T.R.N.C

NEAR EAST UNIVERSITY
İNSTITUTE OF HEALTH SCIENCES

The Evaluation of Drug interaction in prescriptions dispensed in community pharmacies of Suleymaniyah, North of Iraq

A THESIS SUBMITTED TO THE GRADUATE INSTITUTE OF HEALTH SCIENCES NEAR EAST UNIVERSITY

BY:

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

NICOSIA 2015

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ACKNOWLEDGEMENTS

Millions of thanks to Almighty ALLAH- Who has blessed me with the knowledge and power to perform and complete not only project, but also other tasks and Who has always guided me in difficult times of which I have never imagined in my life.

The love and care that my parent~ and family have been endowing me throughout my life has been a major cause behind my success.

I deeply acknowledge the valuable advices and the guidance provided by my Teacher Prof. Dr Rumeysa Demirdamar regarding the project development.

I am very grateful to my advisor Assoc. Prof. Bilgen Basgut the head of clinical pharmacy and pharmacology department of the faculty of pharmacy at Near East University Cyprus for her encouragement throughout my university Career.

Special acknowledgement to Dr. Abdi Karim Muhammad Daud (PhD scholar) and Dr Syed Sikandar Shah for his major contribution in the completion of this project.

I am also very thankful to Kurdistan Peshmaraga. Finally I am very thankful to Louhai and Ala Sardar and many individual who helped me in the completion of my project, and all my family members and friends for their encouragement and prayer without which nothing would have been possible.

DALSHAD MOHAMED

ABSTRACT

The project titled as "The Evaluation of drug interaction in prescriptions dispensed in community pharmacies of Suleymaniyah, North of Iraq" was conducted in different community pharmacies under the ministry of health at northern Iraq city of Suleymaniyah.

Drug-drug interactions (DDis) are an impoıtant type of adverse drug events. Yet overall incidence and pattern of DDis in North of Iraq 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 was to analyise 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 North of Iraq city of Suleymaniyah.

The study is an observational retrospective study; the prescriptions of 1800 patients were collected and screened for cardiovascular disease patients using at least one cardiovascular related medication. Prescriptions were collected randomly from 50 community pharmacies out of nearly 149 registered pharmacies in the ministry of health at northern Iraq city of Suleymaniyah. 141 prescriptions were retrospectively analyzed for drug-drug interactions using three different drug-drug interaction data bases namely Medscape, Lexi-comp and Drugs.com or Drug Interactions Identifier. Relevant drug interactions were graded.);;;~ their level of severity (major, moderate and minor). Statistic workup is carried using graph pad prism version 6.07 and descriptive methods.

It is concluded that the rate of adverse drug reactions increases exponentially after a patient has been on multiple medications; therefore it is very important to make efforts to reduce polypharmacy, However the number of medications cannot always be reduced without doing harm. This is why the understanding of the basis for drug interactions is so important. Clinicians should be aware of the potential interactions and this will enhance the use of rational drug therapy and better drug combinations.

Key words: DDis, Adverse drug events, prescriptions, cardiovascular drugs, pharmacokinetic, pharmacodynamics.

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S.#	ABBREV ATIONS	EXPLANATION
1	AD Rs	Adverse drug reactions
2	AC Els	Angiotensin converting enzyme ihibitors
3	CYP	Cytochrome P Enzyme
4	CPA	Consumer Protection Act
5	DD Is	Drug drug interactions
6	IRB	Institutional Review Board
7	TDM	Therapeutic Drug Monitoring
8	NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

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Introduction

1.1. Drug Interactions

In brief explanation, drug-drug interactions (DOI) is defined as the effect of one drug altered by another drug due to concurrent or concomitant administration of two or more drugs known as "drug interactions". It can also be defined as the modification of pharmacological activity of one drug by concomitant or concurrent administration of two or more drug is known as "drug interactions".

DDis occur when the effect of one drug is changed by the presence of another drug. The outcome can be harmful if the DOI causes an increased toxicity of the drug .However, a reduction in therapeutic efficacy due to a DOI may be just as harmful as an increase, others can be beneficial and valuable, DDis are rare and therefore we use the expression potential (p) DOI. (Hamilton et al., 1998) pointed out that exposure to DDIs was associated with a significantly increased risk of hospitalization. According to Pirmohamed et al one percent of all hospital admissions were caused by DDls, corresponding to 16% of all patients admitted with ADRs including DDls. (Pirmohamed et al., 1996) In a recent review, incidences of up to 2.8% of hospital admissions were found to be caused by ADRs due to DDIs. (Jankel CA et al., 1993) Lepori et al showed that 21% of all drug-related hospital admissions in a Swiss hospital were caused by DDIs, 1.3% of all admissions. (Lepori et al., 1993)

*1.2. **Risk Factors for Drug Interactions***

In these recent years, the use of medicine has been increased rapidly. It is the modification of the effect of one drug (the object drug) by the prior concomitant administration of another (precipitant drug). Or modification of pharmacological activity of one drug by the concomitant or concurrent administration of two or more drug is known as drug (inter action) cause of 2/3 ADR is drug interaction and drug interaction 4th cause of disease. (Ehne et al,. 1990) declares that drug interaction refer to the ability of one drug to alter the effect of

another. The result of drug interaction synergistic or antagonistic effects may be harmful or beneficial. (Ehne etal,.1990) states some drug interactions beneficial other are harmful .
Two drugs that produce overtly similar· effects will sometimes produce exaggerated or diminished effects when used concurrently. (Tallarida et al., 2000)

A drug interaction is a pharmacological response which cannot be explained by the action of a single drug but may be 'due to two or more drugs acting at the same time however the effects of a drug may also be changed by the presence of food, drink or by some environmental chemical agent. The outcome of a drug interaction may be harmful if the interaction results in increased efficacy or toxicity of one or more drugs. However, reduction in efficacy due to a drug interaction can sometimes be just as harmful. (Johnson et al., 1995) The clinical importance of drug interactions is evident when one considers that up to 8% of hospital admissions are due to adverse drug reactions and over 20% of these are due to drug interactions.(Leape et al. 1995). The incidence of drug interactions is difficult to quantify as this may depend on the "clinical significance" of the interaction. (Johnson et al. 1995) However the greater the number of drugs taken surely increases the risk of a drug interaction occurring.

Several factors may increase the likelihood of a clinically significant drug interaction and include:

A) Drugs with a narrow therapeutic index i.e. where a small margin exists between therapeutic and toxic drug levels.

B) High risk patients. The patient characteristic which has the most attitudes on drug interactions is age. Certain patient groups e.g. the elderly may have an increased risk of suffering a clinically significant drug interaction due to poly-pharmacy. It is likely that for patients taking 2-5 drugs daily the incidence of a potential drug interaction is 19%. This rises to over 80% for those taking 6 or more drugs according to Krahenbuhl et al Renal or in particular, hepatic impairment, either age-related or otherwise may affect the ability to metabolize drugs. Patients with severe underlying disease may be less tolerant of changes in plasma concentration of their therapy (ASHP, 1995). The disease being treated and any concomitant diseases may also influence drug interactions as can the patients pre-existing clinical status.

