CHAPTER

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Important Drug Interactions Every Physician Must Know

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Today's physician has to choose from a bewildering array of drugs. New drugs are formulated and introduced into the market every year. Any given patient is being treated with a multitude of drugs. The reasons for this are many; longer life spans, clustering of diseases in a patient, mushrooming of sub-specialities and the incessant promotional campaigns by pharmaceutical companies. All of this exposes patients to deleterious side effects of polypharmacy. Also, many of the commonly used drugs have clinically important interactions when used together. These interactions can decrease or enhance the efficacy of either of the two interacting drugs and predispose the patient to lower therapeutic efficacy or drug toxicity, respectively. An attempt is being made to generate awareness among physicians about important drug interactions. It is not possible to enumerate all such interactions; however, interactions of the commonly prescribed drugs viz. anti-diabetics, anti-hypertensives, cardiovascular drugs, anti-tubercular, anti-epileptic, warfarin, newer oral anticoagulants, and anti-infectives have been presented in tabular form. The detailed mechanisms of these interactions have not been discussed as we want this chapter to be a desktop, ready-reckoner for the busy physician to be used in the clinic. A summary of the very important and must-remember drug interactions is given in the end.

ANTI-DIABETIC, ANTI-HYPERTENSIVE AND CARDIOVASCULAR DRUGS

Patients with type 2 diabetes mellitus often require multifactorial pharmacological treatment due to different co-morbidities. Relevant drug interactions are predominantly related to sulfonylureas, thiazolidinediones and glinides. Metformin has a very low interaction potential. With the exception of saxagliptin, dipeptidyl peptidase-4 (DPP-4) inhibitors also show a low interaction potential. Incretin mimetics and sodium–glucose cotransporter-2 (SGLT-2) inhibitors

Table 1: Drug interactions of Anti-diabetic Drugs

Antidiabetic Drug	Interacting Drug	Clinical Effect	Clinical Relevance	Clinical Management
Sulfonylureas	Fluconazole, H2-antagonists, sulfonamides, clarithromycin, verapamil	Increased efficacy of sulfonylureas, hypoglycemia	Moderate	Dose reduction of sulfonylurea, blood glucose monitoring
	Rifampicin, phenytoin, carbamazepine	Decreased efficacy of sulfonylureas, hyperglycaemia	Moderate	Increase dose of sulfonylurea, blood glucose monitoring
	Non-selective beta-blockers	Decreased efficacy of sulfonylureas, hyperglycemia	Moderate	Blood glucose monitoring
Metformin	Iodinated contrast media	High risk of contrast induced nephropathy	High	Contraindicated 48 hours prior and 48 hours after use of contrast media
Thiazolidinediones	Calcium channel blockers, NSAIDs	Fluid retention, heart failure	High	Avoid combination, close monitoring
DPP-4 inhibitors*	Diltiazem, Atazanavir, ritonavir, clarithromycin	Increased efficacy of DPP-4 inhibitors, hypoglycemia	Moderate	Dose reduction of DPP-4 inhibitor, blood glucose monitoring
	Rifampicin	Decreased efficacy of DPP-4 inhibitors, hyperglycemia	Moderate	Increase dose of DPP-4 inhibitor, blood glucose monitoring
	GLP-1 analogues	Increased risk of pancreatitis	Moderate	Avoid use together

