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ORIGINAL RESEARCH

A Detailed Description of Evidence-Based Reported Drug Interaction and Impact in a Tertiary Care Hospital in Kolkata

Dr. Sayantan Ghosh[1], Dr. Arpan Dutta Roy[2], Mr. Soumyajeet Paul[3]*, Mr. Tamal Nayak[4], Dr. Prolay Paul[5], Mr. Kunal Mukherjee[6], Mr. Priyabrata Biswas[7], Dr. Dinesh Kumar Yadav[8]

[1]Clinical Pharmacologist & Co-ordinator AMC, NCC-PvPI Department of Pharmacology AMRI Hospitals Ltd., Mukundapur

[2]Chief Clinical Pharmacologist, Departmental head of Clinical Pharmacology and research, Ruby general hospital, E. M. Bypass, Sector I, Kasba Golpark, Kolkata, West Bengal 700107

[3]Ex-Intern, Dept. of Clinical Pharmacology,Ruby general hospital, E. M. Bypass, Sector I, Kasba Golpark, Kolkata,West Bengal 700107
Email: jishnu.paul.in@gmail.com

[4]Clinical Research Coordinator Ruby general hospital, E. M. Bypass, Sector I, Kasba Golpark, Kolkata, West Bengal 700107

[5]Clinical Pharmacologist, Narayana Hrudayalaya Hospitals, Bangalore, Karnataka 560099

[6]Clinical Pharmacologist, Ruby general hospital, E. M. Bypass, Sector I, Kasba Golpark, Kolkata, West Bengal 700107

[7]Senior Clinical Pharmacist, Ruby general hospital, E. M. Bypass, Sector I, Kasba Golpark, Kolkata, West Bengal 700107

[8]Clinical Pharmacologist Fortis Hospital, Anandapur, Kolkata, West Bengal 700107

Abstract:

Drug interactions are said to occur when the pharmacological activity of a drug is altered by the concomitant use of another drug or by the presence of some other substances. The presence of multiple prescribers, multiple pharmacological effects of a single drug, multiple diseases, poor patient compliance, advancing age of the patient, polypharmacy, and some drug-related problems are some of the factors affecting drug interaction. Drug interactions can lead to ineffective therapeutic response and serious adverse events and therefore, early detection and careful monitoring of it can prevent its occurrence and amplify the therapeutic response. In this study, potential drug-drug interactions were detected and monitored regularly during daily rounds and the relevant interactions were then informed to the consultant physicians, along with the corrective measures. Regular follow-up was done for the patients and the measured taken were well documented. Before this initiative, the concept of drug interaction monitoring was not present in the hospital. However, with the conventional method of the study, the system has been recently updated with an automated referral system. As the study shows a positive impact on the improvement of the patient's quality of treatment and betterment of healthcare, this process of drug interaction monitoring and clinical pharmacy practice will be continued. The role of a clinical pharmacist is to prevent and detect interactions and provide reliable advice on interaction management that can greatly add to patient safety and well-being.

Keywords: Drug-interactions, Polypharmacy, Therapeutic monitoring, Toxicity monitoring, Clinical Pharmacist

