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POTENTIAL DRUG-DRUG INTERACTIONS AMONG ADULT PATIENTS ADMITTED TO MEDICAL WARDS AT A TERTIARY TEACHING HOSPITAL IN ETHIOPIA

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ABSTRACT

Introduction: A Drug-drug interaction (DDI) is a decrease or increase in the pharmacological or clinical response to the administration of two or more drugs that are different from the anticipated response they initiate when individually administered.
Objectives: To assess the prevalence and factors associated with potential DDIs among adult inpatients admitted to the medical wards of a tertiary teaching Hospital in Ethiopia.
Methods: A retrospective cross-sectional study design was employed on adult Patients who were admitted to the medical ward in one year period. A total of 384patients' medical records were checked for a possible DDI using Micromedex DrugReax® drug interaction database and analyzed consecutively using SPSS version 20.0.
Results: Among 384 adult Patients enrolled in the study, 209 (54.4%) of them had medications with at least one potential DDI in their prescriptions. Of the 209 potential DDI, 26.3% were with a minimum of one major potential DDI. The median number of potential DDI per patient was 2.2. Overall, 296 potential DDI were identified in the current study. Among 296 identified potential drug-drug interactions, most of the interaction (49.7%) had good documentation. The number of medication prescribed per patient showed a significant ($p< 0.001$) association with the occurrence of potential DDIs.
Conclusion: More than half of the patients' prescription contains potentially interacting medications. This study, additionally, revealed that there is a significant association between potential DDIs and number of medications prescribed per patient.

Keywords: Drug-drug interactions, pharmacokinetic interaction, pharmacodynamic interaction, internal medicine

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1. INTRODUCTION

Drug interactions are the possibility that pharmacological effect of one drug might be altered by another agent, present concurrently. It can involve interactions between drugs and disease, drugs and chemicals in the environment, drugs and nutrients, and drugs and drugs [1]. Concurrently administered drugs may act independently, or interact with each other [2]. Drug–drug interaction (DDI) is thus defined as a pharmacological or clinical response to the administration of two or more drugs that are different from the response they initiate when individually administered[3].

The interaction may increase or decrease the effects of the involved drugs and sometimes may cause unexpected toxicity, side effects or failure of the pharmacological therapy [4]. Such DDIs can be classified as pharmacokinetic, pharmacodynamic and pharmaceutical, based on the mechanism of interaction [1]. Clinically significant DDIs might pose a potential harm to Patients [5]. Moreover, it may present with harmful outcomes, resulting in an estimated cost of more than 1 billion USD per year to governmental health care systems expenditure [6].

A drug interaction, which is an emerging threat to public health [6], can occur within a couple of minutes or can take several weeks to develop [7]. There are various

factors contributing factors to the occurrence of DDIs. This includes polypharmacy, use of non-prescription drugs, drug abuse and patient noncompliance [5,8]. Tamblyn et al. [9] reported that about one-quarter of inappropriate drug combinations were resulted from contemporaneous prescribing by different physicians. Patient factors that increase the risk for drug interactions include being critically ill, age, genetic factors, renal function, hepatic function, alcohol consumption, smoking, diet, environmental factors, individual variations, hypoxemia, or metabolic disturbances, and being elderly [5,8,10]. Some of the factors have shown consistent association with the presence of potential DDIs [11].

The risk of DDI rose from 13% for Patients taking two medications to 82% for Patients taking seven or more medications [12]. Drug interactions are considerable cause of adverse drug reactions (ADRs) and hospital admission [13]. In some studies[14, 15], DDIs have been reported to be responsible for up to 3% of hospitalizations. Besides, hospitalized Patients are more likely to be affected by these DDIs because of severe and multiple illnesses, co-morbid conditions, chronic therapeutic regimens, polypharmacy and frequent modification in therapy [16]. It is imperative to determine the prevalence of DDIs in adult patients. Despite a very few studies done in Ethiopia to evaluate the potential DDIs, there is no enough study that shows the situation of Potential DDI in inpatient wards. Thus, this study aimed to assess the prevalence and factors associated with potential DDI among adult inpatients admitted to medical wards of a tertiary teaching Hospital in Ethiopia

2. MATERIAL AND METHODS

2.1. Study Settings and Design

A retrospective cross sectional study was employed on Patients admitted to the medical unit of inpatient ward of Saint Paul's Hospital Millennium Medical College (SPHMMC). SPHMMC is the second largest tertiary medical teaching hospital in the country which is located in the capital city, Addis Ababa. It was inaugurated in July 1947 and equipped with 250 beds. The study was conducted from Mayto June 2016.