C) Genetic characteristics relating to approximately 10% of the population, may affect some drug interactions e.g. grapefruit juice and terfenadine resulting in an increased risk of cardio toxicity.

1.3. Mechanism of Drug-Drug Interactions

1.3.1. Pharmacokinetic Interactions

Pharmacokinetic interactions may occur during administration, absorption, distribution, metabolism or elimination of a drug. Interactions Pharmacokinetics is 'what the body does to the drug'. These interactions occur when one drug (the agent) alters the concentration of another drug (the object) with clinical significances. Altered bioavailability this occurs when the amount of the object drug reaching the systemic circulation is affected by a perpetrator drug. For orally administered drugs this occurs when absorption or first-pass metabolism is altered. Drugs with low oral bioavailability are often affected while those with high bioavailability are infrequently affected. (Bend et al., 2012)

1.3.2. Altered clearance

This occurs when the metabolism or excretion of the object drug is affected by a perpetrator drug. Object drugs with a narrow therapeutic index are particularly susceptible, as modest changes in concentration may be clinically essential. Perpetrator drugs known to 'strongly affect drug metabolism are more likely to cause large concentration changes and hence clinical consequences.

1.3.3. Altered distribution

This occurs when the concentration of drug at the site of action is altered without necessarily changing its circulating concentration. This is particularly an issue for drugs with intracellular or central nervous system targets. Some drugs cause significant changes in the cell membrane transport of other drug.

1.3.4. Metabolism

Changes in drug metabolism are the most important causes of surprising drug interactions. These occur by changing drug clearance or oral bioavailability. There are several enzyme families involved in drug metabolism, and the Cytochrome P450 (CYP) enzyme family is the most important. Inhibition of a Cytochrome P450 enzyme increases the concentration of some drugs by decreasing their metabolism. Example; Drug inhibition of Cytochrome P450 enzymes is also used therapeutically. (Smith et al., 1997)

1.3.5. CYP450 Systems

The Cytochrome P450 (CYP) family of hememonooxygenases comprises the most important group of phase 1 enzymes. These enzymes are characterized by a maximum absorption wavelength of 450 nm in their reduced state in the presence of carbon monoxide. The term Cytochrome P-450 refers to a group of enzymes which are located on the endoplasmic reticulum. The metabolic enzymes are also present in high concentrations in the enterocytes of the small intestines with small quantities in extra hepatic tissues (kidneys, lungs, brain etc.). (Einarson et al., 1993)

1.3.6 .Enzyme Inhibition

Inhibition based drug interactions constitute the major proportion of clinically impo~t drug interactions. Drug metabolism by CYP450 can be inhibited by any of the following three mechanisms. The first is mutual competitive inhibition caused by co administration of drugs metabolized by the same CYP450 is enzyme. Inhibition most often occurs as a result of competitive binding at the enzyme's binding site. In this case, blood concentrations of both drugs may be increased. Competitive inhibition depends on the affinity of the substrate for the enzyme being inhibited, the concentration of substrate required for inhibition, and the half-life of the inhibitor drug. The onset and offset of enzyme inhibition are dependent on the half-life and time to steady the state of the inhibitor drug. The time to maximum drug interaction (onset and termination) is also dependent on the time required for the inhibited drug to reach a new steady state. The inhibited drug to reach a new steady state is the enzyme-inhibitor complex. In the case of competitive inhibition by a given concentration ofl

is marked when the substrate concentration is low and becomes less marked with an increase in the substrate concentration.

The second inhibition mechanism, and less common mechanism of inhibition, is the inactivation of CYP450 by the drug metabolite fanning a complex with CYP450. Noncompetitive inhibition' is a pattern of inhibition where the inhibitor binds to the same enzyme as the drug but the binding site is different, resulting in a conformation change of the protein, etc.

The degree of inhibition does not depend on the substrate concentration. The third mechanism of inhibition is the uncompetitive inhibition, a pattern of inhibition where the inhibitor binds only to the enzyme forming a complex with the drug. (Remmer et al., 1966)

1.3.7. Enzyme Induction

Drug interactions involving enzyme induction are not as common as inhibition based drug interactions, but equally profound and clinically important. (Smith et al., 1997) Enzyme induction occurs when hepatic blood flow is increased, or the synthesis of more CYP450 enzymes is stimulated. Like inhibitors, inducers tend to be lipophilic, and the time course of the interaction is dependent on the half-life of the inducer. A complicating factor is that the time course of induction is also dependent on the time required for enzyme degradation and new enzyme production. The half-life of CYP450 enzyme turnover ranges from .l~(days. Enzyme induction is also influenced by age and liver disease. The ability to induce drug metabolism may decrease with age, and patients with cirrhosis or hepatitis may be less susceptible to enzyme induction. (Edwards et al., 2006) The most common mechanism is transcriptional activation leading to increased synthesis of more CYP 450 enzyme proteins. If a drug induces its own metabolism, it is called auto induction. If induction is by other compounds, it is called foreign induction. Metabolism of the affected drug is increased leading to decreased intensity and duration of drug effects. If the drug is a pro-drug or is metabolized to an active or toxic metabolite, then the effect or toxicity is increased. Some drugs-called "enzyme inducers"-are capable of increasing the activity of drug metabolizing enzymes, resulting in a decrease in the effect of certain other drugs. Examples of enzyme inducers include aminoglutethimide, barbiturates, carbamazepine, glutethimide, griseofulvin, phenytoin, primidone, rifabutin, rifampin, and troglitazone. Some drugs, such as ritonavir,

may act as either an enzyme inhibitor or an enzyme inducer, depending on the situation. Drugs metabolized by CYP3A4 or CYP2C9 are particularly at risk to enzyme induction. In some cases, especially for drugs that undergo extensive first-pass metabolism by CYP3A4 in the gut wall and liver, the reduction in serum concentrations of the object drug can be profound. Some drugs are converted to toxic metabolites by drug metabolizing enzymes. For example, the analgesic acetaminophen is converted primarily to non-toxic metabolites, but a small amount is converted to a cytototoxic metabolite. Enzyme inducers can increase the formation of the toxic metabolite and increase the risk of hepatotoxicity as well as damage to other organs. (Lehne et al., 2007)

1.1.3.1.Pharmacodynamic Interactions

Pharmacodynamics i.e., "what the drug does to the body'. These interactions occur between drugs with improver or opposite effects. The brain is the organ most commonly cooperated by pharmacodynamics interactions. Pharmacodynamics interactions between drugs with additive effects may be intentional. Combining drugs with differing effects can result in loss of drug effect. •

Additive: An effect in which two substances or action used in which two substances or actions used in combination produce total effect the as sum of the individual effects

Synergistic: The use of two or more drugs that produce a greater effect of one drug used alone.

