Drug-Drug Interaction Analysis of Collected Prescriptions from Different Regions of Bangladesh

By

Mahmudul Islam
13346021

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Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Mahmudul Islam
13346021

Approval

The project titled “Survey on Prescription Analysis Regarding to Drug-Drug Interactions” submitted by Mahmudul Islam (13346021) of Summer, 2013 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on December 2020.

Examining Committee:

Supervisor:

Dr. Md. Aminul Haque
Assistant Professor, Department of Pharmacy
Brac University

Program Coordinator:

Dr. Hasina Yasmin
Professor, Department of Pharmacy
Brac University

Departmental Head:

Dr. Eva Rahman Kabir
Professor & Chairperson, Department of Pharmacy
Brac University

Ethics Statement

This study does not involve any sort of animal trial.

Abstract

Drug-drug interactions is one of the major kinds of drug interactions which is particularly originated from faulty prescription. In Bangladesh, drug-drug interactions are firing up very rapidly which is eventually damaging our health sector day by day. Drug-drug interactions are not just altering the therapeutic benefits but also creating adverse drug events which is taxing on our healthy lifestyle. The principal objective of this study is to portray the present synopsis of Bangladesh regarding to the drug-drug interactions and the unsafe healthcare systems by evaluating random prescriptions chosen from different regions of Bangladesh. Expectantly, this investigational study can deliver an insight to the current healthcare personnel and researchers, so that they can overcome this health hazard in near future.

Keywords: Prescription analysis; Polypharmacy; Drug-drug interaction; Classification of DDI; Rational use of drugs; ADR.

Dedication

This work is dedicated to my lovely parents for their perpetual love and constant support.

Acknowledgement

First and foremost, I would like to thank the Almighty Allah for giving me strength and patience to complete this project with proper knowledge and wisdom, which I hope, will reflect through my project.

It was a great journey working with my project and the support of a lot of people who are thankfully acknowledged here.

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List of Acronyms

DDI	Drug-Drug Interaction
NSAID	Non-Steroidal Anti-inflammatory Drug
CDS	Clinical Decision Support
ADR	Adverse Drug Reaction

Chapter 1

Introduction

1.1 Preface

Prescription is more than just a piece of paper written lots of life saving medications. It speaks on behalf of the physician through the patients. It's a connection between them and stairs to the healthy lifestyle. Unfortunately, it is being devastated and decayed by the same entities that are used to cure ailments. And they are drugs, which are interacting amongst themselves altering the therapeutic outputs and creating the barrier of health hazards every single day.

1.2 Drug-Drug Interaction

To start with, drug-drug interactions which is the most common type of drug interactions, particularly defined as the alteration in drug's activity when it is dispensed along with other drugs. This can lead to increased or decreased absorption of the drug as well as it can delay which might cause adverse drug reactions. Drug-drug interactions is a possible reason behind this adverse drug reactions (ADRs), which is responsible for almost 3-5% of total ADRs. The Boston collaborative Drug Surveillance program conducted a study which shows 83,200 drug exposure in approximate 10,000 patients and found more than 3600 ADRs, of which 6.5% were accountable of drug interactions (Rana et al., 2014). Drug-drug interaction may alter the therapeutic response both pharmacokinetically or pharmacodynamically (Abu, 2016). Safety studies while drug development, prescription analysis, post-marketing surveillance are the ongoing approaches used to recognize drug-drug interactions (Celebi, 2019).

Table 1: Examples of drug-drug interactions and their ADR (D et al., 2012)

SL. NO.	Drug-1	Drug-2	Severity of DDIs	ADR (Adverse Drug Reaction)
1.	Furosemide	Digoxin	Moderate	Nausea and vomiting
2.	Alprazolam	Digoxin	Major	Vomiting
3.	Theophylline	Levofloxacin	Major	Nausea, palpitation

1.3 Prescription and prescribing process

To evaluate the drug-drug interactions, 'Prescription' is the trump card which represents a vital interconnection between patients and physicians as a means of diagnosis and prophylaxis of the disease to achieve maximum healthcare. Prescribing medicines requires high level of skills and precision as it provides both safety and efficacy of the prescribed medicines to the patients. Irrational use of medicines has now become a global problem which leads to unnecessary wastage of resources and this needs to be monitored to increase the therapeutic benefits and decrease subsequent adverse effects. By periodically surveying the prescriptions several aspects can be identified like, polypharmacy, drug-drug interactions, adverse drug reactions etc. (Sumana, 2015). Prescribing medicines is a complex process which consists a series of steps like:

- Selecting the drugs that is correct for the particular patients
- Selecting the most applicable drug from various drug groups
- Setting appropriate dose and dosing schedule
- Following up the patient, so are the drugs

Creating awareness among the patients and providing proper knowledge relating to both drug use and abuses (S. et al., 2016).

1.4 Risk factors for DDIs

There are some risk factors for potential DDIs and they are:

1. Number of prescribed medicines
2. Age (very young or elderly), especially female gender
3. Existing illness or conditions
4. Number of prescribing physicians
5. Genetic factors
6. Cardiovascular diseases
7. Decreased renal and hepatic functions
8. Former interactions
9. Metabolic conditions like obesity, hypothyroidism
10. Drugs having narrow therapeutic index (Himanshu et al., 2015).

1.5 Polypharmacy

Polypharmacy is also a big reason behind this drug-drug interaction which is defined as the prescription consists of numerous medications taken by a patient simultaneously. It is a common occurrence in almost 20-40% of elderly patients. Another study taken place in Netherland shown that the existence of prevailing DDIs increased from 10.5% to 19.2% within the years of 1992 and 2005 (Becker et al., 2008). Around 287, 074 subjects enrolled in a retrospective study in Australia that indicated hazardous drug pairs that were prescribed to almost 1.5% of the total test subjects (Roughead et al., 2010). Another study from Swiss shown that, about 1.11% moderate and major DDIs found per patient where almost 47% of the total DDIs were took place during hospitalization (Vonbach et al., 2008). Geriatric patients are more

likely to be affected by potential DDIs and the occurrence ranges from 3 to 69%. They also rely on combination of drugs which makes them more susceptible to chronic illnesses both physically and psychologically (Miller et al., 2007). Another retrospective study in New York published clinically significant DDIs in 2006 which says, 63 out of 153 patients(41%) requires dosage adjustment as they were taking antiretroviral therapy due to AIDS. (Gebretsadik et al., 2017).

1.6 Prescribing cascades

Polypharmacy also increases the chances of 'prescribing cascades' which is a series of events where side effects of the drugs are mistaken as symptoms of another problem which leads to further prescriptions which consequently gives further side effects and so on.

