EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 7
Issue: 6
385-391
Year: 2020

A RETROSPECTIVE CROSS-SECTIONAL STUDY TO ANALYZE ADVERSE DRUG REACTIONS REPORTED AT TERTIARY CARE HOSPITAL

[1]Dr. Virendra Kushwaha, [2]*Dr. Pooja Agrawal, [3]Dr. Pushpendra Pushkar, [4]Dr. Tanvi Azmi, [5]Sumit Kumar

[1]Department of Pharmacology, Government Medical College, Azamgarh, Uttar Pradesh, India.
[2*,3,4,5]Department of Pharmacology, GSVM Medical College, Kanpur, Uttar Pradesh, India.

***Corresponding Author: Dr. Pooja Agrawal**
Department of Pharmacology, GSVM Medical College, Kanpur, Uttar Pradesh, India.

Article Received on 31/03/2020 **Article Revised on 20/04/2020** **Article Accepted on 10/05/2020**

ABSTRACT

Objectives: To analyze the pattern and nature of adverse drug reactions (ADRs) reported to ADR monitoring center (AMC) of tertiary care hospital in Kanpur. **Materials and Methods:** This study is a retrospective cross-sectional analysis of all ADRs reported to AMC, Department of Pharmacology, GSVM Medical College, Kanpur during 12 months duration (July 2018 to June 2019). These ADRs were analyzed for the pattern, system organ class involved, suspected drug/drugs, type of reactions, seriousness and causality assessment. **Results:** A total of 408 ADRs were reported from 299 patients. The majority of the patients (84.950%) were between 19-60 years with female preponderance (54.515%). As per the WHO-UMC causality assessment system, 84.615% ADRs were probable while 15.385% ADRs were possible and 3 patients (1.003%) suffered from serious ADRs. The gastrointestinal (36.520%) was the most affected system, followed by the nervous system (15.931%), skin & subcutaneous tissue (14.706%), psychiatric (13.971%) and general (10.539%) disorders. The majority of ADRs were of type-A (86.275%) while remaining of type-B (0.490%), type-C (0.490%) and type-F (0.245%). **Conclusions:** We can prevent these 'avoidable' reactions by safe prescribing and enthusiastic participation in pharmacovigilance. The concept of ADR reporting is still new in India and reporting of ADRs is scarce. There is a need for active participation of all the departments of this tertiary care hospital for ADRs reporting. This study warrants further research in the northern part of India for the development of possible intervention strategies so that the burden of ADRs can be reduced.

KEYWORDS: ADR, adverse drug reaction monitoring center, Pharmacovigilance Programme of India, NCC-PvPI, WHO-UMC.

INTRODUCTION

According to DJP Barker, an English physician and epidemiologist, ''There are three actions of a drug: The one you want, the one you don't want, and the one you don't know about."[1] All drugs carry some risk of harm and sometimes, adverse effects related costs, such as hospitalization, surgery and lost productivity, exceed the cost of the medications. Therefore, it's important to monitor their effects, both intended and unwanted, to get an evidence-based assessment of risk/benefit ratio. Today it is well recognized that a reliable pharmacovigilance system is essential for rational, safe and cost-effective use of medicines and therefore has clear advantages in relation to cost for public health.[2,3]

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem. World Health Organization (WHO) established its Programme for International Drug Monitoring (PIDM) in response to the thalidomide disaster detected in 1961. WHO promotes PV at the country level, together with the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC).[4]

The Pharmacovigilance Programme of India (PvPI) has a broad objective to safeguard the health of more than 1.27 billion people of India. Adverse Drug Reactions (ADRs) are reported from all across the country to National Coordinating Centre -PvPI (NCC-PvPI), Indian Pharmacopoeia Commission (IPC), Ghaziabad. It also works in collaboration with the WHO-UMC, Sweden to contribute to the global ADRs data base. NCC-PvPI monitor the ADRs among the Indian population and helps the regulatory authority of India (Central Drugs Standard Control Organization, CDSCO) in taking decisions for safe use of medicines.[5]

