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NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

Potential Drug - Drug Interaction in Pediatric Patients of a Teaching Hospital in Northern Cyprus

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Mentor
Assist. Prof. Dr. AbdiKarim Abdi

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

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Abstract

Introduction: Drug–drug interaction (DDI) is an important factor that may cause treatment failure or the development of side effects. Hospitalized infants and children are typically exposed to numerous distinct medications during inpatient admissions, increasing their risk of having potential drug-drug interactions (PDDIs)

Aim: To describe the frequency, types, and related information of potential drug-drug interactions (PDDIs) in pediatric unit in Near East University Hospital (NEUH) in Northern Cyprus and to assess the associated factors with PDDIs in hospitalized pediatric patients.

Method: A retrospective study was carried in Near East University Hospital (NEUH). Patients' information and data was obtained from patient archives. There were 332 pediatric patients admitted to NEUH during the period of 1st September 2017 and 1st September 2018. 230 patients were eligible and were included in the analysis.
All drugs the patients used during their hospitalized period were assessed using three different drug-drug interaction databases; Lexi.com, Drugs.com, and Medscape. All screening and documenting was done by a research pharmacist.

Result: Out of 332 patients, 230 cases (69.2%) were fitting the inclusion criteria and screening for DDI was carried. Regarding the gender of the patients, 112 out of 230 were male which represent 48.7% of the sample, while 118 out of 230 were female which reflect 51.3% of the sample. Regarding the number of interactions in the three different tools, Lexicomp identified 64 (27.8%) patients to have interactions while Drugs.com and Medscape identified 57 (24.8%) and 53 (23%) patients' interactions, respectively. According to the Lexicomp, Drugs.com, and Medscape the highest number of interactions were significantly noticed in young children with percentage of 70.00%, 50%, 57.5% respectively and $p<0.05$. Longer staying period and higher number of medications used were significantly associated with more interactions in the study group ($p <0.05$).

Conclusion: Hospitalized patients are commonly exposed to PDDIs, but the subsequent probability of occurrence and magnitude of patient harm requires further empirical substantiation. Although that our data showed low prevalence rates of DDIs, life-threatening interactions may develop. While Medscape detect more major interactions than other two databases, Lexicomp was the most inclusive of all three data bases and was more users friendly and better guided to clinical recommendations than the others.

Key Words: Drug-drug interaction, Drug related problem, Pediatric, Prevalence, medication safety, clinical pharmacist, Northern Cyprus.

STATEMENT (DECLARATION)

Hereby I declare that this thesis study is my own study, I had no unethical behavior in all stages from planning of the thesis until writing thereof, I obtained all the information in this thesis in academic and ethical rules, I provided reference to all of the information and comments which could not be obtained by this thesis study and took these references into the reference list and had no behavior of breeching patent rights and copyright infringement during the study and writing of this thesis.

Rim Diri

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ABBREVIATIONS

Abbreviations	Explanation
DDIs	Drug-drug interactions
DRPs	Drug-Related Problems
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PH	Potential Hydrogen
CYP	Cytochrome P450
ADR	Adverse Drug Reaction
GI	Gastrointestinal
UTI	Urinary tract infection
GFR	Glomerular Filtration Rate
P-gp	P-glycoprotein
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences
IRB	Institutional Review Board
FDA	Food and drug administration
WHO	World Health organization
PK	Pharmacokinetic
PD	Phamacodynamic

Classification of Diseases and Related Health Problems

J02	Acute pharyngitis
J69.0	Aspiration pneumonia NOS
P24.	Neonatal aspiration pneumonia
J12	Viral pneumonia
J13	Pneumonia due to Streptococcus pneumonia
J15	Bacterial pneumonia
A09	Infectious gastroenteritis
G00	Bacterial meningitis
J45.	Asthma
N39.0	Urinary tract infection
NOS(K52.9)	Gastroenteritis

1. INTRODUCTION:

Drug interactions occur when the side effects or effects of one drug are changed by the presence of another compound, namely drugs, food, drinks, herbs, or environmental chemicals.

There are several types of interactions and different factors affected (i.e. enhance) drug interaction such as such as smoking or environmental factors. Other than that, drugs can interact with herbals, foods, supplements and drug excipients.

Several changes occurs regarding the term interaction even drug interaction refers generally to drug drug interaction, these changes includes pharmacokinetics or pharmacodynamics or both. From the previous brief introduction we define the drug interaction as an alteration of the patients response to the specific drug with or without the presence of other substance. (Askari M., 2013).

Due to increasing in the quality of life of population and number of the drugs the chance of drug interactions increased dramatically. Interactions between two or more concomitantly administered drugs may rise or reduce therapeutic effect as well as undesired effects. Drug-drug interactions (DDIs) make patient safety at risk by leading to toxicity or a decreasing therapeutic benefit and may increase the mortality and morbidity, especially in elderly and frail patients.

Fatal adverse drug effects rank between the fourth and sixth major cause of death in the US, and it is mentioned that around third percentage of all adverse effects of the drugs are a direct result of interactions between drugs (Scripture, 2006).

Three different results coming from DDI; alteration of therapeutic or adverse effect (Increasing or decreasing) or specific adverse effects rose because of the presence of two or more interactions which is not presence in the absence of this interaction. (Blower, 2005), the risk of the interaction results increased if the toxic effect of the drug increased due to this interaction. For instance, there is a huge increase in the risk of acute muscle damage if patients taking statins start taking azole (antifungals), a reduction in efficacy as a result of interaction can sometimes be just as harmful as an increase, for example, patients taking Warfarin who are given Rifampin needs more warfarin to maintain

sufficient anticoagulation (Preston, 2015). Drug-drug interaction is divided into two main types of interaction: pharmacokinetic which include a change of absorption, distribution, metabolism, and elimination, and the second type is pharmacodynamic there is a change in the pharmacological effect of a drug.

The risk of interactions among inpatients pediatric is high due to plentiful of drugs consumed which increase the risk. The second reasons of the high incidence of DDI among pediatrics is the presence of different specific reasons such as; the information of drug use among this population is low comparing to adult patients, the dose of drugs used in pediatrics mainly calculated depending on their weight and off labeled use of the drug among pediatrics (Feinstein J et al, 2015).

This study aims to describe the frequency, types, and related information of potential drug-drug interactions (PDDIs) in pediatric unit and assess the associated factors for PDDIs in hospitalized pediatric patients.

2. Background

2.1 Drug-drug interactions:

The attention and consideration of DDI among health care providers, scientists increased these days around the world (Ansari.J,2010).

The number of drugs discovered increased every day, this increment leads to increase the interactions between them. This leads to as a consequence to provide different way rather than the memory of doctors or pharmacists to prevent the occurrence of any interactions (Ansari.J,2010).

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2.2. Mechanism of Drug-drug Interactions

Pharmacological interactions are classified into pharmacodynamics and pharmacokinetic interactions (Scott, 2013). Pharmacokinetics (PK) interactions occurred when one or more of the four components of the PK of the drug (absorption, distribution, metabolism and elimination) is altered because of the presence of the other drug (Hansten PD, 2006).

Being familiar with the mechanisms of DDIs is important for the healthcare professionals to take an appropriate action and recognize the importance of the interaction by weighing the risks and benefits to the patient (Lal, 2008). For instance, prescribers may change the medication, dose, time and consequence of the treatment regimen. Also, when administering of combination therapy, knowing the mechanisms of any interacting drug is important for the prediction and avoidance of toxic outcomes (Angela D. M., 2011).

Special awareness is needed when prescribing drugs with high opportunity for

interactions such as anticoagulants, antiepileptic, antifungals, antibiotics ,antihistamines, NSAIDs, HIV protease inhibitors, proton pump blockers, anticancer drugs, hypoglycemic agent. Furthermore, populations like elderly patients, critically ill, and patients with chronic disease should be monitored closely for DDIs because of polypharmacy or changed renal/hepatic metabolism (Lal, 2008).

2.3 Pharmacodynamic interactions

Pharmacodynamic interactions occur between drugs with similar or opposite pharmacological effects (Corrie, 2017).

2.3.1 Additive or synergistic Pharmacodynamic Interaction

When the effect of two drugs is greater than the effect of each agent given alone (1+1=2); this interaction is considered as additive. An example of additive DDI is the combination of aspirin (antiplatelet) with heparin (anticoagulant); this may increase the chance of bleeding (Scott, 2013).

Even drugs with different pharmacological action but have common side effect; their side effect will be potentiated. As an example, amitriptyline (tricyclic antidepressant) and thioridazine (antipsychotic), both drugs have anticholinergic effects and can result in heat stroke in hot, humid climates or psychoses, in addition to the common side effects like dry mouth and blurred vision. Similarly, adverse effect of two drugs may also be additive as ototoxicity when using ethacrynic acid and streptomycin or nephrotoxicity when using tobramycin and cephalothin (Pleuvry, 2005).

However, the pharmacodynamic interaction may be aimed, if the drug's effects are to the same direction, this will lead in potentiating their effect (synergistic effect) (Cascorbi, 2012) More specifically, synergism occurs when the effect of two combined drugs exceeds the sum of the effects of each drug given alone (1+1=3). This interaction is aimed particularly in the use of antibiotics (Scott, 2013).

For instance, sulphonamide antibiotics and trimethoprim are bacteriostatic but when combined their effect will be bactericidal (Pleuvry, 2005).

In contrast, the combination of nitroglycerin, isosorbide (nitrates) and sildenafil may result in unwanted synergistic DDI and life-threatening drop in blood pressure.

