Potential drug-drug interactions among patients with chronic kidney disease admitted at National Hospital: a retrospective study in Tanzania

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Abstract

Background: Drug related problems such as drug-drug interactions (DDI) are likely to occur in chronic kidney disease (CKD) patients due to polypharmacy practice. The DDI increases the risk of morbidity, mortality, prolonged hospital and cost of treatment. In most cases, the potential drug-drug interactions (pDDI) are not checked during prescribing or dispensing of polypharmacy for CKD patients in developing countries like Tanzania. Therefore, we documented the pattern and potential drug-drug interactions (DDIs) among CKD patients admitted at Muhimbili National Hospital (MNH).

Methods: The study retrospectively reviewed 198 files for CKD patients admitted at MNH between January 2017 and December 2018. The social-demographic characteristics and comorbidities were documented using a checklist. Prescriptions with polypharmacy were reviewed and prescribed medicines were documented. Medscape drug interaction checker was used for pDDIs. The SPSS version 23.0 was used to carry out statistical analysis.

Results: The study involved a total of 306 prescriptions with polypharmacy with a mean(±SD) of 6.21(±1.22) medicines per prescription. Majority of patients (77.2%) were in stage 5 of chronic kidney disease. Frequently prescribed medicines were pantoprazole 135(44.1%), furosemide 133(43.5%), ferrotone 101(33.0%), calcium carbonate 91(29.7%), amlodipine 121(39.5%), nifedipine 83(27.1%), bisoprolol 46(15.0%) and clonidine 38(12.4). The prevalence of pDDIs was 94.1%. The total of 1743 potential drug-drug interactions was observed with a mean of 6.03(±2.12) interactions per prescription. Majority of the pDDIs were moderate (67.5%) whereas, 29.5%, 2.6% and 0.3 were minor, serious and contraindicated respectively. The occurrence of pDDIs was associated with stroke (P-value=0.038), diabetes mellitus (p-value=0.049) and hypertension with diabetes mellitus (p-value=0.047).

Conclusion: The prevalence of pDDIs was high among the CKD patients. The determinants of pDDIs among CKD patients were hypertension, diabetes mellitus and stroke. Interaction checkers should be incorporated in health system to guide the prescribing and dispensing of medicine for CKD patients.

Background

Chronic kidney disease (CKD) is among the leading course of morbidity and mortality worldwide(1,2). The global prevalence of CKD ranges between 11% and 13% while the prevalence of CKD in Tanzania was 13.6%(3,4). The mortality attributed to CKD has been increasing from time to time, for example, there was an increase of 32% of mortality in ten years from 2005 to 2015 (5). It has been estimated that, about 10 million people die from kidney disease each year(2,3). Lack of access to proper management of CKD has been reported to be a challenge due to expenses, making the condition worse in developing countries like Tanzania (2). In 2010, about 7 million patients with end stage kidney disease (ESKD) died due to lack of access to dialysis(2).

The CKD is accompanied with other diseases such as cardiovascular (hypertension, heart failure and stroke) and diabetes mellitus (1,3,4,6). Therefore, prescriptions with more than one medicine for treatment

of these patients is a common practice. An average of 6–8 medicines have been reported to be prescribed to CKD patients (7–10). When the prescription contains five or more medicines is referred to as polypharmacy (11). In developing countries the prevalence of polypharmacy is above 80% (9–11). The risk of pDDIs rises to 40.0% among patients taking five drugs and 80.0% in patients with more than five drugs(12). The prevalence of pDDIs among patients receiving polypharmacy has been reported to be between 59–89.1% (9). The pDDIs predispose CKD patients into severe morbidity, increased mortality rate, high treatment cost and prolonged hospital stay (10). The severity of these interactions may be affected by the renal status of the patients. The mild interaction experienced by renal competent patients may be life threatening in patients with impaired renal disease since their pharmacokinetic responses to the drugs are altered (6).

