Original Article

A study of harmful drug–drug interactions due to polypharmacy in hospitalized patients in Goa Medical College

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Abstract

Introduction: Concomitant use of multiple drugs is often indicated to manage comorbid conditions and enhance efficacy. Such concomitant use of multiple drugs (five or more drugs) has been defined as "polypharmacy." Polypharmacy has been associated with adverse consequences such as greater healthcare costs, increased risk of adverse drug events, drug–drug interactions (DDIs), medication nonadherence, reduced functional capacity, and multiple geriatric syndromes. This study evaluated number of potential harmful DDIs due to polypharmacy.

Materials and Methods: A prospective, cross-sectional, observational study was performed from July 2011 to June 2012. Approval was obtained from the Institutional Ethics Committee, Goa Medical College. Drug interactions were identified using a computerized DDI database system Lexi-Comp version: 2.4.1. Quantitative data analysis was done by the SPSS for Windows version 17.0.

Results: Seven hundred and fifty-one out of 5424 (13.85%) prescriptions were observed to have polypharmacy with highest rates observed in the Department of Medicine. The median age of patients was 55.60 ± 13.86 (range 10–108 years). A total number of drugs per prescription ranged from minimum of 5 to maximum of 16 drugs, with an average of 7.96 ± 1.75. A large number of 596 prescriptions contained 6–9 drugs per prescription. Drugs involved in potential DDIs in our study included aspirin, antacids, beta-blockers, 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, calcium channel blockers, angiotensin-converting enzyme inhibitors, ondansetron, and H2 blockers.

Conclusion: Patients taking multiple medications experience unique pharmacotherapy. Personalized drug prescribing strategies and close monitoring of patients taking drugs with potential DDIs are keys to optimal therapeutic result.

Keywords: Adverse effect, drug–drug interactions, polypharmacy, super-polypharmacy

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INTRODUCTION

Concomitant use of multiple drugs is often indicated in the management of diseases. Such concomitant use of multiple drugs has been defined as "polypharmacy." A commonly applied definition of polypharmacy is "the concomitant use of five or more drugs." Other less commonly used definitions use the phrases "six or more medications," "potentially inappropriate medication combination," or

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"use of more medications than are medically necessary." Polypharmacy often results in heightened risk of drug-related problems.[1,2] The main causative factors behind it are physiologic changes associated with aging (reduced renal elimination, reduced hepatic function, reduced total body water, reduced lean body mass, diminished vision and hearing), frequency of medical comorbidities, communication barriers, and multiple prescribers. Polypharmacy also results in greater healthcare costs, increased risk of adverse drug events, drug–drug interactions (DDIs), medication nonadherence, decreased functional capacity, and many geriatric syndromes.[3]

DDI is said to occur when two or more drugs interact in such a manner that efficacy or toxicity of one or more of the drugs is altered. DDIs are considered as preventable medication-related problems. DDI can be harmful either by increasing the toxicity of a drug or by reducing its efficacy. Chances of DDIs are proportionate to the number of drugs prescribed. A study by Nolan and O'Malley showed that patients who took ten or more medications had over a 90% probability of having one or more clinically significant DDIs. Such DDIs often have severe consequences including hospital readmissions. Multiple studies in over 370,000 patients showed that 2.2%–70.3% may subject to potential DDIs. Up to 11.1% of patients actually experienced symptoms that may have been attributable to the effects of a DDI.[4,5]

This study evaluates the potential DDIs due to polypharmacy in inpatients of three departments of a tertiary care government center in India.

What this study adds

The studies evaluating association between polypharmacy, potential DDI, and multimorbidity are few. An Italian study evaluating hospitalized elderly patients showed significant associations between specific disease clusters and polypharmacy.[6] Elderly patients with diabetes, coronary heart disease, and cerebrovascular diseases had greater likelihood of polypharmacy as compared to those without diabetes and cerebrovascular diseases. In another study by Vyas *et al.*, although highest rates of polypharmacy were found among elderly over 65 years, younger individuals between 50 and 64 years of age were also significantly more likely to report polypharmacy when compared to young individuals in the age range of 22–39 years. In addition, the prevalence of multimorbidity was similar between 65 and older (9.0%) and adults in the 50–64 age group (8.2%). These two findings taken together suggest that multimorbidity in 50–64 age group was very similar to those of elderly, and the association between multimorbidity and polypharmacy is similar across the two groups. An Australian study documented that multimorbidity was prevalent (4.4% for 20–39 years of age and 15.0% for 40–59 years of age) in the younger adults as well. Results of Vyas *et al.* are similar to Australian study by Doan *et al.*, which showed that multimorbidity was associated with polypharmacy adults across all ages and need to be further evaluated.[7,8]

Our study adds Indian data about potential for harmful DDI due to polypharmacy practiced in hospitalized patients in government medical institute setting.

