NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF CLINICAL PHARMACY

EVALUATION OF POTENTIAL DRUG-DRUG INTERACTION IN THE INTENSIVE CARE UNIT AT AL METHNAB GENERAL HOSPITAL IN AL-QASSIM REGION, SAUDI ARABIA

M.Sc. THESIS

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Approval

We certify that we have read the thesis submitted by Alaa Harmoush titled "**Evaluation of Potential Drug- Drug Interaction in the Intensive Care Unit at Al Methnab General Hospital in Al-Qassim region, Saudi Arabia"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Health Sciences.

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Declaration

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

Alaa Harmoush

29/06/2021

DEDICATION

I am grateful to Almighty Allah for giving me so many blessings the knowledge, wisdom, and strength.

It is with genuine gratitude and warm regard that I dedicate this thesis to my loving parents, Hisham Harmoush and Ayat Wannos whose words of encouragement and push for tenacity ring in my ears. My sister Doha was my inspiration to pursue my master's degree. My brothers Gafaar, Hamzah, Hadi and Mustafa have never left my side.

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Alaa Harmoush

ABSTRACT

Evaluation of Potential Drug-Drug Interaction in the Intensive Care Unit at Al Methnab General Hospital in Al-Qassim region, Saudi Arabia

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Critically ill patients are often administered multidrug regimens to provide the best effective pharmacotherapeutic support. Drug-drug interaction (DDI) occurs as a result of polypharmacy therapy and can lead to treatment failure or death.
***Aim*:** This study aims to assess the frequency of DDIs, mechanism and severity of interaction in patients at intensive care unit at Al Methnab General Hospital.

Method: A retrospective observational study was conducted in the Intensive Care Unit (ICU) for a period of 35 months from 01 January 2018 to 30 November 2020 in Al Methnab General Hospital, for all patients who admitted to the (ICU). Five different drug-drug interaction checker databases were used to check DDIs; Lexicomp, Micromedex, Drug.com, Medscape and Epocrates. A Pearson Chi square test was performed to evaluate the associations between categorical variables. The level of significance was defined as ($\alpha = 0.05$).

Result: Out of 524 patients, 314 patients match the inclusion criteria and screening for DDI in five different tools was carried, Micromedex recorded (231, 73.6%) patients have interactions while Lexicomp recorded (256,81.5%) patients, Drugs.com recorded (284, 90.4%) and in Epocrates and Medscape (275,87.6%), (283,90.1%) patients' interactions, respectively. Most of interactions were pharmacodynamic. There was a significant association with the occurrence of DDIs and factors such as age, gender, number of the number of administered drugs, Length of Stay (LOS) and the patient outcomes.

Conclusion: We found that ICU patients have a high risk of occurrence Drug-drug interactions. Clinical pharmacists have an essential role to play in reducing the incidence of DDIs, and the medical community as a whole should pay attention to this issue.

Key words: drug-drug interactions, intensive care unit ICU, clinical pharmacist.

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Abbreviations

Abbreviations	Explanation
ADEs	Adverse Drug Events
ADR	Adverse Drug Reaction
ARDS	Acute Respiratory Distress Syndrome
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CPOE	Computerized Physician Order Entry
CVP	Central Venous Pressure
CYP450	Cytochrome P450 Monooxygenase
DDIs	Drug-Drug Interactions
DI	Drug Interaction
DRPs	Drug-Related Problems
ECG	Electrocardiogram
FDA	Food and Drug Administration
FFP	Fresh Frozen Plasma
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
LMWH	Low Molecular Weight Heparin

LOS	Length of Stay
ME	Medication Error
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PD	Pharmacodynamic
PDDIs	Potential Drug-Drug Interactions
PEG	Percutaneous Endoscopic Gastrostomy
PICC	Peripherally Inserted Central Catheter
PK	Pharmacokinetics
PRBC	Packed Red Blood Cells
SPSS	Statistical Package of Social Sciences

CHAPTER I
INTRODUCTION

1.1 Background

Drug interactions represent a significant and widely under recognized source of medication errors.

An interaction occurs when the effects of one drug are altered by the presence of another drug, herbal medicine, food, drink, or some chemical factor in the environment. (Baxter, 2010) Drug interactions can reduce the effectiveness of a drug, induce unexpected adverse effects, or increase the efficacy of a particular medication. (FDA, 2004)

Drug interactions fall into three broad categories:

Drug-drug interactions: occur when two or more drugs react with each other.

Drug-food/beverage interactions: result from drugs reacting with foods or beverages.

Drug-condition interactions: may occur when an existing medical condition makes certain drugs potentially harmful. (FDA, 2004)

If the interaction increases the toxicity of the drug, the consequence can be hazardous. A decrease in efficacy as a result of an interaction might sometimes be just as damaging as an increase. The phrase 'drug interaction' is also used to describe the physicochemical interactions that occur when medications are combined with intravenous fluids, resulting in precipitation or inactivation. (Baxter, 2010)

These unwanted interactions are harmful and undesirable, but there are certain interactions that can be beneficial and valuable, such as the deliberate co-prescription of antihypertensive medications and diuretics to produce antihypertensive effects that may not be possible with either medicine alone. (Baxter, 2010)

Drug interactions are an avoidable cause of patient harm. Drug interactions should be considered both in the differential diagnosis of symptoms (for interactions that have already occurred) and when prescription changes are made (for potential interactions).

Software checkers for drug interactions are widely available, but have limited clinical utility.

Routine care includes monitoring patients for drug toxicity or loss of efficacy.

Checking for changes in symptoms, biomarkers of effect, or medication concentrations shortly after a prescription modification aids in the early detection of drug interactions and reduces harm. (Merlo et al., 2001)

In clinical practice, there are five "rules" for managing potential drug-drug interactions:

1. Any existing drug interactions in a specific patient have already occurred. As a result, they are included in the differential diagnosis.
2. Combining knowledge of drug pharmacological effects and patient physiology enables the detection of probable pharmacodynamic drug-drug interactions.
3. Drugs having a narrow therapeutic index are more vulnerable to pharmacokinetic drug-drug interactions.
4. A small number of drugs are important ‘perpetrators’ of pharmacokinetic drug-drug interactions.
5. A prescription decision to start or stop a medicine can result in a drug interaction.

2.1 Aim of The Study

The majority of probable drug interactions can be recognized by applying clinical pharmacology concepts and appropriate clinical care. Increased vigilance by physicians and clinical pharmacists while changing medications improves the chance of detecting undesirable drug interactions before they cause serious harm. Knowing a few medicines well and making judicious use of available information is more beneficial than relying entirely on computerized decision support for managing drug interactions. (B.D. et al., 2012)

CHAPTER II
LITERARURE REVIEW

2.1 Drug-related problems

According to pharmaceutical care network of Europe (PCNE), DRP is defined as, “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (PCNE V9.1, 2020)

DRP became an area of interest when cases of aplastic anemia were reported following the use of chloramphenicol and congenital malformations following thalidomide treatment in 1960. (MacTavish et al, 2020)

Patients with polypharmacy and comorbidities are considerably more likely to develop DRPs. As a result, particular care is required to prevent DRPs in these patients. (Hailu et al., 2020)

DRPs have been linked to higher healthcare costs and hospital admissions, as well as longer hospital stays, lower quality of life, and higher mortality. (Naples et al., 2016)

To resolve DRPs, the cause must be recognized and the DRPs must be categorized appropriately. The classification of DRPs is critical for this reason. DRPs are classified in several ways. However, there is no single standardized classification in the world. (Basger et al., 2015)

Because it is updated and amended on a regular basis, the PCNE classification system is widely used and has improved usability and internal consistency. It is critical for DRP documentation in the pharmaceutical care process. (Van Mil et al., 2004)

Identifying, resolving, and preventing DRPs has been recognized as a critical process in pharmaceutical treatment. Clinical pharmacists are appropriately qualified to conduct medication reviews in patients, and they have been shown to improve the usage of high-risk drugs as well as the accuracy of prescription regimens. (Weddle et al., 2017)

Experience from developed countries has demonstrated that incorporating clinical pharmacists in patient care and clinical pharmacist intervention resulted in lower DRPs and associated costs. (Martínez et al., 2015)

DRPs include medication errors (MEs), adverse drug events (ADEs) and adverse drug reactions (ADRs). (Deax et al., 1995) DRP is further subdivided into intrinsic

and extrinsic toxicity. The interaction of the pharmaceutical chemical and/or pharmacological properties of the medication itself with the human biosystem is referred to as intrinsic toxicity or ADRs. (Edwards & Aronson, 2000) On the contrary, Extrinsic toxicity, often known as MEs, refers to difficulties produced by inappropriate drug usage, whether by a healthcare practitioner or a patient. (Resar, R. K., Rozich, J. D., Simmonds, T., & Haraden, 2006)

The patient has been harmed as a result of a medication in ADR and ADE. In more depth, ADR is damage from dosing that is "commonly used in humans", whereas damage related to any dose of a drug is ADE, whether that dose is "commonly used in humans" or not. So ADR is a subtype of ADE. (Aseeri et al., 2020) These terms have more precise definitions in Table 1, and their relationship is shown in Figure 1.

Definitions of DRPs are shown in Table I, and the relationships between these terms are given in Figure I.

Table 1 Definitions of drug-related problems

Drug-related problem	An event or condition concerning medication therapy that actually or potentially interferes with expected consequences. (Luz et al., 2015)
Medication error	Any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not (Puccini et al., 2019)
Adverse drug reaction	Any harmful and unanticipated response to a medicine that occurs at levels commonly used in humans for prophylaxis, diagnosis, or therapy, or for the alteration of physiological function, provided that this noxious response is not the result of a medication error. (Brouwers, 2000)
Adverse drug event	An injury related to the use of a drug, although the causality of this relationship may not be proven (Cortes et al., 2020) (Kang et al., 2020)

Medication errors are defined as problems that involve a mistake in the process from the prescribing to the administration of the drug (Puccini et al., 2019). Problems that occur even when no errors have been made in the process of drug distribution are

called ADRs (Brouwers, 2000). Adverse drug events (ADEs) are defined as problems related to the use of a drug, but without evidence of the causality (Puccini et al., 2019).

Despite these definitions, the term "ADR" is used in the literature (e.g. (Tchambaz et al., 2005))– and also in our studies – as a more general term. Consequently, DRPs due to medication errors such as drug-drug interactions (DDIs) are included in the definition of an ADR.

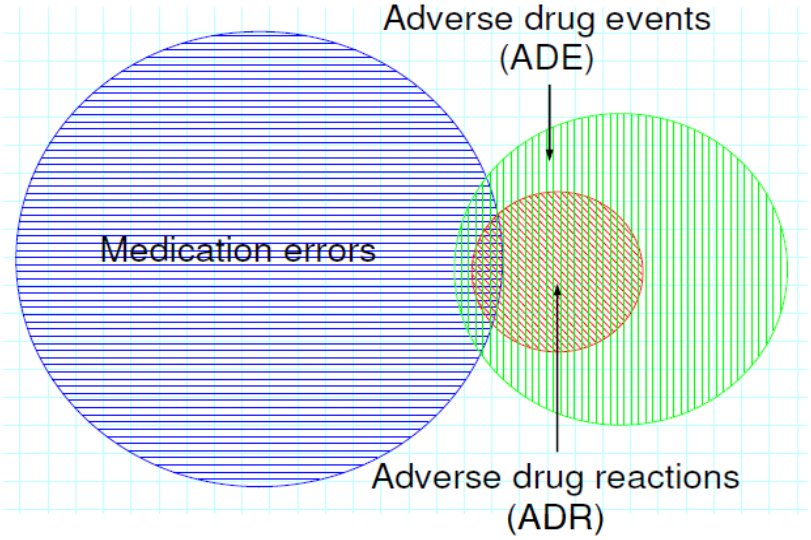

Figure 1 Relationship between the terms medication errors, adverse drug reactions and adverse drug events (according to (Tchambaz et al., 2005))

Drug-induced morbidity has become a widespread issue that imposes a significant financial burden on society. (Ernst & Grizzle, 2001) . According to Classen et al., ADEs dramatically lengthen hospital stays, increase treatment costs and increase risk of death by nearly twofold. (Pestotnik et al., 2015). Some studies suggest that medication errors or ADRs cause between 7,000 and 100,000 deaths annually in the United States (Tong et al., 2021). According to Lazarou et al., ADRs are the fourth to sixth largest cause of death in the United States. (Costa et al., 2021).

The subject of drug-drug interactions (DDIs) has gained a great attention recently from the scientific, regulatory, and health care communities around the world. (Iviacgregor et al., 1971).

Drug interaction was described as a clinically significant change in the effect of one drug caused by the coadministration of another. Potential drug interaction was

defined as the simultaneous administration of two medications known to interact, regardless of whether adverse outcomes occurred. Drug interactions can be generally classified as pharmacokinetic (the delivery of one drug to its site of action is influenced by another) or pharmacodynamic (response of the one drug is modified by the other without changes in the pharmacokinetics of the first drug). (Hines & Murphy, 2011)

Although some drug interactions may be employed for therapeutic purposes, others may increase the effects of a medicine, resulting in toxicity. Patients on statins, for example, face a significant increase in the risk of severe muscle damage if they begin taking azole antifungals. (Baxter, 2010)

Or inhibit the effects of a drug, leading to a diminished therapeutic benefit, Patients taking warfarin who are given rifampicin (rifampin) require more warfarin to maintain adequate anticoagulation, whereas patients taking 'tetracyclines' or 'quinolones' must avoid antacids and milky foods (or separate their ingestion) because admixture in the gut can reduce or even abolish the effects of these antibacterial. (Baxter, 2010)

2.2 Adverse Drug Reactions

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "an unintended and harmful reaction suspected to be caused by a drug taken under normal conditions." (Dey et al., 2018)

ADRs have been identified as a substantial public health issue all over the world. It is estimated that approximately 2 million significant ADRs occur among hospitalized patients in the United States each year, resulting in over 100,000 fatalities. (Dey et al., 2018)

According to national USA Vital Statistics System statistics, the rate of ADR-related mortality increased from 0.08 to 0.12 per 100,000 people between 1999 and 2006. A study of 22 observational studies conducted in European countries discovered a similarly wide range of ADRs leading to hospitalization, ranging from 0.5 percent to 12.8 percent. (Formica et al., 2018)

A major study of nearly 20,000 patients admitted to hospital in the United Kingdom discovered that ADRs cause an average of eight additional days of hospitalization and cost around € 706 million each year, including ADRs deemed potentially

preventable. (Pirmohamed et al., 1998)

Preventable ADRs can occur as a result of medication errors, drug interactions, underlying diseases, or patient characteristics (idiosyncratic reactions and allergies, including unintended effects occurring at recommended doses), errors in prescribing or dispensing, poor adherence, and poor patient safety monitoring. (Report, 1997)

Detecting probable adverse drug reactions (ADRs) in drug candidates early in the development process can improve drug safety, reduce patient risks, and save money for pharmaceutical corporations. (Dey et al., 2018)

2.3 Medication Errors

Medication errors (MEs) are an important part of DRPs. Medical error is defined as an unintentional act (whether by omission or commission) or an act that does not achieve the expected result, failure to achieve a planned act as expected (an error of execution), the use of an incorrect plan to achieve a goal (an error of planning), or a deviation from the treatment process that may or may not harm the patient. Patient harm due to medical error can occur on an individual level as well as on a system level. The role of error can be complex. While many errors are insignificant, one error can end the life of someone with a long-life expectancy or hasten their imminent death. (Makary & Daniel, 2016)

Health care delivery is not infallible. Errors are prevalent in most healthcare systems and are considered to be the seventh leading cause of mortality in the World. (Rockville, 2000)

The high percentage of medication errors in hospitals is a well-known and important issue of patient safety. Longer hospital stays, higher costs, substantial morbidity, and even mortality have all been associated with medication errors. (Prgomet et al., 2017)

The Institute of Medicine (IOM) highlighted the significance of this problem in 1999, when its report, "To Err is Human: Building a Safer Health System," called public attention to the importance of patient safety. The medical community reacted with great awareness to this. (Kohn et al, 1999)

The annual global cost of medication errors is estimated to be $42 billion. (World Health Organization, 2017) Medication errors, for example, cause injury to at least 1.5 million people in the United States each year. (Aspden, Wolcott, Bootman, & Cronenwett, 2007). They have been recognized as an issue in Turkey as well. (Unes,

2014)

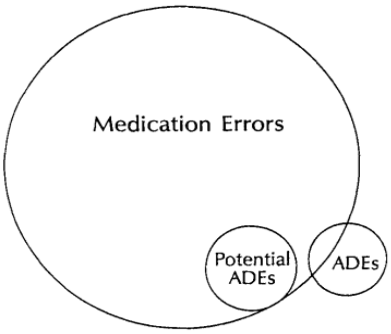

Figure 2 The relationship between MEs, ADEs, and potential ADE (Falconer, 2019)

2.3.1 Classification of medication errors

To give an inpatient a single dose of a drug, 80 to 200 distinct processes must be completed correctly.

