Original Research

Evaluation of drug therapy problems among hypertensive patients in a Nigerian secondary healthcare centre

Kosisochi Chinwendu Amorha [1]*, Chinyere Euphemia Anyanwu [2], Ebere Emilia Ayogu [1], Deborah Oyine Aluh [1]

[1] Department of Clinical Pharmacy and Pharmacy Management, Faculty of Pharmaceutical Sciences, University of Nigeria Nsukka, PMB 410001, Enugu State

[2] Department of Pharmacy, General Hospital, Gbagada, Lagos State

* **Corresponding Author:** Dr. Kosisochi Chinwendu Amorha; Phone Number: +234-8038539349;
Email: kosisochi.amorha@unn.edu.ng

Abstract

Background: High blood pressure (HBP) is responsible for over 7.1 million deaths annually. Drug therapy problems (DTPs) interfere with the therapeutic control of HBP. This study aimed to evaluate drug therapy problems among hypertensive patients in a secondary healthcare centre in Lagos State.

Methods: This was a retrospective study carried out in a secondary health facility in Lagos State, Nigeria from 1st January 2017 through 31st December 2018. Data were extracted from the patients' folders using the Pharmaceutical Care Network Europe (PCNE) Classification tool Version 7.0, DRP-PCNE V 7.0 and analyzed with the IBM SPSS Version 25.0.

Results: 250 patient folders were assessed. Drug therapy problems were found in 181 of the 245 folders included in the study (73.9%). The mean ± SD age of patients was 58.65 ± 12.35 years. The mean ± SD number of drug therapy problems per patient was 3.18 ± 1.17. Treatment effectiveness was the most frequently encountered category of drug therapy problems (96.6%, n = 177). There was a moderate positive correlation between the total number of drug therapy problems encountered and the number of drugs taken by the patients (r = 0.546, P < 0.001). The number of drugs taken by a patient was a significant predictor of the number of drug therapy problems encountered (F [2, 134] = 37.205, P < 0.001).

Conclusion: There was a high prevalence of drug therapy problems among hypertensive patients. Patients with co-morbidities and those taking multiple medications should be monitored for potential or manifest drug therapy problems.

Keywords: Drug therapy problems, Hypertension, Drug interactions, Nigeria

INTRODUCTION

The global prevalence of hypertension is expected to rise from 26.4% in 2000 to 29.2% in 2025. [1,2] This predicted increase is attributed to the increasing incidence of hypertension in Low-and-Middle-Income Countries (LMIC). Globally, hypertension is responsible for greater than 10% of all premature deaths. Being a risk factor for cerebrovascular, cardiovascular and renal diseases, hypertension poses an important public health problem. [3,4]

Despite the recent advances in the diagnosis and treatment of hypertension, it remains an undertreated disease. The rising number of anti-hypertensive drugs and more complex drug regimens have led to an increased number of side effects and adverse drug reactions. Most patients with hypertension suffer from other co-morbidities that require combining anti-hypertensive agents with other medications. [4] Co-morbidities like diabetes and obesity are associated with uncontrolled hypertension. [4] Many patients with hypertension will require more than one anti-hypertensive agent to achieve optimal blood pressure control. Medication therapy with multiple drugs can lead to drug therapy problems (DTPs), such as adverse drug reactions and drug-drug interactions. [5]

The Pharmaceutical Care Network Europe (PCNE) classification Version 6.2, defined drug-related problem as 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes. [6] DTPs can be classified into seven: need additional drug therapy, unnecessary drug therapy, ineffective drug, too low or too high dosage, adverse drug reactions, and non-compliance. [7] DTPs have posed an important barrier to the therapeutic control of high blood pressure. Timely identification of the DTPs can improve the outcomes of therapy. Studies on DTPs using the PCNE classification system have been carried out in Malaysia. These include a study on patients with co-morbid type II diabetes mellitus and hypertension and a study on patients with diabetes, hypertension or hyperlipidemia. [8,9] Other international studies have used the same instrument, but none of them has focused on DTPs in patients with hypertension. [10,11] A study by Ganiyu *et al.*, (2014) on drug therapy problems among diabetics and hypertensives revealed a high incidence of drug therapy problems in the study participants. [12] Unnecessary drug therapy, wrong drug therapy, need for additional drug therapy, non-adherence to drug therapy, and drug interactions were majorly spotted in descending order of occurrence. [12]

