PHARMACOVIGILANCE: A STATISTICAL STUDY OF ADVERSE DRUG REACTIONS OF ANTIHYPERTENSIVE AND ANTIDIABETIC DRUGS IN GADHINGLAJ RURAL REGION

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ABSTRACT

Adverse drug reactions to drugs are the curse of drug development and can lead to life-threatening illnesses. which then causes the discontinuation of therapy. ADR of drugs can affect not only patients' health but also other health professionals and pharmaceutical companies. The main aim of this study is to find the ADRs in hypertension and diabetes disease. Hypertension is seen to be the most common condition but can lead to serious conditions like myocardial infraction, stroke, renal failure, and death if it is not treated at the right time. Diabetes is caused due to the production of an insufficient amount of insulin or due to a poor body response to the insulin that is made by the pancreas. This study is important because ADRs of hypertension and diabetes drugs help to reduce or overcome the damage caused by taking medication for the treatment of specific disease conditions. The survey was conducted in Gadhinglaj rural areas (villages). First of all, we selected the hospitals where hypertensive and diabetic patients are treated. In this survey, we interacted with doctors to collect information about adverse drug reactions found in patients who are taking antihypertensive and antidiabetic medications. After completing the survey, we know which drugs have the most adverse drug reactions. We also find out which ADRs are frequently experienced. All the data we gathered here is used by a non-parametric test, i.e., by the Kruskal-Wallis Test. To observe the null hypothesis, we determine the rejected null hypothesis. We came to the conclusion that hypertensive and diabetic patients require extensive care and therapy, as well

as good counselling. In the case of antihypertension, amoxetine, a calcium channel blocker, is the primary medicine of choice, indicating the majority of ADRs when compared to other pharmacological classes. In the case of anti-diabetic drugs, we learn that metformine is the most commonly used, but it has more ADRs such as edema.

KEYWORDS: Pharmacovigilance, Antihypertensive, Antidiabetic, Adverse drug reaction.

INTRODUCTION

The evolution of society's response to illness and disease throughout history is illustrated through the history of medicine. We have covered how medical research has improved and transformed our lives in the paragraphs that follow. Early medicinal traditions may be found in India, China, Egypt, and Babylon. The Hippocratic Oath, which was composed in ancient Greece in the fifth century BCE, served as the direct model for the oaths of office taken today by new physicians. Another Indian medicinal system is called Ayurveda, which means "full wisdom for long life." As an alternative kind of medicine in India, unani medicine is quite similar to Ayurveda. During the Middle Ages, unani medicine established strongholds and received royal support.[1,4]

Lifestyle: Evolved?[5]

The term "lifestyle illnesses" refers to conditions whose development is mostly dependent on a person's daily routine and results from an unsuitable interaction between that person and their surroundings. Bad eating habits, inactivity, poor body mechanics, and a thrown off biological clock are the major causes of lifestyle illnesses. More years are being spent by people coping with disease and disability. In 2015, the world's top risk factors for early mortality and bad health included high blood pressure, smoking, high blood sugar, a high

body mass index, and under-nutrition in children. It is crucial that the medical community participate in preventative initiatives. A multitude of health problems related to lifestyle can develop into chronic non- communicable illnesses with potentially fatal outcomes.

Cardiovascular system

Avoidable risk factors	Risk factors	Other risk factors
1.High Blood Pressure	Age	Unwanted presence of homocysteine in blood
2.Use of tabaco	Heredity or family history	Lipoprotein
3.Sanitary lifestyles	Gender	Thrombophilia
4.Use of alcohol	Nationality	
5.Unhealthy diet		