Collection of the adverse event information from the healthcare professionals/ patients, and performing follow up to get supplementary detailed information for scientific evaluation is achieved by the Adverse Drug Reactions Monitoring Centres (AMCs). AMCs are coordinated by NCC-PvPI and are the Medical Council of India approved medical colleges & hospitals, medical/central/autonomous institutes, public health programmes or corporate hospitals.[6]

Being a large country with unique diversity, it is important to recognize any difference in the pattern and nature of ADRs from this vast majority of the populace and comparing it to the existing database. This retrospective study is a preliminary effort in this direction and was undertaken to scientifically evaluate the pattern and nature of ADRs reported to our AMC.

MATERIALS AND METHODS

A retrospective cross-sectional study was carried out in the Department of Pharmacology, GSVM Medical College, Kanpur. The data was extracted from the filled suspected ADR reporting forms which were reported to our AMC during 12 months duration (July 2018 to June 2019). The ADR information was also entered in VigiFlow® software for reporting to NCC-PvPI. The type, number, seriousness, and pattern of ADR reported, at different levels as per system organ class (SOC), and the medication suspected to cause ADR has been studied. The seriousness of ADRs was classified as per WHO criteria. Rawlins and Thompson classification was used to classify the ADRs into various types. The WHO-UMC causality assessment system was used to classify ADRs into various causality categories. Confidentiality was maintained at all levels. Descriptive statistics was used to analyze the extracted data.

RESULTS

A total of 408 ADRs were reported from 299 patients. The profile of patients suffering from ADRs is shown in Table 1. The majority of patients (84.950%) were in the age group 19-60 yrs while only 15.050% patients were either children, adolescent or >60yrs of age. There was a preponderance of ADRs in females as compared to males (54.515% vs. 45.485%) As per the WHO-UMC causality assessment system, ADRs were either with probable or possible causality. There were no ADRs which categorized into certain, unlikely, unclassified or unclassifiable causality. Out of 299 patients, 3 patients (1.003%) suffered from serious ADRs.

Table 1: Profile of patients (N=299) suffering from ADRs.

Characteristics		N (%)
Age (in years)	0-18	19 (6.355)
	19-60	254 (84.950)
	>60	26 (8.696)
Gender	Male	136 (45.485)
	Female	163 (54.515)
Causality	Possible	46 (15.385)
	Probable	253 (84.615)
Seriousness of ADRs	Yes	3 (1.003)
	No	296 (98.997)

The frequency of ADRs based on the SOCs is shown in Figure 1. As per SOC, most commonly reported ADRs were related to gastrointestinal system disorders (36.520%), followed by nervous system disorders (15.931%). The ADRs related to skin & subcutaneous tissue disorders, psychiatric disorders, and general disorders were followed with 14.706%, 13.971%, and 10.539%, respectively. Other disorders contributed to 8.333% of ADRs altogether.

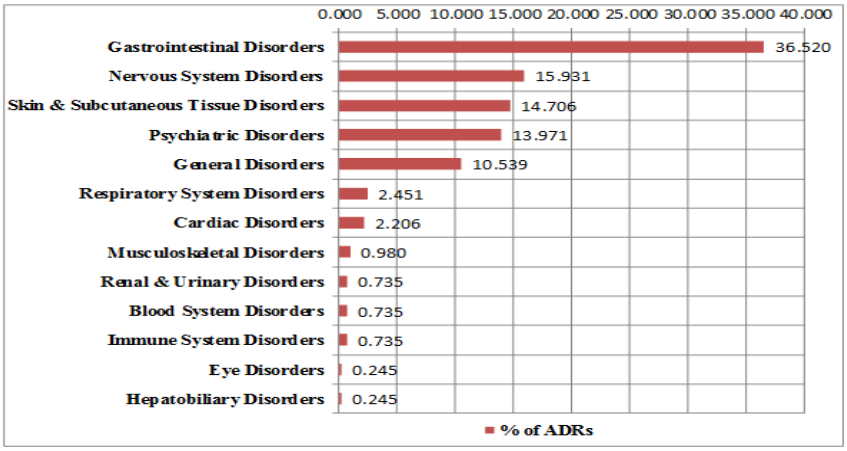

Figure 1: Frequency of adverse drug reactions based on the system organ classes.