In Nigeria, there is a paucity of literature on DTPs and contributing factors in hypertensive patients. Identifying risk factors for DTPs will create opportunities for designing effective interventions to address problems related to drug therapy, thereby maximizing patient care. The objective of this study was to identify drug therapy problems and determine their predictors among hypertensive patients in a secondary healthcare centre in Lagos State.

METHODS

Study design/setting

This was a retrospective study conducted in a secondary health facility in Lagos State, Nigeria, to evaluate drug therapy problems among hypertensive patients from 1st January 2017 through 31st December 2018.

Sample size and selection

To calculate the sample size, the prevalence of DTPs among hypertensive patients of 80.7% was used from a previous study. [13] The sample size for the study was determined using Raosoft® sample size calculator. [14] At a 95% confidence interval, and the degree of accuracy set to 0.05, a sample size of 245 was estimated. Two hundred and fifty (250) folders were randomly selected from all the available folders.

Eligibility criteria

(i) Diagnosis of hypertension and being managed in the secondary healthcare centre;
(ii) Patients aged ≥ 18 years;

Data collection/study instrument

Data were extracted from the patients' folders using the Pharmaceutical Care Network Europe (PCNE) Classification tool Version 7.0, DRP-PCNE V 7.0. [15] The DRP-PCNE V 7.0 has three primary domains for problems, eight primary domains for causes and five primary domains for interventions. It also has a section called "Acceptance of the Intervention Proposals" which has three domains.

Data analysis

Data were analyzed using the IBM SPSS Version 25.0. Descriptive statistics, such as mean ± standard deviation, were used to summarize data. Linear regression test was used to determine the predictors of DTPs with statistical significance set as $P < 0.05$. Potential drug interactions were assessed using Epocrates® Online MultiCheck® drug interaction checker.

Ethical approval

Ethical approval with assigned number ADM/DCST/HREC/APP/2761 was obtained from the Health Research Ethics Committee of the Hospital. The confidentiality of data was maintained all through the study period.

RESULTS

A total of 250 folders were evaluated; 5 folders were not included due to incomplete information. Drug therapy problems were reported in 181 of the 245 folders included in the study (73.9%). The mean ± SD age of patients was 58.65 ± 12.35 years. The mean ± SD number of drugs taken by the patients was 5.69 ± 1.79. The mean ± SD number of DTPs per patient was 3.18 ± 1.17.

Socio-demographic and clinical characteristics of patients

The patients were mostly females (68.5%, n = 124) and were 65 years old and below (70.2%, n = 127). The most common co-morbidity was Diabetes mellitus (17.1%, n = 31). The drug therapy problems were mostly manifest drug therapy problems (95.6%, n = 173) and were most frequently discovered by the pharmacist (73.5%, n = 133). The demographic data and clinical characteristics of the patients are shown in Table 1.

Table 1: Socio-demographic and clinical characteristics of patients, N = 181

Variable	n (%)
Gender	
Male	57 (31.5)
Female	124 (68.5)
Age	
Elderly (>65 years)	54 (29.8)
Non-Elderly (≤65 years)	127 (70.2)
Co-morbidities	
None	96 (53.0)
Diabetes mellitus	31 (17.1)
Peptic ulcer disease	14 (7.7)
Stroke	7 (3.9)
Heart failure	12 (6.6)
Chronic Kidney Disease	2 (1.1)
Hyperlipidemia	7 (3.9)
Asthma	4 (2.2)
Osteoarthritis	8 (4.4)
Problem discovered by	
Pharmacist	133 (73.5)
Physician	48 (26.5)
Type of Problem	
Potential	8 (4.4)
Manifest	173 (95.6)

