Basic Pharmacology

A 79-year-old man is admitted with acute shortness of breath of unknown origin. On examination his respiratory rate is 24 breaths per minute. On auscultation there is multiple crackles and wheezes. He is treated with A) nebulised salbutamol, B) intravenous hydrocortisone, C) furosemide and D) morphine, as well as inhaled E) salmeterol.

Which drug theoretically produces a pharmacological action first?
Receptors

A) Salbutamol-cellular receptor-delivered to site of action
B) Hydrocortisone-nuclear receptor-manufacture proteins
C) Furosemide-needs to cause luminal Na gradient
D) Morphine-cellular receptor-needs to diffuse across BBB
E) Salmeterol-Prodrug-needs to be metabolised
## Drugs-Mechanism of Action

<table>
<thead>
<tr>
<th>Site of Action</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell Surface Receptors</td>
<td>Morphine</td>
<td>ACE Inhibitors</td>
</tr>
<tr>
<td>Nuclear receptors</td>
<td>Steroids</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Enzymes</td>
<td>NAC, GTN</td>
<td>NSAID’s, statins</td>
</tr>
<tr>
<td>Ion channels</td>
<td>Minoxidil</td>
<td>Calcium Channel blockers</td>
</tr>
<tr>
<td>Transporter Channels</td>
<td></td>
<td>SSRI’s</td>
</tr>
<tr>
<td>Transduction Proteins</td>
<td></td>
<td>Sildenafil</td>
</tr>
</tbody>
</table>

BASIC SCIENCES FORM PART OF THE CURRICULUM
Pharmacokinetics and Pharmacodynamics

• Kinetics-What the body does to the drug
  – Absorption
  – Distribution
  – Metabolism
    • Phase 1-largely oxidative processes
    • Phase 2-adding on large sugar moieties
  – Excretion

• Dynamics-What drugs do to the body (and each other)
  – Affects each of the stages above
Case History

Man stopped for drinking and driving. Noted to have difficulty staying in his lane. His blood alcohol concentration was 95 mg/dL. (Limit 80 mg/dL). Also taking co-codamol tablets. Claims that a drug interaction is responsible for his raised blood alcohol.

Is his excuse valid or should he be convicted?
CONVICTED

Pharmacokinetics
Codeine slows gastric Emptying
Therefore less alcohol absorbed
Should have lower BAC!!

Pharmacodynamics
Codeine interacts with alcohol increasing CNS effects
An 18 year old woman with PCOS attends the acute medical clinic with anaemia and loose black stools. She is taking a combination of iron sulphate, metformin, and doxycycline. She has recently started drinking grapefruit juice as part of a health drive. Her doctor is concerned that her anaemia has not improved. What is the most likely explanation?

a) Chronic peptic ulcer disease
b) Drug interaction - metformin and FeSO4
c) Drug Interaction - FeSO4 and doxycycline
d) Poor drug compliance
e) The grapefruit juice impairing Fe absorption
Drug Interactions

• Absorption
  – Gastric emptying
  – Insoluble complexes

• Distribution
  – First Past Effects

• Metabolism
  – Phase I and 2 Processes

• Excretion
A 58 year old lady was diagnosed as having atrial fibrillation 2 weeks previously. She was started on warfarin and amiodarone. She has no significant past medical history apart from recurrent urinary tract infections for which she takes prophylactic trimethoprim and cranburry juice. She also takes ranitidine for mild gastro-oesophageal reflux disease. She attends the Emergency Department following a minor nosebleed. Her INR is 3.9. The ED SpR asks for advice regarding what he needs to do.

A. No action required
B. Stop amiodarone
C. Stop ranitidine
D. Stop the cranberry juice
E. Stop trimethoprim
Answer D

INR out of range minor bleed some action required

Amiodarone, trimethoprim and cranberry juice will all interact and increase the INR.

Amiodarone, interaction is dependent on the concentration of amiodarone. Owing to the long-half life of amiodarone and the implication that she has only just been diagnosed unlikely to cause at present time – watch out 3 months down the line.