2.2 Study Population

All adult Patients receiving inpatient care at internal medicine ward of SPHMMC were the source population of the study and adult Patients admitted to the internal medicine wards from May 1, 2015 to April 30, 2016 were considered as the study population. All Patients exposed to two or more concomitant drugs during their stay in the ward were eligible for the study.

2.3 Sample Size and Sampling Procedure

A single proportion formula was employed for sample size estimation. A total sample size of 384was estimated with considering the P as 0.5 at 95%CI and 5% margin of error. The respective patient cards were selected throughsystematic random sampling techniques using the patient admission registration catalogue as a sampling frame.

2.4 Data Collection Tools

Data was collected from the patient medical chart using a structured and pretested data abstraction format. The data was collected by the principal investigator and two traineddata collector nurses.

2.5 Operational Definitions

Contraindicated DDI: The drug-pair is contraindicated for concurrent use.

Major DDI: The effects are potentially life threatening or capable of causing permanent damage.

Moderate DDI: It may cause deterioration in patients' clinical status and additional treatment or extension of hospital stay.

Minor DDI: The effects are usually mild. Consequences may be bothersome or unnoticeable but should not significantly affect the therapeutic outcome [17, 18].

Excellent Documentation: controlled studies have clearly established the existence of the interaction

Good Documentation: documentation strongly suggests the interaction exists, but well-controlled studies are lacking

Fair Documentation: available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or, documentation is good for a pharmacologically similar drug [17,18].

2.6 Analysis of potential DDIs

Medications were screened for potential DDIs using drug interaction software, Micromedex Drug Reax® (Thomson Reuters Inc., 2011). Micromedex Healthcare Series Greenwood Village/CO). Micromedex is used to check and describe the type and severity of drug-drug interaction[19].

2.7 Statistical analysis

The collected data was first checked for completeness then compiled, processed and analyzed using SPSS for Windows version 20.0. Descriptive statistics (frequencies, percentage, mean and standard deviation) were used to present counts, proportions and averages. Chi-squared test was used to identify potential factors having association with potential DDIs.

2.8 Ethical Consideration

Ethical clearance was obtained from Ethical Review Committee of the School of Pharmacy, Addis Ababa University as well as from the Department of Internal Medicine in SPHMMC. Privacy and confidentiality was ensured during review of patients' chart by data collectors. Thus, name and address of Patients was not recorded in the data collection format. Moreover, the data collectors and the principal investigator provided appropriate drug information to heath care professionals when necessary.

3. RESULTS

3.1 Demographic information

A total of 384 adult Patients were enrolled in the study. Among these, 193(50.2 %) of the Patients were females.

Patients' age ranges from 15 to 85 years (mean age; 41.37 ±16.208 years). The major diagnosis for these patients were renal disorder, cardiovascular disorder and infectious disease with a frequency of 89 (23.2%), 85 (22.13%) and 78 (203%), respectively (Table 1).

Table 1: Socio-demographic characteristics of Adult Patients admitted to Medical wards of SPHMMC, June 2016 (N=384)

Variable		Frequency	Percentage (%)
	Male	193	50.2
	Female	191	49.8
Age category (years)			
	15-24	56	14.8
	25-44	178	46.4
	45-64	96	25.0
	≥65	53	13.8
Co-morbidity	Present	55	14. 32
	Absent	329	85.68
Number of prescribed medications per patient	≤ 4	262	68.23
	≥5	122	31.77
Major Diagnosis	Renal disease	89	23.18
	Cardiovascular	85	22.13
	Infectious	78	20.3
	Gastrointestinal	32	8.34
	Hematologic	26	6.77
	Thromboembolic	22	5.73
	Liver	20	5.21
	Diabetes Mellitus	14	3.65
	Stroke	14	3.65
	Others*	4	1.04

