Potential Drug-Drug Interactions among Medications Prescribed to Adult Filipinos at a Primary Care Clinic in a Government Teaching Hospital

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ABSTRACT

Background. A drug-drug interaction (DDI) is a pharmacologic or clinical response to the administration of a drug that can result in adverse outcomes. DDIs are considered preventable adverse drug reactions because these interactions can be learned, predicted and recognized.

Objective. To determine potential drug-drug interactions (pDDI) among medications prescribed to adult patients consulting at a primary care clinic in a government teaching hospital.

Methods. This was a 6-month retrospective cross-sectional study of drug prescriptions based on medical records of adult Filipinos who were seen and managed at a primary care clinic in a government teaching hospital. Medical charts were systematically selected based on a sampling frame with inclusion and exclusion criteria.

Results. A total of 1,490 medical records of adult Filipino patients were included in the study. There were a total of 261 unique prescriptions based on generic formulations and an overall total of 5,978 drugs for a 6-month period of clinic consultations. An average of 4 medications (SD±1.63) were prescribed for every consultation recorded in the medical chart. From the charts that were reviewed, 23% of all adults were given a prescription of 4 drugs (N=348/1490), 26% had 3 drug prescriptions (N=386/1490) and 18% had two drugs, respectively, per clinic visit. Overall, 714/9054 (7.88%) medication pairs were seen to have potential drug interactions. The top three most common drug pairs with pDDI were amlodipine-simvastatin, losartan/hydrochlorothiazide-metformin and aspirin-furosemide. Five hundred twenty-five drug pairs had pharmacodynamic interactions (525/714) while 94 drug pairs (15%) had pharmacokinetic interactions.

Conclusion. Potential drug-drug interactions were observed in 8% of medications prescribed to adult Filipinos seen at Family Medicine Clinic in a government hospital. Seventy-four percent (74%) of the drug pairs with pDDIs were pharmacodynamic and 15% were pharmacokinetic interactions.

Key Words: drug-drug interaction, outpatient clinic, primary care clinic

INTRODUCTION

Multiple medication prescriptions are common because of the increasing number of comorbid conditions in the aging population. Unfortunately, this increases the potential for unrecognized drug-drug interactions (DDIs), which can lead up to 3% of all hospital admissions resulting in increased healthcare cost and possible drug-related mortality.[1] DDIs are also one of the unseen sources of medication errors and are considered to be a subset of adverse drug reactions.[2]

Drug-drug interactions are the pharmacologic or clinical response to a drug resulting in adverse outcomes.[3] Although potential DDIs (pDDI) may not have an actual clinical effect, the incidence of DDI-related adverse drug

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reactions in elderly outpatients was documented at 6% and the prevalence of clinically important pDDIs can be as high as 47.4%.[4] Clinically significant interactions may lead to gastrointestinal bleeding, hypotension, nephrotoxicity, myopathy or electrolyte imbalance such as hyperkalemia.[4,5] The consequences of clinically relevant drug-drug interactions are preventable by identifying and preventing potential DDIs among prescription drugs starting at the outpatient setting.

In outpatient practice, pDDIs have been documented from 13% to 63% among adults greater than 45 years old and as high as 83% in a medical outpatient facility of a tertiary care teaching hospital.[2,6,7] Analysis of a drug database in Iran showed that for every 10,000 prescriptions, about 7 clinically relevant drug-drug interactions were identified.[8] A study conducted in Europe also showed around 2.2% of primary care physicians inadvertently prescribed multiple drugs with pDDIs in a year.[9]

DDIs are considered preventable adverse drug reactions because the interactions can be learned, predicted and recognized thru the use of well-established, currently available DDI databases.[10] A prescription analysis study in primary care clinic of a government teaching hospital can contribute to the identification and recognition of pDDIs to help improve medication safety via healthcare providers feedback. Likewise, training interventions may be designed and implemented to prevent co-prescription of drugs with pDDIs. It may also be a useful tool in quality assurance activities to identify high-risk patients and address practices resulting in adverse outcomes. Hence, the overall objective of this study was to determine potential drug-drug interactions among medications prescribed to adult patients consulting at a primary care clinic in a government teaching hospital.