Aim of this study

This study focuses on evaluating the rates of polypharmacy across two age groups <60 and >60 years which may lead to DDIs. Systematic screening of case papers of patients admitted in the hospital wards can give a bird's eye view of the potential DDIs due to polypharmacy in admitted patients. Exact data on how polypharmacy led to toxicity or loss of efficacy or both were not evaluated and are beyond the scope of the study. This analysis was done in the Departments of Medicine, Surgery, and Orthopaedic of Goa Medical College to observe the rates of polypharmacy and its associations with harmful DDIs in admitted patients.

Objectives

- To estimate the rate of polypharmacy among patients admitted to medicine, surgery, and orthopedic wards of Goa Medical College
- To determine the age-wise determination of polypharmacy in admitted patients, as per two age groups - <60 and >60 years
- To analyze the polypharmacy prescriptions for potential for harmful DDIs and see association if any with the number of drugs prescribed for the patients
- To enlist the commonly encountered DDIs and classify them into "X" (combinations to be avoided), "D" (combinations to be modified), and "C" (combinations to be monitored) categories depending upon their risk rating.

MATERIALS AND METHODS

Data source

A prospective cross-sectional observational study was performed from July 2011 to June 2012. Approval was obtained from the Institutional Ethics Committee, Goa Medical College, before study initiation. Data were obtained from the Medical Record Department of Goa Medical College, Bambolim, Panjim, Goa.

Data collection

Discharge papers of all the patients admitted in the medicine, surgery, and orthopedics wards of Goa Medical College during the study period were considered for the study. These departments had maximum rates of inpatient admissions in the hospital; hence, due to logistical constraints, inpatient records of these three departments were considered. Intravenous fluids were considered as drugs in the prescription count.

Inclusion criteria

Prescriptions were considered under polypharmacy if:

- Five or more drugs were prescribed at the same time in one single prescription during hospital stay
- The said prescription was continued for minimum period of 3 days.

Exclusion criteria

Multidrug therapies involving antimalignancy chemotherapy were excluded from the study.

Data analysis

Demographic information (age and sex) was obtained from the clinical records.

Factors studied were:

- Patient characteristics (gender, age)
- Prescription characteristics (number of drugs per prescription).

Drug interactions were identified using a computerized DDI database system (Lexi-Comp version: 2.4.1, Lexi-Comp, Inc., Hudson, OH, USA). This computer program describes all potential interactions and states whether information is available on specific drugs within a class of drugs. It also briefly indicates the clinical relevance of the interaction, whether the interaction has been well established in the literature and gives literature citations.

Classification of drug–drug interactions

Based on the profile of medications prescribed, the DDIs were identified and classified according to Lexi-Comp database. As per the Lexi computer database, all the three categories of DDI were considered as harmful.

According to severity and rating, DDIs were classified as:

- X: Avoid combination altogether
- D: Consider therapy modification
- C: Monitor given therapy.

Statistical analysis

Quantitative data analysis was done by the SPSS for Windows version 17.0 (SPSS Inc., Chicago, IL). Mean with 95% confidence interval was used to summarize age. Frequencies expressed as percentages were used to summarize sex-, age-, department-wise distribution of polypharmacy. Descriptive analysis performed to assess frequency of categorical variables such as number of drugs prescribed, total number of DDIs per prescription, and severity of DDIs. Chi-square test was used to find the association between elderly, number of drugs, and DDIs. Pearson correlation was used to find the correlation between numbers of drugs with DDI present and its severity. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 5424 prescriptions were collected from the three departments and analyzed during the study period.

Analysis of polypharmacy

Altogether, 751 prescriptions out of 5424 (13.85%) prescriptions were observed to have polypharmacy with highest rates observed in the Department of Medicine. The median age of patients was 55.60 ± 13.86 (range, 10–108 years). Four hundred and seventy-six patients were male (63.4%) and 275 (36.6%) were females. Percentage of elderly patients (age 60 or more) was 41.5% as compared to 58.5% of patients with age <60 years.