ADRs, arranged according to SOCs, with their frequencies and suspected drug/drugs are shown in Table 2. Out of all 408 ADRs, vomiting (8.088%) and headache (8.088%) were the most commonly reported ADRs, followed by nausea (5.882%), itching (4.412%), anxiety (4.412%) and anorexia (4.412%).

Table 2: Adverse Drug Reactions (N=408) with their Frequency and Suspected Drug/Drugs.

Adverse drug reaction	Frequency-N (%)	Suspected drug/drugs
Skin and subcutaneous tissue disorders- N=60 (14.706%)		
Itching	18 (4.412%)	Ceftriaxone (4), Ciprofloxacin (3), Levofloxacin (2), Paracetamol, Drotaverine, Glimeperide, Metformin (3), Azithromycin, Ibuprofen, Piperacillin
Rash	14 (3.431%)	Ciprofloxacin, Piperacillin, Amlodipine, Sitagliptin, Glimeperide, Prednisolone, Sodium picosulfate, Diclofenac, Rabeprazole, Metronidazole, 5-FU, Levofloxacin, Nevirapine, Ceftriaxone
Urticaria	2 (0.490%)	Metformin, Azithromycin
Alopecia	9 (2.206%)	Cyclophosphamide, 5-FU (2), Gemcitabine, Paclitaxel (3), Ifosfamide, Cisplatin
Lip swelling	5 (1.225%)	Diclofenac, Ketoconazole (2), Prednisolone, Ibuprofen
Flushing	2 (0.490%)	Dipenhydramine, Metformin
Hirsutism	1 (0.245%)	Phenytoin
Pigmentation	7 (1.716%)	5-FU (2), Epirubicin, Ifosfamide (2), Paclitaxel, Cyclophosphamide
Pigmentation nail	2 (0.490%)	Cyclophosphamide, 5-FU
Gastrointestinal disorders- N=149 (36.520%)		
Dry mouth	5 (1.225%)	Cheston cold, Tiotropium, Sodium picosulfate, Pantoprazole, Cetrizine
Constipation	14 (3.431%)	Sitagliptin, Ifosfamide, 5-FU (4), Cisplatin, Atenolol (2), Dicyclomine, Ciprofloxacin (2), Metronidazole, Paclitaxel
Vomiting	33 (8.088%)	Ciprofloxacin, Epirubicin, Cisplatin (7), Paclitaxel (2), Carboplatin (3), Ifosfamide, Cyclophosphamide, Gefitinib, Atenolol (2), Amoxicillin (3), Diclofenac, Desogestrel, Metformin , Ibuprofen (2), Dicyclomine, Fluconazole, Prednisolone (2), Metronidazole, Adriamycin
Nausea	24 (5.882%)	Albendazole, Cisplatin (6), Prednisolone (2), Aspirin, Erythromycin, Amoxicillin (3), Ibuprofen (2), Adriamycin, 5-FU, Metformin, Atenolol, Paracetamol (2), Diclofenac, 5-FU + Cyclophosphamide
Gastritis	3 (0.735%)	Etoricoxib (2), Diclofenac
Dyspepsia	7 (1.716%)	Metoprolol(2) , Losartan, Clonazepam, Diclofenac, Metronidazole, Renerve
Flatulence	11 (2.696%)	Nucoxia, Aceclofenac, Metoprolol, Sitagliptin, Atenolol, Ibuprofen (2), Ciprofloxacin, Diclofenac, Ketorolac, Adriamycin
Bloating	2 (0.490%)	Norflox + Tinidazole, Diclofenac
Loose stool	15 (3.676%)	Amoxicillin (8), Fluconazole, Prednisolone, Glimepiride, Olmesartan, Saxagliptin, Cyclophosphamide, Adriamycin
Diarrhoea	13 (3.186%)	Paclitaxel (3), Cisplatin (3), Ibuprofen, Ketoconazole, Atenolol, Fluconazole, Amlodipine, Carboplatin, Adriamycin
Abdominal pain	17 (4.167%)	Losartan, 5-FU (2), Epirubicin, Amoxicillin, Albendazole, Ibuprofen (2), Clotrimazole, Azithromycin, Fluconazole, Hydrocortisone, Ciprofloxacin, Paracetamol, Metronidazole, Aceclofenac, Cyclophosphamide
Teeth discoloration	1 (0.245%)	Amoxicillin
Tongue discoloration	1 (0.245%)	Prednisolone
Swollen tongue	1 (0.245%)	Metronidazole
Black stool	1 (0.245%)	Norfloxacin + Tinidazole
Excessive salivation	1 (0.245%)	5-FU
Nervous system disorders- N=65 (15.931%)		
Dizziness	16 (3.922%)	Ciprofloxacin, Carboplatin, Amlodipine, Levofloxacin,

