Slide 1

Drug Interactions
Year 2 Clinical Pharmacology

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Slide 2

Objectives

- Explain the potential for interacting drugs to cause beneficial and harmful effects
- Recognise the main ways in which interactions occur (e.g. pharmacokinetic, pharmacodynamic)
- Identify the importance of liver metabolism as a point of interaction between drugs
- Identify sources of information about drug interactions

Slide 3

A 32 year old Chinese woman who was treated with radioactive iodine for an overactive thyroid gland develops hypothyroidism. She is commenced on thyroxine and attends a follow-up clinic appointment. Her thyroid function test results are:

freeT4: 8.0 pmol/L (10.0 - 20.0)
TSH: 8.8 mIU/L (0.30 - 4.00)

Which over-the-counter medicine could account for this result:

A. Ferrograd
B. Healtheries Osteo
C. Mylanta
D. Red 8 Soy Protein Isolate
E. All of the above

Slide 4

What is a drug interaction?

A change in one drug's effect when administered with another drug, food or other substance.

Slide 5

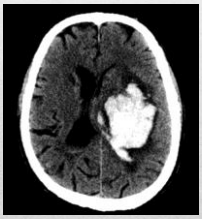
Interactions may be…

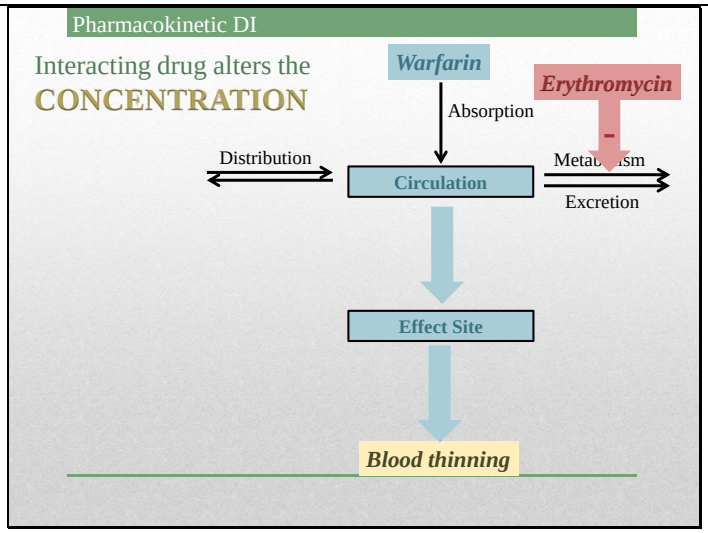
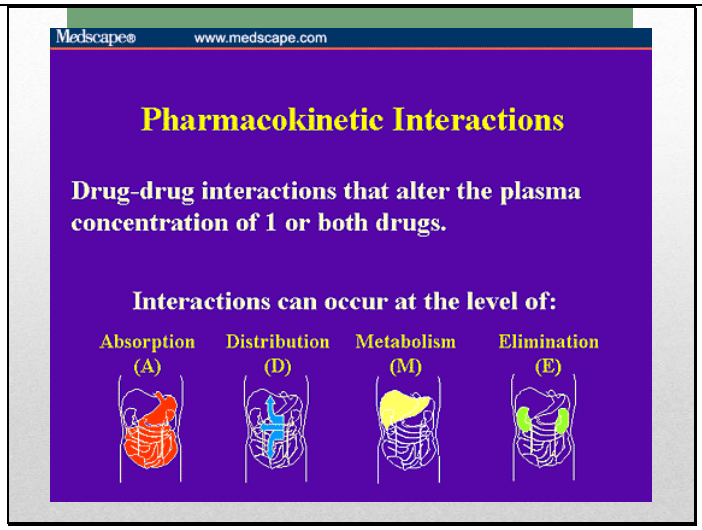
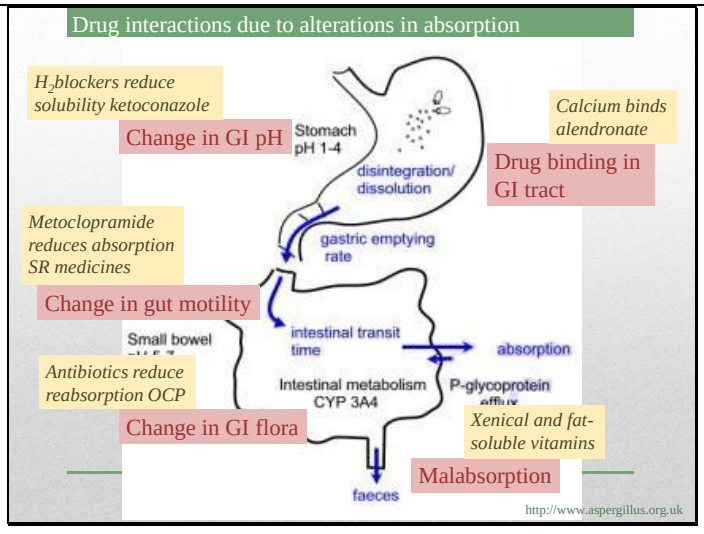
	Additive or Synergistic (=increased effects)	Antagonistic (=lessened effects)
Beneficial	**POTENTIATION** *e.g. combination antibiotics*	**ANTAGONISM** *e.g. "antidote" for overdose*
Undesirable	**TOXICITY** *e.g. diuretics and NSAIDs worsening renal impairment*	**LOSS OF EFFECT** *e.g. carbamazepine reducing warfarin's blood thinning effect*

