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DRUG THERAPY PROBLEMS AND THEIR PREDICTORS AMONG HYPERTENSIVE PATIENTS ON FOLLOW UP IN DIL-CHORA REFERRAL HOSPITAL, DIRE-DAWA, ETHIOPIA

Abadir Hussen and Fekede Bekele Daba [*]

School of Pharmacy, Institute of Health, Jimma University, Jimma, Ethiopia.

ABSTRACT: Background: The objective of this study was to assess drug therapy problems (DTPs) and their predictors among hypertensive patients on follow up at Dil-Chora Referral Hospital, Ethiopia. **Methods:** Hospital based cross-sectional study involving medical record review was conducted from February-to-April 2015 using a structured questionnaire and this was complemented by a face-to-face interview. Adult hypertensive patients aged ≥18 years who were on follow-up for at least 3-months were enrolled in the study using a convenient sampling method. Data analysis was done using SPSS software version 16.0. Multiple logistic regressions were fitted and odds ratios with 95%CI were calculated to identify factors associated with DTPs. **Results:** The study included 271 hypertensive patients. Mean age was 57.73±12.13. One hundred sixty three (60.1%) were females. More than half of the respondents (50.6%) had comorbid condition and diabetes was the most common. More than 71% of patients were found to have at least one DTP and the mean number of DTPs per patient was 1.39±1.28. Need additional drug therapy(62.4%) and non-adherence(32.8%) were the two most common DTPs. Presence of comorbidity (AOR=5.74, 95%CI; 2.49-13.00), taking ≥3 medications per day (AOR=7.04, 95%CI; 2.33-21.25), and uncontrolled blood pressure (BP) (AOR=7.68, 95%CI; 3.70-15.90) were factors associated with DTPs. **Conclusions:** DTPs are common among hypertensive patients on follow up and the most common were need additional drug therapy and non-adherence to medications. Pharmacist interventions in drug therapy would help physicians in early identification and prevention of DTPs so that a joint effort between physicians and pharmacists should be made.

INTRODUCTION: Despite the development of many effective anti-hypertensive drugs, occurrence of DTPs is frequent in patients with hypertension and may introduce a significant risk to patients, which adversely affect quality of life, increase hospitalization and overall health care cost [1]. A DTPis any undesirable event experienced by a patient which involves, or is suspected to involve, drug therapy, and that interferes with achieving the desired goals of therapy.

DTPs are categorized into unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, dosage too high, adverse drug reaction and noncompliance [2].

Although the recent advances in the diagnosis and treatment of hypertension have been shown to prevent cardiovascular diseases and to extend life, hypertension still remains an inadequately managed worldwide disease. Worldwide, 13.5% of all premature deaths are attributable to high BP. The WHO has estimated that about 62% of cerebrovascular disease and 49% of ischemic heart disease burden worldwide are attributable to suboptimal control of BP levels [3]. In developing countries, its morbidity and mortality are increasing from time to time due to changes in life style and

sedentary life [4]. About 80% of this burden occurred in low- and middle-income countries [5, 6]. The levels of awareness, treatment and control of hypertension vary between countries and are particularly low in some economically developing countries. Although there is shortage of extensive data, 10.5% of the Ethiopian population has been estimated to have hypertension [5, 7].

Few studies indicated that prevalence of hypertension is increasing among the urban population of Ethiopia because of increased risk factors including smoking, excessive use of alcohol, lack of exercise and obesity. Because of competing priorities from infectious diseases and nutritional problems, the prevention and control of chronic diseases like hypertension is extremely low among developing nations including Ethiopia [8]. Even in developed countries, up to 67% of hypertensive patients being treated have no adequate control of their diseases [1, 5, 9].