Despite the inevitable polypharmacy practice among CKD patients there is still a critical need to minimize the number of prescribed medicines for these patients in order to reduce risk of associated outcomes (10). As there is an increasing prevalence of kidney diseases in developing countries (1,4) and the ongoing improvement of nephrology services in Tanzania, the need of studies on the pattern and potential of DDIs is important in order to closely monitor the prescribed medicines among CKD patients. However, to our understanding there are no sufficient published evidence on the pattern and pDDIs among CKD patients admitted at MNH.

Methods

Study design and setting

This was a retrospective study that was conducted to CKD patients admitted at nephrology unit, MNH. MNH is a National Referral Hospital, Research Center and University Teaching Hospital, which admits 1,000 to 1,200 patients per week. The MNH has well established nephrology department, in which it offers specialized medical and dialysis services to CKD patients. In recent years, MNH have been performing successfully renal transplants to patients with ESKD. The study was conducted from November 2018 to July 2019 involving CKD patients admitted between January, 2017 and December, 2018.

Sampling and data collection

The study involved consecutive medical files of CKD patients admitted in nephrology unit at MNH. Considering the 80% prevalence of pDDIs among CKD patients and 6% margin of error, the minimum of 198 files were included in the study (12,13). All prescriptions that were present in the medical file were evaluated for pDDIs. Prescriptions that had less than five medicines or incomplete were excluded from the study.

Socio-demographic characteristics and clinical information such as age, sex, marital status, education level, occupation, history of smoking, alcohol consumption, comorbidities and stage of CKD were recorded from patient file. The prescribed medicines were recorded from the prescription by their generic names.

Assessment of pDDIs

The pDDIs were assessed using Medscape interaction checker, WebMD LLC. This is an online software program that provided the four categories of pDDIs; minor, moderate, serious and contraindicated. The software allows checking interactions between two drugs. Since we included prescriptions with at least five drugs, various combination of drugs on each prescription were checked. As per the Medscape interaction checker software, “minor interaction” meant the significance of interaction was not known, “moderate interactions” required the physician to monitor the patient closely (use the combination with caution) while “serious interaction” required to use alternative/monitor closely, the contraindicated interaction was to avoid concomitant administration of drugs.

Data analysis

Descriptive statistics were done, and frequency distribution table and graphs were used to summarize the results in Microsoft Excel, cleaned and analyzed by SPSS (statistical package for social sciences) version 23.0 software. Chi-Square and Fischer Exact tests were used for analysis of categorical variables. To describe the prevalence of pDDIs, we calculated the percentages of pDDIs by patient. Categorical variables with a p-value of < 0.2 were subjected to logistic regression models to identify factors associated with pDDIs. The p-value < 0.05 at 95% Confidence interval was deemed significant.

Results

Social demographic information

In total, 198 patient files of CKD patients were studied (table 1). Majority (59.1%) were female aged between 51–61 years old (38.4%) with a mean (± SD) of 52.82 (± 15.59) years. More than half of the patients (66.7%) were married. More than 50.0% of the patients were alcohol takers and only few (11.1%) had a history of smoking. Most of the patients’ information on occupation (86.4%) and education level (84.3%) were missing.

Medical condition and chronic kidney disease stage

The majority (72%) of CKD patients were under conservative care while 28% were on maintenance dialysis (Fig. 1) and no any patient was found under renal transplant. Hypertension and diabetes were present in 90.4% and 31.3% patients respectively, with 30.8% having both hypertension and diabetes. Most of them 77.2% were in stage-5 of CKD, followed by stage-4 (15.7%) and stage-3 (6.6%) and no patient had stage one (table2).

Prescribed medications and potential drug-drug interactions

Overall, 306 prescriptions with polypharmacy were obtained from 198 patient files with a mean (± SD) number 1.55(± 1.147) prescriptions per patient. In total, 1900 medicines were prescribed with mean (± SD) of 6.21(± 1.22) medicines per prescription. Frequently prescribed medicines were pantoprazole (44.1%),

furosemide (43.5%), amlodipine (39.5%), ferrotone (33.0%), calcium carbonate (29.7%), nifedipine (27.1%), bisoprolol (15.0%) and clonidine (12.4).

