CASE STUDY 1 - AKI

Mr Anthony Brown is a 54 year old male is admitted to hospital at 09:00 this morning with community acquired pneumonia. You are a prescribing pharmacist in the acute medical unit, working alongside a doctor to review Mr Brown.

1. What is Mr AB's CrCl in ml/min and what stage of AKI is he currently in? (Baseline creatinine = 120 µmol/L / Baseline eGFR = 20ml/min/1.73m^2)

$$\frac{(140-54) \times 70 \times 1.23}{270}$$

= 27ml/min

AKI Stage 2 as 2-2.9x baseline creatinine

Note: **For UEA workshops/exams always use actual body weight**. In practice IBW may be used in some cases e.g. extremes of muscle mass, but use of ABW/IBW is still debated in practice and varies – see prescribing in renal impairment in the BNF for more information.

2. The doctor wants to prescribe co-amoxiclav IV for Mr AB's CAP. Using the BNF and the renal drug handbook extracts, what are the recommendations for dosing?

BNF	RHB
1.2 g initially, then 600 mg every 12 hours (eGFR 10-30ml/min/1.73m^2)	1.2g every 12 hours (CrCl 10-30ml/min)

Note: In practice we would use RHB dosing.

There is an argument for using a higher dose as their CrCl isn't far from 30ml/min & we are expecting this to improve – drug dependent as to what you would do in practice, for an anti-biotic you may choose to go higher to treat the infection. For UEA workshops/exams stick to resource recommendations but be aware of the practicalities of prescribing in practice.

3. Using the drug chart written in A&E earlier today, prescribe the co-amoxiclav as per your recommendation in Q2. The prescription should start at 18:00 this evening.
   [ANSWER ON DRUG CHART]
   Note: Duration could be between 5-7 days. BNF duration for CAP for PO dosing is 5 days, however as the patient has been hospitalized and needing IVs, 7 days would be acceptable.

4. Using the drug chart, identify any actual and potential pharmaceutical care issues for your patient. Using the tables below to help you document the issue(s) and the action(s).
   Where you recommend the patient to start on any **NEW** medication, please also complete details of the monitoring parameters for the new drug, otherwise leave it blank. (the number of boxes below does NOT give any indication to the number of issues to be identified)

Issue	**Action required**
No allergy status	Add allergy status from history onto the chart (also ensure verbal check with patient)

Issue	**Action required**
Perindopril prescribed in AKI and hypotensive state	Hold perindopril Monitor renal function & blood pressure. Re-start once AKI and bp resolve due to long term reno protective benefit for T2DM patients.
Monitoring parameters	
Therapeutic	**Toxic**
	BP target <140/90

Issue	**Action required**
Simvastatin not EBM according to guidelines (and over 10mg ON) Note: Would hold in AKI if risk of rhabdomyolysis, in this patient no need to hold necessarily, but may be held while in AKI & unwell as no harm in doing so	Change to atorvastatin 20mg ON as per EBM. No dose reduction required (consider aspirin review as lack of evidence for primary prevention)
Monitoring parameters	
Therapeutic	**Toxic**
Lipid profile – Total cholesterol + LDL + HDL (target >40% reduction in non-HDL cholesterol) Lack of CV event	LFTs, myopathy/muscle pain, creatinine kinase (CK)

Issue	Action required
Metformin C/I in CrCl <30ml/min (Note in RHB = 25% of dose if CrCl 10-45ml/min, however in 'other information' states manufacture C/I – appears some debated research however current practice is manufacturer recommendation) No SGTL2I	Hold metformin and monitor CrCl and blood glucose. Re-start once CrCl >30ml/min. Once recovered consider initiation of Dapagliflozin 10mg OD as per T2DM guidelines, and when starting dapagliflozin, consider stopping gliclazide, dependent on glucose control, as this may take over glycaemic control with the metformin. No need to hold gliclazide due to AKI as mostly cleared by the liver – in practice high doses may be reduced for safety as a small % is excreted by the kidney/if blood glucose if low or borderline.

Monitoring parameters	
Therapeutic	**Toxic**
Blood glucose (4-7mmol/L) HbA1c (target 48mmol/mol)	Blood glucose <4mmol/L Counsel patient regarding: MHRA warning for Fournier's Gangrene (keep genital area dry/clean and be aware of symptoms such as itching and irritation that indicate infection) Sick day rules – hold while acutely unwell particularly in D&V (provide with patient information leaflet linked on Bb for information)

Issue	Action required
Apixaban should be reduced to 2.5mg BD as CrCl 15-29ml/min.	Reduce dose to 2.5mg BD. Monitor CrCl and increase back to 5mg BD dosing once AKI resolved. If worsens below 15ml/min then switch to LMWH.

Monitoring parameters	
Therapeutic	**Toxic**
Lack of CVA	Hb, bleeding signs, ORBIT score

Issue	Action required
Ibuprofen OTC – can cause AKI, MHRA advise avoid in renal impairment where possible	Stop taking ibuprofen PRN, can cause AKIs by pre-renal route (reduced perfusion) or intrinsic AKI if severe acute reduced perfusion (acute interstitial nephritis). Prescribe paracetamol PRN as a replacement for pain management. (500mg-1g QDS PRN, or 1g QDS PRN would be acceptable dosing for this patient)

Monitoring parameters	
Therapeutic	**Toxic**
Pain score	Weight (<50kg reduce dose) Liver impairment (reduce dose)

5. **Once you have confirmed the care issues with a facilitator,** amend the drug chart accordingly to carry out your actions.
   [ANSWERS ON DRUG CHART]
   Note: You do not have to demonstrate changes exactly as shown, as long as you have made your changes clear e.g. 'Hold, signed & dated' from the next dose, so there is no chance a nurse would give the next dose + your details are on the front page as a prescriber so that who your signature belongs to is clear.

CASE STUDY 2 – CKD

Ms Ali Rai is a 64 year old female with CKD stage 5 who is starting on dialysis. She will be having haemodialysis three times a week and her history is below. You are a non-prescribing pharmacist at the clinic reviewing Ms Rai.

1. For each of the following drugs, check both the SPC and Renal Drug Handbook and document in the tables below the dosing advice given in each resource.

Drug: Aspirin	
SPC	**RHB**
C/I in severe renal impairment	Dose as in normal renal function

Drug: Ramipril	
SPC	**RHB**
Slightly dialysable. Initial dose 1.25 mg/day and the maximal daily dose is 5 mg; should be administered few hours after haemodialysis is performed.	Initial dose 1.25 mg daily and increase according to response.

Note: ‘dialysable’ = capable of diffusing through dialysis membrane

Drug: Bendroflumethiazide	
SPC	**RHB**
Use with caution in renal impairment (severe renal insufficiency is a contraindication to use)	Unlikely to work.

Note: From teaching - ineffective CrCl<30ml/min (BNF 01.24)

Drug: Atorvastatin	
SPC	**RHB**
No adjustment of dose is required	Not dialysed. Dose as in normal renal function

Drug: Bisoprolol	
SPC	**RHB**
In patients with severe renal impairment (CrCl <20ml/minute), the dose should not exceed 10mg once daily.	Dose as in normal renal function

Provided below are Ms Rai’s pre-dialysis blood test results.

2. Using the results above, what treatment would you recommend giving to Ms Rai prior to dialysis treatment and why? Please include in your answer any toxic or therapeutic monitoring parameters for new medication recommended.

- Reduced Hb due to low erythropoietin levels in the blood, causing less RBC proliferation in the bone marrow.
  Treat with IV recombinant human erythropoietin e.g. Eprex 50units/kg 3x weekly (maintenance 75-300units/kg weekly).
  Target: Hb 100-120g/L.
  Toxic: Hb >120g/L (can lead to CV events & clots), joint pain, high bp (dose-dependent)

- Reduced ferritin – low iron stores due to mainly reduced absorption, **need to replace this first** for epo injection to be effective.

IV iron therapy e.g. Ferinject (indicated when <200mcg/L)
Target: Ferritin 200-500mcg/L
Toxic: high bp, skin, anaphylaxis, hypophosphataemia

3. Post- dialysis, Ms Rai’s bp is 150/92. Using the information provided, including your answers to Q1, critique the management of Ms Rai’s hypertension. Any new medication proposed should have toxic and therapeutic monitoring parameters written.

Target <130/80 mmHg as CKD, HTN and ACR >70mg/mmol
Bendroflumethiazide contra-indicated – stop.
Ramipril – 5mg max dose in SPC, no max dose in RDHB. Check how pt is tolerating, check toxic parameters e.g. potassium, before up-titrating if able to tolerate. Note: not concerned over effects on CrCl as already ESRF.
Add in CCB e.g. amlodipine 5mg OD (BP target <130/80mmHg, toxic parameters: ankle oedema, dizziness, headaches)
Note: SGTL2 inhibitor – not in this patient as CKD5 would be under the guidance of eGFR 25-75 at start of treatment

Using your answers to questions 2 and 3, fill in the below SBAR form.

CASE STUDY 3 – CKD

SITUATION	e.g. I am (x) from (x). I am reviewing (x) and need to discuss issues (x) … I am (student name) a pharmacist in clinic today. I am reviewing one of our patients named Ali Rai and would like to a discuss a few issues I have found with you.
BACKGROUND	e.g. (x) is an (x) patient. Their last set of observations/blood tests were (x). Ms Rai is a CKD stage 5 patient starting their first haemodialysis session today. In their pre-dialysis bloods, they have a low haemoglobin and low ferritin, and their blood pressure remained high after dialysis at 150/92.
ASSESSMENT	e.g. I think the problem is (X) These results suggest Ms Rai is experiencing renal anaemia and needs replacement erythropoietin and iron therapies. Also, as her blood pressure target would be <130/80 I suggest we optimise her anti-hypertensive therapies to help bring this under control.
RECOMMENDATION	e.g. I recommend that we (x) with a target of (x) and follow up (x) I would recommend that we give 1g of Ferinject IV then start Eprex at 50units/kg three times a week and titrate to a maintenance weekly dose. To control her blood pressure, I recommend that we stop her bendroflumethiazide as this will be ineffective at this stage of CKD. Also, I recommend we up titrate her ramipril to 7.5mg OD or add in a calcium channel blocker, such as amlodipine 5mg OD, with follow up in a weeks' time to assess her blood pressure control.

Mx Kai Harrison, aged 66 (DOB: 22.01.1958, address: 12 Flatplace Gardens, Flatplace, FP6 7NQ) has CKD stage 5 and receives haemodialysis 3 times a week. They are visiting the clinic for their dialysis and are complaining of severe itching. You are a prescribing pharmacist reviewing their recent blood test results and clinical observations.

Using the test results above, explain why their calcium and phosphate are out of range, and how this should be managed. For any new medications recommended, include any therapeutic and toxic monitoring parameters.

- Raised phosphate levels (hyperphosphataemia) due to kidneys inability to excrete phosphate

Prescribe a phosphate binder e.g. calcium acetate 1-2 tablets three times a day with meals, dose depending on meal size
Therapeutic: Phosphate target 1.1-1.7mmol/L in dialysis patients, pruritis control
Toxic: GI side effects (constipation/nausea/diarrhoea), Hypercalcaemia (>2.6mmol/L)

NOTE: If pruritis management mentioned, creams/gabapentinoids/antihistamines can be used off-label but no NICE guideline. Jan 2024: Approval of Difelikefalin for pruritis in CKD patients on haemodialysis – activating opioid K receptors. STUDENTS DO NOT NEED TO KNOW PRURITIS TREATMENTS & WILL NOT BE EXAMINED ON, THIS IS FOR INFORMATION ONLY (this is stated in screencasts also)

- Reduced calcium level (hypocalcaemia) due to low activated vitamin D levels, and a high level of sequestering by phosphate.

Prescribe activated vitamin D or partially activated vitamin D (e.g. alfacalcidol 1mcg OD)
Target corrected calcium 2.2-2.6mmol/L
Toxic: Calcium >2.6mmol/L, abdominal pain, nausea

- Counselling for all new drugs – indication, dose, frequency, side effects

~~Details for individual medication~~
AVOID OTC: NSAIDs

The next week, you are reviewing Mx Harrison's pre-dialysis blood tests at the clinic.

Using the blood test results above, what pharmaceutical issue(s) can you identify and what action(s) would you take? For any new medications, state any therapeutic and toxic monitoring parameters.

Phosphate remains high despite treatment

- Check adherence, phosphate binders notorious for low adherence due to tablet burden & GI side effects
- If poor adherence – counsel & encourage adherence if they are able to tolerate
- If they cannot tolerate/have good adherence but ineffective – use alternative

e.g. Sevelamer 800mg, 3-6 tablets TDS (2.4-4.8g daily in 3 divided doses)
Therapeutic: Phosphate target 1.1-1.7mmol/L in dialysis patients, pruritis control
Toxic: GI side effects (constipation/nausea/diarrhoea)
~~**Don't forget diet – referral to renal dieticians for dietary advice & lowering intake of high phosphate**~~ ~~(Note: students are not expected to know any more detail than this regarding dietary advice)~~

BIOCHEMISTRY Collection LAB No 31/01/2023 1671	Total protein **51*** (60-80) g/dl	Albumin **27*** (35-50) g/dl	Bilirubin **65*** (3-20) µmol/l	ALP **370*** (20-100) IU/l	AST **212*** (5-40) IU/l
	ALT **60*** (5-30) IU/l	GGT **246*** (5-45) IU/l	PT **22*** (10-15) secs	Hb **9.9*** (14-18) g/dl	WBC 10.3 (4-11) x 10^9/l
	Na 134 (134-145) mmol/L	K 4.7 (3.6-5.0) mmol/L	Urea 6.8 (1.7-7.1) mmol/L	Creatinine 123 (55-125) µmol/L	

No result for ammonia. Would expect urea to decrease as it is not produced by the liver and ammonia to rise as it is what the liver converts to urea. This leads to encephalopathy as ammonia crosses the BBB. Some patients do not have increased ammonia but display symptoms of HE – there is believed to be other mechanisms by which HE occurs, i.e. increased permeability of the BBB.

1. What signs/symptoms and lab test results are consistent with alcoholic liver disease?

Sign/symptom/blood test result	**Brief description of pathophysiology behind the result/presentation seen for the patient**
Medical history – continued excessive alcohol intake. Signs/symptoms: ● **confusion** [⇒ alcohol withdrawal/ encephalopathy/W-K syndrome], ● **jaundice** [impaired metabolism], (When thinking about some of the symptoms of liver disease we need to consider their causes. The liver receives ~75% of its blood from the hepatic portal vein which drains the capillary bed of the gut, arterial blood comes from the hepatic artery. Normally large volumes of blood flow through the liver uninterrupted however in many liver diseases, vascular resistance is increased due to inflammatory damage (fibrosis) with the formation of some new blood vessels. This can further develop to cause disrupted architecture loss of function and random, disordered regeneration of the hepatocytes and of circulation. This leads to increased portal vein hypertension ⇒ formation of collateral circulation (smaller thin-walled veins and the formation of new, disorganised thin walled vessels) and other symptoms of the disease…) ● distended abdomen [⇒ **ascites**], ● **spider naevi**, ● **palmer erythema**, ● **peripheral oedema** Blood tests: ● ↑ Bil,ALP [⇒ ↓ bilary secretion],	Alcohol withdrawal – minor - CNS hyperactivity (insomnia, tremor, anxiety, diaphoresis, palpitations). Seizures. Delirium tremens (DTs) – hallucinations, confusion, disorientation, tachypnoea, hypertension, agitation, severe tremor, diaphoresis – can be fatal. Encephalopathy can be due to ammonia crossing the BBB, as it cannot be broken down to urea in the liver and due to the disrupted blood flow through the liver meaning it enters the systemic circulation. Wernicke-Korsakoff syndrome. This is a neurological syndrome due to the deficiency of vitamin B (thiamine) due to malnutrition. Impaired liver cannot effectively conjugate and excrete bilirubin therefore it is increased in the circulation and appears in the skin and in the sclera of the eyes. Number of causes. Activation of renin/ang/aldesterone system due to the reduced renal blood flow seen when there is the disordered anatomy of the hepatic/collateral blood flow. This leads to retained sodium and water. Secondary hyperaldosteronism – due to this activation. This means that there is fluid retention and is exaggerated as the liver would normally metabolise aldosterone which cannot happen as liver failing. Reduced albumin – reduces the osmotic pressure in the plasma and causes leakage and oedema/accumulation in tissues – peritoneal cavity. Due to the portal hypertension, this accumulation occurs around the abdomen. Due to the vascular changes as described above. Dilation of vessels on the skin. Usually found on the torso. Can be seen in other situations pregnancy/COC use. Due to the altered circulation. As above (What is another symptom of the collateral system? - Bleeding oesophageal varices.) Alk phos - v. high in biliary obstruction and also found in other tissue.

● ↑ ALT, AST, GGT [⇒ liver cell damage], ● ↓ albumin [is the liver working?], ● ↑ PT [⇒ ↓ function] [is the liver working?], ● ↓ Hb [aneamia/bleeding] ● Electrolyte abnormalities	Bili – jaundice (yellowing of skin) when >35 micromol/L. Transaminases – AST in hepatocytes and other tissue not just liver. ALT more specific to liver. Seen in cholestatic jaundice and cirrhosis. Ratio AST/ALT>2 alcohol injury, <1 other disease. GGT very high in biliary obstruction and lower increases in alcohol/drug tox/hepatitis/cirrhosis/cholestatis. Also, in other tissue. Elevated when patients drink but reduce after 3-6 weeks of abstinence-good for monitoring adherence. Where enzymes are found in other tissue LFTs must be interpreted with the whole patient picture – MHx, signs etc. Albumin made only by liver, 20-26 day half life means reductions are indicative of long term damage. How long it takes for the blood to clot. It is increased when there is a lack of underlying clotting factors. Depends on factor 2, 7, 9 and 10, increasing if these factors are not produced. These require vitamin K (fat soluble vitamin needing bile salts for absorption) – administration of vit K can indicate the type of damage there is, i.e. give Vit K no response = hepatocellular damage as it is not able to produce the clotting factors, whereas, if the issue is cholestasis where there is a deficiency in bile salts (needed to absorb vit K) the PT will decrease. Bone marrow suppression in end stage disease. May appear low as dilutional effect of excessive fluid intake.

What would your thoughts be if the patient had signs of liver disease but LFTs are not raised?

- Severe liver impairment, there are not the hepatocytes present to produce the enzymes and so may appear to be normal.

2. Comment on the choice of 'once only' medication used to control the agitation, tremor and nausea. Explain what alternative recommendations you would make to the junior doctor?

Symptoms highly likely to be due to alcohol withdrawal – anxiety, agitation, sweating, hypertension, tremor, tachycardia, restlessness, insomnia, N&V, confusion.

Regularly drinking 15 units/day and or a score of >15 on the Severity of Alcohol Dependence Questionnaire SADQ (appendix 2) tells us how likely they are to get withdrawal and predict severity. This can be used to determine doses of treatment.

Healthcare professionals can use the clinical Institute Withdrawal Assessment of Alcohol Scale – CIWA-Ar (Appendix 1) to help determine when a dose of benzodiazepine.

Treatment is symptom control (benzo) and supportive care - correct fluid and electrolyte abnormalities.
Benzodiazepines – control psychomotor agitation and prevent progression to more severe adverse effects.
Diazepam is a benzodiazepine.
However, diazepam long acting [half-life 20-100hr] + ↑ risk of masking encephalopathy. It is also prone to abuse.

In acute alcohol withdrawal syndrome recommend a reducing regime of chlordiazepoxide. This is also a long acting benzodiazepine and is more effective than shorter acting ones at preventing seizures and delirium. They have less rebound than shorter acting agents. Chlordiazepoxide has a more gradual onset of psychotropic effects, less potential for misuse and less toxic in overdose.

There is an accumulation risk in elderly and those with liver failure. Shorter acting agents such as oxazepam [half-life about 3-21hrs] can be used. **Therefore, for this patient oxazepam would be best however will require close observation to avoid withdrawal symptoms.**

You want to use the lowest possible dose without causing sedation as this increase's likelihood of encephalopathy.

See separate oxazepam prescription and NNUH guidance on the doses that are given. Some patients as a standard regime whereas other (where specially trained staff are available to monitor the patient) a symptom triggered regime may be used. This involves reviewing the patient for symptoms and giving doses if necessary using the clinical Institute Withdrawal Assessment of Alcohol Scale – CIWA-Ar (Appendix 1).

Fixed dose chlordiazepoxide could therefore be between 20-40mg QDS starting dose and then decreased over 9-10 days.

Due to the hepatic impairment in this patient the symptom triggered approach is preferred and the use of the dose.

Do not send home with supply – issue of dependence and risk of respiratory depression (especially when used with alcohol).

Drug: Lactulose

Appropriateness: Appropriate treatment of hepatic encephalopathy [↓ pH of intestine & therefore ↓ ammonia-forming bacteria, reduction in absorption of the now ionised molecules, ↑ gut transit time & therefore ammonia absorption].

Other options - Rifaximin (added when optimised lactulose not working) and phosphate enema.

Issues	Action required
Dose potentially too low as signs of HE. Must check stool chart/assess stool frequency/consistency.	Speak to Dr to get dose amended to achieve 2-3 loose stools per day [up to 50ml tds]. Likely to be too low a starting dose – start 20ml bd-tds to 30-50mL TDS. Ensure avoidance of precipitating factors – dehydration, hypokalaemia, GI haemorrhage, CNS drugs, high protein diet, constipation.

Monitoring parameters

Therapeutic	Toxic
Symptoms of encephalopathy, stool chart (aim 2-3 loose stools per day)	Stool chart - avoid diarrhoea causing dehydration/hypovolaemia Adherence s/e abdo pain, flatulence, N&V

Drug: Pabrinex IVHP (vit B and C given over 30 mins)

Appropriateness: B vitamins are appropriate for use in a patient with alcoholic liver disease as alcoholism is associated with vitamin B1 deficiency which can lead to Wernicke's encephalopathy and Korsakoff's psychosis (Wernicke-Korsakoff syndrome). IV form, dose dependent on likelihood of the syndrome.

Issues	Action required
Risk of anaphylaxis with IV pabrinex. Dose potentially too low.	Speak to Dr regarding a dose change considering probable withdrawal and risk of WKS. As per NNUH guidelines – 2 pairs TDS for 3 to 5 days. Alongside oral thiamine 100mg TDS, continued for 3-6 after abstinence is achieved or long-term if drinking continues.

