A STUDY ON CLINICAL PATTERN OF ADVERSE DRUG REACTIONS TO THE DRUGS USED FOR HYPERTENSION AND ASSESSMENT OF MEDICATION KNOWLEDGE IN SUCH PATIENTS.

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Conflicts of Interest: Nil

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ABSTRACT
The aim of the present study was to monitor adverse drug reactions associated with antihypertensive drugs. due to its high prevalence, Hypertension is a major health problem throughout the world and very less studies has been aimed at assessing the patient's knowledge and awareness about hypertension and adherence to antihypertensive medication among hypertensive patients. Hypertension is a major health problem and risk factor for stroke, coronary heart diseases and antihypertensive treatment is used to reduce renal and cardiovascular diseases by lowering blood pressure. Occurrence of adverse reactions among hypertensive patients could prevent or delay patients from achieving desired therapeutic goals. The study was conducted by one to one patient interview using a questionnaire-based medication knowledge form, Adverse Drug Reaction Monitoring Form drafted according to the World Health Organisation Monitoring Guidelines. A total of 86 adverse drug reactions were observed in 127 hypertensive patients during the 6 month study. In this study the ADRs were found probable (51.16%), possible (32.56%), unclassifiable (11.63%) and unlikely (4.65%) by using WHO causality assessment scale. By using Naranjo algorithm scale it was found that ADRs were possible in 77.91% and probable in 22.09% of cases. This study also found that amlodipine was responsible for most of the ADRs and among the entire ADRs reported headache was the commonest followed by dizziness, pedal oedema, fatigue, abdominal pain, dry cough, breathlessness, bradycardia, muscle cramps, sedation, diarrhoea and irritation all over the body. After counseling by clinical pharmacist medication knowledge was found to be increased.

Keywords: Adverse drug reaction, medication knowledge, hypertension

INTRODUCTION
Hypertension is defined as systolic blood pressure of ≥ 140 mm Hg and diastolic blood pressure of ≥ 90 mm Hg, though the risk appears to increase even with blood pressure above 120/80 mm Hg. Hypertension or high blood pressure is a major public health problem due to increased morbidity, mortality. It is an iceberg condition and the prevalence of hypertension has been considered as an increasing “silent killer” problem. Reasons for this growing trend is due to the unhealthy lifestyle practices, lack of awareness, distorted public health system, physicians not following the standard guidelines in treating hypertension and non-compliance to hypertension therapy. Keeping the blood pressure at an optimum level helps to prevent cardiovascular complications like stroke, myocardial infarction (MI), renal failure and mortality; this has been confirmed in epidemiological and interventional studies.1,2 In developed countries, diastolic pressure is more than 90 mm Hg in about 25% adults; this prevalence is almost same in developing countries, where it is seen in 10% to 20% adults. Hypertension accounts for 20-50% of all deaths. Hypertension is present in all populations and it steadily increases during the first two decades of life. With advancing age, the prevalence of hypertension also increases. Systolic blood pressure is higher for adult males than females, but in older individuals, the age related rate rise is steeper for females. A middle aged or elderly individual has 90% chance of developing hypertension in his or her lifetime. Both genetic and environmental factors play a major role to produce regional and racial changes in blood pressure and prevalence of hypertension. In India the prevalence of hypertension was 35 in males and 36 in females per 1000 in rural population and 60 in males and 70 in females per 1000 in the urban population3,4,5.
Classification

A. Essential or primary hypertension:
A patient is said to have essential hypertension when no particular cause of hypertension can be found.

B. Secondary hypertension:
A patient is said to have secondary hypertension when a particular cause of hypertension can be found.

Risk factors:
Risk factors of hypertension include age, gender, hereditary factors, race, overweight, increased salt and saturated fat intake, decreased intake of dietary fiber, alcohol consumption, sedentary lifestyle, high socio-economic status and environmental stress.