Drugs involved in drug therapy problems

Among the hypertensives, the most frequently implicated drugs causing drug therapy problems were Diuretics (41 %, n = 55) and Beta-blockers (19.4%, n = 26). Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (25.4%, n = 34), Anti-thrombotics (23.9%, n = 32) and Aspirin (23.9%, n = 32) were the most commonly implicated drugs among the additional drugs used by the patients. The mean number of DTPs per patient was 3.18 ± 1.168. The drugs involved in DTPs are shown in Table 2.

Table 2: Drugs involved in drug therapy problems, N = 134

Drug Class	n (%)
Anti-hypertensives	
ACEI	12 (9.0)
ARB	23 (17.2)
BB	26 (19.4)
CCB	10 (7.5)
Diuretics	55 (41.0)
CAA	8 (6.0)
Additional drugs	
PPIs	9 (6.7)
NSAIDs	34 (25.4)
Anti -thrombotics	32 (23.9)
Aspirin	32 (23.9)
Biguanides	12 (9.0)
Anticonvulsants	11 (8.2)
Corticosteroids	2 (1.5)
Cardiac glycosides	2 (1.5)

ACEI – Angiotensin-Converting Enzyme Inhibitors; CCB – Calcium Channel Blockers, ARB –Angiotensin Receptor Blocker, BB – Beta Blocker, CAA – Centrally Acting Antihypertensive, PPIs – Proton Pump Inhibitors, NSAIDs – Non-steroidal Anti-Inflammatory Drugs

Drug-related problems in hypertensive patients according to PCNE 7.0 Classification

The most common type of treatment effectiveness problem was 'Effect of drug not optimal' (92.3%, n = 167). Adverse events were reported in eight patients (4.4%). The most commonly encountered drug selection problem was 'Inappropriate drug according to guideline/formulary' (30.9%, n = 56). Dose selection problems were not very common, 'Dose too high' was found in six folders (3.3%). Concerning treatment duration, 'Duration too long' was most frequent (49.7%, n = 90). Drugs were under-administered in 48 patients (26.5%). Among the patient-related DTPs, 'Patient unable to use the drug as directed' was the most commonly encountered drug therapy problem (18.8%, n = 34), Table 3.

Table 3: Drug therapy problems in hypertensive patients according to PCNE 7.0 Classification

Code	Problem	n (%)
P1	**Treatment effectiveness**	**177 (96.6)**
	No effect of drug treatment	6 (3.3)
	Effect of drug treatment not optimal	167 (92.3)
	Unnecessary drug treatment	2 (1.1)
	Untreated indication	2 (1.1)
P2	**Adverse event**	**8 (4.4)**
P3	**Others**	**2 (1.1)**
	Unclear problem/complaint.	2 (1.1)
C1	**Drug Selection**	**109 (60.2)**
	Inappropriate drug according to guidelines/formulary	56(30.9)
	Inappropräte drug (within guidelines but otherwise contraindicated)	6 (3.3)
	Inappropriate combination of drugs, or drugs and food	10 (5.5)
	Inappropriate duplication of the therapeutic group or active ingredient	7 (3.9)
	Synergetic or preventive drug required and not given	28 (15.5)
	New indication for drug treatment presented	2 (1.1)
C2	**Drug form**	**2 (1.1)**
	Inappropriate drug form	2 (1.1)
C3	**Dose selection**	**9 (5.0)**
	Drug dose too low	2 (1.1)
	Drug dose too high	6 (3.3)
	Dosage regimen not frequent enough	1 (0.6)
C4	**Treatment duration**	**96 (53.0)**
	Duration too short	6 (3.3)
	Duration too long	90 (49.7)
C5	**Dispensing**	**4 (2.2)**
	Prescribing error (necessary information missing)	4 (2.2)
C6	**Drug use process**	**66(36.5)**
	Inappropriate dosing interval	2 (1.1)
	Drug under - administered	48 (26.5)
	Drug over - administered	2 (1.1)
	Drug not administered at all	12 (6.6)
	Wrong drug administered	2 (1.1)
C7	**Patient - related**	**106 (58.6)**
	Patient forgets to use drugs	4 (2.2)
	Patient uses unnecessary drug	9 (5.0)
	Patient takes food that interacts	3 (1.7)
	Patient uses drug in a wrong way	30 (16.6)
	Patient cannot afford drug	26 (14.4)
	Patient unable to use drug as directed	34 (18.8)

