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ADVERSE DRUG REACTIONS OF NEUROLOGY MEDICATIONS AND THEIR ASSESSMENT: AN OVERVIEW

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ABSTRACT

Pharmacovigilance is one of the important areas of health care system and also a new discipline in pharmaceutical industry. It is defined as "science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems". The aim of pharmacovigilance is to enhance patient care and safety related with use of medicines. Adverse drug reaction (ADR) is defined as any response to a drug which is noxious and unintended and to which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. Studies shows that frequency and identification of ADR have been mainly reported in the departments like medical wards, geriatric department, surgery department, psychiatry department, pediatric department, ICU. ADR may influence all age groups mainly geriatrics and pediatrics. In India, study conducted among the inpatients of department of neurology. Neurology department includes antiepileptic, anti-psychotics, Parkinson's disease etc. Epilepsy is a common neurological disorder in which nerve cell activity in the brain is disturbed causing seizures. Antipsychotics are drugs used to treat symptoms of psychosis such as hallucination, delusion, paranoia or confused thoughts. In clinical practice, psychotropic drugs are mostly prescribed. Psychosis commonly seen in Parkinson's disease patients. In Parkinson's disease patients, antipsychotics are mainly prescribed. The assessment of causality relationship is often highly subjective, based on an individual clinician's assessment. Causality assessment is the method by which the extent of the relationship between a drug and a suspected reaction is estimated. Causality assessment can be done by using Naranjo's algorithm, World Health Organization (WHO) causality assessment scale and Karch and Lasagna's causality assessment scale.

KEYWORDS: Pharmacovigilance, ADR, Causality assessment.

INTRODUCTION

Drugs have been used since ages for the successful management of human illness. Unfortunately, drugs have contributed to the occurrence of various iatrogenic diseases.[42] Use of drugs always carries a certain amount of risk which may be intended or unintended.[26] Health care professionals should be well aware of the burden that adverse drug reactions play in the health service which marks the important of post marketing surveillances thereby ensuring continuous drug safety.[43]

Pharmacovigilance is one of the important pillars of health care system. Pharmacovigilance is the science which includes gathering, exploring, assessing and evaluating information from health care professionals and patients on adverse reactions of medicines, biological products, vaccines, medical devices etc.[33] Pharmacovigilance is a new field in pharmaceutical industry. The term "Pharmacovigilance" was first introduced in the year 1970.[37]

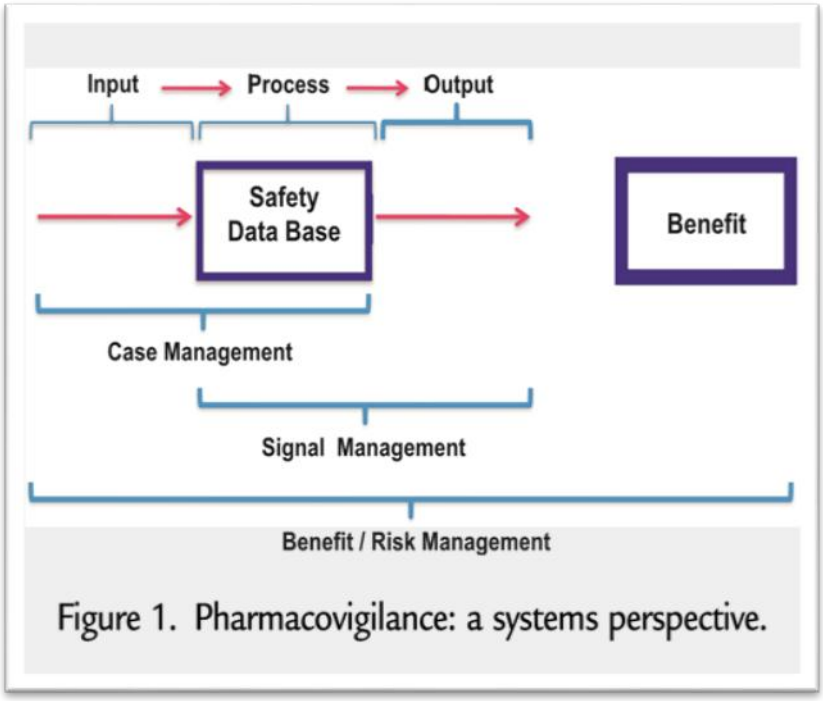

Figure 1. Pharmacovigilance: a systems perspective.