* Especially for Saxagliptin

Table 2: Drug Interactions of Anti-hypertensive Drugs

Drug	Interacting Drug	Clinical Effect	Clinical Relevance	Clinical Management
Beta-blockers	Verapamil, Diltiazem	Additive bradycardia, AV block	High	Avoid using together, monitor heart rate, BP and ECG
	Antidiabetic drugs, including insulin and GLP-1 analogues	Suppression of neuroglycopenic symptoms - tremor, sweating, palpitations (hypoglycemia unawareness)	High	Monitor blood sugars
	Bronchodilators	Decreased bronchodilator activity, bronchial spasm	Moderate	Avoid use in asthma, COPD. Use selective beta-blockers
Verapamil, Diltiazem	Digoxin	Increased digoxin levels, digoxin toxicity (mainly with verapamil)	High	Avoid use together, decrease digoxin dose by upto 50%, monitor digoxin levels
	Carvedilol, Metoprolol	Hepatic interaction leading to high blood levels of Verapamil	Moderate	Use atenolol, bisoprolol or nebivolol (also when using potent hepatic enzyme inducers or inhibitors)
Diuretics	Digoxin	Increased digoxin toxicity due to hypokalemia	High	Monitor blood potassium levels
	Aspirin (with thiazide diuretics)	Increased blood uric acid levels	Moderate	Monitor blood uric acid levels
	NSAIDs	Lowering of anti-hypertensive effect of loop diuretics	Moderate	Monitor BP, avoid use of NSAIDs, use acetaminophen
	Steroids	Hypokalemia, lowering of anti-hypertensive effect due to sodium retention	Moderate	Avoid use together, monitor serum potassium levels and BP, supplement potassium
	Aminoglycoside antibiotics	Ototoxicity (when used with loop diuretics)	Moderate	Avoid use together, monitor for ototoxicity
ACEIs, ARBs	Diuretics	Additive hypotensive action	Moderate	Monitor BP closely, do not use together in volume depleted patients
	Potassium sparing diuretics	Hyperkalemia when used together	High	Monitor blood potassium levels, avoid use together in renal function derangement

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Table 2: Drug Interactions of Anti-hypertensive Drugs

Drug	Interacting Drug	Clinical Effect	Clinical Relevance	Clinical Management
	ACEIs, ARBs	Hyperkalemia when used together	High	Monitor blood potassium levels, avoid use together in renal function derangement
	NSAIDs	Reduced antihypertensive action due to sodium and fluid retention	Moderate	Avoid use together
	High-dose aspirin	Reduced antihypertensive action due to sodium and fluid retention	Moderate	Avoid use together
Clonidine	Centrally acting depressant agents (hypnotics, tranquillizers, neuroleptics, anti-epileptics, some anti-depressants, H1-anti-histaminic agents, alcohol)	Additive sedative effects	High	Avoid use together, instruct patient to avoid driving, use machinery, prevent falls

ACEIs - Angiotensin Converting Enzyme Inhibitors, ARBs- Angiotensin Receptor Blockers, HR - Heart Rate, BP - Blood Pressure, NSAIDs - Non-Steroidal Anti-Inflammatory Drugs, HIV - Human Immunodeficiency Virus

Table 3: Drug interactions of commonly used cardiovascular drugs

Drug	Interacting Drug	Clinical Effect	Clinical Relevance	Clinical Management
Atorvastatin	Verapamil, clarithromycin itraconazole, fluconazole, ciclosporine	Rhabdomyolysis	High	Avoid use of macrolides and azoles, use rosuvastatin
Clopidogrel	Proton Pump inhibitors	Decreased efficacy of clopidogrel	Moderate	Avoid use of PPIs with clopidogrel, add aspirin or use prasugrel
Amiodarone	Digoxin	Increased digoxin concentration, Digoxin toxicity	High	Avoid use together, decrease digoxin dose by upto 50%, monitor blood digoxin levels and for clinical digoxin toxicity
Sildenafil	Nitrates	Severe hypotension	High	Contraindicated for use together
	Amiodarone, itraconazole	Increased plasma sildenafil level	Moderate	Avoid use together
Digoxin	Clarithromycin, ciclosporine, itraconazole	Increased digoxin concentration, Digoxin toxicity	High	Avoid use together, decrease digoxin dose by upto 50%, monitor blood digoxin levels and for clinical digoxin toxicity

comprise a very low interaction potential and are therefore recommended as an ideal combination partner from the clinical–pharmacologic point of view.