A large number of medications are proven to reduce increased BP and the risk of associated adverse cardiovascular events. Although safe and effective drugs and evidence-based treatment guidelines are available, the management of hypertension with medications remains suboptimal [10]. DTP is one of the biggest obstacles in therapeutic control of BP. DTPs themselves will complicate the health problem burden of hypertensive patients. Inpatients with hypertension, non-compliance, adverse drug reactions, improper drug selection and drug interactions are the most common problems related to medications.

Early identification of the DTPs and their causes can enhance the prevention and management of DTPs. Categorizing DTPs will also enable the practitioners, in collaboration with the patient, in constructing a pharmaceutical care plan that improves the patient's treatment outcome. Following appropriate interventions, intensive follow-up to assess therapeutic response and adverse effects is most important. In this regard, clinical pharmacists can play an important role in identifying, resolving and preventing DTPs through careful pharmaceutical care practice. In the study area, studies are scarce and little is known about the prevalence of DTPs and its contributing factors in patients with hypertension.

Thus, the aim of study was to assess the prevalence of DTPs and its predictors among hypertensive patients on follow up.

METHODS: The study was conducted in Dil-Chora Referral Hospital (DCRH) found in Dire-Dawa city, one of two federal city administrations of the country, Ethiopia. A hospital based cross-sectional study designinvolving retrospective chart review of 271adult hypertensive patients aged ≥18 years and face-to-face interviewswere carried out. Data was abstracted from medical record charts of patients who were on follow up at chronic care unit and visited the hospital from February to April 2015, using structured data collection format. The data abstracted included patients' socio-demographics, presence of comorbidities, lifestyle factors, presence of concurrent medications, relevant laboratory results and other related clinical factors.

Data entry and analysis were done using SPSS software version 16.0. Descriptive statistics was calculated for demographic and clinical characteristics of patients. Categorical data were expressed as percentages and continuous data were expressed as mean ± standard deviation. Bivariate and multivariate logistic regression analysis was employed.

All variables with a p-value <0.25 in the bivariate logistic regression analysis were further entered into the multivariate model to control confounding effects. The association of independent predictors and DTPs was done by multivariate logistic regression analysis and the odds ratio (OR) with 95% confidence intervals (CI) was calculated to determine the association between the variables and p-value <0.05 was taken as statistically significant association.

Ethical Clearance: The study was conducted after ethical approval was obtained from Ethics Review Committee of College of Health Sciences, Jimma University. Prior to data collection, written consent was obtained from all patients. Record card number was used as patient identifier and name of the patients was excluded to keep and respect confidentiality of all information obtained. For data analysis, a code number that had been given to each patient's data collection instrument was used.

RESULTS:

Demographic, lifestyle and other clinical characteristics: This study included a total of 271 hypertensive patients. One hundred sixty three (60.1%) were females and 108 (39.9%) were males. Mean age was 57.73 ± 12.13 years old and the age ranged from 25 and 94 years. Two hundred three (74.9%) were married, 132 (48.7 %) were unable to read and write, 127 (46.9%) were unemployed and 208 (76.8%) were Orthodox Christians. Regular physical activity was reported by only 7.4% of patients. Smoking and alcohol consumption were reported by 12.9% and 12.5% of patients, respectively **Table 1**.

TABLE 1: SOCIODEMOGRAPHIC AND LIFESTYLE CHARACTERISTICS OF THE STUDY PARTICIPANTS (N=271)

Characteristics	Category	n	(%)
Age	19-64	85	(31.4)
	≥65	186	(68.6)
Sex	Male	108	(39.9)
	Female	163	(60.1)
Occupation	Retired	68	(25.1)
	Unemployed	127	(46.9)
	Merchant	28	(10.3)
	Farmer	4	(1.5)
	Employee	44	(16.2)
Educational status	Unable to read & write	132	(48.7)
	Primary education	61	(22.5)
	Secondary education	59	(21.8)
	Tertiary education	19	(7.0)
Religion	Orthodox	208	(76.8)
	Muslim	56	(20.7)
	Protestant	7	(2.6)
Marital Status	Married	203	(74.9)
	Single	32	(11.8)
	Divorced	4	(1.5)
	Widowed	32	(11.8)
Residence	Urban	261	(96.3)
	Rural	10	(3.7)
Lifestyle characteristics	Physical exercise	20	(7.4)
	Smoker	35	(12.9)
	Alcohol user	34	(12.5)
	Khat user	64	(23.6)
	Coffee	173	(63.8)
	Traditional medicine	33	(12.2)

