Which drug-drug interactions the General Practitioners should know

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Martin CS Wong MBChB, MD, MPH, MSc, MBA, FHKAM (Fam Med)
School of Public Health and Primary Care
Faculty of Medicine
Chinese University of Hog Kong

Outline of content

- **Introduction:**
  - What is drug-drug interaction?
  - What is polypharmacy?
- **Issues on drug-drug interaction in various areas:**
  - Who are more vulnerable to drug-drug interaction?
  - What are the most common drug-drug interactions?
  - Drug-related factors and underlying mechanisms of interactions
  - Strategies to avoid drug-drug interaction
- **Future direction of development to enhance safer prescriptions**

Common drugs used in GP

- Antihypertensive agents
- Oral hypoglycemic agents
- Lipid-lowering agents
- Anticonvulsants
- Psychiatric medication –
  - antidepressants, anxiolytics, antipyschotics
- Antibiotics
- Oral contraceptive pills
- Aspirin
- Warfarin

What is drug-drug interaction

- **Drug-drug interaction:**
  - Possible whenever a person takes two or more medications concurrently.
  - A situation in which a substance (e.g. a drug) affects the activity of a drug when both are administered together.
- A large number of drugs are introduced every year, and new interactions between medications are increasingly reported

What is drug-drug interaction

- **Precipitant drugs** modify the **object drug**'s absorption, distribution, metabolism, excretion, or actual clinical effect.
- **Precipitant drugs**
  - **Nonsteroidal anti-inflammatory drugs, antibiotics** and, in particular, **rifampicin** are common precipitant drugs prescribed in primary care practice.
- **Object drugs**
  - Drugs with a **narrow therapeutic range** or **low therapeutic index** are more likely to be the objects for serious drug interactions.
  - Object drugs in common use include **warfarin**, **fluoroquinolones**, **antiepileptic drugs**, **oral contraceptives**, **cisapride,** and **3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors**[1].

1. Ament PW, Bertolino JG, Liszewski JL. Am Fam Physician. 2000 Mar 15; 61(6):1745-54.

Polypharmacy

- **Poly-pharmacy**
  - The simultaneous use of multiple drugs to treat a single ailment or condition.
  - Polypharmacy is becoming more and more common in our locality due to the emergence of multi-morbidities in the population.
  - Potential drug-drug interactions have increased over time and there are particular at-risk groups who are more vulnerable to **the consequences** of these interactions
    - Elderly; psychiatric patients, ≥ 5 drugs; multiple physicians/pharmacists; recently hospitalized patients; multiple comorbidities, low education level, impaired vision

What is drug-drug interaction

- **Types of pharmacological interactions:**
  - **Synergistic**: When the interaction causes an increase in the effects of one or both of the drugs
  - **Antagonistic**: When the interaction causes a decrease in the effects of one or both of the drugs
  - A **new effect** can be produced

1. Montané E, Barriocanal A, Isern I, Parajon T, Costa J. J Clin Pharm Ther. 2009 Aug; 34(4):485-7.

Categories of drug-drug interactions

- There are a number of mechanisms by which drugs interact with each other
- Most of them can be divided into 2 general categories
- Either type of drug interaction can result in adverse effects in some individuals.

- **Pharmaco-dynamic:**
  - When one drug enhances or decreases the effect of another drug at its **site of action** without altering the drug's concentration in the body.
  - When pharmacodynamic drug interactions occur, two drugs have additive or antagonistic pharmacologic effects.
  - E.g. **Propranolol** (a β -blocker) diminishes the effect of **albuterol** (a β -agonist) through antagonism at the β -2 receptor site in the lungs[1,2].

1. Tatro DS: Drug Interaction Facts. St. Louis, Mo., Facts and Comparisons, 2000
2. Hansten PD, Horn JR: Drug Interactions Analysis and Management: A Clinical Perspective and Analysis of Current Developments. St. Louis, Mo., Facts and Comparisons, 2002Kroner BA. Common drug pathways and interactions. Diabetes Spectrum 2002 Fall 2002;15(4):249.

Categories of drug-drug interactions

- **Pharmacokinetic:**
  - When one drug enhances or interferes with the absorption, distribution, metabolism, or excretion of another drug resulting in a change in **drug concentration in the body**.
  - E.g. The ability of **phenobarbital** to decrease the effect of **warfarin** by increasing its metabolism through hepatic enzyme induction.
- As most drugs are **detoxified by the liver**, the most important of the pharmacokinetic drug interactions involve **drug metabolism**.
- This is **influenced by genetics**, which explains why some patients suffer adverse consequences from some drug combinations and others do not.

