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Drug Interaction Management in Critically Ill Patient

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Drug interaction in critically ill patient is very common and affecting patients Physically, Mentally and Financially. There are various measures which has been taken to minimize this burden on patient, such as books being prepared which include various drug interaction, maintain websites and database that provides information regarding drug interactions. With the use of these website and databases the drug interaction can be managed. It is common practice that side effects of drug interaction are being managed by additional drugs, the main reason behind it could be non-availability of alternative drugs or costlier alternative. These factors remain the main cause of treatment failure in majority of patients leading to prolong. The current study was performed for the duration of 12 months, from this study it was identified that 113 types of major drug interactions commonly found in total 250 prescriptions which were evaluated and managed accordingly. Suggestions being prescribed by various sites were, avoid concomitant use of drug, use alternative therapy, and monitor closely for any adverse effect. During suggestion made by the Clinical Pharmacist, for the same drug interactions it was identified that more of drug therapy adjustment can be done then provided by the online database. The parameter on which the drug interactions management are being suggested were focused on just type of drug interaction and its effect, it does not include the actual pharmacodynamic and pharmacokinetic changes in therapy. The suggestion made by the clinical pharmacist were includes drug removal, drug dosage changes, alternative therapy, alternative route of administration, change in time interval etc. From this study it

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was concluded that the drug interaction management can be done at various stages of treatment with proper therapy modification by the clinical pharmacist, and if done properly it will improve the overall outcome of patient health care.

Keywords: Drug interaction; antagonism; adverse drug reaction; critical ill patients.

1. INTRODUCTION

The treatment of critically ill patient is never been simple, these patients require special arrangements at hospital and expensive drug therapy. It becomes more difficult for a health care system to provide a good and satisfactory treatment to these patients as there are increase chance of Drug Interactions (DIs) with addition of every drug in the patient drug therapy. It is a known fact symptom either as disease condition or as side effect of drug interaction being treated with additional drugs rather than any other means. The impact of drug interactions has been very well studied and documented in various research articles. These research articles have shown that how it is being affecting patients physically, Mentally and financially. Any effect from a drug interaction also affects the decision making in the drug therapy, causing additional burden on the doctors who certainly relay on the gold standards and guidelines provided by various health care statutory bodies [1-3]. The DIs can be divided in majorly two categories Pharmacokinetic drug interactions and Pharmacodynamic drug interactions. Both of which may lead to increase the toxicity of the drug or decrease its effectiveness. There are various mechanisms through which either of increase or decrease of drug effects can be achieved. By understanding Pharmacokinetic and Pharmacodynamic properties of the drug it is possible to predict the effect of drug on the patient. The Pharmacokinetic drug interactions can be elaborated more as, the changes in the concentration of drug in the various body masses such as body fluids and body tissues. These changes generally occur during the process of drug absorption, drug distribution and elimination of the drug. For Pharmacokinetic interaction to occur metabolism of drug is necessary and for this to occur the drug should undergo through two phase of metabolism which are Phase I and Phase II metabolism. The Phase I includes the oxidative transformation of the drug and the Phase II increases the polarity of the drug by the means of conjugation reaction with the endogenous groups like glucuronides or sulfates. When it comes to Pharmacodynamic drug interactions, it is usually associated with alteration in safety and efficacy of the drug. Which may or may not include alteration in the drug Pharmacokinetic profile. Generally, when two drugs of same objective in a treatment given together can produce additive or synergistic effects on patient body, such effects can be considered under Pharmacodynamic drug interactions. DIs can be managed by understanding mechanism through which the interaction is occurring. The understanding of pharmacokinetic and pharmacodynamic properties and applying same on the individual patient can help in reduction of drug interaction and related effects drastically. With the understanding of pk and pd properties of drugs which are interacting a clinical pharmacist can provide a proper drug therapy of prescribed drugs. The prepared drug therapy may include changes in drug dosage, route of administration, different salt formation, addition or removal of drug if necessary [4]. The availability of various drug interaction related information providing database has gain popularity in the recent decade. The provided drug interaction database does contain information for severity, possible effect of interaction on patient, mechanism of drug interaction and source of information form where it has been collected. The very crucial part of provided information on drug interaction is first its management and second its source of information with appropriate justification. The database does lacks in quality of these two parameters. This lacuna can be fulfilled with the help of clinical Pharmacist actively managing drug interaction at the bedside with constant monitoring of the drug chart at the hospital [5]. The practice of Evidence based medicine is a part of the evolutionary medical care. It is necessary to keep in check the type of evidence available for the drug interactions also and keep them updating. The updated version for classification of evidence as per by Centre for Evidence Based Medicine: Levels of Evidence (March 2009) can be used to classify the level of evidence provided in various online drug interaction database to provide necessary strength to the claim of drug interaction. The current study is an attempt of provide best possible management of drug interactions to the critically ill patient with the help of the online drug

interaction data bases and various research articles available online.