More than half of the respondents (50.6 %) had comorbid conditions. Diabetes (35.1%) was the most common comorbid condition followed by peptic ulcer disease (3.7%) and stroke (3.3%). Seventy eight (28.8%) had at least one previous history of hospitalization. BP status of 173 (63.8%) patients was not controlled according to JNC 7 guidelines **Table 2**.

TABLE 2: CLINICAL CHARACTERISTICS OF THE STUDY PARTICIPANTS (n = 271)

Characteristics		n	(%)
Presence of co morbidity	Yes	137	(50.6)
	No	134	(49.4)
Type of co morbidity	Diabetes mellitus	95	(35.1)
	Peptic ulcer disease	10	(3.7)
	Stroke	9	(3.3)
	Heart failure	5	(1.8)
	Chronic kidney disease	4	(1.5)
	Other[a]	14	(5.2)
Duration with hypertension since diagnosis (year)	< 1	23	(8.5)
	1-3	111	(40.9)
	4-6	100	(36.9)
	7-9	19	(7.0)
	≥10	18	(6.6)
BP status	Controlled	98	(36.2)
	Uncontrolled	173	(63.8)
Previous hospitalization	None	193	(71.2)
	Once	63	(23.2)
	Twice and more	15	(5.5)

Others[a] Asthma=4, Gouty arthritis=3, HIV/AIDS=2, UTI=2, soft skin infection=2 and Diarrhea=1

Medications use: The average number of overall medications per patient was 2.57 ± 1.05 and ranged from 1 to 5 medications. The most frequently prescribed antihypertensive medication was hydrochlorothiazide (41.4%), followed by enalapril (28.9%) and nifedipine (19.7%). Most patients (62.7%) were receiving combination of two or more antihypertensive medications and 101 (37.3%) were prescribed with monotherapy.

The most commonly prescribed dual antihypertensive therapy was a combination consisting of enalapril and hydrochlorothiazide and the most common triple therapy was a combination consisting of enalapril, hydrochlorothiazide and atenolol **Table 3**. The most commonly prescribed concurrent medications were antidiabetics, 95 (35.1%) and NSAIDs, 27 (9.9%) **Table 4**.

TABLE 3: PATTERN OF ANTIHYPERTENSIVE MEDICATION USE AMONG STUDY PARTICIPANTS

Characteristics		n	(%)
Medications prescribed	Hydrochlorothiazide	196	(41.4)
	Enalapril	137	(28.9)
	Nifedipine	93	(19.7)
	Atenolol	36	(7.6)
	Spironolactone	5	(1.1)
	Furosemide	4	(0.8)
	others[a]	2	(0.4)
	Total drugs	473	(100)
Monotherapy	Enalapril	42	(41.6)
	Hydrochlorhiazide	36	(35.6)
	Nifedipine	21	(20.8)
	Atenolol	2	(1.9)
	Total	101	(100)
Dual therapy	Enalapril + Hydrochlorothiazide	70	(50.0)
	Nifedipine + Hydrochlothiazide	55	(39.3)
	Atenolol + Hydrochlothiazide	8	(5.7)
	Others[b]	7	(5.0)
	Total	140	(100)
Triple therapy	Enalapril + Hydrochlorothiazide + Atenolol	17	(56.7)
	Nifedipine + Hydrochlothiazide + Atenolol	7	(23.3)
	Enalapril +Nifedipine + Hydrochlothiazide	4	(13.3)
	Enalapril +Spironolactone + Furosemide	2	(6.7)
	Total	30	(100)