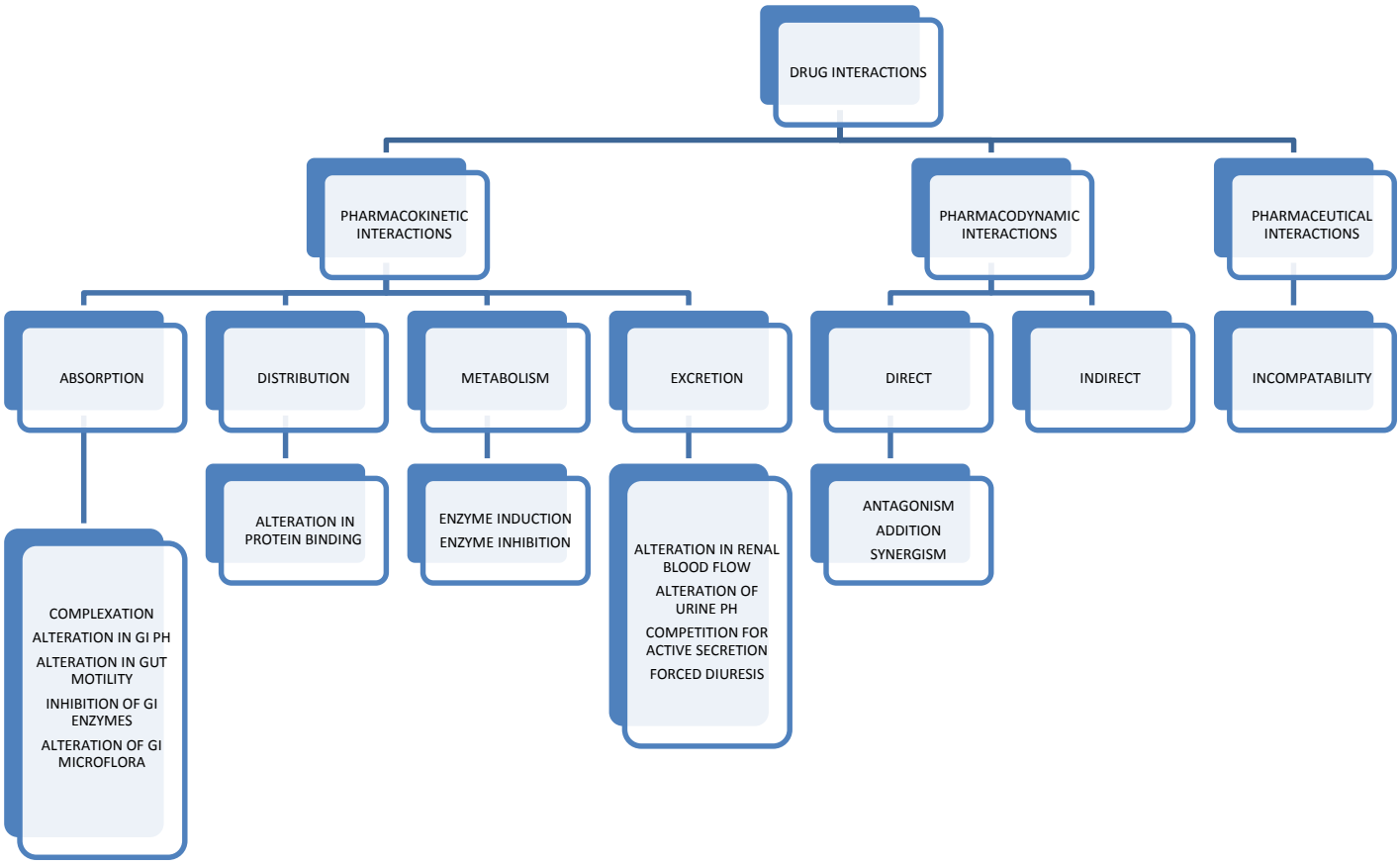
Introduction:

Drug interactions are said to occur when the pharmacological activity of a drug is altered by the concomitant use of another drug or by the presence of some other substances [1]. The drug whose activity is affected by such an interaction is called the object drug and the agent which precipitates

such an interaction is referred to as the precipitant [2]. Drug interactions may include drug-drug interactions, food-drug interactions, chemical-drug interactions, drug-laboratory test interactions, and drug-disease interactions. The presence of multiple prescribers, multiple pharmacological effects of a single drug, multiple diseases, poor patient compliance, advancing age of the patient, polypharmacy, and some drug-related problems are some of the factors affecting drug interaction [2,3].

Drug interactions can be effectively managed by identifying the patient risk factors, taking drug history, maintaining complete patient medication records, updating knowledge about pharmacological actions, considering therapeutic alternatives, individualizing the therapy, and performing therapeutic and toxicity monitoring [4]. Drug interactions can lead to ineffective therapeutic response and serious adverse events and therefore, early detection and careful monitoring of it can prevent its occurrence and amplify the therapeutic response. The role of a clinical pharmacist is to prevent and detect interactions and provide reliable advice on interaction management that can greatly add to patient safety and well-being. Pharmacists have a good educational base to develop expertise in drug interactions and make a very valuable contribution to patient management. While all practicing pharmacists need to develop basic and specialized skills in this area and add to the national and international knowledge pool [5,6].