Antagonistic: The use of second drug reduces the effects of another. The second drug has an antagonistic effect. The second drug may bind to the same receptor as the first drug, thus preventing the agonist response. (Bend et al., 2012)

1.4. Consequences of Drug-Drug Interaction

I Increase in toxicity.

2. Decrease effectiveness.

3. Organ damage especially kidney damage and liver.

4 Increase cost.

From a pharmacokinetic angle, the major effects of drug-drug interactions can be understood in terms of causing the quality of drug to be abnormally slow or fast. The major consequence is a high or low plasma and tissue level of the drug. If the metabolism of drug impeded due to enzyme inhibition, then a high plasma level of the drug may be follow. One of the major effects will be increased- pharmacological activity, and this may or may not be a problem, depending on the therapeutic window. Of course not only the desired effect may be increased but also the undesirable side effect. If activation of pro-drug is inhibited, then a lower level of therapeutic effectiveness might be estimated. Another possibility is that when the major pathway of metabolism of drug is blocked, secondary pathway may become more favorable. This can be a problem if the secondary path way leads to a toxic production. Another possibility is that the increased level of a drug due inhibition of the P450 involved in its oxidation may lead to inhibition of another P450. Although direct evidence for such a situation has not been presented. When level of P450 (or for that matter another enzyme) is induced, the major consequence is a lack of therapeutic effectiveness. Although this might seem to be a common event, the number of real clinical situations in which this has been a problem is rather limited. Another possibility with a pro-drug is that activation may be too rapid and seriously high level of active drug could result. this could be problem, as one of the primary reasons for developing pro-drug is to avoid transiently high level of active drug .however no good example of clinical problems resulting from a phenomenon- of this type are known yet. There are two other possibilities that can be considered in regard to issues of drug-drug interactions. One involves P450 are induced or inhibited by drug and then cause decrease or increase the effective of the substrate. (Lehne et al., 2007)

2. Rational Drug Use

The concept of rational drug use during the past few years has been the topic of various state & worldwide. Various studies conducted in developed as well as in developing countries during past few years regarding the safe & effective use of drugs show that irrational drug use is a global phenomenon & only few prescriptions justify rational use of drugs.

2.1.3. Definition

In simplest words rational use means "prescribing right drug, in adequate dose for the sufficient duration & appropriate to the clinical needs of the patient at lowest cost. The concept of rational drug use is age old, as evident by the statement made by the (Alexandrian physician Herophilus 300 B.C) that is "Medicines are nothing in them but are the very hands of god if employed with reason & prudence."

Rational drug use attained more significance nowadays in terms of medical, socio economical and legal aspect. Factors that have led sudden realization for rational drug use are.

1. Drug explosion - Increase in the number of drugs available has incredibly complicated the choice of appropriate drug for particular indication.

2. Efforts to prevent the development of resistance - Irrational use of drugs may lead to the early end of highly effective & lifesaving new antimicrobial drug due to development of resistance.

3. Growing awareness: - Today, the information about drug development, its uses & adverse effects travel from one end of the earth to the other end with amazing speed through various media.

4. Increased cost of the treatment - Increase in cost of the drug increases economic burden on the public as well as on the government. This can be reduced by rational drug use.

5. Consumer protection Act. (CPA):- Extension of CPA in medical profession may restrict the irrational use of drugs.

2.1.4. Reasons for Irrational Use of Drugs

1. Lack of information - Unlike many developed countries we don't have regular capacity which provides us up to date unbiased information on the currently used drugs. Majority of our practitioners rely on medical representatives. There are differences between pharmaceutical concern & the drug regulatory authorities in the interpretation of the data related to indications & safety of drugs.

2. Faulty &inadequate training & education of medical graduates - Lack of proper clinical training regarding writing a prescription during training period, dependency on diagnostic aid, rather than clinical diagnosis, is increasing day by day in doctors.

3. Poor communication between health professional & patient - Medical practitioners & other health professional giving- less time to the patient & not explaining some basic information about the use of drugs.

4. Lack of diagnostic facilities/Uncertainty of diagnosis - Correct diagnosis is an important step toward rational drug therapy. Doctors posted in remote areas have to face a lot of difficulty in reaching to a precise diagnosis due to non-availability of diagnostic facilities. This promotes poly-pharmacy.

5. Demand from the patient - To satisfy the patient expectations and demand of quick relief, clinician prescribe drug for every single complaint. Also, there is a belief that "every ill has a pill" All these increase the tendency of polypharmacy.

6. Defective drug supply system & ineffective drug regulation - Absence of well-organized drug regulatory authority & presence of large number of drugs in the market leads to irrational use of drugs.

7. Promotional activities of pharmaceutical industries: The satisfying promotional programs of the various pharmaceutical industries influence the drug prescribing. Dean Bet al., 2000)

2.1.5. Consequences of Irrational Drug Use

Irrational use of drugs may lead to:

1. Ineffective & unsafe treatment.
2. Exacerbation or prolongation of illness.
3. Distress & harm to patient.
4. Increase the cost of treatment.

2.1.6 The Importance of Drug Interactions in Rational Drug Use

It is well accepted that the promotion of rational drug use lead to improvements in the quality and efficiency of healthcare services.

Rational drug use require patient receives medications appropriate to their clinical needs in dose that meet their own individual requirement for an adequate period time and at lowest cost to them and their community.(Einarson et al., 1993)

So the main points that must be met to ensure rational drug therapy are:

1. Right patient.
2. Right diagnosis,
3. Appropriate dose.
4. Appropriate dosage form.
5. Appropriate route of administration.
6. Appropriate duration of treatment.
7. Appropriate information to the patient.
8. Adequate follow up.

Or simply meaning prescribing the right drug in adequate dose for the sufficient durfil'ionand appropriate to the clinical needs of the patient at lowest cost.(Fattinger Ket al.,2000)

3. Materials and methods

1.1 Study Design :

The study is an observational retrospective study; the prescriptions of 1800 patients were collected and screened for cardiovascular disease patients using at least one cardiovascular related medication. Prescriptions were collected randomly from 50 community pharmacies out of nearly 149 registered pharmacies in the ministry of health at northern Iraq city of Suleymaniyah.

Prescriptions matching inclusion criteria; that contain at least one cardiovascular related medication were included; prescriptions containing only one drug were also excluded since there is no pair of medications to be compared with. Prescriptions were retrospectively analyzed for drug-drug interactions using three different drug-drug interaction data bases namely Medscape, Lexi-comp and Drugs.com Drug Interactions Identifier.