According to WHO, Pharmacovigilance is defined as "science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems". Pharmacovigilance is derived from Greek word "Pharmakon" means medicinal substances and "Vigila" (Latin word) means to keep watch.[35]

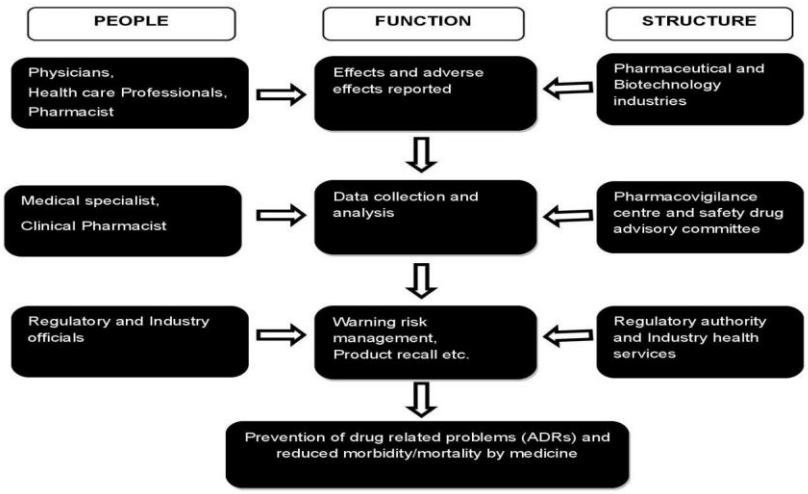

Figure 2: A typical Pharmacovigilance setup.[39]

AIM

- To enhance patient care and safety related with use of medicines.
- To promote education, understanding and to provide effective communication to health professional and public.[41]

Pharmacovogilance

Pharmacovigilance is mainly concerned with ADRs. Monitoring of effects of drugs, reactions, use and adverse effects which will result in increase in degree pf morbidity and may leads to mortality, thus are essential to increase benefits and reduce risks. The drug regulatory agencies are responsible for having a well-established pharmacovigilance system for ADR monitoring.[34]

History of pharmacovigilance

The history of Pharmacovigilance started 1848 in north England there was a young child Hannah Greener died after receiving chloroform anesthetic before removal of an infected toenail. Chloroform is a better and safer

anesthetic used, but it was not correctly recognized at that time what killed her. Later in 1960's most countries of UK faced another drug tragedy i.e., Thalidomide tragedy. The drug Thalidomide was used for morning sickness in pregnancy. After thalidomide treatment resulted in severe birth defects such as Phocomelia in thousands of children.[34]

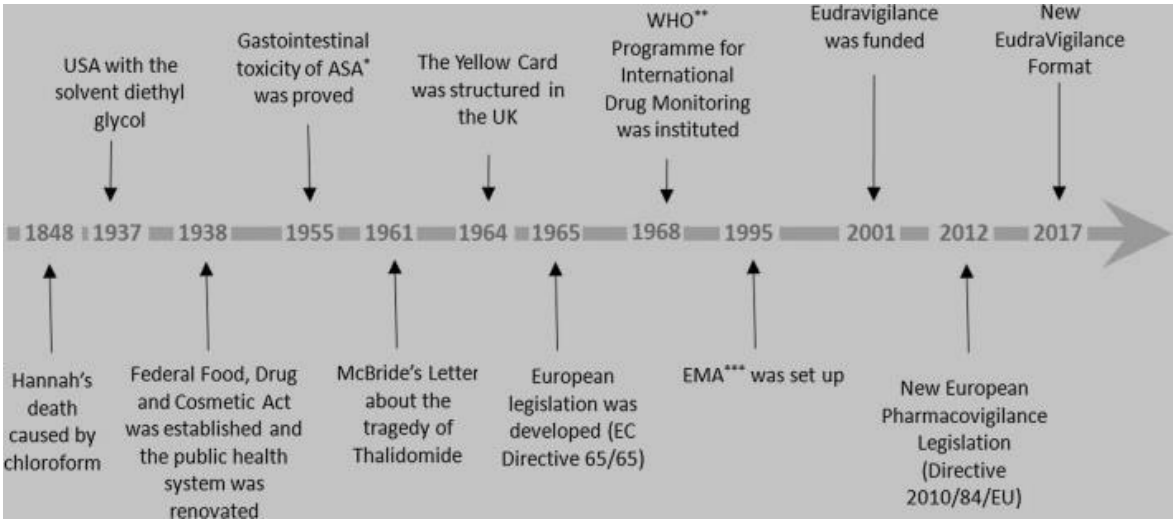

Figure 3: Timeline of the historical evolution of Pharmacovigilance.