Figure 1: pattern of drug interactions [1,2]



1.1 Types of drug interaction:

These classifications are as per the guidelines. The relevance of a particular drug interaction to a specific individual will be determined by the clinical pharmacist [1,2].

Table 1: Classification of drug interactions

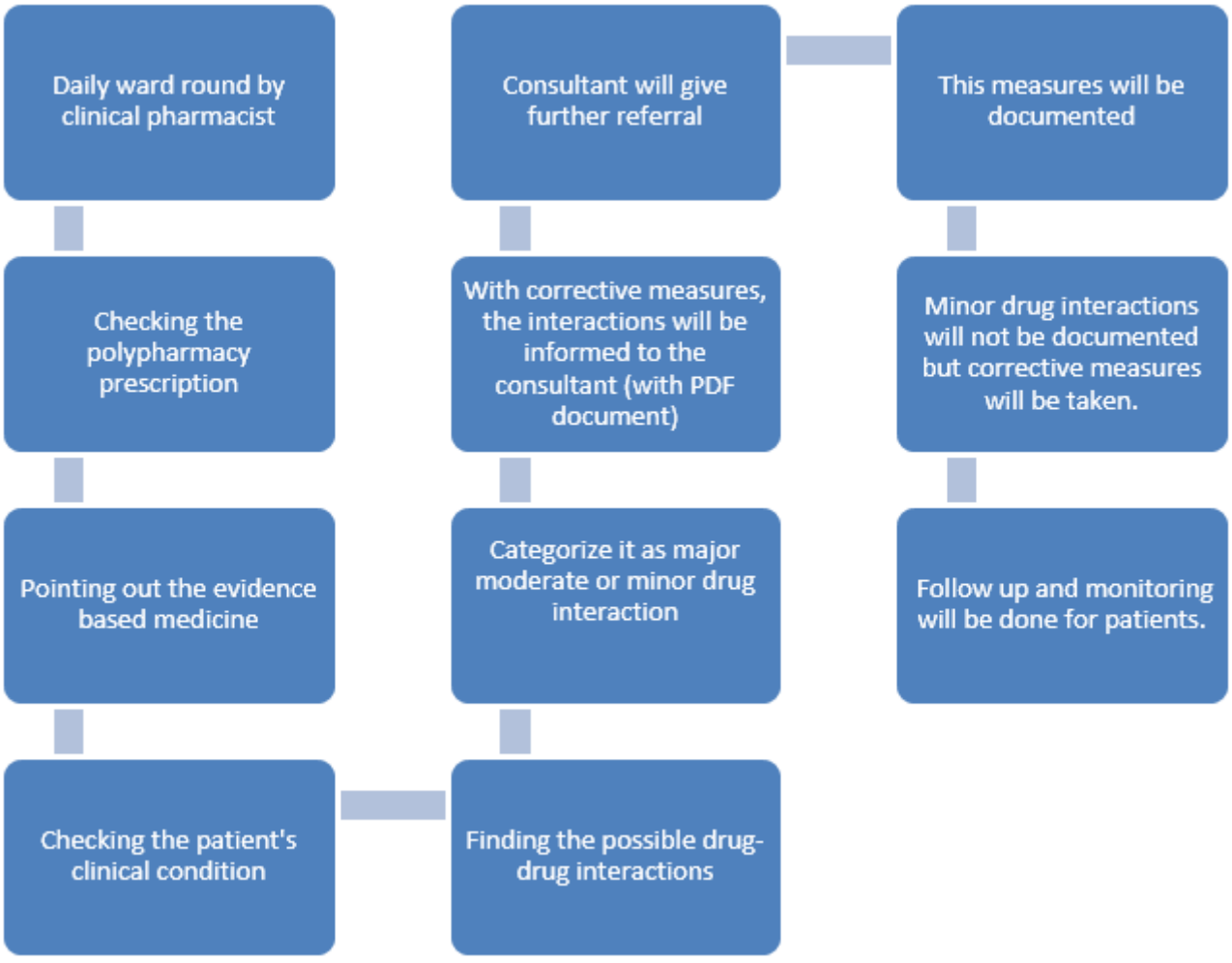
MAJOR	MODERATE	MINOR
Highly clinically significant. Avoid combinations; the risk of the interaction outweighs the benefit.	Moderately clinically significant. Avoid combinations, use them only under special circumstances.	Minimally clinically significant. Minimize risk and consider an alternative drug, take steps to circumvent the interaction risk, and /or institute a monitoring plan.