2.3.2 Opposing or antagonistic Pharmacodynamic Interaction

When one drug diminishes or eliminates the effect of another this DDI, this interaction is defined as antagonistic (1-1=0). This DDI occur at the receptor level. Co-administration of a beta-agonist (as albuterol or salmeterol), with a beta-blocker (aspropranolol or metoprolol) may reduce the effects of both drugs by competing for the same (Scott, 2013).

In addition, when two drugs work on different receptor systems, exert opposite effects on different receptor systems and physiologically oppose the function of one another; this considered as functional antagonism. Hyperglycemia caused by glucocorticoids may oppose the actions of hypoglycemic agents.

2.4 Pharmacokinetic interactions

Pharmacokinetic interactions occur when one drug interfere with the absorption, distribution, metabolism or excretion (collectively known as ADME) of the other drug (Corrie, 2017).

2.4.1 Drug absorption interactions

Interactions at drug absorption level may lead to sub therapeutic serum concentration of the interacting drugs and occur due to the following factors:

2.4.1.1 Changes in gastrointestinal pH:

H2-receptor blocker, proton pump inhibitors, and antacids containing Al/Mg change the gastric pH and it may significantly reduce the bioavailability of other drugs. As a result, gastric acid modifying agents may reduce the absorption of ketoconazole, itraconazole, and salicylic acid (Lal, 2008).

2.4.1.2 Changes induced by chelation and adsorption:

Chelating lead to the formation of complexes which can affect the absorption of one of the two combined drugs. Metal ions (as calcium, magnesium, aluminum, iron) founded in antacids, preparations containing magnesium salts, aluminum and calcium preparations can decrease the absorption of tetracyclines (as doxycycline or minocycline) in the digestive tract by the formation of complexes that are poorly absorbed (Bokor-Bratić, 2000).

2.4.1.3 Changes in gastrointestinal motility

Increase the gastric motility can reduce the absorption of a drug by decreasing the time in which the drug will be in contact with mucosal area of absorption. For example, metoclopramide reduce the absorption of digoxin and theophylline because it speeds up the gastric emptying (Johnson, 1984).

2.4.1.4 Transporter based interactions

Multidrug efflux transporters such as P-glycoprotein (P-gp) are involved in this type of DDIs. Induction or inhibition of these proteins also results in DDIs. Rifampicin is P-gp inducer and may lead to the reduction of digoxin its plasma levels (Greiner, 2002); while verapamil is P-gp inhibitor and increases the digoxin levels (Lal, 2008).

2.4.2 Drug distribution interactions

Often, transportation of drugs is mediated by binding to plasma and tissues proteins such as albumin, α1-acid glycoprotein, and lipoproteins (Palleria, 2013).competition for plasma protein and displacement of a drug from its binding site results a transient increase the concentration of free (active) drug (Scott, 2013).

Co-administration of warfarin and diclofenac shows pharmacological displacement interaction. Since, warfarin and diclofenac have the same affinity for albumin, using diclofenac in patients previously used warfarin for a long time may displace the warfarin from its binding site and increases the plasma concentration of free warfarin. As a

consequence, serious hemorrhagic reactions may be developed (Palleria, 2013).

2.4.3 Drug metabolism interactions

The cytochrome P450 (CYP450) family is involved in most DDIs. CYP isoforms commonly mediate DDIs are CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (Gad, 2008). Many of these interactions occurred due to inhibitions or inductions of these isoforms.

2.4.3.1 Effect of enzyme induction on drug-drug interactions:

Inducers of CYP450 increase the rate of metabolism and facilitate the clearance of the substrate from the system because inducers stimulate the production of the CYP isoform. Thus, the response to the substrate decreases and the drug will be ineffective.

Several drugs can induce the enzyme CYP 450 such as: troglitazone, griseofulvin, glutethemide, barbiturate….. This induction of the enzyme lead to sever drug interaction when at the same time the patients used warfarin, verapamil, quinidine because of the lower substrate concentration in the plasma (Lal, 2008).

2.4.3.2 Effect of enzyme inhibition on drug-drug interactions:

On the other hand, CYP450 inhibitors reduce the metabolism and extend the activity of the substrate. This may increase toxicity especially if the drug affected has a low therapeutic index, such as phenytoin (Gad, 2008). CYP1A2 inhibitors can promote the toxicity risk of theophylline or clozapine; CYP2C9 inhibitors promote the toxicity risk of phenytoin and warfarin; while CYP3A4 inhibitors promote the toxicity risk of a larger number of drugs like carbamazepine, lovastatin and simvastatin, rifabutin, cisapride, cyclosporine, ergot, protease inhibitors and alkaloids (Lal, 2008).

Many of the commonly prescribed drugs their clearance is mediated by the CYP3A family, particularly CYP3A4 (Gad, 2008) .For instance, Ketoconazole is a selective inhibitor for CYP3A4 that responsible for the metabolism of cyclosporine. This interaction is common in transplant patients. As a result, less than 25% of the dose of

cyclosporine is needed if ketoconazole is co-administered (Pleuvry, 2005).

2.4.4 Drug elimination interactions

Drugs are eliminated mainly by kidney and bile, but bile elimination has no significant DDIs (Lal, 2008).

Alterations of renal excretion mediated by changes in protein binding (discussed before), or inhibition of tubular secretion, or changing in the kidney blood flow or urinary pH. The action of penicillin is prolonged by the co-administration of probenecid is the classical. Probenecid was designed to compete with the active transport mechanism that secretes acids (penicillins) into the renal tubule. Other acidic drugs as aspirin, indomethacin, and sulphonamides; if co-administered together the plasma concentrations of each other will be increased. NSAIDs inhibit prostaglandin production which important for renal capillary vasodilatation. As a consequence, the renal blood flow may be reduced. This interaction is significant for renally excreted drugs with a low therapeutic index, such as lithium (Scott, 2013).

2.5 Incidence of drug -drug interactions in pediatrics:

Drug drug interactions (DDI) occurred when one change the effect of the other one when both of them are taken at the same time by the same patient (Alvim MM, et al., 2015).

Administration of more than one drug is common in practice, which may increase the possibility of the interactions occurrence, these interactions may lead to increase the hospitalization and cost due to presence of adverse effect like increase/decrease the effect of the drug a result of the interaction (Moura C et al,2011) (Ganeva M et al., 2013).

Several factors can increase the incidence of interactions among pediatric patients such as:
a) The huge number of drugs that they consumed during one hospitalized period.
b) Due to their different PK parameters than adult, the efficacy of drug may altered among them.
c) The off labeled use of drugs are higher in pediatrics compared to adult.

Due to high risk of hospitalization among pediatric patients, and different factors can increase the hospitalized days such as diseases like epilepsy, or drugs used like asthma drugs, the hospitalization period may increase which result in big range of the prevalence of DDI among our population from 3.8% to 75% (LangerovaÂ P et al., 2013) (Yeh ML et al.,2014) (Dai D, et al,2016).

Regarding the gender of the patients, Micromedex and Drug Interaction Facts both reported that male patients with hematological disease are at higher risk of interaction because of more drugs they administered even not used for hematological diseases and more days they stayed in hospitals (FernaÂnde et al, 2014).

Dia D in 2016 and the team conducted a study to report the prevalence of interactions among pediatrics in pediatric intensive care unit (PICU), their findings concluded that the hospitalized periods may affected by ethnicity of the patients such as Caucasians in addition to the diseases and number of drugs the patients used during the hospitalized days which increase the risk of drug interactions as a result (Dai D, et al., 2016).

Emergency Department (ED), considered as an integral department for the presence of drug interactions since most of the pediatric who entered the ED have sever condition which make them exposed to more drugs and increase the staying period before transferring them to other departments which lead to increase the risk of the DDI. (Morales-Ríos, O et al., 2018).

2.6 The role of pharmacist in managing drug Interactions

Pharmacists are considered an integral part of the team, although their level of involvement in the critical care practice is variable (Sanghera N et al.,2006).
A few small studies have shown that a pharmacist's involvement in critical care rounds is associated with fewer adverse effects and alone may be associated with lower mortality among ICU patients (Tripathi, S., et al.,2015).

The American Academy of Pediatrics in 2003 proposed that inclusion of a pharmacist in the critical care team can help decrease medication errors. To date, however, descriptions in the pediatric literature of a clinical pharmacist's role in this team have remained limited.

The literature supported the presence and emerging the pharmacists as a health care provider in the pharmaceutical care plan for the patients. Since a few articles consider the involving the pharmacists in pediatric patients, only few articles will be included (Krupicka MI, et al.,2002).

In 2004, to evaluate the presence of the pharmacists as an integral part of health care team, clinical pharmacists and students were enrolled in a study. The findings supported the pharmacists as an integral part since 223 of the interaction were prevented by the pharmacists and 91% of their interventions were accepted by the physicians, and around $500000 were saved due to the valuable of the pharmacists interventions (Condren ME, et al.,2004).

In 2012, a study conducted to assess the efficacy of interpreting pharmacists as a part of health care team for 2 months, the average of the interventions daily were 21 and 202% were the drugs reconciliation (Cunningham KJ.,2012).

The pharmacists roles exceeds the medication errors to include enhancing patients adherence in different countries such as Egypt, China and Canada, also pharmacists have a positive impact in the days of admissions for the pediatric patients in addition to drugs interventions (Zhang C et al.,2012).

In Canada, a study conducted in the oncology clinic, the pharmacists had positive effect on the patient care (83% of the interventions). Also pharmacists were able to recognize 99% of the DRP which equal to 165 in the 58 pediatric patients (Taylor TL,et al., 1999).

Condren and Boger evaluated the impact of a multidisciplinary asthma education program involving a pediatrician, pharmacist, and a nurse in a pediatric clinic. This retrospective analysis included 57 patients and compared outcomes in terms of decreased hospitalizations, emergency room visits, and systemic corticosteroid use for the year prior to enrollment in the clinic to 1 year. (Condren M, &Boger J.,2005).