1.7 Rational use of drugs

Rational use of drugs can resolve this matter effectively as it implies the deliverance of the least number of drugs to the patient that are committed to give maximum therapeutic effects in shortest period of time. This procedure must meet the following five standard criteria. They are:

- Right diagnosis
- Proper prescribing
- Actual dispensing
- Suitable packing
- Patient adherence (S. et al., 2016).

1.8 Risk-benefits assessment

Assessment of the drug-drug interactions is important to presume the risk-benefits balance alteration. If the drug concentrations get higher, side effects can get increased. On the other hand, if one drug accelerates other drug's clearance, patient might not get desired therapeutic output. One survey from Centers for Disease Control and Prevention (CDC) apprised that, around 20% of the U.S adults takes three medicines or more than that. Besides that, 40% of the geriatric patients who are 65 years or older taking five or more medicines along with multiple preexisting illnesses (*CDER Conversation: Evaluating the Risk of Drug-Drug Interactions | FDA*, n.d.). Pharmaceutical companies conduct numerous amounts of in-vitro studies to assess the potential drug-drug interactions for the investigational drugs before they are launched in the market for consumers. The drug is withdrawn from the market if it is proved to be responsible for major drug interactions. Post-marketing surveillance assess these interactions depending upon the severity and the other subsequent risk factors. Some drugs are even withdrawn from the market for some serious adverse drug events like, the antihistamines terfenadine, asteminzole, the gastrointestinal medicine cisapride, the CVS drug cerivastatin, mibefradil etc. (Coloma et al., 2013). US FDA employs some effective measures to communicate drug interactions. 'Drug interaction' section includes relevant drug interactions where 'clinical pharmacology' section speaks for the nature of in-vitro clinical studies which provides the clinical recommendations. There are some other sections that explains a lot if there is a chance for potential DDIs like, 'contraindications', 'warnings and precautions' section (*CDER Conversation: Evaluating the Risk of Drug-Drug Interactions | FDA*, n.d.).

1.9 Classification of drug-drug interaction

On the basis of the severity, DDIs are classified into the following:

1. **Major**: This is a life-threatening situation by the interactions of the prescribed medicines which needs to be taken care of immediately. Using of alternative medicine is suggested.
2. **Moderate**: This DDIs may lags the clinical improvements of the patient. This may not fatal but it surely can affect patient's other medicines and treatments. Requires monitoring.
3. **Minor**: This DDIs are very general and doesn't require much attentions (D et al., 2012).

Drug-drug interactions are so common these days that almost every prescription got at least one DDIs which is perhaps no one is aware of. Here is some prevalent DDIs given below on the basis of their severity:

Table 2: Examples of DDI based on severity (D et al., 2012)

SL. NO.	**Drug combinations**	**Severity**	**Outcomes of DDIs**
1.	Furosemide + Theophylline	Minor	Concentration of theophylline altered (Jänicke et al., 1987).
2.	Aspirin + Furosemide	Moderate	Weakens the diuretic effects of furosemide and increase the risk of acute renal failure, salicylate toxicity (Reddy & Kuriakose, 2019).
3.	Aspirin + Insulin	Moderate	Hypoglycemia (H. Hammadi et al., 2012).
4.	Azithromycin + Ondansetron	Major	Prolongation of QT interval.
5.	Hydrocortisone + Furosemide	Moderate	Risk of hypokalemia (Ramalingam et al., 2018).

An example of serious drug-drug interactions can be seen when a patient is prescribed in combination of digoxin and spironolactone where spironolactone reduces the drug clearance of digoxin and consequently increasing digoxin toxicity (Hedman et al., 1992). A moderate drug-drug interaction can be seen while giving iron and pantoprazole where pantoprazole surely reduces gastrointestinal acidity but also reduces bioavailability of the iron. Aspirin also interacts with clopidogrel less significantly yet it may cause severe bleeding as aspirin intensifies the antiplatelet properties of clopidogrel. If the drugs interact in a serious manner, combination must be avoided and alternate drugs must prescribe. Prescriber should be very observant to these interactions to make sure patient's safety (H S et al., 2014).

1.9.1 Classification of DDIs based on mechanism

However, drug-drug interactions are divided into pharmacodynamic and pharmacokinetic DDIs by their mechanism. Pharmacokinetic DDIs represents the plasma concentration of interacting drugs that might increase or get decreased whereas pharmacodynamics DDIs represents either synergistic or antagonistic effects that are to be produced by the interacting drugs (Farooqui et al., 2018).

Pharmacokinetic DDIs is interaction where drugs obstruct with each other's absorption, distribution, metabolism and elimination.

Absorption interactions:

- Formation of insoluble metabolites and complexes: When bisphosphonates are co-administered with calcium, bisphosphonates lose its bioavailability
- Inhibition of active transporters: Metformin uptakes inhibited by repaglinide that interferes with organic cation transporter (OCT1)

- Inhibition of efflux transporters: Verapamil affects the P-glycoprotein efflux pump which consequently reduces the efflux of digoxin and therefore concentration of digoxin increases.

Distribution interactions:

- Competitive binding: Phenytoin and valproate compete for the same binding sites which incline to dislocate phenytoin.

Metabolic interactions:

- Competition for the same CYP450 enzymes: Metabolism of warfarin is inhibited by macrolides by competing for the same CYP450 3A4
- Inhibition of metabolic enzymes: Carbamazepine enhances the rate of the metabolism of warfarin and oral contraceptive

Interactions related to elimination:

- Competition for active transporters: Probenecid decreases the active secretion of β-lactams and cephalosporin
- Solubility interference: When acetazolamide is administered urine turns alkaline which traps the salicylate ions in excess (Levêque et al., 2010).

Pharmacodynamic DDIs does not concern ADME profile of the drugs. When one drug alters the pharmacodynamics response of another and it is in the same concentration as the former. Pharmacodynamic drug-drug interactions can either go with synergistic or antagonistic which resembles increased or decreased activity respectively.

Homodynamic: Binds to the same receptor site

- Antagonism: Opioids and naloxone competes for the same receptor site just like ibuprofen and aspirin

Allosteric modulation: Binds to the same receptor but different sites

- Agonist effect: Barbiturates and benzodiazepine can be a proper example.

Heterodynamic: Binds to the different receptors yet affects the second messenger system.

- Antagonistic effect: Glucagon influences β-blockers by acting on cyclic AMP second messenger system.

Second messenger effects: Binds to the different receptor or messenger systems. However, exerts the same physiological process.

- Synergistic effects: Sedative agents reduces the scale of consciousness. For example, combination of benzodiazepines and propofol.

- Antagonistic effects: Acetylcholinesterase on neuromuscular blocks the effects of non-depolarizing agents.