Methodology:

The study objective was to develop a series of biologically based hypotheses about clinically important drug-drug interactions. Data were collected between July 2020 to December 2021, during daily rounds for the admitted patients in the hospital and all the relevant demographic and clinical data like the demographic details, number of drugs, number of comorbid conditions, and duration of hospital stay were collected and documented. Prescriptions with polypharmacy and multiple diseased states were identified and the patient's clinical condition was assessed. In the next step, potential drug-drug interactions were identified and categorized using electronic databases such as the Micromedex Drug-Reax System. Along with the corrective measures, the relevant interactions were then informed to the consultant physicians and regular follow-up was done for the patients. The measures taken were documented properly.

- Inclusion Criteria: Admitted patients.
- Exclusion criteria: Day Care and Out-Patient and Minor drug interactions

Figure 2: The process followed to detect and categorize the drug interactions



Results and Discussion:

In the given study, about 26 types of clinically significant drug interactions were observed within a period of about 18 months. The frequency of drug interactions was found to be more in patients with multiple prescribed drugs, multiple diseased conditions, old age and compromised renal state. Hence, in such cases early detection and careful therapeutic and toxicity monitoring play an important preventive role. **Table 2** shows the details of all the documented drug interactions. After finding the possible interactions in the current study, corrective and preventive measures had been taken by adjusting the dose and frequency of the drug and stopping the drug as per the clinical condition of the patient, if required. The whole process has been carefully documented by the clinical pharmacist in a detailed manner for further references.

Table 2: Description of documented drug interactions

Sl. No.	Drug-Interaction	Mechanism of action	Severity	Effect	Inference	Actions taken
1.	Voriconazole + ivabradine	As voriconazole is a potent inhibitor of CYP450, it may significantly increase the plasma concentration of ivabradine.	Major	Toxicity and bradycardia	Both these drugs are contraindicated. As the half-life of ivabradine is 6 hours, the dose should be adjusted according to that.	Voriconazole is administered after 6 hours of ivabradine exposure.
2.	Naproxen+ methotrexate	The proposed mechanism is inhibition of renal elimination of methotrexate and its metabolite, 7-hydroxymethotrexate. Naproxen will increase the plasma concentration of methotrexate and will show toxicity.	Major	GI toxicity, bone marrow toxicity, anemia.	7.5-15mg/week can be given as a safe dose to a patient. Naproxen should not be given before the dose of methotrexate. The half-life of naproxen is 3-9 hours, so dose adjustment is required considering that.	On the day of administration of methotrexate, naproxen is not administered. It is instead administered on the next day.