2. METHODOLOGY

The Intensive Care Unit of Dhiraj General Hospital was the site of data collection for this study. The study was a retrospective observation study conducted for the duration of 12 months (November 2019 to October 2020). The objective of the study was to identify common drug interaction in critically ill patient, To identify the level of evidence references used by various drug interaction database, and to identify type of drug interaction categories in major and moderate type. Total 251 cases were analysed for the drug interactions. The drug interaction was identified with the help of various drug interaction data providing websites Micromedex and Medscape. The selection of Critically Ill patient was made on the basis of inclusion and exclusion criteria. Inclusion criteria: Patient admitted at Intensive care unit, only patient who were 18 year and above included in the study. The Patient admitted in ICU will be considered Critically Ill. Exclusion criteria: Those patient drug charts which does not containing drug interaction was not included. The identified drug interaction was assessed for its severity and interaction with Major and Severe type of drug interaction were selected for further analysis. Drug interaction found to be Major or Severe then provided with Management from either source of online drug interaction database and Clinical Pharmacist approach of information retrieval from research article and available medical books. The gathered information was then provided to treating doctor who will manage patient treatment accordingly. Descriptive statistics was applied for the analysis of data.

3. RESULTS

In this study total 345 drug interaction were identified from 251 prescription out of which 113 were Major and 232 were Moderate type of interaction (Fig 1). Total 24 type of Major drug interaction were found to be most frequent (Table 1).

Total number of drug interaction found was 345 out of which 113(32.75%) was Major or Severe, 232(67.24%) was Moderate.

Table 2 shows all major drug interactions, common types of disease conditions possible effect of drug interaction on the patient, management give as per the online database, frequency of drug interactions and level of evidence of the interactions.

This table shows Highest Level of Evidence provided for drug interaction in online data base. The level of Evidence has been provided on the basis of chart provided by Centre for Evidence Based Medicine: Levels of Evidence (March 2009). Majority of drug interaction provide in online database were having a poor level of evidence i.e., 71 drug interaction was having level 5 evidence followed by 15 drug interactions were having level 3b and only 10 drug interactions were having level 1b evidence.

4. DISCUSSION

In this study 251 prescriptions were included from which total 345 drug interactions was found. Out of those 345-drug interaction 113 were major drug interactions and 232 were moderate drug interactions. 1/3rd of total interaction was major drug interaction. In a similar study conducted at Cardiothoracic ICU has shown that 1/4th of the total interaction found were major drug interaction [6]. Another study conducted in ICU have shown that 15 percent of total drug interaction were highly significant [7]. Another similar study has shown that 54 percent of potential drug-drug interaction occurred in ICU patient and from those interaction 90 percent of interactions can be set in 20 set of potential drug interactions types [8]. The study also shows that the most common type of effect form drug interaction was QT interval prolongation, Increased risk of bleeding and cardiac arrythmias. Majority of patients were suffering from Cardiovascular, Neurological and Nephrological disease conditions. The most frequent major drug interaction found were Aspirin with Furosemide, Aspirin with Clopidogrel, Aspirin with Heparin, Aspirin with Ramipril, Aspirin with Spironolactone and Aspirin with Heparin. Similar study has shown most common drug interaction were between antihypertensive, anticoagulants and antiplatelet agents [9]. In a study conducted at United Kingdom on combination therapy of clopidogrel and aspirin shows significant increase in bleeding time through synergistic antiplatelet action [10]. Similar study conducted titled antagonism of spironolactone induced natriuresis by aspirin has been observed. The study has shown that 1/3rd reduction in sodium excretion can affect the treatment of patient adversely for the patient treated with spironolactone for ascites

or edema [11]. Another study shows that Dexamethasone, Ciprofloxacin, Tramadol, Moxifloxacin, Diclofenac, Pantoprazole and Theophylline [12]. The level of evidence provided by the online database for the given major drug interaction were majorly of poor level of evidence i.e., 71 drug interaction with level 5 evidence followed by 15 drug interactions of 3b, 10 drug interaction of 1b, 6 drug interaction of 4 and 5 drug interaction of 2b. Article reviewed for the identification of level of evidence of the drug interaction in Table 1 [13-51].

