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Pharmacovigilance for Health Care Professional Students

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ABSTRACT

Pharmacovigilance is a science which ultimately deals with effective health care with safe drugs. A better understanding of this among the health care professional students (medical, dental, pharmacy, nursing and physiotherapy students) is mandatory for effective implementation. This article attempts to facilitate the attitude and aptitude of the targeted students by making definitions of pharmacovigilance, requirements and the reporting information easy. It is essential that public/ health care givers need more awareness about this so as to enable them to report any adverse reaction however mild it is, in an unhesitant way. This will help to restrict the use of drugs producing adverse reactions, there by rendering safe health care.

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Introduction

Pharmacovigilance a relatively a new entity and is fast developing. It mainly deals with drug safety there by effective health care. It will be ideal, that health care professional students have a better insight of pharmacovigilance right from student days so that at the end of the course they will be able to implement the same effectively. This article is written with this motto. Pharmacovigilance as the terminology itself explains, a vigilance on pharmacotherapy.

The main problem in safe drug therapy is the occurrence of adverse effects more prominently when ever new drugs are used during phase IV of the clinical trial (post marketing surveillance). Adverse drug reaction (ADR) is unexpected, undesirable action when a drug is administered. Any drug, no matter how vital its therapeutic actions, has the potential to do harm [1]. This can be a simple form like skin rashes to most severe one i.e. fatal anaphylactic reaction. Further, increased frequency in occurrence and severity of known ADRs can be considered for inclusion during the pharmacovigilance. The following *modus operandi* shall be a useful guide.

Definitions [2]

Pharmacovigilance: concerned with the detection, assessment and prevention of adverse reactions to the drugs.

Adverse drug reaction (ADR) is the unexpected, undesirable action when a drug is administered which may mandate stoppage of the drug and choose alternate drug.

Side effect is any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological proprieties of the drug and does not necessitate stoppage of the drug.
Adverse event or experience is defined as any untoward medical occurrence that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment.

Serious adverse events can be defined as those which lead to

- Either life-threatening or fatal events
- Prolong hospital admission
- Persistent incapacity or disability and
- Provision for misuse leading to dependence.

Aims of Pharmacovigilance

- Detection of unknown adverse reactions and interactions.
- Detection of increases in frequency of known adverse reactions.
- Identification of risk factors and possible mechanisms underlying adverse reactions.
- Analyze risk / benefit aspect and to make available the information required for rational prescribing and regulation.

- Educate the clinicians, paramedical personnel and public on pharmacovigilance.
- To assist the regulatory authorities to monitor and take necessary actions for safe therapy.

Birth of Pharmacovigilance

'*Not all hazards can be known before a drug is marketed*' (Committee on Safety of Drugs, Annual Report 1969, 1970.) The birth of pharmacovigilance came from the disaster caused by thalidomide in 1961. Thalidomide had been introduced and welcomed as a safe and effective hypnotic and anti-emetic. It rapidly became popular for the treatment of nausea and vomiting in early pregnancy. Tragically, the drug proved to be a potent human teratogen that caused major birth defects in an estimated 10,000 children in the countries in which it was widely used in pregnant women [3]. This incident called for the first systemic International efforts to address drug safety issues. In 1963, Sixteenth World Health Assembly adopted a resolution that reaffirmed the need for monitoring adverse drug reactions (ADR) and disseminating ADR information. In 1968, World Health Organisation (WHO) Pilot Research Project for International Drug Monitoring was created. The pilot project was developed into the WHO Programme for International Drug Monitoring and co-ordinated by the Uppsala Monitoring Centre (UMC) in Uppsala, Sweden.

Pharmacovigilance emerged from WHO technical report based on a consultation meeting held in 1971. In 1992 pharmacovigilance was formally introduced into the research and academic world and now there is increasing integration into clinical practice. Literally *pharmakon* (Greek) means "drug;" and *vigilare* (Latin) means "to keep awake or alert, to keep watch." Leading to the term pharmacovigilance.

Until August 2011, 106 countries had become member of this WHO pharmacovigilance program. Presently 33 countries have applied for membership and are considered as associate members. [4]

History of Pharmacovigilance in India

India entered into pharmacovigilance by 1986. A formal ADR monitoring system was introduced with 12 regional centres, each covering a population of 50 million. However, no significant progress was made. Subsequently in 1997, India joined the World Health Organization and Adverse Drug Reaction monitoring program based at Uppsala, Sweden but went unsuccessful. Hence, from 2005 WHO sponsored and World Bank – funded National Pharmacovigilance Programme (NPP) of India was made operational. Finally revived and restructured pharmacovigilance program of India (PvPI) was started in 2010.

