Confidence and Accuracy in identification of adverse drug reaction (ADR) reported by inpatients

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Abstract – The project entitled "confidence and accuracy in identification of ADRs reported by inpatients" was carried out in Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan. The basic objectives of the study were to determine type and frequency of ADRs reported by inpatients, their level of confidence and accuracy and factors responsible for these aspects. Standard proforma was designed for collection and evaluation of patient data which comprises patient demographic data, chief complaints, Biochemical tests , list of medications , drug interactions , suspected adverse events , visual analogue scale, face rating scale and Naranjo algorithm. During the project 25 cases containing ADRs reported by patients were selected. In current study percentage of male and females were sixty and fourty percent respectively and it was observed that majority of individuals were in the age category of 51..60 (28%), 21-30 years (20%) , 11-20 years (12%) , 61-70 years (20%) , 71-80 years (8%) and 31-40 years (4%). From this study it was noted that prominent concurrent diseases were hypertension, ischemic heart diseases, gastro intestinal disorders and hepatic abnormalities. While incidence of ADRs were more common with injections/infusions (57%) as compare to oral dosage forms. During analysis of 25 cases, 55 drug interactions were recorded in which percentage of serious interactions, minor interactions and those interactions that require close monitoring were 7%, 26% and 67% respectively. Confidence of patients during reporting ADRs were identified using VAS and face rating scale in which percentage of high , medium and lower confidence were 32% , 39% and 29% respectively. Relation between ADE and suspected drugs were measured using Naranjo scale in which percentage of definite, probable, possible and doubtful ADRs were 3%, 48%, 46% and 3% respectively.

Keywords – Cofidence, drug interaction, Adverse Drug, Hypertension, ischemic

1. Introduction

1.1 Adverse Drug Reaction

Drug related problems i.e. ADRs is the most prevalent clinical problem in addition these are one of the major cause of mortality and morbidity [1]. In recent times the responsiveness of community is focused on Adverse drug reactions (ADR) because recently bill is approved by US senate that compel pharma companies to provide ADR related information to consumer. After the Tragedy of thalidomide in 1960s (its teratogenic effect), the interest of health care professionals is highly stimulated [2].

According to WHO ADR is defined as "any reaction produced by drug which is harmful, undesirable and occur at normal therapeutic measured quantity used in individuals for prophylaxis, diagnosis or therapy of sickness [3].The use of phrase 'at dose normally used in man' differentiate harmful effects produced by drug at normal dose from toxic effect produced by poisoning. The definition of ADRs proposed by WHO has been condemned because this definition did not mentioned ADRs caused by pharmacologically inactive components of medicinal product i.e. excipients .The use of term 'drug' in the WHO definition also omitted the use of alternative treatments such as Herbal products [4, 5].

So to overcome the defects in WHO definition of ADRs , it can be defined as "an considerably injurious or undesirable response, due to involvement associated to the use of medicinal substance, which forecasts harm from imminent administration and warn stoppage or particular treatment, or modification of the doses or withdrawal of therapeutic entity" [6]. The term "adverse reactions" and "adverse effects" are interchangeable, but ADE is seen from medication perspective whereas ADR is perceived from patient of view. However, these both terminologies should be distinguished. An ADR is an hostile result which is attributed to action of drug, while an ADE is an detrimental effect in patient taking drug, but this adverse consequence may or may not be caused by it [6].

1.2 Epidemiology

Drug related problems are responsible for majority of

fatality and diseases, in addition 6.5% of hospital admissions are attributed to these DRPs which ultimately cause burden on economy [7, 8]. A study conducted in United Kingdom (UK) showed that annual total cost of drug induced hospital admission was around £466 million [9]. According to another study conducted in 1996 the estimated cost due to ADR induced morbidity and mortality was $76.6 billion in ambulatory setting in USA [10]. The institute of medicine in US revealed that 44,00 to 98,000 deaths occur due to medical errors. Out of these deaths ADRs were responsible for 7000 deaths [11]. American pharmaceutical system performed retrospective study by examining 39 studies it was noted that 106,000 peoples died due to ADRs in 1994 [11] . Due to such mortality and morbidity it was found that in US ADRs is the fourth leading cause of death after cardiovascular disease, cancer and strokes [12] These assessments formed the basis of a major reform of the European regulatory system for pharmacovigilance, which was carried out in July 2012. In another study 3695 hospitalized patients were analyzed it was found that 14.7% of patients in surgical or medical wards experienced ADRs during their stay in hospital. Older patients, women and patients admitted to surgical wards were more prone to these ADRs [13, 14].

It is very challenging to determine the incidence of ADRs in primary health care center. In some cases, studies totally dependent on patient's ADRs report and for this purpose information are obtained either through telephone surveys or postal questionnaires. By this method information about the incidence and prevalence of ADRs can be obtained but demerit of this method is, lack of information due to unresponsiveness of ambulatory patients. However, the incidence of ADRs are about 25% in US and 30% in UK. According to studies carried out in 2007 it was noted that in primary care setting the prevalence of all ADE including ADR was 14.9% per 1000 person per month [15].

In addition, the average residence time of patients, suffering from ADR remained 20 days as compared to 8 days, and the costs associated with ADR in hospital were estimated at £ 171 million per year for NHS in England [16] . Expenses to the NHS related with admissions due to ADRs have been estimated as £466 million every year [17]. Another study performed in 2017 revealed that average incidence rate of ADR occurrence in India was 0.218%. Among them the ADRs which leads to hospital admission were 0.046% and ADRs during hospitalization were 0.212% [14]. A prospective study was conducted in Pakistan According to which the incidence of ADRs due to polypharmacy was 10.5% [18]. Another forthcoming cross-sectional examination was directed in Pakistan as indicated by which 18.09% anti-infection agents related ADEs were found in Hospitalized patients [14, 19].