Prescription, transcription, preparation, dispensation, and administration are the five basic stages of hospital medicine utilization. An error can occur at any point in this process. A medication error is any error in the medication process, regardless of whether there are negative effects or not. The majority of errors happen during the administration stage (median of 53% of all errors), followed by prescription (17%), preparation (14%), and transcribing (11%). (Moyen et al., 2008)

2.3.1.1 Prescribing errors: are errors that occur in the selection and prescription of a drug, as well as in monitoring therapy. Administrative and procedural errors, dosage errors, and therapeutic errors are the three types of prescribing errors. (Franklin & Puaar, 2020)

Administrative and procedural errors:

- General (readability)
- Patient data (patient mix-up)
- Ward data and prescriber data
- Drug name
- Dosage form and route of administration (Paul MacDowell, Ann Cabri, 2013)

- **Dosage errors:**

- Strength
- Frequency
- Dosage too high/low
- No maximum dosage in “at need” prescription
- Length of therapy
- Directions for use (Al-Ramahi et al., 2017)

- **Therapeutic errors:**

    - Indication
    - Contra-indication
    - Monitoring
    - Drug-drug interaction
    - Incorrect monotherapy
    - Duplicate therapy (Hayes et al., 2009)

2.3.1.2 Transcription errors: These errors can occur when transcribing or interpreting a medicine prescribed by the physician. (Shawahna et al., 2019) (Kelly, 1995)

2.3.1.3 Dispensing errors: Dispensing error can occur at any stage of the dispensing process (from obtaining the prescription in the pharmacy to supplying a dispensed medicine to the patient). (James et al., 2009)

Dispensing errors are classified to:

- Wrong drug
- Wrong dosage form
- Wrong strength
- Wrong time

2.3.1.4 Administration errors: An administration error occurs when the drug received by the patient differs from the prescription medication. These errors are committed by nurses or doctors in the hospital, or by patients in the outpatient sector (non-compliance). (Koyama et al., 2020)

Classification of administration errors:

- Omission
- Unordered
- Wrong preparation
- Wrong dosage form
- Wrong route of administration
- Wrong administration technique
- Wrong dosage
- Wrong time (at least 60 minutes early or late)
- Compliance/adherence (Chua et al., 2009)

Dean et al. investigated the causes of prescribing errors and discovered that the majority of errors were caused by lapses in attention or by prescribers omitting relevant rules. Workplace, workload, whether they are prescribing for their own patient, communication within their team, physical and mental well-being, and a lack of expertise were all highlighted as risk factors by physicians. Inadequate training, a low perceived relevance of prescribing, a hierarchical organization of the medical team, and a lack of self-awareness were also recognized as system problems. (Dean et al., 2002)

2.3.2 Medication errors in Intensive Care Units (ICUs)

Medication errors are more prevalent among patients in intensive care units (ICUs), where critically ill patients are prescribed twice as many medications as patients outside of intensive care units (ICUs). (Moyen et al., 2008)

This is due to the criticality of the patients in these units, the broad, dynamic, and complex pharmacotherapy used to treat them, and the service organization (excessive care burdens, communication issues, frequent staff changes, etc.), all of which is compounded by the urgency of the work required done in these units. (Ohta et al., 2014)

Intensive care units (ICUs) are particularly prone to error and their repercussions, which can be inherently hazardous to ICU patients. Critically ill patients admitted to the ICU accumulate an average of 1.7 medical errors daily, and many patients experience possibly life-threatening errors during their hospital stay. The most common type of error in the ICU is medication errors, which account for 78 percent of major medical errors. (Tully et al., 2019) Up to 70% of prescription errors are

detected by nurses and pharmacists. (Leape et al., 2013)

Potassium chloride, heparin, magnesium sulfate, vasoactive medicines, sedatives, and analgesics were identified as the medications having the highest risk of errors in multicenter studies. (Ridley et al., 2004) Antibiotics are commonly provided empirically in the ICU, and errors can have serious consequences for both individual patients and the population. (Kollef et al., 1999)

Patients are provided these drugs in a stressful, complex, challenging environment that is stewardship by several professionals and who often treat patients in crisis. (Kane-gill & Weber, 2006)

It's imperative to remember that critically ill patients have fewer defenses than other people. They have little participation in their medical treatment and lack the physiological reserve to sustain further harm. (Moyen et al., 2008)

2.4 Drug-drug Interactions

DDIs occur when the effects of one drug are altered by the presence of another drug. The result can be detrimental if the DDI increases the toxicity of the drug. A decrease in therapeutic efficacy caused by a DDI, on the other hand, may be just as damaging as an increase. When oral anticoagulants are taken with an inducing drug, for example, an unintentional decrease in anticoagulation is noticed. While such a DDI is undesirable, others, such as the co-prescription of antihypertensive medicines and diuretics to achieve a greater antihypertensive impact, can be helpful and valuable. (Shaik et al., 2016)

Because epidemiological data on the unfavorable clinical outcome of DDIs are few, we employ the expression potential (p)DDI. According to Hamilton et al., exposure to pDDIs was related with a considerably higher risk of hospitalization. (A. Hamilton, 1998). According to Pirmohamed et al., DDIs were responsible for 1% of all hospital admissions, which equates to 16% of all patients admitted with ADRs (including DDIs) (Pirmohamed et al., 2004). According to a recent study, ADRs related to DDIs are responsible for up to 2.8 percent of hospital admissions. (Janke & Fitterman, 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 V,1999)

2.4.1 Risk factors for drug-drug interactions

2.4.1.1 Patient-related factors:

Polypharmacy: Disease therapy is typically accompanied by the use of multiple drugs; nevertheless, this may raise the risk of DDIs. (Moriarty et al., 2018). According to recent sources in the United States, the number of people who take three or more prescription medications has risen from 11.8% in 1988–1994 to 20.8% in 2007–2010. In addition, the number of people taking five or more medications has risen from 4.0% to 10.1% during this period. (Percha & Altman, 2013)

According to Goldberg et al., patients taking two drugs had a 13 percent risk of DDIs, 38% had a risk of DDIs with five medications, and 82% had a risk of DDIs with seven or more medications. Taking three or more drugs, as well as patients older than 50 years old taking two or more medications, were found to be significant risk factors for adverse DDIs, according to the report. (Goldberg et al., 1996)

It is critical to identify and monitor patients who are exposed to polypharmacy; they must be continuously managed to avoid events caused by drug interactions. (Jansen & Martin, 2015)

Age: Age is considered to be a major risk factor for DDI. DDI can be found at any age, but the risk is higher in the elderly as the frequency of polypharmacy increases. In the Netherlands, 25% of elderly outpatients who took more than one drug and were referred to a diagnostic clinic for impaired cognition, functional dependence, or both; and were discovered to have ADR or decreased effectiveness of the drug, perhaps as a result of DDI (Salem et al., 2013)

The incidence of DDI increases after age 44 and the highest incidence occurs in patients over 74 years of age. (Aparasu et al., 2007) In contrast, due to the immature enzymatic metabolism system, the risk of DDI is common in very young patients (< 5 years). (Shapiro & Shear, 2002)

DDIs based on disease conditions of the patient: Recently, a 2013 study evaluating DDI in inpatients at a university hospital in southern India showed that the highest average number of DDI occurred in patients with cardiovascular disease with comorbid conditions, followed by cardiovascular disease (without comorbid Diseases). In detail, patients with cardiovascular and respiratory diseases had the highest mean number of DDIs (7.33), followed by prescriptions for patients with cardiovascular disease (6.34) and then prescriptions for liver disease (6.00).

(Kulkarni et al., 2013)

Furthermore, the incidence of DDIs is substantial and common in patients with chronic kidney disease (CKD) who also have another comorbid.; commonly hypertension and cardiovascular diseases. (Winkelmayer, 2010) Another disease associated with the risk of DDI is congestive heart failure (CHF). The drugs used in CHF are essential to pharmacological improvements and clinicians cannot rule out any of them. Polypharmacy in the treatment of CHF is inevitable and patients can develop undesirable cases such as hypotension, hyperkalemia, and renal insufficiency.(Garfinkel et al., 2015) Additionally, cancer patients often take multiple drugs to treat cancer, drug-induced toxicity, cancer-related syndromes, and other comorbidities. Therefore, they face the risk of DDI. (Correa et al., 2018).

Other risks include female sex (women are more at risk than men), genetics, organ dysfunction, the use of medications with a narrow therapeutic index (such as warfarin, digoxin, and cyclosporine), metabolic or endocrine risk conditions (such as hypothyroidism, hypoproteinemia), and acute medical issues (as dehydration). (Shapiro & Shear, 2002),(Goldberg et al., 1996) ,(Tulner et al., 2008).

2.4.1.2 Practice-related risk factors

Patients who consult different doctors have the opportunity to obtain DDI. As the number of physicians or pharmacists involved in dispensing the medication increases, the risk of DDI may increase. (Kylstra et al., 2007) In addition, new medications added to present drug therapy in hospitalized patients increase the risk of potential drug interactions. (Kulkarni et al., 2013)

More specifically, when computer alerts are too frequent or infrequent, and workload increases, the possibility of DDIs increases. (Kylstra et al., 2007)

2.4.2 Mechanism of Drug-drug Interactions

Pharmacological interactions are interactions between the drugs inside the body. Pharmacological interactions are classified into pharmacodynamics and pharmacokinetic interactions. (Roberts & Gibbs, 2018) A pharmacokinetic interaction occurs when one drug affects the absorption, distribution, metabolism, or excretion of another. A pharmacodynamic interaction occurs when two medications have additive or antagonistic clinical effects. (Corrie & Hardman, 2017)

The awareness of the mechanisms of DDIs and recognize the value of the interactions by weighing the risks and the benefits to the patient is vital for

healthcare professionals for appropriate action. It might be clinically useful in which can help to decrease side effects and undesirable effects by adjusting the dose or finding an alternative drug. According to Corrie & Hardman (2020),

Anticoagulants, antiepileptics, antifungals, antibiotics, antihistamines, NSAIDs, HIV protease inhibitors, proton pump blockers, anticancer medications, and hypoglycemic agents require special consideration when prescribed. Furthermore, populations such as the elderly, critically ill, and patients with chronic disease should be constantly monitored for DDIs due to polypharmacy or altered renal/hepatic metabolism. (Roberts & Gibbs, 2018)

The mechanisms of drug interactions may be considered in three groups/drug interactions are generally known in terms of three broad classes of underlying mechanisms:

- ❖ Pharmacodynamic interactions: is the relationship between drug concentration and drug response;
- ❖ Pharmacokinetic interactions: are those where the effects of one drug are changed by the presence of another drug at its site of action
- ❖ and pharmaceutical interactions: is relating to chemical or physical incompatibility between the drug preparations being used.

2.4.2.1 Pharmacodynamic interactions

Pharmacodynamic interactions occur between drugs with similar or opposite pharmacological effects. (Niu et al., 2019)

Pharmacodynamic interactions can be classified into three main areas:

- interactions that occur at a single receptor site;
- interactions occurring at a variety of receptor sites;
- and the general non-specific interactions mediated through unspecified sites of action.

The variety of actual and potential drug interactions in terms of pharmacodynamics is limitless.

- **Additive or synergistic Pharmacodynamic Interaction**

Additive DDIs refer to the resulting effect of two Co-administered medications that is greater than the effect of each drug given separately (1+1=2). (Zheng, 2020)

Examples of additive DDIs are sleeping pills combined with alcohol, which can induce more sleepiness than either the sleeping pills or the alcohol alone, or aspirin (antiplatelet) combined with heparin (anticoagulant), which can increase the risk of bleeding. (Zheng, 2020)

Synergistic DDI describes a situation in which the combined effect of two drugs is greater than the total effects of each drug given alone (1+1=3). (Zheng, 2020)

Synergistic DDIs are frequently used in pharmacological therapy. Medicinal cocktails have been developed and are frequently utilized to treat ailments from HIV to cancer. (Zheng, 2020)

This interaction is focused specifically at the use of antibiotics. The findings corroborate that meropenem, when combined with an aminoglycoside, is synergistic against *P.aeruginosa.* (Tam et al., 2004)

- **Opposing or antagonistic Pharmacodynamic Interaction**

  When one medicine lowers or suppresses the effect of another, this is referred to be antagonistic DDI (1+1=0). (Snaprud et al., 1994)

  This DDI takes place at the receptor level, when two drugs compete for the same receptor. Functional antagonism occurs when two medications work on distinct receptor systems, exert opposite effects on various receptor systems, and physiologically oppose one another's function. (Schille et al., 1990)

  Antagonistic DDIs may be therapeutic in reversing hazardous medication effects. Vitamin K, for example, is a reversal agent for the anticoagulant warfarin, while naloxone is an antidote for narcotic overdose. (Zheng, 2020)

- **Alteration in drug transport mechanisms**

  A mechanism for DDIs is drug competition with each other for uptake at the site of action. Noradrenergic receptors are one example of this class. Medications that work through the noradrenaline reuptake mechanism in combination with tricyclic antidepressants that suppress this reuptake process may reduce the effectiveness of drugs that require it. (B.W Fox and M. Fox, 1984)

- **Changes in fluid and electrolyte balance**

  Digitalis and loop diuretics are used to treat heart failure and edema. Loop diuretics reduce plasma K+, which may exacerbate digitalis toxicity. (Pittler, 2010)

  Often, pharmacodynamic interactions are a significant concern to elderly patients

because of changes in the homeostatic mechanisms that make them more sensitive to the effects of the combined drugs. Additive DDIs are particularly important in elderly patients with impaired physiological functions. When two or more anticholinergic drugs (such as tricyclic antidepressants and antihistamines) are administered together, elderly men with pre-existing prostatitis may experience urine retention. (Seymour & Routledge, 1998) Furthermore, older adults on NSAIDs had a 4.1 relative risk of developing a peptic ulcer, compared to only 1.1 in patients taking corticosteroids. (Griffin et al., 2013). Thus, the use of two medications together raises the potential of peptic ulcer. by a factor of 15 when compared to nonusers of either drug. (Piper et al., 2016)

2.4.2.2 Pharmacokinetic interactions

When a drug modifies the disposition (absorption, distribution, metabolism, and elimination) of a co-administered drug, this is referred to as a pharmacokinetic drug-drug interaction. (Ubeaud-séquier et al., 2010)

Pharmacokinetic interactions can cause plasma medication concentrations to rise or fall. It can result in serious side effects or decreased treatment efficacy. (Ubeaud-séquier et al., 2010)

These interactions are classified by (T.N. Calvey and N.E. Williams, 2012) based on their impact on the processes of

- Dissolution or absorption
- Distribution
- Metabolism
- Elimination

- **Drug absorption interactions**

Interactions at the level of drug absorption can result in subtherapeutic serum concentrations of the interacting agents, and they can occur as a result of the following factors: (Baxter, 2006)

Changes in gastrointestinal pH:

A range of factors, particularly regional gastrointestinal (GI) pH, influence medication oral bioavailability. Minor changes in the GI pH profile can have a significant impact on the dissolution and absorption of medicines with pH-dependent

dissolution and absorption. Therefore, precise knowledge of GI pH levels and their variability under different dosing settings is critical for formulation scientists and researchers in order to appropriately design and target drug release and quantify the effect of GI pH on a drug's in vivo plasma pharmacokinetic profile. (Abuhelwa et al., 2016)

All antacids can cause drug interactions by modifying gastrointestinal pH, hence altering drug dissolution of dosage forms, decreasing gastric acid hydrolysis of medicines, or influencing drug excretion by altering urine pH. (Maton & Burton, 1999)

Changes induced by chelation and adsorption:

Chelation results in the formation of complexes, which can affect the absorption of either medicine when combined.

