Early Identification and Prevention of Drug-to-Drug Interactions in a tertiary care hospital.

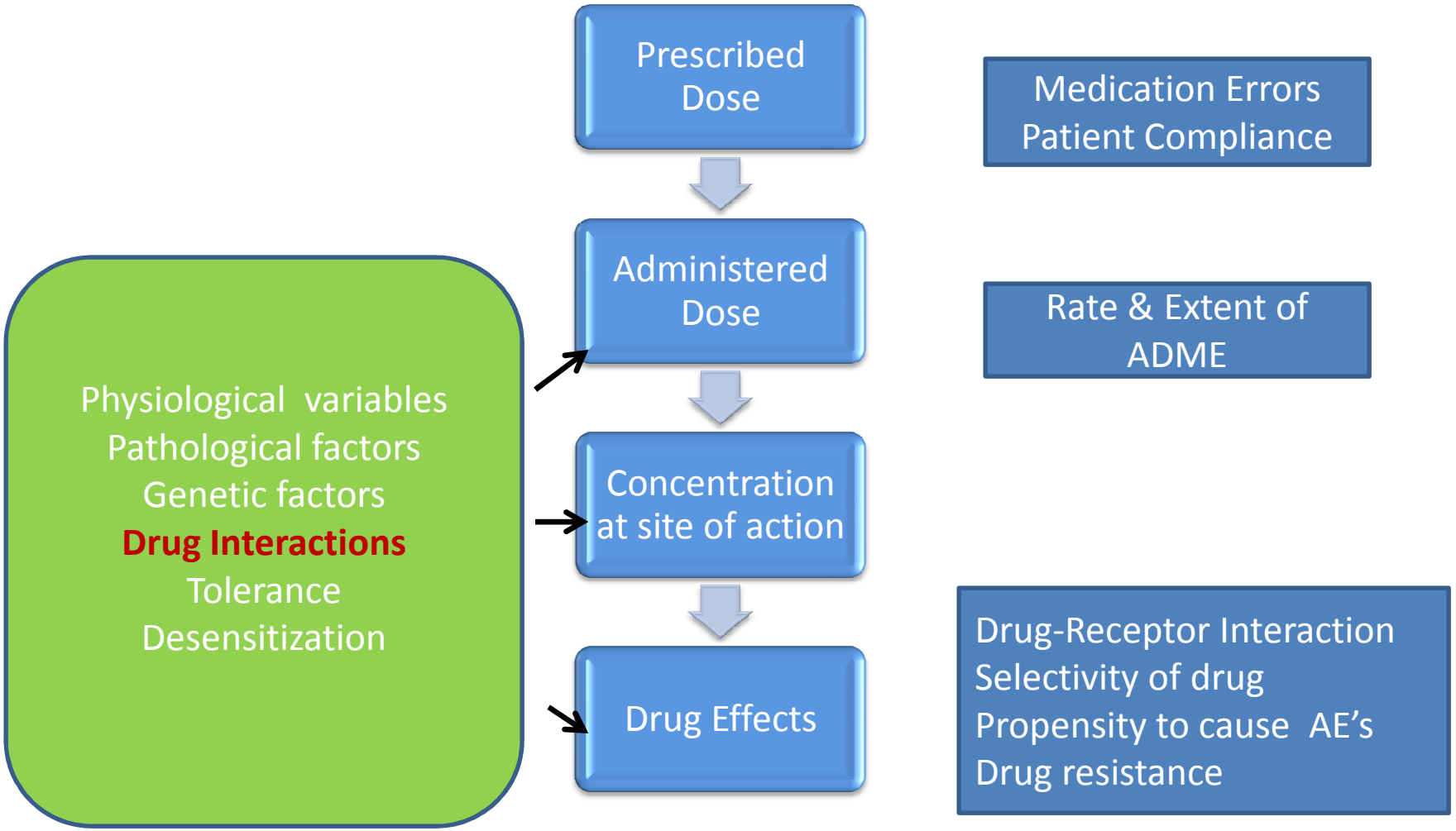
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Introduction

Therapeutic success and safety result from integrating evidence of efficacy and safety with knowledge of the individual factors that determine response in a given patient

Factors that determine drug response



- Drug interactions can occur with prescription and non-prescription drugs, as well as supplements and nutraceuticals

- Drug interactions can cause toxicity, or inhibit the drug effect

- Drug interactions always should be considered when unexpected responses to drugs occur.
- Drug interactions may be pharmacokinetic or pharmacodynamic.
- **Understanding the mechanism of drug interactions provides a framework for preventing them**

Objective

- To emphasize the importance of early identification and prevention of Drug – Drug Interactions.

