Drug therapy problems among patients with cardiovascular disease admitted to the medical ward and had a follow-up at the ambulatory clinic of Hiwot Fana Specialized University Hospital: The case of a tertiary hospital in eastern Ethiopia

Tamene Gelchu[1] and Jemal Abdela[2] iD

Abstract

Background: Pharmacotherapy is important in reducing morbidity and mortality related to cardiovascular diseases. However, these advantages are limited by drug therapy problems that can impact on a patient's quality of life, prolong hospital stays, and increase the overall burden of healthcare expenditures. Therefore, this study was aimed to assess drug therapy problems among patients with cardiovascular diseases who were hospitalized and received follow-up at the ambulatory clinic of Hiwot Fana Specialized University Hospital.

Methods: An institution-based cross-sectional study design was used to collect data from patients with cardiovascular diseases who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of Hiwot Fana Specialized University Hospital. The collected data were coded, entered, and analyzed using SPSS version 16. The associations of selected categorical variables were done using binary logistic and multivariate logistic regression analyses.

Results: Out of 216 study participants, females accounted for 123 (57%), whereas 93 (43%) of them were males. Among cardiovascular diseases identified in the medical ward and ambulatory clinics of Hiwot Fana Specialized University Hospital, congestive heart failure 96 (44.4%) and hypertension 93 (43.1%) were the two most commonly diagnosed disorders. Of the total participants involved in the study, 131 (60.65%) had drug therapy problems. Among the seven classes of drug therapy problems assessed, the most commonly observed was the need for additional drug therapy 76 (58%); followed by cases related to unnecessary drug therapy and noncompliance both of which were estimated to be 16 (12.2%). In addition, of independent variables, only the use of more than three drugs was significantly associated in both binary logistic (crude odds ratio = 0.41, 95% confidence interval = 0.234–0.719, p = 0.002) and multivariate logistic regressions (adjusted odds ratio = 4.86, 95% confidence interval = 1.625–14.536, p = 0.005) as compared with those patients who were using less than three drugs.

Conclusion: The findings of the study indicated that more than half of the study participants experienced drug therapy problems, for which 58% required additional drug therapy. The risk of drug therapy problem is found to increase with the use of more than three drugs. Since these problems are adversely affecting the treatment outcome of patients, this is an area which requires special attention and the cooperation of healthcare professionals to tackle it.

Keywords

Drug therapy problem, cardiovascular disease, unnecessary drug therapy, noncompliance, need additional drug therapy, ineffective drug product, ineffective dose

Introduction

Cardiovascular diseases (CVDs) remain the biggest cause of death worldwide. According to estimates in a report by the World Health Organization in 2011, approximately 17.1 million people die of CVDs each year, representing 30% of all deaths. Of these deaths, approximately 7.3 million people die of coronary heart disease and 6.2 million people die

[1]School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia
[2]Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, Harar, Ethiopia

Corresponding author:
Jemal Abdela, Department of Pharmacology and Toxicology, School of Pharmacy, College of Health and Medical Sciences, Haramaya University, P.O. Box 235, Harar, Ethiopia.
Email: abdelajemal07@gmail.com

mainly from heart disease and stroke, which are projected to remain the single leading cause of death.[1] CVDs account for 7%–10% of all adult medical admissions in African hospitals, of which heart failure constitutes approximately 3%–7%.[2] According to a study conducted in Ethiopia in 2015, ischemic heart disease, hemorrhagic stroke, and ischemic stroke were among the top causes of premature mortality and age-standardized deaths.[3] In addition, studies conducted in Addis Ababa, the capital of Ethiopia, also indicated that 75% of CVD deaths were due to myocardial infarction, stroke, and hypertensive heart disease.[4,5]

Even though a drug may have a significant role for curative, preventive, or diagnostic purposes, it may also have debilitating, negative effect on the health of patients if it is not used properly.[6,7] Moreover, the availability of a wide range of drug products and drug consumers as well as complicated regimens of drugs can contribute to more adverse drug events (ADEs) and drug interactions that may create difficulty in the follow-up of the patients.[8]