Metabolism of medications

- **Cytochrome P450 (CYP450) enzyme system**
  - Responsible for the oxidative-reductive metabolism of medications.
  - Primarily concentrated in the liver & small intestines.
  - Four isoenzymes (CYP3A4, CYP2C9, CYP1A2, and CYP2D6) are responsible for the majority of drug metabolism[1].
- **CYP3A4** metabolizes the greatest number of medications and endogenous substances in the body
  - accounting for most CYP450 enzymes in the liver and small intestines (60% & 70%, respectively)[2].
- **Substrate**
  - A substrate is the medication being metabolized by the enzyme system.
  - E.g. **Warfarin, statins** (e.g. lovastatin [Mevacor] and simvastatin [Zocor]), and **theophylline** are examples of substrates.

1. Bottoroff M, Hansten P: Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors: the role of metabolism-monograph for physicians. Arch Intern Med 160:2273–2280, 2000
2. White CM: An evaluation of CYP3A4 drug interactions with HMG-CoA reductase inhibitors. Formulary 34:343–352, 2000

CYP450 Isoenzymes

- **Enzyme Inhibitor: drug toxicity**
  - A medication that decreases enzyme activity and leads to increased concentrations of the substrate.
  - E.g. Some **macrolide antibiotics** (e.g., erythromycin and clarithromycin [Biaxin]), **cimetidine** (Tagamet), and **azole antifungals** (e.g., fluconazole [Diflu-can], itraconazole [Sporanox], and ketoconazole [Nizoral]).

- **Enzyme Inducer: ↓effectiveness of medications**
  - medication that increases the number of enzymes and leads to decreased concentrations of the substrate. Notorious enzyme inducers are **rifampicin** (Rifadin, Rimactane), **carbamazepine** (Tegretol), **phenytoin** (Dilantin), and **phenobarbital.**

Epidemiology

In the UK,

- By estimation, ~1 /10 admissions to geriatric units involved a drug-related illness
- About 1/3 of these patients later considered that they had not recovered fully from the adverse effect or drug interaction [1]

In the US,

- Prevalence of polypharmacy in the older people is around 68% in 2006 [2]

In Hong Kong,

- There is an increase in the prevalence of polypharmacy in older adults from **32%** more than a decade ago to **65%** in 2010 [3]

[1] Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. Age Aging 1980; 9: 73-80.
[2] Streinman MA, Landefeld CS, Rosenthal GE, et al. Polypharmacy and prescribing quality in older people. J Am Geriatr Soc 2006;54:1516-1523.
[3] Ko CF, Ko PS, Tsang ML. A survey on the polypharmacy and use of inappropriate medication in a geriatric out-patient clinic. J Hong Kong Geriatr Soc 1996; 7:28-31.

Antihypertensive drugs

Table 3. Frequently reported side-effects of antihypertensive drugs*

Class of drug	Symptoms
Diuretics, e.g. bendrofluazide, frusemide	Impotence, decreased libido, lethargy, constipation, nausea, dizziness
Beta-adrenoceptor blocking drugs, e.g. propranolol, atenolol	Bradycardia, bronchospasm, peripheral vasoconstriction, gastrointestinal disturbances, fatigue, sleep disorders
Vasodilator antihypertensive drugs, e.g. hydralazine hydrochloride	Tachycardia, fluid retention, nausea and vomiting, headache
Centrally acting antihypertensive drugs, e.g. methyldopa	Dry mouth, depression, drowsiness, diarrhoea, fluid retention, failure of ejaculation, liver damage, parkinsonism
Alpha-adrenoceptor drugs, e.g. doxazosin, prazosin	Postural hypotension, dizziness, headache, fatigue, nausea, urinary incontinence
Angiotensin-converting enzyme inhibitors, e.g. captopril, enalapril	Rash, dry cough, nausea, vomiting, constipation, headache, dizziness, fatigue
Calcium channel blockers, e.g. verapamil, nifedipine	Headache, flushing, dizziness, ankle oedema
Angiotension receptor antagonists, e.g. losartan, valsartan	Dizziness, hypotension, hyperkalaemia,
Potassium channel activators, e.g. nicorandil	Transitory headache, cutaneous vasodilation, nausea, vomiting, dizziness, weakness

Source: *British National Formulary* (1998)

Allen H. Promoting compliance with antihypertensive medication. Br J Nurs. 1998;7:1252–1258.

