NEAR EAST UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CLINICAL PHARMACY

ASSESMENT OF POTENTIAL DRUG-DRUG INTERACTIONS IN THE RESPIRATORY CLINICS

M.Sc THESIS

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NICOSIA

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Approval

We certify that we have read the thesis submitted by Mohaned Shafie M. ElZubeir titled **"Assesment of Potential Drug-Drug Interactions in the Respiratory Clinics"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Educational Sciences.

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Abstract

Assesment of potential drug-drug Interactions in respiratory clinics

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SUMMARY

Purpose

This study aimed to assess the risk of possible drug-drug interactions upon admission and during hospitalization in patients with respiratory diseases treated at the Near East Hospital(NEUH) in the Turkish Republic of Northern Cyprus (TRNC).

Method

Out of 270 patients, we retrospectively analyzed 236 eligible patients with respiratory diseases (ages 17 to 98) at the NEUH. The data collected was only for patients hospitalized in the respiratory clinics between December 1st, 2021, and December 1st, 2022. Drugs.com and medscape.com interaction checkers were used for screening potential drug-drug interactions (pDDIs). The detected drug-drug interactions (DDIs) were categorized based on their severity.

Results

pDDI was detected in 202 patients out of 236. The mean age of patients was equal to or more than 60 years old, the length of hospital stay was 0-5 days and the number of medications in a prescription for a patient was 5-9. According to drugs.com, the most common type of interaction was major (53.8%) and moderate (22.9%). Using medscape.com, 47% and 30.5% were recorded for monitor closely and serious interaction, respectively. There was a significant association between the occurrence of pDDIs and the number of prescribed medications.

Conclusion

The current study revealed a significant frequency of pDDIs in respiratory clinics. Patients with polypharmacy were at high risk for DDIs. Education, automated prescribing systems, medication information, and pharmaceutical care are all essential methods suggested for minimizing the harm caused by DDIs.

***Key Words**:* Drug interactions, Respiratory clinics, NEUH, TRNC

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List of Abbreviations

DDI: Drug-drug interaction

pDDI: Possible drug-drug interactions

DRPs: Drug-Related Problems

ADE: Adverse Drug Event

ADR: Adverse Drug Reaction

MAOIs: Monoamine Oxidase Inhibitor

FQ: Fluoroquinolone

CPs: Cephalosporins

LMWH: Low Molecular Weight Heparins

OTC: Over the counter

NEUH: Near East University Hospital

TRNC: Turkish Republic of Northern Cyprus

SPSS: Statistical Package for Social Sciences

FDA: Food & Drug Administration

MRRH: Mbarara Regional Referral Hospital

CHAPTER I

This section provides a concise overview and foundational context about possible interactions between medications in patients who are hospitalized at the internal clinic. It covers the problem statement, the importance of the study, its objectives, constraints, the inquiries the research seeks to address, and the clarification of terminology.

Introduction

A drug-drug interaction occurs when two or more drugs interact, resulting in altered drug effectiveness or toxicity. Although most drug-drug interactions are preventable, they can potentially cause serious harm to patients. The prevalence of potential DDIs has been estimated at between 15 and 45 % of hospitalized patients (Zheng et al., 2017).

DDIs are more common in elderly patients, patients hospitalized for a longer time, and/or receiving multiple drugs daily. Potential drug-drug interactions are more likely to affect hospitalized patients due to multiple factors such as comorbid conditions, chronic therapeutic regimens, polypharmacy, and modifications in therapy (Diksis et al., 2019). Drug-drug interactions are divided into pharmacodynamic and pharmacokinetic interactions. PD interactions occur when the combination of medications causes additive or antagonistic pharmacological effects and influences efficacy. PK interactions occur when there are changes in absorption, distribution, metabolism, and elimination. Drug-drug interactions are often predictable; thus, they can be avoided or managed (Diksis et al., 2019).

Many DDIs happen at the drug clearance level, especially for drugs that undergo metabolism. The CYP450 enzyme system, responsible for metabolizing various drugs, including antibiotics, can be inhibited, induced, or saturated by the drugs. Antibiotics primarily metabolized by a specific P450 isoform may experience significant changes in their serum concentration as drug clearance is either increased or decreased due to alterations in enzyme activity. These enzymes are found in high concentrations in the liver, but the intestinal mucosa also contains CYP450 enzymes and is a site where numerous drug-drug interactions affecting bioavailability can occur (Michael et al. Reed, 2012).

DDIs can result in adverse clinical outcomes, accounting for 5% of hospital admissions (Lazarou J et al., 1998). In 1995, the med watch program of the FDA recorded 6,894 deaths attributed to adverse drug reactions (ADRs), which encompassed DDIs, within the United States (Chyka PA, 2000). Research has shown possible DDI rates ranging from 2.2% to 30% in hospitalized patients and 9.2% to 70.3% in ambulatory patients (Jankel et al. LK, 1993). pDDIs are identified through retrospective chart checks, while actual DDIs are defined based on clinical evidence confirmed by laboratory testing or symptoms (Qian Y et al., 2010).

Treating a disease may require the administration of multiple medications.(Juurlink DN, 2006). Polypharmacy refers to using five or more medications by a patient and the risk of clinically significant DDIs increases with the number of drugs prescribed. (Georgiev et al., 2022; Pedersen et al., 2021). Polypharmacy poses a considerable risk of DDIs that can have significant health implications. Several factors can heighten the likelihood of adverse drug interactions, including using medications with a narrow therapeutic index, the severity of underlying medical conditions, and the patient's age (particularly in the elderly population). These factors increase the risk of detrimental drug interactions (Juurlink DN, 2006). Thus the prevalence of polypharmacy and DDIs are likely to increase due to the aging population and more aggressive treatment of chronic diseases (Pedersen et al., 2021).

The prevalence of pDDI is close to 40% in patients taking five medications and increases to 80% in patients taking seven or more medications (Diksis et al., 2019).

Hospitalized patients have more complicated treatments due to one or more diseases and are more commonly treated with polypharmacy; therefore, hospitalized patients are more likely to be exposed to drug-drug interactions (Santos et al., 2020).

Studies on DDI patterns have been conducted in various clinics, but clinically important DDIs affecting hospitalized pulmonary patients are not extensively studied (Hamid et al., 2020). This is particularly relevant for patients with chronic obstructive respiratory disorders, such as asthma and chronic obstructive pulmonary disease (COPD), that require combinations of medications with different mechanisms of action for effective treatment (van der Molen and Cazzola, 2012). Utilizing drugs from various classes can result in three primary types of interactions:

synergistic, antagonistic, and additive effects. Synergy refers to an interaction that goes beyond the anticipated additive effect, while antagonism describes an effect weaker than expected when combined (Calzetta et al., 2018). The initial step in evaluating synergy and/or antagonism involves quantifying the additive effect. In this context, the Bliss Independence criterion and the Unified Theory have established techniques for determining the additive effect of drugs targeting the respiratory system. However, only the Bliss approach can offer statistical significance (Calzetta et al., 2015). The rationale behind combining therapies is to trigger a synergistic interaction between individual components, a strategy to enhance the effectiveness of agents and, potentially, decrease the required drug dosages and the likelihood of adverse events (Calzetta et al., 2018). Nonetheless, it is crucial to be cautious and avoid the overlap of drug toxicities (Chou, 2006).

Based on extensive research and comprehensive analysis of published findings, it is well established that asthma and COPD often coincide with a range of additional health conditions, including cardiovascular disease (CVD), depressive disorders, type 2 diabetes mellitus (T2DM), osteoporosis, malignant pulmonary neoplasms, skeletal muscle wasting, and cachexia. Many of these associated conditions are linked to systemic inflammation, which can impact the severity and intensity of asthma and COPD (Cazzola M, 2010). Although the underlying connection involving systemic inflammation is recognized, the precise mechanisms by which it affects asthma, COPD, and related comorbidities, particularly CVD and T2DM, are still not fully understood.

The primary approach to treating asthma and COPD involves bronchodilators, sometimes in combination with each other or inhaled corticosteroids (ICS). The current consensus suggests that even if CVD or T2DM is present, these lung disorders should be managed according to standard protocols.

Nevertheless, instances of adverse cardiovascular events in individuals with asthma or COPD who are using LABA or LAMA should prompt medical professionals to assess the associated risk. This is because LABA and LAMA, despite their selectivity, can influence the heart due to the presence of β1 and β2 adrenergic receptors and M2 and M3 muscarinic receptors in the heart. This impact may hold particular significance for those with pre-existing heart conditions, although

individuals with heart failure often experience reversible bronchoconstriction that responds to inhaled β2-agonists. This could reduce cardiac workload (Adimadhyam S et al., 2014). Moreover, evidence suggests that dual bronchodilation enhances regional ventilation and blood flow in the pulmonary microcirculation in patients with pulmonary hyperinflation, a common occurrence in both asthma and COPD. This, in turn, might contribute to improvements in cardiac filling and overall cardiac output (Vogel-Claussen J et al., 2019).

Effectively overseeing patients who have both asthma or COPD along with other concurrent medical conditions requires consistent monitoring of medication adherence and a comprehensive review of their prescribed medications during each medical encounter. It is crucial to take all necessary measures to minimize the potential for negative impacts on the airways and the organs affected by these additional health issues. Amid the ongoing focus on addressing chronic respiratory conditions in patients by targeting treatable traits, it is vital to recognize that comorbidities represent significant extrapulmonary treatable traits that necessitate specialized treatment when they are present (Cazzola M et al., 2017).

Pharmacokinetic Drug-Drug Interactions

Pharmacokinetics refers to the processes that occur within the body to affect the action of a drug. Clinical implications occur when one drug, known as the perpetrator, modifies the concentration of another drug, referred to as the object (Ben D et al., 2012).

Altered Bioavailability

This situation arises when a perpetrator drug decreases the quantity of the object drug that enters the bloodstream. This commonly occurs when orally administered medications are affected by absorption or first-pass metabolism disruptions. Drug interactions frequently influence medications with low oral bioavailability, whereas those with high bioavailability are seldom affected. For example, drugs such as alendronate and dabigatran possess low oral bioavailability. When alendronate is co-administered with calcium, its bioavailability decreases, leading to the possibility of no alendronate being absorbed. On the other hand, when dabigatran is co-

administered with verapamil, it enhances bioavailability, potentially increasing the risk of bleeding (Ben D et al., 2012).

Altered Clearance

This occurs when a perpetrator drug disrupts the metabolism or excretion of the object drug. Object drugs with a narrow therapeutic index are particularly susceptible because even slight changes in their concentration can have a significant clinical effect (Table 1). Perpetrator medications that have been demonstrated to influence drug metabolism significantly are more likely to cause substantial shifts in concentration and, consequently, result in clinical consequence. Identifying these possible instigators of pharmacokinetic drug-drug interactions is of utmost importance (Polasek et al., 2011).

Drug Class	Example
Antiarrhythmics	Amiodarone
Anticoagulants	Warfarin
Antiepileptics	Phenytoin
Aminoglycoside antibiotics	Gentamicin

Table 1.

Examples of Drug Classes That Contain Narrow Therapeutic Index Drugs.

Metabolism

The most common causes of unanticipated drug interactions are changes in drug metabolism. These occur as a result of changes in medication clearance or oral bioavailability. The cytochrome p450 enzyme family is acknowledged as the principal and most consequential group of enzymes engaged in drug metabolism. (see Table 2). Inhibiting a cytochrome p450 enzyme raises medication concentration by lowering metabolism. Clarithromycin, for example, is a potent inhibitor of CYP3A4-catalyzed simvastatin metabolism, increasing the risk of myopathy (Jacobson TA, 2004). Drugs' inhibition of cytochrome p450 enzymes are also

employed for medicinal purposes. Ritonavir, a potent cyp3a4 inhibitor, decreases the metabolism of other protease inhibitors, improving their effectiveness in treating HIV (so-called 'ritonavir-boosted' regimens) (Walmsley S et al., 2022). When a cytochrome p450 enzyme is induced, it enhances the metabolism of specific medications, reducing their concentration. For instance, drugs like carbamazepine, phenytoin, and St. John's wort, CYP3A4 inducers, can increase the metabolism of combination oral contraceptives. This increase in metabolism raises the risk of an unexpected pregnancy. (Sabers A., 2008). Some popular CYP3A4 inhibitors include macrolides (clarithromycin and erythromycin), azole antifungals such as ketoconazole and Itraconazole, and grapefruit juice. Bupropion and paroxetine inhibit the CYP2D6 enzyme, whereas no medications induce it. Fluconazole inhibits the CYP2C9 and CYP2C19 enzymes, whereas rifampicin induces them. Finally, ciprofloxacin and fluvoxamine inhibit CYP1A2 metabolism, but phenytoin and rifampicin induce it (Polasek TM et al., 2011).