The prevalence of pDDIs among CKD patients was 92.4%. Total of 1743 potential drug-drug interactions were observed with a mean (± SD) of 6.03 ± 2.12 interactions per prescription. Majority of the pDDIs were moderate interactions (67.5%). The minor, serious and contraindicated were 29.5%, 2.6% and 0.3% respectively.

The most common interactions observed were between furosemide and calcium carbonate (3.1%), pantoprazole and ferrotone (2.9%), bisoprolol and furosemide (1.8%) and clonidine and metoprolol (0.8%) (Table 3). Other interactions observed were between ciprofloxacin and ondansetron (serious), metronidazole and tolvaptan (serious), hydralazine and bisoprolol (moderate) and clonidine and atenolol (serious).

On logistic regression analysis, CKD patients who had stroke were at 2-fold risk of experiencing pDDIs compared with those who had no stroke (aOR, 2.09; 95% CI,1.78–36.76; p = 0.007). The pDDIs were high among CKD patients with diabetes mellitus (aOR,1.17; 95%CI, 1.09–9.96; p = 0.04) and when hypertension occurred co-currently with diabetes (aOR, 1.19; 95% CI,1.09–9.96; p < 0.03). Other comorbidities such as HIV infection and heart failure were not significantly associated with pDDIs.

Discussion

This study retrospectively assessed the prevalence and pattern of pDDIs among CKD patients admitted at MNH in Tanzania. The prevalence of pDDIs was 92.4%, and most of the pDDIs were moderate and minor interactions. This was much higher than a Pakistan study(12) that reported incidence of 78.5%. The lower pDDI rate in Pakistan study could have been due to the use of Micromedex Drug-Reax® system, unlike our study that used Medscape drug interaction checker to screen the drug-drug interaction profiles. A study done on comparison of drug-drug interaction software programs had shown differences regarding accuracy and comprehensiveness between the programs with disagreement in the severity of the interactions(16). Although variations exist in study designs of previous study, a high prevalence of pDDIs has been observed in CKD patients, which supports our study findings.

The high prevalence of stage 5 patients could be because the early stages 1–3 of CKD are usually asymptomatic thereby making the patients present at health facilities with CKD at advanced stages. Also the study was conducted at the National referral hospital which receives most of patients in their late stages from the countryside. Most of these patients were on conservative care since most of CKD patients could not afford dialysis.

We found that, a mean (± SD) of 6 ± 1.29 medicines per prescription which is lower than a study in Nigeria(10) which reported a mean (± SD) of 10.06 (± 3.97) medications. The number of medications in this study was close to a Palestine study(15) which reported a mean of 7.87 (± 2.44) medicines. This demonstrated how common polypharmacy is among CKD patients. The mostly prescribed medicines

were useful in improving the quality of life of CKD patients. Among commonly prescribed medications in the study were calcium carbonate and furosemide similar to other studies (10,12,15). CKD patients at stage 3 to 5 are associated with cardiovascular events with edema, anemia and bone resorption which could have attributed to diuretics, beta-blockers, calcium channel blockers, ferrotone and calcium carbonate being prescribed (4,6).

Patients who had hypertension with diabetes, diabetes and stroke had increased risk of pDDIs. Since drugs were used in the treatment of CKD and comorbidities, concomitant administration of these drugs increased the risk of pDDIs. The drug-related problems could worsen the CKD and comorbidities (17). Therefore, care should be take when prescribing drugs to CKD patients with these comorbidities and pharmacist should be full involved in order to advice appropriately in reducing the number of medications (9,18).

Study limitation

Our study used Medscape interaction checker software program which was free and easily accessible in our settings. The software allowed only two drugs to be checked. Some interactions are dose dependent; the software did not have the option to check interactions related to doses. The software program did not take into account the time interval between drug administration; it assumes tow drugs are taken at the same time. In addition, there is no ideal software program for checking pDDIs. The outcome of interaction and the approach taken by the health care provider in case of adverse drug reaction associated with pDDIs was not documented.

Conclusion

The prevalence of pDDIs was high among the CKD patients. The most common pDDIs were moderate and minor interactions and required close monitoring. Stroke, diabetes and hypertension with diabetes increased the chances of pDDIs, thus, health care providers need to pay special attention when attending patients with these commodities. Electronic drug interaction tools such as Medscape drug interaction checker should be available in the pharmacy section of hospitals.