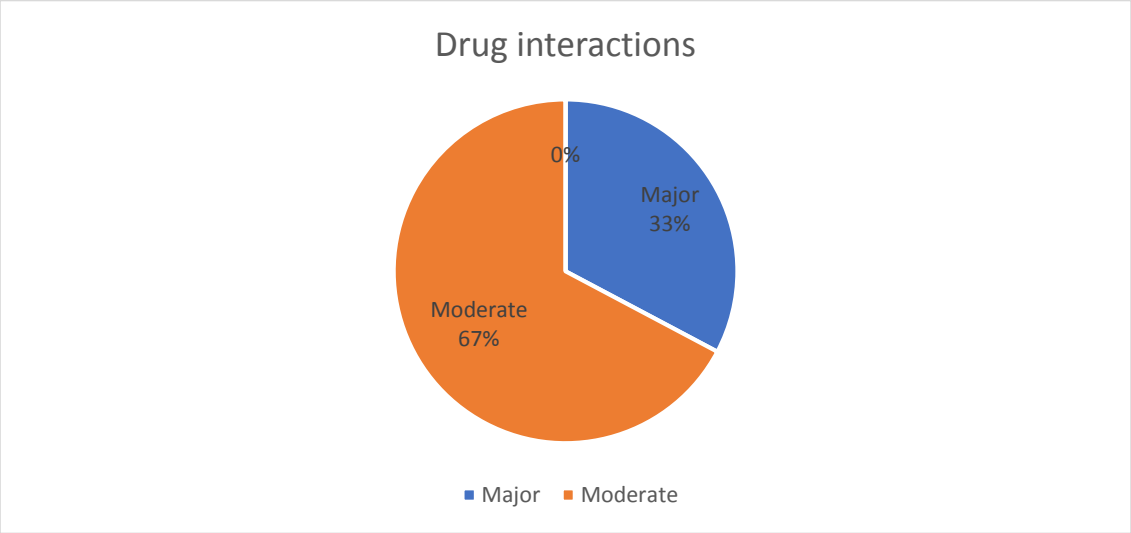

Fig. 1. Type of Drug interaction Identified

Table 1. The common major drug interactions were found to be between following drugs

S. No	Interacting Drugs	No. of Interaction Found (Percentage)
1.	Aspirin & Furosemide	24 (9.6%)
2.	Aspirin & Clopidogrel	22(8.8%)
3.	Aspirin & Heparin	17(6.8%)
4.	Aspirin & Ramipril	17(6.8%)
5.	Aspirin & Spironolactone	15(6%)
6.	Clopidogrel & Heparin	15(6%)
7.	Atorvastatin & Budesonide	10(4%)
8.	Ramipril & Spironolactone	10(4%)
9.	Ceftriaxone & Heparin	08(3.2%)
10.	Metronidazole & Ondansetron	06(2.4%)
11.	Metronidazole & Phenytoin	06(2.4%)
12.	Ondansetron & Tramadol	06(2.4%)
13.	Ofloxacin & Ondansetron	05(2%)
14.	Aspirin & Torsemide	04(1.6%)
15.	Digoxin & Spironolactone	04(1.6%)
16.	Heparin & Warfarin	04(1.6%)
17.	Piperacillin & Heparin	04(1.6%)
18.	Aspirin & Enalapril	03(1.2%)
19.	Aspirin & Prasugrel	03(1.2%)
20.	Atropine & Glycopyrrolate	03(1.2%)
21.	Ceftriaxone & Warfarin	03(1.2%)
22.	Digoxin & Metoprolol	03(1.2%)
23.	Domperidone & Ondansetron	03(1.2%)
24.	Heparin & Nitroglycerine	03(1.2%)

The frequent drug interactions were between, Aspirin & Furosemide, Aspirin & Clopidogrel, Aspirin & Heparin 17, Aspirin & Ramipril 17, Aspirin & Spironolactone

Table 2. Identified drug interaction along with management as per online database and Pharmacist management

