T.R.N.C

NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

Potential drug-drug interactions in cardiovascular patients prescriptions dispensed in community pharmacies in Almarj of Libya

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BY:

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In Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmacology

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Master of Science in Pharmacology

Advisor:

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DEDICATION

To the spirit of my dear father God’s mercy

To my lovely mother

To my husband

To my dear children, Ragd, Reham, Mohammed, and Salh

To my sisters, brothers, and friends

Approval

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Hania Abdelwahid

ABSTRACT

The project titled as "Potential drug-drug interactions in cardiovascular patients prescriptions dispensed in community pharmacies in Almarj of Libya". was conducted in different community pharmacies under the ministry of health at Almarj of Libya.

The drug is the cause of drug interactions (DDIs) adverse reactions by a group of drug. They are predictable often, and thus can be avoided or manageable. Various studies suggest that cardiovascular patients are more often reported with potential DDIs as compared to patients with other diseases. The possible reason behind higher potential DDI rate in cardiovascular diseases may involve elder age, multiple drug regimen, and pharmacokinetic or pharmacodynamic nature of drugs used in cardiology. Yet overall incidence and pattern of DDIs in Libya has not been well documented and little information is available about the strategies that have been used for their prevention. Most of the studies world widely were done for hospitalized patient to measure the incidence of drug-drug interactions. The primary objective of the study was to analysis the frequency of drug interactions in prescribed drugs for cardiovascular diseases outpatients and to correlate the frequency of drug interactions with demographic features of patients and to identify risk factors for such interactions in Almarj of Libya. Also, to evaluate the nature, type, and prevalence of potential DDIs (pDDIs) in prescriptions dispensed in community pharmacies in Almarj of Libya.

In this study, the prescriptions of 1305 of patients were collected and screened for cardiovascular disease patients using at least one cardiovascular drug. Prescriptions were collected from 29 pharmacies registered in the Ministry of Health at Almarj of Libya, from January to March 2016. 133 prescriptions were retrospectively analyzed for drug-drug interactions using Drugs.com databases. Categorized DDIs according to their level of significance into three classes (minor, moderate, major). The data were processed using SPSS software version 20.

In conclusion, the present study has recorded a high prevalence of pDDIs in the prescriptions contain cardiovascular drugs. Most of the interactions were of moderate interactions. Patients with old age, and increased number of prescribed drugs were more exposed to pDDIs, therefore it is very important to make effort to reduce polypharmacy. The physicians should be more aware of potentially harmful DDIs,

especially cardiovascular drugs. Close monitoring of patients is recommended to manage and prevent negative clinical consequences of these interactions. Pharmacists can contribute to the prevention and detection of drug-related problems.

Key words: DDIs, prescriptions, cardiovascular drugs, pharmacokinetic, pharmacodynamics

ÖZET

"Libya'nın Almarj toplum eczanelerde reçete kardiyovasküler hastaların reçetelerine Potansiyel ilaç-ilaç etkileşimleri" başlıklı proje. Libya Almarj sağlık bakanlığı altında farklı eczanelerden gerçekleştirilmiştir.

Bu çalışmada, hastanın 1305 reçeteleri toplandı ve en az bir kardiyovasküler ilaç ile kardiyovasküler hastalık hastalar için taranmıştır. Reçeteler 133 reçete retrospektif Drugs.com veritabanlarını kullanarak ilaç-ilaç etkileşimleri için analiz edildi, Ocak-Mart 2016 için Libya Almarj Sağlık Bakanlığı kayıtlı 29 eczanelerden toplanmıştır. üç sınıfa (minör, orta, büyük) içine önem düzeylerine göre kategorize DDIS. Veriler SPSS yazılım sürümünü 20 kullanılarak işlendi.

Reçeteler kardiyovasküler ilaçlar ihtiva de Sonuç olarak, bu çalışma pDDIs yüksek oranda kaydetti. etkileşimlerin en orta etkileşimleri edildi. yaşlılık ve reçete edilen ilaçların artan sayıda olan hastalar daha nedenle polifarmasiden azaltmak için çaba çok önemlidir, pDDIs maruz bırakıldı. hekimler potansiyel olarak zararlı DDIS, özellikle kardiyovasküler ilaçların daha farkında olmalıdır. hastaların dikkatle izlenmesi yönetmek ve bu etkileşimlerin olumsuz klinik sonuçları önlemek için tavsiye edilir. Eczacılar uyuşturucuya bağlı sorunların önlenmesi ve tespiti katkıda bulunabilir.

Anahtar Kelimeler: DDIs, reçeteler, kardiyovasküler ilaçlar, farmakokinetik, farmakodinamik

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LIST OF ABBREVIATIONS:

DDIs : Drug-Drug Interactions

PDDIs: Potential Drug-Drug Interactions

GIT: Gastrointestinal tract

CYP450: Cytochrome p-450

NSAIDs: Non-Steroidal Anti-Inflammatory Drugs

MAOI: Monoamine oxidase inhibitors

NM blockers: Neuromuscular blockers

ACEI: Angiotensin converting enzyme inhibitors

ADRs: Adverse drug reactions

TDM: Therapeutic Drug Monitoring

PPIs : Proton Pump Inhibitors

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1. Introduction

1.1. Drug interactions

The interaction occurs when the effects of one drug is altered by the presence of another drug, herb, food, or drink, the type of interaction between the drugs themselves (DDIs) these modification being specified when a drug administered with another drug, this type of interaction may cause an unexpected side effect.

Drug interactions according to the mechanism can be classified into two categories; pharmacokinetic or pharmacodynamic; the mechanisms of pharmacokinetic interaction include a change of absorption, distribution, metabolism, or elimination; and on the other hand the category the pharmacodynamic interaction is an alteration of pharmacological effect without a change in plasma concentration (Ashraf & Lionel, 2004).

The interactions between drugs (drug–drug interactions) may be useful or harmful; the harmful of drug–drug interactions is important because this type cause 10–20% of the adverse drug reactions require hospitalization (Pirmohamed M et al, 2004). Not only that but dug-drug interactions can also cause partial or complete cancellation of the effectiveness of the treatment; the disease treatment usually requires to uses more than one drug, but polypharmacy carries a high risk of DDIs with serious consequences for health. Some factors, such as the administration of drugs with low therapeutic index and age of the patient (usually elderly) can increase the potential of the risk of drug interactions (Juurlink DN et al, 2003), the potential DDIs can be determined by using the Drug Interactions Checker within the Drugs.com database, this database classified into three levels: major, moderate and minor.

Some published studies reported the rates of potential DDIs ranging from 2.2% to 30% in hospitalized patients and from 9.2% to 70.3% in Outpatients (Jankel CA & Fitterman LK, 1993); And according to various studies the cardiovascular patients are more often reported with potential DDIs as compared to patients with other diseases (Ismail et al, 2012b). The possible reason behind higher potential DDI rate in cardiovascular diseases might include older age, multi-drug regimen, and pharmacodynamic or pharmacokinetic nature of drugs used in cardiology (Faulx & Francis, 2008).

1.2. Mechanism of drug–drug interactions

1.2.1. Pharmaceutical Drug Interactions

The pharmaceutical interactions occur before drugs administered to the patient; Incompatibility between two drugs mixed in an IV fluid, these can be physical interactions (for example with visible precipitate) or chemical with no visible sign of a problem, example, adding drug classes to the IV infusion. These involve certain antibiotics, glucocorticosteroids, and antihistamine-antiemetic that interact with dextran in solutions and are broken down or form complexes (Chicago & Wolters, 2010).