The vast majority of hypertensive patients are treated with antihypertensive drugs for many years. Other therapeutic agents are frequently used simultaneously, thus giving

Table 4: Drug Interactions of Warfarin

Drugs with moderate to high risk of increased INR and/or bleeding tendency when used concomitantly with warfarin

Drug	Clinical Management	Drug	Clinical Management
Metronidazole	Monitor INR when starting or stopping, decrease dose of warfarin by 30% when adding metronidazole	Methylsalicylate (topical)	Monitor INR when starting or stopping, avoid use together
Amiodarone	Monitor INR when starting or stopping, decrease dose of warfarin by 25% when adding amiodarone	Ranitidine	Monitor INR when starting or stopping, use alternative (famotidine)
Aspirin (> 6 gms/day), NSAIDs	Use lower doses of aspirin, monitor for bleeding, use COX-2 inhibotors	Rosuvastatin	Monitor INR when starting or stopping, decrease dose of warfarin by 20% when adding rosuvastatin, use atorvastatin
Clopidogrel	Monitor for bleeding	Sulfamethoxazole (with or without trimethoprim)	Severe interaction, Monitor INR, decrease dose of warfarin by 25% when adding sulfamethoxazole
Ciprofloxacin, levofloxacin	Monitor INR when starting or stopping, decrease dose of warfarin by 15% when adding ciprofloxacin	Tramadol	Monitor INR when starting or stopping, decrease dose of warfarin by 20% when adding tramadol
Phenytoin	Initially INR is increased, later on with long term use it is decreased - monitor INR, use alternative anti-epileptic drug	Lactulose	Monitor INR when starting or stopping
Clarithromycin	Monitor INR when starting or stopping, decrease dose of warfarin by 15% when adding clarithromycin	Fenofibrate	Monitor INR when starting or stopping, decrease dose of warfarin by 15% when adding fenofibrate
Lansoprazole	Monitor INR when starting or stopping	Fluconazole	Monitor INR when starting or stopping, decrease dose of warfarin by 20% when adding fluconazole
Leflunomide	Monitor INR when starting or stopping	Isoniazid	Monitor INR when starting or stopping, decrease dose of warfarin by 15% when adding isoniazid
Levothyroxine	Monitor INR when starting or stopping	Itraconazole	Monitor INR when starting or stopping, decrease dose of warfarin by 25% when adding itraconazole

rise to the possibility of drug-drug interactions. The potential for drug-drug interactions increases with rising age, since elderly patients receive larger number of drugs, but also because the renal excretion of several therapeutic agents is impaired in the elderly, as a result of diminishing kidney function. Tables 1, 2 and 3 summarise drug interactions of common anti-diabetic, anti-hypertensive and cardiovascular drugs.

DRUG INTERACTIONS OF WARFARIN

Warfarin has been the mainstay of oral anticoagulant therapy for the past 60 years and it is most commonly used to treat or prevent thrombosis or thromboembolism in patients with venous thromboembolism, atrial fibrillation and prosthetic heart valves. However, this drug is efficacious only when the dosage is maintained within a narrow therapeutic index, measured by the international normalized ratio (INR). Multiple challenges exist in appropriately achieving and maintaining therapy

Table 5: Drug Interactions of Warfarin

Drugs with moderate to high risk of decreased INR and/or clotting tendency when used concomitantly with warfarin

Drug	Clinical Management	Drug	Clinical Management
Azathioprine	Monitor INR when starting or stopping; 2 to 3 fold higher dose of warfarin may be required	Rifampicin	Monitor INR when starting or stopping; increase dose of warfarin by 25-50% when adding rifampicin
Carbamazepine	Monitor INR when starting or stopping, increase dose of warfarin by 50% when adding carbamazepine	Sulfasalazine	Monitor INR when starting or stopping; may need to increase dose of warfarin by 50%
Propylthiouracil	Monitor INR when starting or stopping	Methimazole	Monitor INR when starting or stopping