Methods

- In our institute, clinicians whenever they suspect a drug related therapeutic issue, they refer the case to Dept of Clinical Pharmacology & Therapeutics, for opinion on dosage adjustment in special populations/ suspected drug-drug interactions/suspected ADRs and/or rechallenge options etc.,

- Of the cases referred in the last two years, data of the cases with potential drug to drug interactions are presented.

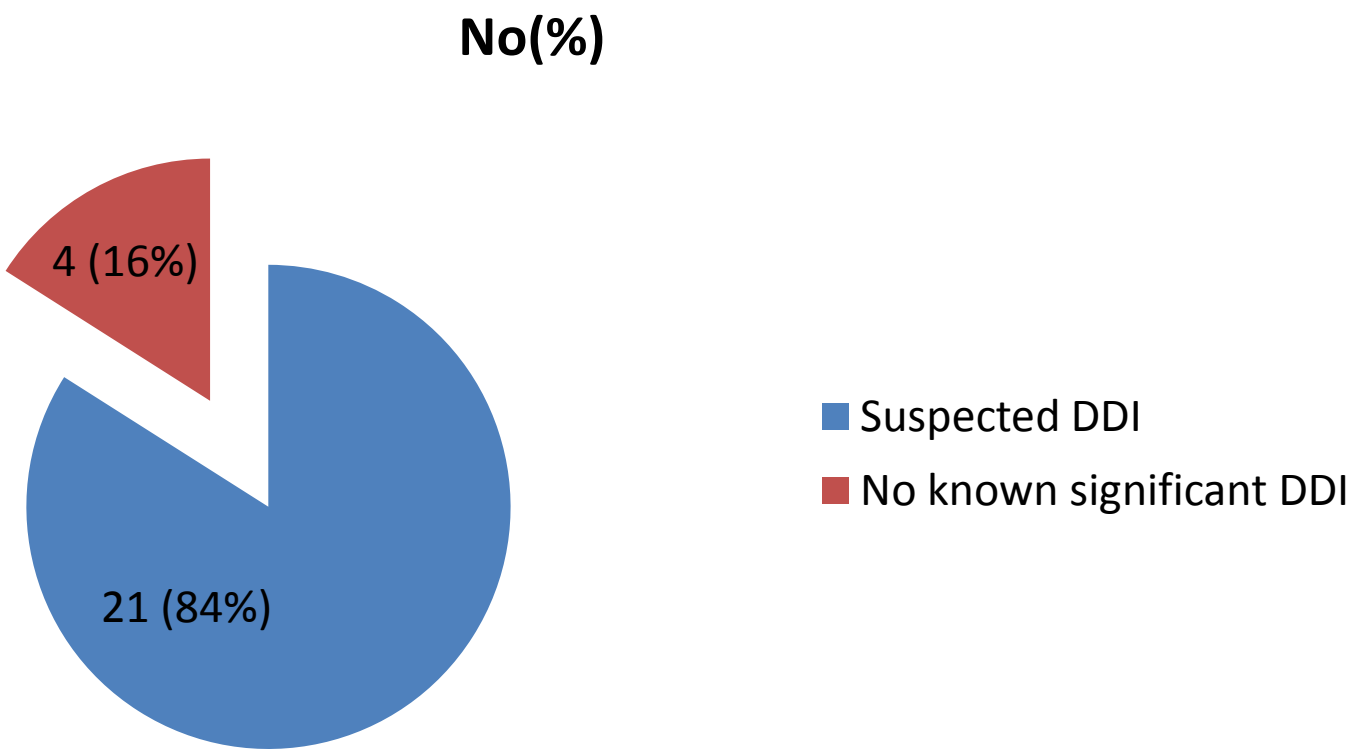
- In these cases referred, a comprehensive prescription review was done, and opinion regarding suspected drug-drug interaction , with anticipated outcomes and further management was suggested.

In this presentation, an effort is being made to present the data of cases with suspected drug to drug interactions and their clinical outcomes.

Results

- Total number of cases referred were 124 in the last two years.