Additive physiological effects: Different mechanisms and receptor systems to get the opposing physiological effects.

- Co-administration of glyceryl trinitrate (GTN) with noradrenaline for the patients from coronary artery bypass grafting (CABG) surgery.

Vasopressors and vasodilators is also a good example under this pharmacodynamics interactions (Niu et al., 2019).

Table 3: Additive interactions and their outcomes (Cascorbi, 2012)

SL. NO.	Substance 1	Substance 2	Possible interactions
1.	NSAIDs	SSRIs	Risk of bleeding (De Jong et al., 2003).
2.	ACE inhibitors	Spironolactone	Hyperkalemia (Wrenger et al., 2003).
3.	NSAIDs	Glucocorticoids	Risk of gastric bleeding (Kataoka et al., 2000).
4.	TCAs	Less-potent neuroleptics	Anticholinergic effects enhanced (Overø, 1972).
5.	Quinolones	Macrolides	Prolongation of QT-interval that might leads to torsade de pointes (Niedrig et al., 2016).

Table 4: Antagonistic interactions and their outcomes (Cascorbi, 2012)

SL. NO.	Substance 1	Substance 2	Possible interactions
1.	Acetylsalicylic acid	Ibuprofen	Decreased effects aspirin and increase risk of gastrointestinal ulcers (Alqahtani & Jamali, 2018).

2.	ACE inhibitors	NSAIDs	NSAIDs affects prostaglandins which reduces the anti-hypertensive effects of ACE inhibitors (Shionoiri, 1993).
3.	Phenprocoumon	Vitamin K	Phenprocoumon antagonizes vitamin k by thinning the blood affecting clotting factors (Dupont, 2007).
4.	Levodopa	Classical neuroleptics	Decreased effects of levodopa by pharmacodynamic antagonism (Lucca et al., 2015).

1.10 Wastage of Resources and Economical impact

Drug-drug interactions is not only decaying to a healthy body but also to a healthy economy as well. In 1999, Institute of Medicines (IOM) published a shocking report that says, around 44, 000 to 98,000 people dies per year due to medical errors. Since then, medication errors are regarded as a major subcategory of all sorts of medical errors. In 1995, Johnson and Bootman employed an expert panel and decision analysis model which estimated $76.6 billion as the direct costs for drug-related morbidity and mortality. This analysis model updated the information where the costs for drug misadventures jumped to $177.4 billion by 2000.

Medication errors, regarded as a subcategory of medical errors held responsible for more than 7,000 deaths per year in the United States of America. There was a DDI case reported involving the interactions between fluoxetine and selegiline which required 15 days of hospitalization, emergency services, ambulance services, electrocardiogram, laboratory tests, magnetic resonance imaging and consultations gathering a total medical expenditure of $17, 213. All this unnecessary wastage of resources for a single case of DDI (Malone et al., 2005).

Most pharmacies rely on prospective drug utilization review (PDUR) software to analyze potential medication errors and adverse drug reactions. But for being inconsistent to real time fluctuation, efficient solutions and recommendations is often not so much helpful in the management of potential drug-drug interactions. It creates a confusion with important alerts about DDIs and 'noise' or false alerts. Due to this enormous volume of messages, pharmacist often overrides the messages, sometimes even the important ones. Study says, in community pharmacies around 88% PDUR alerts are ignored by the pharmacists (Malone et al., 2005).

1.11 Rationale of this Study:

The main objective of this study is to achieve:

1. Make an approach to detect and quantifying DDIs in regular prescription
2. Make an effort to draw the attention of the healthcare professionals for the welfare of public health

1.12 Literature review:

The motive of this part is to review the previous researches and studies with current study. This literature review is like a connection established between the past and the present study.

In the research work of “Potential drug-drug interactions and their risk factors in pediatric patients admitted to the emergency department of a tertiary care hospital in Mexico”, the main purpose was to estimate the prevalence of potential DDIs and estimate the associated risk factors in Mexico. However, there are no research or investigative study in children admitted to the emergency department (Morales-Ríos et al., 2018).

In another research work of “Recommendations for selecting drug–drug interactions for clinical decision support”, the main objective was to outline the focal information that were required to guide clinical decision support (CDS) and recommended more researches to identify the potential DDIs and reduce repetitive and less-relevant alerts (Tilson et al., 2016).

In the research work of “Study of Drug-Drug Interactions in Prescriptions of General Practitioners and Specialists in Iran 2007-2009”, samples were collected from 33 different medical universities in Iran. Between the year of 2007 and 2008, around 0.77% of prescriptions found with potential drug-drug interactions out of which 0.67% were clinically significant and requires special monitoring (Ahmadizar et al., 2011).

Chapter 2

Methodology

2.1 Design of the study

All the samples were collected from different places for this study. Those were examined thoroughly by using "Medscape drug interaction checker" in order to find all the possible drug-drug interactions. Stockley's drug interaction index were also used to justify clinically important drug-drug interactions. Setting this main concern, an evident comparison between the severities of the drug-drug interactions can be obtained and emphasized.

2.2 Collection of data

All the samples were collected indiscriminately by visiting different government hospital outdoor and from the chamber of qualified doctors and other medical centers. Apart from the information related to the doctors and the patients along with the clinics and the hospitals were kept off the record. The names or any sort of personal regarding to the patients or physicians remained undisclosed. Additionally, all the sample data were collected from the year of 2019 to get the most updated results.

2.3 Estimation of end results

The main objective was to present the most recent drug-drug interactions that were obtained after the analysis of the collected prescriptions. The potential DDIs were classified depending upon the severity- major, minor, moderate. Results helped to draw out the potential DDIs occurrences. Apart from that, study findings were represented in bar diagram, pie chart and tabular form as well. Although, some DDI results mentioned some of the repetition of the drugs of same therapeutic class. The Medscape drug interaction checker and Stockley's drug interactions index were used to identify and justify clinically potential drug-drug interactions.

Medscape is selected in the detection of potential DDIs because it is considered too likely to be used in medical practices for its easy interface and free online access at any time. Interactions are shown by the interacting drugs, their severity, and mechanism of action as well as general recommendations.

2.4 Statistical Investigation

All the data findings about the DDIs were both shown in percentages and numerical value in tables accompanied by Microsoft Excel 2016.

Chapter 3

Result

A total of four hundred prescriptions were collected from multiple government hospital outdoor, diagnostic clinic and medical centers of multiple divisions around the country. The prescriptions were analyzed on the basis of the drug-drug interactions that were found within the total sample. The whole drug-drug interactions and their subsequent findings are expressed in both graphical and tabular form right below.