Total number of drugs per prescription ranged from minimum of 5 to maximum of 16 drugs, with an average of 7.96 ± 1.75. Five hundred and ninety-six prescriptions contained 6–9 drugs per prescription. More than ten drugs per prescriptions were observed in 79 prescriptions.

Analysis of drug–drug interactions

Potential for DDIs was present in 706 out of 751 (94%) prescriptions with polypharmacy. A minimum of one potential DDI to a maximum 25 potential DDIs could be identified in a single prescription in the 706 prescriptions. Most of the prescriptions ($n = 205$) had 5–7 harmful DDIs [Figures 1 and 2].

A total of 305 prescriptions (97.75%) in elderly patients had DDIs as compared to 401 prescriptions (91.34%), with DDIs in patients <60 years of age. This finding is coherent with results of other studies depicting increase in polypharmacy proportional to age. Department-wise, 403 prescriptions from the medicine department had DDIs as compared to 159 from surgery and 144 from orthopedics [Figure 3].

Out of 706 prescriptions with DDIs, 79 prescriptions had more than ten drugs, followed by 323 prescriptions with 8–10 drugs and 304 prescriptions with 5–7 drugs [Table 1].

Sixteen out of 706 (2.3%) prescriptions had at least one DDI classifiable as "X" (combination should be contraindicated), whereas 415 prescriptions had at least one DDI of "D" type where drug therapy should be modified [Table 2] and 688 prescriptions had at least one DDI classifiable as "C" where drug therapy has to be monitored [Table 3].

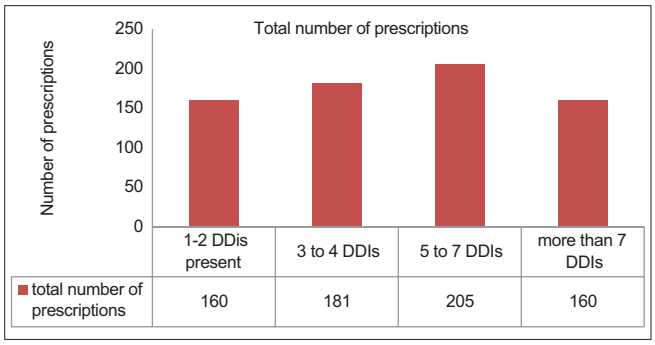

Figure 1: Group of patients as per number of drug–drug interactions

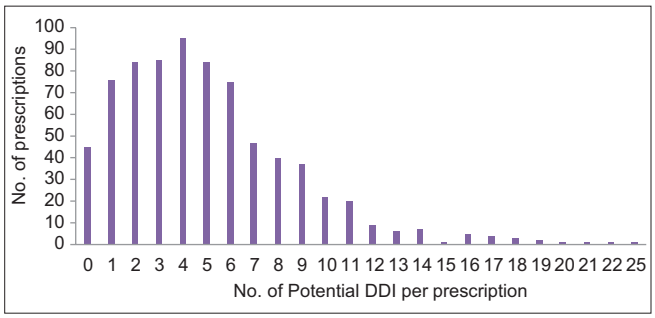

Figure 2: Number of drug–drug interactions per prescription with polypharmacy

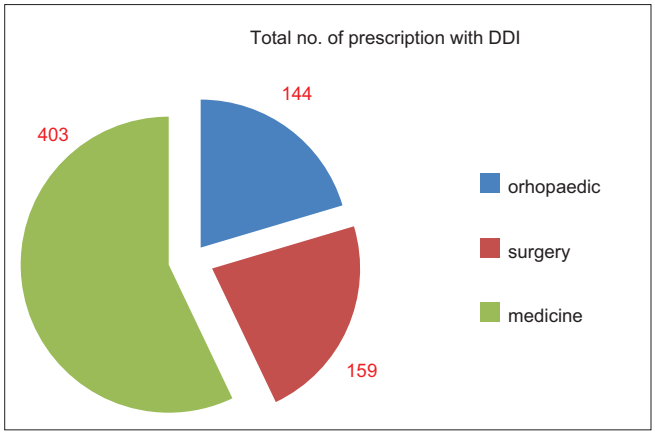

Figure 3: Department-wise breakup of drug–drug interactions

Table 2 enlists the common DDIs encountered in "X" category where these combinations have to be avoided.