Abbreviations

DDI, potential drug-drug interaction; ESKD, end stage renal disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease

Declarations

Ethics approval and consent to participate

Approval to conduct this study was sought from the Ethical Committee of Muhimbili University of Health and Allied Sciences. The permission to conduct the study and access to patient information was granted

by MNH.

Consent for publication

Not applicable

Availability of data and material

The dataset generated and/or analyzed during this study is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

WPM designed the study, data analysis and drafted the manuscript. JEM coordinated and monitored data collection. MK, WK, HM, GMB, AIM and RM participated in study design, supervision of the study, interpretation of data and manuscript development. All authors read and approved the final manuscript.

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Not applicable

Authors' information (optional)

Not applicable

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Tables

Table 1. Social demographic information

Variables	Number of patients N=198	Percentage
Gender		
Males	81	40.9%
Females	117	59.1%
Marital status		
Single	14	7.1%
Married	132	66.7%
Widowed	42	21.2%
Divorced	10	5.1%
Age (years)		
<18	4	2.0%
19-35	24	12.1%
36-50	51	25.8%
51-65	76	38.4%
> 65	43	21.7%
Education level		
Tertiary level	14	7.1%
Secondary level	6	3.0%
Primary level	11	5.6%
Not recorded	167	84.3%
Alcohol use		
Yes	112	56.6%
No	86	43.4%
Smoking		
Yes	21	10.6%
No	177	89.4%

Table 2. Chronic kidney disease stage and Co-morbidities

Variables	Number of patients N=198	Percentage
CKD stage (eGFR)[a]		
Stage 1 (>90 ml/min/1.73 m^2)	0	0.0%
Stage 2 (60-89 ml/min/1.73 m^2)	1	0.5%
Stage 3 (30-59 ml/min/1.73 m^2)	13	6.6%
Stage 4 (15-29 ml/min/1.73 m^2)	31	***15.7%***
Stage 5 (< 15 ml/min/1.73 m^2)	153	**77.3%**
Co-morbidity		
Hypertension	179	***90.4%***
Diabetes mellitus	62	***31.3%***
Heart failure	5	2.5%
HIV	38	19.2%
Stroke	9	4.5%
Hypertension and diabetes mellitus	61	***30.8%***
Hypertension and HIV	18	9.1%
Hypertension, diabetes mellitus and HIV	7	3.5%

[a]The eGFR as described by Pronovost et al (14)

Table 3. Pharmacological effect of common drug-drug interaction among CKD patients

Prescribed drugs	Frequency	Interaction category	Pharmacological effect of DDI
Furosemide+calcium carbonate	54	Minor	Furosemide decreases levels of calcium carbonate by increasing renal clearance
Pantoprazole+Ferrotone	50	Minor	Pantoprazole decreases the level of ferrotone by increasing gastric pH
Bisoprolol+furosemide	31	Moderate	Bisoprolol increases and furosemide decreases the serum potassium
Metoprolol+ furosemide	27	Moderate	Metoprolol increases and furosemide decreases serum potassium
Pantoprazole+ efavirenz	23	Minor	Efavirenz increases the level of pantoprazole by affecting hepatic enzyme CYP2C19
Clonidine+metoprolol	14	Serious	Either increases the toxicity of the other by unspecified mechanism, can increase the risk of bradycardia
Furosemide+metolazone	12	Moderate	Both decreases serum potassium
Bisoprolol+clonidine	11	Serious	Either increases toxicity of the other by unspecified mechanism, can increase the risk of bradycardia
Fluconazole+ pantoprazole	4	Minor	Fluconazole increases the level of pantoprazole by affecting hepatic enzyme CYP2C19
Ceftriaxone+calcium carbonate	3	Contraindicated	Risk of potentially fatal particulate precipitation in lungs and kidney
Carvedilol+efavirenz	3	Serious	Efavirenz increases the level of carvedilol by affecting hepatic enzyme CYP29/10 metabolism
Nifedipine+tolvaptan	2	Serious	Nifedipine increases the level of tolvaptan by affecting hepatic/intestinal enzyme CYP3A4 metabolism
Ceftriaxone+calcium gluconate	2	Contraindicated	Risk of potentially fatal particulate precipitation in lungs and kidney
Aspirin + enalapril	2	Serious	Interacts by pharmacodynamics antagonism, aspirin reduces the synthesis of vasodilating renal prostaglandins. May result in renal function deterioration especially in elderly.

