

# Drug-Drug interaction among admitted patients at primary, district and referral hospitals' medical wards in East Gojjam Zone, Amhara Regional State, Ethiopia

SAGE Open Medicine

Volume 9: 1–6

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DOI: 10.1177/20503121211035050

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## Abstract

**Objectives:** This study was aimed to assess the type, prevalence, characteristics of drug interaction and factors associated from admitted patients in medical wards at primary, district and referral hospitals in East Gojjam Zone, Amhara Regional State, Ethiopia.

**Methods:** A facility-based retrospective cross-sectional study design was conducted among admitted patients in medical wards at different hospitals of East Gojjam Zone from September 2019 to February 2020. Patient-specific data were extracted from patient medical prescription papers using a structured data collection tool. Potential drug–drug interaction was identified using [www.drugs.com](http://www.drugs.com) as drug–drug interaction checker. Data were analyzed using SPSS version 23.0. To identify the explanatory predictors of potential drug–drug interaction, logistic regression analysis was done at a statistical significance level of  $p$ -value  $< 0.05$ .

**Results:** Of the total 554 prescriptions, 51.1% were prescribed for females with a mean ( $\pm$  standard deviation) age of  $40.85 \pm 23.09$  years. About 46.4% prescriptions of patients had one or more comorbid conditions, and the most frequent identified comorbid conditions were infectious (18.6%) and cardiac problems (6.3%) with  $0.46 \pm 0.499$  average number of comorbid conditions per patient. Totally, 1516 drugs were prescribed with  $2.74 \pm 0.848$  mean number per patient and range of 2–6. Two hundred and forty-two (43.7%) prescriptions had at least one potential drug–drug interaction, and it was found that 292 drug interactions were presented. Almost half of the drug–drug interaction identified was moderate (50%). Overall, the prevalence rate of drug–drug interaction was 43.7%. Older age (adjusted odds ratio = 8.301; 95% confidence interval (5.51–12.4),  $p = 0.000$ ), presence of comorbidities (adjusted odds ratio = 1.72; 95% confidence interval (1.10–2.68),  $p = 0.000$ ) and number of medications greater or equal to 3 (adjusted odds ratio = 2.69; 95% confidence interval (1.42–5.11),  $p = 0.000$ ) were independent predictors for the occurrence of potential drug–drug interaction.

**Conclusion:** The prevalence of potential drug–drug interaction among admitted patients was relatively high. Pharmacodynamic drug–drug interaction was the common mechanism of drug–drug interaction with moderate degree. Therefore, close follow-up of hospitalized patients is highly recommended.

## Keywords

Drug–drug interaction, medical wards, comorbidity

Date received: 28 January 2021; accepted: 7 July 2021

## Introduction

The administration of drugs is one of the medical interventions made for betterment of the patients. Even though medications play a major role in the cure, palliation and inhibition of disease, they also expose patients to drug-related problems (DRPs).<sup>1</sup> The prescribing practice of two or more

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medications to a single patient can lead to morbidity and mortality.<sup>2</sup> Adverse drug interaction is a major cause of morbidity and mortality.<sup>3</sup> Although lots of effort is made to prevent the possible negative consequences of drugs, everything about the drugs is impossible to be ascertained. One of the main issues that cannot be addressed with the preclinical and clinical study is drug–drug interaction (DDI), a condition in which a substance alters the activity of another drug when both are concurrently administered.<sup>4</sup> Early detection and recognition of clinically important DDI is vital to identify patients who are at higher risk for such events to avoid negative outcomes. The reduction in the quality of education, which is one of the issues of Ethiopia, could affect the quality of drugs prescribed for patients. DDI is a bit complex science which needs the intellectuals' effort and capability to aware the pharmacokinetic, pharmacodynamics and pharmaceutical drug interactions. DDIs related mortality and morbidity are becoming common now days. DDI is the cause for the increment of patient hospitalization and therapeutic cost, and reduction in the efficacy of concomitant drugs which in turn compromise the quality of life of the patients.<sup>5</sup>

Many new drugs are manufactured from the factories yearly and the information regarding these drugs are not easily accessible from different reference materials including books, standard treatment guide lines and drug formularies by the health professionals working at different health care facilities. Hence, vigorous and accurate information regarding the potential adverse impacts of coadministration of drugs is required to reduce the health impacts and costs of adverse events. Different studies have been conducted at different study settings to develop practical decision, support tools, and improve clinicians' knowledge of prevalent and clinically important pDDIs encountered in their daily practice. Since there was no a single study revealing the pDDIs of drugs prescribed at the study settings, this study was conducted to determine the type, prevalence, and characteristics of pDDIs and associated factors among inpatients receiving different medications at the medical wards of primary, district and referral hospitals in East Gojjam Zone, Amhara Regional State, Ethiopia.

