

Spontaneous reporting system:
Spontaneous reporting system of ADRs is one of the basic methods for post marketing surveillance and is a method to generate signals of unrecognized ADRs. Withdrawals due to safety problems are often based on data from spontaneous reporting systems. It offer many advantages (i.e. they are inexpensive, simple to operate, potentially cover all drugs and whole patient population, including special subgroups do not interfere with prescribing subgroups).

It has be estimated that in United Kingdom where since 1964, the yellow card spontaneous reporting system works, only 10-15% of even severe reactions are reported.\(^{22}\)

Indian scenario:
Monitoring of adverse drug reactions in India starts two decades ago in 1982. Under the chairmanship of drug controller of India, five centers were established with the idea of monitoring program nationwide. It considered of three phases: first one being monitoring of reactions in the institutes, second one in governmental bodies and third phase proposed including general practitioners.
The ADR reporting in India is below 1% compared to the worldwide rate of 5%. The PvPI launched in India for the safety of billion patients. In July 2010, The central drug Standard Control Organization (CDSCO), New Delhi has initiated a Nationwide Pharmacovigilance program under aegis of Ministry of Health and Welfare, Government of India with all institute of Medical Sciences (AIIMS), New Delhi as a National Coordinating Centre (NCC) to monitor ADR. For the successful production of this program, NCC shifted from AIIMS, New Delhi to the Indian Pharmacopeia Commission, Ghaziabad (UP), in April 2011, under aegis of Uppsala Monitoring Centre- World Health Organization (UMCWHO).  

The UMC-WHO, Sweden maintaining the international database of ADR reports received ADRs report data from several National Pharmacovigilance of different countries.  

The program has a three tier structure consisting of peripheral, regional and zonal Pharmacovigilance centre in addition to the nation Pharmacovigilance advisory committee and the national Pharmacovigilance centre based at CDSCO, New Delhi all centers can report alarming or critical adverse drug reactions to the national Pharmacovigilance center directly so that regulatory decisions can be taken promptly. Under the program peripheral Pharmacovigilance centers will be established in teaching and non-teaching hospitals, clinics and pharmacies in each state and union territory. Each peripheral Pharmacovigilance centre will record adverse events and forward the adverse drug reaction forms and relevant information to its respective regional Pharmacovigilance centre on a weekly basis.

The regional Pharmacovigilance centers would cover five regions of the country; North, South, East, Central, West, and South and will be responsible for recording adverse drug reaction data locally and scrutinizing data received from the peripheral Pharmacovigilance centers situated in their respective regions. Each regional Pharmacovigilance centre will subject its data to causality assessment and also report to its Zonal Pharmacovigilance centre.

Each zonal Pharmacovigilance centre would also prepare reports for the National Pharmacovigilance center and conduct special Pharmacovigilance projects on any drug of special concern to the National Pharmacovigilance Program.

The national Pharmacovigilance center would recommend the central drugs standard control organization regarding regulatory actions base on the adverse drug reaction data generated in the country and periodic safety update reports submitted by pharmaceutical companies. It would disseminate relevant information through adverse drug reaction news bulletins, drug alerts and seminars. As a part of international collaboration, the National Pharmacovigilance centre will network with national Pharmacovigilance bodies from other countries and also provide data for the World Health Organization International Drug Monitoring program.

Besides it, the causality assessment is the method by which the extent of relationship between a drug and a suspected drug reaction is established.

- Underreporting:
  One of the major deficiencies of spontaneous reporting program is the failure of health professionals to identify and report drug. It is a serious issue. The lack of awareness and knowledge on how to report ADRs led to poor reporting. Inman listed seven purported reasons for failure to report adverse drug reactions. These are called seven deadly sins. According to this description signs are caused due to the attitude of Professionals toward their activities, lack of knowledge related to the problems associated with ADE reporting and the disinterest shown by professionals. This includes:

I. Financial incentives: reporting rewards
II. Legal aspects: fear of getting involved into legal costs
III. Complacency: the belief that before the commercialization, ADE reporting is well documented for a drug.
IV. Diffidence: the belief that a particular drug was certainly involved in the adverse drug event.
V. Indifference: the belief that a single case observed by an individual doctor might not contribute to medical knowledge.

