INTRODUCTION

Drug–drug interaction is a specific term for adverse effect which is used when efficacy or toxicity of one drug is modified by another drug. Potential drug interactions can be predicted based on various properties of interacting drugs like bioavailability, mechanism of action, route of elimination etc. Thus, it is very important to prevent drug interactions which can affect patient management and should be recognized early and managed appropriately by selecting alternative therapeutic strategies. It is very common when multiple drugs are used especially in intensive care unit (ICU). The complex regimen of drugs in the ICU predisposes the critically ill patients to serious drug interactions. Drugs may affect the absorption, distribution, metabolism and elimination of interacting drug with suspected drug. Critically-ill patients are at an increased risk of adverse events from drug–drug interactions due to the large number of medications being taken and their effects on organ function.

EPIDEMIOLOGY

The incidence and prevalence of drug–drug interactions in ICUs are variable which depends upon the methodology of data collection (Prospective cohort or retrospective chart review) by auditing medication chart and presence of surveillance system in ICU. Polypharmacy is one of the most important cause of drug–drug interactions in ICUs, while daily scrutiny of drugs prescribed and keeping it to minimum is essential step to prevent potential drug interactions in ICUs. In another retrospective study, it was reported that medication errors were significantly more in ICUs than in general medical unit, thereby emphasizing the need for a surveillance system for detecting clinically significant drug interactions in order to pre-empt these adverse effects and take corrective measures to change route, time and dose of interacting drug.

Severity of Drug-Drug interactions:

Type I: Unknown: No known interaction
Type II: Minor: No action needed: It would have limited clinical effects.
Type III: Moderate: Monitor Therapy: The interaction may result in exacerbation of the patients’ condition and require an alteration in therapy.
Type IV: Major: Consider therapy modification: It may be life-threatening and require medical intervention to minimize or prevent serious adverse events.
Type V: Contraindicated: Avoid combination: The drugs are contraindicated for concurrent use.

Risk factors of drug-Drug interactions:

1. Number of Medications received
2. Duration of treatment
3. Age (Very young or very old)
4. Number of Prescribing Physicians
5. Stage of Disorder
6. Multiple Diseases
7. Previous drug interactions
8. Overweight
9. Dehydration
10. Poor Nutrition
11. Hypotension
12. Congestive Heart Failure
13. Liver and Kidney Damage
14. Genetic Make-up
15. High Alert Medication

Mechanism of Drug-Drug Interactions: Drug interactions may be either Pharmacokinetic or Pharmacodynamics. A Pharmacokinetic Interaction occurs when one drug alters the...
absorption, distribution, metabolism or elimination of another drug.

A Pharmacodynamics interaction arises when one drug changes the pharmacologic response of another drug in an Additive, Synergistic or antagonistic way. Potential drug interaction is a situation in which a drug action is likely to be altered by the concurrent administration of another drug. Clinically relevant Drug interaction means where unwanted drug reaction alters the course of treatment and intervention of any form is required.

**Effects- Hospital Stay and Cost:**

In a study of hospitalized cancer patients, there was a strong positive association between length of stay and potential drug-drug interactions. Interactions between drugs and subsequent laboratory tests also led to an increase in the duration of hospital stay. Longer ICU stay may require extra laboratory tests, medications and utilisation of healthcare resources, all leading to added cost to the patient. According to studies, potential Drug-Drug interactions are very frequent among hospitalized patients. The rate of Drug-Drug interactions are directly related to number of prescribed drugs and length of hospital stay and cost among other factors. The Development and implementation of Guidelines/Protocols and computer based screening could help Physicians and Pharmacists to prevent potentially dangerous drug interactions and help patients. Many Drug-Drug interactions have adverse drug consequences which result in prolonged hospital stay and healthcare burden on society. Many studies shows that hospital admissions of Elderly population for drug toxicity usually occurs due to drug-drug interactions. The healthcare professional must develop their own system of approach to prevent undesirable drug-drug interactions to reduce healthcare burden.