1.2.2. Pharmacokinetic interactions

Pharmacokinetic DDIs include modification of drug absorption, distribution, metabolism and elimination by a second drug resulting in a change (increase or decrease) of the primary drug concentration and are often difficult to predict (Strain JJ et al, 2004).

1.2.2.1. Drug interactions affecting absorption

Drugs are mostly given by oral route for absorption via the mucous membranes of the gastrointestinal tract (GIT); There are many of factors can affect absorption of drugs involves changes in pH, altered intestinal bacterial flora, Complexation, and alteration of gastrointestinal motility. In some cases, the absorption of a drug may be reduced, which lead to a reduction in therapeutic activity, but in some others case, a delay in absorption may occur, but the amount of absorbed drug is not affected. This delay in drug absorption can be unwanted when a rapid effect is needed to relieve acute symptoms, such as pain (Van-Boxtel CJ et al, 2008; Hussar DA, 2005).

1.2.2.2. Changes in pH

Drugs are weak bases or weak acids, the gastrointestinal pH can alter the extent of their absorption. Drug absorption through the mucous membranes depends on the non-ionized form of a drug is more lipid-soluble and will be absorbed more readily than the ionized form. Change in gastric pH due to an administration of antacids, histamine H_2-receptor antagonists or proton pump inhibitors (PPIs) may reduce absorption of weakly

acidic drugs (Hansten PD & Hayton WL, 1980). Itraconazole and ketoconazole require acidic pH for optimal absorption. Their bioavailability can be decreased by other drugs that increase gastric pH such as antacids and omeprazole (Carlson JA et al, 1983; Sorkin EM et al, 1983); The interaction between antibiotic tetracycline and cimetidine. Cimetidine is a potent H2-receptor antagonist that prevent gastric acid secretion, which leads to raising gastric pH, these kinds of drug interactions can lead to treatment failure of antibiotics (Alpert P, 1997); So, antacids associated interactions can be minimized by keeping an interval of two to three hours between the administration of antacids and the potential interaction of drugs.

1.2.2.3. Altered intestinal bacterial flora

The metabolism of certain drugs occurs by the action of bacterial flora in the GI tract, certain antibiotics reduce intestinal flora and may lead to the change in drug absorbed (Finegold SM, 1970; Danos EA, 1992). 40% or more of the patients receiving digoxin dose is metabolized by the intestinal flora. Antibiotics can cause in kill a large number of the normal flora of the intestine, that lead to increase digoxin concentration and increase its toxicity (Lindenbaum J et al, 1981).

1.2.2.4. Complexation or chelation

Drugs may form non-soluble complexes by chelation in the gastrointestinal tract. The chelation includes forming a ring structure between the metal ion and organic molecule which leads to an insoluble compound that is unable to permeate the intestinal mucosa due to lack of drug dissolution (Knupp CA & Barbhaiya RH , 1997); Concurrent use of iron supplements may reduce absorption levodopa and methyldopa combinations, with a resultant reduction in efficacy; Tetracycline can form complexes with iron, magnesium, calcium and aluminum these are present in many antacids. And this leads to reduction absorption of antibiotic, but that may lead to reducing the antibacterial effects of tetracycline (Alpert P, 1997).

1.2.2.5. Effect on gastrointestinal motility

The drugs which affect the gastric emptying rate may alteration the rate of absorption of a drug from the gastrointestinal tract by influencing the dissolution rate of tablets and passage into the small intestine. As an example of that the Laxatives which decrease

absorption of other drugs by increasing their passage through the intestine, and also metoclopramide increases gastric emptying and increases the absorption rate of propranolol, acetaminophen, and lithium (Van-Boxtel CJ et al, 2008 ; Hussar DA, 2005).

1.2.2.6. Displaced protein binding

Many drugs highly bound to plasma proteins. Generally, acidic drugs (i.e. penicillin, clindamycin, and doxycycline) strongly bind to albumin and basic drugs (i.e.erythromycin) to the alpha-1-acid glycoprotein.

The drug displacement interaction can be defined as a reduction in the extent of plasma protein binding of one drug caused by the presence of another drug that competes for the same binding sites that lead to an increased free or unbound concentration of the displaced drug (Stewart CF et al, 1991; Mandel MA, 1976). As an example of this kind of interaction phenylbutazone has a great affinity for bound to plasma proteins more than warfarin. If both drugs are taken at the same time that will increase the plasma concentrations of warfarin, which leads to increased inhibition of coagulation and bleeding.

1.2.2.7. Drug interactions affecting metabolism

This reaction occurs when the two drugs are metabolized by the same enzyme and affect the metabolism on each other; thus, it is important to determine the identity of the CYP that metabolizes a particular drug and to avoid co-administering drugs which are metabolized by the same CYP (McElnay JC & D'Arcy PF, 1983). The main site for drug metabolism is the liver.

Metabolism converts lipophilic compounds to ionized metabolites for renal elimination; The drug metabolizing activity can be a classified into two phases phase I reactions and phase II reactions, phase I reactions include oxidation, reduction, and hydrolysis, the formed metabolite can be excreted into urine or can undergo phase II reaction. phase II reaction consists of conjugation (i.e., glucuronidation, Sulfation). Cytochrome P-450 enzymes are the most important enzymes include in phase-I metabolism, cytochrome P450 is a family of isozymes responsible for the metabolism of several drugs. That is located in the smooth endoplasmic reticulum of many tissues. In the presence of carbon

monoxide, they have an absorption maximum at wavelength 450 nm and are therefore called P-450. DDIS includes alterations in phase I metabolism by inhibition or induction of cytochrome P-450 enzymes (CYP450)

Although this group has more than 50 enzymes, six of these enzymes metabolize 90 percent of drugs. There are Six different P450 isozymes that play important roles in drug metabolism which have been specified, these isozymes are: CYP1A2, CYP2C19, CYP2E1, CYP3A4, CYP2D6, and CYP2C9, the isozymes are located in the liver, kidneys, skin, gastrointestinal tract, and lungs (DiPiro JT, 1999). Drugs that inhibit CYP enzymes can increase the plasma concentrations of certain other drugs metabolized by same enzymes and prolonged pharmacological drug effect, induction of CYP enzymes can decrease the plasma concentrations and drug effects (Armstrong SC et al, 2003; Abernethy DR & Flockhart DA, 2000).

1.2.2.8. Enzyme inhibition:

Isoenzyme CYP inhibition activity is an important source of drug interactions that lead to dangerous adverse events, the most common form of inhibition being by competing on the same isoenzyme; Enzyme inhibition is the decrease in the rate of metabolism of a drug by another one, this will lead to an increase of the concentration of the target drug and lead to the increase of its toxicity; If the two drugs are substrate for the same CYP isoenzyme then metabolism of one or both the drugs might delay.