## Methods

The study was conducted at three Primary (Bichena, Yejube and Lumame) hospitals, one district (Shegaw Motta) and one referral (Debre Markos) hospitals in East Gojjam Zone, Ethiopia. Shegaw Motta Hospital is 372 km far from Addis Ababa to Northwest direction and it has a latitude and longitude of 11°5'N 37°52'E and 11.083°N 37.867°E, respectively, with an elevation of 2487 m (8159 feet) above sea level. The hospital has more than 500,000 catchment populations. Debre Markos Compressive Specialized Hospital is the only specialized hospital in East Gojjam Zone specifically in Debre Markos town located 300 km far from Addis

Ababa, the capital of Ethiopia. This hospital serves more than 3.5 million people in its catchment area. Bichena Primary Hospital is also one of the hospitals found in the regional state of Amhara, and it renders service for four surrounding districts, namely, Enemay, Enarj Enawga, Debay Tilatgen and Shebel Berenta. Lumame and Yejube Primary Hospitals are also located in East Gojjam Zone 35 and 27 km far from Debre Markos town, respectively.<sup>6–8</sup>

In this study, a health facility–based retrospective cross-sectional study design was conducted from September 2019 to February 2020. The source population of this study were all prescriptions received by patients admitted at different wards of the selected hospitals while the study population were all prescriptions dispensed to patients admitted at different wards of the selected hospitals during the study period. All prescriptions of patients attending the hospital during the study period were included and prescriptions with a single drug and without full patient information were excluded. DDIs were the dependent variable whereas socio-demographic characteristics of the patients, concomitant diseases, number of drugs prescribed and qualification of the prescribers were considered as independent variables.

Sample sizes were determined based on the World Health Organization (WHO)<sup>9</sup> which states that for the study of DDI from prescriptions, it is recommended to take 600 prescriptions from the study area, and as result, a total of 600 prescriptions were considered as sample size among which 120 prescriptions (allocated 600 prescriptions to each of the 5 hospitals) were taken from each hospital. In order to take the required number of prescriptions from each hospital, first, the 6-month prescription papers were selected, assembled with their respective months, and then from the assembled prescription, 120 prescriptions were withdrawn from each hospital using random sampling technique.

To maintain the quality of data, a half-day training was given to data collectors (who were pharmacy professionals). In addition, a pretest was carried out by taking 60 prescription papers at Finote Selam Hospital in order to check the validity of data collection checklist. The data collection process was controlled by the principal investigator. The collected data were checked daily to approve its completeness, accuracy and clarity. Data entry to the drug interaction checker ([www.drugs.com](http://www.drugs.com)) software was done via a double entry method, that is, two individuals entered and checked the pDDIs of drugs of each prescription to make the results more reproducible.

Data were entered using Epi Data version 3.1, and then exported to SPSS version 23. Descriptive statistics was used to summarize the findings in the form of tables and figures. To observe the effect of independent variables on the outcome variable, bivariate analysis was performed and variables with *p*-value less than 0.25 were considered for multivariate analysis. *p* < 0.05 was considered as a cut-off value for statistically significant association. Ethical approval

**Table 1.** Nature of pDDI and demographic variables.

Demographic variables	Mean $\pm$ SD	Total (%)
Age	40.85 $\pm$ 23.09	554 (100)
Male	1.54 $\pm$ 0.5	272 (49.1)
Female	1.59 $\pm$ 0.493	282 (50.9)
Number of drugs prescribed	2.74 $\pm$ 0.848	1516 (100)
Potential for DDI	1.56 $\pm$ 0.496	292 (100)
Presence of comorbid	0.46 $\pm$ 0.499	257 (46.4)
Educational status		
Nurses	1.62 $\pm$ 0.486	367 (66.2)
Medical doctors	1.40 $\pm$ 0.492	127 (22.9)
Emergency surgeon	1.55 $\pm$ 0.503	55 (9.9)
Midwives	1.80 $\pm$ 0.447	5 (0.9)

pDDI: potential drug–drug interaction; DDI: drug–drug interaction; SD: standard deviation.

for this study was obtained from the Institutional Research Ethics Review Committee (IRERC) of Health Sciences College, Debre Markos University (approval no. HSC/R/C/Ser/Co/328/106/12) and the requirement for written consent from the subjects was waived off by the Institutional Research Ethics Committee.