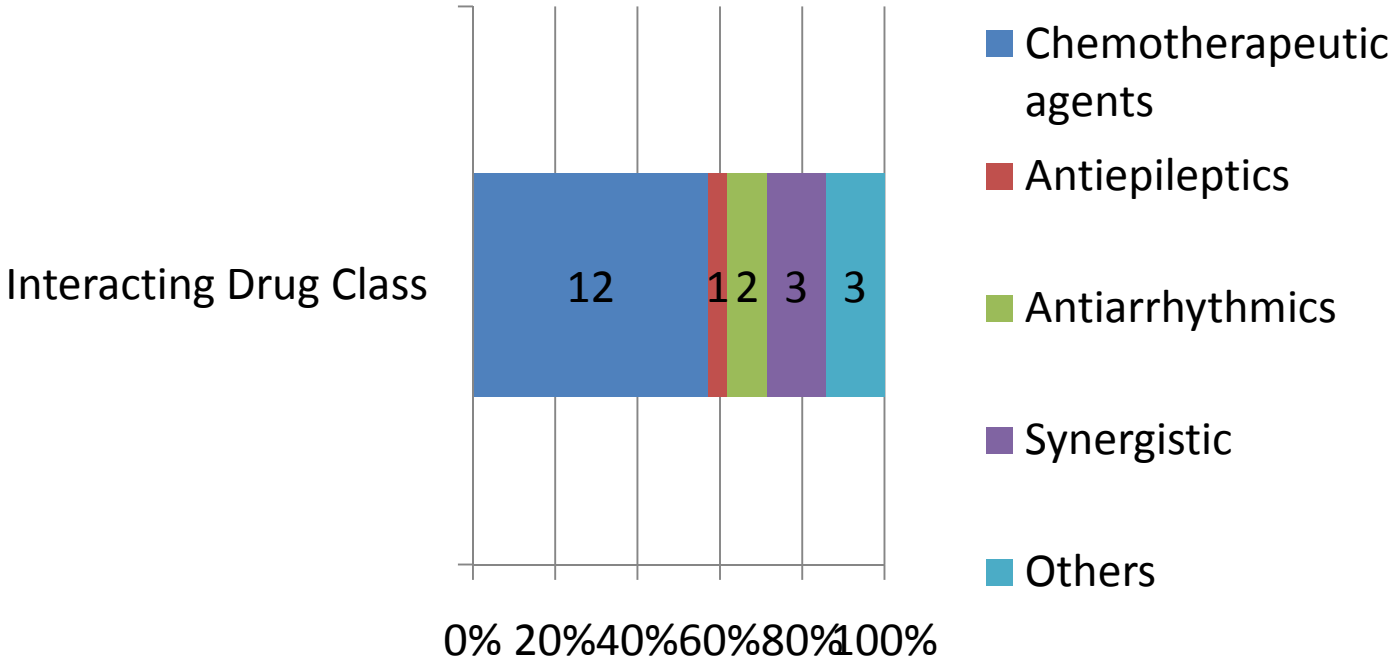
Purpose of referral	OP	IP		No of cases
		Ward	ICU	
Dosage adjustment due to renal dysfn	5	10	8	23
Dosage adjustment due to hepatic dysfn	-	3	11	14
Dosage adjustment due to both renal and hepatic dysfn	1	2	6	9
Drug-drug Interactions	**7**	**8**	**10**	**25**
Guiding therapy acc to STG	2	8	16	26
ADR (Rechallenge suggestions)	3	17	7	27
Total	18	48	58	124

