Drug-drug interaction, adverse drug reaction and their determinants among adult hypertensive patients; Multicenter study in Ethiopia

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Abstract

Background

Hypertensive patients are at high risk of adverse drug interaction (ADR) and drug-drug interaction (DDI) because of high tendency to use multiple drugs; this can undermine the quality of patients' care. The aim of the study was to assess the magnitude of ADR, DDI, and their determinants among adult hypertensive patients at selected hospitals in Ethiopia.

Methods

A hospital-based cross-sectional study was conducted using chart reviews and patient interviews. DDIs were identified and classified using the Medscape online DDI checker. Written informed consent was obtained, and multivariate logistic regression was performed with statistical significance at $p \leq 0.05$.

Results

Among a total of 543 hypertensive patients ADR was reported in 32.2%, with the most common being weakness (33.7%), followed by gastric irritation (33.1%), and headache (30.3%). Nearly half of the patients (47.9%) experienced at least one DDI. A total of 789 DDIs with mean of 3.03 ± 2.22 was identified in the study participants. Enalapril plus metformin was found as the most common contributing for DDI. Multivariable logistic regression analysis showed that patients with comorbid conditions, (AOR = 2.42; 95%CI: 1.25–4.67; p = 0.008), increasing number of concurrent medications use (AOR = 6.93; 95%CI: 4.50–10.69; p < 0.001), use of furosemide (AOR = 14.42; 95%CI: 4.38–47.48; p < 0.001), metformin (AOR = 23.57; 95%CI: 7.53–73.72; p < 0.001), and propranolol (AOR = 7.56; 95%CI: 1.12–50.61; p = 0.037) were significantly associated with higher odds of DDI. Increasing age (AOR = 1.017; 95%CI: 1.000–1.034; p = 0.044) and presence of comorbid conditions (AOR = 1.506; 95%CI: 1.001–2.264; p = 0.049) as well as, the use of enalapril (AOR = 1.751; 95%CI: 1.143–2.683; p = 0.010), nifedipine (AOR = 2.359; 95%CI: 1.013–5.492; p = 0.047), hydrochlorothiazide (AOR = 1.712; 95%CI: 1.112–2.635; p = 0.015) and increased number of concurrent medications (AOR = 1.287; 95%CI: 1.091–1.519; p = 0.003) were significantly associated with higher odds of ADRs.

Conclusion

This study found a high prevalence of DDI and ADR; with nearly half experiencing DDIs and about one-third reporting ADRs with different independent predictors. These findings highlight the need for regular medication review and close clinical monitoring to improve medication safety and optimize hypertension management.

Introduction

World Health Organization (WHO) report shows hypertension affects 1 in 3 adults worldwide. Globally 56%(1), in the USA (per the new definition of hypertension) 49.64% (2), in Africa 36% (1), and in Ethiopia 30% (3) of adult population has hypertension. Hypertension is, a deadly condition which leads to 10.8 million avoidable deaths every year out of 41 million death from non-communicable disease (NCD) and different morbidities (stroke, heart attack, heart failure, kidney damage) and enormous economic costs(1). Appropriate hypertension management will save lives and improve wellbeing (1). In-appropriately treated hypertension has worst health outcomes(4), which is higher in Africa (5).

Appropriate hypertension management through ensuring that people receive appropriate ant-hypertensive therapy and free from drug-drug interaction (DDI) and adverse drug reaction (ADR) to BP goal achievement has been highly recommended (6–10). Thus, by improving BP control alone, the global health care savings have been estimated at $100 billion per year (11), and it can assure the achievement of Sustainable Development Goal (SDG) target 3.4; one third reduction in premature mortality by 2030 from NCD (1, 11).

DDI is defined as the qualitative or quantitative modification of the effect of a drug by the simultaneous or successive administration of a different drugs. This may result in the alteration of therapeutic effect and safety of either or both drugs. It is a great concern among hypertensive patients due to the tendency of receiving multidrug therapy(12). However, it is important to remember that DDI may be beneficial or harmful. Thus, WHO recommends that the problem can be significantly minimized by implementing careful attention to the identification and resolution of DDIs (13, 14). DDI studies among hypertensive patients out of Ethiopia showed that the prevalence is as high as 47.6% to 89.06% (13, 15, 16), where majority of them were significant in severity (85.36%) to 95.42%. A lots of antihypertensive medication have been contributing for DDI (13, 15–17).

Even though it is highly recommended to have surveillance on DDI among hypertension patients to take appropriate intervention, the available data in Ethiopia is limited(12) (to our knowledge only one study before 10 years in single hospital (18) and no study in West Shoa Zone. The other studies on DDI were not specific to antihypertensive (it is general or related with cardiovascular disease)(19–22). In fact, those data showed high prevalence of DDI in Ethiopia among patients with cardiovascular disease (CVD) (19–22); Addis Ababa 90.1% (19) and at Dessie Referral Hospital, Ethiopia 1.63 DDI per patient (23).