The main research questions addressed were:

- Frequency of DDI in patients using cardiovascular medications in Suleymaniyah of north Iraq
- Types of DDIs occurring, there severity and risk factors associated
- Efficacy of three different DOI databases in identifying DDIs

Relevant drug interactions were graded by their level of severity (major, moderate and minor) with categories of minor interaction if the risk of the adverse outcome appeared small, moderate interaction if the administration of the drug was avoided unless it was determined that the benefit of the administration outweighed the risk and major interaction if an interaction that would likely require a change in therapy or use of additional clinical or laboratory monitoring.

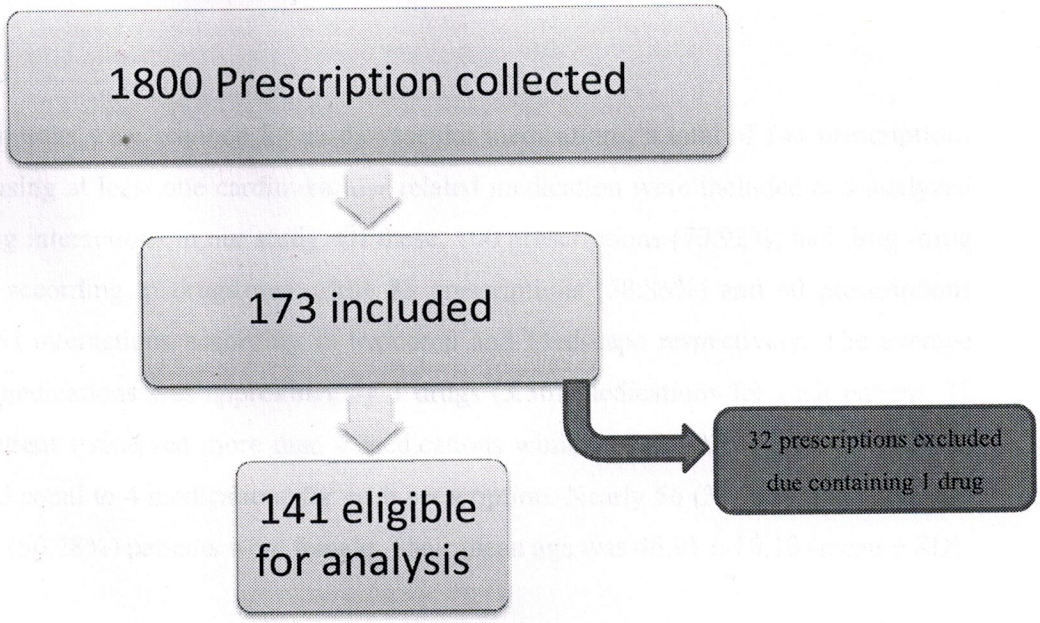
The primary objective of the study was to analyise the frequency of drug interactions in prescribed drugs for cardiovascular diseases patients regardless of whether they :~ally occurred clinically or their consequences that happened actually. Other objectives were to correlate the frequency of drug interactions with demographic features of patients, and to identify risk factors for such interactions. This study did not cover potential interactions between drugs and complementary/alternative medications, herbs, or food. Nor the clinical impact of these interactions were recorded or found in registry.

1.2 Data collection

Prescriptions were collected from 50 community pharmacies at Suleymaniyah city the second capital city of north of Iraq, available data on prescriptions included selected patient

demographics, physician identification, and the name, strength, and quantity of the medications dispensed.

A drug- drug interaction was defined- by the following definition: a "pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the 2 agents when given alone. The clinical result of a drug-drug interaction may manifest as antagonism, synergism, or idiosyncratic.



For each of the prescriptions analyzed, all drugs were tabulated and inserted in an excel sheet Interactions were screened with three different data bases manually.

Statistical analysis

The values are given as a percentage of total interactions. Chi square test or fisher's exact test was used as an appropriate for categorizing the Data. $P < 0.05$ was accepted as statistically significant.

1.3 Ethical Considerations:

Confidentiality was guaranteed during the study and furthermore patient's persistent privacy, a Letter of moral clearance was submitted to 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. Just Initials were utilized during the study without recording patient's location or other related not clinical essential individual data.

Results

1800 prescriptions were scanned for cardiovascular medications, a total of 141 prescriptions of patients using at least one cardiovascular related medication were included and analyzed for drug-drug interactions in our study. Of these, 100 prescriptions (70.92%) had drug -drug interactions according to drugs.com while 83 prescriptions (58.86%) and 60 prescriptions (42.55%) had interactions according to lexicomp and Medscape respectively. The average number of medications was approximately 3 drugs (3.36) medications for each patient. 31 (21.98%) patient's received more than 4 medications while 110 (78.02%) patients received less than and equal to 4 medications for each prescription. Nearly 56 (39.71%) patients were male and 85 (60.28%) patients were female. Their mean age was 46.91 ± 10.10 (mean± SD).

A total number of 202 interactions were noted according to drugs.com while the number of interactions which were evaluated according to lexicomp and Medscape were 135 and 116 respectively.

Relevant drug interactions were graded by their level of severity. 42 (20.79%) were minor interactions, 152 (75.24%) were moderate interactions and 8 (3.96%) were major interactions according to drug.com as shown in Table no 2. According to lexicomp 7 (5.18%) were minor interactions, 119 (88.14%) were moderate interactions and 9 (6.66%) were major interactions. Similarly 110 (88.79%) were moderate interactions followed by 10 (8.62%) minor interactions followed by 3 (2.58%) according Medscape respectively.

According to our prescriptions drugs.com provided significantly higher number of interactions when it was compared with other data bases (Lexicomp and Medscape). Depend on that we used drugs.com for evaluating the mechanism of interactions.