Clinical features:
Most hypertensive patients will not have any specific symptoms. Headache is the commonest symptom seen in patients with severe hypertension; other symptoms include palpitations, dizziness, impotence and easy fatigability.

Treatment:

Lifestyle interventions:
Lifestyle changes help in prevention and treatment of hypertension. Hence, they are advised for individuals with prehypertension and for hypertensive individuals as an addition to drugs.

Lifestyle changes to manage hypertension:

- Reduction of Weight with body mass index (BMI) < 25 kg/m²
- Salt restricted diet < 6 g of NaCl/day
- Follow DASH (Dietary Approaches to Stop Hypertension) diet plan.
  Diet should include vegetables, fruits and products with reduced amount of fat.
- Reduction of alcohol consumption
- Regular physical activity

Pharmacotherapy:

Drug therapy is recommended for individuals with blood pressure ≥140/90 mmHg. Choice of antihypertensive agents and their combinations should depend on age, severity of hypertension, cardiovascular risk factors, comorbid conditions, cost, side effects and frequency of dosing. The antihypertensive drugs include α-blockers, β-blockers, CCBs (calcium channel blockers), diuretics, ACE inhibitors (Angiotensin converting enzyme inhibitors), ARBs (Angiotensin receptor blockers) etc.; these are either used as monotherapy or as combination therapy.

Antihypertensive drugs:
Lowering of blood pressure by antihypertensive drugs helps to prevent blood vessel damage and to reduce morbidity and mortality. Antihypertensive drugs acts by interfering normal arterial pressure regulation. Knowledge of mechanisms of antihypertensive drugs helps to predict their efficacy and toxicity resulting in rational use of these drugs.

Classification of antihypertensive drugs:

Diuretics:
- Thiazides and related agents: Hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide, methylclothizadie and metolazone.
- Loop diuretics: Furosemide, torsemide, bumetanide, and ethacrynic acid.
- K⁺ sparing diuretics: Spironolactone, amiloride and triamterene.

Sympatholytic drugs:
- β-blockers: Metoprolol, betaxolol, nadolol, bisoprolol, esmolol, timolol, nebivolol, penbutolol, atenolol, pindolol and propranolol.
- α-blockers: Prazosin, terazosin, doxazosin, phenoxybenzamine and phenolamine.
- Mixed α and β receptor blockers: Labetalol and carvedilol.
- Centrally acting adrenergic agents: Methyldopa, clonidine, guanabenz and guanfacine.
- Adrenergic neuron blocking agents: Guanadrel and reserpine.

Current status of Pharmacovigilance in India:
In the world, India stands fourth among producers of pharmaceuticals. It is rising as one of the clinical trial hub in the world. Our country introduces many new drugs and hence there is a need for an energetic pharmacovigilance system in the country to guard the people from the possible harm that may be caused by some of these new drugs. Evidently conscious about the extent of the task, the Central
Drugs Standard Control Organization (CDSCO) has started a well planned and highly participative National Pharmacovigilance Program. It is mainly based on the recommendations made in the WHO document titled “Safety Monitoring of Medicinal Products Guidelines for Setting up and Running a Pharmacovigilance Centre”. Pharmacovigilance has not come up well in India and the subject is in its early stage. The rate of pharmacovigilance in India is less than 1% when compared with the world rate of 5%. This is because of lack of knowledge about the subject and also deficiency in training. Now a days in India, pharmacovigilance situation has been progressing step by step than what it was in the past.

Antihypertensive drugs are more prone for development of adverse drug reactions (ADRs); this decreases the available treatment options and also reduces the compliance of the patients; this in turn hinders blood pressure control. Hypertension is a disorder that requires long term therapy; this predisposes to ADRs. As many studies do not include pregnant ladies, the elderly and patients with many diseases, the study population may not be the real world where drug has to be used eventually; hence, safety monitoring has to be done to get information regarding ADRs to have a better treatment module and to prevent morbidity and mortality due to ADRs. Currently, ADR monitoring in India is in its infancy stage.

