OUT-PATIENTS UTILIZATION OF ANTI-HYPERTENSIVE DRUGS IN A TERTIARY HOSPITAL IN NORTH-WESTERN NIGERIA

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ABSTRACT

Despite the availability of the wide range of anti-hypertensive drugs and simplifying prescribing decision by the Seventh Joint National Committee (JNC7), hypertension and its complications are still important causes of adult morbidity and mortality in sub-Saharan Africa. Drug utilization studies promote rational drug use which in turn minimizes the negative medical, social and economic consequences in management of chronic diseases like hypertension. The study was designed to evaluate the out-patients utilization of anti-hypertensive drugs in a tertiary hospital in north western Nigeria. This retrospective longitudinal study covered a period of five years (January, 2010 to December, 2014). Data was collected from the Medical Out-patients Department (MOPD) of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto State in north western Nigeria. A total of 3316 encounters were analyzed using ATC/DDD method. Prescriptions written for females were 63.2%, while the mean age of the patients was 51.68±11.39. Diabetes was the highest comorbidity encountered. The mean number of drugs per prescription was 2.2. There was significant difference between the mean number of drugs prescribed in 2010 and 2012 ($p<0.05$). The year 2010 had the highest percentage (80.2%) of drugs prescribed by generic names. Amlodipine and lisinopril were the most utilized antihypertensive drugs with 281.8 and 215.8 DDD/1000 patients/ day respectively. The trend of antihypertensive use was found to be normal. This study showed that there was rationality in antihypertensive drugs use in this facility. However, targeted education of the prescribers and dissemination of treatment guidelines could facilitate rational use of antihypertensive drugs and adherence to treatment guidelines.

KEYWORDS: *Antihypertensive drugs, Drug utilization, Hypertension, Treatment guideline*

INTRODUCTION

Drug utilization, as defined by the World Health Organization (WHO), is the "marketing, distribution, prescription and use of drugs in society, with special emphasis on the resulting medical, social and economic consequences" [1-2]. The principal aim of drug utilization research is to facilitate the rational use of drugs in populations **Invalid source specified.** which became a respectable subject for consideration at international congresses in pharmacology and epidemiology **Invalid source specified.**. This is pertinent especially in chronic diseases like hypertension.

Hypertension is one of the major health problems and, being the most common cardiovascular disease, it results in high morbidity and mortality in world population **Invalid source specified.**. It is an established risk factor for cardiovascular diseases such as myocardial infarction, arrhythmias, angina pectoris; cardiac and renal failure **Invalid source specified.**. Available data indicate that untreated hypertension shortens life expectancy by approximately five years **Invalid source specified.**. The global prevalence of hypertension is on the increase. In 2000, 972 million people had hypertension with a prevalence rate of 26.4% **Invalid source specified.**. These are projected to increase to 1.54 billion affected individuals and a prevalent rate of 29.4% in 2025. The prevalent rate

increases with age and it is higher in blacks (30%) than in white (25%) **Invalid source specified.**. A study conducted in 2009 in Sokoto North-Western Nigeria indicated that the prevalence rate of hypertension was 24.8**Invalid source specified.**.

According to Intercontinental Marketing Service (IMS) data, the leading group of drugs utilized worldwide is anti-hypertensives **Invalid source specified.**, which are usually co-prescribed along with antidiabetic drugs as a result of the co-existence of hypertension and diabetes **Invalid source specified.**.

Several evidence-based studies have demonstrated appropriate use of anti-hypertensives prevents or delays the emergence of hypertension related complications, thereby improving the quality and quantity of the patients' life. However, despite the availability of a wide range of these drugs, hypertension and its complications are still important causes of adult morbidity and mortality in sub-Saharan Africa **Invalid source specified.**, especially in Nigeria where healthcare services are sub-optimal for the rapidly expanding populations [14-15].