Prodrugs

Certain drugs are converted to their active form by cytochrome p450 enzymes. Prodrugs are particularly vulnerable to alterations in metabolism because they usually rely on a specific enzymatic pathway. If the process of transforming a prodrug into its active state is blocked, it can cause insufficient levels of the active medication, leading to treatment failure. One instance is tamoxifen, which is converted into its active form called endoxifen by the enzyme cyp2d6. Using the potent cyp2d6 inhibitor paroxetine alongside tamoxifen has been associated with a rise in breast cancer mortality (Kelly CM et al., 2010).

Excretion

Certain medications are eliminated from the body in their active state, typically through urine or the biliary tract. Effects on renal tubular function or urine pH might cause changes in renal drug clearance. Probenecid, for example, lowers the renal clearance of anionic medicines like methotrexate and penicillin (Ben D et al., 2012).

Altered distribution

This occurs when the drug's concentration at the active site changes without altering the circulating concentration. This poses a particular challenge for medications that target intracellular or central nervous system sites. Some medications significantly alter the transport of other pharmaceuticals across cell membranes. Verapamil is an example of this, as it inhibits efflux transporters like p-glycoprotein, resulting in elevated levels of substances such as digoxin and cyclosporine. Likewise, probenecid inhibits anion transporters like oat-1, resulting in higher levels of substrates like methotrexate and penicillin. Drug interactions mediated by transporters are not as well comprehended as those mediated by metabolism (Ben D et al., 2012).

Pharmacodynamic drug-drug interactions

Pharmacodynamics refers to the effects of a drug on the body. Pharmacodynamics interactions occur when two medications exhibit additive or antagonistic effects. Among these interactions, the brain is the organ most commonly affected, with potential harm resulting from such interactions. Intentional or unintentional pharmacodynamic interactions can arise from the combined use of medications that have additive effects. Intentional examples include the deliberate combination of antihypertensive drugs. However, unintentional interactions can also arise, such as serotonin syndrome resulting from the unintended combination of tramadol and an SSRI. When medications with opposing effects are combined, it can lead to a loss of drug effects. For example, the co-administration of a nonselective beta-blocker with a beta2 agonist can diminish the bronchodilation effect of the latter (Fallowfield JM and Marlow HF, 1996). Consideration of medication effects by organ is a suitable method for identifying pharmacodynamic interactions. Taking into consideration whether these drugs have an impact on the same organ, such as the brain. By doing so, this can assess interactions between medications that operate through different mechanisms, such as combining an anticholinergic and a benzodiazepine. (Hilmer SN et al., 2007).

Categories of DDIs

Drug-drug interactions can be sorted into two broad categories:

- Pharmacokinetic drug interactions refer to situations where one drug influences the pathway or route taken by another drug within the body. This can include hindering the elimination or metabolism of the second drug or even impeding its absorption. As a result of pharmacokinetic drug interactions, the affected drug may exhibit unexpectedly high or low levels in the body, potentially leading to significant side effects or ineffective treatment.
- Pharmacodynamics drug interactions of how the body reacts to a drug, encompassing the connection between the concentration at the target location and its subsequent effects, including the strength and duration of the positive and negative outcomes (Campbell, 2017). These interactions can involve one drug counteracting the therapeutic benefit of another (e.g., Drug A treats high blood pressure, but Drug B increases blood pressure) or two drugs with similar effects working together to produce an unfavorable outcome (e.g., both Drug A and Drug B causing low blood pressure, resulting in excessively low blood pressure). When respiratory medications are utilized correctly, the occurrence of DDIs is minimal. The primary interactions observed among various respiratory drugs involve additive effects, particularly with anticholinergic drugs and those that prolong the QTc interval (Horn et al., 2018).

Other DDIs can result in antagonistic effects. For instance, beta-agonists, commonly present in various inhalers, promote bronchodilation, while beta-blockers cause bronchoconstriction. When patients taking beta-blockers require inhalers, they may need higher doses to achieve desired outcomes since these medications counteract

each other. Combining nonselective beta-blockers, which affect cardiac and respiratory muscles, is not recommended with beta-agonist medications. Cardio-selective beta-blockers primarily target cardiac muscles and have a limited impact on the respiratory system at lower doses. However, as the dosage increases, selective beta-blockers can affect cardiac and respiratory functions (Short PM et al., 2013). Table 1 lists significant respiratory medicine DDIs (Horn et al., 2005), (Pruitt B., 2018).

Alpha/beta-agonists, such as epinephrine and beta-blockers, can have contraindications and DDIs. Monoamine oxidase inhibitors (MAOIs) may cause hyperglycemia and can interact with other medications like antidepressants, particularly Bupropion sustained release, also used as a smoking cessation aid. Certain antidepressants may interact with cyp2d6 inhibitors or inducers and CYP2D6 substrates. Varenicline, used for smoking cessation, may also interact with MAOIs. Among antihistamines, cetirizine and desloratadine may lead to additive anticholinergic effects, while QT interval-prolonging agents like codeine and dextromethorphan can interact with cyp2d6 inhibitors or inducers. Being aware of these contraindications, DDIs, and warnings is crucial to ensure the safe and effective use of these medications (Short PM et al., 2013)

Prevention and Management of Drug- drug Interactions

It is advisable to proactively manage drug interactions before administering medications. Product labels and monographs usually provide information regarding common or significant drug interactions and strategies to prevent such interactions. Drug-drug interaction checkers are valuable resources for evaluating potential interactions and can be used to assess individual drugs or compare different products. In certain situations, managing drug interactions may involve temporarily discontinuing one of the medications or adjusting the timing of administration. However, certain interactions may require more intricate management approaches, such as conducting blood tests or closely monitoring for particular side effects. Research findings indicate that most patients demonstrate incorrect inhalation usage (Hanania N., 2018), (Lehman S., 2018). Regularly review the proper use of respiratory medications, such as inhalers, with patients.

Providing the patients with education on the correct techniques to prevent adverse reactions and errors. During each visit, it is important to reevaluate all medications that patients are taking to minimize the occurrence of additive or antagonistic reactions. Multiple prescribers may prescribe similar medications or provide overlapping recommendations, necessitating a comprehensive assessment. Patients should be encouraged to disclose all prescription drugs, over-the-counter medications, supplements, and vitamins that they are using, as they may not perceive certain substances as important or only disclose medications related to a specific prescriber. It is crucial to recognize that all substances that patients consume or apply to their bodies have the potential to interact. Through medication counseling and reconciliation, the likelihood of unknown interactions and adverse effects can be reduced (Kelsey F., 2008).

Role of clinical pharmacist in DDIs

In collaboration with the prescriber, the clinical pharmacist is responsible for informing patients about potential side effects and providing appropriate guidance if

they arise. Leveraging their extensive understanding of medications, pharmacists can correlate unexpected symptoms patients report with potential adverse effects of their prescribed drug regimen. In clinical pharmacy, this practice aims to minimize ADRs by avoiding medications with known side effects in susceptible individuals. Consequently, pharmacists play a significant role in preventing, identifying, and reporting DDIs (Palanisamy S et al., 2009). A critical role of a clinical pharmacist is to identify, handle, and prevent interactions between different medications (known as drug-drug interactions or DDIs) to safeguard patient well-being and achieve the best therapeutic outcomes. Drug-drug interactions arise when one medication's effects are influenced by the presence of another medication, potentially leading to unfavorable effects, diminished efficacy, or even toxicity. The responsibilities of a clinical pharmacist in addressing drug-drug interactions encompass various key aspects including evaluating and analyzing medications, risk assessment and tailoring treatment to individual patients. Upon identifying a potential drug interaction, clinical pharmacists collaborate with prescribers to suggest appropriate actions. This could involve modifying dosages, altering medication schedules, monitoring specific lab parameters, or opting for alternative medications with lower interaction risks. Clinical pharmacists document their evaluations, recommendations, and interventions tied to drug interactions in the patient's medical records. They also keep tabs on patients for indications of adverse effects or shifts in therapeutic responses and may adjust interventions based on patient outcomes (Margo L et al., 2012).

To sum up, the role of a clinical pharmacist in overseeing drug-drug interactions is pivotal in ensuring the safe and productive utilization of medications, minimizing potential risks, and optimizing patient care.

Management options for drug interactions include:

1. Avoiding the combination: In specific drug interactions, the risks always outweigh the benefits, and it is best to avoid the combination altogether. Since drug classes often vary in their potential for interactions, it is usually possible to select an alternative drug that does not interact with either the main drug or the secondary drug involved (Hazlet TK et al., 2001)

2. Adjusting the dosage of the main drug: Sometimes, it is safe to administer both interacting drugs if the dosage of the main drug is appropriately adjusted (Ansari J, 2010).

3. Spacing out dosing times to prevent interaction: When specific drug interactions involve binding in the gastrointestinal tract, the interaction can be avoided by administering the main drug at least 2 hours before or 4 hours after the secondary drug. This way, the main drug can be absorbed into the bloodstream before the secondary drug becomes active (Ansari J, 2010).

4. Monitoring for early detection: In cases where it is necessary to use interacting drug combinations, careful laboratory or clinical monitoring can help detect signs of the interaction at an early stage. This allows for prompt dosage adjustments or discontinuation of the drugs if needed (Ansari J, 2010).

5. Providing information on patient risk factors: Physicians and pharmacists draw from clinical experience and published studies to identify risk factors that increase the likelihood of adverse outcomes from interacting drug combinations (Doucet J et al., 1996). For example, evidence suggests that statin-induced myopathy risk rises with higher serum concentrations of the statin. Therefore, it is advised not to exceed

20 mg of simvastatin daily in patients concurrently taking verapamil (Orloff DG, 2002).

6. Enhancing computerized screening systems: Despite some limitations, efforts should be made to improve computerized drug interaction screening systems for more effective identification of potential interactions (Chrischilles EA et al., 2002).

7. Computerized drug interaction screening systems often identify many drug interactions, but many pharmacists perceive that many of these interactions may not hold significant clinical relevance.

8. Incorrect handling of drug class differences: Most drug classes exhibit heterogeneous interactions, as individual drugs within the same class are often metabolized by different cytochrome p450 isozymes or ABC transporters. For instance, statins provide a good example, with simvastatin and lovastatin being extensively metabolized by CYP3A4, atorvastatin moderately metabolized by cyp3a4, fluvastatin metabolized by CYP2C9, and pravastatin and rosuvastatin not metabolized by cytochrome P450 isozymes (Williams J and Feely J, 2002). Consequently, it is seldom justified to consider all members of a drug class as interacting together in the context of drug interactions. However, it is a common practice for reviews and computer systems to group all statins as interacting with cyp3a4 inhibitors, even though the risk primarily applies to lovastatin, simvastatin, and a lesser extent, atorvastatin (Pasternak RC et al., 2002).

Statement of the Problem

Potential drug-drug interactions represent a prevalent concern, especially in multi-drug prescriptions. While not all DDIs are clinically significant, alterations resulting from changes in prescribed medications can lead to adverse drug reactions, thus presenting significant clinical challenges. DDIs are thought to account for 2-5% of hospital admissions among elderly patients (Becker et al., 2007), (Olivier et al., 2009), (Bénard-Laribière et al., 2015) and 1% of hospital admissions in the general population (Dechanont et al., 2014). Nowadays, demographic, and epidemiological shifts have resulted in an increasing proportion of the population being old and suffering from chronic comorbidities (Global Burden of Disease Study, 2015). This aging population is projected to increase drug consumption, the prevalence of polypharmacy and chronic polypharmacy (Haider et al., 2007; Nobili et al., 2011; Maher et al., 2014). The older population is particularly vulnerable to the potential impact of drug interactions because of physiological changes that affect pharmacokinetics and pharmacodynamics and the high prevalence of polypharmacy (Hohl et al., 2001).