Iron-drug interactions with clinical importance can occur in a wide range of individuals and involve a wide range of medications. Concurrent iron consumption significantly reduces the bioavailability of a variety of medicines. Tetracycline, tetracycline derivatives (doxycycline, methacycline, and oxytetracycline), penicillamine, methyldopa, levodopa, carbidopa, and ciprofloxacin are all affected medications with different chemical structures and clinical effects. The creation of iron-drug complexes is the primary mechanism of these drug interactions (chelation or binding of iron by the involved drug). A wide range of other important and widely used medications, including thyroxine, captopril, and folic acid, have been shown to form stable complexes with iron. (Campbell & Hasinoff, 1991)

Changes in gastrointestinal motility

Prokinetic drugs in the gastrointestinal tract improve the pace of gastric emptying as well as upper intestinal motility. These actions are expected to boost the initial rate of absorption of orally delivered medicines while decreasing total bioavailability. (Greiff & Rowbotham, 1994)

Increased gastric motility can decrease the absorption of a drug by reducing the time the drug is in contact with the absorption area of the mucous membrane; For example, metoclopramide reduces the absorption of digoxin and theophylline because it accelerates gastric emptying. (Baxter, 2006)

Transporter based interactions

P-glycoprotein (P-gp) and other multidrug efflux transporters are involved in this kind of DDI. Induction or inhibition of these proteins also results in DDIs. Rifampicin is a P-gp inducer and may lower digoxin levels in the blood, whereas verapamil is a P-gp inhibitor and raises digoxin levels. (Eichelbaum et al., 2002)

- **Drug distribution interactions**

  Distribution is the movement of the absorbed drug through the bloodstream and its transport throughout extracellular or intracellular compartments to the site of action. (Triplitt, 2006)

  Many drugs bind substantially to plasma proteins in the bloodstream, such as albumin. When a drug binds to these plasma proteins, it is not actively distributed to the site of action, and only the "free" drug can exert an effect (Triplitt, 2006). In theory, combining two highly protein-bound medicines can cause one to displace the other from its protein binding site, increasing the concentration of the unbound drug and changing its apparent distribution volume (Zhao & Long, 2020). This increases the amount of "free" medication that can be used to induce an effect. (Triplitt, 2006)

  Distribution interactions can be significant for drugs that have extremely rapid distribution, narrow safety margins, and possibly nonlinear kinetics. (Triplitt, 2006)

  Crizotinib, ceritinib, alectinib, brigatinib, and entrectinib are highly protein-bound (90%) and may interact with other highly protein-bound medications such as phenytoin and warfarin. (Zhao & Long, 2020)

- **Drug metabolism interactions**

  Most DDIs involve the cytochrome P450 (CYP450) family. CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are the most prevalent CYP isoforms that mediate DDIs. Many DDIs are associated with CYP enzyme inhibition or induction. (Back et al., 2008)

  Effect of enzyme induction on drug-drug interactions:

  Drug-drug interactions (DDI) occur when one medication interferes with the activities of a metabolizing enzyme involved in the clearance of another drug. DDIs can occur as a result of the process of enzyme induction, which refers to the increased expression of a drug metabolizing enzyme as a result of drug or chemical exposure. Increased clearance and thus decreased exposure to a co-administered

object medication results from DDI driven by enzyme induction. (Finch et al., 2015)

Co-administration with rifampin, a significant inducer of cytochrome P450 isoform 3A (CYP3A), for example, results in lower concentrations of HIV protease inhibitors, oral contraceptives, azole antifungals, and a variety of other medications metabolized by CYP3A. (Finch et al., 2015)

The negative implications of enzyme induction can include decreased efficacy due to medication concentrations falling to subtherapeutic levels and/or higher toxicity due to increased production of reactive metabolites. (Ripp SL., 2008)

Effect of enzyme inhibition on drug-drug interactions:

Inhibition is the reduction of enzyme activity caused by a direct contact with a medication. This process normally starts with the initial inhibitor dose, and the start and end points of inhibition are related to the half-lives of the medicines involved. (Pirmohamed & Park, 1999)

When single oral doses of metoprolol (50 mg), a beta-adrenoceptor blocking agent, and/or propafenone (150 mg) were given to healthy participants, there was a two-fold reduction in the oral clearance of metoprolol when propafenone was added. When propafenone is additionally administered, the dose of metoprolol should be lowered. (Wagner et al., 1987)

Similar drug-drug interactions have been observed when thioridazine and propranolol (CYP2D6), fluoxetine and desipramine (CYP2D6), omeprazole, and diazepam (CYP2C19), tolbutamide and phenytoin (CYP2C9), and diltiazem and cyclosporin (CYP3A) (Campana et al., 1996) are used together. (Bibi, 2008)

- **Drug elimination interactions**

Drugs are excreted primarily by the kidneys and bile ducts, but biliary excretion does not have important DDIs. (Luecke & Wosilait, 1979) Changes in renal excretion are mediated by changes in protein binding (as previously stated), tubular secretion inhibition, or changes in renal blood flow or urine PH. Penicillin's effect is classically prolonged by co-administration of probenecid. The active transport mechanism that secretes acids (penicillins) into the renal tubule was designed to compete with probenecid. Other acidic medications, such as aspirin, indometacin, and sulphonamides, will raise each other's plasma concentrations if administered concurrently. (EMA, 2012; Scott et al., 2013) (Luecke & Wosilait, 1979)

2.4.2.3 Pharmaceutical Interactions

Pharmaceutical Interactions are due to chemical or physical reactions that take place in vitro which may be responsible for the loss of drugs activity, for their aggregation, or precipitation in solution. It sometimes has serious consequences (T.N. Calvey and N.E. Williams, 2012). Pharmaceutical Interactions occur prior drugs are administered to the patient, and it depends on the properties of the drugs and its pharmaceutical form (Becker, 2011).

- **Chemical**

Chemical deterioration or decomposition

Most drugs, even anesthetic agents, must be stored before use and in many occasions may undergo deterioration or decomposition. However, decomposition is likely to occur more slowly when stored in a powder or solid form (T.N. Calvey and N.E. Williams, 2012).

- **Physical**

Solvent system polarity

Solvent system polarity (the solubility of a drug or drug solvent in aqueous solution) may be important when relatively insoluble agents such as diazepam or propofol are existing in organic solvents and are then added to aqueous solutions. In these conditions, precipitation may occur, and its extent will depend on the relative volume and concentration of both drug and aqueous solution (T.N. Calvey and N.E. Williams, 2012).

2.5 Intensive Care Unit

Since their widespread introduction more than half a century ago, Intensive Care Units (ICUs) have become an integral part of the health care system. (Murthy et al., 2015)

An ICU is an organized system for the provision of care to critically ill patients that provides intensive and specialized medical and nursing care, an enhanced capacity for monitoring, and multiple modalities of physiologic organ support to sustain life during a period of life-threatening organ system insufficiency. While an ICU is based

in a defined geographic area of a hospital, its activities often extend beyond the walls of the physical space to include the emergency department, hospital ward, and follow-up clinics. (Marshall et al., 2017)

The birth of intensive care medicine was a process that took place in Copenhagen, Denmark, during and after the poliomyelitis epidemic in 1952/1953. (LASSEN HC, 1953)

The birth of intensive care medicine, as it is generally acknowledged today, was the result of a succession of unconventional methods and solutions hastily improvised by a Danish hospital in order to cope with the over- whelming medical and organizational challenges of the poliomyelitis epidemic of 1952. If 1952 can therefore be considered as the annus mirabilis of intensive care, the event was far more gradual in detail: A last desperate attempt to save the life of a 12-year-old turned out surprisingly well. This led to the organization of a single- disciplinary unit to treat polio patients with respiratory failure. This unit developed into a multidisciplinary recovery room and finally ended up as a multidisciplinary intensive care unit. The entire process took just 17 months, and—more surprisingly—the honors for this remarkable achievement are widely conferred on only one man, who is recognized for having designed and performed each of these revolutionary steps: Dr. Bjo¨rn Ibsen, also commonly known as the ‘‘father of intensive care medicine’’. (Reisner-se, 2011) (LASSEN HC, 1953)

Intensive care, also known as critical care, is a multidisciplinary and inter professional specialty dedicated to the comprehensive management of patients having, or at risk of developing acute, life-threatening organ dysfunction. Intensive care uses an array of technologies that provide support of failing organ systems, particularly the lungs, cardiovascular system, and kidneys. While the specialty has developed expertise in the comprehensive management of disorders such as sepsis and the Acute Respiratory Distress Syndrome (ARDS), its common expertise is the pathophysiology and support of organ dysfunction, more than the specific management of the diseases responsible for the acute illness; the primary goal of intensive care is to prevent further physiologic deterioration while the underlying disease is treated and resolves. (Weil et al., 1952)

To define intensive care as a multidisciplinary specialty is to recognize that while its practitioners share common expertise in the management of acute organ system insufficiency, they may also come from various specialty backgrounds that provide

additional clinical expertise. (Haupt et al., 2003)

Intensive care is not just a clinical specialty, but a system of care delivered by a skilled interprofessional team that includes physicians, nurses, respiratory therapists, physiotherapists, pharmacists, microbiologists, social workers, ethicists, spiritual care, and many others.

As the discipline of intensive care has matured, its scope has broadened. Intensivists and other critical care practitioners now play an active role in the resuscitation of acutely unstable patients in the emergency department or on the hospital ward, and in the rehabilitation of survivors of critical illness. Their expertise extends beyond the treatment of the patient to the support of the family, the provision of compassionate care at the end of life, and developing societal preparedness for future crises. Originally defined by the geographic locale where care was provided, intensive care has become a specialty without walls. Yet central to its success is the availability of a dedicated space where patients with acute organ dysfunction can be cared for, by a skilled team of health care providers, and often for an extended period of time. (Marshall et al., 2017)

2.5.1 Who to admit?

Intensive care is appropriate for patients requiring or likely to require advanced respiratory support, patients requiring support of two or more organ systems, and patients with chronic impairment of one or more organ systems who also require support for an acute reversible failure of another organ. Early referral is particularly important. If referral is delayed until the patient's life is clearly at risk, the chances of full recovery are jeopardized. (Smith & Nielsen, 1999)

Factors to be considered when assessing suitability for admission to intensive care

- Diagnosis
- Severity of illness
- Age
- Coexisting disease
- Physiological reserve
- Prognosis
- Availability of suitable treatment

- Response to treatment to date
- Recent cardiopulmonary arrest
- Anticipated quality of life
- The patient's wishes (Smith & Nielsen, 1999)

2.5.2 Common disease in intensive care unit:

Some of the common illnesses which may require treatment in the ICU:

- Sepsis
- Traumatic Brain Injury
- Shock
- Stroke
- Ruptured Brain Aneurysm
- Trauma
- Post-operative Intensive Care
- Cancer-related Intensive Care
- Heart Failure
- Respiratory (Lung) Failure
- Neonates, after any surgery. (Ottawa Hospital, 2020)

Risks and complications of critical illness

- Deep Vein Thrombosis (blood clot)
- Kidney Failure
- Infections
- Liver Failure
- Stomach Ulcers
- Skin ulcers (pressure ulcers)
- Weakness
- Confusion
- Medication Side Effects
- Procedural Complications (Ottawa Hospital, 2020)

2.5.3 Common medication in Intensive Care Unit

Patients admitted to the intensive care unit (ICU) frequently have a number of critical

medical issues. Pharmacotherapy is an essential part of critical care medicine. ICU patients are vulnerable and cannot tolerate the comorbidities that result from a failure medication treatment. The concern of pharmacotherapy in the ICU is that patients may be receiving medical treatment as well as a lot of medicine at the same time. (Zhou et al., 2018)

To summarize the information regarding the most regularly encountered pharmaceuticals in the ICU, we divided them into five categories: analgesics and sedatives, antifungal drugs, cardiovascular drugs, gastroenterological drugs, and anticonvulsant drugs. (Zhou et al., 2018)

- Analgesics and Sedatives: Opioid analgesics (Morphine, Fentanyl, Tramadol), Sedatives (Propofol, Midazolam, Lorazepam, Diazepam)
- Antipsychotics (Haloperidol)
- Antifungal Drugs (Voriconazole)
- Cardiovascular Drugs: Anticoagulant drugs (Warfarin, Enoxaparin), Antiplatelet drugs (Clopidogrel), Antiarrhythmic drugs (Metoprolol, Carvedilol), Vasoactive drugs (Vasopressin, Dopamine, Norepinephrine), Vasodilators (Nitroglycerin), Statins (Simvastatin)
- Gastroenterological Drugs: Proton pump inhibitors (PPIs) (pantoprazole, lansoprazole, omeprazole, esomeprazole), Ondansetron
- Anticonvulsant Drugs (Phenytoin, Carbamazepine, Valproic acid)
- Inotropes (Dopamine-Dobutamine)

One of the most important and common medicines in ICUs also:

- Fluids Crystalloids (Dextrose 5%- Normal Saline)
- Fluids Colloids (Albumin 5%)
- Blood Products (Packed Red Blood Cell (PRBC)- Fresh Frozen Plasma (FFP)- Cryoprecipitate) (Zhou et al., 2018)

2.6 drug–drug interaction software programs

More years of pharmacy education seemed to improve the ability to detect drug interactions. However, none of the pharmacists or students was able to detect all potentially interacting pairs in a profile containing 8 or 16 drugs (Weideman et al.,

1999). It is likely that every physician and pharmacist cannot remember and understand all potential DDIs and therefore cannot take corrective actions accordingly. They may be more familiar with drugs used in their specialty but not with drugs used in other specialties (Kheshti et al., 2016).

Therefore, an improvement in the clinicians' ability to detect DDIs can reduce the chance of ADEs, preserve patients' safety, and prevent related medical and legal problems. (Weideman et al., 1999)

One of the tools that clinicians trust into review patients' medication sheet for DDIs is computerized DDI software. Drug-drug interaction (DDI) screening programs are an important tool to check prescriptions of multiple drugs. By manual review of drug regimens by pharmacists, without the use of utility (e.g., drug interaction reference and computer program), only 66% of DDIs in a 2-drug regimen can be correctly identified and the proportion decreases substantially as the number of drugs increases (Halkin et al., 2001).

In order to reduce the number and to improve the management of DDIs, physicians primarily have to be aware of the presence of a DDI. A DDI screening program implemented as clinical decision support system would be highly desirable. (Kra et al., 2008)

While a DDI screening program can be highly desirable, there is concern about variation between programs and about quality and effectiveness of the information. Thus, clinicians should be aware of the advantages and limitations of the DDI applications. (Kheshti et al., 2016)

Halkin *et al*. showed that using DDI screening programs by physicians and pharmacists could decrease 67.5% of hazardous DDIs. What is important is that these programs vary in accuracy and the information within interaction monographs. (Halkin et al., 2001)

The category of potential DDI for drug interaction pairs often differs among drug interaction database programs. When assistance from a drug interaction database program is needed, physicians should recognize this limitation and check more than one program. (Monteith & Glenn, 2019)

2.7 Clinical pharmacist:

Clinical pharmacy is the practice of pharmacists who provide patient care that optimizes drug therapy while also promoting health, wellness, and disease prevention. Clinical pharmacists rely on their professional connections with patients to provide guidance on how to effectively satisfy the needs and desires of individual patients. (Madhav University, 2018)

Role of Clinical Pharmacist:

- Therapeutic Drug Monitoring (TDM)
- Rational drug use
- Medication outcomes and comparative effectiveness
- Pharmacoepidemiology
- Medication Therapy Management
- Medication outcomes
- Hematology and Oncology Pharmacists
- Pharmacogenomics & Pharmacoeconomics
- Pharmacokinetics and pharmacodynamics
- Transitions-of-care Services (Madhav University, 2018)

Clinical pharmacists are licensed practitioners with advanced education and training who practice in all types of patient care settings with a priority on comprehensive drug management. These specialized pharmacists are concerned with ensuring optimal drug utilization, emphasizing dosing, monitoring, identifying adverse effects, and improving economic efficiency in order to achieve optimal patient outcomes. Clinical pharmacists are gaining prominence as essential members of the patient care team for ambulatory and acute care patients around the world. (Jacobi, 2016)

2.7.1 Clinical Pharmacist Roles within the Health Care System

Clinical pharmacists use evidence-based medicine guidelines, evolving sciences, advancing technology, and relevant legal, ethical, social, cultural, economic, and professional considerations to help patients accomplish their treatment goals.

Furthermore, whether working independently or in consultation or collaboration with other healthcare practitioners, clinical pharmacists assume duty and obligation for managing pharmaceutical therapy in direct patient care settings.

Because the clinical pharmacist is the most experienced about the medication's therapeutic use and provides the health-care system with unique information and skillsets, it is necessary to assume the role of specialists in drug therapy.