It is therefore necessary to evaluate the utilization pattern of anti-hypertensives using universal indicators, which are independent on the investigator or time of measurement **Invalid source specified.**. This is to find out whether the drugs' use is rational or not, to enable evidence-based interventions can be made where necessary in our healthcare institutions. Anti-hypertensive drugs consumption expressed in defined daily dose and prescribed daily dose per thousand hypertensive patients per day (DDD and PDD/THPD); drug utilization 90% (DU90%) and anti-hypertensive cost per PDD and total coast will help the hospital management in making rational drug budget and procurement so that the patients can at any time obtain cost-effective anti-hypertensive medications at the right time and in the right quantity. Researchers can also to make basic comparisons between situations in different areas or at different times. The above mentioned issues stimulated the undertaking of the present study which is aimed at evaluating the out-patients' utilization of anti-hypertensive drugs in a tertiary health institution in north-western Nigeria.

METHOD

Study setting

The study was conducted at the Medical Records Unit of the Medical Outpatients Department (MOPD) of Usmanu Danfodiyo University Teaching Hospital (UDUTH), Sokoto. The hospital is a tertiary healthcare facility located in the capital city of the state, offering health services to the residents of the State and neighbouring States especially Kebbi, Zamfara and Katsina.

Sample description

Prescriptions of patients attending Cardiology Out-Patient Clinics of the hospital made the sample of this study.

Sampling technique

A systematic random sampling was employed. Chronological list of 6,790 encounters copied from the patients' folders over the five years study period was prepared as a sample frame. A sample of 3,395 patients' encounters was drawn from the sample frame.

Study design

This retrospective longitudinal study covered a period of five years between 1st January, 2010 and 31st December, 2014. Hypertensive patients' folders were identified from the MOPD register. The folders were removed from the shelves using a six (6) digit patient's hospital number. A total of 6,790 encounters written within the study period were copied out from the case folders and recorded in data collection forms adopted from WHO guidelines on how to investigate drug use in health facilities **Invalid source specified.**. A chronological list was prepared; a sample of 3,395 encounters was withdrawn using a systematic random sampling, out of which 3316 encounters met the inclusion criteria. Prescriptions obtained were sorted and classified in accordance with WHO Anatomical Therapeutic Chemical/ Defined Daily Dose (ATC/DDD) classification system **Invalid source specified.**. Cost of the prescribed drugs was gotten from National Health Insurance Scheme (NHIS) and the Hospital's drugs price list.

Eligibility criteria

Inclusion criteria

Only prescriptions of patients who were diagnosed of hypertension and prescribed at least one anti-hypertensive drug were included in the study.

Exclusion criteria

All illegible, improperly and incompletely written prescriptions were noted and excluded from the final analysis.

Ethical approval

Written ethical approval (UDUTH/HREC/2014/No. 261) was obtained from the hospital ethical committee before the commencement of the study. Confidentiality and anonymity of the patients' information was maintained during and after the study.

Assessment of Drug use Indicators

The following drug use indicators were assessed according to WHO guidelines on how to investigate drug use in health facilities **Invalid source specified.**.

i. Prescribing indicators: Average number of drugs per encounter, Percentage of drugs prescribed by generic name, Percentage of encounters with an antibiotic prescribed, Percentage of encounters with an injection prescribed, Percentage of drugs prescribed from National Essential Drug List (NEDL).

ii. Facility indicators: Availability of copy of Essential Drug List (EDL), Availability of key drugs.

iii. Complementary indicators: DDD per thousand hypertensive patients, Average drug cost per encounter.

Statistical analysis

The data was sorted, coded and entered into Statistical Package for the Social Sciences (SPSS) for Windows 16.0 and subsequently analyzed. Descriptive statistics (including frequency and percentages, mean and standard deviation), Chi square, Cross-tab and T-test were used in the data analysis.