3.1 Prescriptions with potential DDIs

In this survey, 400 prescriptions were collected as a sample. Among them, 161 prescriptions were found with no interactions which is around 40.25% of the total sample. On the contrary, 239 prescriptions were found with a mix of multiple interactions which is 59.75% of the total sample and that is quite high and alarming for our health sector.

Table 5: Number of prescriptions with DDIs and their percentages

No. of prescriptions	Interaction status	Percentage (%)
161	No	40.25
239	Yes	59.75

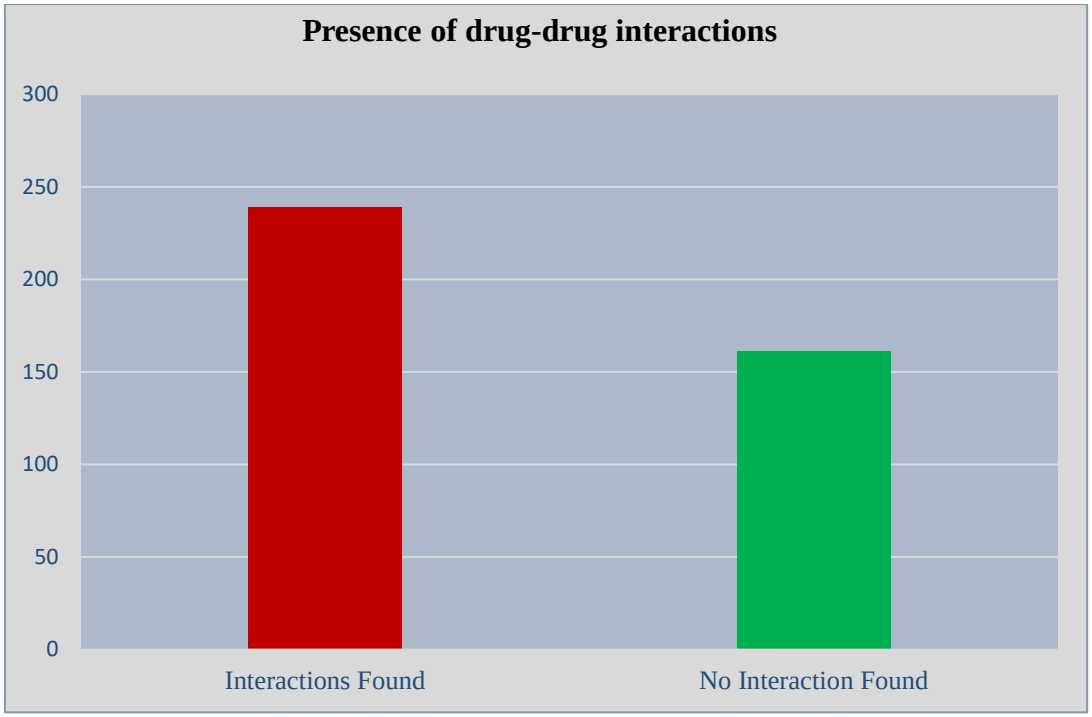


Figure 1: Number of drug-drug interacting prescriptions

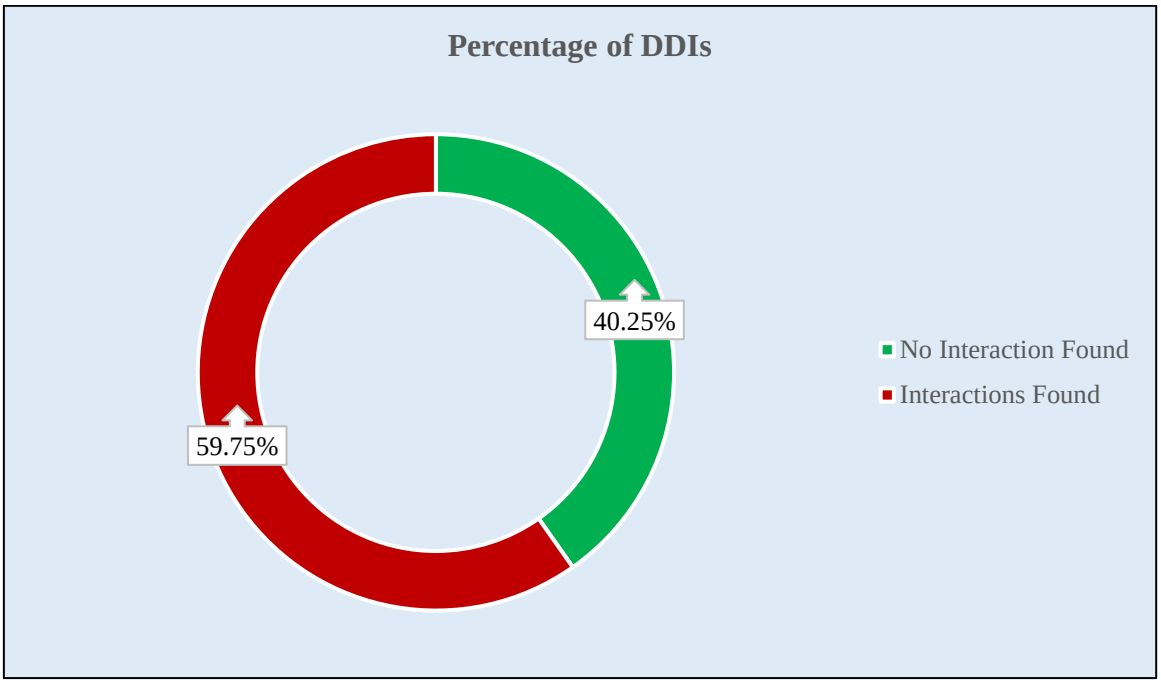


Figure 2: Percentages of the total drug-drug interactions

3.2 Categorization by the severity of DDI

However, these 239 prescriptions which is around 59.75% of the total sample. Here, three stages of severity were mentioned and the total part of interacting prescriptions were distributed into 51.46% of minor interactions, 73.64% of moderate interactions and 5.02% of major interactions. Minor interactions pose almost no threat at all but moderate interactions require monitoring and major interactions suggests to use alternative medicines.

