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Frequency of ADRs among Monotherapy and Combinations therapy Hypertensive Patients from Private Tertiary Care Hospital of Hyderabad, Pakistan

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Abstract: The objective of current study was to evaluate the frequency of adverse drug reactions (ADRs) among monotherapy and combinations therapy patients who had confirmed Hypertension from private tertiary care hospital of Hyderabad, Sindh, Pakistan.

Methodology:

A qualitative based study was explained descriptively and sample was taken on the basis of purposive technique, a total of 940 hypertensive patients were taken from the out-door patients who were taken atleast one antihypertensive medication. The duration of study was 2 years. The questionnaire were designed with the help of experts on the basis of study aims i.e. to evaluate the frequency of ADRs.

Results:

Out of 940 patients, 53.94% were belonged to male gender i.e. maximum, 76.91% were living in urban areas. Maximum patients were recruited from cardiac out-patient department i.e. 57.87%. The maximum age of enrolled patients was between 49 to 58 years i.e. 37.13%. 61.06% were on various antihypertensive combinations therapy. Among monotherapy Telmisartan was the most common prescribing drug and among dual therapy the most common was Valsartan+Amlodipine. Among triple therapy enalapril+hydrochlorothiazide+Atenolol was the most common prescribing medicines. Out of total patients, 17.49% ADRs were among monotherapy, 16.44 were among dual therapy, 20.74% were among triple therapy and 19.12% were among quadruple therapy patients.

Conclusion:

It was concluded that maximum ADRs were due to combination therapy so the data reflects clearly that proper guidelines should be follow while prescribing the antihypertensive medications so the prevalence of ADRs will be reduced.

Keywords: Adverse Drug Reactions, Monotherapy, Hypertension, Combination therapy, Private Hospital

1. INTRODUCTION

Every individual is now conscious about health. Now a days the burden of diseases is increased due to so many factors such as unhygienic food, malnutrition, fast foods, depression, work load, unemployment and many more[1]. The high pressure of blood leads to cardiovascular morbidities. It is estimated that each year more than 17 million mortalities take place throughout the world. Hypertension may also be defined as in the light of American heart Association that the blood is one of the root cause to initiate the power in blood arteries particularly their walls. Moreover the pressures exerted by the blood in the arteries are more that ultimately caused the high blood pressure or also called hypertension[2]. In one of developed countries about 100 millions of people have pre hypertension. High blood pressure may also be defined as the systolic pressure more than 140mmHg and diastolic pressure more than 90mmHg. The word systole means pumping and diastole means relaxation. The normal pressure of blood in arteries is 120/80mmHg and still the causes/factors for this chronic disease i.e. hypertension is still questionable for another terms is commonly used i.e. silent killer[3].

Table: 01: Adult based Classification of Hypertension[4]

Category	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure(mmHg)
Optimal	Less than 120	Less than 80
Normal	Between 120–129	Between 80–84
High normal	Between 130–139	Between 85–89
Grade 1 hypertension (mild)	Between 140–159	Between 90–99
Grade 2 hypertension (moderate)	Between 160–179	Between 100–109
Grade 3 hypertension (severe)	Greater than and Equal to 180	Greater than and Equal to 110
Isolated systolic hypertension	Greater than and Equal to 140	Less than 90

Drugs/Medicines are the most important tool to relieve the morbidities or any serious illness. But there are always two sides of the coin benefits as well as some hazardous effects so same drugs had benefits as well as adverse effects. These are double standards said by some old peoples. For this to detect and evaluate the adverse drug reaction is also important for drug safety[5]. WHO may also described the ADRs i.e. any reaction to

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a drug that is harmful and unplanned and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function. To treat hypertension there are so many classes and the initial treatment of a hypertensive patients starts from diuretics and among diuretics the most important is Thiazide and loop diuretics. But with the good effects there are some side effects of these treatments like erectile dysfunction is the common ADR of Thiazide diuretics, hypotension is due to ACE inhibitors and headache, dizziness and hypoglycemia was due to CCBs[6,7].

Table 2: Time Span of Hypertension between sample population.

Time Span of Hypertension between sample population.					
	Hospitals	**Duration of HTN**	**Frequency**	**Percent**	**Cumulative Percent**
Valid	PTCH (n=940)	Less than 1 Year	152	16.17%	16.17%
		≥1≤3 Years	263	27.98%	44.15%
		≥3≤5 Years	370	39.36%	83.51%
		More than 5 Years	155	16.49%	100%

Table 3: Frequency of Blood pressure lowering medications.