*ASA: Acetylsalicylic acid; **WHO: World Health Organization;
***EMA: European Medicines Agency

Pharmacovogilance in India

Pharmacovigilance Programme of India (PvPI), which started functioning 14 July 2010, associated with the All India Institute of Medical Sciences (AIIMS), New Delhi, as the National Coordination Centre (NCC). In order to track ADRs all over India, the PvP had 22 ADR monitoring centres (AMCs), including AIIMS, New Delhi. The NCC was later shifted from AIIMS to the Indian Pharmacopoeia Commission (IPC), Ghaziabad, on 15 April 2011. The main aim of the program was safety of drugs to match the global drug safety monitoring standard.[40]

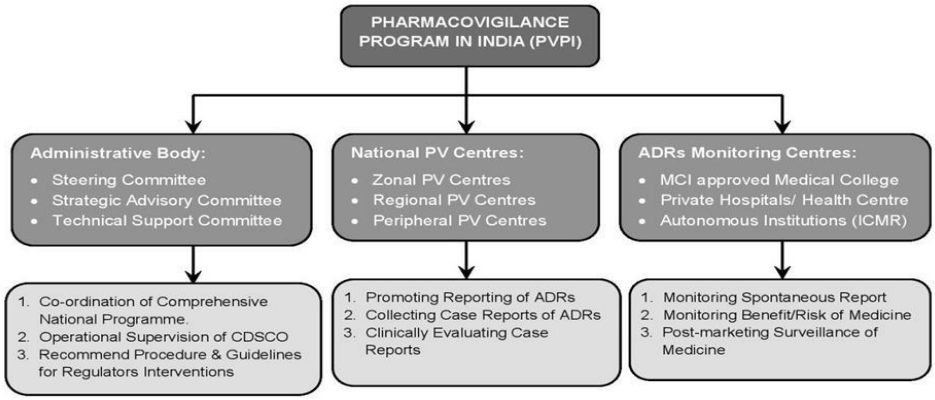

Figure 4: Pharmacovigilance in India.

Methods in pharmacovigilance for monitoring of ADRs

1. Passive surveillance

- **Spontaneous reports**

This type of reporting system was developed after thalidomide tragedy and the main aim is to evaluate safety of drugs. Spontaneous reporting is mainly used for detection of signals of new, rare and serious ADRs of medicines. Through this method all the drugs in the market are evaluated throughout the lifecycle.

- **Case series**

This method mainly employed in developing a hypothesis between post-marketing drugs and outcomes of drugs.

- **Stimulated reporting**

This type of system encourages and facilitates health care professionals to report ADR in certain situations. Mainly employed for reporting of ADR during post marketing phase.

2. Active surveillance

This type of system includes a pre-organized process to detect serious adverse events/ reactions. Through this method more information about individual adverse events can be reported.

3. Comparative observation studies

This method includes cross section studies, cohort studies and case control studies. Cross section is conducted to provide information between the exposure of drug and outcome in ecological studies. Case control can easily detect adverse events. Cohort studies are used to evaluate safety in particular populations such as children and patients with comorbidities.[36]

Adverse Drug Reaction (ADR)

Adverse drug reaction has become an economic burden to the developing countries like India and it was the main cause of morbidity. According to studies from India and other countries, Polypharmacy has the greater risk of ADR.[1] An Adverse drug reaction (ADR) is defined as any response to a drug that is noxious and unintended and that occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function.[5] Pharmacists plays important role in identifying drug related problems (DRPs) which involves resolving actual DRPs and prevents potential DRPs by Pharmaceutical care process. ADR monitoring helps to evaluate the effectiveness and risk of medications, enhance safe and provides rational use of drugs and improves general patient care and well-being. Identification and reporting of ADR prevents drug related problems in future. Drug related problems may arise from all stages of the medication from prescription to follow up of the treatments. Studies shows that frequency and identification of ADR have been mainly reported in the departments like medical wards, geriatric department, surgery department, psychiatry department, pediatric department, ICU. An ADR may result from single or multiple use of drugs. ADR may influence all age groups mainly geriatrics and pediatrics.[1] ADR in geriatrics may due to polypharmacy, comorbid disease, altered pharmacokinetic and pharmacodynamic changes. Pediatrics experience ADR especially the neonates are due to immature organ development and instabilities in pharmacokinetics and pharmacodynamics. CNS drugs administered during pregnancy may cause teratogenic effects on the fetus.[5] According to different studies, about 50-80% of ADR can be prevented. In India, study conducted among the inpatients of department of neurology. Of the 250 patients reviewed, 108 (43%) patients experienced at least one ADR. Among which 106 (98.1%) patients experienced ADR during their hospital stay and 2 (1.9%) patients were admitted due to the occurrence of ADRs. Determination of ADR is based on cessation of therapy, due to an adverse event or treatment failure.