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### Class of drugs having drug interactions is as under:

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) Antimicrobials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Ampicillin</td>
<td>Allopurinol</td>
<td>Increases incidence of skin rashes</td>
<td>Monitor the patient for symptoms if symptoms appears use alternate antibiotics.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Probencid</td>
<td>Retards renal excretion of ampicillin</td>
<td><strong>Avoid</strong> concurrent use and monitor the patient and reduce ampicillin dose if required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone</td>
<td>Inactivates ampicillin in IV solution</td>
<td><strong>Don't</strong> use in same IV solution</td>
</tr>
<tr>
<td>2</td>
<td>Aminoglycosides: Eg- Gentamycin, Tobramycin</td>
<td>Loop diuretics: Furosemide</td>
<td>Produces additive toxicity (ototoxic, nephrotoxic)</td>
<td>Reduce the dose and <strong>Avoid</strong> concurrent use</td>
</tr>
</tbody>
</table>

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*Baweja et Al. Drug-Drug Interactions In Medical ICU*
<table>
<thead>
<tr>
<th>3</th>
<th>Bacteriostatics: Tetracycline, Erythromycin, Clindamycin</th>
<th>Bactericidal: Beta lactum antibiotics (eg-Penicillin G)</th>
<th>Decrease in bactericidal action</th>
<th>Don’t use concurrently</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Cefoperazone, ceftriaxone</td>
<td>Oral anticoagulants: Warfarin</td>
<td>Additive hypoprothrombinaemia that leads to bleeding</td>
<td>Monitor INR and reduce dose of anticoagulant</td>
</tr>
<tr>
<td>5</td>
<td>Ciprofloxacin Norfloxacin Perflloxacin</td>
<td>Theophylline, Warfarin</td>
<td>Toxicity of theophylline and warfarin</td>
<td>Reduce the dose of theophylline and warfarin</td>
</tr>
<tr>
<td>6</td>
<td>Chloramphenicol</td>
<td>Warfarin, phenytoin, Sulfonylurea</td>
<td>Concentration of warfarin, phenytoin, and sulfonylurea increases that leads to toxicity.</td>
<td>Avoid concurrent use or monitor and reduce dose of object drugs</td>
</tr>
<tr>
<td>7</td>
<td>Clarithromycin, Ciprofloxacin, Erythromycin, Metronidazole, Cotrimoxazole</td>
<td>Warfarin</td>
<td>Increased effect of warfarin.</td>
<td>Select alternative antibiotics</td>
</tr>
<tr>
<td>8</td>
<td>Clindamycin</td>
<td>Erythromycin, Clarithromycin, Chloramphenicol</td>
<td>Mutual antagonism of antibacterial action</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>9</td>
<td>warfarin, phenytoin, Sulfonylurea</td>
<td>Pancuronium</td>
<td>Exaggerated neuromuscular blockade</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>10</td>
<td>Metronidazole, Tinidazole, Cefoperazone</td>
<td>Alcohol</td>
<td>Bizarre or disulfiram like reactions</td>
<td>Avoid Alcohol by patient</td>
</tr>
<tr>
<td>11</td>
<td>Fluoroquinolones, Tetracycline</td>
<td>NSAID’s</td>
<td>Increased CNS toxicity and seizures are reported</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>12</td>
<td>Tetracycline</td>
<td>Diuretics: Furosemide</td>
<td>Blood urea rises</td>
<td>Should be Avoided or don’t use concurrently</td>
</tr>
<tr>
<td>13</td>
<td>Isoniazid</td>
<td>Aluminium hydroxide</td>
<td>Inhibit isoniazid absorption.</td>
<td>Avoid combination or space administration by 2-4 hours</td>
</tr>
<tr>
<td>14</td>
<td>Rifampin</td>
<td>Anti-seizure drugs: phenytoin, Phenobarbital, Carbamazepine</td>
<td>Decrease in level of phenytoin, Phenobarbital, Carbamazepine</td>
<td>Monitor drug level regularly</td>
</tr>
<tr>
<td>15</td>
<td>Amphotericin B</td>
<td>HIV protease inhibitors (efaviranz)</td>
<td>Decreased activity of HIV protease</td>
<td>Can use other rifamycins eg-rifabutin</td>
</tr>
<tr>
<td>16</td>
<td>Griesofulvin</td>
<td>Phenobarbitone</td>
<td>Phenobarbitone reduces oral absorption and induces metabolism of Griesofulvin.</td>
<td>Avoided as failure in griesofulvin therapy</td>
</tr>
<tr>
<td>17</td>
<td>Itraconazole, Fluconazole, Ketoconazole</td>
<td>Simvastatin, Lovastatin</td>
<td>Risk of myopathy and rhabdomyolysis</td>
<td>Monitor for myopathy and myoglobinuria (dark urine) if symptoms persists choose another antifungal like terbinafine</td>
</tr>
<tr>
<td>18</td>
<td>Chloroquine</td>
<td>Antiepileptics</td>
<td>Antagonism of antiepileptic effect</td>
<td><strong>Avoid</strong> Combination</td>
</tr>
<tr>
<td></td>
<td>Neostigmine, Pyridostigmine</td>
<td>Antagonism action</td>
<td><strong>Avoid</strong> Combination</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Mefloquine</td>
<td>Quinidine, Quinine,</td>
<td>QTc lengthening that leads to cardiac arrest</td>
<td>Must be <strong>Avoided</strong></td>
</tr>
</tbody>
</table>