Table 6: Clinically important Drug Interactions of Anti-epileptic Drugs

What AEDs do to other drugs

AED	Interacting drug	Clinical effect	Clinical relevance	Clinical management
Carbamazepine, Phenytoin	Oral Contraceptives (OCP) (estrogen containing)	Loss of contraceptive efficacy	High	Avoid use together, use OCP with high dose oestrogen, use alternative method of contraception, use AEDs which do not interact with OCPs*
Carbamazepine	Warfarin**	Loss of warfarin efficacy, lower INR	Moderate	Avoid use, monitor INR, increase dose of warfarin, use levetiracetam, oxcarbazepine
Phenytoin	Warfarin**	Unpredictable effect, INR may increase or decrease	Moderate	Avoid use, monitor INR, use levetiracetam, oxcarbazepine
Carbamazepine, Phenytoin	Cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisolone	Reduced serum concentrations of steroids	Moderate	Monitor clinically for loss of efficacy
Carbamazepine, Phenytoin	Amiodarone, atorvastatin, digoxin, metoprolol, nifedipine, nimodipine, verapamil	Reduced serum concentrations of interacting drugs	Moderate	Monitor clinically for loss of efficacy
Carbamazepine, Phenytoin	Doxycycline, itraconazole, metronidazole, albendazole			
Valproic acid	Amitriptyline, meropenem, imipenem	Increased serum concentration of interacting drugs	Moderate	Avoid use together

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Table 6: Clinically important Drug Interactions of Anti-epileptic Drugs

What AEDs do to other drugs				
AED	**Interacting drug**	**Clinical effect**	**Clinical relevance**	**Clinical management**
What other drugs do to AEDs				
AED	Interacting drug	Clinical effect	Clinical relevance	Clinical management
Phenytoin	Rifampicin	Lower serum phenytoin levels	Moderate	Avoid use together, monitor serum phenytoin levels
Phenytoin	Clarithromycin, fluconazole, fluoxetine, isoniazid	Phenytoin toxicity	High	Avoid use together, monitor serum phenytoin levels
Phenytoin	Allopurinol, amiodarone, diltiazem, omeprazole	Phenytoin toxicity	Moderate	Avoid use together, monitor serum phenytoin levels
Carbamazepine	Rifampicin	Lower serum carbamazepine levels	Moderate	Avoid use together, monitor serum carbamazepine levels
Carbamazepine	Dextropropoxyphene	Carbamazepine toxicity	High	Avoid use together
Carbamazepine	Haloperidol, Risperidone, fluoxetine	Carbamazepine toxicity	Moderate	Avoid use together
Carbamazepine	Clarithromycin (NOT Azithromycin), fluconazole, isoniazid, metronidazole	Carbamazepine toxicity	High	Avoid use together
Carbamazepine, lamotrigine, phenytoin, valproic acid	Sertraline	AED toxicity	Moderate	Avoid use together
Valproic acid	OCP, Meropenem	Loss of efficacy of Valproic acid, seizures No effect on OCP efficacy	Moderate	Avoid use together, increase dose of valproic acid
Lamotrigine	OCP	Loss of efficacy of lamotrigine, seizures May lead to loss of OCP efficacy at doses > 300mg/day	High	Avoid use together, increase dose of lamotrigine Use other AEDs which do not interact with OCPs*
Lamotrigine	Rifampicin	Lamotrigine toxicity	Moderate	Dose reduction of lamotrigine by 50%, slow up-titration of lamotrigine
What AEDs do to other AEDs				
AED	Interacting drug	Clinical effect	Clinical relevance	Clinical management
Valproic acid	Lamotrigine	Lamotrigine toxicity	Moderate	Dose reduction of lamotrigine by 50%, slow up-titration of lamotrigdine

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Table 6: Clinically important Drug Interactions of Anti-epileptic Drugs