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Drug interactions in Hypertension

- **Calcium-channel blockers** (CCBs), **β –blockers**, **ACE inhibitors**, & **angiotensin receptor blockers** (ARBs) are metabolized by CYP450.
- Drug concentrations may change when combined with:
  - Enzyme inhibitors (**azole antifungal**, **cimetidine, erythromycin**)
    → Decrease drug concentrations
  - Enzyme inducers (**rifampin**, **carbamazepine**, **phenobarbital, phenytoin**)
    → Increase drug concentrations [1]
- Diuretics & hydrophilic β–blockers (nadolol & atenolol) are not subject to CYP450 interactions [2].

[1] Flockhart DA, Tanus-Santos JE. Implications of cytochrome P450 interactions when prescribing medication for hypertension. Arch Intern Med 2002;162:405–412.
[2] Kroner BA. Common drug pathways and interactions. Diabetes Spectrum 2002 Fall 2002;15(4):249.

Drug interactions in Hypertension

- **β –blockers**
  - In larger doses can antagonize the effects of β-antagonists
    → lead to broncho-constriction
  - In combination with amiodarone (Cordarone), diltiazem, digoxin, & verapamil
    → can have increased effects on heart rate, & possibly lead to significant bradycardia [1]
- **Thiazide, loop diuretics, ACE inhibitors, ARBs, β –blockers, & peripheral α-blockers**
  - Interact with nonsteroidal anti-inflammatory drugs (**NSAIDs**)
    → NSAIDs Inhibit the renal prostaglandins, & promote sodium & water retention, antagonizing the actions of the antihypertensives [2,3].

[1] Anderson JR, Nawarskas JJ. Cardiovascular drug-drug interactions. Cardiol Clin 2001;19:215–234
[2] Houston MC. Nonsteroidal anti-inflammatory drugs and antihypertensives. Am J Med 1991;90 (Suppl. 5A):42S–47S.
[3] Oates JA. Antagonism of antihypertensive drug therapy by nonsteroidal anti-inflammatory drugs. Hypertension 1988;11 (Suppl. II):II4–II6.

Table 1. Clinically Significant Drug Interactions in the Treatment of Dyslipidemia[1,2,5,6,32,33*]

Medication	Interacting Medication	Mechanism	Effects	Recommendations**
Atorvastatin, lovastatin, or simvastatin	Macrolide antibiotics (erythromycin or clarithromycin)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antibiotic or temporarily stop statin or change to pravastatin or fluvastatin
	Azole antifungals (fluconazole, ketoconazole, or itraconazole)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antifungal (topical or terbinafine) or temporarily stop statin or change to pravastatin or fluvastatin
	Cyclosporine	Unknown	Myopathy or Rhabdomyolysis	Change to pravastatin or fluvastatin
	Verapamil or diltiazem	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antihypertensive or change to pravastatin or fluvastatin
	Gemfibrozil	Unknown	Myopathy or Rhabdomyolysis	Counsel patient and monitor CPK and myalgias
	Protease inhibitors (indinavir, nelfinavir, ritonavir, saquinavir, amprenavir†)	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Change to pravastatin or fluvastatin
	Nefazodone	Inhibition of statin metabolism	Myopathy or rhabdomyolysis	Alternative antidepressant or counsel patient and monitor CPK and myalgias, or change to pravastatin or fluvastatin
	Niacin	Unknown	Myopathy or rhabdomyolysis	Counsel patient and monitor CPK and myalgias
Lovastatin, simvastatin, fluvastatin, gemfibrozil, or fenofibrate	Warfarin	Inhibition of warfarin metabolism	Increased INR with potential for bleeding	Counsel patient and monitor INR

Kroner BA. Common drug pathways and interactions. Diabetes Spectrum 2002 Fall 2002;15(4):249.

Other drug interaction

Atypical antipsychotics

- Researches showed a relationship between increased glucose levels & treatment with the **atypical antipsychotics clozapine** (Clozaril) & **olanzapine** [1]
- A few cases of hyperglycemia have been reported with **risperidone** (Risperdal) & **quetiapine** (Seroquel) [1]

[1] Lindenmayer, JP, Nathan, AM, Smith RC. Hyperglycemia associated with the use of atypical antipsychotics. J Clin Psychiatry 2001; 62 (Suppl. 23): 30-38.