Figures

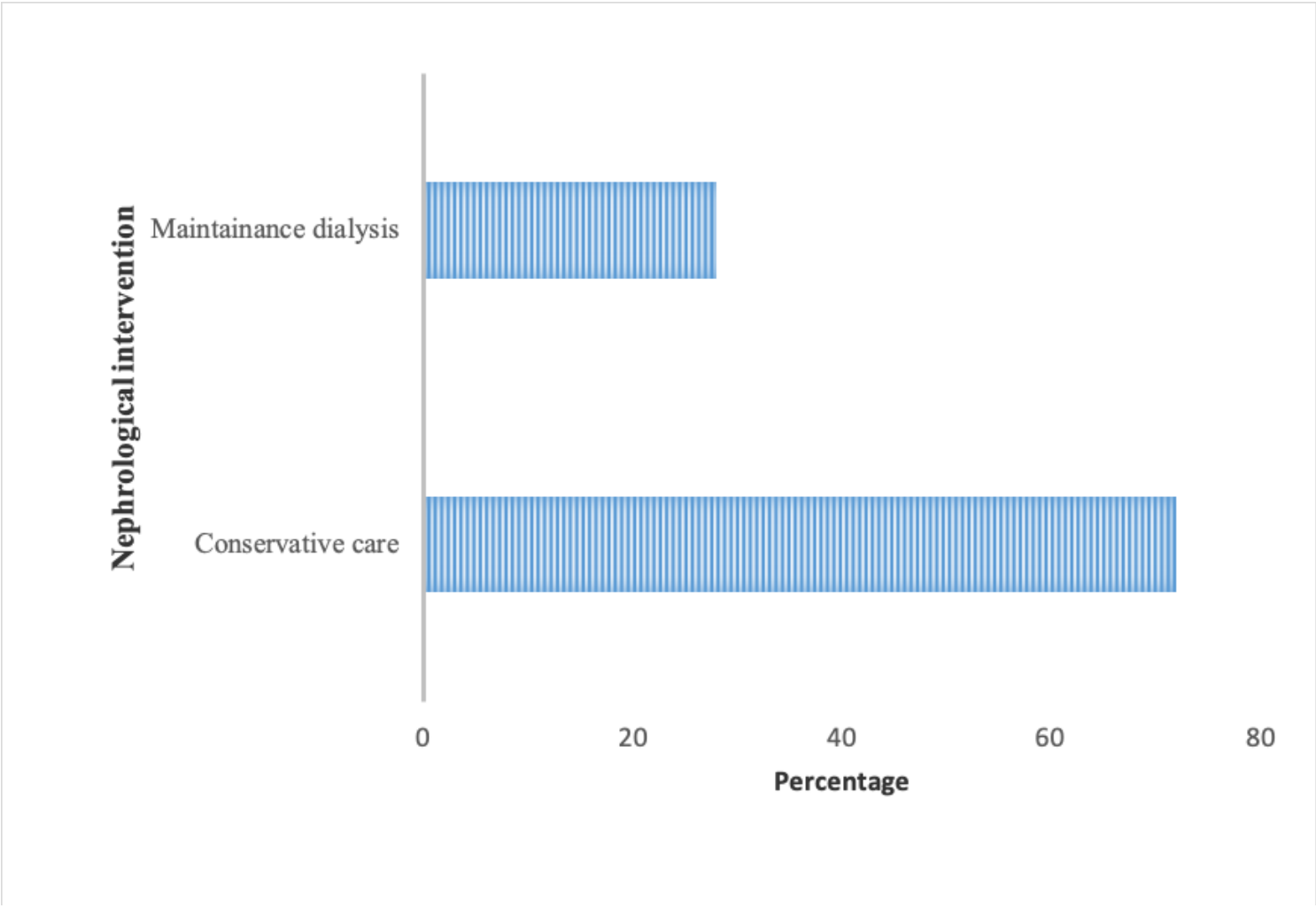

Figure 1

Nephrological intervention among CKD patients at MNH