Monitoring parameters

Therapeutic	Toxic
No signs/symptoms of WKS	Anaphylaxis Injection site reactions

Drug: Vitamin K injection (phytomenadione)

Appropriateness: As clotting factors are made in the liver; impairment may mean that these are not produced and increase a patient's risk of bleeding. Mr AM's prothrombin time is elevated.
In patients with alcoholic liver disease, which increases their risk of major bleeds such as oesophageal varices, you want to reduce the risk of bleeding wherever possible. This may not work if their liver damage is extensive as it is due to a lack of liver production of clotting factors and not a lack of vitK absorption.
IM – not appropriate as it increases the risk of bleeding and haematoma formation.

Issues	Action required
Method of administration not appropriate. It increases the risk of bruising and bleeding in a patient already at increased risk of this.	Ask dr to prescribe IV. Ensure avoidance of aspirin/NSAID and anticoagulants

Monitoring parameters

Therapeutic	Toxic
Prothrombin time – reducing to normal	Method of administration

Drug: Spironolactone 100mg od

Appropriateness: First line treatment for ascites (add in furosemide if desired effect of optimised spiro not seen and if other areas of oedema). To get rid of the accumulated fluid. It is an aldosterone antagonist and as this is part of the cause, it means it is a first line choice.
Fluid restriction.
Paracentesis.

Issues	Action required
None - appropriate choice & starting dose for treatment of ascites	

Monitoring parameters

Therapeutic	Toxic
weight loss [aim 0.5-0.75 kg/day or 1-1.5 kg/day if peripheral oedema] needs to be steady to prevent hypovolaemia and reduced K+ and Na+,	U&E's [RF and K+/Na+] gynaecomastia s/e

abdominal girth	

3. Document any additional pharmaceutical care issues and actions in the table below

Issues	Action required
Continuation of thiamine to reduce the risk of V-K syndrome	Ensure supply of thiamine 100mg TDS for discharge.
Referral to DAL to help with dependence on alcohol.	Refer to DAL team.
Multivitamins – due to potential malnutrition.	
To reduce the risk of bleeding from the collateral circulation we should aim to reduce the portal blood pressure using low dose – carvedolol or propranolol (cautiously titrated as drug undergoes extensive first pass metabolism so need to monitor effect in a liver patient).	Check whether the medical team are thinking of initiating (carvedolol 6.25 mg) or propranolol (40mg BD) adjust according to HR.

Mr AM has not lost enough weight since he was admitted and asks how he should increase the spironolactone.

4. What advice would you give the junior doctor?

Spironolactone takes 2-3 days to have effect, therefore continue for at least another day.
If desired reduction in weight/girth not seen, ↑ by 100mg every 2 days until diuresis achieved [max 600mg per day, although in practice doses this high rarely used – single dose or divided if causes GI side-effects]
Add in furosemide if still no weight loss [especially if also peripheral oedema].

Caution not to cause hypovolaemia due to risks associated with encephalopathy.

What other drugs should the doctor and Mr AM be recommended to avoid or use with caution due to his liver cirrhosis?

You need to consider which function of the liver have been lost in your patient. For the patient in this workshop with cirrhosis, they have lost their metabolic, excretory and synthetic capabilities. Therefore, careful consideration is required for any drug that relies on these properties.

- **Hepatotoxic** – see separate sheet for details of the types of hepatoxicity some drugs can cause.
- **Anything affecting clotting/bleeding** eg. NSAIDs, warfarin, DOACs, clopidogrel, heparin, corticosteroids SSRI's (increased risk of upper GI bleeding and decreased serotonin uptake into platelets reducing their ability to form clots)– patient is likely to have clotting abnormalities (reduction in clotting factor production, and splenomegaly causing low red cells, white cells and platelets). Portal hypertension can cause splenomegaly and therefore low counts – increased bleed risk, and development of a collateral circulation in delicate blood vessels of the oesophagus and stomach which can rupture and cause excessive bleeding – risk with drugs causing GI bleeding.
- **Anything causing GI ulceration** e.g. NSAIDs, corticosteroids, aspirin, bisphosphonates.

Why are NSAIDs particularly problematic?
– GI irritation and GI bleeding, sodium and water retention.

- **Anything that affects CNS** e.g. opioids, tricyclic antidepressants, sedating antihistamines, benzodiazepines and other hypnotics, antipsychotics – use with caution in those at risk of developing encephalopathy. Responsiveness to the pharmacological action of some drugs may lead to increased susceptibility of the brain. If the metabolic capacity of the liver is impaired (acute liver failure of cirrhosis) a patient is at risk of becoming encephalopathic or of worsening encephalopathy. The brain is more sensitive to the sedative effects of any drug due to increased permeability of the BBB, cerebral blood flow and receptor sensitivity. The CNS side effects, sedation and confusion, can increase the risk or worsen the grade of encephalopathy by compounding the CNS depressant effects. Decreased metabolism also increases the risk of this happening.

What are your views on modified release opioid analgesia?

- Not ideal due to long period to wear off that can mask the adverse effects for longer. If deterioration is noted in the patient, you cannot do much about it until the drug has worn off (unless you reverse the analgesia with naloxone).
- Most opioids are metabolised in the liver and have a high intrinsic clearance/high first pass effect, therefore when metabolism is impaired, or blood flow is reduced (for high extraction ratio drugs), clearance of the opioid is decreased resulting in prolonged duration and toxicity. Portal hypertension (and increased systemic exposure) may increase oral bioavailability and toxicity risk. Therefore, it is difficult to predict pharmacokinetics.
- Paracetamol – data is conflicting regarding the safety in liver disease and dosing will be guided by local policy. Theoretically liver enzyme induction (by chronic alcohol or enzyme inducing drugs) may enhance the production of toxic metabolites. Caution is necessary in patients that cannot eliminate the toxic metabolite due to decreased glutathione, i.e. malnourished patients. In practice we reduce the dose in patients less than 50 kg, malnourished and those with liver disease to 500mg QDS or TDS or 15 mg/Kg.

- **Over diuresis and electrolyte abnormalities** e.g. high dose furosemide, bumetanide (inappropriate starting doses and/or titration). These drugs will disturb the fluid-electrolyte balance which can lead to encephalopathy in susceptible (cirrhotic or acute failure patients), i.e. dehydration, hyponatraemia, hyper or hypokalaemia.
- **Drugs that lower the seizure threshold** e.g. tramadol, phenothiazine antipsychotics and some antidepressants. These may accumulate due to cirrhosis or acute liver failure and are particularly problematic in alcoholic patients who have an increased risk of seizure due to alcohol withdrawal.

- **Causing constipation** e.g. opioid analgesics, tricyclic antidepressants, sedating antihistamines, 5HT3 antagonists, calcium channel blockers, antispasmodics-hyoscine, antimuscarinics-Parkinsons drugs. Constipation prevents the clearance of toxic waste products in the bowel that can accumulate and cross the BBB to cause or worsen HE
- **Highly protein bound drugs** i.e. phenytoin, ibuprofen, prednisolone, verapamil are unable to bind plasma proteins and albumin therefore increasing the free drug.

- **High sodium content drugs**, especially an issue with IV preparations and soluble tablets. These can cause fluid retention and worsen ascites.
- **Nephrotoxic drugs** – patients with cirrhosis or acute liver failure are at risk of hepatorenal disease and are also more susceptible to renal impairment than those without renal impairment.

You are the pharmacist on the transplant ward and seeing this patient for the first time. His inpatient chart has been provided. Mr P S is a renal transplant recipient. He received his new kidney last night. He is 6 foot 2 inches tall and his creatinine result this morning is 180 micromol/L.

1. Using your knowledge, the screencasts and BNF, complete the table below for the drugs prescribed for Mr PS:

Drug	Indication / Drug class / brief mechanism of action / key monitoring parameters (therapeutic and toxic)
Basiliximab	**Indication:** Induction immunosuppression. **Drug class:** Monoclonal antibody immunosuppressant **Mechanism of action:** Chimeric monoclonal antibody against IL-2 (interleukin-2 receptor antagonist). Inhibits T-cell proliferation. **Therapeutic monitoring parameters:** Lack of acute rejection **Toxic monitoring parameters:** infections, hypersensitivity, BP, FBC (anaemia) Given at induction **and** 4 days after.
Advagraf (tacrolimus)	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Calcineurin inhibitor **Mechanism of action:** Inhibits early T-cell activation by inhibiting calcineurin, an enzyme involved in the transcription of genes encoding IL-2 and other cytokines. **Therapeutic monitoring parameters:** Lack of rejection, trough tacrolimus levels 5-15 (20) ng/mL **Toxic monitoring parameters:** Cr, eGFR, Ur, urine output (nephrotoxicity*, hyperkalaemia), GI, FBC, blood glucose (DM), BP, headache, tremor, seizures, peripheral neuropathy (neurotoxicity*), interactions (cyp 3A4 & p-glycoprotein), trough tacrolimus levels 5-15 (20) ng/mL, lipids, BP, hirsutism, gum hyperplasia NH Day 1 UV light, lymphoproliferative disease/neoplams, vaccination, avoiding live vaccines, brand (must be the same), formulation (they are not equivalent) *can be dose dependent **metabolised in the liver (CYP-3A4) and p-glycoprotein – care with interactions. Highly plasma protein bound. Usually long term.
Mycophenolate mofetil	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Antiproliferative drug **Mechanism of action:** Inhibits inosine monophosphate dehydrogenase which is the rate limiting enzyme in the production of guanine nucleotide synthesis. Action is said to be lymphocyte specific. **Therapeutic monitoring parameters:** Lack of rejection **Toxic monitoring parameters:** method of administration as teratogenic, neoplasms, infections, FBC (neutropenia may require dose reduction cessation, leucopenia, anaemia), GI (D&V), interactions (drugs interfering with MPA enterohepatic recirculation-colestyramine/antibiotics), (potentially, not done regularly - MPA monitoring), contraception, LFT, renal function, avoid live vaccines UV light Usually long term.
Prednisolone	**Indication:** Part of the triple immunosuppressant maintenance therapy. **Drug class:** Corticosteroid **Mechanism of action:** Is anti-inflammatory and affects most of the cells involved in the initiation of an episode of rejection. At maintenance doses, corticosteroids block the release and inhibit the action of cytokines – interleukins and interfere with T-cell activation. (Review year 2 material) **Therapeutic monitoring parameters:** Lack of rejection **Toxic monitoring parameters:** BP (hypertension), U&E (hypernatraemia, hypokalaemia), bone mineral density, eye examination (glaucoma), weight (fluid retention), lipids, blood glucose/HbA1c, GI, tapering course (adrenal suppression), psychiatric adverse reactions, Cushing's syndrome - moon face/thinning of the skin, malignancy, infections, chicken pox, avoid live vaccines, interactions (cyp 3A) Steroids are tapered down quite quickly but is done on a patient-by-patient basis, depending on the level of organ match, graft function and overall patient condition. Starting at 20mg immediately post-transplant, this can be reduced to 15mg at discharge (about day 5), and the further reduction is dictated by the doctor review that occurs in the twice weekly clinic appointments).
Dalteparin	**Indication:** VTE prophylaxis **Drug class:** LMWH **Mechanism of action:** LMWH – binds antithrombin III, which preferentially potentiates the inhibition of factor Xa and IIa. Factor Xa usually catalyses the conversion of prothrombin to thrombin. Decreased thrombin leads decreased fibrin and clot formation. **Therapeutic monitoring parameters:** Lack of VTE/clotting post surgery **Toxic monitoring parameters:** weight, platelets (thrombocytopenia), U&E (K+ inc), signs of bleeding and bruising, Cr/eGFR LMWH used while in hospital and changed to **aspirin 75mg OD (lifelong) at discharge**.

Co-trimoxazole	**Indication:** Prophylaxis against *pneumocystis jirovecii pneomonitis*. Classified as a common fungal lung infection in the environment causing illness in immunosuppressed patients. **Drug class:** Antibiotic. Sulfamethoxazole and trimethoprim combination drug. **Mechanism of action:** The two parts have different points of inhibition in the formation/utilisation of folate required by PJP to make DNA. **Therapeutic monitoring parameters:** No pneumocystis jiroveci infection **Toxic monitoring parameters:** headache, hyperkalaemia, rash, N&D – common. Less common but important – LFTs (hepatic necrosis), skin (life threatening skin and cutaneous adverse effects i.e. Stevens-Johnsons syndrome), FBC (blood dyscrasias Usually used for 6 months.
Lansoprazole	**Indication:** GI protection against therapy associated with GI disturbance (i.e. steroids) and surgery **Drug class:** Proton pump inhibitor **Mechanism of action:** Activated PPI reacts with the sulphydryl group of the H+/K+ ATPase (proton pump) responsible for the transport of hydrogen ions out of the parietal cells. **Therapeutic monitoring parameters:** No ulcer formation due to surgery or corticosteroids **Toxic monitoring parameters:** GI infection, Mg, osteoporosis, LFT, FBC, GI, use (stop when able), interaction with tacrolimus (metabolised by 3A4 and 2C19) Stop once steroids completed.
Nystatin (oral fluconazole is considered in those patients on highly immunosuppressive treatment, i.e. alemtuzumab)	**Indication:** prophylaxis against *Candida spp.* Increased risk due to high dose steroids and immunosuppression. **Drug class:** Antifungal **Mechanism of action:** Oral polyene that binds ergosterol in the fungal cell membrane resulting in increased permeability, cell leakage and cell death. **Therapeutic monitoring parameters:** No oral/GI candida **Toxic monitoring parameters:** usually very well tolerated. Large doses can lead to N/V/D Usually used for 1 month
Paracetamol	**Indication:** Base line pain relief. **Drug class:** Analgesia **Mechanism of action:** Central COX inhibition **Therapeutic monitoring parameters:** Pain control **Toxic monitoring parameters:** weight, max dose, alcohol, malnutrition, (LFT, FBC) PRN at discharge.
Fentanyl	**Indication:** Post operative pain relief **Drug class:** Opioid analgesia **Mechanism of action:** Strong and potent opioid agonist **Therapeutic monitoring parameters:** Pain relief **Toxic monitoring parameters:** constipation, RR, drowsiness, flushing, N&V, skin reactions, palpitations Mainly hepatically metabolised making it a safer opioid pain relieve in patient with potentially poor renal function. Used first few days pot surgery.
Meptazinol	**Indication:** Post operative pain relief step down **Drug class:** Weak opioid analgesia **Mechanism of action:** Mixed opioid agonist/antagonist action. **Therapeutic monitoring parameters:** Pain relief **Toxic monitoring parameters:** As above PRN at discharge.

The type/combination of immunosuppression required depends upon the type of graft and organ and therefore the intensity of the immune response.

Allograft – same species but different individuals – degree of immune response and likelihood of rejection therefore depend on the degree of histocompatibility of the donor and recipient and the type of organ (eyes trigger little immune response/heart, kidney, liver are highly vascular and elicit a greater response). Matching tries to allocate patients to organs with the best match to minimise the immune response. But wherever there is even slight differences (i.e. non-identical individuals) the transplantation of an organ will provoke an immune response. For this reason patients receive immunosuppression. This will be needed for as long as the graft is functioning but will vary over time (both in dose and the number of drugs required) - immediately after transplant patients are at the highest risk of rejection so the highest doses and higher target levels (i.e. for tacrolimus) are required. Over time, doses/target levels may be able to be reduced.
Patients receive 'induction' immunosuppression at the time of transplant and are then started on a maintenance regime.
Maintenance therapy consists of a **COMBINATION** of the different classes of immunosuppression, i.e. a calcineurin inhibitor plus an anti-proliferative plus a corticosteroid.

As more immunosuppressive drugs were developed it was found that by using a combination the patient had a more positive outcome in terms of **reduced rejection** and **reduced side effects** due to not requiring as high a dose when used in combination as opposed to when used alone.

The drug chart shows the typical triple immunosuppression therapy for a patient post kidney transplant (note – different transplant centres may use slightly different regimes.

1. Identify any Pharmaceutical care issues with this prescription and document the action you would like to take.

Issues	Action required
Second dose of basiliximab not prescribed. To complete the course, the second dose should be given on day 4 (as per BNF).	Ask prescribers to prescribe basiliximab 20mg on day 4.

Issues	Action required
Advagraf is the modified release, **ONCE** a day tacrolimus preparation currently prescribed BD. This will lead to toxicity if it is not amended.	Dose stated in the BNF: 200-300 micrograms/Kg/day, therefore it should be 14mg to 21mg **ONCE** a day in the morning and closely monitor ask prescriber to amend. (0.15mg/kg PO Od is an example of dosing discussed in the screencast – this would equate to 10-11mg once daily for this patient)

Issues	Action required
Mycophenolate mofetil dose is incorrect it should be given twice a day. BNF dosing: 1g BD PO. Dosing discussed in the screencast: 750mg BD.	Ask prescriber to amend and prescribe a twice daily dose 750mg to 1g BD (based on local protocol).

Issues	Action required
Dalteparin dose too low based on the patients current renal function. Patient with a renal function over 20ml/min (and weight over 50kg) should receive 5000 units daily.	Ask prescriber to prescribe 5000 units once a day. Ensure starting Aspirin 75 mg OD occurs at discharge when the dalteparin is stopped.

Issues	Action required
No stop dates for supportive therapy on drug chart which may lead to inappropriate continuation of therapy.	Add stop dates - Co-trimoxazole generally 6 months, nystatin generally 4 weeks. Although this is the general rule, patients continue to be monitored in clinic and therapy adapted to patient needs.

Issues	Action required
Potentially missing valganciclovir depending on CMV status of patient and donor.	(See next question)
Monitoring parameters	
Therapeutic	**Toxic**
Lack of cytomegalovirus (PCR)	RF, Hb (anaemia), FBC (neutropenia, leukopenia, thrombocytopenia, pancytopenia), contraception, s/e D, N&V, dermatitis, cough, headache, loss of appetite, infection (V.common)

In addition to the above drugs, Mr PS is also started on prophylactic valganciclovir. In renal transplant patients this is used if either the patient or the donor is seropositive for Cytomegalovirus, CMV. This is done by measuring a patient's CMV IgG. CMV is a member of the herpes virus family which can be passed on via body fluids, tissue donation or it can be congenital. For immunocompetent individuals the primary infection is generally asymptomatic but can manifest as mononucleosis syndrome. An individual's immunity controls viral replication.
In those who are immunosuppressed it can cause severe illness. This can be especially detrimental for transplant recipients as CMV is associated with increased graft rejection. Renal clearance accounts for the majority of valganciclovir excretion.

1. 3. Using the patient's renal function, (using the Cockcroft and Gault equation) and the table below, please check what dose of valganciclovir the patient should receive and prescribe it on your drug chart.

CrCl (ml/min)	**Maintenance/Prevention dose of valganciclovir**
≥ 60	**900 mg (2 tablets) once daily**
40 – 59	**450 mg (1 tablet) once daily**
25 – 39	**450 mg (1 tablet) every 2 days**
10 – 24	**450 mg (1 tablet) twice weekly**
< 10	**not recommended**

Valcyte 450 mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk) – accessed 9/1/23

-Using Cockroft and Gault:
(140-55) x 1.23 x 72kg / 180 = 41.82 mL/min = 42mL/min
Therefore, 450mg ONCE a day would be the recommended dose.

The patient's renal function is likely to be quite variable after a transplant. Some patients require dialysis either periodically due to high potassium in the 24-48 hours post op or if their renal function does not improve (and therefore electrolytes imbalances occur). However, for the majority of patients their renal function can improve towards a normal range within 5 days and so calculations and adjustments are required during their hospital stay and then in their follow-up clinics post discharge.
Generally, this drug will be received for 3 months, high risk patients receive it for 6 months. CMV PCR is used to monitor CMV status of the patient.
If a patient develops the infection and receives treatment, once two negative results have been received they will continue with prophylaxis for a further 11 weeks.
Prescribe valganciclovir appropriately on your drug chart.

1. Mr PS is ready to be discharged tomorrow and you need to counsel him on his new medication. List the important counselling points for Advagraf, mycophenolate mofetil and prednisolone

Please review lecture slides and relevant monographs in the BNF

Advagraf –
Inform the patient of what the medicine is, its indication, how important it is, dose, frequency, potential important side effects (FOR EACH DRUG YOU ARE EXPECTED TO STATE THE IMPORTANT SIDE EFFECTS) and what needs to be done if they occur.*
Take ONCE a day on an empty (food reduces bioavailability) stomach (upon waking), wait approximately 1 hour afterwards before eating or having other medicines.
Swallow whole.
Stress that clinic check-ups are important so their therapy can be closely monitored.* Monitoring is required for efficacy and toxicity monitoring as CNI are nephrotoxic, can cause HTN, hyperlipidaemia, tremor, neurotoxicity and diabetes.
On clinic days do NOT take until bloods have been taken (Bloods need to be a trough level, i.e. immediately prior to next dose). Remember to bring dose with to take after sample has been taken.
Make sure you take this regularly and are aware of the correct dose for you-doses are variable and change dependent upon the levels.*
Make sure you have adequate supply as you must not run out.*
Ensure you **always** have the same BRAND, check when collecting medication.
Ensure you take the correct strength, as it is available as 0.5mg, 1mg, 3mg and 5mg.
Avoid grapefruit juice-inhibits cyp450 and causes the increase in tacrolimus levels.
Avoid excessive exposure to sun light (UV light)-increased risk of cancers.*
Avoid use of live vaccines.*
Avoid high risk foods, those that could cause infection – unpasteurised cheese/milk, lightly cooked meat etc.*
Ensure any medical professional treating you is aware of this medicine as it has MANY interactions.*

Mycophenolate Mofetil
In addition to the * above.
Swallow whole do not crush or chew.
Food does not have an effect on this medication.
For men (our patient) - Importance of appropriate contraception during treatment and for 90 days after.
Importance of FBC monitoring.
Recognition and reporting of infection or unexplained bruising and bleeding.

Prednisolone
In addition to the * above.
Take in the morning.
Take with or after food.
Ensure you have adequate supply; these must not be stopped abruptly.
Ensure the patient has a steroid card and they are aware of the important information it contains.
Ensure you know what dose you should be taking as it is likely that this will change relatively frequently dependent upon your clinical condition.

* as for all transplant immunosuppression

PHA-7001B Central Nervous System

Alzheimer's Diseases

Learning objectives

- Use the appropriate criteria to ensure the acetylcholinesterase inhibitors are used within their license
- Consider the ethical issues around autonomy when prescribing for patients with disorders that affect cognition and respond appropriately
- Identify and manage adverse drug reactions associated with the treatment of dementia
- Identify appropriate pharmacological and non-pharmacological interventions for disturbing neuropsychiatric behaviours

Mr TP is a 74 year old man. His wife has approached the pharmacy, accompanied by Mr TP, while out shopping as she is worried about his memory and would like to buy a supplement to help. You invite them into you consulting room to find out more.