Purpose of the Study

The study is aimed to detect and assess the incidence and patterns of pDDIs for respiratory clinic patients at the NEUH.

Significance of the Study

The results of this study can be used to identify the most common DDIs in respiratory clinics. It is essential for patient safety, optimal treatment outcomes, and efficient healthcare resource utilization. It allows healthcare professionals to minimize risks, tailor treatment plans, and improve patient care. The results of this study will serve as the basis for future literature reviews and other academic contributions to the topic. Future clinical pharmacists specializing in respiratory diseases can use the study results to develop strategies for bridging knowledge gaps, misinformation and to improve pharmacists' attitudes toward recognizing DDIs and other drug-related problems.

Limitations of study

First, because our study is retrospective, we could not perform an intervention and monitor patient clinical outcomes. In addition, the only source of our knowledge was the patient's files, which prevented us from contacting the patients and identifying further issues. Finally, we cannot generalize our study findings due to the study being conducted only in NEUH so, cannot be generalized to general population to further describe the incidence of DDIs.

Definitions of terms

Drug-drug interaction: A drug interaction can be defined as an unwanted reaction between two or more medications when both are administrated together in a combination regimen that may alter or change the desired therapeutic outcomes. This harmful reaction can sometimes occur between medications, foods, supplements, and beverages. DDIs can affect how the medications work and lead to undesirable adverse outcomes.

Adverse Drug Event (ADE) is "an injury from drug use. The term ADE includes harm caused by adverse drug reactions, overdoses, and harm from drug use (including dose reductions and discontinuations of drug therapy). ADE may result from medication errors, but most do not.

Adverse Drug Reactions (ADR) are any unintended, harmful events attributed to the use of medicines – that occur as a cause of and during a significant proportion of unscheduled hospital admissions.

Medication Error is any preventable event that may cause or lead to inappropriate medication use or patient harm.

Pharmacodynamic Interactions: The alternation of the pharmacological effects of one medication that is altered by the presence of another drug in combination therapy may result in toxicity or changes in therapeutic outcomes.

Pharmacokinetic Interactions: When the medications interfere with the absorption, distribution, metabolism, and elimination, better known as ADME, of another drug, this is known as pharmacokinetics interactions; in other words, it is the alternation of disposition of co-administrated medications that result in changes of the medications' plasma concentrations.

Respiratory Medicine is a medical specialty focused on diagnosing, treating, and managing diseases and disorders affecting the respiratory system. This includes conditions related to the lungs, airways, and respiratory muscles.

CHAPTER II

Literature Review

This chapter presents research-based conceptual definitions, descriptions, and existing literature on the subject matter.

Theoretical Framework

DDI constitutes one of the potential mechanisms leading to often preventable ADE and health damage (Edwards IR & Aronson JK, 2000). Multiple drug therapies are very common for the treatment of various medical illnesses. Such therapy is a potential source of DDIs. DDIs have recently garnered significant attention from regulatory bodies, scientific researchers, and healthcare communities worldwide (Farkas D et al., 2008). Many new drugs are launched every year, and novel drug interactions are becoming more common. As a result, clinicians can no longer rely solely on memory to avoid dangerous drug interactions. Precipitant medications alter the object drug's absorption, distribution, metabolism, excretion, or clinical effect. Nonsteroidal anti-inflammatory medications, antibiotics, and, in particular, Rifampin, are frequently prescribed in primary care. Drugs with a narrow therapeutic index are more prone to significant drug interactions. Object drugs in common use include Warfarin, Fluoroquinolones, antiepileptic drugs, oral contraceptives, cisapride, and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (Ament PW et al., 2000).

The pharmacist and the prescriber are responsible for ensuring that patients are aware of the potential side effects and are equipped with the necessary information to handle them if they arise. Due to their comprehensive knowledge of medications, pharmacists can link atypical symptoms patients report to potential adverse effects of their drug therapy. Clinical pharmacy practice also ensures that ADRs are reduced by avoiding medications with probable side effects in vulnerable patients. As a result, pharmacists play an essential role in ADR prevention, detection, and reporting (Palanisamy S et al., 2009).

This study aims to identify and assess the incidence and patterns of pDDI in patients at respiratory clinics. 236 eligible patients' medical files, out of 270, were analyzed, and data of the patients admitted to respiratory clinic between Dec 1st,

2021, to Dec 1st, 2022 was collected. Patients' age, gender, hospital stay, and medications administered on the first day of hospital admission were analyzed. Drugs.com and Medscape.com drug interaction checkers were used to detect pDDIs and categorize them based on their severity.

Related Research

A study conducted by Chatsisvili analyzed 1,553 prescriptions. 213 prescriptions were identified to have one or more pDDIs, leading to 287 moderate DDIs. Potentially harmful medications were present in 18.5% of the prescriptions. Major DDIs accounted for 1.9% of all prescriptions and 10.5% of all identified DDIs, while moderate DDIs accounted for 16.6% of all prescriptions and 89.5% of all detected DDIs. The frequency of DDIs increases with the number of medications in a prescription. Amiodarone, known to interact with potassium-wasting diuretics, digoxin, simvastatin, and acenocoumarin, was the most common medication involved in serious DDIs. The study concludes that implementing a suitable surveillance system is necessary to monitor such interactions effectively (Chatsisvili et al., 2010).

A retrospective study by Lubinga et al. in Western Uganda examined 235 patients. The study revealed an overall prevalence of pDDIs of approximately 23%, with 54 out of 235 hospitalization admissions indicating at least one potential DDI on the drug charts. 10.6% of the identified interactions were determined to occur via a pharmacodynamic mechanism, and the recommended management strategies were either "use with caution" (11.9%) or "modify treatment/monitor" (10.6%). The study found that having a primary diagnosis of cardiovascular disease and being prescribed four or more medications were associated with pDDI. The study concluded that while potential DDIs were common, most were not clinically significant. Nevertheless, patients with cardiovascular disease and those taking multiple medications should be closely monitored (Lubinga et al., 2011).

Dirin et al. conducted a study investigating pDDIs in prescriptions dispensed in both community and hospital pharmacies in east Iran. Of the 2,796 prescriptions reviewed, 1,163 (41.6%) had at least one drug-drug interaction. 1,576 interactions were detected in the examined prescriptions, and approximately 66% were categorized as category C. The study's conclusion emphasized the role of polypharmacy in facilitating these interactions or using multiple medications, which

was a significant contributing factor. The probability of drug interactions increased with the number of items per prescription. According to the survey, approximately 48% of the prescriptions analyzed consisted of 3-4 medication items, with an average of 4.18 items per prescription. Previous research studies have demonstrated that the occurrence of potential drug interactions in patients taking two or more medications ranges from 24.3% to 42%. This suggests that the pDDIs rise as the number of drugs increases. Category C interactions were the most prevalent in the study, constituting 66% of all interactions observed in the analyzed settings (Dirin et al., 2014).

Research Questions

i. What are the most common potential drug-drug interactions among patients admitted to the respiratory clinic department?
ii. What factors contribute to the increased risk of DDIs?

CHAPTER III

Methodology

This chapter provides details regarding the research design, participants or sample, data collection and analysis procedures, and the approach employed to analyze the findings.

Research Design

A retrospective observational study was conducted on patients (aged 17 and above) hospitalized at the respiratory clinic between December 1st, 2021, to December 1st, 2022 at the NEUH in the TRNC.

Inclusion Criteria

- Patients admitted to the respiratory clinic of NEU Hospital
- Patients hospitalized in the respiratory clinic for 12 months (from Dec1st, 2021, till Dec1st, 2022)

Exclusion Criteria

- Incomplete patient files

Sample Size and Data Collection

The Raosoft software calculator with 5% margin of error, 95% cofidence level and 270 population size was used to estimate the required sample size. The recommended sample size was 159. Data were collected from the medical records of all patients admitted to respiratory clinics throughout 12 months (Dec 1st, 2021, to Dec 1st, 2022). The nucleus program of the NEU hospital system was used to assist

in collecting the data. The approximate time needed to complete the data collection for each patient was approximately 5 minutes.

Patients' ages, genders, primary diagnoses, concurrent disease states and medications were recorded.

Only the first-day prescription was analyzed for drug-drug interactions.

Statistical Data Analysis Procedure

The collected data was inputted into a Numbers Spreadsheet and subsequently analyzed using Statistical Package for Social Sciences (SPSS) version 28.0 for macintosh apple.

Guidelines and references used to determine drug-drug interactions.

Online databases were utilized to investigate possible drug-drug interactions.

1. Drugs.com
2. Medscape.com

The potential drug-drug interactions were grouped into four categories based on severity for each database.

- Drugs.com (No interaction, Major interaction, Moderate interaction and Minor Interaction)
- Medscape.com (No interaction, Serious interaction, Monitor closely and Minor interaction)

Ethical Considerations

Ethical approval for this research study was approved on 30th November 2022 from the Scientific Research Ethical Committee of Near East University Hospital (NEU/2022/108-1639). Throughout the study, strict measures were taken to ensure patient privacy and confidentiality. No private patient information was recorded. The study solely utilized patients' file numbers, age, gender, diagnosis, and medications as data points.

CHAPTER IV

Findings and Discussion

Demographic Data

The study collected 236 patients' data that's eligible out of 270, from December 1st, 2021, till December 1st, 2022. Only the first-day prescription was utilized to identify any possible drug-drug interactions. Results indicate that out of the 236 patients, 51.7% were male, and 48.3% were females. Moreover, approximately 73.3% of the patients included in the study belonged to the age group equal to or greater than 60. Of all the patients, 62.7% had hospital stays ranging from 0 to 5 days, while 22.9% remained hospitalized for longer than ten days. Most patients (61.4%) were prescribed 5-9 medications per prescription, followed by 22.5% prescribed 10-14 medications. Finally, the most common diagnosis as to why the patients were admitted to the respiratory clinic was due to several respiratory disorders such as Asthma, COPD and Pneumonia. The mean of total number of medications taken was (2.21± 0.70). 62.7% of the patients stayed at the hospitals between 0-5 days, 14.4% stayed between 6 to 9 days, and 22.9% stayed for 10 or more days. The mean of hospitalization days was (1.60 ± 0.83), with the number of medications recorded during the hospitalization period (2.21± 0.70) ranging from 5 to 9 drugs per prescription. Finally, the most common diagnosis as to why the patients were admitted to the respiratory clinic was due to several respiratory disorders such as asthma, COPD, and pneumonia.

Drug Interactions

202 patients (85.6%) had DDI, while 34 (14.4%) had no DDIs. The study results show the frequency of DDIs and severity according to two online databases for checking drug interactions. The two online databases used in the study were drugs.com & medscape.com drug interaction checkers. According to drugs.com, 53.8% of major DDI were identified, followed by moderate (22.9%) and minor (0.8%). (Table 5). The most common drug classes responsible for the major interactions were corticosteroids + macrolides, causing 50 DDIs and corticosteroids

+ FQ (budesonide + moxifloxacin), resulting in 20 DDIs. As for the moderate interaction, CPs + PPIs resulted in 32 DDIs. Penicillin + macrolide accounted for most of the minor interactions resulting in 8 DDIs, 4 times by ampicillin + clarithromycin and 4 times by piperacillin/tazobactam + clarithromycin. (Table 6).

While using medscape.com, the results showed that most of the DDIs were monitor closely (47%), serious interactions (30.5%) and minor interactions (3.4%). According to medscape.com, the highest interaction recorded was monitor closely, accounting for 111 DDIs (47%), followed by serious interaction that was responsible for 72 DDIs (30.5%) and 8 minor interactions DDIs (3.4%). (Table 5). Corticosteroids + PPI causing 73 DDIs. LMWH + corticosteroids were the drug classes responsible mainly for the moderate interactions resulting in 50 DDIs. As for the serious interaction, 21 DDIs from the drug combination of CPs + LMWH were recorded. Macrolides and corticosteroids were also accountable for 28 serious DDIs. Diuretics + corticosteroids & corticosteroids + macrolides were mainly responsible for the minor interactions resulting in 40 DDIs and 30 DDIs, respectively. (Table 6).

