

# Assessment of Potential Drug–Drug Interactions and Their Predictors in Chronic Outpatient Department of Dessie Referral Hospital, Dessie, Northeast Ethiopia

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**Objective:** To assess the prevalence and predictors of Potential drug–drug interactions (DDIs) at the chronic outpatient department of Dessie Referral Hospital, Dessie, Northeast Ethiopia.

**Patients and Methods:** A cross-sectional study was carried out on the medical records of patients treated in the chronic ambulatory department of Dessie Referral Hospital (DRH), from March 1/2019 to May 30/2019. Ethical clearance was granted from the department of pharmacy, college of medicine, and health sciences, Wollo University. Lexi-comp computer program database was used to detect pDDIs. SPSS version 22 was used to produce a descriptive analysis of the background data and logistic regression to identify predictors of pDDIs.

**Results:** In this study, the medical record of 300 patients has been reviewed and 489 pDDIs have been identified. The prevalence of pDDIs per patient was 1.63. Of all the identified pDDIs, the moderate severity interactions were the majority, 88.55% (n=433) followed by 8.38% (n=41) of minor, 2.66% (n=13) of major, and 0.41% (n=2) of contraindicated drug interactions. Taking three or more drugs at a time has been found as a statistically significant predictor of the occurrence of pDDIs.

**Conclusion:** A high rate of moderate severity pDDIs have been recorded. A system of checks and balances should be developed and executed for all those who are involved in prescribing, dispensing, and administration of medications for effective identification and prevention of pDDIs.

**Keywords:** patient safety, polypharmacy, prevalence, drug selection

## Introduction

Because of their greater impact on medical and societal issues, adverse drug events (ADEs) in recent decades have become a major area of concern in the health care system.<sup>1,2</sup> ADEs carries a significant burden of inpatient hospital care, raise total health care cost, and leads to increased loss of life. A retrospective analysis of a large inpatient database estimated that ADE is responsible for the hospitalization of 6.28% of all patients. The costs due to preventable adverse drug reactions (ADRs) in the out-patient setting might stretch to € 8515 and 9.2 days of hospital stay.<sup>3,4</sup>

A significant percentage of ADEs are preventable if adequate emphasis is given and detected early.<sup>3,5</sup> Potential Drug–Drug Interactions (pDDIs) constitute one of

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the often preventable Causes of ADEs.<sup>6,7</sup> Stockley's drug interaction definition declares that interaction is said to occur when the pharmacological effects of one drug are changed by the presence of another drug, herbal medicine, food, drink, or by some environmental chemical agent(s).<sup>8</sup>

Drug–drug interactions (DDIs) are classified based on their mechanism of interaction as, pharmacokinetics and pharmacodynamics, but there are few unknown mechanisms of interactions.<sup>8–10</sup> Based on the severity and significance of interactions, pDDIs can be rated as, severe, moderate, and minor.<sup>9,11–13</sup> The occurrence of pDDIs ranges from 19.3% to 91.6% across different health settings and patients.<sup>11,14</sup> The rate of hospital admissions in the general population due to pDDIs stretches to 1.1%.<sup>15</sup> The prevalence of clinically important potential pDDIs was found to be 47.4% and the incidence of DDI-related ADRs in chronic geriatric patients reaches about 6.5% and most of the events presented important clinical consequences.<sup>16</sup>

The prevalence of pDDIs relates to the severity of the illness, age of the patient, the health care setting, number of medications, and length of hospital stay, presence of multiple comorbidities, and gender of the patient.<sup>7,11,17,18</sup>

Although pDDIs has been reported in different populations, there are no known data from Ethiopia and relatively little from under-developed nations. Therefore, the study aimed to measure the prevalence, clinical significance, and associated factors of pDDIs in the chronic outpatient department of DRH, Dessie, Northeast Ethiopia.

## Patients and Methods

A cross-sectional study was carried out at the outpatient department for 3 months (March–May 2019) in DRH, Dessie, Northeast Ethiopia. DRH is the biggest hospital in the Northeast region of the country. The study was approved by the ethical committee of the department of pharmacy, college of medicine and health sciences, Wollo University. It was approved through a letter written on January 28, 2019, with a reference number of WU phar/205/19. The ethical committee waived the need for patient consent provided that data collectors ensured privacy and confidentiality during the review of patients' records. As a result, the name and addresses of patients were not recorded in the data collection forms.

The chronic outpatient department has three rooms, which can serve 100 patients per day. Patients who visited the chronic outpatient department during the study period

were included. Those with incomplete medical records were excluded from the study.