Moreover, this expertise is employed pro-actively to ensure and advance rational drug therapy use, so avoiding many of the medication therapy disasters that occur as a result of inappropriate therapeutic decisions made at the time of prescribing.

This expertise also extends to non-traditional treatments that are not part of conventional medicine.

Finally, it specifies that a clinical pharmacist produces therapeutic assessment suggestions and recommendations, and it emphasizes the fact that there are regular consultations between the evaluation of drug therapy in everyday practice with patients and healthcare professionals. (Saseen et al., 2017)

2.7.2 The Role of Pharmacists in Discovering and Preventing DRPs and DDIs:

Clinical pharmacists have been shown in studies to be effective at identifying, solving, and preventing clinically significant drug-related problems, which has a positive impact on patient outcomes such as improved health and economic outcomes, a reduction in medicine-related adverse events, improved quality of life, and reduced morbidity and mortality.

Clinical intervention is the process of a pharmacist identifying, and making a recommendation in an attempt to prevent or resolve a DRPs. (Al-ateya, 2018)

Some studies conducted in Indian hospitals revealed numerous evidences of drug-related problems, as well as a significant influence of pharmacist intervention on minimizing drug-related problems and improving overall patient care. (Dahal et al., 2013)

The objective of this research was to determine and assess the significance of clinical pharmacist intervention in medical wards, as well as the effectiveness of pharmacist participation in multidisciplinary health care teams during inpatient care. (Alagiriswami et al., 2009)

The study reveals that incorporating clinical pharmacist services in patients' care can considerably aid in identifying, resolving, and preventing DRPs in the hospital, hence improving patient outcomes. Moreover, the clinical pharmacist's

recommendations throughout the intervention were well accepted by the physician, indicating that a collaborative approach between physician and pharmacist can deliver superior patient care outcomes. The study emphasizes the significance of clinical pharmacists in the health care sector, as well as their essential role in patient care. (Dahal et al., 2013)

According to a study published in the International Journal of Clinical Pharmacy in 2013, clinical pharmacists were able to link a patient's current diagnosis, laboratory values, and medical history with their pharmacotherapy drugs. As a result, the clinical pharmacist can discover and assist in the resolution of more DRPs than any other automated system, such as Computerized Physician Order Entry systems (CPOE). (Cornu & Steurbaut, 2014)

2.7.3 The Role of Clinical Pharmacists in ICU:

In today's intensive care unit (ICU), there are multiple disciplines that come together and work as a team to improve patient care, with one of the integral players being pharmacy.

Critical care pharmacists are considered essential members of the multi-professional ICU team. Limitation in resources and reimbursement may result in reductions in hospital personnel. However, the critical care pharmacists have demonstrated their contribution to drug therapy management, reduction of drug expenditures, and impact on patient and medication safety. There appear to be many ICUs without a dedicated critical care pharmacist, signifying an important gap in the critical care team and a missed opportunity for optimal utilization of pharmaceuticals. (Horn & Jacobi, 2006)

The daily responsibilities of pharmacists continue to evolve as the pharmacy profession moves from product-focused to patient-focused care.

In those institutions that provide clinical pharmacy services, patients in the intensive care unit (ICU) are the most frequently monitored by pharmacists. (Rosa & Antonio, 2007)

In conclusion, we found that the introduction of a critical care pharmacist to assess the compliance to guidelines in a quality care bundle was associated with a reduction in the duration of mechanical ventilation, as well as ICU and hospital length of stay. This strategy was also associated with a significant reduction in healthcare costs.

(Louart et al., 2017)

2.7.4 Justifying critical care pharmacy services:

The American College of Clinical Pharmacy (ACCP) and the Society of Critical Care Medicine (PC) published a joint position paper outlining the fundamental, desired, and optimal tasks of critical care pharmacists. These organizations promote pharmacists to participate in activities that enhance patient safety and the optimization of the medication-use process. Examples of pharmacist involvement include assuring a safe, accurate, and rapidly responsive drug distribution system for critically ill patients, the development of multidisciplinary guidelines for stress ulcer prophylaxis, sedation, hemoglobin management, antifungal use, and biotechnological approaches to sepsis. Research and teaching are essential higher level (more specialized) responsibilities of ICU pharmacists that distinguish desired and optimal levels of critical care pharmacy services. There is currently no data on the enhanced patient outcomes/safety of delivering daily teaching to ICU team members/staff, nor on the utility of pharmacist-driven research as independent investigators. This position paper serves as a foundation for justifying pharmacy services.

An effective approach to justifying critical care pharmacists is emphasizing their role in the prevention of ADEs and medication errors. The incidence of ADEs in the ICU is reported to be 19 events per 1,000 patient-days, as compared with 10 events per 1,000 patient-days in non-ICU patients. Since pharmacists have been shown to reduce the number of ADEs by 66%, and ADEs are associated with a high incidence of mortality, the critical care pharmacist ensures added patient safety and potential annual cost savings of US $ 270,000.

The addition of a critical care pharmacist must be marketed as potential cost savings since administrator are required to cost justify additional personnel. There are at least ten studies discussing the economic benefit of critical care pharmacists. Critical care pharmacists have the potential to save between US $ 25,140 and US $ 318,891 annually. (Kane et al., 2003)

CHAPTER III

METHODOLOGY

3.1 Study design

A retrospective observational study was conducted in the Intensive Care Unit (ICU) for a period of 35 months from 01 January 2018 to 30 November 2020. The data were gathered from patient files at the archive and electronic system records in Al Methnab General Hospital, for male and female who admitted to the Intensive Care Unit (ICU).

3.2 Setting

This study has been conducted in Al-Qassim region, Saudi Arabia, ' Al Methnab General Hospital.

The medical center is a government hospital in Saudi Arabia with an 82,000 square meter closed area, 130 total beds, an Intensive Care Unit with 6 beds, 2 operating theaters, and a 14-bed intensive care facility with Neonatal intensives.

3.3 Study subjects

All the ICU files of patients admitted within the stipulated study period were analyzed.

- Inclusion Criteria:
  - Patients who are admitted to the intensive care unit in Al Methnab General Hospital from 1st January 2018 to 30th November 2020.
  - Patients who are 18 years or older.
  - Patients who were using two medications or more.
  - Patients who stay 24H or more in the ICU.
- Exclusion Criteria:
  - Patients Who had an incomplete file

3.4 Data collection tool

The ICU electronic medical system records all the information that is necessary when prescribing medications. Using this as a data collection tool allowed the researchers to collect information on all medications used in the ICU.

The information was taken from the patient's medical record and entered into a special data entry format. The following information was collected:

- Patient demographic details: Age, Gender
- Date of admission to ICU and date of discharge from ICU (to assess the LOS)
- Diagnosis at admission and Diagnosis during ICU
- The Patient's final condition
- Lab test results.
- Drugs using during ICU.

Drugs information recorded were; name of the drugs, DDI severity, mechanism of drug interaction, risk rating, recommendation for the PDDI.

Generic name was used in all study procedure.

3.5 Study procedure

All drugs the patients used during their hospitalized period in ICU were enters into five different drug-drug interaction checker; Lexicomp, Micromedex, Drug.com, Medscape and Epocrates. All screening and documenting done by the researcher.

3.6 Drug-drug interaction identification and categorization

Collected retrospective data was analyzed using Lexi-interact tool of Lexicomp (copyright 2021, Wolters Kluwer Clinical Drug Information, Inc), IBM Micromedex drug int. (Copyright IBM corporation 2018), Epocrates drugs interaction check (copyright 2020, LLC), Medscape interaction checker (Copyright © 1994-2021 by WebMD LLC) and Drugs.com database (Copyright © 2000-2021 Drugs.com).

Mechanisms of DDI were categorized to Pharmacodynamic, Pharmacokinetic, Pharmaceutical and Unknown.

Lexicomp classified interaction levels into five categories (A, B, C, D, and X), with interaction levels X, D, and C being very important therapeutically and clinically significant, necessitating the modification of drugs and dosages or the avoidance of combinations. While, IBM Micromedex categorized the severity into 4 levels

(Contraindicated, Major, Moderate and Minor). Based on Epocrates, the classifications of severity interaction are 4 as well (Contraindicated, Avoid/Use Alternative, Monitor/Modify and Caution Advised). Another database that categorized the severity into 4 levels (Contraindicated, Serious, Monitor Closely and Minor) is Medscape. On the other hand, Drugs.com database classified the DDIs severity into 3 sectors (Major, Moderate and Minor).

Table 2 Interaction levels categories by Lexicomp

Risk rating	**Action**	**Description**
A	No interaction	No evidence of pharmacodynamic or pharmacokinetic interactions between the agents has been found.
B	No action needed	Data show that the listed drugs can interact with one another, however there is little to no evidence of clinical risk as a result of their concurrent usage.
C	Monitor therapy	Data show that the listed drugs can interact with one another in a clinically significant way. The benefits of taking these two drugs together generally exceed the hazards. To identify potential detrimental impacts, a suitable monitoring plan should be created. In a small number of patients, one or both drugs' dosages may need to be adjusted.
D	Modify regimen	Data show that the two drugs may have clinically significant interactions with one another. To establish if the advantages of concomitant therapy outweigh the dangers, a patient-specific assessment must be performed. Specific activities must be made in order to reap the benefits and/or reduce the toxicity caused by the agents' concurrent use. These efforts may include intensive monitoring, empiric dosage adjustments, and the selection of alternate medications.
X	Avoid combination	Data show that the listed drugs can interact with one another in a clinically significant way. The dangers of using these medicines concurrently usually outweigh the benefits. These medications are typically regarded as contraindicated.

Table 3 Interaction levels categories by IBM Micromedex drug interaction

Risk rating	Action	Description
Contraindicated	Avoid combination	The drugs are contraindicated for concurrent use.
Major	require medical intervention	The interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects.
Moderate	require an alteration in therapy	The interaction may result in exacerbation of the patient's condition
Minor	not require a Major alteration in therapy	The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects

Table 4Drug Interaction Classification according severity in Drugs.com database

Severity	Action	Description
Major	Avoid combination	The interaction is highly clinically significant, and the risk outweighs the benefit.
Moderate	Usually avoid combinations	It is moderately clinically significant; usage only in exceptional conditions.
Minor	No action need	Minimally clinically significant, assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

Table 5 Drug Interactions Categories by Medscape

Severity	Description
Contraindicated	Concurrent usage of the medications is not permitted.
Serious	Avoid or Use Alternate Drug.
Monitor Closely	Data indicate that the specified drugs have pharmacodynamic or pharmacokinetic interactions.
Minor	Unknown Significance

Table 6 Drug Interactions Categories by Epocrates

Severity	Description
Contraindicated	contraindicated for concurrent use
Avoid/Use Alternative	life-threatening interaction
Monitor/Modify	Monitor the patient closely and may require medical intervention
Caution Advised	monitor the patient

3.7 Statistical analysis

Microsoft Excel 2016 was used to record and analyze the data, and statistical methods were utilized to evaluate the data, including the calculation of descriptive statistics such as the frequency and percentage for categorical variables. A Pearson Chi square test was used to assess the relationships between categorical variables. The level of significance was set at $\alpha = 0.05$. The SPSS (Statistical Package for Social Sciences Demo Version 22.0) program was used for all calculations and analyses.

3.8 Ethical Consideration

During the study, patients' privacy and confidentiality were protected. The study was approved by the ALQASSIM region's National Committee of Bioethics, which recognized it as an observational study. There was no documentation of patient data. During the study, just the patients' file numbers, age, and gender were used. The medical record and patient profile were authorized for retrieval from the archives of the Al Methnab General Hospital ICU department.

CHAPTER IV

RESULTS and FINDING

4.1 Demographics of the patients:

There were 524 patients admitted to ICU between 1st Jan. 2018 to 30th Nov. 2020, only 314 patients were matched the inclusion criteria and included in the analysis and screened for Potential Drug-Drug Interaction (PDDI) in five different tools.

Regarding the gender of the patients, 184 out of 314 were male which reflect 58.6% of the sample, while 130 out of 314 were female which reflect the percentage of 41.4%.

Referring to the age categories of the patients, most of the patients 42.7% (n=134) were 65 years old or older, and 35-64 years age group was 41.4% (n=130) while only 15.9% (n= 50) were between 18-34 years old.

The days of hospitalized was categorized into three groups <3 days, 3-7days and >7 days. Most of the patients 45.2% (n=142) stayed in hospital less than 3 days, while 38.5% (n=121) of patients stayed 3-7 days and 16.2% (n=51) of patients stayed in hospital more than 7 days.

The number of medications used during hospitalization was diverse between the patients, most of the patients 56.4% (n=177) used 6-10 drugs during their hospitalization, while 24.8% (n=78) used more than 10 drugs and only 18.8% (n=59) used 2-5 drugs during their hospitalization.

Out of 314 patients enrolled in the study, 56.4% (n=177) stayed alive, while 19.4% (n=61) dead and 24.2% (n=76) referral. [see table 7].

Table 7 General demographic characteristics of the patients

Characteristics	*Frequency*	*Percent %*
Gender		
Female	130	41.4%
Male	184	58.6%
Age (years)		
18 to 34 Years	50	15.9%
35 to 64 Years	130	41.4%
≥ 65	134	42.7%
Hospital stay LOS (days)		
< 3 Days	142	45.2%
3-7 Days	121	38.5%
> 7 Days	51	16.2%
Prescribed medications per patient		
2-5	59	18.8%
6-10	177	56.4%
> 10	78	16.2%
Final status of patient		
Alive	177	56.4%
Dead	61	19.4%
Referral	76	24.2%

4.2 Drug interactions:

According to the number of potential interactions in the five different tools, Micromedex recorded n=231 (73.6%) patients have potential interactions while Lexicomp recorded n=256 (81.5%) patients, Drugs.com recorded n=284 (90.4%) and in Epocrates and Medscape n=275 (87.6%), n=283 (90.1%) patients have potential interactions, respectively.

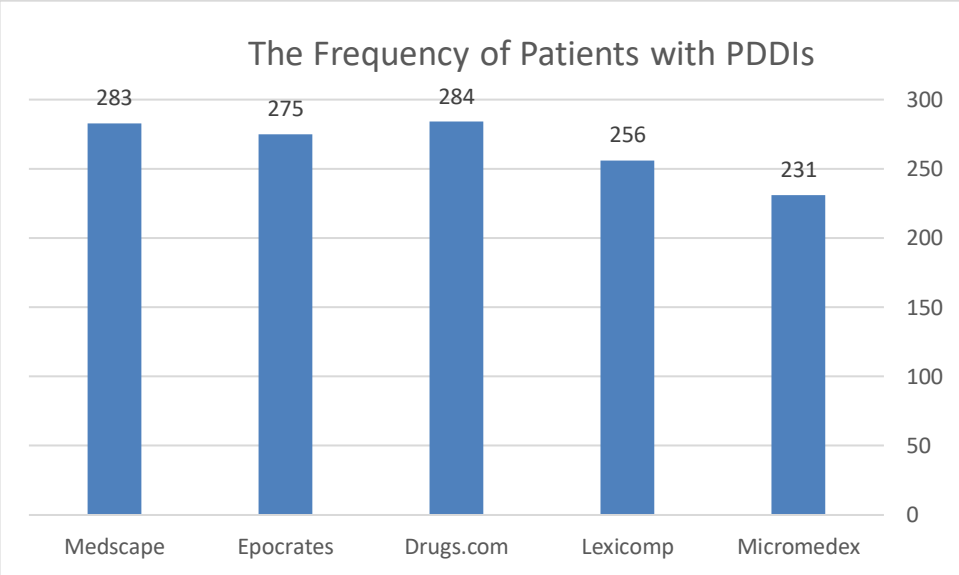

Figure 3The frequency of PDDIs

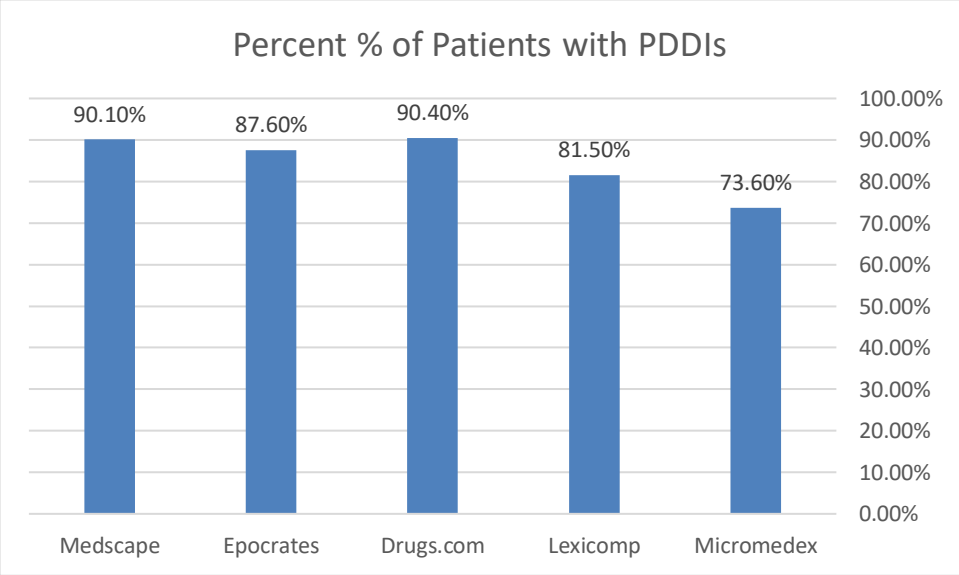

Figure 4 The percentage of PDDIs

For Micromedex, the most frequent interactions were between (Clopidogrel × Acetylsalicylic Acid) for 41 times (Clopidogrel × Enoxaparin sodium) for 25 times (Clopidogrel × Omeprazole) for 18 times. For Lexicomp, the most frequent interactions were between (Enoxaparin sodium × Acetylsalicylic Acid) for 40 times (Omeprazole × Clopidogrel) for 23 times (Enoxaparin sodium × Clopidogrel) for 19 times. For Drug.com, the most frequent interactions were between (Enoxaparin sodium× Acetylsalicylic Acid) for 59 times (Enoxaparin sodium × Clopidogrel) for 34 times (Clopidogrel × Omeprazole) for 18 times. For Epocrates, the most frequent interactions were between (Enoxaparin sodium × Acetylsalicylic Acid) for 63 times (Enoxaparin sodium × Clopidogrel) for 38 times (Clopidogrel × Acetylsalicylic Acid) for 19 times. For Medscape, the most frequent interactions were between (Enoxaparin sodium × Ceftriaxone) for 42 times (Enoxaparin sodium × Clarithromycin) for 13 times (Enoxaparin sodium × Acetylsalicylic Acid) for 12 times. [see table 8]

