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NEAR EAST UNIVERSITY

INSTITUTE OF HEALTH SCIENCES

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

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Master of Science in Pharmacology

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NICOSIA 2016

Approval

Thesis submitted to the Institute of Health Sciences of Near East University in partial fulfillment of the requirements for the degree of **Master of Science in Pharmacology.**

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ACKNOWLEDGEMENT

I am very thankful to Almighty Allah who provided me all the resources and gave me courage to complete this project. My research work would not have been possible without the help, support, and guidance of many people to whom I want to convey my deepest gratitude. I owe my deepest gratitude and much respect to Assoc. Prof. Bilgen Basgut myco –adviser, for his valuable time, encouragement, and guidance given to me during my training and research time. I must also thank all my professors at my master degree in Near East University. Finally, I would like to express my deepest heartfelt gratitude to my brothers, sisters, and my friends KERALA, SALAH, ANDADEL.

DEDICTION

To the Spring that never stops giving, to my mother who weaves my happiness with strings from her merciful heart... to my mother. To whom he strives to bless comfort and welfare and never stints what he owns to push me in the success way who taught me to promote life stairs wisely and patiently, to my dearest father.

To whose love flows in my veins, and my heart always remembers them, to my children BODOUR, MOHAMMED and MAREM and to my best friend HANIA.

ABSTRACT

The project titled as"Potential drug-drug interactions in cardiovascularpatients prescriptions dispensed in community pharmacies in Albyd of Libya. It was conducted in different community pharmacies under the Ministry of Health in Albyd of Libya.

Drug-Drug Interactions (DDIs) are adverse reactions caused by a combination of drugs; they are often predictable and therefore avoidable or manageable.Various studies suggest that cardiovascular patients are more often reported with pDDIs as compared to patients with other diseases.

The possible reason behind higher pDDI rate in cardiovascular diseases may include 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 but the primary objective of the study will to be 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 Albyd of Libya.

The objective of this study is to evaluate the nature, type and prevalence of potential DDIs in prescriptions dispensed in community pharmacies in Libya.

This study was conducted in 32 community pharmacies under the Ministry of Health in Albyd of Libya. They were collected in 1369 prescription to patients randomly. Prescription matching inclusion criteria, It was sort prescription that contain a cardiovascular drug and excluded those involving one drug, Prescription were retrospectively analyzed for drug-drug interaction using Drugs.com data base, these database are categorized three categories (minor, moderate, major). The collected data will be transferred to computer and analyzed using suitable statistical analysis. Overall incidence of drug interaction was 76.5% from that 2.17% was major interaction, 68% was moderate and the rest had minor interactions. Increase in number of drugs in each prescription caused to a significant increase in the incidence of drug interactions.

It is conclude knowledge of drug interactions and replace them with other drugs and reduce the number of drugs that can reduce to a large extent these interactions.

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

OZET

Libya Albyd toplum eczanelerde reçete cardiovascularpatients reçete "Potansiyel ilaç-ilaç etkileşimleri başlıklı proje. Bu Libya Albyd Sağlık Bakanlığı altında farklı eczanelerden gerçekleştirilmiştir.

Bu çalışmanın amacı, Libya'da halk eczanelerde reçete reçeteler doğa, türü ve potansiyel DDIS sıklığını değerlendirmektir.

Bu çalışma Libya Albyd Sağlık Bakanlığı'na bağlı 32 eczanelerden gerçekleştirilmiştir. Onlar rastgele hastalara 1369 reçete toplanmıştır. Reçete eşleştirme dahil edilme kriterleri, O bu veritabanı üç kategori kategorize edilir sıralama bir ilaç içerenler, Reçete geriye dönük Drugs.com veri tabanı kullanılarak ilaç-ilaç etkileşimi için analiz edildi kardiyovasküler ilaç içeren ve dışlanan reçete oldu (küçük, orta, büyük) . Toplanan veriler bilgisayar ortamına aktarılarak ve uygun istatistiksel analiz kullanılarak analiz edilecektir. ilaç etkileşimi insidansı, yani 2.17 den% 76.5,% majör etkileşim oldu% 68 orta ve dinlenme küçük etkileşimleri vardı. Her reçete ilaçların sayısındaki artış ilaç etkileşimleri görülme sıklığında önemli bir artış sağlamıştır.

Bu ilaç etkileşimlerinin bilgi sonucuna ve diğer ilaçlarla değiştirmek ve büyük ölçüde bu etkileşimlerin azaltabilir ilaç sayısını azaltmak olduğunu.

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

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LIST OF ABBREVIATIONS

ADRs: adverse drug reactions.

ACE:angiotensin converting enzyme

DDIs: Drug-Drugs interaction.

GIT: gastrointestinal tract

HCL: Hydrochlorothiazide.

NSAIDS: Nonsteroidal anti-inflammatory drugs.

TDM: Therapeutic Drug Monitoring.

pDDIs:Potential drug-drug interactions.

CNS:central nervous system

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

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES

BY:

HANAN ALI SALEH ALI

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

NICOSIA 2016

1. Introduction

1.1. Drugs interaction

Drug-Drugs interaction (DDIs) is one of the most frequently appearing challenge that may alter the pharmacokinetic and pharmacodynamics of the drugs.

Drug interactions may result when two or more drugs are taken together. These interactions are not limited to the co-administration of two or more drugs, and can be occur in the forms drug interactions with drug, drug with food, drug with a disease, and drug with environmental factors, for that Drug-Drug Interactions (DDIs) are common adverse drug reactions which have an important influence on patient safety and healthcare costs (Esteghamat et al., 2012).

There are many definitions of DDIs, one of the definition of drug- drug interactions (DDIs) in both field of pharmacokinetic or pharmacodynamic is the effects of drugs on each other, which may lead to undesirable effects, and low efficacy or increased toxicity (Edwards IR& Aronson JK.,2000).

Pharmacokinetic interactions result from changes in a drug's absorption, distribution, metabolism, or excretion. On the other hand Pharmacodynamic interaction is a result of the impact of combined treatment at a site of biological activity and yield altered pharmacological actions at standard plasma concentrations, although drug 0antagonism or potentiation of the effects of drugs.