Therefore, investigating adverse drug reactions (ADRs), drug–drug interactions (DDIs), and their determinants is essential to quantify the magnitude of the problem and enable early intervention to optimize antihypertensive therapy. These findings provide valuable evidence to support healthcare providers in improving patient care and minimizing ADRs and DDIs during clinical management.

Methods and Participants

Study area, period and design:

A hospital-based cross-sectional study was conducted in 5 selected public hospitals (multi-center study) in the West Shoa Zone, Oromia, Ethiopia, from January 01 2024 to April 30, 2024. West Shoa Zone has ten public hospitals in general which serves around 3.6 million populations. From the 10 hospitals, by lottery method 5 hospitals, namely, Guder Primary Hospital, Ambo University Referral Hospital, Ambo General Hospital, Ginchi Primary Hospital and Bako Primary Hospital were included to the study. The selected hospitals have separate outpatient departments for the treatment and follow-up of chronic diseases including hypertension. So the data for this study was collected from the outpatient department of chronic diseases follow up.

Study Participants Recruitment, Sampling and Data Collection Procedure

Adult hypertensive patients (≥ 18 years) on pharmacologic treatment for at least 6 months and on follow up during data collection period were included by systematic random sampling methods from selected hospitals with inclusion criteria (proportional allocation was made for each hospitals). Pregnant mothers, refuse to participate in the study, patients with cognitive impairment, seriously ill patients (admission) that made it impossible to conduct a reliable interview and patients with incomplete medical records were excluded.

Study variables:

Dependent variables were, DDI and ADR, while independent variables were: sociodemographic, disease related factors, presence of metabolic syndrome (BMI or WHR), drug related factors (number and type of drug used), and behavioral factors (alcohol, khat, and tobacco use habit).

Sample size and sampling procedure

Sample size was calculated for different objectives and/ or predictor variables and then the largest sample size (588) was selected as a final sample size. For determinant factor double population formula was used with 95% C.I and 80% powers from study at Nekemte, Ethiopia (8).

Determinant factor	p-value	AOR	%outcome exposed	%outcome un-exposed	Power (%)	95%c.I	Sample size
Sex	0.005	1.89	44%	31.5	80	95	233
Age	0.030	0.38	37	63.9	80	95	51
Adherence to drug	0.032	3.14	66.3	41.1	80	95	58
Physical exercise	0.02	2.8	37.9	24.2	80	95	176

A single population formula was used to calculate the sample size for BP control rate. The assumptions considered during the calculation of the sample size were 95% confidence level, 5% margin of error, and p = 36.4%; prevalence of uncontrolled hypertension from the study carried out in Nekemte, Ethiopia(8).

$$n = \frac{(Z\alpha/2)^2\, p\,(1-p)}{w^2} = \frac{(1.96)^2\, X\,(0.364x0.636)}{(0.05)^2} = 356$$

Where;

a. N is the size of the population that the sample is to represent = 13748 hypertensive patients in West Shoa in 2015 E.C from DHIS 2.
b. Design effect= 1.5, thus 1.5*356= 534 (2 stage sampling)
c. 10% for non-response rate = 54 +534 = 588

The sample size for each hospital was proportionally allocated with the ratio of 588/11360= 0.052. Systematic random sampling method (every K^{th}) was used to select the study participants from each selected hospitals.

Data Collection Tool, Process and Quality Control

The data collection tool used for this study was annexed as supplementary material (data collection tool). Data was collected with semi-structured questionnaire through patient interviews and medical record reviews. A medical chart review and a data abstraction tool was filled for each eligible patient to get relevant information like co-morbid condition/s, BP and laboratory values, medication/s. Patients were interviewed to obtain socio-demographic, disease-related, behavioral/ lifestyle and compliance to medication/salt related information. The pretest was done on 5% of the total sample to ensure the quality and agreement of the data abstraction format with the objective of the study and adjustments were done accordingly.

The identification of DDI was done based on the 'Medscape online drug interaction checker'(24). All concurrent medications were entered into Medscape, which classifies DDIs by severity: (1) Contraindicated – risks outweigh benefits; (2) Serious – avoid or modify therapy; (3) Significant – monitor for adverse effects or reduced efficacy; (4) Minor – minimal or unknown clinical impact. Polypharmacy was defined as the use of ≥ 5 medications concurrently(25). ADRs were defined as any harmful or unintended drug response perceived by the patient to be caused by their medications(24). ADR is considered based on patient report after probing that the compliant was started after the use of the offending drug (any drug used by patient).

Data Processing and Analysis:

The data was entered, cleaned and analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0. Descriptive statistics including frequency, percentages, mean and standard deviation (SD) were used to summarize study variables. Multivariate logistic regression was done for variables with p-value less than 0.25 and known predictors from previous study to determine factors associated with DDI with p-values ≤ 0.05 for statistical significance.

Results

Socio-demographic and clinical characteristics of study participants

The details of the socio demographic characteristics of the study participants was available elsewhere in other document 'Psychometric property of Hill bone high blood pressure therapy compliance scale' because it was done simultaneously. A total of 543 hypertensive patients were included in the study with response rate of 92.3%. The mean (± SD) age of the participants was 56.5 ± 12.3 years.