		Cyclophosphamide, Albendazole, Dicyclomine (2), Metformin, Dipenhydramine, Atenolol, Amoxicillin, Sodium picosulfate, Salmeterol, Norfloxacin + Tinidazole, Olmesartan
Headache	33 (8.088%)	Dericip, Aceclofenac, Doxorubicin, Docetaxel, Oxaliplatin (2), Cisplatin (3), Montelukast, Atenolol, Ifosfamide, Etoricoxib (2), Ibuprofen, Clarithromycin, 5-FU, Glibenclamide (3), Desogestrel (2), Hydrochlorthiazide, Enalapril, Itraconazole, Tranexamic acid, Pantoprazole, Salmeterol, Efavirenz, Sildenafil, Cyclophosphamide, Salbutamol, Ciprofloxacin
Tingling	6 (1.471%)	5-FU (2), Paclitaxel (2), Metformin (2)
Numbness	1 (0.245%)	Paclitaxel
Tinnitus	1 (0.245%)	Cisplatin
Vertigo	4 (0.980%)	Pregabalin, Albendazole, Hydrochlorthiazide, Glibenclamide
Paraesthesia	4 (0.980%)	Paclitaxel (2), 5-FU, Gemcitabine
Musculoskeletal disorders- N=4 (0.980%)		
Muscle spasm	1 (0.245%)	Rabeprazole
Leg pain	3 (0.735%)	Atorvastatin, Carboplatin, 5-FU
Blood system disorders- N=3 (0.735%)		
Decreased Hb	1 (0.245%)	Azathioprine
Thrombocytopenia	2 (0.490%)	Cefotaxime (2)
Cardiac disorders- N=9 (2.206%)		
Palpitation	9 (2.206%)	Cefotaxime, Glibenclamide (2), Glipized+Metformin, Amlodipine, Metformin, Dicyclomine, Etoricoxib, Carvedilol
Psychiatric disorders- N=57 (13.971%)		
Confusion	2 (0.490%)	Aspirin, Dicyclomine
Anxiety	18 (4.412%)	Gemcitabine (2), Dextromethorphan, Montelukast, Dicyclomine, Levofloxacin, Paclitaxel, Cisplatin, Glipizide, Amlodipine (2), Metformin, Sitagliptin (2), 5-FU, Metronidazole, Ibuprofen, Ceftriaxone
Anorexia	18 (4.412%)	5-FU (2), Oxaliplatin, Carboplatin (3), Cyclophosphamide (3), Cisplatin, Docetaxel , Gemcitabine, Paclitaxel, Ceftriaxone, Cetrizine, Oxaliplatin, Adriamycin (2)
Slurred speech	1 (0.245%)	Clonazepam
Irritability	2 (0.490%)	Glibenclamide, Glipized+Metformin
Nervousness	3 (0.735%)	Glibenclamide, Indapamide, Levofloxacin
Lethargy	4 (0.980%)	Aspirin, 5-FU, Diclofenac, Metformin
Drowsiness	4 (0.980%)	Lorazepam, Cetrizine (2), Clonazepam
Hypersomnia	2 (0.490%)	Cefpodoxime, Sitagliptin
Insomnia	3 (0.735%)	Atenolol, Salbutamol, Glipizide
Renal and urinary disorders- N=3 (0.735%)		
Nephrotoxicity	1 (0.245%)	Colistin
Painful urination	1 (0.245%)	Losartan
Hematuria	1 (0.245%)	Ibuprofen
Respiratory disorders- N=10 (2.451%)		
Dyspnoea	7 (1.716%)	Carvedilol, Azithromycin, Tranexamic acid, Diclofenac, Metformin, Ibuprofen, Ceftriaxone
Apnoea	1 (0.245%)	Cefotaxime
Cough	1 (0.245%)	Enalapril
Throat pain	1 (0.245%)	Salmeterol
General disorders- N=43 (10.539%)		
Fever	5 (1.225%)	Albendazole, Clotrimazole, Dipenhydramine, Amoxicillin, DNS
Therapeutic failure	1 (0.245%)	Advate (Factor VIII)
Mucositis	6 (1.471%)	Cisplatin (2), Paclitaxel, 5-FU (2), Carboplatin
Weakness	4 (0.980%)	Glibenclamide, Glipized+Metformin, Fluconazole, Clonazepam
Body pain	9 (2.206%)	Sitagliptin, Carboplatin, Paclitaxel (2), Atorvastatin (2),