The important to study came out due to many reports over the world in which the high rate of fatalities, for example the med watch program of Food and Drug Administration reported that there are 6894 fatalities due to adverse drug reactions (ADRs) including DDIs in the United States in 1995 (Chyka PA., 2000).

Some various studies showed that cardiovascular patients are often reported with DDIs as compared to patients with other diseases (Ismail et al., 2013a, b; Ismail et al., 2012a, b).

The studies found that the higher DDI rate in cardiovascular diseases, the possible reason behind that may include multiple drug regimen, elder age, and pharmacokinetic or pharmacodynamic nature of drugs used in cardiology (Faulx

&Francis, 2008) becuase cardiovascular drugs are often involve in DDIs (Baxter and Preston, 010;Mendell et al., 2011).

It was understood for decades, it was not easy to identify the effects of DDIs on patients, but, recently the technology allowed to a more thorough understanding of drug-metabolizing is forms and effects in this regard, and there is a large number of drug databases and semi-structured resources which help to know and determine the effects of drug interactions (K. Baxter &Stockley., 2010). The existence of DDIs potential can be identified Drug Interactions Checker using inside Drugs.com data base, these database are categorized three categories, Major, moderate and minor interaction. (Kennedy-Dixon T et al., 2015).

1.2. Mechanisms of drug interactions

Drug interaction is caused by pharmaceutical, pharmacokinetic and pharmacodynamic processed.

1.2.1. Pharmaceutical Drug Interactions

It occurs before drug is actually administered to the patient and generally represents incompatibilities of drug administered by intravenous infusion.

These incompatibilities apparent as an increase in turbidity or measured haze, particulates, and color changes. Ultimate consequence is not established however at the very least is presumed to increase the potential for vein irritation. For example: If sodium thiopentone and either vecuronium or pancuronium are together administered they may form a white precipitate that can flow into intravenous tubing. This precipitate may cause a problem of embolism to the patient (pharmainfo.net, 2016).

1.2.2. Pharmacokinetic interactions

Pharmacokinetics involve the effect of a drug on another drug includes absorption, distribution, metabolism and excretion.

1.2.2.1. Altered GIT absorption

Certain drugs combinations can affect the rate or extent of drug absorption with one or more of these mechanisms (Welling PG, 1984).

1.2.2.1.1. Altered pH

The rate of drugs absorption via passive diffusion is limited by the dissolution or solubility of a compound in gastric fluid solubility. Basic drug is more soluble in acidic fluid, and acidic drug is more soluble in basic fluid, thus compounds that create an environment with a specific pH might reduce the solubility of compounds needing an opposing pH for absorption. But drugs solubility does not completely ensure absorption because only un-ionized molecule is absorbed.

The non-ionized form of drugs is more lipids soluble and more readily absorbed from GIT than the ionized form does; and as an example of this type of interaction include antacid and ciprofloxacin, antacid reduced ciprofloxacin absorption due to reduced dissolution (Lee BL, Safrin S, 1992).

1.2.2.1.2. Chelation and Adsorption

Drugs might form insoluble complexes via Chelation in the gastrointestinal tract. Chelation includes the formation of a ring structure between a metal ion and an organic molecule, and those results in an insoluble compound those are unable to penetrate the intestinal mucosa because of the deficiency of drug dissolution.

There are many examples of this type of interaction which include the complication of tetracycline and iron, and by this mechanism, tetracycline antibiotic is decreased by up to 80% (NeuvonenPJ & Gothon, 1970; Campbell N & Hasinoff BB1991).

On case of Adsorption, it is a process of ion binding or binding hydrogen; and this may occur between Infection control, such as penicillin, cephalexin, sulfamethoxazole, and tetracycline or Absorbents such as cholestyramine, the reason behind that because this process can significantly reduces antibiotic exposure (Questran, 1993; Parsons RL& Paddock GM, 1975). Due to that the concomitant administration of absorbents and antibiotics must be avoided.

1.2.2.1.3. Altered in Gastric Emptying and Intestinal Motility

The absence or presence of food can affect the absorption of drug by a variety of mechanisms (Fraga Fuentes MD, Garcia Diaz B, de Juana Velasco P, et al, 1997). Meals can be high in fat significantly increases the extent of absorption Compounds that dissolve in fat (Welling PG ,1984), that happen because the primary site of drugs absorption are the small intestine, also the changes in gastrointestinal motility and gastric emptying might have significant effects on drug exposure.

The fast gastrointestinal transit effected by prokinetic agents like, domperidone, and metoclopramide mightlowering the extent of absorption of poorly soluble drug or drug that is absorbed in a limited area of the intestine in gastric emptying (Tonini M, 1996).

1.2.2.1.4. Changes in Gut Flora

Metabolism of certain drugs occurs by the action of microbial flora in the GI tract. The Certain antibiotics reduce the GI flora and may lead to alteration in amount of drug being absorbed. For example, tetracycline and other broad-spectrum antibiotics have been found to enhance the effect of concomitantly administered anticoagulants (Delie F, Rubas, 1997; Lu AY, 1998).

In some patients (about 10%), a portion of digoxin is inactivated by GI flora. Concurrent use of erythromycin or tetracycline may lead to increased serum digoxin levels most probably by reducing the GI-flora-induced metabolism of digoxin (Hall SD, Thummel KE, Watkins PB, et al, 1999).

1.2.2.2. Drug interactions affecting distribution

Protein Binding and Displacement

Some drugs and their metabolites are highly bound to plasma proteins as a rule, acidicdrugs bind mostly to albumin and basic drugs to alpha-1-acid glycoprotein. Drugs displacement interactions are defined as a decrease in extent of plasma proteinbinding of one drug caused by the presence of another drug which competes for the same binding sites, resulting in an increased free or unbound concentration of the displaced drug. For example, methotrexate is highly bound to plasma protein and may be displaced from protein binding sites by salicylates. As a result, free form of

methotrexate likely increased that may lead to toxicity. None the less, salicylates reduce renal excretion of methotrexate, which is more important mechanism for this interaction (Stewart CF, et al., 1991; Mandel MA, 1976).

1.2.2.3. Drug interactions affection drug metabolism

The main site of drug metabolism is the liver. Metabolism generally converts lipophilic compounds into ionized metabolites for elimination. Drug-metabolizing activity can be classified to Phase I and Phase II reactions:

- Phase I reactions involve oxidation, reduction, and hydrolysis.
- Phase II reactions include conjugation (Wilkinson G, 2005).

