



## EVALUATION OF THE RELATIVE INCIDENCE OF ADVERSE EFFECTS LEADING TO TREATMENT DISCONTINUATION OF RECOMMENDED ANTIHYPERTENSIVE DRUGS

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### ABSTRACT

This study aimed at evaluating the incidence of adverse effects leading to treatment discontinuation of antihypertensive drugs within the same therapeutic class. Individual medical records were searched to identify those hypertensive patients who had been commenced on antihypertensive therapy during a 24-month period and who had subsequently for a reason(s) discontinued the therapy. The results showed variation in discontinuation rates for drugs within same class, and that might be related to the relative frequency of specific adverse effects. Cough was the reason cited for discontinuation of angiotensin converting enzyme inhibitors, with losopril appearing to be better tolerated than captopril (39% vs 48%); peripheral oedema with calcium channel blockers, with amlodipine appearing to be better tolerated than nifedipine (29% vs 38%) and bradycardia with beta adrenergic receptor blockers, with propranolol better tolerated than atenolol (0% vs 48%). Diuretics showed the lowest discontinuation rate (3.3%) mainly due to hypokalemia, with thiazide better tolerated than frusemide (11% vs 43%).

Prescribers should verify their use of antihypertensive drugs to ensure that they prescribe drugs with lower adverse effect rates, in order that patients with hypertension continue using the medication in the long term, thereby reducing the risk of developing cardiovascular complications associated with uncontrolled blood pressure.

**Keywords:** antihypertensive drugs, adverse effect, discontinuation, treatment

### INTRODUCTION

Hypertension is a medical condition where the systolic blood pressure (SBP) is more than 140 mm Hg and the diastolic blood pressure (DBP) is more than 90 mm Hg<sup>1</sup>. Uncontrolled hypertension can lead to heart disease, stroke, renal failure and retinopathy<sup>2</sup>. These are the principal causes of death in all developed countries and are emerging as a prominent public health problem in developing countries ranking third with mainly 16% of all deaths<sup>3</sup>. The prevalence of hypertension in Nigeria varied extensively between studies, ranging from a minimum of 12.4% to a maximum of 34.8%<sup>4</sup>. Antihypertensive drugs are medicines that lower blood pressure. There are various categories of antihypertensive drugs and each has some adverse effects. The UK Commission on Human Medicine defines an adverse drug reaction (ARD) as an unwanted or harmful reaction experienced after the administration of a drug or combination of drugs under normal condition of use and suspected to be related to the drug<sup>5</sup>. Among the recommended and most widely used antihypertensive drugs are the diuretics, the angiotensin converting enzyme (ACE) inhibitors, the calcium channel blockers (CCBs), the beta adrenergic receptor blockers, and the angiotensin II receptor antagonists ARBs<sup>6,7</sup>. Despite the plethora of blood pressure (BP) lowering agents, satisfactory control of hypertension is often difficult to achieve. This is in part due to the adverse effects associated with the various antihypertensive drugs, which are a cause for the discontinuation of treatment<sup>8</sup>. Several studies<sup>9-12</sup> had been carried out on adverse drug reactions (ADRs) related to antihypertensive drugs in some parts of the world, the results demonstrated high frequency of ADRs in antihypertensive treatment, but with significant differences between the various drug groups<sup>13</sup> and between antihypertensive drugs within the same therapeutic group, leading to the discontinuation of treatment.<sup>14</sup>

Maiduguri is a metropolitan city in the north eastern Nigeria, a region which to the best of our knowledge has not been evaluated for incidence of adverse effects of antihypertensive drugs. Therefore, the objective of this retrospective study was to evaluate the relative incidence of adverse effects of antihypertensive drugs, leading to treatment discontinuation among patients diagnosed with hypertension, who attended the Cardiology Unit of the Department of Medicine, University of Maiduguri Teaching Hospital (UMTH) Maiduguri.

### MATERIALS AND METHOD

#### Setting

The retrospective study was carried out at the Cardiology Unit of the Department of Medicine, University of Maiduguri Teaching Hospital (UMTH) Maiduguri Borno State, Nigeria.