METHODS

Study Design, Sample size and Data Collection

This was a six-month retrospective cross-sectional study of drug prescriptions of adult Filipinos who were seen and managed at a primary care clinic in a government tertiary teaching hospital. Medications prescribed to all outpatient consultations were reviewed and aggregated.

Documentations of a minimum of two drug prescriptions in the last recorded clinic visit were included. Medical charts were systematically selected based on the sampling frame of daily clinic census. Excluded were charts with prescriptions for surgical, anesthesia procedures and subspecialty referrals.

The study period comprised of six months of outpatient consults. A nurse research assistant was trained on data collection. However, due to time and resource limitations, the days for data gathering were limited to only 3 days per week. Clinic days were randomly selected using MS Excel™ random number generator.

The calculated sample size was 1,284 unique prescriptions based on a previous study prevalence of DDIs at 83.42%, a desired precision of 5% and confidence level of 95%. An additional 20% was added to account for prescriptions that will be excluded during data collation. Eighteen (N=18) records per day were systematically selected for inclusion, depending on the total number of patients' clinic consultation per day.

Potential drug-drug interactions (pDDIs) were checked using currently available databases such as Lexi-Comp™ Drug Interactions, Medscape® online and Epocrates® drug interaction checker. The severity of the pDDIs were categorized into serious, significant (close monitoring), or minor. The groupings were then further classified as to the main mechanism of interaction: either pharmacokinetic or pharmacodynamic interactions.

Data were encoded in Microsoft Excel™ 2016 spreadsheet and analyzed using Stata™ version 14. Nominal data were analyzed using descriptive statistics (frequency, proportions and cross tabulations) while numerical data were reported using mean, median and standard deviation. Multivitamins and other supplement forms were excluded from the analysis of the drug pairs based on the original study protocol.

Study Outcomes

Primary outcomes included the overall frequency of pDDIs in the six-month study period, average number of drugs prescribed per patient consult, and pDDIs per category of mechanism. Secondary outcomes included the average age of patients who had undergone consultations, top three most common diagnoses, and most common drugs that were prescribed.

Ethical Considerations

The research underwent ethical review by the University of the Philippines Manila Research Ethics Review Board (CODE: 2016-458-01). Permission to conduct the study and access medical charts was secured from the respective hospital offices. Confidentiality and anonymity of medical records was ensured thru paper coding of all data collection forms. The conduct of data collection, gathering, processing and management was in accordance with the Implementing Rules and Regulations of the Data Privacy Act of 2012.

RESULTS

A total of 1,490 medical records of adult Filipino patients were included in the study. Records of consultations (< 0.05%) with single or no drug prescription were excluded from data collection.

There were a total of 261 unique prescriptions based on generic formulations and an overall total of 5,978 drugs for the entire 6-month period of outpatient consultations.

The average age of adult patients who came in for consultations at the Family Medicine Clinic was 57.82 years (SD± 11.72), the oldest being 95 years old. Sixty-five percent

Table 1. Distribution of Potential Drug-Drug Interactions based on Mechanism and Severity in 5978 drugs prescribed among Adult Filipino patients consulting at the Primary Care Clinic of a Tertiary Government Hospital, February to July 2017

Severity/Mechanism	Serious	Significant	Minor	Total N (%)
Pharmacodynamic	245 (46.7%)	228 (43.4%)	52 (9.9%)	525 (100%)
Pharmacokinetic	24 (25.5%)	63 (67.0%)	7 (7.4%)	94 (100%)
Pharmacokinetic/Pharmacodynamic	0	15 (24.2%)	47 (75.8%)	62 (100%)
Unspecified	1 (3%)	32 (97%)	0	61 (100%)
Overall	270	338	106	714

(65%) were females while 3% of the medical records (N=41) had no documentation of patient's physical gender.

Non-communicable diseases (NCDs) were the top diagnoses based on the medical records reviewed. Hypertension was the most common primary diagnosis, comprising 73% (N=1085/1490) of all records, while diabetes was second at 25% (primary diagnosis or as comorbid, N=378). Other diagnoses included dyspepsia, heart failure, dyslipidemia, pneumonia, chronic stable angina, pulmonary tuberculosis and degenerative osteoarthritis.

Drug Prescriptions

An average of 4 medications (SD±1.63) were prescribed for every consultation. Accordingly, 23% (N=348/1490) of all adults who came in for an outpatient consult were given a prescription for 4 drugs, 26% (N=386/1490) had 3 drugs and 18% (268/1490) had two 2 drugs prescriptions. Four (4) patients had a prescription for 10 medications.