The formulas for calculating the DDD/ 1000 Patients/Day (DTD) is shown below:

a. DDD/ 1000 Patients/Day (DTD) =

$$\frac{Total\ amount\ of\ drug\ used\ during\ the\ study\ period\ (mg,units)\times 1000}{DDD\ (mg,units)\times No.of\ days\ \times total\ sample\ size}$$

RESULTS

Two thousand and ninety six 2096 (63.2%) prescriptions were written for females (see Table 1). There was significant difference between the proportion of the male and female prescriptions (*p<0.05*). The year 2014 had the highest prescriptions written for females 453 (65.2). The mean and range of ages of the patients for all the years were 51.68±11.39 and 18 to 95 years

respectively. Diabetes was the highest comorbidity encountered 818 (24.7) (see Table 1).

The number of drugs per prescription was between 1 and 5, with mean value of 2.2, 2.2, 2.4, 2.2 and 2.2 drugs in 2010, 2011, 2012, 2013 and 2014 respectively, while 2.2 is the mean value for all the years. There was significant difference between the mean number of drugs prescribed in 2010 and 2012 (*p<0.05*). The year 2012 has the highest mean number of drugs per prescription, while two drugs per prescription were the commonest, five drugs per prescription was the least. Key drugs were generally available.

Mean prescriptions for injections and antibiotics over the years were 0.7% and 4.9% respectively. The year 2013 had the highest percentage of encounter with antibiotics (7.1), while 2014 had the highest percentage of encounter with injections (see Table 2). An anti-malarial injection (α -β-arteether) accounted for most of the injections encountered; penicillins were the most commonly encountered antibiotics.

Percentages of drugs written in generic name encountered were 80.2, 73.1, 74.2, 72.2 and 74.3 in 2010, 2011, 2012, 2013 and 2014 respectively, while 74.7 was the mean percentage of drugs written in generic name over the years. The year 2013 had the least (72.2%) percentage of drugs written in generic name despite having larger sample size than 2010, 2011, and 2012 (see Table 2).

A mean percent of 72.2 of the anti-hypertensive drugs prescribed over the five years were in the Nigerian National Essential Drugs List (NEDL). The year 2011 had the highest percent (78.7) of anti-hypertensives prescribed from NEDL.

Mean drug cost per prescription was ₦ 2991.3 for all the years (see Table 2). There was significant difference between the mean drug cost per prescription across the years (*p<0.05*). The year 2014 had the highest average cost of anti-hypertensives per prescription ₦ 3021.1.

Aspirin was the most commonly prescribed non anti-hypertensive drug, followed by analgesics/antipyretics, anti-diabetics, antimalarials, multi-vitamins and antibiotics.

The DDD/1000 patients/ day were 293.9, 259.0, 300.3, 240.3 and 240.3 in 2010, 2011, 2012, 2013 and 2014 respectively. The mean and total DDD/1000 patients/ day for all the years were 270 and 1350.0 respectively.

Five classes of anti-hypertensive drugs fell within DU90% segment while 2 classes fell beyond DU90%. Outpatient utilization of anti-antihypertensive drugs within DU90% and total

DU90% over the years were 1215.7 and 1350.0 DDDs/1000 patients /day respectively. Amlodipine (C08CA01) 281.8 DDDs/1000 hypertensive patients /day was the most consumed anti-hypertensive drug over the years with highest consumption in 2012.

The trend of anti-hypertensive consumption shows a relatively normal pattern over the years (see Figure 1).

CCBs (C08CA) and ACEIs (C09AA), 34.3% and 18.9% respectively, were the most utilized therapeutic subgroups, followed by thiazide diuretics (14.5%) (C03AA). Beta-blockers (C07A) (3.5%) were second to the least group utilized in this study. ARBs (CO9CA) (3.0%) were the least group utilized. Amiloride+Hydroclorthiazide (*Moduretic®*) was the most utilized FDC, while Amlodipine+Valsartan+HCT (*Exforge HCT®*) was the least utilized FDC (see Table 3.4). There were copies of NEDL; about 100% availability of drugs.