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
1.	Acetaminophen + Isoniazid	Tuberculosis, Diabetes II	Increase risk of Hepatotoxicity	Acetaminophen use should be avoided or limited in patients taking isoniazid.	01	05
2.	Amikacin + Mannitol	Acute left sided subdural hemorrhage	Increase risk of Renal toxicity	Avoid concomitant use of amikacin and mannitol	01	05
3.	Amiodaron + Ondansetron	Diabetes Mellitus, Hypothyroidism	QT Interval Prolongation	Avoid Concomitant administration of Amiodarone	01	05
4.	Amiodaron + Warfarin	Rheumatic Heart Disease	Increase risk of bleeding	Avoid or Use Alternative Drug	02	2b
5.	Amlodipine + Clarithromycin	Peptic Ulcer, Hypertension	Increase risk of Hypotension	Dosage adjustments should be done if coadministration is clinically warranted	01	1b
6.	Amlodipine + Digoxin	Rheumatic Heart Disease	Increase risk of bradycardia or complete heart block	Avoid or use Alternative drug	01	05
7.	Amlodipine + Domperidone	Cerebrovascular Accident	Increase risk of QT interval Prolongation, Ventricular Arrhythmias	Domperidone Should be initiated at lowest possible dose and titrated with caution. Discontinue Domperidone if the patient experiences dizziness, Palpitations, Syncope.	01	05
8.	Augmentin + Warfarin	Rheumatic Heart Disease	Increased risk of bleeding	Frequent Monitoring of INR is recommended	02	1b

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
9.	Aspirin + Clopidogrel	Ischemic heart disease	Increased risk of Bleeding	Use low dose of aspirin	22	05
10.	Aspirin + Digoxin	Heart Failure, Ischemic Heart Disease, Hypertension	Increase serum potassium	Monitoring Serum Digoxin level	02	05
11.	Aspirin + Duloxetine	Cerebrovascular Accident, Hemiparesis	Increase Risk of Bleeding	Monitor Signs of Increased Bleeding	01	05
12.	Aspirin + Enalapril	Cerebrovascular Disease, Diabetes Mellitus	Significant decrease renal function	Avoid or Use Alternative Drug.	03	1b
13.	Aspirin + Furosemide	Congestive Heart Failure, Hypertension, IHD	Reduced Diuretic Effectiveness and Possible Nephrotoxicity	Monitor for signs of worsening renal function, assure diuretic efficacy.	24	1b
14.	Aspirin + Glimepiride	Congestive Cardiac Failure, Diabetes Mellitus	Increase risk of hypoglycemia	Use Caution, Monitoring	02	05
15.	Aspirin + Heparin	Congestive Cardiac Failure, Acute Myocardial Infarction, Ischemic Heart Disease	Increase risk of Bleeding	Monitor patients closely for any signs of bleeding	17	2a
16.	Aspirin + Metformin	Congestive Cardiac Failure, Diabetes Mellitus	Increase risk of hypoglycemia	Monitor blood sugar carefully	02	5
17.	Aspirin + Prasugrel	Cerebrovascular Accident, Hemiparesis	Increase risk of Bleeding	If coadministration is required, Monitor for bleeding	03	5
18.	Aspirin + Prednisolone	Recurrent Cerebrovascular Accident	Increase risk of Gastro Intestinal Ulcer	Use Caution, Monitoring	01	3b
19.	Aspirin + Ramipril	Congestive Cardiac Failure, Diabetes	Significant Decrease in Renal Function	The clinician should weigh the benefits	17	1b

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
		Mellitus, Ischemic Heart Disease		against the risks of combining these two agents		
20.	Aspirin + Spironolactone	Congestive Cardiac Failure, Diabetes Mellitus	Hyperkalemia, Possible Nephrotoxicity	Monitor Sign Symptoms of Hyperkalemia and Renal Toxicity	15	1b
21.	Aspirin + Tirofiban	Anterior wall myocardial infarction, Diabetes, Coronary artery bypass grafting	Increase Risk of Bleeding	Patients should be closely monitored for signs and symptoms of active bleeding.	01	05
22.	Aspirin + Torsemide	Congestive Cardiac Failure, Diabetes	Nephrotoxicity	Monitor for signs of worsening renal function and assure diuretic efficacy, including appropriate effects on blood pressure.	04	1b
23.	Atorvastatin + Budesonide	Acute Myocardial Infarction, Heart Failure, Ischemic Heart Disease	Increase effect of Budesonide	Use Caution and Monitor	10	05
24.	Atorvastatin + Digoxin	Dilated Cardio Myopathy	Tachycardia, Cardiac arrhythmias	Reduce digoxin dosage 15 to 30%, continue monitoring digoxin plasma concentration	02	3b
25.	Atorvastatin + Fluconazole	Neuropathy with Cerebrovascular Accident	Increased risk of Myopathy or Rhabdomyolysis	If concomitant use is necessary, use the lowest atorvastatin dose necessary and closely monitor patients for signs or symptoms of muscle pain, tenderness, and weakness.	01	05