3.	Linezolid+ serotonergic agents	As linezolid is a MAO-A inhibitor, it increases the level of serotonin.	Major	Major changes in blood pressure and heart rate.	Monitoring of the patient is required with corrective actions like frequency and dosage adjustment following the pharmacokinetic characteristics of the drug. The drug can also be substituted.	3rd generation cephalosporins are administered instead of linezolid.
4.	Linezolid+ duloxatine	As linezolid is a MAO-A inhibitor, the serum concentration of serotonin will be increased.	Major	Serotonergic syndrome, like a sudden change in blood pressure and heart rate with anxiety and tremors.	Monitoring of the patient is required with corrective actions like frequency and dosage adjustment following the pharmacokinetic characteristics of the drug. Drugs can also be substituted or stopped.	Linezolid was stopped.
5.	Linezolid+ levodopa	Linezolid increases the level of serotonin in the plasma.	Major	Serotonergic syndrome, like a sudden change in blood pressure and heart rate with anxiety and tremor.	Routine monitoring of the patient is required and the dose, frequency of the drug should be changed.	As linezolid has a half-life of 4 hours, levodopa will be given after 4 hours of the interval of linezolid.
6.	Diltiazem + methylprednisolone	Concurrent use may result in an increased concentration of methylprednisolone and enhanced adrenal suppressant effects.	Moderate	By inhibition of CYP3A4 mediated metabolism of methylprednisolone.	Dose reduction should be done in case of long-term therapy and persistent symptoms.	Dose of methylprednisolone was reduced.
7.	Atorvastatin + ranolazine	Concurrent use may result in an increased risk of atorvastatin	Moderate	CYP3A4 mediated metabolism of	If concomitant use is necessary, serum creatinine kinase levels	Spacing between the drugs were done.

		exposure and myopathies.		atorvastatin is inhibited.	and muscle strength should be monitored.	
8.	Haloperidol + quetiapine	Concurrent use leads to an increased risk of QT-prolongation.	Major	Additive effects on QT-interval	Coadministration should be avoided to present the risk of serious cardiac events.	Spacing between the drugs were done.
9.	Duloxetine + Ondansetron	Concurrent use of duloxetine and serotonergic agents may result in an increased risk of serotonin	Major	Additive serotonergic effects	All patients on duloxetine therapy should be monitored for serotonin syndrome,	The patient was carefully monitored.
					during initiation. Discontinue treatment with duloxetine and any concomitant serotonergic agent if symptoms occur and initiate supportive treatment.	1120
10.	Amiodarone + quetiapine	Concurrent use of quetiapine and QT interval prolonging agents may result in an increased risk of QT prolongation.	Major	Additive effects on QT interval.	Coadministration should be avoided to prevent an increased risk of serious cardiac effects.	Quetiapine was stopped.
11.	Hydroxychloroquine + quetiapine	Concurrent use of quetiapine and QT interval prolonging agents may result in an increased risk of QT prolongation.	Major	Additive effects on QT interval.	Coadministration should be avoided to prevent an increased risk of serious cardiac effects.	Quetiapine was stopped.
12.	Amiodarone + Voriconazole	Concurrent use of amiodarone and QT prolonging agents may result in an increased risk of QT prolongation and torsade de pointes.	Major	Additive effects on QT interval.	Concomitant administration of amiodarone and a QT prolonging agent should be avoided since the interaction is possible even	Voriconazole was discontinued.

					after the discontinuation of amiodarone.	
13.	Linezolid + Atorvaststin					
14.	Amitriptyline + Hydroxychloroquine	Concurrent use of amitriptyline and QT prolonging agents may result in an increased risk of QT prolongation.	Major	Additive effects on QT interval.	Hydroxychloroquine is not recommended in patients taking other drugs that are arrhythmogenic.	Hydroxychloroquine was stopped.
15.	Levofloxacin + Hydrocortisone	Concurrent use may result in an increased risk of tendon rupture.	Major	Additive effect of risk for tendon rupture.	Fluoroquinolones should be discontinued if the patient experiences pain, swelling, inflammation, or rupture of a tendon.	The patient was regularly monitored for any of the mentioned signs.
16.	Gabapentin + Tramadol	Concurrent use of gabapentin and CNS depressants may result in respiratory depression.	Major	Additive CNS depression.	If gabapentin was coadministered with another CNS depressing agent, especially an opioid and in patient with underlying respiratory impairment, monitor for symptoms of respiratory depression and sedation, consider initiating gabapentin at a low dose.	Dose of gabapentin was reduced.
17.	Tramadol + Hydroxychloroquine					
18.	Posaconazole + Rivaroxaban					
19.	Torsemide + Amikacin	Concurrent use results in an increased risk of ototoxicity.	Moderate	Unknown	Avoid concomitant use, since torsemide, a loop diuretic, increases the	Signs of ototoxicity were being carefully monitored.