Midazolam and erythromycin both are substrates for 3A4 isoenzyme so, there is competition for sites enzyme and inhibited the metabolism of midazolam (Olkkola KT et al, 1993). Omeprazole is a strong inhibitor of three of the CYP isozymes responsible for warfarin metabolism; If the two drugs in combination this will increase the plasma concentrations of warfarin, which leads to increase inhibition of blood clotting and the risk of bleeding. This inhibition of metabolism of the drug may lead to increase plasma concentration, prolonged pharmacological effect of the drug, and increased toxicities (Levine M & Sheppard I, 1984; Massey EW, 1983).

1.2.2.9. Enzyme Induction:

Drug interactions caused by P450 induction generally results in reduced therapeutic effect by acceleration metabolism. Metabolism of the affected drug is increased which

leads to decreased intensity and duration of drug effects; If the drug is a prodrug or it is metabolized to toxic or an active metabolite this leads to increase the effect or toxicity. The enzyme induction will effects by age and liver disease, and the ability to induce drug metabolism may decrease with age, and patient with cirrhosis or hepatitis. Certain drugs, such as phenobarbital, rifampin, and carbamazepine, are able to increase the synthesis of one or more CYP isozymes, that will lead to the increase of drug metabolism and decrease effect certain other drugs.

Phenytoin increases metabolism of theophylline leading to decrease its level and decrease its action. Also, increase metabolism of warfarin by many drugs such as phenytoin, rifampin, and barbiturates. As a result, this interaction reduced the effect of anticoagulant and may need to increase the dose of warfarin (Levine M & Sheppard I, 1984 ; Massey EW, 1983). Consequences of increased drug metabolism include, decreased plasma drug concentrations, decreased drug activity if the metabolite is inactive, decreased therapeutic drug effect, and increased drug activity if the metabolite is active (Finkel et al, 2009). common substrates, inducers, inhibitors of CYP in Table Number 1.

Table1. Examples of common substrates, inducers, inhibitors of CYP isoforms (Baxter K & Lee A, 2008 ; Tredger JM & Stoll S, 2002 ; Wilkinson G, 2005).

CYP isoform	**Substrate**	**Inhibitor**	**Inducer**
CYP 3A group (includes 4,5,7)	Atorvastatin, simvastatin clarithromycin, erythromycin, diltiazem, verapamil, nifedipine, losartan, sildenafil, progesterone	Itraconazole, ketoconazole Clarithromycin, erythromycin Diltiazem, verapamil Grapefruit juice	Rifampicin Carbamazepie Phenytoin Phenobarbitol Efavirenz St John's Wort
CYP 2D6	Carvedilol, metoprolol, paroxetine, venlafaxine, antidepressants Cimetidine, Codeine	Bupropion, quinidine Fluoxetine, paroxetine, cimetidie, amiodarone, Duloxetine,	Rifampicin
CYP 2C9	Diclofenac, ibuprofen, naproxen, Warfarin, diazepam	Fluconazole, Amiodarone, isoniazid	Rifampicin
CYP 2C19	Proton pump inhibitors, Diazepam, Citalopram, warfarin	Proton pump inhibitors Cimetidine, ketoconazole Chloramphenicol	Carbamazepine Rifampicin
CYP 1A2	imipramine, clozapine, theophylline, warfarin	ciprofloxacin Cimetidine, amiodarone erythromycin,	Tobacco smoke Broccoli

1.2.2.10. Drug interactions affecting excretion

Drugs are excreted mainly through kidneys. Renal elimination of drugs include glomerular filtration, tubular secretion, and tubular reabsorption. Rates of glomerular filtration can be affected by changes in renal blood flow, and extent of protein binding (Van Ginneken CA & Russel FG, 1989).With drugs highly bound to protein, this will increase the unbound fraction and may be lead to an increase in glomerular filtration and increased drug elimination. The most drug excretion through renal filtration. Nearly most electrolytes and water are reabsorbed from the renal tubules back into the circulation. but, polar compounds, cannot diffuse back into the circulation and are excreted (Kirby WMM et al, 1971).

Active tubular secretion in the proximal tubule is important in the elimination of many drugs, the drugs combine with a specific protein to pass through the proximal tubules, when a drug has a competitive interaction with the protein, that is responsible for active transport of another drug, this will reduce a drug excretion and increases its concentration besides its toxicity; These two compounds may compete for the same carrier and cause inhibition of secretion of the other, The competition may be used therapeutically; The Probenecid is used to block renal tubular secretion of some drugs (e.g. penicillin) and thus prolong its duration of action (Kampmann J et al, 1972).

Tubular reabsorption, lipid soluble drugs undergo passive tubular reabsorption from tubular lumen into systemic circulation; The ionized drugs are reabsorbed less than non-ionized drugs, and urine pH can change the reabsorption of weak acids and bases. The amphetamines and quinidine are weak bases. Their excretion is increased by acidifying agent (by ammonium chloride) while reduced by alkalinizing agent (by sodium bicarbonate). Phenobarbital and salicylates are weak acids, their excretion is decreased by acidifying agent while increased by alkalinizing agent (Bendayan R, 1996).

1.2.3. Pharmacodynamic interactions

Pharmacodynamic interactions (actions of a drug on the body) can be defined the effects of one drug are change by the presence of another drug at its site of action. These reactions generally include synergistic, additive or antagonistic effects of drugs acting on the same receptors or physiological systems (Baxter K & Lee A, 2008).

1.2.3.1 Additive and Synergistic Interactions:

In case of taking two or more drugs with similar pharmacological effects, In additive effects, this may lead to excessive response and toxicity, drugs acting on same receptors or having same mechanisms e.g. combination of NSAIDs and warfarin lead to increased risk of bleeding (Buresly K et al, 2005). Antihypertensive (captopril & diuretic), tyramine + MAOI. Increased neuromuscular (NM) blockade with aminoglycosides and NM blockers (Dupuis JY et al, 1989).

1.2.3.2 **Potentiation:** Drug which increases the effect of other drug.(e.g. physostigmine and Acetylcholine).

1.2.3.3 Antagonism: effect of two or more drugs is less than a total of the effects of the individual drugs. For example, action of a selective beta-2 receptor agonist (albuterol), is antagonized by a non-selective beta receptor antagonists (propranolol) (Kroner B, 2002). Other examples involve reduction of antihypertensive effect of ACE inhibitors and loop diuretics by NSAIDs (Shionoiri H, 1993).

1.3. Other types of drug interaction

Food-drug interaction: this kind of interaction happens when a drug affects the body that have specific type of food, for example, tyramine and MAO inhibitors (foods that include the substance tyramine) will slow down the enzymes that metabolize MAO inhibitors (a type of antidepressant medication) and can cause a dangerous rise in blood pressure. Also, calcium and antibiotics drink a glass of milk when you take a tetracycline antibiotic prescription, the calcium in milk bind to tetracycline which makes a compound that is impossible for your body to absorb and antibacterial effects may be lost (Banner Health, 2.3.2016).

Drug-Disease Interactions: Sometimes, drugs that are useful in one disease are harmful in another disorder. Such as, some beta-blockers taken for heart disease or hypertension can worsen asthma (Merck Manual, 2.3.2016).

Herb-drug interactions: The herbs are often administered with therapeutic drugs, raising the potential herbal-drug interaction. For example, ginkgo is used by elderly because of its ability to improve cognitive function in people with Alzheimer's disease

(LeBars P et a, 1997; Sastre J et al, 1998), and to improve blood flow in people with peripheral vascular disease. Patients taking ginkgo with other products that affect platelet activity, such as vitamin E (>1200 IU), warfarin, low molecular weight heparins, and aspirin, you should be warned about the potential interaction of those products with ginkgo, that may be lead to unusual bleeding (Foster S, 1996).