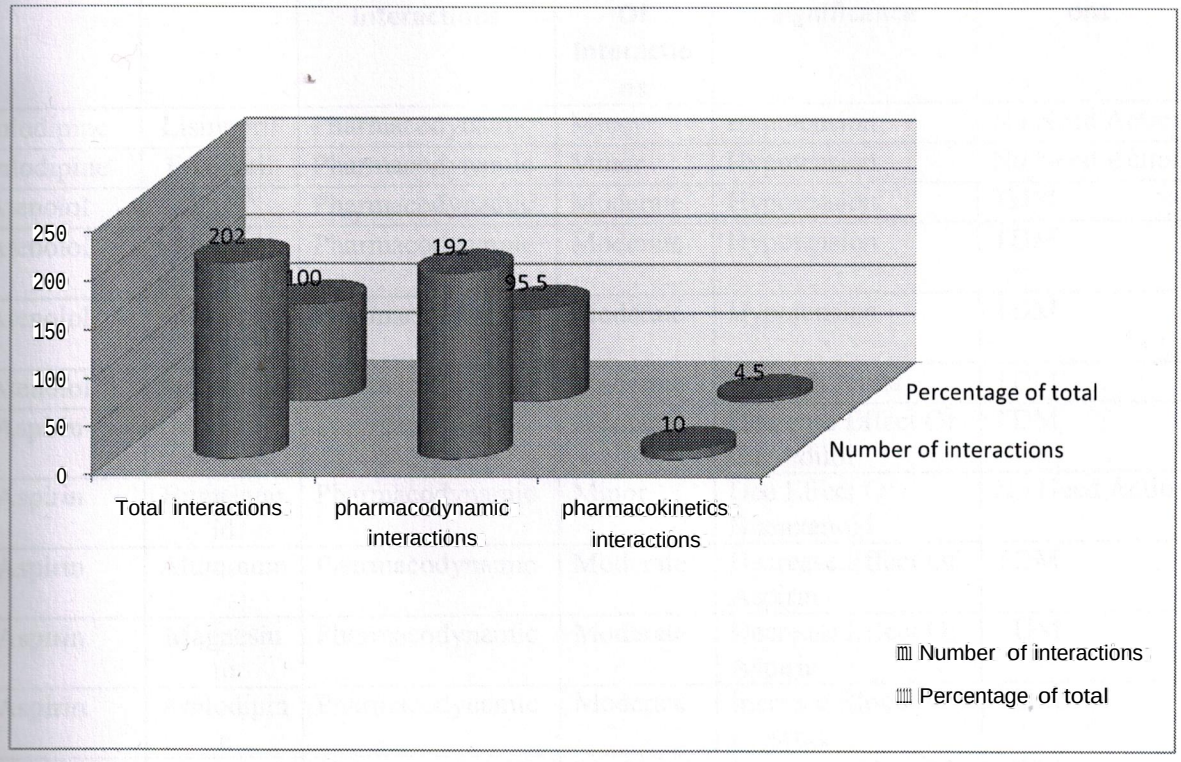
Table.1 Number of interactions according to severity of interactions with different databases

Table.1 Number of interactions according to severity of interactions with different databases

Name of Database	Number of prescriptions with interactions	Total number of interactions	Minor interactions	Moderate interactions	Major interactions
Drugs.com	100****	202	42**	152*	8
Lexicomp	83	135	07	119	9
Medscape	60	116	10	103	3

Number of prescriptions with interactions according to Drugs.com having **** $p<0.0001$, **<O.Ol, *$p<0.05$ were considered statically significant having when compared to all other groups.

Figure L'The **number of interactions according to mechanism of drug interactions (Drugs.com)**



Pharmacodynamics interactions having ****p<0.0001 were considered significa~JŞ-higher than pharmacokinetics interactions according to Drugs.com.

Of the total of 202 interactions (Drug.com) 10 (4.95%) were pharmacokinetics interactions and 192 (95.5%) were pharmacodynamics interactions as shown in figure 3. The most common interactions were noted between aspirin and diuretics 27 (13.36%), of which 16 (59.25%) interactions were in-between aspirin + enalapril followed by aspirin + captopril 7 125.92%) respectivdy.

Table2. Drug interactions, Outcomes, Clinical significance (Drugs.com) and Recommendations

Drug A	Drug B	Mechanisms Of Interactions	Outcome Of Interactions	Clinical Significance	Recommendations
Amlodipine	Lisinopril	Pharmacodynamic	Minor	Hypotension	No Need Action
Amlodipine	Enalapril	Phannacodynamic	Minor	Hypotension	No Need Action
Atenolol	HCT	Pharmacodynamic	Moderate	Hypotension	TDM
Atenolol	Candesartan+ HCT	Phannacodynamic	Moderate	Hypotension	TDM
Atenolol	Amitriptyline	Pharmacodynamic	Moderate	Hypotension	TDM
Atenolol	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Aspirin	Carvedilol	Phannacodynamic	Moderate	Decrease Effect Of Carvedilol	TDM
Aspirin	Bumetanoid	Phannacodynamic	Minor	Dec Effect Of Bumetanoid	No Need Action
Aspirin	Aluminum	Phannacodynaınic	Moderate	Decrease Effect Of Aspirin	TDM
Aspirin	Magnesiuın	Pharmacodynamic	Moderate	Decrease Effect Of Aspirin	TDM
Aspirin	Amlodipine	Pharmacodynamic	Moderate	Increase Blood Pressure	TOM
Aspirin	Glimepiride	Pharmacodynaınic	Moderate	Increase Effect Of Glimepiride	TOM
Aspirin	Valsartan	Pharmacodynamic	Moderate	Reduce Effect Of Valsartan In Lowering Blood Pressure	TDM
Aspirin	Glimepiride	Pharmacodynamic	Moderate	Increase Effect Of Gliınepiride	TDM
Aspirin	Lisinopril	Pharmacodynamic	Moderate	Reduce Hypotensive Effect Of Lisinopril	TOM
Aspirin	Carvedilol	Pharmacodynamic	Minor	Decrease Effect Of Carvedilol	No Need Action
Aspirin	Losaıtan	Phannacodynamic	Moderate	Decrease Effect Of Losartan	TOM
Aspirin	Clopidogril	Pharmacodynarnic	Moderate	Leads To Bleeding	TDM
Eaalapril	Aspirin	Pharmacodynamic	Moderate	Decrease Effect Of	TDM

				Enalapril	
Enalapril	Metformin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Enalapril	Amiloride	Pharmacodynamic	Moderate	Hyperkalemia	TDM
Enalapıil	HCT	Pharmacodynamic	Minor	Hypotension	No Need Action
Enalapril	Diltiazem	Pharmacodynamic	Minor	Hyperkalemia	No Need Action
Enalapıil	Glyburide	Pharmacodynamic	Moderate	Hypoglycemia	TOM
Enalapril	(Magnesium Salicylate	Phannacodynamic	Moderate	Reduce Effect Of Enalapril	TDM
Enalapıil	Amitriptyl ime	Pharmacodynamic	Moderate	Hypotension	TOM
Enalapril	Prednisolo ne	Pharmacodynamic	Moderate	Reduce Effect Of Enalapril	TOM
Enalapril	Oigoxin	Pharniacokinetic	Moderate	Increase Concentration Of Digoxin In Blood	TDM
Enalapril	Oexameth asone	Pharmacodynamic	Moderate	Reduce Effect Of Enalapril (Cause NaAndH20 Retention	TDM
Enalapril	Piro xi cam	Pharmacodynamic	Moderate	Increase Adverse Toxic Effects Of NSAIDs	TDM
HCT	Omeprazo le	"Pharmacodynamic	Moderate	Hypomagnesaemia	TDM
HCT	Carvedilol	Pharmacodynamic	Moderate	Hypotension And Bradycardia	TDM~
HCT	Glimepiri de	Pharmacodynamic	Moderate	Reduce Effect Of Glimepiride	TDM
HCT	Sitagliptin	Pharmacodynamic	Moderate	Reduce Effect Of Sitagliptin	TDM
HCT	Lansoprazole	Phannacodynamic	Moderate	Hypomagnesaemia	TDM
HCT	Metoprolo 1	Phannacodynamic	Moderate	Hypotensive And Bradycardia And Increse Risk Of Hyper Glycaemia	TOM
\	\\C1	G\~b\\ü(le	\l\.\affi\aCCKl'jl\'affi\C	Mackrate	Reduce Effect Of Glyburide	1'DM
	HCT	Metfonnin	Phannacod ynamic	Moderate	Reduce Effect Of Metformin	TDM
L	HCT	Glimepiri de	Phannacod ynamic	Moderate	Reduce Effect Of Glimepiride	TOM