#### Data collection process

Ethical clearance was obtained from the Ethics and Research Committee of the hospital prior to the commencement of the study. The methodology was adopted from Baqir [14] with modifications. Patients with hypertension (who were not diagnosed with co-morbid diseases such as diabetes mellitus, dyslipidemia, heart failure and hepatic dysfunction) were identified from the Cardiology Unit, medical records system using clinical codes. Individual records were then searched to identify those patients who had been commenced on antihypertensive therapy during 24-month period (January 2008-December 2009) and who had subsequently discontinued that therapy. Though a sample size determination formula:  $nf = n/1+n/N$  ( $nf$  = sample size for population less than 10,000;  $n$  = sample size for population greater than 10,000 and  $N$  = estimate for population of study) was supposed to have been used for a target population of less than 10,000, because of the precision desired in the study

the entire population, comprising 1164 patients' folders, was used.

Further scrutiny of the patients' records was then undertaken to ascertain the reason(s) for the discontinuation of antihypertensive therapy. A self-designed data collection format (appendix I) was used for collection of all relevant data.

**Data analysis**

The data obtained were statistically analyzed using Statistical Package for Social Sciences SPSS Version 16, and the results were presented as frequency and percentage of adverse effects experienced from each class of antihypertensive drugs. Proportions were compared using chi-square analysis, p-values < 0.05 were considered significant.

**Table 1: Distribution of adverse drug effect within each class of antihypertensive**

Class of antihypertensive drug	Total exposure (prescriptions) of drugs	Any documented of adverse drug effect (incidence) within class of antihypertensives	
		No	Yes
Diuretics	749	714 (95.3%)	35 (4.7%)
ACEI	716	628 (87.7%)	88 (12.3%)
Beta-adrenergic receptor blockers	429	398 (92.8%)	31 (7.2%)
CCBs	372	331(89.0%)	41 (11.0%)
CAAs	114	111 (98.2)	3 (2.6%)
α- adrenergic blocker	65	61 (93.8%)	4 (6.2%)
<b>Total</b>	<b>2460</b>		<b>202 (8.2%)</b>

P ≥ 0.05 (CI=95%; df= 6)

**Table 2: Rate of discontinuation of treatment due to adverse drug effect within each class of antihypertensive**

Class of antihypertensive drug	Total exposure (prescriptions) of drugs	Frequency (percentage) of discontinuation of treatment due to adverse drug effect of antihypertensive	
		No	Yes
Diuretics	749	10 (1.3%)	25 (3.3%)
ACEI	716	1	87 (12.2%)
Adrenergic beta-receptor blockers	429	7 (1.6%)	24 (5.5%)
CCBs	372	8 (2.2%)	33 (8.9%)
CAAs	114	3 (2.6%)	0 (%)
adrenergic α-receptor blockers	65	0	4 (6.2%)
<b>Total</b>	<b>2460</b>		<b>173 (7%)</b>

P ≥ 0.05 (CI=95%; df= 6)

**Table 3: Distribution of specific adverse drug effect experienced from Angiotensin I converting enzyme inhibitor (ACEI) (n = 88)**

ACEI	Frequency of specific adverse drug effect experienced (percentage)			
	Hypotension	Dry cough	Headache	Abdominal pain
Captopril	7(8. %)	42 (47.7%)	0	0 (0%)
Linopril	3 (3.4%)	34 (38.6%)	0 (0%)	0 (0%)
Ramipril	0 (0%)	2 (2.3%)	0 (0%)	0 (0%)
<b>Total (n = 88) 100%</b>	<b>10 (11.4%)</b>	<b>78 (88.8%)</b>	<b>0 (0%)</b>	<b>0 (0%)</b>

P ≥ 0.05 (CI=95% df= 2)

**Table 4: Distribution of specific adverse drug effect experienced from Calcium channel blockers (n =41)**

Calcium channel blocker	Frequency of specific adverse drug effect experienced (percentage)			
	Bradycardia	Headache	oedema	Abdominal pain
Nifedipine	2 (5.9%)	19 (55.9%)	13 (38.2%)	0 (0%)
Amlodipine	1 (14.3%)	2 (28.6%)	2 (28.6%)	2 (28.6%)
<b>Total (n = 41)</b>	<b>3 (7.3%)</b>	<b>21 (51.2%)</b>	<b>15 (36.6%)</b>	<b>2 (4.9%)</b>

P ≥ 0.05 (CI=95% df= 3)