VI. Ignorance: the belief that only serious reports or unexpected ADE reporting is required.

VII. Lethargy: lack of interest or time to report ADE or other excuses.

However it is estimated that only 6-10% of all ADRs are reported in all over the world and India is also the part of it while its contribution is not up to mark. This is due to lack of a reporting culture among healthcare professionals in India. So there is questionnaire based on Knowledge, Attitude and Practice (KAP) is used to increase the reporting of ADRs.

Our study is aimed at exploring Attitude, Awareness and Knowledge of health care professionals to report ADR in Tertiary Care Teaching Hospital.

**Knowledge**: Means theoretical or practical understanding of the subject matter.

**Attitude**: A predisposition or a tendency to respond positively and negatively towards a certain idea, object, person and situation.

**Practice**: Application of Knowledge or practical approach to the subject matter.

**Safety monitoring of herbal medicine**: Now a day’s herbal medicines are very popular in general public but the safety of these remedies are major issue for public health. The use of herbs I traditional medicines continues to expand rapidly across the world. In various national health care settings for the health of patients, herbal products have a very large share almost prescribed medicines. Monitoring of herbal safety relate to address specific challenges such as botanical nomenclature, quality, adulteration, labeling issues, prescriber differences and under-reporting.

**Guidelines for India’s Pharmacovigilance**: Many countries have formulated their own Pharmacovigilance guidelines with the aim to have a systemic process of safety reporting. The ICH has six guidelines pertaining to various aspects of drug safety.

- **E2A**: clinical safety data management: definitions and standards for expedited reporting
- **E2B**: clinical safety data management: data elements for transmission of individual case safety reports
- **E2C**: clinical safety data management: periodic benefit-risk evaluation report (PBRER)
- **E2D**: post approval safety data management
- **E2E**: Pharmacovigilance Planning in preparation for the early post marketing period of a new drug and
- **E2F**: development safety update report

The USFDA has title 21 code of federal regulations (mainly part 312- investigational new drug part 314- applications for FDA approval to market a new drug) and the EMEA has entire volume 9A for Pharmacovigilance in humans. In contrast India has only a small section of schedule Y dedicated to drug safety, which when viewed in light of contemporary global practice, seems to have many lacunae. It is thus a felt need that CDSCO must formulate a detailed Pharmacovigilance guideline. Such guideline shall incorporate all relevant areas of pre and post marketing safety, address to current lacunae and bring about clarity on issues as discussed above. Most importantly, the guideline shall be in tune with the current international norms, so as to support India’s growth as any participate in multinational clinical trials.

**Haemovigilance**: As well as Pharmacovigilance, Haemovigilance is an important part of ADR monitoring. Haemovigilance is an urgent need of the country to identify and prevent occurrence and recurrence of transfusion related ADRs, so as to increase the safety and quality of blood transfusion. This system includes monitoring, reporting, investigation, identification, and analysis of adverse drug reaction. This Haemovigilance program is being seen in the context of ‘biovigilance’.

**CONCLUSION**: ADRs and Pharmacovigilance study have become prominent and one of the most important aspect of patient care. The awareness of
the reporting centre is crucial due to large population of doctors were ignorant of PV centers. The attitude should be improved more among the hospital staff in the developing countries. Lack of motivation and training toward ADR reporting and Pharmacovigilance discourages them from reporting. Proper training and established proper policies or standard operating procedures will ensure reporting of ADRs with more quality. ADR reporting made compulsory by doctors until there is no strict rules and regulations success of Pharmacovigilance program is questionable. Now a day’s many of other branches like Haemovigilance, biovigilance and herbal Pharmacovigilance are comes in market to provide patient care.

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How to cite this article:

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