Table 1: Patients' Demographic Data

Patients' Characteristics	N=3316					
	Year of prescription					
	2010	**2011**	**2012**	**2013**	**2014**	**Total across the years**
Mean age of the patients (yrs)	51.58±10.64	51.76±10.27	51.12 ±10.98	52.41±11.80	51.48±12.89	51.68±11.39
Gender n (%)						
Male	249 (41.2)	238 (35.4)	238 (36.4)	253 (36.7)	242 (34.8)	1220 (36.8)*
Female	356 (58.8)	435 (64.6)	415 (63.6)	437 (63.3)	453 (65.2)	2096 (63.2)*
Comorbidities n (%)						
Diabetes	127 (21.0)	150 (22.3)	161 (24.7)	214 (31.0)	166 (23.9)	818 (24.7)
Heart failure	43 (7.1)	44 (6.5)	66 (10.1)	107 (15.5)	138 (19.9)	398 (12.0)
Others	12 (2.0)	15 (2.2)	2 (0.3)	6 (0.9)	0 (0)	35 (1.1)

There is significance difference between the proportion of encounters written for male and female at (*p<0.05*)**;** no significant difference between the mean age (*p<0.05*); Diabetes was the highest comorbidity encountered.

Table 2: Drug use indicators data

Core indicators	N=3316					
	Year of prescription					
	2010	**2011**	**2012**	**2013**	**2014**	**All years**
Prescribing Indicators						
Average number of drugs prescribed (n)	2.2*	2.2	2.4*	2.2	2.2	2.2
Drugs prescribed by generics (%)	80.2*	73.1	74.2	72.2*	74.3	74.7
Encounters with antibiotics (%)	4.1	3.1	4.4	7.1*	5.9	4.9
Encounters with injections (%)	0.3	0.1	0.9	0.9	1.2	0.7
Drugs prescribed from National Essential Drug List (%)	75.7	78.7*	77.2	68.1	61.4*	72.2
Complementary indicators						
Average drug cost per Prescription (₦)	2169.1*	2830.4*	3669.8*	3196.9*	3021.1*	2991.3*
Facility indicators *Availability of EDL* *Key drugs availability (%)*	Yes 100					

*There was significant difference between the mean number of drugs prescribed in 2010 and 2012 (*p<0.05*); 2010 has the highest % of drugs prescribed by generic names with 2013 having the least generic prescriptions; there was significant difference between the mean drug cost per prescription (₦) across the years (*p<0.05*). EDL=essential drug list.
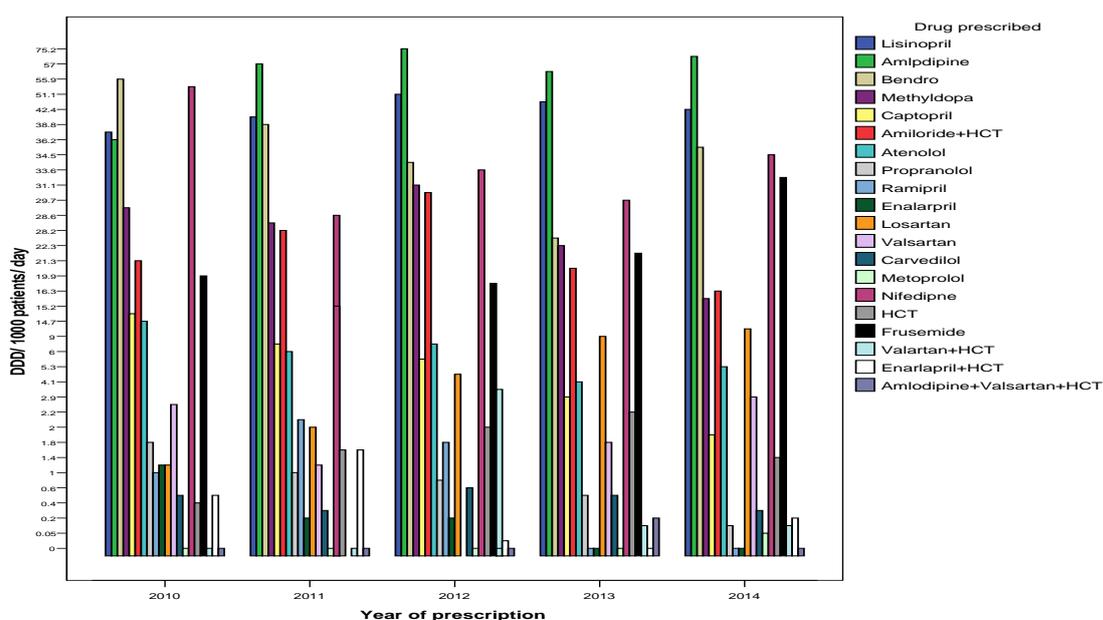