Others[a]: Methyldopa (1), Propranolol (1)
Others[b]: Enalapril+Atenolol (3), Nifedipine+Spironolacton (2) Enalapril+Furosemide (1) Spirinolactone+Furosemide(1)

TABLE 4: PATTERN OF CONCURRENT MEDICATION USE AMONG STUDY PARTICIPANTS (n = 271)

Characteristics	n	(%)
Antidiabetic medications	95	(35.1)
NSAIDs	27	(9.9)
Vitamins	17	(6.3)
Proton-pump inhibitors	13	(4.8)
Antibiotics	5	(1.8)
Others[a]	7	(2.6)

Abbreviations: NSAIDs, Non-Steroidal Anti-Inflammatory Drugs
Others[a]: digoxin, cough syrup, salbutamol, simvastatin

DTPs and associated factors: One hundred ninety three (71.2%) patients were found to have DTP and the mean number of DTPs per patient was 1.39 ± 1.28 with the maximum of 5. The most frequent category of DTP was the needs for additional drug therapy (62.4 %). The possible causes of this DTP were mostly need of preventive drug therapy, followed by need of synergistic drug effect and untreated indication. Noncompliance to medications (32.8%) was the second most frequent category of DTPs and the most commonly reported reasons were forgetfulness and feeling worse from the medications use **Fig. 1**.
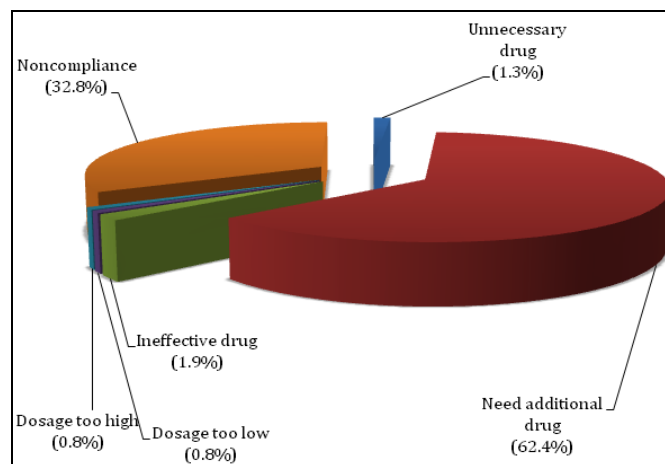

FIG. 1: THE MOST COMMONLY IDENTIFIED TYPES OF DRUG THERAPY PROBLEMS

Among a total of 378 drug therapy problems (DTPs) identified, 182 were "needs for additional drug therapy [141 were need of preventive drug therapy, 91 were need of synergistic drug effect and 41 were untreated indication that needs drug therapy]; 124 were "noncompliance to medications" [101 were due to forgetting to take medications and 23 were feeling worse from the medications use]; 7 were "ineffective drug" [4 were due to use of ineffectiveness drug for the medical condition and 3 were due to use of drugs instead of which more effective drugs available] and 5 were "unnecessary drug" [3 were use of multiple drug products unnecessarily and 2 were use of a drug with no valid medical indication].

Multivariate analysis showed that the presence of comorbid condition (s), use of multiple number of medications and uncontrolled BP were significantly associated with the occurrence of DTPs. Accordingly, out of 137 patients with comorbid conditions, 125 (91.2 %) were appeared to have at least one DTP. Analysis was done to see the association between the presence of comorbid condition and the occurrence of DTP.

Thus, study participants who had comorbid condition (s) were 5.74 times at increased risk of developing DTPs compared with those without comorbid conditions(AOR= 5.74, p< 0.001).

With respect to BP control, 146 of 173 (84.4 %) patients with uncontrolled BP were found to have at least one DTP. This was found to be significantly associated with DTPs (AOR= 7.68, p<0.001) compared to patients with controlled BP.