Many new antihypertensive drugs are now available, which alter quality of life of the patient in a better way. Thus a regular scrutinization is needed by systematic audit that gives feedback to doctors, which will help to prescribe drugs rationally and to avoid ADRs.

Adverse Drug Reactions: Classification, Mechanism And Interactions

The World Health Organization (WHO) defines a drug/medicine such as “any substance in a pharmaceutical product that is used to modify or explore physiological systems or pathological states for the benefit of the recipient.” As per WHO following are the definitions for adverse event/adverse experience (AE) and adverse drug reaction (ADR).

Adverse Event (Or Adverse Experience)

"Any unwanted medical occurrence that may induce during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment."

Adverse Drug Reaction (ADR)

A response to a drug which may be noxious and unintended, and which occurs at doses generally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) guideline of Clinical Safety Data Management (E2A guidelines) further describes the definition of adverse drug reactions (ADR) during the pre-approval (before marketing of the pharmaceutical product) phase.

Classification of ADR

Pharmacological Classification

Type A (Augmented): commonest type (up to 80%) of ADR which is predictable by the pharmacological mechanisms, e.g., hypoglycaemia caused by insulins or oral hypoglycaemics, or hypotension by beta-blockers, NSAID induced gastric ulcers. These type of adverse drug reactions are dose dependent henceforth severity increases with dose. Such ADRs are preventable in most part by slow introduction of low dosages. Sometimes regarded as Type I ADRs.

Type B (Bizzare): ADR is not expected from the known pharmacological mechanisms e.g. aplastic anaemia hepatitis caused by halothane caused by chloramphenicol, neuroleptic malignant syndrome caused by some anaesthetics and antipsychotics. Such ADRs are unrelated to dose. (Type 2 ADRs.)

Type C (Continuous drug use): ADR occurs due to continuous drug use. Such type of ADR may be irreversible, unexpected, unpredictable, e.g dementia by anticholinergic medications.

Type D (Delayed): ADR is characterized by the delayed occurrence even after the cessation of treatment, e.g., ophthalmopathy after chloroquine, or pulmonary/peritoneal fibrosis by methyserzide, corneal opacities after thioridazine

Type E (End of dose): ADR is usually characterized by withdrawal reactions. Such ADRs occur typically with the depressant drugs, e.g., seizures on alcohol or benzodiazepines.

Medication knowledge:

Medication knowledge is the information that patients possess about the medications which he or she is taking. It includes information about the name of the drug, indication for uses, dose, dosage regimen, adverse effects, precautions to be taken during treatment, contraindications and storage.
conditions. Patient educational status and awareness affects medication knowledge. The specialized skills of clinical pharmacists have proved to be beneficial for improving treatment outcomes. Because of their skills in identifying drug interactions, their excellent position of direct contacts and trust by patients, pharmacist can thus help patients remove evident adherence barriers and incorporate interventions into the care of their patients.

Objective: This study was aimed to characterize the adverse reactions experienced in antihypertensive patients and to assess their causality, severity, and preventability. To assess the patient’s medication knowledge related to antihypertensive drugs and the impact of clinical pharmacist mediated counseling on their medication knowledge.

Methods:
The study was observational, prospective and follow up study. This study was conducted at sms hospital Hospital, Jaipur, Rajasthan. 127 patients were recruited from OPD of department of medicine, at sms hospital Hospital, Jaipur, Rajasthan. Inclusion Criteria: Patients whose informed consent received, Patients with history of hypertension, Patients whose blood pressure are uncontrolled despite the use of medication, Patients who are experiencing adverse effects due to antihypertensive drugs, Patients of age above 18 years and either sex, Patients taking one or more antihypertensive medications at least for 1 month, Willingness to participate.

Exclusion Criteria: Patients on treatment for hypertension for more than one year, Pregnant and lactating mother, Patients who did not completely fill out questionnaire, Patients did not consent to participate.

The study duration was done for a period of 6 months.