Based on the age categories and according to drugs.com, the age group (17-19 years old) recorded 2 no interactions, 2 major, 0 moderate and 0 minor interactions. As for the 20-29 years old, they recorded 3 no interactions, 8 major interactions, 1 moderate and 1 minor interaction. 7 no interactions, 10 major, 1 moderate and 0 minor interactions were the results of the age group between 30-39 years old. 40-49 years old age group recorded 4 no interactions, 7 major, 1 moderate and 0 minor interactions. 50-59 years old age group results were that 5 had no interactions, 8 major, 3 moderate and 0 minor interactions. Finally, the age group with the highest DDI (173 DDI) was the age group equal to or above 60. 32 patients had no interaction, 92 had major, 48 had moderate, and 1 had minor interactions.

Using medscape.com, the age group (17-19 years old) recorded 1 no interaction, 2 serious interactions, 1 monitor closely and 0 minor interactions. As for the 20-29 years old, they recorded 3 no interactions, 3 serious interactions, 6 monitor closely and 0 minor interactions. 4 no interactions, 7 serious interactions, 5 monitor closely and 2 minor interactions were the results of the age group that is between 30-39 years old. The 40-49 age group recorded 5 no interactions, 3 serious interactions, 3 closely monitored, and 1 minor interaction. 50-59 years old age group results were that 1 patient had no interactions, 3 had serious interactions, 11 required close

monitoring moderate, and 1 had 1 minor interaction. Finally, the age group with the highest DDI (173 DDI) was the age group equal to or above 60. 31 patients had no interaction, 54 had serious interactions, 85 had monitor closely, and 3 had minor interactions.

Table 2.

Illustrates the DDI According to Drugs.com and Its Effect on Different Age Groups.

		Drugs.com Interactions				
		No interaction	Major interaction	Moderate interaction	Minor interaction	No interaction
Age	17-19	2	2	0	0	2
	20-29	3	8	1	1	3
	30-39	7	10	1	0	7
	40-49	4	7	1	0	4
	50-59	5	8	3	0	5
	Equal or more than 60	32	92	48	1	32
Total		53	127	54	2	53

Table 3.

DDIs According to Medscape.com and their Effect on Different Age Groups.

		Medscape.com DDIs			
		Serious interaction	Monitor closely	Minor interaction	No interaction
Age	17-19	1	2	1	0
	20-29	3	3	6	1
	30-39	4	7	5	2
	40-49	5	3	3	1
	50-59	1	3	11	1

Table 3 (Continued).

	Equal or more than 60	31	54	85	3
Total		45	72	111	8

Table 4.

General Characteristics of the Patients in the Respiratory Clinic.

	Characteristics	**Frequency**
Gender	Male	112 (51.7%)
	Female	114 (48.3%)
Age	17-19	4 (1.7%)
	20-29	13 (5.5%)
	30-39	18 (7.6%)
	40-49	12 (5.1%)
	50-59	16 (6.8%)
	Equal to or greater than 60	173 (73.3)
Hospital Stay	0-5 days	148 (62.5%)
	6-9 days	34 (14.4%)
	Equal to or more than 10 days	54 (22.9%)
Prescribed medications per patient	Equal to or less than 4 medications	26 (11%)
	5-9 medications	145 (61.4%)
	10-14 medications	53 (22.5%)

Table 4 (Continued).

	Equal to or more than 15 medications	12 (5.1%)

Table 5.

Prevalence of Potential Drug-Drug Interactions in Respiratory Clinics.

	Type of Prevalence	**Frequency**
	DDIs (present)	202 patients (85.6%)
	No DDIs	34 patients (14.4%)
Drugs.com	No interaction	53 (22.5%)
	Major interaction	127 (53.8%)
	Moderate interaction	54 (22.9%)
	Minor interaction	2 (0.8%)
Medscape.com	No interaction	45 (19.1%)
	Serious interaction	72 (30.5%)
	Monitor closely	111 (47%)
	Minor interaction	8 (3.4%)

Table 6.

Most Common Medications that are Responsible for the pDDIs.

	Severity	Most common DDI	Effects	Managements
Drugs.com	Major Interaction	Corticosteroids + Macrolides (x20 ddis) Corticosteroids + FQ (x50 ddis)	Hypercorticism such as acne, thinning of skin Tendinitis	Budesonide alternative, progressive dosage reduction Caution is recommended
	Moderate Interaction	CPs + PPI (x32 ddis)	May increase gastric pH	Alternative antibiotic
	Minor Interaction	Penicillin + Macrolide (x8 ddis)	-	Monitoring
Medscape.com	Serious interaction	Macrolides + Corticosteroids (x28 ddis) Penicillins + LMW Heparins (x19 ddis) Cephalosporins + LMWHeparins (x21 ddis)	Increased level of corticosteroid Anticoagulation Anticoagulation	Avoid or use of alternative drug Avoid or use of alternative drug Avoid or use of alternative drug
	Moderate Interaction	PPI + Corticosteroids (x83 ddis) LMWH + Corticosteroids (x50 ddis)	Increase gastric pH Decreased anticoagulation effects	Monitor closely Use with caution/Monitor
	Minor Interaction	Corticosteroids + Diuretic (x40 ddis) Corticosteroids + Macrolides (x30 ddis)	Hypokalemia Decreased effect of macrolides	- -

Table 7.

Frequency of Gender.

Gender			
	Frequency	Percent	Valid Percent
Male	122	51.7	51.7
Female	114	48.3	48.3
Total	236	100.0	100.0

Table 8.

Frequency of Type of Diseases.

Types of Diseases			
	Frequency	Percent	Valid Percent
Respiratory disorder	134	56.8	56.8
More than 1 disorder	87	36.9	36.9
Endocrine disorder	1	.4	.4
Electrolyte imbalances	1	.4	.4
Mental health condition	2	.8	.8
Oncological disorder	6	2.5	2.5
GI disorder	2	.8	.8
Eye condition	1	.4	.4

Table 8 (Continued).

Toxicities	1	.4	.4
Cerebrovascular disease	1	.4	.4
Total	236	100.0	100.0

Table 9.

Frequency of DDIs According To Drugs.com.

Drugs.com DDIs			
	Frequency	Percent	Valid Percent
No interaction	53	22.5	22.5
Major interaction	127	53.8	53.8
Moderate interaction	54	22.9	22.9
Minor interaction	2	.8	.8
Total	236	100.0	100.0

Table 10.

Frequency of DDIs According To Medscape.com.

Medscape.com DDIs			
	Frequency	Percent	Valid Percent
No interaction	45	19.1	19.1
Serious interaction	72	30.5	30.5
Monitor closely	111	47.0	47.0
Minor interaction	8	3.4	3.4
Total	236	100.0	100.0

Figure 1.

DDIs Frequency Identified by Drugs.com.

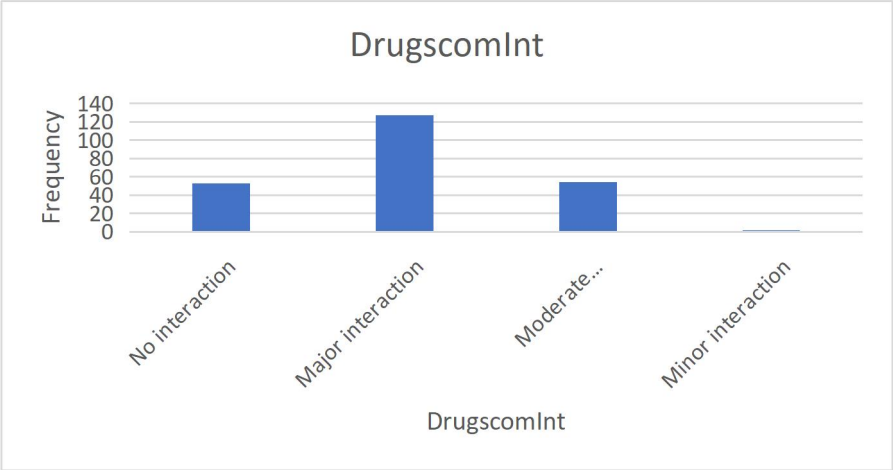

Figure 2.

DDIs Frequency Identified by Medscape.com.

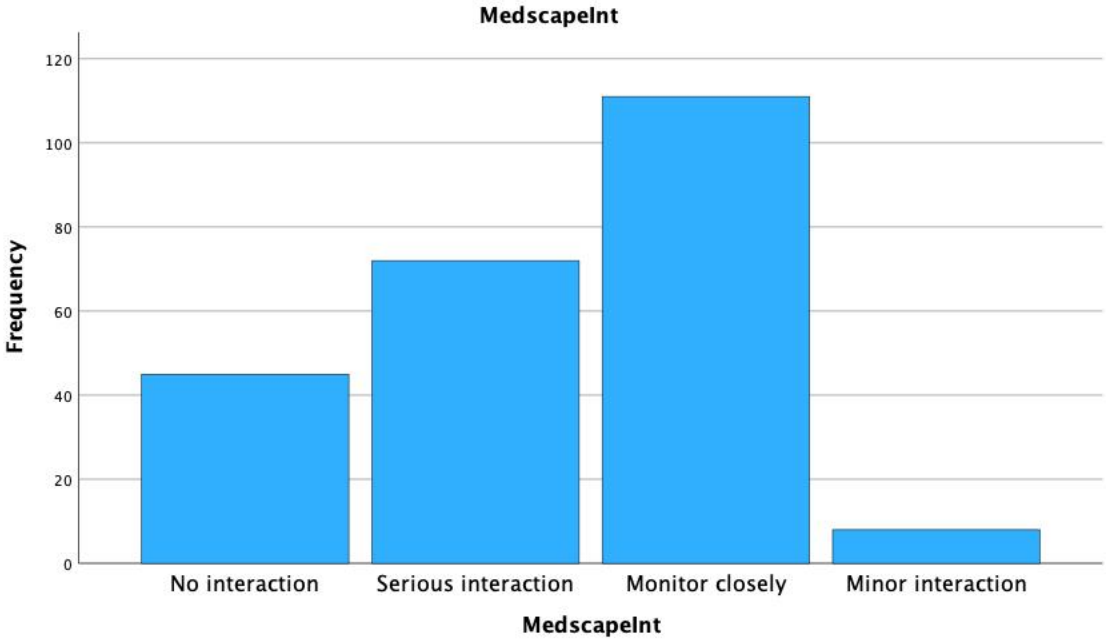

Figure 3.

Frequency of Genders.

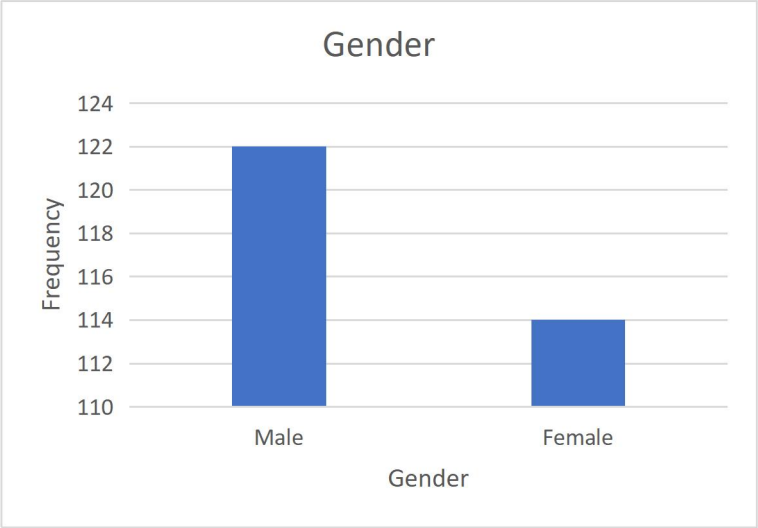

Figure 4.

Frequency for Types Of Diseases.