Table 6: Number of prescriptions based on severity of the DDIs with percentages

Severity	Number prescriptions	Percentage (%)
Minor	123	51.464
Moderate	176	73.640
Major	12	5.020

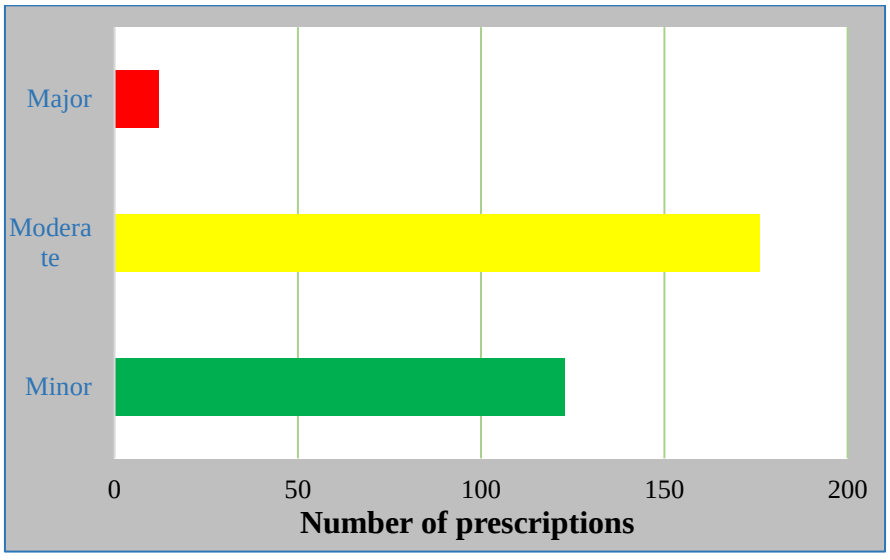


Figure 3: Number of prescriptions based on severity of DDIs

3.3 Categorization by the presence of multiple interactions

Besides, there were multiple interactions of same type found in the same prescriptions which are considering as multiple drug-drug interactions. Around 31 multiple minor interactions were obtained along with 67 and 2 multiple moderate and multiple major interactions respectively. And this seems quite unhealthy and risky for the patients which need to be monitored and controlled effectively to achieve maximum therapeutic benefits. Multiple minor interactions may be tolerated but for multiple moderate and major interactions, they need to be handled by alternating the prescribed medicines.

Table 7: Number of multiple-interaction and their percentages

Interaction Status	Number of prescriptions	Percentage (%)
Multiple Minor	31	12.970
Multiple Moderate	67	28.033
Multiple Major	2	0.837

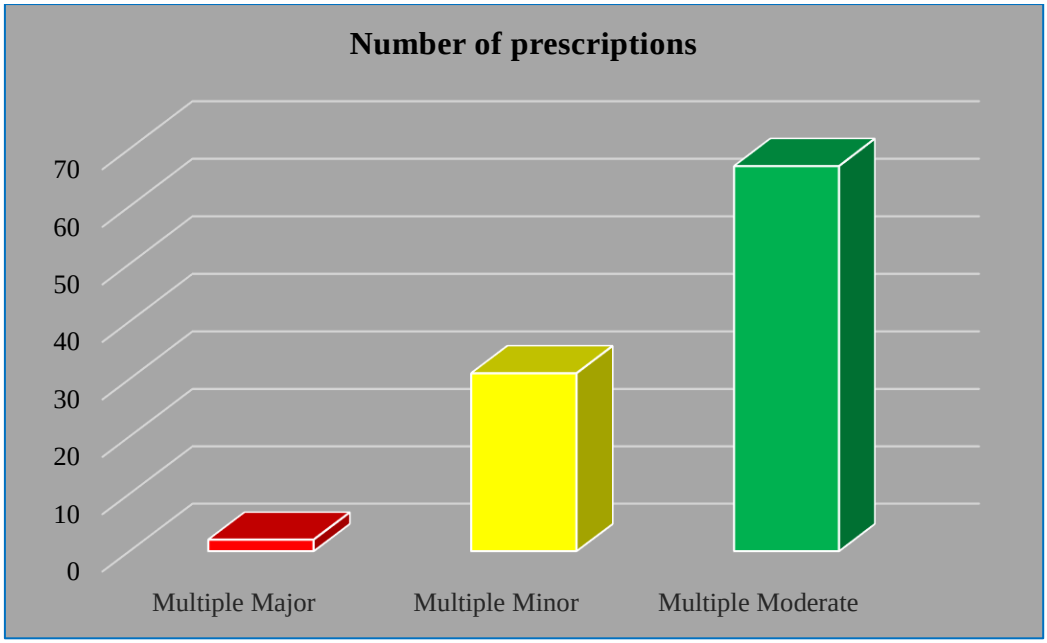


Figure 4: No. of prescriptions based on the existence of multiple interactions

Very often physicians prescribe numerous medicines which increase the chances of potential drug-drug interactions. Drug-drug interactions is one of the major concerns among all the other prescription errors. Going through the survey, lots of prescriptions found with not just potential DDIs but also multiple DDIs.

Table 8: Few examples of DDIs found from the samples

SL. No.	**Drug-1**	**Drug-2**	**Severity**	**Mechanism of interaction**
1.	Voriconazole	Esomeprazole	Moderate	Voriconazole affects the hepatic enzyme CYP2C19 and consequently, level of esomeprazole gets increased (Qi et al., 2017).
2.	Esomeprazole	Cefuroxime	Moderate	Esomeprazole increases the gastric pH which in turns, decreases the level of

				cefuroxime (Wedemeyer & Blume, 2014).
3.	Escitalopram	Azithromycin	Major	Escitalopram increases the toxicity of azithromycin by QTc interval (Sbaih et al., 2018).
4.	Fenofibrate	Atorvastatin	Major	Increase the risk of serious condition like rhabdomyolysis and liver damage as a side effect (Patiño-Rodríguez et al., 2015).
5.	Itraconazole	Fexofenadine	Minor	Itraconazole increases the level of fexofenadine by P-glycoprotein efflux transporter (Shimizu et al., 2006).

For instance, a prescription was collected from a registered consultation and diagnostic center which consists a total of four interactions including one major, one moderate and two minor interactions. Here, Fluconazole and Moxifloxacin were prescribed together which exerts a major drug-drug interaction and suggestive for the use of alternative medicine. Also, fluconazole interacts moderately with proton pump inhibitor esomeprazole and increase the effects of it by affecting CYP2C19 metabolism, a hepatic enzyme (Stergiopoulou et al., 2009). Furthermore, clonazepam, a benzodiazepine hypnotic was prescribed within this same prescription. Both Esomeprazole and Moxifloxacin interacts with it where the level or effects of clonazepam increases by decreasing metabolism and affecting CYP2C19 metabolism respectively. These two interactions pose less threat as their significance are pretty minor (Gee et al., 2015).