Classification OF ADR

Pharmacological Classification

1. Type A(Augmented)

This is the commonest type (up to 70%) of ADR which is predictable by the pharmacological mechanisms, e.g., hypotension by beta-blockers, hypoglycemia caused by insulins or oral hypoglycemics, or NSAID induced gastric ulcers. These type of adverse drug reactions are dose dependent hence severity increases with dose. Such ADRs are preventable in most cases by slow introduction of low dosages. Sometimes it is referred to as Type I ADRs.

2. Type B (Bizarre)

This type of ADR is not expected from the known pharmacological mechanisms e.g., hepatitis caused by halothane, aplastic anaemia caused by chloramphenicol, neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics. Such ADRs are unrelated to dose. Sometimes referred to as Type 2 ADRs.

3. Type C (Continuous drug use)

This type of ADR is mainly due to continuous drug use. This can be irreversible, unexpected, unpredictable, e.g., tardive dyskinesias by antipsychotics, dementia by anticholinergic medications.

4. Type D (Delayed)

This type of ADR is characterized by the delayed occurrence even after the cessation of treatment, e.g., corneal opacities after thioridazine, ophthalmopathy after chloroquine, or pulmonary/ peritoneal fibrosis by methysezide.

5. Type E (end of dose)

This type of ADR is commonly characterized by withdrawal reactions. Such ADRs occurs with the depressant drugs, e.g. hypertension and restlessness in opiate abstainer, seizures on alcohol or benzodiazepines withdrawal; first dose hypertension caused by alpha-blockers (Prazosin) or ACE inhibitors.

6. Type F (Failure of therapy)

This type of ADR results from the ineffective treatment, e.g., accelerated hypertension because of insufficient control. These are also called lack of efficacy.

Severity classification

- **Mild / Minor:** No antidote, therapy or prolongation of hospitalization is needed.
- **Moderate:** It includes change in drug therapy, specific treatment, or an increase in hospitalization by at least one day.
- **Severe:** It is potentially life threatening, causing permanent damage or requiring intensive medical care.

Seriousness classification

- **Unexpected ADR:** It is an ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/ regional product labeling or investigator's brochure.
- **Expected ADR:** An ADR whose nature, severity, specificity, or outcome is consistent with the term or

description used in the local/ regional product labeling or investigator's brochure.[25]

Mechanism of ADR

The classification of adverse effects of drugs into Type A and Type B reactions is useful in diagnosis and management of adverse reactions and in understanding underlying mechanisms.

Type A Reactions

- **Pharmaceutical causes**

The pharmaceutical cause for the occurrence of these reactions usually involves alteration in the quantity of drug available for systemic absorption or an influence in the release rate so as to produce a local toxicity at the site of absorption. The availability of drug for systemic absorption is influenced by the various factors such as particle size in the particular pharmaceutical preparation, the nature and the quantity of excipients, coating materials.

- **Pharmacokinetic causes**

It is the study of absorption, distribution, metabolism and excretion of drugs. Henceforth any alteration in absorption, distribution, and elimination may produce type A reactions.

a) Absorption: Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation. The rate and extent of drugs absorption from the gut is determined by its pharmaceutical and physicochemical characteristics. Changes in gastrointestinal motility can influence the extent of absorption through its effect on gastric emptying or on small intestinal motility.

b) Distribution: Distribution is reversible transfer of a drug between the blood and the extravascular fluids and tissues. Extravascular distribution is depend on various factors such as: physicochemical characteristics, regional blood flow, tissue binding, plasma protein binding and active transport. Tissue binding of drugs is known to be responsible for the pathogenesis of some adverse reactions and this mechanism is of wider importance. Tissue drug binding results in localization of a drug at a specific site in the body. A number of drugs bind irreversibly with the tissues; for example, oxidation products of paracetamol, phenacetin, chloroform, carbon tetrachloride and bromobenzene bind covalently to hepatic tissues.

c) Metabolism: It is the conversion of drug from one chemical form to another. The chemical changes are usually affected enzymically in the body and thus, the definition excludes chemical instability of a drug with in the body. Example conversion of penicillin to penicilloic acid by the bacterial penicillinase and mammalian enzymes is metabolism but its degradation by the stomach acid to penicillanic acid is chemical instability. The most important pathway of biotransformation of drugs through liver is oxidation by cytochrome P-450 group of iso enzymes. Drugs, which undergoes metabolism by this route, include oral, anti-coagulants, phenothiazines, tricyclic anti-depressants, many anti-convulsants, benzodiazepines and most barbiturates.

d) Drug Elimination: Drugs and /or their metabolites are removed from the body by excretion. Excretion is defined as the process whereby drugs and /or metabolites are irreversibly transferred from internal environment to external environment. The principle organ of excretion are kidneys, the drug may be removed from the body through bile or by metabolism by the liver to metabolites which are then excreted.