Trimethoprim increases INR but taking regularly therefore dose should account for this

Cranberry juice increases INR, owing to cytochrome P450 interaction. Takes variable dose intermittently
Drug Food Interaction

Grapefruit/Cranberry Juice

- **Inhibits** several CYP450 isoenzymes
- ↓ Clearance of many drugs
  - Simvastatin (myositis)
  - Amiodarone (long QT)
- May lead to ↑ exposures to drug of up to 16 fold!
Proportion of Drugs Metabolized by CYP450 Isozymes

- CYP2D6: 19%
- CYP2C19
- CYP2C9
- CYP2E1
- CYP2B6
- CYP2A6
- CYP3A4: 36%
- CYP1A2
# CYP 450 Drug Interactions

## Inducers
- **P** — Phenytoin
- **C** — Carbamazepine
- **B** — Barbituates
- **R** — Rifampicin
- **A** — Alcohol (chronic use)
- **S** — Sulphonylureas & St John’s Wort

## Inhibitors
- **O** — Omperazole
- **D** — Disulfiram
- **E** — Erythromycin
- **V** — Valproate
- **I** — Isoniazid
- **C** — Cimetidine + Ciprofloxacin
- **E** — Ethanol (Acutely)
- **S** — Sulphonamides

*Do not underestimate alternative therapies!*
CYP450 Pharmacogenetics

- Variation in CYP450 expression accounts for a great deal of inter-patient variability in drug response
- Examples include:
  - Warfarin response (CYP2C9/CYP3A4)
  - Response to codeine (CYP2D6)
An overweight 58 year old lady is admitted following a fall. She had recently started the cabbage leaf diet. She has a past medical history of arthritis for which she has been taking co-codamol 30/500 for a number of years and hypertension. She had recently stopped taking diltiazem owing to concerns regarding her heart rate. Her present medication consists of co-codamol 30/500 and bendroflumethiazide. On examination she has a respiratory rate of 8 breaths per minute and pin-point pupils.

What is the most likely reason for her fall?

A. Drug interaction between co-codamol and bendroflumethiazide
B. Drug interaction between her new diet and her medication
C. She had taken an overdose of co-codamol
D. Unmasked cardiac arrhythmia following cessation of diltiazem
E. Unmasked drug sensitivity to codeine following cessation of diltiazem
E. Unmasked drug sensitivity to codeine following cessation of diltiazem

Answer E
Codeine is metabolised by CYP2D6. This enzyme exhibits polymorphism. Ultrarapid metabolises may become intoxicated with opiate as a greater proportion of the drug is metabolised to morphine. Diltiazem is an inhibitor of this enzyme.
Codeine Metabolism

- Different rates of metabolism for \textit{CYP2D6}
  - Ultrarapid \(1\text{-}7\%\)
  - Extensive \(50\%\)
  - Intermediate \(40\%\)
  - Intermediate/Poor \(7\text{-}10\%\)
  - Poor \(10\%\)
Mother who killed her baby?

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J. Leeder

In April, 2005, a full-term healthy male infant, delivered vaginally, showed intermittent periods of difficulty in breastfeeding and lethargy starting on day 7. During a well-baby paediatric visit on day 11, the paediatrician noted that the baby had regained his birthweight. On day 12, however, he had grey skin and his milk intake had fallen. He was found dead on day 13. Postmortem analysis

Codeine and breastfeeding

In 2006, Gideon Koren and colleagues published a Case Report in The Lancet on the death of a neonate whose mother was taking codeine and who was genetically an ultrarapid metaboliser of codeine to morphine. Koren and colleagues suggested that the baby died from morphine transferred during breastfeeding—a conclusion that led to widespread concerns in obstetric and paediatric circles. We have doubts about this conclusion. Furthermore, another

100 mg morphine daily would result in a therapeutic neonatal morphine concentration. We and others agree with this assessment.