Drug therapy problems (DTPs) are defined as any unintended effects encountered by a patient during treatment.[9] DTP can occur at all steps of the treatment process, mainly during prescribing, transcribing, dispensing, and patient use of medication therapy.[10] These problems significantly influence the treatment outcomes of the patient and the ability to achieve the desired therapeutic goals.[9] Approximately, 20% of patients face DTPs after discharge from the hospital.[11] DTPs increase patients' healthcare expenditures as well as morbidity and mortality.[12] DTPs are classified based on the possible cause of the problem[11] and may be related to; the choice of formulation, under or overtreatment, inappropriate dosing, drug interactions, noncompliance, and harm caused by ADEs.[13]

In a study conducted in Singapore, which involved 347 patients, DTPs were found to be one of the major reasons for admission that resulting in 71.9% of patient admissions.[14] Similarly, an observational study conducted in hospitals in the Netherlands indicated that out of 13,000 unintended admissions, 714 (5.6%) were most likely due to issues related to drug therapy. Of these drug-related admissions, 46.5% were potentially preventable.[15] Furthermore, in the United States, around 44,000 people reportedly died each year in the hospitals as a result of medical problems that were preventable as indicated by different studies.[16,17] The literature review conducted on DTPs has demonstrated that about 28% of cases encountered at the emergency ward were drug-related problems such as adverse drug reactions (ADRs), of which 70%–90% were potentially preventable.[18] A cross-sectional study conducted in Lahore, Pakistan also indicated that more than half (58.4%) of the ADEs were preventable. Accordingly, 43.6% of the ADEs were definitely preventable, whereas 14.8% were probably preventable and less than half (41.6%) were non-preventable ADEs or ADRs.[19]

Coming to our country Ethiopia, a study conducted in Felege Hiwot Referral Hospital among cardiovascular patients identified a total of 105 DTPs.[20] An additional study conducted in Jimma Referral Hospital showed that of 257 participants, 189 (73.5%) had developed DTPs.[8] Similarly, findings from a medical ward of Gondar University Referral Hospital indicated that of 256 participants engaged in the study, 169 (66.0%) of patients had drug-related problems.[7] This could imply that DTPs are common in our settings. Therefore, this study was targeted to assess DTPs among patients with CVD who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of Hiwot Fana Specialized University Hospital (HFSUH).

Methods

Study design and study period

The study was conducted using institutional-based cross-sectional study design among patients with CVDs who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH that is located in Harar town, which is 526 km away from Addis Ababa, the capital of Ethiopia. The hospital provides internal medicine, surgery, pediatrics, emergency, maternity, family planning, gynecologic/obstetric, ambulatory clinic, dental, psychiatric, physiotherapy, tuberculosis (TB), and human immunodeficiency virus (HIV) services to the people of eastern Ethiopia, especially those from both Hararghe zone and Harari region. The data were collected from March 1 to 30, 2017.

Source population. All patients who were admitted to the medical ward and those who had a follow-up at the ambulatory clinic of HFSUH in the study period.

Study population. All patients with CVDs who were admitted to the medical ward and those who had a follow-up at the ambulatory clinic of HFSUH during the study period.

Eligibility criteria

Inclusion criteria
- Patients who were admitted with CVD to the medical ward and who had taken cardiovascular drug therapy;
- Patients with CVD who received follow-up at the ambulatory clinic of HFSUH;
- Patients with age ⩾18 years old.

Exclusion criteria
- Patients with incomplete medical records;
- Patients who were seriously sick and unable to respond for questions;
- Patients with age < 18 years old.

Sample size and sampling technique

The sample size was calculated using a single proportion formula with the assumption of 50% prevalence of DTPs among patients with CVDs, 95% confidence interval (CI), 5% margin of error, and 10% of contingency for non-response rate. Based on this assumption, the calculated sample size was found to be 216.

Convenience sampling technique was used as per inclusion criteria and data collection period. Data abstraction questionnaires assessing sociodemographic characteristics, vital signs, relevant laboratory test, diagnosis, current medical conditions, medication prescribed, the effectiveness of drugs, regimens, duration of treatment, comorbid illness, and categories of DTPs were used. These questionnaires are not validated; however, it was pretested in separate similar hospital in Harar town to check whether there is any ambiguity with the questions and to modify it accordingly. The data were collected by reviewing patients' medical records and asking the patients' pertinent information related to adherence and compliance, and other issues based on the objective of the study. Two clinical pharmacists were involved in the data collection.