What AEDs do to other drugs

AED	Interacting drug	Clinical effect	Clinical relevance	Clinical management
Valproic acid	Carbamazepine	Carbamazepine toxicity	Moderate	Monitor serum levels of affected AEDs
Carbamazepine, Phenytoin	Benzodiazepines, lamotrigine, pregabalin, topiramate, valproic acid	Reduced serum concentration of interacting AEDs, Loss of efficacy of AED, breakthrough seizures	High	Monitor serum levels of affected AEDs

*Levetiracetam, pregabalin, gabapentin, valporate, and topiramate at doses < 200 mg/day do not interact with OCPs ** Oxcarbazepine and Levetiracetam have not been reported to interact with warfarin. Valproic acid may increase bleeding tendency by interfering with platelet function and clotting factor disturbances

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Table 7: Drug Interactions of Anti-tubercular Drugs

ATT Drug	Interacting Drug	Clinical Effect	Clinical Management
Rifampicin	Verapamil, Amlodipine, Nifedipine, diltiazem	Reduced levels of calcium channel blockers	Monitor BP, increase dose of calcium channel blockers, use alternative anti-hypertensive
	Beta- blockers (NOT Atenolol)	Reduced levels of beta-blockers	Monitor BP, increase dose of beta-blockers, use atenolol
	Sulfonylureas	Decreased efficacy of sulfonylureas, hyperglycaemia	Monitor blood sugar, add other drugs
	Phenytoin, carbamazepine, valproic acid, benzodiazepines	Lower serum levels of AEDs, breakthrough seizures	Monitor serum levels of AEDs
	Digoxin	Reduced serum digoxin levels	Monitor clinically and serum digoxin levels
	OCPs	Reduced efficacy of oestrogen and progesterone containing OCPs	Avoid use together, use additional method (barrier), injectable progesterone may be used
	Corticosteroids	Reduced efficacy of steroids	Increase dose of steroids
	Cyclosporine	Reduced efficacy of ciclosporine	Increase dose of ciclosporine
	Itraconazole, fluconazole, macrolides	Marked reduction in blood levels of anti-fungals	Use higher doses of anti-fungals
Isoniazid	Phenytoin, Carbamazepine	Marked rise in blood levels of phenytoin and carbamazepine, AED toxicity	Monitor clinically and blood AED levels, reduce dose
Pyrazinamide	Zidovudine	Decreased levels and efficacy of pyrazinamide, loss of efficacy in HIV-TB co-infected patients	Increase dose of pyrazinamide, avoid use of zidovudine (use Tenofovir)

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Table 7: Drug Interactions of Anti-tubercular Drugs			
	Cyclosporine	Reduced levels of ciclosporine	Increase dose of ciclosporine
	Thiazide diuretics	Increased uric acid levels in blood	Increase dose of allopurinol
Quinolones	Calcium, Iron containing oral preparations, antacids	Reduced absorption of Quinolones	Space out the drugs by 2-4 hours
	Drugs that prolong QT interval**	Further QT prolongation, risk of TDP	Avoid use together, monitor by ECG, Moxifloxacin is contraindicated
	Amiodarone	Increased risk of arrhythmia	Avoid use together

**Drugs that prolong QT interval: Imidazoles, tricyclic antidepressants, atypical antipsychotics, amiodarone & other anti-arrhythmics, some antidepressants (citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, trazodone, venlafaxine) alfuzosin, chlorpromazine & domperidone, galantamine, haloperidol, indapamide, lithium, methadone, quinine sulphate, tamoxifen, tizanidine, co-trimoxazole. Other Non-drug risk factors for prolonged QT interval: Family history, electrolyte abnormalities (hypokalaemia, hypocalcaemia, hypomagnesaemia), cardiac ischaemia, cardiomyopathies, hypothyroidism and hypoglycaemia.