- **Pharmacodynamic Causes**

Hemorrhage or perforations of peptic ulcers in association with administration of non-steroidal anti-inflammatory drugs or corticosteroids are a typical example. Others include bronchoconstriction in association with beta-blockers in patients with obstructive airway disease and neuromuscular blockade precipitated by aminoglycoside antibiotics in individuals with myasthenia gravis or in patients with who have recently been given muscle relaxants.

Type B Reaction

- **Pharmaceutical Causes**

The main pharmaceutical cause of Type B adverse drug reaction includes decomposition of the active constituents, toxic effects of excipients, and effects produced byproducts of the active constituents of the preparation. Though some drugs are remarkably stable, many undergo degradation during prolonged storage or in adverse climatic conditions. Administration of a decomposed drug is more likely to result in therapeutic failure when the products are devoid of pharmacological properties. However, in few cases, decomposition products may be toxic for e.g., paraldehyde ad tetracycline. In pharmaceutical preparations excipients may also cause toxicity for example additives such as propylene glycol, carboxymethylcellulose, and tartrazine may cause hypersensitivity reactions in man.

- **Pharmacokinetic causes**

Drug metabolism can be considered to be a detoxification process in that it converts therapeutically active compounds to inactive metabolites, which can then be excreted harmlessly from the body. In certain circumstances, the drug-metabolizing enzymes can convert a drug to a toxic, chemically reactive metabolite (CRM), a process known as bioactivation. Bioactivation or toxicological activation is the formation of highly reactive metabolites which interact with the tissues to precipitate one or more of the several forms of toxicities such as carcinogenesis and teratogenesis. An imbalance between bioactivation and bio inactivation leading to toxicity may be created by taking a drug overdosage. This leads to the formation of large amounts of chemically reactive metabolites and leading to cell damage. An excellent example is paracetamol which causes hepatotoxicity when taken in overdosage.

- **Pharmacodynamic causes**

Type B adverse reactions may be due to pharmacodynamic differences between individuals. The reactions may be generic, immunological, or neoplastic

and teratogenic in origin. An example for the genetic basis of occurrence of Type B reactions is hemolysis in patients with deficiency of glucose 6- phosphate dehydrogenase in their red blood cells. The example for immunological basis of occurrence of Type B reaction include penicillin induced anaphylaxis.

Neurologic Drugs and Associated ADRS

Drugs that are used in antiepileptic, antipsychotic, anti-parkinsonism, anxiolytic includes extrapyramidal symptoms, insomnia, sedation and depression.[5]

Anti-epileptics

Epilepsy is a common neurological disorder in which nerve cell activity in the brain is disturbed causing seizures. Epilepsy can be defined as a chronic seizure disorder or group of disorder characterized by seizures that usually recur unpredictably in the absence of consistent provoking factor. A seizure is a paroxysmal event characterized by abnormal excessive, hypersynchronous discharge of cortical neuron activity.[36]

Table 1: Drugs used in Epilepsy.

DRUGS	TRADE NAME	DOSAGE	MECHANISM	SIDE EFFECTS
Phenytoin	Dilantin	625mg/day	Voltage gated sodium channel blockade	Ataxia, allergy, Hyperplasia, insomnia, Drug induced lupus, Sedation, seizures, Cognitive deficits
Levetiracetam	Keppra	500mg BID	Binding to SV2A	Hair loss, anxiety, Irritability, depression, Headache, nausea, Sedation, weakness
Valproic acid	Depakene	750-2250mg/day	Voltage gated sodium channel blockade	Hepatic failure, Hypothermia, depressed Cognition, pancreatitis
Carbamazepine	Carbatrol	400-800mg/day	Voltage gated sodium channel blockade	Heart block, aplastic Anemia, Stevens Johnson syndrome (SJS)
Gabapentin	Bigvin tab Bestochem	300-3600mg TID	Voltage gated calcium channel inhibition	Anxiety, peripheral edema, dizziness, Hepatotoxicity, Sedation