The pharmacists' role exceeds the medication errors to involve the education for the diseases such asthma, optimizing the usage of inhalers, and patients counseling. the summation of the pharmacists roles lead to significantly decrease in stayed days of asthmatic patients, number of visiting and using systematic corticosteroids.(Condren M, &Boger J.,2005).

In adults the pharmacists interventions leads to reduction in poly pharmacy and this is established in the literature while in children there is no enough evidence (Costello I, et al.,2004).

A retrospective study was conducted in outpatient pediatric clinics that assessed the implementation of an electronic medical record-based quality improvement intervention for documentation of a medication reconciliation process (Rappaport D,et al.,2011) .

The authors found improvement in documentation of medication reconciliation depending on the type of visit, the person placing the medication order, and quality-based incentives. Although the data are limited, medication reconciliation may be one of the main components for identifying polypharmacy in pediatric patients.

Next, a single-center, prospective pilot study published in 2012 reviewed a pharmacist-managed medication reconciliation program for pediatric patients in outpatient clinics (Provine AD, et al.,2014).

The pharmacist on duty was responsible for speaking with the patient, family, caregiver, or retail pharmacy after a physician or nurse completed a medication history (MH) review. If there were any medication changes or interventions, the pharmacist updated the electronic medical record. A total of 100 MHs were included in the study and the mean number of medications documented prior to the pharmacist intervening was 4.4±3.3.

After the pharmacist finalized the MH, the mean number of medications dropped to 4.3±3.9. It took an average of 15 minutes for the pharmacy to complete each MH.

2.7 Pediatric overview:

Rates of chronic conditions in pediatrics have been steadily increasing and medications used to treat these conditions have also shown a proportional increase (Perrin JM, et al.,2014).

Most clinical trials for approving medications by the US Food and Drug Administration (FDA) focus on the safety and efficacy of solitary medications in adults. However, data from these trials are often times extrapolated for use in pediatric patients who have different pharmacokinetic processes and physical profiles.

Clinical trials that focus on the safety, efficacy, and dosing parameters in pediatric patients are lacking, prompting use of "off-label" prescribing by physicians.

With the limited availability of evidence-based protocols and practice guidelines, clinicians often rely on their best clinical judgment when managing pharmacotherapy for pediatric patients with multiple and/or complex disease states (Horace, A. E., et al.,2015).

The FDA has developed mandates for pediatric research and is providing incentives for researchers to improve the quality and quantity of available data. As research increases and more medications become available for use in pediatrics, the issue of poly pharmacy is becoming more of a concern (Horace, A. E., et al.,2015).

The British National Formulary for Children, for example, provides doses for neonates (u nder 1 month in age), then for children from 1 month to 4 years, and for children 4 year t o 10 years. Many entries do not, however, follow this age division. For example, the US FDA classification is neonate (birth to 1 month), infant (1 month to 2 years), children (2 t o 12 years) and adolescent (12 to < 16 years) (Knoppert, D., et al.,2007).

2.7.1 Pharmacokinetic in pediatrics:

Due to the difference in PK parameters and the alteration during the pediatric life, special considerations taken by physicians in the prescription and dosing of the drugs.

These alterations in the physiological systems lead to consider pediatric as special population.

2.7.1.1 Absorption:

The low number of clinical studies assesses the absorption mechanism in pediatrics lead to not fully understand the mechanism in this population.

The concentration of the absorbed drug in young children is low, this result comes from the low intestinal transit time in this group of population i.e. sustained release drugs and low soluble drugs (Pedersen S &Steffensen G., 1987).

Regarding the acidity of the stomach, the pH =3 after 24-48 hour after the birth then increase to reach 7 after 10 days then again decrease at 2 years age (Strolin Benedetti Met al., 2005) , (Bartelink IH et al.,2006).

These alterations on the acidity of the stomach among this population can lead to significant effect in the absorption of different drugs. The concentration of penicillin which is an acidic drug measured in newborns and infants and children, the concentrations were higher in newborns which have higher pH compared to the other two groups (Lange D et al., 1997).

Also itraconazole which is a basic drug can be affected by the acidity of the stomach, the higher the concentrations found in lower pH such as in newborn. The concentration of the mentioned drug is lower than the predicted value in this population (Lange D et al., 1997).

Comparing to the adults, the bile secretions is lower in neonates, the data showed that 2-4mM in the neonates while 3-5mM in the adults (Perez de la Cruz Moreno M et al.,2006).

The absorption in the younger patients may be affected negatively comparing to the adult since the absorption is positively proportional with the bile salt concentration. this is affect mainly the low soluble drugs such as hydrocortisone (ZughaidH,et al., 2012) .

Referring to the intestinal permeability, during the first week the permeability decreases after being high enough at the birth (van Elburg RM, et al., 2003).

The studies conducted on the rats demonstrated that the reduction of the surface area is the hidden reason for this reduction (Zakeri-Milani P et al.,2007).

The sugar absorption test was used to measure the permeability of intestine in preterm babies. Regardless the mechanism of the absorption the test result showed that higher absorption were in preterm babies comparing to health ones (Corpeleijn WE et al.,2011).

2.7.1.2 Distribution:

Both duration of action and efficacy of drugs are related in a way or other to distribution. Different studies compare the distribution of drugs in both adult and pediatric, a study included 45 different drugs to see the difference in distribution of these drugs in adult and pediatric populations, the data showed that the volume of distribution were higher in all childhood age groups compared to adult in theses 45 drugs (Ginsberg G, et al.,2002).

The distribution of drugs affected by the body composition, to be specify, infants with higher percentage of fat in their bodies will have higher volume of distribution of lipophilic drugs compared to adult with lower percentage of fat (Batchelor, H. K., et al.,2015).

Several drugs have low protein binding in pediatrics such as salicylates, nafcillin, sulfisoxazole and phenytoin. Since these drugs have low protein binding this means more free drugs can penetrate tissues as a consequence larger volume of distribution. Table 1 showed the difference between adults and pediatric in protein of the body. (Batchelor, H. K., et al.,2015).

Table 1. A comparison between adults and pediatric protein (Radde IC et al.,1985)

Parameter	Neonate	Infant	Child
Total protein	Decreased	Decreased	Equivalent
Plasma albumin	Decreased	Equivalent	Equivalent
Plasma globulin	Decreased	Decreased	Equivalent
α1-glycoproteinacid	Decreased	No data available	Equivalent
Free fatty acid	Increased	Equivalent	Equivalent
Unconjugated bilirubin	Increased	Equivalent	Equivalent

The data of different studies showed that the protein of the liver increased with the age from newborn to adult from 26 mg for each g to be 40 mg for each g for the adults (Barter ZE et al.,2007).

2.7.1.3 Metabolism:

Generally drugs that are highly metabolized are administered at a lower mg kg^{-1} dose in newborns compared with preschool children due to these differences in enzyme levels. However, the hepatic clearance of drugs can be higher in infants and preschool children as liver blood flow is increased compared with adults, owing to the larger ratio of liver to total body mass in the former population (Gibbs JP, et al., 1997).

This can increase the first pass effect where a drug is cleared on first passage through

the liver although the level of enzyme activity will influence this parameter. The observed age-dependent clearances for theophylline, caffeine, carbamazepine, and valproic acid seem to reflect liver size to body weight differences rather than differences in intrinsic clearance per gram of liver weight (Rane A, 1992).

However, the specific metabolic pathways need to be understood to enable extrapolation of adult data into pediatric populations. The example of the grey baby syndrome resulting from dosing chloramphenicol to neonates at doses extrapolated from adult data is often used to highlight the importance of understanding ontogeny of metabolic pathways (Batchelor, H. K., et al.,2015).

Differences in enzyme expression and activity can result in altered metabolism of drugs(e.g. midazolam and zidovudine or production of metabolites in pediatric populations that are not observed in adults (e.g. caffeine production in newborns receiving theophylline, differences in metabolite production in children with valproic acid, paracetamol, chloramphenicol ,cimetidine and salicylamide (Benedetti MSetal., 2007)(Batchelor, H. K., et al.,2015).

There are several extensive reviews on metabolism within pediatric populations including ontogeny of drug metabolizing enzymes and age related changes in the metabolism of drugs (DeWildt SN,2011).

Age and diet can affect the bacterial colonization in the gut, this difference in colonization depending on the age affect the drug metabolism by those bacteria (Kurokawa K et al., 2007).

Drugs such as midazolam, nifedipine and verapamil can be affected negatively by the metabolism mechanism in both gut lumen and the wall, this negative effect affect both bioavailability and pharmacological effect (Von Richter O, et al., 2001).

2.7.1.4 Eliminations:

Kidneys are the major organ for the excretion of the drugs and their metabolites.

The neonates have a GFR of 2- 4ml min^{-1} 1.73m^{-2}, and after one week it will increase to 4 – 8 ml min^{-1} 1.73m^{-2}, the equivalent to adult level at the first year of birth. This was the result of the article compared three different drugs and their phase II metabolites clearance by kidney (Anderson BJ &Holford NHG, 2013).

Comparing to the adults, newborns have lower kidney functions due to incomplete function of their kidneys. These finding were differ from the preschool and infants which they have similar or a higher level of the renal elimination compared to adults (SomogyiA et al., 1985) (Patsalos PN.,2004).

This similarity in renal clearance was because of kidney function were more preschool children compared to the adults.(Batchelor, H. K. 2015).

