Adverse Drug Reaction Scenario at ADR Monitoring Centre of Tertiary Teaching Hospital at Raipur

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ABSTRACT

Drugs are approved for clinical use after passing stringent protocol of preclinical and clinical trials so that they are safe for human consumption. But they provide limited information as they are conducted under strictly controlled conditions and largely focus on efficacy evaluation and adverse drug reactions being secondary parameters assessed. Some ADR can be detected only after Long term use in a large population and in specific patient groups due to genetic variability or difference in life style and food habits, concomitant disease prevalence and medication use . We are reporting the scenario of spontaneous suspected ADRs reported at ADR Monitoring Center (AMC) of Pt JNM medical college Raipur, Chhattisgarh, India.

A retrospective, cross sectional observational study of ADRs reported spontaneously between June 2014 and May 2015 done at our AMC. The study protocol was approved from Institutional ethical committee. Odds ratio and Percentages were calculated. Of the total of 26 suspected ADRs received, 61.5% (n=16) were females. Only 11.53% (n=3) were serious. The most common ADR presented were with dermatological symptoms 65.38% (n=17) and the most common offending class of drug was of musculoskeletal class -NSAIDs -38.46% (10). 53.84 % (n=14) ADRs were possible, 26.92% (n=7) were probable, 15.38% (n=4) were certain and 3.84% (n=1) was unclassified. 57.69% (15) patients had received generic formulation and 73.07 % (n=19) ADRs were due to single drug formulation.

Measures to improve adverse drug reaction detection and reporting by all healthcare professionals should be undertaken, to ensure patient's safety.

Keywords: *Adverse Drug Reaction (ADR), ADR Monitoring Center (AMC), health care professionals. National Coordinating Center – NCC, Pharmacovigilance program of India (PvPI), Central Drugs Standard control Organization (CDSCO).*

INTRODUCTION

Adverse drug reactions have been identified as a top safety priority because these events are the most common type of iatrogenic injury, increasing morbidity, mortality leading to increased or prolonged hospitalization and pharmacoeconomic burden. Studies have indicated that ADRs occur almost daily among indoor and outdoor patients. However, despite the high morbidity and mortality, health care professionals often do not recognize, report or appropriately treat instances of drug-related harm.

The World Health Organization defines Adverse drug reaction as a response which is noxious and unintentional, and undesired effect to a drug, which occur at doses used in human for the prophylaxis, diagnosis or therapy[1]. This definition underlines the fact that the phenomenon is noxious (differentiating adverse drug reaction from side-effects which can also be beneficial) and that it includes doses prescribed clinically, excluding accidental or deliberate overdose [2].

Pharmacovigilance is a science relating to the detection, assessment, understanding and prevention of adverse drug reaction or any other possible drug related problems. The ultimate goal of this activity is to improve the safe and rational use of medicines, thereby improving patient care and public health [3]. Recently, the concerns of Pharmacovigilance have been widened to include herbal, traditional and complementary medicines, blood products, biological, medical devices and vaccines. Many other issues like substandard medicines, medication errors, lack of efficacy, use of medicines for indications that are not approved and for which there is inadequate scientific basis, case reports of acute and chronic poisoning, abuse and misuse of medicines, and adverse interactions of medicines with chemicals, other medicines and foods and drinks are also of relevance to the science of Pharmacovigilance [4].

ADRs and causality assessment are important component of Pharmacovigilance, contributing to better evaluation of the risk-benefit profiles of medicines. Evaluating ADR reports are essential part of Pharmacovigilance as it helps to collates and analyze data to arrive at an inference for regulatory purposes [5]. There is diversity in results

around the globe and, it is due to the rigor with which ADR are sought, detected and reported.

Globally, the size of the database for Pharmacovigilance in developed countries are big enough to perform data mining and to check if any drug has been found to be causally associated with and significantly responsible for any serious and unknown side effects. As per 2012, there are over 7 million adverse reaction reports in the WHO individual case safety reports (ICSR) data base [6].