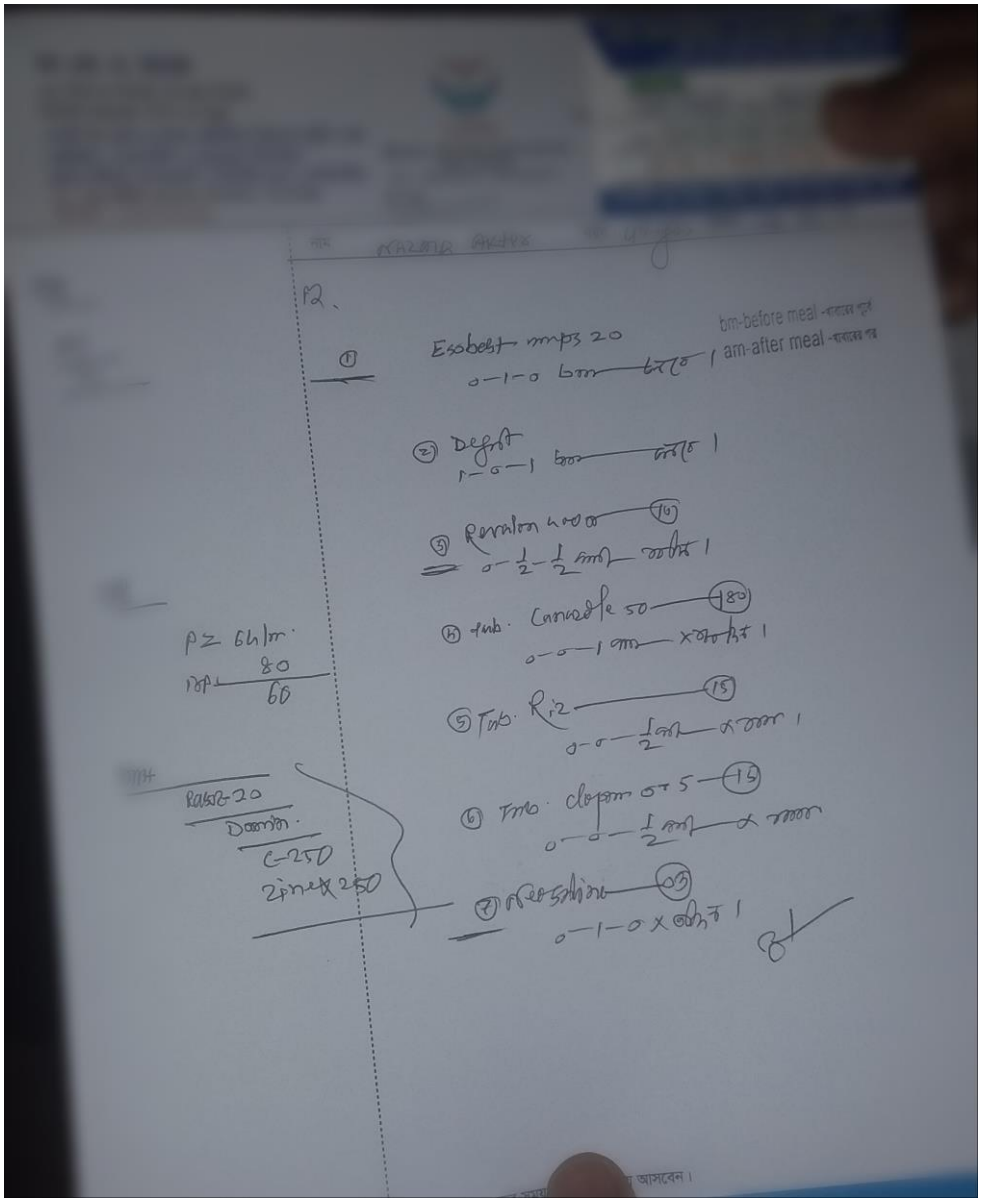


Figure 5: A prescription with the existence of multiple interactions

Chapter 4

Discussion

This survey represents the drug-drug interactions which is one of the most alarming prescription errors that is decaying the public health every single day. A proper prescription plays indispensable role in maintaining patient's health and safety which take quite the opposite side when drug-drug interactions goes unchecked. However, errors are possible because 'to err is human' but possible health hazard should be lessen to a minimal. The current plot of Bangladesh is pretty down on luck because out of all the samples more than fifty percent of them found drug-drug interacted. This study was to establish a knowledge of the current possible DDIs and their subsequent occurrences in the health sector, especially in the process of treatment of different individuals. Interactions that have been found while analyzing the prescription were further categorized on the basis of their severity and existence of multiple drug-drug interactions.

This study consists of 400 samples among which 239 prescriptions found with potential and multiple series of drug-drug interactions and rest remain disengaged. And so, the total percentage of interacted prescriptions were 59.75% and rest 40.25% prescriptions were just fine. There was a total of 176 prescriptions where moderate interactions were found, 123 and 12 prescriptions were found with minor and major DDIs respectively.

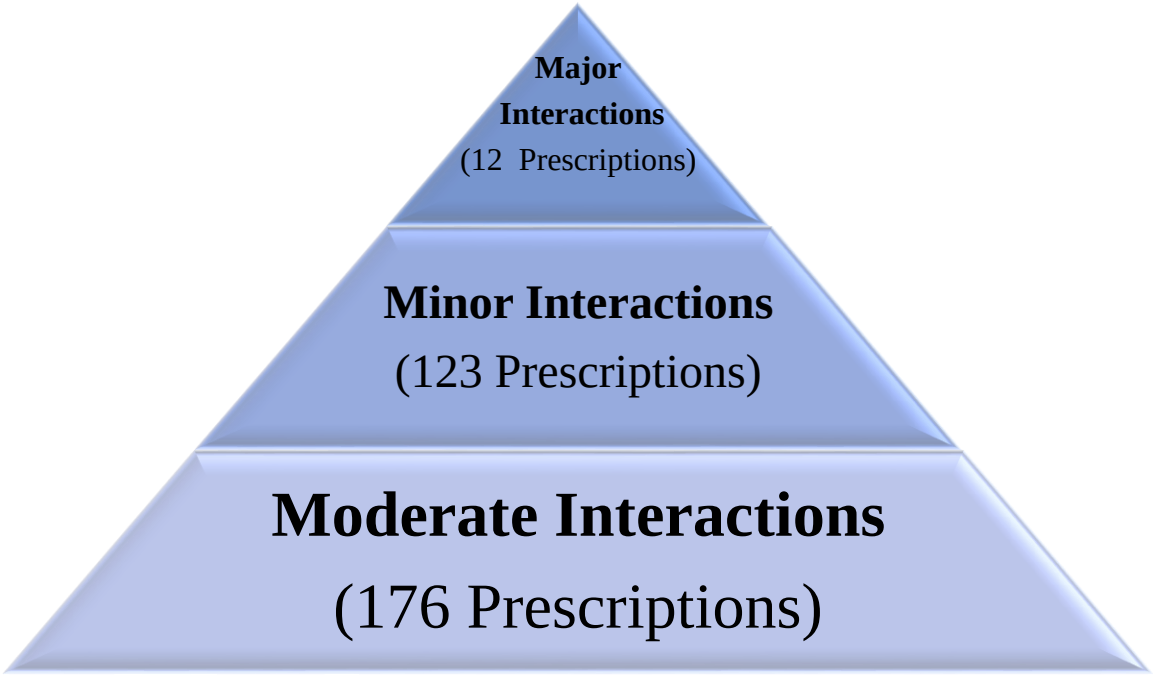


Figure 6: Delineation of the classification of DDI based on severity

Furthermore, out of every severity, they are again categorized upon the existence of same type of interaction multiple times. Multiple moderate interactions are mostly found while analyzing the sample prescriptions, secondly multiple minors and lastly multiple majors which appeared in 67, 31 and 2 prescriptions respectively.