Mr TP is a pleasant man who chats easily to you and doesn't share his wife's concerns. He does concede that he is a bit more forgetful but puts this down to advancing age and isn't concerned. Mrs TP explains that her husband forgot to pick the grandchildren up from school 3 times last month and when he collected her from the hairdressers last week, he forgot where he left the car. She also reports that, despite being very easygoing usually, he is more snappy and short-tempered lately. Mr TP smiles when his wife tells you this, and rolls his eyes at you. He tells you that this is because he gets told off a lot more than he used to and smiles at his wife.

Mrs TP has read that fish oil is good for memory and would like to buy it for him.

You probe further and find that there is a history of Alzheimer's disease in the family. Mr TP's own father died from AD when he was 81 years old. In asking about his general health, you find out that Mr TP has had a persistent cough recently and is a bit chesty following a cold, but otherwise is well with regular medication for blood pressure only. He does not drink alcohol or smoke.

You reassure them but explain that memory changes such as these need to be investigated by the GP in case there is a simple cause that is easily taken care of and refer them on. What tests will the GP undertake to determine the likely cause of his current symptoms?

Question 1

Will need to rule out organic causes of cognitive decline before considering Alzheimer's disease e.g. **Electrolyte imbalances**- all U&Es (renal failure or hyperuraemia can ppt confusion)	

Metabolic disturbances-
 Vit B12 and folate (low levels can cause memory impairment and mood changes),
 TFTs (rule out hypothyroidism as a cause of dementia-like presentation)
 Blood glucose (diabetes is a risk factor in itself but too stringent control can lead to confusion in the elderly i.e. hypos)
 LFTs (rule out any metabolic dysfunction e.g. hyperammonaemia in liver cirrhosis)

Infective screen- CRP, FBC, temperature, urine MSU (dipstick no longer recommended as diagnostic tool for UTI in patients >65years),
FBC
Imaging (not realistic in GP surgery but may refer)- CT brain to rule out stroke/tumour can also help identify cause i.e. small vessel disease suggestive of vascular dementia.
Full medical history- identifying any risk factors e.g. FH, genetic component, alcoholism etc
When all organic causes have been ruled out formal behavioural and cognitive assessment and potential referral to a specialist memory service e.g. specialist psychiatrist/old age psych.
The severity of Alzheimer's disease can be assessed using several methods, depending on the setting for example research utilises ADAS-cog **or** clinical practice and the outcome being assessed.
Clinical practice uses a variety of measures, often along with clinically based assessments such as biographical interview e.g.
 AMTS (abbreviated mental test score) is often used acutely to determine whether memory problems present (10 questions).
 Severity is frequently defined by Mini Mental State Examination (MMSE) score:
- mild Alzheimer's disease: MMSE 21–26
- moderate Alzheimer's disease: MMSE 10–20
- moderately severe Alzheimer's disease: MMSE 10–14
- severe Alzheimer's disease: MMSE less than 10

A few days later, Mrs TP returns to your pharmacy. She has a prescription for co-amoxiclav 625 mg TDS (21). She thanks you for your referral and says that, after asking lots of questions and listening to Mr TP's chest, the doctor gave him this prescription. She asks you whether this is to help his memory, and how long will it take to work. What do you tell her?

Question 2

The doctor may have found signs of a chest infection and given a course of antibiotics is to treat. Acute infection can, especially in older people, lead to changes in memory and behaviour (older people do not have the in-built reserve to fight off infection as well as younger people therefore even the smallest of insults can knock them back and precipitate confusion/induce delirium).
That is why it is important to treat infection and rule out other organic causes before embarking upon treatment to help with cognition.
After asking whether Mr TP is allergic to penicillin (he's not), you explain that his chest should start sounding better after a few days, but that he should complete the course even

if his symptoms disappear completely before the end of 7 days

You are on duty 3 weeks later when a prescription comes over from the surgery for Mr TP. It requests:

Ebixa® treatment initiation pack (op) MDU

According to this drug's license, what has Mr TP been diagnosed with and would you like to clarify the prescriber's intentions?

Question 3

According to this drug's license, Mr TP has been diagnosed with moderate to severe dementia of the Alzheimer's type. This suggests that he has significant cognitive impairment and does not fit with your impression of Mr TP a few weeks ago, who was independent with his ADLs and responding appropriately to conversation, with only mild memory impairment and behavioural symptoms.
You should contact the GP to ensure that he has selected the correct treatment. Only acetylcholinesterase inhibitors are licensed for the treatment of mild-moderate dementia of the Alzheimer's type and the GP may have selected the wrong product in error.

The doctor thanks you for you call and says that the memory clinic recommended ‘pharmacological memory support’ in their letter to her and she hadn’t been aware of the different licenses. However she agrees with you that an acetylcholinesterase inhibitor would be more appropriate given the severity of his symptoms and would be happier with that. She asks you to make a recommendation. What do you recommend?

Question 4

Mr TP has no cardiovascular issues of note, and no swallowing difficulties that suggest he would need a non-solid formulation. He takes an antihypertensive each day without problems and so a cost effective, once daily formulation would seem sensible.
While donepezil, rivastigmine or galantamine are all clinically fine, NICE endorse that “treatment should normally be started with the drug with the lowest acquisition cost (taking into account required daily dose and the price per dose once shared care has started i.e. between memory specialist potentially and GP)”.
The most cost effective choice is donepezil tablet 5 mg OD (considering OD administration and acquisition- now that they are all available in generic this is not as much of a problem).
NICE recommendation and licencing for memantine:
Memantine monotherapy is recommended as an option for managing Alzheimer's disease for people with:
 moderate Alzheimer's disease who are intolerant of or have a contraindication to AChE inhibitors **or**
 severe Alzheimer's disease.

The doctor supplies you with a prescription the following day and Mr TP comes to collect it. He asks you if he can speak to you privately. You invite him into the consultation room.

He tells you that he knows that the memory specialist thinks he has lost his mind but he doesn’t agree and has no intention of taking this medication. He

claims that the specialist asked a lot of silly questions and just because he didn't have the answers on the tip of his tongue and needed to think about them, they have claimed him to be senile and started this medication.

He acknowledges that his wife really wants him to take the medication and so he tells that he is going to keep collecting the prescription so that his wife doesn't suspect anything but that he is going to throw the tablet away each day. That way, everyone is happy. He expects you to be complicit in this and not tell his wife or the GP. What do you tell him?

Question 5

You may not reveal anything about his medical condition or medication to a third party without his consent unless you consider there to be a real and imminent danger to his health or the health of the public.
However, it is not ethical to continue to dispense a prescription that you know that the patient is not taking. It breaches a number of bioethical principles including fidelity and justice.
Mr TP is not lacking in capacity and is currently capable of making his own decision about how he would like his health to be managed. He is able to refuse to take the medication if he wants to and is able to understand the consequences of both taking and not taking it.
Explain to him that the medicine is proposed to improve his memory and slow down the disease. It works well in some people, and not at all in others. **On average, about half of the patients that take it tend to decline slower that it's thought they would without it.**** (3rd improve,3rd non decline, 3rd no response)
Tell him that it is his choice about whether he takes the medication or not and that the GP would support him in any decision he made, as would you, but that it would not be ethical for you to continue to supply it to him knowing that he did not intend to take it. In this situation, you would need to inform the GP of his intentions.
Suggest he involves his wife- it is likely he will need her support further down the line as the disease progresses.

Mr TP decides not to accept the medication and thanks you for your support.

A year later, you receive a prescription for

Donepezil 5 mg OD (28)

It is collected by Mrs TP. She explains that his condition has deteriorated over the last year and he now accepts that medication may be helpful. She is keen to ensure Mr TP gets the best from this medication. What information do you give her about the use of donepezil?

Question 6

The tablet should be taken in the evening. At least a month at 5mg OD will be needed to determine whether there is any effect and that it is well tolerated. A higher dose can then be trialled after 1 month (4 weeks)
Mr TP will continue to be reassessed to see if there is any benefit (approx. every 3 months).
Common side effects include nausea, diarrhoea and headache. Advice you could provide to combat these nausea- Stick to simple foods - avoid fatty or spicy meal, diarrhoea- ensure you drink plenty of fluid and headache- simple analgesia may help.
He may also experience some changes in his mood or behaviour and experience strange dreams. If any of these things happen and are distressing, they will go away if the medicine is stopped.
Manufacturer information:
"Therapy with donepezil should only be started if a caregiver is available who will regularly monitor drug intake for the patient. Maintenance treatment can be continued for as long as a therapeutic benefit for the patient exists. Therefore, the clinical benefit of donepezil should be reassessed on a regular basis. Discontinuation should be considered when evidence of a therapeutic effect is no longer present. Individual response to donepezil cannot be predicted"

Mrs TP asks you if this will stop Mr TP ending up like his father, who spent the last few years of his life very unwell in a nursing home, with no recognition of family and friends and this was very hard on every one. What do you tell her?

Question 7

It is important that expectations of treatment are realistic to ensure that over-

reliance on drugs doesn't limit social interventions that are also helpful.
It is ok to explain to Mrs TP that Alzheimer's Disease is neurodegenerative and that patients do deteriorate over time. However it is impossible to predict the rate of decline and so Mr TP may yet experience years of reasonable health.

8 months later Mrs TP returns with an FP10 HP prescription for

Oxybutynin 5 mg TDS

You ask to speak to Mrs TP and enquire about the health of her husband. She says he is doing ok, still on the donepezil but not as well as he was. He needs to be supervised a lot of the time and is having increasingly angry outbursts. He had minor op recently and the ward staff noticed that he was a bit incontinent which was upsetting for him, and the hospital prescribed this to help.

Should you dispense this? What could be the cause of his urinary symptoms and what action should you take?

Question 8

Due to pro-cholinergic effects, urinary incontinence is a common side effect of acetylcholinesterase inhibitors. It would resolve upon withdrawal of donepezil but then any benefits Mr TP may be experiencing would be lost.
An anticholinergic such as oxybutynin would counteract the pro-cholinergic effects of the donepezil on his urinary tract. However, oxybutynin crosses the blood brain barrier and will also counteract any effects that the donepezil is having in supporting Mr TP's cognition. (mechanism of action of oxybutynin= anticholinergic action in blocking the muscarinic effects of acetylcholine on smooth muscle)
Options include:
1) If you dispense the oxybutynin, it will render the donepezil useless but

6 years after your first contact with Mr TP and his wife, his PMR is flagged to you while undertaking an audit of appropriate antipsychotic medication prescribed in elderly patients. You see that for the last 4 months, on days you weren't on duty, the following medication has been dispensed:

Ebixa® 20 mg OD
Risperidone 0.5 mg prn
Lorazepam 1 mg up to QDS prn for aggressive behaviour
Amlodipine 10 mg OD
Senna ii ON
Fybogel I BD

Does anything concern you about this record? What other information would you like to find out? How would Mr TP's neuropsychiatric symptoms be measured?

Question 9

Ebixa® 20 mg OD -(max, S/E constipation)
Risperidone 0.5 mg prn-(see below review, max dose, S/E constipation common)
Lorazepam 1 mg up to QDS prn for aggressive behaviour- (see below, check dose taking, must not be stopped suddenly, max dose in elderly usually 2mg/24 hr and susceptibility of S/E greater with A/D, can cause paradoxical effect of aggression)
Amlodipine 10 mg OD- S/E constipation common
Senna ii ON- Laxatives to be reviewed, constipation common with current meds prescribed, stool chart, lifestyle, diet, fluids etc
Fybogel I BD

The use of antipsychotics is challenging in patients with dementia because it increases their risk of stroke significantly. As a result, only risperidone is licensed to treat persistent aggression in in patients with moderate to severe AD but **only for 6 weeks**, up to a maximum of 1mg BD.
You would like to ring Mrs TP and ask how Mr TP is getting on, and ask the

following:
What are his symptoms are like at the moment?
What is the normal daily dose of risperidone being used?
How is she using the lorazepam and risperidone – in what order and for what type of behaviour? . If Lorazepam considered to be weaned off, talk here how to do it safely (patient currently could take max recommended adult dose)
Is the issue worse at night time or during the day? – Sundowning?
Is Mrs TP getting enough rest to allow her to cope with Mr TP's symptoms?
Does Mrs TP have enough support at home to continue to care for Mr TP? – Day-care Centre ?
Assessment of the severity of Mr TP would be via the Neuropsychiatric Inventory (NPI) which is a validated test administered to Mrs TP to find out how she distressing perceives his behaviour to be. Also consider conducting carer givers distress test with Mrs TP.

You find Mrs TP in reasonable spirits. She explains that the hospital, during Mr TPs last admission for a UTI, started risperidone as his behaviour on the ward became very disturbing indeed and he slapped a healthcare assistant. The GP must've thought it good to carry on as it's on his repeat. She gives a dose of 0.5 mg at night to help him get off to sleep and doesn't use the lorazepam as the label says it's for aggressive behaviour, which he doesn't exibit.

Why do you think his behaviour deteriorated so much in hospital?

What should you next course of action be?

Question 10

The UTI itself may have contributed to worsening symptoms of dementia. The unfamiliar hospital environment may have also caused Mr TP to feel anxious and worried, which manifested in symptoms of disturbing behaviour. This can often happen when a patient is placed in an unfamiliar environment.
Risperidone is only licensed for 6 weeks use and so is now being used off license. It also increases the risk of stroke in Mr TP.
You explain to Mrs TP that it is likely that the Risperidone was prescribed to manage his unsafe behaviour in hospital and that it isn't really the right choice to just get him settled. You can discuss alternative methods to help with sleep, such as sleep hygiene methods and non-pharmacological approaches. Potentially a low dose short-term sleeping aid may be an option, such as Zopiclone, however, should be used with caution and regularly monitored as there is an increased risk of falls in elderly and AD patients.

You communicate this to his GP

Mrs TP is worried that her husband might show some aggressive behaviour in the future while at home and asks for your advice if there are any non-pharmacological management that might help. What advice do you give?

Question 11

Non Pharmacological Therapies

- ❑ **Cognitive/Emotion-oriented Interventions:**
- *Reminiscence Therapy*
- *Simulated Presence Therapy (SPT)*
- *Validation Therapy*
- *Reality Orientation Therapy*
- ❑ **Sensory Stimulation Interventions:**
- *Acupuncture*
- *Aromatherapy*
- *Light Therapy*
- *Massage and Touch Therapy*
- *Music Therapy*
- *Snoezelen Multisensory Stimulation Therapy*
- *Transcutaneous Electrical Nerve Stimulation (TENS)*
- ❑ **Behavior Management Techniques:**
- ❑ **Other Psychosocial Interventions:**
- *Animal-assisted Therapy (AAT)*
- *Exercise*
- ❑ **Various Interventions Targeting a Specific Behavioral Symptom**
- *Wandering*
- *Agitation*
- *Inappropriate Sexual Behavior*

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- *Aromatherapy*
- *Light Therapy*
- *Massage and Touch Therapy*
- *Music Therapy*
- *Snoezelen Multisensory Stimulation Therapy*
- *Transcutaneous Electrical Nerve Stimulation (TENS)*
- ❑ **Behavior Management Techniques:**
- ❑ **Other Psychosocial Interventions:**
- *Animal-assisted Therapy (AAT)*
- *Exercise*
- ❑ **Various Interventions Targeting a Specific Behavioral Symptom**
- *Wandering*
- *Agitation*
- *Inappropriate Sexual Behavior*

Non Pharmacological Therapies

- ❑ **Cognitive/Emotion-oriented Interventions:**
- *Reminiscence Therapy*
- *Simulated Presence Therapy (SPT)*
- *Validation Therapy*
- *Reality Orientation Therapy*
- ❑ **Sensory Stimulation Interventions:**
- *Acupuncture*
- *Aromatherapy*
- *Light Therapy*
- *Massage and Touch Therapy*
- *Music Therapy*
- *Snoezelen Multisensory Stimulation Therapy*
- *Transcutaneous Electrical Nerve Stimulation (TENS)*
- ❑ **Behavior Management Techniques:**
- ❑ **Other Psychosocial Interventions:**
- *Animal-assisted Therapy (AAT)*
- *Exercise*
- ❑ **Various Interventions Targeting a Specific Behavioral Symptom**
- *Wandering*
- *Agitation*
- *Inappropriate Sexual Behavior*

Nonpharmacological treatment of isb

Behavioural modifications

For public behaviours:

- Sensitive explanation of inappropriateness and gentle redirection
- Avoid confrontation
- Do not ignore these behaviours
- Distraction
- Single rooms for patients
- Avoid inappropriate external cues like over-stimulating television or radio programs.
- Modified clothing: trousers which open in the back or are without zippers may be helpful.
- Provide adequate social activity.
- Encourage family and friends to visit.
- Provide simple and repeated explanations of why such behaviours are unacceptable.

Mrs TP asks you what support services are available for Patients and their Carers. What support services are available and how would you signpost Mrs TP?

Question 12

Dementia friend- learning abut dementia to help the community
Dementia UK
Alzheimer's Society
Pilgrim friends- care homes and residential homes
NHS website
Age UK
Young Dementia UK
Alzheimer's research UK

Charities and voluntary organisations provide valuable support and advice on their websites and via their helplines:

- Alzheimer's Society's National Dementia Helpline on 0300 222 1122
- Age UK's Advice Line on 0800 055 6112 (free)
- Independent Age on 0800 319 6789 (free)
- Dementia UK Admiral Nurse Dementia helpline on 0800 888 6678 (free)
- Carers Direct helpline on 0300 123 1053 (free)
- Carers UK on 0800 808 7777 (free)

Talk to other carers

Sharing your experiences with other carers can be a great support as they understand what you're going through. You can also share tips and advice.

If it's difficult for you to be able to attend regular carers groups, join one of the online forums:

- Carers UK forum
- Alzheimer's Society Talking Point forum

Task 1 - Risks of seizures and seizure classification

Consider what factors may increase the risk of seizures in a patient or trigger a seizure?

Head trauma Stroke
Brain tumours
Infection e.g. meningitis
Multiple sclerosis – degenerative brain disorders
Triggers Flickering lights
Sleep deprivation
Alcohol, recreational drugs
Drugs – common drugs that lower seizure threshold – tramadol, Quinolones and Carbapenems

Complete the following table with the classification of seizures.

Generalised seizures		
Motor	Tonic seizures	Stiffness and extension of limbs Consciousness is impaired Seizures are brief lasting only seconds
	Atonic seizures	Sudden loss of muscle tone Seizures are brief
	Myoclonic seizures	Abrupt muscle jerks affecting upper limbs Do not affect consciousness
	Clonic seizures	Loss of consciousness and rhythmic symmetrical shaking of limbs, face and neck due to rapidly alternating muscle contraction and relaxation
	Tonic-clonic seizures	Initial tonic phase – person loses consciousness, becomes rigid and falls to ground Clonic phase – jerking of muscles Convulsions last 2-3 minutes, person remains unconscious for up to a few hours
Non-motor	Absence seizures	Person will stop moving and have a fixated stare, usually lasts for about 10 seconds
Focal Seizures		
Simple focal seizures (awareness)	Motor onset	Change in muscle activity of some sort, such as jerking (clonic), stiffness (tonic), loss of muscle tone (atonic), automatisms (repeated or automatic movements e.g. lip smacking, repetition of words/phrases, pacing), irregular big movements like jumping/thrashing/rocking movements (hyperkinetic), Sudden flexing and/or extending of the muscles in the trunk and close to the trunk of the body (epileptic spasms). Quick, involuntary muscle jerk (Myoclonic)
	Non-motor onset	can include changes in heart rate, breathing, or color (autonomic); blank stare, stop talking or stop moving (behavioural arrest): confusion, slowed thinking, or& problems talking and understanding (cognitive changes); sudden fear, dread, anxiety/pleasure (emotional); or changes in hearing, vision, taste, tingling, or pain (sensory).
Complex focal seizures (impaired awareness)	Motor onset	Change in muscle activity of some sort, such as jerking (clonic), stiffness (tonic), loss of muscle tone (atonic), automatisms (repeated or automatic movements e.g. lip smacking, repetition of words/phrases, pacing), irregular big movements like jumping/thrashing/rocking movements (hyperkinetic), Sudden flexing and/or extending of the muscles in the trunk and close to the trunk of the body (epileptic spasms). Quick, involuntary muscle jerk (Myoclonic)
	Non-motor onset	Changes in heart rate, breathing, or colour (autonomic); blank stare, stop talking or stop moving (behavioural arrest): confusion, slowed thinking, or& problems talking and understanding (cognitive changes); sudden fear, dread, anxiety/pleasure (emotional); or changes in hearing, vision, taste, tingling, or pain (sensory).

Task 2 Management of epilepsy

Miss PT, a 27 year old woman has been newly diagnosed with focal seizures and the epilepsy consultant is considering prescribing

Zonisamide 100mg once daily.
You are a hospital pharmacist reviewing the patient's notes, and can see is not on any regular medication:

1) Is the choice of therapy appropriate, if not what would you recommend?

No this is not appropriate as Zonisamide is 2nd line monotherapy option. This should only be considered if 1st line monotherapy options are not successful or not tolerated.
More appropriate first line choice would be levetiracetam or lamotrigine – also safe in patients in child-bearing potential in case they get pregnant whilst on it.

Other issue to consider – Zonisamide requires women to be on highly effective contraception (e.g. intrauterine devices – copper coil, levonorgesterol IUD or progesterone implant).
NOTE – it is 'non-enzyme inducer' AED so the drug does not alter the efficacy of the contraception. It is its teragenic effects that require the need for highly effective contraception

Also side effects of Zonisamide– risk of heat stroke (need to counsel about adequate hydration), hypersensitivity reactions, blood disorders, etc.

2) After a few months, Miss PT's therapy changes and is stabilised on carbamazepine 100mg TWICE daily. What counselling points would you cover with the patient?

- Not stopping the medication abruptly,
- Needs to stay on the same brand of medication (category 1 AED) – discuss supply of medication
- Potential side effects of medication –see BNF, SPC (drowsiness, fatigue, GI discomfort, leucopenia, eosinophilia, thrombocytopenia, etc)
- Risk of hypersensitivity syndrome (look out for rashes), also monitor for blood dyscrasias – to seek medical attention if they experience a fever, rash, mouth ulcers, bruising or bleeding develop

3) What additional non-pharmaceutical advice would you give Miss PT?