Ethical considerations: Ethical approval was obtained from the Ethics and Research Committee of the Hospital, and informed consent was obtained from each patient verbally. The quality of the data and its confidentiality were ensured by keeping the patients’ identity coded with their initials only. The data were fully anonymized and aggregated. Any information about any patient was kept strictly confidential and not shared with unauthorized individuals. The patient's right to confidentiality, information and privacy were respected.

Study procedure:. Patients of either sex diagnosed with hypertension visiting at Out Patient Department of sms hospital, Jaipur after satisfying the inclusion and exclusion criteria, explained in detail about the study and informed written consent was obtained from each patient before recruiting them in to the study. Details of prescribed antihypertensive drug or drugs like brand name or generic name, dose, route of administration, diagnosis, laboratory results, any adverse drug reactions, any other medications were recorded in case report form. Also noted down the information of patient demographic details such as age, gender, weight, height, BMI, education, occupation, family history, past medical history, personal habits of smoking and alcohol, and contact details. A Medication Knowledge Assessment Questionnaire consisted of 5 questions to assess the knowledge of patient regarding the Medications.

Casuality assessment of ADRs
Casuality assessment of ADRs reported in patients prescribed with antihypertensive drugs by using WHO-UMC causality assessment scale and Naranjo scale.

i. **WHO-UMC system for causality assessment:**

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

**Probable/ Likely:**
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required

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

**Unlikely:**
- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable
- Disease or other drugs provide plausible
Sharma V. et al.  

Socioeconomic status of patients studied: Socioeconomic status of the patients studied were grouped as per their monthly per capita income according to modified Prasad classification 2013. Out of 127 patients, 67 (52.76%) belonged to class III. Number of patients in other classes were 34 (26.77%) in class IV, 11 (8.66%) in class II, 8 (6.3%) in class V and 7 (5.51%) in class I as shown in Table 2.

Number of patients receiving monotherapy of antihypertensive drugs: In present study 96 (75.59%) patients had received single drug for the treatment of hypertension. Amlodipine was the most commonly used drug which was prescribed for 84 (87.5%) patients. Other drugs prescribed as monotherapy were ramipril for 3 (3.14%) patients, nifedipine for 2 (2.08%) patients, telmisartan for 2 (2.08%) patients, metoprolol for 2 (2.08%) patients, losartan for 1 (1.04%) patient, nebivolol for 1 (1.04%) patient and furosemide for 1 (1.04%) patient as shown in Figure 3.

Number of patients receiving two drug combination therapy of antihypertensive drugs:

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### Scoring Scale:

- **0** = Doubtful ADR
- **1** = Possible ADR
- **2** = Indicative ADR
- **3** = Probable ADR
- **4** = Possible ADR
- **5** = Probable ADR
- **6** = Possible ADR
- **7** = Probable ADR
- **8** = Definite ADR
- **9** = Definite ADR

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### Conditional/ Unclassified:
- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination

### Unassessable/ Unclassifiable:
- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

### ii. Naranjo Causality Scale:

a. Are there previous conclusive reports on this reaction?
   - Yes (+1), No (0), Do not know or not done (0)

b. Did the adverse event appear after the suspected drug was given?
   - Yes (+2), No (-1), Do not know or not done (0)

c. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?
   - Yes (+1), No (0), Do not know or not done (0)

d. Did the adverse reaction appear when the drug was readministered?
   - Yes (+2), No (-1), Do not know or not done (0)

e. Are there alternative causes that could have caused the reaction?
   - Yes (-1), No (+2), Do not know or not done (0)

f. Did the reaction reappear when a placebo was given?
   - Yes (-1), No (+1), Do not know or not done (0)

g. Was the drug detected in any body fluid in toxic concentrations?
   - Yes (+1), No (0), Do not know or not done (0)

h. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?
   - Yes (+1), No (0), Do not know or not done (0)

i. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
   - Yes (+1), No (0), Do not know or not done (0)
Out of 127 patients two drugs were prescribed for 22 (17.32%) patients. Amlodipine + atenolol was most commonly prescribed two drug combination which was prescribed for 6 patients (27.26%). Other two drug combinations prescribed were amlodipine + furosemide for 5 patients (22.72%), telmisartan + hydrochlorothiazide for 3 patients (13.63%), amlodipine + ramipril for 2 patients (9.09%), enalapril + hydrochlorothiazide for 1 patient (4.55%), amlodipine + losartan for 1 patient (4.55%), telmisartan + amlodipine for 1 patient (4.55%), losartan + hydrochlorothiazide for 1 patient (4.55%), carvedilol + ramipril for 1 patient (4.55%) and amlodipine + nebivolol for 1 patient (4.55%) as shown in Figure 4.

Number of patients receiving three drug therapy of antihypertensive drugs:

Out of 127 prescriptions three drugs were prescribed for 7 (5.51%) patients. In that losartan + hydrochlorothiazide + amlodipine was the most commonly prescribed three drug combination prescribed for 3 patients (42.84%). Other three drug combinations prescribed were ramipril + amlodipine + atenolol for 1 patient (14.29%), amlodipine + atenolol + furosemide for 1 patient (14.29%), bisoprolol + ramipril + furosemide for 1 patient (14.29%) and telmisartan + amlodipine + hydrochlorothiazide for 1 patient (14.29%) as shown in Figure 5.

Number of patients receiving four drug therapy of antihypertensive drugs:

The four drug combinations were the least prescribed. Four drugs were prescribed only for 2 (1.58%) patients. Telmisartan + hydrochlorothiazide + amlodipine + atenolol and telmisartan + hydrochlorothiazide + amlodipine + metoprolol were the two four drug combinations prescribed for 2 patients as shown in Figure 6.

Adverse drug reactions recorded: In present study it has been observed that 86 ADRs developed for different types of antihypertensive drugs during the period of six months. Showed ADRs to antihypertensive drugs, 55 (63.95%) were female and 31 (36.05%) were male as shown in Figure 7.

Age distribution of patients developing ADRs to antihypertensive drugs: ADRs to antihypertensive drugs were observed most commonly in age group of 61–70 years (n = 40, 46.51%). Other age groups affected were 51–60 years (n = 24, 27.91%), 71–80 years (n = 13, 15.12%) and 41–50 years (n= 9, 10.46%) as shown in Figure 8.

ADRs shown on treatment with different classes of antihypertensive drugs: CCBs were found to be the commonest therapeutic class of antihypertensive drugs associated with ADRs (n = 54, 62.79%). Other groups associated with ADRs were ARBs (n = 11, 12.79%), β-blockers (n = 10, 11.63%), ACE inhibitors (n = 6, 6.98%) and diuretics (n = 5, 5.81%) as shown in Figure 10. Among individual drugs amlodipine was found to be the commonest drug associated with ADRs (n = 41).

ADRs to antihypertensive drugs affecting various systems: In present study ADRs to antihypertensive drugs associated with central nervous system (n = 37, 43.03%) were found to be the most frequent [headache, dizziness, sedation and giddiness]. Other systems associated with ADRs were musculo-skeletal system (n = 25, 29.07%) [pedal edema, fatigue and muscle cramp], respiratory system (n = 11, 12.79%) [dry cough and breathlessness], gastrointestinal system (n = 8, 9.3%) [abdominal pain and diarrhoea], cardiovascular system (n = 4, 4.65%) [bradycardia] and skin (n = 1, 1.16%) [irritation all over the body] as shown in Figure 11.

WHO causality assessment scale: According to WHO causality assessment scale most of the ADRs were “probable” 44 (51.16%), followed by “possible” 28 (32.56%), unclassifiable 10 (11.63%) and unlikely 4 (4.65%) as shown in Figure 12.