In a meta-analysis of 39 prospective studies from hospitals in the United States, it was shown that ADRs ranked from the fourth to sixth leading cause of death and accounted for 6.7% of all admissions and 6-15% hospitalized patients experience ADR [7]. In Europe also 8% - 12% of patients admitted to hospitals suffer from adverse effects and 100,800–197,000 Europeans die per year in hospitals due to adverse drug reactions. Many more are harmed without fatal consequences [8]. While similar figures are not available for India, it is logical to conclude that the figures in relative and absolute numbers would be much higher in view of high levels of unmonitored and indiscriminate drug use widely prevalent in the country. Medicinal Product Records in WHO-Drug dictionary, March 1, 2006, for the Top 15 Countries shows that in spite of India having 40,800 Medicinal Product with 14,500 Product Names and 2,100 Combination of Ingredients, Compared to United States with 72,700 Medicinal Product, 9,100 Product Names and 3,800 Combination of Ingredients [9]. India is way behind them in reporting ADRs.

In such a scenario, the Pharmacovigilance program initiated by Central DrugsStandard control Organization (CDSCO) of Indian government promises to maintain a close watch over the use of drugs and their effects on people. The Pharmacovigilance Program of India (PvPI) was launched in April 2011, with a broad objective to safe guard the health of people of India. Adverse drug Reactions (ADRs) from Monitoring centers are reported from all over the country to National Coordinating Center - NCC-PvPI, which work in collaboration with the global ADR monitoring centre (WHO-UMC) Sweden to, contribute in the global ADRs data base. NCC-PvPI monitors the ADRs among Indian population and helps the regulatory authority of India (CDSCO) in taking decision for safe use of medicines.

As per information furnished by Medical Council of India (MCI), the total number of doctors registered (allopathic) in the country till 31st July, 2011, is 8,56,065 out of which approximately six lac are presently active practitioners. The current doctor-population ratio has been worked out to be approximately 1:2000 in India[10]. This is way behind the 1:600 doctor patient ratio as recommended

by the World Health Organization (WHO) by 2015. This disproportionate shortage of health care professionals in India, leads to health care professionals being overburden with clinical care, and reporting an ADR becomes secondary and, adds to the workload compounded by lack of interest, lack of knowledge about when and where to report, and false fear of legal problems deter them to participate in thePharmacovigilance program.

When assessing a suspected ADR, the clinician should always evaluate the following aspects [2, 11]

- Temporal relationship between the use of the drug and the occurrence of the reaction (time to onset),
- The differential diagnosis (of causes other than the suspected drug),
- The selection of the responsible drug on the basis of pattern of the event or by exclusion, dechallenge and rechallenge.
- The pattern of the adverse event must fit the known pharmacology or allergy pattern of one of the suspected drugs or of chemically or pharmacological related compounds.

Drug interactions may cause altered drug bioavailability, distribution, clearance and additive or antagonistic pharmacodynamic effects. A recently published study indicated that the percentage of drug-drug interactions identified as cause of ADRs was 15% [12]. The aim of the causality assessment is to establish a level of probability regarding the suspicion that a certain drug is responsible for an adverse event. WHO-UMC[13] developed a causality system which we will be following, takes into account the clinical-pharmacological aspects. According to this scale ADRs can be of these 6 types certain, probable/likely, possible and unlikely/doubtful, conditional/ unclassified, and unassessable/unclassifiable. Methods to evaluate ADRs using data from clinical trials, medical records, and computerized databases of medication users and nonusers must be developed to complement spontaneous reporting systems. Without these methods, potentially important ADRs will remain undetected and spurious associations between adverse outcomes and medications or devices will remain unchallenged [14].

MATERIAL AND METHOD

Spontaneously reported Suspected ADRs forms received between June 2014 to may 2015 from prescribing clinicians of government hospital and private set up were analyzed for demographic profile, causality using WHO-UMC scale and The Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO was used for drug utilization studies. International Classification

of Disease (ICD -10) was used for coding the diagnosis. Spontaneous ADR reporting forms issued by Indian pharmacopeia commission were used to collect the ADRs.

OBSERVATIONS AND RESULTS

A total of 26 suspected ADRs were received in one year at our monitoring center.