HCT	Carvedilol	Pharmacod ynamic	Moderate	Carvedilol(Hyper kalemia) And HCT (Hypokalemia)	TDM
HCT	Cholecalci ferol(D3)	Pharmacodynamic	Moderate	Hypercalcemia	TDM
HCT	Glimepiri de	Phannacodynamic	Moderate	Decrease Effect Of Glimepiride	TDM
Omeprazole	Glyburide	Pharmacokinetic	Minor	Hypoglycemia	No Need Action
Omeprazole	Glyburide + metformin	Phannacokinetic	Minor	Hypoglycemia	No Need Action
omeprazole	Clopidogri l	Pharmacokinetic	Major	Decrease Anti Platelet Effect Of Plavix	Change Therapy
Omeprazole	Ciprofloxa cm	Pharmacodynamic	Minor	Reduce Effect Of Ciprofloxacin	No Need Action
Atorvastatin	Omeprazo le	Pharmacokinetic	Major	Increase Blood Level Of Atorvastatin(Liver Damage)	Change Therapy
Piroxicam	Amlodipin e	Pharmacodynamic	Moderate	Reduce Effect Of Amlodipine	TOM
Piroxicam	Valsartan	Pharmacodynami c	Moderate	Reduce Effect Of Valsartan	TOM
Diltiazem	Atorvastat in	Pharmacokinetic	Moderate	Oiltiazem May Increase Blood Level Of Atorvastatin Cause Liver Damage And Rhabdomylosis	TDM
Magnesium	Clopidogri l	Pharmacodynamic	Moderate	Unusual Bleeding	TOM
Metoprolol	Magnesiu m	Phannacod ynamic	Minor	Reduce Effect Of Metoprolol	No Need Action
Phenyltoloxami ne	Tramadol	Phannacodynamic	Moderate	Respiratory-Depressant	TDM
(Magnesium Salicylate	Aluminu ill Hydroxide	Phannacod ynamic	Moderate	Reduce Effect Of Magnesium Salicylate	TDM
Aluminum Hydroxide	Ranitidine	Pharmacokinetic	Minor	Reduce Concentration Of Rani tidine	No Need Action
Lansoprazole	Atorvastat in	Pharmacokinetic	Moderate	Increase Concentration Of Atorvastatin	TDM

Sitagli ptin	Glimepiri de	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Ooxycycline	Rifampici n	Pharmacokinetic	Moderate	Reduce The Serum Concentration Of Ooxy Cycline	TDM
(Magnesium Salicylate	Ooxye yeli ne	Pharmacodynamic	Moderate	Reduce The Effect Of Doxycycline	TOM
Phenyltoloxam ime	Tram ado!	Pharmacodynamic	Moderate	Respiratory-Depressant	TOM
Metoprolol	(Magnesiu m Salicylate	Pharmacodynamic	Moderate	Reduce Effect Of Metoprolol	TOM
Rifampicin	Tramadol	Phaımacokinetic	Moderate	Reduce Effect Of Tramadol	TDM
Phenyltoloxam ime	Amitriptyl ime	Pharmacod ynamic	Moderate	Increse Side Effect Such As (Dry Mouth)Heatintolear nee)	TDM
Carvedilol	Enalapril	Pharmacodynamic	Moderate	No	TDM
Metoprolol	Glyburide	Pharmacodynamic	Moderate	Increase Risk Of Hypoglycemia	TDM
Metformin	Metoprolo l	Pharmacodynamic	Moderate	Increase Risk Of Hypoglycemia	TDM
Furosemide	Omeprazo le	Phaımacodynamic	Moderate	Hypomagnesaemia	TDM
Metoprolol	Valsartan	Pharmacodynamic	Moderate	Increase Morbidly And Mortality	TOM
Captopril	Magnesiu m	Pharmacodynamic	Minor	Do Not Usually Cause Harm	No Need Action
Captopril	Aluminum	Pharmacodynamic	Minor	Do Not Usually Cause Haım	No Need Action
Dexamethason e	Albuterol	Pharmacodynamic	Minor	Additive Hypokalemia	No Need Action
Ciprofloxacilin	Metoprolo l	Pharmacokinetic	Minor	Increase Metoprolol Concentration	No Need Action
Melatonin	Chlordiaz epoxide	Phaımacodynamic	Minor	Enhancement Of Sedation And Impairment Memory	No Need Action
Metoprolol	Chlordiaz enoxide	Pharmacodynamic	Moderate	Hypotension	TOM
Furosemide	Enalapril	Pharınacod ynarnic	Moderate	Hypo tension	TDM

Lisinopril	Mixtard Insulin	Pharmacodynarnic	Moderate	Hypoglycemia	TDM
Propranolol	Carbarnazepine	Pham1acodynamic	Moderate	Hypotension	TDM
Propranolol	Carbimazole	Pham1acodynarnic	Moderate	Hypotension	TDM
Metformin	Valsartan + hydro cholorothiazide	Pharmacodynamic	Moderate	(HCT) Increase Blood Sugar Level	TDM
Valsartan + hydro cholorothiazide	Enalapril	Pharrnacodynamic	Moderate	Hypotension (Hyperkalemia)	TDM
Lisinopril	Amiloride	Pharmacodynamic	Major	Hyperkalernia	Change Therapy
Captopril	Aspirin	Phannacodynamic	Moderate	Diminish Effect Of Enalapril	TDM
Atorvastatin	Clopidogril	Pharmacodynamic	Moderate	Reduce Effect Of Clopidogril	TDM
Furosemide	Digoxin	Pharmacodynamic	Moderate	Hypokalernia Hypomagnesaemia	TDM
Spironolactone	Candesartan	Pharmacodynamic	Major	Hyperkalemia	Change Therapy
Bunıetanoid	Carvedilol	Pharmacodynamic	Moderate	Hypotension	TOM
Spironolactone	Carvedilol	Phannacodynarnic	Moderate	Hypotension	TDM
Furosemide	Diazepam	Pharmacodynamic	Moderate	Hypotension	TDM
Furosenıide	Carvedilol	Phannacodynamic	Moderate	Hypotension	TDM
Diazepanı	Carvedilol	Phannacodynamic	Moderate	Hypotension	TDM
Lisinopril	Candesartan	Phannacodynamic	Major	Hyperkalemia, Hypotension	Change Therapy
HCT	Lisinopril	Pharmacodynamic	Major	Hypotension	Change Therapy
Diltiazem	Lisinopril	Pharmacodynamic	Minor	Hypotension	No Need Action
Candesartan	Aspirin	Phannacodynamic	Moderate	Reduce Effect Of Candesartan	TDM
Ramipril	Metfonnin	Pharmacodynamic	Moderate	Hypoglycemia	TDM
Lisinopril	Metformin	Phannacodynamic	Moderate	Hypoglycemia	TDM