1.3 Classification of "ADRs"

There are numerous means to classify it such as:

- Extended Rawlins-Thompson Classification of ADRs
- DoTS system
- EIDOS- Mechanistic classification of ADRs [20].

1.3.1Extended Rawlins-Thompson Classification of ADRs:

According to this system of classification ADRs are divided into the following types.

- Type-A (Dose related or augmented)
- Type-B (Non-dose related or bizarre)
- Type-C (Dose-related and time related or chronic)
- Type-D (Time-related or delayed)
- Type-E (Withdrawal or end of use)
- Type-F (Unexpected failure of therapy or failure) [20].

1.3.1.1 Type- A (Dose related or Augmented)

These type of DRPs are common, occur due to pharmacological action of drugs and are predictable and have low fatality rate. These reactions are typically because of inaccurate dose or impaired drug elimination. The word "side effects" is frequently referred to minor such type of reactions. There are two sub-classes of type A adverse drug reaction [21].

1.3.1.1.1 Exaggerated Desired Effect

These problems take place as a result of overstimulation of specific receptor by drugs. Examples Bleeding due to warfarin, orthostatic hypotension with antihypertensive like Amlodipine, day time dizziness cause by sleeping pills and hypoglycemic shock after insulin etc [22].

1.3.1.1.2 Unwanted Outcome

The presence of an unwanted pharmacologic impact, known as parallel incitement, such reaction can occur after an optimum dose or at slightly higher than normal quantity in vulnerable individuals. It is because of the activation of untargeted receptors by the medicaments. For instances constipation caused by morphine, gastric discomfort due to non-steroidal anti-inflammatory drugs (NSAIDs), asthmatic attack due to propranolol and loss of libido with antidepressants [23].

1.3.1.2 Type- B (Non-dose related or Bizarre)

Types B reactions are rare and are not related to the pharmacologic action of drugs. These reactions are unpredictable and have high mortality. These reactions are also called pharmacologically unexpected, unpredictable or idiosyncratic adverse reactions. There are two sub-classes of type B reactions [24].

1.3.1.2.1 Immunologic

Immunologic mechanisms are involved in such type of adverse drug reactions. Anaphylactic shock due to penicillin in susceptible patient is the example of such reaction [25].

1.3.1.2.2 Peculiar

The term peculiar is regularly utilized in a wide sense to assign subjectively irregular unfavorable response that happen in explicit individual and mechanism of which is still unknown. These responses are typically very uncommon and sometimes might be because of a hereditary or procured protein abnormality along with production of harmful metabolites. Example include primaquin induced hemolytic anemia in individuals having congenital deficiency of glucose-6-phosphate dehydrogenase (G6PD) enzyme [25].

Table 1; Comparison of type A and B reactions

	Type A	Type B
Dose dependent	Yes	No
Morbidity	High	Low
Pharmacologically predictable	Yes	No
Incidence	High	Low
Mortality	Low	High
Management	Dose reduction	Withhold and avoid in future
Drug example		
Naproxen	Agramulocytosis	G.I hemorrhage
Warfarin	Bleeding	Breast necrosis
Chlorpromazine	Hepatotoxicity	Sedation

1.3.1.3 TypeaC:

These categories of ADRs are uncommon and correlated to the cumulative amount of drug as well as duration of therapy. Examples include

1. Corticosteroids induced suppression of Hypothalamic-pituitary-axis.
2. Bisphosphonates induced Necrosis of jaws.

Such ADRs can be prevented either by withdrawal of drug or reducing its dose [26].

1.3.1.4 Type-D (Time-related or Delayed)

Such type of ADRs are rare and are usually dose related, and occur sometime after use of drug. These type of Reactions are difficult to manage. Examples of these ADRs include

1- Tardive dyskinesia
2- Carcinogenesis
3- Teratogenesis
4- Lomustine induced Leukopenia [26].

1.3.1.5 Type-E (End-of use)

These sort of problems are unusual and occur shortlyonce drug is stopped. These ADRs can be managed by reintroducing drug and then slowly withdrawn. Examples of these ADRs include

1- Withdrawal symptoms of Opiates or Benzodiazepines

1.3.1.6 Type-F (Unexpected failure of therapy)

These type of DRPs are more common, dose relate and often caused by drug interaction. Examples include failure of oral contraceptives in the presence of enzyme inducer, antibiotics etc and failure of prodrug due to enzyme inhibitor [26].

1.3.2DoTS system

According to this system ADRs are classified with respect to Dose, Timing and patient susceptibility. Rather than the Rawlins–Thompson grouping, which is characterized distinctly by the properties of the medication and the response, the DoTS classification gives a beneficial format to analyze different factors that both depict a reaction and influence the liability of individual patient [27].

1.3.2.1 Dose relatedness

Generally immunological and some unfavorable medication responses have been considered not to be related to dose of the drug. Conversely the effect of drug involves interactions between chemical entities follow the law of mass action, this indicate that both useful and harmful effects of drugs are related to the dose of the drugs. Examples of some immunologic responses that are concentration dependent are: Hayfever due to increased pollengrain count; Hepatitis B vaccine induced immunogenic responses; plus type IV allergic skin reactions [28].

It is noteworthy that after phase iv clinical trial (post marketing servialence) the doses of 20% newly marketed drugs have been reduced due to their toxicity. On the basis of dose relatedness Adverse drug reactions (ADRs) are divided into ;

• Toxic effects which include effects related to use of drugs at doses above the therapeutic dose,

• Collateral effects which include effects of drugs that occur at normal therapeutic dose and

• Hyper susceptibility reactions which include responses which happen at sub-therapeutic concentration in liable individuals [29].