DTPs were identified and classified using the Cipolle's and Strand's method[9,21] and discussion held by clinical pharmacists on the identification of DTP. Then, these pharmacists further refined DTP identification and classification method to the study setting based on treatment guidelines and literature reviews.[22–24] The identification of DTP was based on a review of patients' medical and medication records, assessment of laboratory investigations, and patient's interview about medication experience. Specific information about medication therapies, such as the recommended drug of choice, recommended dosages, frequency of administration, duration of therapy, drug interactions, and ADEs were compared based on details from the standard pharmacotherapy textbooks, and guidelines of hypertension and heart failure management.[22,25–27]

Data entry and analysis

The data were cleaned, coded, entered, and analyzed using SPSS version 16. Categorical variables were described by frequencies and percentages, whereas the associations of selected categorical variables were done using binary logistic and multivariate logistic regressions.

Operational definitions

Adverse drug event is any injury related to the use of a drug, even if the causality of this relationship is not proven.[28]

Adherence is drug-taking behavior of a patient measured with the Morisky scale in which when a patient says no at least for one of the questions, he or she is noncompliant.[9]

Contraindication is a medical condition in which specific drugs are not going to indicated because it may be associated with severe medical complication.[29]

Comorbidity is the presence of one or more additional disease or disorders co-occurring with a primary disease.[30]

Adverse drug reaction refers to any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy.[31]

Dosage includes the dose given, frequency of administration, and duration of therapy.

Definition of terms related to DTPs[9,21]

- Unnecessary drug therapy—the drug therapy is unnecessary because the patient does not have a clinical indication at this time.
- Need for additional drug therapy—additional drug therapy is required to treat or prevent a medical condition or illness from developing, or the clinical condition required initiation of drug therapy.
- Ineffective drug—the drug product is not being effective at producing the desired response or the medical condition is refractory to the drug product.
- Inappropriate dosage—refers to dosages both too low and too high.

  ○ Dosage too high—indicates that the dose is too high and resulting in undesirable effects.
  ○ Dosage too low—refers to the dose is too low to produce the desired response.

- Noncompliance—the patient is not able or willing to take the drug therapy as intended.
- Drug–drug interaction—occurs when the effect of one drug is changed due to the presence of other co-administered drugs, food, or drinking substance.

Results

Sociodemographic characteristics of patients

Of the total patients involved in the study, 93 (43%) of them were males, whereas 123 (57%) were females. Approximately, 164 (75.9%) of the study participants were married. Of 216 participants engaged in the study, 83 (38.4%) of them had attended secondary school, whereas 80 (37%) of them were illiterate. Sixty-five (30.1%) of the study participants were aged >58 years. Out of the 123 females participated in the study, 10 (8.1%) were pregnant and 9 (7.3%) were breastfeeding (Table 1).

Table 1. Sociodemographic characteristics of patients admitted to the medical ward and those who had a follow-up at the ambulatory clinic of HFSUH, Harar town, from March 1 to 30, 2017 (N = 216).

Sociodemographic variable			N (%)
Sex	Male		93 (43)
	Female	Pregnant	10 (8.1)
		Nonpregnant	104 (84.6)
		Breastfeeding	9 (7.3)
Age	≤58		151 (69.9)
	>58		65 (30.1)
Marital status	Single		47 (21.8)
	Married		164 (75.9)
	Widowed		–
	Divorced		5 (2.3)
Religion	Orthodox		83 (38.4)
	Protestants		41 (19)
	Muslims		91 (42.1)
	Others		1
Educational status	Illiterate		80 (37)
	Primary		35 (16.2)
	Secondary		83 (38.4)
	Tertiary		18 (8.3)
Ethnicity	Amhara		57 (26.4)
	Oromo		135 (62.5)
	Gurage		9 (4.2)
	Tigre		10 (4.6)
	Others		5 (2.3)
Social drug (substance) use	Yes		97 (44.9%)
	No		119 (55.1%)

HFSUH: Hiwot Fana Specialized University Hospital.
"Others" in religion indicated Catholic Christian, "Others" in ethnicity indicated Adare.