- Driving -Need to inform the DVLA. Also - need to be seizure free for at least 1 year before being able to drive. If weaned off antiepileptics then the patient should not drive during that period or for a further 6 months.
- Consider situations that may provoke a seizure and avoid e.g. sleep deprivation, alcohol, contact sports.
- Consider risk of seizures at home e.g. having baths (risk of seizure while in bath), any risk of hitting windows/glass panes during seizure
- Consider age – check to see if patient needs:
  - Contraceptive advice (types of contraception she could have are progesterone-only injection, Levongesterol IUD, and Cu-IUD)
  - Or if patient has plans to have a baby – advice that she needs to discuss with consultant a plan. Potential she may need to change AED

4) Mr PS, a 55 year old man who takes carbamazepine 400mg BD, presents to your pharmacy with a prescription for ciprofloxacin 500mg BD 7/7 for a UTI. Is the prescription appropriate?

- There is an interaction between carbamazepine and ciprofloxacin – ciprofloxacin can lower the seizure threshold and therefore should be avoided in patients with epilepsy.

NOTE – it will not appear in as an interaction in the online BNF. It is a drug-disease interaction. Stockleys mentions that quinolones in general are known to induce seizures and therefore are generally not recommended in pts with epilepsy.

- As carbamazepine can be used for neuropathic pain as well as epilepsy then need to establish if the patient is taking carbamazepine for epilepsy, consider if patient has cultures and sensitivities/allergies but
- If alternative antibiotic therapy available would consider switching - possibly Trimethoprim but that causes hyponatraemia with carbamazepine; nitrofurantoin may be the best alternative depending on pt's renal function.
- Key message – you have drug-drug interactions AND drug-condition interactions

5) Mr HG has recently started on lamotrigine therapy and tells you that he has developed a severe rash over his trunk of his body. What would you advise?

- Check if anything else new has started/changed – i.e. any other possible causes of the rash
- But rash is a rare but reported ADR of lamotrigine – would need to see GP urgently as would need to stop but need to consider an alternative therapy as well

6) Mr TB has been admitted to hospital with uncontrolled seizures, he has had 2 seizures in the past month. He is taking phenytoin 300mg OD and has been on phenytoin for the past year. His phenytoin level is checked and the level is 10mg/L (10-20mg/L)

- What would you want to check before interpreting his phenytoin level?

- Dose changes - check if there has been a recent dose change – can take 5-14 days to reach steady state after dose changes
- Other interactions - As phenytoin interacts with other drugs has any new drugs been recently started? Albumin levels – as phenytoin is highly protein bound – then if the patient has low albumin then the level will not reflect the true free concentration
- Adherence - Has the patient been taking their medication?

- Time of level – should be pre- dose trough level (because of long half-life and helps ensure measurements are taken consistently at the same time when the serum concentrations are least likely to vary). Usually within 1 hour of the dose being due.
- Formulation – check if patient is taking tablets or capsules – difference in phenytoin base levels

The doctor tells you he wants to increase the patient's dose to 500mg OD, what would you expect to happen to the therapeutic drug level?

Phenytoin doesn't display linear pharmacokinetics therefore would not expect a dose increase to result in a predictable increase in the therapeutic level – it also displays saturable (zero order) pharmacokinetics.

1) Mr CT is nil by mouth and is currently unable to take his medication, he is taking carbamazepine m/r 200mg BD. What would you recommend?

Carbamazepine is available as a suppository though not dose equivalent – 100mg tablet = 125mg suppository [stated in the BNF in indication section]
Therefore would need to give 125mg FOUR times a day – but would need to monitor clinical response

2) Mr SY has been taking sodium valproate 1g TWICE daily for generalised tonic-clonic seizures, but he is not achieving seizure control and the consultant decides to add in lamotrigine, what factors do you need to consider when you adding in another antiepileptic?

- Higher risk of liver toxicity when more than one antiepileptic used with valproate
- Is it appropriate for the seizure type the patient has? Don't want to exacerbate seizures
- Valporate can increase plasma concentration of lamotrigine therefore need to consider dose titration.
- Is the sodium valproate to be discontinued? will then need to consider reducing valproate slowly.

- Time of level – should be pre- dose trough level (because of long half-life and helps ensure measurements are taken consistently at the same time when the serum concentrations are least likely to vary). Usually within 1 hour of the dose being due.
- Formulation – check if patient is taking tablets or capsules – difference in phenytoin base levels

Task 4 Patient scenarios

In this task you will be assigned one out of the three scenarios to work through and prepare to feedback to the rest of the group. Please assign a spokesperson from your group to provide feedback.

You are the responsible pharmacist of a community pharmacy, and a patient has presented the prescription below to be dispensed and collected. They are a regular patient and you recognise them. Please assume the prescription is both legally and clinically correct.:

Scenario 1: You have taken in the prescription, and as per your pharmacy SOP have checked her PMR record and seen she usually has Epilim© brand of Sodium Valproate dispensed.

Unfortunately, this is currently out of stock with your supplier, and you only have the generic version in stock. Discuss in your groups:

- What things do you need to consider in order to dispense this prescription safely?
- What additional counselling points (if any) would you need to discuss with the patient

Things to discuss

Sodium valproate is a MHRA category 2 medicine, and the Epilepsy summary section of the BNF advises the following:

"For these drugs, the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer taking into account factors such as seizure frequency, treatment history, and potential implications to the patient of having a breakthrough seizure. Non-clinical factors as for Category 3 drugs should also be considered - differences between alternative products (e.g. product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence. In addition, difficulties for patients with co-morbid autism, mental health problems, or learning disability should also be considered."

So, check with the patient:

Have they had the generic brand ever in the past?

How controlled is their epilepsy? When was the last time they had a seizure?

How confident are they with their medication? Will a difference in colour, shape or taste of the tablet cause any issues? (potentially show the patient the tablets)

Do they have any concerns about having a generic brand?

If all the above are ok – dispense the medication, make a note on the patient's PMR and consider letting the GP know that a different brand has been dispensed due to lack of stock so that they are aware.

Additional counselling points:

Reassure the patient that the generic and branded version of the medication have the same drug in it, but the appearance is different

If they do start experiencing change in their seizures – frequency, duration, symptoms, to contact their GP/Epilepsy specialist asap

If they do find after a a few days/weeks they are getting confused about how to take their medicine because of the difference in the brand to contact the pharmacy so you can support them.

Scenario 2: You have taken in the prescription, and followed your pharmacy SOP in relation to dispensing, labelling and checking the prescription. As part of your SOP for processing prescriptions for Sodium Valproate you are required to talk to patients of child-bearing potential every time they present a prescription. Discuss in your groups:

- What are the key points that should be discussed with the patient?
- What materials/information must be provided to the patient with every prescription?

- What materials/information must be provided to the patient with every prescription?

Things to discuss with the patient:
Check the patient is taking the medication ok and have no adherence problems

Check the patient has a signed and up to date Acknowledgement of Risk form (should be done annually). Also new regulations state the 2 prescriber need to sign off in relation to continued use of this in patients under 55 yrs.

If child-bearing potential (pt is 34 so there is the potential of this) - counsel patient about the risks in pregnancy while taking the medication and on a pregnancy prevention programme as they need to be on adequate contraception (barrier method like condoms are not enough) – need to be only **HIGHLY EFFECTIVE contraception** e.g. IUD (Cu or LNG), implant, female sterilisation. Pill/patch/vaginal rings can be used but condoms must be used alongside them as not classed as 'highly effective'.

If patient is not aware of the need for adequate contraception and has not seen their doctor in the last year, the patient must not stop taking the drug, and the drug must be dispensed as normal but refer them for a review with their doctor

If the patient wants to become pregnant refer patient urgently to their GP and/or specialist for a review.

Remind the patient they should have a review with their specialist every year

Note: The prescription is for 56 – how many would be supplied to the patient?
Sodium valproate (all tablet forms) is now a special container (the whole box now not just the strips). Therefore you would supply 60 against this prescription.

Same principle apply for pts taking valproic acid for bipolar disorder.

Other resources to provide to patient:

Patients must be provided with a patient alert card every time they have the medicine dispensed.

Also patient information leaflet (this is a standard for all medicines)

Scenario 3: The patient explains that they are no longer on Sodium valproate (so no longer need the previous prescription) and have recently had a baby. She asks you to dispense the new prescription (see below) and wants some advice around whether it is safe to breastfeed. She is also worried about having a seizure while looking after the baby.
Discuss in your groups:

- What information would you discuss with the patient around breastfeeding whilst taking Levetiracetam?
- What additional information and precautionary measures would you need to advise the patient on in relation to looking after the baby?

Breastfeeding whilst on Levetiracetam
Looking at the SPC for Levetiracetaam it says:

"Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding". (https://www.medicines.org.uk/emc/product/2293/smpc#PREGNANCY)

So make sure patient is aware of the risks, check if she has discussed it with her epilepsy specialist and midwife. If needed refer patient back to epilepsy specialist if no discussion has been carried out.

Additional information

- Bathing - the N+N hospital recommend patients shower if washing alone. If taking a bath, it is recommended they have someone else with them(9).
  - This is because if they were to have a seizure whilst in the bath they could potentially drown, and therefore showers are preferred.
- Feeding – sitting on the floor when feeding, with the mother's back against the wall for support, and using cushions either side reduce risk of the child falling onto hard floor if the mother was to have a seizure
- Changing nappies – changing the baby on the floor not using a changing unit or the bed
- Going outside – having a length of cord attached to the wrist that will stop the pram from running away if the mother was to have a seizure

TASK 1

A retired nurse who cared for her husband with Parkinson's will be attending the workshop. Below is a brief testimonial account of her experiences:

Context

My husband P. was diagnosed with Parkinson's in 2003 & passed away in 2011. I am giving my experience of living and caring with someone who had Parkinson's.

As a carer, whilst my aim was always to ensure P was as independent as possible, in the later years when the disease progressed at a faster rate, his needs became greater and my role as a carer became more intense.

Background history of ourselves

P was always in good health – attendance at our GP practice was rare. P was the eldest of 6 children.

He was self – employed – sole trader– running a worldwide business - building, designing underwater equipment for the oil industry & providing training to workers offshore around the world.

He was a very confident person. Both of us looked after his mother for several years, who

had Parkinson's and Lewy Body Dementia, until her death in 2003

In 2003 P went to see his GP because of the difficulty he was having forming chords when playing his guitar – having played it since 16yrs old. His GP referred him to a neurologist at Addenbrookes who diagnosed Parkinson's. P was 53 years old when diagnosed this was also the year that his mum died

P was very stoical and carried on, never complained about his illness but got very frustrated when his symptoms restricted some activities. I had experience in a caring role as a registered nurse and had spent 34 years working in the NHS at the point P was diagnosed.

On reflection the symptoms that were apparent before P's diagnosis were: Loss of smell, His writing was very small, Problems with his stomach - GP investigated stomach ulcer, Constipation, Often knocking into/ against things/ clumsy, Not swinging arms when walking

Caring for someone with Parkinson's

Whilst I took on the role willingly, the fact is I too suffered significant loss in terms of opportunities and the future they we had planned.

As a carer I needed factual, credible information and support as much as the person afflicted by Parkinson's disease. Some of this was provided by our families, the local branch of the charity Parkinson's UK PUK, their carers group provided tips and hints on managing some of the challenges and other support came from the local neurological/ multidisciplinary team.

Communication and negotiation skills were particularly important in order to balance the needs of both P and myself. I was also aware of the need to look after my own health by getting enough sleep and exercise which was not always possible and I would cancel dentist appointments etc. simply because I could not leave P alone or his condition on the day limited his ability to move easily.

When first diagnosed I didn't worry about immediate incapacity as I thought it would have a slow progression and it would be a while before he would need high levels of care & he may never need the highest level. Both of us kept busy working.

I was still working full time and had not contemplated leaving work/ retiring for a few years. As the disease progressed at a faster pace than I had anticipated I decided to leave work the plans we had made for the future now changed. The post I was in required me to give 6 months' notice to my employer – so predicting the right time to do this was very difficult.

Both of us faced a different retirement from the one we had expected.

I don't mean luxuries in any kind of material sense, but luxuries in the terms of just the things we wanted to do together and share together. So as time went on I spent a lot of time kind of worrying about, "How will I approach him giving up his business. How will we wind it up? Will he have the energy capacity and memory to do this or help me to do it? He was very reluctant to let it go. What were the risks of making faulty equipment that could endanger others' lives? What were his vulnerabilities? What were the financial consequences? What other symptoms was he experiencing and afraid to share and what symptoms lay before him? What would he be like if he just couldn't do things? How will he manage to make himself understood?

As we were both aware of the mental health decline in his mum, how would P cope with that? Was there a risk of suicide?

It would have helped me hugely during that time to feel like I could just have gone and talked to somebody who had opened the door to saying, "Do you want to just come in and talk about how you feel or what you're worrying about? Even just knowing then that I could have gone back, and maybe said, I don't think I needed a huge amount of help, but I do think it would have made a huge difference if I could just have talked to somebody at that time.

Long before there were serious physical needs, I had to learn the difficult balance between the desire to help against the perceived value of encouraging independence. I suppressed any fears about the future in an attempt to keep P from descending into depression.

I did not want to interfere, seem bossy or cause him further worry and anxiety but all the time had to weigh up just how much to do for him and how much to leave to him to get on with doing things. We usually saw his consultant and professionals together as P sometimes had difficulty expressing himself. Initially he wasn't owning up to his doctor about all the problems he was having so after discussion with him we agreed how we would manage this and would have several discussions leading up to his appointments. I contributed with my observations, and we agreed a list of symptoms/ difficulties we would discuss with the professionals in the hope it might possibly make a small difference to his treatment and maximise the 10-minute session we had with the Doctor. This did help with his drug regimen in a way that improved the control of his symptoms. Getting the right medication and adjusting dosages & timings was necessary.

As the illness progressed P needed help with such things as bathing, dressing, cutting up food and mobility.

Whenever medication was changed he would get much worse for a few days. Even switching from tablets to capsules of the same strength caused some confusion as the later stages of the disease and required a lot of time, patience and persuasion for him to take them.

TASK 2 Mr AB is admitted to the acute medical unit after a fall. His GP repeat medication list is provided below, and his inpatient drug chart is provided on Blackboard. His wife confirms that he takes his medication as per the GP medication list.

- Sinemet 12.5/50 2 tablets TDS at 06:00, 12:00, 18:00
- Half Sinemet CR 25/100 ON
- Aspirin 75mg OM
- Simvastatin 20mg ON
- Salbutamol 100mcg Evohaler® PRN
- Tamsulosin 400mcg OM

Recently discontinued:

- Sinemet 12.5/50 1 tablet TDS at 06:00, 12:00, 18:00

1. Identify any discrepancies between the drug chart (on Blackboard) and repeat medication slip.

- Simvastatin prescribed OM rather than ON (Q 1)
- Tamsulosin prescribed in mg not mcg (Q 2)
- Sinemet = co-careldopa NOT co-beneldopa (Q 3)
- Pt normally takes normal release Sinemet 125mg (2 x 62.5) TDS and MR at night-time.
- Morning dose prescribed at 08:00- should be 06:00

Starting dose of Sinemet is usually 125 mg TDS (100mg L Dopa & 25mg carbidopa)

If changing from different levodopa, discontinue at least 12 hours (24 hours for slow-release preparations) before starting therapy.

The easiest way to do this is to give 'Sinemet' as the first morning dose after a night without any levodopa.

2. Identify any other pharmaceutical care issues associated with his current drug chart.

- Metoclopramide charted TDS PRN and doses given (contraindicated in Parkinson's) (Q4)
- Need to select an alternative anti-emetic i.e., domperidone. Most others e.g., prochlorperazine and metoclopramide are DA antagonists. (Q 4)
- Day 1- 08:00, 12:00 dose of co-beneldopa not given (4 indicates no stock)
- indication for aspirin?

You have a discussion with Mr AB's wife, as she is concerned that since increasing his dose of Levodopa therapy, he has been feeling dizzy and nauseous. Summarise an appropriate management and monitoring approach in response to this information.

Nausea, vomiting and orthostatic hypotension are the most commonly encountered side effects of levodopa therapy.

These adverse events may be circumvented by increasing the levodopa more slowly or co-prescribing domperidone.

Levodopa therapy stimulates dopamine receptors found in the peripheral areas of the gut and vomiting centre.

Metoclopramide is contraindicated in PD as it blocks dopaminergic transmission. Suggest domperidone 10mg TDS as alternative antiemetic if necessary (domperidone also reduces dopaminergic transmission but does not pass the blood brain barrier therefore safe to use in PD).

This patient would benefit from referral to a Parkinson's/ neurology specialist. It is likely that the patient may have developed postural hypotension as a result of the increased levodopa dose from 50mg to 100mg at 06:00, 12:00 and 18:00. We could suggest reducing to his original dose of 50mg TDS and increasing by 50mg a day (i.e. - initially 100mg at 06:00, 50mg 12:00 and 18:00 for example).

Tamsulosin also causes postural hypotension – you may suggest that the doctor reviews this for ongoing suitability.

During his admission, Mr AB is therefore referred for assessment by the speech and language therapist (SALT). SALT recommends thickened fluids and pureed meals. Summarise below your recommendations for the FY2 regarding how best to manage his Parkinson's medication. + check non parkinsons med

Co-careldopa tablets are dispersible in water – so thicken fluid as necessary, stop statin, aspirin (stop, dispersible), dompeidone available as suspension

Mr AB is becoming increasingly agitated and confused has removed his nasogastric tube multiple times so the decision is made to convert his oral Parkinson's medications to a transdermal patch. Use the OPTIMAL Calculator 2, for patients who cannot have an NG tube to calculate a suitable dose of Rotigotine patches.

LINK: OPTIMAL Calculator

Task 1 Post-Operative Analgesia

Mr SH is a 65yr old male admitted to the surgical admissions unit for planned left leg amputation due to uncontrolled diabetes causing gangrene.

Prior to admission:

Medical History:
Hypertension
Type 1 diabetes mellitus

Drug History:
Ramipril 5mg DAILY
Simvastatin 40mg DAILY
Novorapid 8 units with meals
Lantus 18 units at night

Background to case:

Mr SH is planned to go to emergency theatre though he is complaining of uncontrolled pain, he is currently prescribed;

- Paracetamol 1 g QDS PO
- Codeine 30 mg QDS PO

1. What signs and symptoms of pain might we see for this patient? What changes or additions can be made to Mr SH's medications to control his pain pre-operatively?

Patient reported pain Blood pressure, pulse rate (increased) respiratory rate (increased) Can increase codeine dose OR switch to alternative e.g. Tramadol/dihydrocodeine Consider adding an NSAID (+PPI) PRN morphine

2. Mr SH has his lower leg amputated and is returned to the ward and initiated on a Patient Controlled Analgesia (PCA) pump. What factors do you need to consider before starting a patient on a PCA?

Disadvantages of a PCA – patient may not be responsive enough to use PCA, may be scared of self-administration. Consider manual dexterity as well in terms of use Advantages: Patient is able to respond to pain quicker, therefore faster alleviation of time, less time consuming for nurses. Able to easily titrate according to patient response/need

3. What monitoring parameters would you advise for the PCA to monitor for therapeutic effect and toxicity?

Therapeutic effect: Pain score: should be minimal, definitely less than 4 whilst being able to move, cough etc. If pain score is 5-8 consider additional analgesic dose and/or treatment. If pain score is 8 or over, refer for advice e.g. anaesthetist, pain team. Could give an additional small bolus doe of morphine. Toxicity: Sedation: Alert/Voice/Pain/Unresponsive Respiratory depression: Normal resp rate usually taken as 10-14 breaths per minute. Toxicity indicated by RR < 8 breaths per minute. Naloxone may be prescribed PRN in case of respiratory depression. Constipation: need to ask patient about 'normal' frequency of bowel movement. Monitor frequency, if constipated may need Rx e.g an oral laxative or enema. Pruritis:

4. What are the treatment options for step down analgesia once the PCA is removed?

Paracetamol PO 1G QDS (or every 4-6 hours) and any ONE weak opiate option from the following: Codeine PO 30-60mg QDS(or every 4-6 hours) Tramadol PO 50-100mg QDS (or every 4-6 hours) Dihydrocodeine PO 30-60mg QDS (or every 4-6 hours) Ibuprofen PO 400mg TDS + PPI

Task 2 – Neuropathic pain

You are working in a GP surgery conducting a pain clinic, Mr SH attends, he recently had a below knee amputation of his left leg. He was discharged from hospital on paracetamol and ibuprofen. He is reporting that despite taking these regularly he is feeling pain and itching in his amputated leg.

1. What is the likely cause of Mr SH pain? What would you recommend in terms of Mr SH's pain management?

He is experiencing phantom limb syndrome – where pain is experienced in the lost limb, this can present as burning, itching and pain in the missing limb.

Thought that the pain could be due to the peripheral nerves in the stump which are sensitive to stimuli

Non-pharmacological treatment can help with this such as relaxation, medication, physical exercise.

Analgesics are still appropriate though normally would use drugs suitable for neuropathic pain e.g. gabapentin, pregabalin, duloxetine, amitriptyline.

In terms of other analgesia he could use PRN tramadol for breakthrough pain

Consider stopping the ibuprofen.

Mr SH returns a month later. Alongside the paracetamol he has been taking the tramadol and amitriptyline as you prescribed. He started with amitriptyline 25mg ON and increased weekly to his current dose of 75mg ON. He has been taking tramadol 100mg up to QDS and it works when he takes it, although says he tries to take it as little as possible as he is not keen on taking opioids. He reports that the amitriptyline hasn't helped much with the pain but is making him drowsy for the majority of the morning.

2. What would you do next in the management of Mr SH pain?

Offer Mr SH a different agent – gabapentin or duloxetine would be the options;

Gabapentin – commonly causes drowsiness – a titrating dose can minimise this. As he had problems with drowsiness from the amitriptyline it would be prudent to start at 300mg OD day one then BD day 2 up to TDS day 3. The dose can be further titrated by 300mg every 2-3 days to a maximum 3.6g per day

Duloxetine – licenced for diabetic neuropathy only – other indications off label
60mg OD, may increase to 120mg per day

Task 3 – Palliative care

Mrs Josie Barratt, an 84 year old lady, has been admitted from her care home with declining medical condition and pain. Investigations show progression of her cancer.