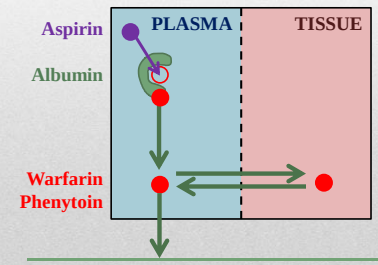
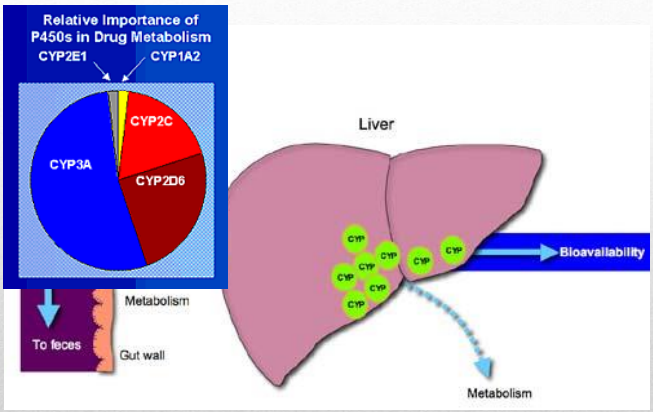
Slide 6

An 87 year old NZ European woman is brought to the Emergency Department by ambulance. Her INR is 6 (therapeutic range 2-3) and this is her CT scan. Her daughter tells you she is usually on warfarin and has recently been taking some other tablets. Which of the following is it most likely to be?

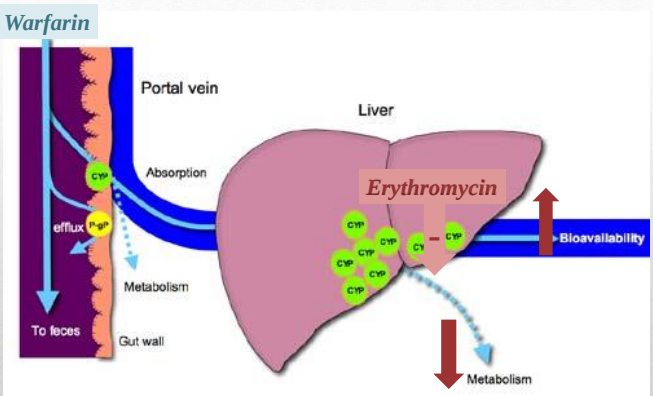
A. St John's wort
B. Aspirin
C. Erythromycin
D. Amoxycillin
E. Paracetamol