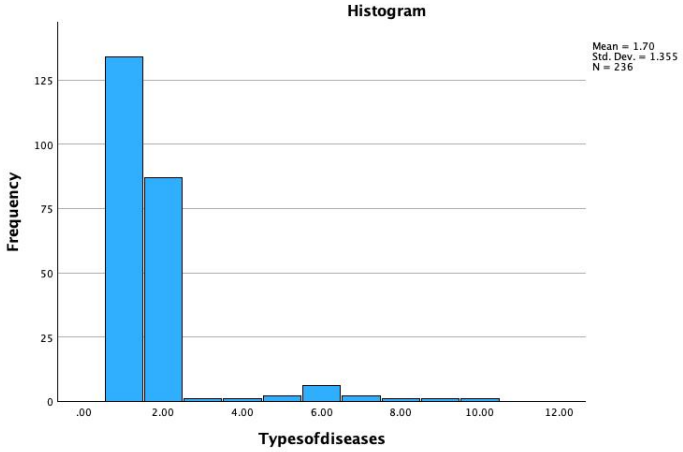

Table 11.

Descriptive Statistics for Age, Hospital Stay & Total Number of Medications.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	236	1.00	6.00	5.2966	1.33247
Hospitalstay	236	1.00	3.00	1.6017	.83681
TotalNumberMeds	236	1.00	4.00	2.2161	.70251

Table 12.

Continuous Data for Age.

Age			
	Frequency	Percent	Valid Percent
17-19	4	1.7	1.7
20-29	13	5.5	5.5
30-39	18	7.6	7.6
40-49	12	5.1	5.1
50-59	16	6.8	6.8
Equal or more than 60	173	73.3	73.3
Total	236	100.0	100.0

Table 13.

Continuous Data for Hospital Stay.

Hospital Stay			
	Frequency	Percent	Valid Percent
0-5 days	148	62.7	62.7
6-9 days	34	14.4	14.4
Equal or more than 10 days	54	22.9	22.9
Total	236	100.0	100.0

Table 14.

Continuous Data for Total Number of Medications.

Total Number of Medications			
Equal or less than 4 meds	Frequency	Percent	Valid Percent
5-9 meds	26	11.0	11.0
10-14 meds	145	61.4	61.4
Equal or more than 15 meds	53	22.5	22.5
Total	12	5.1	5.1
Equal or less than 4 meds	236	100.0	100.0

Comparing Frequencies of Drugs Using Different Drug-Interaction Checkers Databases For Types of Medications.

1.Drugs.com

Table 15.

Frequency & Severity of Drugs Interactions Using Drugs.com

Drugs.com Statistics				
		Major Interactions	Moderate Interactions	Minor Interactions
N	Valid	348	1047	131

Table 16.

Drugs.com Major Interactions Drugs.

Drugs.com (Major Interactions)			
	Frequency	Percent	Valid Percent
Cortiocsteroids	129	37.1	37.1
FQs	114	32.8	32.8
Macrolides	34	9.8	9.8
Anit-histamines	10	2.9	2.9
LMWH	7	2.0	2.0
SSRIs	7	2.0	2.0
ARBs	6	1.7	1.7
Diuretics	5	1.4	1.4
NSAIDs	5	1.4	1.4
5-HT3 antagonsit	4	1.1	1.1

Table 16

Electrolyte supplement	4	1.1	1.1
Antipsychotics	3	.9	.9
CCBs	2	.6	.6
Beta-blockers	2	.6	.6
Antidiabetics	2	.6	.6
Opioid analgesics	2	.6	.6
Antiplatelets	2	.6	.6
Iodinated contrast agent	2	.6	.6
Prokinetic agents	2	.6	.6
ACEIs	1	.3	.3
Local anasthetic	1	.3	.3
Statins	1	.3	.3
Sympathomimetics	1	.3	.3
General anasthetic	1	.3	.3
Herbal supplement	1	.3	.3
Total	348	100.0	100.0

Table 17.

Drugs.com Moderate Interactions Drugs.

Drugs.com (Moderate Interactions)			
	Frequency	Percent	Valid Percent
Corticosteroids	206	19.7	19.7
Diuretics	137	13.1	13.1
PPIs	95	9.1	9.1
FQs	57	5.4	5.4
CPs	48	4.6	4.6
Beta-blockers	44	4.2	4.2
ARBs	41	3.9	3.9
CCBs	39	3.7	3.7
NSAIDs	38	3.6	3.6
Antihistamines	33	3.2	3.2
Antidiabetics	29	2.8	2.8
Macrolides	26	2.5	2.5
Antipsychotics	26	2.5	2.5
Bronchodilators	22	2.1	2.1
Anticholinergics	18	1.7	1.7
ACEIs	16	1.5	1.5
Anticonvulsants	16	1.5	1.5
LMWH	12	1.1	1.1
Statins	12	1.1	1.1
5-HT3 antagonists	11	1.1	1.1
SSRIs	11	1.1	1.1
General Anasthetic	11	1.1	1.1
Anticoagulants	10	1.0	1.0
Alpha blockers	10	1.0	1.0
Electrolyte supplements	8	.8	.8
Probiotics	7	.7	.7
Antidiarrheals	6	.6	.6

Table 17

Antifungals	6	.6	.6
Antiplatelets	5	.5	.5
Sympathomimmetic agent	5	.5	.5
Opioid	4	.4	.4
Cardiac glycoside	4	.4	.4
BDZs	4	.4	.4
Prokinetic agents	3	.3	.3
LTRAs	3	.3	.3
PDE5i	3	.3	.3
Antiarrythmics	3	.3	.3
Thyroid medication	3	.3	.3
Herbal supplement	2	.2	.2
Acetylcholinesterase inhibitor	2	.2	.2
Iron supplements	2	.2	.2
Penicillins	1	.1	.1
Protectants	1	.1	.1
Alkylizing agent	1	.1	.1
Nitrofuran antibiotics	1	.1	.1
Nitroimidazole antibiotics	1	.1	.1
Fibrates	1	.1	.1
Local anasthetic	1	.1	.1
Nitrates	1	.1	.1
Iodinated contrast agent	1	.1	.1
Total	1047	100.0	100.0

Table 18.

Drugs.com Minor Interactions Drugs.

Drugs.com (Minor Interactions)			
	Frequency	Percent	Valid Percent
Bronchodilators	15	11.5	11.5
FQs	12	9.2	9.2
Macrolides	11	8.4	8.4
Corticosteroids	10	7.6	7.6
Diuretics	10	7.6	7.6
Penicillins	9	6.9	6.9
Prokinetic agents	8	6.1	6.1
Beta-blockers	8	6.1	6.1
NSAIDs	7	5.3	5.3
PPIs	5	3.8	3.8
CCBs	5	3.8	3.8
Analgesics	5	3.8	3.8
PDE5i	5	3.8	3.8
Antihistamines	3	2.3	2.3
ACEIs	2	1.5	1.5
SSRIs	2	1.5	1.5
ARBs	2	1.5	1.5
LABAs	1	.8	.8
Opoids analgesics	1	.8	.8
Cardiac glycosides	1	.8	.8
Antidiabetics	1	.8	.8
LTRAs	1	.8	.8
Antimuscarinic agents	1	.8	.8
Anticholinergics	1	.8	.8
Thyroid medications	1	.8	.8
Local anasthetics	1	.8	.8

Table 18

Inorganic compounds	1	.8	.8
Tetracyclines	1	.8	.8
LMWH	1	.8	.8
Total	131	100.0	100.0

2-Medscape.com

Table 19.

Frequency & Severity of Drugs Interactions Using Medscape.com

Medscape.com Statistics				
		Serious Interactions	Monitor Closely	Minor Interactions
N	Valid	248	1285	515

Table 20.

Medscape.com Serious Interaction Drugs.

Medscape.com (Serious Interactions)			
	Frequency	Percent	Valid Percent
Macrolides	54	21.8	21.8
LMWH	41	16.5	16.5
Corticosteroids	40	16.1	16.1
CPs	20	8.1	8.1
Penicillins	15	6.0	6.0
FQs	13	5.2	5.2
5-HT3 antagonists	13	5.2	5.2
Beta-blockers	8	3.2	3.2

Table 20

CCBs	8	3.2	3.2
SSRIs	8	3.2	3.2
Antipsychotics	6	2.4	2.4
Cardiac glycoside	3	1.2	1.2
Statins	3	1.2	1.2
General Anasthetic	3	1.2	1.2
Probiotics	2	.8	.8
Alpha 2 agonist	2	.8	.8
Antiplatelets	2	.8	.8
Sympathomimetic agents	2	.8	.8
PPIs	1	.4	.4
Analgesics	1	.4	.4
Antihistamines	1	.4	.4
Iron supplements	1	.4	.4
Antiarrythmics	1	.4	.4
Total	248	100.0	100.0

Table 21.

Medscape.com Monitor Closely Drugs.

Medscape.com (Monitor Closely)				
		Frequency	Percent	Valid Percent
Corticosteroids	486	37.8	37.8	37.8
FQs	123	9.6	9.6	9.6
PPIs	122	9.5	9.5	9.5
LMWH	79	6.1	6.1	6.1
Macrolides	59	4.6	4.6	4.6
Beta-blockers	42	3.3	3.3	3.3
Diuretics	39	3.0	3.0	3.0
NSAIDs	35	2.7	2.7	2.7

Table 21

ARBs	27	2.1	2.1	2.1
Bronchodilators	22	1.7	1.7	1.7
CCBs	22	1.7	1.7	1.7
Antipsychotics	22	1.7	1.7	1.7
Antiplatelets	20	1.6	1.6	1.6
Antihistamines	19	1.5	1.5	1.5
CPs	18	1.4	1.4	1.4
Statins	18	1.4	1.4	1.4
Penicillins	16	1.2	1.2	1.2
Antidiabetics	14	1.1	1.1	1.1
Anticonvulsants	11	.9	.9	.9
ACEIs	10	.8	.8	.8
Cardiac glycoside	9	.7	.7	.7
Electrolytes	9	.7	.7	.7
SSRIs	8	.6	.6	.6
Opioids	6	.5	.5	.5
LTRAs	5	.4	.4	.4
Alpha blockers	5	.4	.4	.4
Anticholinergics	5	.4	.4	.4
NMB	5	.4	.4	.4
5-HT3 antagonist	4	.3	.3	.3
General Anasthetics	4	.3	.3	.3
Antifungals	3	.2	.2	.2
Prokientic agent	2	.2	.2	.2
Anticoagulants	2	.2	.2	.2
Antiarrythmics	2	.2	.2	.2
Protectants	2	.2	.2	.2
Analgesics	1	.1	.1	.1
Antidiarrheals	1	.1	.1	.1
PDE5i	1	.1	.1	.1
Antioxidants	1	.1	.1	.1
Supplements	1	.1	.1	.1
Alpha 1&2	1	.1	.1	.1

Table 21

adrenergic agonists				
BDZs	1	.1	.1	.1
Iron supplements	1	.1	.1	.1
Sympathomimmetic agent	1	.1	.1	.1
Acetylcholinesterase inhibitor	1	.1	.1	.1
Total	1285	100.0	100.0	100.0

Table 22.

Medscape.com Minor Interaction Drugs.

Medscape.com (Minor Interactions)			
	Frequency	Percent	Valid Percent
Corticosteroids	174	33.8	33.8
Diuretics	79	15.3	15.3
LTRAs	52	10.1	10.1
Macrolides	50	9.7	9.7
Analgesic	25	4.9	4.9
Antidiabetics	21	4.1	4.1
LMWH	18	3.5	3.5
PPIs	17	3.3	3.3
Penicillins	9	1.7	1.7
CPs	9	1.7	1.7
FQs	6	1.2	1.2
NSAIDs	6	1.2	1.2
Beta-blockers	6	1.2	1.2
Bronchodilators	5	1.0	1.0
Prokientic agent	5	1.0	1.0
Antipsychotic	4	.8	.8
Anticonvulsants	4	.8	.8
Anticoagulants	3	.6	.6

Table 22

Electrolytes	3	.6	.6
CCBs	2	.4	.4
ACEIs	2	.4	.4
SSRIs	2	.4	.4
Antifungals	2	.4	.4
Thyroid medications	2	.4	.4
Antioxidants	2	.4	.4
Statins	1	.2	.2
Antihistamines	1	.2	.2
PDE5i	1	.2	.2
Nitroimidazole antibiotics	1	.2	.2
Antiarrythmics	1	.2	.2
Mucolytic agents	1	.2	.2
Nitrates	1	.2	.2
Total	515	100.0	100.0

Table 23.