1.4. Risk factors for drug interactions

Many factors can increase the probability of drug interactions. They include the use of several drugs, old age or very young, some diseases can alter drug absorption, metabolism, and elimination, and response the body to drugs (Merck Manual, 2.3.2016).

- **Polypharmacy:** it is now common (concomitant use of > 5 drugs), it is often necessary to manage certain diseases (Aronsson JK, 2006). However, the greater number of co-prescribed medicines increase the risk of potential drug interaction, the risk of potential drug interaction in patients taking 2 - 5 drugs have to be 19%, but the risk rises to > 80% for those taking > 6 drugs (NMIC Bulletin, 2000).
- **Age**: Infants and very young children are at risk of the high rate of adverse drug reactions because their ability to metabolize medications are not fully developed. Newborns cannot metabolize and eliminate the antibiotic chloramphenicol. Older people are at high risk of an adverse drug reaction for many reasons, they have many health problems and thus to be taking many prescription and over-the-counter drugs, also, as people age, the liver is less able to metabolize many drugs, and the kidneys are less able to eliminate drugs from the body ((Merck Manual, 2016).
- **Narrow therapeutic index drugs**: Where there is a small margin between therapeutic and toxic drug levels e.g. Digoxin, Insulin, Lithium, Antidepressant, Warfarin
- **Specific illness** E.g. Hepatic disease, Renal dysfunction.

1.5. Prevention of drug-drug interactions

It is not easily to remember all the clinically important interactions and how they occur, but there are some broad general principles that may be helpful for prescribers in order to reduce risk to the patient (Baxter K, 2006).

- The most important developments in our ability to detect DDIs include computer programs. Many medical systems have already demonstrated that the use of computers may be lead to decreases in medical errors, including DDIs (Flammini S et al, 1999).
- Avoiding the combination: For some drug interactions, the risk of the interaction outweighs the benefit, and the combination should be avoided (Hazlet TK et al, 2001). Atenolol and verapamil together may lead to increased side effects, this can cause fatigue, headache, weight gain, shortness of breath, chest pain, decreased or increased heartbeat.
- Spacing dosing times to avoid the interaction: Some drug interactions including binding in the gastrointestinal tract, to avoid the interaction can give one drug at least 2 h before or 4 h after the other drug. In this way, the first drug can be absorbed into the circulation before the second drug appears.
- Monitoring for early detection: In some cases, when it is needed to administer interacting drug combinations, the interaction can be managed through clinical or laboratory monitoring for the evidence of the interaction. In this way, the appropriate dosage changes can be made, or the drugs stopped if necessary.
- Drugs that have a narrow therapeutic index (e.g. anticoagulants, anticonvulsive agents, digoxin), in this matter it needs to take care when initiating such a drug or co-prescribing with another drug (Doucet J et al, 1996).
- Knowledge of drugs which inhibits metabolism enzymes or inducer.
- Remember that chronically ill patients and the elderly are at increased risk of drug interactions (Teeling M, Feely J , 2008).

1.6. Consequences of drug-drug interactions

Drug interactions may lead to decrease or an increase in benefits or side effects of certain drugs, when drug interaction increases the benefit of the drugs administered without increasing side effects, and can be combined with each of the drugs to increase the control of the condition that is being treated, for example, medications that reduce blood pressure by different mechanisms can be combined because the effect of lowering the blood pressure of both drugs achieved may be better than with either drug alone, example diuretics, beta-blocker.

Drugs that reduce the absorption or increase metabolism or elimination of other drugs tend to reduce the effects of other drugs, this may lead to treatment failure; For example, increase metabolism of warfarin by many drugs such as phenytoin, rifampin, and barbiturates. As a result, interaction reduced the effect of the anticoagulant.

Therapeutic effect of one drug reduced by another drug, example albuterol and propranolol. Albuterol is taken by those with asthma to dilate the bronchi. Beta blocker (propranolol) is for cardiovascular disorders and can act in the lung to block the effects of albuterol.

Conversely, drugs that increase the absorption or reduce eliminate or metabolism of other drugs, increase the concentration of other drugs in the body, and more side effects, cimetidine inhibit metabolism theophylline, increase the serum concentration theophylline and toxicity. Sometimes, medications interact because they produce similar side effects. Thus, when it is the combination of two drugs that produce similar side effects, and increased the severity of side effects (RxList , 12.3.2016).

2. Materials and methods

2.1. Study Design:

This study was conducted on prescriptions of different community pharmacies in Almarj of Libya, the prescriptions of 1305 of patients were collected and screened for cardiovascular disease patients using at least one cardiovascular drug. Prescriptions were collected from 29 pharmacies registered in the Ministry of Health at Almarj of Libya, from January to March 2016.

Prescriptions matching inclusion criteria, containing at least one cardiovascular drug were included in this study, and also, prescriptions that contain only one drug were excluded from the study since there are no medications to be compared with. Prescriptions were retrospectively analyzed for drug-drug interactions using Drugs.com database (Dalshat, 2015).

The main research questions addressed were:

- Frequency of DDIs in patients using cardiovascular drugs in Almarj of Libya.
- Types of DDIs according to severity and risk factors associated.

Categorized DDIs according to their level of significance into three classes (minor, moderate, major) with categories of major interaction is highly clinically significant, which likely to require a change in treatment or laboratory monitoring, avoid combinations if the risk of the interaction outweighs the benefit, moderate interaction is moderately clinically significant, usually avoid combinations unless if the benefit of administration outweighed the risk, and minor interactions are minimally clinically significant. There are many drug-drug interaction databases namely Medscape, Lexi-comp, and drugs.com, this study used drugs.com, because it's utilized is a worldwide acceptable and validated, not only that also it provides accurate and independent information on more than 24,000 prescription drugs.

The main objective of this study was to analysis the frequency of drug interactions in prescribed drugs for cardiovascular disease patients. Other objectives were to correlate the frequency of drug interactions with demographic features of patients, and to identify risk factors for such interactions. This study did not include the potential interactions between drugs and complementary medications, herbal or food.

2.2. Data collection:

Prescriptions 1305 were collected and screened for cardiovascular disease patients using at least one cardiovascular drug. Prescriptions were collected from 29 community pharmacies in Almarj of Libya.

A total of 157 prescriptions contain cardiovascular drugs, 24 prescriptions contain only one drug, and 133 prescriptions of patients using at least one cardiovascular drug.