Table 8: Drug Interactions of common Anti-infective agents			
Anti-infective Drug	**Interacting Drug**	**Clinical Effect**	**Clinical Management**
Clarithromycin, Azithromycin	Atorvastatin	Risk of rhabdomyolysis	Avoid use together, use rosuvastatin
	Warfarin*	Increased INR, bleeding tendency	Monitor clinically and by INR
	NOACs - Dabigatran, Rivaroxaban, Apixaban	Increased risk of bleeding	Monitor clinically
	Phenytoin, carbamazepine	Increased blood levels of AED with clarithromycin and erythromycin, AED toxicity	Avoid use together, monitor clinically and blood AED levels, use Azithromycin
	Drugs that prolong QT interval**	Further QT prolongation, risk of TDP	Avoid use together, monitor by ECG
Trimethoprim and Co-trimoxazole	Warfarin*	Increased INR, bleeding tendency	Monitor clinically and by INR
	Methotrexate	Methotrexate toxicity	Monitor clinically for signs of liver and haematological toxicity
	Amiodarone	Increased rosk of arrhythmia	Avoid use together
Itraconazole, Fluconazole	Atorvastatin	Risk of myopathy	Avoid use together
	Warfarin	Increased INR, bleeding tendency	Monitor clinically and by INR
	NOACs - Dabigatran, Rivaroxaban, Apixaban	Increased risk of bleeding	Not recommended, Monitor clinically
	Drugs that prolong QT interval**	Further QT prolongation, risk of TDP	Avoid use together, monitor by ECG
Linezolid	Rifampicin	Low blood levels of linezolid, therapeutic failure	Increase dose of linezolid, use alternative antibiotic
Meropenem	Valproic acid	Reduced blood levels of valproic acid, loss of seizure control	Contraindicated

NOACs - Newer Oral AntiCoagulants, TDP - torsades de pointes, INR - International Normalised Ratio, PPIs - Proton Pump Inhibitors; *Penicillins and cephalosporins are preferred drugs when patients are on warfarin and NOACs

Table 9: Very Important Drug Interactions of the "Red Alert" Drugs - Summarised

Drug	Comments
Warfarin	Monitor INR and patient closely when adding metronidazole, ciprofloxacin, co-trimoxazole, clarithromycin, doxycycline, fluconazole, azathioprine, rifampicin, isoniazid, carbamazepine, phenytoin, sulfasalazine, amiodarone Adjust dose of warfarin, at the outset, when adding these drugs Switch to LMWH or UFH
Atorvastatin	Do not use with verapamil, clarithromycin, itraconazole, fluconazole, ciclosporine Monitor CPK levels Switch to rosuvastatin (with warfarin, atorvastatin may be better) when adding any of these drugs
Clarithromycin	Do not use with atorvastatin, digoxin, warfarin, dabigatran, rivaroxaban, apixaban, colchicine, phenytoin, carbamazepine and drugs that prolong QT interval May use azithromycin or other antibiotic in patients taking any of these drugs
Itraconazole, Fluconazole	Do not use with atorvastatin, dabigatran, rivaroxaban, apixaban, digoxin Use carefully with warfarin, carbamazepine, phenytoin, rifampicin
Digoxin	Do not use with clarithromycin, itraconazole, ciclosporine, verapamil, diltiazem Use carefully with diuretics, amiodarone, rifampicin, phenytoin, carbamazepine
Rifampicin, Isoniazid	Use carefully with hepatotoxic drugs Use carefully with phenytoin, carbamazepine, warfarin, digoxin, calcium channel blockers, oral contraceptives, corticosteroids, sulfonylureas, macrolide antibiotics, azole antifungals
Carbamazepine, phenytoin	Do not use with clarithromycin, oral contraceptive pills Use carefully with warfarin, itraconazole, isoniazid, rifampicin
Amiodarone	Use carefully with digoxin, warfarin, carbamazepine, phenytoin and drugs that prolong QT interval
Sildenafil	Do not use with nitrates
Allopurinol	Do not use with azathioprine

LMWH - Low Molecular Weight Heparin, UFH - UnFractionated Heparin, CPK - Creatine Phospho-Kinase

within this narrow index. Recent data have identified genetic variants that may reduce a person's requirement for warfarin.Furthermore, once a suitable dosage of warfarin has been established, control of therapy can be affected by changes in intake of vitamin K, development of acute medical conditions (e.g., fever, diarrhea), changes in certain chronic medical conditions (e.g., heart failure) and interactions with prescription, nonprescription and herbal products. Tables 4 and 5 list important interactions of warfarin with other drugs.