DISCUSSION

Polypharmacy is commonly seen in hospitalized patients and carries a high risk of DDIs and drug–disease interactions. These may cause harmful effects, inadequate therapeutic effects, dose missing, overdosing, DDIs, and adverse drug reactions (ADRs). WHO limits the average number of drugs per prescription to be within the range of 1.4–2.4.[9]

We analyzed 5424 prescriptions of patients admitted in medicine, surgery, and orthopedic wards of Goa Medical College from July 2011 to June 2012. Polypharmacy was seen in 751 (13.85%) prescriptions with maximum rates observed in the Department of Medicine. Many patients (n = 596) had 6–9 drugs prescribed and 79 prescriptions had super-polypharmacy (more than ten drugs per prescription). This can be explained by the fact that admitted patients have a multitude of comorbidities, are managed by specialists, and need a multiple number of drugs for prevention and control of the disease.

A prospective, observational study from the cardiology department in a hospital from South India reported an incidence of 30.67% of potential DDIs.[10] In Brazil, few short-term studies reported potential interactions among selected groups of patients. These reports suggest rates of DDIs occurred in 22% for psychiatric and 32% for pediatric patients.[11-13] Furthermore, there was a study done in Mexico City on 624 ambulatory patients over 50 years of age with nonmalignant pain syndrome. The study showed that 80.0% of patients had prescriptions implying one or more potential DDIs and found that advanced age, polypharmacy, and having cardiovascular disorders were the common factors associated with increased rates of DDIs.[14]

In a study done in Canadian hospital in general medical wards, rate of potential DDIs has been almost 60% which is relatively higher rate compared to our study. Similar studies conducted in the emergency departments found frequency of potential drug interactions was in the range of 16%–47%.[15]

Table 1: Comparison of DDIs with number of drugs used

Total number of drugs per prescription	Total number of Drug-drug interactions (DDIs) per prescriptions				
	1-2 DDIs	3 to 4 DDIs	5 to 7 DDIs	More than 7 DDIs	Total
5 to 7 drugs	115 (37.5%)	99 (32.6%)	73 (24.0%)	17 (5.6%)	304
7 to 10 drugs	44 (13.6%)	76 (23.5%)	113 (35.0%)	90 (27.9%)	323
More than 10 drugs	11 (1.3%)	6 (7.6%)	19 (24.1%)	53 (67.1%)	79
Total	160 (22.7)	181 (25.6%)	160 (29.0%)	160 (22.7%)	706

Another study done in Singapore showed that drug-related problems, which include ADRs, unnecessary drug therapy, untreated conditions, and inappropriate choice of drugs reported an incidence rate as high as 25%.[16] Our study had relatively less incidence of DDIs (13.85%).

These differences in the incidences of interactions may be a consequence of the enrollment of younger patients in our study compared to the other studies which enrolled elderly patients.

In our study, 751 prescriptions had polypharmacy and 706 prescriptions showed the presence of a potential DDI. It is a well-known fact that more the number of drugs in a given prescription, more are the chances of having DDIs. Studies show that the rates of potential drug interactions for patients receiving two or more drugs range from 24.3% to 42%.[17]

According to risk rating, we analyzed the DDIs into X, D, C category according to combinations that should be avoided, that should be modified, or that should be monitored, respectively. Drugs involved in potential DDIs in our study included some drugs which are frequently used in primary care, such as aspirin, antacids, beta-blockers, 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitors, calcium channel blockers, angiotensin-converting enzyme inhibitors, ondansetron, and H2 blockers. Other DDIs involved drugs often used together with regular drugs such as calcium salts and iron salts.

Table 2: Common potential DDIs where combinations are contraindicated

Drug-drug interaction	Frequency	Severity	Mechanism of DDI
Carbamazepine/Tramadol	6	Major	PK/PD
Benzodiazepines/Olanzapine	2	Major	PD
Ranolazine/Phenytoin	11	Moderate	PK
Ivabradine/Ranolazine	1	Major	PD
Amiodarone/Ondansetron	1	Major	PD
Artesunate/Ondansetron	1	Major	PD
Prazosin/Tamsulosin	3	Major	PD

The most prevalent type of interactions observed in our study was type C and D, prevalent in 94% of patients having polypharmacy. Dirin *et al.* conducted a study in Iran showed that 48% of prescriptions had 3–4 drug items, with an average of 4.18 items per prescription. The most prevalent type of interactions observed in their study was type C, accounting for 66% of all interactions, followed and only 0.14% of all interactions were due to type X interactions.[18] Similarly, Morteza-Semnani *et al.* reported high percentage of major potential drug interactions ranging from 0.83% to 17%.[19] Twenty-five cases of potential DDIs implicated in our study belong to X category [Table 4], where the combinations are to be avoided totally. Physicians, patients, and pharmacists should be aware of the consequences of these DDIs and closely monitor the patients:

Tramadol/carbamazepine

Six patients in our study had this drug combination administered. According to tramadol prescribing information, tramadol and carbamazepine should not be used together. These drugs could theoretically interact through several mechanisms. Carbamazepine can reduce tramadol systemic concentrations by inducing tramadol metabolism (e.g., through CYP3A). Tramadol has also been associated with seizures, so its administration could decrease or counteract antiseizure effects of carbamazepine. Finally, both drugs are central nervous system (CNS) depressants,

Table 3: Number of DDIs where combination needs modification - Category D

Drug-drug interactions	DDI wherein Drug therapy needs to be modified Category D				Total
	Not present	1 or 2 DDIs	3 to 5 DDIs	More than 5 DDIs	
Present	291	223 (31.6%)	159 (22.5%)	33 (4.7%)	706
Absent	45 100%	0	0	0	45
Total	63 8.4%	218 29.0%	273 36.4%	197 26.2%	751

Table 4: Number of DDIs where combination needs monitoring - Category C

Drug-drug interaction	DDI wherein drug therapy needs to be monitored Category C				Total
	DDI not present	1 or 2 DDIs	3 to 5 DDIs	More than 5 DDIs	
Present	18 2.5%	218 30.9%	273 38.7%	197 27.9%	706
Absent	45 100%	0	0	0	45
Total	63 8.4%	218 29.0%	273 36.4%	197 26.2%	751

so their combination could increase the risk of significant CNS depression.

Lorazepam/olanzapine

Our study analyzed two cases of this interaction. A case report describes a 31-year-old female who fainted and lost consciousness for approximately 2 h, following oral administration of lorazepam (2.5 mg single dose) and olanzapine. Olanzapine prescribing information recommends avoiding concomitant administration of intramuscular (IM) olanzapine and parenteral benzodiazepines due to the risk of excessive sedation and cardiorespiratory depression (87). Wagstaff *et al.* have discussed IM olanzapine in their review article and mentioned that concomitant administration of IM olanzapine and parenteral benzodiazepine had not been studied and therefore had not been recommended.

Ranolazine/phenytoin

Eleven cases of this combination were noted in our analysis. Combined use of ranolazine with phenytoin (strong CYP3A4 inducer) should be avoided since these agents may substantially reduce ranolazine concentrations (likely to subtherapeutic levels). Data described in the ranolazine product labeling show that coadministration of rifampin (600 mg daily) and ranolazine (1000 mg twice daily) resulted in a 95% decrease in ranolazine plasma concentrations. Although studies with other strong CYP3A inducers have not yet been published, it is expected that a similar effect would be observed.

Prazosin/tamsulosin

Three such cases were noted. Concomitant use of alpha-1 blockers was avoided. Additive pharmacologic effects (e.g., hypotension, syncope) might be anticipated. The prescribing information for several alpha-1 blocking agents recommends against concomitant use with other alpha-1 blockers. No such drug interaction has been reported in literature so far.

Ivabradine with ondansetron, amiodarone with ranolazine, artesunate with ondansetron

One case each of these combinations was noted (three cases). The concomitant use of highest risk QTc-prolonging agents with any other QTc-prolonging agent should be avoided. Concomitant use is expected to substantially increase the risk for serious toxicities, including the development of torsades de pointes or other significant ventricular tachyarrhythmias.

Suggested practice

Studies have suggested that medication use can be improved by better communication among patients, physicians, and pharmacists. Measures can be taken to limit polypharmacy to its truly legitimate and appropriate needs. This is an emerging area of research, frequently called de-prescribing.

Several measures may reduce polypharmacy and inappropriate medication use in the nursing homes or hospitals. A new medication should be prescribed only when it is necessary. An appropriate diagnosis should be recorded for each medication prescribed. There would be needed to be more vigilant in the selection of medications so as to avoid potential DDIs and drug–disease interactions. When patients are transferred from acute hospitals, all medications should be reviewed for appropriate clinical indications. Regular medication review by trained physicians to discontinue unnecessary medication could also reduce polypharmacy and inappropriate medication use in nursing homes. Appropriate interventional strategies such as educational, managerial, or regulatory should be made to practice evidence-based prescribing and close monitoring of patients taking drugs with potential DDIs and ADRs. Policymakers and stakeholders should develop drug use policies and intervention measures such as implementation of computer-based software to be used in assisting clinical decision-making. These strategies however may require greater specialist input into medical assessment within hospitals and may have resource implications.