## Results

### Demographic characteristics

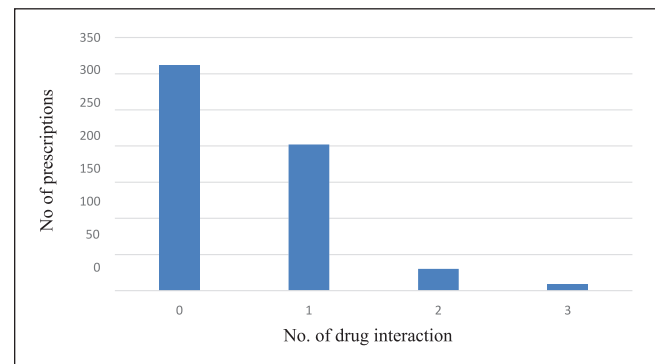
Among the 600 collected prescriptions, only 554 prescriptions were taken for data analysis as the remaining were discarded due to illegible handwriting that was not included as exclusion criteria. The patients' age ranged from 0.01 to 89 years and the mean age in years was 40.85  $\pm$  23.09. The majority of the patients in this study belonged to age group of <55 years which accounts 60.1%. Nearly half of the patients (51.1%) were females. Of the total 554 cases in the prescriptions, 46.4% of them had one or more comorbid conditions. The most frequent identified comorbid conditions were infectious (18.6%) specifically consists of severe/non-severe community acquired pneumonia and cardiac problems (6.3%). The average number of comorbid conditions per patient was 0.46  $\pm$  0.499. More than half (66.2%) of the prescriptions were prescribed by nurses followed by medical doctors (22.9%) (Table 1) which revealed the reality in Ethiopia where; although rapid expansion, there are inadequate physicians specially at district and primary hospitals.

### Drugs' use pattern

The majority of the prescriptions (48%) contained two drugs and the mean number of drugs prescribed per patient was 2.74  $\pm$  0.848, ranging from two to six drugs (Table 2). Number of drugs prescribed was positively correlated with increasing age and presence of concomitant diseases (Pearson's correlation coefficient  $r=0.222$ ,  $p=0.000$  and

**Table 2.** Number of drugs prescribed per prescription (N=554) at hospitals of East Gojjam Zone, 2019.

Number of drugs per prescription	Frequency	%
2	266	48.00
3	191	34.5
4	76	13.7
5	19	3.4
6	2	0.4

**Figure 1.** Number of drug interactions in a prescription in medical wards of primary, district and referral hospitals.

$r=0.26$ ,  $p=0.000$ , respectively). Among the drugs prescribed, ceftriaxone was administered to more than half of (62.27%) the patients.

### Drug interactions

Two hundred and forty-two (43.7%) prescriptions had prescribed drugs with the pDDI. The number of pDDIs within the identified prescription was 292 with mean of 1.56  $\pm$  0.496 (Table 2). Of the total prescriptions, 36.5%, 5.4% and 1.8% had one, two and three drug interactions, respectively (Figure 1). Out of the total pDDI identified, 39.04%, 11.6% and 7.9% were at pharmacodynamic, pharmacokinetic and pharmaceutical levels, respectively. The mechanism of the majority of drug interaction (42.8%) was unknown, followed by additives (38%) and antagonism (15.8%) (Figure 1).

With regard to degree of severity, from the total 292 pDDIs identified, 13 were major (4.5%), 146 were moderate (50%) and 133 (45.5%) were minor interactions (Figure 2).