CLINICALLY IMPORTANT DRUG INTERACTIONS INVOLVING ANTI-EPILEPTIC DRUGS (AEDS)

Patients with difficult-to-treat epilepsy benefit from combination therapy with two or more antiepileptic drugs (AEDs). Additionally, virtually all epilepsy patients will receive, at some time in their lives, other medications for the management of associated conditions. In these situations, clinically important drug interactions may occur. Carbamazepine and phenytoin induce many cytochrome P450 (CYP) and glucuronyl transferase (GT) enzymes, and can reduce drastically the serum concentration of associated drugs which are substrates of the same enzymes. Valproic acid may cause clinically relevant drug interactions by inhibiting the metabolism of selected substrates, most notably lamotrigine and carbamazepine. Compared with older generation agents, most of the recently developed AEDs are less likely to induce or inhibit the activity of CYP or GT enzymes. Levetiracetam, gabapentin and pregabalin have not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions. The interactions listed below are not complete and may be variable in each individual patient. Hence, close clinical monitoring and measurement of serum levels of the affected drug is warranted. Table 6 lists the important interactions of anti-epileptic drugs.

ANTI-TUBERCULAR DRUGS AND THEIR INTERACTIONS

The most well-known drug interaction of anti-tubercular drugs is amongst themselves - hepatitis - caused by combined hepatotoxic potential of isoniazid, rifampicin, and pyrazinamide. When one considers the drugs used for the treatment of tuberculosis, the important interactions are almost exclusively caused by rifampicin. Rifampicin is a potent liver enzyme inducer that increases the activity of the microsomal enzymes so that the pace of metabolism and excretion of other drugs metabolised by the same enzyme system is increased. Isoniazid is an enzyme inhibitor. Ethambutol and pyrazinamide have few significant drug interactions. Table 7 enumerates the common and important interactions of anti-tubercular drugs.

DRUG INTERACTIONS OF COMMONLY USED ANTI-INFECTIVE DRUGS

Antibiotics and antifungals are prescribed very commonly and on top of many other drugs which the patient is already consuming. Therefore, drug interactions are bound to occur and patient may have adverse consequences. Listed below (Table 8) are some of the commonly used antibiotics and anti fungal drugs and their important drug interactions.

MANAGING DRUG INTERACTIONS

Because of the variability in individual metabolism, many interactions will not be obvious in most individuals, but when an interaction occurs, it may lead to considerable morbidity, or mortality. The usual way to manage the potential interaction is through conscientious monitoring and general awareness of the clinical symptoms of toxicity. If a new medicine has been added and a new symptom occurs, be suspicious of an interaction, not just an adverse effect. When about to prescribe a potentially interacting medicine (see red alert drugs and Table 9 below), one should ask the following questions:

1. Is the combination really necessary—what are the alternatives?
2. What are the likely adverse effects of high dosages of the target medicine (how hazardous)?
3. What clinical monitoring does the patient need to know about to report back to you?
4. What objective monitoring needs to be done, and when?

THE "RED ALERT" DRUGS

The following medicines should 'ring alarm bells' as having important interactions:

- Warfarin
- Statins - atorvastatin
- Macrolide antibiotics - clarithromycin, azithromycin
- Calcium channel blockers - verapamil, diltiazem
- Azole antifungals - itraconazole, fluconazole
- SSRIs - fluoxetine
- Amiodarone
- Digoxin
- Rifampicin, Isoniazid
- Antiepileptic medicines - particularly carbamazepine, phenytoin; less so valproate

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