Note:* Solid tumor (n=2), airway obstruction (n=1) and neurologic(n=1)

3.2 Prevalence of Potential Drug-Drug Interactions

In this study, a total of 296 Potential DDIs were identified. Among 384 adult Patients admitted in medical wards, 209(54.4%) of them had prescriptions with at least one potential DDI irrespective of how severe the interactions are. In majority of cases, one to two Potential DDIs per patient were identified with median of 2.2 potential DDIs per patient with a range of 1-9 (Table 2).In the pharmacologic intervention, 101 (26.3%), 159 (41.4%) and 33 (8.6%) interacting drug pairs were having major, moderate and minor severity potential DDIs, respectively (Table 3).

Table 2: Prevalence of potential DDIs among adult Patients admitted to medical wards of SPHMMC, June 2016 (N=209)

Variables	Frequency	Percentage (%)
Number of PDDIs per Patient		
1	98	46.90
2	42	20.10
3	27	12.9
4	19	9.10
5	12	5.74
6	4	1.90
7	3	1.44
8	3	1.44
9	1	0.48
PDDIs per Patient mean	2.2, range (0-9)	

Table 3: Severity, documentation, onset and mechanisms of identified potential DDI for Patients admitted to medical ward of SPHMMC, 2016(n=296)

Level	Frequency	Percentage (%)
Severity		
Contraindicated	2	0.7
Major	105	35.5
Moderate	157	53.0
Minor	32	10.8
Documentation		
Excellent	38	12.8
Good	147	49.7
Fair	111	37.5
Onset		
Rapid	49	16.5
Delayed	116	39.2
Non-specific	131	44.3

3.3 Levels and mechanism of Potential DDIs

The identified potential DDIs were categorized into different levels according to onset, severity, scientific evidence and mechanism of interaction, using the online drug interaction checker; Micromedex. Almost half (147; 49.7 %) of the potential DDI exhibited good scientific evidence availability while 116 (39.2%) showed a delayed onset (Table 3). Most (142; 53.4%) of the interactions were pharmacokinetic in mechanism.

3.4 Drugs with major drug-drug interaction

Digoxin and spironolactone (14.3%) are found to be the most encountered concurrently prescribed drugs with a good documentation. Drug interactions between RHZ and efavirnezas well as atorvastatin andwarfarin are interactions found to have an excellent evidence of documentation (table 4).

Table 4: List of frequently prescribed treatment combinations having major potential drug -drug interaction

List of drugs with Major DDI	Frequency n (%)		Documentation	Type of DDI	Expected effect
	frequency N=70	percentage			
Digoxin+ Spironolactone	15	14.3	Good	PKI	Increasing the risk of digoxin toxicity
Aspirin + Heparin	12	11.4	Fair	PDI	Increased risk of bleeding
Cotrimoxazole + Fluconazole	10	9.5	Fair	PDI	Increased risk of cardiotoxicity
Atorvastatin + Warfarin	5	4.7	Excellent	PDI	Increased risk of bleeding
Azithromycin + Metronidazole	5	4.7	Fair	PDI	Increased risk of QT-interval prolongation and arrhythmias.
Enalapril + Spironolactone	5	4.7	Good	PDI	may result in hyperkalemia
Aspirin + Warfarin	5	4.7	Fair	PDI	Increased risk of bleeding
Aspirin + Clopidogrel	5	4.7	Fair	PDI	Increased risk of bleeding
RHZ + Efavirnez	5	4.7	Excellent	PKI	Decreased serum Efavirenz concentrations
Metronidazole + Warfarin	5	4.7	Good	PKI	Increased level of warfarin
Chloroquine + Ondansetron,	1	0.95	Fair	PDI	Increased risk of QT prolongation
Ceftazidime + Warfarin	3	2.8	Good	PDI	Increased risk of bleeding
Ciprofloxacin + Insulin	4	3.8	Fair	PDI	Enhanced effect of insulin
Fluconazole + Gentamicin	3	2.8	Good	Unknown	Decreased level Gentamicin
Ciprofloxacin + Metronidazole	4	3.8	Fair	PDI	Increased risk of arrhythmia
RHZ + Acetaminophen	3	2.8	Excellent	PKI	Increased risk of hepatotoxicity
Clopidogrel + Omeprazole	3	2.8	Excellent	PKI	Lesser effect of clopidogrel
Carbamazepine + Tramadol	3	2.8	Fair	PKI	Decreased level and effect of tramadol
Haloperidol + Tramadol	3	2.8	Fair	PDI	Increased risk of CNS depression
Dexamethasone + Efavirnez	1	0.95	Fair	PKI	Decreased level and effect of efavirenz
Simvastatin + Warfarin	3	2.8	Excellent	PKI	Increased INR
Carbamazepine + Simvastatin,	3	2.8	Good	PKI	Reduced simvastatin exposure