Factors that predispose to drug interaction

Elderly patients (enhanced drug effect)

Table I. Some drug interactions of clinical importance in the elderly that result in an enhanced drug effect

Drug A	May interact with drug B	Effect of interaction	Mechanism of interaction
ACE inhibitors	NSAIDs	Hyperkalaemia, reduced renal function	Additive nephrotoxic effects
Antidepressants (tricyclic)	Enzyme inhibitors[a]	Increased effect of A	Reduced clearance of A
Antihypertensive agents	Vasodilators (e.g. nitrates for angina) antipsychotics and some antidepressants	Postural hypotension	Combined hypotensive effects
Aspirin (acetylsalicylic acid) [low dose]	NSAIDs	Peptic ulceration	Additional risk of peptic ulceration
Carbamazepine	Enzyme inhibitors,[a] verapamil	Increased effect of A	Reduced clearance of A
Corticosteroids (oral)	NSAIDs (including aspirin)	Peptic ulceration	?Corticosteroid prevents healing
Cyclosporin	Enzyme inhibitors[a]	Increased effect of A	Reduced clearance of A
Digoxin	Amiodarone, diltiazem, verapamil	Increased effect of A	Reduced clearance of A
Digoxin	Diuretics (loop and thiazides)	Increased effect of A (e.g. arrhythmias)	Diuretic-induced hypokalaemia
Diuretics (potassium-sparing)	ACE inhibitors, potassium supplements	Hyperkalaemia, impaired renal function	Combined potassium-elevating effects
Lithium	NSAIDs, thiazide diuretics	Increased effect of A	Reduced clearance of A
Phenothiazines and butyrophenones	Anticholinergic drugs (e.g. some antihistamines and tricyclic antidepressants)	Excessive anticholinergic effects (e.g. constipation, urinary hesitancy, dry mouth, confusion, etc.)	Combined anticholinergic effects
Phenytoin	Enzyme inhibitors[a]	Increased effect of A	Reduced clearance of A
Quinolones	NSAIDs	Seizures	Pharmacodynamic interaction at CNS effector site
Theophylline	Enzyme inhibitors,[a] quinolones	Increased effect of A	Reduced clearance of A
Warfarin	See table III		

a Examples of common inhibitors include amiodarone, fluconazole, miconazole, ketoconazole, erythromycin, clarithromycin, sulphonamides, cimetidine and ciprofloxacin.

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

Reference: Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. Drug Aging 1998;12(6):485-94.

Elderly patients (reduced drug effect)

Table II. Some drug interactions of clinical importance in the elderly that result in a reduced drug effect

Drug A	May interact with drug B	Effect of interaction	Mechanism of interaction
Antidepressants	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A
Antihypertensives [e.g ACE inhibitors, thiazides and β-adrenoceptor antagonists (β-blockers)]	NSAIDs	Reduced effect of A	Pharmacodynamic antagonism of antihypertensive effect of A
Calcium antagonists	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A
Corticosteroids (oral)	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A
Cyclosporin	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A
Digoxin	Cholestyramine, colestipol	Reduced effect of A	Reduced absorption of A
Quinolones	Cholestyramine, colestipol	Reduced effect of A	Reduced absorption of A
Theophylline	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A
Thyroxine	Enzyme inducers[a]	Reduced effect of A	Increased clearance of A

a Examples of common inducers are rifampicin (rifampin), phenobarbital (phenobarbitone), phenytoin, primidone and carbamazepine.

Abbreviation: NSAIDs = nonsteroidal anti-inflammatory drugs.

Reference: Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. Drug Aging 1998;12(6):485-94.

Dangerous drug combinations among elderly patients

- **Causing hypotension**
  - ≥ 2 of the following groups: tricyclic antidepressants, nitrates, calcium antagonists, ACEI, α-adrenoceptor antagonists (alpha-blocker)
- **Causing additive sedative effects**
  - May lead to falls, confusion, aspiration pneumonias, dizziness, apathy & incontinence
- **Causing anticholinergic effects**
  - E.g. Antipsychotic medications, some antiarrhythmic preparations, some tricyclic antidepressant, some antihistamines & some antiparkinsonism agents
- **Drug with a narrow therapeutic index**
  - E.g. Thephylline, phenytoin or digoxin
- **Any elderly patient receiving anticoagulants**
  - E.g. Warfarin

Reference: Seymour RM, Routledge PA. Important drug-drug interactions in the elderly. Drug Aging 1998;12(6):485-94.