Why Does India Need Pharmacovigilance

India is the second largest in population and has more patients suffering from diabetes, cancer, cardio vascular events and stroke which helped it to emerge as a hub for clinical trials. A study conducted by Rabo India Finance, a subsidiary of the Netherlands-based Rabo Bank, to emphasise that India is the ideal destination for clinical trials stated " Pharmaceutical companies outsource the clinical trial projects to India since they are very

much attracted to the fact that India offers nearly 700,000 speciality hospital beds, 221 medical colleges, skilled English speaking medical professionals". India is the fourth major producer of pharmaceuticals in the world. Approximately more than 6,000 licensed drug manufacturers and over 60,000 branded formulations are available in India. 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.

India is a largest hub for 'Herbal' and 'Traditional' medicines. There is a face belief that Natural/Herbal means 'Safe'. However, the possibility of these herbal and traditional medicines getting adulterated with allopathic medicines, steroids, non steroidal anti inflammatory drugs and heavy metals should be excluded. There is an increasing concurrent use of herbal and traditional medicine along with other prescribed medications which could lead to serious adverse drug reactions. These demand for a strong pharmacovigilance system which could effectively monitor the safety of the medicines.

In the past, there was no real urgency for the government to establish a strong pharmacovigilance system since most of the drugs introduced in India had a long term use in western markets and India's regulatory agencies and drug companies followed the safety assessments based upon them. In recent years, the time lag of availability of drugs in India after launching in western market is dramatically decreased, so that the much needed long term safety data is no longer available. Moreover, now India-based drug companies have their own Research and Development (R &D) wing and they have increased their capacity to develop and launch new drugs on their own. This advocates the importance of developing adequate Indian standards for pharmacovigilance to detect adverse drug reactions. [5]

Outcomes of pharmacovigilance

Main outcome of the pharmacovigilance system is *Signal detection*. WHO defines *Signal* as "Reported information on a possible casual association between an adverse event and a drug, the relationship being unclear or incompletely documented previously". These generated signals are communicated in scientific publications so that the clinicians will be more cautious in using those specific drugs. Depending on the severity of the signal the regulatory authorities take necessary actions which ranges from including them in prescription information, as a package insert or black box warnings or withdrawal of the drug from market.

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Table:1 Important Drugs Which Caused Serious Adverse Drug Reactions and are Withdrawn [6]

Drugs	Class	Serious adverse drug reactions	Year of entry into market	Year of ADR and withdrawal
Elixir Sulfanilamide	Antimicrobial agent	Killed 107 people (prepared with diethylene glycol)	1937	1937
Chloramphanicol	Antimicrobial agent	Aplastic anemia	1949	1950
Thalidomide	Hypnotic	Phocomelia	1950	1961
Diethylstilbestrol	Synthetic non steroidal estrogens	Adenocarcinoma of the cervix and vagina (In utero exposure, manifestation after 20 years)	1940	1970
Practolol	Beta blocker	Oculo-mucocutaneous syndrome	1967	1975
Terfenadine	Second-generation antihistamine	Causes ventricular arrhythmias	1985	1998
Astemizole	Second-generation antihistamine	Ventricular arrhythmias – Torsades de pointes	1977	1999
Troglitazone	Oral anti diabetic agent	Hepatic failure	1990	2000
Cisapride	Pro kinetic drug	Torsades de pointes	1980	2000
Phenylpropanolamine	Appetite suppressant	Stroke	1970	2005
Cerivastatin	Lipid lowering agent	Rhabdomyolysis	1990	2001
Fenformin	Oral anti diabetic agent	Fatal lactic acidosis.	1970	2003
Rofecoxib	Selective COX2 inhibitor	Myocardial infarction	1999	2004
Valdecoxib	Selective COX2 inhibitor	cardio vascular events and stroke fatal skin reaction	2001	2005
Quinine containing preparations	Anti malarial drug	Cardiac arrhythmias, thrombocytopenia, hypersensitivity	1940	2007
Pergolide	Anti parkinsonism agent	Heart Valve damage	1988	2007
Sibutramine	Oral anorexiant	Cardiovascular events and stroke	1997	2011
Gatifloxacin	Anti microbial agent	Diabetes, liver damage, hallucinations	1999	2011
Nimesulide	Selective COX2 inhibitor	Children <12 years has been banned due to risk of severe hepatotoxicity.	1985	2011