DDI=Drug-drug interaction; PKI= Pharmacokinetic interaction; PDI= Pharmacodynamic interaction; RHZ=rifampicin+isoniazide and pyrazinamide

3.5 Association of DDI with predicting factors

Univariate logistic regression analysis was done between independent and dependent variables. Table 5 below shows that there is association of the occurrence of one or more potential DDIs with the number of medications prescribed per patient who took more than four medications [odds ratio (95% *CI*)=7.034 (2.130, 11.089) and *P*=0.001], but other variables like sex,co-morbidity and age have no association with potential DDIs.

Table 5: predicting factor of potential DDI in medical wards of SPHMMC, 2016(n=384)

Variable	Potential DDI		P value	OR(95%CI)
	yes	no		
Sex			0.321	
Male	88	105	-	1.00
Female	121	70	0.540	4.650 (0.320–0.810)
Age			0.078	
15-24	29	28	-	1.00
25-44	87	91	0.561	0.538 (0.085, 3.409)
45-64	54	42	0.345	0.718 (0.150, 3.442)
≥65	39	17	0.07	0.563 (0.115, 2.747)
Polypharmacy			0.001	
≤ 4	110	152	-	1.00
≥5	99	23	0.001	7.034 (2.130–11.089)*
Co-morbidity			0.639	
Present	29	26	-	1.000
Absent	180	149	0.639	0.72(0.43,1.2)

4. DISCUSSION

The current study determined the prevalence of potential DDI in adult Patients admitted to medical wards. In a sample of 384 medication charts, the study revealedthat prevalence of potential DDIs was 54.30%. Although the methodology vary from those used in other studies, the result isin concordance with previously cited studies [20-22], which reported prevalence potential DDIs with the range of 52.17% to 66%. A prospective study conducted in the medication charts in medicine wards of Bangalore, India showed that 52.17% (n=230) of hospitalized Patients were exposed to 330 potential DDIs [20].

Among the 296 DDIs identified, 2 (0.7%) of them were contraindicated combinations, 105(26.2%) were major, 111 (42.6%) were moderate and 23 (8.6%) were minor interactions. The finding was comparable with Jimmy et al [20] in which prevalence major drug interaction was 24.85%.The prevalence of moderate drug interaction in the current study, however, is slightly higher than study done northern Ethiopia by Teka et al.,2016 [23].

The clinical significance of potential DDIs in our study is superior in comparison to study done in Brazilian teaching hospital which revealed a 3.4% of major DDIs from a total 887 interacting combinations [24]. Similarly, the clinical significance of current study is much higher than a study conducted in Indian tertiary care hospital which reported 0.14%, 3.6%, and 27.9% of contraindicated, major and moderate level of clinical significance, respectively [25]. Thus, the current study is instrumental to make awareness on the dangerous potential interactions that could compromise the clinical outcome and pose adverse effect on patients.

In this study, the most frequently prescribed major DDI in this study was concurrent use of digoxin with spironolactone. Concomitant use of digoxin and spironolactone may result in increased digoxin exposure andenhance the risk of digoxin toxicity [26]. The second most common interaction identified were aspirin and heparin. Concomitant use of heparin, an anticoagulant, with an NSAID increases the risk of gastrointestinal bleeding due to the potential for decreased platelet function and decreased coagulation [19]. However, the concurrent clinical use these two drugs might be inevitable. Therefore, close monitoring and evaluation of patient's response is vital.