1   61.5% (n=16) were females and 38.5% (n=10) were males.
2   69% (n=18) patients were adults between the age group 14-60 yrs Geriatric patients >60 yrs were 23.07% (n=6) and 7.69% (n=2) were of pediatric age group <14 yrs.
3   Only 11.53 %(n=3) were serious and had to be hospitalized, and 88.46 % (n=23) were not serious.
4   The most common diseases as per System organ classification(SOC)were of musculoskeletal system connective tissue and bone disorder 57.69%(n=15), followed by 15.38 (n=4) cases were of infection and infestation , 7.69% (n=2) cases each of respiratorytract illness, GIT disorders, and surgical procedures and 3.84% (n=1) was of investigation.(fig 1)
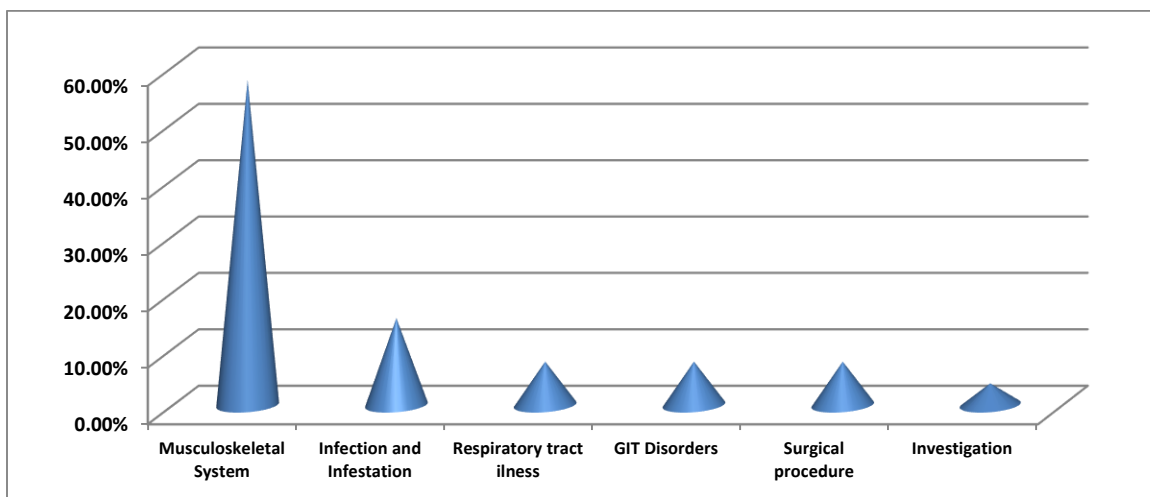

Fig. 1: Disease for which Drugs were prescribed with percentage of patients.

5. The most common ADRs 65.38% (n=17) were with dermatological symptoms (itching, urticaria, peticihal hemorrhage), 26.92% (n=7) had peripheral edema and a similar number of patients has GIT irritation and hyperacidity, 7.69% (n=2) had involvement of eye and a similar number had involvement of musculoskeletal system, 3.84%(n=1) had cardio toxicity.(fig 2)
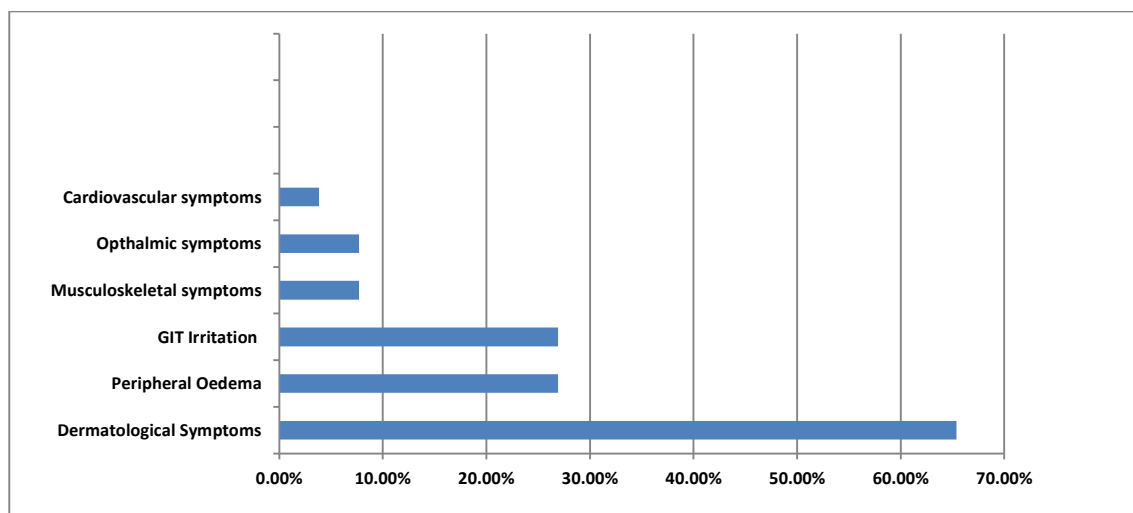

Fig. 2: System involved in ADR with percentage

One patient with dermatological manifestation has fixed drug reaction (hyper pigmented circular lesion) on boththe sole after oral Aceclofenac 200 mg   for osteoarthritis. The drug was stopped and the reaction waned gradually. The patient self administered Paracetamol after 2 weeks for analgesia and the reaction reappeared.