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Pharmacovigilance Programme of India (PvPI)

The Central Drugs Standard Control Organization (**CDSCO),** Directorate General of Health Services under the aegis of Ministry of Health & Family Welfare, Government of India in collaboration with Indian Pharmacopeia commission, Ghaziabad initiated a nation-wide pharmacovigilance programme for protecting the health of the patients by assuring drug safety. The programme is coordinated by the Indian Pharmacopeia commission, Ghaziabad as a National Coordinating Centre (NCC). The centre will operate under the supervision of a Steering Committee.

Goal and Objectives of Pharmacovigilance Programme of India (PvPI) [7]

Goal:

To ensure that the benefits of use of medicine outweighs the risks and thus safeguard the health of the Indian population.

Objectives:

- To monitor Adverse Drug Reactions (ADRs) in Indian population
- To create awareness amongst health care professionals about the importance of ADR reporting in India.
- To monitor benefit-risk profile of medicines.
- Generate independent evidence based recommendations on the safety of medicines.
- Support the CDSCO for formulating safety related regulatory decisions for medicines.
- Communicate findings with all key stakeholders.
- Create a national centre of excellence on par with global drug safety monitoring standards.

ADR Monitoring centres –

- MCI approved medical colleges and hospital
- Private tertiary care hospitals
- Public health programmers
- Autonomous institute like ICMR
- In-house / outsourced industry based pharmacovigilance centre.

ADR Monitoring Cell (AMC) under Pharmacovigilance Programme of India (PvPI)

Total number of AMC's 60. Out of which 43 are government AMCs and 17 are Non government AMC's**.** [7]

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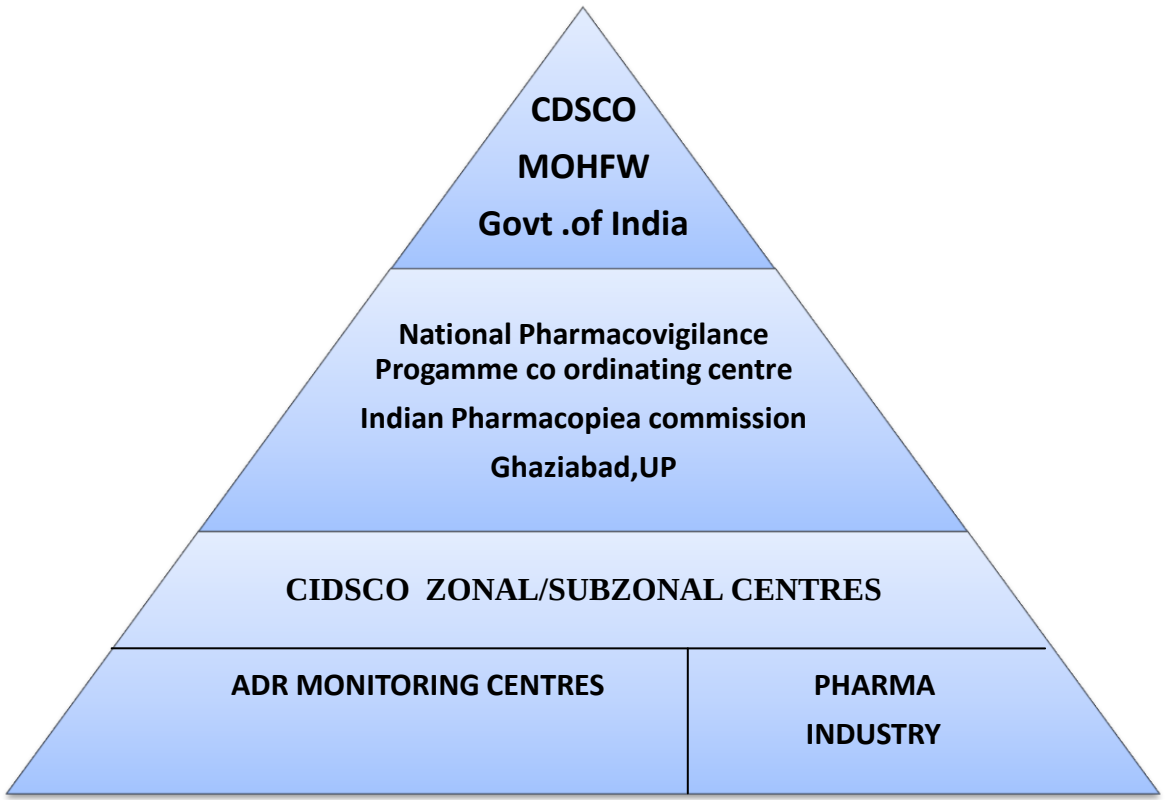
Pharmacovigilance Programme of India (PvPI) Structure:



CDSCO – Central Drug Standard Control Organisation.
MOHFW – Ministry Of Health & Family Welfare.
Zonal /Sub Zonal centres – North, South, East, West.

Pharmacovigilance – Team Work

The key members in this team are:

- Government and regulatory authorities,
- Pharmaceutical companies,
- Drug retailers, pharmacists,
- Health professionals, Private tertiary hospitals , Medical colleges,
- Medical and pharmaceutical associations,
- Poison and Drug information centre,
- General public and patients
- Researchers ,activist groups
- Non government organizations
- Media, politicians , lawyers
- World Health Organization.

Initiation of Pharmacovigilance Process:

Reporting:

How to report Adverse Drug Reactions:

Whenever a clinician / health care professional comes across an ADR he/she must fill the ADR case report form which is available online www.cdsco.nic.in/pharmacovigilance.htm . It is also made available in all clinical departments in MCI approved medical colleges, tertiary care hospitals, can also be directly obtained from pharmacovigilance centers.The filled report forms to the pharmacovigilance centre nearby.

ADR form is the predesigned structured form issued by PvPI to record the adverse drug effects. ADR case report form must at least contain the following items:

- Patient information's: Name, age, sex, relevant medical history, risk factors.
- Adverse event: its nature, severity and exact site, date of onset, duration and outcome.
- Suspected drugs and route of administration, dosage, duration of treatment.
- Concomitant medications used.
- Details of reporter.

What to Report:

- All adverse experiences with any drug (one must report even if he/she is not certain about the cause).
- All suspected drug interactions
- Serious adverse reactions which include:
    1. Death,
    2. Life-threatening (real risk of dying),
    3. Hospitalization (initial or prolonged),
    4. Disability (significant, persistent or permanent),
    5. Congenital anomaly,
    6. Intervention to prevent permanent impairment or damage.

Who all can report and whom to report:

Health care personals like doctors including dentist, nurses, and pharmacist are the main source of information. The programme does not accept reports from lay member of public or anyone else who is not a health care professional.