Correlation between patient characteristics and the number of drug therapy problems encountered

There were significant weak positive correlations between the total number of DTPs encountered in a patient and the presence of co-morbidity, the type of co-morbidity, type of anti-hypertensive taken by the patient, the type of DTP, the type of additional drugs taken by the patient. There was a moderate positive correlation between the total number of drug therapy problems encountered and the number of drugs taken by the patients (r = 0.546, P < 0.001). There was a weak positive correlation between the number of drugs taken by a patient and the presence of co-morbidity (r = 0.450, P < 0.001). Details of correlation among variables are shown in Table 4.

Table 4: Correlation between patient characteristics and the number of drug therapy problems encountered

		Sum DTP	Co-morbidity	Type of Anti hypertensive	Problem discovered by	Type of problem	Type of co- morbidity	Type of Add. drugs	Number of drugs
SumDTP	r	0.381	0.322	0.318	0.274	0.321	0.418	0.546	
	P	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	< 0.001*	
Type of Co-morbidity	N	177	177	177	177	177	177	177	
	r	1	0.084	0.057	0.263	0.653	0.072	0.450	
	P		0.261	0.449	< 0.001*	< 0.001*	.338	< 0.001*	
	N		181	181	181	181	181	181	
Type of Anti-hypertensive	r		1	0.141	0.194	0.092	0.552	0.305	
	P			0.059	0.009*	0.217	< 0.001*	< 0.001*	
	N			181	181	181	181	181	
Problem discovered by	r			1	0.118	0.000	0.136	0.208	
	P				0.113	0.995	0.069	0.005*	
	N				181	181	181	181	
Type of problem	r				1	0.189	0.248	0.185	
	P					0.011*	0.001*	0.013*	
Type of co-morbidity	N					181	181	181	
	r					1	.033	0.263	
	P						.657	< 0.001*	
	N						181	181	
Type of Additional drug	r						1	0.327	
	P							< 0.001*	
	N						181	181	

*P < 0.05; r = Pearson Correlation; Add. = Additional

Predictors of drug therapy problems

A linear regression established that the number of drugs taken by a patient could significantly predict the number of DTPs experienced by patients $F_{(2, 134)} = 37.205$, $P < 0.001$.

The number of drugs taken by the patient explained 30 % of the variability in the predicted drug therapy problems. The regression equation was: predicted DTPs = 1.381 + 0.365 (Number of drugs taken by the patient) + (-0.004) × (Age). The predictors of the number of DTPs are shown in Table 5.

Table 5: Predictors of drug therapy problems

Model	Unstandardized Coefficients		Standardized Coefficients	t	P	95% Confidence Interval	
	B	Std. Error	Beta			Lower Bound	Upper Bound
(Constant)	1.381	0.413		3.346	0.001	0.566	2.195
Age	-0.004	0.006	-0.044	-0.681	0.497	-0.017	0.008
Number of drugs	0.365	0.042	0.552	8.604	< 0.001	0.281	0.449

a. Dependent Variable: SumDTP
SumDTP: Total number of drug therapy encountered in a patient