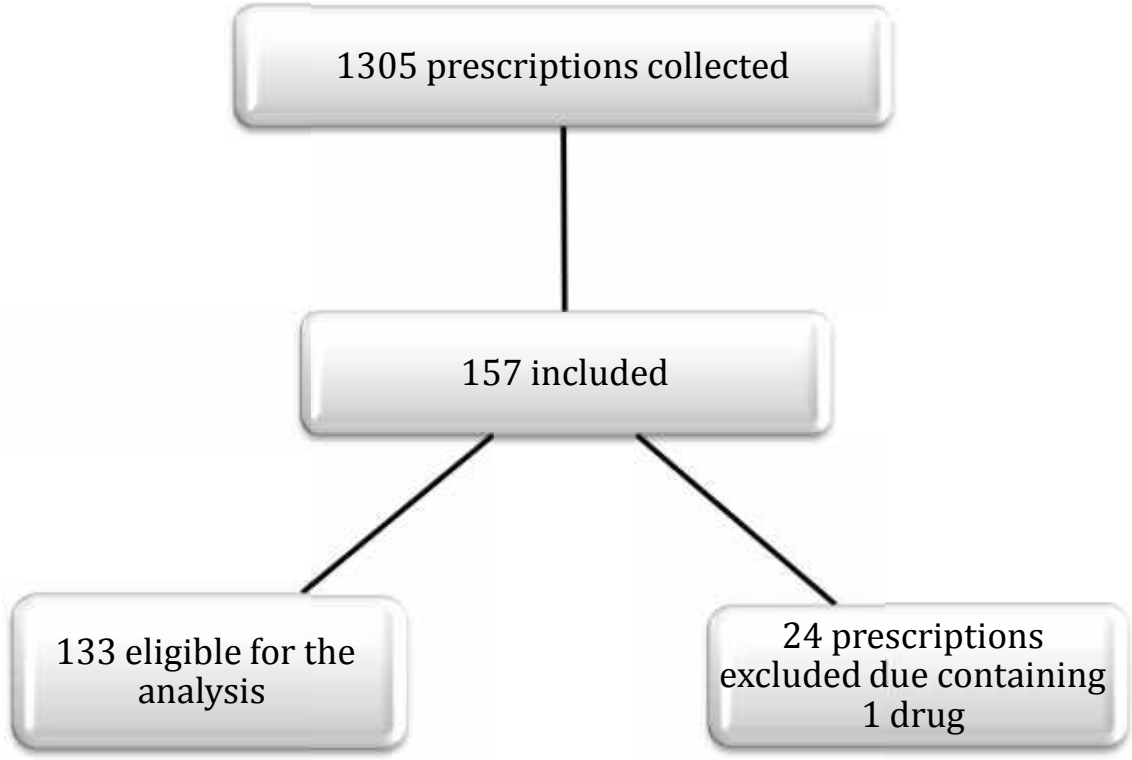


Figure 1: Data collection

For each of the prescriptions analyzed, all drugs were tabulated and inserted in an excel sheet. Interactions were checked with drugs.com database.

2.3. Data analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 20) software. Data were described using frequency distribution. Chi-square tests and fisher's exact tests were used for comparisons, Pearson Chi-square test were used for correlation analysis.

2.4. Ethical Considerations

Confidentiality was assured during the study and also patient's privacy, a Letter of ethical clearance was obtained from the Institutional Review Board (IRB) of Near East University Hospital that assigned this research as being just observational study and hence viewed as not requiring moral regard. Only Initials were used during the study without recording patient's location or other related not clinical essential individual data. Approval letters is given as shown in the Appendix.

3. Results

During this study, 1305 prescriptions were collected and screened for cardiovascular drugs. From total of 157 prescriptions contain cardiovascular drugs, 24 prescriptions contain only one drug were excluded from the study and 133 prescriptions of patients using at least one cardiovascular drug have been included and analyzed for drug-drug interactions in our study. 75.2% out of it, 100 prescriptions, has drug-drug interactions according to drugs.com. While, there was no significant association of pDDIs with specific gender in our study, 78 (58.6%) patients were male where 55 (41.4%) patients were female, number patients were between 30 and 85 years old of age, i.e. Figure 2. A total number of 175 interactions were noted according to drugs.com. Relevant drug interactions were graded by their level of severity moderate pDDIs were most prevalent 116 (66.3%) followed by minor pDDIs 54 (30.8%), and major pDDIs recorded in 5 (2.9%), as shown in Table 2.

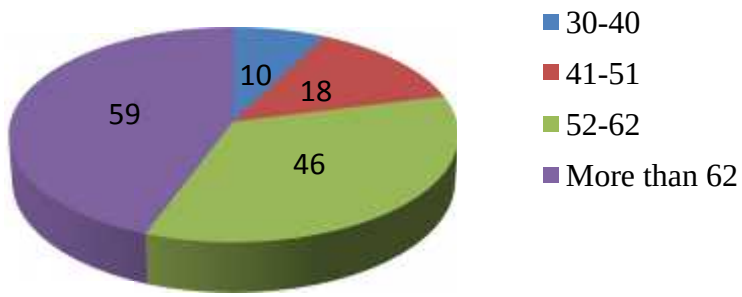
In this study was a significant association between number of drugs and potential DDIs, 69 (51.9%) patients received 2 drugs, 41 (59.4%) prescriptions had drug interactions, 40 (30.1%) patients received 3 drugs, 35 (87.5%) prescriptions had interactions, patients received 4 drugs or more, all prescriptions had drugs interactions, as shown in Table 2.

The total interactions according to Drugs.com were 175, 152 (86.9%) were pharmacodynamics interactions and 23 (13.1%) were pharmacokinetics interactions, as shown in Table 3.

There is positive correlation between age and number of interactions (Figure 3) because of polypharmacy increase in the elderly ($p < 0.001$). The most common interactions were between aspirin and bisoprolol 17 (9.7%), aspirin and enalapril 13 (7.4%) furosemide and aspirin 12 (6.9%), and lisinopril and aspirin 11(6.3%).

Figure 2 .Demographic characteristics of patients

A: Age



B: Gender

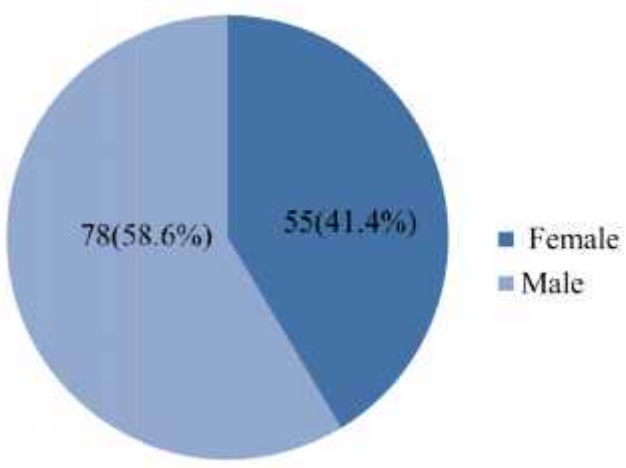


Table 2: Number of interactions according to severity of interactions (Drugs.com)

Number of drugs	Number of prescriptions	Number of prescriptions have interactions	Number of prescriptions no have interactions	Number of interactions	Minor interactions	Moderate interactions	Major interactions
2	69	41 (59.4%)	28 (40.6%)	41	8 (19.51%)	32 (78.05%)	1 (2.44%)
3	40	35 (87.5%)	5 (12.5%)	70	27 (38.57%)	41 (58.57%)	2 (2.86%)
4	18	18 (100%)	0	38	11 (28.95%)	26 (68.42%)	1 (2.63%)
5	5	5 (100%)	0	23	7 (30.43%)	15 (65.22%)	1 (4.35%)
6	1	1 (100%)	0	3	1 (33.3%)	2 (66.7%)	0 0%
Total	133	100*	33	175	54 (30.8%)	116# (66.3%)	5 (2.9%)