1.3.2.2 Time relatedness

The pharmacological effects of drug depend upon the concentration as well as time course of its presence at the site of action. For example the diuretic effect of furosemide at particular dose is greater when infused than when given directly by bolus [30]. Furthermore the incidence of methotrexate toxicity is higher when administered frequently at low doses whileupon administration of large one dosage, incidence of toxicity is low . Time relatedness of drug reactions are of two types which are:

1.3.2.2.1 Time independent reactions

These types of responses take place at any time in the course of therapy and are not dependent on duration of treatment. Such kind of responses happen either when pharmacological reaction is changed without alteration in quantity of drug for instance digoxin toxicitydue to hypokalemia or when the extent of medication modifies at the location of activity for example digoxin induced hazards happen because of nephrologic problems [30].

1.3.2.2.2 Time dependent reactions

This kind of drug related problem include the following cases .

• Rapid reactions:

These reactions takes place when medication is administered speedily, for instance redness and itching of skin , face etc. caused by vancomycin .

• First dose reactions:

Such type of reactions takes place when drug is administered for the first time to a patient. Examples include first dose induced hypotension associated with ACE inhibitors and allergic responses [31].

• Early reactions:

These reactions appear in the beginning of therapy and disappear with continuing treatment due to development of tolerance. Example headache associated with nitrates.

• Intermediate reactions:

Intermediate reactions occur after certain time of treatment. Yet if reaction has not occurred then chances of such reactions will be less. Examples include type II hypersensitivity reactions i.e. reduction of platelets count caused by quinine, type III hypersensitivity reactions i.e. penicillin induced tubule interstitial nephritis and type IV reactions i.e. antihistamine induced cutaneous hypersensitivity [32].

• Late reactions:

Such reactions take place infrequently at the start of therapy however the incidence of these reactions increases with recurrent exposure. Examples of late reactions include adverse effects of corticosteroids i.e. Osteoporosis, Diabetes etc. and hypertensive attack after withdrawal of clonidine or methyl Dopa [32].

• Delayed reactions :

These reactions occur after sufficient time of exposure even if drug therapy is stopped prior to appearance of reaction. Examples of such reaction include In utero vaginal carcinoma in womendue to Diethylstilbosterole and Teratogenesis (malformation of hand and feet) due to thalidomide.

1.3.2.3 Susceptibility:

The incidences of adverse drug reactions among exposed population are not same. For instance penicillin cause anaphylaxis only in susceptible individuals, toxicity of isoniazid is greater in slow acetylater etc. Several factors are involved in susceptibility which include age, gender, genetic variations, exogenous factors and disease etc [32].

1.3.3EIDOS- Grouping of ADRs based on mechanism:

This system describe mechanism through which ADRs occur and depends on the following five key components [33].

1.3.3.1 The Extrinsic species (E)

Hostile drug responses occur when foreign chemical agent such as medications enters into body. The extrinsic entities may include:

• The drug itself i.e. Indomethacin induced Renal impairment, Thalidomide induced birth defects.

• An excipients i.e. castor oil (CremophoroEL) can cause IgE mediated allergic reaction.

• An adulterant i.e. Lead or Arsenic in Herbal products can cause toxicities.

• A degradation product i.e. expired product in expired tetracycline can cause renal tubular damage.

• Derivatives (metabolite) of active pharmaceutical agent (API) i.e. Metabolite of paracetamol NAPQI (N-acetyl para amino benzoquinone isoamine) induced hepatotoxicity in childrens , metabolite of isoniazid “hydrazine” cause hepatotoxicity [33].

1.3.3.2 Intrinsic species (I)

The intrinsic entities include Endogenous molecules (Nucleic acids, Enzymes, Receptors), Extracellular species (water, H-ions), Physical or physicochemical factors (tissue damage etc.).

1.3.3.3 Distribution (D)

When intrinsic and extrinsic species found in same place so they interact and response is produced. Example: Histamine antagonist i.e. chlorphenermine (extrinsic factor) produce drowsiness when cross blood brain barrier and bind with H1 receptors (Intrinsic factor) in central nervous system (CNS) but newer antihistamines like Loratidine, cetirizine etc. are unable to reach CNS and therefore does not produce drowsiness [33].

1.3.3.4 Outcome of the interaction (O)

When intrinsic factor combines with extrinsic factor it leads to generation of Hostile outcome that could cause pathological or physiological modifications.

1.3.3.5 Sequelae (S)

The consequences of the harmful alterations made by medication establish last step in this arrangement and explain clinically conspicuous incompatible drug related problems then Sequelae can be classified using DoTS system.

1.4 Risk factors of adverse drug reactions

1.4.1Age

Children and elder patients are more prone to ADRs because of physiological alteration which affect pharmacokinetic and pharmacodynamics of drugs. In elders the incidence of ADRs are more due to hepatic and renal impairments [29]. Furthermore elders suffer from multiple diseases due to which they require many drugs which increase the risk of ADRs due to drug interactions. There is relative increase in fat proportion of the body in old age which intern increase the distribution of many drugs i.e. Benzodiazepines, Opioids and Antipsychotics etc. So if doses are not adjusted it will produce toxic effects. In infants and young children organs (Liver etc.) are not fully developed due to which they are susceptible to ADRs. There are many factors which prone infants to ADRs , some of which are [34].

- Neonates under the age of eight weeks have under developed renal tubular function so drugs like aminoglycosides, ACE inhibitors, NSAIDs and digoxin should be avoided.
- Neonates have low plasma proteins (i.e. albumen) , care should be taken in case of highly protein binding drugs i.e. NSAIDs.
- Neonates below the age of 8 weeks have immature blood brain barrier [29].