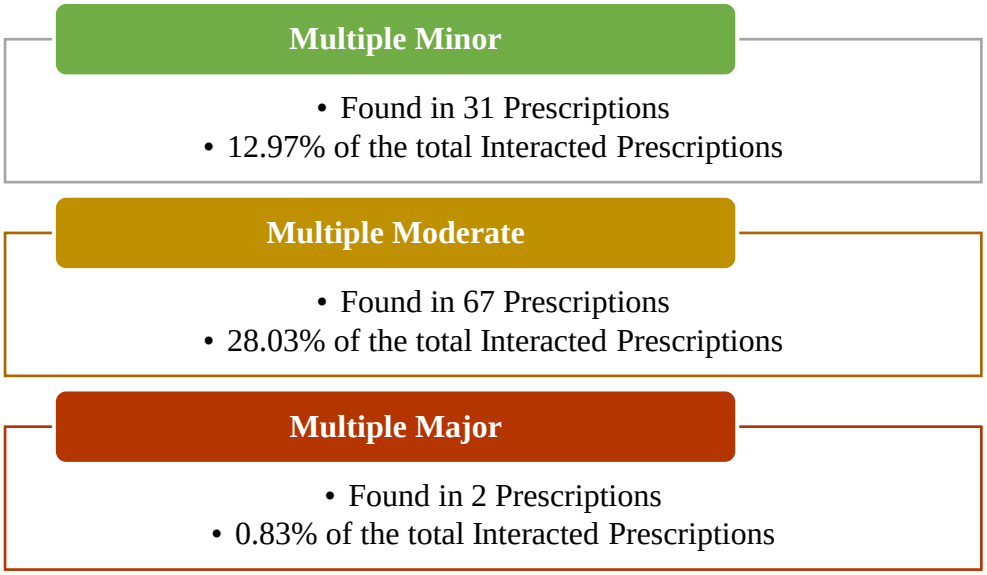


Figure 7: Comparison among the existence of multiple DDIs

A faulty prescription representing a major drug-drug interaction including some other multiple interactions is given below. Here, amitriptyline and fluconazole is interacting a major DDI by increasing QT interval. Basically QT interval is the time required for an electrical system to fire an impulse through the ventricles and causing ventricular depolarization to the completion of repolarization (Morrison et al., 1997). This combination must be avoided and alternative drug must be used. Additionally, the combination of fluconazole and amitriptyline also exerted some other moderate and minor DDIs. Fluconazole increases the effect of amitriptyline because it affects hepatic enzyme CYP2C19 and CYP3A4 metabolism. Moreover, it interacts with chlordiazepoxide and decreases metabolism. As a result, the concentrations or level of chlordiazepoxide increases (Robinson et al., 2000).

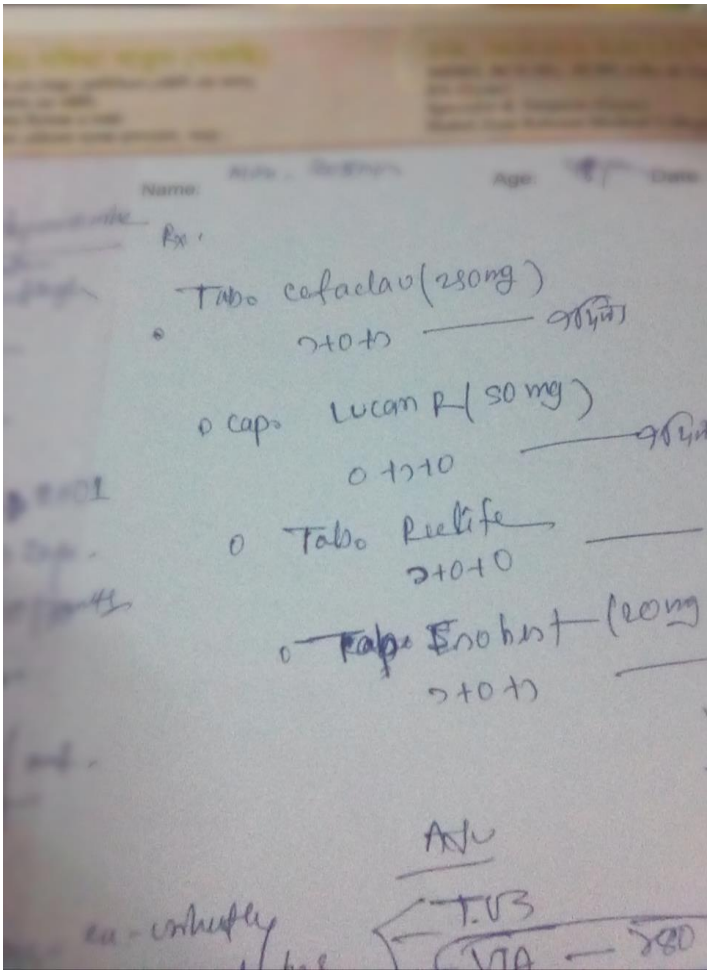
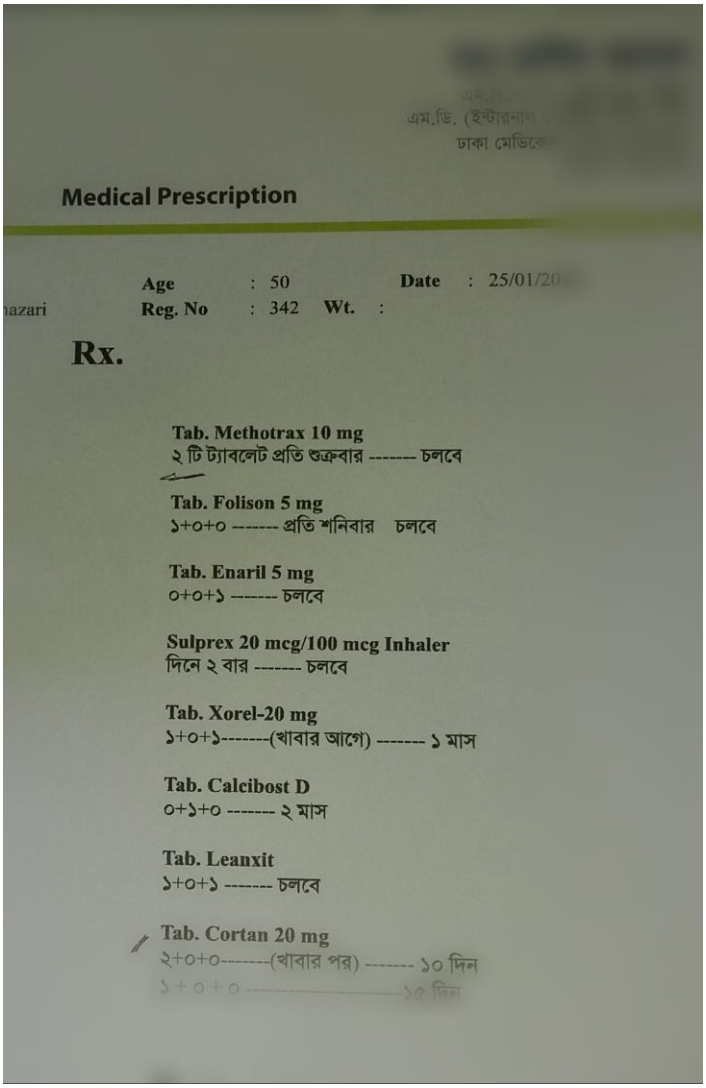