* P <0.001 when compared number of prescriptions have no interaction

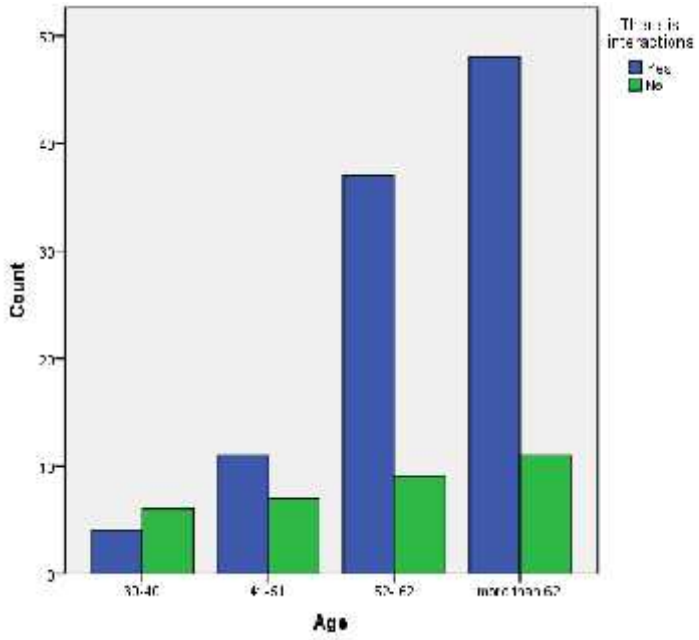
# p <0.001 when compared to other severity of interactions

Table 3: Number of interactions according to the mechanisms of drug interactions (Drugs.com)

Number of drugs	Number of interactions	Pharmacodynamic	Pharmacokinetic
2	41	36 (87.8%)	5 (12.2%)
3	70	63 (90%)	7 (10%)
4	38	36 (94.7%)	2 (5.3%)
5	23	15 (65.2%)	8 (34.8%)
6	3	2 (66.7%)	1 (33.3%)
Total	175	152* (86.9%)	23 (13.1%)

* P <0.001 when compared to pharmacokinetic interactions

Figure 3 . The number of interactions according to age



In this study was a significant association between age and potential DDIs, If the patient's age from 30 to 40 years, rate pDDIs was 7.5%, from 41 to 51 years was 13.5%, from 52 to 62 years was 34.6%, and more than 62 years was 44.4%.

Table 4: Drug interactions, outcomes, clinical significance (Drugs.com) and recommendations

Drug A	Drug B	Mechanisms of interactions	Outcome of interactions	Clinical significance	Recommendations
Aspirin	Enalapril	Pharmacodynamic	Moderate	Decrease effect of enalapril	Blood pressure monitoring. The lowest therapeutic dosage of aspirin should be used
Aspirin	Digoxin	Pharmacokinetic	Moderate	Increase plasma digoxin concentrations	Monitor digoxin level
Aspirin	Atenolol	Pharmacodynamic	Minor	High doses of aspirin may decrease effects of atenolol	No need action
Aspirin	Verapamil	Pharmacodynamic	Moderate	Unusual bleeding	TDM
Aspirin	Telmisartan	Pharmacodynamic	Moderate	Aspirin decrease effects telmisartan	TDM
Aspirin	Bisoprolol	Pharmacodynamic	Minor	High doses of aspirin may decrease effects of bisoprolol	No need action
Aspirin	Losartan	Pharmacodynamic	Moderate	Reduce the effects of losartan	Monitor blood pressure
Aspirin	Insulin regular	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring of blood glucose
Aspirin	Insulin isophane	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring of blood glucose
Aspirin	Amlodipine	Pharmacodynamic	Moderate	Increase blood pressure	aspirin dose should be kept to a minimum in patients with hypertension and monitor blood pressure
Aspirin	Nitroglycerin	Pharmacodynamic	Minor	Aspirin may enhance the antihypertensive effect of nitroglycerin	No need action
Aspirin	Spironolactone	Pharmacodynamic	Minor	Decreased spironolactone effectiveness	No need action
Aspirin	Carvedilol	Pharmacodynamic	Minor	High doses of aspirin decrease effects of carvedilol	No need action
Aspirin	Nifedipine	Pharmacodynamic	Moderate	Decrease effect	Monitor blood

				of nifedipine	pressure
Aspirin	Captopril	Pharmacodynamic	Moderate	Aspirin decrease the vasodilator and hypotensive effects of captopril	Blood pressure monitoring. The lowest therapeutic dosage of aspirin should be used.
Aspirin	Ramipril	Pharmacodynamic	Moderate	Decrease vasodilator and hypotensive effects of ramipril	Blood pressure monitoring and reduce dosage of aspirin
Aspirin	Lisinopril	Pharmacodynamic	Moderate	Reduce vasodilator and hypotensive effect of lisinopril	Blood pressure monitoring and reduce dosage of aspirin
Aspirin	Furosemide	Pharmacodynamic	Minor	Lasix effects may be reduced by aspirin	No need action
Aspirin	Clopidogrel	Pharmacodynamic	Moderate	Leads to bleeding	Monitored closely for signs of bleeding
Aspirin	Candesartan	Pharmacodynamic	Moderate	Reduce the effects of candesartan	TDM
Atenolol	Amlodipine	Pharmacodynamic	Moderate	Additive antihypertensive action	TDM
Atenolol	Furosemide	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Atenolol	Insulin regular	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring of blood glucose
Atenolol	Verapamil	Pharmacodynamic	Major	Reductions in heart rate, cardiac conduction, and cardiac contractility	Avoid combinations
Atenolol	HCT	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Amiloride	Valsartan	Pharmacodynamic	Major	Hyperkalemia	Monitoring of serum potassium
Amlodipine	Enalapril	Pharmacodynamic	Minor	Hypotension	No need action
Amiloride	Candesartan	Pharmacodynamic	Major	Hyperkalemia	Monitoring of serum potassium
Amlodipine	HCT	Pharmacodynamic	Minor	Hypotension	No need action
Amlodipine	Lisinopril	Pharmacodynamic	Minor	Hypotension	No need action
Amlodipine	Bisoprolol	Pharmacodynamic	Moderate	Additive antihypertensive action	TDM
Bisoprolol	Furosemide	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Bisoprolol	Spironolactone	Pharmacodynamic	Moderate	Hypotension	TDM
Bisoprolol	Insulin regular	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring of