Frequency of Blood pressure lowering medications.					
Hospitals	**Status**		**Frequency**	**Percent**	**Cumulative Percent**
PTCH (n=940)	Monotherapy		366	38.94%	38.94%
	Combinations Therapy (n=574)	Dual Therapy	371	39.47%	78.41%
		Triple Therapy	135	14.36%	92.77%
		Quadruple	68	7.23%	100%

2. METHODOLOGY

A qualitative based study was explained descriptively and sample was taken on the basis of purposive technique i.e. purely depending upon the aims and objectives. The sampling was taken from a renowned private hospital of Hyderabad Sindh Pakistan. A total of 500 bed hospital where various specialties of patients were treated. Based on patient flow, a total of 940 hypertensive patients were taken from the out-door patients who were taken atleast one antihypertensive medication. The duration of study was 2 years. The questionnaire were designed with the help of experts on the basis of study aims i.e. to evaluate the frequency of ADRs. The structured questionnaire has various sections that cover the patient's bio data, medications history, current medications and detection of adverse drug reaction. Those patients having aged 18 or more than were included in the study and also having confirmed hypertension. There is no any gender difference while taking sample from hospital. The complicated patients such as mental retard, nephrotoxic, cancer and AIDs patients were excluded from the study. The research study was also approved from the research committee and data were analyzed descriptively and statistically.

3. RESULTS AND DISCUSSION

Out of total of 940 patients i.e. enrolled from private tertiary care hospital (PTCH), the male frequency was 507 patients (53.94%) and female was 433 patients (46.06%). Based on locality 723 (76.91%) patients was belonged to urban and 217 (23.09%) was from rural areas. Moreover 544 (57.87%) patients were from cardiac out-patient department and 396 (42.13%) patients from medicine out-patient department. Maximally the age of patients were from 49 to 58 years i.e. 349 (37.13%). As far as history of hypertension was concerned, out of total patients, 201 (21.38%) patient had 1 parent hypertension, 102 (10.85%) patients had 2 parents, 505 had no any hypertension in their families and 132 (14.04%) patients don't know about the status

Table 4: List of Antihypertensive medicines Prescribed among Monotherapy Patients (n=366)

Prescribed Medicines	**Frequency**	**Percent**	**Cumulative Percent**
Furesimide	10	2.73%	2.73%
Spironolactone	4	1.09%	3.82%
Hydrochlorothiazide	7	1.91%	5.73%
Atenolol	38	10.38%	16.11%
Propanolol	48	13.11%	29.22%
Amlodipine	26	7.10%	36.32%
Nifidipine	11	3.00%	39.32%
Enalapril	22	6.01%	45.33%
Perindopril	4	1.09%	46.42%
Ramipril	34	9.29%	55.71%
Candesartan	12	3.28%	58.99%
Lisinopril	17	4.64%	63.63%
Captopril	9	2.5%	66.13%
Telmisartan	58	15.84%	81.97%
Bisoprolol	5	1.35%	83.32%
Carvedilol	3	0.82%	84.14%
Valsartan	12	3.3%	87.44%
Felodipine	5	1.36%	88.8%
Verapamil	6	1.64%	90.44%
Benzopril	3	0.82%	91.26%
Losartan	26	7.10%	98.36%
Metoprolol	6	1.64%	100.00%
Total	**366**	**100.0%**	

Table 4 described the frequency of mono therapy medications that was prescribed to hypertensive patients. Out of 366 monotherapy patients the maximum patients i.e. 58 (15.84%) were on Telmisartan followed by Propanolol and its frequency was 48 (13.11%). While the frequency of monotherapy medication were discussed in above table.

Table 5: List of Antihypertensive medicines Prescribed as Dual Therapy in combined therapy Patients (n=371)

Prescribed Medicines	Frequency	Percent	Cumulative Percent
Valsartan+Amlodipine	49	13.21%	13.21%
Atenolol+Chlorthalidone	21	5.66%	18.87%
Telmisartan+hydrochlorothiazide	38	10.24%	29.11%
Valsartan+hydrochlorothiazide	8	2.16%	31.27%
Amlodipine+Perindopril	19	5.12%	36.39%
Lisinopril+hydrochlorothiazide	33	8.89	45.28%
Losartan+hydrochlorothiazide	11	2.97%	48.25%
Enalapril+hydrochlorothiazide	35	9.43%	57.68%
Candesartan+hydrochlorothiazide	7	1.90%	59.58%
Amlodipine + Telmisartan	32	8.62%	68.20%
Losartan+ Spiranolactone	9	2.42%	70.62%
Candesartan + Spiranolactone	5	1.35%	71.97%
Propanolol+ Frusemide	10	2.70%	74.67%
Amiloride + hydrochlorothiazide	8	2.16%	76.83%
Amlodipine+ Ramipril	19	5.12%	81.95%
Enalapril + Frusemide	11	2.96%	84.91%
Frusemide + Amiloride	16	4.31%	89.22%
Lisinopril + Verapamil	12	3.23%	92.45%
Ramipril+Hydrochlorothiazide	28	7.55%	100%
Total	**371**	**100.0%**	