### Factors associated with pDDIs

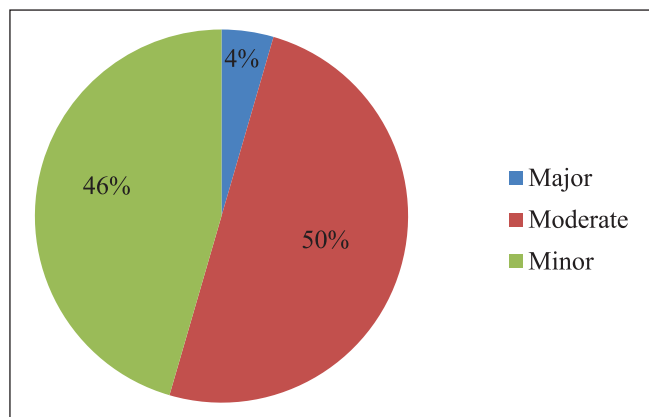
According to the multivariate logistic regression, age category  $\geq 50$  years, presence of comorbidities and prescribing two or more drugs for a patient showed statistically significant association with the prevalence of pDDIs (Table 3). Gender did not associate with the increased risk of pDDI.

## Discussion

One of the components of rational use of drugs is the prescribing of drugs without pDDIs. Drug interactions are the major causes of mortalities and morbidities to patients admitted at different levels of hospitals.<sup>10</sup> Administration of two or more drugs to a hospitalized patient can frequently lead to DDI, which further compromises the overall health condition of the patients. This study used www.drugs.com software to evaluate potential drug interactions of drugs administered to admitted patients at East Gojjam zonal hospitals. In this study, majority of the patients belonged to age group of <55 years, which was in line to other study.<sup>11</sup> The overall prevalence of pDDI in this study was 43.7% which was lower than findings from Tikur Anbesa Specialized Hospital (78.2%) and greater than a study from different settings in Thailand (27.9%) and Iran (20.3%).<sup>10</sup> The discrepancy in the prevalence of DDI among different studies might be related to the differences in the availability of alternative drugs, absence of clinical pharmacists, drug information software, and patient load at these hospitals and the differences in the nature and type of diseases of patients. The finding in this study revealed that the

most frequent comorbid condition was infectious (18.6%) followed by cardiac problems (6.3%) which is in line with the previous study.<sup>10</sup> A study done at Saint Paul's Hospital Millennium Medical College (SPHMMC) confirmed that the major diagnosis for these patients was renal disorder, cardiovascular disorder and infectious disease with a frequency of 23.2%, 22.13% and 20.3%, respectively.<sup>12</sup> In another study, although the common comorbidities were diabetes mellitus (19.2%), coronary artery disease (CAD) (5.6%) and chronic kidney disease (CKD) (1.6%), the average number of comorbid conditions per patient was  $0.45 \pm 0.70$  which was almost the same with the findings of this study, that is,  $0.46 \pm 0.499$ .<sup>13</sup> This study showed that the mean number of medications per prescription was  $2.74 \pm 0.848$  with the range of 2 and 6 which was much lower than India ( $6.53 \pm 2.15$ ) and Taiwan ( $5.8 \pm 2.4$ ).<sup>14</sup> But, the average number of drugs prescribed in this study was almost similar with that of Ayder Comprehensive Specialized Hospital (ACSH), which was reported as 2.73.<sup>3</sup> Differences in study settings, number and type of comorbidity as well as the prescribing culture might explain the discrepancy in the findings.

The level of DDIs is usually classified as pharmacokinetic, pharmacodynamic and pharmaceutical outcomes. The findings of this study revealed that levels of pharmacodynamic, pharmacokinetic and pharmaceutical drug interactions were found to be 39.04%, 11.6% and 7.9%, respectively. Similar to this study, a study from Indian revealed that the level of pharmacokinetic and pharmacodynamic interactions was identified as 19.14% and 80.86%, respectively.<sup>15</sup> Another study conducted among hypertensive patients in a tertiary care teaching hospital, Ethiopia, revealed that 37.3% and 22.7% of the identified pDDI were pharmacodynamic and pharmacokinetics.<sup>13</sup> Kibrom and Huluka<sup>12</sup> stated that more than half of (53.4%) of the interactions were at pharmacokinetic level, which was different from findings of this study. A study in Pakistan showed that 53.3% of the drug interaction was found to be pharmacodynamics followed by pharmacokinetics (40.2%) which was similar in pattern with that of a study from SPHMMC.<sup>16</sup> A study in India also



**Figure 2.** Distribution of DDIs according to the degree of severity ( $n=554$ ).

**Table 3.** Logistic regression analysis of factors associated with pDDIs ( $n=554$ ).

Variables		Exposure to DDIs		Bivariate and multivariate analysis (95% CI)			
		Exposed	Not exposed	COR	p-value	AOR	p-value
Sex	Male	126	145	0.799 (0.571–1.119)	0.192	1.194 (0.773–1.844)	0.425
	Female	116	167				
Concomitant diseases	Yes	181	76	9.24 (6.247–13.590)	0.000*	1.72 (1.10–2.68)	0.000*
	No	61	236				
Age	<50	72	261	1.00		1.00	
	>50	170	51				
Number of medications	2–3	163	294	1.00		1.00	
	>3	79	18				

pDDI: potential drug–drug interaction; CI: confidence interval; COR: crude odds ratio; AOR: adjusted odds ratio.