		Adriamycin, 5-FU + Cyclophosphamide, Cisplatin
Swelling	9 (2.206%)	Diclofenac, Piperacillin, Glibenclamide, Minocycline, Azithromycin (2), Tranexamic acid, Pantoprazole, Olmesartan
Chest pain	1 (0.245%)	Omeprazole
Increased sweating	4 (0.980%)	5-FU, Clarithromycin, Amlodipine, Glibenclamide
Chill	4 (0.980%)	DNS (4)
Immune system disorders- N=3 (0.735%)		
Anaphylactic reaction	1 (0.245%)	Gastrografin
Hypersensitivity	2 (0.490%)	Levofloxacin, Glimepiride
Eye disorders- N=1 (0.245%)		
Blurred vision	1 (0.245%)	Prednisolone
Hepatobiliary disorders- N=1 (0.245%)		
Jaundice	1 (0.245%)	Isoniazid

ADRs are classified into various types and are shown in Figure 2. Out of all 408 ADRs, the majority of ADRs were of type-A (N=352, 86.275%) while remaining of type-B (N=53, 0.490%), type-C (N=2, 0.490%) and type-F (N=1, 0.245%).

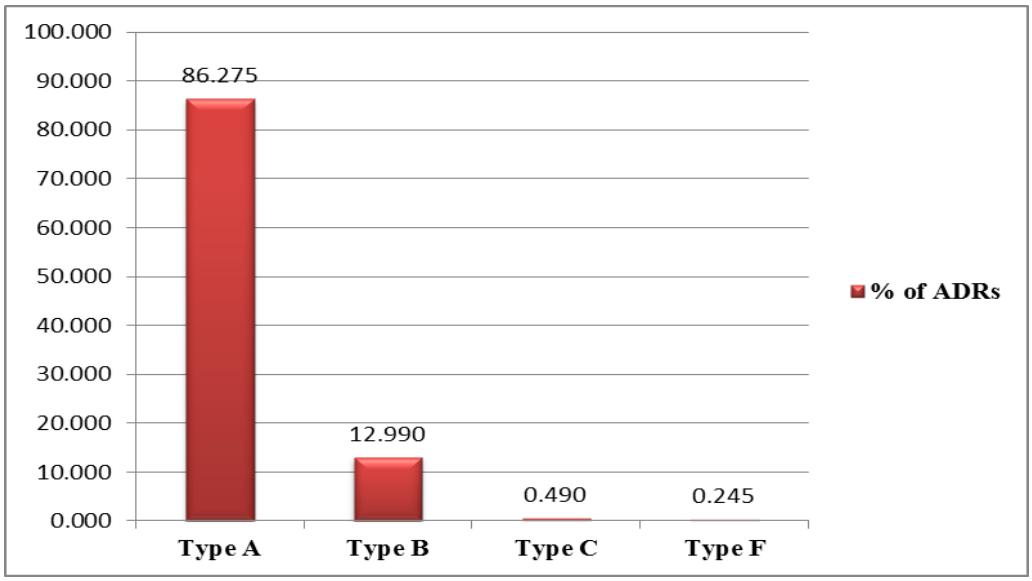

Figure 2: Types of Adverse Drug Reactions.