Ranitidine	Metformin	Phannacodynamic	Minor	Increase Effect Of Metformin	No Need Action
Levothyroxine	Omeprazole	Phannacodynamic	Minor	Decrease Concentration Of Levothyroxine	No Need Action

TDM .... Therapeutic drug monitoring

HCT ..... Hydrochlorothiazide

NSAIDs ... Non-steroidal anti- inflammatory drugs

Similarly common interactions 18 (8.91%) were also noted between anti diabetics and diuretics, of which 11 (61.11%) interactions were in-between HCT (Hydrochlorothiazide) + metformin followed by 07 (38.88%) between HCT and Glimepiride.

Discussion

DDis occur when the effect of one drug is changed by the presence of another drug. The outcome can be harmful if the DDI causes an increased toxicity of the drug .However, a reduction in therapeutic efficacy due to a DDI may be just as harmful as an increase, others can be beneficial and valuable, DDis are rare and therefore we use the expression potential (p) DDI. Hamilton et al Pointed out that exposure to DDis was associated with a significantly increased risk of hospitalization. Drug-Drug interactions are associated with potential severe events and even death. These can be prevented with rational prescribing and the knowledge of the untoward effects which occurs secondary to these. Drug interaction mechanisms are divided into two main types, phannacodynamics and pharmacokinetics depending on the principles that determine drug behavior in human body. (Baxter k, 2006)

Pharmacodynamics interactions include mechanisms where the effect of one drug is altered by a second drug at its site of action without changes in the drug concentration. These interactions can result in antagonistic, synergistic or additive effects. (Pinnohamed Met al., 1998)

Pharmacokinetic interactions include mechanisms where the absorption, distribution, metabolism or excretion of one drug is altered by a second drug, and results in changes in the

drug concentration. (Hans ten P et al, 201 0). A large proportion of potentially clinically significant drug interactions are reported to occur by alterations in the drug metabolism through inhibition and induction of enzymes and drug transport proteins in the liver. (Faber KN et al, 2003). The outcome of changed metabolism depends on the drug, for instance inhibition of an active drug can Jead to rises in the concentration to toxic levels, while for a pro-drug that is activated via the enzyme inhibition can lead to reduced efficacy. Among the most important enzymes involved in the metabolism are cytochrome P450 enzymes (CYP). They are responsible for the metabolism in approximately 50% of drugs used clinically. (Sjöqvist F et al, 2008). Simply we can say that the effects of the drug combination may be: synergistic or additive; antagonistic or reduced; or altered or idiosyncratic, and it may result in beneficial effects or adverse reactions.

The drug-drug interactions are classified as mild, moderate and severe according to their severity and undesirable effects. Mild drug-drug interactions limit the clinical effects. The manifestations include an increase in the frequency or the severity of the adverse effects, but these usually do not require a change in the therapy. Moderate drug-drug interactions may result in exacerbation of the disease of the patient and/or a change in the therapy. The severe drug-drug interactions are life threatening and/or they require medical treatment or an intervention to minimize or to prevent the severe adverse effects.(ASHP, 1995).

The result of drug interaction synergistic or antagonistic effects may be harmful or beneficial. Two drugs that produce overtly similar effects will sometimes produce exaggerated~ diminished effects when used concurrently. (Tallarida et al, 2000). The clinical importance of drug interactions is evident when one considers that up to 8% of hospital admissions are due to adverse drug reactions and over 20% of these are due to drug interactions. The incidence of drug interactions is difficult to quantify as this may depend on the "clinical significance" of the interaction. (Johnson JA et al, 1995).However the greater the number of drugs taken surely increases the risk of a drug interaction occurring. Several factors may increase the likelihood of a clinically significant drug interaction and include: Drugs with a narrow therapeutic index i.e. where a small margin exists between therapeutic and toxic drug levels. A high risk patient, the patient characteristic which has the most attitudes on drug interactions is age, renal or hepatic impairments or other particular diseases. Genetic characteristics relating to approximately 10% of the population, may affect some drug

interactions e.g. grapefruit juice and terfenadine resulting in an increased risk of cardio toxicity (Bates DW et al, 1997). Drug-drug interactions may leads to Increase of toxicity, decrease effectiveness, Organ damage especially kidney damage and liver and increase cost. Drug -drug interaction have been reported to account for 14% of all hospitalized admission and been described as a fourth to "seven leading cause .of deaths in Sweden and in the united states and it leads to a mean length of hospital stay of 6-13 days and therefore also more expensive.

(Mjörndal T et al, 2002). In Germany, drug related hospital admissions were estimated to cost an average of 3700 euro per stay and 2200 euro per single drug-related problem in Sweden (Schneeweiss et al, 2002).

Similarly the studies performed on inpatient prescriptions, four assessed the overall incidence of potential DDIs in prescriptions for all groups of patients in all departments and for all drug classes, the median incidence of potential DDIs in these studies was 19.2% (Rafeian Met al, 2001). The focus of one study in inpatient setting was on pediatric patients DDIs were 21 %.(Valizadeh F et al, 2008). The two studies that focused on potential DDis in hospitalized patients in the hematology and oncology departments reported the incidence of 38% and 63%. (Hadjibabaie et al, 2013).

Among the studies performed in outpatient settings, nine studies assessed the overall incidence of potential DDIs in prescriptions in the population for all types of drugs. Ourc' study show that (70.92%) of prescriptions had drug -drug interactions according to drugs.com which were comparable to study carried in Iran which show an incidence of (88.5%) potential DDis in prescriptions. According to Johnell K et al drugs that have been reported to be involved in potential drug-drug interactions (45%) are cardiovascular agents (including enalapril, digoxin, ramipril, furosemide and spironolactone) which also show comparison to our results which were 59%. In contrast another study conducted by Ebrahim et al show an evidence of potential drug-drug interaction due to NSAIDs were (49%) which show variation from our study in which most common interactions were noted due to NSAIDs were (13.36%).

