Cambridge University Hospitals NHS
NHS Foundation Trust

Nausea and Vomiting in Pancreatic Cancer

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Aims of the session

- Assessment of the patient with pancreatic cancer and symptoms of either nausea or vomiting or both to determine best treatment options

- How those treatment options might be best provided, assessed and escalated if necessary

Nausea and Vomiting

Nausea and vomiting management

1. Evaluation to identify cause(s)
2. Treatment of reversible causes
3. Non-pharmacological management
4. Pharmacological management

1) Identify cause(s)

Related to disease	Related to treatment	Concurrent causes
Gastric stasis Bowel obstruction Hepatomegaly Constipation Pain Anxiety Raised ICP Cough Hypercalcaemia	Chemotherapy Radiotherapy Drugs NSAIDs Opioids Antibiotics Iron TCA SSRI Digoxin	Infection Gastritis Candidiasis Uraemia Alcohol excess or withdrawal

Clinical pictures

Chemical picture	Mechanical picture	Raised ICP
Severe, persistent nausea Little relief from vomiting Smaller volume vomitus Retching	Early satiety Relatively little nausea Larger volume vomitus Undigested food Faeculent vomitus Abdominal colic	Early a.m. headache

Always take a detailed nausea and vomiting history

Identifying cause(s)

Chemical picture

- Drugs, chemotherapy
- Hypercalcaemia, uraemia

Raised ICP picture

- Space occupying lesion
- Cranial radiotherapy

Mechanical picture

- Malignant obstruction
- Gastric stasis
- Constipation

Movement-related picture

- Vestibular disease
- Transport

2) Treat reversible causes

- Drugs
- Anxiety
- Constipation
- Hypercalcaemia
- Raised intracranial pressure
- Tense ascites
- Severe pain
- Infection
- Cough
- Reflux

Always correct these first!

3) Non-pharmacological management

- Relaxation
- Calm, reassuring environment
- Small snacks, bland food
- Avoid odours and control of malodour
- Attention to food preparation
- Mouth care
- Acupuncture and acupressure (P6)
- NG / PEG tubes
- Surgery / stents

4) Pharmacological management

First line antiemetics

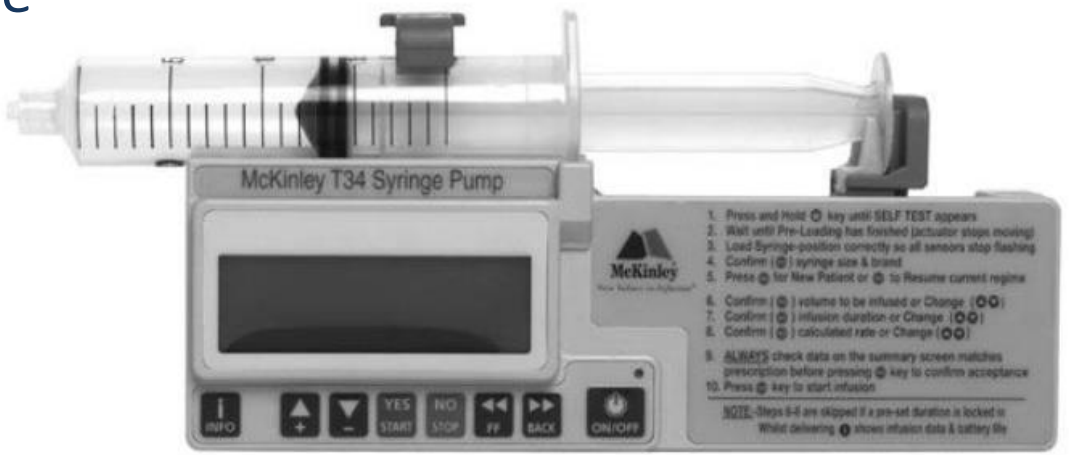
- Metoclopramide
- Cyclizine
- Haloperidol