PMH
Alzheimer's disease
Hypertension
Stage 4 breast cancer
Weight – 56kg
Medications charted;
Amlodipine 5mg OD – held as hypotensive
Zomorph 40mg BD
Codeine 30mg QDS
Oramorph 1.25mg 4 hourly PRN – she has been taking this every 4 hours

1. Comment on Josie's analgesia regime and make recommendations to adjust therapy.

Use of 2 regular opiates is not rational

The oramorph dose for breakthrough pain is not sufficiently high enough

She is using the oramorph regularly which indicates that the regular opioid dose is not controlling her pain and should be increased

From the BNF;
Codeine 100mg = morphine 10mg
Codeine 120mg = morphine 12mg
Oramorph 1.25mg x 6 = 7.5mg
12 + 7.5 = 19.5 mg

Increase regular dose by 19.5mg / day – round to Zomorph 50mg BD

Increase oramorph dose to 1/10 to 1/6 regular daily dose = 10-16mg – 10-15mg 2-4 hourly PRN

Monitor for side effects of therapy and consider medications if needed;
AVPU
Resp rate
Bowels
Nausea/vomiting

The following day Josie's medication regime has been adjusted however she has declined further, and anticipatory medications have been commenced;

Zomorph 50mg BD
Oramorph 5-10mg 2 hourly PRN
Midazolam S/C 2.5 – 5mg 2 hourly PRN
Hyoscine butylbromide S/C 20mg 2 hourly PRN
Levomepromazine S/C 6.25mg 2 hourly PRN
Morphine S/C 5mg 2 hourly PRN

After the weekend when you attend the ward you find Josie is no longer tolerating oral intake and the nursing staff had trouble getting her to take her Zomorph this morning, when you check her chart you find she has had regular doses of midazolam – 5mg every 4 hours and levomepromazine 6.25mg every 12 hours. The doctor has prescribed the following syringe driver;

Diamorphine 50mg
Midazolam 30mg
Levomepromazine 12.5mg
To 17mL sodium chloride 0.9%

2. Comment on the appropriateness of the drugs in the syringe driver use the extract from 'The Syringe Driver: Continuous subcutaneous infusions in palliative care' by Dickman & Schneider to consider the stability of the combination

From the BNF;

Morphine PO 10mg = Diamorphine parenteral 3mg
Morphine 100mg = Diamorphine 30mg

Dose of diamorphine is too high, especially as it has only just been increased and she has not been using any PRN morphine

Reduce diamorphine dose to 30mg

Compatibility;
Diamorphine 30mg
Midazolam 30mg
Levomepromazine 12.5mg

SD book;
Compatible

Josie continues to suffer nausea and has been having an additional 2 dose of levomepromazine 6.25mg BD. The doctor changes the syringe driver prescription to;

Diamorphine 50mg
Midazolam 30mg
Levomepromazine 25mg
To 17mL sodium chloride 0.9%

3. Comment on the compatibility of this combination

Compatibility;
Diamorphine 30mg
Midazolam 30mg
Levomepromazine 25mg

SD book;
Concentrations;
Diamorphine 1.76mg/mL
Midazolam 1.76mg/mL
Levomepromazine 1.47mg/mL

Last line shows laboratory compatibility of this combination. Changing the diluent to WFI would also be acceptable.

Diamorphine (A), Levomepromazine (B), and Midazolam (C)

Drug	Concentration (mg/mL)	Diluent	Dose in syringe (mg)	Volume in syringe (mL)	Outcome	Data type
A	1.76	*NaCl*	30	17	✓[P] (24 hours)	CLIN
B	0.74		12.5			
C	3.53		60			
A	3.53	WFI	60	17	✓[P] (24 hours)	CLIN
B	7.35		125			
C	1.47		25			
A	10.00	*NaCl*	150	15	✓[P] (24 hours)	CLIN
B	0.42		6.25			
C	0.33		5			
A	16.47	*NaCl*	280	17	✓[P] (24 hours)	CLIN
B	0.37		6.25			
C	1.76		30			
A	40.00	*NaCl*	800	20	✓[P] (24 hours)	CLIN
B	7.50		150			
C	3.00		60			
A	85.29	WFI	1450	17	✓[P] (24 hours)	CLIN
B	0.74		12.5			
C	1.76		30			
A	94.12	WFI	1600	17	✓[P] (24 hours)	CLIN
B	2.94		50			
C	1.76		30			
A	137.14	WFI	2400	17.5	✓[P] (24 hours)	CLIN
B	3.43		60			
C	2.14		37.5			
Comment: Physically compatible at the stated concentrations.						
A	0.50	WFI	Physically compatible and chemically stable [by HPLC] for 24 hours at ambient temperature			LAB[33]
B	0.31					
C	0.50					
A	5.00	*NaCl*	Physically compatible and chemically stable [by HPLC] for 24 hours at ambient temperature			LAB[33]
B	2.50					
C	1.50					

Task 1 Post-Op Analgesia & Neuropathic Pain

Mr Stuart Hale is a 61yr old male, date of birth 18/01/1963, admitted to the surgical admissions unit for planned lower left leg amputation.

Address: Flat 3b, Bengal Tower, Flatplace, FL8 0LK

Medical History:
Hypertension
Type 1 diabetes mellitus
CKD 3 (baseline eGFR = 55ml/min/1.73m^2)
Drug History:
Ramipril 5mg OD
Furosemide 20mg OD
Simvastatin 40mg OD
Novorapid 8 units with meals
Lantus 18 units at night
Note: Caused by uncontrolled diabetes causing damage to nerves (easy to injure) and blood vessels, restricting blood flow can cause cell death or lack of immune cell delivery to infection sites impaired wound healing = gangrene.

Mr SH is planned to go to theatre though he is complaining of uncontrolled pain, he is currently prescribed:

- Paracetamol 1 g QDS PO
- Codeine 30 mg QDS PO

1. What signs and symptoms of pain might we see for this patient? What changes or additions can be made to Mr SH's medications to control his pain pre-operatively?

Patient reported pain, pain score. Blood pressure, pulse rate (increased) respiratory rate (increased). Check adherence. Could try an alternative weak opioid (tramadol/dihydrocodeine) however low doses as renally impaired. Stronger opioid if severe pain - PRN oxycodone liquid (1.25-2.5mg 2hrly PRN) (not morphine as CKD3). NOT NSAID as CKD.

2. Mr SH has his lower leg amputated and is returning to the ward.
   He is about to be initiated on:
   Patient Controlled Analgesia (PCA) pump: Morphine - bolus 1mg, lockout 5 minutes.
   Morphine 10mg/5ml liquid, 2.5mg PO 4 hourly PRN.
   What pharmaceutical care issues can you identify regarding the two prescriptions above?

Pharmaceutical Care Issue	Action
CKD3 with baseline eGFR<60 & morphine chosen as the opioid (risk of accumulation due to impaired renal excretion)	Switch to fentanyl (NNUH guidance = 20mcg/ml concentration = 20mcg (1ml) dosing with 5 minute lockout) Note: If neuropathic pain – ketamine may be used also in the PCA alongside opioid (neuropathic pain not currently indicated)

Pharmaceutical Care Issue	Action
Oral morphine also charted	Assess whether oral or PCA route is most appropriate and stop one of the prescriptions. Whichever prescription continues – less renally excreted opioid (if PCA then fentanyl, if PO then oxycodone liquid)

Pharmaceutical Care Issue	Action
Other prescriptions not in place for opioid side effects and for non-opioid analgesia	Anti-emetic PRN in case of N&V side effects e.g. cyclizine 50mg TDS PRN – protocols for PO/IV/IM depending on route availability. Other considerations depending on signs/symptoms – naloxone for reversal, chlorphenamine for itching (4mg QDS PRN), laxatives if using opioid regularly (stimulant and osmotic e.g. laxido and senna – not bulk forming) Non-opioid analgesia e.g. paracetamol 1g QDS PRN

3. What are the treatment options for step down analgesia once the PCA is removed?

Paracetamol PO 1G QDS (or every 4-6 hours) (>50kg, LFTs in range) Depending on PCA usage: Strong opioid: oxycodone liquid 1.25-2.5mg 2 hourly PRN Weak opioid: Codeine PO 15-30mg QDS(or every 4-6 hours) Tramadol PO 50mg QDS (or every 4-6 hours) Dihydrocodeine PO 30mg QDS (or every 4-6 hours)

NOT Ibuprofen PO 400mg TDS – CKD3
NOTE: On discharge – aim to step down to a weak opioid with paracetamol, dependent on pain level. May be discharged with both and instructed to step down to codeine once able. ALL SHORT TERM prescriptions & follow ups arranged if necessary.

You are a now a prescribing pharmacist in Mr SH's GP surgery. He is attending your pain clinic 1 month post-op. Despite taking his analgesia prescriptions regularly, he is feeling pain and itching in his amputated leg; he describes the pain as mostly a tingling sensation but sometimes a sharp shooting pain.

4. What is the likely cause of Mr SH pain? What would you prescribe for Mr SH's pain management?

Phantom limb syndrome – pain is experienced in the lost limb, this can present as burning, itching and pain in the missing limb. Thought that the pain could be due to the peripheral nerves in the stump which are sensitive to stimuli – treated as neuropathic pain.
Pharmacological options: Amitriptyline/Gabapentin/Pregabalin/Duloxetine
Amitriptyline MOST appropriate as:
Duloxetine off-label use (BNF only has doses for diabetic neuropathy, not 'neuropathic pain' as with the others)
Gabapentin/Pregabalin have renal clearance issues – BNF recommends dose reductions for these drugs, however, has no recommendation for amitriptyline as this is not an issue.
Non-pharmacological treatment can help with this such as relaxation, medication, physical exercise.

5. Write a prescription which is the most appropriate option for controlled Mr Hale's pain, at the lowest recommended dose. You will follow up with Mr Hale in 1/52.
   You are prescribing in: Flatplace Pain Clinic, Flatplace, FP10 7PT

Legal requirements – Indelible ink/Date/signed/address & particulars of prescriber/name and address of patient/Age if under 12 (DOB & age of 12 above are good practice)

Task 2 – Opioid overdose

You are working as an on-call pharmacist when a junior doctor from A&E calls you regarding a patient who has come in with suspect opioid overdose. They tell you that she has found unconscious in her bedroom by her housemate, who also found an empty bottle of morphine liquid. She was supplied with this two days ago on discharge from hospital. She has no prior history of using regular opioids. She appears pale and her lips have started to turn blue.
The doctor wants to prescribe naloxone but does not know what dose to give.

1. What signs/symptoms exhibited in the information above, and on the patient's NEWS2 chart, suggest that she is in opioid toxicity? Calculate the patient's latest NEWS score as part of the answer this question

2. Using the NNUH guideline, what dose of naloxone would you recommend?

Latest NEWS2 Score = 10

Physical appearance – pale skin, blue lips – indicating hypoxia
Unconscious
Low respiratory rate <8 breaths per minute – activation of μ-opioid receptors in the brain stem that help to co-ordinate breathing
Low oxygen saturation on air on admission (increasing slowly now on oxygen)
Tachycardia
Clear indication of opioid use – empty bottle 24hours after discharge (typical bottle 100ml (10mg/5ml) = 200mg morphine)

NOTE: Another symptom not mentioned in this case – pin-point pupils. 3-5mm normal, opioids give you 2-3mm, direct response of pupil constricting to light & consensual response of the other eye constricting (should see dilation once light removed).
Benzos / cocaine / ketamine / antihistamines = dilation (stimulants).

Task 3 – Palliative care

Mrs Josie Barratt, an 84 year old lady, has been admitted from her care home with declining medical condition and pain. Investigations show progression of her cancer.
PMH
Alzheimer's disease
Stage 4 breast cancer
Weight – 56kg
eGFR = 77ml/min/1.73m^2
Medications charted:
Amlodipine 5mg OD – held as hypotensive
Zomorph 30mg BD
Codeine 30mg QDS
Oramorph 1.25mg 4 hourly PRN – she has been taking 1.25mg every 4 hours for 3/7

1. Comment on Josie's analgesia regime and make recommendations to adjust therapy.

Issues:

- Use of 2 regular opiates is not rational
- She is using the oramorph regularly which indicates that the regular opioid dose is not controlling her pain and should be increased
- The oramorph dose for breakthrough pain is not sufficiently high enough

From the BNF:
Codeine 100mg = morphine 10mg
Codeine 120mg = morphine 12mg
Oramorph use over 24 hours = 1.25mg x 6 = 7.5mg

12 + 7.5 = 19.5 mg
Increase regular dose by 19.5mg / day – round to 20mg/day as cannot halve a capsule
New dose = **Zomorph 40mg BD**
Increase oramorph dose to 1/10 to 1/6 regular daily dose = 8-13mg – Approximately **Oramorph 10mg 2-4 hourly PRN**

+ STOP CODEINE
Monitor for side effects of therapy and consider medications if needed:
AVPU, Resp rate, Bowels, Nausea/vomiting
~~Note: You may also see dexamethasone used in oncological pain control (as per specialist teams only – not expected to~~ recommend or dose this, just to be aware of use)

You attend the consultant ward round on Friday morning where you find that Josie is struggling to swallow her Zomorph capsules. The consultant wishes to change this to an equivalent buprenorphine patch and has asked you to prescribe this for her.

2. Using the 'Prescribing in Palliative Care' chapter in the BNF, what dose of buprenorphine patch do you prescribe?

Zomorph 40mg BD = 80mg morphine over 24 hours
Rounded to nearest 84mg morphine = buprenorphine '35' patch

Buprenorphine 35mcg/hour patch once weekly

Notes: If renal function was impaired we would prescribe fentanyl patch. Patches can be 72hrly/weekly/96hrly so check patch directions (majority buprenorphine weekly, fentanyl 72hrly).
Continuous release – e.g. patient concerned that their patch was changed two days early, is this a problem? No, just a waste of drug.

After the weekend, you attend Monday's ward round to find that Josie has unfortunately deteriorated and has been moved to a palliative care approach. Anticipatory injections have been started as follows:
Buprenorphine 35mcg patch once weekly
Oramorph 10mg 2 hourly PRN
Midazolam S/C 2.5 – 5mg 2 hourly PRN (restlessness/agitation)
Hyoscine butylbromide S/C 20mg 2 hourly PRN (secretions)
Levomepromazine S/C 6.25mg 2 hourly PRN (nausea & vomiting)
Morphine S/C 5mg 2 hourly PRN (pain/SOB)
Over the weekend, nurses report that she has become quite agitated, and her patch is rubbing off when she moves around causing her to be in pain when this goes unnoticed. She has received 4 injections of 5mg midazolam over the last 24 hours. The consultant wishes to start her on a 24 hour syringe driver which contains midazolam and morphine and asks you to prescribe the appropriate driver.

3. Identify and explain the appropriate medications, including dosages, diluent and size of syringe driver that you would prescribe. Use the compatibility table on the next page, and the prescribing in palliative care chapter of the BNF to make your recommendation.

Answer:
Morphine 42mg (In practice would be rounded to 40mg or 45mg as a multiple of 5 for administration purposes – rounding up/down would depend on clinical condition & level of pain)
Midazolam 20mg
Dilute to 17ml with WFI (17ml in 20ml syringe driver)

BNF Chapter:
Buprenorphine '35' patch = 84mg morphine
10mg PO Morphine = 5mg IV/SC Morphine
84mg PO Morphine = 42mg SC Morphine
Using 5mg x 4 midazolam over 24 hours = 20mg SC midazolam
Water for injection diluent in 17ml in 20ml driver as per compatibility chart

- **Most patients will require much lower doses.** Refer to relevant guidelines to obtain the usual dose range to prescribe for each drug. Use minimum effective dose and review according to response.
- Mixing of drugs in this manner is unlicensed but is supported by clinical practice.
- Seek specialist advice from a clinical pharmacist if the doses needed are greater than those stated in the tables.

Task 1 - Nausea and vomiting in pregnancy

Mrs SP, a 25-year-old female, 8^{+3} gestation, enters the patient enters the community pharmacy that you are working in and asks for some advice on the morning sickness she is experiencing. She tells you that she started feeling sick about week 4 and feels sick most of the day. Luckily, she has only been sick a few times.
She has no relevant PMHx, DHx and NKDA.

1) What advice would you give Mrs SP?

- It usually begins between 4–7th weeks, peaks between 9–16th weeks, and resolves by 16–20 weeks of pregnancy. Onset of symptoms after 11 weeks of gestation usually suggests an alternative cause of symptoms unrelated to pregnancy.
- IT IS NOT - Hyperemesis gravidarum describes the most severe end of the spectrum of symptoms, and is a diagnosis of exclusion characterized by:
    - Prolonged, persistent and severe nausea and vomiting unrelated to other causes.
    - Weight loss (usually at least 5% of pre-pregnancy body weight).
    - Dehydration and electrolyte imbalance.
- Risk factors – multiple pregnancy, first pregnancy, Hx of HG, FH, obesity.
- Possible maternal complications if there are severe symptoms include weight loss, electrolyte imbalance, acute kidney injury, nutritional and vitamin deficiencies, gastro-oesophageal reflux disease, venous thromboembolism, and impact on psychosocial functioning.
- Possible fetal complications if there is hyperemesis gravidarum include preterm delivery, low birthweight, and small-for-gestational age.

Assess the impact – duration, severity, oral intake, hydration, urine output, sleep, co-morbidities (i.e. DM = DKA risk).

Reassure it usually resolves by 16-20 weeks.
Self help:
Rest as needed, and try to avoid sensory stimuli that may trigger symptoms, such as odours, heat, and noise.
Try eating plain biscuits or crackers in the morning.
Try eating bland, small, frequent protein-rich meals which are high in carbohydrate and low in fat.
Cold meals may be more easily tolerated if nausea is smell-related.
Drinking little and often, rather than large amounts. Ginger (can be taken in fresh, tea, capsule, or syrup form).
Acupressure (such as over the P6 point on the ventral aspect of the wrist using a wrist band or finger pressure).
Avoid contributing medication.
Advise on dyspepsia (if contributing) – small frequent meals (3 hours), not late, avoid irritants (caffeine, fruit juice, carbonated drinks), food diary. Raise the head of the bed. Potentially alginate product.
Fresh air.

2) In what situations would you need to refer the patient to the GP?

Unable to keep anything down/fluids.
Risk/is dehydrated/low BP.
Co-morbidity that increases risks i.e. diabetes, epilepsy
Persistent high volume and/or suspicious colour of vomit
Unable to do daily tasks.- especially if patient has other children, care of the other children and the foetus could be at risk
Concomitant drugs that increase risks when vomiting/unable to keep essential medication down.
Potentially patients that have struggled to conceive and the patient is incredibly anxious about losing the baby
Prescription medication to help with morning sickness being ineffective.

2 Weeks later Mrs SP comes back to the pharmacy with a prescription.

3) Which antiemetics would you expect to see prescribed by the GP?
For each suggestion, provide detail of important cautions/contraindications, side effects, interactions and counselling.

*Green-top guideline RCOG No 69
**CKS – only drug licensed for N&V in pregnancy

***CYCLIZINE** – first line – Antihistamine (H1) block the histamine receptors of the vestibular system (that's why they work for travel sickness), but also in the vomiting centre (NTS-nucleus of the solitary tract). There is also antimuscarinic action (leading to s/e). Increase in oesophageal sphincter tone.

Various indications – motion, narcotc analgaesia/GA in PONV, radiotherapy, vestibular disorders.

Dose - Po 50mg TDS (RCOG) (can be given IV, PR and by subcutaneous/intravenous infusion)

Antiemetic effect in 2 hours and lasts approximately 4-6 hours.

Cautions – (due to anticholinergic effect) – may ppt glaucoma, caution in urinary retention, GI obstruction, HTN, epilepsy (as convulsions reported) and prostatic hypertrophy. Severe HF and recent MI – may reduce CO (inc.HR). Hepatic impairment/failure – increased risk of encephalopathy.

Side effects - Children and elderly (increased risk of cognitive impairment and mortality) are more susceptible.

(peripheral) dry mouth, nose, eyes and throat, blurred vision, tachycardia, constipation and urinary retention; (central) drowsy, dizzy, incoordination, EPSE – mechanism unclear (dystonia, dyskinesia), tremor, convulsions, dizziness, decreased consciousness, confusion, agitation. There have been reports of euphoric or hallucinatory effects – potential for abuse. N&V. Arrhythmias. Hypotension, hypertension. Photosensitive skin reactions reported – protect skin from the sun.

Interactions - with alcohol – increases toxicity of alcohol (do not use in acute alcohol use). Interaction with other CNS depressants – additive effects (hypnotics, anaesthetics, antipsychotics, TCA, opioid analgesia). Enhanced additive side effects with other anticholinergic drugs.

Driving and machinery – can cause drowsiness and impaired function, if affected do not drive or operate machinery.

*__PROMETHAZINE__ (Phenergan) – first line – Antihistamine (H1) block the histamine receptors of the vestibular system (that's why they work for travel sickness), but also in the vomiting centre. Also, antimuscarinic and antidopaminergic activity.

Indications – nausea, vomiting vertigo labyrinthine disorders, motion sickness. Not licensed for under 2-year-olds due to the risk of respiratory depression, and children under 6 yrs should not be given cough and cold remedies with it in MHRA warning 2009).

Dose - Adult – RCOG recommends 12.5-25mg every 4- 8 hours for morning sickness. Different doses for motion sickness).

PO, IV.

Cautions - (due to anticholinergic effect) – may ppt glaucoma, caution in urinary retention, GI obstruction, HTN, epilepsy (as convulsions reported) and prostatic hypertrophy.

Contraindications - in CNS any depression.

Side effects, interaction and warning – as above.

*__PROCHLORPERAZINE__ – first line – Phenothiazine – first generation antipsychotic mainly blocks D2 dopamine antagonist, H1, muscarinic and noradrenergic receptor antagonism.

Indications – N&V in migraine, labyrinthine disorders, prevention and treatment of N&V

PO, IM, buccal, PR (not equivalent)

Dose - Po 5-10mg 6-8 hourly (RCOG)

Contraindications - CNS depression

Cautions – conditions predisposing to seizures, cardiac failure, CVD (may predispose to arrhythmias), DM (may raise blood glucose), epilepsy (can lower seizure threshold), myasthenia gravis (due to anticholinergic effect), PD (antagonism), susceptibility to closed angle glaucoma, prostatic hypertrophy, stroke risk, elderly, hepatic impairment (extensively metabolised in the liver), renal impairment (increased cerebral sensitivity).

Side effects - Nervous system s/e are most commonly reported – dystonia, dyskinesia, Parkinsonism's, tardive dyskinesia, insomnia, agitation, convulsions.

Antimuscarinic s/e (interactions with drugs that potentiate this). Drowsiness (esp. when first used). Photosensitisation of the skin. Haematological (leucopenia, neutropenia). Hypotension. Hyperprolactinaemia – potentially leading to galactorrhoea, gynaecomastia, amenorrhoea and impotence. Hypotension.

Cardiac disorders including, potentiation of the QT interval leading to serious arrhythmias (interactions with drugs that potentiate this).

Additional care where patients have mental health issues requiring treatment – specialist advice would be sought. Additional care when considering interactions.

Interactions - CNS depressant effects of alcohol, sedatives etc intensified. Levodopa = antagonism.