In the present study, 74(27.7%), 87(32.6%) and 39(14.6%) of Potential DDIs are identified to exhibit pharmacokinetic, pharmacodynamic and unknown mechanism of interactions, respectively. This is different from a similar study done in Addis Ababa, whereby 49.8% of interaction mechanisms were pharmacokinetic type, while 44.6% and 5.6% of them were pharmacodynamic and unknown mechanisms, respectively[27]. This difference could be due to lack of

available treatment alternative in the study hospital for the high level of pharmacokinetic interaction[28].

There was significant association between polypharmacy (taking five drugs or more) and occurrence of drug- drug interaction (P<0.001)]. Different studies [29-31] also indentified that polyphatmacy increases the likelihood of potential DDIs occurrence. But, in the present study there was no association between age of patient and gender with the occurrence of drug-drug interaction. This study somewhat different from study conducted in Brazilian teaching hospital [20], which reported positive association of potential DDI with the patient's gender and age.

5. CONCLUSION AND RECOMMENDATION

The findings of this study showed that the prevalence of potential DDIs among Patients admitted to medical wards was higher. This study also revealed presence of a significant association between DDI and number of medications prescribed per patient. Most of the interactions were of moderate-to-major severity. Major DDIs are considered clinically important and should be avoided by health care professionals. Health professionals should closely scrutinize drugs prescribed for patients. Identifying and preventing potentially harmful DDIs is a vital component of a pharmacist's mission which can be assisted by the presence DDI software in the workstations of pharmacists.

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Author Contributions

SK and ZT participated in the study design and literature reviewing. SK conducted the study. All authors were involved in data acquisition, analysis, interpretation, and write-up. All authors approved the final manuscript.

Ethical Approval and Consent to Participate

Ethical approval was obtained from the Research Ethics Committee of the School of Pharmacy, Addis Ababa University as well as the Department of Internal Medicine. A permission letter was also received from SPHMMC administrator for the study.

Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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REFERENCES

1. Cora SYW. Drug Interactions in Palliative Care. HKSPM Newsletter. 2010; 1:12-16
2. Cristina L, Jacomini L, Antonio da Silva N. Drug interactions: a contribution to the rational use of synthetic and biological immunosuppressant. Rev Bras Reumatol. 2011; 51:161-174.
3. David S., Tatro P.D. Publisher: Lippincott Williams & Wilkins; 2012. Drug Interaction Facts 2013: The Authority on Drug Interactions
4. Hussar Daniel A. Drug Interactions. In J. Swarbrick (Ed.), Encyclopedia of Pharmaceutical Technology (p. 1392). (2007) Informa Healthcare USA.
5. Qorraj-Bytyqi H, Hoxha R, Krasniqi S, Bahtiri E, Kransiqi V. The incidence and clinical relevance of drug interaction in pediatrics.JPharmacolPharmacother.2012; 3:304-7.
6. Kothari N, GangulyB. Potential Drug-Drug Interactions among Medications Prescribed to Hypertensive Patients. J Clin Disgn Res.2014; 8(11):HC01–HC04.
7. Strandell J. Drug interaction surveillance using individual case safety reports. Linköping: Linköping University Electronic Press; 2011; 1252.
8. Bista D, Palaian S, Shankar PR, Prabhu MM, Paudel R, Mishra P. Understanding the essentials of drug interactions: A potential need for safe and effective use of drugs. KUMJ.2006; 4: 421-430.
9. Tamblyn RM, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. Can Med Assoc J. 1996; 154:1177–84
10. Tom-Revzon C. Drug Interactions. Pediatrics in Review.2006; 27:315-17.
11. Mahendra Kumar BJ, kumaraswamy M, Mahadevamma L. incidence and pattern of potential drug interactions of antimicrobial agents in the department of medicine in a tertiary care teaching hospital: a prospective study. Asian J Pharm Clin Res. 2011; 4:31-36
12. Cristiano Moura C, Acurcio F, Belo N. Drug-Drug Interactions Associated with Length of Stay and Cost of Hospitalization. J Pharm Pharmaceut Sci. 2009; 12:266-272.
13. Jankel CA, Fitterman LK. Epidemiology of drug–drug interactions as a cause of hospital admissions. Drug Saf 1993; 9: 51-59
14. Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug–drug interactions in a Medicaid population. Pharmacotherapy. 1998; 18:1112–20
15. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalised patients: a meta-analysis of prospective studies. JAMA. 1998; 279: 1200-1205
16. Zwart-van-Rijkom JEF, Uijtendaal EV, Ten Berg MJ, Van Solinge WW, Egberts ACG. Frequency and nature of drug-drug interactions in a Dutch university hospital. Br J ClinPharmacol. 2009; 68:187–193.
17. Teixeira JJV, Crozatti MTL, dos Santos CA, Romano-Lieber NS (2012) Potential Drug-Drug Interactions in Prescriptions to Patients over 45 Years of Age in Primary Care, Southern Brazil. PLoS ONE 7(10):e47062. doi:10.1371/journal.pone.0047062
18. Patel VK, Acharya LD, Rajakanan T, Surulivelrajan M, Guddattu V, Padmakumar R. Potential drug interactions in patients admitted to cardiology wards of a south Indian teaching hospital. Australia's Med J.2011; 4:9-14.
19. Micromedex® Healthcare series(internet database) version 2.0 Greenwood Village, Colorado: Thomson Helathcare Inc;2016 http://www.micromedexsolutions.com
20. Jimmy OD, Shabha Rani RH, Indira R, Ramjan S. Study of drug-drug interactions in the medication charts in medicine wards at tertiary care hospital, Bangalore. IJOPP.2012; 5.
21. Soherwardi S, Chogtu B, Faizal P. surveillance of the Potential Drug-Drug Interactions in the Medicine Department of a Tertiary Care Hospital. JCDR.2012; 6: 1258-1261.
22. Vonbach P, Dubied A. Krahenbuhl S. Prevalence of drug-drug interaction at hospital entry and during stay of patients