On this basis, total conversion of the codeine in the present case would have produced only 60 mg morphine daily and neonatal blood morphine concentration well within the therapeutic range.4 Breastmilk morphine was 87 μg/L when retrospectively measured in this case, but post-mortem morphine in the baby was disproportionately high (70 μg/L). Therapeutic doses of morphine in neonates are

dosing, it suggests a life-threatening overdose.36

Did the drug cause death? Codeine and breastfeeding

A breastfeeding mother takes codeine with paracetamol, and her baby dies. Was either drug the cause? Gideon Koren and colleagues blamed maternal codeine ingestion for the death of a 13-day-old breastfed baby.33 Postmortem blood contained paracetamol

Postmortem change in drug concentration is a "toxicological nightmare," and interpretation is correspondingly difficult. Postmortem blood differs greatly from blood used for drug analysis in life, because of coagulation, sedimentation, haemolysis,
Drug-Drug Interaction: Pharmacodynamic

- Interactions either enhance or reduce therapeutic outcome through actions on the receptors

- Drug interactions can occur via different receptors or different tissues
32 year old lady admitted from a psychiatric hospital following an overdose of paracetamol. Her present medication consists of haloperidol and amiodarone for intermittent SVT. The psychiatrist recommends she is started on an antidepressant. Which of the following medication is the most appropriate

a) Amitriptyline
b) Doxepin
c) Fluoxetine
d) Mirtazapine
e) Venlafaxine
a) Amitriptyline
b) Doxepin
c) Fluoxetine
d) Mirtazapine
e) Venlafaxine

BNF-all antidepressants equally efficacious

What other issues:
Haloperidol and amiodarone both affect QTc, adding in a third drug which also affects cardiac conduction ...
QTc Interval Prolongation

- Genetic and Acquired Forms
- Ion channel and sympathetic abnormalities
- QTc lengthened by many anti-arrhythmics
- Other drugs also prolong QT
- Any drug that impairs metabolism of a QTc prolonging drug may cause LQTS
Prolonged QT-interval

<table>
<thead>
<tr>
<th>Antiarrhythmic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
</tr>
<tr>
<td>quinidine, disopyramide, procainamide</td>
</tr>
<tr>
<td>Class III</td>
</tr>
<tr>
<td>sotalol, amiodarone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-antiarrhythmic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
</tr>
<tr>
<td>erythromycin, bactrim</td>
</tr>
<tr>
<td>Antifungal</td>
</tr>
<tr>
<td>ketoconazole,itraconazole</td>
</tr>
<tr>
<td>Antihistamine</td>
</tr>
<tr>
<td>terfenadine, astemizole</td>
</tr>
<tr>
<td>Psychiatric drugs</td>
</tr>
<tr>
<td>tricyclic antidepressants, phenothiazines, haloperidol</td>
</tr>
<tr>
<td>Cholinergic antagonists</td>
</tr>
<tr>
<td>cisapride, organophosphates</td>
</tr>
<tr>
<td>Other drugs</td>
</tr>
<tr>
<td>cocaine, arsenic</td>
</tr>
</tbody>
</table>
Clinical Toxicology
Overdose UK

<table>
<thead>
<tr>
<th>Region/Primary care trust</th>
<th>Poisoning Per 100,000 pop</th>
</tr>
</thead>
<tbody>
<tr>
<td>England</td>
<td>22.4</td>
</tr>
<tr>
<td>Redcar and Cleveland</td>
<td>56.7</td>
</tr>
<tr>
<td>Leicestershire County and Rutland</td>
<td>19</td>
</tr>
</tbody>
</table>
A 21 year old student is brought into the Emergency Department by friends with an excruciating tooth ache, not controlled with paracetamol and ibuprofen as well as fever and rigors. Over the previous 2 days she has ingested 32 500 mg paracetamol tablets and 16 200 mg ibuprofen tablets which have failed to control her symptoms. She is a known epileptic on carbamazepine and leviteracetam. She asks for “pain-killers” to be prescribed until she can see her dentist in 2 days time. Owing to the number of paracetamol taken blood tests are performed 4 hours after she took her last paracetamol tablet. 2 hours later the following results are available;

- Urea 3.2 mmol/L (3.2-8.5)
- Creatinine 60 umol/L (45-105)
- ALT 91 iu/L (<50)
- Alk Phos 81 iu/L (<130)
- Paracetamol 25 mg/L

What is the most appropriate drug to be prescribed?