The cytochrome P-450 (CYP) family of enzymes plays important role in metabolism, it contains a large number of oxidative enzymes involved in the degradation and biosynthesis of many endogenous substances (e.g. vitamins, lipids steroids) (Wilkinson G, 2005).

These also metabolize ingested substances such as drugs and food; they are divided into families and subfamilies on the basis of the similarity of their amino acid sequences. CYP1, CYP2, and CYP3 are the main sub-families of cytochrome P-450 system which responsible for about 90% of the drug metabolism. Six isoforms, (CYP1A2, YP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) are involved in the metabolism of a large proportion of drugs (Spina E, Santoro V, D'Arrigo C, 2008; Keltner NL, Moore RL2010).

Each enzyme individuals generally have the privacy of the substrate, i.e. drugs metabolized by CYP 2D6 may interact with each other but not with CYP 3A4 drugs, the activity of CYP enzymes is modulated by some factors such as age, diet , gender, use of alcohol or tobacco as well as chronic illness have also been implicated in modulating activity, because CYP function is thus crucial in determining the way a drugs are handled by the body; every new drug is undergo a process of evaluation to determine which, if any, CYP enzymes are include in its metabolism (CPMP/EWP, 2009).

Importance of the CYP system of metabolism for drugs interactions lies in the fact that the activity of CYP enzymes can be blocked (inhibited) or increased (induced) by

certain drugs or exogenous substances, and this results Change in plasma level expected of a drug affected, whenever they are used in association with the inhibiting /inducing substance.

The substrates are normally metabolized by the major isoforms and commonly used inducing and inhibiting substances for each isoform. Usually enzyme inhibition quickly and results in the accumulation happens Drug affected and the risk of toxicity. Enzyme induction may take several days or weeks to achieve maximum effect and reduces efficacy of the affected drug for some time after stood up of the inducer drug (Wilkinson G, 2005).

Examples:- of common substrates, inducers, inhibitors of CYP isoforms

(Baxter K, Lee A, 2008; Wilkinson G, 2005; Tredger JM, Stoll S, 2002)

CYP isoform	Substrate	Inhibitor	Inducer
CYP 3A group (includes 4,5,7)	Atorvastatin, simvastatin Clarithromycin, erythromycin, Losartan, progesteronein Diltiazem, verapamil, nifedipine	Itraconazole, ketoconazole Clarithromycin, erythromycin Diltiazem, verapamil Grapefruit juice	Rifampicin Carbamazepine Phenytoin Phenobarbitol St John's Wort
CYP 2D6	Carvedilol, metoprolol, timolol,Tricyclic antidepressants Codeine, dextromethorphan,	Bupropion, quinidine Cimetidine, amiodarone, sertraline	Rifampicin
CYP 2C9	Diclofenac, ibuprofen, naproxen glibenclamide Warfarin, diazepam	Fluconazole Amiodarone	Rifampicin
CYP 2C19	Diazepam, warfarin	Cimetidine, ketoconazole	Rifampicin

1.2.2.4. Drug interactions affecting excretion

Renal elimination of drugs involves glomerular filtration, tubular secretion, and tubula reabsorption.

Glomerular Filtration

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 highly protein-bound drugs a significant increase in the unbound fraction can lead to an increase in glomerular filtration and subsequent increased drug elimination (Kirby WMM et al, 1971).

Tubular Secretion

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 this drug excretion increasing its concentration, and its toxicity. Two compounds may compete for the same carrier and cause inhibition of secretion of the other, this competition may be used therapeutically, Probenecid is used to block renal tubular secretion of some drugs (e.g. penicillin) and thus prolong its duration, .(Kampmann J et al, 1972).

Tubular Reabsorption

Lipid soluble drugs undergo passive tubular reabsorption from tubular lumen into systemic circulation. Ionized drugs are reabsorbed less than non-ionized drugs, and urine pH can change the reabsorption of weak acids and bases. The excretion of weak bases are increased with urine acidification (i.e. by ascorbic acid and salicylates) and decreased with urine alkalization (i.e. by calcium carbonate, sodium bicarbonate, antacids, and thiazide diuretics); the excretion of weak acids (aminoglycoside, and sulfonamides)is increased with urine alkalization and decreased with urine acidification.(Bendayan R,1996).

1.2.3. Pharmacodynamic Interactions

In pharmacodynamic interactions, the effects (actions of a drug on the body) of one drug will be changed by the presence of another drug at its site of action. In some instances the interacting drugs compete for particular receptors (e.g., beta-2 agonists, such as albuterol, and beta-blockers, such as propranolol). In other situations there will be more indirect reactions occurrence that involves interference with some physiological mechanisms (Corrie K, Hardman JG, 2011; Delafuente JC, 2003), and the classification of these interactions is more difficult as compared with pharmacokinetic interactions. The following classifications are subtypes of pharmacodynamic interactions.

1.2.3.1. Additive or Synergistic Interactions

If the pharmacological effects of two drugs are similar, their co-administration may lead to additive response. For example, excessive drowsiness can be caused by the concomitant use of drugs having CNS depressant properties such as antidepressants, antihistamines, hypnotics, antiepileptic (Patsalos PN, Perucca E, 2003; Burrows GD, Davies B, 1971 Silverman G, Braithwaite R, 1972).

1.2.3.2. Antagonistic or Opposing Interactions

In opposing interactions the drug which has an agonistic action at a receptor type will interact with another drug has antagonistic action at that receptor type. For example, an action of albuterol (a selective beta-2 receptor agonist) is antagonized by propranolol, non-selective beta receptor antagonists (Kroner B, 2002). For example Warfarin produces its anticoagulant which effected by competitively inhibits the effect of vitamin-K. Effect of warfarin is antagonized if the intake of vitamin-K is increased (Juurlink DN, 2007). Other examples include reduction of antihypertensive effect of ACE inhibitors and loop diuretics by NSAIDs (Shionoiri H, 1993); and reduction of blood glucose lowering effects of antidiabetics by glucocorticoids (Lansang MC, Hustak LK, 2011).