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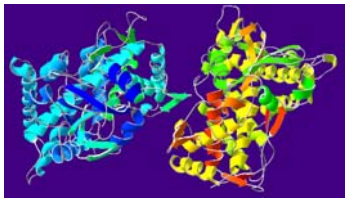
Warfarin & interactions in the elderly

Table III. Some clinically important interactions with warfarin (after Routledge,[39] with permission)

Interacting drug	Result of interaction on the effects of warfarin	Probable mechanism(s)
Cholestyramine, colestipol	Reduced anticoagulant effect	Impaired absorption and increased elimination of warfarin. Long term treatment may cause impaired vitamin K absorption and enhance the anticoagulant effect
Barbiturates Carbamazepine Phenytoin (see also below) Primidone Rifampicin (rifampin)	Reduced anticoagulant effect	Induction of warfarin metabolism
Amiodarone Azapropazone Chloramphenicol Cimetidine Ciprofloxacin Clarithromycin Dextropropoxyphene Erythromycin Fluconazole Itraconazole Ketoconazole Mefenamic acid Metronidazole Miconazole Phenylbutazone Sulfinpyrazone Sulphonamides [e.g. in cotrimoxazole (trimethoprim-sulfamethoxazole)]	Increased anticoagulant effect	Inhibition of warfarin metabolism
Bezafibrate Clofibrate Danazol Thyroxine Gemfibrozil Phenytoin (see also above) Salicylates/aspirin (acetylsalicylic acid) [high dose] Stanozolol Tamoxifen	Increased anticoagulant effect	Pharmacodynamic potentiation of anticoagulant effect
NSAIDs (including aspirin at all doses)	Increased risk of bleeding	Additive effects on coagulation and haemostasis
Oral contraceptives, vitamin K	Reduced anticoagulant effect	Pharmacodynamic antagonism of anticoagulant effect

Genotypic variations in the isozymes of cytochrome P450

- The cytochrome P450 (CYP450) enzyme system is responsible for the oxidative-reductive metabolism of medication
- Primarily concentrated in liver and small intestines.
- >30 human CYP450 enzymes have been identified.
- Only 4 isoenzymes (CYP3A4, CYP2C9, CYP1A2 & CYP2D6) are responsible for the majority of drug metabolism [1]



Cytochrome P450 Oxidase (CYP2C9) [2]

[1] Kroner BA. Common drug pathways and interactions. Diabetes Spectrum 2002 Fall 2002;15(4):249.
[2] Wikipedia tfe. Cytochrome P450. 2012; Available at: http://en.wikipedia.org/wiki/Cytochrome_P450. Accessed November 14, 2012.

Genotypic variations in the isozymes of cytochrome P450

- CYP3A4 metabolizes the greatest number of medications & endogenous substances in the body, accounting for most CYP450 enzymes in the liver and small intestines [1,2]
- Inheriting abnormal alleles of cytochrome P450 can alter drug metabolism & lead to drug interaction [3]

[1] White CM. An evaluation of CYP3A4 drug interactions with HMGG-CoA reductase inhibitors. Formulary 2000; 34: 343-352.
[2] Kroner BA. Common drug pathways and interactions. Diabetes Spectrum 2002 Fall 2002;15(4):249.
[3] Ansari JA. Drug Interaction and Pharmacist. J Young Pharm 2010 Jul-Sep; 2(3):326-331.

Genotypic variations in the isozymes of cytochrome P450

Table 1. Pharmacogenetics of Phase I Drug Metabolism.*

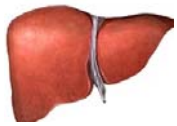
Drug-Metabolizing Enzyme	Frequency of Variant Poor-Metabolism Phenotype	Representative Drugs Metabolized	Effect of Polymorphism
Cytochrome P-450 2D6 (CYP2D6)	6.8% in Sweden 1% in China[17]	Debrisoquin[15] Sparteine[16] Nortriptyline[23] Codeine[27,28]	Enhanced drug effect Enhanced drug effect Enhanced drug effect Decreased drug effect
Cytochrome P-450 2C9 (CYP2C9)	Approximately 3% in England[29] (those homozygous for the *2 and *3 alleles)	Warfarin[29,30] Phenytoin[31,32]	Enhanced drug effect[29-32]
Cytochrome P-450 2C19 (CYP2C19)	2.7% among white Americans[33] 3.3% in Sweden 14.6% in China[17] 18% in Japan[33]	Omeprazole[34,35]	Enhanced drug effect[36,37]

* Examples of genetically polymorphic phase I enzymes are listed that catalyze drug metabolism, including selected examples of drugs that have clinically relevant variations in their effects.