Figure 8: Representative prescription for major DDI

From another prescription, moderate DDI can be seen with some other minor interactions. Methotrexate, a drug from the therapeutic class of antimetabolites that interacts with PPI rabeprazole which particularly decreases the renal clearance (Inhibitors, 2012). Consequently, the concentrations or levels of methotrexate increases. Methotrexate also interacts with folic acid which is a vitamin-B preparations. Folic acid reduces the therapeutic effects of methotrexate by the mechanism of pharmacodynamic antagonism which is a minor DDI. Folic acid and their derivatives may affect the clinical responses when methotrexate is administered systematically (Khanna et al., 2005).



Medical Prescription

Age : 50 Date : 25/01/20
Reg. No : 342 Wt. :

Rx.

Tab. Methotrax 10 mg
২ টি ট্যাবলেট প্রতি শুক্রবার ------- চলবে

Tab. Folison 5 mg
১+০+০ ------- প্রতি শনিবার চলবে

Tab. Enaril 5 mg
০+০+১ ------- চলবে

Sulprex 20 mcg/100 mcg Inhaler
দিনে ২ বার ------- চলবে

Tab. Xorel-20 mg
১+০+১-------(খাবার আগে) ------- ১ মাস

Tab. Calcibost D
০+১+০ ------- ২ মাস

Tab. Leanxit
১+০+১ ------- চলবে

Tab. Cortan 20 mg
২+০+০-------(খাবার পর) ------- ১০ দিন

Figure 9: Representative prescription for moderate and minor DDIs

4.1 Genetical influences on DDIs

An individual's genetic configuration can affect the pharmacokinetics and pharmacodynamics and thus alter the therapeutic response of a drug. For example, Chinese people tends to become more drunk and dizzy when they consume alcohol because their ethnic differences in metabolizing ethanol by alcohol dehydrogenase (Ansari, 2010). Pharmacogenetics describes the inherited traits and genetic polymorphisms. On the other hand, pharmacogenomics explains the entire spectrum of genes. In the management of drug-drug interactions, Pharmacogenetics

can do a lot by focusing on enzyme metabolism and transporters where pharmacogenomics focuses on drug and dosage personalization for a specific disease. A familiar DDI may not take place in every individual. It's because there are some factors that somewhat controls drug interactions. They are like age, physiology, drug dosage, lifestyle, genes, duration of combined therapy etc. (Jeiziner et al., 2020).

4.2 Responsibilities of the Healthcare Professionals

Before commencing any new prescription or over-the-counter drug, healthcare provider or pharmacist should be well aware of, even if it is some vitamins or other sort of dietary supplements. Every medications or supplements should be checked if there is any kind of 'Drug Interaction Precaution' labeled as a primary warning. Finally, it will be very helpful for the patients if they go one pharmacy for all the prescriptions medicines and OTCs. That's how they can review their list of medicines simply by asking the pharmacist in charge for any kind of potential DDIs.

Not just the patients or the physicians but also the pharmacists have a role to play in maintaining the possible drug-drug interactions in susceptible patients. They have their vast knowledge in medicines which they need to apply on evaluating prescriptions as well as following up with patients to know the existing side effects or any kind of unexpected adverse drug reactions (ADR). That is how pharmacist can take part in managing potential DDIs simply by detection, prevention and reporting ADRs is there is any.

4.3 Responsibilities of the Community Pharmacists

Community pharmacist can perform some steps to achieve patient's health and safety by some essential assessments like:

- Devising a safe and effective medication treatment plan

- Monitoring and assessing the patient's response to the medication
- A thorough medication review to detect and resolve drug related problems
- Educating the patients giving proper knowledge and guidelines to use his or her medications
- Providing 24 hours help and support services over the phone, when it is not possible to appear physically by anyone
- Healthcare provider or the physician in charge should be well aware of the addition or discontinuation of any medication and certain changes in patient's lifestyle e.g., exercise, diet etc.
- Try to avoid prescribing multiple medications that increases the chances for DDIs (Ansari, 2010).

Chapter 5

Limitations of the study

- This study was mostly emphasized on potential DDI occurrence rather than their clinical consequences
- As the sample data were collected from a particular time, results cannot be generalized for the past or the future
- The results cannot be inferred to other country or their healthcare centers
- Since the data were collected only once, obtained results might vary time to time
- Selection of the sample might get biased because the study included patients with complete medical records

Chapter 6

Conclusion

On the whole, this study illustrates the universality of drug-drug interactions around the country which is pretty high indeed. It is not very hard to presume the current situation of healthcare services of Bangladesh. From this study, simple but necessary awareness can be raised amongst the current and future healthcare providers. Most of the prescriptions are required to be monitored and double checked by the healthcare professionals to ensure there is no interactions. The use of computerized interactions screening systems can be a beneficial tool in assessing the prescription regarding to drug-drug interactions and adverse drug reactions. Patients should also be aware and well educated about the medications they are taking. It's never too late to change the perspective towards the proverb, 'There is a pill for every ill'.

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