Information picked from the medical records included demographic characteristics, diagnosed main disorder, and other comorbidities, and number and type of prescribed drugs. All drugs were checked for pDDIs. The Ethiopian standard treatment guideline was used for grouping of patient diagnosis; accordingly, patients were categorized into six groups: Cardiovascular, Endocrine, Neurologic, Cardiovascular and endocrine, Cardiovascular and neurologic, and the others.

In the hospital, there is no any pDDIs screening and detection mechanism. Pharmacy professionals simply dispense prescribed medication without reconciliation of interactions. In this study, pDDIs were identified using Lexi-comp's Drug–Drug Interactions Checker computer application.<sup>19</sup> The detected DDIs were classified as level: X–interaction, D–interaction C–interaction, and B–interaction. Detected pDDIs were manually checked for the presence of sound scientific literature. Based on the severity of the pDDIs, interactions' were grouped according to Lexicomp<sup>®</sup> classification as:

X–interaction (avoid combination) – the risks associated with concomitant use of these agents usually outweigh the benefits. These agents are generally considered contraindicated.

D–interaction (consider therapy modification) – a patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks. Specific actions must be taken to realize the benefits and/or minimize the toxicity resulting from the concomitant use of the agents and considered as major interactions.

C–interaction (monitor therapy) – the benefits of concomitant use of these two medications usually outweigh the risks. An appropriate monitoring plan should be implemented to identify potential negative effects and considered them as moderate interactions.

B–interactions (no action needed) – data demonstrate that the specified agents may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use and generally classified as minor interactions.

Data analysis was done using the computer program SPSS version 22. The frequencies and percentages of the demographic characteristics, main diagnosis, number of drugs per patient, and the prevalence of the pDDIs are summarized in tables. Initially, a univariate analysis was

performed for each independent variable, and variables having a p-value less than 0.25 were fitted into a multivariate logistic regression to determine the presence of an association between variables. The number of drugs per patient, diagnosis, and the age of the subjects are summarized with an odds ratio of 95% confidence interval. P-value was set at 0.05 or less.

## Operational Definition

Chronic outpatient department: it is the part of a hospital designed for the treatment of outpatients with chronic health problems who visit the hospital for diagnosis or treatment, but do not require a bed at the time or to be admitted for overnight care.

Polypharmacy: regular use of at least four medications.

## Results

During the study period, 315 chronic outpatients came to DRH. Of those, the medical records of 15 patients were discarded because of incompleteness.

## Sociodemographic and Clinical Data

From the total 300 patients, 176 were females and their ages ranged from 18 to 84 years, and the mean age was  $51.54 \pm 15.568$  years. The majority of the study participants (54.7%) came with cardiovascular diseases and nearly half (49.3%) were diagnosed with two disease conditions. The number of drugs per patient ranged from 2 to 7 and the mean number of it was  $3.24 \pm 1.153$ . Polypharmacy was practiced in 46 (15.3%) participants (Table 1).

## Prevalence and Severity of Potential DDIs

A total of 973 drugs were prescribed for 300 chronic ambulatory patients and 489 pDDIs were identified. The prevalence of pDDI per patient was 1.63 (489/300). Regardless of the severity of interactions, 228 (76%) patients had at least one pDDIs. Based on the severity of pDDIs, 433 (88.55%) and 41 (8.38%) interactions are classified as moderate and minor interactions, respectively (Table 2).

## Common Interacting Drug Combinations

Among 31 drug combinations which were responsible for 489 potential DDIs, 280 (57.3%) were contributed by:

**Table 1** Sociodemographic and Clinical Data of the Study Subjects

Variables	Value	Frequency	Percentage (%)
Sex	Male	124	41.3
	Female	176	58.7
Age, Years	Mean $\pm$ SD (Range)-	51.54 + 15.568	
	18–41	77	25.7
	42–54	77	25.7
	55–63	74	24.7
	$\geq 64$	72	24.0
Comorbid conditions	Absent	126	42.0
	Present	174	58.0
Number of drugs per patient	Mean (Range)	3.24 $\pm$ 1.153 (2–7)	
	2–3	185	61.7
	4–5	104	34.7
	$\geq 6$	11	3.6
Disease Type	Cardiovascular	164	54.7
	Endocrine	31	10.3
	Neurologic	19	6.3
	Cardiovascular + endocrine	61	20.3
	Cardiovascular + neurologic	11	3.7
Others *	14	4.7	
Type of regimen	Simple	185	61.7
	Polypharmacy	115	38.3

Note: \*Others: respiratory and hematology.

enalapril + hydrochlorothiazide (46), aspirin + enalapril (34), spironolactone + enalapril (57), enalapril + furosemide (69), metformin + enalapril (32) and metformin + glibenclamide (42). The most serious drug interactions were found among salbutamol with propranolol and carbamazepine with nifedipine (Table 3).