**(II) Anticoagulants**

| 1 | Warfarin | Ciprofloxacin, Clarithromycin, Erythromycin, Metronidazole, Cotrimoxazole | Increased effect of warfarin | Select alternative antibiotics |
|     | Amiodarone, Antifungal, Isoniazid, Omeprazole, Tamoxifen, Statins, Griesofulvin | May increase **INR** in plasma | Dose of warfarin should be **reduced** |
|     | Aspirin | Increased **INR** and bleeding | **Reduce** dose of warfarin |
|     | Ampicillin | Risk of bleeding due to decrease in vitamin k production in gut | Use with caution |
| 2 | Heparin | Vitamin k | Antagonism action with each other | Combination must be **Avoided** |

**(III) Autacoids and related drugs**

| 1 | Aspirin | Probenecid | Uricosuric action of probenecid (inhibit tubular secretion of uric acid) | Use other NSAID’s |
|     | Spironolactone | Aspirin block spironolactone action | Use other NSAID’s |
| 2 | Acetaminophen (Paracetamol) | Anti T.B drugs eg-Rifampicin, Isoniazid | Increase risk of liver disease | Use alternate NSAID’s |
|     | Zidovudine | Increased zidovudine levels | Use alternate NSAID’s like aspirin |
| 3 | Azathioprine | Rifampicin | Organ Transplants rejections can happen. | **Avoid** Combination |
| 4 | Probencid | Acyclovir | Probencid may decrease renal clearance of acyclovir | Monitor Acyclovir if toxicity persists reduce the dose |
| 5 | Diclofenac sodium | Furosemide | Diclofenac counteract diuretic effect of furosemide | Better to replace diclofenac with other analgesic like paracetamol |
| 6 | NSAID’s eg- Aspirin, Ibuprofen, Ketoprofen, Naproxen | Methotrexate, Cyclosporine, Digoxin | Reduces kidney clearance of methotrexate, cyclosporine and digoxin | Monitor the patient for toxicity |

**(IV) Antidiabetic drugs**
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glibenclamide</td>
<td>Bosentas</td>
<td>Increase in hypoglycaemic effect</td>
<td>Use with caution</td>
</tr>
<tr>
<td>2</td>
<td>Insulin</td>
<td>Lithium</td>
<td>Increase in hypoglycaemia</td>
<td>Use with caution</td>
</tr>
</tbody>
</table>