Fig. 3: Fixed Drug Eruption after Aceclofenac (both Feet)

6   The most common offending class of drug according to The Anatomical Therapeutic Chemical (ATC) classification was 42.30% (n=11) musculoskeletal class including NSAIDs (n=10) and Ibandronate (n=1), followed by 30.76% (n=8) anti-infective class including anti-bacterial, antiretroviral (Zidovudine+ lamivudine+ Nevirapine), Anti leprotic drug Dapsone, anti-filarial -DEC. 7.69% (n=2) of minerals and vitamins class   followed by 3.84%(n=1) each total 5 , of anti-neoplastic agents (Doxorubicin), , blood forming agent (Ferrous ascorbate), sex hormone group (ethinyl estradiol +desogestrel) , Dye –Iohexol, and unknown herbal preparation.(fig 4)
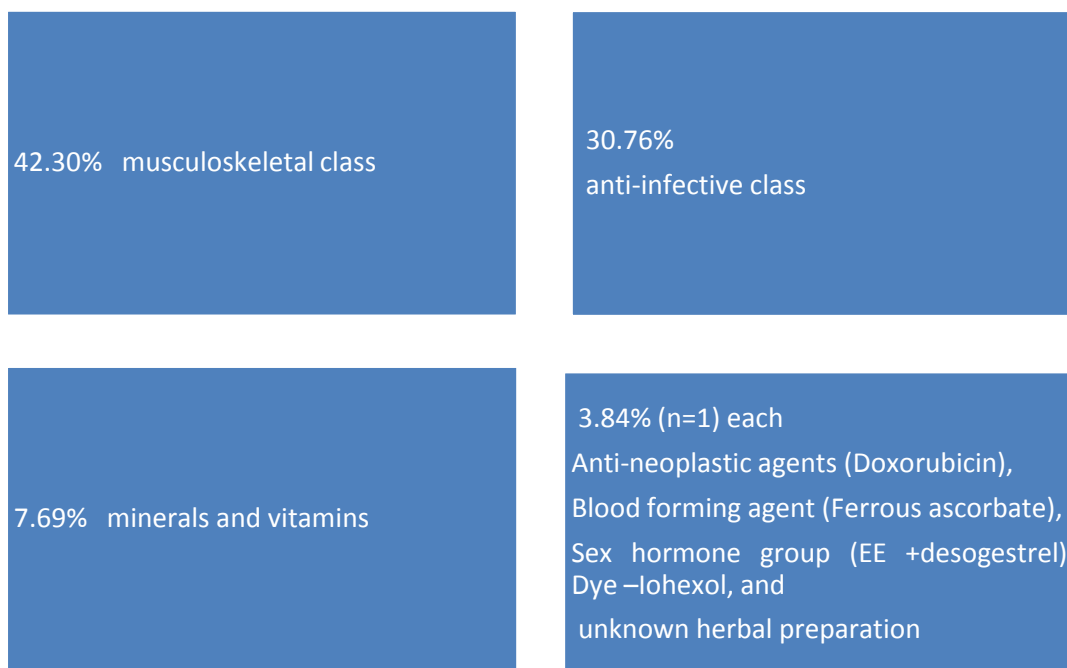
42.30%   musculoskeletal class

30.76%
anti-infective class

7.69%   minerals and vitamins

3.84% (n=1) each
Anti-neoplastic agents (Doxorubicin),
Blood forming agent (Ferrous ascorbate),
Sex hormone group (EE +desogestrel)
Dye –Iohexol, and
unknown herbal preparation

Fig. 4: Offending drugs.

7   50% (n=13) patients had acute onset of ADR, ie, after taking one dose only, followed by 15.38 % (n=4) patients reporting after 3 doses and a similar number reported after 6 doses. 7.69% (n=2) reported after 2 doses and a similar number with 4 doses.Only one patient reported with unknown dose.