Diabetes

| Avoidable risk factors	Risk factors	Other risk factors
Inadequate diet	Age	Low immunity
Over weight	Hereditary	Non affordable treatment
Sanitary lifestyle	Nationality	
Hyperlipidemia		
Hypertension		
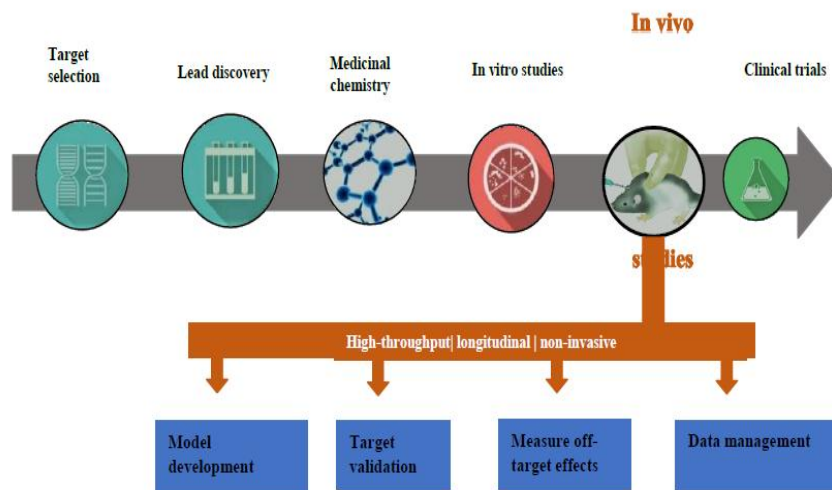
Drug development[3]

(WHO) defines pharmacovigilance as the "Pharmacological science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.".[9,10]

ADR Definition[11]

According to the World Health Organization (WHO) definition, an adverse drug reaction (ADR) which has been in use for about 30 years, is 'A response to a drug that is noxious and unintended and occurs at doses normally used in human for the prophylaxis, diagnosis, and treatment of disease, or for modification of physiological function.'

Classification of adverse drug reactions[12]
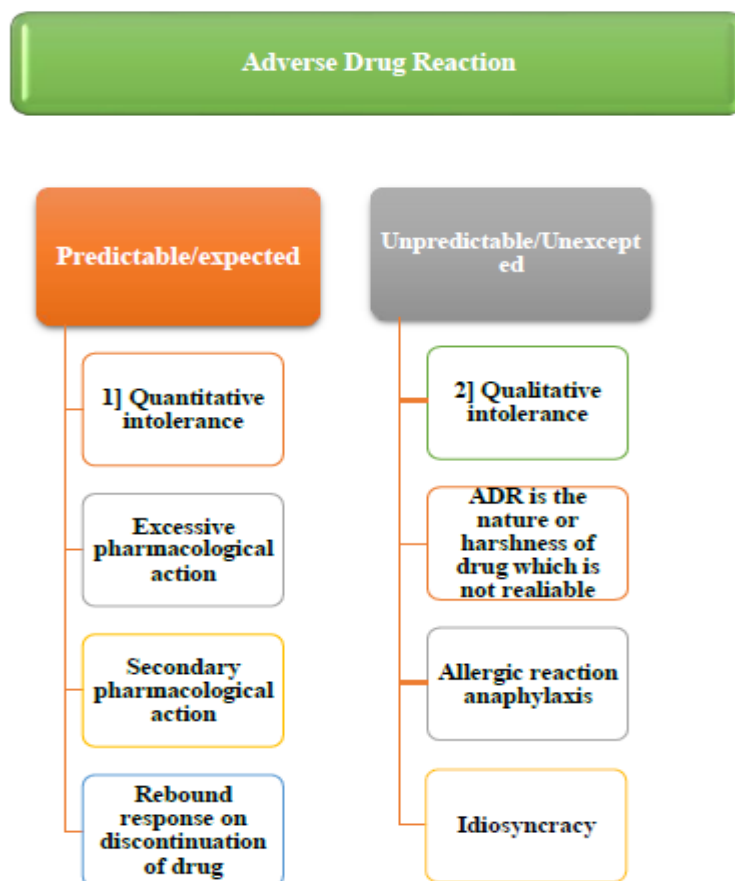
In the 21st century, people's lives suffered from many lifestyle diseases. In the present study, we have focused on hypertension and diabetes because of their reputation to suffer large populations on a global scale.

Hypertension[6,8]

Traditional definitions of hypertension include a persistent rise in blood pressure (BP) above 140/90 mm Hg. This criterion identifies a subset of people whose risk of cardiovascular illness attributable to hypertension is high enough to require medical treatment. One billion people may have hypertension according to estimates of its prevalence worldwide, and the condition may be responsible for 7.1 million annual fatalities. According to the World Health

Organization (WHO), there is minimal difference in the prevalence of cardiovascular disease (CVD) and ischemic heart disease (IHD) among men and women when sub-optimal blood pressure (> 115 mm Hg SBP) is present. One of the illnesses that are most frequently diagnosed in basic healthcare institutions is hypertension. Adult patients receiving primary care in rural locations had a somewhat high incidence of hypertension.