**(V) Cardiovascular drugs**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ACE inhibitors</td>
<td>K+(potassium) diuretics</td>
<td>Hyperkalemia</td>
<td>Monitor k+ level regularly</td>
</tr>
<tr>
<td>2</td>
<td>Amiodarone</td>
<td>Antimalarial drugs: Chloroquine</td>
<td>Increase risk of ventricular arrhythmia</td>
<td>Avoided</td>
</tr>
<tr>
<td></td>
<td>Simvastatin</td>
<td></td>
<td>Increase in concentration of simvastatin leads to myopathy and rhabdomyolysis</td>
<td>Use alternate statins like rosuvastatin</td>
</tr>
<tr>
<td></td>
<td>Levofloxacin, Moxifloxacin, Ofloxacin</td>
<td></td>
<td>Increased risk of QTc prolongation</td>
<td>Use alternative antibiotics like ciprofloxacin</td>
</tr>
<tr>
<td>3</td>
<td>Clonidine</td>
<td>Chlorpromazine, Imipramine</td>
<td>Decrease in antihypertensive action of clonidine</td>
<td>Concurrent use Avoided</td>
</tr>
<tr>
<td>4</td>
<td>Cholestyramine</td>
<td>Corticosteroids like Methylprednisolone, Hydrocortisone</td>
<td>Raises blood sugar</td>
<td>Concurrent use Avoided</td>
</tr>
<tr>
<td>5</td>
<td>Digoxin</td>
<td>Calcium</td>
<td>Increased effect of digoxin</td>
<td>Avoid concurrent use.</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td></td>
<td>Plasma concentration of digoxin becomes double so toxicity can occur</td>
<td>Reduce the dose of Digoxin, can be reduced up to half</td>
</tr>
<tr>
<td></td>
<td>Diuretics, Corticosteroids</td>
<td></td>
<td>Hypokalemia, digitalis arrhythmia can be precipitated</td>
<td>Potassium may be given prophylactically</td>
</tr>
<tr>
<td></td>
<td>Propanolol, Verapamil, Diltiazem, Disopyramide</td>
<td></td>
<td>May depress AV conduction and oppose positive Inotropic action</td>
<td>Avoid the combination</td>
</tr>
<tr>
<td>6</td>
<td>Beta-blockers: Atenolol</td>
<td>Lidocaine</td>
<td>Bradycardia and Hypotension</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>7</td>
<td>Diuretics</td>
<td>Cotrimoxazole</td>
<td>Higher incidence of hypertension</td>
<td>Should be Avoided</td>
</tr>
<tr>
<td>8</td>
<td>Propranolol</td>
<td>Adrenaline with local anaesthetic</td>
<td>Rise in BP due to decrease in adrenaline vasodilation activity in systemic circulation</td>
<td>Avoid adrenaline having local anaesthetics.</td>
</tr>
<tr>
<td>9</td>
<td>Nitrates: Glyceryl trinitrate, Isosorbide dinitrate, Isosorbide mononitrate</td>
<td>Sildenafil, Tadalafil</td>
<td>Dramatic hypotension</td>
<td>Must be Avoided onset of interaction effect soon after taking sildenafil</td>
</tr>
<tr>
<td>10</td>
<td>Thiazide diuretics: Hydrochlorothiazide, Indapamide, Chlorthalidon</td>
<td>Lithium</td>
<td>Increase in toxicity of lithium</td>
<td>Decrease lithium dose by 50% and monitor level of lithium</td>
</tr>
<tr>
<td>11</td>
<td>Verapamil, diltiazem</td>
<td>B-Blockers: Propranolol, Metoprolol, Atenolol</td>
<td>Additive sinus defects, marked bradycardia, AV-block</td>
<td>Avoided</td>
</tr>
</tbody>
</table>

**(VI) Cytotoxic drugs**
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Doxorubicin, daunorubicin, Epirubicin, idarubicin</td>
<td>Methadone</td>
<td>Acute cardiac toxicity, cumulative dose-dependent toxicity.</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>2</td>
<td>Daunorubicin, Doxorubicin, Epirubicin, Sorafenib</td>
<td>Venlafaxine</td>
<td>Synergistic effect of QTc prolongation. Increasing venlafaxine levels will predispose patients to toxicity. Monitor for QTc prolongation</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cisplatin</td>
<td>Celecoxib, Amiloride, Vancomycin, Furosemide, Hydrochlorothiazide</td>
<td>Both potentiate nephrotoxicity and ototoxicity</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cyclophosphamide</td>
<td>Chloramphenicol</td>
<td>Retard metabolism of cyclophosphamide</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>5</td>
<td>Gefitinib, imatinib, desatinib</td>
<td>Tramadol</td>
<td>Increases tramadol concentration. Monitor the patient for tramadol induced serotonin syndrome if symptoms persist use other alternatives of tramadol like NSAID's.</td>
<td></td>
</tr>
</tbody>
</table>

### S.No. Drugs Interacting drugs Clinical effect Precautions

#### (VII) Gastrointestinal drugs

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Omeprazole</td>
<td>Phenytoin, Diazepam, Warfarin</td>
<td>Omeprazole increases the oxidation of Phenytoin, Diazepam, Warfarin</td>
<td>Monitor the patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clarithromycin</td>
<td>Clarithromycin increases plasma concentration of omeprazole</td>
<td>Monitor the patient</td>
</tr>
<tr>
<td>2</td>
<td>Metoclopramide</td>
<td>Levodopa</td>
<td>Abolish therapeutic effect of levodopa</td>
<td>Avoid concurrent use</td>
</tr>
</tbody>
</table>