Table 8 Most frequently identified potential interactions

	Drug 1	Drug 2	Frequency	Severity	Mechanism of interaction	Interaction Effect	Clinical Management
Micromedex	Aspirin	Clopidogrel	41	Major	PD	Increased risk of bleeding	Monitoring of blood counts
	Clopidogrel	Enoxaparin	25	Major	PD	Increased risk of bleeding	Discontinue the antiplatelet agent prior to initiating a LMWH if possible. If discontinuation is not possible, monitoring for signs or symptoms of bleeding and evaluate promptly.
	Clopidogrel	Omeprazole	18	Major	PK	Reduced plasma concentration of clopidogrel active metabolite and reduced antiplatelet activity.	Avoid concomitant use
Lexi-comp	Aspirin	Enoxaparin	40	Moderate	PD	Agent with antiplatelet properties may enhance the anticoagulant effect of Enoxaparin	Discontinue antiplatelet agent prior to initiating enoxaparin whenever possible. If concomitant administration is unavoidable, monitor closely for signs and symptoms of bleeding.
	Clopidogrel	Omeprazole	23	Major	PK	Omeprazole may diminish the antiplatelet effect of Clopidogrel. Omeprazole may decrease serum concentrations of the active metabolites of	Avoiding concurrent use with omeprazole due to the possibility that combined use may result in decreased clopidogrel effectiveness.

						Clopidogrel.	
	Clopidogrel	Enoxaparin	19	Moderate	PD	Agent with antiplatelet properties may enhance the anticoagulant effect of Enoxaparin	Discontinue antiplatelet agent prior to initiating enoxaparin whenever possible. If concomitant administration is unavoidable, monitor closely for signs and symptoms of bleeding.
Drugs.com	Aspirin	Enoxaparin	59	Major	PD	May potentiate the risk of bleeding complications	Should preferably be avoided. Close clinical and laboratory observation for bleeding complications is recommended if concurrent therapy is necessary.
	Clopidogrel	Enoxaparin	34	Major	PD	May potentiate the risk of bleeding complications	Any agent that can enhance the risk of hemorrhage including other anticoagulants should be discontinued prior to initiation of LMWH therapy. If coadministration is necessary, it should be undertaken with caution and only after thorough assessment of risks and benefits. Close clinical and laboratory observation for bleeding complications is recommended.

	Clopidogrel	Omeprazole	18	Major	PK	Coadministration with (PPIs) may reduce the cardioprotective effects of clopidogrel. May decreased effectiveness of clopidogrel	Should preferably be avoided. PPIs should only be considered in high-risk patients and only after thorough assessment of risks versus benefits.
Epocrates	Aspirin	Enoxaparin	63	Avoid	PD	Combination may increase risk of GI or other bleeding, include life-threatening	Use alternative or monitor bleeding signs and symptoms
	Clopidogrel	Enoxaparin	38	Avoid	PD	Combination may increase risk of bleeding, include life-threatening	Use alternative or monitor bleeding signs and symptoms
	Aspirin	Clopidogrel	19	Monitor	PD	Combination may increase risk of GI or other bleeding, include life-threatening	Monitor bleeding signs and symptoms
Medscape	Enoxaparin	Ceftriaxone	42	Serious	PD	Cephalosporins may decrease prothrombin activity.	Avoid or use alternative drug
	Enoxaparin	Clarithromycin	13	Serious	PK	Clarithromycin increases effects of Enoxaparin	Avoid or use alternative drug
	Enoxaparin	Aspirin	12	Monitor	PD	Increase anticoagulation.	Use caution and monitor closely

4.3 Drug-drug interaction according to Micromedex

4.3.1 PDDIs in Micromedex according to demographic characteristics

Out of 314 patients, 231 (73.6%) patients had PDDIs according to Micromedex, there are 894 PDDIs. Among the 231 patients with PDDIs, 132 (57.1%) were male whereas 99 (42.9%) were female. [see table 9]

Patients aged between 35 to 64 years old had the highest number of PDDIs (44.2%), followed by patients 65 years of age or older (42.9%), and patients aged between 18 to 34 years old had the lowest number of PDDIs (12.9%). [see table 10]

Patients whose stay in the ICU was less than three days had the highest rate of PDDIs (46.8%), followed by patients who stays between 3 to 7 days (40.3%), and the lowest number of PDDIs was in patients who stays more than seven days (12.9%). [see table 11]

Patients who took 6 to 10 drugs had the highest number of PDDIs (55.8%), followed by patients who took more than 10 drugs (31.2%), and the least number of PDDIs were in patients who took 2 to 5 drugs (13%). [see table 12]

You can have a look at Table 13 which shows the relationship between the incidence of PDDI and the patient's final condition.

Table 9 PDDIs distribution among patient's gender in Micromedex.

			Micromedex interaction		Total
			No	Yes	
Gender	Female	N	31	99	130
		%	23.8%	76.2%	100.0
	Male	N	52	132	184
		%	28.3%	71.7%	100.0
Total			83	231	314

The female patients who had PDDIs according to Micromedex were 76.2% while 71.7% of the male patients had PDDIs. These findings demonstrated that there is no association between the presence of PDDI and gender ($X2= 0.76$, $p >0.05$).

Table 10 PDDIs distribution among patient's age in Micromedex.

			Micromedex interaction		Total
			No	Yes	
Age	18-34	Count	20	30	50
		%	40.0%	60.0%	100.0
	35-64	Count	28	102	130
		%	21.5%	78.5%	100.0
	65	Count	35	99	134
		%	26.1%	73.9%	100.0
Total			83	231	314

The patients between 18-34 years old who had PDDIs according to Micromedex were 60.0% while 78.5% of patients between 35-64 years old had PDDIs, and 73.9% of patients 65 years of age or older had PDDIs. These findings demonstrated that there is a significant difference between the presence of PDDIs and different age ($X2= 6.3$, $p < 0.05$)

Table 11 PDDIs distribution among LOS in Micromedex.

			Micromedex interaction		Total
			No	Yes	
Length of stay (days)	< 3	N	34	108	142
		%	23.9%	76.1%	100.0%
	3-7	N	28	93	121
		%	23.1%	76.9%	100.0%
	>7	N	21	30	51
		%	41.2%	58.8%	100.0%
Total			83	231	314

The patients who stayed between 3-7 days or less than 3 days in the ICU and who had PDDIs according to Micromedex were 76.9% and 76.1%, respectively, while 58.8% of patients who stayed more than 7 days had PDDIs. These findings

demonstrated that there is a significant difference between the presence of PDDIs and length of stay (X2= 6.8, p < 0.05).

Table 12 PDDIs distribution among medication number in Micromedex.

			Micromedex interaction		Total
			No	Yes	
Medication number	2-5	N	29	30	59
		%	49.2%	50.8%	100.0%
	6-10	N	48	129	177
		%	27.1%	72.9%	100.0%
	>10	N	6	72	78
		%	7.7%	92.3%	100.0%
Total			83	231	314

The patients who used more than 10 drugs and who had PDDIs according to Micromedex were 92.3%. In addition, 72.9% of patients who used 6-10 drugs had PDDIs while 50.8% of patients who used 2-5 drugs had interactions. These findings demonstrated that there is a significant association between the presence of PDDIs and the number of medications (X2= 29.79, p < 0.05).

Table 13 PDDIs distribution among patient's status in Micromedex

			Micromedex interaction		Total
			No	Yes	
Status	Alive	N	51	126	177
		%	28.8%	71.2%	100.0
	Dead	N	19	42	61
		%	31.1%	68.9%	100.0
	Referral	N	13	63	76
		%	17.1%	82.9%	100.0
Total			83	231	314

The patients who lost their lives and have PDDIs according to Micromedex were 68.9% while 71.2% of patients who stayed alive and 82.9% of patient who referred had PDDIs. These findings demonstrated that there is no association between the prevalence of PDDIs and the patient's final condition ($X2= 4.6$, $p > 0.05$).

4.3.2 PDDIs in Micromedex according to Mechanism of interactions and severity

Regarding mechanism of interaction, the most frequent mechanism recorded on Micromedex was pharmacodynamic 44.7% (n=400) while the pharmacokinetic interactions were 37.8% (n=338), 1.5% (n=14) were pharmaceutical interactions and the remaining was unknown mechanism. Referring to the severity of DDI founded, most of the PDDI 46.8% (n=419) were major in severity, and moderate was only 45.7% (n=409) of the total interactions reported using Micromedex. [see table 14]

Table 14 Mechanism of interactions and severity in Micromedex

Micromedex	**N (894)**	**%**
Mechanism of interactions		
Pharmacokinetic	338	37.8%
Pharmacodynamic	**400**	**44.7%**
Pharmaceutical	14	1.5%
Unknown	142	15.8%
Severity		
Contraindicated	20	2.2%
Major	**419**	**46.8%**
Moderate	409	45.7%
Minor	46	5.1%

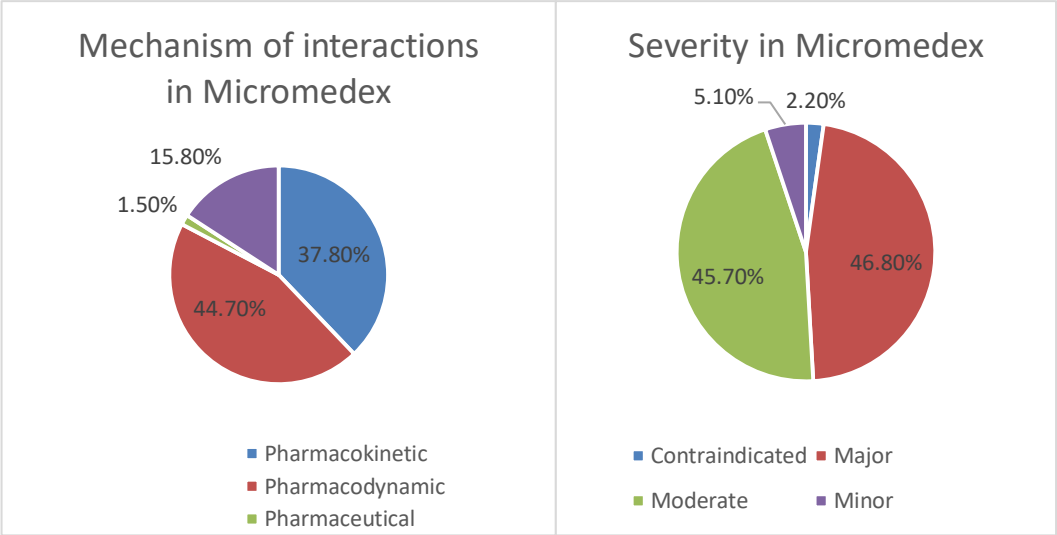

Figure 5 Mechanism and severity of PDDIs in Micromedex

4.4 Drug-drug interaction according to Lexicomp

4.4.1 PDDIs in Lexicomp according to demographic characteristics

According to Lexicomp, 256 (81.5%) out of 314 patients had PDDIs, resulting in 1239 PDDIs. There were 147 (57.4%) male patients and 109 (42.6%) female patients among the 256 patients with PDDIs. [see table 15]

Patients 65 years of age or older had the highest number of PDDIs (45.7%), followed by patients aged between 35 to 64 years old (43.4%), and patients aged between 18 to 34 years old had the lowest number of PDDIs (10.9%). [see table 16]

Patients who stayed in the ICU for fewer than three days had the highest rate of PDDIs (43%), followed by those who stayed for three to seven days (41.4%), and those who stayed for more than seven days had the lowest rate of PDDIs (15.6%). [see table 17]

Patients who took 6 to 10 drugs had the highest number of PDDIs (59%), followed by patients who took more than 10 drugs (29.7%), and the least number of PDDIs were in patients who took 2 to 5 drugs (11.3%). [see table 18]

You can have a look at Table 19 which shows the relationship between the incidence of PDDI and the patient's final condition.

Table 15 PDDIs distribution among patient's gender in Lexi-comp.

			LEXI interaction		Total
			No	Yes	
Gender	Female	N	21	109	130
		%	16.2%	83.8%	100.0
	Male	N	37	147	184
		%	20.1%	79.9%	100.0
Total			58	256	314

The female patients who had PDDIs according to Lexi were 83.8% while 71.7% of the male patients had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and gender (X^2= 0.79, p >0.05).

Table 16 PDDIs distribution among patient's age in Lexi-comp

			Lexi interaction		Total
			No	Yes	
Age	18-34	N	22	28	50
		%	44.0%	56.0%	100.0
	35-64	N	19	111	130
		%	14.6%	85.4%	100.0
	65	N	17	117	134
		%	12.7%	87.3%	100.0
Total			58	256	314

The patients between 18-34 years old who had PDDIs according to Lexi were 56.0% while 85.4% and 87.3% of patients between 35-64 years old and 65 years of age or older had PDDIs. These findings demonstrated that there is significantly difference between the presence of PDDIs and age (X^2= 25.8, p < 0.05).

Table 17 PDDIs distribution among LOS in Lexi-comp.

	Lexi interaction		Total
	No	Yes	

Length of stay (days)	< 3	N	32	110	142
		%	22.5%	77.5%	100.0
	3-7	N	15	106	121
		%	12.4%	87.6%	100.0
	>7	N	11	40	51
		%	21.6%	78.4%	100.0
Total			58	256	314

The patients who stayed more than 7 days or less than 3 days in the ICU and who had PDDIs according to Lexi-comp were 78.4% and 77.5%, respectively, while 87.6% of patients who stayed between 3-7 days had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and length of stay (X^2= 4.8, p > 0.05).

Table 18 PDDIs distribution among medication number in Lexi-comp

			Lexi interaction		Total
			No	Yes	
Medication number	2-5	N	30	29	59
		%	50.8%	49.2%	100.0
	6-10	N	26	151	177
		%	14.7%	85.3%	100.0
	>10	N	2	76	78
		%	2.6%	97.4%	100.0
Total			58	256	314

The patients who used more than 10 drugs and who had PDDIs according to Lexi were 97.4%. In addition, 85.3% of patients who used 6-10 drugs had PDDIs while 49.2% of patients who used 2-5 drugs had PDDIs. These findings demonstrated that there is a significant association between the presence of PDDIs and the number of medications (X^2= 55.88, p < 0.05).