Driving and machinery – can cause drowsiness and impaired function, if affected do not drive or operate machinery.

Administration of buccal (administration instructions).

*__CHLORPROMAZINE__ – first line – Phenothiazine - first generation antipsychotic mainly blocks D2 dopamine antagonist, H1, muscarinic and alpha-adrenergic receptor antagonism.

Indication – N&V in palliative care.

Dose - Po 10-25mg every 4-6 hours (RCOG)

Po, IM, PR (not equivalent)

Similar cautions and CI to above for prochlorperazine.

Contact sensitisation – avoid handling.

Interactions – Potentiation of effects with drugs with similar pharmacology.

Chlorpromazine is generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects; whereas, prochlorperazine has fewer sedative and antimuscarinic effects and more pronounced extrapyramidal effects.

**DOXYLAMINE/PYRIDOXINE (Xonvea) – First-line – H1 receptor receptor blocker and vitamin B6 (water soluble vitamin).

The only drug licensed for N&V in pregnancy.

***DOMPERIDONE** – Second line - Dopamine antagonist. Works on the chemoreceptor trigger zone but does not cross the BBB. Increases GI transit due to peripheral receptor antagonism (prokinetic).

Dose - Po 10mg up to TDS (every 8 hours) (RCOG) max1 week

Not for children and those weighing less than 35 Kg (not as effective and alternative should be considered – not shown to be any more effective in controlling N&V than ORT)

Contraindications - cardiac disease (i.e. CCF as this increases the risk of ventricular arrhythmias), where cardiac conductance is/could be impaired, bradycardia (increases the risk of arrythmias), GI haemorrhage, GI obstruction (where stimulation harmful), receiving other medicines known to increase QT (amiodarone, citalopram, erythromycin, methadone) or have prolonged QT, potent cyp 3A4 inhibitors/caution with all CYP3A4 inhibitors (azoles, protease inhibitors and macrolides) (domperidone is a substrate for it and it is its main metabolic pathway), hepatic impairment (hepatically metabolised), prolactinoma (a prolactin-releasing pituitary tumour).

Caution - >60yrs increased risk of ventricular arrhythmias, severe renal impairment (dose and frequency reduction required), electrolyte abnormalities (correct before use as this could increase the risk of arrhythmias), drugs causing electrolyte abnormalities and bradycardia.

Side effects - c=dry mouth, uc=anxiety, breast abnormalities (galactorrhoea, pain, tenderness), diarrhoea, drowsiness, rash; frequency unknown=arrhythmias, QT prolongation, urinary retention, gynaecomastia, menstrual cycle disorders, seizure, hyperprolactinaemia. Movement disorder (EPSE) – rare as it doesn't cross the BBB

Identify signs of arrhythmia and get help – i.e. palpitations and syncope

2014 European safety review 2014– risk of serious adverse drug reactions including increased QT and sudden cardiac death. Implemented measures to balance risk:benefit.

Lowest effective dose for the shortest time (greater doses increase the risk of arrhythmias) – max 1 week.

Absorption is delayed if taken after eating, therefore best to take on an empty stomach.

Interactions – anything prolonging QT, cyp 3A4 inh (macrolides, azoles), drugs causing electrolyte abnormalities.

***METOCLOPRAMIDE** – Second line – Dopamine antagonist in the CTZ (some direct action on the gut to act as a prokinetic). This can cross the BBB to cause the movement disorders described in it's side effects. Also inhibits serotonin in the CTZ.

Indications – N&V+ migraine, delayed CINV, RINV, PONV prophylaxis

Dose – 5- 10mg every 8 hours (RCOG)

Po, IM, IV

MHRA/CHM 2013 – risk of neurological adverse effects (Acute dystonic reactions - EPSE, tardive dyskinesia etc.) – restricted dose and duration. Prescribe short term (up to 5 days), 10mg up to TDS (at least 6 hours apart) (max daily dose is 500 mcg/kg), iv bolus over at least 3 minutes, oral liquid should be measured using an appropriate oral syringe.

Metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Usually with higher doses/prolonged use. Treatment must be stopped if signs appear.

Contraindications - 3-4 days post GI surgery, GI haemorrhage, obstruction, perforation – stimulated GI motility in these patients is a risk. Epilepsy (can cause seizures). Parkinson's disease.

Cautions - asthma (can cause bronchospasm), bradycardia and conductance disorders (increased risk of arrhythmias), children and elderly (increased risk of neurological adverse effects), Parkinson's disease (causes movement disorders), uncorrected electrolyte imbalance (increased risk of arrhythmias), young adults (increased risk of neurological adverse effects), renal impairment & hepatic impairment (risk of accumulation).

Side effects - c = asthenia, depression, drowsiness, diarrhoea, hypotension, menstrual cycle abnormalities, parkinsonism, EPSE; uc=arrhythmia, hallucinations, bradycardia, hyperprolactinaemia, decreased level of consciousness, r=confusion, seizure, nk= AV block, cardiac arrest, QT prolongation

Renal and hepatic dose adjustments required.

Interactions - Levodopa (plus other medicines used for Parkinson's disease) and metoclopramide – antagonism. Alcohol potentiates sedative effect. Central nervous system depressants – morphine, anxiolytics, sedative H1 antihistamine, sedative antidepressants – sedative effect potentiated. Anticholinergics and agents acting to slow GIT will antagonise the prokinetic effect. Additive effect to other drugs causing EPSE's. Strong CYP2D6 inhibitors (fluoxetine, paroxetine) monitor as this is the main route of metabolism.

Ability to operate machines/drive may be impaired

*__ONDANSETRON__ – Second line – 5HT3 antagonist acting in the GIT (vagal afferents) and CNS (CTZ).

Indications - Moderate and severely emetogenic chemotherapy and radiotherapy, PONV

Dose – PO (RCOG) 4-8mg every 6-8 hours for up to 5 days

Po, IV (doses not equivalent)

MHRA/CHM 2020 – small increased risk of cleft palate when used in the first 12 weeks.

MHRA guidance from August 2012, highlights a dose-dependent risk of QT prolongation, cardiac arrhythmias, including Torsade de Pointes with ondansetron. Ondansetron should be avoided in patients with congenital long QT syndrome.

Caution - if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include: electrolyte abnormalities, use of other medicines that prolong QT interval or may lead to electrolyte abnormalities, congestive heart failure, bradyarrythmias and medicines which lower the heart rate. This is dose dependent.

Side effects - c=constipation, headache, warmth/flushing; uc=arrhythmias, hypotension, movement disorders, seizure, r=QT prolongation

Dose adjust in hepatic impairment

Interactions - Many enzymes are responsible for metabolism therefore if one is reduced then the others can compensate. Potent inducers will clear it quicker, i.e. phenytoin, carbamazepine and rifampicin. Other serotoninergic drugs

*Doses as per the RCOG. For other indications please refer to the BNF or product literature (SPC).

Task 2 - Antiemetics use in Parkinson's disease

1) Mr BS, a 63 year old gentleman phones his specialist nurse to discuss a new adverse effect that he is experiencing after an increase in the strength of his medication. He reports a constant feeling of nausea and has been sick once.

DHx: Co-beneldopa 100/25 tablets – 1 TDS (was 50/12.5 QDS)
Co-beneldopa CR 100/25 capsule – 1 ON

The doctor wants to prescribe an antiemetic for Mr BS to use before he can be seen in clinic in a couple of days time.
Which antiemetic would you recommend and why?
Why would other antiemetics be considered inappropriate?

Parkinsons disease is a progressive neurodegenerative condition resulting from the death of dopaminergic cells of the substantia nigra in the brain. This leads to symptoms such as motor symptoms (hypokinesia, bradykinesia, rigidity, rest tremor and postural instability) and non-motor symptoms (dementia, depression, sleep disturbance, bladder and bowel dysfunction, speech, and language changes, swallowing problems and weight loss).

Domperidone – It acts on and blocks peripheral dopamine receptors of the chemoreceptor trigger zone in the area postrema (surface of brain stem but outside the physiological BBB). This is where dopamine agonists, such as levodopa, exerts it effect to cause vomiting. It also acts as a prokinetic.
Other potentially appropriate agents include:
Cyclizine – as above
Ondansetron – as above
Antiemetic that should not be used in Parkinson's disease:
Metoclopramide, prochlorperazine, chlorpromazine – D2 agonists - highly likely to worsen Parkinson's disease – as they are dopamine antagonists crossing the BBB.

2) Provide detail of important cautions/contraindications, side effects, interactions and counselling of the medication recommended.

Domperidone – As above

Cyclizine – As above

Ondansetron – As above

Task 3 – Antiemetics during cancer chemotherapy
Chemotherapy induced nausea and vomiting (CINV) is an important area of patient management for patients undergoing cancer treatment. CINV is classified into 5 categories:

Acute – N&V occurring within 24 hours of chemotherapy administration.
Delayed – N&V occurring at least 24 hours after administration of chemotherapy and often peaking between 48 to 72 hours.
Breakthrough – N&V occurring within 5 days post chemotherapy despite optimal antiemetic use (requires rescue antiemetics).
Refractory – N&V occurring in subsequent chemotherapy cycles despite maximum antiemetic.
Anticipatory – N&V triggered by sensory stimuli associated with chemotherapy.

1) What treatment **strategies** (not treatments) can be used in their management? As a HCP, what factors influence your decisions about management of CINV?

Assess the patient for risks – age <50, female, history of motion sickness or motion sickness, emesis with prior treatment. Alcohol (>5 drinks/week) / smoking lowers the risk of CINV.

Assess the regime - Antineoplastic regime (depends on dose, concomitant drugs, route, drug, frequency) being used – high risk of cinv (>90%) – cisplatin, cyclophosphamide, carmustine; moderate (30-90% of patients) – carboplatin, doxorubicin, oxaliplatin. There are also drugs with low and minimal emetic effects.

Prophylactic strategies – PREVENTION is easier than treatment.

Dose given before, after and into the future. Breakthrough and rescue therapies are also provided.
The likelihood and timings of drug/regime N&V will also have come from the clinical trials. The protocols will contain details of the types of antiemetics to use when.

The greater the risk the more drugs are used in combination.

2) For the THREE main types of antiemetic used for the prophylaxis of acute and delayed CINV? Describe why they are effective for CINV (consider their MOA).
For each suggestion, provide detail of important cautions/contraindications, side effects, interactions and counselling.

It is a complex process, involving peripheral and central mechanisms to cause N&V. Believed to involve neurotransmitters (serotonin, substance P, dopamine) and receptors (5HT3 and NK-1) as well as acetylcholine, histamine….

5HT are released from enterochromaffin cells in the GIT mucosa as a response to chemotherapy/radiotherapy. These bind 5HT3 receptors located at the end of the vagal afferent nerves. These travel to the nucleus of the solitary tract (NTS)/VC.

Chemoreceptors in the area prostrema, located outside the BBB can be directly activated by chemotherapy and released 5HT. = acute

Substance p, present in the peripheral and central nervous system is also released in response to chemotherapy, This binds to neurokinin 1 receptors on the NTS and CTZ. Predominantly important in delayed CINV. It also acts in the GIT so may have a role in acute N&V.

There are national guidelines available European and American societies and networks and specialist centres will have their own adaptations of these.

Dexamethasone – The exact mechanism of how this works is unknown. Potential due to management of the inflammatory mediators (eicosanoids) produced after chemo or radiotherapy.

Generally taken for short periods of time.

5HT3 receptor antagonist – Ondansetron, polonosetron (second generation – longer half life), granisetron
Work at receptors in the periphery and centrally preventing activation of the CTZ.

Action is important in acute CINV and to a lesser extent in delayed CINV.

Neurokinin-1 antagonists – aprepitant (125, 80, 80), fosaprepitant (injectable pro-drug)
Highly selective and centrally acting.
Used in combination for acute with dex and 5HT.

Substance p is considered to be the neurotransmitter involved in delayed CINV, therefore also used for delayed.

S/E diarrhoea, fatigue and nausea.
Aprepitant is metabolised by and a moderate inhibitor of cyp 3A4. Also other effects on other CYP enzymes. It can cause an increase in plasma dexamethasone levels (reduction of dex required).

Task 4 – Antiemetics (Medicine and Surgery)
On the ward, Mr JL, a 75 year old gentleman, returned from surgery yesterday lunchtime. He has had a THA (total hip arthroplasty). The NIC (nurse in charge) catches you as you get to the ward to get some cyclizine ordered for this patient as he is feeling nauseous and was sick about 30 minutes ago.

You review his chart (DHX and MR completed by pharmacy technician):

Prescribed medication		Potential indication
Digoxin 500mcg BD (3 doses given)	New	AF – is this the best choice?
Apixaban 2.5mg BD	New	AF
Paracetamol 1g QDS	DHx	Pain
Ibuprofen 400mg TDS	New	Pain
Trelegy Ellipta I puff OD	DHx	COPD
Salbutamol 100mcg QDS PRN	DHx	COPD
Cyclizine 50mg TDS PRN	New	N&V
Morphine PCA 3mg (5-minute lock out)	New	Pain

1) What could be the potential cause(s) of the N&V?

Surgery,
NBM,
anaesthesia,
dehydration,
blood loss,
electrolyte imbalance
Opiate analgesia/post operative pain relief
Renal impairment
Digoxin toxicity
Digoxin
Apixaban
NSAID

2) What additional checks would you like to make and why?

Renal function
Fluid balance/hydration status
COPD control – requirement for digoxin over beta blocker/calcium channel blocker
Digoxin level – 0.5-2ng/L, level 6-8 hours post dose
Electrolytes – Potassium
Pain score – can treatment be stepped down?

3) What advice would you give to the house officer?

Determine the underlying cause of the problem and treat that.

Level and hold the digoxin. Restart at a lower dose once in range and patient feeling better/or consider selective beta blocker or rate limiting calcium channel blocker rather than digoxin (need to consider COPD control).

Manage all underlying issues as highlighted from above investigations.

Task 5 - Antiemetics in the community pharmacy
For each of the 4 following situations, please provide details of the most appropriate medication to treat travel sickness based on the specific scenario:

1) A family going on a 3-hour journey. Their 2 and a half year old suffers with sickness on journeys longer than 20 minutes.

Not joy-rides as 3 years and up
Not Kids Kwells – 4yrs +
Not Sturgeron (cinnarizine) – 5yrs +
Not Scopoderm patch – 10yrs +
Not Promethazine teoclate tablets (Avomine) – 5yrs+

Promethazine HCl ok in liquid form, 5mg night before travel and morning if needed - ALERT – be cautious when selling Promethazine Hydrochloride OTC (Phenergen) as risk of abuse. Parents using it to sedate children inappropriately! Many pharmacists will refuse to sell it in general because of this.

- Main piece of advice to tell parents is that it will make the child feel very drowsy. There are of course other side effects – please read info leaflet carefully.
- Also, that it is long acting and therefore they should stick to the dosage instructions even if they feel it isn't working.
- It will make your skin more photosensitive so use protective sun creams and be careful when going outside.
- There is a list of conditions that are listed as contraindicated or cautioned – most especially asthma and epilepsy. Important to be aware of.

Advice in terms of administration of travel sickness medication for children

- Think about the formulation – majority of formulations licensed for children will be chewable tablets, sublingual, or liquid form. Some involve tablet form but they need to be cut in half – consider talking to the parents about tablet cutters to help give an appropriate dose.

More general advice for travel sickness with children

- Non-pharmaceutical measures should be used first, before pharmaceutical measures if possible.
- Remove/reduce things that make them feel sick – reading books, playing on phones/playstations etc during the journey. Think about using ginger biscuits, having the car well ventilated, making regular stops.
- Also travel sickness bands for children is another alternative.

2) Patient HP, a 25 year old comes in for advice before going on a cruise for a week around the Mediterranean. They do not want to take tablets more than once a day.

Hyoscine patch (Scopoderm®)

- Apply patch 5-6hours before going on your journey
- Must be applied to clean, dry, hairless skin behind the ear
- Wash hands thoroughly after applying the patch
- Do not touch the patch once it has been applied to the skin – if you do wash hand immediately. (if any was to get into the eyes it may affect your vision temporarily)
- When you remove the patch, wash your hands AND the skin it was applied to thoroughly.
- As each patch lasts 3 days, if you need to change the patch after 3 days use the area behind the other ear for the 2nd patch.
- Use only one patch at a time
- Drowsiness may persist up to 24hours after removing the patch

Promethazine Teoclate (Avomine) – for the prevention of travel sickness take one tablet at night, starting the evening before you travel. (Different instructions if you are treating travel sickness –

- Dosage for treating travel sickness – 25mg taken at onset of motion sickness, then 25mg for 2 further doses.
- Dose should be taken in the EVENING, starting on the evening of onset. (because of the drowsiness)

Promethazine Hydrochloride (Phenergan) prevention of motion sickness

- 20-25mg dose to be taken at bedtime on night before travel, and repeat following morning if necessary

NOTE – the 2 different types of promethazine have slightly different licencing's and indications. Important to be clear and distinguish between them both

3) Patient LN, a 19 year old comes into your pharmacy stating that they have forgot to pack their travel tablets, they are going on a coach trip soon and want something to work quickly.

Joyrides or Kwells as hyoscine products which work within 30 minutes

- For joyrides – chew tablet before swallowing 20mins before travelling. FYI
- Kwells 'kids' and adults– can be sucked, chewed or swallowed 30mins before travelling

4) Patient BP comes in wanting advice on which travel sickness tablets to buy for a journey they are planning. They are travelling to Calais and catching the ferry between Dover and Calais, however the patient is prone to getting sea sick. What is the most appropriate to recommend and what advice must you give the patient?

Most appropriate would be Kwells/Joy-rides as the patient could drive to the Port, then take the tablet 30mins before getting on the Ferry, allowing the tablets to be effective. The hyoscine butylbromide acts quicker than other travel sickness tablets and is shorter acting (~6hours)

Things to consider – though Hyoscine butylbromide is less sedating than cinnarizine or promethazine, it can still make you sleepy. Therefore, you must counsel the patient about not driving after taking the tablet as it could affect their driving skills. This may not be wanted by the patient as they have to continue their journey on from Calais etc. If this is the case non-pharmacological methods should be used.

What would you advise if they needed to drive and were also car sick?

(1) they stop driving until they feel better as none of the medication recommend driving whilst on it. Or (2) they could use travel sickness bands. Or (3) they get someone else to drive and take some travel sickness medication and don't drive until this has worn off.

General advice and non-pharmacological things to use to prevent travel sickness:
General advice:

- Focus on objects in the distance like the horizon
- Do not look at moving objects – e.g. passing cars
- Make sure the vehicle is well ventilated – windows open
- Don't read or play games or electronic devices during the journey
- Don't eat large heavy meals just before a journey
- Try and sleep on the journey
- Take regular breaks during the journey

Other advice

- Travel sickness bands – meant to work like acupuncture (Nei-Kuan P6 acupressure point). Different types available and children versions too (e.g. Sea-bands)
- Ginger biscuits
- Peppermint tea

Other things to consider when selling travel sickness tablets:

- What other medication are they on or conditions? This may seem obvious, but it is important to know what conditions as well as medication may interact with these products. Many of the travel sickness products are contraindicated in patients with glaucoma and prostatic enlargement. In addition, often products state that patients with CNS disorders (e.g. seizures) should consult a doctor before taking.
- How long is the journey? Important to know how long the different tablets work for to be able to recommend the most appropriate one and how long they take to work:

Drug	How long does it take to work	Duration of effect
Hyoscine butylbromide tablets	~20-30mins	6hours
Cinnarizine 15mg tablets	2 hours	8 hours
Promethazine Hydrochloride	Taken the night before travelling	6-8hours

- How alert do they want to be during the journey? If they are going site seeing and they are going to be on a coach all day – yes they need a long acting travel sickness pill but they don't want to be drowsy over the whole day and miss everything. Therefore, this is why it is important to take on board the patient's preferences and to inform the patient of how sedating some travel sickness tablets are.
- Will they be driving within 12-24hours of taking the travel sickness tablet? Some travel sickness tablets take longer to wear off and patient should not drive for certain periods of time after taking travel sickness tablets.

5) Patient JK, a 24 year old comes into your pharmacy complaining of nausea associated with a migraine and wants something to help them feel better. What would you recommend?

Migraleve Pink tablets – contain paracetamol, codeine and buclizine (anti-emetic). Must ascertain that they have been diagnosed with migraines by GP.

Alternatively – Buccastem M tablets – prochlorperazine buccal tablet licensed OTC for nausea and vomiting in previously diagnosed with migraines (18yrs +)

- Administration – between upper lip and gum. Good blood supply in the mouth and therefore acts quickly. (Also bypasses liver therefore no 1st pass metabolism)
- Only 8 in a pack (shows it should be used for very short term use).

- **migraitan or Imigran (sumatriptan)** as a migraine alternative however this is for use at onset of symptoms mostly. A special questionnaire must be used to determine if it is safe for the patient to use. As you know its main action is to stop the migraine rather than stop N&V.
- link to the questionnaire is here -
https://www.bristol-labsconsumercare.co.uk/wp-content/uploads/Migraitan-Questionnaire-13-08-18.pdf
- Guidance - https://www.bristol-labsconsumercare.co.uk/wp-content/uploads/Migraitan-Questionnaire-Guidance-13-08-18.pdf
- Generally if the symptoms are very severe/new onset/not responding to treatment we would be referring the patient to the GP as there is very little more we can offer OTC. Using travel sickness medication will not help (due to how they work) as well as being out of license.

(motilium OTC or domperidone – that was removed from P meds a while ago now and it is POM.)

6) Patient WD comes into your pharmacy complaining of N&V. Upon questioning you determine that it appears they may have consumed a 'dodgy' kebab. The patient does not have any relevant medical or drug history and no allergies. The patient asks whether they can have some travel sickness medicine to help.
   a) What is your response? Explain the underlying reason for this response.
   b) What advise should you give?

a) These preparations are unlicensed for this indication so could not be sold for this.
b) Eat when you feel ready. Dry bland food. Maintain fluid intake. Could have oral rehydration. Rest.