\*Significant at  $p < 0.05$ .

showed that 42.8% of the drug interaction was pharmacokinetics and 29.62% was pharmacodynamics.<sup>17</sup> In this study, www.drugs.com software detected that 42.8% of the drug interaction mechanism was unknown followed by additives (38%) and antagonism (15.8%) which was in line to that of a study in Indian where 16.78% of the mechanism was unknown.<sup>17</sup> But, a study from Pakistan identified among the pharmacodynamics DDI, 80.6% were synergistic, 19.3% were additive or antagonistic in nature and 6.4% were having unknown in mechanism.<sup>16</sup> The degree of DDI findings indicated that the majority (50%) of the identified drug interaction was moderate, whereas 45.5% and 4.5% of the interactions were categorized as minor and major, respectively. A study in Pakistan identified that 4.33% of the interaction was categorized as major and 66.12% and 29.53% of the DDIs were grouped as moderate and minor, respectively<sup>10</sup> which was almost similar in pattern with the findings of this study. About 45.0% pDDIs were moderate and nearly one-third were major in severity, according to the study conducted at Jimma University Medical Center.<sup>18</sup> A report from ACSH indicated that 5.7% prescriptions had major DDIs, and 35% moderate, 14.5% minor and 3.7% unknown.<sup>3</sup> The discrepancy of DDIs in level, mechanism and degree among different studies and the findings of this study might be attributed to the different diagnosis that requires different pairs of medications, number of drugs prescribed per patient, availability of therapeutically alternative drugs, knowledge and skills of prescribers and dispensers, presence of comorbidities, and the patients' condition like age and gender.

Among the factors that affected the drug interactions of this study, patients with comorbidities were 1.72 times more likely to be exposed to those who did not have comorbidities. In addition, groups of patients with age category of >50 had 8.3 times more likely to be affected by the consequences of DDIs as compared to those patients with age of less than 50 years. Moreover, those patients who took two or more drugs were 2.7 times at more risk to develop DDI. The findings of different literatures were in line with that of this study where older age, use of more drugs and presence of concomitant diseases were statistically associated with the occurrence of DDI.<sup>11,16,18</sup>

### Limitations of the study

Since we used the recommendation by WHO to take a minimum sample size of 600 to assess prescriptions at health facilities, simply we took 600 prescriptions and sample size calculation was not performed. Another major restraint in this study was having prescriptions with missed patient information such as age, sex, identified disease, comorbidities and prescribed drugs, and to alleviate the associated problems, those prescriptions were disregarded. Currently, available DDI checkers identified only the severity of the interaction and not the consequent and the mechanism of the interaction. Most importantly, the study was not limited to

specific age groups, and it would have been better if more sample size was taken but unable to do this owing to financial deficits.

## Conclusion and recommendations

The prevalence of potentially DDIs among admitted patients was relatively high at primary, district and comprehensive specialized referral hospital medical wards. The majority of the DDI was moderate in severity and the health professionals have to take it into account while prescribing and dispensing of drugs to the patients, particularly those with comorbidities, old age and taking three or more drugs. Therefore, healthcare facilities have to develop and implement cautionary guidelines and software-based screening techniques to prevent the adverse outcomes of potentially harmful DDIs.

## Acknowledgements

The authors gratify the Debre Markos University for covering the data collection cost for the study. The authors extend their thanks to health facility administrators for their willing and collaboration during data collection.

## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Ethical approval for this study was obtained from the Debre Markos University, Health Sciences College Institutional Research Ethics Review Committee prior to the study and the approval number was HSC/R/C/Ser/Co/328/106/12.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This paper was funded by Debre Markos University.

## Informed consent

Informed consent was not sought for this study because we used and assessed prescription papers for data collection and the requirement for written consent from the subjects was waived off by the Institutional Research Ethics Review Committee.

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