Table 19 PDDIs distribution among patient's status in Lexi-comp

			Lexi interaction		Total
			No	Yes	
Status	Alive	N	42	135	177
		%	23.7%	76.3%	100.0
	Dead	N	8	53	61
		%	13.1%	86.9%	100.0
	Referral	N	8	68	76
		%	10.5%	89.5%	100.0
Total			58	256	314

The patients who lost their lives and had PDDIs according to Lexi-comp were 86.9% while 76.3% of patients who stayed alive and 89.5% of patient who referred had PDDIs. These findings demonstrated that there is association between the prevalence of PDDIs and the patient's final condition. (X^2= 7.9, $p < 0.05$).

4.4.2 PDDIs in Lexicomp according to Mechanism of interactions and severity

Regarding mechanism of interaction, the most frequent mechanism recorded on Lexicomp was pharmacodynamic 82.4% (n=1021), while the pharmacokinetic interactions were 6.5% (n=81), pharmaceutical interactions were identified in 0.5% (n=7) and the remaining was unknown mechanism. Referring to the severity of drug interactions founded, most of them 61.4% (n=761) were category C in severity, and D category was 22.1% (n=274) of the total interactions reported using Lexicomp. [see table 20]

For the severity of interaction category X, 14 interactions were detected between (Labetalol hydrochloride* Salbutamol) 2 times, (Ipratropium bromide* Tiotropium) 2 times, and for the following each one occurred only once (Linezolid * Metoclopramide hydrochloride), (Clarithromycin* Tamsulosin hydrochloride), (Nifedipine * Phenytoin Sodium), (Azithromycin*Clarithromycin), (Diclofenac sodium* Meloxicam), (Chloroquine *Clarithromycin), (Dabigatran * Enoxaparin sodium), (Gemfibrozil *Simvastatin), (Clarithromycin*Simvastatin), and (Chlorphenamine *Ipratropium bromide)

Table 20 Mechanism of interactions and risk rating in Lexi-comp

Lexicomp	N (1239)	%
Mechanism of interactions		
Pharmacokinetic	81	6.5%
Pharmacodynamic	**1021**	**82.4%**
Pharmaceutical	7	0.5
Unknown	130	10.5%
Risk rating		
A	0	0.0%
B	190	15.3%
C	**761**	**61.4%**
D	274	22.1%
X	14	1.1

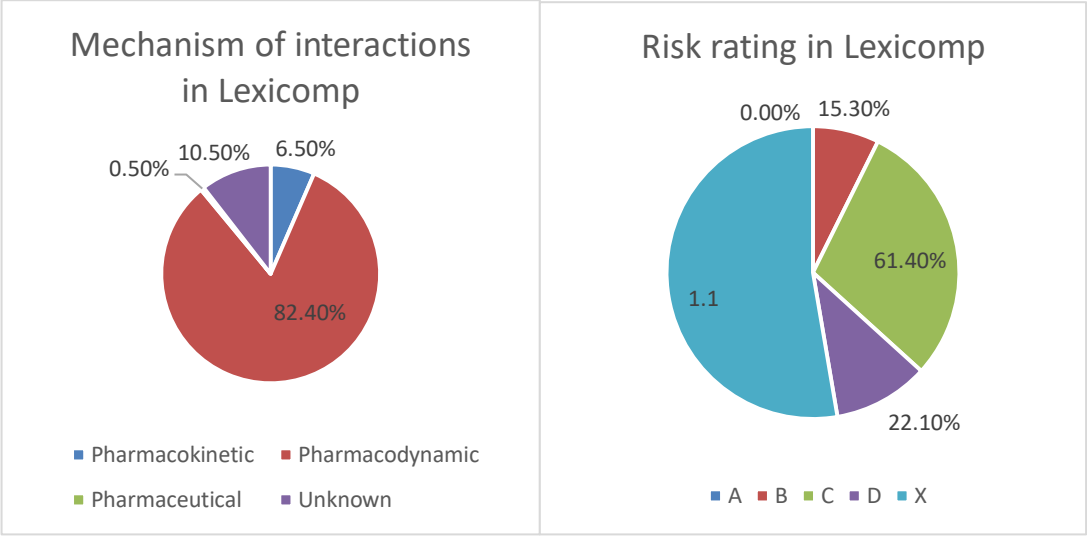

Figure 6 Mechanism and risk rating of PDDIs in Lexi-comp

4.5 Drug-drug interaction according to Drugs.com

4.5.1 PDDIs in Drugs.com according to demographic characteristics

According to Drugs.com, PDDIs were found in 284 (90.4%) of 314 patients, resulting in 1847 PDDIs. Of the 284 patients with PDDIs, there were 161 (56.7%) male patients and 123 (43.3%) female patients. [see table 21]

Patients 65 years of age or older had the most PDDIs (44.1%), followed by patients aged between 35 to 64 years old (40.1%), and patients aged between 18 to 34 years old had the fewest PDDIs (15.8%). [see table 22]

Patients who stayed in the ICU for fewer than three days had the largest number of PDDIs (43.7%), followed by those who stayed for three to seven days (40.8%), and those who stayed for more than seven days had the lowest rate of PDDIs (15.5%). [see table 23]

Patients who took 6 to 10 medications had the highest number of PDDIs (58.1%), followed by patients who took more than 10 drugs (27.5%), and the fewest PDDIs were in patients who took 2 to 5 drugs (14.4%). [see table 24]

You can have a look at Table 25 which shows the relationship between the incidence of PDDI and the patient's final condition.

Table 21 PDDIs distribution among patient's gender in Drugs.com.

			Drugs.com interactions		Total
			No	Yes	
Gender	Female	N	7	123	130
		%	5.4%	94.6%	100.0
	Male	N	23	161	184
		%	12.5%	87.5%	100.0
Total			30	284	314

The female patient who had PDDIs according to drugs.com were 94.6% while 87.5% of the male patients had PDDIs. These findings demonstrated that there is a significant association between the presence of PDDIs and gender (X^2= 4.4, p <0.05).

Table 22 PDDIs distribution among patient's age in Drugs.com.

			Drugs.com		Total
			No	Yes	
Age	18-34	N	5	45	50
		%	10.0%	90.0%	100.0

	35-64	N	16	114	130
		%	12.3%	87.7%	100.0
	65	N	9	125	134
		%	6.7%	93.3%	100.0
Total			30	284	314

The patients between 18-34 years old and 65 years of age or older who had PDDIs according to drugs.com were 90.0% and 93.3%, respectively, while 87.7% of patients between 35-64 years old had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and different age (X^2= 2.4, p > 0.05).

Table 23 PDDIs distribution among LOS in Drugs.com.

			Drugs.com interaction		Total
			No	Yes	
Length of stay (days)	< 3	N	18	124	142
		%	12.7%	87.3%	100.0
	3-7	N	5	116	121
		%	4.1%	95.9%	100.0
	>7	N	7	44	51
		%	13.7%	86.3%	100.0
Total			30	284	314

The patients who stayed more than 7 days or less than 3 days in the ICU and who had PDDIs according to Drugs.com were 86.3% and 87.3%, respectively, while 95.9% of patients who stayed between 3-7 days had PDDIs. These findings demonstrated that there is a significant difference between the presence of PDDIs and length of stay. (X^2= 6.7, p < 0.05)

Table 24 PDDIs distribution among medication number in Drugs.com

			Drugs.com interaction		Total
			No	Yes	
Medication number	2-5	N	18	41	59
		%	30.5%	69.5%	100.0
	6-10	N	12	165	177
		%	6.8%	93.2%	100.0
	>10	N	0	78	78
		%	0.0%	100.0%	100.0
Total			30	284	314

The patients who used more than 10 drugs and who had PDDIs according to Drugs.com were 100%. In addition, 93.2% of patients who used 6-10 drugs had PDDIs while 69.5% of patients who used 2-5 drugs had PDDIs. These findings demonstrated that there is a significant association between the presence of PDDIs and the number of medications (X^2= 39.7, $p < 0.05$).

Table 25 PDDIs distribution among patient's status in Drugs.com

			Drugs.com		Total
			No	Yes	
Status	Alive	N	18	159	177
		%	10.2%	89.8%	100.0
	Dead	N	6	55	61
		%	9.8%	90.2%	100.0
	Referral	N	6	70	76
		%	7.9%	92.1%	100.0
Total			30	284	314

The patients who lost their lives and have PDDIs according to Drugs.com were 90.2% while 89.8% of patients who stayed alive and 92.1% of patient who referred had PDDIs. These findings demonstrated that there is no association between the prevalence of PDDIs and the patient's final condition. (X^2= 0.32, $p > 0.05$).

4.5.2 PDDIs in Drugs.com according to Mechanism of interactions and severity

Regarding mechanism of interaction, the most frequent mechanism recorded on Drugs.com 63.9% (n=1181) was pharmacodynamic, while the pharmacokinetic interactions were 21.6% (n=400), the pharmaceutical interactions were 13.5% (n=250) and the remaining was unknown mechanism. Referring to the severity of PDDIs founded, most of them 64.3% (n=1189) were moderate in severity, and major was 18.4% (n=340). [see table 26]

Table 26 Mechanism of interactions and severity in Drugs.com

Drugs.com	**N (1847)**	**%**
Mechanism of interactions		
Pharmacokinetic	400	21.6%
Pharmacodynamic	**1181**	**63.9%**
Pharmaceutical	16	0.8%
Unknown	250	13.5%
Severity		
Minor	318	17.2%
Moderate	**1189**	**64.3%**
Major	**340**	18.4%

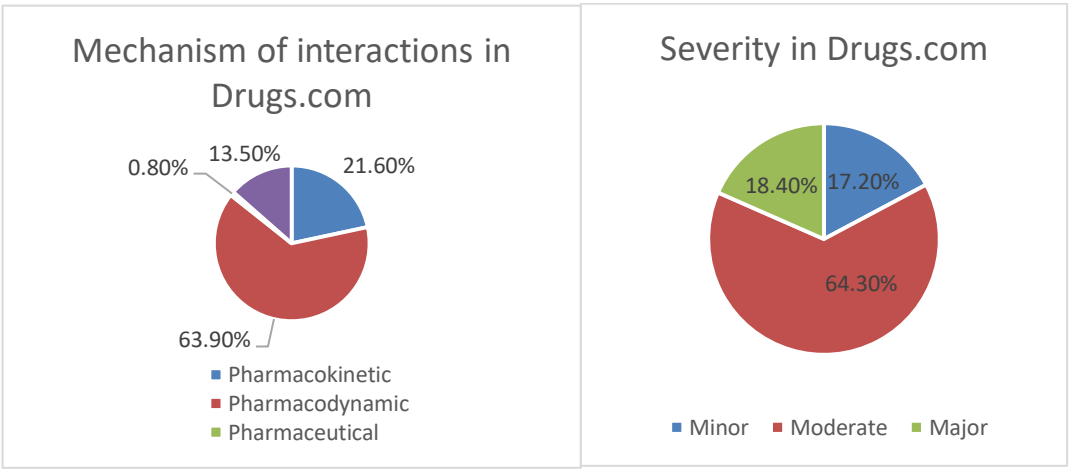

Figure 7 Mechanism and severity of PDDIs in Drugs.com

4.6 Drug-drug interaction according to Epocrates

4.6.1 PDDIs in Epocrates according to demographic characteristics

Out of 314 patients, 275 (87.6%) patients had PDDIs according to Epocrates, there are 1706 PDDIs. Among the 275 patients with PDDIs, 158 (57.5%) were male whereas 117 (42.5%) were female. [see table 27]

Patients 65 years of age or older aged had the highest number of PDDIs (45.5%), followed by patients age between 35 to 64 years old (41.8%), and patients aged between 18 to 34 years old had the lowest number of PDDIs (12.7%). [see table 28]

Patients whose stay in the hospital was less than three days had the highest rate of PDDIs (44%), followed by patients who stays between 3 to 7 days (40.4%), and the lowest number of PDDIs was in patients who stays more than seven days (15.6%). [see table 29]

Patients who took 6 to 10 drugs had the highest number of PDDIs (58.9%), followed by patients who took more than 10 drugs (28%), and the least number of PDDIs were in patients who took 2 to 5 drugs (13.1%). [see table 30]

You can have a look at Table 31 which shows the relationship between the incidence of PDDI and the patient's final condition.

Table 27 PDDIs distribution among patient's gender in Epocrates.

			Epocrates		Total
			No	Yes	
Gender	Female	N	13	117	130
		%	10.0%	90.0%	100.0
	Male	N	26	158	184
		%	14.1%	85.9%	100.0
Total			39	275	314

The female patient who had PDDIs according to Epocrates were 90% while 85.9% of the male patients had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and gender (X^2= 1.1, p >0.05).

Table 28 PDDIs distribution among patient's age in Epocrates.

			Epocrates		Total
			No	Yes	
Age	18-34	N	15	35	50
		%	30.0%	70.0%	100.0
	35-64	N	15	115	130
		%	11.5%	88.5%	100.0
	65	N	9	125	134
		%	6.7%	93.3%	100.0
Total			39	275	314

The patients between 18-34 years old who had PDDIs according to Epocrates were 70.0% while 88.5% of patients between 35-64 years old had PDDIs, and 93.3% of patients 65 years of age or older had PDDIs. These findings demonstrated that there is significantly association between the presence of PDDIs and different age (X2= 18.3, $p < 0.05$).

Table 29 PDDIs distribution among LOS in Epocrates.

			Epocrates		Total
			No	Yes	
Length of stay (days)	< 3	N	21	121	142
		%	14.8%	85.2%	100.0
	3-7	N	10	111	121
		%	8.3%	91.7%	100.0
	>7	N	8	43	51
		%	15.7%	84.3%	100.0
Total			39	275	314

The patients who stayed more than 7 days or less than 3 days in the ICU and who had PDDIs according to Epocrates were 84.3% and 85.2%, respectively, while 91.7% of patients who stayed between 3-7 days had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and length of stay ($X^2= 3.1$, $p > 0.05$).

Table 30 PDDIs distribution among medication number in Epocrates

			Epocrates		Total
			No	Yes	
Medication number	2-5	N	23	36	59
		%	39.0%	61.0%	100.0
	6-10	N	15	162	177
		%	8.5%	91.5%	100.0
	>10	N	1	77	78
		%	1.3%	98.7%	100.0
Total			39	275	314

The patients who used more than 10 drugs and who had PDDIs according to Epocrates were 98.7%. In addition, 91.5% of patients who used 6-10 drugs had PDDIs while 61% of patients who used 2-5 drugs had PDDIs. These findings demonstrated that there is a significant association between the presence of PDDIs and the number of medications (X^2= 49.6, $p < 0.05$).

Table 31 PDDIs distribution among patient's status in Epocrates

			Epocrates		Total
			No	Yes	
Status	Alive	N	30	147	177
		%	16.9%	83.1%	100.0
	Dead	N	6	55	61
		%	9.8%	90.2%	100.0
	Referral	N	3	73	76
		%	3.9%	96.1%	100.0
Total		N	39	275	314

The patients who lost their lives and have PDDIs according to Epocrates were 90.2% while 83.1% of patients who stayed alive and 96.1% of patient who referred had PDDIs. These findings demonstrated that there is association between the prevalence of PDDIs and the patient's final condition. (X^2= 8.7, $p < 0.05$).