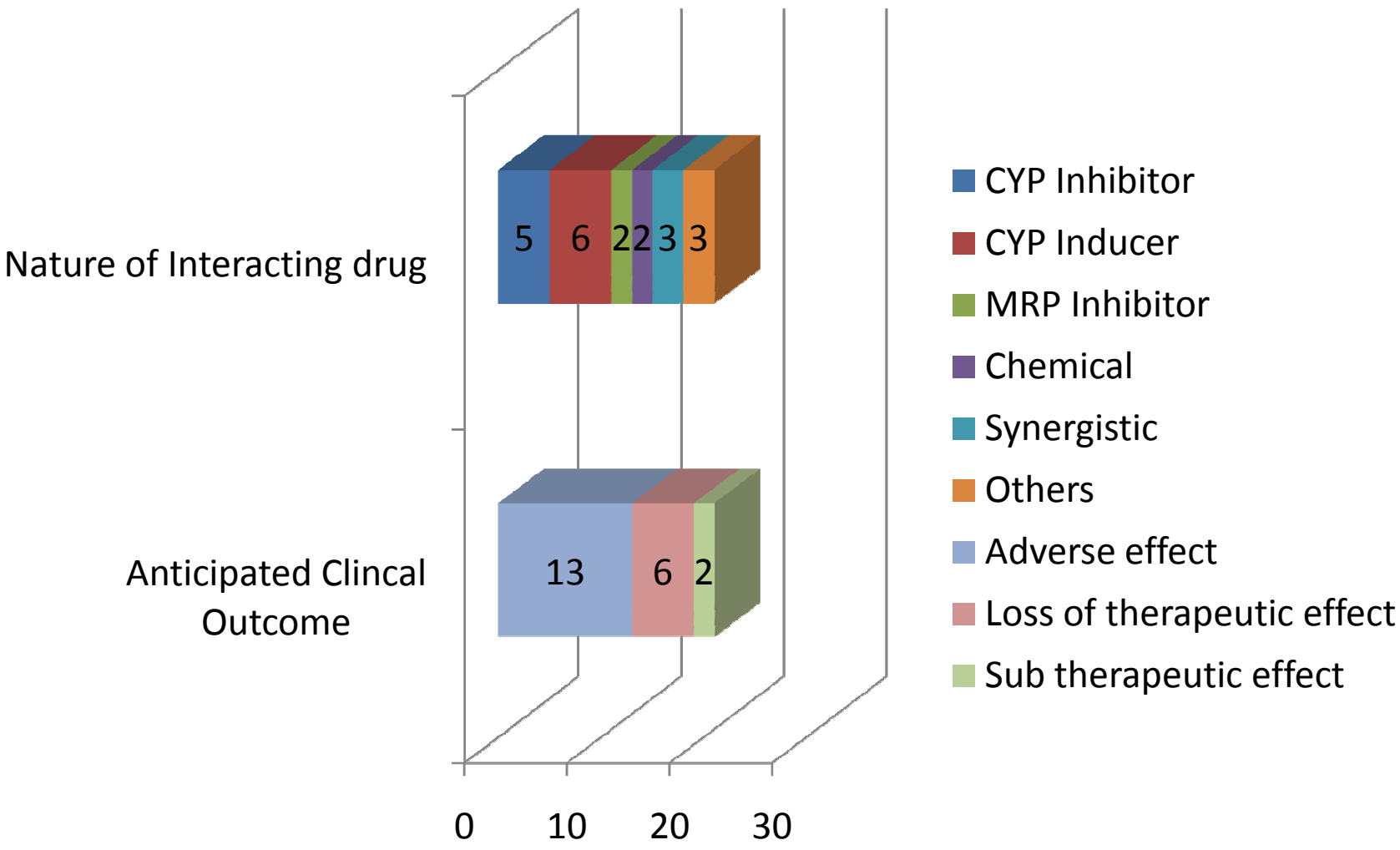

No(%)
4 (16%)
21 (84%)
Suspected DDI
No known significant DDI

Patient Characteristics (n=21)

Mean Age	**41.9 yrs**
Gender Male Female	 11 (52.4%) 10 (47.6%)
Mean number of drugs prescribed OP Ward ICU	 6.5 8.3 10.1

Drug- Drug Interaction Details (n=21)




Nature of Interacting drug
Anticipated Clincal Outcome
5
6
2
2
3
3
13
6
2
0
10
20
30
CYP Inhibitor
CYP Inducer
MRP Inhibitor
Chemical
Synergistic
Others
Adverse effect
Loss of therapeutic effect
Sub therapeutic effect

CYP Inhibitor mediated interactions

- Voriconazole – Warfarin
- Ritonavir – Attorvastatin
- Ketoconazole – Sulphonylureas
- Ritonavir – Rifabutin
- Amiodarone - Warfarin

CYP Inducer mediated interactions

- Rifampcin – Fluconazole
- Rifampcin – Voriconazole
- Carbamazepine – Warfarin
- Rifampcin – Lopinavir/r
- Rifampcin - Nevirapine
- Ritonavir – Phenytoin

MRP Inhibitor mediated interactions

- Ganciclovir – Tenofovir
- Ritonavir - Tenofovir

Synergistic interactions

- Amphotericin B – Amikacin
- Moxifloxacin – Quetiapine
- Ganciclovir – Zidovudine

Chemical interactions

- Sucralfate – Levofloxacin
- Fe + Multivit - Levofloxacin

Other mechanisms

- Amiodarone – Digoxin
- Pencillin V – Warfarin
- Ganciclovir – Amphotericin B

- Ganciclovir- Tenofovir
- Voriconazole- Warfarin
- Ritonavir- Tenofovir
- Ritonavir- Attorvastatin
- Ketoconazole – Sulphonylureas
- Amiodarone – Digoxin
- Pencillin V – Warfarin
- Amphotericin B – Amikacin
- Moxifloxacin – Quetiapine
- Ritonavir – Rifabutin
- Ganciclovir- Zidovudine
- Ganciclovir- Amphotericin B
- Amiodarone- Warfarin

Adverse effects

- Rifampcin – Fluconazole
- Rifampcin- Voriconazole
- Ritonavir- Phenytoin
- Carbamazepine – Warfarin
- Lopinavir/r – Rifampcin
- Rifampcin – Nevirapine
- Fe + mulltivit – Levofloxacin
- Sucralfate - Levofloxacin

Loss of Therapeutic effect

Mechanism of interactions causing adverse effects (n=13)

Pharmacokinetic interactions (n=8)

- Ganciclovir- Tenofovir
- Voriconazole- Warfarin
- Ritonavir- Tenofovir
- Ritonavir- Attorvastatin
- Ketoconazole – Sulphonylureas
- Amiodarone – Digoxin
- Ritonavir – Rifabutin
- Amiodarone- Warfarin

Pharmacodynamic interactions (n=5)