Slide 7		
Slide 8		
Slide 9		

Slide 10	**Interactions due to Drug Distribution** Drug displaced from protein binding → Transient increase free drug → Increased rate of elimination of free drug → Restored previous level free drug  **Only clinically relevant when interpreting drug concentrations.** **Total drug concentration will be reduced**	
Slide 11	**Drug Interactions due to Hepatic Metabolism**  http://www.doctorfungus.org/thedrugs/antif_interaction.php. Shimada T et al. J Pharmacol Exp Ther 1994; 270 (1): 414.	
Slide 12	**Core concepts** • **Substrate**: An agent that is metabolized by an enzyme into a metabolic end product and eventually excreted. • **Inhibitor**: An agent which interferes with the ability of a given enzyme to metabolize a given substrate. **Leads to decreased drug metabolism → increased concentrations of drug.** • **Inducer**: An agent which causes an increase in the production of the enzyme(s) responsible for metabolizing a given substrate. **Leads to increased drug metabolism → decreased concentrations of drug.**	

Slide 13	**Time course of effect may vary**
	• The introduction of enzyme **inhibitors** generally leads to rapid increases in the blood levels of substrates.
	• The onset and time to maximal drug interaction are determined by:
	  • Half-life and time to steady state of the inhibitor drug
	  • Time required for the substrate to reach a new steady state.
	• Enzyme **induction** causes increased synthesis and therefore an increased amount of the induced enzyme.
	• Maximum effect may not be reached for 2-3 weeks (and take 2-3 weeks to 'wear off').	

Slide 14	• Her daughter brings her medicines in and amongst them you find a bottle of erythromycin tablets that were prescribed a week ago. • You recall that erythromycin can interact with other medicines and you look it up: **Explanation** Several pharmacokinetic studies suggest that erythromycin causes a minor increase in the effects of warfarin. Case reports suggest that some patients have a marked increase in the anticoagulant effects of warfarin when they take erythromycin.	
Slide 15		

Slide 16

CYP 3A4

SUBSTRATES	INDUCERS	INHIBITORS
• macrolide antibiotics	• carbamazepine	• macrolide antibiotics
• calcium channel blockers	• phenytoin	• calcium channel blockers
• statins NOT pravastatin	• phenobarbitone	• HIV antivirals
• benzodiazepines	• rifampicin	• azoles
• HIV antivirals	• St John's Wort	• grapefruit juice
• cyclosporine		
• warfarin		

- **Clinical relevance**: A small number of patients have increased blood thinning with erythromycin. Avoid the combination or monitor at 3–5 days.

http://www.rnzcgp.org.nz/assets/documents/Publications/JPHC/June-2009/JPHCJune09Insert24WEB.pdf

Slide 17

CYP 2C9, 2C19

SUBSTRATES		INDUCERS		INHIBITORS	
2C9	2C19	2C9	2C19	2C9	2C19
•warfarin	•warfarin	•carbamazepine	•phenytoin	•amiodarone	•omeprazole
•NSAIDs	•PPIs*	•rifampicin	•rifampicin	•fluoxetine	•fluoxetine
•OHA*	•anti-depressants	•St John's Wort		•fluconazole	•ketoconazole
•phenytoin	•anti-epileptics			•isoniazide	

- **Clinical relevance**: When amiodarone is added to warfarin an increase in blood thinning is seen in most patients. Monitor weekly for 4 weeks (onset seen in about 2 weeks).

