Slide 1	# *Medicine Interactions* Professor Mark McKeage Department of Pharmacology and Clinical Pharmacology and Auckland Cancer Society Research Centre *MBChB221B 29 Sept 2020*	
Slide 2	## *Learning goals* • Define drug interaction • Understand mechansims and classification of drug interactions • Know some important examples • Appreciate how adverse effects from drug interactions can be prevented • Know where to source information for prescribers about drug interactions	
Slide 3	## Drug Interactions • **Definition:** when effects of one drug are changed when administered with another drug, food or another substance • Effects on the drug concerned; may be increased, decreased or a new effect produced • Drug-Drug • Drug-Food • Drug-Herb • Relevant terminology – Syngergism, potentiation, additivity, antagonism • Clinical Significance – Mostly harmful, sometimes useful	

Slide 4

Classification of Drug Interactions:

Pharmacokinetic

- Drug interaction due to an effect of one drug on the absorption, distribution, metabolism or elimination of another drug

Pharmacodynamic

- Drug interaction due to the effects of two or more drugs on the same receptor or physiological system, without change in drug concentration

Pharmaceutical

- drug interaction occurring in syringes or infusion fluids

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Altered Absorption

- One drug may alter the rate or *degree* of absorption of another drug from the gastrointestinal tract
- Decreased absorption may lead to loss of therapeutic activity
- Increased absorption may lead to exaggerated and/or prolonged activity and/or toxicity

- **Clinical examples**
- Metal chelate formation, between metal-containing antacids or supplements decreasing absorption of antibiotics, eg. aluminium hydroxide (perpetrator drug) and doxycycline or ciprofloxacin (susceptible drugs)
- P-glycoprotein inhibition, by a perpetrator drug increasing the bioavailability of a susceptible drug, eg. ciclosporin and loperamide, respectively

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Induced Drug Metabolism

- One drug may alter the metabolism of another drug by inducing enzyme activity
- Induction of drug metabolising enzymes occurs over several days or a few weeks, frequently involves cytochrome P450 enzymes and is regulated at the level of transcription
- Clinical consequences depend on activity of metabolites

Clinical examples

- Perpetrator classes drugs
  - Anticonvulsants, Antimicrobials for TB and HIV, Natural Health Products
- Perpetrator drugs
  - Phenytoin
  - Carbamazapine
- Susceptible drugs
  - Ethinyloestradiol/levonorgestrel (reduced contraceptive effect)
  - Warfarin (reduced anticoagulant effect)
  - Gefitinib (reduced anticancer effect)

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Inhibited Drug Metabolism

- One drug may interact with another drug by inhibiting drug metabolism
- Drug interactions due to inhibited drug metabolism frequently involve the cytochrome P450 enzymes and have rapid onset within hours of concurrent drug administration
- Inhibition of drug metabolism may cause exaggerated or prolonged responses or increased toxicity

- **Clinical examples**
- CYP450 perpetrator drug classes
  - Perpetrators: Macrolides, azole antifungals, protease inhibitors, antidepressants, grapefruit juice
  - Susceptible: Anticoagulants, oral hypoglycaemics, statins
  - eg. Erythromycin inhibits simvastatin metabolism (increased toxicity)
  - eg. Fluconazole inhibits warfarin metabolism (increased effect)
- Aldehyde dehydrogenase
  - Eg. Metronidazole inhibits alcohol metabolism producing dysphoria

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Altered Elimination

- One drug may alter the effects of another drug by interfering with renal or biliary elimination
- Drug interactions due to altered renal or biliary elimination may competition for renal tubular secretion
- Altered elimination may slow drug clearance causing exaggerated and/or prolonged activity and/or increased toxicity

- **Clinical examples**
  - Inhibition of drug elimination of transporter substrate drugs by inhibitors
- P-Glycoprotein (P-gp)
  - eg. inhibition of renal elimination of digoxin by erythromycin (digoxin toxicity)
- Solute carrier transporters (SLC)
  - eg. inhibition of renal elimination of penicillin by probenecid (increased penicillin concentration)

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Pharmacodynamic Drug Interactions

• One drug may effect another drug by them acting on the same physiological system, without any change in drug concentration

• May occur from drug actions on the same or different receptors

•May result in potentiation or antagonism of drug effects

- **Clinical examples**
- **Same receptor**
  - Beta2-adrenoceptor agonist and antagonist
  - eg. salbutamol and atenolol
- Same target tissue
  - **Multiple CNS depressants**
  - Eg. Alcohol plus other recreational drugs
  - Eg. Polypharmacy in elderly
  - eg. diazepam and nortriptyline
  - **Blood coagulation**
  - Eg. Warfarin and Aspirin

Slide 10	**How to reduce harm from drug interactions?** – Know the key concepts – Know the perpetrator drugs most often involved • Azole antifungals; Macrolides; Anticonvulsants; etc – Know about drugs with low therapeutic index • Anticoagulants; Antiarrhythmics; Antiepileptics; Antineoplastics; Aminoglycosides; Immunosuppressants; – Know the drugs you frequently prescribe – Know drugs of low risk for common problems – Know how to recognize high risk patients • Extremes of age; number of medicine; organ impairment	
Slide 11	**Know where to find drug information** • New Zealand Formulary • http://nzf.org.nz/nzf_1.html • Medsafe datasheets • http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp • Also: • Hospital medicine information service • Prescribing and dispensing software • Tables are available online	
Slide 12	Short answer question example Your 75 year old grandfather has been discharged from hospital after an acute myocardial infarction. He has been prescribed simvastatin. He has been told to avoid grapefruit juice. As you are medical student he asked you why. 1) What do you tell him? 2) If you don't know where could you obtain information for prescribers about this? 3) How could grapefruit juice interact with simvastatin? 4) What are the potential clinical consequences? 5) What type of drug interaction is this? 6) Define drug interaction	