Based on the age-adjusted Charlson comorbidity index (CCI), patients were almost equally distributed between the low-risk (42.7%) and moderate-risk (42.9%) categories, with fewer in the high-risk group. About half (50.8%) had at least one chronic comorbid condition, most commonly a single condition (83%). Diabetes mellitus was the leading comorbidity (50.4%), followed by heart failure (19.6%) and asthma/Chronic Obstructive Pulmonary Disease (COPD) (14.1%) (Table 1).

Table 1
clinical characteristics of study participants at selected hospitals of West Shoa Zone, January to April 30/2024, Ethiopia (N = 543)

Variables Categories		Frequency	%
Age based Charlson CI risk classification score (N = 543)	low risk (0–2 score)	232	42.7
	moderate risk (3–4 score)	233	42.9
	high risk (> = 5 score)	78	14.4
	Median (IQR), min-max	3[2–4], 1–10	
Chronic Co-morbid condition based on CCI (N = 543)	No	267	49.2
	Yes	276	50.8
Number of comorbid condition (N = 276)	1	229	83.0
	2	37	13.4
	≥ 3	10	3.6
List of chronic common co-morbid condition based on CCI (top 10)(N = 276)	DM	139	50.4
	Heart failure	54	19.6
	Asthma/COPD	39	14.1
	Gastritis/PUD	22	8.0
	Stroke/TIA	21	7.6
	CKD	13	4.7
	Rheumatic/connective tissue disease	13	4.7
	IHD	10	3.6
	PVD	8	2.9
	HIV/AIDS	7	2.5
	Others#	15	5.4

Note: **other#**- (hemiplegia, Cancer, Dementia/Alzheimer, Depression); COPD-chronic obstructive pulmonary disease; DM-diabetes mellitus; PUD-peptic ulcer disease; TIA-transient ischemic attack; CKD-chronic kidney disease, IHD-ischemic heart disease; PVD-peripheral vascular disease; HIV/AIDS-Human immune virus/ Acquired immune deficiency syndrome;

Prevalence of Drug-drug interaction and Adverse Drug Reaction

Among 543 patients, 16.0% were identified to have polypharmacy. Nearly half of the patients (47.9%) experienced at least one drug-drug interaction (DDI), regarding the severity of DDI, significant interactions being the most common (85.4%), and 17.3% experiencing serious interactions. There was no contra-indicated type of DDI identified. The mean number of DDIs per patient with interactions (among 260 patients) was 3.03 ± 2.22 (range 1–12), with a total of 789 DDIs identified in the study participants.

Regarding adverse effects, 32.2% of patients reported at least one adverse drug reaction, with the most common being weakness (33.7%), gastric irritation (33.1%), headache (30.3%), and ankle swelling (10.3%) (Table 2**).**

Table 2
Drug-drug interaction and patient reported ADR among hypertensive patients at selected hospitals of West Shoa Zone, Ethiopia (N = 543)

Variables	Category	Frequency	Percentages
Poly pharmacy (N = 543)	No	456	84.0
	Yes	87	16.0
Overall drug-drug interaction (N = 543)	No	283	52.1
	yes	260	47.9
Severity of drug-drug interaction (N = 260)	Minor	83	31.9%
	Significant	222	85.4%
	Serious	45	17.3%
Number of drug-drug interaction per patient (N = 260)	1	73	28.1%
	2	58	22.3%
	3	52	20.0%
	4	31	11.9%
	≥ 5	46	17.7%
	Mean ± SD (min. to maximum)	3.03 ± 2.22 (1–12)	
Summary of drug-drug interaction	Sum (total DDI)	789 DDI identified	
	Average per patients with DDI (260)	3.04 DDI	
	Average per sample (543)	1.45 DDI	
Total number of DDI by level of severity (N = 260)	Minor	153	0.6 DDI*
	Significant	584	2.3 DDI*
	Serious	52	0.2 DDI*
Adverse drug reaction (self-report) (N = 543)	No	368	67.8
	Yes	175	32.2
Type of adverse drug reaction reported by patients (N = 175)- Multiple response	Weakness	59	33.7%
	Headache	53	30.3%

Note: **DDI***- average drug-drug interaction per 260 patients; DDI- drug-drug interaction; **Other$**- (chest pain, urinary retention, shortness of breath, constipation, hyperkalemia, synchro/seizure, liver toxicity, dry mouth)

Variables	Category	Frequency	Percentages
	Erectile dysfunction	5	2.9%
	Gastric irritation (GI compliant)	58	33.1%
	Dry cough	9	5.1%
	Ankle swelling	18	10.3%
	Generalized body edema	10	5.7%
	Skin itching/ allergic reaction	11	6.3%
	Hypotension	3	1.7%
	Dizziness	5	2.9%
	Pain/tingling of extremities	3	1.7%
	Others$	11	6.2%

Note: **DDI***- average drug-drug interaction per 260 patients; DDI- drug-drug interaction; **Other$**- (chest pain, urinary retention, shortness of breath, constipation, hyperkalemia, synchro/seizure, liver toxicity, dry mouth)

Common drugs contributing for DDI and it clinical consequence

Among the identified drug–drug interactions (DDIs), the most frequently observed combination was enalapril plus metformin, accounting for 89 cases (34.2%), which was associated with increased metformin toxicity and a heightened risk of hypoglycemia and lactic acidosis. This was followed by amlodipine plus metformin in 69 cases (26.5%), where amlodipine reduced the therapeutic effect of metformin through pharmacodynamics antagonism, potentially leading to hyperglycemia.