- Pencillin V – Warfarin
- Amphotericin B – Amikacin
- Moxifloxacin – Quetiapine
- Ganciclovir- Zidovudine
- Ganciclovir- Amphotericin B

Mechanism of interactions causing loss of effect

- All the interactions that lead to loss of therapeutic effect/ subtherapeutic were **pharmacokinetic** by mechanism

Rifampcin – Fluconazole

Rifampcin- Voriconazole

Ritonavir- Phenytoin

Carbamazepine – Warfarin

Rifampcin - Lopinavir/r

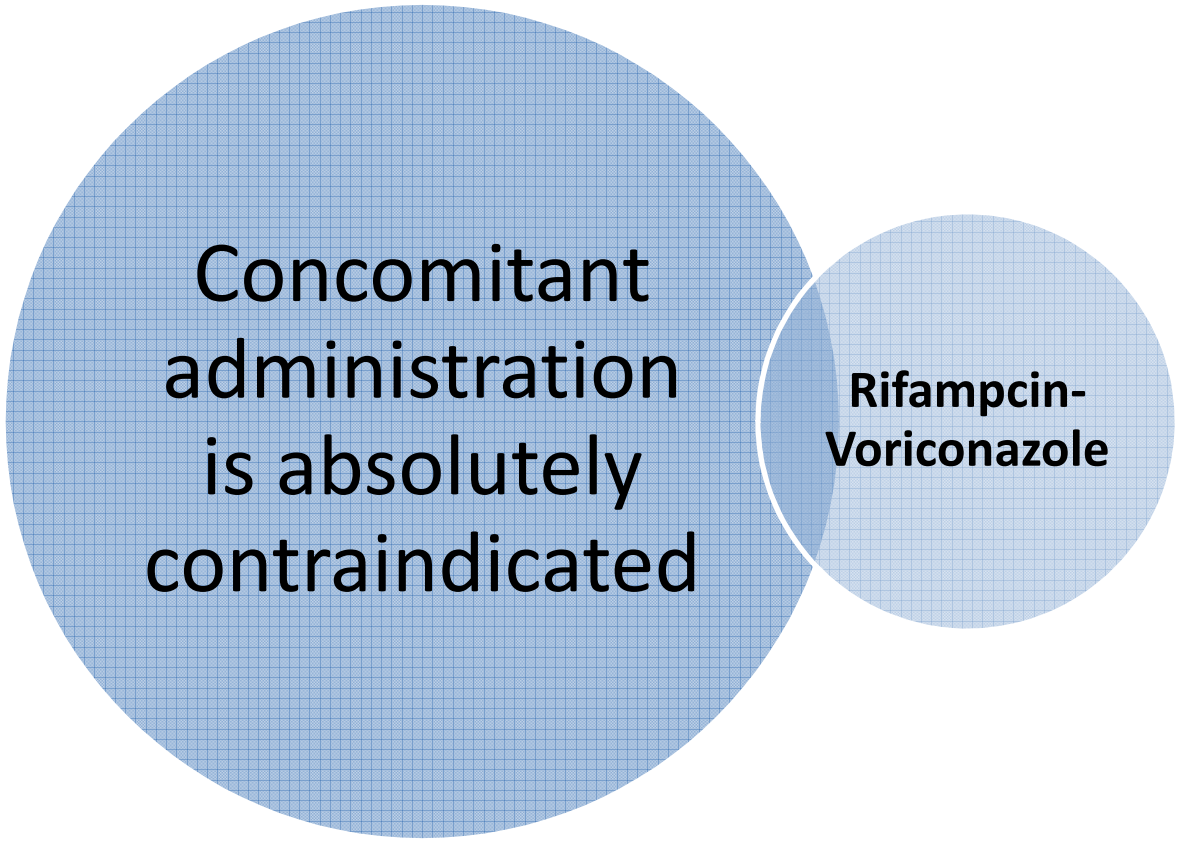
Rifampcin – Nevirapine