Common CVDs, family history, laboratory test, and comorbid illness observed among patients with CVD admitted to the medical ward and those who had a follow-up at the ambulatory clinic of HFSUH. Among CVDs identified, the most common were congestive heart failure (CHF; 44.4%) and hypertension (43.1%). Approximately, 10 (4.6%) of participants reported a family history of cardiovascular disorders, whereas few of them also reported the presence of diabetes mellitus. Nearly, more than half of the patients had no relevant laboratory test, whereas most of them had documented vital sign. Out of the patients attending the medical ward and ambulatory clinic of HFSUH, diabetes (17.6%) and pneumonia (15.3%) were the two leading comorbidities. Regarding the number of drugs prescribed per patient, 137 (63.4%) patients were prescribed with more than three drugs (Table 2).

DTPs among patients with CVD who were admitted to the medical ward and those who had a follow-up at the ambulatory clinic of HFSUH. Out of 216 participants involved in the study, DTPs were observed in approximately 131 (60.65%) patients, in whom the ratio of DTPs per patient was 0.6. Of DTPs identified in this study, the need for additional drug therapy accounted for 76 (58%), followed by unnecessary drug therapy and noncompliance—both of which accounted for 16 (12.2%) (Table 3).

Factors associated with DTPs among patients with CVD who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH. To identify independent factors predicting the likelihood of DTPs, binary logistic and multivariate logistic regressions were conducted. In binary logistic regression, the risk of DTP among patients using more than three drugs was decreased by 0.410 (crude odds ratio (COR); 95% CI = 0.234–0.719, p = 0.002) as compared with those who were received less than three drugs. However, in multivariate logistic regression, patients who were received greater than three drugs were 4.86 times more likely to develop DTPs than those who were using three or fewer drugs (Adjusted odds ratio [AOR]; 95% CI = 1.625–14.536, p = 0.005) (Table 4).

Discussion

Drug-related problems are a major healthcare challenge and most of them are preventable.[32–35] A large number of reports illustrated the incidence, prevalence, and preventability of drug therapy-related losses of life.[36,37] Inappropriate medication use has been associated with hospitalization[35,38,39] and untoward drug effects that have adversely affected the quality of life of patients. This has been shown to cause

Table 2. The most common CVDs, number of drugs prescribed, family history, laboratory test, and vital sign of patients admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH, Harar town, from March 1 to 30, 2017 (N = 216).

Category of variables		N (%)
Working diagnosis	CHF	**96 (44.4)**
	HTN	**93 (43.1)**
	IHD	**9 (4.2)**
	Stroke	**6 (2.8)**
	VTE	**10 (4.6)**
	ACS	**1**
	AF	**1**
Family history of the patients	CVD	**10 (4.6)**
	DM	**6 (2.8)**
	Others[a]	**200 (92.6)**
Relevant laboratory test	Yes	**100 (46.3)**
	No	**116 (53.7)**
Vital sign is documented	Yes	**144 (66.7)**
	No	**72 (33.3)**
Common comorbid illness	DM	**38 (17.6)**
	Anemia	**18 (8.3)**
	Dyspepsia	**13 (6)**
	Pneumonia	**33 (15.3)**
Number of drugs prescribed	≤3	**79 (36.6)**
	>3	**137 (63.4)**

CHF: congestive heart failure; HTN: hypertension; IHD: ischemic heart disease; VTE: venous thromboembolism; ACS: acute coronary syndrome; DM: diabetic mellitus; CVD: cardiovascular disease; AF: atrial fibrillation; HFSUH: Hiwot Fana Specialized University Hospital.
[a]Cases not related to cardiovascular disease.

Table 3. DTPs among patients with CVD who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH, Harar town, from March 1 to 30, 2017 (N = 131).