1.2.4. Other types of drug interaction

One type of food that classified under food drug interaction known to be clinically important is grapefruit juice (inhibitor of CYP 3A especially in gut) and drugs metabolized by CYP 3A (Kiani J and Imam S, 2007), these results are higher than expected blood levels of certain drugs, e.g. nifedipine which gives a greater than expected response.

Tobacco is inducing CYP1 A2 activity, which may result in lower blood levels than expected of affected drugs (Kroon L, 2007) e.g. when theophylline is prescribed to a smoker, there is a risk of toxicity when the patient stopped smoking unless the dose is reduced, because the plasma levels of theophylline increase. In recently, the risk of herb-drug interactions has been brought to the fore with St John's Wort that is a known inducer of CYP 3A4. Patient taking drug metabolized by this system, run the risk of reduced efficacy if St John's Wort is used at the same time; It was found that this has disastrous consequences for patients with HIV or in post-transplant patients (Izzo AA, 2004). And there have been reports of increased bleeding with the use of concomitant wayfaring with any garlic or Ginkgo biloba (Teeling M, Feely J, 2008).

Alcohol is known to increase the sedative effect of central nervous system depressants and the hypotensive effect of many anti-hypertensive agents (e.g.ß-blockers, ACE inhibitors, calcium channel blockers) (BNF 56, 2008).

1.3. Risk Factors for Drug Interactions

1.3.1. High Risk Patient

What distinguishes a patient who has a greater impact on drug Interactions are age. Certain patient groups, for example, older people may have an increased the risk of drug-drug interactions due to polypharmacy.

It is estimated that of the patients who take medication daily 2-5 incidence of potential drug-drug interaction is 19% this rate rises to more than 80 % of those who drank six or more drugs. Renal or, hepatic impairment, either age-related or otherwise may affect the ability to metabolize drugs (Aust P, 1994; SMRC, 1999; Aust P, 1994), the disease being treated and any concomitant diseases may also influence drug interactions.

1.3.2. High Risk Drugs

Drugs with a narrow therapeutic index:

In this case there is a small margin between Therapeutic drug levels and toxic (e.g. Digoxin, Warfare).

1.4. Consequences of Drug-Drug Interactions

There are 3 possible outcomes when drug-drug interactions occur and they are the following:

1. One drug may intensify the effects of the other.
2. One drug may reduce the effects of the other.
3. The combination may produce a new response not seen when either drug is given alone.

1.4.1. Intensification of Effects

When a patient is taking two medications, one drug may intensify the effects of the other. This type of interaction is often termed potentiative. Potentiative interactions may be beneficial or detrimental. A potentiative interaction that enhances therapeutic effects is clearly beneficial. A potentiative interaction that intensifies adverse effects is clearly detrimental.

Example of increased therapeutic effect:

Sulbactam and ampicillian (antibiotics) represents a beneficial potentiative interaction. When administered alone, ampicillin undergoes rapid inactivation by bacterial enzymes. Sulbactam inhibits those enzymes, and therefore prolongs and intesifies ampicillin's therapeutic effects.

Example of increased adverse effects:

Warfarin and aspirin when taken together represents a potentially detrimental protentiative interaction. Like warfarin, aspirin also suppresses clotting. So if taken at the same time the risk of spontaneous bleeding is significantly increased.

1.4.2. Reduction of effects

Interactions that result in reduced drug effect are often termed as inhibitory.

Example of reduced therapeutic effects:

Albuterol and propranolol represents a detrimental inhibitory interaction. Albuterol is taken by those with asthma to dilate the bronchi. Propranolol (beta blocker) is for cardiovascular disorders and can act in the lung to block the effects of albuterol.

Example of reduced adverse effects:

Naloxone and morphine sulfate is an example of a beneficial inhibitory interaction.

1.4.3. Example of unique response:

The combination of two drugs produces a new response not seen with either agent alone. Alcohol and disulfiram (Antabuse) when taken together many unpleasant and dangerous responses can happen (Engrade,2016).

1.5. How to prevent drug interactions

It is very difficult to remember all known clinically significant interactions and how they occur. However, there some general principles petition, which may be useful for prescribers in order to minimize the risk to the patient.

- There are some computer programs that used to determine and identify DDIs e.g. (drug.com)
- Be aware for drugs known to have a narrow therapeutic index (e.g. anticoagulants, anticonvulsive, agents, digoxin). And also take caution when initiating that a drug or co-prescribing another drug with it.
- Be alert of commonly used drugs known to be enzyme inducers (e.g. Rifampicin) or inhibitors (e.g. verapamil, amiodarone).
- Remember that elderly patients and people with chronic illnesses are at increased risk of drug interactions.
- If there is no possible alternative combination, the patient closely monitored for signs of toxicity or reduced efficacy measure drug levels, (e.g. phenytoin,

lithium) or outcome if possible. Conditioning the relevant dose (s) in accordance with the individual's response.

- Always ask about the use of over-the- counter (OTC) medicines and herbal remedies or alternative.
- Start or stop the medicine is prescribing Resolution, which may lead to drug interactions.
- Dose related events may be managed by changing the dose of the affected drug.
- The potential for the severity of some of the reaction requires immediate Stop combination.
- Time's doses spacing to avoid interaction: For some drugs interactions include binding in the gastrointestinal tract, to avoid one interaction can give medicine object at least 2 hours before or 4 hours after drug precipitant. In this way, the drug object can be absorbed into the circulation before the precipitant drug appears. (General considerations, 2006; . NMIC Bulletin 2000; . Warfarin Taro 20/03/2016).

2. Materials and method

2.1. Study Design

This study was conducted in 32 community pharmacies under the ministry of health in Albyd of Libya. Data were collected from 1369 prescription to patients randomly. Prescription matching inclusion criteria, it was sort prescription that contain a cardiovascular drug and excluded those involving one drug, because that contain a single drug where there is no drug-drug interaction.