Table 05 described the frequency of dual therapy medications and the results showed that maximum patients were on Valsartan + Amlodipine and its frequency was 49 (13.21%).

Table 06: List of Antihypertensive medicines Prescribed as Triple Therapy in combined therapy Patients (n=135)

Prescribed Medicines	Frequency	Percent	Cumulative Percent
Valsartan+ hydrochlorothiazide+Amlodipine	15	11.11%	11.11%
Atenolol+Chlorthalidone+Telmisartan	10	7.41%	18.52%
Telmisartan+hydrochlorothiazide+Propanolol	7	5.18%	23.7%
Valsartan+hydrochlorothiazide+Atenolol	16	11.85%	35.55%
Losartan+hydrochlorothiazide+ αMD	24	17.78%	53.33%
Enalapril+hydrochlorothiazide+Atenolol	29	21.48%	74.81%
Amlodipine + Telmisartan+Metoprolol	5	3.70%	78.51%
Propanolol+Hydrochlorothiazide+Telmisartan	8	5.93%	84.44%
Ramipril+Hydrochlorothiazide+Propanolol	21	15.56%	100%
Total	**135**	**100.0%**	

Table 06 described the frequency of triple therapy medications and the results showed that maximum patients were on Enalapril + Hydrochlorothiazide + Atenolol and its frequency was 29 (21.48%)

Table 7: List of Antihypertensive medicines Prescribed as Quadruple Therapy in combined therapy Patients (n=68)

Prescribed Medicines	Frequency	Percent	Cumulative Percent
Valsartan+Amlodipine+ Atenolol+Chlorthalidone	24	35.29%	35.29%
Atenolol+Chlorthalidone+Telmisartan+ αMD	10	14.71%	50%
Telmisartan+hydrochlorothiazide+Propanolol+αMD	7	10.29%	60.29%
Amlodipine+Telmisartan + Enalapril+hydrochlorothiazide	12	17.65%	77.94%
Candesartan+hydrochlorothiazide+ Amlodipine+ Propanolol	15	22.06%	100%
Total	**68**	**100.0%**	

Table 07 described the frequency of quadruple therapy medications and the results showed that maximum patients were on Valsartan + Amlodipine + Atenolol+ Chlorthalidone and its frequency was 24 (35.29%).

Table 8: Class wise List of Antihypertensive medicines Prescribed in Monotherapy and Combinations therapy Patients.

Monotherapy Frequency	Combinations Therapy Frequency		
	Dual Therapy	Triple Therapy	Quadruple Therapy
Diuretics (DUs)=21	ARBs + DUs=78	ARBs + CCBs+ DUs= 15	ARBs + CCBs+BBs+DUs= 39
Beta Blockers (BBs)=100	BBs+DUs=31	ARBs+DUs+BBs=41	BBs+DUs+ARBs+αMD=17
Calcium Channel Blockers(CCBs)=48	ARBs+CCBs=81	ARBs+DUs+ αMD=24	ARBs+CCBs+ACEIs+DUs=12
Angiotensin Converting Enzyme Inhibitors (ACEIs)= 138	CCBs+ACEIs=50	ACEIs+DUs+BBs=50	
Angiotensin receptor blockers (ARBs)= 59	ACEIs+DUs=107	CCBs+ARBs+BBs=5	
	DUs+DUs=24		
Total=366	**Total=371**	**Total=135**	**Total=68**

Table No 08 described the frequency of prescribing status of antihypertensive medications based on class and the results clearly stated that among monotherapy the ACEIs inhibitors were mostly prescribed and the frequency was 138, among dual therapy the ACEIs+DUs were mostly prescribed and the frequency was 107, among triple therapy patients, the ACEIs+DUs+BBS were mostly prescribed and the frequency was 50 and in last among quadruple therapy, the ARBs+CCBs+BBs+DUs class were maximally prescribed and the frequency was 39.