**Table 5: Distribution of specific adverse drug effect experienced from Beta-adrenergic receptor blocker (n = 31)**

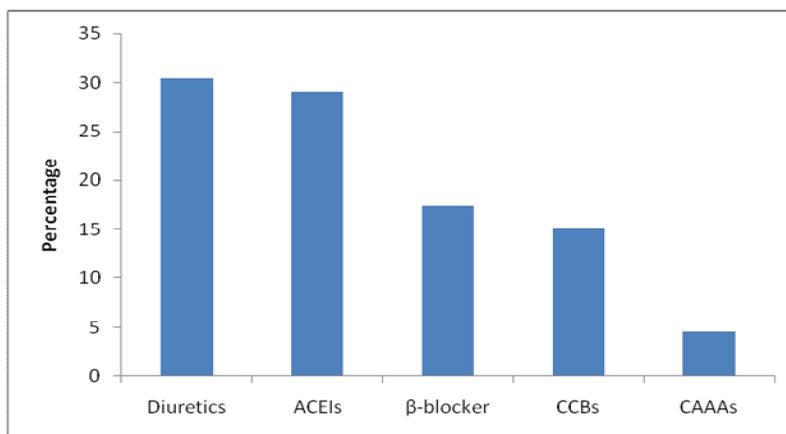
Beta-adrenergic receptor blocker	Frequency of specific adverse drug effect experienced (percentage)			
	Hypotension	Bradycardia	Insomnia	Fatigue and cold extremities
Atenolol	5(16.1 %)	15 (48.4%)	7(22.5%)	0
Propranolol	3 (9.7%)	0 (0%)	0 (0%)	0 (0%)
Cavidalol	0 (0%)	0 (0%)	1 (3.2%)	0 (0%)
<b>Total (n = 31) 100%</b>	<b>8(25.8%)</b>	<b>15 (48.4%)</b>	<b>8(25.8%)</b>	<b>0 (0%)</b>

P ≥ 0.05 (CI=95% df= 4)

**Table 6: Distribution of specific adverse drug effect experienced from Diuretics (n =35)**

Diuretics	Frequency (percentage)of specific adverse drug effect experienced			
	Dehydration	Hypokalaemia	Hypouricaemia	Fatigue
Bendroflumethiazide	3 (8.6%)	4(11.4%)	4(11.4%)	2(5.7%)
Frusemide	3(8.6%)	15(42.9%)	1(2.8%)	3(8.6%)
Hydrochlorothiazide	0	0	0	0
Spirinolactone	0	0	0	0
<b>Total (n = 35) 100%</b>	<b>6(17.2%)</b>	<b>29(54.3%)</b>	<b>5(14.2%)</b>	<b>5(14.2%)</b>

P ≥ 0.05 (CI=95%; df= 3)



**Figure 1: Percentage distribution of classes of anti hypertensive drugs**

ACEIs – Angiotensin converting enzyme inhibitors; β-blockers – Beta-adrenergic receptor blockers; CCBs – Calcium channel blockers; CAAAs – Centrally acting adrenergic antagonists

## RESULTS

One thousand, one hundred and sixty-four (1164) patients (728 males and 536 females with the mean age of  $47 \pm 14.2$ ) had 2460 exposures (prescriptions) of various classes of antihypertensive drugs. The most frequently prescribed were: diuretics 749 (30.4%), ACE inhibitors 716 (29.1%), followed by beta blockers 429 (17.4%), calcium channel blockers (CCBs) 372 (15.1%) and centrally acting adrenergic agonists (CAAs) 114 (4.6%) [Figure1]. The distribution of frequency and percentage of adverse effects experienced from each class of antihypertensive drugs are shown in Table 1. Also the rates of discontinuation of treatment due to adverse effects within class of antihypertensive drugs are shown in Table 2, while the distribution of proportions of specific adverse effects due to various drugs within each class of antihypertensive drugs are as shown in Tables 3 to 6.