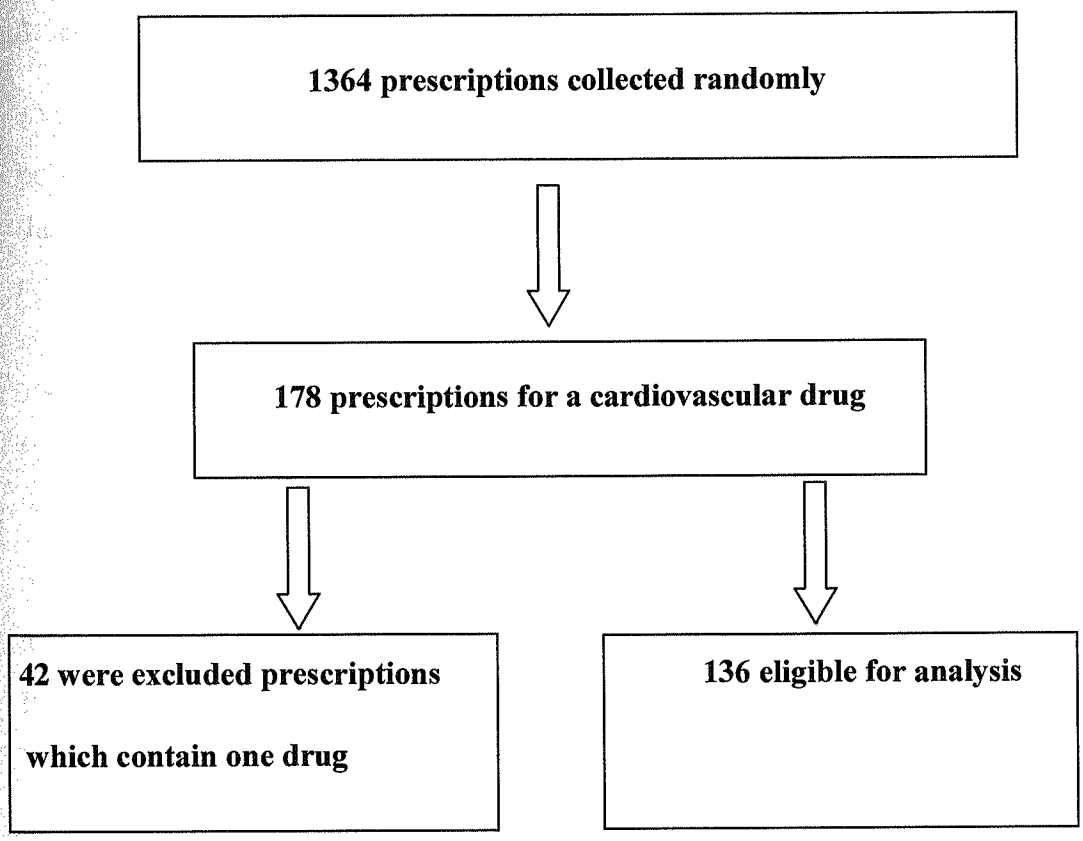
Prescription were retrospectively analyzed for drug-drug interaction using Drugs.com database, there are many drug-drug interaction databases namely Medscape, Lexi-comp, and drugs.com, This study used drugs.com, because its utilized a worldwide a acceptable and validated as found from some related studies (Dalshat, 2015), not only that but also it provides accurate and independent information on more than 24,000 prescription drug, these database are categorized three categories, major interaction is highly clinically significant and this combination should be avoided because the risk of the interaction outweighs the benefits; second one moderate interaction is moderately clinically significant and should be avoided, but may be used only under

special circumstances and the third category minor Interaction is minimally clinically significant.

The main objective of this study is the analysis and the pace of drug interaction in prescription drugs, which include cardiovascular, regardless of whether they actually occurred clinically or consequences of what actually happened actually. This study did not include interaction between drug and complementary, herbal or food.

2.2. Data collection

The prescription was collected from 32 community pharmacies in Albyd of Libya.



Each of the prescriptions analyzed, has all the drug and scheduling in the excel sheet. It was examined interaction with www.drug.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

Ensures secrecy during the study, and moreover gave Privacy persistent patient , Letter of moral clearance was submitted to the Institutional Review Board (RB) of Near East University Hospital The appointment of this research as simply a descriptive study , and therefore do not require seen as immoral. And it used only the initials during the study site without registering any basic clinical data of the patient or other person. Approval letters is given as shown in the Appendix.

3. Results

1364 prescriptions collected and screened for cardiovascular drugs, A total of 178 prescriptions contain cardiovascular drugs, 42 prescriptions contain only one drug, that excluded from the study, and 136 prescriptions of patients using at least one cardiovascular drug that included and analyzed for drug-drug interactions in our study. 103 prescriptions (76.5%) had drug-drug interactions according to drugs.com. There was no significant association of pDDIs with specific gender in our study, 72 (52.9%) patients were male while 64 (47.1%) patients were female, number patients were between 40 and 80 years old of age (Figure 1).

A total number of 230 interactions were noted according to drugs.com. Relevant drug interactions were graded by their level of severity moderate pDDIs were most prevalent 158 (68.70 %) followed by minor pDDIs 67 (29.13%), and major pDDIs recorded in 5 (2.17%) , as shown in Table 2.

In this study there is a significant association between number of drugs and potential DDIs, 68 (50%) patients received 2 drugs, 44 (64.7%) prescriptions had drug interactions, 56 (41.4%) patients received 3 drugs, 47 (83.9%) prescriptions had interactions, patients received 4 drugs or more, all prescriptions had drugs interactions, as shown in Table 2.

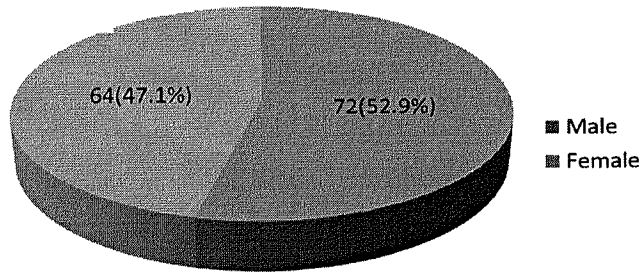
The total interactions according to Drugs.com were 230, 190 (82.6%) were pharmacodynamics interactions and 40 (17.4 %) were pharmacokinetics interactions,

as shown in Table 3. There is positive correlation between age and number of interactions (Figure 2) because of polypharmacy increase in the elderly ($p<0.001$)

The most common interactions were noted between aspirin and diuretics 21(9.13%), of which 17(7.39%) interactions were in-between aspirin and beta-blockers followed by aspirin and enalapril 7(3.03%) respectively.