DISCUSSION

Studies about DTPs in hypertensive patients are limited, especially in Low- and Middle-Income countries (LMICs). DTPs were found in 181 of the 245 folders included in the study, which represents about three-quarters of the sampled patient folders. The mean ± SD number of drug therapy problems per patient was 3.18 ± 1.17, which is much higher than previous studies on DTPs in Nigeria, Southern Ethiopia, Malaysia and Eastern Ethiopia. [16 – 19] The mean number of DTPs is, however, lower than the value obtained (11.2 per patient) among ambulatory patients in Jordan. [20] The variation in the number of drug therapy studies across studies may be attributed to the differences in the classification system study designs and settings. Notwithstanding the variations, interventions are necessary to reduce the number of DTPs. Despite the accessibility of effective medical therapy for hypertension, many hypertensive patients are undertreated, globally. This might have stemmed from DTPs such as non-adherence, improper drug selection, and drug interactions. DTPs in medication therapy for hypertensive patients may prevent or delay patients from achieving optimal therapeutic outcomes, increase hospital admission rates and lead to extended stays in the hospital. These, in turn, lead to poor health outcomes, lower quality of life, increased healthcare cost. [13] In this study, there were more female than male patients. The prevalence of hypertension is more in males than females before the age of 50 years, but with increasing age, the prevalence increases and becomes higher in women. [21 – 23] Mechanisms that have been identified as responsible for gender differences in hypertension include the kidney's role as shown by transplant studies from men into women and vice versa, the role that *relaxin* plays in women, and the role that developmental programming (changes in utero or early in life) plays in mediating hypertension. [24 – 26] The average age of the patients in this study was 58 years, and about one-third of them were above 65 years old. Older adults account for the majority of hypertension-associated morbidity and mortality – because of the high prevalence of hypertension among the elderly. [27] Key mechanisms associated with ageing such as inflammation, oxidative stress, and endothelial dysfunction have been linked to the development of hypertension. [28 – 30] The most common co-morbidity among the patients was diabetes mellitus. This is consistent with a similar study among hypertensive patients in Malaysia. [18] The co-morbid presence of hypertension and diabetes mellitus is high in the general population. [31] Hypertension is significantly higher in diabetics, while non-diabetic individuals with hypertension are 2.5 times more likely to develop diabetes mellitus within five years than individuals without hypertension. [32] Hypertension and diabetes mellitus co-morbidity increases the risk of macrovascular complications and facilitates the development and progression of diabetic nephropathy and retinopathy. [31] Early and aggressive anti-hypertensive treatment is thus mandatory in diabetic and prediabetic groups. Since some anti-hypertensive agents such as Beta-blockers have been associated with reduced sensitivity to insulin and other deleterious effects, the metabolic effects of antihypertensive medications should be considered when choosing the proper drug regimens for patients with co-morbid hypertension and diabetes. [33] Diuretics were the most commonly prescribed anti-hypertensives implicated in DTPs while non-steroidal anti-inflammatory drugs (NSAIDs) were the most commonly encountered additional drugs. Diuretics are a popular, heterogeneous class of antihypertensives currently recommended as a first-line option in the treatment of hypertension. [34] NSAIDs, by inhibition of prostaglandins and bradykinin, cause vasoconstriction of the afferent renal arteriole and decrease the ability of the kidney to regulate glomerular blood flow. The administration of an NSAID plus diuretic or ACEI or ARB may decrease the hypotensive effect of the anti-hypertensive agent and may lead to acute kidney failure. [35] Aspirin and antithrombotics were the second most implicated additional drugs in the DTPs encountered. This corresponds with findings from other similar studies among hypertensive patients with co-morbidities. [9, 18] The most common DTP encountered was 'Effect of drug

therapy not optimal'. This result is in agreement with studies conducted in Jordan, Eastern Ethiopia and Southern Ethiopia where patients being not in optimal therapy was the most commonly observed DTP. [17, 19, 20] It is, however, contrary to other studies on DTPs among patients with chronic diseases where 'use of unnecessary drugs' was a common type. [19, 36, 37] The use of unnecessary drugs was encountered only twice. The most common patient-related DTP was non-adherence resulting from patients taking their drugs in the wrong way. This could be due to insufficient patient education or awareness of the disease condition, inefficient patient counselling process by pharmacists dispensing medications, a financial constraint on the part of the patients.