Antiepileptic Drug Treatment (AED) helps to control seizures in 60%-95% of epileptic patients. ADR experienced in AED treatment can be dose dependent and are reversible. AED depends on various factors which includes patient convenience, risk of ADR and correct epilepsy diagnosis. Different studies proves that patients who shows AED related adverse reactions may vary from less than 10% to more than 70%. According to cross sectional survey conducted in India, about 788 epileptic patients undergone chronic AED therapy while 80 experienced at least one ADR.[20] Valproic acid (VPA) can be used for the treatment of various types of seizures. Common AEDs prescribed in combination with VPA includes carbamazepine, topiramate, phenytoin, lamotrigine. VPA can also be used to treat bipolar disorder in alone or in combination with antipsychotic agents. VPA have some advantages such as it shows efficacy with a favorable safety profile and relatively low drug-drug interactions. Most common symptoms of VPA toxicity such as anorexia, nausea, vomiting, increased convulsions, jaundice, coma can develop. Several VPA ADRs include unusual bleeding, fever, itching, confusion, swollen glands, depression.[23]

Anti-psychotics

Antipsychotics are first line therapy for psychotic disorders in children and adolescents. In the non-psychotics group antipsychotics are only considered as adjuvant therapy. Antipsychotic drugs=neuroleptics =major tranquilizers. Antipsychotics decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive treatment. The major MOA of antipsychotic drugs are they affect dopamine by blocking dopamine receptors.[28] Antipsychotic actions are due to blockade at dopamine or serotonin receptors. Many of antipsychotic agents also block cholinergic, adrenergic and histaminergic receptors causing ADR.[4] Antipsychotics are drugs used to treat symptoms of psychosis such as hallucination, delusion, paranoia or confused thoughts. They are used in treatment of schizophrenia, several depression and severe anxiety. In clinical practice, psychotropic drugs are mostly prescribed.[3]

Table 2: Drugs used in Psychosis.

DRUGS	TRADE NAME	DOSAGE	MECHANISM	SIDE EFFECTS
TYPICAL ANTIPSYCHOTICS [29]				
• Chlorpromazine	Thorazine Promacid Neurazine	300-800mg	Blocks dopamine receptors in all parts of the brain	Agitation, Dizziness, Blank facial Expression
• Thioridazine	Mellaril	200-700mg		Drowsiness, Dry mouth, Nausea
• Haloperidol	Haldol	1-100mg		Blurred vision, dry mouth, loss of appetite, Increased saliva
ATYPICAL ANTIPSYCHOTICS				
• Olanzapine	Zyprexa	5-10 mg/day	Blocks dopamine and serotonin receptors in the brain	Anticholinergic Symptoms, Diabetes, Sedation Hyperlipidemia
• Risperidone	Risperdal consta	1mg BD	Decrease serotonergic and dopaminergic pathway activity in brain	Acute parkinsonism, Elevated prolactin, Weight gain

Psychotropic drugs show a number of ADR. Due to non-adherence or discontinuation of therapy, psychotropic drugs cause ADR. Pharmacovigilance in psychiatry plays an important role to ensure safety and efficacy of drugs [18]. It is proved that at least 26 million people are suffering from schizophrenia in worldwide. Nowadays, second generation antipsychotics (SGA) have been largely replaced with conventional antipsychotics for the treatment of schizophrenia, autism, bipolar disorder because of its better safety profile. Risperidone is the most common SGA. It is a combination of dopamine and serotonin. The main adverse effects related to risperidone are weight gain, hyper prolactinemia, extrapyramidal symptoms (EPSs). These ADRs may leads to severe complications such as metabolic syndrome, diabetic mellitus (DM), sexual dysfunction and cardiac problems. Neuropsychiatric disorders (NPD) includes both psychotic and nonpsychotic disorders [6]. The psychotic disorders like schizophrenia, delusional disorders and psychosis and nonpsychotic disorders like Autism Spectrum Disorders (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Tourette Syndrome (TS) and Obsessive Compulsive Disorder (OCD).

Parkinson's disease

Parkinson's disease is a progressive disease of nervous system marked by tremor, muscular rigidity and slow, imprecise movement. It was mainly affected by elderly people. Parkinson's disease which was first described in "An essay on shaking palsy" in 1817 by a London Physician James Parkinson [30]. It was mainly associated with degeneration of basal ganglia of brain and a deficiency of neurotransmitter dopamine. Psychosis commonly seen in Parkinson's disease patients. The long-term cumulative prevalence rate is 60% and reported prevalence rate is 20-40%. In Parkinson's disease patients, antipsychotics are mainly prescribed.