For example, digoxin a drug excreted viaP-gp within the tubular cell of the kidney, preschool children had to exposure to three times higher doses of the drug compared to adults due to higher kidney function related to the body weight (Chae KM& Tharp MD,2000).

GFR is also predicted by the CrCl, in children where the advice was to decrease the dose of the drugs if the CrCl is lower than the normal range. In addition to that, the acidity of the urinary also affects the reabsorption of weak acid or weak base drugs which had influence in the clearance of the drugs (Batchelor, H. K. 2015).

In infants the urine is more acidic compared to the adults which more reabsorption of the weak acid drugs occurred (Alcorn J & McNamara PJ. 2008).

2.7.2 Pharmacodynamics in pediatric

Describe the relationship between the dose of the drug or its concentration and the response which may be desirable response (effectiveness) or unfavorable response (toxicity).

Age-dependent changes and Development can alter the action and the response to a drug. Little information available about the effect of human age changes on interactions between drugs and receptors and the impact of these interactions (Kearns, G. L et al., 2003).

For example, famotidine has different PD profile in neonates, this difference came from the difference in glomerular filtration rate because of the decrement in plasma clearance of the drug (James, L. P., et al.,1998).

2.8 Most prescribed drugs used in pediatrics:

Antibiotics:

In childhood period most of the children receives antibiotics as the major drug category prescribed to this population (Chaietal., 2012).
Several studies demonstrated the frequent usage of this class of drugs leads to different diseases later and different physiological changes (Biedermann and Rogler, 2015).

The epidemiological studies in US showed that one child received at least one antibiotic during his childhood period which equal to 25% of the total drugs given to children, and the total number of antibiotics given were 74.5 million in outpatients clinics (Hicks et al., 2013).
Several studies illustrated that a huge percentage of antibiotics which equal to around 50% of them are useless and no need to be prescribed.(Kronman et al., 2014).

The viral upper respiratory tract infections were the most common disease with unnecessary prescribed antibiotics and 30% of the children received unnecessary antibiotic in each visit to outpatient clinics (McCaig et al.,2003).

The misused of broad spectrum antibiotics and prescribed them in cases that narrow spectrum can show a positive response have been increased significantly (Hersh et al., 2013).

Children with same infectious diseases still received different antibiotics even after adjusting different factors affect the drug of choice such as; age, socio demographics factors and co morbidities. This vastly differentiates of antibiotic usage rely on the visit and clinical practice (Fierro et al., 2014; Gerber et al., 2014).

Misusing and wrong antibiotics usages lead to increased risk of drug resistance in addition to adverse events. In USA every year around 140,000 visits to ED were because of antibiotics adverse events which encompass around to 20% of all visits related to adverse events of drugs usages (Shehab et al., 2008).

The World Health Organization (WHO) mentioned that one of the three biggest problem face the human being is antimicrobial resistant. Another finding that focused on the antibiotics resistant that the using of antibiotics during the childhood will increase the resistance as the age of the patients increased, with more risk increment in the cesarean delivery as the genes of resistance increased (Ba¨ ckhed et al., 2015).

2.9 Previous Studies:

Changing or alterations in PK or/and PD of the drug by the presence of another drug is called drug interaction. As the number of drugs increased in one prescription, the risk of interaction increased. The pediatric populations are at high risk of interaction since one patient administers different drugs on one admission.

A study was conducted in 2013 by Petra Langerová et al, to assess and evaluate the drug interaction, 6078 patients enrolled in their study. During their days of admission the total number of prescriptions was 19522. 3.83% of the patients had a drug interaction and 0.47% of the interactions were moderate to severe. (Langerová et al., 2013).

To measure the factors that increased the risk of interactions, the findings showed that the number of prescription in each visit, the number of visits in a year and the patients age had a significant effect in increasing the risk of interaction($p<0.0001$), ($p<0.0001$) and ($p=0.008$), respectively. Regarding the classification of interaction, only 12.7% of the interaction classified as a moderate to severe interaction while 37.3% of them were mild (Langerová et al., 2013).

In 2011, a total of 43 hospitals enrolled in a study to assess the interaction in pediatric population, the total patients who fitted the inclusion criteria were 498 956 in those hospitals. The results showed that around half of the patients (49%) had at least one interaction, and 5% of the patients had contraindicated interaction. The classifications of interactions were mild, moderate and major with percentage of 11%, 28% and 41%, respectively. (Feinstein, MD, 2011).

In 2014, a total of 150.6 million prescription sheets were evaluated, 19. 4 million (2.85%) prescriptions were met the inclusion criteria. the findings of this study showed that 672,020 potential DDI occurred which means one drug interaction in each three prescription as an estimated average. The most common interactions were between aspirin and aluminum/magnesium hydroxide with a percentage 4.42% (Yeh ML et al., 2014).

Regarding the significant level of interaction, the data showed that the interaction between digoxin and furosemide were the most common interaction belong to level 1 in significant (20.14%). the reason for classified this interaction as a level 1 is that the loop diuretics such as furosemide increase the K^+ and Mg^{2+} excretion which affect the contractility of the heart muscle and leads to exacerbate the effect of digoxin in inducing arrhythmias. (Yeh ML et al., 2014).

Close monitoring of the K^+ and Mg^{2+} level in plasma with providing supplements in case of sever excretion can reduce the severity of the interaction.

The second and third most common interactions were between cisapride with furosemide 6.02% of the interaction and cisapride with erythromycin 4.85%, respectively. In the classes of the drug interaction, paracetamol with anticholinergic drugs were the most common with 6.62% percentage and aspirin with NSIADs and anti-acids were the second and third most common with 5.40% and 4.46%, respectively (YehML et al., 2014).

3 MATERIAL AND METHOD

3.1 Study design:

A retrospective observational study in Near East University Hospital.

3.2Inclusion criteria:

- Patients < 12 years old.
- Patients who used more than one drug during his/ her hospitalized period.

3.3 Exclusion criteria:

- Patients who take only one medication.
- Patients who their files were uncompleted.

3.4 Sampling

All patient admitted to the pediatric units matching the inclusion criteria within the study time frame (September 2017 to September 2018) were included in the analysis.

3.5 Data collection instrument:

Data were collected using a report form (appendix), which includes demographic data of the patients; age, gender, number of medications used during the hospitalized period and staying periods.

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

Generic name was used in all study procedure.

3.6 Study procedure:

All drugs the patients used during their hospitalized period were enters into three different drug-drug interaction checker; lexi.com, Drugs.com, medscape.com. All screening and documenting done by the researcher.

Mechanisms of DDI in All software used were categorized to Pharmacodynamic, Pharmacokinetic and Unknown. Based on Lexicomp classification interaction level into 5 categories (A, B, C, D and X), interaction level of X, D and C were Very important clinically and need to modify the medications and dosages or avoid combination [Table 2]. In Drugs.com database DDIs are classified according to the severity of interaction into major, moderate, minor [Table 3], while in Medscape they were classified to minor, monitor closely and serious.

Table 2.Interaction levels categories by Lexicomp (Wolters Kluwer Clinical Drug Information, Inc)

Interaction Levels	**Action**	**Description**
X	Avoid combination	The risks associated with concomitant use of these agent usually outweigh the benefits
D	Consider therapy modification	patient-specifics assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risk
C	Monitor therapy	Data demonstrate that the specific agent may interact with each other in a clinically significant manner. the benefits of concomitant use of these two medications usually outweigh the risk
B	No action needed	Data demonstrate that the specific agent may interact with each other, but there is little to no evidence of clinical concern resulting from their concomitant use
A	No known interaction	Data have not demonstrated either pharmacodynamic or pharmacokinetic interaction between the specified agents

Table 3. Drug Interaction Classification according severity in Drugs.com database Severity

severity	**Action**	**Description**
Major	Avoid combination	Highly clinically significant, the risk of the interaction outweighs the benefit
Moderate	Usually avoid combinations	Moderately clinically significant, use it only under special circumstances.
Minor	No action need	Minimally clinically significant, assess risk and consider an alternative drug, take steps to circumvent the interaction risk and/or institute a monitoring plan.

Table 4. Drug Interaction Classification according severity in Medscape database Severity

severity	**Action**	**Description**
Minor	No action needed	Can be used, the interaction may occurred, then use alternatives.
Monitor Closely	Use in caution	Moderate clinically significant, usually needs monitoring when used
Serious	Should be avoided	High risk of serious interactions, should not used and consider alternatives.

3.7 Ethics approval:

Ethics approval for this study was obtained from the Institutional Review Board (IRB) of Near East University Hospital (YDU/2018/62-656). Research was conducted in accordance with the Declaration of Helsinki. Patients' privacy was taken in consideration by the researchers.

3.8 Statistical analysis:

The collected and analyzed data were conducted using Microsoft Excel 2016 and Statistical Package for the Social Sciences (SPSS), software version 20.0.

Frequency analysis was carried out to investigate the descriptive characteristics of study sample. To describe categorical variables such as gender frequency and percentage was used.

For the continuous data such as hospitalized period and number of medications, descriptive statistics such as arithmetic mean, standard deviation, median, minimum and maximum values were calculated.

Independent samples Mann Whitney U test was applied for the comparison of staying periods and number of medication between two categorical variables.

To test the association between different categorical variables, Pearson Chi-square and Fischer exact test were performed.

Related analysis result of each statistical method is shown in their corresponding tables throughout the text. Level of significance was accepted to be 0.05 for the whole study.

4 Result

4.1 Demographics of the patients:

332 patient files were screening during the study period, only 230 were matched the inclusion criteria and were screened for DDI in three different tools.

Regarding the gender of the patients, 112 out of 230 were male which reflect 48.7% of the sample, while 118 out of 230 were female which reflect the percentage of 51.3%.