There were associations between the number of DTPs encountered and the type and number of co-morbidities present in a patient which is in concordance with findings from other similar studies. [20, 38] This can be explained by the fact that the medications used in the management of the co-morbidities (e.g. diuretics, digoxin, insulin, and oral antidiabetics) are risk factors for DTPs among patients.

A linear regression established that the number of drugs taken by a patient could significantly predict the number of drug therapy problems. This concurs with an Ethiopian study where the number of comorbidities and drugs taken significantly predicted the occurrence of a DTP. [39] It is also in concordance with several other studies where the number of drugs

taken by the patient significantly predicted the occurrence of drug therapy problems. [13, 40, 41]

An increased number of drugs increases the pill burden for the patient and increases the likelihood of non-adherence, increased toxic effects, and drug interactions. Therefore, patients with co-morbidities and patients taking a large number of medications should be carefully monitored for DTPs to avoid deleterious effects. To identify and solve the problems of drug interactions, pharmacy departments need to utilize drug interaction software. Patients should be advised to adopt effective reminder strategies such as the use of mobile alarm and alarm clock since forgetfulness is a commonly cited reason for non-adherence. Financial access was documented as one of the barriers to adherence. Physicians should consider the finances of their patients in prescribing anti-hypertensive medications, and generic prescribing should be encouraged to improve adherence.

LIMITATIONS OF THE STUDY

Some limitations are acknowledged in the current study. This study utilized the retrospective study design, and thus relied solely on information available in the patient medical records and data from laboratory results. Since one secondary healthcare facility was used, the assessment may not have been comprehensive enough and should be generalized cautiously. Furthermore, actual interventions were not carried out, and the acceptance rate of other healthcare providers to these interventions

were not assessed. In addition to orthodox medications, many patients in African settings often resort to alternative therapy involving the use of traditional remedies to manage their ailments which may also contribute to DTPs. [42] These types of remedies are not readily documented in the patients' case notes.

CONCLUSION

Drug therapy problems were reported in about three-quarters of the assessed patient folders. Treatment effectiveness was the most frequently encountered category of DTPs. 'The effect of drug treatment not being optimal', 'the duration of treatment being too long' and 'inappropriate combination of drugs, or drugs and food' were the most common causes of DTPs. The most commonly implicated drugs causing DTPs were Diuretics and Beta-Blockers. There were significant positive correlations between the total number of DTPs encountered in a patient and the presence of co-morbidity, the type of co-morbidity, type of anti-hypertensive taken by the patient, the number of drugs patient was taking, the type of DTP, the type of additional drugs taken by the patient. The number of drugs taken by a patient was a significant predictor of the number of DTPs encountered.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008.