A. acetylcysteine  
B. co-codamol  
C. diclofenac  
D. metronidazole  
E. tramadol
Answer A

This patient has taken a staggered overdose of paracetamol. She is at increased risk of liver damage owing to her long-term requirement for carbamazepine. She urgently requires acetyl cysteine to be administered.
Paracetamol Overdose

[Chemical diagram showing the metabolism of paracetamol (acetaminophen) with pathways for sulfate and glucuronide conjugation, and hepatoxic free NAPQI metabolite formation.]
High Risk Patients for Complications

Excess acetaminophen intake

• Taking liver enzyme-inducing drugs
  – chronic alcohol use
  – carbamazepine, phenobarbital, phenytoin, isoniazid, rifampin

• Malnourished-
  – anorexia, cystic fibrosis, hepatitis C, HIV positive

• Not Eaten for a few days.
Stimulant Drugs

• Drugs acting on the adrenergic system
  – Adrenaline
  – Sympathiomimetics
  – Beta-2 agonists
  – Cocaine
  – Ecstasy
Effects of adrenaline

- fear, excitement
- tremor
- palmar sweating
- vasoconstriction
- heart rate, BP
- arrhythmia
- pupil size
- salivary flow
Stimulants

Cathinones - Mephedrone
Aka: butylone, M1, MDPV, Methylone, pyrovalerone.
Adrenergics

• agitation, hallucination, seizures
• tremor, muscle over-activity
• hyperthermia
• tachycardia, hypertension
• pupillary dilation

• Early death from arrhythmia
  adrenergic hyperstimulation
  hyperkalaemia

• Later death from hyperthermia/rhabdomyolysis
A young patient is admitted from a night-club having taken “Buzz” a new Cathinones derivative. On examination she is confused, sweating and hot to the touch. Her heart rate is 130 beats per minute, respiratory rate 20 per minute and temperature is 39°C. Neurologically she has no focal neurology apart from mild ankle clonus. She suffers a brief convulsion.

What treatment does she immediately require?

A. Dantrolene  
B. Haloperidol  
C. Diazepam  
D. Esmolol  
E. Normal Saline

Answer – Serotonin Syndrome - initially iv fluids
Serotonin Actions

Central Nervous System: Modulates attention, behaviour and thermoregulation

Peripheral Nervous System: Vascular tone and gastric motility

Excess Serotonin $\rightarrow$ Serotonin Syndrome
Clinical Presentation

- Classic clinical triad:
  - Mental status changes
  - Autonomic hyperactivity
  - Neuromuscular abnormalities

- Wide ranging symptoms

- Hyperreflexia (greater in lower extremities)
- Clonus (greater in lower extremities)
- Tremor (greater in lower extremities)
- Increased bowel sounds; may have diarrhea
- Autonomic instability; often hypertensive
- Tachycardia
- Diaphoresis
- Agitation
- Mydriasis
Serothonin Syndrome

Management

1) Stop causative agent
2) Good supportive care
   -iv fluids, oxygen, monitoring etc
3) Control autonomic instability
   -sodium nitroprusside, esmolol
4) Control hyperthermia
   -diazepam/dantrolene
5) Consider antidotes
   -cyproheptadine- 5-HT1A and 5-HT2A
Confusion memory loss
Movement Disorders
Temperature (sex)
Frontal Cortex
Nigrostriatal
Dopamine Blockade
Hypothalamus
Autonomic nervous system
Blood Pressure
Heart Rate
Respiratory Rate

Neuroleptic Malignant Syndrome
Neuroleptic Malignant Syndrome

• Presentation
  – Hx antidopaminergics: gradual process
  – O/E pyrexia, confusion, rigidity, autonomic instability (pallor, tachy, labile BP, sweats)