1.4.2Gender

Normally physiology of women is different from that of men such as females have lower body weight, organ size, more body fat, different gastric motility and low glomerular filtration rate (GFR). These variation affect the pharmacokinetic and pharmacodynamics of drug making females more prone to ADRs . According to studies conducted by Rademaker it was found that risk of ADRs are 1.5_1.7 times greater in women as compare to men. Females have longer Q-T interval than men, due to this difference women are more susceptible to drug induced torsade de pointes and ventricular arrhythmias etc [35].

1.4.3Ethnicity

Genetic makeup greatly varies from race to race which cause inter-individual differences due to polymorphism in gene encoded for drug receptors, transporters and drug metabolizing enzymes [36]. Examples of ADRs associated with ethnicity include high incidence of ACE-inhibitors induced angioedema in black patients and high risk of statin (rosuvastatin) induced myopathy in Asian patients [29].

1.4.4Comorbidities

Co-morbidities such as renal and hepatic impairment significantly increase the incidence of ADRs. Recently Zhang et al conducted studies to determine different factors responsible for repeated admissions to hospital due to ADRs [37]. It was noticed that co-morbidities such as cardiac failure, diabetes, hepatic, renal and chronic pulmonary diseases were responsible for ADRs induce hospital re-admission rather than advanced age [36].

1.4.5Alcoholism and smoking

Alcohol can alter the metabolism of drugs and assist the development of ADRs. Chronic consumption of alcohol causes induction of CYP540 enzymes while acute consumption of alcohol cause inhibition of microsomal enzymes. When alcohol is used with other medications it can enhance their harmful effects like nausea, vomiting, head ach, loss of co-ordination etc. Similarly smoking also increase the incidence of ADRs by altering metabolism because of its strong inducing effect on hepatic microsomal P450 iso-enzymes [38].

1.4.6Poly-pharmacy

According to WHO, polypharmacy is defined as the concurrent use of five or more different prescription medications. As a result of co-morbidities and chronic illness older patients are more prone to ADRs due to polypharmacy [39]. From recent studies confirmations have been obtained that incidence of ADRs in elder patients were 6% upon administration of two drugs, while this incidence raised up to 50% when five drugs are administered and become 100% when 8 or more drugs are administered concurrently [39].

1.4.7Drug interactions

Majority of ADRs due to drug interactions which may result hospitalization and increase the cost of therapy. These types of ADRs are mostly preventable by careful analysis of prescribed medication. Example of ADRs due to drug interaction include the risk of statins induced rhabdomyolysis increase when used with enzyme inhibitors e.g fluconazole ,erythromycin, cimetidine etc [39].

1.5 Direct patient reporting of ADRs

Self-generated reporting of drug related problems such as ADRs is an essential system of pharmacovigilance which is achieved in UK through YCS and regulated by MHRA. Throughout the world Health care system mostly depend on spontaneous reporting system (SRS) for recognition of unknown and severe DRPs and for documentation of associated risk factors for the purpose of prevention of ADRs in future. Patient reporting has initiated as a source of ADRs reporting because health care professionals were not effectively reporting ADRs through spontaneous reporting system [40]. Patients can deliver detailed information about the possible adverse effects of drugs and act as valuable source of information. For example, physicians are unaware about over-the-counter medications or complementary or alternative drugs but patient report can provide detailed information about such drugs. According to analysis performed by Health regulatory International (HRI) it was observed that patient deliver significantly clearer and detailed explanations of his/her experiences than health care experts while

reporting doubted, showing eagerness to describe their knowledge's [40].

Different studies were conducted for the purpose of comparing the reporting of paroxetine induced ADRs by patients and health care professionals. As a result of such studies nine new ADRs were identified both by patients and health professionals and it was observed that patient report ADRs earlier (average difference in lag 373 days) than health professionals [41]. A group of researchers in Scotland carried out various studies on antidepressants, anticonvulsants and analgesics and found that patients consistently report their suspected symptoms to general practitioners [41]. Furthermore, general practitioners were unable to record all reported symptoms that patient has stated as possibly produced by an ADR. Patient reports submitted to MHRA during the first 2 years of scheme were compared which showed that they were more likely to describe the effects of ADR than those reported by health professionals. After comparison of submitted ADR reports it was observed that patients report large number of ADRs to many drug. However, proportion of reactions evaluated by the MHRA was same for both patients and health professionals. In general, patient reports make a useful contribution to pharmacovigilance [41].

Majority of general practitioners were not able to submit suspected ADRs to regulatory authorities, to counteract this problem direct patient reporting was initiated. Furthermore, most of individuals identified suspicion of ADR through issues relating to timing, as indicated in the methods used by pharmacovigilance specialists or by getting data about the drug from patient information leaflet (PIL) [42, 43].

1.6 To determine confidence of patient

Various methods can be used to measure the confidence of patient with respect to reporting of ADRs. In current study two methods are used in this regard which are; Visual analogue scale and Faces rating scale.

1.6.1Visual analogue scale

Visual analogue scale is an estimation tool that attempt to quantify those characteristics that we cannot measure it directly i.e. subjective characteristics. VAS was introduced for the first time in 1921 known by the name "graphic rating method" [44]. Visual analogue scale is commonly used for the measurement of pain but it is also used to measure the confidence of patient during ADR reporting, by quantifying the level of discomfort they perceive. bVAS can be used in many ways such as in form of numbers (numerical rating scales), meter shaped scales and graphic rating scales. The simple form of VAS is consisting of 10cm straight line, ends of line are considered as extreme limit of condition to be measured i.e. pain or other discomfort etc. Usually such scales line is oriented from left to right where left end indicates no discomfort while right end indicates extreme discomfort [44, 45].