Categories of variables		N (%)
Types of DTP	Unnecessary drug therapy	16 (12.2)
	Need for additional drug therapy	76 (58)
	Ineffective drug products	9 (6.9)
	Inappropriate dose	14 (10.7)
	ADR	–
	DI	–
	Noncompliance	16 (12.2)
Common DTP among patients with comorbidity	Need for additional drug therapy	16 (12.2)
	Ineffective drug products	2 (0.9)

HFSUH: Hiwot Fana Specialized University Hospital; DTP: drug therapy problems; ADR: adverse drug reaction; DI: drug interaction; CVD: cardiovascular disease.

considerable morbidity and mortality in the inpatient and ambulatory clinics of health facilities.[28,40–42] Taking this into account, this study was intended to evaluate the occurrence of DTPs among patients with CVD who were hospitalized as well as those who had a follow-up at the ambulatory clinic of HFSUH. In addition, the study identifies factors related to the development of DTP such as age, sex, pregnancy, breastfeeding, comorbidity, and the number of medications prescribed per patient.

The study identified that a large number of the study participants were presented with CHF and hypertension. This finding is higher than the results reported from other studies of which the prevalence of CHF and hypertension were less than 30%.[43,44] However, it is consistent with a study conducted in Jordan.[45] In addition, our study also indicated that the most prevalent comorbidities among patients with CVDs were diabetes and pneumonia. These conditions put the patients at high risk of DTPs due to the need for multiple drugs to manage these health problems parallel to other CVDs. This could explain why most of the study participants in this study received three or more drugs. These results are in agreement with a study conducted in the northwest of

Table 4. Factors associated with DTPs among patients with CVDs who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH, Harar town, from March 1 to 30, 2017.

Variables		COR (95% CI)	p-value	AOR (95% CI)	p-value
Sex	Male	1	0.197	1	**0.268**
	Female	0.693 (0.397–1.209)		0.735 (0.467–1.567)	
Age	≤58 years	1	0.898	1	**0.119**
	>58 years	1.04 (0.574–1.883)		0.362 (0.101–1.298)	
Pregnancy	No	1	0.384	1	**0.420**
	Yes	1.867 (0.458–7.606)		2.776 (0.232–33.201)	
Breastfeeding	No	1	0.521	1	**0.950**
	Yes	1.6 (0.38–6.732)		1.085 (0.083–14.143)	
Social drug (substance) use	No	1	0.429	1	**0.715**
	Yes	0.801 (0.463–1.387)		0.810 (0.261–2.514)	
Number of drugs prescribed	≤3	1	0.002	1	**0.005***
	>3	0.410 (0.234–0.719)		4.860 (1.625–14.536)	
The presence of comorbid illness	No	1	0.085	1	**0.104**
	Yes	0.416 (0.153–1.129)		0.278 (0.059–1.304)	

HFSUH: Hiwot Fana Specialized University Hospital; COR: crude odds ratio; AOR: adjusted odds ratio; CI: confidence interval; DTPs: drug therapy problems; CVDs: cardiovascular diseases.
*$p < 0.05$ is considered to be statistically significant.

Ethiopia in which most patients experienced more than one comorbid illness and received more than five drugs.[7]

Coming to DTP, the study identified different types of DTPs among patients who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic of HFSUH. These were unnecessary drug therapy, the need for additional drug therapy, ineffective drug therapy, inappropriate dose, and noncompliance with the treatment. These all have detrimental effects on the treatment outcome of the patients in addition to forcing them to make unnecessary healthcare expenditures. According to this study, more than half of the study participants experienced DTPs in which the ratio of DTPs per patient was 0.6. However, this finding is lower than the results reported from studies conducted in the southwest[8] and the northwest of Ethiopia.[7] Moreover, our finding is also lower than a report from another study which indicated that the number of DTPs per patients was 2.5.[46] This difference is probably related to the small sample size that was used in our study, which attributed to relatively lower DTPs compared with studies conducted in other areas.