## DISCUSSION

A total of 202 (8.2%) adverse drug effects were observed in 1164 hypertensive patients (728 males and 536 females) from the total of 2460 antihypertensive drug exposures (prescriptions) and the mean age of  $47.66 \pm 14.23$  during the period of 2003-2004 in UMTH. A higher percentage of adverse drug effects occurred in females 116 (57.4%) than 86 (42.57%) of males, the finding was in agreement with that reported by Raghu et al<sup>15</sup> and Prasad et al<sup>16</sup> respectively, which revealed that a higher percentage of adverse drug effect occurred in females (58.80%) than males (41.2%). Also the incidence of discontinued treatment occurred more in females 17 (10.2%) than males 14 (8.4%), though the observed difference between the sex groups was not statistically significant ( $p > 0.05$ ). Theoretically women were thought to be at greater risk of adverse drug reaction than men, which might be due to gender related differences in pharmacokinetics, immunology and hormonal factors. However, a recent survey by Walker and Whittlesea<sup>5</sup> revealed that the overall tolerability of low to moderate-dose antihypertensive medicines was similar in men and women. Of the total of 202 adverse drug effects observed across the different classes of antihypertensive drugs (Table 1), the most commonly implicated were ACE inhibitors with an incidence of 12.3%, followed by calcium channel blockers (CCBs) 11.2% and beta-adrenergic receptor blockers 7.2%. The least implicated were diuretics (4.7%), even though they were the most commonly prescribed. These findings were consistent

with those reported by Singhal et al<sup>17</sup> in which CCBs and ACE inhibitors were the most often implicated with highest incidence of adverse drug effect but contrast to findings of Prasad et al<sup>16</sup> in which beta-blockers and ACE inhibitors were associated with higher incidences of ADRs.

The overall rate of discontinuation of treatment due to adverse effects across the different classes of antihypertensive drugs was (7%), i.e. of the total of 202 observed adverse effects, 173 (84.2%) resulted in discontinuation of treatment. ACE inhibitors were the most commonly discontinued therapeutic class (12%) followed by CCBs (8.9%), adrenergic  $\alpha$ -receptor blockers (6.2%), beta adrenergic receptor blockers (5.5%) and diuretics (3.3%). This demonstrated that users of diuretics had the lowest rate of discontinuation of treatment with the greatest tolerability. This finding concurred with another study<sup>18</sup> which reported the lowest rates of discontinuation due to diuretics

In this study, the most common reason cited for discontinuation of ACE inhibitors was cough, thus, supporting the finding by Alderman<sup>19</sup>. Lisinopril appearing to be better tolerated than captopril with discontinuation rates of 39% vs 48% respectively [absolute risk reduction (ARR) calculated to be 9%, number need to harm (NNH) = 9, i.e. for every eight patients treated with captopril instead of lisinopril one patient will discontinue treatment due to cough]. Though the incidence of headache (56%) was higher than peripheral oedema (38%) in hypertensive patients treated with CCBs, peripheral oedema was the main reason cited in the patients' records for discontinuation of the treatment. This finding was supported by the reports of stus<sup>20, 21</sup> which revealed that peripheral oedema was the most common reason cited for discontinuation of CCBs. Within CCBs, the rate of discontinuation was higher with nifedipine than amlodipine (38% vs 28%) respectively (ARR) = 10%, implying the later was better tolerated than the former. This finding concurred with the report of a study by Hosu et al<sup>22</sup> that a higher incidence of adverse drug reactions with attendant rate of discontinuation was associated with nifedipine compared to amlodipine.

Within beta-adrenergic receptor blockers, the most common reason cited for discontinuation of treatment was bradycardia, with propranolol appearing to be better tolerated than atenolol 48% vs 0% respectively. On the contrary, another study<sup>23</sup> revealed that impotence was a common complaint with this class of drugs.

Within the diuretics class, frusemide recorded the highest incidence of adverse drug reactions mainly hypokalaemia (43%), followed by Bendroflumethiazide (11%), and with the lowest incidence reported in Hydrochlorothiazide (3%). There was statistical significant difference in the distribution of hypokalaemia. Though the major adverse drug reaction of diuretics recorded in this study was hypokalaemia, a previous study<sup>24</sup> reported the incidence of impotence as high as 31%. Overall, the discontinuation rates for the antihypertensive drugs within therapeutic class varied, and this might be related to the relative frequency of adverse effects of each drug. This finding is in agreement with that reported by Baqir.<sup>14</sup> The important factors in the management of hypertension are achieving a targeted level of blood pressure control and ensuring the patient remains using the drug over a long term. This study shows that selecting drugs with the lowest incidence of adverse effects from within the same therapeutic class may lead to persistence with treatment and achieving blood pressure control. Thus, the risk of developing cardiovascular complications can be reduced.

## CONCLUSION

Therefore, the evaluation of the relative incidence of adverse effects and treatment discontinuation among the antihypertensive drugs offer the best opportunity to detect differences among the individual drugs within the same therapeutic class.

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