Figure 1: Trend of anti-hypertensive drugs (C02) utilization over five years (2010-2014). The figure shows normal trend in anti-hypertensive drugs use

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Table 3: Utilization of anti-hypertensives (C02) expressed as percentage and number of DDD/1000 patients/day (2010-2014)

No.	ATC Code	Generic name	2010	2011	2012	2013	2014	DDD/1000 Patients/Day	Percentage (%)
1	C08CA01	Amlodipine	36.2	57.0	75.2*	56.2	57.2	281.8**	20.9*
2	C09AA03	Lisinopril	38.1	39.3	51.1	44.9	42.4	215.8	16.0
3	C03AA01	Bendroflumethiazide	55.9	38.8	34.1	23.7	35.0	187.5	13.9
4	C08CA05	Nifedipine	54.6	28.6	33.6	29.7	34.5	181.0	13.4
5	C02AB01	Methyldopa	28.9	28.5	31.1	22.3	15.7	126.5	9.4
6	C03EA01	Amiloride+HCT	21.3	28.2	30.5	20.6	16.3	116.9	8.7
7	C03CA01	Furosemide	19.9	15.2	18.1	21.6	31.7	106.5	7.9
	Within DU90% Segment								90.1
8	C07AB03	Atenolol	14.7	6.0	7.1	4.1	5.3	37.2	2.8
9	C09AA01	Captopril	15.1	7.1	5.4	2.9	1.9	32.4	2.4
10	C09CA01	Losartan	1.3	2.0	4.8	9.0	11.3	28.4	2.1
11	C09CA03	Valsartan	2.4	1.3	3.9	1.8	2.9	12.3	0.9
12	C03AA03	Hydrochlorothiazide	0.4	1.7	2.0	2.2	1.4	7.7	0.6
13	C09AA05	Ramipril	1.0	2.1	1.8	-	-	4.9	0.4
14	C07AA05	Propranolol	1.8	1.0	0.8	0.5	0.1	4.2	0.3
15	C07AG02	Carvedilol	0.5	0.3	0.6	0.5	0.3	2.2	0.2
16	C07AB52	Metoprolol	-	-	-	-	0.05	2.4	0.2
17	C09AA02	Enalapril	1.3	0.2	0.2	-	-	1.7	0.1
18	C09BA02	Enalapril+HCT	0.5	1.7	0.004	-	0.2	0.05	0.0
19	C09DA03	Valsartan+HCT	-	-	-	0.1	0.1	0.2	0.0
20	C09DX01	Amlodipine+Valsartan+HCT	-	-	-	0.2	0.1	0.2	0.0
		Total	293.9	259.0	300.3*	240.3	256.5	1350.0	
	DU90% Segment							**Beyond**	9.9
	DU90% + Beyond DU90%							**Total= within**	100

Amlodipine was the most consumed drug over the years with the highest consumption in 2012; 7 drugs made up the DU90 segment (71.4% from NEDL). HCT= hydrochlorothiazide