#### (VIII) Drug acting on Nervous System

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Amitryptiline</td>
<td>Phenobarbital, Valproic Acid, Carbamazepine</td>
<td>Antagonism of anticonvulsant effect</td>
<td>Avoid combination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol</td>
<td>Chances of ventricular arrhythmia</td>
<td>Avoid</td>
</tr>
<tr>
<td>2</td>
<td>Baclofen</td>
<td>MAO inhibitors: Selegiline</td>
<td>Depression in brain function</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>3</td>
<td>Antipsychotic(neuroleptics): eg-chlorpromazine, Haloperidol, Risperidone</td>
<td>Levodopa</td>
<td>Block action of levodopa</td>
<td>Avoid concurrent use</td>
</tr>
<tr>
<td>4</td>
<td>Benzodiazepine: Clonazepam</td>
<td>Sodium valproate</td>
<td>Provoked psychotic disorder</td>
<td>Avoid concurrent use</td>
</tr>
</tbody>
</table>

### S.No. Drugs Interacting drugs Clinical effect Precautions

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Clonazepam</td>
<td>Sodium valproate</td>
<td>Absence status may be precipitated</td>
<td>Avoid concurrent use</td>
</tr>
</tbody>
</table>

<p>| 7     | Duloxetine           | Tamoxifen         | Duloxetine inhibit conversion of tamoxifen to endoxifen that leads to toxicity | Avoid if possible. Venlafaxine can be used in place of duloxetine |</p>
<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drugs</th>
<th>Interacting drugs</th>
<th>Clinical effect</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Respiratory drugs</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Theophylline</td>
<td>Erythromycin, Ciprofloxacin</td>
<td>Tremors occurs</td>
<td>Reduce the dose of theophylline or choose alternate antibiotics</td>
</tr>
<tr>
<td>2</td>
<td>Aminophylline</td>
<td>Ascorbic acid, Chloropromazine, Promethazine, Morphine, Penicillin G, Erythromycin, Tetracycline, Pethidine</td>
<td>Combination in same infusion is chemically unstable</td>
<td>Avoid using in same infusion</td>
</tr>
<tr>
<td>3</td>
<td>Salbutamol(albuterol)</td>
<td>Metoprolol</td>
<td>Antagonistic pharmacological action</td>
<td>Avoid combination if not possible must space the administration by 2-4 hours and monitor the patient</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>Miscellaneous drugs</strong></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Cyclosporine</td>
<td>Potassium Diuretics, ACE Inhibitors, Amiloride</td>
<td>Marked Hyperkalemia</td>
<td>Monitor the K+ level of patient if symptoms of hyperkalemia occurs reduce the dose</td>
</tr>
<tr>
<td>2</td>
<td>Pyridoxine(vitamin B6)</td>
<td>Levodopa</td>
<td>Reduce efficacy of levodopa</td>
<td>Avoid use of Vitamin B6 in patients on levodopa</td>
</tr>
<tr>
<td>3</td>
<td>Nicotinic acid Gemfibrozil</td>
<td>Statins: Simvastatin, Rosuvastatin, Fenofibrate, Clofibrate, Cholestyramine</td>
<td>Increase risk of Myopathy</td>
<td>Caution in concurrent use</td>
</tr>
<tr>
<td>4</td>
<td>Live Vaccines</td>
<td>Azathioprine, Bleomycin, Cyclophosphamide</td>
<td>Can leads to impairment in immune system</td>
<td>Avoid combination</td>
</tr>
<tr>
<td>No.</td>
<td>Drug Interaction</td>
<td>Effect</td>
<td>Corrective Measure</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
<td>--------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Oral contraceptive pills, Rifampin, Antibiotics</td>
<td>Decreased oral contraceptive effectiveness</td>
<td>Avoid combination if possible, if necessary use high contraceptive dose (&gt;35 mcg of ethinyl estradiol) or alternative method of contraception</td>
<td></td>
</tr>
</tbody>
</table>

**PREVENTION:**

During multiple drug therapy some precautions must be considered:

1. Concurrent administration of drug should be avoided, if not possible, care must be taken and therapeutic drug monitoring must be done to observe the patients for any interaction.

2. Dose titration must be done in case of possibility of any drug interaction.

3. Any suspicious new symptoms must be observed clinically and modification in therapy should be considered according to the situation.

4. Do not ignore any symptoms if its due to interaction as they can lead to adverse outcomes.

**CORRECTIVE MEASURES**

Drug–Drug interaction knowledge base development should include patient specific information such as patient demographics, Risk factors, laboratory values, radiology reports, electrocardiogram information and Hemodynamic values. Physician and Pharmacist alerts may differ to find out the most clinically relevant information that would benefit patients, additionally, in ICU set up the alert system should be more efficient. Importance of Pharmacokinetics in preventing Drug–drug interactions and the evaluation of Interactions with biological drugs should be considered in future direction to prevent drug interaction.

**REFERENCES**