Diabetes[7]

Diabetes mellitus is a chronic condition caused by an inherent or acquired insulin shortage or the development of insulin resistance. This insufficiency causes elevated blood glucose levels,which harms many of the body's systems, including the blood vessels and neurons. According to recently published data, around 150 million individuals worldwide have diabetes mellitus, and this figure is expected to treble by 2025. The majority of this rise will occur in developing nations as a result of population expansion, ageing, bad diets, obesity, and sedentary lifestyles. While most persons with diabetes in wealthy nations will be 65 or older by 2025, the majority in underdeveloped countries will be 45-64 years old and afflicted in their most vulnerable years 2.

Kruskal wallis method

The Kruskal-Wallis test is the non-parametric alternative to the One-Way ANOVA test.   The test is non-metric if it doesn't presume your data comes from a specific distribution. The null hypothesis is calculated using this procedure. Which is employed to determine whether a value is critical, that is, larger or lower than the H critical value.

Although health science has evolved over the years there are some obstacles are yet to overcome like adverse drug effects and lifestyle diseases; so, in this research we are focusing-on study of ADRs for the benefit of medical science.

Objective
- The goal of this study is to look into the numerous adverse drug reactions associated with antihypertensive and anti-diabetic medications.
- Drugs with fewer ADRs will be identified.
- To encourage the use of drugs in a sensible and safe manner
- To figure out what types of ADRs there are and how common they are.
- Identification of risk variables that may predispose, induce, or influence the onset, severity, and occurrence of ADR

MATERIALS AND METHOD

The survey was conducted at Gadhinglaj rural areas (Villages) first of all we have selected the hospitals where the hypertensive and diabetic patients are commonly available. In present survey, we have interacted with expert doctors to collect the information about adverse drug reactions found in patients who are under the antihypertensive and antidiabetic medication. After successful completion of the survey, we came to know exact scenario about drugs adverse drug reactions, we also found out which ADRs are frequently experienced.

Sr. no.	Activity	Rationale
1.	Selection of disease category	Now a days most population is suffering from hypertension and diabetes so we have selected the hypertension and diabetes diseases for the study of ADRs
2.	Selection of hospital	We have selected the hospitals where hypertensive and diabetic patients are treated.
3.	Questionnaire	Prepared question bank to collect the data for the doctors. The question is related with patients, ADRs found in Antihypertensive and anti-diabetic medications, which ADRs are frequently experienced.
4.	Preparation of ADRs report form	Prepare the adverse drug reaction form to collect information about the ADRs found in patient.
5.	Data collection	Data is collected with the help of survey form and questionnaire
6.	Data study	Study the data of adverse drug reaction, record the information in chart and plot the graph.
7.	Compilation of data	Study both the category of drugs and their ADRs and make the conclusion.
8.	Statistical Study	Data is calculated by using non parametric test i.e., Kruskal Wallis Test

Data collection

Table no. 1: Total no. of patients and their ADRs due to Anti-hypertensive Drugs.

`Sr. no.	Anti-hypertensive Drug	Total no. of patients	Total no. of ADRs
1	Amlodipine	105	11
2	Nefidipine	30	03
3	Atenolol	45	02
4	Metoprolol	50	03
5	Propranolol	60	04
6	Ramipril	30	01
7	Telmisartan	70	03
8	Losartan	55	04
9	Furosemide	35	02
10	Hydrochlorothiazide	20	01

Table no. 2: Total no. of patients and their ADRs of Anti-diabetic drugs.

Sr. no.	Anti-diabetic drugs	Total no. of patients	Total no. of ADRs
1	Glimepride	175	05
2	Metformin	150	09
3	Voglibose	100	05
4	Pioglitazone	40	02
5	Vildagliptin	60	02

According to class of drugs[13]

Table no. 3: Adverse Drug reaction and therapeutic class of Anti-hypertensive medication.