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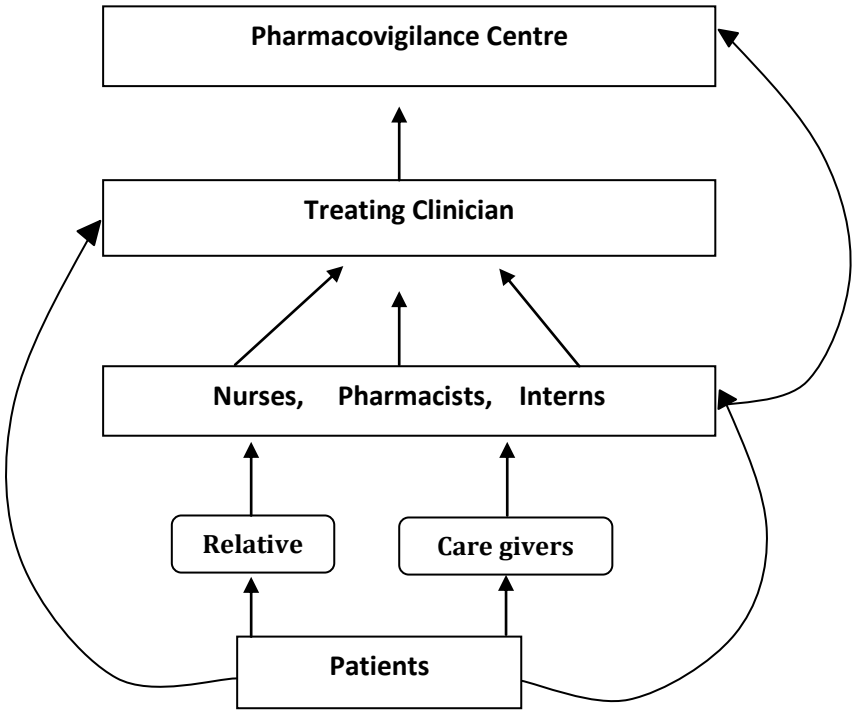
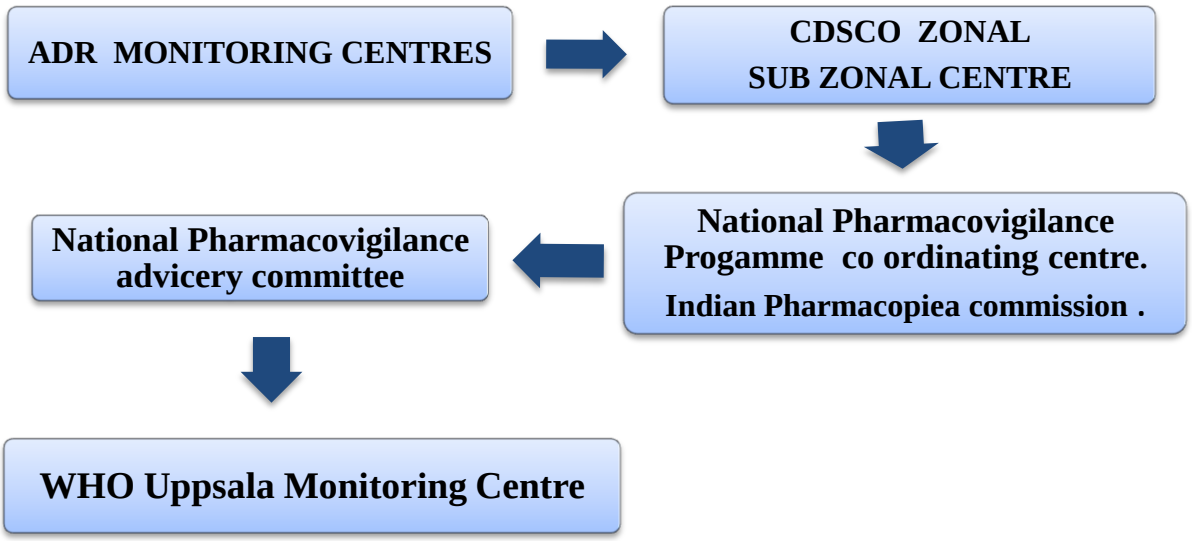


What happens to the submitted report?

The submitted report from one of the ADR monitoring centre goes to CDSCO Zone/Subzone offices in Region level (north, south, east or west centres) that will carry out the causality analysis. This information shall be forwarded to the National Coordinating centre (Indian Pharmacopeia Commission, Ghaziabad). The data will be statistically analyzed and forwarded to the global pharmacovigilance database managed by WHO Uppsala Monitoring Centre in Sweden.



The final report based on the analyzed data will be periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health and