Of the DTPs identified in this study, the most prevalent one was the need for additional drug therapy; followed by unnecessary drug therapy and noncompliance. This finding is concordant with a study conducted in the Southwest of Ethiopia at Jimma University Specialized Hospital[8,47] as well as a study conducted in Jordan among patients with chronic disease[48] in which the need for additional drug therapy was higher than other categories of DTPs. However, in terms of the need for additional drug therapy, our finding is higher than what is reported in a study conducted in the northwest of Ethiopia.[7] This study also reported a higher prevalence of inappropriate dosage and

noncompliance[7] than the findings of our study. Similarly, a study carried out at Ambo General Hospital showed that a higher percentage of unnecessary drug therapy and a lower prevalence of the need for additional drug therapy[49] compared with the results of our study. This difference might be ascribed to factors such as the level of knowledge of health professionals among these health facilities regarding the appropriate indication of drugs, the proper selection of drugs as per cases observed, and issues related to comorbidities as well as the patient's condition.

With regard to variables influencing the occurrence of DTPs among patients with CVD; only the use of multiple drugs was significantly associated in both binary logistic and multivariate logistic regressions. In binary logistic regression analysis, the likelihood of developing DTPs among patients using more than three drugs is decreased by 0.410 (95% CI = 0.234–0.719, p = 0.002), whereas in multivariate logistic regression analysis, those patients who received greater than three drugs were 4.86 times more likely to experience DTPs than those who were using three or fewer drugs (95% CI = 1.625–14.536, p = 0.005). The most probable explanation for the difference between unadjusted and AOR is due to the presence of confounding factors which masked the true effect of a risk factor of multiple drugs used as a predictor of DTPs in binary logistic regression. However, when multiple variables are run at a time using multivariate logistic regression, possibly the confounding factors were controlled and changed the direction of the association between multiple drugs used and DTPs. This finding is in agreement with the study done in Jordan where the number of medications used were strongly linked to treatment-related problems[12] as well as the study conducted in the northwest of Ethiopia in which the number of medications per patient is associated with the risk of DTPs

(AOR = 9.088; 95% CI: 1.012–81.623; p = 0.033).[7] In addition, the finding of our study is also in agreement with another study conducted in the southwest of Ethiopia in which the use of more than five drugs per day per patient was found to be a predictor of the occurrence of DTPs (AOR = 5.23; 95% CI = 1.15–23.75).[8]

Limitation of the study

Limitations of this study include the following: first, the study only covers patients who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic, and it only involves a single health facility. Second, except questionnaires used to assess categories of DTPs those that are adapted from pharmaceutical care practice,[9] the remaining questionnaires are not validated and prepared based on the objective of the study. Due to this reason, the tools may have their own limitation. Therefore, further studies are recommended to involve different facilities using standardized tools to identify the most important factors likely to be associated with the occurrence of DTPs among hospitalized patients and patients attending ambulatory clinics in order to generate sufficient evidence that can be generalized to a larger population.

Conclusion

The prevalence of DTPs was common among patients who were admitted to the medical ward and those who had received follow-up at the ambulatory clinic, in which approximately 60.65% of patients developed DTPs. Of all the DTPs which occurred, the need for additional drug therapy was the most prevalent and accounted for 58%, whereas the proportion of almost all other DTPs was lower. Since these problems are adversely affecting the treatment outcome of patients, this is an area which requires special attention and the cooperation of healthcare professionals to tackle it.

Ethical approval

Ethical approval for this study was obtained from Institutional Health Research Ethics Review Committee of College of Health and Medical Sciences, Haramaya University. An official letter was obtained from the School of Pharmacy (ref. No. SOP 980/02/2017) and given to HFSUH administration to secure permission.

Informed consent

Verbal informed consent was obtained from all subjects before the study. However, written informed consent was not obtained because it is expected that the study involved participants who are illiterate and cannot understand written informed consent. Therefore, by considering this expectation, the Institutional Health Research Ethics Review Committee waived verbal informed consent proposed during proposal submission.