• Blood test changes in NMS
  – CK usually >1000iu/L
  – WCC >10x10⁹L
  – ↑ALT, Alk Phos, LDH, Na⁺, K⁺, H⁺
  – ↓Mg++, Ca++, Na⁺, serum iron
## Summary

<table>
<thead>
<tr>
<th></th>
<th>Neuroleptic malignant syndrome (NMS)</th>
<th>Serotonin syndrome (SS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causative agents</strong></td>
<td>Dopamine antagonist</td>
<td>Serotonin agonist</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Days to weeks</td>
<td>Within 24 hours</td>
</tr>
<tr>
<td><strong>Neuromuscular findings</strong></td>
<td>Bradyreflexia, severe muscular rigidity</td>
<td>Hyperreactivity (tremor, clonus, reflexes)</td>
</tr>
<tr>
<td><strong>Treatment agents</strong></td>
<td>Supportive Care, Dantrolene</td>
<td>Supportive Care, Benzodiazepine, Cyproheptadine</td>
</tr>
<tr>
<td><strong>Resolution</strong></td>
<td>Days to weeks</td>
<td>Within 24 hours</td>
</tr>
</tbody>
</table>
32 year old Eastern European is admitted with symptoms of acute paranoia, sweating, tremor and myoclonus. His friends state he is a known drug abuser?

Which agent is he most likely to have taken?

a) Butane Gas
b) Diazepam
c) Heroin
d) Methanol
e) Synthetic cannabinoid
Synthetic Cannabinoids

Pandora's Box Herbal Incense

Name: Pandora's Box Herbal Incense

This Product is Hazardous and Not for Human Consumption!

Drop menu below for bulk discounts.

1g = £8.00
3g = £22.00
6g = £40.00

Add to Cart
SYNTHETIC CANNABINOIDs

RELATED TERMS: X, TAI HIGH HAWAIIAN HAZE, SPICE, MARY JOY, EXODUS DAMNATION, ECSESS, DEVIL'S WEED, CLOCKWORK ORANGE, BOMBAY BLUE EXTREME, BLUE CHEESE, BLACK MAMBA, ANNihilation, AMSTERDAM GOLD.

THE DRUG  THE EFFECTS  THE RISks  THE LAW

What are the effects of synthetic cannabinoids?
Synthetic cannabinoids act like THC, the active substance in cannabis. They may be stronger than typical cannabis and because these substances are so new, they may have completely unknown effects. Typical cannabis effects include:

- Some can make you feel happy and relaxed
- Some can make you feel hungry
- Some can make you get the giggles
- Some can make you become very talkative
- Others get more drowsy
- Mood and perception can change
- Concentration and coordination may become difficult
- Some will have quite bad reactions. Paranoia, panic attacks and forgetfulness are all associated with using cannabis.
Features

- CNS: agitation, tremor, anxiety, confusion, somnolence, syncope, hallucinations, changes in perception, acute psychosis, nystagmus, convulsions and coma.
- Cardiac: tachycardia, hypertension, chest pain, palpitations, ECG changes.
- Renal: acute kidney injury.
- Muscular: hypertonia, myoclonus, muscle jerking and myalgia.
- Other: cold extremities, dry mouth, dyspnoea, mydriasis, vomiting and hypokalaemia.
- Loss of eyesight and speech have also been reported (Westerbergh and Hulten, 2011).
Management

• ABCDE
• Cooling
• CNS agitation etc-Diazepam
• Cardiac-monitor check QTc interval NaHCO$_3$
• Hypertension-Diazepam, NO$_3$
• Renal-rehydrate

... and wait
Other Overdoses

• SCE examine writers have more tricyclic overdoses than anyone else
• Don’t forget about salicylate and NSAID overdoses
• Remember basic principles
  – Absorption- decontamination
  – Distribution- dialysis
  – Metabolism-drugs
  – Excretion-urine alkalinisation
Summary

• Remember basic pharmacology
• Don’t panic about drug interactions
• Remember we’re not all the same
• Think clinically
• Think what would I do in practice