The combination of aspirin and enalapril was observed in 38 patients (14.6%) and was linked to pharmacodynamics antagonism with possible acute kidney injury, classified as significant to serious in severity. Similarly, glyburide plus atorvastatin occurred in 37 cases (14.2%) and increased the risk of atorvastatin-induced myopathy.

Interactions involving antihypertensive and diuretic agents were also common. Enalapril plus furosemide was identified in 31 cases (11.9%), posing a risk of acute hypotension and renal insufficiency due to synergistic effects. Enalapril plus glyburide, reported in 27 cases (10.4%), increased the risk of hypoglycemia, while enalapril plus insulin was seen in 16 cases (6.2%) with a similar synergistic hypoglycemic effect.

Antidiabetic drug combinations contributed substantially to DDIs; metformin plus insulin was identified in 18 cases (6.9%), significantly increasing hypoglycemia risk. Cardiovascular drug combinations such as aspirin plus metoprolol (17 cases; 6.5%) and metoprolol plus furosemide (11 cases; 4.2%) were associated with alterations in serum potassium levels.

Less frequent but clinically relevant interactions included propranolol or bisoprolol plus amlodipine (9 cases; 3.5%), which may synergistically lower blood pressure and cause hypotension; nifedipine plus metformin (7 cases; 2.7%), associated with reduced glycemic control; and atorvastatin plus amitriptyline (10 cases; 3.8%), which increased amitriptyline exposure. In addition, combinations involving aspirin or spironolactone with furosemide were noted in 16 cases (6.2%), potentially affecting serum potassium levels.

Overall, the majority of identified DDIs were classified as significant in severity, underscoring the need for careful medication review and close clinical monitoring in patients receiving multiple chronic therapies **(**Table 3**).**

Table 3
List of top-15 drugs contributed to DDI, their Prevalence, and Expected Negative Effects among hypertensive patients at selected hospitals of West Shoa Zone, Ethiopia (N = 543)

List of common drugs contributed to DDI	Prevalence of DDI (%)	Clinical consequence of DDI	Severity of DDI per Medscape checker
Enalapril + metformin	89 (34.2)	Increased metformin toxicity: Increases risk for hypoglycemia and lactic acidosis.	Significant
Amlodipine + metformin	69 (26.5)	Amlodipine decreases effects of metformin by pharmacodynamics antagonism-hyperglycemia.	Significant
Aspirin + enalapril	38 (14.6)	Increase risk of acute renal insufficiency, pharmacodynamics antagonism	Significant-serious
Glyburide + atorvastatin	37 (14.2)	Increase risk of atorvastatin myopathy	Significant
Enalapril + furosemide	31 (11.9)	Increase risk of acute renal insufficiency & hypotension (synergism)	Significant
Enalapril + glyburide	27 (10.4)	Enalapril increase risk of hypoglycemia (synergism)	Significant
Metformin + insulin	18 (6.9)	Increased risk of hypoglycemia (synergism)	Significant
Aspirin + metoprolol	17 (6.5)	Increased serum potassium(synergism)	Significant
Enalapril + insulin	16 (6.2)	Increases risk for hypoglycemia(synergism)	Significant
Aspirin/ Spironolactone + Furosemide	16 (6.2)	Affect serum potassium (Unclear effect)	Significant
Atenolol/Propranolol/bisoprolol + amlodipine	13 (5.0)	Synergize BP reduction / hypotension	Significant

Note: **Others#-** (folic acid + methotrexate, amitriptyline + metformin, amitriptyline + metformin, hydrochlorothiazide + metoprolol, indomethacin + albuterol, amitriptyline + tramadol, amlodipine + phenytoin, valproic acid + phenytoin, amoxicillin + hydrochlorothiazide, artemether/lumefantrine + primaquine, aspirin + hydrochlorthiazide. aspirin + albuterol/propranolol/bisoprolol, phenytoin + amlodipine/atorvastatin/valproate, prednisolone + HCT, propranolol + insulin), Amitriptyline + albuterol, Diclofenac/dexamethasone + enalapril, CBZ + atorvastatin, Beclomethasone + HCT, Beclomethasone + furosemide, Gabapentine + amitriptyline, Tramadol + albuterol, Indomethacin + enalapril, CBZ + amlodipine, Albuterol + furosemide, Indomethacin + HCT, Furosemide + HCT, Nifedipine + atorvastatin, carbamazepine + HCT/enalapril, phenobarbito + amlodipine/carbamazepine, Metoprolol + albuterol, Metformin + HCT).