DISCUSSION

The mean age of the patients in this study was as within the middle age, a finding that is consistent with many literatures that show hypertension is mostly a disease of the middle age and the elderly people [20-22]. There were more females' prescriptions than males, similar to studies conducted in some other geopolitical zones in Nigeria **Invalid source specified.**, and different from a similar study conducted in south eastern Nigeria **Invalid source specified.**. This difference may be due to the fact that male patients mostly have longer visit interval (up to four months) as observed during the data collection, possibly because of their tight schedules compared to females, hence more prescriptions for females. It may also be due to poor attitude of males not accessing health care early and not keeping clinic follow-up appointment. The highest number of

female prescriptions in 2014 than 2013, 2012, 2011 and 2010 was due to the largest sample size used. Diabetes was the highest comorbidity encountered in this study as it was in many other studies [25-26]. The mean number of drugs prescribed (2.2) for all the years was an indication that poly pharmacy is less likely in the facility considering the recommendations of JNC 8 hypertension treatment algorism **Invalid source specified.** .

Percentage of drugs written by generic name was high for all the years, even higher than that of a study conducted in south western Nigeria which shows (56.9%) **Invalid source specified.**. Though hundred percent generic prescribing is advocated as generic drugs are identical or within an acceptable bioequivalent range to their brand-name counterpart with respect to pharmacokinetic and pharmacodynamics properties **Invalid source specified.**, this relatively shows a less

Table 4: Utilization of anti-hypertensives (C02) by therapeutic subgroups and fixed dose combinations (2010-2014)

ATC Code	Therapeutic subgroup	Drugs Prescribed	Percentage (%)	DDD/1000 Hypertensive Patients/Day
C09AA	ACEIs	Lisinopril	16.0	215.8
		Captopril	2.4	32.4
		Enalapril	0.1	1.7
		Ramipril	0.4	4.9
		Total	**18.9**	**254.8**
C08CA	CCBs	Amlodipine	20.9	281.8
		Nifedipine	13.4	181.0
		Total	**34.3****	**462.8****
C03AA	Thiazide Diuretics	Bendroflumethiazide	13.9	187.5
		Hydrochlorothiazide	0.6	7.7
		Total	**14.5**	**195.2**
C03CA01	Loop DU	Furosemide	7.9	106.5
		Total	**7.9**	**106.5**
C02AB	Centrally acting α AA	Methyldopa	9.4	126.5
		Total	**9.4**	**126.5**
C07A	β-Blockers	Atenolol	2.8	37.2
		Carvedilol	0.2	2.2
		Propranolol	0.3	4.2
		Metoprolol	0.2	2.4
		Total	**3.5**	**46**
C09CA	ARBs	Losartan	2.1	28.4
		Valsartan	0.9	12.3
		Total	**3.0***	**40.7***
Fixed Dose Combinations (FDC)				
C03EA	PSD+TDU FDC	Amiloride+HCT	8.7*	116.9*
C09BA	ACEIs+TDU FDC	Enalapril/HTC	0.0	0.05
C09DA	ARBs+TDU FDC	Valsartan/HTC	0.0	0.2
C09DX01	CCBs+ARBs+TDU FDC	Amlodipine+Valsartan+HCT	0.0	0.2
		Total	**8.7**	**117.4**

CCBs (C08CA) were the most utilized therapeutic subgroup, and Amlodipine (C08CA01) is the agent most utilized in the group; ARBs (CO9CA) was the least group utilized. Amiloride+HCT (*Moduretic*®) was the most utilized FDC, while Enalapril/HTC (Thiapril®) was the least utilized FDC.

likelihood for the prescribers to prescribe anti-hypertensives with trade name in this facility. The year 2013 had the least drugs written with generic name despite having larger sample size than other years. This may be due to the increased influence of many companies marketing their different anti-hypertensive brands in the year as well as difference in prescribers' behaviour.