*PPI s= proton pump inhibitors
OHA=oral hypoglycaemic agents
http://www.rnzcgp.org.nz/assets/documents/Publications/JPHC/June-2009/JPHCJune09Insert24WEB.pdf

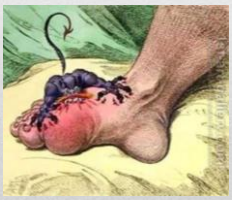
Slide 18

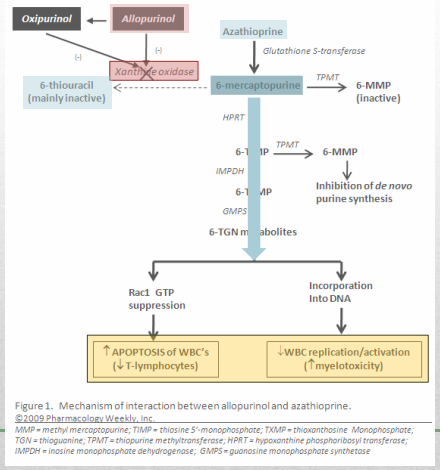
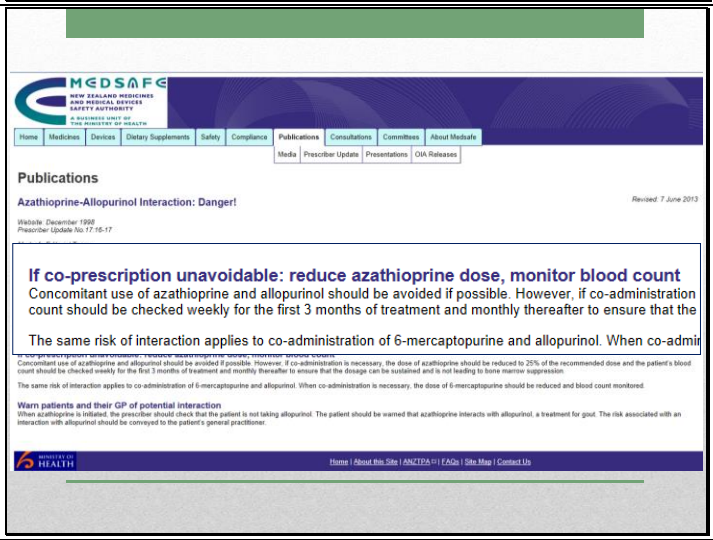
CYP 2D6

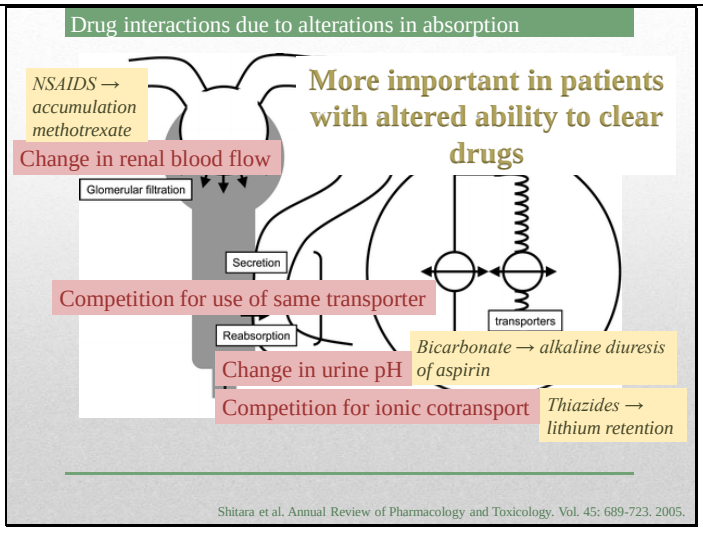
SUBSTRATES	INDUCERS	INHIBITORS
• beta blockers		• amiodarone
• tricyclic antidepressants		• SSRIs
• antipsychotics		• cimetidine
• opiates		