List of common drugs contributed to DDI	Prevalence of DDI (%)	Clinical consequence of DDI	Severity of DDI per Medscape checker
Metoprolol + furosemide	11 (4.2)	Affect serum potassium (Unclear effect)	Significant
Atorvastatin + amitriptyline	10 (3.8)	Atorvastatin will increase the level or effect of amitriptyline	Significant
Nifedipine + metformin	7 (2.7)	Amlodipine decreases effects of metformin by pharmacodynamic antagonism-hyperglycemia.	Significant
Digoxin + furosemide	6 (2.3)	Hypokalemia increases digoxin effects & Affect serum potassium (Unclear effect)	Significant
Aspirin + spironolactone	5 (1.9)	Both increase serum potassium	Significant
Others#	92 (35.4)		

Note: **Others#-** (folic acid + methotrexate, amitriptyline + metformin, amitriptyline + metformin, hydrochlorothiazide + metoprolol, indomethacin + albuterol, amitriptyline + tramadol, amlodipine + phenytoin, valproic acid + phenytoin, amoxicillin + hydrochlorothiazide, artemether/lumefantrine + primaquine, aspirin + hydrochlorthiazide. aspirin + albuterol/propranolol/bisoprolol, phenytoin + amlodipine/atorvastatin/valproate, prednisolone + HCT, propranolol + insulin), Amitriptyline + albuterol, Diclofenac/dexamethasone + enalapril, CBZ + atorvastatin, Beclomethasone + HCT, Beclomethasone + furosemide, Gabapentine + amitriptyline, Tramadol + albuterol, Indomethacin + enalapril, CBZ + amlodipine, Albuterol + furosemide, Indomethacin + HCT, Furosemide + HCT, Nifedipine + atorvastatin, carbamazepine + HCT/enalapril, phenobarbito + amlodipine/carbamazepine, Metoprolol + albuterol, Metformin + HCT).

Common drugs contributing for DDI and its potential effect on Blood pressure

Among the study participants (N = 260), most DDIs had no potential effect on blood pressure (188; 72.3%), while 16.9% (44 cases) decreased BP and 10.8% (28 cases) increased BP. Interactions between CVD and non-CVD drugs were the most frequent (100; 38.5%), followed by within-CVD interactions (71; 27.3%) and all-class interactions (70; 26.9%); non-CVD interactions were least common (19; 7.3%). Among DDIs affecting BP (N = 72), significant severity predominated (41; 56.9%), with minor (29; 40.3%) and serious (2; 2.8%) interactions occurring less frequently (Table 4**).**

Table 4
clinical effect of DDI on BP and common class of drugs contributing for DDI among hypertensive patients at selected hospitals of West Shoa Zone, Ethiopia (N = 260)

Variables	Categories	Frequency	Percentages
DDI effect on BP (N = 260)	No effect	188	72.3
	Decreased	44	16.9
	Increased	28	10.8
Type of DDI by therapeutic class (N = 260)	All type	70	26.9
	CVD with Non-CVD	100	38.5
	non CVD	19	7.3
	Within-CVD	71	27.3
Level of DDI effect on BP (N = 72)	Serious	2	2.8
	Significant	41	56.9
	Minor	29	40.3

Predictors of Drug-drug interaction (DDI)

Binary logistic regression was performed to screen candidate variables for multivariable logistic regression. Variables with a p-value ≤ 0.25 in the bivariable analysis, as well as variables identified as significant predictors in previous studies (including polypharmacy and overall number of medications used), were entered into the multivariable model to identify independent predictors of drug–drug interactions (DDIs).

Multivariable logistic regression analysis showed that patients with comorbid conditions (AOR = 2.42; 95% CI: 1.25–4.67; p = 0.008), an increasing number of medications (AOR = 6.93; 95% CI: 4.50–10.69; p < 0.001), use of furosemide (AOR = 14.42; 95% CI: 4.38–47.48; p < 0.001), metformin (AOR = 23.57; 95% CI: 7.53–73.72; p < 0.001), and propranolol (AOR = 7.56; 95% CI: 1.12–50.61; p = 0.037) were significantly associated with higher odds of DDI. In contrast, use of enalapril (AOR = 0.28; 95% CI: 0.13–0.60; p = 0.001), amlodipine (AOR = 0.27; 95% CI: 0.13–0.57; p = 0.001), hydrochlorothiazide (AOR = 0.49; 95% CI: 0.24–0.98; p = 0.044), and beclomethasone (AOR = 0.18; 95% CI: 0.03–0.89; p = 0.036) were associated with reduced odds of DDI (Table 5).