Referring to the age categories of the patients, more than half of the patients 127 (55.2%) were neonate (0-1 month) and infants (1-2 years) were32 (13.9%) while 40 (17.4%) were young child (2-6 years) and child (6-12) were 31 (13.5%).

Regarding the disease of the patients who had interactions, pneumonia was the most cause for hospitalization (33, 14.34%), 10 patients were hospitalized because of they were premature (4.34%), 9 patients had GI (3.91%), 4 had pharyngitis (1.73%) , 4 had UTI (1.73%) , 2 had epilepsy (0.86%),2 patients had surgery(0.86%) ,1(0.43%) patient had asthma , 1(0.43%) patient had coma and 1(0.43%) patient entered the hospital duo to meningitis.

The mean days of hospitalized was (2.8 ± 4.5) with the mean number of medications used during hospitalization (3.6 ± 2.0) ranging from 2 medications used to 13,14 and 15 drugs used recorded once.

4.2 Drug interactions:

According to the number of interactions in the three different tools, Lexicomp recorded 64 (27.8%) patients have interactions while Drugs.com and Medscape recorded 57 (24.8%) and 53 (23%) patients' interactions, respectively.

According to Lexicomp, the highest number of interactions were noticed in young children with percentage of 70.00%% of drug interaction founded and neonates has only 7.87% interactions among the drugs they used. These findings can conclude that there is an association between the age and the interactions in lexicomp ($X2=66.28$, $p < 0.05$). (Figure 1).

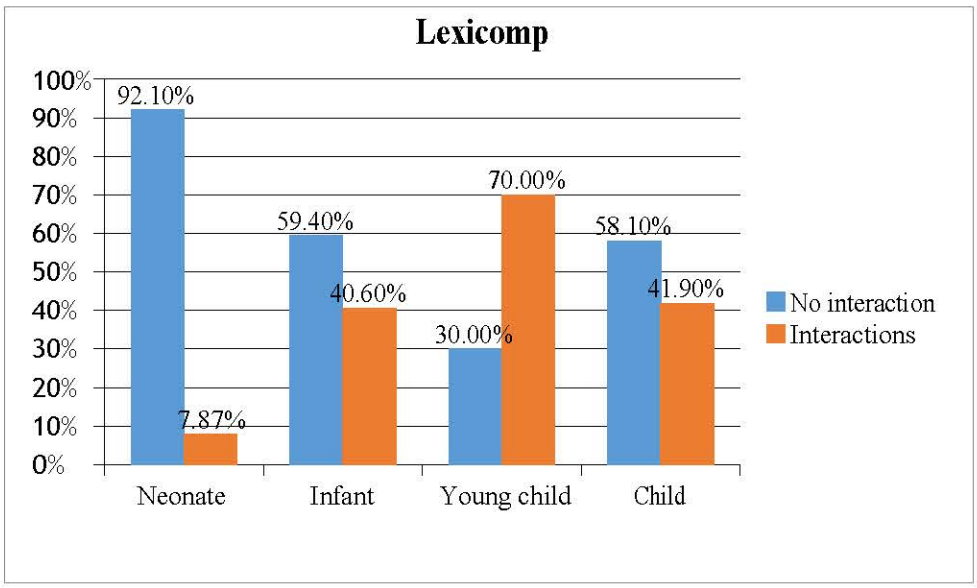

Figure 1.The interaction of drugs in Lexicomp within age groups

The mean ± SD number of the drugs used according to the patients age groups was for (3.02 ± 1.43) for the neonate and (4.09 ± 2.21) for infants. While the mean ± SD number of the drugs used found to be in young children and children was (5.07 ± 2.37) (4.00 ± 2.50), respectively.

The gender of the patients showed that only 71.4% of the male have no interaction and 72.9% of the females recorded no interaction without any associations between the gender and interactions (X^2 = 0.06 p=0.8).

According to the Drugs.com, the total number of interactions recorded was 57 (24.80%), this percentage was divided into four different age groups as following: 50% of the young children have interaction and only 13.4% of the neonates have interactions. While out of the infants and child only 34.37% and 29.03% have interactions, respectively. These findings indicated that there is a dependence between age groups and presence of interactions(X^2 = 24.37, p <0.05). Table5

Table 5.The interactions within age groups in Drugs.com

	Neonate	Infant	Young child	Child
No interaction	(110)86.61%	(21)65.62%	(20)50.00%	(22)70.96%
Interactions	(17)13.40%	(11)34.37%	(20)50.00%	(9)29.03%

According to the gender, only 25% of the male patients have interaction, while 24.6% of the female reported interaction during their hospitalized period. This result can indicate that there is no dependence between gender and presence of interaction regarding Drugs.com ($X^2 = 0.006$, $p = 0.94$).

According to Medscape, only 23% of the drugs used during the hospitalized period recorded interaction, these interactions ranged between one interaction till 7 interactions for one patient.

Referring to the age of the patients, the 92.10% of the neonate recorded that there is no interaction while only 7.87% of the neonate recorded interactions. Moving to young children the interaction was little higher than have not interaction 57.5% and 42.5%, respectively.

In children and infants, both age categories recorded that there was no interaction more than there is interaction 70.96% and 65.62%, respectively. From these findings we can conclude that there is an association between age groups and presence of interactions ($X^2 = 46.20$, $p < 0.05$). Figure 2.

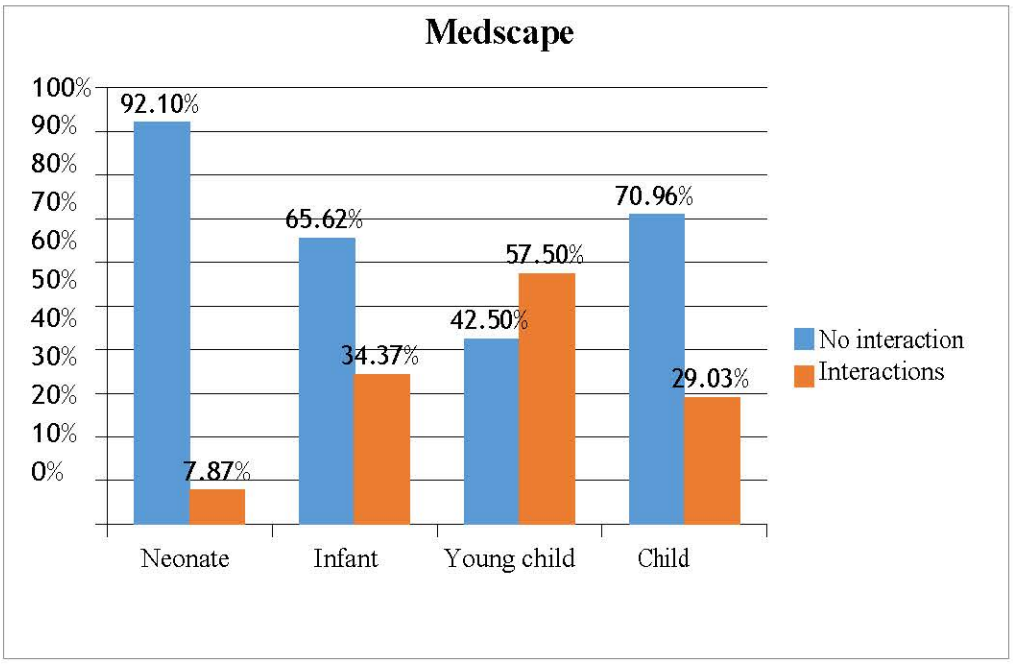

Figure 2. The interaction of drugs in Medscape within age groups

For Lexicomp, the most frequent interaction were between (budesonide × salbutamol) for 29 times (clarithromycin × budesonide) for 23 times (prednisolone × salbutamol) for 18times (clarithromycin × prednisolone) for 16 times (clarithromycin × ranitidine) for 10 times.

For Drug.com, the most frequent interaction were between (salbutamol × clarithromycin) for 26 times (clarithromycin × budesonide) for 25 times (prednisolone × salbutamol) for 16 times (clarithromycin × prednisolone) for 14 times (gentamycin × ampicillin+ sulbactam) for 12 times.

For Medscape, the most frequent interaction were between (salbutamol × ibuprofen) for 20 times (prednisolone × clarithromycin) for 18 times (prednisolone × ibuprofen) for 14 times (gentamycin× ibuprofen) for 4 times (gentamycin× midazolam) for 3 times.

The continuous data such as number of medications used during the hospitalized periods demonstrated that the mean ± SD number of the drugs used in male was significantly higher than female (3.45 ±1.96) (3.85± 2.11) ($p < 0.05$). While the staying period showed that there is no significant difference in mean between both genders ($p > 0.05$).

The data of presence of interaction regarding lexicomp showed that mean ± SD of the number of medication used was significantly higher in patients with interactions than those with no interaction (5.85 ± 2.56 Vs 2.81 ± 0.84; $p < 0.05$). Similar to number of drugs, the staying period showed that there is a statistically significant difference between mean ± SD of staying period for those who have interaction comparing to those who didn't recorded any interaction (5.17 ± 6.88 Vs 2.01± 2.89; $p < 0.05$).

The data of presence of interaction regarding Drugs.com showed that mean ± SD of the number of medication used was significantly higher in patients with interactions than those with no interaction (6.01 ± 2.68 Vs 2.88 ± 0.88, $p < 0.05$). Similar to number of drugs, the staying period showed that there is a statistically significant difference between mean ± SD of staying period for those who have interaction comparing to those who didn't recorded any interaction (6.63 ± 7.90 Vs 1.66 ± 1.25; $p < 0.05$).