					ototoxic potential of other ototoxic drugs like aminoglycoside antibiotics.	
20.	Fluconazole + Alprazolam	Concurrent use of alprazolam and CYP3A4 inhibitors may result in increased alprazolam exposure.	Major	Inhibition of CYP3A4 mediated metabolism of alprazolam	Concomitant use should be avoided so as to reduce the risk of adverse effects. If concomitant use is unavoidable, dose reduction should be considered.	The dose of alprazolam was reduced.
21.	Fluconazole + Atorvastatin	Concurrent use may result in an increased risk of myopathy or rhabdomyolosis	Major	Unknown	If concomitant use is necessary, use the lowest atorvastatin dose and closely monitor patients for signs of muscle pain, tenderness, and weakness.	Dose of atorvastatin was reduced.
22.	Quetiapine + Ivabradine	Concurrent use of quetiapine and QT interval prolonging agents may result in an increased risk of QT prolongation.	Major	Additive effects on QT interval.	Coadministration should be avoided to prevent an increased risk of serious cardiac effects.	Quetiapine was stopped.
23.	Amitryptyline + Ivabradine	Concurrent use of quetiapine and QT interval prolonging agents may result in an increased risk of QT prolongation.	Major	Additive effects on QT interval.	Coadministration should be avoided to prevent an increased risk of serious cardiac effects. And closely monitor the cardiac functions.	The patients ECG was carefully monitored.
24.	Prednisolone + Levofloxacin	Concurrent use may result in an increased risk of tendon rupture.	Major	Additive effect of risk for tendon rupture.	Fluoroquinolones should be discontinued if the patient experiences pain, swelling, inflammation, or	The patient was regularly monitored for any of the mentioned signs.

					rupture of a tendon.	
25.	Spironolactone + Ramipril	Concurrent use of potassium-sparing diuretics and ACE Inhibitors may result in hyperkalemia	Major	Increased potassium retention due to lowered aldosterone levels.	Concomitant use should be avoided and serum potassium levels should be regularly monitored.	The drugs were spaced.
26.	Clarithromycin + Eplerenone	Concurrent use of eplerenone and strong CYP3A inhibitors may result in increased serum levels of eplerenone	Contraindicated	Inhibition of CYP3A mediate eplerenone metabolism	Concomitant use of both is contraindicated.	Clarithromycin was changed.
27.	Clarithromycin + Ivabradine	Concurrent use of ivabradine and strong CYP3A4 inhibitors that prolong the QT-interval may result in increased exposure of ivabradine and increased risk of QT-prolongation.	Contraindicated	Inhibition of CYP3A4 mediated metabolism of ivabradine and additive QT-interval prolongation	Concomitant use of both is contraindicated.	Clarithromycin was changed.
28.	Clarithromycin + Atorvastatin	Concurrent use may result in increased atorvastatin exposure and increased risk of myopathy or rhabdomyolysis.	Major	Inhibition of CYP3A4 mediated atorvastatin metabolism by clarithromycin.	Evaluate the risk-benefit ratio of using both of the drugs together and do not exceed atorvastatin doses of 20 mg. Regularly monitor the signs and symptoms of myopathy or rhabdomyolysis.	Atorvastatin was used at the lowest possible dose.

Conclusion:

Early detection of potential drug interactions will provide a broad picture of the risks, improve therapeutic outcomes, minimize the drug adverse effects and treatment cost, and also assist the clinicians in designing the treatment regimen. Before this initiative, the concept of drug interaction monitoring was not present in the hospital. However, with the conventional method of the study, the system has been recently updated with an automated referral system. The clinical pharmacist will be automatically informed if any patient is prescribed more than twelve drugs at a time. As the study shows a positive impact on the improvement of the patient's quality of treatment

and betterment of healthcare, this process of drug interaction monitoring and clinical pharmacy practice will be continued.

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