4.6.2 PDDIs in Epocrates according to Mechanism of interactions and severity

Regarding mechanism of interaction in Epocrates, the most frequent mechanism recorded were pharmacodynamic 76.1% (n=1298) while the pharmacokinetic interactions were 20.2% (n=346), the pharmaceutical interactions were 0.8% (n=15) and the remaining was unknown mechanism. Referring to the severity of drug interactions founded, most of them 68.9% (n=1176) were belonged to category monitor/ modify, while avoid/ use alternative category were 19.1% (n=327) and caution advised were 10.4% (n=178). [see table 32]

Table 32 Mechanism of interactions and severity in Epocrates

Epocrates	**N (1706)**	**%**
Mechanism of interactions		
Pharmacokinetic	346	20.2%
Pharmacodynamic	**1298**	**76.1%**
Pharmaceutical	15	0.8%
Unknown	47	2.7%
Severity		
Contraindications	25	1.4%
Avoid/ use alternative	327	19.1%
Monitor/ Modify	**1176**	68.9%
Caution advised	178	10.4%

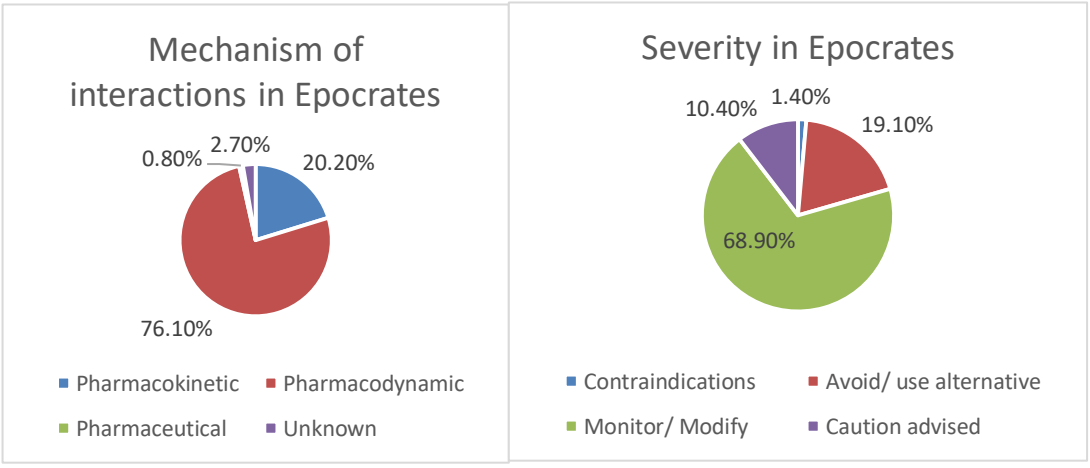

Figure 8 Mechanism and severity of PDDIs in Epocrates

4.7 Drug-drug interaction according to Medscape

4.7.1 PDDIs in Drugs.com according to demographic characteristics

According to Drugs.com, PDDIs were found in 283 (90.1%) of 314 patients, resulting in 1671 PDDIs. Of the 283 patients with PDDIs, there were 163 (57.6%) male patients and 120 (42.4%) female patients. [see table 33]

Patients 65 years of age or older had the most PDDIs (44.2%), followed by patients aged between 35 to 64 years old (41%), and patients aged between 18 to 34 years old had the fewest PDDIs (14.8%). [see table 34]

Patients who stayed in the ICU for fewer than three days had the largest number of PDDIs (44.5%), followed by those who stayed for three to seven days (40%), and those who stayed for more than seven days had the lowest rate of PDDIs (15.5%). [see table 35]

Patients who took 6 to 10 medications had the highest number of PDDIs (59%), followed by patients who took more than 10 drugs (27.2%), and the fewest PDDIs were in patients who took 2 to 5 drugs (13.8%). [see table 36]

You can have a look at Table 37 which shows the relationship between the incidence of PDDI and the patient's final condition.

Table 33 PDDIs distribution among patient's gender in Medscape

			Medscape		Total
			No	Yes	
Gender	Female	N	10	120	130
		%	7.7%	92.3%	100.0
	Male	N	21	163	184
		%	11.4%	88.6%	100.0
Total			31	283	314

The female patient who had PDDIs according to Medscape were 92.3% while 88.6% of the male patients had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and gender (X^2= 1.1, p > 0.05).

Table 34 PDDIs distribution among patient's age in Medscape.

			Medscape		Total
			No	Yes	
Age	18-34	N	8	42	50
		%	16.0%	84.0%	100.0
	35-64	N	14	116	130
		%	10.8%	89.2%	100.0
	65	N	9	125	134
		%	6.7%	93.3%	100.0
Total			31	283	314

The patients between 18-34 years old who had PDDIs according to Medscape were 84% while 89.2% of patients between 35-64 years old had PDDIs, and 93.3% of patients 65 years of age or older had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and different age (X^2= 3.7, p > 0.05).

Table 35 PDDIs distribution among LOS in Medscape.

			Medscape		Total
			No	Yes	
Length of stay (days)	< 3	N	16	126	142
		%	11.3%	88.7%	100.0
	3-7	N	8	113	121
		%	6.6%	93.4%	100.0
	>7	N	7	44	51
		%	13.7%	86.3%	100.0
Total		N	31	283	314

The patients who stayed more than 7 days or less than 3 days in the ICU and who had PDDIs according to Medscape were 86.3% and 88.7%, respectively, while 93.4% of patients who stayed between 3-7 days had PDDIs. These findings demonstrated that there is no association between the presence of PDDIs and length of stay (X^2= 2.6, p > 0.05).

Table 36 PDDIs distribution among medication number in Medscape

			Medscape		Total
			No	Yes	
Medication number	2-5	N	20	39	59
		%	33.9%	66.1%	100.0
	6-10	N	10	167	177
		%	5.6%	94.4%	100.0
	>10	N	1	77	78
		%	1.3%	98.7%	100.0
Total			31	283	314

The patients who used more than 10 drugs and who had PDDIs according to Medscape were 98.7%. In addition, 94.4% of patients who used 6-10 drugs had PDDIs while 66.1% of patients who used 2-5 drugs had PDDIs. These findings demonstrated that there is a significant association between the presence of PDDIs and the number of medications (X^2= 48.2, $p < 0.05$).

Table 37 PDDIs distribution among patient's status in Medscape

			Medscape		Total
			No	Yes	
Status	Alive	N	23	154	177
		%	13.0%	87.0%	100.0
	Dead	N	2	59	61
		%	3.3%	96.7%	100.0
	Referral	N	6	70	76
		%	7.9%	92.1%	100.0
Total			31	283	314

The patients who lost their lives and had PDDIs according to Medscape were 96.7% while 87% of patients who stayed alive and 92.1% of patient who referred had PDDIs. These findings demonstrated that there is no association between the prevalence of PDDIs and the patient's final condition. (X^2= 5.2, $p > 0.05$).

4.7.2 PDDIs in Medscape according to Mechanism of interactions and severity

Regarding mechanism of interaction in Medscape, the most frequent mechanism recorded were pharmacodynamic 53.9% (n=902) while the pharmacokinetic interactions were 23.2% (n=388), the pharmaceutical interactions were 0.7% (n=12) and the remaining was unknown mechanism. Referring to the severity of drug interactions founded, most of them 64.1% (n=1071) were belonged to category monitor closely, while serious category was 17.5% (n=294) and Minor were 15.9% (n=266). [see table 38]

Table 38 Mechanism of interactions and severity in Medscape

Medscape	N (1671)	**%**
Mechanism of interactions		
Pharmacokinetic	388	23.2%
Pharmacodynamic	**902**	**53.9%**
Pharmaceutical	12	0.7%
Unknown	369	22.1%
Severity		
Minor	266	15.9%
Monitor Closely	**1071**	**64.1%**
Serious	294	17.5%
Contraindicated	41	2.4%

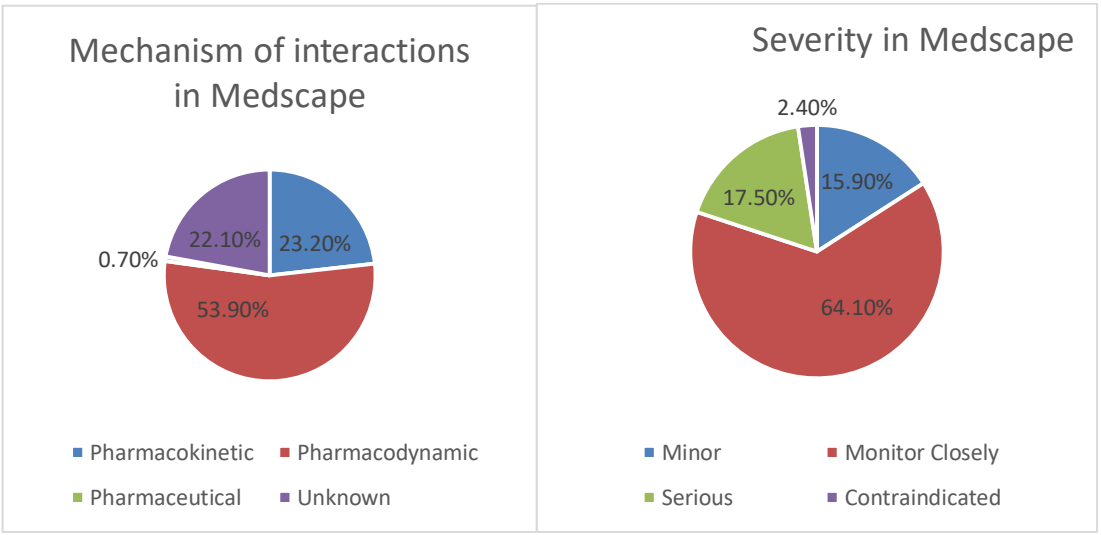

Figure 9 Mechanism and severity of PDDIs in Medscape

CHAPTER V
DISCUSSION

A significant scope of clinical pharmacy practice is to rationalize drug use. Individualizing drug therapy is the main service of clinical pharmacy which aimed to discover, evaluate, solve and prevent PDDIs. PDDIs can prevent the rational prescribing and lead to possible serious incidents and even death. It is quite usual to use drug combinations with the capability to interact in medical practice.(Mamo & Alemu, 2020) Despite not all DDIs detected in a patient may occur, their identification is relevant since they can raise the risk for adverse drug reactions (ADRs), toxicity, or loss of treatment efficacy. This can increase days of hospital stay and costs in addition to adverse consequences for patients. The occurrence of DDIs among ICU patients is a vital issue that demands more attention by healthcare practitioners. PDDIs occur at high rates in the ICU as a result of many reasons including severity of disease of ICU patients and complicated regimens of multiple medications used. Accordingly, if this PDDIs is not specified; This can lead to subsequent treatment failure or adverse drug reactions.(Mamo & Alemu, 2020) (Karajizadeh, M., Zand, F., Sharifian, 2021)

The present study was designed with the aim of investigating the prevalence of potential PDDIs among patients admitted to the ICUs. Based on the results of this study, the prevalence of PDDIs in ICUs is high, 81.50% according to Lexicomp, 73.60% according to Micromedex, and 90.40%, 87.60%, 90.10% according to Drugs.com, Epocrates and Medscape respectively.

A vast majority of ICU patients are exposed for PDDIs. In previous studies, the incidence of PDDIs among ICU patients was considered as high. An 8 months study of PDDIs in the intensive care unit in Belgium, showed that 79% of 275 ICU patients are exposed to PDDIs on day 3. (Vanham et al., 2016). Abideen et al., used Lexi-comp system showed that prevalence of PDDIs for ICU patients of Narayana Hrudayalaya (NH) Hospital in India was 90.02%. (Abideen et al., 2015) Another study of PDDIs in patients admitted in the adult ICU of Clinics Hospital of the State University of Campinas (HC-UNICAMP) in care hospital in Brazil by Rodrigues et al., reported that the incidence of PDDIs was 89%. (Rodrigues et al., 2011). While

45.5% of ICU patients were found to have PDDIs according to study conducted in Turkey (GülçebİE et al., 2016). This is comparable to Smithburger et al study in USA, in which 46.3% PDDIs in ICU patients was also reported (Smithburger et al., 2012)

In terms of mechanisms, PDDIs could be categorized into pharmacodynamic, pharmacokinetic, pharmaceutical and unknown interactions. The pharmacokinetics affect the processes of absorption, distribution, metabolism and excretion, while pharmacodynamics occurs when the effects of a drug changed in presence of another one at the site of actions. The majority of PDDIs recorded in our study were caused by the pharmacodynamic mechanism. Pharmacodynamic interactions caused 44.7% (n=400/894) while pharmacokinetic interactions caused 37.8% (n=338/894), unknown 15.8% (n=142/894) and pharmaceutical interactions 1.5% (n=14/894) were responsible for a smaller number of PDDIs in Micromedex database. In Lexi-comp, pharmacodynamic interaction caused 82.4% (n=1021/1293) while pharmacokinetic interaction caused 6.5% (n=81/1239), pharmaceutical interactions 0.5% (n=7/1239) and 10.5% (n=130/1239) with an unknown mechanism of interaction. Drugs.com database showed that pharmacodynamic interactions caused 63.9% (n=1181/1847) of PDDIs, pharmacokinetic interactions caused 21.6% (n=400/1847), unknown 13.5% (n=250/1847) and pharmaceutical interactions 0.8% (n=16/1847) of PDDIs. In Epocrates pharmacodynamic interactions caused 76.1% (n=1298/1706) while pharmacokinetic interactions caused 20.2% (n=346/1706), pharmaceutical interactions 0.8% (n=15/1706) and 2.7% (n=47/1706) with an unknown mechanism of interactions. The last database, Medscape, exhibited that 53.8% (n=902/1671) of PDDIs was pharmacodynamic interactions, pharmacokinetic interactions, pharmaceutical interactions and an unknown mechanism of interactions caused 23.2% (n=388/1671), 0.7% (n=12/1671) and 22.1% (n=369/1671), respectively. The results of the other studies were close to the results of our study at the mechanism level and showed the pharmacodynamic caused the greatest number of PDDIs in ICU patients. A prospective cross-sectional study was performed at the intensive care units of 2 teaching hospitals in Peshawar, namely Khyber Teaching Hospital (KTH) and Hayatabad Medical Complex (HMC), Peshawar, Pakistan, between January 2014 and January 2015 on 520 patients (260 from each hospital) showed that 70% of DDIs in KTH and 71.7% of PDDIs in HMC caused by pharmacodynamic interaction while pharmacokinetic interaction 32% and 27%, and an unknown mechanism of interaction caused 1% and 1.3%. (Shakeel, Khan, et al., 2018). Another study

conducted in Malaysia documented that the pharmacodynamics-related DDIs were more common (66.90%) than pharmacokinetics-related DDIs (24.20%). (Hasan et al., 2012). On the other hand, a prospective study carried out in an ICU of a pulmonary teaching hospital in Iran surveyed 195 patients, the total incidence of pharmacokinetics interactions was 71.4%. (Baniasad, 2014).

At the level of a severity of drug-drug interactions, in our study the most PDDIs in 1847 interactions found were moderate (n=1189; 64.30%) followed by major 18.40% (n=340), minor 17.20% (n=318) according to Drugs.com database. A retrospective search over a period of 6 months, showed a close comparison to our study, 66.6% in total PDDIs were classified as moderate severity, 23.7% were minor and only 9.7% were of major severity.(Ali et al., 2020).

According Lexi-comp, DDIs are classified by risk rating of interaction into five level A, B, C, D, X. A retrospective study on 72 patients found 222 PDDIs, combination should be avoided (X), combination must consider therapy modification (D) and combination which must be monitor (C) were found to be 7.20% (16), 35.59% (79) and 57.21% (127) respectively. (Abideen et al., 2015). A similar result was obtained in our study. 61.4% of PDDIs were reported as type C (n=761) in compare to 1.1% of PDDIs of X (n=14), 22.1% of interactions of D (n=274) and 15.3% PDDIs of B (n=190). No need to worry when medications have interaction on level C, usually the benefits of concomitant two drugs outweigh the risks. To prevent any negative consequences, an effective monitoring strategy must be implemented. Dosage adjustments of one or both drugs may be necessary for patients. Also, An observational and prospective study detected 72.2% category C (n=125), 21.4% category D (n=37), and 6.4% category X (n=11) risk category interactions.(Gülçebİ et al., 2016)

Micromedex categorized the severity into 4 levels (Contraindicated, Major, Moderate and Minor). For this study, the results were as follows: 46.8% (n=419/864) were major, 45.7% (n=409/864) were moderate and 5.1% (n=46/864), 2.2% (n=20/846) were minor and contraindicated, respectively. Likewise, a cross sectional study was conducted at the critical care units of four tertiary care hospitals in Peshawar, Pakistan; a total of 3019 PDDIs were observed, 46.3% (1398) were of major severity, 50.8% (1533) were of moderate severity, 2.7% (82) were of minor severity while 0.2% (6) PDDIs were contraindicated. (Shakeel, Khan, et al., 2018). The findings of a recent study in 2018 were as follows: Total PDDIs = 1171,

contraindicated = 6 (1%), major = 715 (61%), moderate = 428 (36%), and minor = 22 (2%) PDDIs. (Wagh BR et al., 2019).

Based on Epocrates, the classifications of severity interaction are 4: Contraindicated, Avoid/Use Alternative, Monitor/Modify and Caution Advised. Our findings were monitor/modify 68.9% (n=1179/1706), avoid/use alternative 19.1% (n=327/1706) and caution advised and contraindicated were 10.4% (n=178/1706), 1.4% (n=25/1706), respectively. Likewise, a recent study published in 2017, showed that the most PDDIs were monitor/modify with mean 8.22 ± 7.43 and the fewer common PDDIs were contraindicated with mean 0.01 ± 0.10. (Opančina et al., 2017).