Number of medications use by patients was among factors contributed to the occurrence of DTPs. The study found that 124 of 271 (45.8 %) patients were taking three or more drugs per day and this was significantly associated with DTPs. Thus, patients taking three or more medications per day were about 7 times more likely to develop DTPs compared with patients taking less than three medications(AOR= 7.04, P= 0.001) **Table 5**.

TABLE 5: FACTORS ASSOCIATED WITH DTPS AMONG HYPERTENSIVE PATIENTS ON FOLLOW UP

Characteristics	No DTP n (%)	DTP n (%)	AOR (95% CI)	P-value
Presence of co morbidity				
No	66 (49.3)	68 (50.7)	1	
Yes	12 (8.8)	125 (91.2)	5.74 (2.49, 13.00)	<0.001
Number of medication				
< 3	66 (24.4)	81 (29.9)	1	
≥ 3	12 (9.7)	112 (90.3)	7.04 (2.33, 21.25)	0.001
Blood pressure				
Controlled	51 (52)	47 (48)	1	
Uncontrolled	27 (15.6)	146 (84.4)	7.68 (3.70, 15.90)	<0.001

The following variables were entered into a binary logistic regression model: age, gender, marital status, educational level, religion, occupation, residence, number of medications per day, Presence of co-morbidity, BP status.
Abbreviations: DTP, drug therapy problem; AOR, adjusted odds ratio; CI, confidence interval

DISCUSSIONS: This study revealed that a total of 378 DTPs were identified in 193 patients and 71.2% of the study participants had at least one DTP. The mean number of DTPs per patient was 1.39. Prevalence of DTPs in this study was less compared to prevalence report from other study setting of Ethiopia, which was 80.7% [11], and a study from Malaysia also reported 90.5 % [12].These findings indicate that management of patients with hypertension is more complicated and prone to different DTPs. The differences in prevalence might be related to different factors including differences in the size of the study population, the study period, as well as professionals involved in the identification of DTPs. Clinical pharmacists are crucial in the identification of DTPs since they are trained with adequate pharmacotherapeutic knowledge and pharmaceutical care services. Therefore, pharmacists in the hospital setting are suitable in the identification and resolution of DTPs [13].

The need of additional drug therapy was the most common category of DTPs. It accounts for 62.4% of the total DTPs (236/378). It was also common in two other studies done at different hospitals of

Ethiopia which were reported as 32.6% and 90.7% [14, 15]. From these reports, it has been shown that there are variations in the prevalence among different settings.Such discrepancies might be explained in terms of availability of comprehensive treatment guidelines and professionals involved in the identification of DTPs particularly availability of clinical pharmacists in the clinical settings.

Recognition of possible indications for theneed of additional drug therapy is substantial in this study setting. As it was reported, among 236 of a need of additional drug therapy as a DTP, majority (59.7%) was indicated to prevent the onset of a new medical condition. Addition of antiplatelet and statin therapy in the prevention of cardiovascular complications such as myocardial infarction and/or stroke in patients with diabetes, ischemic heart disease was common. Requiring synergistic effect (38.6 %) and untreated indication (1.7 %) were also the second and third indications for the need of additional drug therapy.

This implies that, determining whether a patient is actually requiring drug therapy is not an easy task and is a complex problem. This is because different factors including presence of comorbidities or

taking large number of medications might complicate such problems as evidenced by the current study. Therefore, it needs basic knowledge of the objective disease and different comorbid conditions as well as an expert knowledge of pharmacotherapy and skills of pharmaceutical care practice. In this regard, clinical pharmacists are well suit hence their expertise is focused in the disciplines of pharmacology, pharmacotherapy, and pharmaceutical care practice.