8   At the time of receiving the ADR forms, 73.07 %(n=19) patients were recovering, 23.07% (n=6) had recovered, and one patient (with cardio toxicity due to doxorubicin) was still suffering. No Fatality was reported.

9   As per the Causality assessment by WHO UMC scale, 53.84 %(n=14) ADRs were possible, 26.92 % (n=7) were probable, 15.38% (n=4) were certain and 3.84 %(n=1) was unclassified.

10 57.69% (n=15) patients had received generic formulation and 42.30(n=11) had taken Branded Formulation

11 73.07 % (n=19) ADRs were due to single drug formulation and 26.92% (n=7) were due to fixed drug combinations (fig 5).
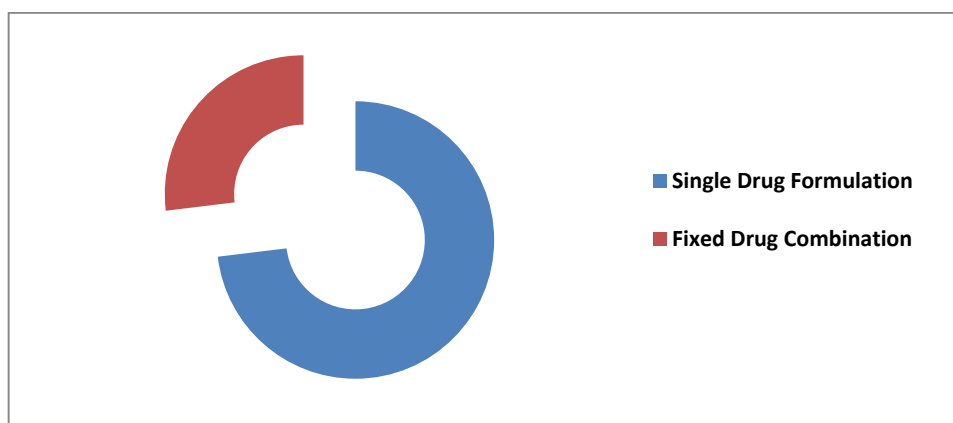
■ **Single Drug Formulation**

■ **Fixed Drug Combination**

Fig. 5: Type of Drug Formulation

DISCUSSION

In our study 61.5% were females and 38.5% were males, showing female preponderance but statistically not significant, (OR=1.600, 95% CI = 0.6132-4.1747, p=0.3368 (P <0.05) and the finding is consistent with other studies. [15, 16]

Age distribution pattern shows only 7.69% were of pediatric age, 69% patients were adults between the age group 14-60 yrs, and 23.07% were

elderly above 60 yrs of age as compared to 21% reported by Schneider JK, Moin LC et al [17]. These findings are consistent with recent studies [18, 19]. The reason why higher incidence is observed in adults could be that they have more accessibility to medical health care and awareness to come back to the treating physician to report ADR.

Adverse drug reactions are an important cause of hospitalization. In our study 11.53% were serious and had to be hospitalized. Other studies have reported a higher admission rate of up to 30% [20, 21]. The difference could be due to under reporting of ADRs. *The serious ADRs were due to use of Doxorubicin for Hodgkin's disease, Lamivudine/ Nevirapine/ Zidovudine for HIV infection and Oxaceprol (NSAID) for use in osteorthritis.* There are several ways in which doxorubicin is believed to cause cardiomyopathy, including oxidative stress, down regulation of genes for contractile proteins, and p53 mediated apoptosis. The drug dexrazoxane is used to mitigate doxorubicin's cardio toxicity. Lamivudine/ Nevirapine/ Zidovudine Tablets 150mg/ 200mg/300mg may cause skin reactions and allergic reactions, which in the worst case can be serious and life-threatening. Fatalities have been reported. Such reactions may appear in form of rash accompanied by other side effects such as fever, blistering, mouth sores and requires discontinuation of this combination.

The most common presentation of ADRs were dermatological manifestations seen in 65.38% followed by gastro intestinal system (Gastric irritation and hyper acidity) and renal disorder (peripheral edema) 26.92% in each. This is consistent with other studies [15, 22]. However Suh et al [23] reported gastrointestinal (24%), dermatologic (19%), and immune systems (15%) as the major organ systems affected.