Etiology

- Heredity
- Antipsychotic drugs (or neuroleptic agents)
- Encephalitis in response to brain trauma, tumors, hydrocephalus or ischemia
- Arteriosclerosis
- Neurotoxins such as cyanide, manganese and carbon monoxide
- Drugs like reserpine (hydro press), methyldopa (aldomet), haloperidol (Haldol) and phenothiazine (Thorazine).[31]

Table 3: Drugs used in Parkinson's disease.

DRUG	TRADE NAME	DOSAGE	SIDE EFFECTS
Levodopa	Levopa C	300-600mg	Nausea, dizziness, headache, somnolence
Promethazine	Phenergan	25mg	Severe drowsiness, weak/Shallow breathing, confusion, Agitation, nightmares, seizures
Selegiline	Emsam	5mg	Abnormal involuntary movements, nausea, fainting, Abnormal pain, dry mouth

Detection and Monitoring of ADR

Pre-marketing studies

During the development of new drugs, their safety and efficacy is tested in animal models. This information is obtained from various tests such as acute toxicity, carcinogenicity, mutagenicity, teratogenicity. Clinical trials are carried out prior to the release of new drug and only not more than 4000 individuals have been exposed to new drug. This implies that clinical trials only have the power to identify adverse reactions of a frequency greater than 0.5-1.0%.

Post-marketing surveillance

Adverse reactions of drugs used in the market are detected by healthcare professionals and patients using spontaneous reporting systems. The two epidemiological methods that are commonly used are cohort studies and case-control studies. In cohort studies, patients exposed a particular drug are followed up and adverse reaction frequencies are compared to an unexposed, control population. In case- control studies, the individuals affected by adverse reactions are identified as cases. Each case is matched with control population randomly recruited from study base. Both cases and control are investigated based on their exposure to possible causative agent prior to occurrence of event. The odds ratio is calculated.

In the hospital set-up, healthcare professionals should be very vigilant in detecting Adverse Drug Reactions. Adverse Drug Reactions may be detected during ward rounds with the medical team or during review of the patient's chart. Patient counselling, medication history interview and communicating with other health care professional may provide additional clues, which may be useful in the detection of Adverse Drug Reactions.

To assist the detection of Adverse Drug Reactions, healthcare professionals should closely monitor patients who are at high risk. These include;

- Patients with renal or hepatic impairment
- Patients taking drugs which have the potential to cause Adverse Drug Reactions, for example, those with a narrow therapeutic range
- Patients who have had previous allergic reactions
- Patients taking multiple drugs
- Pregnant and breastfeeding woman

The first step in the detection of Adverse Drug Reactions is collection of data. The data to be collected includes the patient's demographic information; presenting complaints; past medication history; drug therapy details including over-the-counter, current medication on admission; and lab data such as haematological, liver, and renal function tests.

Details of the suspected Adverse Drug Reactions such as time of onset and duration of reaction, nature and severity of reaction; details on the suspected drug including dose, frequency, time of administration, duration of treatment, plasma concentration of the drug; previous report on reactions; data on any other causes including risk factors and predisposing factors are useful.

All of the above can be obtained from the following sources of information:

- Patient's case notes and treatment chart
- Patient interview
- Laboratory data sources
- Communication with the healthcare professionals[26]

Reporting Of ADRS

Indian Pharmacopoeia Commission (IPC), Ghaziabad is the National Coordination Centre (NCC) for Pharmacovigilance Programme of India (PvPI). 150 ADR Monitoring Centre (AMCs) are introduced in various medical institutions/ hospitals across India to monitor and collect ADR reports under NCC- PvPI.[44]

- **What to report**

All known/ unknown, serious, non- serious, frequent or rare reaction caused due to use of vaccine or drug must be reported. Events that need to be reported include life threatening condition or death, hospitalization of patient and all suspected drug interaction.

- **When to report**

All spontaneous ADRs should be reported within 10 days. All suspected ADR should be reported as soon as possible and other serious ADR needs to be reported within 7 days. All non- serious ADR must be reported within 30 days.