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
26.	Atropine + Glycopyrrolate	OP Poisoning	Increase the risk of additive anticholinergic effects, including worsening of narrow-angle glaucoma and urinary retention.	Avoid unnecessary use with other anticholinergic agents	03	05
27.	Atropine + Potassium Chloride	OP Poisoning	Retention of Potassium Chloride tablet in GI can cause lesions in GI tract.	Avoid solid dosage of Potassium Chloride	01	05
28.	Azithromycin + Levofloxacin	Iron Deficiency Anemia	Increased risk of QT Interval prolongation and arrhythmias	Avoid	01	05
29.	Azithromycin + Enoxaparin	Rheumatic Heart Disease	Increased risk of Bleeding	Avoid or Use Alternate drug	01	05
30.	Azithromycin + Warfarin	Rheumatic Heart Disease	Increased risk of Bleeding	Avoid or Use Alternate drug	02	1b
31.	Azithromycin + Digoxin	Rheumatic Heart Disease	Increased Vomiting and Cardiac arrhythmias	Avoid or Use Alternate drug	01	3b
32.	Azithromycin + Heparin	Heart Failure, COPD, Hypokinesis	Increased risk of Bleeding	Avoid or Use Alternate drug	01	05
33.	Azithromycin + Ivabradine	Balloon Mitral Valvotomy	Increased risk of QT Interval prolongation and arrhythmias	Use caution	01	05
34.	Azithromycin + Metronidazole	Acute Kidney Injury, Hypertension, Antepartum Hemorrhage	Increased risk of QT Interval prolongation and arrhythmias	Susceptible patients may require ECG monitoring	01	05
35.	Azithromycin + Norfloxacin	Upper respiratory tract Infection, Kidney Stone	Increased risk of QT Interval prolongation and arrhythmias	If concomitant therapy is required, closely monitor ECG for QT interval prolongation.	02	05

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
36.	Carvedilol + Diltiazem	Alcoholic Cardiomyopathy, Heart Failure	Increased risk of hypotension, bradycardia	Modify therapy and Monitor Closely	01	3b
37.	Carvedilol + Metoprolol	Decompensated cardiomyopathy	Increase risk of Hypotension	Avoid or Use Alternate drug	01	05
38.	Cefoperazone + Heparin	Small Vessel Disease, PTCA	Increased risk of Bleeding	Monitor if required use alternative antimicrobial	02	05
39.	Ceftriaxone + Heparin	Myocardial Infarction, Rheumatic Heart Disease, Cerebrovascular Accident	Increased risk of Bleeding	Avoid or Use Alternate drug	08	05
40.	Ceftriaxone + Calcium Carbonate	Meningitis	Ceftriaxone – Calcium Precipitates	Contraindicated	01	05
41.	Ceftriaxone + Warfarin	Rheumatic Heart Disease	Increased risk of bleeding	Avoid or Use Alternate drug	03	05
42.	Ciprofloxacin + Ondansetron	Rabies, Dysphagia	Increased risk of QT interval prolongation, Bradyarrhythmia's	Avoid or Use Alternate drug	01	05
43.	Clarithromycin + Clopidogrel	Lower Respiratory tract Infection	Decrease activity of Clopidogrel, Increase risk of thrombotic event	Avoid or Use Alternate drug	01	05
44.	Clarithromycin + Heparin	Lower respiratory tract infection, Heart Failure	Increased risk of bleeding	Avoid or Use Alternate drug	02	05
45.	Clarithromycin + Ondansetron	Lower respiratory tract infection, Heart Failure	Increased risk of QT interval prolongation, Bradyarrhythmia's	Avoid or Use Alternate drug	02	05
46.	Clarithromycin + Rosuvastatin	Lower respiratory tract infection, Heart Failure	Increased risk of Myopathy or Rhabdomyolysis	Avoid or Use Alternate drug	01	05
47.	Clonazepam + Midazolam	OP Poisoning	Increased risk of hypoventilation	Use Caution/Monitor	01	3b