In our study one patient reported with fixed drug eruption (FDE), and study [24] show that FDE is one of the most typical cutaneous drug adverse reactions. This localized drug-induced reaction is characterized by its relapse at the same sites. The most common drug implicated is paracetamol, followed by the non-steroidal anti inflammatory drugs. The time between drug intake and skin symptoms is on average, two days.

The most common offending class 42.30% (n=11) of drug according to ATC classification belonged to musculoskeletal class including NSAIDs (n=10) and Ibandronate (n=1), followed by 30.76% (n=8) anti-infective class including anti-bacterial, antiretroviral (Zidovudine+lamivudine+ Nevirapine), Anti leprotic drug Dapsone, anti-filarial -DEC. 7.69% (n=2) were of minerals and vitamins class followed by 3.84% (total 5, 1 each from anti-neoplastic agents (Doxorubicin), blood forming agent (Ferrous ascorbate), sex hormone group (ethinyl estradiol +

desogestrel), Dye – Iohexol, and unknown herbal preparation. Classen et al also found NSAIDs as the most offending drug[25]. While Murphy andFrigo reported that rash and antibiotics were most common [26].

In Causal relationship only 15.38% (n=4) drugs were established with certainty for ADR, 53.84 %(n=14) suspected drugs were- possible which is higher than probable -26.92 % (n=7) and 3.84 %(n=1) were unclassified. A similar study showed Causality of 63% of ADRs as possibly drug-related [27]. Another study reported 56.7% ADRs as probable followed by 43.3% as possible [28].

57.69% patients received generic formulation and 42.30% had taken Branded Formulation. We could not find any study during internet search which showed the difference in ADR incidence due to brand or generic prescription, though studies do report of increased incidence of ADRs due to generic switch from branded. Ken G. Makus reported adverse reactions on a brand-to-generic switch of lamotrigine for epilepsy, presenting as loss of seizure control[29].Another study by Luca Gallelli[30] reports that the use of generic drugs could be related with an increased days of disease or might lead to a therapeutic failure.

We also found that 73.07 % ADRs were due to single drug formulation and 26.92% were due to fixed drug combinations. It is a well known fact that Most FDCs increases chances of adverse drug effects and drug interactions compared with both drugs given individually as they have the following demerits [31]

- Dosage alteration of one drug is not possible without alteration of the other drug.
- Differing pharmacokinetics of constituent drugs pose the problem of frequency of administration of the formulation.

CONCLUSION

In India ADR monitoring and reporting is in its infancy and needs rigorous attitude of ADR monitoring centers towards sensitizing the health care professionals right from the beginning of medical career and by continuing medical education to highlight the importance and moral responsibility to report ADRs.

Measures to improve detection and reporting of ADR by all health care professionals should be undertaken, to ensure patient's safety. The success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions. To date, the mainstay of pharmacovigilance has been spontaneous reporting by health professionals. To detect the full spectrum of complications from pharmaceutical treatment and to gain a representative picture, all sectors of the health-care system need to be involved. This includes public and private

hospitals, general practitioners, pharmacies, nursing homes, retail dispensaries and providers of traditional medicine. The patients and the general public also must be made aware to report any ADR.

REFERENCES

1.   Definitions – WorldHealthOrganization www.who.int/ medicines/areas/quality_safety/safety.../definitions.pdf. Accessed July 2015.

2.   Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000; 356:1255–1259.

3.   Rehan HS, Chopra D, Kakkar A; Physician's guide to pharmacovigilance: Terminology and causality assessment. European Journal of Internal Medicine, 2009; 20: 3-8

4.   World Health Organization- 2006 The Safety of Medicines in Public Health Programmes. page 21. *www.who.int/medicines/areas/quality.../Pharmacovigil ance_B.pdf. Accessed July 2015*

5.   Arimone Y, Begaud B, Miremont-Salame G, Fourrier-Reglat A, Moore N, Molimard M et al.; Agreement of expert judgment in causality assessment of adverse drug reactions. Eur J ClinPharmacol., 2005; 61: 169-173.

6.   Uppasala Monitoring Center. Wikipedia. *Accessed July 2015*

7.   Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA.1998 Apr 15; 279:1200-5.