## Factors Associated with Potential DDIs

Multivariate analyses showed that patients taking more than three concomitant drugs (polypharmacy) are at higher risk of pDDIs (adjusted odds ratio (AOR) (95% confidence interval (CI) =5.794 (2.719–12.348)) and  $P < 0.001$ ), but other variables did not show significant association with pDDIs (Table 4).

**Table 2** Prevalence and Severity of pDDIs

Potential DDIs		Frequency	Percentage (%)
Prevalence	Yes	228	76
	No	72	24
Severity	Contraindicated	2	0.41
	Major	13	2.66
	Moderate	433	88.55
	Minor	41	8.38
	<b>Total</b>	<b>489</b>	<b>100%</b>

## Discussion

This study aimed at assessing the prevalence and severity of pDDIs in outpatient settings. Drug interaction is a very

important issue in drug therapy. In this study, 973 drugs were prescribed for 300 chronic outpatients visiting DRH and 489 pDDIs were identified. This study showed that the overall prevalence of at least one pDDI in 76% (228/300) of study participants would have resulted from the combinations of the prescribed drugs. This is lower than reports in Saudi Arabia (90.64%),<sup>20</sup> however, comparable with a result of studies conducted at the internal medicine ward of Gondar University hospital (78%) and Black Lion tertiary hospital (78.02%).<sup>10,21</sup> This might indicate the need for equal attention of pDDIs during the prescription of medicines for chronic patients visiting the outpatient department and admitted patients. But, lower figures were reported by other studies in Brazil (26.5%),<sup>22</sup> in

**Table 3** Common Interacting Drug Combinations

Severity	Combinations	Frequency	Potential Adverse Outcome
Contraindicated	Propranolol + salbutamol	1	Constriction of bronchi
	Carbamazepine + nifedipine	1	Decrease nifedipine
Major	Amlodipine + phenytoin	6	Increase phenytoin concentration
	Amlodipine + simvastatin	3	Increase simvastatin concentration
	Meloxicam + furosemide	2	Diminish diuretic effect
	Risperidone + carbamazepine	1	Depression
	Indomethacin + methotrexate	1	Methotrexate increase
Moderate	Enalapril + furosemide	69	Hypotension/nephrotoxicity
	Spironolactone + enalapril	57	Hyperkalemia
	Enalapril + hydrochlorothiazide	46	Enhance nephrotoxicity
	Metformin + glibenclamide	42	Hypoglycemia
	Aspirin + enalapril	34	Nephrotoxicity
	Metformin + enalapril	32	Lactic acidosis
	Spironolactone + digoxin	23	Increase digoxin
	Metformin + HCT	19	Hyperglycemia
	Furosemide + digoxin	19	Increase cardiac glycoside
	Phenobarbital + carbamazepine	14	CNS Depression
	Phenytoin + phenobarbital	14	CNS depression
	ASA + furosemide	13	Decrease loop diuretics
	Metoprolol + digoxin	12	Bradycardia
	Atenolol + digoxin	12	Bradycardia
	ASA + metformin	9	Hypoglycemia
	ASA + NPH	7	Hypoglycemia
	Atenolol + nifedipine	6	Hypotension
Spironolactone + atorvastatin	5	Increase spironolactone effect	
Minor	NPH + enalapril	13	Hypoglycemia
	Beclomethasone + salbutamol	5	Hypokalemia
	Atenolol + PTU	7	Increase atenolol
	PTU + propranolol	7	Increase propranolol
	Aspirin + phenytoin	5	Increase phenytoin
	Indomethacin + amlodipine	4	Diminish hypertensive

**Abbreviations:** ASA, aspirin; HCT, hydrochlorothiazide; NPH, neutral protamine hagedorn insulin; PTU, propylthiouracil.