1) Complete the table below calculating the number of units of alcohol from each entry in the alcohol diary:

	alcohol consumed	**Number of units**
Monday	2 large glasses wine & one small beer	**8.6**
Tuesday	None	
Wednesday	2 small beers & one G&T	**3.3**
Thursday	3 double G&Ts	**6**
Friday	3 small beers & 2 large G&Ts	**7.4**
Saturday	Bottle of wine	**9 or 10**
Sunday	2 small beers & 1 large G&T	**4.3**

2) How many units are being consumed per week? (The figure will be a guide as the strength and (ABV) and size of measures is unknown) approx. 40
3) What is the AUDIT C score? 10

CASE STUDY 1
WN is a new admission to the acute psychiatric ward

WN is a 22-year-old male trainee accountant and was admitted to hospital with a possible psychotic episode

a. Friends found him naked in his bedroom cutting himself and called an ambulance. He was taken to Casualty
b. In Casualty WN was given 1mg lorazepam and 5mg haloperidol I/M (to calm him down and reduce agitation), after he was aggressive towards nursing staff. WN was transferred to a mental health ward
c. WN didn't know where he was and could not recollect previous events. He was rambling and talking about insects that he needed to cut out of his arms. His mood was elevated and lively.

Family History

d. Good schooling, achieved well, math's degree. Family are caring and his mother takes antidepressants

Social History

e. Lots of friends, smokes, alcohol consumption: 'a few beers per week'

Drug History

f. WN stated that he is on a reducing methadone script and doesn't want his parents to know that he had "got into a bit of trouble with heroin". He is currently taking methadone 20mg a day maintenance
g. He confesses to taking cocaine as well
h. He has been smoking cannabis since his mid-teens
i. **Fluoxetine 20mg** - he has been taking this since he was 16yrs

Previous Medical History

j. Depression since he was 16 years' old

What would you do to confirm WN has been taking opioids, cocaine and cannabis?

- Urine drug screen which will confirm all illicit drugs
- Contact the pharmacy who dispenses the prescription to confirm dependence and check what dose is on the script
- Once dependence is confirmed, you can suggest the ward staff use withdrawal scales (COWS) to monitor symptoms of withdrawal as he has not taken methadone for 4 days

You contact the community pharmacist who informs you that WN did not collect his methadone script for 4 days. The junior doctor suggests prescribing 20mg/d methadone. Do you agree with this dose and what is the rationale for your answer?

- You inform the medical staff about possible loss of tolerance after 3 days
- Community pharmacies should not dispense methadone after 3 missed doses
- Ask WN if he has used heroin instead of methadone or if he has purchased any street methadone, this could affect the dose prescribed. However, WN may not be communicative.
- Inform drug agency he has not collected his prescription for 4 days
- WN has been confirmed as positive for opioids but his tolerance may be reduced
- You would recommend prescribing a **reduced dose** and titrate against withdrawals using the COWS withdrawal scales
- Remember that once tolerance is reduced with opioids then there is a risk of overdose

You discover that WN is on a reducing script for methadone. The lead nurse asks you to have a chat to WN about his methadone dose. What do you discuss?

- WN has already missed 4 days methadone and this may be an opportunity for him to take a reduced dose to help with the methadone reduction
- If you are able to, discuss with WN and aim for a reduction
- However, be aware as he is currently experiencing a psychotic episode, withdrawal symptoms may be difficult to ascertain and WN may be difficult to engage.

WN has been smoking cannabis since his teens. What is his risk of psychosis?

- There is evidence that cannabis use increases the risk of psychosis
- Teenagers are particularly vulnerable because the brain is still developing up until about the age of 21years
- Schizophrenia and Cannabis:
- Schizophrenia has many possible causes e.g. genetics, environmental, trigger
- Cannabis leads to dopamine being released
- Many symptoms of schizophrenia are caused by excess dopamine
- Cannabis (THC) can induce psychosis, especially highly concentrated versions e.g. skunk
- Cannabis alone does not cause schizophrenia
- **But** it can be a trigger factor (combining with other factors) to precipitate psychosis
- Risk may be higher if started early or high doses are taken
- There is no evidence of a rise in schizophrenia with increased use of cannabis (1996- 2005-date)

Summary and advice:

- Use by vulnerable young people should be discouraged
- Around a third of FEP (First Episode Psychosis) had their first symptoms after cannabis
- In someone with schizophrenia, stopping cannabis may cause clear improvement
- Cannabis should be avoided if it makes psychotic symptoms worse
- If compliance is good, positive schizophrenia symptoms are unchanged, occasional use is probably OK (pragmatic remark!)
- But more research is needed e.g. Are there brain changes? Memory impairment? Cognitive impairment? Are these pre-existing, permanent or reversible? How relevant is age of first use?

WN responds very well and is discharged from the ward after 5 days.
He is also discharged on methadone 10mg daily and his regular fluoxetine 20mg daily.
Before discharge, the nurse asks you to have a chat with WN to discuss his medication and illicit use.

2) What will you discuss?

Mental state of WN- you will learn this in the depression session(s)

- WN is currently taking fluoxetine 20mg daily - ask him about his mental health and whether he feels this is an adequate dose, could increase to 40mg depending on mood. Think about switching if not effective at 40mg/d. 20mg is optimum in most people

- **Remember to optimise the dose before switching to another antidepressant**

- Self-medication with alcohol and illicit substances is often a sign that mental health is not being well controlled, or sleep is poor
- May need antipsychotic in long term to avoid relapse and psychosis should be monitored

- Overshadowing effect of physical health - this means that physical health in a patient is often over shadowed and neglected by the mental health

Illicit substances

- **Cocaine** is associated with cardiac rhythm disturbances and best avoided when taking methadone. It is a stimulant and if taken in excess it can deplete dopamine stores in the brain thus causing psychosis. This can be difficult to distinguish from schizophrenia (covered in the schizophrenia sessions)
- **Poly-substance** misuse increases the risk of accidental overdose and self-harm
- **Cannabis -** effects on mental health- see lecture material
- Carry out an **AUDIT-C** questionnaire on WN and give him advice on alcohol consumption. Alcohol is a depressant which has long term health risks (you should detail the risks here)
- You could signpost him to an agency specialising in alcohol misuse
- Point out that he would be putting his professional career in jeopardy by using substances
- Signpost to **psychological** therapies - this may help with regard to stimulants and cannabis misuse

Harm minimisation

- Education and advice, storage of methadone
- Pharmacists are key individuals in the success of methadone treatment
- How does he use illicit drugs? Smoking or injecting? (smoking less harm than injecting)
- **Driving -** DVLA should be notified if a patient is suffering from an acute illness - patient responsibility
- **Adherence** to prescribed medication
- **Smoking cessation advice - risk to health**

CASE STUDY 2

MN comes into your pharmacy and asks you for some herbal Nytol® to help her sleep

- MN is a regular customer and in conversation with MN you ask her how she is as her husband died 3 months ago
- She stated that she has poor sleep is and can't function during the day, she asks for some herbal Nytol®
- She is currently off sick from work
- She appears anxious
- You notice from her prescription that she is currently taking zopiclone and diazepam. She states that she is worried about getting addicted to them so doesn't take them very much
- She confesses that alcohol is helping her but then she wakes up feeling low

Family History

- Mother alive and well, her father died from liver disease. Husband died from cancer 3 months ago, she has two children at University

Social History

- MN has some friends but can't face them. She doesn't smoke but consumes alcohol

Drug History

- Diazepam 2mg four times each day when required for agitation
- Zopiclone 3.75mg bedtime when required to help sleep

You have some time and ask MN if she would like a consultation? She is very grateful as she doesn't like to bother her GP again.

- Nytol is diphenhydramine 50mg, an antihistamine, 20 minutes before bedtime
- Nytol Herbal is Hops, Valerian, Passion Flower ('3 natural active ingredients')

1) During the consultation you calculate that MN has an audit C score above 10 – what would this indicate?

- 10 (This is important for you to know what a score of 10 means after undertaking an AUDIT-C)- indicates higher risk from alcohol consumption

1) What would you say to MN in a brief intervention about her alcohol misuse
   - Discuss **Audit C** and what it means
   - Often just discussing her use and number of units recommended will decrease consumption. She may be unaware she is consuming so much
   - She has had a recent bereavement and may be self-medicating with alcohol to help her with the trauma. Query whether she might need an antidepressant
   - Genetic and/or environmental component? Father alcoholic

The potential benefits of cutting down alcohol:
Physical:
Sleep better, More energy, Lose weight, Reduce risk of injury, Improve memory, Better physical shape,
Reduce risk of high BP, Reduce risk of cancer, Reduce risk of liver disease, Reduce risk of brain damage
Psychological/Social/Financial:
Improved mood, Improved relationships, Reduce risk of drink driving, Save money
Support her in making a plan for a reduction:
Sign post to AA, Use an alcohol diary to record consumption and reduction
Use alcohol with lower ABV (ie lower percentage)
Allow 2 alcohol free days together as recommended by guidelines

'Frames' can be used a guide for brief interventions

a. Feedback: on an individual's alcohol use and the risk of harm from their current rate of consumption or drinking pattern
b. Responsibility: emphasise that drinking is by choice
c. Advice: increase the individual's self-belief and CONFIDENCE in their ability to change their drinking behaviour
d. Menu: offer alternative goals and coping STRATEGIES i.e. 2 drink free days together, once adequately treated with an antidepressant then the need for alcohol as a coping mechanism will be reduced
e. Empathy: role of the pharmacist showing non-judgemental approach
Self-efficacy: installing optimism that chosen goals can be achieved

1) Would you sell MN some Nytol®? - please justify your answers

- There would be no need for Nytol if diazepam and zopiclone were taken in the short term
- Taking Nytol combined with prescribed meds and alcohol will increase sedation
- Advise against Nytol, although is a short-term option

2) What would you say to MN about her diazepam and zopiclone usage?
https://bnf.nice.org.uk/treatment-summary/hypnotics-and-anxiolytics.html

- Re-assure her that they are both safe in the short term 2-4 weeks and the risk of tolerance and addiction will then be reduced
- Caution her against taking benzos and z drugs with alcohol as this can cause respiratory depression/overdose and so it is not safe to do so
- MN may need an antidepressant to help with anxiety, diazepam and alcohol are not the long-term answer
- Give advice on sleep hygiene and by reducing alcohol consumption will improve her sleep. Insomnia is very common after a bereavement and so zopiclone taken regularly in the short term would help her

3) Two weeks later, MN returns to see you and is feeling much better but she has a prescription for thiamine 100mg a day. She is unsure what it is for and is asking for information about it. What do you say to her?

People at high risk of drinking alcohol often have low levels of thiamine, because of:

- Poor eating habits, vomit, alcohol can damage stomach lining- hence poor absorption of thiamine which can lead to Wernicke's (uncontrollable eye movements, poor co-ordination (ataxia), confusion and memory loss
  - Ocular disturbances (ophthalmoplegia)
  - Changes in mental state (dementia)
  - Unsteady stance and gait (ataxia)
  - Can lead to Korsakoff's psychosis – irreversible
- Emphasize the importance of a good diet and explain why thiamine is necessary

- Also 100mg/d better as 50mg BD or 25mg TDS/QDS
- This is also a good opportunity to discuss her alcohol consumption again and perhaps perform another Audit C

Depression workshop

ANSWERS

Person Centered Medicine from Bench to Bedside (PHA-6020Y)

Clinical Workshop

The purpose of the lecture material and workshop is for you to:

- To improve your understanding and knowledge of depression and its management
- Review case studies. From the case studies the questions will direct you to:
    a. Identify care issues
    b. Formulate care interventions

Pre-task activity 1

80-year-old man with a history of cardiac disease is suffering from depression and poor sleep.	
Possible treatment	**More than one answer may apply**
SSRI	Y
TCA	N (anticholinergic side effects) • orthostatic hypotension • urinary retention • Longer half-lives and decreased oral clearance values in elderly observed. Slower metabolism in elderly • TCAs affect cardiac contractility. Some TCAs linked to ischaemic heart disease and sudden cardiac death. Avoid in coronary artery disease. • Contraindicated in patients with recent MI
Psychological therapy	Y
Zopiclone	Y
Sleep hygiene	Y
Diazepam	N (accumulation in the elderly)- low accumulation and delayed washout of diazepam in elderly, slower metabolism in elderly Risk of Falls
Pregabalin	N-for GAD (*Generalized Anxiety Disorder*)

Pre-task activity 2

EN has been struggling to get off to sleep whilst waking extremely early. He has also lost his appetite and 6kg in weight. He is unable to concentrate for long periods of time.	
Possible treatment	**More than one answer may apply**
SSRI	Y (seems likely EN is suffering from depression) **Moderate depression**
Psychological therapy	Y
Zopiclone	Y
Sleep hygiene	Y
Promethazine	N

1st agent ▼ 2nd agent ▶	SSRI	TCA *	Venlafaxine	Duloxetine	Mirtazapine	Reboxetine**	Agomelatine
SSRI with the exception of fluoxetine	Discontinue first SSRI gradually and stop - start second SSRI at low dose the following day [2] ***or*** Immediate switch [8,9,15]	Discontinue SSRI gradually and stop - start TCA the following day. If the SSRI being stopped is paroxetine or fluvoxamine, ideally leave a gap of a few days [3] ***or*** Cross-taper cautiously with very low dose of TCA* [2]	Cross-taper cautiously, starting with venlafaxine 37.5mg daily and increase very slowly [2] ***or*** Immediate switch (caution if fluoxetine or paroxetine used) [8,9]	Immediate switch starting with duloxetine 60mg daily has been well tolerated [2,3,10]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]
Fluoxetine 20mg daily §	Stop fluoxetine abruptly – start second SSRI at half the normal starting dose 4 to 7 days later [2]	Stop fluoxetine abruptly – start TCA at low dose 4 to 7 days later and increase dose very slowly [2,3,9]	Stop fluoxetine abruptly – start venlafaxine 37.5mg daily and increase dose very slowly [2]	Immediate switch starting with duloxetine 60mg daily has been well tolerated [2]	Cross-taper cautiously starting with mirtazapine 15mg daily [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]
TCA*	Gradually reduce the dose of TCA to 25-50mg daily - start SSRI then slowly withdraw TCA* over next 5 to 7 days [3]	Cross-taper cautiously [2]	Cross-taper* cautiously, starting with venlafaxine 37.5mg daily [2]	Cross-taper cautiously starting with duloxetine* 30mg daily and increase dose very slowly [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]
Venlafaxine	Cross-taper cautiously starting with half the normal starting dose of SSRI e.g. paroxetine 10mg daily [2] ***or*** Immediate switch (caution if fluoxetine or paroxetine	Cross-taper* using a very low starting dose of TCA e.g. amitriptyline 25mg daily [2]		Discontinue venlafaxine gradually and stop – start duloxetine 30mg daily the following day and increase dose slowly [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]	Cross-taper cautiously [2]

Case study 1

Sandra is a 32-year-old lady with two young children. She is married and works part-time in a supermarket. Her husband has recently been made redundant which has caused some worries for the family. She has recently been very tense and short tempered and is finding it difficult to concentrate at work. Sandra feels most of her problems are because she hasn't been sleeping well and as a result is always tired with no energy.

Her husband convinces her to visit her GP which she reluctantly agrees to as she feels she would be wasting their time. At the surgery she admits to having felt down a lot recently and perhaps her symptoms have been going on for longer than she realised. On further questioning the GP discovers Sandra feels her husband is better at looking after their children than she is and most nights she lies awake dreading the day ahead. She has even had thoughts of preferring to be dead than continuing to feel this way.

Sandra doesn't take any medication and apart from these symptoms is fit and well and usually a happy character.

The GP diagnoses Sandra with a moderate depression and prescribes Citalopram 20mg OM.

1. From the information provided about Sandra, identify the likely causes, signs and symptoms of her depression.

Causes	Signs	Symptoms
Psychological aspects	**Objective – what you see**	**Subjective – how the patient feels**
1. life events (+ve and -ve) Husband made redundant	Agitation	Poor concentration
2. psychological stressors • disruption in normal activities: • Difficulty in concentration at work • Poor sleep, no energy	Poor concertation/poor sleep	Fatigue
	Anxiety	Agitation
Genetic factors	Self-neglect	Sleep disturbance
- predisposition		Poor memory
Biological factors		Self-neglect (children)
1. hormonal influences		Negative thinking, anhedonia **(lack of interest/enjoyment from life experiences),** suicidal thoughts
3. monoamine hypothesis (The monoamine hypothesis of depression predicts that the underlying pathophysiologic basis of depression is a depletion/imbalance in the levels of neurotransmitters such as serotonin, norepinephrine, and/or dopamine in the central nervous system.)		Anxiety

4. What information would you as a pharmacist provide to Sandra before initiating citalopram?

   How might it make her feel?

- Take your dose once a day in the morning. If you take it at night, it can affect your sleep and you will not sleep as well.
- If you feel sick when you first start taking citalopram, this should only last for a few days. It can help by taking your dose with or after food.
- The effect of citalopram will probably start in a few days and may start to be noticeable in a week or so but then continues to build up over the next few weeks (2-6 weeks to assess response)
- Missed doses.
- Citalopram is not addictive.
- If you carry on taking it for eight weeks or more and suddenly stop you may experience discontinuation effects (feeling dizzy or lightheaded, vertigo, feeling sick, headache, 'electric shocks' in the head, not sleeping, stomach cramps, flu-like symptoms, and increased or more vivid dreaming).
- Exploring how she feels taking antidepressants and addressing any concerns. (Stigma around mental health medications: feeling judged, being embarrassed, medication adherence)

5. What non-pharmacological interventions/advice could you give for Sandra's depression?

1. **Guided Self Help:** Printed or digital materials that follow the principles of guided self-help including structured cognitive behavioral therapy (CBT), structured behavioral activation (BA), problem-solving or psychoeducation materials. These can be delivered in person, by telephone, or online.
   Patient can also be guided about mental health charities (for e.g. Mind) that can provide them with further support if needed.
   Emergency and crisis helpline information should be given to patients.
2. **Group or individual cognitive behavioral therapy (CBT):** Focuses on how **thoughts, beliefs, attitudes, feelings, and behaviour interact**, and teaches coping skills to deal with things in life differently.
   a. May be helpful for people who can recognise negative thoughts or unhelpful patterns of behaviour they wish to change.
3. **Group or individual behavioral activation (BA):** Focuses on identifying the link between an **individual's activities and their mood.** Helps the person to recognise patterns and plan practical changes that reduce avoidance and focus on behaviours that are linked to improved mood.
   May be helpful for people whose depression has led to social withdrawal, doing fewer things, inactivity, or has followed a change of circumstances or routine.
4. **Group exercise:** Does not directly target thoughts and feelings. Moderate intensity aerobic exercise.
   May allow peer support from others who may be having similar experiences.
5. **Interpersonal psychotherapy (IPT):** Focus is on identifying how **interpersonal relationships or circumstances are related to feelings of depression**, exploring emotions, and changing interpersonal responses.
   May be helpful for people with depression associated with interpersonal difficulties, especially adjusting to transitions in relationships, loss, or changing interpersonal roles.
6. **Counselling:** Focus is on **emotional processing and finding emotional meaning**, to help people find their own solutions and develop coping mechanisms.
   Provides empathic listening, facilitated emotional exploration and encouragement.
   May be useful for people with psychosocial, relationship or employment problems contributing to their depression.

Non- Pharmacotherapy

Subthreshold, Mild, Moderate and severe depression (as per NICE)

- **Social support (very important)**

Low intensity Psychosocial and Psychological Interventions (initial steps, milder depression)

- Guided self-help (books and leaflets)
- Being active
- Computer based CBT

High Intensity Psychological Interventions

- Psychological therapies, CBT, Interpersonal Therapies (IPT) relaxation therapy, anxiety management, mindfulness-related therapies and counselling
- General support and advice e.g. on financial matters, to reduce stress

Severe and complex depression (as per NICE)

- High Intensity Psychological Interventions
- ECT (electroconvulsive therapy) for acute severe depression
- TMS (transcranial magnetic stimulation) may possibly be useful.

6. Sandra has requested if can be switched from citalopram tablets to citalopram oral drops. How would you switch this?

Citalopram liquid comes as drops. Before giving or taking the liquid, the drops should be mixed with water, orange juice or apple juice.

Citalopram Oral Drops have approximately 25% increased bioavailability compared to tablets

Citalopram dose as tablets	The same citalopram dose as drops	How many drops for that dose
10 mg	8 mg	4 drops
20 mg	16 mg	8 drops
30 mg	24 mg	12 drops
40 mg	32 mg	16 drops

A week later Sandra approaches the Pharmacy counter and asks to buy some ibuprofen for her backache.

7. Would you sell her the ibuprofen, and if not, why?

No- SSRI use roughly double the risk of upper GI bleeds, and this is increased to 3-fold by concurrent NSAIDs,
Advise Paracetamol 1gram QDS instead.

Explore patient's history. History of GI bleeds? Would be worth exploring what they have tried in the past and how long they plan to use it for. Also, whether they are already on a gastroprotection)

- Can also consider gel as topical application rather than oral if ibuprofen is really needed.

After 4 weeks Sandra returns to the GP for a review. She feels there has been some improvement but not enough for her to say she feels significantly better.

8. Consider the options available now. Decide on the best course of action and provide a rationale for your decision.

- Check adherence and ask about side effects.
- Continue treatment for another 2 weeks.
- Check any further changes in personal life that could have caused further deterioration in mood.
- Increase the dose to 40mg OM if there are no significant side effects.
- Switch to another antidepressant

The GP decided to increase the citalopram dose to 40mg and review in two months, but two months later the doctors want to change Sandra to an alternative antidepressant after she failed to respond sufficiently to the higher dose of citalopram.