Naranjo scale: According to Naranjo scale 67 (77.91%) ADRs were “Possible”, 19 (22.09%) were “Probable” and none were “Definite” as shown in Figure 13.
Table 1: Demographic profile of the patients studied

<table>
<thead>
<tr>
<th>1.</th>
<th>Age in years</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>41 - 50</td>
<td>10</td>
</tr>
<tr>
<td>ii.</td>
<td>51 - 60</td>
<td>34</td>
</tr>
<tr>
<td>iii.</td>
<td>61 - 70</td>
<td>65</td>
</tr>
<tr>
<td>iv.</td>
<td>71 - 80</td>
<td>16</td>
</tr>
<tr>
<td>v.</td>
<td>81 - 90</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2.</th>
<th>Sex</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Male</td>
<td>95</td>
</tr>
<tr>
<td>ii.</td>
<td>Female</td>
<td>32</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3.</th>
<th>Body mass index in Kg/m²</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Normal weight (18.5 – 24.9)</td>
<td>73</td>
</tr>
<tr>
<td>ii.</td>
<td>Overweight (25 – 29.9)</td>
<td>44</td>
</tr>
<tr>
<td>iii.</td>
<td>Underweight (&lt;18.5)</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 2: Socioeconomic status and comorbid conditions of the patients studied

<table>
<thead>
<tr>
<th>1.</th>
<th>Socioeconomic status (Prasad classification)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>Class I</td>
<td>7</td>
</tr>
<tr>
<td>ii.</td>
<td>Class II</td>
<td>11</td>
</tr>
<tr>
<td>iii.</td>
<td>Class III</td>
<td>67</td>
</tr>
<tr>
<td>iv.</td>
<td>Class IV</td>
<td>34</td>
</tr>
<tr>
<td>v.</td>
<td>Class V</td>
<td>8</td>
</tr>
</tbody>
</table>

Figure 1: Bar diagram showing the number of prescriptions of antihypertensive drugs by generic and brand names

Figure 2: Pie diagram showing the percentage of prescriptions of antihypertensive drugs as monotherapy and combination therapy
Figure 3: Bar diagram showing the number of prescriptions of antihypertensive drugs as monotherapy

Figure 4: Bar diagram showing the number of prescriptions of antihypertensive drugs as two drug combination therapy
Figure 5: Bar diagram showing the number of prescriptions of antihypertensive drugs as three drug combination therapy

Figure 6: Bar diagram showing number of prescriptions of antihypertensive drugs as four drug combination therapy
Figure 7: Pie diagram showing the percentage of males and females who experienced ADRs due to use of antihypertensive drugs

Figure 8: Bar diagram showing the age wise distribution of patients who experienced ADRs due to use of antihypertensive drugs
Figure 9: Pie diagram showing the percentage of ADRs experienced in patients who received monotherapy and combination therapy of antihypertensive drugs.

Figure 10: Bar diagram showing the number of ADRs experienced with different classes of antihypertensive drugs.
Figure 11: Bar diagram showing system-wise distribution of ADRs to antihypertensive drugs

Figure 12: Bar diagram showing the causality assessment of ADRs due to antihypertensive drugs by WHO-UMC Causality assessment scale
Figure 13: Bar diagram showing the causality assessment of ADRs due to antihypertensive drugs by Naranjo scale

Certain
- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible
- Event definitive pharmacologically or phenomenologically
- Rechallenge satisfactory, if necessary Probable/Likely
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not required Possible
- Event or laboratory test abnormality, with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal may be lacking or unclear

Unlikely
- Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable
- Disease or other drugs provide plausible explanations

Conditional/ Unclassified
- Event or laboratory test abnormality
- More data for proper assessment needed, or
- Additional data under examination Unassessable/Unclassifiable
- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory
- Data cannot be supplemented or verified

WHO: World Health Organization
UMC: Uppsala Monitoring Centre
Naranjo algorithm or adverse drug reaction probability scale - The total score calculated from this table defines the category as: Possible (total score 1–4), Probable (total score 5–8), Definite (total score >9)

