Slide 1	**Adverse Medicine Reactions** Professor Mark McKeage Department of Pharmacology and Clinical Pharmacology and Auckland Cancer Society Research Centre	
Slide 2	Learning goals • Define adverse drug reaction • Understand mechanisms and classification of adverse drug reactions • Know some important examples • Appreciate how adverse drug reactions can be prevented • Know where to source information for prescribers about adverse drug reactions	
Slide 3	**Adverse Drug Reactions** Definition: A noxious or unintended response to a drug, which occurs at doses normally used in humans for the prophylaxis, diagnosis or treatment of diseases or for the modification of physiological function. Significance: •Common (9-28% of hospitalised patients) • Associated with long-term disability and death.	

Slide 4

Adverse Drug Interactions: Classification

- **Type A (Augmented pharmacological effect)**
  Related to the main pharmacological action of the drug, or cytotoxicity of the drug or metabolites
- **Type B (Bizarre)**
  Unrelated to the main pharmacological action of the drug
- **Type C (Chronic effects)** Adverse effects associated with long-term therapy
- **Type D (Delayed effects)** Effects appearing along time after treatment
- **Type E (End of treatment effects)** withdrawal reactions
- **Type F (Failure of treatment)**

Slide 5

Type A Adverse Drug Reactions

- Related to the main pharmacological action of a drug or the cytotoxic action of the drug or its metabolites
- predictable
- dose-related
  eg. bleeding with warfarin
  hypoglycaemia with insulin
  confusion and drowsiness with nortriptyline

Slide 6

Type A Adverse Drug Reaction

<u>Cytotoxicity</u>:

- drug or reactive metabolites may directly damage cells
- form covalent bonds or alter target molecules by non-convalent interaction
- hepatic metabolism generates high levels of metabolites in the liver → hepatotoxicity
- polar drugs/metabolites are concentrated within the nephron → nephrotoxicity

Slide 7	**Type A Adverse Drug Reactions** **Clinical example: Paracetamol Hepatoxicity**: • converted by hepatic CYPs to toxic alkylating intermediate* • metabolite inactivated by conjugation to reduced glutathione • in overdose, glutathione is rapidly depleted • excess metabolite binds covalently to liver macromolecules causing cell damage and acute hepatic necrosis • prevented by N-acetylcysteine that facilitates glutathione synthesis *N-acetyl-p-benzoquinonimine (NABQ1)	
Slide 8	**Type A Adverse Drug Reactions** **Clinical example: Gentamicin nephrotoxicity**: • Aminoglycoside antibacterial ribosomal protein synthesis inhibitor • Excreted unchanged in urine by glomerular filtration • Cytotoxic at high concentrations to proximal renal tubules causing nephrotoxicity • Gentamicin dose needs to be adjusted according to blood level monitoring and renal function	
Slide 9	**Type B Adverse Drug Reactions** • Bizarre • Not related to the main pharmacological action of a drug • not predictable • not dose related • allergic reactions or pharmacogenetic variability	

Slide 10	**Adverse Drug Reactions** **<u>Allergic Reactions</u>:** • initial exposure and sensitisation • allergic reaction occurs on repeated exposure • symptoms and signs resemble allergic disease eg. acute hypersensitivity, skin rash, haematological reaction • antibiotics, non-steroidal anti-inflammatory drugs, radio-contrast agents, anaesthetic agents	
Slide 11	**Type B Adverse Drug Reactions** **Clinical example: Benzylpenicillin Allergy**: • skin rash 1:10; anaphlaxis 1:5000; death 1:50,000 • antibodies directed to penicilloyl-protein complex or penicillin polymers • many types of allergic reaction eg. acute anaphylaxis haemolytic anaemia serum sickness rash	
Slide 12	**Type B Adverse Drug Reactions** **Clinical example: Carbamazepine Skin Reaction**: • Sodium channel blocker used for epilepsy • Occasional life-threatening severe skin reactions – Stevens-Johnson syndrome, Toxic Epidermal Necrolysis – Blistering and peeling of skine leading to dehydration, sepsis, multiple organ failure and death – Immune-mediated adverse drug reactions – Genetic susceptibility among those with HLA-B*1502 allele	

Slide 13	**Type C Adverse Drug Reactions (Chronic effects of Long-Term Therapy)** • Long-term treatment may alter receptor expression and/or tissue sensitivity to drugs • adverse drug reactions can occur during therapy or after withdrawal of the drug	
Slide 14	**Type C Adverse Drug Reaction (Chronic effect)** • Clinical example: haloperidol-induced dyskinesia • Dopamine receptor antagonist used for psychosis • Tardive dyskinesia - Late neurological syndrome associated with long-term anti-psychotic use that persists after cessation of treatment • Involuntary movements of the lips, jaw and tongue • Possibly due to compensatory increase in dopaminergic system	
Slide 15	**Type E Adverse Drug Reaction (End of treatment effect) Withdrawal Reactions** • Withdrawal reaction • Abrupt cessation of treatment can cause symptoms because of the unopposed change in receptor expression or tissue sensitivity • Clinical example: dexamethasone-induced adrenocorticoid insufficiency • acute adrenocorticoid insufficiency upon sudden withdrawal of dexamethasone due to adrenal atrophy • Dexamethasone must be gradually reduced and withdrawn to allow return of adrenocorticoid function	

Slide 16	**Type D (Delayed) Adverse Drug Reactions** **<u>Carcinogenesis</u>** Drug may cause cause by: a) causing mutations by covalently modifying DNA in growth regulatory proto-oncogenes or tumour suppressor genes, or; b) by promoting cell proliferation	
Slide 17	**Delayed ADR due to Carcinogenesis** • Clinical example: Doxorubicin (topoisomerase inhibitor) or Cyclophosphamide (DNA binder) induced secondary cancers • Both common components of combination chemotherapy • Both mutagenic and carcinogenic • Secondary cancers presenting after a long delay after treatment, most commonly acute myelogenous leukaemia • Survivors of childhood cancer >10 times increase risk of secondary cancer for 30 years after initial treatment compared to normal population	
Slide 18	**Type D (Delayed) Adverse Drug Reactions** **Teratogenecity:** • fetal malformations • damage resulting from drugs prescribed during pregnancy • Clinical example: doxycycline-induced tooth discolouration and malformation – Antibacterial ribosomal protein synthesis inhibitor – Disposition of doxycycline in growing bones and teeth by binding calcium causes tooth staining and hypoplasia in unborn child	

Slide 19	**Adverse Drug Reactions** **<u>Risk Factors</u>:** • fetus or neonatal • elderly • previous drug reactions • liver or kidney disease • number of drugs given	
Slide 20	**Adverse Drug Reaction Monitoring** Some important adverse reaction are not recognised before approval for marketing Post-marketing monitoring aims to detect serious or unexpected adverse drug reactions New Zealand: - Voluntary reporting of serious or unexpected reactions or interactions - Intensive Medicines Monitoring Programme	
Slide 21	**Summary** • adverse drug reactions are unwanted effects of drugs • they can arise via mechanisms related (Type A) or unrelated (Type B) to the main mechanism of action of the drug • adverse drug reactions are predicted and therefore can often be anticipated • monitoring programs aim to identify significant adverse drug reactions after marketing	

Slide 22	## Short answer question example • An 87 year old NZ European woman is brought to Emergency Dept by ambulance. She is unconscious and was found on the floor by a cleaner. The ambulance officer noted she was taking glipizide. • What is the main mechanism of action of glipizide? • What is the main clinical use of glipizide? • What Type A (Augmented pharmacological effect) adverse drug reaction would be expected from glipizide?	