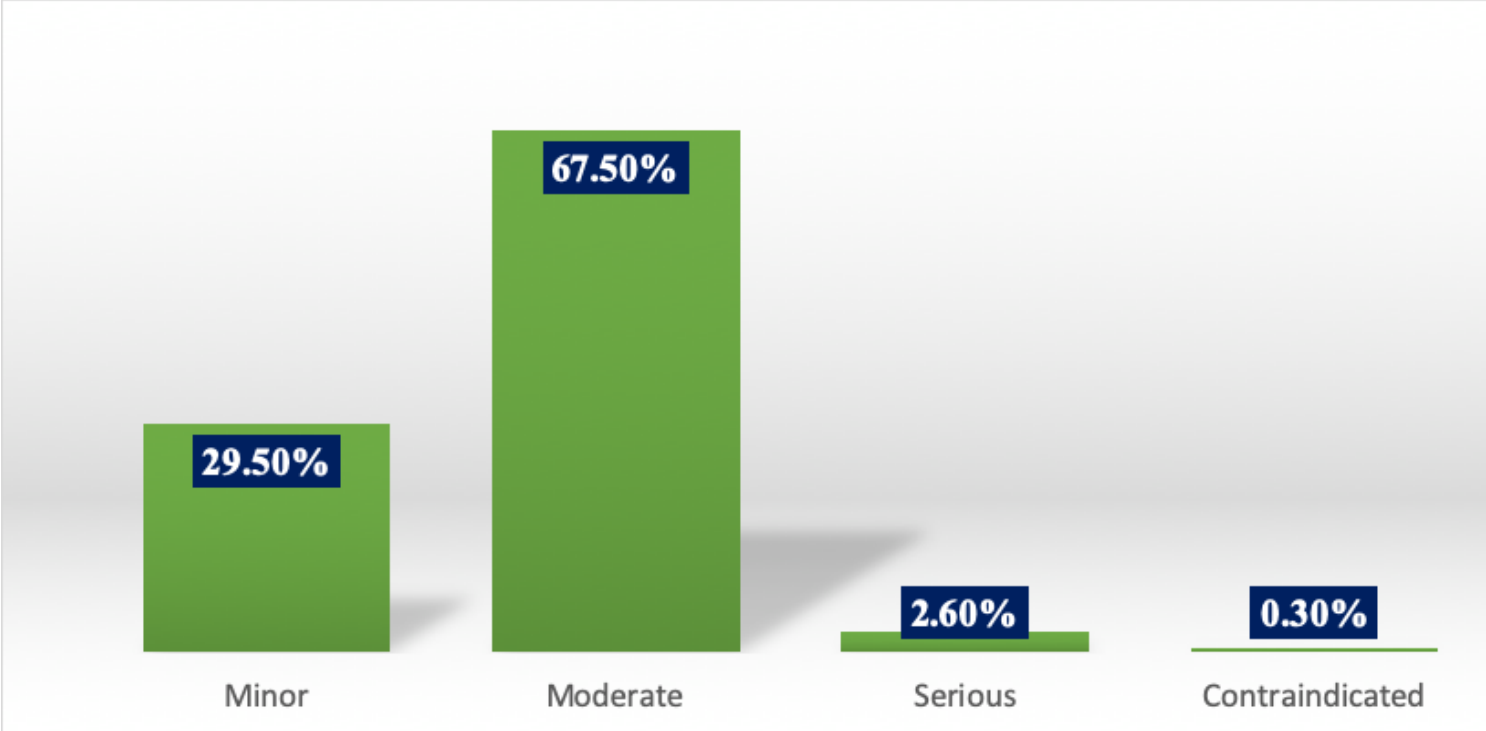

Figure 2

pattern of potential drug-drug interactions