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
48.	Clonidine + Metoprolol	Ischemic Heart Disease, Left Ventricular SYSTOLIC Dysfunction	Increase risk of Bradycardia	Avoid or use Alternate Drug	01	05
49.	Clopidogrel + Diltiazem	Heart Failure, Diabetes Mellites	Increased risk of thrombotic events	Use Caution	02	2b
50.	Clopidogrel + Duloxetine	Cerebrovascular Accident, Hemiparesis,	Increased Risk of Bleeding	Monitor patient for any signs of bleeding	01	05
51.	Clopidogrel + Fluconazole	Neuropathy with Cerebrovascular Accident	Increased risk of thrombotic events	Consider avoiding concomitant use.	01	05
52.	Clopidogrel + Heparin	Small Vessel Disease, Congestive Cardiac Failure	Increased Risk of Bleeding	Monitor patients closely for signs or symptoms of blood loss	15	05
53.	Clopidogrel + Nicardipine	Small Vessel Disease, Cerebrovascular accident	Increase the risk of atherothrombotic events	Use caution if clopidogrel and nicardipine are used concurrently and monitor patients for loss of clopidogrel efficacy.	01	2b
54.	Clopidogrel + Warfarin	Left Side Deep Vein Thrombosis	Increased Risk of Bleeding	Monitor patients closely for signs or symptoms of blood loss	01	05
55.	Dexamethasone + Tramadol	Vasculitis with Polyarteritis Nodosa, Guillen Barre Syndrome, Hypertension	Decreased effectiveness of tramadol	Use Caution and Monitor	02	05
56.	Dextromethorphan + Haloperidol	Schizophrenia, Left Side Hemiparesis	Exacerbation of dextromethorphan adverse effects (CNS excitement, mental confusion, respiratory	Monitor patient for signs and symptoms of dextromethorphan toxicity	02	3a

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
			depression, nervousness, tremors, insomnia, diarrhea).			
57.	Diclofenac + Prednisolone	Systematic Lupus Erythematosus	Increased risk of gastrointestinal ulcer or bleeding	Use Caution and Monitor	02	05
58.	Digoxin + Bisoprolol	Rheumatic Heart Disease, Decompensated Cardiac Myopathy	Increase risk of bradycardia	Avoid or use Alternative drug	01	05
59.	Digoxin + Diltiazem	Alcoholic Cardiomyopathy, Heart Failure	Increased risk of complete heart block	Reduce the oral digoxin dose by approximately 15% to 30% or modify the dosing frequency.	01	3b
60.	Digoxin + Metoprolol	Rheumatic Heart Disease, Decompensated Cardiac Myopathy	Increased risk of bradycardia and possible digitalis glycoside toxicity	Avoid or use Alternative drug	03	3b
61.	Digoxin + norepinephrine	Rheumatic Heart Disease, Decompensated Cardiac Myopathy	Increased risk of cardiac arrhythmias	Individualize the dosage of digoxin	01	5
62.	Digoxin + Spironolactone	Alcoholic cardiomyopathy	Increased risk of cardiac arrhythmias	Reduce the digoxin dose by approximately 15% to 30%, or modify the dosing frequency and continue monitoring	04	3b
63.	Diltiazem + Budesonide	Ischemic Heart Disease, Lower Respiratory Infection	Closely monitor for signs and symptoms of corticosteroid excess	Use Alternative	02	5
64.	Diltiazem + Nebivolol	Lower respiratory tract infection, Rheumatic	Increase risk of Bradycardia	Avoid or use Alternative drug	01	1b

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
		Heart Disease				
65.	Diltiazem + Metoprolol	Hypertension, Left side Hemiparesis	Increase risk of Bradycardia	Avoid or use Alternative drug	02	1b
66.	Domperidone + Hydroxychloroquine	Systemic Lupus Erythematosus	Increased risk of QT – Interval prolongation	If concomitant use is required, consider close ECG monitoring at baseline and during therapy	02	04
67.	Domperidone + Ondansetron	Dengue, Menorrhagia	Increased risk of QT – Interval prolongation	initiated at the lowest possible dose and titrated with caution. If coadministration cannot be avoided, monitor ECG for signs of QT interval prolongation	03	05
68.	Enalapril + Telmisartan	Hypertension	Hypotension, Syncope, Hyperkalemia, acute renal failure	Avoid or use Alternative drug	01	1a
69.	Enoxaparin + Warfarin	Rheumatic Heart Disease	Increased risk of bleeding	Avoid or use Alternative drug	02	05
70.	Escitalopram + Ondansetron	OP Poisoning	Increased risk of QT – Interval prolongation	Avoid or Use Alternate Drug.	02	05
71.	Fluconazole + Ondansetron	Paraquat Dichloride Poisoning	Increased risk of QT – Interval prolongation	Avoid or use alternative, ECG Monitoring	01	05
72.	Fluconazole + Tramadol	Vasculitis with Polyarteritis nodosa	Increased risk of respiratory depression.	Consider reducing the dose of tramadol and closely monitor for seizures, serotonin syndrome, or respiratory depression	01	05
73.	Fluconazole + Clopidogrel	Neuropathy, uremia electrolyte imbalance,	Increased risk of thrombotic event	Avoid or use alternative, ECG Monitoring	01	05