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Questionnaires</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Are there previous conclusive reports on this reaction?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2.</td>
<td>Did adverse drug reaction (ADR) appear after the suspected drug was administered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>3.</td>
<td>Did ADR improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4.</td>
<td>Did the adverse reaction appear when the drug was readministered?</td>
<td>2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>5.</td>
<td>Are there any alternative causes (other than the drug) that could have caused the reaction?</td>
<td>-1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6.</td>
<td>Did the reaction reappear when placebo was given?</td>
<td>-1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7.</td>
<td>Was the drug detected in the blood (or other fluids) in concentration known to be toxic?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8.</td>
<td>Was the ADR more severe when dose was increased or less severe when dose was decreased?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9.</td>
<td>Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10.</td>
<td>Was the adverse event confirmed by any objective evidence?</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Comparison of the Mean Medication Knowledge Score of Patients

Mean medication knowledge score was assessed at baseline, first follow up and second follow up. It was observed that there was significant improvement in the mean medication knowledge score of the patients at each follow ups (p < 0.001). Mean score increased from 29.66 at baseline to 49.82 at first follow up and 64.60 at second follow up.

**Table 3: Comparison of the mean medication knowledge score of patients at baseline and first follow up**

<table>
<thead>
<tr>
<th>Mean baseline score ± SE</th>
<th>Mean first follow up score ± SE</th>
<th>Difference of means</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.66 ± 2.085</td>
<td>49.82 ± 1.900</td>
<td>20.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 4: Comparison of the mean medication knowledge score of patients at first follow up and second follow up**

<table>
<thead>
<tr>
<th>Mean first follow up score ± SE</th>
<th>Mean second follow up score ± SE</th>
<th>Difference of means</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>49.82 ± 1.900</td>
<td>64.60 ± 1.850</td>
<td>14.79</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 5: Comparison of the mean medication knowledge score of patients at baseline and second follow up**

<table>
<thead>
<tr>
<th>Mean baseline score ± SE</th>
<th>Mean second follow up score ± SE</th>
<th>Difference of means</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.66 ± 2.085</td>
<td>64.60 ± 1.850</td>
<td>34.94</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Results show that there is consistent improvement in the medication knowledge of the patients at every visit. After applying ‘ANOVA’ test for repeated measures analysis, it is found that the difference in means is highly significant. This shows that there is definite positive impact of patient counselling and patient information leaflets on the medication knowledge of patients. The results of our study show that there is poor medication knowledge in the patients at baseline. After counselling, there is significant improvement in the medication knowledge of the patients. There is direct correlation of Medication Knowledge with Medication Adherence in the patients.

**Conclusion:**
In this study the ADRs were found probable (51.16%), possible (32.56%), unclassifiable (11.63%) and unlikely (4.65%) by using WHO causality assessment scale. By using Naranjo algorithm scale it was found that ADRs were possible in 77.91% and probable in 22.09% of cases. This study also found that amlodipine was responsible for most of the ADRs and among all the ADRs reported headache was the commonest followed by dizziness, pedal oedema, fatigue, abdominal pain, dry cough, breathlessness, bradycardia, muscle cramps, sedation, diarrhoea and irritation all over the body. The study was conducted for a period of 6 months. The data was collected using a case record form. The study included patients of all age group. The results of this study reveal that there is Significant improvement in the medication knowledge in patients after counselling by the pharmacist. If counselled appropriately, pharmacist can bring about major change in the adherence related attitude of the patients. There is definite relationship between the medication related knowledge and medication adherence. Hence improving the medication knowledge can lead to greater awareness and hence better medication adherence. The results at baseline showed that there was less knowledge and awareness to treatment in patients regarding their medications. As the drug therapy is mainstay of hypertension it is very much essential to educate patients regarding their medications to improve their knowledge about the medications. Factors like age, gender, family history affect the knowledge of the patients regarding their medications. Pharmacist’s efforts can contribute to the optimization of disease management for the patients thereby helping them to improve their medication adherence and hence in long term quality of life.

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