					blood glucose
Bisoprolol	Insulin isophane	Pharmacodynamic	Moderate	Hypoglycemia	Monitoring of blood glucose
Bisoprolol	HCT	Pharmacodynamic	Moderate	Hypotension	TDM
Carvedilol	Furosemide	Pharmacodynamic	Moderate	Hypotension	TDM
Carvedilol	Spironolactone	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Candesartan	Spironolactone	Pharmacodynamic	Major	Hyperkalemia	Monitoring of serum potassium
Captopril	Furosemide	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Digoxin	Enalapril	Pharmacokinetic	Moderate	Increase the blood levels and effects of digoxin	TDM
Digoxin	Furosemide	Pharmacodynamic	Moderate	Hypokalemia	Monitoring of serum potassium
Digoxin	Spironolactone	Pharmacokinetic	Minor	Increase plasma digoxin concentrations	Monitored for signs and symptoms of digoxin toxicity
Digoxin	Lisinopril	Pharmacokinetic	Moderate	Increased plasma digoxin levels	TDM
Enalapril	Furosemide	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Enalapril	Nifedipine	Pharmacodynamic	Minor	Hypotension	No need action
Enalapril	HCT	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Furosemide	Metformin	Pharmacokinetic	Moderate	Increase plasma concentrations of metformin	TDM
Furosemide	Ramipril	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Digoxin	Ramipril	Pharmacokinetic	Moderate	Increase the blood levels and effects of digoxin	TDM
Furosemide	Hydralazine	Pharmacokinetic	Minor	Increase in the plasma clearance of furosemide	No need action
Furosemide	Lisinopril	Pharmacodynamic	Moderate	Hypotension	Monitoring of blood pressure
Furosemide	Insulin regular	Pharmacodynamic	Moderate	Hyperglycemia	Monitoring of blood glucose
Furosemide	Insulin isophane	Pharmacodynamic	Moderate	Hyperglycemia	Monitoring of blood glucose
Digoxin	Telmisartan	Pharmacokinetic	Moderate	Increase the serum concentrations of digoxin	TDM
Furosemide	Warfarin	Pharmacokinetic	Minor	Plasma warfarin	No need action

				concentrations and warfarin effects may be increased	
Nifedipine	Simvastatin	Pharmacokinetic	Moderate	Increase the plasma concentrations of simvastatin	TDM
Warfarin	Spironolactone	Pharmacodynamic	Minor	Decrease effect of warfarin	No need action
Lisinopril	Spironolactone	Pharmacodynamic	Major	Hyperkalemia	Monitoring of serum potassium

HCT: Hydrochlorothiazide

4. Discussion

Interactions between drugs (DDIs) are drug modification affected when administered with another drug. Interactions between drugs may be useful or harmful. The harmful of drug–drug interactions are important they also cause 10–20% of the adverse drug reactions require hospitalization. Drug interactions can be pharmacokinetic or pharmacodynamic (Ashraf & Lionel, 2004).

Pharmacodynamic interactions, the effects of one drug are change by the presence of another drug at its site of action without a change in plasma concentration. These interactions generally include additive, synergistic or antagonistic effects (Baxter K & Lee A, 2008).

Pharmacokinetic interactions include change of drug absorption, distribution, metabolism and elimination by a second drug resulting in a change (increase or decrease) in the drug concentration (Strain JJ et al, 2004). A large proportion of potentially clinically significant drug interactions are reported to occur by alterations in the drug metabolism through inhibition and indication of enzymes. The outcome of changed metabolism depends on the drug, inhibition of an active drug can lead to rises in the concentration and toxicity, induction of CYP enzymes can decrease the plasma concentrations and drug effects (Armstrong SC et al, 2003; Abernethy DR & Flockhart DA, 2000). Cytochrome P-450 enzymes are the most important hepatic enzymes include in phase-I metabolism, they are responsible for the metabolism of many drugs. Many factors may increase the drug interaction include polypharmacy, age, drugs with a narrow therapeutic index, and renal or hepatic diseases.

The objective of this study was to determine the prevalence of DDIs in prescriptions for cardiovascular drugs, the prevalence of DDIs in prescriptions was 75.2% in this study, moderate pDDIs were most prevalent 116 (66.3%), 54 (30.8%) were minor interactions, and 5 (2.9%) were major interactions.

pDDIs prevalence rate in our study (75.2%) was higher than that reported by some other studies ranging from 19% to 51% in whole hospital settings (Cruciol-Souza JM & Thomson JC. A, 2006; Zwart, et al 2009; Fokter N et al, 2010). 31% to 47% in emergency department (Hohl CM et al, 2001). Prevalence of major pDDIs in our study (2.9%) nearly similar with some studies which reported a rate of 3.1% to 13% of DDIs (Cruciol-Souza JM & Thomson JC , 2006 ; Fokter N et al, 2010 ; Vonbach P et al, 2008).

Many studies support this high prevalence rate of pDDIs in patients with cardiovascular diseases. And also few other studies suggest that cardiac patients are at higher risk of pDDIs as a number of cardiovascular drugs are associated with drug drug interactions due to multiple drug therapy (Becker ML et al ,2007 ; Straubhaar B et al ,2006). A similar study done in the Department of Cardiology, Hazara, Pakistan, rate prevalence pDDIs was 77.5% pDDI (Ismail et al , 2012b). A study in the south Indian hospital, the prevalence rate pDDIs was 30.67% in the cardiac patients (Patel et al , 2011). A study done to evaluate pDDIs in the patients with hypertension found 75% patients presented with one or more pDDIs (Carter BL et al ,2004). A study analyzed medication to patients with heart failure, for pDDIs using computerized DDIs screening program. pDDIs were recorded in 68% to 88.8% patients at different stages from admission to discharge (Straubhaar B et al , 2006). Another study evaluate the prevalence of pDDIs in patients prescribed with antihypertensive drugs. It was found that 55% to 84% patients were exposed to at least one or more pDDIs(Carter BL et al, 2002). 43.4% prevalence rate for pDDIs was observed during the study in patients with heart disease in the Iranian hospital (Namazi, 2012).

In this study, moderate pDDIs were most prevalent 116 (66.3%), followed by minor pDDIs 54 (30.8%), and 5 (2.9%) were major interactions, comparable to another study, moderate interactions were 67.4%, major interactions were 7.7%, and 24.2% were minor interactions (Stanton LA et al, 1994). A study investigated prevalence and levels of pDDIs in 265 elderly patients diagnosed with arterial hypertension. Total 240

(90.6%) patients were presented with at least one pDDI, moderate interactions were most common (83%) followed by major interactions (16%), previous studies prevalence of DDI, study analyzed 100 patients' data and found total 180 pDDIs. Moderate pDDIs were most common (56.7%) followed by minor pDDIs (25%) and major pDDIs (18.3%) (Bacic-Vrca V et al , 2010).

The total of interactions in our study was 175 interactions152 (86.9%) were pharmacodynamics interactions, and 23 (13.1%) were pharmacokinetics interactions which were similar to another study pharmacodynamics were (91.7%) and (5.3%) were pharmacokinetics (Davies EC et al, 2009). In another study investigation ADRs leading to hospital admissions, all drug interactions considered responsible for the ADR were pharmacodynamics (Stanton LA et al, 1994).

In our study found some factors related with pDDIs that include patients' age, and polypharmacy. Our findings concerning association of pDDIs with elder patients are supported by other studies also (Bacic-Vrca et al, 2010 and Mallet et al, 2007). A study performed at Switzerland in cardiovascular patients also showed that patients with old age were at higher risk for pDDIs (Egger et al, 2007).

Patients taking multiple medications in this study were at higher risk of pDDIs. A study conducted in the Cardiology Department in Switzerland found that the incidence of pDDIs increased with increase in number of drugs prescribed (Egger et al, 2007). A study conducted at USA in patients with hypertension reported similar association (Carter et al , 2004). Another study investigated pDDIs in patients, prescribed with drugs commonly used for the management of hypertension. They found that increased number of prescribed drugs were significantly associated with the presence of one or more pDDIs(Carter et al , 2002). A study investigated the association between number of medications and pDDIs in elderly population. They found a strong correlation between number of medications and probability of pDDIs (Johnell K & Klarin , 2007).