In this study, non-adherence to antihypertensive agents was the second most common DTP category accounting for 32.8% of all DTPs, as measured by MMAS-8. According to the report of the majority of respondents, forgetting to take the medications at the right time and feeling worse while taking the medications were the major contributing factors. Studies from two settings of Ethiopia were reported lower rates of non-adherence (26% and 19%) than the current study [11, 16]. On the contrary, other literature findings were reported higher rates of non-adherence [17, 18]. There are also other findings with comparable results non-adherence rate [19, 20].

These commonly reported rates of non-adherence of patients to the prescribed medications in different study settings indicate that there is a worldwide medication adherence problem. Studies, particularly in Ethiopia have documented non-adherence as a major concern in the treatment of patients with hypertension. Presence of comorbid conditions and use of multiple medications might contribute, as also are the case in the current study. In this regard, pharmacists, in cooperation with physicians and other health care professionals, should invest their time more on ensuring their patients' adherence to their treatments based on individualized approach.

Variations in the rates of non-adherence might be due to differences in the socio economic status and literacy level of the study patients; differences in accessibility to health facilities; differences in the adequacy of hospital facilities including the availability of essential medications and availability of adequate practitioners who are equipped with the skills of tracking non-adherence problems. The precision of the method for measuring adherence, the way of employing the questionnaire whether face-to-face interviewor self-

reporting by the patient, as well as the subjective nature of the self-reported questionnaire might also contributed to the differences in the rate of non-adherence among different study settings.

More than half of studied patients were found to have comorbid conditions. As this study revealed, there was significant association between the presence of comorbid conditions and the occurrence of DTPs. As a result, patients with comorbidities were 5.74 times more likely to experience DTPs compared with those without comorbidities. It is obvious that, in the presence of co morbidities, patients are exposed to large number of antihypertensive and concurrent medications that might increase the pill burden to the patient. This might in turn increase the likelihood of adverse drug effects that would enforce the patient not to take the medications as agreed upon. These, in addition to other factors, might contribute to the occurrence of DTPs.The association between the presence of comorbid conditions and the occurrence of DTPs was consistent with other literature results [11, 13, 17].

The average number of medications per patient was 2.57. Study from other setting of Ethiopia also reported 2.96 [11]. As to the current study, the number of medications taken per day showed a statically significant association with the occurrence of DTPs. Different study findings also showed that use of higher number of medications significantly affected DTPs [11, 13]. Patients taking multiple medications with frequent daily administration often have a complex drug schedule and are at high risk of experiencing DTPs. This might be due to intolerance of additive toxic effects of concurrent medications, possibility of drug interactions that might bring about changes to the required dose range and its desired effects and other related factors. Patients with multiple disease conditions and patients taking large number of medications should be closely monitored for DTPs to avoid clinically significant harmful consequences.

Uncontrolled BP increases the risk for cardiovascular disease, including heart attack and stroke. In the current study, despite taking antihypertensive, BP of about 64 % of patients was uncontrolled. Consequently, this group of patients

were found to be 7.68times at increased risk of experiencing DTPs compared with patient group with controlled BP. Uncontrolled BP might be related to different factors. It might be attributable to adherence behaviour of patients. It is more likely that non-adherent patients are at high risk of not achieving BP control. In the treatment of hypertension, poor adherence affects the clinical outcome; hence 32.8% of DTPs were non-adherence with the prescribed medications. The significant association between adherence level and BP control was also supported by other studies [21].Therefore, close monitoring of patients with hypertension is vital in order to trace any possible factor that could contribute to the poor control of BP while taking appropriate management. By doing so, it could be possible to prevent CV complications as well as minimize the occurrence of DTPs that might be resulted due to poor BP control.

CONCLUSION: Management of patients with hypertension is prone to different DTPs for several reasons, including presence of comorbidity, large number of concurrent medications, uncontrolled BP and other patient related factors. In this study, relatively higher prevalence of DTPs was identified and the most common were need of additional therapy and non-compliance to medications, highlighting the importance of considering drugs as a possible cause of health problems in hypertensive patients and the need for their rational use.

COMPETING INTERESTS: There is no any conflict of interests among the authors.

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