Table 9: ADRSs reported in Monotherapy and Combinations therapy Patients

ADRs	Monotherapy Frequency	Combination Therapy Frequency		
		Dual therapy	Triple therapy	Quadruple therapy
Present	64(17.49%)	61 (16.44%)	28 (20.74%)	13 (19.12%)
Absent	302(82.51%)	310 (83.56%)	107 (79.26%)	55 (80.88%)
Total	**366(100%)**	**371 (100%)**	**135 (100%)**	**68 (100%)**

Table No 09 showed the ADRs reported among mono and combinations therapy patients. Out of 366 monotherapy patients 64 (17.49%) were experienced various ADRs while in combinations therapy patients such as among dual therapy out of 371 patients 61 (16.44%) were experienced ADRs, in triple therapy patients out of 135 patients 28 (20.74%) were experienced ADRs and in quadruple therapy patients out of 68 patients only 13 (19.12%) patients were experienced various ADRs.

Table 10: Drug wise ADRs reported in Monotherapy and Dual therapy Patients

Monotherapy	Frequency	Dual Therapy	Frequency
Furesimide	1 (1.56%)	Valsartan+Amlodipine	12 (19.67%)
Spironolactone	2(3.12%)	Atenolol+Chlorthalidone	2(3.28%)
Hydrochlorothiazide	3(4.69%)	Telmisartan+hydrochlorothiazide	6(9.83%)
Atenolol	6(9.40%)	Valsartan+hydrochlorothiazide	3(4.92%)
Propanolol	10(15.62%)	Amlodipine+Perindopril	4(6.56%)
Amlodipine	7(10.94%)	Lisinopril+hydrochlorothiazide	5(8.20%)
Nifedipine	2(3.12%)	Losartan+hydrochlorothiazide	1(1.64%)
Enalapril	5(7.81%)	Enalapril+hydrochlorothiazide	9(14.75%)
Perindopril	0	Candesartan+hydrochlorothiazide	1(1.64%)
Ramipril	3(4.69%)	Amlodipine + Telmisartan	9(14.75%)
Candesartan	1(1.56%)	Losartan+ Spiranolactone	1(1.64%)
Lisinopril	4(6.25%)	Candesartan + Spiranolactone	1(1.64%)
Captopril	0	Propanolol+ Frusemide	1(1.64%)
Telmisartan	12(18.75%)	Amiloride + hydrochlorothiazide	1(1.64%)
Bisoprolol	0	Amlodipine+ Ramipril	0
Carvedilol	0	Enalapril + Frusemide	1(1.64%)
Valsartan	2(3.12%)	Frusemide + Amiloride	2(3.28%)
Felodipine	1(1.56%)	Lisinopril + Verapamil	0
Verapamil	1(1.56%)	Ramipril+Hydrochlorothiazide	2(3.28%)
Benzapril	0		
Losartan	4(6.25%)		
Metoprolol	0		
Total	**64(100%)**	**Total**	**61 (100%)**

Table No 10 described the frequency of ADRs from various antihypertensive medications among mono and dual therapy patients. It was clearly stated in above table that most of ADRS were reported in those patients who were taken Telmisartan 12(18.75%) followed by Propanolol 10(15.62%). While in dual therapy patients most of ADRs were due to Valsartan+Amlodipine and its frequency was 12 (19.67%) moreover remaining frequencies were mentioned in above table.

Table 11: ADRs reported from Triple Therapy and Quadruple therapyPatients

Prescribed Medicines (Triple therapy)	ADRs reported	Prescribed Medicines (Quadruple therapy)	ADRs reported
Valsartan+ hydrochlorothiazide+ Amlodipine	2(7.14%)	Valsartan+Amlodipine+ Atenolol+Chlorthalidone	4(30.77%)
Atenolol+Chlorthalidone+Telmisartan	3(10.71)	Atenolol+Chlorthalidone+Telmisartan + αMD	3(23.08%)
Telmisartan+ hydrochlorothiazide+Propanolol	3(10.71)	Telmisartan+hydrochlorothiazide+Propanolol +αMD	1(7.69%)
Valsartan+ hydrochlorothiazide+ Atenolol	7(25%)	Amlodipine+Telmisartan + Enalapril+hydrochlorothiazide	2(15.38%)
Amlodipine+Perindopril+αMD	0	Amlodipine+Perindopril+Telmisartan+αMD	0
Lisinopril+hydrochlorothiazide+ αMD	0	Candensartan+hydrochlorothiazide+ Amlodipine+ Propanolol	3(23.08%)
Losartan+hydrochlorothiazide+ αMD	2(7.14%)		
Enalapril+hydrochlorothiazide+Atenolol	6(21.43%)		
Amlodipine + Telmisartan+Metoprolol	1(3.57%)		
Propanolol+Hydrochlorothiazide+Telmisartan	1(3.57%)		
Ramipril+Hydrochlorothiazide+Propanolol	3(10.71%)		
Total	**28(100%)**	**Total**	**13(100%)**