in internal medicine. International Journal of Internal Medicine. 2008; 19:413–420.
23. Teka F, Teklay G, Ayalew E, Teshome T. Potential drug–drug interactions among elderly patients admitted to medical ward of Ayder Referral Hospital, Northern Ethiopia: a cross sectional study. BMC Res Notes. 2016; 9:431
24. Cruciol-Souza MJ, Thomson JC. Prevalence of Potential Drug-Drug Interactions and its Associated Factors in a Brazilian Teaching Hospital. J Pharm Pharmaceut Sci. 2006; 9:427-433.
25. Kapadia J, Thakor D, Desai C, and Dikshit RK. A Study of Potential Drug-Drug Interactions in Indoor Patients of Medicine Department at a Tertiary Care Hospital. J App PharmSci.2013; 3:089-096.
26. Hedman A, Angelin B, Arvidson A, Dahlqvist R. Digoxin-interactions in man: spironolactone reduce renal but not biliary digoxin clearance Eur J ClinPharmacol. 1992; 42:481.https://doi.org/10.1007/BF00314854
27. Tesfaye ZT, Nedi T. Potential drug–drug interactions in inpatients treated at the Internal Medicine ward of TikurAnbessa Specialized Hospital. Drug Healthc Patient Saf.2017; 9:71-76.
28. Abu-ElsoudN. Drug-drug Interaction Management in Internal Medicine Specialty Asian Journal of Pharmaceutics. 2017; 11(Suppl3) ;S566.
29. Obreli-Neto PR, Nobili A, de Oliveira Baldoni A, Guidoni CM, de LyraJúnior DP, Pilger D, Duzanski J, Tettamanti M, Cruciol-Souza JM, Gaeti WP, Nakamura Cuman RK. Adverse drug reactions caused by drug–drug interactions in elderly outpatients: a prospective cohort study. Eur J Clin Pharmaco. 2012; 68(12):1667–1676.
30. Kashyap M, D'Cruz S, Sachdev A, Tiwari P. Drug–drug interactions and their predictors: results from Indian elderly inpatients. Pharm Pract. 2013; 11(4):191–195.
31. Ibielli P, Rozenfeld S, Matos GC, FdeAcurcio A. Potential drug–drug interactions among elderly using antihypertensives from the Brazilian list of essential medicines. Cad Saude Pub. 2014; 30(9):1947–1956.