A high percentage of the prescribed anti-hypertensive drugs over the years were in the NEDL, even though it was less than values from other regions [28-29], yet implying a relatively good adherence to national guidelines. The year 2012 has the highest average cost per prescription. The result shows high average cost of anti-hypertensives per patient per prescription. There were significant differences between the mean costs across the years ($p<0.05$). Patients with low socioeconomic status may fall victims of poor management and outcome of their hypertensive care. The high frequency of aspirin 75mg, analgesics/antipyretics, anti-diabetics, antimalarials, multi-vitamins and antibiotics prescriptions of no anti-hypertensive drugs could be due to the fact that aspirin 75mg has been used as cardio-protective to decrease the risk of further cardiovascular events in patients with hypertension **Invalid source specified.**; most patients present with pains; diabetes is the major comorbidity encountered, the region is malaria endemic; patients present with loss of appetite and infections especially in those with diabetes.

The year 2012 had the highest number of DDD/1000 patients/ day, which implied the highest anti-hypertensive consumption.

Five classes of anti-hypertensive drugs fell within DU90% segment while 2 classes fell beyond DU90%. The appearance of loop diuretic (furosemide) and α-adrenergic blocker (methyldopa) within DU90% is a deviation from the JNC recommendation **Invalid source specified.**. However, methyldopa is enlisted in the NEDL **Invalid source specified.**. Amlodipine (C08CA01) 281.8 DDDs/1000 hypertensive patients /day was the most consumed anti-hypertensive drug over the years with highest consumption in 2012. CCBs (C08CA) either singly or in combination with other classes of antihypertensive drugs were the most utilized therapeutic subgroup, followed by ACEIs (C09AA). Amlodipine (C08CA01) and Lisinopril (C09AA03) were the agents most utilized in CCBs and ACEIs respectively. This is in agreement with some studies in Nigeria [22-23], while contrary to studies in other regions of the country and another

study in Malaysia where diuretics and β-blockers were found to be the most utilized therapeutic subgroup [16,24]. The high use of CCBs and ACEIs in this study agrees with the recommendations of the JNC 8 **Invalid source specified.**. Although the general recommendation by JNC 7&8 and 2010 Institute for Clinical Systems Improvement (ICSI) is that thiazide diuretics (C03AA), which were the third leading prescribed anti-hypertensives in this study, be the initial drug in the absence of compelling indications [18,25] physicians appeared more cognizant of the long term cardio- and renovascular benefits inherent in using ACEIs in a high cardiovascular risk group such as black hypertensive **Invalid source specified.**.

Alpha (α) adrenergic blockers (methyldopa) enjoys little utilization and does not have much relevance in JNC 7 & 8. It is generally neither an initial drug nor one of the drug class recommendations for compelling indications based on various clinical data. Their long-term effects on morbidity and mortality do not seem superior to placebo. They should not be used as monotherapy for treating hypertension due to an increased risk of heart failure and contraindicated in patients with autonomic dysfunction **Invalid source specified.**.

ARBs (CO9CA) were the least group utilized in this study as reported by other studies **Invalid source specified.** and this may be due to their relative high cost compared to other therapeutic group. Amiloride+HCT (*Moduretic®*) was the most utilized FDC, while Amlodipine+Valsartan+HCT (*Exforge HCT®*) was the least utilized FDC (see Table 4.4). This may also be due to the low and high cost of *Moduretic®* and *Exforge HCT®* respectively.

RECOMMENDATIONS

Other studies should be carried out in this facility to determine the association between the utilization pattern and clinical and economic outcomes in the hypertensive patients. Governments at all levels should introduce hypertensive care program to subsidise the direct cost of anti-hypertensive drugs.

CONCLUSIONS

There was no poly pharmacy in the overall utilization of anti-hypertensives over the study period. Prescribers were less likely to prescribe anti-hypertensives by trade names as most of the drugs were prescribed by generic names. Most of the drugs

used were in the NEDL. Amlodipine (C08CA01) was the most utilized drug over the five (5) years study period. This study showed that there was rationality in the use of antihypertensive drugs in this facility. However, targeted education of the prescribers and dissemination of treatment guideline could facilitate even better rational use of antihypertensive drugs.

CONFLICT OF INTEREST

The authors declare that there are no conflict of interest in the conduct and reporting of this work

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