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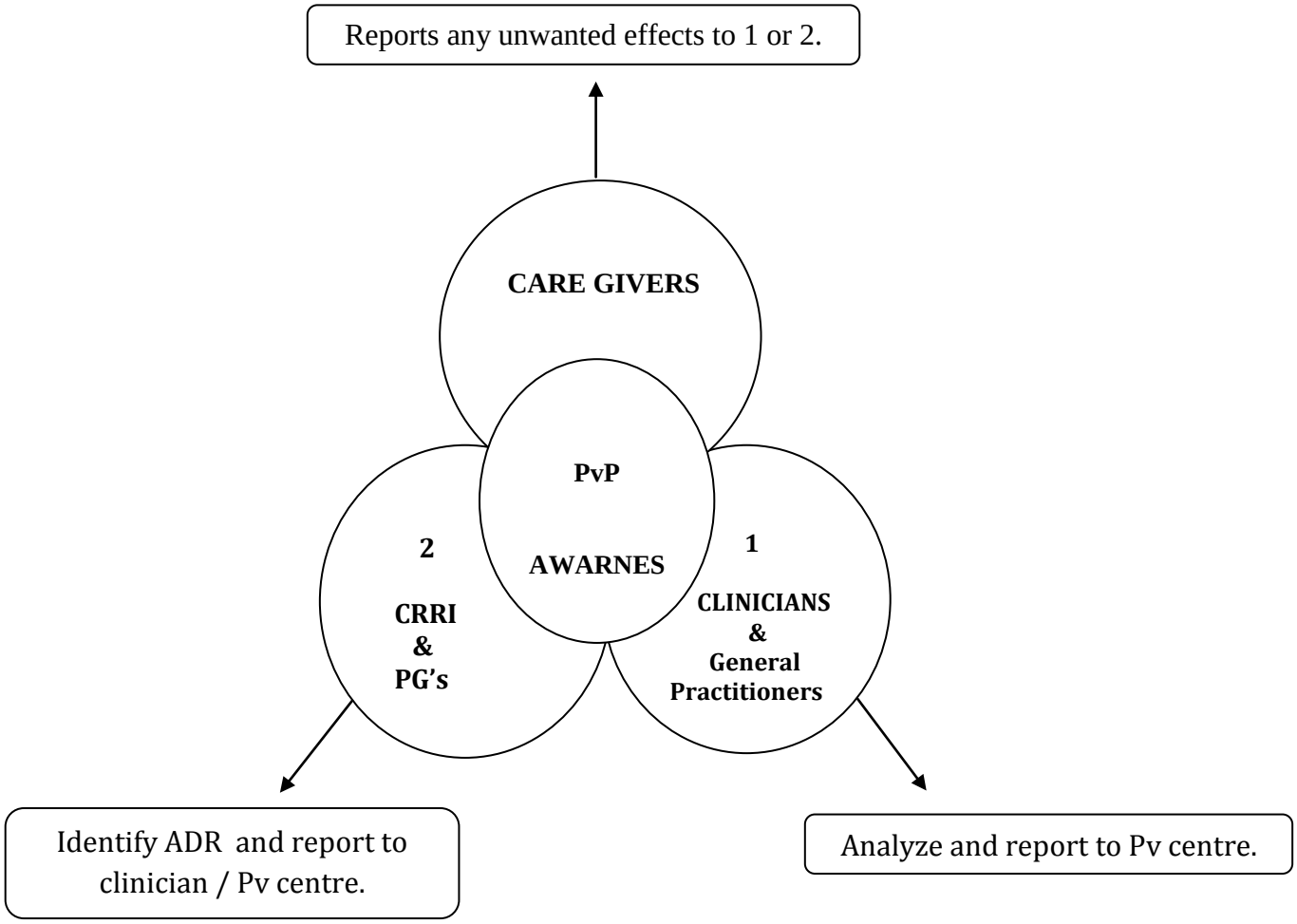
Family Welfare. The Committee can suggest any regulatory interventions such as withdrawal/banning of the drug.

How to start the Pharmacovigilance Programme of India (PvPI)

Sensitization programs – Teaching and learning pharmacovigilance plays a vital role. Interactive techniques like academic detailing, continuing medical education (CMEs) and frequent remainders are very essential. These programs must be attended by:

- All health care workers, clinicians in various clinical departments in medical colleges, hospitals including CRRIs.
- General Practitioners
- Paramedical staffs like nurses, pharmacist and social workers.
- Undergraduate and post graduate students
- General public and care givers

This program must sensitize the above mentioned participants about the basic understanding, process work flow and importance of pharmacovigilance.



Simple steps to avoid ADRs for clinicians, General Practitioners, Post Graduate students

- Prescribing the well known drugs, minimal drugs whenever possible by following the principles of essential drug concept and implement rational drug therapy.
- Changing a well known drug to unfamiliar drug only on a valid reason.
- Updating drug reactions and interactions by constant updating of knowledge with the help of books and reference materials.
- Prescribing with caution the anticoagulants, hypoglycaemic, and drug affecting the CNS because they can exhibit a large variety of interactions and adverse reactions. Careful monitoring of patients with such reactions must be undertaken.
- Watching interaction of drugs with certain food stuffs, alcohol and even with house hold chemicals.
- Reviewing, the entire drug used on him, Special notice must be made for over the counter drugs and herbal preparations.
- Providing special attention and care whenever prescribing to children, elderly, pregnant and nursing women, seriously ill and patients with hepatic and renal diseases. Consider periodic monitoring in these patients.
- When the patients show signs or symptoms which are not clearly explained by the course of their illness, think of adverse drug reaction.
- Consider stopping the drug while suspecting an adverse reaction and please notify the adverse drug reaction to pharmacovigilance centre.