Relationship Between Total Number of Medications and Hospital Stay.

		Ranks		
	TotalNumberMed	N	Mean Rank	Sum of Ranks
Hospital Stay	Equal or less than 4 meds	26	70.83	1841.50
	5-9 meds	145	88.72	12864.50
	Total	171		

Test Statistics[a]	
	Hospital Stay
Mann-Whitney U	1490.500
Wilcoxon W	1841.500
Z	-1.982
Asymp. Sig. (2-tailed)	.048

a. Grouping Variable: TotalNumberMeds

		Ranks		
	TotalNumberMeds	N	Mean Rank	Sum of Ranks
Hospitalstay	10-14 meds	53	30.88	1636.50
	Equal or more than 15 meds	12	42.38	508.50
	Total	65		

Test Statistics[a]	
	Hospital Stay
Mann-Whitney U	205.500
Wilcoxon W	1636.500
Z	-2.195
Asymp. Sig. (2-tailed)	.028

a. Grouping Variable: TotalNumberMeds

Table 24.

Relationship Between Age & Hospital Stay.

Ranks				
	Age	N	Mean Rank	Sum of Ranks
Hospital Stay	17-19	4	8.50	34.00
	20-29	13	9.15	119.00
	Total	17		

Test Statistics[a]	
	Hospital Stay
Mann-Whitney U	24.000
Wilcoxon W	34.000
Z	-.555
Asymp. Sig. (2-tailed)	.579
Exact Sig. [2*(1-tailed Sig.)]	.871[b]

a. Grouping Variable: Age

b. Not corrected for ties.

Ranks				
	Age	N	Mean Rank	Sum of Ranks
Hospital Stay	30-39	18	15.06	271.00
	40-49	12	16.17	194.00
	Total	30		

Test Statistics[a]	
	Hospital Stay
Mann-Whitney U	100.000
Wilcoxon W	271.000
Z	-.573
Asymp. Sig. (2-tailed)	.566
Exact Sig. [2*(1-tailed Sig.)]	.755[b]

a. Grouping Variable: Age

b. Not corrected for ties.

Ranks				
	Age	N	Mean Rank	Sum of Ranks
Hospital Stay	50-59	16	74.91	1198.50
	Equal or more than 60	173	96.86	16756.50
	Total	189		

Test Statistics[a]	
	Hospital Stay
Mann-Whitney U	1062.500
Wilcoxon W	1198.500
Z	-1.719
Asymp. Sig. (2-tailed)	.086

One Way Anova Test – is a type of analysis in SPPS used to compare and determine if there's any significant difference between two sample's means.

Table 25.

Comparison of Age & Types of Interactions from Drugs.com using One Way Anova Test.

Descriptives Age & Drugs.com DDIs

					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
No interaction	53	4.9434	1.53692	.21111	4.5198	5.3670	1.00	6.00
Major interaction	127	5.2598	1.36401	.12104	5.0203	5.4994	1.00	6.00
Moderate interaction	54	5.7778	.74395	.10124	5.5747	5.9808	2.00	6.00
Minor interaction	2	4.0000	2.82843	2.00000	-21.4124	29.4124	2.00	6.00
Total	236	5.2966	1.33247	.08674	5.1257	5.4675	1.00	6.00

ANOVA Age

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	22.649	3	7.550	4.439	.005
Within Groups	394.589	232	1.701		
Total	417.237	235			

Table 26.

Comparison of Age & Types of Interactions from Medscape.com using One Way Anova Test.

Descriptives Age & Medscape.com DDIs								
					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
No interaction	45	5.1111	1.46508	.21840	4.6710	5.5513	1.00	6.00
Serious interaction	72	5.2778	1.39640	.16457	4.9496	5.6059	1.00	6.00
Monitor closely	111	5.4505	1.18888	.11284	5.2268	5.6741	1.00	6.00
Minor interaction	8	4.3750	1.59799	.56497	3.0390	5.7110	2.00	6.00
Total	236	5.2966	1.33247	.08674	5.1257	5.4675	1.00	6.00

ANOVA Age					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	10.996	3	3.665	2.093	.102
Within Groups	406.241	232	1.751		
Total	417.237	235			

Table 27.

One Way Anova Test for Hospital Stay & Gender.

Descriptives Age & Medscape.com DDIs								
					95% Confidence Interval for Mean			
	N	Mean	Std. Deviation	Std. Error	Lower Bound	Upper Bound	Minimum	Maximum
Male	122	1.6639	.86827	.07861	1.5083	1.8196	1.00	3.00
Female	114	1.5351	.80022	.07495	1.3866	1.6836	1.00	3.00
Total	236	1.6017	.83681	.05447	1.4944	1.7090	1.00	3.00

ANOVA Hospital					
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.978	1	.978	1.400	.238
Within Groups	163.581	234	.699		
Total	164.559	235			

Table 28.

Crosstabulation Count Between Gender & Hospital Stay.

Case Processing Summary						
			Cases Missing		Total	
		Valid				
	N	Percent	N	Percent	N	Percent
Gender* Hospitalstay	236	100.0%	0	0.0%	236	100.0%

Gender * Hospitalstay Crosstabulation Count					
		Hospital Stay			
		0-5 days	6-9 days	Equal or more than 10 days	Total
Gender	Male	73	17	32	122
	Female	75	17	22	114
Total		148	34	54	236

Table 29.

Crosstabulation Count Between Gender & Drugs.com DDIs.

Case Processing Summary						
	Valid		Cases Missing		Total	
	N	Percent	N	Percent	N	Percent
Gender* Drugscomddis	236	100.0%	0	0.0%	236	100.0%

Gender * Drugs.com DDIs Crosstabulation Count						
		Drugs.com DDIs				
		No interaction	Major interaction	Moderate interaction	Minor interaction	Total
Gender	Male	30	70	21	1	122
	Female	23	57	33	1	114
Total		53	127	54	2	236

P-value: 0.152

Table 30.

Crosstabulation Count Between Gender & Medscape.com DDIs.

Case Processing Summary						
			Cases Missing		Total	
		Valid				
	N	Percent	N	Percent	N	Percent
Gender* Medscape.com DDIs	236	100.0%	0	0.0%	236	100.0%

Gender * Drugs.com DDIs Crosstabulation Count						
		Medscape.com DDIs				
		No interaction	Serious interaction	Monitor closely	Minor interaction	Total
Gender	Male	23	34	63	2	122
	Female	22	38	48	6	114
Total		45	72	111	8	236

P-value: 0.274

Table 31.

Crosstabulation Count Between Age & Drugs.com DDIs.

Age * Drugs.com DDIs Crosstabulation Count						
		Drugs.com DDIs				
		No interaction	Serious interaction	Monitor closely	Minor interaction	Total
Age	17-19	2	2	0	0	4
	20-29	3	8	1	1	13
	30-39	7	10	1	0	18
	40-49	4	7	1	0	12
	50-59	5	8	3	0	16
	Equal or more than 60	32	92	48	1	173
Total		53	127	54	2	236

Table 32.

Crosstabulation Count Between Age & Medscape.com DDIs.

Age * Medscape.com DDIs Crosstabulation Count						
		Medscape.com DDIs				
		No interaction	Serious interaction	Monitor closely	Minor interaction	Total
Age	17-19	1	2	1	0	4
	20-29	3	3	6	1	13
	30-39	4	7	5	2	18
	40-49	5	3	3	1	12
	50-59	1	3	11	1	16
	Equal or more than 60	31	54	85	3	173
Total		1	2	1	0	4

Table 33.

Anova Comparison Between Age & Severity of Interactions using Drugs .com.

Descriptive Statistics				
	N	Minimum	Maximum	Mean
Age	236	1.00	6.00	5.2966
Drugscomddis	236	.00	3.00	1.0212
Valid N (listwise)	236			

Report				
	Age			
Drugscomddis	Mean	N	Std. Deviation	% of Total Sum
No interaction	4.9434	53	1.53692	21.0%
Major interaction	5.2598	127	1.36401	53.4%
Moderate interaction	5.7778	54	.74395	25.0%
Minor interaction	4.0000	2	2.82843	0.6%
Total	5.2966	236	1.33247	100.0%

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
Age* Drugs.comDDIs	Between Groups (Combined)	22. 649	3	7.550	4.439	.005
	Within Groups	394.589	232	1.701		
	Total	417.237	235			

Table 34.
Anova Comparision of Age & Severity of Interaction using Medscape.com.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	236	1.00	6.00	5.2966	1.33247
Medscapeddis	236	.00	3.00	1.0212	.82387
Valid N (listwise)	236				

Report				
	Age			
Medscapeddis	Mean	N	Std. Deviation	% of Total Sum
No interaction	5.1111	45	1.46508	18.4%
Serious interaction	5.2778	72	1.39640	30.4%
Monitor closely	5.4505	111	1.18888	48.4%
Minor interaction	4.3750	8	1.59799	2.8%
Total	5.2966	236	1.33247	100.0%

ANOVA Table						
		Sum of Squares	df	Mean Square	F	Sig.
Age* Medscape.comDDIs	Between Groups (Combined)	10.996	3	3.665	2.093	.102
	Within Groups	406.241	232	1.751		
	Total	417.237	235			

Table 35.

Total Number of Medications & Severity of interaction Using Drugs.com

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
TotalNumberMeds	236	1.00	4.00	2.2161	.70251
Drugscomddis	236	.00	3.00	1.0212	.69922
Valid N (listwise)	236				

Report				
Drugscomddis TotalNumberMeds	Mean	N	Std. Deviation	% of Total Sum
Equal or less than 4 meds	.4231	26	.94543	4.6%
5-9 meds	1.0621	145	.67926	63.9%
10-14 meds	1.1509	53	.49599	25.3%
Equal or more than 15 meds	1.2500	12	.45227	6.2%
Total	1.0212	236	.69922	100.0%

ANOVA Table						
		Sum of Squares	df	Mean Square	F	Sig.
Drugscomddis * TotalNumberMeds	Between Groups (Combined)	11.064	3	3.688	8.241	<.001
	Within Groups	103.830	232	.448		
	Total	114.894	235			

Table 36.

Total Number of Medications & Severity of Interactions using Medscape.com.

Descriptive Statistics				
	N	Minimum	Maximum	Mean
TotalNumberMeds	236	1.00	4.00	2.2161
Medscapeddis	236	.00	3.00	1.3475
Valid N (listwise)	236			

Report				
Medscapeddis TotalNumberMeds	Mean	N	Std. Deviation	% of Total Sum
Equal or less than 4 meds	.4615	26	.90469	3.8%
5-9 meds	1.4690	145	.80842	67.0%
10-14 meds	1.4340	53	.60477	23.9%
Equal or more than 15 meds	1.4167	12	.51493	5.3%
Total	1.3475	236	.82387	100.0%

ANOVA Table						
		Sum of Squares	df	Mean Square	F	Sig.
Medscapeddis * TotalNumberMeds	Between Groups (Combined)	23.001	3	7.667	13.030	<.001
	Within Groups	136.507	232	.588		
	Total	159.508	235			

Table 37.

Comparision Between Hospital Stay & Severity of Interaction using Drugs.com.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Hospitalstay	236	1.00	3.00	1.6017	.83681
Drugscomddis	236	.00	3.00	1.0212	.69922
Valid N (listwise)	236				

Report				
Drugscomddis Hospitalstay	Mean	N	Std. Deviation	% of Total Sum
0-5 days	1.0000	148	.69985	61.4%
6-9 days	1.1471	34	.74396	16.2%
Equal or more than 10 days	1.0000	54	.67293	22.4%
Total	1.0212	236	.69922	100.0%

ANOVA Table						
		Sum of Squares	df	Mean Square	F	Sig.
Drugscomddis * Hospitalstay	Between Groups (Combined)	.629	2	.315	.642	.527
	Within Groups	114.265	233	.490		
	Total	114.894	235			

Table 38.