Guttmacher AE & Collins FS. Inheritance and drug response. N Engl J Med 2003; 348:529-37

Liver or renal diseases

- Liver: major site of reactions of drug metabolism
- Kidney: many drugs and drug metabolites are excreted in the urine via renal tubular secretion.
- Various diseases causing renal or hepatic insufficiency may alter drug metabolism.
  - The blood concentrations of drugs that are metabolized in the liver and / or excreted in the urine via renal tubular secretion may be altered if either of these organs is not functioning correctly



Delafuente JC. Critical Reviews in Oncology. Hematology 2003. 48. 133-143

Liver or renal diseases

Drug-disease interactions

- **Metformin *(Glucophage)***
  - Absolutely contraindicated in patients with renal dysfunction & in those with congestive heart failure requiring pharmacological treatment
  - Temporarily discontinued in patients undergoing procedures involving administration of intravenous iodinated contrast materials which can decrease renal function [1]
- **Corticosteriods**
  - Increase plasma glucose levels in DM patients
  - Affect glucose control by decreasing glucose utilization & increasing gluconeogenesis [2]
  - Routinely monitor the blood glucose levels of patients

[1] Glucophage package insert, Bristol-Myers Squibb Company, Princeton, N. J. Revised May 2001.
[2] Pandit MK, Burke J, Gustafson AB, Minocha A, Peiris AN. Drug-induced disorders of glucose intolerance. Ann Intern Med 1993;118:529 539

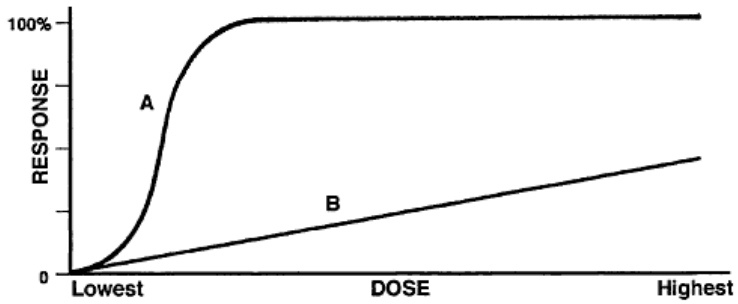
Drugs with narrow therapeutic index

- Narrow therapeutic index: small difference between the therapeutic and toxic dosages of the drugs
  - E.g. Digoxin, Lithium [1]
- **Drug interactions in hypertension:**
  - **Thiazide diuretics, ACE inhibitors, & ARBs** can increase **lithium** concentrations by interfering with lithium's renal excretion [2][3]
  - Patients who are on ACE inhibitors or ARBs & lithium should have lithium levels checked and should seek medical attention for signs of lithium toxicity
    - Nausea, vomiting, diarrhea, coarse tremor, slurred speech and disorientation

[1] Seymour RM & Routledge PA. Important Drug-drug Interactions in the Elderly. Drugs & Aging 1998 Jun. 12(6): 485-494.
[2] Tatro DS. Drug interaction facts 2000. St. Louis, Mo. Facts and comparisons, 2000
[3] Hansten PD, Horn JR. Drug interactions analysis and management: A clinical perspective and analysis of current developments. St. Louis, Mo., Facts and comparisons, 2002

Steep dose-response curves

- Occurs when the small changes in the dosage of a drug produce large changes in the drug's concentration in the patient's blood plasma



Overall management strategies of drug-drug interaction

- **Recognition of the interaction:**
- Drug interactions are **complex** and **chiefly unpredictable**
- A known interaction may not occur in every individual - can be explained because there are several **factors that affect the likelihood that a known interaction will occur**
  - genes,
  - physiology,
  - age,
  - lifestyle (diet, exercise),
  - underlying diseases,
  - drug doses,
  - the duration of combined therapy, and
  - the relative time of administration of the two substances (Sometimes, interactions can be avoided if two drugs are taken at different times).

Overall management strategies of drug-drug interaction

- **Decision making:**
- Regarding whether to prescribe, dispense, or administer the interacting combination
  - If the outcome were possible death, the risk would likely outweigh the benefit
  - If the outcome were increased drowsiness, the benefit would appear to outweigh the risk

- **Follow-up monitoring:**
- When patients are prescribed drugs known to interact, they should be monitored appropriately and counseled about signs and symptoms that should trigger a call to the health care provider.

Overall management strategies of drug-drug interaction

- **Appropriate patient counseling:**
- Patients should also be advised to have **all of their prescriptions filled at one pharmacy** so their drug regimens can be **routinely screened** for drug interactions.
- At the very least, they should keep **an updated list of their medications** with them to share with all health care providers.

- **Patient engagement:**
- For patients, they should not be afraid to use their drugs because of the potential for drug interactions.
- Patients should use all the best available information to minimize the risk of such interactions and to improve the success of their therapy

Management options

- **Avoiding the combination entirely:**
- For some drug interactions, the risk always outweighs the risk, and the combination should be avoided.
- Select a **no interacting alternative** for either the object drug or the precipitant drug.
- In today's managed care environment, **drug formularies** may limit alternatives or make them cost-prohibitive.
- This is not necessarily bad because drugs can be costly:
  - drug interactions are not generally regarded as contraindications unless the outcome is extremely serious.