DISCUSSION

Out of 299 patients, the majority of patients (84.950%) were in the age group 19-60 yrs, this was similar in other studies too.[3,7-14] The reason for the majority of reported ADRs in this age group is maybe multi-drug therapy or diseases like cancer, diabetes, hypertension, asthma or other chronic diseases.

There was a preponderance of ADRs in females (54.515%). Several other studies have also found similar results.[3,7-9] While some studies showed a male preponderance.[10-16] Thereby concluding that the influence of gender is just an incidental finding and it does not affect the number of ADR reported. However, demographic factors such as age, gender and pregnancy status can help to predict as well as prevent the risk of an ADR occurrence.

According to the WHO-UMC causality assessment system, maximum reported ADRs were probable (84.615%) while some were possible (15.385%). This was comparable to several other studies.[7-10,16] While some studies found maximum reported ADRs as possible.[3,13-15] One study found probable (45.48%) and possible (47.22%) ADRs almost equally.[12] Out of 3 serious ADRs, the seriousness of one ADR was life threatening anaphylactic reaction due to CT contrast media, Gastrografin (Diatrizoate Meglumine and Diatrizoate Sodium Solution). The seriousness of the other 2 ADRs was hospitalization/prolonged. Outcomes of all serious ADRs were either recovered or recovering.

In our study, the GI was the most affected system followed by the nervous system and skin & subcutaneous tissue disorders. This finding of the GI system being the most affected SOC was consistent with one study.[13] However, in many other studies most commonly reported ADRs were related to skin & subcutaneous tissue disorders.[3,7,8,10,12,16]

The most commonly reported ADRs in this study were nausea & vomiting, headache, and itching of the GI,

nervous system and skin & subcutaneous tissue disorders, respectively. Most of these ADRs are preventable with adequate foresight and monitoring. Identifying the patients who are likely to be susceptible to the adverse effects and interventions that reduce the risk of an ADR occurrence can be an important way to reduce the risk of any harm to the patient.[17]

Out of all 408 ADRs, the most common type of ADR was type-A and a similar result was seen in another study.[13] One study classified the majority of ADRs as type-B.[16] In our study, we came to know of type-C ADRs (N=2) which were hirsutism and jaundice due to phenytoin and isoniazid, respectively. One ADR was of type-F which was a therapeutic failure in case of Advate (Factor-VIII).

We can prevent these 'avoidable' reactions by safe prescribing and enthusiastic participation in PV. Another approach to avoid exposing individuals to doses of drugs that could be harmful to them is by the means of two new disciplines of broad interest: pharmacogenetics and pharmacogenomics. Individualized therapy is becoming more of a possibility and there is increasing evidence that pharmacogenetics will be extremely important in the health service and one day it may be considered unethical not to carry out such tests routinely. It might also substantially reduce the need for hospitalization, and its associated costs, because of adverse drug reactions.[17,18]

CONCLUSIONS

The concept of ADR reporting is still new in India and reporting of ADRs is scarce. There is a need for active participation of all the departments of this tertiary care hospital for ADRs reporting. This study warrants further research in the northern part of India for the development of possible intervention strategies so that the burden of ADRs can be reduced. The limitation of our study is that it is a retrospective analytical study; still, this study would definitely give an insight into the pattern of ADRs in a tertiary health care center and may help to increase awareness for further pharmacovigilance studies.

ACKNOWLEDGEMENT

The authors are indebted to the IPC, NCC-PvPI and all Departments of GSVM Medical College, Kanpur.