Fe + mulltivit – Levofloxacin

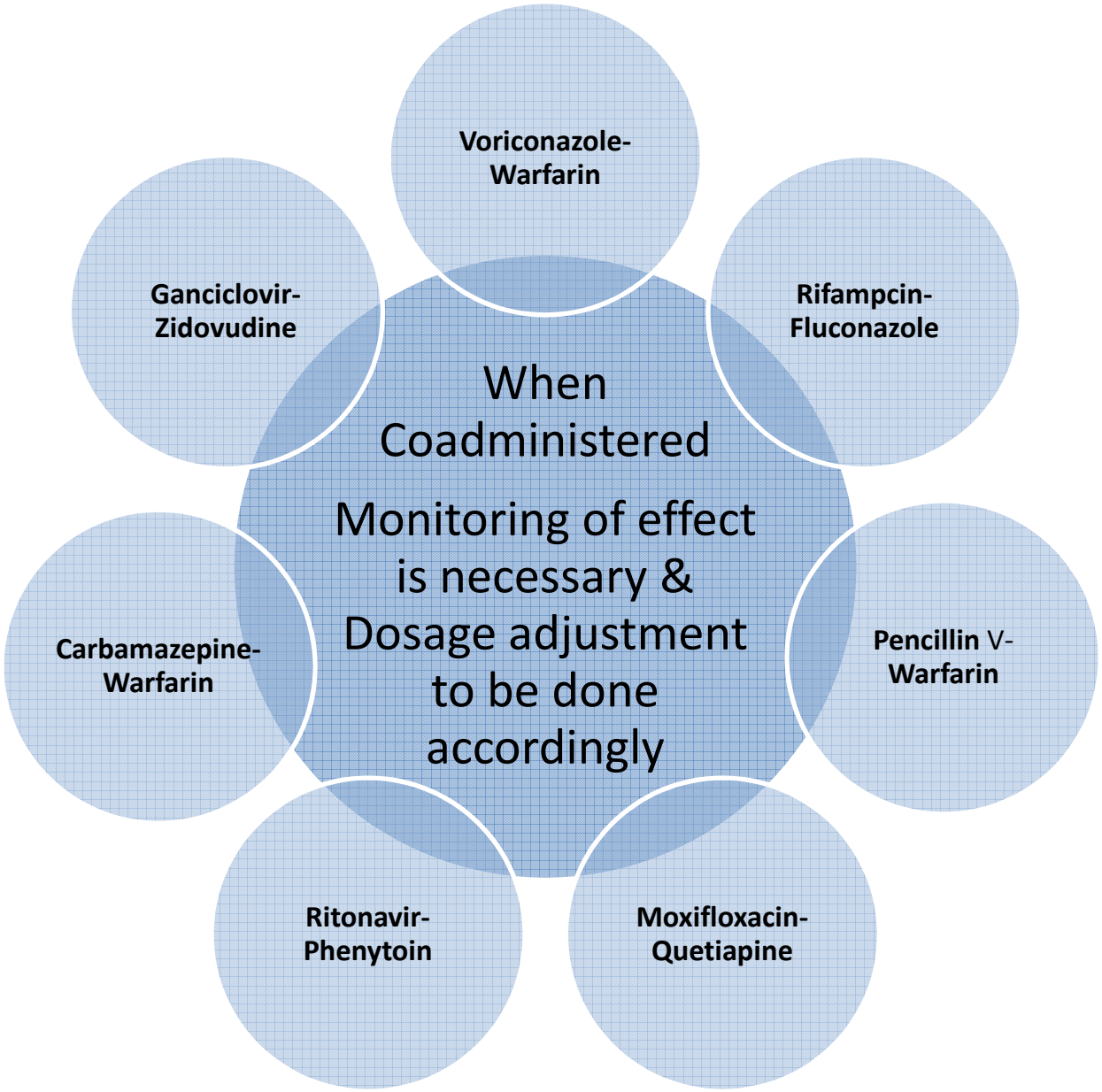
Sucralfate - Levofloxacin

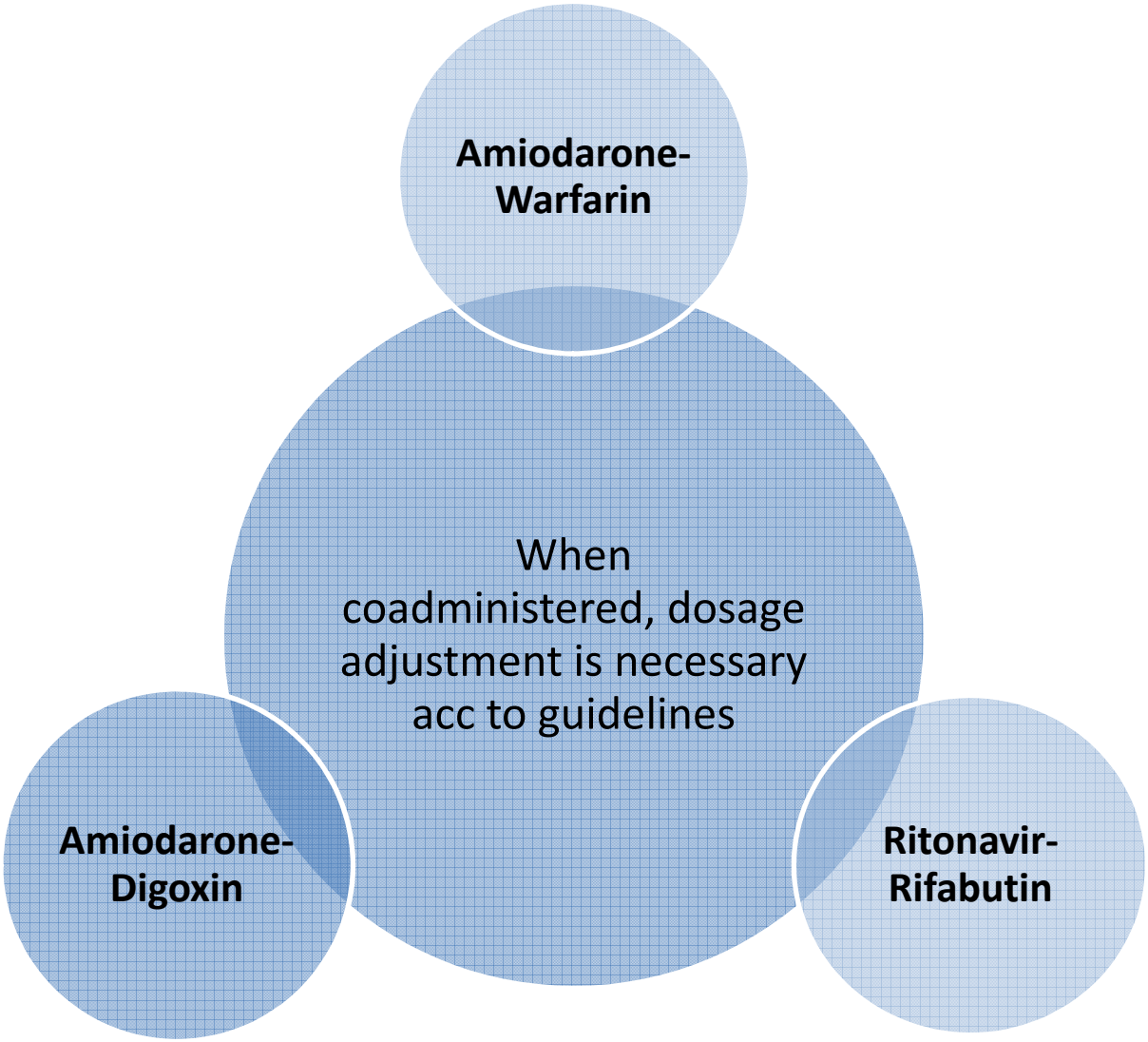
Strategies that need to be employed when drug interactions are suspected among the prescribed drugs

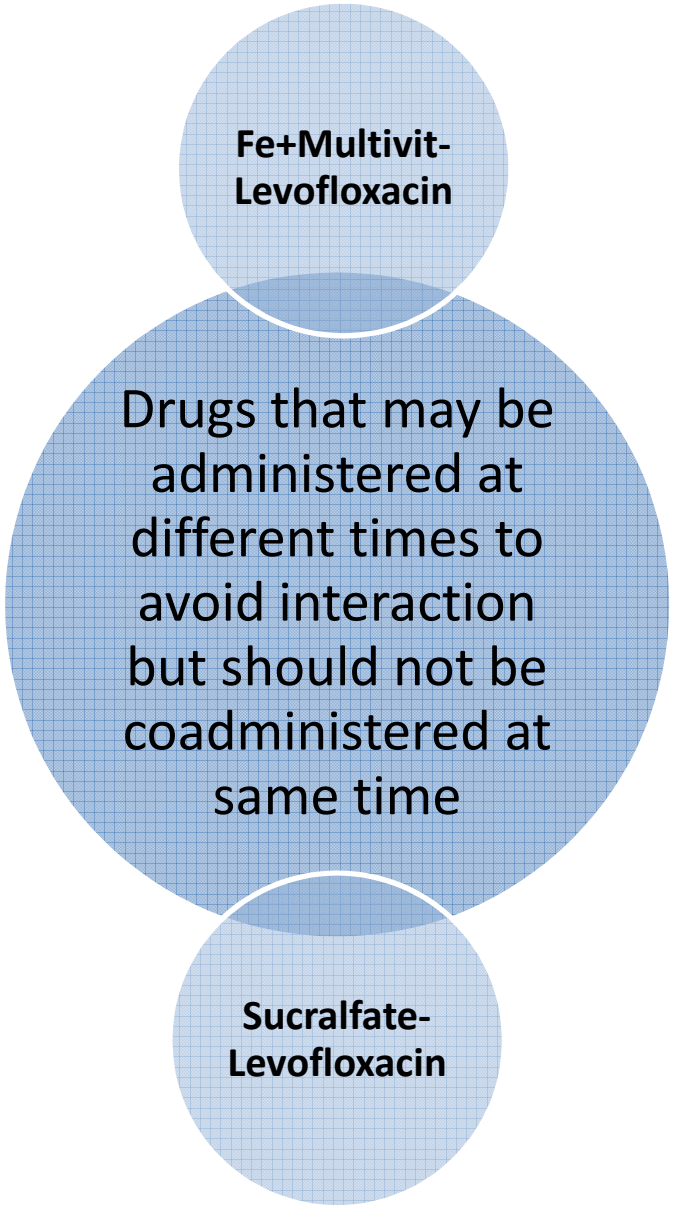
1. When coadministration is contraindicated, one of the interacting drugs must be withdrawn.
2. When coadministration needs to be avoided, one of the interacting drugs may be withdrawn
3. In some cases, the drugs if coadministered, intensive monitoring of anticipated effect is to be done and dosage of the interacting drugs may be tailored accordingly.
4. In some cases, if the interacting drugs are to be coadministered, dosage adjustment is required, in such cases dosage may be adjusted according to the guidelines
5. In some cases, coadministration of interacting drugs should not be done, but administration of the drugs at different times is needed to avoid the interaction.