Medscape drug interaction checker categorized the severity into four levels Contraindicated, Serious, Monitor Closely and Minor. According to Opančina et al study, the vast majority were monitor closely with mean 20.35 ± 15.21 (Opančina et al., 2017). This is comparable to our study where the majority of PDDIs were monitor closely 64.1%, then serious PDDIs 17.5%, then minor 15.9%, and the least PDDIs were contraindicated 41%.

Gender, age, length of stay in ICU and an increasing number of medications are a risk factor for PDDIs, although not all of them have a statistically significant association with PDDIs.

In our study, age was significantly associated with presence of PDDIs according Micromedex (X^2= 6.3, $p < 0.05$), Lexi-comp (X^2= 25.8, $p < 0.05$) and Epocrates, (X^2= 18.3, $p < 0.05$), and no associated with PDDIs according to Drugs.com (X^2= 2.4, $p > 0.05$) and Medscape interaction checker (X^2= 3.7, $p > 0.05$). We divided patients into three age groups, the highest number of PDDIs were in patients 65 years of age or older according to all PDDIs databases, except for Micromedex, where the highest rate of PDDIs were for patients between the ages of 35 and 64. Unlike most studies that have shown that there is no relationship between age and interactions. A study published in 2020 found no statistically significant relationship between the number of drug interactions and age ($P > 0.05$) according to Lexi-comp. (Tahmasebivand et al., 2020). Another study used Lexi-comp and Micromedex showed no significant differences were found in the different age groups, i.e., 0–30, 31–60, > 60 years ($p = 0.148$) in terms of the occurrence of PDDIs. (Hasan et al., 2012)

In our sample, 184 patients (58.6%) were male and 130 (41.4%) were female. Male patients had more PDDIs, but there was no statistically significant association

between gender and the presence of PDDIs according to all interaction databases (Micromedex (X^2= 0.76; p >0.05), Lexi-comp (X^2= 0.79; p >0.05), Epocrates (X^2= 1.1; p >0.05) and Medscape (X^2= 1.1; p > 0.05)), except for Drugs.com interaction database (X^2= 4.4; p <0.05). Several studies have come to similar conclusions. A published Iranian study indicated that no statistically significant relationship between the number of drug interactions and gender (P > 0.05).(Tahmasebivand et al., 2020). Also, another study conducted by Shakeel et al., showed that the association of PDDIs with gender ($p \geq 0.05$) were insignificant. (Shakeel, Khan, et al., 2018)

The other result of this study showed that the duration of stay in the intensive care unit has statistically insignificant association with PDDIs (Shakeel, Aamir, et al., 2018). Conversely, previous research has found different results. Significant association have been founded between the length of stay in the ICU and the presence of PDDIs, as in the study conducted in Malaysia which found that the duration of ICU stay < 3 days, 3–7 days and > 7 days showed a significant difference (p = 0.001) in the occurrence of DDIs. (Hasan et al., 2012). Similarly, we divided the patients in our study into three groups regarding to the length of stay, < 3 days 45.2% (n=142), 3–7 days 38.5% (n=121) and > 7 days 16.2% (n=51), We found that PDDIs are most frequent for patients stays for less than 3 days compared to longer days of ICU stay. This is because PDDIs may have been reduced with extended days in hospital due to the role of clinical pharmacists and health care providers in detecting and resolving PDDIs. However, the statistical association between the presence of PDDIs and length of stay was insignificant according to three databases which are Lexi-comp (X^2= 4.8, p > 0.05), Epocrates (X^2= 3.1, p > 0.05) and Medscape (X^2= 2.6, p > 0.05), while the findings demonstrated that there is significantly association between the presence of PDDIs and length of stay according to Micromedex and Drugs.com, (X^2= 6.8, p < 0.05), (X^2= 6.7, p < 0.05) respectively.

It is important that the current study showed a significant association between the number of administered drugs and the presence of PDDIs according to all drug interaction databases used in this study.

It is important that the current study showed a significant correlation between the number of drugs taken and the presence of PDDIs according to all drug interaction databases used in this study (Micromedex (X^2= 29.79, p < 0.05), Lexi-comp (X^2= 55.88, p < 0.05), Drugs.com (X^2= 39.7, p < 0.05), Epocrates (X^2= 49.6, p < 0.05) and Medscape (X^2= 48.2, p < 0.05)). Most of the patients in our study administered 6 to

10 medications (n=177; 56.4%) and Majority of PDDIs were encountered in this group. Studies by Gülçebİ et al., Tahmasebivand et al., Hasan et al., and Shakeel et al. were agreed with our finding. (Gülçebİ et al., 2016) (Tahmasebivand et al., 2020) (Hasan et al., 2012) (Shakeel, Aamir, et al., 2018). The reason for this significant relation was the presence of polypharmacy. Increased prescription drug numbers have contributed to increased polypharmacy probabilities.(Chavda et al., 2015) Polypharmacy is described as the use of more than five medications.(Masnoon et al., 2017) To avoid unfavourable outcomes caused by DDIs, patients who are exposed to polypharmacy should be detected and monitored more closely.(Bjerrum et al., 2008)

We investigated in our study the association between the patient's final state and the number of PDDIs in order to determine if the increased number of PDDIs contributed to the patients' deaths. According to the data of the study, there is a significant association between the presence of PDDIs and the final state of the patients, according to only two of the interaction databases used which are Lexi-comp (X^2= 7.9, $p < 0.05$) and Epocrates (X^2= 8.7, $p < 0.05$). While other databases showed no statistically association. There are multiple studies that address the theme of PDDIs; however, few of them address the death of the patient as a final result of the interaction. (Rosas-carrasco et al., 2011)

Most drug interactions have identifiable factors that alleviate the interaction or render it unlikely to produce adverse consequences. These factors include the way in which the medications are administered, dose, duration of treatment, dosing times, sequence of drug administration, etc. as well as the individual factors such as pharmacogenetics and planned to monitor the patient. Many drug interactions in particular patients can be ignored by considering these factors.

The real question is, did the combination result in harm? If this question is not asked, then there could be a significant narrowing of the already limited armamentarium of drugs available to treat patients in ICUs. If medications with the potential for interactions are ultimately beneficial to the patient, it may be necessary to use it. But reducing suffering and relief of symptoms should be a priority. Although medications aimed at alleviating symptoms can be overused, patients should not suffer because of unfounded fear of adverse effects. Providers need to be aware and vigilant regarding the potential for PDDIs. Close monitoring of patients in such situations is warranted. With the best evidence available yet, there is highly unlikely a report in the studies that exactly fits a specific patient’s situation entirely.

Knowledge of clinical pharmacology, pharmacokinetics, pharmacodynamics, and pharmacogenomics to individualize (personalize) a patient's treatment regimen will be the way of the future. (Bhatt-mehta et al., 2016)

Strength and Limitations:

This is the first study that evaluates PDDIs in ICU in this hospital, and considered unique in using five different interaction checker databases in Saudi Arabia to detecting the PDDIs in ICU.

Since all patients who admitted to the ICU for almost three years were enrolled, the number of patients included in the analysis was considered a good representation of sample size.

COVID-19 was the most important limitation that affected many aspects of the study, as we were given permission to enter the hospital for a relatively short period, and also, we were not allowed to use paper archives to reduce contact and we were limited to electronic archives, which prevented us from including a larger number of patients in the study, because the electronic archive contains only the information of patients who were admitted to the hospital in the past three years only.

In addition, our study was retrospective, and this prevents us from being able to apply an intervention and see the outcomes clinically, and no directly discuss with the prescribers.

One of the study's main limitations is that various variables that influence the incidence of PDDIs, such as patient weight, genetic factors, and major organ function status, were not taken into account.

Another limitation is that this study was conducted in one hospital, so the results might not be generalizable.

CHAPTER VI
CONCLUSION AND RECOMMENDATION

Conclusion: It can be concluded that the prevalence of PDDIs is high in ICUs. Almost all critically ill patients in the intensive care unit are vulnerable to at least one PDDI due to the multiple drug administration that is common in the ICU. However, more empirical evidence is needed to support the likelihood of patient harm and its severity.

As a consequence, physicians, clinical pharmacists, and nurses should be constantly vigilant for PDDIs in patients, especially those in critical care.

Recommendation: Including clinical pharmacists in a hospital, could be of great help to ICU clinicians, as they could regularly search for PDDIs among drugs prescribed to high-risk ICU patients on a daily basis, thus preventing their occurrence.

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APPENDIX

Appendix A

Data collection form

Lab Test:

Lab / Value				
Cr				
PCT				
CRP				
BUN				
Na^{+}				
K^{+}				
Cl^{-}				
Ca^{++}				
Mg^{++}				
INR				
PTT				
WBC				
RBC				
Hgb				
Hct				
MCV				
Plt				
Troponin				
Alb				
AST				
ALT				
Glc				
Trig				
LDL				
CPK-MB				
D-dimer				

Ventilator ◯	Catheter ◯	Urine catheter ◯

NOTE:

DATA COLLECTION FORM

Alaa Hesham Harmoush

Patient Information:

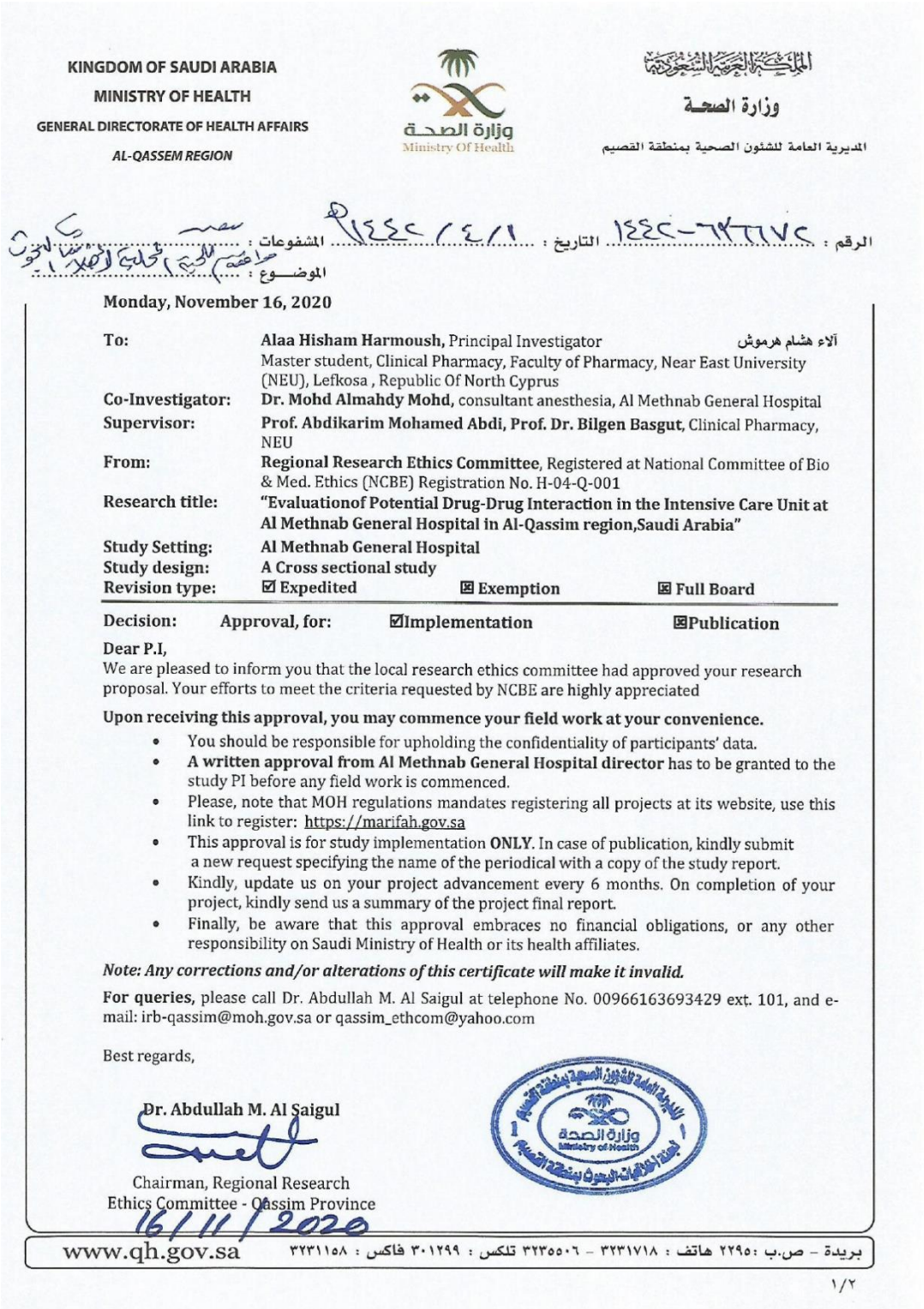
Name:	Number:
Gender: ☐ F ☐ M	Age:
Date of admission: ...../...../..... Date of discharge: ...../...../.....	Length of stay:
Diagnosis at admission:	
Diagnosis during ICU:	
Complications:	
Patient's final condition: ◯ Alive ◯ Dead ◯ Referral	

Medicines prescribed to the patient in ICU:

1.	17.
2.	18.
3.	19.
4.	20.
5.	21.
6.	22.
7.	23.
8.	24.
9.	25.
10.	26.
11.	27.
12.	28.
13.	29.
14.	30.
15.	31.
16.	32.

Appendix B

Ethical approval



KINGDOM OF SAUDI ARABIA
MINISTRY OF HEALTH
GENERAL DIRECTORATE OF HEALTH AFFAIRS
AL-QASSEM REGION

المملكة العربية السعودية
وزارة الصحة
المديرية العامة للشئون الصحية بمنطقة القصيم

وزارة الصحة
Ministry Of Health

الرقم : ١٤٤٢-٦٢٦٦٧٤ التاريخ : ١٤٤٢/٤/١ المشفوعات :
الموضوع :

Monday, November 16, 2020

To:	**Alaa Hisham Harmoush,** Principal Investigator آلاء هشام هرموش Master student, Clinical Pharmacy, Faculty of Pharmacy, Near East University (NEU), Lefkosa , Republic Of North Cyprus
Co-Investigator:	**Dr. Mohd Almahdy Mohd,** consultant anesthesia, Al Methnab General Hospital
Supervisor:	**Prof. Abdikarim Mohamed Abdi, Prof. Dr. Bilgen Basgut,** Clinical Pharmacy, NEU
From:	**Regional Research Ethics Committee**, Registered at National Committee of Bio & Med. Ethics (NCBE) Registration No. H-04-Q-001
Research title:	**"Evaluationof Potential Drug-Drug Interaction in the Intensive Care Unit at Al Methnab General Hospital in Al-Qassim region,Saudi Arabia"**
Study Setting:	**Al Methnab General Hospital**
Study design:	**A Cross sectional study**
Revision type:	**☑ Expedited ☒ Exemption ☒ Full Board**

Decision: **Approval, for:** **☑Implementation** **☒Publication**

Dear P.I,
We are pleased to inform you that the local research ethics committee had approved your research proposal. Your efforts to meet the criteria requested by NCBE are highly appreciated

Upon receiving this approval, you may commence your field work at your convenience.

- You should be responsible for upholding the confidentiality of participants' data.
- **A written approval from Al Methnab General Hospital director** has to be granted to the study PI before any field work is commenced.
- Please, note that MOH regulations mandates registering all projects at its website, use this link to register: https://marifah.gov.sa
- This approval is for study implementation **ONLY**. In case of publication, kindly submit a new request specifying the name of the periodical with a copy of the study report.
- Kindly, update us on your project advancement every 6 months. On completion of your project, kindly send us a summary of the project final report.
- Finally, be aware that this approval embraces no financial obligations, or any other responsibility on Saudi Ministry of Health or its health affiliates.

Note: Any corrections and/or alterations of this certificate will make it invalid.

For queries, please call Dr. Abdullah M. Al Saigul at telephone No. 00966163693429 ext. 101, and e-mail: irb-qassim@moh.gov.sa or qassim_ethcom@yahoo.com

Best regards,

Dr. Abdullah M. Al Saigul
Chairman, Regional Research
Ethics Committee - Qassim Province
16/11/2020

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١/٢

CV

Personal information

Name, surname: Date of birth and place:	Alaa harmoush 25, April,1993, Syria
Current occupation: MSc in clinical pharmacy at neu Address of correspondence: AL Qassim, Saudi Arabia Telephone: +966537938101 E-mail: alaa.harmoush.93@gmail.com	

Education

Year	Grade	University	Field
2013-2018	good	Philadelphia university	BSc