Figure 1 .Demographic characteristics of patients

A: Gender



B: Age

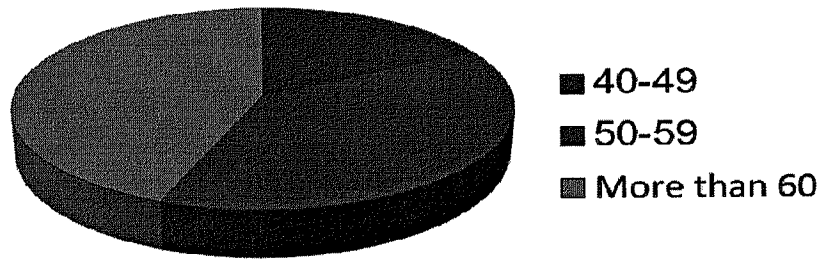


Table.2: Number of interactions according to severity of interactions

Number of drug	Number of prescriptions	Number of prescriptions have interactions	Number of prescriptions no have interactions	Number of interactions	Minor	Moderate	Major
2	68	44 (64.7%)	24 (35.3%)	44	10 (22.7%)	33 (75%)	1 (2.3%)
3	56	47 (83.9%)	9 (16.1%)	124	36 (29.03%)	86 (69.35%)	2 (1.61%)
4	10	10 (100%)	0	50	17 (34%)	32 (64%)	1 (2%)
5	2	2 (100%)	0	12	4 (33.3%)	7 (58.3%)	1 (8.3)
Total	**136**	**103*** **75.73%**	**33**	**230**	**67** **29.13%**	**158#** **68.70%**	**5** **2.17%**

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

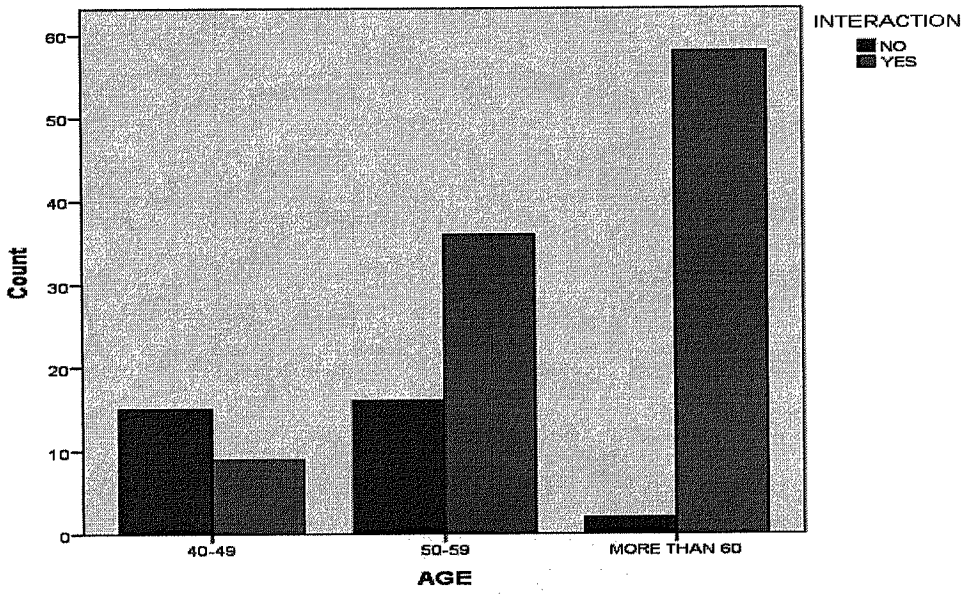
# p <0.001 when compared to other severity of interactions

Table.3: Number of interactions according to the mechanisms and number of drugs.

Number of drug	Number of interactions	Pharmacodynamic	Pharmacokinetic
2	44	39 (88.64%)	5 (11.36%)
3	124	107 (86.29%)	17 (13.71%)
4	50	37 (74%)	13 (26%)
5	12	7 (58.3%)	5 (41.7%)
Total	**230**	**190*** **(82.6%)**	**40 (17.4%)**

* P <0.001 when compared to pharmacokinetic interactions

Figure 2: The number of interactions according to age



There is positive correlation between age and number of interactions because of polypharmacy increase in the elderly ($p < 0.001$).

Table1: Drug interaction, outcomes, clinical significance (Drugs.com) and recommendations.

Drug A	Drug B	Mechanisms of interactions	Outcome of interactions	Clinical significance	Recommendations
Aspirin	Amlodipine	Pharmacodynamic	Moderate	Increase blood pressure	Lowest therapeutic dosage of aspirin and Monitoring blood pressure.
Aspirin	Enalapril	Pharmacodynamic	Moderate	Decrease effect of Enalapril	lowest therapeutic dosage of aspirin and Monitoring blood pressure
Aspirin	Bisoprolol	Pharmacodynamic	Minor	High doses of aspirin`decrease effect of bisoprolol	No need action
Aspirin	Nifedipine	Pharmacodynamic	Moderate	Decrease effect of nifedipine	lowest therapeutic dosage of aspirin and Monitoring blood pressure
Aspirin	Furosemide	Pharmacodynamic	Minor	Decrease effect of Furosemide by aspirin	No need action
Aspirin	Lisinopril	Pharmacodynamic	Moderate	Reduce hypotinsive effect of lisinopril	TDM
Aspirin	Clopidogrel	Pharmacodynamic	Moderate	Leads to bleeding	Monitored closely for signs of bleeding
Aspirin	Telmisartan	Pharmacodynamc	Moderate	Reduce the effects of telmisartan in lowering blood pressure	TDM
Aspirin	Digoxin	Pharmacokinetic	Moderate	Increase plasma digoxin concentrations	TDM
Aspirin	Candesartan	Pharmacodynamic	Moderate	Reduce effect of candesartan	TDM
Aspirin	Carvedilol	Pharmacodynamic	Minor	Reduce effect of carvedilol	No need action
Aspirin	Nitroglycerin	Pharmacodynamic	Minor	Hypotension	No need action
Aspirin	Losartan	Pharmacodynamic	Moderate	Reduce the effects of losartan	TDM