Concomitant administration is absolutely contraindicated
Rifampcin-Voriconazole


Concomitant administration of drugs needs to be avoided
Ganciclovir-tenofovir
Ritonavir-Tenofovir
Ritonavir-Attorvastatin
Ketoconazole-Sulphonylureas
Amphotericin B-Amikacin
Ganciclovir-AMphotericinB
Rifampcin-Lopinavir/r
Rifampcin-Nevirapine


When Coadministered
Monitoring of effect is necessary & Dosage adjustment to be done accordingly
Voriconazole-Warfarin
Rifampcin-Fluconazole
Pencillin V-Warfarin
Moxifloxacin-Quetiapine
Ritonavir-Phenytoin
Carbamazepine-Warfarin
Ganciclovir-Zidovudine


Amiodarone-Warfarin
When coadministered, dosage adjustment is necessary acc to guidelines
Amiodarone-Digoxin
Ritonavir-Rifabutin


Fe+Multivit-Levofloxacin
Drugs that may be administered at different times to avoid interaction but should not be coadministered at same time
Sucralfate-Levofloxacin

Outcomes of Drug Interactions

S.No	Drug – Drug Interaction	Outcome
1	Tenofovir-Ganciclovir Ritonavir- Tenofovir	Elevated Serum Creatinine & Blood Urea leading to acute kidney injury
2	Rifampcin-Voriconazole	Patient who was recovering from CNS aspergillosis, suddenly deteriorated after 20 days of starting ATT
3	Amiodarone - Warfarin	PT was prolonged and INR raised to 8, warfarin was stopped and with PT INR monitoring was restarted after 5 days at a lower dose
4	Ritonavir- Phenytoin	With the optimal dose of phenytoin, the patient's seizures were not under control

S.No	Drug-Drug Interaction	Anticipated outcome
1	Ritonavir-Attorvastatin	↑conc of attorvastatin may lead to rhabdomyolysis
2	Amiodarone-Digoxin	↑Conc of digoxin may lead to digoxin toxicity
3	Amphotericin B -Amikacin	Both drugs are nephrotoxic, so may cause synergistic nephrotoxicity
4	Ganciclovir-Amphotericin B	can cause nephrotoxicity
5	Sucralfate- Levofloxacin Fe+Multivit - Levofloxacin	Can reduce absorption of Levofloxacin, and lead to subtherapeutic conc , resulting in loss of efficacy & dev of resistance as well.

Drug- Drug Interactions that were identified on day one

S.No	Drug-Drug Interactions	Anticipated outcomes that were prevented
1	Rifampcin- Fluconazole	↓ conc of fluconazole, causing subtherapeutic effect
2	Ketoconazole- Sulphonylureas	Can ↑ conc of sulphonylureas, leading to hypoglycemic events
3	PencillinV- Warfarin Voriconazole- Warfarin	↑efficacy of warfarin, causing bleeding episodes
4	Moxifloxacin- Quetiapine	Both the drugs prolong QTc, can cause Torsades pointes
5	Ritonavir -Rifabutin	↑ conc of rifabutin, leading to untoward effects
6	Ganciclovir-Zidovudine	Both cause pancytopenia, so can cause synergistic toxicity
7	Rifampcin -Lopinavir/r	↓conc of ritonavir, making lopinavir ineffective
8	Rifampcin- Nevirapine	↓ Nevirapine conc, making it ineffective
9	Carbamazepine-Warfarin	↓ warfarin conc, causing subtherapeutic effect

Conclusion

- At our hospital, by early identification of drug-drug interactions on day one, we could prevent undesired consequences efficiently in 10 cases and
- By identifying them at a later date, we could still, stop further injury to the patients in rest of the 11 cases.
- As, Drug- Drug interactions is one such factor that can be prevented, if identified early, leading to successful therapeutic outcomes.
- Clinicians should be vigilant regarding DDIs when more than 2 drugs are prescribed and where possible refer the cases to pharmacologists for early identification.

Thank you