ORCID iD

Jemal Abdela ![iD] https://orcid.org/0000-0003-4205-8641

References

1. Abraham RR. Drug related problems and reactive pharmacist interventions for inpatients receiving cardiovascular drugs. *IJBMSP* 2014; 3: 42–48.
2. Feinleib M, Ingster L, Rosenberg H, et al. Time trends, cohort effects, and geographic patterns in stroke mortality—United States. *Ann Epidemiol* 1993; 3(5): 458–465.
3. Misganaw A, Haregu TN, Deribe K, et al. National mortality burden due to communicable, non-communicable, and other diseases in Ethiopia, 1990–2015: findings from the Global Burden of Disease Study 2015. *Popul Health Metr* 2017; 15: 29.
4. Misganaw A, Mariam DH, Araya T, et al. Patterns of mortality in public and private hospitals of Addis Ababa, Ethiopia. *BMC Public Health* 2012; 12: 1007.
5. Misganaw A, Mariam DH and Araya T. The double mortality burden among adults in Addis Ababa, Ethiopia, 2006–2009. *Prev Chronic Dis* 2012; 9: E84.
6. Adibe MO, Igboeli NU and Ukwe CV. Evaluation of drug therapy problems among renal patients receiving care in some tertiary hospitals in Nigeria. *Trop J Pharmaceut Res* 2017; 16: 697–704.
7. Srikanth A. Assessment of drug related problems and its associated factors among medical ward patients in University of Gondar Teaching Hospital, Northwest Ethiopia: a prospective cross-sectional study. *J Basic Clin Pharm* 2017; 8: S016–S021.
8. Tigabu BM, Daba D and Habte B. Drug-related problems among medical ward patients in Jimma University specialized hospital, Southwest Ethiopia. *J Res Pharm Pract* 2014; 3(1): 1–5.
9. Cipolle RJ, Strand LM and Morley PC. *Pharmaceutical care practice: the patient-centered approach to medication management*. New York: McGraw Hill, 2012.
10. Kumar SBP, Dahal P, Venkataraman R, et al. Assessment of clinical pharmacist intervention in tertiary care teaching hospital of Southern India. *Asian J Pharmaceut Clin Res* 2013; 6: 258–261.
11. Basger BJ, Moles RJ and Chen TF. Development of an aggregated system for classifying causes of drug-related problems. *Ann Pharmacother* 2015; 49(4): 405–418.
12. Aburuz SM, Bulatova NR, Yousef AM, et al. Comprehensive assessment of treatment related problems in hospitalized medicine patients in Jordan. *Int J Clin Pharm* 2011; 33(3): 501.
13. Strand LM, Morley PC, Cipolle RJ, et al. Drug-related problems: their structure and function. *DICP* 1990; 24(11): 1093–1097.

14. Koh Y, Fatimah BM and Li SC. Therapy related hospital admission in patients on polypharmacy in Singapore: a pilot study. *Pharm World Sci* 2003; 25(4): 135–137.

15. Leendertse AJ, Egberts AC, Stoker LJ, et al. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. *Arch Intern Med* 2008; 168(17): 1890–1896.

16. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care* 2000; 38(3): 261–271.

17. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients: results of the Harvard Medical Practice Study I. *N Engl J Med* 1991; 324: 370–376.

18. Patel P and Zed PJ. Drug-related visits to the emergency department: how big is the problem. *Pharmacotherapy* 2002; 22(7): 915–923.

19. Iftikhar S, Sarwar MR, Saqib A, et al. Causality and preventability assessment of adverse drug reactions and adverse drug events of antibiotics among hospitalized patients: a multi-center, cross-sectional study in Lahore, Pakistan. *PLoS ONE* 2018; 13(6): e0199456.

20. Tegegne GT, Gelaw BK, Defersha AD, et al. Drug therapy problem among patients with cardiovascular diseases in Felege Hiwot referral Hospital, Northeast, Bahir Dar Ethiopia. *IAJPR* 2014; 4: 2828–2838.

21. Strand LM, Cipolle RJ and Morley PC. *Pharmaceutical care practice*. New York: McGraw Hill, 2012.

22. Gabb GM, Mangoni AA, Anderson CS, et al. Guideline for the diagnosis and management of hypertension in adults—2016. *Med J Aus* 2016; 205: 85–89.

23. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013; 128(16): 1810–1852.

24. Jagadeesh G, Balakumar P and Maung UK. *Pathophysiology and pharmacotherapy of cardiovascular disease*. Berlin: Springer, 2015.

25. DiPiro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: a pathophysiologic approach*. New York: McGraw Hill, 2014.