Comparision Between Hospital Stay & Severity of Interaction using Medscape.com.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Hospitalstay	236	1.00	3.00	1.6017	.83681
Medscapeddis	236	.00	3.00	1.3475	.82387
Valid N (listwise)	236				

Report				
Medscapeddis Hospitalstay	Mean	N	Std. Deviation	% of Total Sum
0-5 days	1.4054	148	.85585	65.4%
6-9 days	1.4118	34	.70141	15.1%
Equal or more than 10 days	1.1481	54	.78686	19.5%
Total	1.3475	236	.82387	100.0%

ANOVA Table						
		Sum of Squares	df	Mean Square	F	Sig.
Medscapeddis* Hospitalstay	Between Groups (Combined)	2.783	2	1.391	2.068	.129
	Within Groups	156.726	233	.673		
	Total	159.508	235			

CHAPTER V

This chapter represents the discussion according to the collected data.

Discussion

This research study effectively assessed the occurrence of drug-drug interactions within the respirator clinic at NEU hospital. Digital clinical databases, specifically Drugs.com and Medscape.com, were employed to analyze these interactions. The escalating concern regarding the prevalence of these interactions among healthcare professionals worldwide is a result of the growing complexity of medication prescriptions, leading to significant adverse outcomes. It is imperative that strategies to mitigate drug-drug interactions extend beyond relying solely on the memory of prescribers and pharmacists. Instead, innovative and diverse approaches should be implemented to proactively prevent the potential harm caused by these interactions (Ansari J, 2010).

This study examined the frequency, and severity of pDDIs in patients' prescriptions at respiratory clinics. It compared the databases of two different drug interaction checkers, which are drugs.com & medscape.com. The results have shown that most patients hospitalized at the respiratory clinics had at least one pDDI throughout their hospitalization in the current research. On average, 85% of the patients had at least experienced a DDI in their prescription.

In relation to the severity of interactions identified by Drugs.com, it was found that 53.8% of the interactions were categorized as major interactions (n=127), while 22.9% were considered moderate interactions (n=54), and a mere 0.8% were labelled as minor interactions (n=2). Moreover, when looking at interactions identified by Medscape.com within the context of the respiratory clinic department, the results were as follows: 30.5% (n=72) were identified as serious interactions, 47% (n=111) were flagged as interactions that require close monitoring, and 3.4% (n=8) were classified as minor drug-drug interactions (DDIs). Each of these identified DDIs has the potential to cause harm in distinct ways. Interestingly, these findings contradict the outcomes of Spanakis M et al.’s research, where major interactions were only observed at a rate of 7%, with moderate interactions at 59%, and minor interactions

at 34%. Another notable discrepancy is in the study conducted by Tina Roblek et al., where significantly fewer major interactions were recorded: serious interactions were noted at a rate of 3.4%, while incidents warranting close monitoring were at a high rate of 91.7% (Tina Roblek et al., 2014). Our study aligns with the results of Ismail et al.'s research, showing major interactions at a rate of 12.8%, moderate interactions at 61.2%, and minor interactions at 26% (Ismail et al., 2011).

Approximately (61.4%) of the patients had between 5-9 medications administered to them, which was the only characteristic that showed a significant correlation with the prevalence of DDIs. Similar research studies show an increasing incidence of DDIs as the number of medications administered increases (Bhagavathula AS et al., 2014). Research conducted globally has indicated that the utilization of multiple medications, known as polypharmacy (involving the use of five or more drugs), and the advanced age of patients (60 years or older) are factors that contribute to a heightened risk of pDDIs (Guthrie B et al., 2015) (Marengoni A & Onder G, 2015). In a study by Rijkom et al., computerized DDIs alerts have demonstrated the potential to prevent adverse drug events in hospital settings. In a study conducted by Ismail et al. (2013), it was found that among 400 medical inpatients, there was an overall prevalence of 52.8% for at least one significant pDDI (Zwart-van Rijkom JE et al., 2009). The most commonly observed type of interactions in our study was major (53.8%) using the drugs.com drug-interaction checker and interactions that require close monitoring (47%) using medscape.com.

The significant divergence in the prevalence percentages of severity can likely be attributed to dissimilarities in the populations studied across the various research endeavors. Within the current investigation, a majority – around two-thirds – of the potential drug-drug interactions (DDIs) identified fall within the moderate category. It's imperative for healthcare providers to take into account the adjustment of therapy and medication dosages for patients affected by major or moderate DDIs, given the potential consequences stemming from these interactions. Moderate DDIs hold the capacity to lead to detrimental results, thus demanding careful supervision of patients diagnosed with such interactions, as these could potentially exacerbate their health conditions.

The category of drugs exhibiting the most prevalent moderate DDIs according to the findings from Drugs.com was corticosteroids, closely followed by diuretic medications. Notably, furosemide from the loop diuretics subgroup, along with budesonide and methylprednisolone, emerged as the primary contributors to moderate DDIs. It is noteworthy that approximately 55% of the identified potential DDIs in this investigation fell within the major or minor classification. Major DDIs possess the capacity to induce severe and even life-threatening consequences, whereas minor DDIs typically result in limited adverse effects and seldom necessitate interventions. Nevertheless, vigilance is essential for monitoring minor DDIs as they occasionally have the potential to lead to significant negative clinical outcomes, particularly among the elderly demographic.

Regarding the class of medications displaying the highest rate of major DDIs based on the information obtained from Drugs.com, corticosteroids took precedence, within which budesonide emerged as the primary agent responsible for major DDIs. In addition, in terms of the category of drugs with the highest frequency of minor DDIs as per Drugs.com's assessment, bronchodilators occupied this position, with ipratropium being the primary causative factor behind minor DDIs.

The outcomes of the present study indicated that there was no significance difference in the occurrence of pDDIs based on gender. This outcome aligns with the discoveries of Abdullah K Rabba et al., who similarly observed no statistically significant variation between genders in their study. However, in contrast, research by Cruciol and Thomson in Brazil revealed a substantially higher prevalence of potential DDIs among females compared to males. The variations in these findings might be attributed to differences in the populations under study or disparities in prescribing practices among physicians (Abdullah et al., 2022; Cruciol & Thomson, 2006).

The findings of this investigation concerning the length of hospitalization revealed an absence of substantial correlation between the duration of stay and the quantity of medications administered. This outcome corresponds with the conclusions drawn by Abdullah K Rabba et al., who likewise found no significant link between the duration of hospitalization and medication usage. Conversely, our results contrast with the outcomes obtained by Tesfaye and Nedi, who indicated a statistically

notable connection between the length of hospital stay and the quantity of medications employed (Abdullah et al., 2022; Tesfaye & Nedi, 2017).

In this research, the impact of age on drug-drug interactions is explored. The study's results revealed a noteworthy connection between age and the occurrence of DDIs, indicating that as age increases, the likelihood of interactions also increases, with this relationship having statistical significance ($p < 0.05$). These findings differ from those of Tesfaye and Nedi, who did not identify a significant link between age and the prevalence of drug-drug interactions (Tesfaye & Nedi, 2017). However, our research outcomes align with the discoveries made by Nobili et al., who also established a notable connection between age and susceptibility to DDIs. These substantial disparities could stem from the fact that the outcomes are more influenced by prescription-related factors rather than characteristics inherent to the patients. While the risk of encountering DDIs remains consistent across various age categories, the severity of health issues among different age groups could differ. The elevated use of multiple medications and heightened health concerns among older individuals contribute to an escalated vulnerability to potential DDIs (Nobili et al., 2009).

CHAPTER VI

Conclusion and Recommendations

This chapter presents conclusions based on the research study results and gives recommendations based on the objective of the research findings.

Conclusion

In conclusion, the current study found a high frequency of DDIs in respiratory clinics. Although most of the interactions were of major severity, large pDDIs were documented in significant numbers and like previous international studies, have demonstrated a notable rise in the occurrence of major DDIs. Patients' exposure to four or more prescription medications emerged as a significant predictor of DDIs.
Mitigating the harm caused by DDIs can be achieved through prescribing medications with a low risk of interactions and implementing diligent monitoring for potential ADRs. Additionally, we advocate for developing and implementing a computerized system that alerts healthcare providers to pDDIs, thereby preventing ADRs in hospital settings. Finally, the main difference between Drugs.com and Medscape.com drug interaction checkers lies in the target audience and the depth of information. Healthcare professionals are more likely to use Medscape for clinical decision-making, while consumers may find Drugs.com more accessible for general drug information and interaction checking.

Recommendations

Insufficient awareness concerning DDIs, a lack of knowledge about patients' medication history, and inadequate communication between primary and secondary healthcare providers, prescribers, and patients may lead to inappropriate drug combinations. Therefore, adhering to proper prescription-writing policies is crucial, minimizing the number of prescribed medications and enhancing physicians' understanding of potentially harmful DDIs., for example, participation in related

educational courses and computerized prescribing systems could help reduce drug interactions. Moreover, the establishment of an efficient drug interaction monitoring system is essential. With their extensive knowledge of medications and safety profiles, pharmacists can play a pivotal role in detecting and preventing drug-related injuries, thereby reducing the incidence of DDIs and mitigating associated risks.

References

1. Abdullah K Rabba, Waffa O Atta, Abdallah D Abukhalil, Aseel N Naser, Aya A Injas, Hani A Naseef, Abdallah D Abukhalil. (2002). A retrospective evaluation of drug–drug interactions in patients admitted to Internal Medicine Departments in Palestinian Hospitals. Sage Journals.

2. Adimadhyam S, Schumock GT, Walton S, et al. (2014). Risk of arrhythmias associated with ipratropium bromide in children, adolescents, and young adults with asthma: a nested case-control study. Pharmacotherapy ; **34**: 315–323.

3. Ament PW, Bertolino JG, Liszewski JL. (2000). Clinically significant drug interactions. *Am Fam Physician.* ;61:1745–54.

4. Ansari, J.A. (2010). Drug interaction and pharmacist. Journal of Young Pharmacists: JYP. 2(3), 326.

5. Becker, M. L., Kallewaard, M., Caspers, P. W. J., Visser, L. E., Leufkens, H. G. M., and Stricker, B. H. C. (2007). Hospitalisations and emergency department visits due to drug-drug interactions: a literature review. *Pharmacoepidemiol. Drug Saf.* 16, 641–651. doi: 10.1002/pds.1351

6. Bénard-Laribière, A., Miremont-Salamé, G., Pérault-Pochat, M.-C., Noize, P., and Haramburu, F. (2015). The EMIR study group on behalf of the French network of pharmacovigilance centres. Incidence of hospital admissions due to adverse drug reactions in France: the EMIR study. *Fundam. Clin. Pharmacol.*29, 106–111. doi: 10.1111/fcp.12088

7. Ben D Snyder, Thomas M Polasek, Matthew P Doogue. (2012). Drug interactions: principles and practice. Volume 35 : Number 3. P85-88.

8. Bhagavathula AS, Berhanie A, Tigistu H, et al. (2014). Prevalence of potential drug–drug interactions among internal medicine ward in University of Gondar Teaching Hospital, Ethiopia. *Asian Pac J Trop Biomed.*;4:S204–8

9. Calzetta L., Matera M.G., Rogliani P., Cazzola M. (2018) Dual LABA/LAMA bronchodilators in chronic obstructive pulmonary disease: why, when, and how. *Expet Rev. Respir. Med.*

10. Cazzola M, Calzetta L, Rinaldi B, et al. (2017). Management of chronic obstructive pulmonary disease in patients with cardiovascular diseases. Drugs ; **77**: 721–732.

11. Chatsisvili A, Sapounidis I, Pavlidou G, Zoumpouridou E, Karakousis VA, Spanakis M, Teperikidis L, Niopas I. (2010). Potential drug-drug interactions

12. Chou T.C. (2006) Theoretical basis, experimental design, and computerized simulation of synergism and antagonism in drug combination studies. *Pharmacol. Rev.*

13. Chrischilles EA, Fulda TR, Byrns PJ, Winckler SC, Rupp MT, Chui MA. (2002). The role of pharmacy computer systems in preventing medication errors. *J Am Pharm Assoc (Wash)* ;42:439–48.