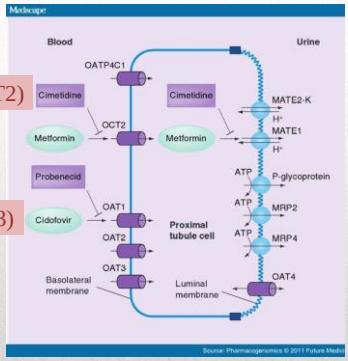
- **Clinical relevance**: If a patient taking a selective serotonin reuptake inhibitor (SSRI) antidepressant is given codeine it cannot be converted to morphine. This results in a lack of pain relief.

http://www.australianprescriber.com/magazine/24/1/article/425.pdf

Slide 19	**Examples of other clinically relevant interactions** • **1A2**: It has been estimated that the average plasma levels of clozapine in smokers are approximately 80% those of non-smokers. Dose reduction is highly recommended in patients who quit or who are hospitalised and unable to smoke. - Substrates: antipsychotics, theophylline - Inducer: tobacco - Inhibitors: amiodarone, cimetidine • **2E1** : Enzyme induction by ethanol increases production of a toxic metabolite of paracetamol and may result in hepatic injury or failure. http://medsafe.govt.nz/profs/PUArticles/December2013SmokingInteractMedicines.htm http://www.australianprescriber.com/magazine/27/1/article/516.pdf	- The hepatotoxic metabolites of paracetamol are produced in the liver largely through the activity of cytochrome P450 2E1. Alcohol inhibits the enzyme while it is present in the body (and theoretically protect the liver). However there is continuing induction of cytochrome P450 2E1 after alcohol has been eliminated from the body (making the liver more sensitive to paracetamol).
Slide 20	**Genetic variation in CYP activity** • There is a **wide variation in enzyme activity** in the normal population • 5-8 fold variation in CYP3A4 activity • 50% variation in CYP2D6 activity • **Poor metabolisers** have blood levels of substrates higher than expected at standard doses • CYP2D6 genetic polymorphism in 5-10% European, 1% Asian population • **Ultraextensive/ultrarapid metabolisers** have blood levels of substrates lower than expected at standard doses. • Extra allelic copies of the wild-type enzyme	This is covered in Nick's lecture
Slide 21	An 27 year old Chinese/Samoan man with Crohn's disease is taking azathioprine. Routine blood tests show a high uric acid level, which can lead to gout and is usually treated with allopurinol. What serious effect can occur as a result of an interaction between azathioprine and allopurinol? A. Hypersensitivity skin reaction B. Pancytopaenia C. Nausea and vomiting D. Renal failure E. Hepatitis  http://dailypaintingpractice.blogspot.co.nz/2010_10_01_archive.html	

Slide 22	**Not all interactions involve CYP450**  Figure 1. Mechanism of interaction between allopurinol and azathioprine. © 2009 Pharmacology Weekly, Inc. *MMP = methyl mercaptopurine; TIMP = thiosine 5'-monophosphate; TXMP = thioxanthosine Monophosphate; TGN = thioguanine; TPMT = thiopurine methyltransferase; HPRT = hypoxanthine phosphoribosyl transferase; IMPDH = inosine monophosphate dehydrogenase; GMPS = guanosine monophosphate synthetase*	
Slide 23	 	
Slide 24	A 64 year old NZ European man is brought to ED following a collapse. He is found to be in atrial fibrillation and is commenced on digoxin. A few weeks later he comes to see his GP as he is experiencing a low mood, and asks about using St John's Wort. What advice would you give him? A. It will not help his mood B. It can reduce the effectiveness of digoxin C. It is a natural product and will not have any adverse effects D. It will increase the levels of digoxin E. It will affect metabolism of digoxin by inducing liver enzymes  	