The most common medications prescribed were for hypertension (29%, N=1729), dyslipidemia (16%, N=950) and diabetes (10%, N=565).

Losartan (N=591), amlodipine (N=471), and enalapril (N=144) were the most common single formulation, while losartan-hydrochlorothiazide (N=187) was the usual dual formulation anti-hypertensive medications prescribed. Atorvastatin (N=462) and simvastatin (N=422) were generally prescribed for dyslipidemia whereas metformin (N=335), gliclazide (N=72), and single formulation sitagliptin (N=54), were most commonly prescribed for diabetes.

Co-amoxiclav, azithromycin and ciprofloxacin were the frequent antibiotics on record. Prescriptions for multi-vitamin supplementation (N=358) were recorded at a higher number compared to antibiotic prescriptions (N=195).

Potential Drug-Drug Interactions (pDDI)

Overall, a total of 714 medication pairs were found to have pDDIs (Table 1). This corresponds to 7.88% of all medication pairs documented in the entire six-month study period. The top three most common combinations were amlodipine-simvastatin (150/710), followed by losartan/hydrochlorothiazide-metformin (49/710), and aspirin-furosemide (Table 2).

Five hundred twenty-five (525) drug pairs had potential DDIs with established pharmacodynamic interactions (525/714). The top five most common pairs identified were amlodipine-simvastatin (N=150), aspirin-enalapril (N=48), losartan-celecoxib (N=37), aspirin-furosemide (N=12) and enalapril-gliclazide (N=11).

Table 2. Top Ten Drug Pairs with the Potential to Cause Drug-Drug Interactions based on Medical Records Review of Outpatient Consultations in a Primary Care Clinic of a Tertiary Government Hospital, February to July 2017

Ranking	Drug Combination	Number of Encounters
1	Amlodipine-simvastatin	150
2	Losartan/HCTZ-metformin	49
3	Enalapril-aspirin	48
4	Losartan-celecoxib	37
5	Metformin-enalapril	21
6	Clopidrogrel-omeprazole	17
7	Aspirin-gliclazide	13
8	Aspirin-furosemide	12
9	Enalapril-gliclazide	11
10	Atorvastatin-digoxin	10

On the other hand, 94 (15%) pairs had probable interactions based on recognized pharmacokinetic mechanisms. Clopidogrel-omeprazole (N=17) and aspirin-gliclazide (N=13) were the two most common drug pairs in this classification.

Ninety percent (90%) of the drug pairs with pharmacodynamic interaction and 9% with pharmacokinetic interaction, were classified as serious. Significant drug interactions were found in 68% of pharmacodynamic, and in 19% of pharmacokinetic interactions.

Modification of therapy was imperative in 218 (30%) out of the 714 prescriptions with pDDIs. Likewise, 454/714 (64%) prescriptions should be closely monitored during therapy for possible adverse outcomes.

DISCUSSION

This prescription analysis study showed that potential drug-drug interactions occured in medications prescribed to adult patients seen at the outpatient clinic. Possible serious and significant interactions have been identified, particularly among commonly prescribed drugs for chronic non-communicable diseases (NCD) such as hypertension, diabetes and dyslipidemia. Clinical responses to more than half of the prescriptions with pDDIs should have been

monitored for pharmacodynamic interactions. Therapeutic plans in 1 of 3 prescriptions should have been modified due to pharmacokinetic mechanisms.

Clinical characteristics of adult Filipinos who consulted the clinic included age greater than 55 years, multiple comorbid diseases and an average prescription of four drugs.

Patients' age group, multiple comorbid disease, combined with four or more medications increase the probability of adverse events and cost of therapeutic management. The increasing number of drug prescriptions among the older population due to several illnesses increases the likelihood of potential drug-drug interaction.