Aspirin	Verapamil	Pharmacodynamic	Moderate	unusual bleeding	TDM
Aspirin	Valsartan	Pharmacodynami	Moderate	Reduce the effects of Valsartan	TDM
Atenolol	Furosemide	Pharmacodynamic	Moderate	hypotension	TDM
Atenolol	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Atenolol	Amlodipine	Pharmacodynamic	Moderate	Decrease blood pressure and heart rate	TDM
Amlodipine	Enalapril	Pharmacodynamic	Minor	Hypotension	No need action
Amlodipine	HCT	Pharmacodynamic	Minor	Hypotension	No need action
Amlodipine	Lisinopril	Pharmacodynamic	Minor	Hypotension	No need action
Amlodipine	Bisoprolol	Pharmacodynamic	Moderate	Hypotension	TDM
Amiloride	**Valsartan**	**Pharmacodynamic**	**Major**	**Hyperkalemia**	**avoid Coadministration**
Bisoprolol	Hydrochlorothiazide	Pharmacodynamic	Moderate	hypotension	TDM
Bisoprolol	Nifedipine	Pharmacodynamic	Moderate	Additive reductions in heart rate, cardiac conduction, and cardiac contractility	TDM
Enalapril	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Enalapril	Hydrochlorothiazide	Pharmacodynamic	Moderate	Hypotension	TDM
Enalapril	Digoxin	Pharmacokinetic	Moderate	Increase the blood levels and effects of digoxin.	TDM
Enalapril	Furosemide	Pharmacodynamic	Moderate	Hypotension	TDM
Enalapril	**Candesartan**	**Pharmacodynamic**	**Major**	**Hypotension, kidney function impairment, and hyperkalemia**	**Generally avoid Coadministration**

Enalapril	Insulin Regular	Pharmacodynamic	Moderate	Hypoglycemic	TDM
Enalapril	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Furosemide	captopril	Pharmacodynamic	Modera	Hypotension	TDM
Furosemide	Ramipril	Pharmacodynamic	Moderate	Hypotension	TDM
Furosemide	Metformin	Pharmacokinetic	Moderate	Increase plasma metformin concentrations	TDM
Furosemide	Lisinopril	Pharmacodynamc	Moderate	Hypotension	TDM
Furosemide	Warfarin	Pharmacokinetic	Minor	Plasma warfarin concentrations and warfarin effects may be increased	No need action
Digoxin	Spironolactone	Pharmacokinetic	Minor	Increase plasma digoxin concentrations	No need action
Digoxin	Lisinopril	Pharmacokinetic	Moderate	Increased plasma digoxin levels	TDM
Digoxin	Ramipril	Pharmacokinetic	Moderate	Increase the blood levels and effects of digoxin	TDM
Digoxin	Furosemide	Pharmacodynamc	Moderate	Hypokalemia and hypomagnesemia	TDM
Digoxin	Telmisartan	Pharmacokinetic	Moderate	Increase the serum concentrations of digoxin.	TDM
Warfarin	Spironolactone	Pharmacodynamc	Minor	Decrease effect of warfarin	No need action
ydrochlorothi azide	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Nifedipine	Simvastatin	Pharmacokinetic	Moderate	Increase the plasma concentrations of simvastatin	TDM
Nifedipine	Lisinopril	Pharmacodynamic	Minor	Hypotension	No need action

Lisinopril	**Telmisartan**	**Pharmacodynamic**	**Major**	**Hypotension, kidney function impairment, and hyperkalemia**	**avoid Coadministration**
Spironolactone	**Candesartan**	**Pharmacodynamic**	**Major**	**Increase potassium levels in the blood**	**avoid Coadministration**
Carvedilol	Spironolactone	Pharmacodynamc	Moderate	Hyprkalemia , hypomrgnesemia and Hypotension	TDM

4. Discussion

One of the definition of drug- drug interactions (DDIs) as a pharmacokinetic or pharmacodynamic is the effects of drugs on each other, which may lead to undesirable effects, and low efficacy or increased toxicity.(Edwards IR& Aronson JK.,2000).

Pharmacokinetic interactions result from changes in a drug's absorption, distribution, metabolism, or excretion. On the other hand Pharmacodynamic interaction is a result of the impact of combined treatment at a site of biological activity and yield altered pharmacological actions at standard plasma concentrations. Although drug interactions happen through an assortment of mechanisms, the effect is the same: the antagonism or potentiation of the effects of drugs.

The important to study came out due to many reports over the world in which the high rate of fatalities, for example the med watch program of Food and Drug Administration reported that there are 6894 fatalities due to adverse drug reactions (ADRs) including DDIs in the United.

Some various studies showed that cardiovascular patients are often reported with DDIs as compared to patients with other diseases (Ismail et al., 2013a,b; Ismail et al., 2012a,b), and the possible reason behind the higher DDI rate in cardiovascular diseases may include multiple drug regimen, elder age, and pharmacokinetic or pharmacodynamic nature of drugs used in cardiology (Faulx &Francis, 2008) becuase cardiovascular drugs are often involve in DDIs (Baxter and Preston, 2010;Mendell et al., 2011).

It was understood that for decades was not easy to identify the effects of DDIs on patients, but, recently the technology allowed to a more thorough understanding of drug-metabolizing is forms and effects in this regard, and there is a large number of drug databases and semi-structured resources which help to know and determine the effects of drug interactions (K. Baxter &Stockley., 2010).

Most of the studies world widely was done for hospitalized patient to measure the incidence of drug- drug interactions but the Studies conducted prescriptions dispensed in community pharmacies very few. The rate and pattern of DDIS in Libya have not been well documented, and little information is available on the strategies that have been used to prevent it.

The primary objective of the study will to be analysis the frequency of drug interactions in prescribed drugs for cardiovascular diseases outpatients in Albyd of Libya. Similarly, studies conducted on prescriptions inpatient , four assess the incidence of potential DDls in prescriptions for all categories of patients in all departments and all varieties of medicines , the average ratio of DDIS potential in these studies was19.2 % (Rafeian M et al. 2001) and the focus was on one study in the development of DDls inpatient children 21 (Valizadeh F et al., 2008) . Both studies reported that the focus on the possibility of DDIS in patients in hospitals in the sections of hematology and oncology in the incidence of 38% and 63%. (Hadjibabaie et al, 2013). Overall prevalence of pDDIs according to drugs.com in this study (76.5%) was higher than that reported by some other studies ranging from 19% to 51% in whole hospital settings(Cruciol-Souza JM, 2006; Zwart-van-Rijkom JEF,2009) 31% to 47% in emergency department(Hohl CM et al., 2001; Goldberg RM et al., 1996); 43% to 60% in internal medicine wards(Vonbach P et al.,2008; Ibanez A .et al., 2008); and 27% to 63% in oncology wards (RiechelmannRPet al., 2005; van-LeeuwenRWet al., 2005).