Drugs	dverse events experienced	Total no. of patients with ADRs	Total no. of patients with ADRs
A] Calcium channel blockers Amlodipine Nefidipine	1.Pedal edema-07 2.Swelling of face-01 3.Minor headache-01 4.Giddiness-02 1.Bardycardia-02 2.Dizziness-01	11 03	105 30
B] Beta- blockers 1.Atenolol Metoprolol Propranolol	1.Hypertension-01 2.Bradycardia-01 1.Bradycardia-02 2.Irritation over whole body-01 1.Braycardia-02 2.Lack of sleep-02	02 03 04	65 50 60
C] ACE inhibitor 1.Ramipril 2.Enalapril	1.Dry cough-021.Dry cough-01	02 01	30 25
D] Angiotensine Receptor Blockers 1.Telmisartan 2.Losartan	1.Dry cough-02 2.Dizziness-01 1.Insomina-01 2.Headache-02 3.naushea and Vomitting-01	03 04	70 55
E] Diuretics 1.Furocemide 2.Hydrochlorothiazide	Dehydration-01 2. Electrolyte in Balance-01 1.Blurred vision-01	02 01	35 20

Table no. 4: Adverse Drug Reaction and Therapeutic class of Anti- Diabetic medication.

Drugs	Adverse events experienced	Total no. of patients with ADRs	Total no. of patients with ADRs
A] Sulfonylureas 1.Glimepride	1.Giddiness-02 2.Hypoglycemia-02 3.Weight gain-01	05	150

B] Bigunide **1.Metformin**	1.vomitting-02 2.Headache-04 3.Dyspepsia-01 4.Diarrhoea-01	09	175
C] α – Glucosidase inhibitors **1.voglibase**	1.Diarrhoea-01 2.Vomitting-01 3.Edema-02 4.Dyspesia-01	05	100
D] Thiazolidinedione activator **1.Pioglitazone**	1.Edema-01 2.Pedal edema-01	02	40
C] Dipeptidyl peptidase-4 (DPP-4) inhibitor **1.Vildagliptin**	1.Hypoglycemia-01 2.Edema-01	02	60

Kruskal wallis method

The non-parametric substitute for the One-Way ANOVA is the Kruskal-Wallis test. The term "non-parametric" refers to a test that makes no assumptions about the distribution of your data.

There is no connection between the two phenomena under study, according to the null hypothesis. The symbol for it is H0.

There is a relationship between two chosen study variables, according to a different theory. H1 or Ha are used to indicate it.

Hypothesis there is relationship between Adverse drug event of antihypertensive and antidiabetic drugs.

Null hypothesis: H0 = There is a link between antihypertensive and antidiabetic adverse drug events.

Alternative hypothesis H1= There is no link between antihypertensive and antidiabetic adverse drug events.

The Kruskal-Wallis test statistic is roughly distributed as chi-square with K-1 degree of freedom df = K-1.

DF = 2-1 = 1

Formula

$$H = \left[\frac{12}{n(n+1)} \sum_{j=1}^{c} \frac{T_j^2}{n_j} \right] - 3(n+1)$$

`Sr. no.	Anti-hypertensive Drug	Total no. of patients	Total no. of ADRs	Percentage ADRs	Ascending order	Ranks
1	Amlodipine	105	11	10	3	1
2	Nifedipine	30	3	10	4	2.5
3	Atenolol	45	2	4	4	2.5
4	Metoprolol	50	3	6	5	4
5	Propranolol	60	4	7	6	5.5
6	Ramipril	30	1	3	6	5.5
7	Telmisartan	70	3	4	7	7.5
8	Losartan	55	4	7	7	7.5
9	Furosemide	35	2	6	10	9.5
10	Hydrochlorothiazide	20	1	5	10	9.5
						55
						R1=55

Sr. no.	Anti-diabetic drugs	Total no. of patients	Total no. ofADRs	Percentage ADRs	Ascending order	Ranks
1	Glimepride	175	5	3	3	1.5
2	Metformin	150	9	6	3	1.5
3	Voglibose	100	5	5	5	3.5
4	Pioglitazone	40	2	5	5	3.5
5	Vildagliptin	60	2	3	6	5
						15
						R2=15

$H=12/10(10+1) [55^2/10+15^2/5]-3(11)$

$H=12/110 [3025/10+225/5]-33$

$H=12/110 [302.5+45]-33$

$H=0.1090 (347.5)-33$

$H=37.90-33$

$H=4.9$

Determine the critical value of H using the table of critical and critical value is 3.841 the criteria for rejection or acceptance of null hypothesis are as follows:
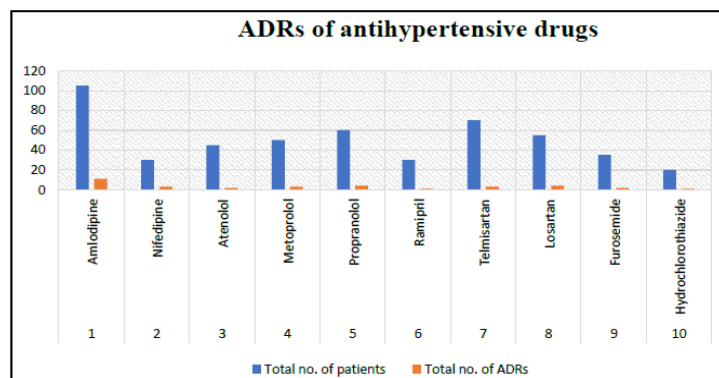
Reject H0: H ≥ critical value