International Journal of Cancer. 127(12): 28932917. 2. Pessinaba S, Mbaye A, Yabeta G-À-D, Kane A, Ndao CT, Ndiaye MB, Harouna H, Bodian M, Diao M, Mbaye MN, Diagne MN, Diack B, Kane M, Niang K, Mathieu JS, Kane A (2013). Prevalence and determinants of hypertension and associated cardiovascular risk factors: Data from a population-based, cross-sectional survey in Saint Louis, Senegal. Cardiovascular Journal of Africa. 24(5): 180183. 3. Awoke A, Awoke T, Alemu S, Megabiaw B (2012). Prevalence and associated factors of hypertension among adults in Gondar, Northwest Ethiopia: A community based cross-sectional study. BMC Cardiovascular Disorders. 12: 113.4. Oliveras A, Schmieder RE (2013). Clinical situations associated with difficult-to-control hypertension. Journal of Hypertension. 31(Suppl 1): S3-8. 5. van Mil F (2005). Drug-related problems⊠: a cornerstone for pharmaceutical care. Journal of the Malta College of Pharmacy Practice. 10: 5-8. 6. Pharmaceutical Care Network Europe (PCNE). Available from: https://www.pcne.org/ (Accessed 9th July 2019)7. Cipolle RJ, Strand L, Morley P, Cipolle R (2004). Pharmaceutical Care Practice: The Clinicians Guide. 2nd ed. New York: McGraw-Hill. 8. Chua SS, Kok LC, Md Yusof FA, Tang GH, Lee SWH, Efendie B, Paraidathathu T (2012). Pharmaceutical care issues identified by pharmacists in patients with diabetes, hypertension or hyperlipidaemia in primary care settings. BMC Health Services Research. 12: 388. 9. Huri

HZ, Wee HF (2013). Drug related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocrine Disorders. 13: 2.10. Eichenberger PM, Lampert ML, Kahmann IV, Van Mil JWF, Hersberger KE (2010). Classification of drug-related problems with new prescriptions using a modified PCNE classification system. Pharmacy World & Science. 32(3): 362372. 11. Chan DC, Chen JH, Kuo HK, We CJ, Lu IS, Chiu LS, Wu SC (2012). Drug-related problems (DRPs) identified from geriatric medication safety review clinics. Archives of Gerontology and Geriatrics. 54(1): 168174. 12. Ganiyu KA, Erah PO and Suleiman IA (2014). Drug therapy problems in patients on anti-hypertensives with antidiabetic drugs in two tertiary health institutions in Niger Delta region, Nigeria. Journal of Pharmaceutical and Allied Sciences. 11: 1.13. Hussein M, Lenjisa JL, Woldu MA, Tegegne GT, Umeta GT and Dins H (2014). Assessment of drug related problems among hypertensive patients on follow up in Adama Hospital Medical College, East Ethiopia. Clinical Pharmacology and Biopharmaceutics. 3: 12214. Raosoft sample size calculator. Available from: http://www.raosoft.com/samplesize.html (Accessed 2nd September 2020)15. Pharmaceutical Care Network, Europe. The PCNE classification for drug-related problem V. 7.0. 2016. Available from: http://www.pcne.org/upload/files/147_DRP-form_ext_V7.pdf

(Accessed 11th May 2017)16. Ogbonna B, Amagba C (2017). Investigation of drug therapy problems in Type 2 diabetes outpatients with co-morbid hypertension in a tertiary hospital in Southeast Nigeria. Value in Health. 20(9): A859.17. Koyra HC, Tuka SB, Tufa EG (2017). Epidemiology and predictors of drug therapy problems among type 2 diabetic patients at Wolaita Soddo University Teaching Hospital, Southern Ethiopia. American Journal of Pharmacological Sciences. 5(2): 40-48.18. Redzuan AM, Ramli AR, Pheng MTH (2017). Drug-related problems in hypertensive patients with multiple co-morbidities. Open Access Journal of Pharmaceutical Research. 1(3): 000113. 19. Shukrala F, Gabriel T (2015). Assessment of prescribing, dispensing, and patient use pattern of anti-hypertensive drugs for patients attending outpatient department of Hiwot Fana Specialized University Hospital, Harar, Eastern Ethiopia. Drug Design, Development and Therapy. 9: 519-523. 20. Al-Azzam SI, Alzoubi KH, AbuRuz S, Alefan Q (2016). Drug-related problems in a sample of outpatients with chronic diseases: A cross-sectional study from Jordan. Therapeutics and Clinical Risk Management. 12: 233-239.21. Ong KL, Cheung BMY, Man YB, Lau CP, Lam KSL (2007). Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension. 49(1): 69-75. 22. Choi HM, Kim HC, Kang DR (2017). Sex differences in hypertension