The average adult prescriptions in the study was comparable to related international literature where the average number of prescriptions for adults aged greater than 45 years old was at 4-6 drugs and up to as high as 11 drug prescriptions per person.[7,11] This prescription pattern create a significant health concern because three to five different types of medications have five times the odds of developing drug interactions (OR 4.74 95%CI 2.90-7.73). The probability of interactions also increases considerably to roughly six-fold (OR 23.03 95% CI 10.42 – 50.91) for patients given six or more drugs.[7] Consequently, the increasing number of drug prescriptions among the older population due to multiple comorbidities similarly enhances the likelihood of potential drug-drug interaction. This risk is also relevant among vulnerable populations, including the elderly hospitalized, cancer patients, patients with heart diseases, and those receiving digoxin, due to high rate of medicine utilization. The problem of potential DDIs also extends to pediatric population: as high as 3.8% with approximately 1 in 200 children significantly at risk for pDDIs.[10]

The occurrence of potential drug interactions may be attributed to several factors related to the health care provider, the patient and/or the properties of the drug. Factors relating to the patient characteristics such as age, gender, genetics comorbid condition such as hypertension and/or concurrent disease affecting drug clearance, increase the probability of potential drug interactions.[2]

On the other hand, selected drug factors also contribute to the development or progress of DDI. This includes narrow therapeutic index, issues of polypharmacy and the sequence of drug administration. Age, gender and specialty of physicians are also factors associated with incidence of DDIs. Physicians known to be male, older, general practitioners and with specialty training in internal medicine and cardiology prescribe medications with more major DDIs.[8] Mousavi et al in 2014 reported that there was a higher percentage of significant clinical DDIs seen among prescriptions given by medical specialists compared to prescriptions by general practitioners.

The list of drug classes associated with potential DDI in the study were comparable with other researches. Non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, proton pump inhibitors (PPI), corticosteroids and cardiovascular drugs are on the top of the list.[10,12]

The drug pairs implicated in potential DDIs commonly prescribed in primary care include ciprofloxacin-theophylline, diclofenac-warfarin, atenolol-amlodipine, metoprolol-amlodipine, aspirin-enalapril, metformin-hydrochlorothiazide, metoprolol-aspirin, aspirin-losartan and aspirin-telmisartan. [2,8,10]

The clinical or adverse effect of drug-drug interactions are predictable based on the mechanisms of actions of the different drug pairs. Amlodipine-simvastatin is the most common drug-pair observed in the study which causes a pharmacodynamic interaction resulting to the amplification of adverse effects of either or both drugs.[13] The combination potentially increases the risk of muscle-related events due to augmented simvastatin levels in the blood. The potential risk of such event may be decreased in prescription using simvastatin doses of 20 mg or less.

On the other hand, some of the drug combinations in the study resulted in a change of the drug's pharmacokinetic properties in the presence of another medication resulting in an increase or lowering of the drug level in the blood.[13]

The combination of omeprazole-clopidogrel is a common prescription for elderly patients as clopidogrel is beneficial for prevention of ischemia related to platelet aggregation while omeprazole is given to prevent gastric irritation. Given together as a pair, omeprazole decreases the blood levels of clopidogrel thus diminishes its effectiveness. Pharmacokinetic interactions are more difficult to anticipate since it is often not predictable from the clinical effects of the drugs involved.

Prescription monitoring may help prevent adverse outcomes in the outpatient setting in the effort to improve the quality of health care delivery. Close monitoring of adult patients and replacement of alternative drugs will help prevent clinically significant interactions.

However, in the absence of an electronic database, the study became labor and time-intensive due to the manual retrieval of medical charts and data extraction. It was also difficult to secure all consultations for the study period due to low resource settings. Hence, study results and feedback to concern health care providers were long-delayed. Likewise, as the outpatient prescription medications were an out-of-pocket expense of patients, the limitations of this study included the lack of verification whether the prescribed medications were actually taken as maintenance medications. As such, patients' compliance to drugs prescribed was not established.

In the setting of Family and Community Medicine residency training, recommendations include the implementation of quality assurance interventions to address prescription patterns and habits of trainees. Interventions should include feedback and quality circle that include senior residents who may monitor pDDIs.

CONCLUSION

Potential drug-drug interactions were observed in 8% of the medications prescribed to adult Filipinos seen at Family Medicine Clinic in a government hospital. Seventy-four percent (74%) of drug pairs with pDDIs had pharmacodynamic and 15% had pharmacokinetic interactions.

Statement of Authorship

Both authors contributed significantly to proposal writing, data collection, data analysis and approval of final version submitted.

Author Disclosure

Both authors declared no conflicts of interest.

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