The data of presence of interaction regarding Medscape showed that mean ± SD of the number of medication used was significantly higher in patients with interactions than those with no interaction (6.26 ± 2.60 Vs 2.88 ± 0.89, $p < 0.05$). Similar to number of drugs, the staying period showed that there is a statistically significant difference between mean ± SD of staying period for those who have interaction comparing to those who didn't recorded any interaction (5.43 ± 6.64 Vs 2.13± 3.44, $p < 0.05$).

Table 6.Mechanism of interactions and severity in Lexicomp

Lexicomp	N (181)	%
Mechanism of interactions		
Pharmacokinetics	74	40.9%
Pharmacodynamics	**82**	**45.3%**
Unknown	25	13.8%
Severity		
N/A	2	1.1%
Minor	21	11.6%
Moderate	**154**	**85.1%**
Major	4	2.2%

Regarding mechanism of interaction, the most frequent mechanism recorded on lexicomp was PD 45.3% while the PK recorded 40.9% and the remaining was unknown mechanism. Referring to the severity of DDI founded, most of the DDI were moderate in severity 85.1% and major was only 2.2% of the total interactions reported using lexicomp. Table 6

Table 7.Mechanism of interactions and severity in Drugs.com

Drugs.com	N (179)	%
Mechanism of interactions		
Pharmacokinetics	28	15.6%
Pharmacodynamics	**99**	**55.3%**
Unknown	52	29.1%
Severity		
Minor	46	25.7%
Moderate	**126**	**70.4%**
Major	7	3.9%

Regarding mechanism of interaction, the most frequent mechanism recorded on Drugs.com was PD 55.3% while the PK recorded 15.6% and the remaining was unknown mechanism. Referring to the severity of DDI founded, most of the DDI were moderate in severity 70.4% and major was 3.9% of the total interactions reported using Drugs.com without any major interactions. Table 7

Table 8.Mechanism of interactions and severity in Medscape

Medscape	**N (109)**	**%**
Mechanism of interactions		
Pharmacokinetics	32	29.4%
Pharmacodynamics	**42**	**38.5%**
Unknown	35	32.1%
Severity		
Minor	11	10.1%
Monitor Closely	**76**	**69.7%**
Serious	22	20.2%

Regarding mechanism of interaction the most frequent mechanism recorded in Medscape was PD 38.5% while the PK recorded 29.4% and the remaining was unknown mechanism.

Table 9.The total number and percentage of major interaction in three different interaction checkers

Program	Total interaction	Major interaction	% of the major interaction
Lexicomp	181	4	2.2
Drugs.com	179	7	3.9
Medscape	109	**22**	**20.1***

* The data showed that there is a significant association between the programs and interaction (X^2 =35.53, $p < 0.05$)

The table 10 shown down demonstrated the risk of interaction (A, B, C, D, X) regarding Lexicomp with mechanism of interaction.

Table 10.Summary of DDI in Lexicomp

No. of drugs	No. of the Patients	No. of interaction*	No. of No Interaction	Mech.			Interaction Levels				
				PK	PD	U	A	B	C	D	X
2	61	1*27 = 27	59	5	12	10	0	17	10	0	0
3	101	2*14 = 28	90	18	8	2	0	10	17	1	0
4	19	3*4 =12	10	6	6	0	1	8	3	0	0
5	14	4*4 =16	5	12	4	0	0	5	10	1	0
≥7	23	5*6 = 30	1	30	0	0	0	6	24	0	0
		6*6 = 36	0	36	0	0	0	11	25	0	0
		7*1 = 7	0	0	7	0	0	2	4	0	1#
		8*2 = 16	0	8	8	0	1	2	10	3	0

PK=Pharmacokinetic, PD = Pharmacodynamic, U=Unknown

* No. of interaction calculated among the patients. # the interaction happened between ipratropium and cetirizine.

5 Discussion and Conclusion

The attention and consideration of DDI among health care providers, scientists increased these days around the world. The number of drugs discovered increased every day, this increment leads to increase the interactions between them. This leads to as a consequence to provide different way rather than the memory of doctors or pharmacists to prevent the occurrence of any interactions (Ansari.J,2010).

In the literature, the studies that evaluated more than one DDI software programs usually emphasized the difference between each software programs that were compared especially on their severity classifications. However, the three DDI software programs evaluated in the present study had similar classification system when evaluating the clinical consequences of each possible DDI (Ansari, J. A. 2010).

A retrospective cross-sectional study assessed the occurrence of PDDIs in pediatric population. The prevalence and nature of PDDIs have been reported in 384 pediatric patients. The study revealed that the overall prevalence of at least one PDDI per patient was 45.8% (Getachew et al 2016). This is comparable to Feinstein et al study, in which 49%PDDI in hospitalized pediatric patients was also reported (Feinstein J et al, 2015).

In our study, the number of interactions occurred according to Lexi comp, Drugs.com and Medscape were (27.8%), (24.5%) and (23%), respectively, which is in contrast to the two above mentioned studies low. This difference in prevalence maybe attributed to the difference in disease type and number of medications used during hospitalized period, where most of our patients were neonates and used just vaccines.

The other result of this study showed that age group has statistically significant association with PDDIs which were occurring more frequently in 2–6 years age group than any other age group of pediatric (P <0.029)(Getachew et al, 2016).

This findings were similar to our findings which found an associations between the presence of interactions and the age groups in three different tools and the most of interactions were occurred in young children (p <0.05). Since most of the young children disease was pneumonia and the mean number of medications used is higher than other age groups, these can indicate the higher percentage of interaction in this group.

Our findings regarding the mechanism of interactions showed that there is no significant association between the presence of interactions and the mechanism in all interaction checker tools (p>0.05) with most frequent mechanism was pharmacodynamic in Lexicomp, Drugs.com and Medscape(45.3%),(55.3%) and (38.5%), respectively.

These findings were unlikely the result of a study was performed in 2016, which conclude that pharmacokinetics interactions were the most frequent interactions among their patients (Getachew et al,2016). This difference occurred since most of our patients were neonates with vaccines as the most frequent drugs used among them.

Of 176 patients having at least one PDDI, major interactions were found in 19.9% (n = 35) of pediatric (Getachew, 2016). These findings were higher in comparison to Ismail et al. in which major interaction was 10.7% (n = 43) (Ismail M et al.,2013).

But they were less than the results of Feinstein et al., which found exposure to the major interaction of PDDIs in 41% of pediatric patients (Feinstein J et al ,2015).
These studies were in contrast to our study, which was only 2.2% of interactions were major regarding Lexicomp and 3.9% and 20.1% were major interaction in both Drugs.com and Medscape, respectively.
Since most of the young children disease was pneumonia and the mean of medications used is higher than other age groups, these can indicate the higher percentage of interaction in this group.

Pharmacists are key players for finding and preventing drug interactions in health care system in developed countries, it is his duty to ensure that the patient is aware of the drug interactions and possible side effects and how to deal with these harmful effects (Aziz, G., et al., 2014).

The American Academy of Pediatrics in 2003 proposed that inclusion of a pharmacist in the critical care team can help decrease medication errors and improve patient outcomes.

There is strong evidence to support the involvement of pharmacists as members of the health care team for pediatric patients. Due to the plethora of data that repeatedly show the worth and need for pharmacists as valued members of health systems (Krupicka MI, et al.,2002).

Despite the availability of electronic drug interaction screening systems, health professionals may still fail to detect potentially harmful combinations. Prescribers and pharmacists must possess the necessary drug interaction knowledge to correctly identify potentially harmful combinations, evaluate the risks for specific patients, and take action to minimize the risk of harm, if appropriate (Hietncapie, A. L., et al.,2012).

Computerized provider order entry in electronic health record (EHR) systems has been identified as one of the interventions with the greatest potential to reduce medication errors and associated harm in the pediatric inpatient setting (Simpao, A. F., et al ,2014).

5.1 Strengths and Limitations:

This is the first study that evaluates three different tools in detecting DDI in pediatric patients in North Cyprus. The number of patients that included in the study considered as a good and reflecting sample size since all patients entered the hospital for one year were enrolled.

This study has some limitations. Since the study design was retrospective, we could not ascertain with any accurate completeness or reliability of the information obtained. As

such, it was possible that we could have under- or over-reported the PDDIs.

As some drugs were prescribed to be taken as required, we could not accurately determine whether these drugs were actually taken with others, which is difficult to make the assessment of drug–drug interaction.

One of the major limitation of this study is different factors that affect the prevalence of interaction were not taken in consideration such as patients weight, genetic factors, major organ function status, and drug compliance .

Another limitation is that this study took place in single hospital so the findings may be unable to be generalized.

This study covered only drug- drug interactions, drug food and drug herbal interactions not assessed.

5.2. Conclusion:

Hospitalized patients are commonly exposed to PDDIs, but the subsequent probability of occurrence and magnitude of patient harm requires further empirical substantiation. Although that our data showed low prevalence rates of DDIs, life-threatening interactions may develop. Though Medscape detect more major interaction than other two checkers, Lexi comp was the most inclusive of all three data bases and was more user friendly and better guided to clinical recommendations than the others. Physicians and pediatricians need reminding of the potential DDIs when prescribing medications to pediatrics and use it when needed.