Role of nursing personnel:

- Nursing personnel are the first member of the medical team who is contacted in most instances.
- Taking medication history before administering.
- Teaching the patient and family member/attendant the signs and symptoms
- Updating regarding drugs(batches) causing ADRs
- Following the manufacturer's guide strictly
- Checking concurrent therapies/polypharmacy
- Avoiding errors of interpretation when administering a drug.
- Withholding the drug whenever an unwanted event occurs and report to respective authority immediately including ADR cell.

Role of pharmacist

- The pharmacist is often the last member of the health care team who communicates with the patient.
- Educating the patient on proper drug intake such as dose, time of administration and precautions.
- Checking the details of the drugs before dispensing.
- Avoiding error of prescription interpretation and drug administration.
- The standard practice of preparing and dispensing drugs is shifting towards pharmaceutical care.
- A clinical pharmacist, not only dispense drugs but also decide the dose and the formulation to be administered besides educating the health care professional on ADRs
- Focusing on drugs, their quality control and dispensing.

Role of care givers

- Care givers and relatives are the first source of information for any health care professional.
- They must be educated about the disease conditions and also about the current therapy with the consent of the patient. They must also be sensitized about, what are all the effects the drug could make other than the desired therapeutic effect so that they can be very vigilant about the side effects and also ADRs. They are advised to report any minor effects even though he/she thinks it might not be from taking the drug.
- Explain well about the reporting system when, where and what to report.

Printing and distribution of reporting forms

During the sensitization program it is necessary to be ready with the availability of the reporting forms which must be distributed to everyone and to be kept in various Out Patient departments (OPD) and also in inpatient wards (IP) of the hospital. The availability of the forms is the very essential during the course of the work process. Make sure the drop boxes are kept ready in all the above mentioned places so that the reporting forms are dropped in them.

Periodic inspection and interaction

Inspection and interaction to be done in a regular interval for reviewing the work progress and also for effective monitoring.

Role of a Pharmaceutical Company

Registered and licensed pharmaceutical company must mandatorily have an in house or out sourced Pharmacovigilance system to ensure liability and safety of their marketed products according to guidelines from Schedule Y. They must collect and evaluate information about suspected ADRs. All these information must be shared with Drug Control General of India (DCGI).

This plays a vital role in the safety of the marketed drugs and this also mandates the inclusion of all possible adverse effects, interactions and contra indications in the prescriber's manual by the pharmaceutical company.

Safety Measures Taken by Pharmaceutical Companies during Marketing their Drugs

Drug information guide - this is paper handouts/pamphlets that must be given to the patients when they buy some specific drugs by the pharmaceutical company through a pharmacist. This conveys risk information that is specific to particular drugs and drug classes which approval information which can help patients to avoid serious adverse effects.

Prescription Information – usually called as prescription labelling or package insert it provides information to the physician about what a prescription medication is supposed to

do, who should and should not take it, and how to use it. Labelling also includes information on a drug's side effects and warnings, and information from the clinical trials of the drug.

Non-prescription Drug Label - For an over-the-counter (OTC), or non-prescription medicine, information printed on the medication bottle or package under the heading Drug Facts is important for taking care of the users. The drug facts tell about what a medicine is supposed to do, who should or should not take it, and how to use it. Safety information and instructions for use are displayed in a uniform and easy-to-read format.

Boxed Warning - This type of warning is also commonly referred to as a "black box warning." It appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks.

Drug withdrawal - It involve situations where there is a reasonable probability that the use of or exposure of the drug, will cause serious adverse health consequences or death. A drug may be recalled due to factors such as problems with packaging, manufacturing, or contamination.

Safety Announcements - The pharmaceutical company must give regular updates on the following with reference to their products

- Early announcements about ongoing safety reviews
- Public health advisories
- Letters to health care professionals
- Patient safety news.

CONCLUSION

To summarize, pharmacovigilance deals with identification and prevention of adverse drug reaction observed when used in large population. This article simplifies the concept to make health care professional students to understand and implement after graduation. Such an act promotes the growth of pharmacovigilance, thereby remembering safe health care for the patients. An inter action between centres shall be beneficial.

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