Many studies support this rate pDDIs high prevalence rate in patients who suffer from cardiovascular disease. These reports have demonstrated that pDDIs are common with cardiovascular (CV) drugs and patients with CV disorders are more likely to be affected by these DDIs because of complex regimens, polypharmacy and comorbid conditions (Straubhaar B et al., 2006; Smithburger PL et a.,l2010).

In this found some of the relevant factors with pDDIs that include patients' age, and polypharmacy.They also found significant associations of pDDIs with various factors in various other studies, and supports our findings with respect to the larger

association pDDIs with patients from other studies also (Bacic-Vrca et al., 2010; Mallet al.,2007). It was reported in this study that old age is a risk factor for pDDIs. A studyconducted at Switzerland in cardiovascular patients also showed that patients with old age were at higher risk for pDDIs (Egger et al., 2007).also found another study conducted in patients taking antihypertensive drugs in edicaid population also found significant association of pDDIs with increase in age (Carter et al., 2002). Patients taking multiple drugs in this study were at higher risk of pDDIs ($p< 0.001$). A study held at Switzerland in a cardiac ward found that incidence of pDDIs increased.

According to another study conducted in the United States in patients with hypertension reported similar association (Carter et al., 2004). other studies have also found similar association of polypharmacy with incidence of pDDIs (Chatsisvili et al., 2010; Cruciol-Souza and Thomson, 2006b; Gagne et al., 2008; Janchawee et al., 2005).

In this study, no statistically significant found on the differences between the gender and DDIS, which Similar to the results of other studies (Ismail et al., 2012b). There are many studies that support our findings. A study In Italy revealed that pDDIs not linked to any specific gender (Nobili et al., 2009).

Also in this study drug screening categories interaction responsible for causing interactions other total of 230 interactions (Drug.com) 40 (17.39) were pharmacokinetics interactions and 190 (82.6) were pharmacodynamics interactions which were comparable to study carried by (Davies EC et al; 2009) the majority were pharmacodynamics (91.7%), pharmacokinetic (5.3%). More than half of the studies have grouped the identified DDIs in terms of severity and report percentage of major, moderate, and minor DDIs separately .The median percentage of major, moderate, and minor DDIs in these studies were 7.7%, 67.4% 24.2% respectively (Riechelmann et al., 2005) which show close comparison to our study in which 67 (29.13%) minor interactions, 158(68.69%) were moderate interactions and 5(2.17%) were major interactions according to drug.com.This study revealed that the overall rate of potential DDIS in cardiovascular patients prescriptions was 76.5%,it was very high should raise some concern, It was found that It has been associated with the occurrence of pDDIs old age and polypharmacy.

5. Strengths and limitations:

To our knowledge, this is the first study to evaluateof drug-drug interactions in prescriptions dispensed cardiovascular diseases patients in community pharmacies at Albyd of Libya. Quality examination we have is that being one of its kind in Albyd of Libya, drug checker first interaction or drug used com is a worldwide accepted and validated well, and drugs, and provides com accurate and independent information on more than 24,000 prescription drugs and medicines without a prescription and natural products.

But though, many limitations had lead less beneficial outcomes for this study, of this, Missing information was a noteworthy limitation particularly data about patient concurrent disease and food intake that's why our study is limited only to drug drug interaction and not drug-disease and drug-food interactions.

our study were limited only to city of Libya and we did not included any patient from other cities. We did not analyze the drug for other group of patients like diabetes mellitus and chronic infections because incidence and pattern of DDIs in Albyd of Libya has not been well documented and little information is available about the strategies that have been used for their prevention.

6. Future Recommendations

- Improve the drug interaction knowledge of health care providers - Improve computerized drug interaction screening systems.
- Provide information on patient risk factors that increase the chance of an adverse outcome.
- Provide information on drug administration risk factors that increase the chance of an adverse outcome.
- Improve patient education on drug interaction.
- Drug products with minimum interacting potentials should be selected.
- Complex regimen should be avoided when possible. An individualized therapeutic Regimen should be selected.
- Patient should be educated regarding the proper use of medications and reporting of adverse outcomes of drug interactions.
- Therapy should be monitored i.e., patients' signs, symptoms and laboratory reports. Should be checked on regular basis.

7. Conclusion

This study revealed that the overall rate of potential DDIS in cardiovascular patients prescriptions was 76.5%,it was very high should raise some concern, It was found that It has been associated with the occurrence of pDDIs old age and polypharmacy Prescription were retrospectively analyzed for drug-drug interaction using Drugs.com data base, total number of interactions were noted according to drugs.com. Relevant drug interactions were graded by their level of severity moderate pDDIs were most prevalent and were pharmacodynamics interactions were most prevalent. Finally, there is a need for more extensive research to identify and reduce the occurrence of associated DDIS factors, design and evaluate the effects of interventions, particularly those that use information technology to increase awareness about DDIs and reduced their incidence. Knowledgeable doctors should be aware of the potential interactions and become substrates, and inhibitors, and inducers of common enzymatic pathways responsible for drug metabolism. By understanding the unique functions and characteristics of CYP enzymes and doctors should be able to anticipate and manage drug interactions. This will enhance the rational use of medicines and treatment for the best drug combinations.

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YAKIN DOĞU ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMALAR DEĞERLENDİRME ETİK KURULU

ARAŞTIRMA PROJESİ DEĞERLENDİRME RAPORU

Toplantı Tarihi : 31.03.2016
Toplantı No : 2016/36
Proje No : 278

Yakın Doğu Üniversitesi Eczacılık Fakültesi öğretim üyelerinden Doç. Dr Bilgen Basgut'un sorumlu araştırmacısı olduğu, YDU/2016/36-278 proje numaralı ve **"Potential drug-drug interactions in prescriptions dispensed cardiovascular diseases patients in community pharmacies in Libya"** başlıklı proje önerisi kurulumuzca değerlendirilmiş olup, etik olarak uygun bulunmuştur.

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