REFERENCES

1. Gupta SK. Post marketing surveillance text book of pharmacovigilance. 1st ed., New Delhi; Jaypee Brothers Medical Publishers (P) Ltd, 2011; 75.
2. Gupta M, Kharb P, Kalaiselvan V, Shridhar M, Singh GN, Kshirsagar N, *et al*. Safety of medicines. Pharmacovigilance Programme of India. The journey travelled and the way forward. WHO Drug Inf, 2018; 32(1): 10-17.
3. Lihite RJ, Lahkar M, Das S, Hazarika D, Kotni M, Maqbool M, *et al*. A study on adverse drug reactions in a tertiary care hospital of Northeast India. Alexandria J Med, 2017; 53: 151-6.
4. Who.int [Internet]: Essential medicines and health products. Pharmacovigilance;c2020 [cited 2020 Mar 07]. Available from: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/
5. Who.int [Internet]: Essential medicines and health products. WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services. Pharmacovigilance Programme of India (PvPI) - Indian Pharmacopoeia Commission, Ghaziabad;c2020 [cited 2020 Mar 07]. Available from: https://www.who.int/medicines/regulation/medicines-safety/about/collab-centres-india/en/
6. Kalaiselvan V, Kumar R, Singh GN. Indian Pharmacopoeia Commission's Partners for Promoting Public Health. Adv Pharmacoepidemiol Drug Saf, 2015; 4: 181.
7. Singh P, Agrawal M, Hishikar R, Joshi U, Maheshwari B, Halwai A. Adverse drug reactions at adverse drug reaction monitoring center in Raipur: Analysis of spontaneous reports during 1 year. Indian J Pharmacol, 2017; 49(6): 432–7.
8. Sutradhar SD, Ray D. A cross-sectional study of patterns of adverse drug reactions reported in the department of pharmacology of a tertiary care teaching hospital in North East India. Int J Compr Adv Pharmacol, 2017; 2(1): 33-35.
9. Roy D, Purkayastha A, Tigga R. Analysis of adverse drug reaction in a tertiary care hospital: a retrospective study. Asian J Pharm Clin Res, 2017; 10(1): 347-9.
10. Saxena K, Tailor C, Mehta C, Gajera P, Srivastava SK. A retrospective analysis of adverse drug reaction reported in a tertiary care hospital. Int J Basic Clin Pharmacol, 2017; 6(5): 1146-50.
11. Pathak AK, Kumar M, Dokania S, Mohan L, Dikshit H. A retrospective analysis of reporting of adverse drug reactions in a tertiary care teaching hospital: one year survey. J Clin Diagn Res, 2016; 10(8): FC01-FC04.
12. Gupta A, Kaur A, Shukla P, Chhabra H. Adverse Drug Reactions pattern in a tertiary level teaching hospital: A Retrospective Study. Indian J Pharm Pract, 2017; 10(1): 27-31.
13. Bhattacharjee P, Das L, Ghosh R, Lalromawii, Das UK. Pattern of adverse drug reactions reported at a tertiary health care teaching hospital of Tripura: a retrospective study. Int J Basic Clin Pharmacol, 2016; 5(4): 1293-9.
14. Behera SK, Rath B, Biswal SB, Mohapatra S. Pattern of adverse drug reactions in a tertiary care hospital in western odisha. Int J Pharm Sci Res, 2018; 9(6): 2471-7.
15. Sriram S, Ghasemi A, Ramasamy R, Devi M, Balasubramanian R, Ravi TK, *et al*. Prevalence of adverse drug reactions at a private tertiary care

hospital in south India. J Res Med Sci, 2011; 16(1): 16–25.
16. Sen M, Singh A, Misra M. Retrospective analysis of adverse drug reactions reported at ADR monitoring centre under PvPI in a tertiary care hospital. Int J Basic Clin Pharmacol, 2018; 7(2): 303-8.
17. Coleman JJ, Pontefract SK. Adverse drug reactions. Clin Med (Lond), 2016; 16(5): 481–5.
18. Wolf CR, Smith G, Smith RL. Science, medicine, and the future. Pharmacogenetics. Brit Med J, 2000; 320: 987–90.