prevalence and control: Analysis of the 2010-2014 Korea national health and nutrition examination survey. PLoS One. 12(5): e0178334. 23. Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, Cheng X, Mu L, Zhang H, Liu J, Su M, Zhao H, Spatz ES, Spertus JA, Masoudi FA, Krumholz HM, Jiang L (2017). Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet. 390(10112): 2549-2558. 24. Wang L, Wang X, Qu HY, Jiang S, Zhang J, Fu L, et al. (2017). Role of kidneys in sex differences in angiotensin II-induced hypertension. Hypertension. 70(6): 1219-1227. 25. Mirabito Colafella KM, Samuel CS and Denton KM (2017). Relaxin contributes to the regulation of arterial pressure in adult female mice. Clinical Science. 131(23): 2795-2805. 26. Dasinger JH and Alexander BT. Gender differences in developmental programming of cardiovascular diseases. Clinical Science. 130(5): 337-348. 27. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. (2016). Executive summary: heart disease and stroke statistics-2016 update: A Report from the American Heart Association. Circulation. 133: 447-454. 28. Chen JH, Hales CN, Ozanne SE (2007). DNA damage, cellular senescence and organismal ageing: Causal or correlative? Nucleic Acids Research. 35(22): 7417-7428. 29. Singh T, Newman AB (2011). Inflammatory markers in population studies of aging. Ageing Research Reviews. 10(3):

319-329. 30. Buford TW (2016). Hypertension and aging. Ageing Research Reviews. 26: 96-111. 31. Bretzel RG (2007). Co-morbidity of diabetes mellitus and hypertension in the clinical setting: A review of prevalence, pathophysiology, and treatment perspectives. Clinical Therapeutics. 29(2): S35-S43. 32. Jones DW, Hall JE (2004). Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 43(1): 1-3. 33. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL (2000). Hypertension and anti-hypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. New England Journal of Medicine. 342(13): 905-912.34. Shrout T, Rudy DW, Piascik MT (2017). Hypertension update, JNC8 and beyond. Current Opinion in Pharmacology. 33: 41-46. 35. Dreischulte T, Morales DR, Bell S, Guthrie B (2015). Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. Kidney International. 88(2): 396403.36. Fog AF, Kvalvaag G, Engedal K, Straand J (2017). Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway. Scandinavian Journal of Primary Health Care. 35(4): 329-335. 37. Al-Taani GM, Al-Azzam SI, Alzoubi KH, Elhajji FWD, Scott MG, Alfahel H, et al (2017). Prediction of drug-related problems in diabetic outpatients in a number of hospitals, using a

modeling approach. Drug, Healthcare and Patient Safety. 9: 65-70. 38. Kaufmann CP, Stämpfli D, Hersberger KE, Lampert ML (2015). Determination of risk factors for drug-related problems: A multidisciplinary triangulation process. BMJ Open. 5(3): e006376. 39. Niriayo YL, Kumela K, Kassa TD, Angamo MT (2018). Drug therapy problems and contributing factors in the management of heart failure patients in Jimma University Specialized Hospital, Southwest Ethiopia. PLoS One. 13(10): e0206120.40. Khdour MR, Jarab AS, Adas HO, Samaro EZ, Mukattash TL, Hallak HO (2012). Identification of drug-related problems: A prospective study in two general hospitals. Current Clinical Pharmacology. 7(4): 276-281.41. Hussen A, Daba FB (2017). Drug therapy problems and their predictors among hypertensive patients on follow up in dil-chora referral hospital, dire-dawa, Ethiopia. International Journal of Pharmaceutical Sciences and Research. 8(6): 2712-2719.42. Osemene KP, Elujoba AA, Ilori MO (2011). A comparative assessment of herbal and orthodox medicines in Nigeria. Research Journal of Medical Sciences. 5(5): 280-285.