Table 5
Predictors of DDI among hypertensive patients at selected hospitals of West Shoa Zone, Ethiopia (N = 543)

Variables	Category	Drug interaction		COR	AOR	95% CI	P-value#
		No (%)	Yes (%)				
Comorbid condition	No	200(75.2)	66(24.8)	1	1	-	
	Yes	83(30.0)	194(70.0)	2.96	2.42	1.25–4.67	0.008
Overall Number of drugs used	Median ± SD	2 ± 0.92	4 ± 1.31	9.65*	6.93	4.50-10.69	0.000
Enalapril	No	176(64.5)	97(35.5)	1	1	-	
	Yes	107(39.6)	163(60.4)	0.24*	0.28	0.13–0.60	0.001
Propranolol	No	281(52.4)	255(47.6)	1	1	-	
	Yes	2 (28.6)	5(71.4)	5.36	7.56	1.12–50.61	0.037
Amlodipine	No	97(43.9)	124(56.1)	1	1	-	
	Yes	186(57.8)	4 (2.2%)	0.26*	0.268	0.13–0.57	0.001
HCT	No	169(45.4)	203(54.6)	1	1	-	
	Yes	114(66.7)	57(33.3)	0.31*	0.49	0.24–0.98	0.044
Furosemide	No	278(55.7)	221(44.3)	1	1	-	
	Yes	5(11.4)	39(88.6)	9.08*	14.42	4.38–47.48	0.000
Metformin	No	278(68.3)	129(31.7)	1	1	-	
	Yes	5(3.7)	131(96.3)	55.40*	23.57	7.53–73.72	0.000
Aspirin	No	277(56.6)	212(43.4)	1	1	-	
	Yes	6(11.1)	48(88.9)	3.12	3.13	0.85–11.52	0.080
Beclomethasone	No	278(53.2)	245(46.8)	1	1	-	
	Yes	5(25.0)	15 (75.0)	0.10	0.18	0.03–0.89	0.036

Note: * -p-value is < 0.05, #- p-value for multivariate logistic regression

Predictors of patient reported adverse drug reaction (ADR)

After running bivariate logistic analysis, the variables with p-value ≤ 0.25 were entered into multivariate logistic regression analysis. Hence, being male (AOR = 0.626; 95% CI: 0.413–0.948; p = 0.027), lack of physical exercise (AOR = 0.615; 95% CI: 0.403–0.940; p = 0.025), the use of glyburide (AOR = 0.370; 95% CI: 0.189–0.726; p = 0.004), and use of beclomethasone (AOR = 0.177; 95% CI: 0.045–0.693; p = 0.013) were associated with a significantly lower likelihood of ADRs. Increasing age, with each one-year increase in age increasing the odds of ADRs by approximately 2% (AOR = 1.017; 95% CI: 1.000–1.034; p = 0.044) and an increase in the number of concurrent medications, with each additional medication increasing the odds by about 29% (AOR = 1.287; 95% CI: 1.091–1.519; p = 0.003). The presence of comorbid conditions (AOR = 1.506; 95% CI: 1.001–2.264; p = 0.049), the use of enalapril (AOR = 1.751; 95% CI: 1.143–2.683; p = 0.010), the use of nifedipine (AOR = 2.359; 95% CI: 1.013–5.492; p = 0.047) and hydrochlorothiazide (AOR = 1.712; 95% CI: 1.112–2.635; p = 0.015) were significantly increased the odds of ADRs (Table 6).

Table 6
Predictors of ADR among hypertensive patients at selected hospitals of West Shoa Zone, Ethiopia (N = 543)

Variables	Categories	ADR		AOR	95% CI	p-value
		No (%)	Yes (%)			
Sex	Female	196 (66.0)	101 (34.0)	1		
	Male	172 (69.9)	74(30.1)	0.626	0.413–0.948	0.027
Age	Mean ± SD	55.86 ± 12.34	57.93 ± 12.25	1.017	1.000-1.034	0.044
Physical exercise	Yes	226 (65.9)	117 (34.1)	1		
	No	142 (71.0)	58 (29.0)	0.615	0.403–0.940	0.025
Comorbid condition	No	193 (72.6)	73 (27.4)	1		
	Yes	175 (63.2)	102 (36.8)	1.506	1.001–2.264	0.049
Enalapril	No	197 (72.2)	76 (27.8)	1		
	Yes	171 (63.3)	99 (36.7)	1.751	1.143–2.683	0.010
Amlodipine	No	149 (67.4)	72 (32.6)	1		
	Yes	219 (68.0)	103 (32.0)	1.506	0.956–2.373	0.078
Nifedipine	No	348 (68.2)	162 (31.8)			
	Yes	20 (60.6)	13 (39.4)	2.359	1.013–5.492	0.047
Hydrochlorothiazide	No	257 (69.1)	115 (30.9)	1		
	Yes	111 (64.9)	60 (35.1)	1.712	1.112–2.635	0.015
Number of concurrent medication	Mean ± SD	1.23 ± 0.42	1.40 ± 0.49	1.287	1.091–1.519	0.003
Glyburide	No	323 (67.2)	158 (32.8)	1		

Variables	Categories	ADR		AOR	95% CI	p-value
		No (%)	Yes (%)			
	Yes	45 (72.6)	17 (27.4)	0.370	0.189–0.726	0.004
Beclomethasone	No	351 (67.1)	172 (32.9)	1		
	Yes	17 (85.0)	3 (150)	0.177	0.045–0.693	0.013

Discussion

This is a first study in its nature of assessing DDI and patient reported ADR among HTN patients in Ethiopian context. This study provides valuable insights into the patient safety related to medication therapy, highlighting its influence on blood pressure (BP) control.