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
		Hypothyroidism				
74.	Fluoxetine + Lithium	Paraquat Dichloride Poisoning	Risk of neurotoxicity	Modify Therapy/Monitor Closely.	02	3b
75.	Fluoxetine + Ondansetron	Paraquat Dichloride Poisoning	Increased risk of QT – Interval prolongation	Avoid or Use Alternate Drug	02	05
76.	Fosphenytoin + Oxcarbazepine	Seizure	Increase risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor)	Use Caution/Monitor	01	2a
77.	Gabapentin + Tramadol	Guillen Barre Syndrome with Hypertension	Coadministration of CNS depressants can result in serious, life-threatening, and fatal respiratory depression	Use Caution/Monitor	01	05
78.	Glycopyrrolate + Potassium Chloride	OP Poisoning	Retention of Potassium Chloride tablet in GI can cause lesions in GI tract.	Contraindicated	01	05
79.	Haloperidol + Ondansetron	Left Sided Hemiparesis, Viral Encephalitis, Cerebral Malaria	QT interval prolongation and an increased risk of serious ventricular arrhythmias	If concurrent therapy is required, ECG monitoring is recommended	03	05
80.	Haloperidol + Tramadol	Left Sided Hemiparesis	Increased risk of respiratory and CNS depression.	Use the lowest dose and shortest duration necessary to achieve treatment goals	02	05
81.	Heparin + Cilostazol	Diabetic Foot	Enhanced risk of hemorrhage.	Contraindicated	01	05
82.	Heparin + Nitroglycerine	Anterior wall myocardial infarction, Heart Failure	May result in a decrease in partial thromboplastin time.	Careful monitoring of PTT and heparin dose adjustment are recommended when heparin and nitroglycerin	03	05

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
				are co-administered		
83.	Heparin + Prasugrel	Anterior wall myocardial infarction, Diabetes	Increased risk of bleeding	Contraindicated	01	3b
84.	Heparin + Tirofiban	Anterior wall myocardial infarction, Diabetes	Increased risk of bleeding	Contraindicated	01	3b
85.	Heparin + Warfarin	Left Side Deep vein thrombosis, Rheumatic Heart Disease	Increased risk of bleeding	Avoid or Use Alternate Drug	04	3b
86.	Isoniazid + Rifampin	Tuberculosis, Diabetes Mellitus	Risk of hepatotoxicity	Use Caution/Monitor	02	3b
87.	Ivabradine + Ondansetron	Sepsis, Acute Myocardial Infarction, Cardiogenic Shock,	Increased risk of QT – Interval prolongation	Use caution	01	5
88.	Labetalol + Metoprolol	Acute kidney injury, Chronic Kidney disease, Hypertension	Increase risk of hypotension	Avoid or Use Alternate Drug	02	5
89.	Lactated Ringer Solution + Ceftriaxone	Meningitis	Ceftriaxone – Calcium Precipitates	Contraindicated	01	4
90.	Levofloxacin + Norfloxacin	Community Acquired Anemia with Iron Deficiency Anemia	Increased risk of QT – Interval prolongation	Avoid or Use Alternate Drug	01	5
91.	Levofloxacin + Ondansetron	Community Acquired Anemia with Iron Deficiency Anemia	Increased risk of QT – Interval prolongation	Avoid or Use Alternate Drug. ECG monitoring recommended with concomitant medications that prolong QT interval, electrolyte abnormalities, CHF, or bradyarrhythmia's.	02	5
92.	Lithium + Ondansetron	Paraquat Dichloride	Increase risk of serotonin	Use Caution/Monitor	02	5

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
		Poisoning	syndrome			
93.	Metronidazole + Ondansetron	Ischemic Stroke, Acute kidney injury, Chronic Kidney disease, Hypertension	Increased risk of QT – Interval prolongation	Susceptible patients may require ECG monitoring	06	4
94.	Metronidazole + Phenytoin	Intracranial Hemorrhage, Hypertension, Acute respiratory failure	Increased risk of Phenytoin toxicity, Arrhythmias	Use Caution/Monitor	06	3b
95.	Moxifloxacin + Ondansetron	Community Acquired Anemia with Iron Deficiency Anemia	QTc Interval Prolongation, can worsen the existing cardiac condition.	Avoid or Use Alternative	01	5
96.	Nifedipine + Phenytoin	Seizure Disorder, Cerebrovascular accident	Decreased Nifedipine Efficacy	Avoid or Use Alternative	03	3b
97.	Norfloxacin + Ondansetron	Community Acquired Anemia with Iron Deficiency Anemia	QTc Interval Prolongation	Avoid, If concomitant therapy is required, monitor ECG for QT interval prolongation	01	5
98.	Octreotide + Ondansetron	Hematemesis, Liver disease	Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia's.	Avoid or Use Alternative	01	3b
99.	Ondansetron + Risperidone	Tuberous Sclerosis	Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia's	Avoid or Use Alternative	02	5
100.	Ofloxacin + Ondansetron	Alcoholic Liver Disease, Pancytopenia	Increased risk of QT – Interval prolongation,	Avoid or Use Alternative	05	5