**Table 4** Factors Associated with pDDIs

Variables		pDDIs		AOR (95% CI)	P-value
		Yes	No		
Age	18–41	50	27	1.00	0.030
	42–54	60	17	2.336 (1.088–5.016)	
	55–63	60	14	2.163 (0.978–4.783)	
	≥64	58	14	2.199 (0.984–4.911)	
Sex	Male	88	36	1.00	0.092
	Female	140	36	1.646 (0.922–2.936)	
Number of drugs	≤3	122	63	1.00	<0.001
	>3	106	9	5.794 (2.719–12.348)	
Comorbid conditions	Absent	85	41	1.00	0.749
	present	143	31	1.104 (0.603–2.022)	

**Abbreviations:** AOR, adjusted odds ratio; CI, confidence interval; pDDIs, potential drug–drug interactions.

Thailand (27.9%)<sup>18</sup> and pediatrics ward of Gondar University hospital (45.8%),<sup>12</sup> this might be partially explained by the difference in availability of drugs, use of less number of drugs per patient in younger age groups.<sup>13</sup>

The result of this study revealed that the prevalence of pDDIs per patient was 1.63. This figure agrees with a finding in Pakistan 1.74<sup>23</sup> and India 1.68.<sup>24</sup> However, the present result is lower than results reported in adult medical wards of Gondar University and Black Lion tertiary hospitals which were 4.2 and 2.9, respectively,<sup>10,21</sup> even though, higher than a finding in Brazil (0.22),<sup>22</sup> and pediatric wards of Gondar University hospital (1.02).<sup>12</sup> This may be due to the differences in the study setting, type, and the number of drugs used by study participants.

All pDDIs were not equally detrimental, though, recognition of the severity of each pDDI was central to assess the clinical importance and appropriate management. The list of interacting drug combinations, particularly prevailing major and moderate interactions, is useful for health care professionals to monitor patient profiles for pDDIs. Of the total 489, pDDIs identified, major interactions covered only 2.66% of the interactions which is

comparable with a finding in Saudi Arabia (2.6%),<sup>20</sup> but much lower when compared with findings in other studies from Gondar University hospital (10–13%) and Black Lion hospital (13.1%). This wide difference may be due to the differences in the study population, two of the studies were conducted in internal medicine wards and the other one was conducted in the pediatrics ward.<sup>10,12,21</sup> Around half of the major severity pDDIs were observed with Amlodipine + phenytoin (6 combinations) which can potentially result in toxicity of phenytoin in chronic patients. Most interacting drug combinations were moderate severity, which covers 88.55% of the identified pDDIs. This figure was higher in comparison to other studies in Ethiopia.<sup>10,12,21</sup> Enalapril was responsible for the occurrence of 238 moderate severity level pDDIs which may result in negative outcomes for the intended treatments. Two contraindicated pDDIs were identified (propranolol + salbutamol and carbamazepine + nifedipine) which may end up in antagonized bronchoconstriction and poor control of hypertension, respectively.<sup>19</sup>

The other result of this study showed that polypharmacy (the use of three or more drugs for a patient) has a statistically significant association with pDDIs in chronic outpatients [AOR = 5.794; 95% CI (2.719–12.348); P = 0.000]. The risk of pDDIs has increased when the number of drugs per individual was more than three which is in line with other studies.<sup>12,16,21,25,26</sup> In this study, other variables like gender, age, and comorbid conditions did not show a statistically significant association with the incidence of pDDIs which did not correspond with findings in Saudi Arabia<sup>20</sup> and Brazil.<sup>16,22</sup>

The limitations of the study should not be overlooked. The drug–drug interactions found were only potential (it is not clear whether they had resulted in any harm to the patients). The results of this study might be slightly underestimated since only prescribed medications were included. The software used for the analysis of pDDIs unable to distinguish between the two different doses scheme. Therefore, dose-dependent pDDIs were not assessed.

This study successfully identified the prevalence, pattern, and factors associated with pDDIs in the outpatient department of DRH. The overall prevalence of pDDIs was found to be 76% and the majority of the pDDIs were moderate in severity. Enalapril was responsible for around half of all the pDDIs identified. Moreover, a statistically significant association was found between the number of drugs prescribed per patient (≥3 drugs per patient) and the occurrence of pDDIs.



Finally, drug–drug interactions are avoidable and the role of pharmacists in its prevention is irreplaceable. However, effective identification and prevention of pDDIs need a systematic check and balances by all those who are involved in prescribing, dispensing, and administration of medications.

## Data Sharing Statement

The data used to generate this result are available from the corresponding author upon reasonable request.

## Ethical Review

This study was approved by the ethical committee of the department of pharmacy, college of medicine and health sciences, Wollo University. The ethical committee waived the need for patient consent provided that data collectors ensured privacy and confidentiality during the review of patients' records. As a result, the name and addresses of patients were not recorded in the data collection forms. This study was done with the consideration and compliance with the declaration of Helsinki.

## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest for this work.

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