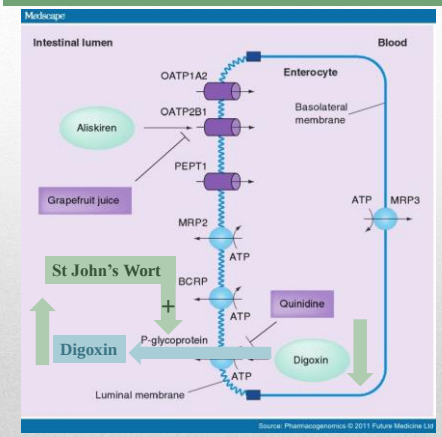
Slide 25	**Drug interactions due to alterations in absorption**  Shitara et al. Annual Review of Pharmacology and Toxicology. Vol. 45: 689-723. 2005.	

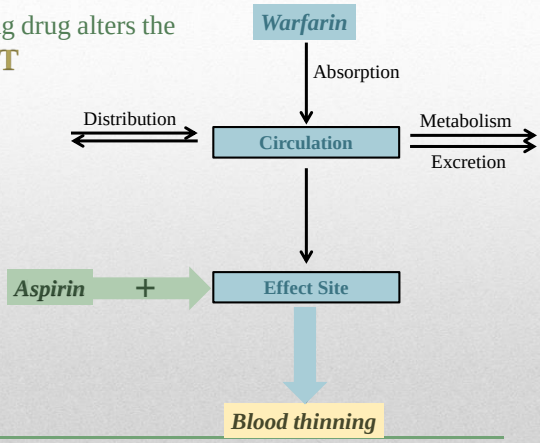
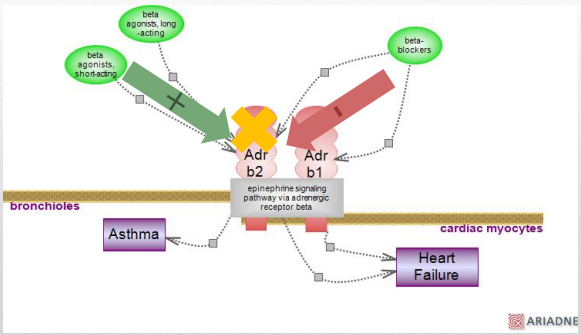
Slide 26	**Transporters**
	Cimetidine increases metformin concentration
	Cationic (e.g. OCT2)
	Probenecid increases penicillin concentration
	Anionic (e.g.OAT1,3)
	• Located in the
	  • Epithelia of intestine, liver and kidney
	  • Endothelia of blood brain barrier and blood placental barrier
	 
	Müller, F and Fromm, MF. Pharmacogenomics. 2011;12(7):1017-1037.	

Slide 27	**Discovery of P-glycoprotein** • P-glycoprotein was first described in tumour cells • Cells had over-expression of P-glycoprotein which reduced the access of cytotoxic drugs • This made the tumours resistant to various anticancer drugs and P-glycoprotein was also known as multidrug resistance protein 1(also ATP Binding Cassette (ABC)B-1)	

Slide 28	**P-glycoprotein has an evolutionary role** • Along with the cytochrome P450 (CYP) P-glycoprotein is believed to be an important evolutionary adaptation against potentially toxic substances • As an efflux transporter it limits the bioavailability of orally administered drugs by pumping them back into the lumen • This promotes drug elimination into the bile and urine and protects a number of tissues such as the brain, testis, placenta and lymphocytes	

Slide 29	• P-glycoprotein pumps drugs across
	  • renal tubules
	  • lumen of gut
	  • liver
	  • blood brain barrier
	
	• **Inducers increase drug efflux → decreased concentrations of drug.**
	
	• **Inhibitors decrease drug efflux → increased concentrations of drug.**
	
	Many drugs that are substrates for CYP3A4 are also substrates for p-glycoprotein.	