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Appendixes

Appendix 1: List of drug-drug interactions identified in Lexicomp

Drug A	Drug B	Mechanism of Interaction	Severity	clinical significance	Recommendation	N
Paracetamol	Lamotrigine	Unknown	Moderate (c)	Acetaminophen decrease serum concentration of lamotrigine	Monitor therapy	1
Ibuprofen	Gentamycin	PK	Moderate (c)	Monitor for increased nephrotic effects of aminoglycosides	Monitor therapy	4
Ibuprofen	Heparin	PD	Moderate (c)	Monitor for signs and symptoms of bleeding	Monitor therapy	2
Ibuprofen	Furosemide	PD	Moderate (D)	Monitor for decreased therapeutic effects of loop diuretics	Consider therapy modification	2
Ceftriaxone	Gentamycin	PD	Moderate (c)	Monitor for increase nephrotoxicity	Monitor therapy	1
Clarithromycin	Budesonide	PK	Moderate (c)	Monitor for signs and symptoms of corticosteroid	Monitor therapy	23
Clarithromycin	Prednisolone	PK	Moderate (c)	Monitor for increased steroid –related adverse effects	Monitor therapy	16
Clarithromycin	Ranitidine	PK	Moderate (c)	Monitor for increased effects of ranitidine	Monitor therapy	10

Clarithromycin	Fluticasone	PK	Moderate (D)	Monitor for increase serum concentration of fluticasone	Consider therapy modification	1
Clarithromycin	Cetirizine Hydrochloride	PK	Moderate (c)	Monitor for increased effects of cetirizine	Monitor therapy	1
Budesonide	Salbutamol	PD	Moderate (B)	Monitor hypokalemia effect of Beta2 agonists	No action needed	29
Budesonide	Furosemide	PD	Moderate (c)	Monitor serum potassium	Monitor therapy	1
Prednisolone	Ibuprofen	PD	Moderate (c)	Monitor for signs of epigastric or abdominal pain	Monitor therapy	15
Prednisolone	Salbutamol	PD	Moderate (B)	Monitor hypokalemia effect of Beta2 agonists	No action needed	18
Salbutamol	Furosemide	PD	Moderate (c)	Monitor hypokalemia effect of loop diuretics	Monitor therapy	1
Ipratropium Bromide	Cetirizine Hydrochloride	PD	Major(X)	Monitor for anticholinergic –related toxicity (urinary retention, consitipation,tachcardia)	Avoid combination	1
Phenytoin	Paracetamol	Unknown	Moderate (C)	Monitor for acetaminophen induced hepatotoxicity	Monitor therapy	1
Phenytion	Phenobarbital	PK	Moderate (C)	Monitor for unwanted effects of additive CNS depression	Monitor therapy	1

Phenytoin	Lamotrigine	PK	Moderate (D)	Monitor for decreased serum concentration of lamotrigine	Consider therapy modification	1
Phenytoin	Ondansetron	PK	Major(D)	Monitor for decreased effects of ondansetron	Consider therapy modification	1
Phenytoin	Levetiracetam	PK	Moderate (c)	Monitor closely for evidence of reduced levetiracetam concentration	Monitor therapy	1
Ondansetron	Paracetamol	PD	Minor (B)	Antiemetic may diminish the analgesic effect of acetaminophen	No action needed	11
Domperidone	Ondansetron	Unknown	Moderate (D)	Domperidone may enhance the QTc-prolonging	Consider therapy modification	1
Levetiracetam	Lamotrigine	PD	Moderate (c)	Monitor for additive CNS depressant	Monitor therapy	1
Caffeine	Adrenalin	PD	Moderate (c)	Monitor blood pressure ,heart rate	Monitor therapy	1
Clonidine	Levodopa+ Benserazide	PD	Moderate (c)	Monitor hypotension effects	Monitor therapy	3
Furosemide	Gentamycin	PK	Moderate (c)	Monitor for toxic effects of aminoglycoside (ototoxicity,nephrotoxicity)	Monitor therapy	4
Furosemide	Levothyroxine	PK	Minor (B)	Monitor free thyroid hormone	No action needed	2

Furosemide	Captopril	PD	Moderate (c)	Monitor for hypotension effects	Monitor therapy	1
Hydroxyzine Hcl	Clarithromycin	Unknown	Minor (B)	Monitor for increase serum concentration of hydroxyzine	No action needed	1
Hydroxyzine Hcl	Phenytoin	PD	Moderate (c)	Monitor for signs of CNS depression	Monitor therapy	1
Valproic Acid	Phenytoin	PK	Moderate (c)	Monitor for evidence of phenytoin toxicity	Monitor therapy	1
Valproic Acid	Levetiracetam	Unknown	N/A (A)	Valproic acid do not appear to affect serum concentration of levetiracetam	No action needed	1
Metoclopramide	Paracetamol	PK	Minor (B)	Gastrointestinal agents may increase the serum concentration of acetaminophen	No action needed	2
Allopurinol	Ampicillin+ Sulbactam	Unknown	Moderate (c)	Monitor for increased of skin rash(hypersensitivity reactions)	Monitor therapy	1
Gaviscon	Gentamycin	PD	Moderate (c)	Monitor for negative respiratory effects	Monitor therapy	1
Pethidine	Paracetamol	PK	Minor (B)	Opioid analgesics may decrease the absorption of acetaminophen	No action needed	1
Tramadol	Paracetamol	PK	Minor (B)	Opioid analgesics may decrease the absorption of acetaminophen	No action needed	1

Tramadol	Pethidine	PD	Major (D)	Monitor for signs of CNS depression	Consider therapy modification	1
Phenobarbital	Levetiracetam	PK	Moderate (c)	Monitor closely for evidence of reduced levetiracetam concentration or effectiveness	Monitor therapy	1
Phenobarbital	Valproic Acid	PD	Moderate (c)	Monitor for increased serum concentration /toxic effects of phenobarbital	Monitor therapy	1
Hydrochlorothiazide	Cholecalciferol	PD	Moderate (c)	Monitor both calcium concentration and response to vitamin D analogs	Monitor therapy	1
Hydrochlorothiazide	Captopril	PD	Moderate (c)	Monitor for symptomatic hypotension and renal failure	Monitor therapy	1
Aspirin	Furosemide	PK	Moderate (c)	Monitor closely for signs and symptoms of salicylate toxicity	Monitor therapy	1
Aspirin	Captopril	PD	Moderate (c)	Monitor for decreased therapeutic effects of ACEI and acute renal failure	Monitor therapy	1
Aspirin	Spironolactone	PD	N/A(A)	Salicylates do not appear to alter pharmacodynamic effects of potassium sparing diuretics	No action needed	1
Spironolactone	Captopril	PD	Major(c)	Monitor hyperkalemia effect of ACEI	Monitor therapy	1

Appendix 2 : list of drug-drug interactions identified in Drugs.com

Drug A	Drug B	Mechanism of Interaction	Severity	clinical significance	Recommendation	N
Paracetamol	Ranitidine	Unknown	Minor	Ranitidine may potentiate the hepatotoxicity of acetaminophen	No action need	5
Ibuprofen	Gentamycin	PK	Moderate	Increase kidney damage risk	Monitor therapy	3
Ceftriaxone	Gentamycin	PD	Moderate	Increase kidney damage risk	Monitor therapy	1
Clarithromycin	Prednisolone	PD	Moderate	Increase side effects of Prednisolone (high blood pressure ,weight gain)	Monitor therapy	14
Clarithromycin	Ampicillin+ Sulbactam	Unknown	Minor	Synergism effects	No action need	1
Clarithromycin	Amoxicillin +Clavulanic acid	Unknown	Minor	Synergism effects	No action need	1
Budesonide	clarithromycin	PK	Moderate	Increase side effects of Budesonide (high blood pressure ,weight gain)	Monitor therapy	25

Prednisolone	Ibuprofen	PD	Moderate	Increase gastrointestinal side effects (bleeding ,ulceration)	Monitor therapy	19
Prednisolone	Midazolam	Unknown	Minor	Decrease plasma concertation of midazolam	No action need	1
Salbutamol	clarithromycin	PD	Moderate	Increase risk of irregular rhythm	Monitor therapy	26
Salbutamol	Prednisolone	Unknown	Minor	Additive hypokalemia effects	No action need	16
Salbutamol	Furosemide	PD	Moderate	Additive hypokalemia effects	Monitor therapy	1
Gentamycin	Ibuprofen	PD	Moderate	Increase kidney damage risk	Monitor therapy	1
Gentamycin	Ampicillin+ Sulbactam	PD	Moderate	Reduce effect of gentamycin	Monitor therapy	12
Ranitidine	Ibuprofen	Unknown	Minor	Decrease ibuprofen concentration	No action need	7
Cholecalciferol (D3)	Phenytoin	PD	Moderate	Desersa effects of Cholecalciferol	Monitor therapy	1
Cholecalciferol (D3)	Phenobarbital	PD	Moderate	Desersa effects of Cholecalciferol	Monitor therapy	1

Cholecalciferol (D3)	hydrochlorothiazide	PD	Moderate	Increase blood calcium levels	Monitor therapy	1
Midazolam	Prednisolone	Unknown	Minor	Decrease plasma concentration of midazolam	No action need	1
Midazolam	Furosemide	PD	Moderate	Increase effect in lowing blood pressure	Monitor therapy	1
Lamotrigine	Phenytoin	PD	Moderate	Decrease serum concentration of lamotrigine	Monitor therapy	1
Phenytoin	Paracetamol	PD	Moderate	Increase hepatotoxicity of acetaminophen	Monitor therapy	1
Phenytoin	Ibuprofen	Unknown	Minor	Increase toxicity of phenytoin (drowsiness, seizures)	No action need	1
Phenytoin	Ceftriaxone	PK	Minor	Increases free plasma level of phenytoin	No action need	1
Phenytoin	Valproic acid	PK	Moderate	Increase toxicity of phenytoin (drowsiness, seizures)	Monitor therapy	1
Ondansetron	Phenytoin	PD	Moderate	Decrease effects of ondansetron	Monitor therapy	1
Lactulose	Ondansetron	PD	Moderate	Increase irregular heart rhythm	Monitor therapy	1