Figure-1: Visual analogue scale

1.6.2 Faces rating scale

Faces rating scale is also called Wong-Baker faces pain rating scale because it was introduced by Donna Wong and Connie Baker for measurement of pain. This scale comprises of six faces ranging from happy face which indicates no discomfort to crying face which shows worst discomfort as shown in figure below. In this method patient is asked to select facial expression that describes their level of discomfort [46].

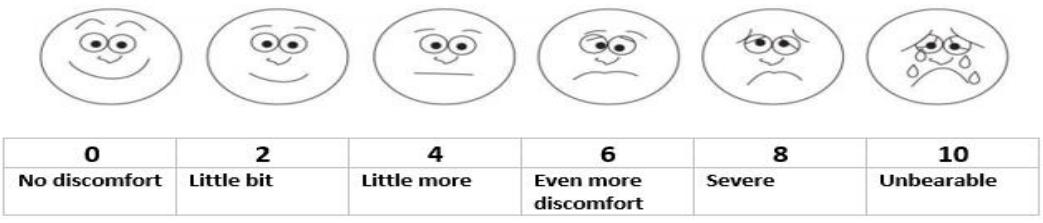


Figure 1 : Face rating scale

1.7 Causality assessment of ADR /Drug-adverse event relation:

This method is the assessment of the possibility that a specific treatment is the reason for scrutinized unfavorable conditions. It involves determination of association between suspected drug and ADE. It is the significant part of pharmacovigilance and assumes a significant role in assessing the hazard-advantage profiles of medications [47].

Studies indicates that length of hospital stay and death rate are 8.25% and 19.18% are higher respectively in those patients who have ADRs. As a result of these ADRs an average rise of 19.86% occur in total medical costs of patients . Nonetheless physicians frequently do not perceive this medication related problem and this failure may result improper management of drug related problems subsequently presenting the patient extra medication danger. To minimize the risk of ADRs in patient it is necessary to determine the casual link between drug and adverse event. For such purpose different causality assessment methods have been established such as Naranjo scale, Kramer's algorithm, Karsh and Lasagna scale and

WHO–UMC causality assessment criteria but the two most widely used are the WHO–UMC and Naranjo probability scale. Many of the accessible techniques are very multifarious and tedious so their use in daily clinical practice has been restricted [47].

1.7.1Naranjo Scale/Algorithm

This ADR Probability Scale was developed in 1991 by Naranjo and colleagues and is often known as Naranjo algorithm. The purpose of this scale was to help standardized assessment of causality for all DRPs. The scale was likewise for use in clinical trials and registration studies. Naranjo scale is commonly used and is simple to apply. This algorithm is comprised of 10 questions, to each question specific score is assigned representing various problems linked to ADRs [48]. Each question has three options i.e. 'yes', 'no' or 'do not know'. At last score of all ten questions is added to determine causality category of adverse drug reaction. A simplified version of the 10 questions is provided below in a table 2.

Table-2: Questioner based on Interpretations of Naranjo Score.

ADRs detection based questioner	Yes	No	Don't Know
Are there any previous reports of this reaction?	+1	0	0
Adverse drug reaction appears after the drug was given?	+2	-1	0
Adverse drug reaction approved when the drug discontinued or taking specific antagonist?	+1	0	0
Did the adverse drug reaction reappear upon re-administering the same drug?	+2	-1	0
Was there any other possible cause of adverse drug reaction?	-1	+2	0
Did the adverse drug reaction reappear upon administration of placebo?	-1	+1	0
Was the drug detected in the blood or other fluids in toxic concentration?	+1	0	0
By increasing or decreasing the dose the reaction become worsened or lessened?	+1	0	0
Did the patient have similar reaction in the past with same or similar agent?	+1	0	0
Was the adverse drug reaction confirmed by any other objective evidence?	+1	0	0

***** The total scores range from -4 to +13, the reaction is considered definite if the score is 9 or higher, probable if 5-8, possible if 1-14, and doubtful if 0 or less.

2. Methodology

2.1 Setting and duration

This report is based on clinical pharmacy clerkship rotations completed during 45 days period from 1st August to 15th September 2019 conducted in all wards of Pakistan Institute of Medical Sciences (PIMS), Islamabad, Pakistan. The title of the study was "Confidence and accuracy in identification of adverse drug reactions (ADRs) reported by in-patients.

2.2 Data collection

Daily visits were made to each ward of the hospital where 4 to 6 interviews were carried out. By doing so total 150 histories were collected out of which only 25 histories i.e. those histories were selected which contain ADRs reported by patient. For data collection patients medication charts were thoroughly studied after which patient were interviewed by using suitable format (questioner).

2.3 Questioner development

A suitable questioner/proforma was designed in order to get information about ADRs reported by patients. Questioner contain different information's such as patient demographic data , prescribed medication , lab reports , suspected Adverse events , suspected drug(s) and Naranjo algorithm [48].

2.4 Data analysis

Current therapy provided in hospital as well as previous medications were analyzed for adverse drug reactions and factors responsible for ADRs. Medscape and BNF were used as source for drug interactions and adverse effects of drugs.

3. Results

we recorded and studied the case histories of 25 patients. The data collected and outcomes of it are given here below.