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
			electrolyte abnormalities, CHF, or bradyarrhythmia's			
101.	Olanzapine + Ondansetron	Alcoholic liver Cirrhosis,	Increased risk of QT – Interval prolongation, electrolyte abnormalities, CHF, or bradyarrhythmia's	Avoid or Use Alternative	01	5
102.	Ondansetron + Escitalopram	Hepatic Encephalopathy, Decreased Intelligence	Increased risk of serotonin syndrome and QT interval prolongation.	Monitoring ECG and for the emergence of serotonin syndrome. Discontinue treatment with ondansetron and institute supportive therapy if symptoms of serotonin syndrome occur	01	5
103.	Ondansetron + Tramadol	Left side Hemiparesis, Acute Pancreatitis, with chronic alcoholic.	Increased risk of serotonin syndrome.	Discontinue tramadol if serotonin syndrome is suspected	06	5
104.	Oxcarbazepine + Phenytoin	Seizure	Increased risk of phenytoin toxicity (ataxia, hyperreflexia, nystagmus, tremor) and decreased effectiveness of oxcarbazepine	Use Caution/Monitor.	01	2a
105.	Pantoprazole + Digoxin	Decompensated Cardiomyopathy	level or effect of digoxin Increased, risk of arrhythmias	Avoid or Use Alternative	02	5
106.	Penicillin G + Warfarin	Rheumatic Heart Disease	Increased risk of bleeding	More frequent monitoring of the patient's INR is	01	1a

Sr. No.	Drug Interaction	Disease Condition	Effect of Drug interaction	Management as per Drug Interaction Database	Frequency of Interactions (In 250 Prescriptions)	Highest level of Evidence
				recommended		
107.	Phenytoin + Nifedipine	Hepatic Encephalopathy, Decreased Intelligence	Phenytoin decreases systemic exposure of nifedipine by about 70%	Avoid or Use Alternative	02	3b
108.	Piperacillin + Heparin	Sepsis, Acute MI, Cardiogenic Shock, Cardio Embolic Stroke	Increased risk of bleeding	Avoid or Use Alternative	04	5
109.	Pyrazinamide + Rifampin	Tubercular Pleural Effusion	may result in severe hepatic injury.	Patients should be monitored throughout the entire course of therapy since a majority of patients have onset of symptoms of liver injury after the fourth week of therapy	02	2b
110.	Ramipril + Spironolactone	Tubercular Pleural Effusion	may result in severe hepatic injury.	Monitor serum potassium levels for persistent elevations in patients on this combination,	10	2b
111.	Spironolactone + Potassium Chloride	Alcoholic Cardiomyopathy, Heart Failure	Increased risk of Hyperkalemia	Avoid or Use Alternative	03	4
112.	Torsemide + Spironolactone	Alcoholic Cardiomyopathy, Heart Failure	Increased risk of Hyperkalemia	Avoid or Use Alternative	01	5
113.	Venlafaxine + Dosulepin	Anxiety, Neurosis, Breathlessness, Decreased Intelligence	Increased risk of serotonin syndrome	Use Alternative	01	5

Table 3. Level of evidence for the identified drug interaction

Sr. No.	Level of evidence	No. of Interactions
1.	1a	02
2.	1b	10
3.	1c	00
4.	2a	03
5.	2b	05
6.	2c	00
7.	3a	01
8.	3b	15
9.	4	06
10.	5	71

5. CONCLUSION

From this study it was concluded that 1/3rd of the total drug interaction was major drug interaction in critically ill patient. The most common drug interaction found were between anticoagulants, antiplatelet and antihypertensive drugs. The level of evidence provided for majority of drug interaction were of level 5, 3b, 1b and 2b. The evidence provided for majority of drug interaction in various database were poor and least reliable.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

Prior to initiation of the study ethical approval was obtained from Sumandeep Vidyapeeth Institution Ethics Committee (SVIEC). Ref. No. SVIEC/IN/PHAR/PHD/19052. The Ethical issue raised by the Ethical committee were, Permission letter from Medical Superintendent for accessing medical records of ICU patients, removal of Informed consent and Patient information sheet from study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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