14. Chyka PA. (2000). How many deaths occur annually from adverse drug reactions in the United States? *Am J Med.* ;109:122–30.

15. Classen DC, Pestotnik SL, Evans RS, Lloyd JF, Burke JP. (1997). Adverse drug events in hospitalized patients. Excess length of stay, extra costs, and attributable mortality. JAMA.277(4):301-6. PMID: 9002492.

16. C.M. Hohl, J. Dankoff, A. Colacone, M. Afilalo. (2001). Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department
Ann. Emerg. Med., 38 (6) pp. 666-671

17. Coleman JJ, Pontefract SK. (2016, October 16). Adverse drug reactions. Clin Med (Lond). (5):481-485. doi: 10.7861/clinmedicine.16-5-481. PMID: 27697815; PMCID: PMC6297296

18. Cruciol-Souza JM, Thomson JC. (2006). Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. J Pharm Pharm Sci; 9(3): 427–433.

19. Diksis, N., Melaku, T., Assefa, D., & Tesfaye, A. (2019). Potential drug–drug interactions and associated factors among hospitalized cardiac patients at Jimma University Medical Center, southwest ethiopia. SAGE Open Medicine, 7, 205031211985735. https://doi.org/10.1177/2050312119857353

20. Dirin MM, Mousavi S, Afshari AR, Tabrizian K. (2014). Potential drug-drug interactions in prescriptions dispensed in community and hospital pharmacies in East of Iran. Journal of Research in Pharmacy Practice.;3(3):104-107.

21. Doucet J, Chassagne P, Trivalle C, Landrin I, Pauty MD, Kadri N, et al. (1996). Drug-drug interactions related to hospital admissions in older adults: A prospective study of 1000 patients. *J Am Geriatr Soc.* 1996;44:944–8.

22. Edwards IR, Aronson JK. (2000). Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* 2000;356:1255–9.

23. Fallowfield JM, Marlow HF. (1996, December 7). Propranolol is contraindicated in asthma. BMJ. 1996 Dec 7;313(7070):1486. doi: 10.1136/bmj.313.7070.1486. PMID: 8973266; PMCID: PMC2353002.

24. Farkas D, Shader RI, von Moltke LL, Greenblatt DJ. (2008). Mechanisms and consequences of drug-drug interactions. In: Gad SC, editor. *Preclinical*

Development Handbook: ADME and Biopharmaceutical Properties. Philadelphia: Wiley; pp. 879–917.

25. Francis J, Abraham S. (2014, December 22) Clinical pharmacists: Bridging the gap between patients and physicians. Saudi Pharm J. o (6

26. Georgiev, K. D., Hvarchanova, N., Stoychev, E., & Kanazirev, B. (2022). Prevalence of polypharmacy and risk of potential drug-drug interactions among hospitalized patients with emphasis on the pharmacokinetics. *Science Progress*, *105*(1), 003685042110701. https://doi.org/10.1177/00368504211070183

27. Gonzaga de Andrade Santos, T. N., Mendonça da Cruz Macieira, G., Cardoso Sodré Alves, B. M., Onozato, T., Cunha Cardoso, G., Ferreira Nascimento, M. T., Saquete Martins-Filho, P. R., Pereira de Lyra, D., & Oliveira Filho, A. D. (2020). Prevalence of clinically manifested drug interactions in hospitalized patients: A systematic review and meta-analysis. *PLOS ONE*, *15*(7). https://doi.org/10.1371/journal.pone.0235353

28. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. (2015). The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med.* 2015;13

29. Haider, S. I., Johnell, K., Thorslund, M., and Fastbom, J. (2007). Trends in polypharmacy and potential drug-drug interactions across educational groups in elderly patients in Sweden for the period 1992 - 2002. Int. J. Clin. Pharmacol. Ther. 45, 643–653. doi: 10.5414/CPP45643

30. Hanania N. (2017, December 14). In COPD, medication delivery matters. American College of CHEST Physicians website. chestnet.org/News/Blogs/CHEST-Thought-Leaders/2017/12/In- COPD-Medication-Delivery- Matters.

31. Hazlet TK, Lee TA, Hansten PD, Horn JR. (2001). Performance of community pharmacy drug interaction software. *J Am Pharm Assoc (Wash)* ;41:200–4.

32. Hilmer SN, Mager DE, Simonsick EM, Cao Y, Ling SM, Windham BG, Harris TB, Hanlon JT, Rubin SM, Shorr RI, Bauer DC, Abernethy DR. (2007, April 23). A drug burden index to define the functional burden of medications in older people. Arch Intern Med.;167(8):781-7. doi: 10.1001/archinte.167.8.781. PMID: 17452540.

33. Ismail M, Iqbal Z, Khattak MB, et al. (2013). Potential drug–drug interactions in internal medicine wards in hospital setting in Pakistan. *Int J Clin Pharm.*;35:455–62

34. Ismail M, Iqbal Z, Khattak MB, Javaid A, Khan TM. (2011). Prevalence, type and predictors of potential drug-drug interactions in pulmonary ward of a tertiary care hospital. Afr J Pharm Pharmacol 2011; 5(10): 1303-1309.

35. Jacobson TA. (2004, November 1). Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol. 94(9):1140-6. doi: 10.1016/j.amjcard.2004.07.080. PMID: 15518608.

36. Jankel CA, Fitterman LK. (1993). Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf.* ;9:51–9.

37. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. (2003). Drug-drug interactions among elderly patients hospitalized for drug toxicity. *JAMA.* ;289:1652–8.

38. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, Paszat LF. (2010, February 8). Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population-based

cohort study. 8;340:c693. doi: 10.1136/bmj.c693. PMID: 20142325; PMCID: PMC2817754.

39. Kelsey F. (2018). Avoiding drug-drug Interactions in patients with respiratory diseases.

40. Lehman S. (2014, December 24). Most people use inhalers and auto-injectors improperly. Reuters website. reuters.com/article/us-health- devices-asthma-allergy/most-people- use-inhalers- and-auto- injectors-improperly-idUSKBN0K213420141224. Published December 24, 2014.

41. Lubinga SJ, Uwiduhaye E. (2011). Potential drug-drug interactions on in patient medication prescriptions at Mbarara Regional Referral Hospital (MRRH) in western Uganda: prevalence, clinical importance and associated factors. African Health Sciences. 2011;11(3):499 – 507.

42. Magro L, Moretti U, Leone R. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. *Expert Opin Drug Saf.* 2012;11:83–94.

43. Marengoni A, Onder G. (2015). Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ.*;350

44. Michael N. Neely & Michael D. Reed (2012) in Principles and Practice of Pediatric Infectious Diseases (Fourth Edition),

45. Nachimuthu S, Assar MD, Schussler JM. (2012). Drug-induced QT interval prolongation: mechanisms and clinical management.*Ther Adv Drug Saf*.;3(5):241-253. doi:10.1177/2042098612454283.

46. Nebeker JR, Barach P, Samore MH. (2004). Clarifying Adverse Drug Events: A Clinician's Guide to terminology, Documentation, and Reporting. Ann Intern Med. 140:795-801.

47. A. Nobili, L. Pasina, M. Tettamanti, U. Lucca, E. Riva, I. Marzonaà , L. Monesià , R. Cucchiani, A. Bortolotti, I. Fortino, L. Merlino, G. Walter Locatelli and G. Giuliani. (2009). Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. Journal of Clinical Pharmacy and Therapeutics. 34, 377–386. doi:10.1111/j.1365-2710.2009.01021.x

48. Olivier, P., Bertrand, L., Tubery, M., Lauque, D., Montastruc, J.-L., and Lapeyre-Mestre, M. (2009). Hospitalizations because of adverse drug reactions in elderly patients admitted through the emergency department: a prospective survey. *Drugs Aging* 26, 475–482. doi: 10.2165/00002512-200926060-00004.

49. Orloff DG. (2002). Label changes for Simvastatin (Zocor) *US Food and Drug Administration.*

50. Pedersen, H. K., Sørensen, A. M., Schelde, A. B., Nyeland, M. E., & Jimenez-Solem, E. (2021). Prevalence and characteristics of drug-drug interactions among hospitalisedpatients in the Capital Region of Denmark. *Adverse Drug Reaction Bulletin*, *Publish Ahead of Print*. https://doi.org/10.1097/fad.0000000000000057

51. Palanisamy S, Arul Kumaran KS, Rajasekaran A. (2009). A study on assessment, monitoring, documentation and reporting of adverse drug reactions at a multi-specialty ertiary care teaching hospital in South India. *Int J PharmTech Res.* ;4:1519–22.

52. Polasek TM, Lin FP, Miners JO, Doogue MP. (2011). Perpetrators of pharmacokinetic drug-drug interactions arising from altered cytochrome P450 activity: a criteria-based assessment. Br J Clin Pharmacol. 71(5):727-36.

doi: 10.1111/j.1365-2125.2011.03903.x. PMID: 21223357; PMCID: PMC3093078.

53. Pruitt B. (2007, May3). Pharmacologic treatment of respiratory disorders.*RT Mag*. rtmagazine.com/2007/05/pharmacological-treatment- of-respiratory-disorders/.

54. Qian Y, Ye X, Du W, Ren J, Sun Y, Wang H, et al. (2010). A computerized system for detecting signals due to drug-drug interactions in spontaneous reporting systems. *Br J Clin Pharmacol.* ;69:67–73.

55. Sabers A. (2007). Pharmacokinetic interactions between contraceptives and antiepileptic drugs. Seizure. 2008 Mar;17(2):141-4. doi: 10.1016/j.seizure. PMID: 18206393.

56. Short PM, Williamson PA, Anderson WJ, Lipworth BJ. (2013). Randomized placebo-controlled trial to evaluate chronic dosing effects of propranolol in asthma.*Am J Respir Crit Care Med*. 187(12):1308-1314. doi: 10.1164/rccm.201212-2206OC.

57. Spanakis M, Ioannou P, Tzalis S, Chouzouri F, Patelarou E, Kofteridis DP, Antoniou KM, Schiza SE, Patelarou A, Tzanakis N. (2023). Evaluation of Drug Interactions in Hospitalized Patients with Respiratory Disorders in Greece. Adv Respir Med. ;91(1):74-92. doi: 10.3390/arm91010008. PMID: 36825942; PMCID: PMC9952796.

58. Tesfaye ZT, Nedi T. (2017). Potential drug– drug interactions in inpatients treated at the Internal Medicine ward of Tikur Anbessa Specialized Hospital. Drug Healthc Pat Saf; 9: 71–76.

59. Tina Roblek, Katja Trobec, Ales Mrhar, Mitja Lainscak. (2014). Potential drug-drug interactions in hospitalized patients with chronic heart failure and chronic obstructive pulmonary disease. DOI: 10.5114/aoms.2014.46212

60. van der Molen T., Cazzola M. (2012). Beyond lung function in COPD management: effectiveness of LABA/LAMA combination therapy on patient-centred outcomes. *Prim. Care Respir. J. : J. General Practice Airways Group.*

61. Vogel-Claussen J, Schonfeld CO, Kaireit TF, et al. (2019). Effect of indacaterol/glycopyrronium on pulmonary perfusion and ventilation in hyperinflated patients with chronic obstructive pulmonary disease (CLAIM). A double-blind, randomized, crossover trial. Am J Respir Crit Care Med ; **199**: 1086–1096.

62. Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, Johnson M, Johnson D, Lalonde R, Japour A, Brun S, Sun E. (2002, June 27). Study Team. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med. 2002 Jun 27;346(26):2039-46. doi: 10.1056/NEJMoa012354. PMID: 12087139.

63. Williams D, Feely J. (2002). Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet.* 41:343–70.

64. Zheng, W. Y., Richardson, L. C., Li, L., Day, R. O., Westbrook, J. I., & Baysari, M. T. (2017). Drug-drug interactions and their harmful effects in hospitalised patients: A systematic review and meta-analysis. European Journal of Clinical Pharmacology, 74(1), 15–27. https://doi.org/10.1007/s00228-017-2357-5

65. Zwart-van Rijkom JE, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts AC. (2009). Frequency and nature of drug–drug interactions in a Dutch university hospital. *Br J Clin Pharmacol* ;68:187–93.

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