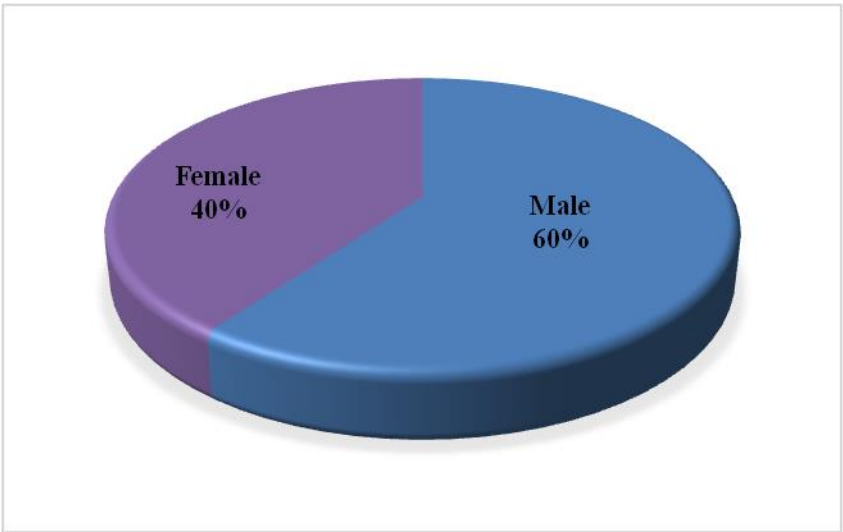


Figure 2: Gender-wise distribution

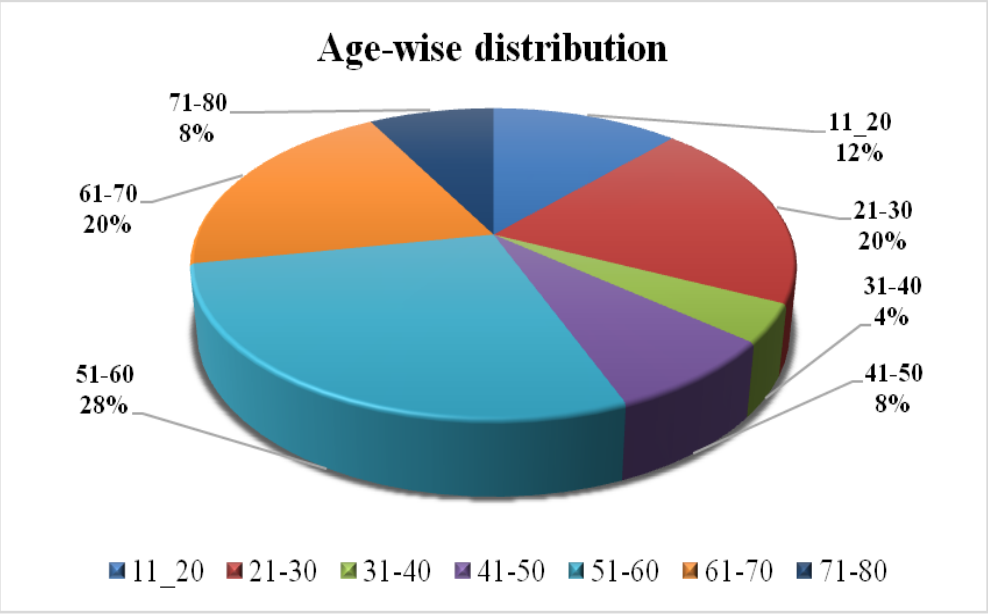
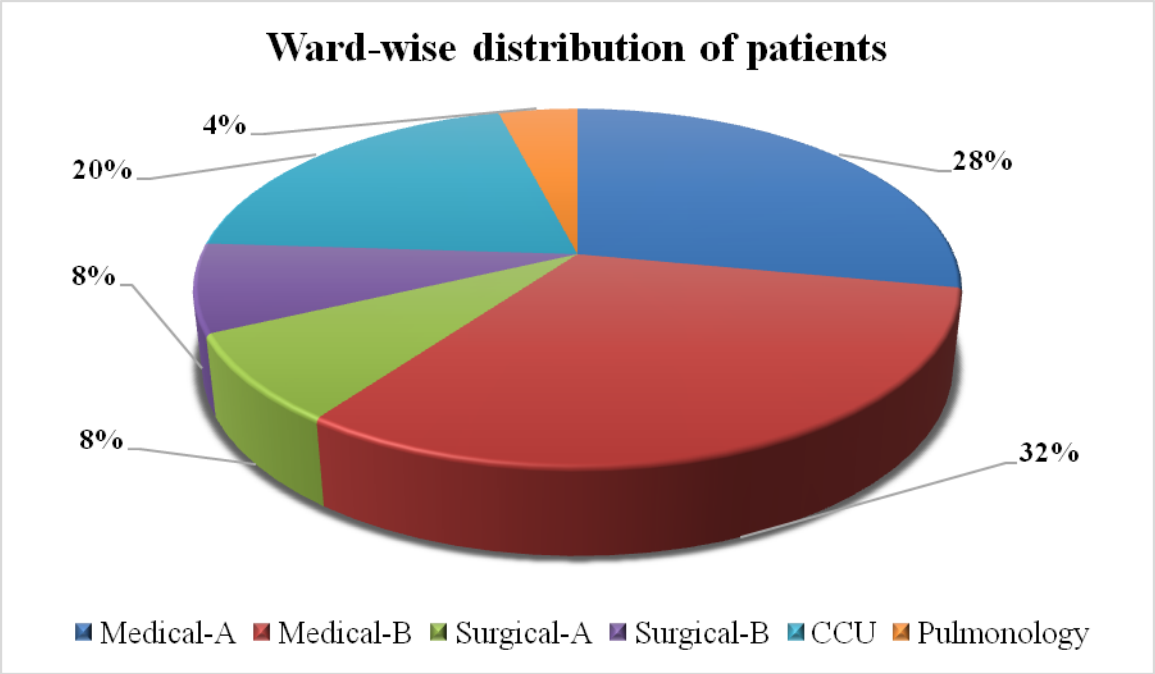