26. Mancini GJ, Gosselin G, Chow B, et al. Canadian Cardiovascular Society guidelines for the diagnosis and management of stable ischemic heart disease. *Can J Cardiol* 2014; 30(8): 837–849.

27. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891–975.

28. Schatz S and Weber R. Adverse drug reactions. *Pharm Prac* 2015; 1: 5–25.

29. World Health Organization. *WHO centre for health development, ageing and health technical report. A glossary of terms for community health care and services for older persons*, Vol. 5. Geneva: WHO, 2004, http://www.who.int/kobe_centre/ageing/ahp_vol5_glossary.pdf

30. Valderas JM, Starfield B, Sibbald B, et al. Defining comorbidity: implications for understanding health and health services. *Ann Fam Med* 2009; 7(4): 357–363.

31. American Society of Health System Pharmacists. ASHP guidelines on adverse drug reaction monitoring and reporting.

American Society of Hospital Pharmacy. *Am J Health Syst Pharm* 1995; 52: 417–419.

32. Hanlon JT, Schmader KE, Ruby CM, et al. Suboptimal prescribing in older inpatients and outpatients. *J Am Geriatr Soc* 2001; 49(2): 200–209.

33. Gandhi TK, Weingart SN, Borus J, et al. Adverse drug events in ambulatory care. *N Engl J Med* 2003; 348: 1556–1564.

34. Rothschild JM, Bates DW and Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; 160(18): 2717–2728.

35. Winterstein AG, Sauer BC, Hepler CD, et al. Preventable drug-related hospital admissions. *Annals of Pharmacotherapy* 2002; 36: 1238–1248.

36. Phillips DP, Christenfeld N and Glynn LM. Increase in US medication-error deaths between 1983 and 1993. *Lancet* 1998; 351(9103): 643–644.

37. Phillips DP, Jarvinen JR and Phillips RR. A spike in fatal medication errors at the beginning of each month. *Pharmacotherapy* 2005; 25(1): 1–9.

38. Grymonpre RE, Mitenko PA, Sitar DS, et al. Drug-associated hospital admissions in older medical patients. *J Am Geriatr Soc* 1988; 36(12): 1092–1098.

39. Col N, Fanale JE and Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. *Arch Intern Med* 1990; 150(4): 841–845.

40. Bates DW, Leape LL and Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *J Gen Intern Med* 1993; 8(6): 289–294.

41. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. *JAMA* 1995; 274(1): 29–34.

42. Gurwitz JH, Field TS, Judge J, et al. The incidence of adverse drug events in two large academic long-term care facilities. *Am J Med* 2005; 118(3): 251–258.

43. Tegegne GT, Yimam B and Yesuf EA. Drug therapy problems and contributing factors among patients with cardiovascular diseases in Felege Hiwot Referral and Jimma University Specialized Hospital, Ethiopia. *Indian J Res Pharm Biotechnol* 2015; 3: 85.

44. Bain KT, Weschules DJ and Tillotson P. Prevalence and predictors of medication-related problems. *Pharmacotherapy* 2006; 2: 4.

45. Starfield B, Lemke KW, Bernhardt T, et al. Comorbidity: implications for the importance of primary care in "case" management. *Ann Fam Med* 2003; 1(1): 8–14.

46. Westberg SM, Derr SK, Weinhandl ED, et al. Drug therapy problems identified by pharmacists through comprehensive medication management following hospital discharge. *J Pharm Technol* 2017; 33: 96–107.

47. Yimama M, Jarso H and Desse TA. Determinants of drug-related problems among ambulatory type 2 diabetes patients with hypertension comorbidity in Southwest Ethiopia: a prospective cross sectional study. *BMC Res Notes* 2018; 11(1): 679.

48. Al-Azzam SI, Alzoubi KH, AbuRuz S, et al. Drug-related problems in a sample of outpatients with chronic diseases: a cross-sectional study from Jordan. *Ther Clin Risk Manag* 2016; 12: 233.

49. Tegegne GT, Gaddisa T, Kefale B, et al. Drug therapy problem and contributing factors among ambulatory hypertensive patients in Ambo General Hospital, West Shoa, Ethiopia. *Glob J Med Res* 2015; 15(4): 20–26.