- **Who can report**

All HCPs including doctors, pharmacists, nurses and mid wives can report ADR. Along with HCPs patient, patient's relatives or any common person after medical confirmation can report.[38]

- **How to report**

Suspected ADR reporting forms for HCPs and consumers are available on website of IPC to report ADR and are available in 10 different languages. ADRs can also be reported via toll free helpline number 1800-180-3024 on weekdays from 9:00 am to 5:30 pm.[44]

- **Where to report**

1. Peripheral PV Centre: It is a primary ADR information gathering centre. It consists of small medical centres, private hospitals, dispensaries, nursing home and pharmacists. ADRs are identified and synchronized by RPCs or ZPCs. All states, Union territory and few leading medical colleges in India have this peripheral centre.
2. Regional PV Centre (RPCs): It is the secondary PV centre and is located in medical college having larger facilities. These are identified and coordinated by zonal centres.
3. Zonal PV Centre (ZPCs): It is the tertiary PV centre and is located in metro city's, medical college having sufficient facility. It is identified by CDSCO and is the first ADR data collection centre. Zonal centre for north and east zone is AIIMS.[38]

Under reporting

One of the major deficiencies of spontaneous reporting program is under reporting. It has been reported that even in countries proper ADR reporting, less than 10 percentage of drug related unwanted events are notified to Pharmacovigilance centres. Under reporting varies due to various factors:

- Reporting of new drugs is higher compared to old drugs.
- Serious adverse reactions are noted more.
- Most commonly Type B reactions are reported
- Reporting is affected due to influence of sponsor.
- Specific drug related problem promotes further reporting which may not be necessarily related to actual frequency.
- Influence of general publicity around the adverse reaction reporting scheme.

Assessing Causality

Causality assessment is the method by which the extent of the relationship between a drug and a suspected reaction is estimated. In eliciting a causality relationship, a temporal or possible association is sufficient for an Adverse Drug Reaction report to be made. The assessment of causality relationship is often highly subjective, based on an individual clinician's assessment. Thus, one clinician's 'possible' may be another clinician's ' unlikely'.

If an Adverse Drug Reaction is suspected, the assessment starts with collection of all the relevant data pertaining to patient demographics; medications including non-prescription drugs (OTC); comprehensive Adverse Drug Reaction details including a description of the reaction, time of onset and duration of the reaction, complications and/ or Sequelae: treatment of the reaction and outcome of the treatment; and relevant investigation reports. The collected data should be utilised to correlate and categorised the relationship between the suspected drug and the Adverse Drug Reaction. It can be done by using one or more causality assessment scales.

Methods for causality assessment of Adverse Drug Reactions are classified into 3 groups

- Opinion of experts, clinical judgment or global introspection methods.
- Algorithms (with or without scaring) or standardised assessment methods.
- Probabilistic or Bayesian approaches

In the first group, the causation is established based on the clinical judgment of the expert (clinical pharmacologist or physicians treating the patient) or panel of experts. The experts consider all the data available pertaining to the suspected Adverse Drug Reaction and express their opinion on the possibility of a drug causing the reaction. Such judgements are based on the knowledge and experience of experts. The tool development by the WHO and Uppsala Monitoring Centre, Visual Analogue Scale Method and Swedish Regulatory Agency Method are examples.

WHO causality assessment scale

CERTAIN

- Event of laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible
- Event definitive pharmacologically or phenomenologically
- Rechallenge (if necessary)

PROBABLE

- Event or lab test abnormality, with reasonable time relationship during intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not necessary

UNLIKELY

- Event or laboratory test abnormality with time to drug value that makes a relationship improbable (but not possible)
- Diseases or other drugs provide plausible explanations

UNASSESSABLE/ UNCLASSIFIABLE

- A report suggesting an adverse reaction
- Cannot be judged because of insufficient or contradictory information
- Report cannot be supplemented or verified

POSSIBLE
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal lacking or unclear

CONDITIONAL/UNCLASSIFIED
- Event or laboratory test abnormality
- More data for proper assessment needed
- Additional data under examination

Algorithms are usually in the form of a questionnaire that enables the user to gather adequate information while assessing the causal relation between the medication and the reaction. Some important algorithm includes Naranjo's, Karch and Lasagna's, Kramer's and French imputation method. Most algorithms share common criteria to arrive at an objective conclusion. No single algorithm is accepted as a ' gold standard' because of the disagreements that exist between the various developed and published algorithms.[26]

	Yes	No	Don't know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
6. Did the reaction re-appear when a placebo was given?	-1	+1	0
7. Was the drug detected in blood (or other fluid) in a concentration known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by objective evidence?	+1	0	0

Naranjo's Causality assessment scale
- Naranjo scale assesses the causality using the traditional categories of the definite, probable, possible, and doubtful.
- A ten-element questionnaire with Yes, No, Unknown replies are developed.
- Based on the replies, the score has been determined into categories.[26]
- Definite ≥ 9, Probable 5–8, Possible 1–4, Unlikely ≤ 0

Limitations of Naranjo scale

The Naranjo scale does not address the points needed in the assessment of the Causality of possible drug interactions.[27]

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