The study revealed that, based on the age-adjusted Charlson comorbidity index (CCI), majority were in low-risk and moderate-risk categories. Low high risk CCI distribution suggests that while many hypertensive patients have comorbidity, most do not have multiple or severe conditions that would substantially increase their mortality risk. Yet, using tools such as the CCI can help clinicians identify high-risk patients who may require more intensive monitoring and tailored interventions to optimize outcomes (26).

Diabetes mellitus (DM) was the leading comorbid condition (50.4%), followed by heart failure (19.6%). This finding was consistent with others studies: a study conducted in Puducherry, India, identified diabetes mellitus (DM) as the most common comorbidity among hypertensive patients, accounting for 19.2% (13), Similarly, a multicenter study in China reported DM as the leading comorbidity, followed by other cardiovascular diseases among hypertensive patients (27, 28). Consistent findings were also observed in a multicenter study in Ethiopia, where DM was the most prevalent comorbidity, affecting 26.7% of hypertensive patients (29). Conversely, when examining comorbidities among patients with DM, hypertension was identified as the most common condition (28, 30). These findings strongly indicate the need for strict clinical attention in hypertensive patients, as the coexistence of hypertension and DM substantially increases cardiovascular risk and premature mortality (28). Furthermore, previous studies have demonstrated that comorbid conditions, particularly DM significantly affect blood pressure control and overall health outcomes among hypertensive patients (28, 29, 31). It is a challenge for achieving guideline-recommended blood pressure targets.

Hypertensive patients with comorbidities and concurrent medication use have a high likelihood of experiencing clinically significant drug–drug interactions (DDIs). Therefore, clinicians and pharmacists must remain vigilant in identifying potential DDIs to minimize their adverse effects (13, 14). In the current study, nearly half of the patients (47.9%) experienced at least one DDI. This prevalence is comparable to

findings from studies conducted in South-West Nigeria (47.6%) (17) and Puducherry, India (48%) DDI(13). However, higher prevalence were reported in studies from Universitas Airlangga Teaching Hospital, Surabaya, Indonesia (89.06%) (16), Addis Ababa, Ethiopia (90.1%) (19), and central Gujarat, India (71.5%) (15). These discrepancies may be attributed to differences in DDI identification tools (Medscape versus Lexicomp Drug Interaction Checker) (16, 32), study populations, and clinical settings particularly studies focusing on elderly patients (> 60 years) or those with cardiovascular diseases (19).

In the present study, significant-severity DDIs were the most frequently observed, accounting for 85.4% of all identified interactions. Among patients who experienced at least one DDI (n = 260), the mean number of DDIs per patient was 3.03. This average number of DDIs per patient is considerably higher than reports from South-West Nigeria (1.3 DDIs per patient) (17), and Dessie, Ethiopia (1.6 DDIs per patient) (23). The observed variation may be attributed to differences in study populations and, more importantly, methodological differences in DDI assessment. For instance, the Nigerian study evaluated interactions only among antihypertensive and antiplatelet medications (17), whereas the current study assessed all medications used by patients, thereby increasing the likelihood of detecting DDIs. With respect to DDI severity, the predominance of significant interactions in the current study is consistent with findings from studies conducted in Indonesia (32), and Dessie, Ethiopia(23), where moderate/significant-severity DDIs were also most common (89.4%). In contrast, studies from central Gujarat, India(15) and Puducherry, India (13), reported a higher proportion of clinically significant DDIs (85.36%). Similarly, a study from Addis Ababa, Ethiopia, conducted among elderly patients with cardiovascular diseases, reported a higher burden of DDI, with 75%, and 83.3% notable proportions of moderate/significant and minor DDIs, respectively (19). These differences may reflect variations in patient age, comorbidity burden, medication complexity, and clinical settings.

The present study identified enalapril plus metformin as the most frequently observed drug combination associated with DDIs, accounting for 34.2% of all interactions. This combination is known to increase metformin toxicity and elevate the risk of hypoglycemia and lactic acidosis. The second most common interacting pair was amlodipine plus metformin (26.5%), in which amlodipine may reduce the therapeutic effectiveness of metformin through pharmacodynamic antagonism, potentially resulting in poor glycemic control and hyperglycemia. Similarly, studies conducted in central Gujarat (15) and Puducherry, India (13) reported atenolol, aspirin, and amlodipine as the most common medications implicated in DDIs among hypertensive patients.

Overall, the majority of identified DDIs in the current study were classified as clinically significant, highlighting the importance of systematic medication review and close clinical monitoring in patients receiving multiple long-term therapies. Among participants who experienced DDIs (N = 260), most interactions had no apparent effect on BP (72.3%); however, 16.9% were associated with a decrease in BP, while 10.8% were associated with an increase in BP. Consistent with previous studies, DDIs in hypertensive patients have been linked to a range of clinically relevant complications, including electrolyte disturbances particularly potassium imbalance (13, 15, 17, 19, 32), increased risk of acute kidney injury (13, 17), interference with blood pressure control (either elevation or reduction of BP) (13–

15, 17, 19, 32), and an increased risk of myopathy (13, 19). These findings further emphasize the critical role of clinicians and pharmacists in proactive DDI screening and individualized patient management.