8.   *Vassiliou A. Patient safety – A strategy for Europe. EJHP Practice. Volume 15 2009/5.*

9.   M Lindquist .VigiBase, the WHO Global ICSR Database System: Basic www.who-umc.org/graphics/24965.pdf. 2008. Accessed July 2015

10.   Doctor-Patient Ratio in the Country - Press Information Bureau pib.nic.in/newsite/PrintRelease.aspx?relid=77859 Accessed July 2015

11.   Talbot J, Waller P. Detection of New Adverse Drug Reactions. 5th Edn, Chichester, UK: John Wiley & Sons, 2004. Br J Clin Pharmacol. 2004 Aug; 58(2): 227.

12.   Passarelli MC, Jacob-Filho W, Figueras A. Adverse drug reactions in an elderly hospitalised population: inappropriate prescription is a leading cause. Drugs Aging 2005; 22: 767-777.

13.   The use of the WHO–UMC system for standardized case causality assessment. Accessed at http://www.who-umc.org/graphics/4409. Pdf acessed july 2015.

14.   BrewerT, Colditz GA. Postmarketing surveillance and adverse drug reactions: current perspectives and future needs. JAMA. 1999; 281(9):824-9.

15.   Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India Br J ClinPharmacol. 2008 Feb; 65(2): 210–216.

16.   Rademaker M. Do women have more adverse drug reactions? Am J ClinDermatol. 2001; 2(6):349-51.

17.   Schneider JK, Mion LC et al Adverse drug reactions in an elderly outpatient population.Am J Hosp Pharm. 1992; 49:90-6.

18.   Singh Surjeet, Wafai Z A. ADVERSE DRUG REACTION MONITORING AT TERITIARY CAR

19.   Jha N, Bajaracharya O, Namgyal T. Prevalence 2002. of adverse drug reactions with commonly prescribed drugs in different hospitals of Kathmandu Valley. Kathmandu University Medical Journal 2007; 5(4); issue 20; 504-10.

20.   Gupta R, Sheikh A, Strachan D, Anderson HR. Increasing hospital admissions for systemic allergic disorders in England: analysis of national admissions data. BMJ. 2003 Nov 15; 327(7424):1142-3.

21.   Wu TY, Jen MH, Bottle A, Molokhia M, Aylin P, Bell D. Ten-year trends in hospital admissions for adverse drug reactions in England 1999-2009.J R Soc Med. 2010 Jun; 103(6):239-50.

22.   Beijer HJM, de Blaey CJ. Hospitalizations caused by adverse drug reactions: a metaanalysis of. observational studies. Pharm world sci 2002; 24: 46-54.

23.   Suh DC, Woodall BS, Shin SK, Hermes-De SantisER. Clinical and economic impact of adverse drug reactions in hospitalized patients. AnnPharmacother. 2000 Dec; 34(12):1373-9.

24.   Brahimi N, Routier E et al., A three-year-analysis of fixed drug eruptions in hospital settings in France, Eur J Dermatol. 2010 Jul; 20(4):461-4. Epub 2010 May 27.

25.   Classen D, Pestotnik S, Evans R, Burke J, and Battles J. Computerized surveillance of adverse drug events in hospital patients. QualSaf Health Care.2005 Jun; 14(3): 221–226.

26.   Murphy BM, FrigoLC. Development, implementation, and results of a successful multidisciplinary adverse drug reaction reporting program in a university teaching hospital. Hosp Pharm. 1993 Dec; 28(12):1199-204, 1240.

27.   Sriram S, Ghasemi A, Ramasam R et al., Prevalence of adverse drug reactions at a private tertiary care hospital in south India. J Res Med Sci. 2011 Jan; 16(1): 16–25.

28.   Kaur S, Kapoor V, Mahajan R et al. Monitoring of incidence, severity, and causality of adverse drug reactions in hospitalized patients with cardiovascular disease Indian J Pharmacol. 2011 Feb; 43(1): 22–26.

29.   Ken G. Makus, John McCormick Identification of adverse reactions that can occur on substitution of generic for branded lamotrigine in patients with epilepsy. Clinical Therapeutics February 2007;29(2), 334–341.

30.   Gallelli L, Palleria C, Antonio De Vuono, Mumoli L, Vasapollo P,et al. Safety and efficacy of generic drugs with respect to brand formulation, JPharmacol Pharmacothe. 2013 Dec; 4(Suppl1): S110–S114.

31.   Chandler S Gautam and Lekha S. Fixed dose drug combinations (FDCs): rational or irrational: a view point. Br J ClinPharmacol. 2008 May; 65(5): 795–796.