Figure 3: Age-wise distribution



Figur-5: Ward-wise distribution of patients

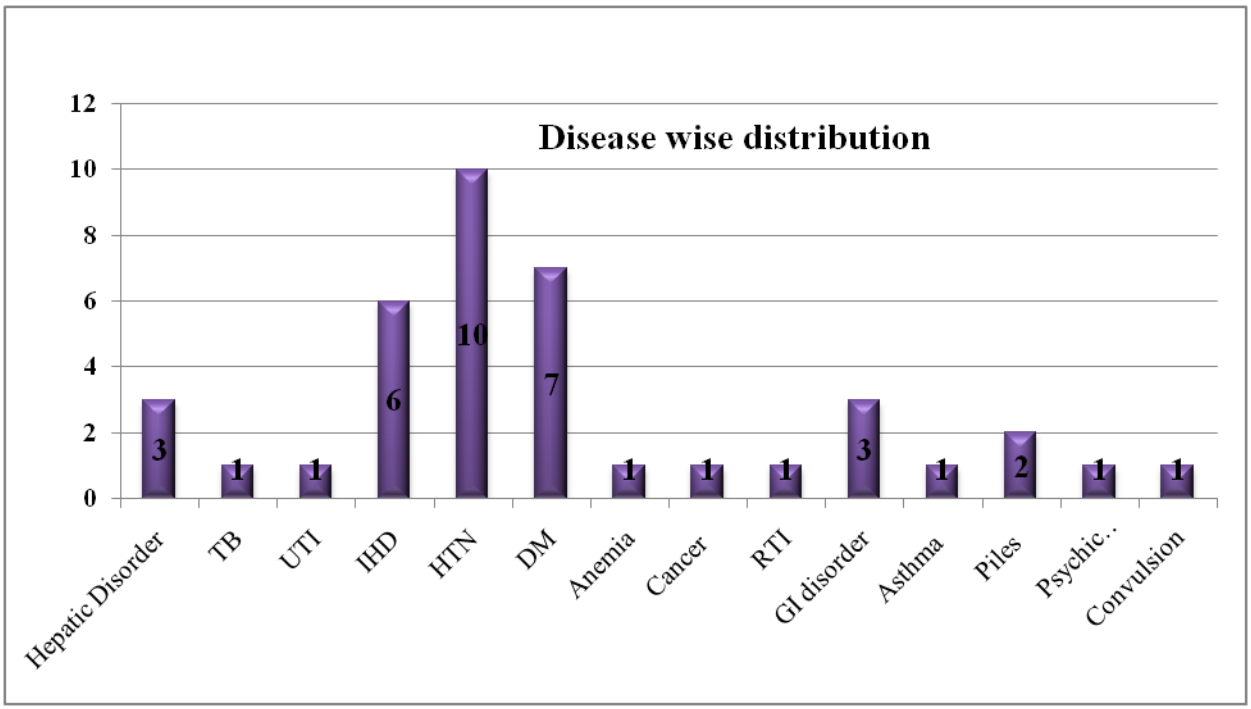


Figure 4: Concurrent diseases

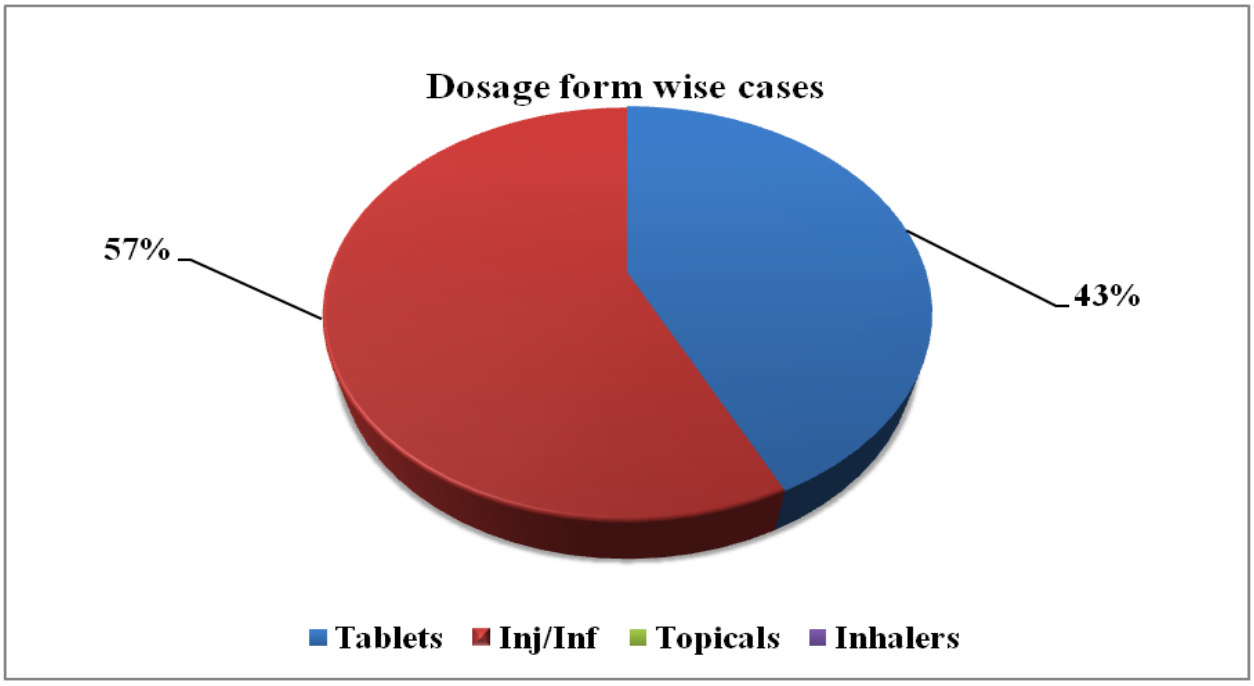


Figure 5: Dosage Form wise ADRs cases

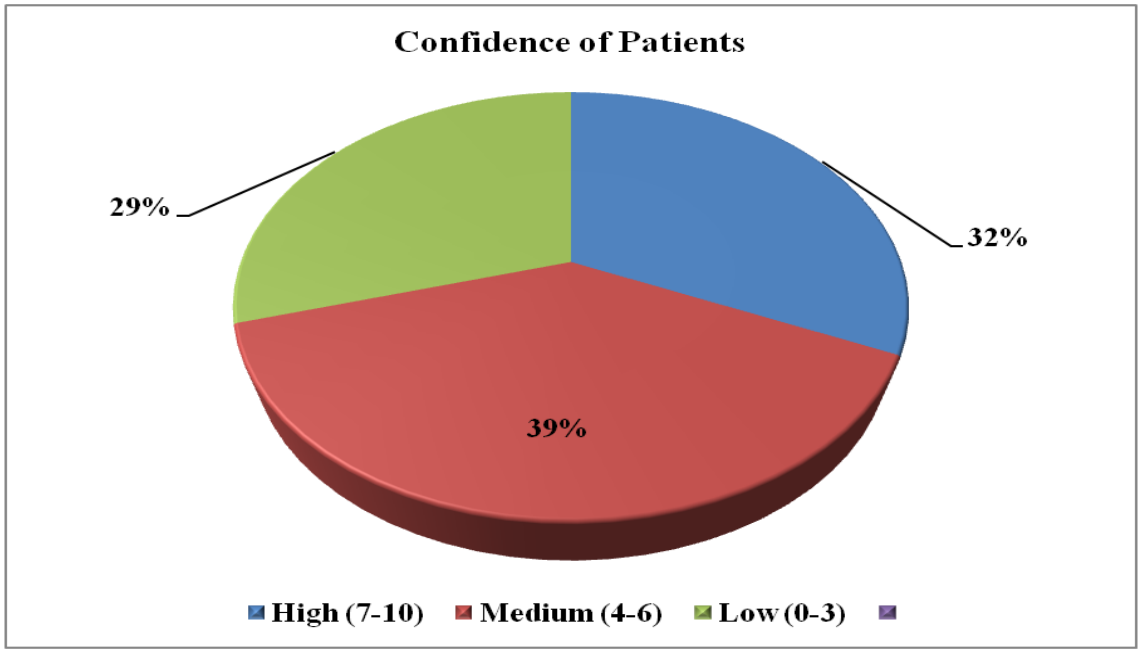


Figure 8: Degree of confidence about ADRs reported by patients

4. Discussion

The purpose of this study is to determine patient experience regarding ADRs specifically their level of confidence in identifying symptoms of ADRs and accuracy by using specific algorithm (Naranjo scale) [48]. In current study 25 cases were selected/ collected from CCU, Pulmonology, Medical and Surgical wards of Hospital. These cases were studied for various parameters. During this study out of 25 cases 15 were male and 10 were female patients, percentages of which are 60% and 40% respectively. According to studies it has been observed that females are more susceptible to ADRs as compare to males but in this case incidence of ADRs seems greater in male than female. Such fluctuation of result may be due to lack of education and cultural barriers that create hindrance for females while reporting ADRs.

Incidence of ADRs was higher in the age group of 51-60 years being 28% . Furthermore, ADRs were most prevalent in patients admitted to Medical-B ward because patients in this ward have large number of co-morbidities. Percentages of cases in Medical-B ward were 32%. The most prevalent concurrent disease was hypertension while second most prevalent diseases were Diabetes mellitus and Ischemic Heart Disease (IHD). Incidences of ADRs were more common with those drugs which require parental administration particularly (injections/infusions) percentage of which was 57%.

During current study total 55 drug interactions were