The present study demonstrated that the presence of comorbid conditions, a higher number of concurrent medications, and the use of furosemide, metformin, and propranolol were significantly associated with increased odds of drug–drug interactions (DDIs). In contrast, the use of enalapril, amlodipine, hydrochlorothiazide, and beclomethasone was associated with reduced odds of DDIs. This apparent protective effect may be attributed to the frequent prescription of these agents as monotherapy or in standardized treatment combinations, which limits exposure to complex multidrug regimens and consequently reduces the likelihood of clinically significant interactions. These findings are consistent with reports from studies conducted in Nigeria and India (13, 17), Indonesia (32), and Dessie, Ethiopia (23), all of which identified the number of prescribed medications as a significant predictor of DDIs. Similarly, the presence of comorbidities has been consistently associated with an increased risk of DDIs (13). Evidence from previous studies further indicates that polypharmacy markedly elevates the risk of adverse drug reactions (ADRs) and DDIs (17).

Moreover, the occurrence of ADRs in 32.2% of patients underscores the importance of careful regimen optimization and continuous clinical monitoring to ensure treatment safety and effectiveness. The most frequently reported adverse effects were weakness (33.7%), gastric irritation (33.1%), and headache (30.3%). Prior studies have shown that ADRs are a major contributor to non-compliance to antihypertensive therapy, which in turn leads to poor blood pressure control (29, 33, 34). In line with the present findings, a study conducted in Gondar, Ethiopia, reported that approximately 20% to 31.1% of patients experienced ADRs, with tiredness, dizziness, and headache being the most common complaints (33, 35).

In the current study, several factors were independently associated with the occurrence of ADRs. These were; increasing age, comorbid conditions, number of concurrent medications, the use of enalapril, nifedipine, and hydrochlorothiazide were significantly associated with a higher risk of ADRs. Increasing age, comorbidities, and a higher number of concurrent medications were significantly associated with an increased risk of ADRs, likely due to age-related pharmacokinetic and pharmacodynamic changes, cumulative drug burden, and a higher likelihood of DDIs(36). Additionally, the use of enalapril, nifedipine, and hydrochlorothiazide was linked to a higher ADR risk, possibly reflecting their known adverse effect profiles, including hypotension, dizziness, electrolyte disturbances, and renal impairment, particularly in older patients with multiple comorbidities(35–37).

Strength and limitation of the study:

This study is done at multicenter which improves generalizability and robustness of its findings. However, the cross-sectional design limits the ability to establish causal relationships, and the reliance on self-reported data may introduce social desirability bias.

Conclusions

This study demonstrates a high burden of DDI and ADR among hypertensive patients. Amlodipine and enalapril were the most commonly prescribed antihypertensive, with clinically important DDIs mainly involving metformin. DDIs were significantly associated with comorbidities, polypharmacy, and use of furosemide, metformin, and propranolol, while enalapril, amlodipine, hydrochlorothiazide. The most common ADR were weakness, gastric irritation and headache. ADRs were significantly associated with age, sex, comorbidities, polypharmacy, and use of enalapril, nifedipine, and hydrochlorothiazide. Overall, these findings underscore the critical need for regular medication review, and close clinical monitoring particularly in patients with multiple comorbidities and concurrent medications to minimize the DDIs and ADRs and improve the safety and quality of hypertension management.

Declarations

Authors' contributions

Conceptualization and fund acquisition: Tefera, GM. Supervising, project administration, study design and formal analysis, investigation, methodology: Tefera, GM, Feyisa, BB, Chala, TS & Beressa, TB. Writing–original draft: Tefera GM. Writing review & editing: Tefera GM, Feyisa BB, Chala, TS & Beressa TB. All authors read and approved the final manuscript.

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Competing interest:

The authors report no conflicts of interest in this work. The authors used ChatGPT only for language improvement.

Clinical trial number:

Not applicable.

Human Ethics and Consent to Participate declarations:

The ethical approval was received from Ambo University Institutional Research and ethics review committee (AU IRERC) with a letter number of AU/C/H/S/RH/M771/2/17/2024. This study adhered to the principles outlined in the Declaration of Helsinki. The study participants were informed of the study purpose, procedures, benefits potential and risks, confidentiality protections, and their right to withdraw at any time. For the data collected from medical records, no patient identifiers such as names or card numbers were used. Then informed written consent was taken.

Consent for publication:

Not applicable.

Availability of data and materials:

All the data used for this manuscript writing was available within the document and its supplementary materials.

Authors' contributions:

Conceptualization and fund acquisition: Tefera, GM. Supervising, project administration, study design and formal analysis, investigation, methodology: Tefera, GM, Feyisa, BB, Chala TS & Beressa, TB. Writing–original draft: Tefera GM. Writing review & editing: GM, BB, Chala TS & TB. All authors read and approved the final manuscript.

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