There was not significant association of pDDIs with specific gender in our study. Various studies have found different results concerning association of any gender with risk of pDDIs. A study done in cardiac patients had found significant association of pDDIs with male patients (Ismail et al , 2012b). On the other hand, a significant association of pDDIs was found with female patients in another study done in Brazil

(Cruciol-Souza and Thomson, 2006a.). A study in Italy revealed that pDDIs are not associated with any specific gender (Nobili et al., 2009).

The present study has recorded a high prevalence of pDDIs in the prescriptions contain cardiovascular drugs was (75.2%). Most of the interactions were of moderate interactions according to severity and pharmacodynamic more than pharmacokinetic interactions. Patients with old age, and increased number of drugs prescribed were more exposed to pDDIs, therefore it is very important to make effort to reduce polypharmacy.

5. Strengths

This study to evaluate drug-drug interaction in prescriptions dispensed cardiovascular diseases patients in community pharmacies in Almarj of Libya which is the first study of its kind in Almarj of Libya. There are many Drug interaction checkers used over the worldwide and they are acceptable and well validated, one of these checkers Drugs.com which provides independent and accurate information on more than 24,000 prescription drugs, natural products and OTC, for all these reasons the researcher use drug.com to check the interactions in this research. Besides that we screened 1305 prescriptions for patients because of the number of those who were also more compared to the sample of registered numbers in other similar studies. Similarly been done in most of the studies on the patient in the hospital to measure the rate of occurrence of drug-drug interactions but in our study we retrospectively analysis the prescriptions of outpatients, which is one of the advantage compared to other studies on the same topic. Furthermore, Prescriptions were retrospectively analyzed for drug-drug interactions using Drugs.com (Dalshad Mohamed, 2015)..

6. Limitations

Many limitations had lead less beneficial outcomes for this study, the missing information and a limitation is particularly noteworthy data about patient concurrent disease and food intake this is why our study is limited only to the drug-drug interaction and not the drug -diseases and food-drug interactions, because the incidence and pattern of DDIs in Almarj of Libya has not been well documented and little information is available about the strategies that have been used for their prevention. And also, our study was limited only to Almarj of Libya and we did not include any patient from other cities. We did not analyze drug interactions for other groups of patients, such as

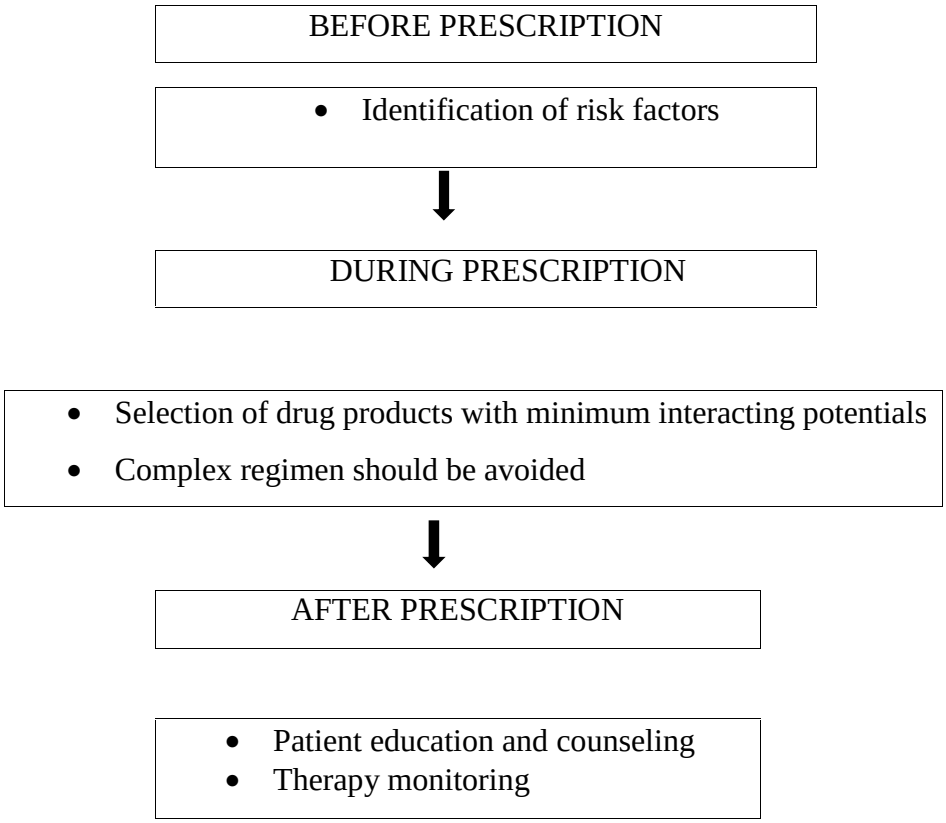
diabetes and chronic infections. The data limited to process through the site Drugs.com due to the reliability of the site in the data analysis, according to some previous studies resulted good results in the same field by using this site (Dalshad Mohamed, 2015).

7. Future recommendations

Identify drug interactions and management of their adverse results is a difficult task for clinical pharmacists. Studies have demonstrated that drug interactions can be predicted on the basis of available published-evidences,pharmacokinetic and pharmacodynamic of drugs (Hisaka A et al, 2010 ; Juurlink DN et al, 2003 ; Peterson JF & Bates DW, 2001 ; Anderson JR & Nawarskas JJ, 2001 ; Ding C, 2011 ; Levy RH & Collins C, 2007). In this way, many drug interactions can be prevented. Away from this, regular monitoring of patients is the best strategy to reduce the potential risks associated with the drug interactions. Following are some general guidelines to identify and management of drug interactions (Figure 4).

- Should identify all risk factors , such as old age, renal and hepatic impairment Severe diseases increase the number of drugs, etc.
- Drug products with minimum interacting potentials should be selected.
- Complex regimen should be avoided when possible. An individualized therapeutic regimen should be selected.
- Monitoring for early detection: In some cases, when it is necessary to administer interacting drug combinations.
- You should educate the patient about the proper use of drugs and reporting of adverse outcomes of drug interactions.
- It should monitor the treatment i.e., patients' signs, symptoms and laboratory reports It should be checked on a regular basis.
- use of computers programs to detect DDIs may be lead to significant decreases in DDIs.
- Spacing dosing times to avoid the interaction.
- Knowledge of drugs which inhibits metabolism enzymes or inducer.

Figure 4: Management of drug interactions



8. Conclusion

In conclusion, the present study has recorded a high prevalence of pDDIs in the prescriptions contain cardiovascular drugs was (75.2%). Most of the interactions were of moderate interactions, major interactions were five interactions according to severity and pharmacodynamic more than pharmacokinetic interactions. Patients with old age, and increased number of prescribed drugs were more exposed to pDDIs, therefore it is very important to make effort to reduce polypharmacy. The physicians should be more aware of potentially harmful DDIs, especially cardiovascular drugs. Close monitoring of patients is recommended to manage and prevent negative clinical consequences of these interactions. Pharmacists can contribute to the detection and prevention of drug-related problems and reduce the rate of DDI and dangerous result associated with them. Finally, there is a need for more extensive research to identify and reduce the factors associated with the incidence of DDIS , and to design and evaluate the effects of interventions particularly those that use information technology to increase awareness about DDIs and decrease their incidence by the drug management team.

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