Reference: Ansari J. Drug interaction and pharmacist. Journal of young pharmacists : JYP 2010;**2(3):326-31.**

Management options

- **Adjusting the dose of the object drug:**
- Sometimes, it is possible to give the two interacting drugs safely as long as the dose of the object drug is adjusted.

- **Spacing dosing times to avoid the interaction:**
- For some drug interactions involving binding in the gastrointestinal tract, to avoid the interaction one can give the object drug at least 2 h before or 4 h after the precipitant drug.
- In this way, the object drug can be absorbed into the circulation before the precipitant drug appears.

Reference: Ansari J. Drug interaction and pharmacist. Journal of young pharmacists : JYP 2010;**2(3):326-31.**

Management options

- **Monitoring for early detection:**
- In some cases, when it is necessary to administer interacting drug combinations, the interaction can be managed through close laboratory or clinical monitoring for the evidence of the interaction.
- In this way, the appropriate dosage changes can be made, or the drugs discontinued if necessary.
- **Improve computerized screening systems:**
- It is clear that computerized drug interaction screening systems have not been as successful as one hoped[1,2].

1. Hazlet TK, Lee TA, Hansten PD, Horn JR. J Am Pharm Assoc (Wash). 2001 Mar-Apr; 41(2):200-4.
2. Chrischilles EA, Fulda TR, Byrns PJ, Winckler SC, Rupp MT, Chui MA. J Am Pharm Assoc (Wash). 2002 May-Jun; 42(3):439-48.

A comment:

- We are not specialists in “drug interactions”!!
- Involve experienced specialists in cases of doubt:
  - Clinical Pharmacologists
  - Pharmacists

- **Community Pharmacists**

Drug Education Enhancement Program for the Elderly (e@DEEP)

- A drug education program provided by trained volunteers
- To find out elderly with drug-related problems and provide subsequent education
- To improve drug knowledge of the elderly
- To provide basic training to volunteers to reduce workload of pharmacists

Educational Slide Show for Patients

- Educational slide show for patients is broadcasted at pharmacy waiting hall to enhance medication safety
- Drug administration and storage Tips

Pharmaceutical Care in some major hospitals in HK

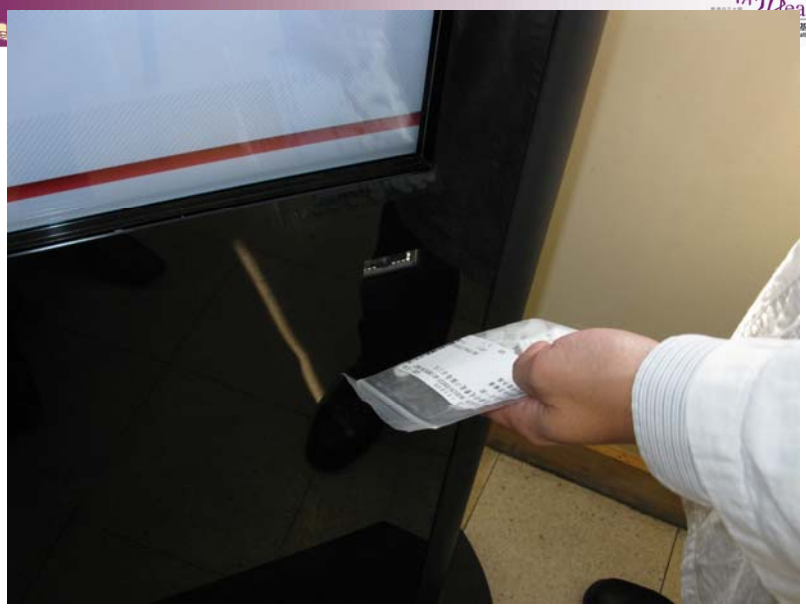
- Identify drug-related problems
- Improve patients' health literacy
- Empower patient
- Enhance patients' drug compliance and self care

Pharmaceutical Care Centre

- Pharmacist to provide drug counseling and pharmaceutical service
- Patients are referred if:
  - Poor clinical control
  - Poly-pharmacy
  - Doctor's referral
  - Self-referral

Drug Info Kiosk

- Empower patients by providing drug education through multi-media
- Enhance medication safety by engaging patients in drug identification
- Encourage patients participation in the discussion of treatment with doctors