recorded, out of which 7% of interactions were of serious nature where such combinations should be avoided or suitable alternative should be used. Whereas majority of interactions (67%) require careful monitoring and 26% of interactions were of minor nature. Total 28 suspected drugs were identified which caused ADRs, majority of ADRs were due to antibiotics and cardiovascular drugs. Out of those, reactions of serious nature are insulin induced hypoglycemic shock (unconsciousness), bisoprolol induced bradycardia and isoniazid induce jaundice.

After analyzing cases in current study it was noted that while reporting ADRs in 39% of cases the level of confidence of patients was medium whereas 32% and 29% of cases showed high and low level of confidence respectively. Relation between ADE and suspected drug were determined by Naranjo Algorithm, from which it was recorded that 48% of cases were probable a 46% were possible while cases of definite and doubtful nature were only 3%.

5. Conclusion and recommendation

Data obtained from the current study confirmed that patient reporting could play beneficial role in pharmacovigilance. From above discussion it is clear that drug related problems are common in hospitals. Unfortunately, there is no proper pharmacovigilance systems in Pakistan due to which majority of health care professionals are not giving attention to identify drug related problems. These can increase hospital stay of patients which create on economy of country and influence compliance of patients.

Based on this project it is also concluded that there is lack of considerations among physicians regarding report of ADRs. Proper system of prescription and dispensing must be introduced for the purpose of reduction of adverse drug reactions and all other drug related problems. Most of these problems can be prevented by careful review of prescription for drug interactions, contraindications and dosage adjustment etc. Furthermore pharmacist shall visit wards to provide drug related information to nurses and physicians.

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Conflict of Interest

The author claiming no conflict of interest.

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