9. What antidepressant would you recommend switching to and provide advice on how to switch to the new antidepressant from citalopram. Also briefly discuss the potential risks that could occur while switching.

		week 1	week 2	week 3	week 4
Withdrawing citalopram	40mg	20mg	10mg	5mg	Nil
Introducing mirtazapine	Nil	15mg	30mg	30mg	45mg (if required)

		week 1	week 2	week 3	week 4
Withdrawing citalopram	40mg	20mg	10mg	5mg	Nil
Introducing sertraline	Nil	25mg	50mg	100mg	150-200mg

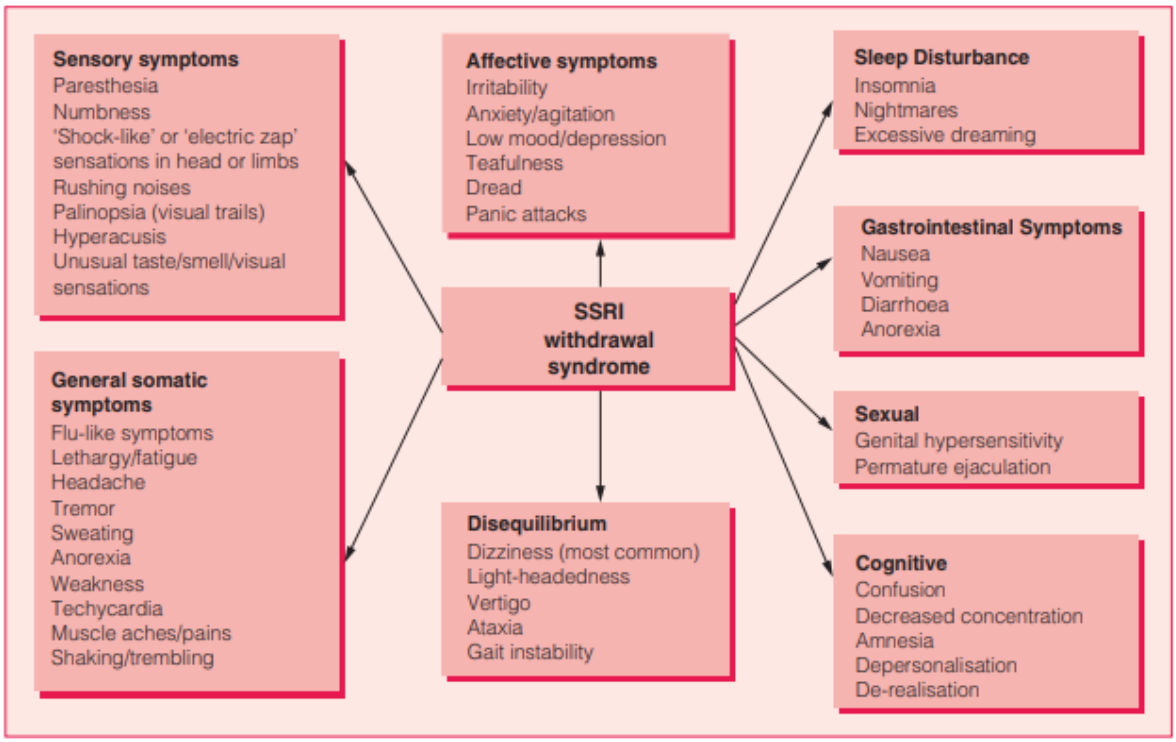
Potential dangers of simultaneously administering two antidepressants include pharmacodynamic interactions (serotonin syndrome, hypotension, drowsiness; depending on the drugs involved) and pharmacokinetic interactions (e.g., elevation of tricyclic plasma levels by some SSRIs).

Serotonin syndrome – symptoms[11]

Increasing severity

Severity	Symptoms
Mild	Insomnia, anxiety, nausea, diarrhoea, hypertension, tachycardia, hyper-reflexia
Moderate	Agitation, myoclonus, tremor, mydriasis, flushing, diaphoresis, low fever (<38.5°C)
Severe	Severe hyperthermia, confusion, rigidity, respiratory failure, coma, death

Withdrawal effects:



Sandra subsequently fails to respond to sertraline and mirtazapine. A fourth antidepressant, venlafaxine, is started and Sandra makes significant improvement. However, her effective dose is 300mg and this is causing her blood pressure to increase.

10. The doctor asks for your advice. What options could you suggest?

Venlafaxine effect on blood pressure: Some increase in postural blood pressure. At higher doses increase in blood pressure

How high is the blood pressure? Employ strategies to reduce BP via
diet change, pharmacotherapy.
How long patient has been on the medication? Is she stable? Risk of relapse if venlafaxine reduced or stopped? Consider reducing the dose if possible?
If all in-effective, then you need to stop the treatment by gradually weaning the patent off venlafaxine.
Discuss if psychological therapies have been explored such as CBT (gold standard with antidepressants)

Case Study 2

You are a pharmacist working in a community pharmacy on a Saturday and a patient walk in and wants to speak to you. She mentions she has been taking paroxetine for a few months. She was due to collect her medications today, but her usual pharmacy was closed. She has had a dose this morning, but she is not sure if she has any left for tomorrow or Monday before she can collect from her usual pharmacy. She is asking if she will be okay to miss one or two doses of her medication.

What would your advice be in this case and what will be your rationale?

- The onset and severity of symptoms are related to the half-life of the antidepressant. Short half-life antidepressants like paroxetine (17-22 hours) and venlafaxine produce symptoms within a day or two, whereas symptoms with fluoxetine can be delayed by 2–6 weeks.
- Antidepressants with short half-lives and cholinergic or noradrenergic effects tend to be associated with more severe withdrawal – venlafaxine, duloxetine and paroxetine are the most often implicated.
- Consider checking patient's records: E-tracker if any prescription available, SCR records etc. Consider making an emergency supply if appropriate.
- Advice patient on the importance on not missing the dose with this medication.
- Even with other mental health medications with longer half-lives- consider psychological impact on patient if missing medication.

Task 1: Features of Bipolar Disorder

1) Complete the table below listing the common features of Hypomania/mania and bipolar depression:

Hypomania/Mania	**Bipolar depression**
Abnormal elevated mood	Decreased energy
Easily distracted	Fatigue
Flight of ideas	Poor sleep
Obsessive pre-occupation with some idea, activity or desire	Lethargy
Overactive and intrusive	Doing less
Risk taking	Anhedonia
	Feelings of wanting to self-harm

Task 2: Medication options

2) Use the list of medication below, to complete the table identifying which medication(s) may be suitable to manage the stated symptoms (each medication may be used once, more than once or not at all).

Medication: lamotrigine, lithium, lorazepam, olanzapine, quetiapine, sodium valproate, SSRIs/SNRIs, TCAs, Zopiclone.

Over activity, intrusive bizarre behaviour	Lorazepam (Short term- calm down)
Lack of sleep/up all night	Zopiclone, lorazepam at night or mood stabilising antipsychotic
Aggression	lorazepam
Mood stabilisation and relapse prevention	Lithium, quetiapine
Low mood	SSRI, SNRI, antipsychotic
Acute mania/hypomania	Quetiapine, olanzapine, lorazepam
Bipolar depression and relapse prevention	Lamotrigine, SSRI, SNRI, quetiapine, olanzapine

Case study 1

SW is 35 years old, known to mental health services and has had repeated admissions to hospital.
She has been lodging with a friend who is in despair at her chaotic behaviour and states that she is spending money on irrelevant goods, she is full of self-importance and is very intrusive into everything that is going on in the house.
She has been admitted to hospital with elevated mood, pressure of speech and increasingly chaotic behaviour.
She is dressed in brightly coloured clothes and wears heavy make-up. She describes a 'cycling' of mood from periods of low to high and she is 'flirtatious' with male members of staff.
SW has a poor diet and she is underweight.
She started lithium therapy 2 months ago and is wearing a support bandage on her leg. She stated that she bounced off a trampoline at the weekend and hurt her leg.
She also says she is using alcohol to get her to sleep as the zopiclone doesn't work anymore. However, she has been trying to reduce her alcohol consumption lately on her GP's advice.

Past Medical History			
Bipolar Affective disorder Insomnia Swollen Ankle			
Drug Allergies		Reaction	
Unknown		Unknown	
Family History			
Mother suffers from bipolar affective disorder			
Social History			
Smoker Alcohol consumption with an audit C score of 12 Drug Screen negative			
Weight	49 Kg	Height	1.4 m
Current medication			
Combined oral contraceptive pill Lithium tablets 200mg at breakfast Thiamine tablets 50 mg daily Zopiclone 7.5 mg bedtime Ibuprofen tables 400 mg three times a day			
Recent blood tests			
Lithium level 0.2 mmol/Litre			

1) Why do you believe the patient has been referred to the acute mental health ward and what are her signs and symptoms of illness? (Include your potential differential diagnosis?

Reason for referral (Signs and symptoms of illness):
Previous bipolar diagnosis
Signs of hypomanic episode:

- Elevated mood
- Over familiar/disinhibition/risk taking
- pressure of speech/increased talkativeness
- Speeding spree
- Grandiose
- Poor sleep
- Intrusive
- Poor diet
- Under weight
- Bright appearance

Differential diagnosis:
Schizophrenia/unipolar depression/alcohol misuse?

1) What are the most likely indication(s) for the current prescribed medication?

Medication	**Indication**
Combined oral contraceptive pill	Contraceptive (Is this enough if she is sexual disinhibited)
Lithium tablets 200mg at breakfast	Acute mania/hypomanic episodes, prophylaxis f bipolar mood disorder
Thiamine tablets 50 mg daily	Prevention of Wernicke's encephalopathy in regular drinkers
Zopiclone 7.5 mg bedtime	Insomnia
Ibuprofen tables 400 mg three times a day	Anti-inflammatory for her leg trampoline injury

2) Please complete the recommended action and ongoing review and monitoring columns for this partially completed care plan (Part 1)

Care intervention	**Recommended Action**	**Ongoing review and monitoring parameters (including frequency)**
Clarification of patients' drug history	● Confirm with GP notes ● Check if patient can confirm medication and allergy status ● Check if any medications have been brought into hospital ● Check contraceptive cover and if had a pregnancy test	Check patients drug chat against history and confirm no unintentional omissions

Lithium (Level, optimisation, dosing)	● Persevere and optimise treatment as the lithium dose if too low. It should be taken at night to minimise renal damage and ensue accurate blood levels
	● Suggest increase lithium to 400mg night then adjust levels according to lithium levels, plasma levels measured after 5-7 days after dose change
	  ● TDM, minimum effective level 0.4-0.8 but can go higher for mania 0.8-1.0
	  ● Blood samples should be taken 10-12 hours post dose
	  ● Dose should be taken at bedtime
		● Plasma levels monitored every 3 months with:
		  ● BMI
		  ● U & Es
		  ● Calcium
		  ● eGFR
		  ● TFTs
		● Poor diet may be restricting fluid which can increase toxicity. Kep hydrated
		● Monitor for signs of toxicity
		  ● Nausea, diarrhoea, blurred vision, polyurea, light headiness, fine resting tremor, muscle weakness and drowsiness
		
		Side effects: thyroid disturbances, weight gain, fine tremor, GIT disturbances, renal disorders – permanent renal damage

Mania control	● Potentially stop lithium (low dose and level, delay onset for mania 5-7 days)	Quetiapine monitoring parameters: Baseline: Oral glucose tolerance test or FPG HbA1c

	● Start mood stabilising antipsychotic such as quetiapine: 300 mg day 1, 600 mg day 2, 800 mg thereafter, while lithium has chance ot work ● Lorazepam may be used as ‘calming agent’ 1mg qds prn (beware tolerance and restrict to 2-4 weeks ● Haloperidol sometimes used (beware EPSE)	Then every 12 months Lipid profile at start and 3 monthly ECG Weight & height – be aware of weight gain

3) Please complete the recommended action and ongoing review and monitoring columns for this partially completed care plan (Part 2)

Care intervention	Recommended Action	Ongoing review and monitoring parameters (including frequency)
Ibuprofen	Interaction with lithium (major interaction and litigation) 2 options: ● Determine is SW taking intermittently, if so ibuprofen time limited ● Could SW make do with Paracetamol 1g QDS (to avoid interaction)	● Monitor pain relief of injured ankle ● If continue with ibuprofen, monitor lithium more regularly until ibuprofen discontinued
Alcohol	● SW self-medicating with alcohol ● Alcohol may be driving her symptoms 9ee dot explain this, not beneficial an once acute illness over may not feel urge. ● Audit C of 12 indicates brief intervention needed ● 14 units per week ● Harm o fuse (depressant and poly substance) ● Signpost to AA, relapse prevention groups ● Alcohol diary ● Alcohol affects mood, if mood managed may not be needed ● Slow reduction (not sudden stop) ● Nalmefene may be beneficial (1-2 hours before drinking)	Monitor regularly (use FRAMES) **F**eedback – use and risk of harm **R**esponsibility – choice **A**dvice – increase self belief/confidence **M**enu – offer strategies, **E**mpathy – non-judgemental **S**elf-efficacy – instal optimise about goal
Thiamine	● Only small amount absorbed so take 2-3 times a day ● Reinforce used to prevent Wenicke's encephalopathy ● Good diet key: ● Poor eating, vomit, alcohol can damage stomach lining – hence poor absorption ● Wernicke's (uncontrollable eye movement, poor coordination, confusion and memory loss) ● Ocular disturbances ● Changes in mental stat ● Unsteady gait ● Can lead to Korsakoff's psychosis (irreversible) 100m TDS thiamine Consider IM/IV pabrinex if heavy drinking	Review thiamine if SW reduces alcohol
Contraceptive	● Effective contraception required while taking Lithium, C/I first trimester ● Discuss alternatives – e.g. Implants ● State risks of pregnancy whilst taking lithium	Ensure adequate contraception continued

4) Please complete the recommended action and ongoing review and monitoring columns for this partially completed care plan (Part 3)

Care intervention	Recommended Action	Ongoing review and monitoring parameters (including frequency)
Weight	Significant weight gain with lithium and quetiapine If problematic, consider aripiprazole 5-10mg increase to 15-30mg (better metabolic profile). Quetiapine more robust for bipolar disorder ● Weight monitoring ● 20% of patient on lithium put on weight, therefore diet and exercise key	Beware of agitation with aripiprazole

Insomnia	● Lack of sleep affecting mood and driving symptoms
	● May have become tolerant to zopiclone (stop and switch to promethazine 25-50mg at night)
	● Alternatively, if quetiapine prescribed then that may be a suitable replacement
	● Sleep hygiene:
	  ● Avoid excessive caffeine, alcohol and nicotine
	  ● Do not stay in bed for prolonged periods if not asleep
	  ● Avoid daytime naps
	  ● A warm bath or gentle exercise may help
	  ● Mak bed and bedroom comfortable
	  ● Regular routine
	  ● Diet high in carbohydrates (nu not a big meal within 2 hours)
	  ● Avoid backlit screens 2 hour prior to bed (inhibit blue light)
		Monitor sleep pattern, hypnotics only used for 2-4 weeks

Non-pharmacological advice	● DVLA notified (acute illness – patients responsibility) ● Help SW identify triggers for illness-mania ● CBT and family therapy may be helpful ● Psychosocial interventions may help Efficacy, side effects, adherence, alternative therapies, increase staying well and reduce relapse Check with nursing staff expected discharge and resolve any adherence issues, inform community support worker of any issues	● Social support ● Monitor engagement with psychologist ● Signpost alcohol support ● Discuss trigger factors ● Financial support ● Employment support ● Engagement with community mental health tams ● Sign post smoking cessation ● Signpost MIND ● Monitor response to treatment and tolerability and adherence every 3-6 months

Drug	Indications
Flupentixol decanoate 200mg IM depot injection fortnightly at lunchtime	Symptoms of psychosis, possible previous diagnosis of schizophrenia, confirm in notes but he has missed the last dose of his depot
Venlafaxine XL 300mg tablets at bedtime	Depression, or possibly negative symptoms of schizophrenia
Lorazepam 1-2mg tablets three times daily when required	Found in agitated state and lorazepam would be useful to calm PP & help with agitation
Zopiclone 15mg tablets at bedtime when required	Suffering from poor sleep, look in medical notes to see how long PP has been using it for? 15 mg ON above max. dose however commonly used.
Haloperidol 5mg tablets three times daily when required	Agitation/violent behaviour

Care intervention	Recommended action	Ongoing review & monitoring parameters (including frequency of monitoring)
PP is experiencing extrapyramidal side effect (EPSE) typically known as DYSTONIA. It is characterised by muscle spasm of the head and neck. When the head is forced sideways it is known as *torticollis*. PP could not look straight ahead and persistently looked up to the left. This may be due to the recent dose increased of the depot plus the addition of haloperidol **(haloperidol can cause marked EPSE c/w flupentixol causing moderate EPSE –seåe appendices- antipsychotics -relative side effects)**	• Acute dystonic reaction must be treated immediately as the condition is quite painful, distressing and uncomfortable but can be life-threatening if left untreated. • Consider prescribing procyclidine (an anticholinergic) either orally or intramuscularly. IM procyclidine (2.5-5mg TDS PRN) may be preferred if PP is unable to swallow and it acts quicker than oral formulations.	Symptoms observation until PP is completely recovered from the acute dystonic reaction. If no improvement with IM procyclidine after 1-2 days, and it is persistent and severe, refer PP to A&E immediately. Monitor for anticholinergic side effects such as urinary retention, constipation, confusion, dry mouth and blurred vision.

Lorazepam 1-2 tds prn	This is obviously useful now while PP is in an acute phase of his illness. How much is PP taking? **Check with the patient** Review lorazepam dose as maximum BNF is 4mg orally in 24 hours. Prescribe 1mg four times daily PRN instead.	Monitor for signs of tolerance and dependence. Advise PP not to take it regularly and only when anxious/agitated and not stop abruptly, should wean off slowly, to avoid discontinuation symptoms.

Non-pharmacological interventions- *Remember as a mental health trust we try to ensure when patients are discharged they are going to suitable living/ accommodation. We have social workers etc who can facilitate this process.*	● DVLA should be notified as PP is suffering from an acute illness and this is PP's responsibility as it could affect the insurance policy ● Smoking cessation – NRT suggestions- when PP is well ● Psychosocial interventions may help reduce stress and help manage symptoms ● Psychotherapy such as 'Living with voices' to help cope with hearing voices and learn how to manage them ● Weight monitoring as PP is over 100kg in weight. ● Discuss alcohol use with PP- respiratory depressant and will not help with low mood ● Presume negative for illicit drugs? It says he is an illicit drug user	● May need social worker involvement: o Social support o Financial support o Employment support ● Monitor engagement with the community mental health team and psychologist ● Sign post for smoking cessation support such as GP or local smoking cessation service ● Sign post to MIND (mental health charity) for support Monitor response to treatment and tolerability every 3 to 6 months in the community as well as adherence to medication. Frequency of monitoring may vary depending on what drug treatment PP is on or switched to. Urine screening for illicit drugs, give advice regarding the detrimental effects of illicit drug use on mental health. Especially cannabis- give more detail here……

Increased risk of QTc interval prolongation and/or ventricular arrhythmias (e.g. Torsade de Pointes) Risk factors: ● Venlafaxine ● Flupentixol ● Antipsychotic polypharmacy ● Antipsychotic at high doses ● Venlafaxine + antipsychotics	Generally, it would be advisable to switch venlafaxine to another antidepressant that does not affect the QTc interval such as sertraline, mirtazapine and duloxetine. However, it may not be appropriate to switch if PP has been stabilised on it and that his ECG results (past and present) were unremarkable. This is because switching to other antidepressants may destabilise PP's depression. It may be advisable to minimise his risk by minimising the number of antipsychotics prescribed. **For instance, stop the haloperidol PRN (see later)** If switching antidepressant is necessary, check drug history to establish which antidepressants PP had tried in the past and their treatment outcome. ●	Monitor ECG when PP is an in-patient on the ward even if he is asymptomatic. Also monitor plasma electrolytes to detect abnormalities. ● Advise PP to report signs and symptoms of QTc prolongation such as heart palpitations, fainting and seizures.

PP is still suffering from psychotic symptoms while having EPSE from the depot and haloperidol. Review the prescription for flupentixol IM depot injection. Also, EPSEs are more common with first-generation antipsychotics than the second-generations. Other risk factors include male gender, younger age, and depot formulation and high doses.	● **2 options: continue with flupentixol or switch to SGA** ● Dose reduction would not be the appropriate approach as PP is suffering from psychotic symptoms, continue with 200mg dose. ● Concern about long-term used of oral procyclidine and need to weigh up the benefits of continuing flupentixol IM depot injection compared with the risk of EPSEs ● May resolve if discontinue haloperidol- (see later) ● Consider switching it to a second-generation antipsychotic depot injection, such as risperidone (fortnightly) or paliperidone (monthly), or even aripiprazole depot o List recommended doses of above depots o If decide to switch to another depot then discuss switching carefully to avoid NMS ● Discuss risks and benefits of switching antipsychotic treatment with PP and the mental health team. ● Review depot c/w oral medication. Presume poor adherence to oral but this should be discussed with PP	If switching to a second-generation antipsychotic: ● Monitor response to treatment ● Monitor EPSEs during switching as flupentixol will remain in PP's system for longer while the new antipsychotic is being introduced. ● Before switching, check ECG, FBC, prolactin and LFTs as baseline. If unremarkable, repeat at 3 months If not switching to a second-generation antipsychotic: ● Continue with the higher dose if EPSE symptoms are controlled and haloperidol is discontinued (see later) ● Monitor symptoms control and EPSEs. ● Check ECG, FBC, prolactin and LFTs as baseline. If unremarkable, repeat at 3 months. ● Consider prophylactic oral procyclidine and monitor anticholinergic side effects ● Monitor medication adherence. Consider clozapine only if it was felt that PP was suffering from treatment resistant schizophrenia & PP would be adherent to medication as clozapine is oral only.
Venlafaxine is prescribed for night time administration. Venlafaxine can cause insomnia, a common side effect.	Consider prescribing venlafaxine XL 300mg for morning administration.	Sleep pattern. In the long term check how effective venlafaxine is at treating PP's depressive symptoms. Check compliance.

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Zopiclone dosage is above BNF limits for insomnia. This appears to be a repeat prescription. Usage probably >4 weeks since initiation.	Consider reducing the dose of zopiclone to the maximum 7.5mg/day. There is no evidence suggesting higher doses are more effective than standard doses. Insomnia may resolve if venlafaxine taken in the morning. Insomnia could be secondary to psychosis and/or depression, if treated appropriately, insomnia should subside. If a hypnotic is necessary, consider switching to an antihistamine such as promethazine as is less addictive and has low risk of dependence. A benzodiazepine (such as nitrazepam and temazepam) may be considered but high risk of dependence and is very addictive. Consider general sleep hygiene advice such as: • Avoid excessive caffeine, alcohol and nicotine use. • Do not stay in bed for prolonged periods if not asleep. • Avoid daytime naps or periods of inactivity • **List all sleep hygiene here**	Monitor and aim for an improvement in sleep pattern.

Review the prescription for haloperidol PRN. Reasons: ● Haloperidol – high risk of EPSEs. ● EPSEs risk increases when co-prescribed with flupentixol. ● PP is suffering acute dystonic reactions ● QTc risk increased with venlafaxine	Consider stopping haloperidol to prevent EPSEs and antipsychotic polypharmacy. If an antipsychotic PRN is necessary, consider using low dose quetiapine (25-50mg) short term as it has a lower risk of EPSEs. QTc is dose dependent so a low dose will minimise risk.	Monitor EPSEs, ECT, NMS and prolactin.

Increased risk of anticholinergic side effects from: ● Procyclidine (if prescribed) ● Flupentixol	Short-term use of procyclidine for acute symptoms may be necessary. Stop it when symptoms improve, and/or if antipsychotic treatment changed. Avoid long-term use if possible Antipsychotics with less anticholinergic side effects may be considered such as risperidone, paliperidone and aripiprazole. They are also available in depot formulation	Monitor for anticholinergic side effects such as urinary retention, constipation, confusion, dry mouth and blurred vision.