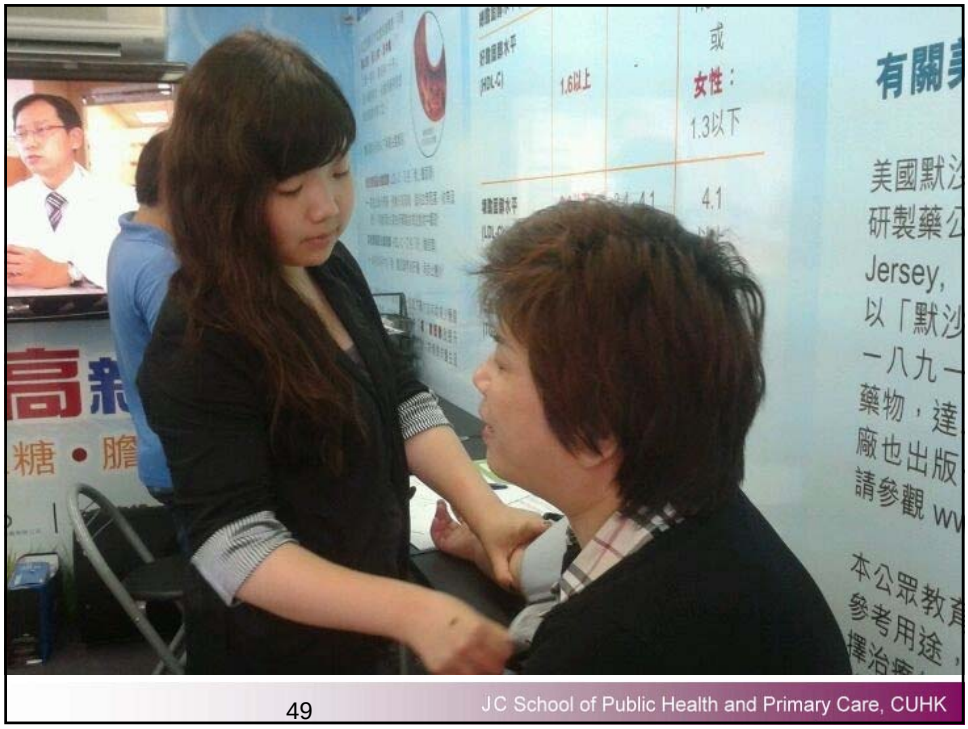



藥物資訊站

Mobile van


ng People Stay Healthy
香港醫院藥劑師學會
藥物教育講座展覽車
認識三高新方向
血壓 • 血糖 • 膽固醇
MSD
全力支持
ISUZU


Alumni Primary School
香港醫院藥劑師學會
藥物教育講座展覽車
MSD



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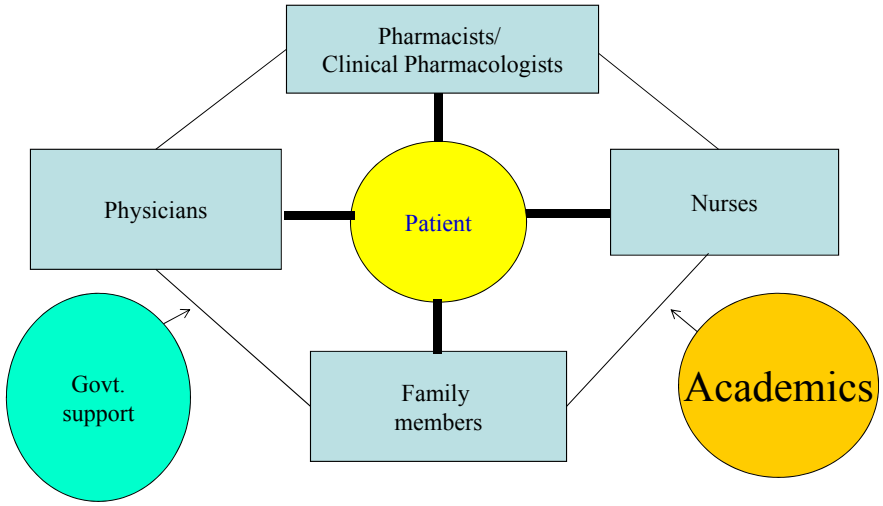
Care for your heart

, CUHK

Home Visits

Video-conferencing

Team approach to interdisciplinary minimization of drug interaction



Source: Carter BL. Adherence, quality of life, cost-effectiveness, and the role of the pharmacist. In Lip & Hall. Comprehensive Hypertension, Mosby, 2007, pp. 1119-1127.

Future direction of development

- Drug interactions can be complex, especially if multiple interactions exist in an individual patient.
- The literature on drug interactions is always changing as new information and new drugs become available.
- Let's join our hands …
- Thank you !!