CONCLUSION

Our study was designed to estimate the rates of polypharmacy in admitted patients and analyze the polypharmacy prescriptions for the presence of harmful DDIs. Polypharmacy was seen in 751 out of 5424 prescriptions with highest rates from the Department of Medicine. Super-polypharmacy (≥10 drugs) was seen in 79 prescriptions. The first step in managing drug interactions is to be aware of patients taking potentially interacting drugs. It is then necessary to assess the clinical significance of the interaction and find the patients actually at risk. Although not all drug interactions are clinically significant, it is important to be alert for those that are. It is impossible to remember all the known important drug interactions. However, knowledge of the main types of drugs that are more likely to be involved will act as a useful alert when prescribing. In addition, it is important to remember that various groups such as the elderly are more susceptible to drug interactions. Application of these principles should reduce serious drug interactions when prescribing.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bushardt RL, Massey EB, Simpson TW, Ariail JC, Simpson KN. Polypharmacy: Misleading, but manageable. Clin Interv Aging 2008;3:383-9.
2. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). Saudi Pharm J 2014;22:83-94.
3. Ruiz B, García M, Aguirre U, Aguirre C. Factors predicting hospital readmissions related to adverse drug reactions. Eur J Clin Pharmacol 2008;64:715-22.
4. Gleason LJ, Luque AE, Shah K. Polypharmacy in the HIV-infected older adult population. Clin Interv Aging 2013;8:749-63.
5. Kafeel H, Rukh R, Qamar H, Bawanty J, Jamshed M, Sheikh R, *et al*. Possibility of drug-drug interaction in prescription dispensed by community and hospital pharmacy. Pharmacology & Pharmacy 2014;5:401-7.
6. Nobili A, Marengoni A, Tettamanti M, Salerno F, Pasina L, Franchi C, *et al*. Association between clusters of diseases and polypharmacy in hospitalized elderly patients: Results from the REPOSI study. Eur J Intern Med 2011;22:597-602.
7. Vyas A, Pan X, Sambamoorthi U. Chronic condition clusters and polypharmacy among adults. Int J Family Med 2012;2012:193168.
8. Doan TN, Lennox NG, Taylor-Gomez M, Ware RS. Medication use among Australian adults with intellectual disability in primary healthcare settings: A cross-sectional study. J Intellect Dev Disabil 2013;38:177-81.
9. Müller M. Polypharmacy, inappropriate prescribing and adverse drug reactions in Austria. Wien Klin Wochenschr 2008;120:713-4.
10. Sharma S, Chhetri HP, Alam K. A study of potential drug-drug interactions among hospitalized cardiac patients in a teaching hospital in Western Nepal. Indian J Pharmacol 2014;46:152-6.
11. Miyasaka LS, Atallah AN. Risk of drug interaction: Combination of antidepressants and other drugs. Rev Saude Publica 2003;37:212-5.
12. Meiners MM, Bergsten-Mendes G. Drug prescription for hospitalized pediatric patients: How can the quality be evaluated? Rev Assoc Med Bras 2001;47:332-7.
13. Dias MF. Potential Drug Interactions in a Hospital Setting [Master's Degree]. Campinas, SP: State University of Campinas; 2001.
14. Hussar DA. Drug interaction. Remington The science and practice of pharmacy. In: Gennaro AR, Marderosian AHD, Hanson GR, Medwick T, Popovich NG, Schnaare RL, *et al*., editors. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 1746-61.
15. Riechelmann RP, Zimmermann C, Chin SN, Wang L, O'Carroll A, Zarinehbaf S, *et al*. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage 2008;35:535-43.
16. Stewart RB, Cooper JW. Polypharmacy in the aged. Practical solutions. Drugs Aging 1994;4:449-61.
17. Dambro MR, Kallgren MA. Drug interactions in a clinic using COSTAR. Comput Biol Med 1988;18:31-8.
18. Dirin MM, Mousavi S, Afshari AR, Tabrizian K, Ashrafi MH. Potential drug-drug interactions in prescriptions dispensed in community and hospital pharmacies in East of Iran. J Res Pharm Pract 2014;3:104-7.
19. Morteza-Semnani K, Saeedi M, Qari Pour U. Evaluation of drug interactions of cardiovascular drugs in insurance prescriptions of Sari city – 1998-1999. Mazandaran Univ Med Sci J 2000;11:93-87.