Accept H0: H ≤ critical value

Here, we accept the null hypothesis because H value is greater than critical value and the final conclusion is, "There is no significant evidence to state that there is no relationship between adverse drug events of antihypertensive and antidiabetic drugs."

RESULT AND DISCUSSION

In graph: drugs and their ADRS

Graph no. 1: Total no. of patients and their ADRs due to Anti-hypertension Drugs.
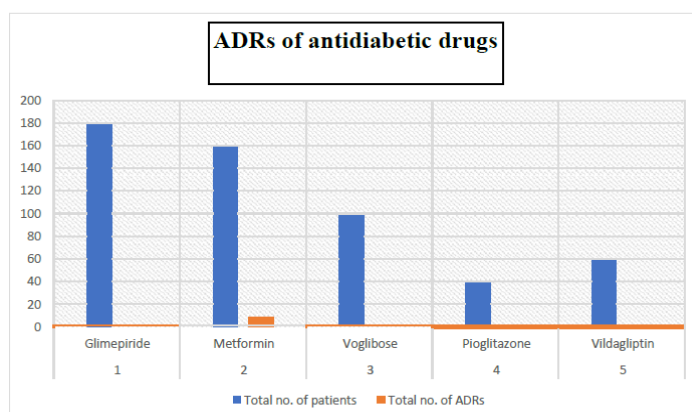
Graph no. 2: Total number of patients and their ADRs due to anti-diabetic drugs.

Photos of survey

Out of a total of 500 antihypertensive patients that attended the hospital during the study period, we found that 105 patients who were taking Amlodipine had 11 patients present with ADRs (11.55%). Likewise, for Nifedipine, 3 out of 30 patients had ADRs (0.9%), for atenolol 2 out of 45 patients had ADRs (0.9%), for Metoprolol 3 out of 50 patients observed ADRs (1.5%), for Propanol 4 out of 60 patients observed ADRs (2.4), for Ramipril 1 out of 30 patients

observed ADRs (0.3%). For Telmisartan, 3 out of 70 patients observed ADRs (2.1%), and for Losartan, 4 out of 55 patients observed ADRs (2.2%). For Furosemide, 2 out of 35 patients observed ADRs (0.7%), and for Hydrochlorothiazide, 1 out of 20 patients observed ADRs (0.2%). According to our survey, we came to know that different classes of anti-hypertensive Drugs show different ADRs, most commonly Bradycardia.

We also surveyed anti-diabetics in the same way we surveyed anti-hypertensive drugs. A total of 525 patients visited the hospital at the time of the survey. So, we observed that 175 patients who are taking Glimepiride medication, out of that 5, showed ADRs (8.75%). Likewise, for Metformin 9 out of 150 patients observed ADRs (13.5%). for Voglibose 5 out of 100 patients observed ADRs (0.5%). For Pioglitazone, 2 out of 40 patients experienced ADRs (0.8%); for Vildagliptin, 2 out of 60 patients experienced ADRs (1.2%). commonly, ADRs for anti-diabeticdrugs.

By using the kruskal wallis test, we observed that there is no relationship between adverse drug reaction, antihypertensive and antidibetic. It determined that our hypothesis is rejected H0: H≥ critical value.

CONCLUSION[7]

We came to the conclusion that hypertensive and diabetic patients require extensive care and therapy, as well as good counselling. In the case of antihypertension, amlodepine, a calcium channel blocker, is the primary medicine of choice, indicating the majority of ADRs when compared to other pharmacological classes. In the case of anti-diabetic drugs, we learn that metformine is the most commonly used, so it has more ADRs such as edema. Our hypothesis is ruled out by these findings, which were obtained using the Kruskal-Walli's test, which revealed that there is no correlation between adverse drug reaction and either an antihypertensive or an antidiabetic.

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