The goal of the present study was to quantify the prevalence of drug interactions in the former scenario. The frequency of potential drug interactions encountered in this study (63% of patients) is of concern at northern Iraq city of Suleymaniyah, as an example of a

developing country. This is the first review study that summarizes the available evidence of DDis in outpatients in northern Iraq. Our study concur with the past studies did on the same subject with slight variations inside of the outcomes. A study by von Euler M et al showed that females have been reported to experience more ADRs than males which were not comparable to our results which showed that males experienced more drug-drug interactions (85.71 %) as compared to female (63.5%). Specific groups such as elderly, elderly with cognitive impairment and individuals with specific diseases such as renal failure are also more likely to experience ADRs. Our study also examined drug interaction categories responsible for causing ADRs.Of the total of 202 interactions (Drug.com) 10 (4.95%) were pharmacokinetics interactions and 192 (95.5%) were pharmacodynamics interactions which were comparable to study carried by Davies EC et al, the majority were pharmacodynamics (91.7%), pharmacokinetic (5.3%). In another small study investigating ADRs leading to hospital admissions, all drug interactions assessed as responsible for the ADR were pharmacodynamics. (Stanton LA et al, 2010). In our study the average number of medications was approximately 3 drugs (3.36) medications for each patient. 31 (21.98%) patient's received more than 4 medications while 110 (78.02%) patients received less than and equal to 4 medications for each prescription which were comparable to study by Ehsan et al, in which mean number of drug for the outpatient setting was 3.16 in 2010, respectively, and 17% of these prescriptions involved more than four drugs in those years.More than half of the studies have grouped the identified DDis in terms of severity and reported the percentage of major, moderate, and minor DDis separately. (Ehsan et al, 2011). The median percentage of major, moderate, and minor DDis in these studies were 7.7%, 67.4%, and 24.2% respectively which show close comparison to our study in which 42 (20.79%) were minor interactions, 152 (75.24%) were moderate interactions and 8 (3.96%) were major interactions according to drug.com.

Considering the data obtained and analyzed from the prescription by the specialist doctors, it's found out that, the drugs interaction, in prescription of internal medicine is relatively higher due to high number of disease for example hypertension as so on, so many drugs prescription may lead to lots of side effect, the second cause is irrational use of drugs by patients. Bate et al, (1995) stated that drug-drug interaction occur when two or more drugs are taken in combination that lead to change in the activity of either or both drugs and lack

cordial relationship between the doctors and pharmacy, lack of the use of drug interaction checker. Duke et al, (1998) claimed that the drug interaction checker should be used when patient use drug. Magnus et al, (2002) stated that computerized alert would be the most effective strategy for preventing drug-drug interaction. Moreover, the case is also true in gynecology, due to the fact that, woman are more susceptible to be infected with infections disease because of their body physiology, therefore, the gynecologist may prescribed more drugs in one prescription which will increase the interaction .but in case of dentistry and dermatology, the drug interactions is relatively less compared to the previously discussed, because of small number of drugs that is normally prescribed for such a diseases like dentistry "and dermatology.

Strengths

This study, evaluating the practical example of drug-drug interaction (Drug.com) at northern Iraq city of Suleymaniyah which is the first study of its kind in North of Iraq. The quality of our examination lies in that beside of being the first of its kind in North of Iraq, the Drug interaction checker or Drug.com utilized is a worldwide acceptable and well validated and Drugs.com provides accurate and independent information on more than 24,000 prescription drugs, over-the-counter medicines and natural products. Beside these we screened more than 1800 prescriptions of patients due to which the number of samples were also more compared to the numbers enrolled in other comparable studies. Similarly most of the studies were done for hospitalized patient to measure the incidence of drug-drug interactions but in our study we retrospectively analyzed the prescriptions of inpatients which are one of the most basic advantage compare to other studies carried out on the same topic. Furthermore, Prescriptions were retrospectively analyzed for drug-drug interactions using three different drug-drug interaction data bases namely Medscape, Lexi-comp, and Drugs.com (Drug Interactions Identifier).

Limitations

This study had. a few limitations. 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. Beside this, our study were limited only to city of suleminayah and we did not included any patient from other cities of north of north of Iraq. We did not analyze the rational use of drug for other group of patients like diabetes mellitus and chronic infections; furthermore, we did not analyze the incidence of actual DD Is & we did not include results of the unpublished studies (e.g. dissertations and conference papers) in the review. This may affect our estimations. Finally, some of the included studies in our review had small sample sizes that might have led to bias. These may have limited the generalizability of our results .

Suggestions from this study:

Due to the lack of studies addressing potential DD1s among northern Iraqian patients, the incidence of adverse events caused by this type of medication errors remains unknown. It is. recommended that future DDis researches investigate the adverse events of DD1s through closely monitoring the patients who are provided with potentially interacting drugs. The prescribers should be aware of the high incidence of DDls in their prescriptions. The prescribers in all health facilities should be advised to use generic name of drug in prescriptions, to prescribe the lowest number of drugs and to avoid symptomatic treatment. They also need to pay attention to patients who are frequently prescribed potentially interacting drugs (e.g. digoxin, beta blockers, NSAIDs, ACEis, and diuretic agents). In the absence of studies assessing communication among the drug management team (physician, nurse, and pharmacist), it is suggested that future studies delve into aspects of this communication. Better communication between the team members could lead to a safe pharmacotherapy plan and reduce the risks of adverse events caused by DDis. In recent years, information technology interventions have been employed to improve medication safety and shown to be effective in reducing the number of potential DD Is. The ministry of public health and population should supervise, monitor and give feedback to health workers, by developing and implementing interventions about drug use in general and prescribing in

particular in order to improve prescribing practices and rational use of drugs. We suggest designing and evaluation of such information technology interventions. Software and computer program can aid prescriber in detecting and managing drug-drug interactions prior to their prescribing, this is recommended here in case of North of Iraq

Conclusion

It is well known that the rate of adverse drug reactions increases exponentially after a patient has been on multiple medications; therefore it is very important to make efforts to reduce polypharmacy. However the number of medications cannot always be reduced without doing harm. This is why the understanding of the basis for drug interactions is so important.

There is a small number of studies on potential DDIs in north of Iraq. The included studies in this review had relatively poor quality and were heterogeneous in their methodologies and reporting. However, almost all studies concluded that the incidence of DDIs in both inpatient and outpatient settings is high. Despite this high incidence, there are a limited number of interventional studies aimed at reducing DOis incidence. Finally, more extensive research is needed to identify and minimize the factors associated with the incidence of DOis, and to design and evaluate the effects of interventions especially those that utilize information technology to increase awareness about DOis and decrease their incidence by the drug management team.

Clinicians should be aware of the potential interactions and become familiar with the substrates, inhibitors, and inducers of the common enzymatic pathways responsible for drug metabolism. By understanding the unique functions and characteristics of CYP enzymes, physicians will be able to anticipate and manage drug interactions. This will enhance the use of rational drug therapy and better drug combinations.

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