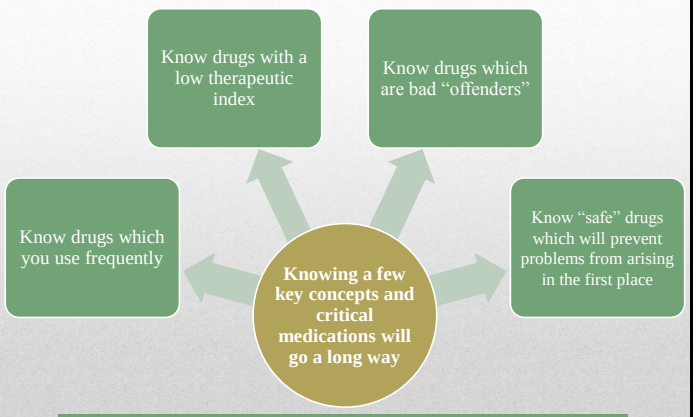
Slide 30	 	

Slide 31	A 50 year old NZ European male presents with low back pain of two weeks duration. His symptoms interfere with his work, personal life and night-time rest and he has bought Tramadol online. You discover that he is taking an anti-depressant (Fluoxetine). Why might you advise him to stop using Tramadol? A. His symptoms will resolve with time B. He is at risk of seizures C. Tramadol is a stronger pain relief than he needs D. He is at risk of low blood pressure E. Medicines bought online are not safe 	
Slide 32	Pharmacodynamic DI Interacting drug alters the **EFFECT** 	
Slide 33	Receptor Mediated DI • Both drugs act through a common receptor 	

Slide 34	**Non-receptor mediated** • Both drugs act upon the same system, but through different receptors Aspirin and warfarin *Inhibit blood thinning* — Bleeding SSRIs and tramadol *Increase serotonin levels* — Seizures and serotonin syndrome Sildenafil and nitrate *Lower blood pressure* — (Severe) hypotension	
Slide 35	**Serious Reactions with Tramadol: Seizures and Serotonin Syndrome** *Prescriber Update 28(1): 11-13.* *October 2007* *Ruth Savage* **Seizures can occur with tramadol, particularly if high doses a … increase the risk of serotonin syndrome. To reduce the likeli … seizure disorders. In patients with risk factors for seizures o …** **Clinical features of serotonin syndrome** Symptoms and signs of serotonin syndrome include at least three of the following: agitation, ataxia, increased sweating, diarrhoea, fever, hyperreflexia, myoclonu … initiating or increasing the dose of a serotonergic medicine.	
Slide 36	**Serotonin Syndrome** • Symptoms and signs include at least three of the following: *agitation, ataxia, increased sweating, diarrhoea, fever, hyperreflexia, myoclonus, or shivering* • More likely if taking two drugs that increase serotonin levels **Medicines known to cause serotonin syndrome** http://http://www.medsafe.govt.nz/profs/PUArticles/TramSerious.htm	

Table 1: Agents causing serotonin syndrome

Antidepressants	mirtazapine, monoamine oxidase inhibitors (including moclobemide), SSRIs, tricyclics, venlafaxine
Antiparkinson agents	amantadine, bromocriptine, carbergoline, levodopa, pergolide, selegiline
Illicit drugs	cocaine, hallucinogenic amphetamines such as MDMA (ecstasy), LSD, etc.
Migraine therapy	dihydroergotamine, naratriptan, sumatriptan, zolmitriptan
Other agents	bupropion, carbamazepine, lithium, morphine, pethidine, reserpine, sibutramine, St. John's wort, tramadol

Slide 37	**Starting or stopping a drug is a prescribing decision that may cause a drug interaction.**	
Slide 38	The good news  http://www.australianprescriber.com/magazine/35/3/85/8	

Slide 39	Sources of information about drug interactions
	• Medsafe datasheets
	  • http://www.medsafe.govt.nz/profs/Datasheet/DSForm.asp
	• New Zealand Formulary
	  • http://nzf.org.nz/nzf_1.html
	• Also:
	  • Hospital medicine information service
	  • Prescribing and dispensing software
	  • Tables are available online	