Heparin	Ibuprofen	PD	Moderate	Increase bleeding	Monitor therapy	2
Heparin	Ampicillin+ Sulbactam	Unknown	Minor	Increase effect of heparin	No action need	4
Fluticasone	clarithromycin	PK	Major	Increase side effect (high blood pressure ,weight gain)	Avoid combination	1
Clonidine	Levodopa+Benserazide	PD	Moderate	Desersa effectiveness of levodopa	Monitor therapy	3
Furosemide	Ibuprofen	PD	Moderate	Reduce hypotensive effect of diuretics	Monitor therapy	1
Furosemide	Ceftriaxone	PD	Moderate	Increase kidney problem	Monitor therapy	1
Furosemide	Gentamycin	PD	Major	Increase side effect of gentamycin (hearing loss, kidney problem)	Avoid combination	5
Furosemide	Captopril	PD	Moderate	Increase lowing blood pressure	Monitor therapy	1
Lansoprazole	clarithromycin	PK	Moderate	Increase plasma concentration of Lansoprazole	Monitor therapy	1

Lansoprazole	Furosemide	PD	Moderate	Increase low blood levels of magnesium	Monitor therapy	1
Hydroxyzine HCl	clarithromycin	Unknown	Moderate	Increase risk of irregular heart rhythm	Monitor therapy	1
Hydroxyzine HCl	Salbutamol	Unknown	Moderate	Increase risk of irregular heart rhythm	Monitor therapy	1
Hydroxyzine HCl	Phenytoin	PD	Moderate	Increase side effects (dizziness, drowsiness)	Monitor therapy	1
Hydroxyzine HCl	Valproic acid	PD	Moderate	Increase side effects (dizziness, drowsiness)	Monitor therapy	1
Pethidine	Tramadol	PD	Major	Increase side effects(respiratory distress ,coma)	Avoid combination	2
Phenobarbital	Phenytoin	PK	Moderate	Alter Phenytoin Levels (loss seizure control)	Monitor therapy	2
Phenobarbital	Levetiracetam	PK	Moderate	Increase side effect such as dizziness ,drowsiness	Monitor therapy	1
Phenobarbital	valproic acid	PD	Moderate	Increase sedation or lethargy	Monitor therapy	2
Hydrochlorothiazide	Furosemide	PD	Moderate	Decrease potassium ,magnesium ad sodium level	Monitor therapy	1

Hydrochlorothiazide	Captopril	PD	Moderate	Addictive lowering blood pressure	Monitor therapy	1
Aspirin	Captopril	PD	Moderate	Aspirin may attenuate the hypotensive effects of ACEI	Monitor therapy	1
Spironolactone	Captopril	PD	Major	Increase level of blood potassium	Avoid combination	1

Appendix 3 : list of drug-drug interactions identified in Medscape

Drug A	Drug B	Mechanism of Interaction	Severity	clinical significance	Recommendation	N
Paracetamol	Lamotrigine	PK	minor	Decrease level of acetaminophen	No action need	1
Paracetamol	Phenytoin	PK	Minor	Decrease level of acetaminophen	No action need	1
Paracetamol	Levertiracetam	PK	Minor	Decrease level of acetaminophen	No action need	1
Paracetamol	metoclopramide	PK	Minor	Increase level of acetaminophen	No action need	1
Ibuprofen	Heparin	PD	Monitor closely	Increase anticoagulation	Use caution	2
Clarithromycin	Hydroxyzine HCl	unknown	Monitor closely	Increase risk of torsades de pointes	Use caution	1
Prednisolone	Ibuprofen	PD	Monitor closely	Increase risk of gastrointestinal ulceration	Use caution	14
Prednisolone	Clarithromycin	PK	Serious	increase prednisolone effects	Use alterative	18
Salbutamol	Ibuprofen	Unknown	Monitor closely	Ibuprofen increase ad salbutamol decrease serum potassium	Use caution	20

Salbutamol	Midazolam	Unknown	Monitor closely	Midazolam increase and salbutamol decrease sedation	Use caution	2
Salbutamol	Hydroxyzine HCl	Unknown	Monitor closely	Hydroxyzine increase and salbutamol decrease sedation	Use caution	1
Gentamicin	Ibuprofen	Unknown	Monitor closely	Ibuprofen increase ad gentamicin decrease serum potassium	Use caution	4
Gentamicin	Midazolam	PD	Monitor closely	Decrease effect of gentamicin	Use caution	3
Gentamicin	Adrenaline	PD	Monitor closely	Decrease serum potassium	Use caution	1
Gentamicin	Furosemide	PD	Serious	Increase ototoxicity ad nephrotoxicity	Use alternative	2
Amoxicillin +clavulanic acid	Clarithromycin	PD	Minor	Decrease effects of amoxicillin	No action need	1
Ampicillin+ Sulbactam	Azithromycin	PD	Minor	Decrease effects of ampicillin	No action need	1
Ampicillin+ Sulbactam	Clarithromycin	PD	Minor	Decrease effects of ampicillin	No action need	1
Cholecalciferol (D3)	Phenytoin	PD	Monitor closely	Decrease effects of vitamin D3	Use caution	1

Cholecalciferol (D3)	Phenobarbital	PD	Monitor closely	Decrease effects of vitamin D3	Use caution	1
Cholecalciferol (D3)	hydrochlorothiazide	PD	Monitor closely	Increase effects of vitamin D3	Use caution	1
Midazolam	Prednisolone	PK	Monitor closely	Decrease midazolam effect	Use caution	2
Lamotrigine	Phenytoin	PK	Monitor closely	Decrease level of lamotrigine	Use caution	1
Phenytoin	valproic acid	PK	Monitor closely	Increase effects of phenytoin	Use caution	1
Ondansetron	Phenytoin	PK	Monitor closely	Decrease level of ondansetron	Use caution	1
Caffeine	Adrenaline	PD	Monitor closely	Decrease sedation	Use caution	1
Fluticasone	Clarithromycin	PK	Monitor closely	Increase effect of fluticasone	Use caution	1
Clonidine	Levodopa+Benserazide	PD	Monitor closely	Increase effect of clonidine	Use caution	3
Furosemide	Ibuprofen	PD	Monitor closely	Ibuprofen increase and furosemide decrease serum potassium	Use caution	1

Furosemide	Salbutamol	PD	Monitor closely	Decrease serum potassium	Use caution	1
Furosemide	Hydrochlorothiazide	PD	Monitor closely	Decrease serum potassium	Use caution	2
Furosemide	Captopril	PD	Monitor closely	Risk of acute hypotension	Use caution	1
Furosemide	Aspirin	PD	Monitor closely	Aspirin increase and furosemide deceases serum potassium	Use caution	1
Lansoprazole	Clarithromycin	PK	Monitor closely	Increase effect of lansoprazole	Use caution	1
Phenobarbital	Phenytoin	PK	Monitor closely	Decrease level of phenytoin	Use caution	1
Acyclovir	Ibuprofen	PK	Minor	Increase level of acyclovir	no action need	1
Levothyroxine	Furosemide	PK	Minor	Increase toxicity of levothyroxine	no action need	1
Pethidine	Tramadol	PD	Serious	Increase sedation	Use alternative	1
Phenobarbital	valproic acid	unknown	Minor	Increase level of phenobarbital	no action need	1

Metronidazole	Ibuprofen	PK	Minor	Increase level of ibuprofen	no action need	1
Captopril	Aspirin	PD	Serious	Decrease in renal function	Use alternative	1
Hydrochlorothiazide	Captopril	PD	Monitor closely	Increase risk of nephrotoxicity	Use caution	1
Spironolactone	Captopril	PD	Monitor closely	Risk of hyperkalemia	Use caution	1
Pseudoephedrine	Salbutamol	PD	Monitor closely	Increase blood pressure and heart rate	Use caution	1
Pseudoephedrine	Hydroxyzine HCl	Unknown	Monitor closely	Hydroxyzine increase and pseudoephedrine decrease sedation	Use caution	1

Appendix 4: Data collection form

A. Demographics		
Patient number #:	Date of admission:	Date of review:
Age:	Gender:	Unit:

B. Patient history	
Current diagnosis:	Past medical history:

C. Medications history		
Number of medication	Generic name	Pharmacological class

D. Drug-Drug interaction						
Is there at least one drug-drug interaction?		Yes ☐ No ☐				
	Drug A	Drug B	Mechanism	Severity	Proposed action	Clinical implication
1	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
2	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
3	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
4	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
5	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
6	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
7	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
8	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
9	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
10	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
11	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
12	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
13	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
14	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				
15	Chronic ☐ Acute ☐	Chronic ☐ Acute ☐				

CURRICULUM VITAE

Name	Rim	Surname	Diri
Place of birth	Syria	Date of birth	1 -1- 1988
Nationality	Syria	Tel	00966550972677
Email	My.sweet88@hotmail.com		

Education Level

	Name of the Institution where he/she was graduated	Graduation year
Postgraduate/ Specialization	_	_
Masters	NEU	2019
Undergraduate	Albaath University	2010
High school	Alsayedeh Aishaah	2005

Job experience

Duty	Institution	Duration (Year-Year)

Foreign Language	Reading Comprehension	Speaking	Writing
Arabic	Very good	Very good	Very good
English	Very good	Very good	Very good

Foreign Language Examination Grade								
YDS	ÜDS	IELTS	TOEFL IBT	TOEFL PBT	TOEFL CBT	FCE	CAE	CPE

	Math	Equally weighted	Non-math
ALES Grade			
Other grade			

Computer Knowledge

Program	Use proficiency
Microsoft office	Very good

ENCLOSURE: Other scientific activities (publication, congress proceedings etc.)