Table No 11 described the frequency of ADRs from various antihypertensive medications among triple and quadruple therapy patients. It was clearly stated in above table that most of ADRS were reported in triple therapy patients who were taken Valsartan+hydrochlorothiazide+Atenolol 7(25%). While in quadruple therapy patients most of ADRs were due to Valsartan+Amlodipine+ Atenolol+Chlorthalidone and its frequency was 4 (30.77%) moreover remaining frequencies were mentioned in above table.

4. DISCUSSION

The current research work shows the prescribing status of antihypertensive medications as well as frequency of ADRs among hypertensive patients at tertiary care hospital of Hyderabad, Sindh Pakistan. Current study showed the status of patients according to gender wise i.e. 53.94% of the patients were belonged to male and 46.06% of the patients were belonged to female gender while various studies were conducted by different authors and described different status. According to another study[8] the male was 50.5% and female was 40.5% and according to sandozi and emani[9] the percentage of male was 47% and female was 53%. Moreover on the basis of age, out of 940 patients, 37.13% were between 49-58 years of age i.e. maximum while another study conducted[10]. The comparison of therapies were also evaluated with the discussed study and it was concluded that current study had less than 50% of the patients were taken monotherapy and more than 50% patients were taken combination therapy which was same with the discussed study. Another study conducted by Yakubu Sani et al[11], which describe that total of 1164 patients were enrolled having dominancy of male gender i.e. 728 and the female patients was 536. Out of total patients 8.2% of the patients experienced various ADRs due to antihypertensive drugs. The most prescribed classes of antihypertensive drugs were diuretic followed by ACE inhibitors. Among ACE inhibitors i.e. Captopril caused hypotension in 8% of the patients, dry cough in 47.7% due to Lisinopril 3.4% of the patients caused hypotension and 38.6% of the patients caused dry cough. While as compared to current study the male patients were more and female patients were less. A total of 17.49% ADRs were reported in monotherapy patients i.e. more than the discussed study and the most prescribed antihypertensive drug was Telmisartan and the percentage was 18.75%..

According to current study the prescribing status were based on different therapies i.e. 38.94% were on monotherapy and 61.06% were on combinations therapies i.e. dual, triple and quadruple therapies. While Krunal *et al* reported that 49.50% of patients were on dual therapy, 33.16% of the patients were on monotherapy and 15.5% of patients were on triple therapy. Further present study described that out of 371 dual therapy patients the most prescribing combination was Valsartan+Amlodipine with 13.21% followed by Telmisartan+hydrochlorothiazide with 10.24% but krunal reported the most combination dual therapy was Enalapril+Atenolol with 22% followed by Enalapril +Amlodipine with 10.83%. Moreover among triple therapy according to current therapy the most prescribing combination was Enalapril+ Hydrochlorothiazide+Atenolol with 21.48% followed by Losartan+hydrochlorothiazide+αMD with 17.78% but krunal reported the most combination triple therapy were Enalapril+Atenolol+Amlodipine with 8% followed by Enalapril+Atenolol+Frusemide with 4.16%. The quadruple therapy was also assessed in current study and it was found that the most common combination was Valsartan+Amlodipine+Atenol+Chlorthalidone with 35.29% while krunal described the Enalapril+Atenolol, Amlodpine+Furosemide with 1.66%[12-13]

5. CONCLUSION

The above study clearly indicates the dominancy of male gender and belonging to urban areas. Majority of patients had hypertension for more than three years. The maximum patients were on combinations therapy, among monotherapy patients telmisartan was the most common prescribing medicine and among dual therapy majority of patients were on valsartan+Amlodipine, among triple therapy patients Enalapril+ hydrochlorothiazide+Atenolol were most common and among quadruple therapy Valsartan + Amlodipine + Atenolol +Chlorthalidine was most common prescribing medicine. The ADRs were mostly detected among triple therapy patients as compared to monotherapy patients. Telmisartan was among monotherapy, Valsartan+ Amlodipine was among dual therapy, Enalapril +hydrochlorothoiazide+Atenolol was among triple and Valsartan+Amlodipine+Atenolol+Chlorthalidone was among quadruple therapy causing most common ADRs.

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