Second line antiemetics

- Levomepromazine
- Ondansetron
- Olanzepine

Miscellaneous

- Hyoscine butylbromide
- Octreotide
- Dexamethasone
- Benzodiazepines



Antiemetic choice

Chemical causes

- **Haloperidol** or metoclopramide
- Ondansetron/granisetron

Bowel obstruction

- **Metoclopramide** (if no colic)
- Hysocine butylbromide (if colic)
- Octreotide
- Dexamethasone
- Ondansetron/granisetron

Raised ICP

- **Cyclizine**
- Dexamethasone

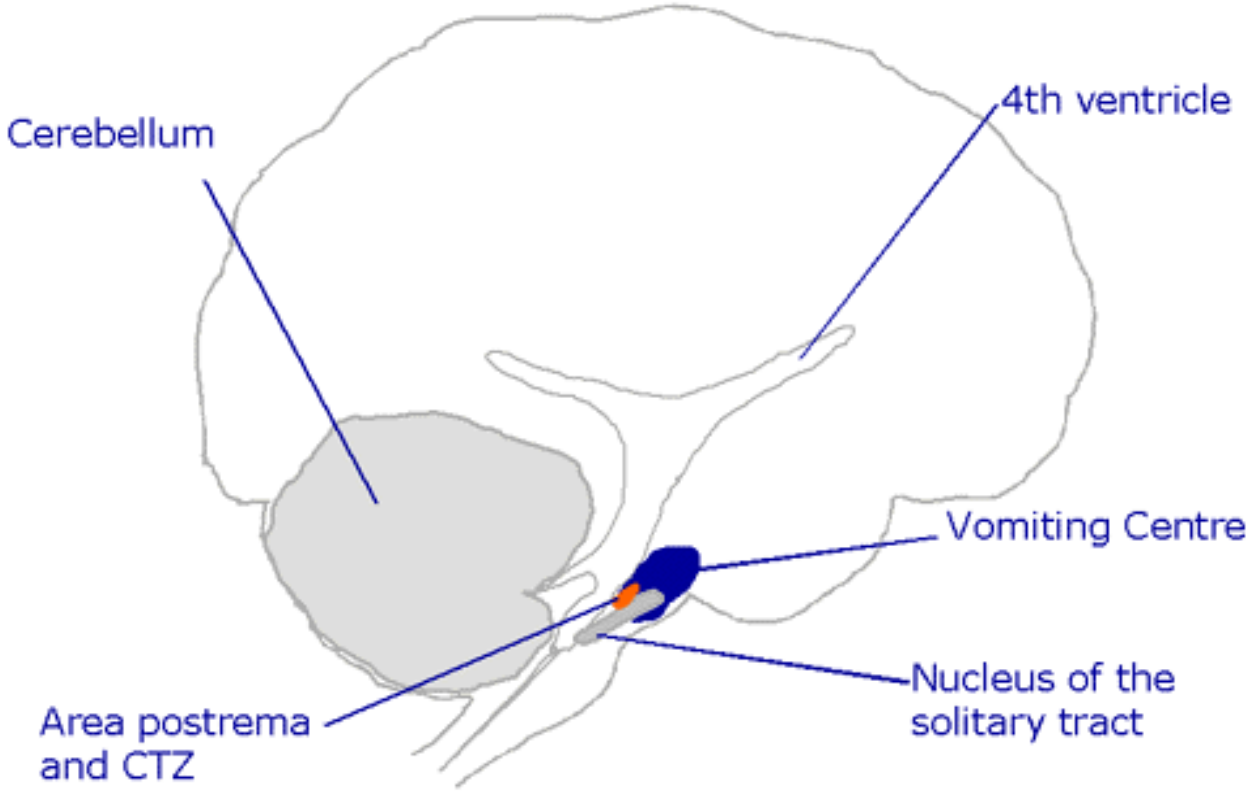
Movement-related

- **Cyclizine**

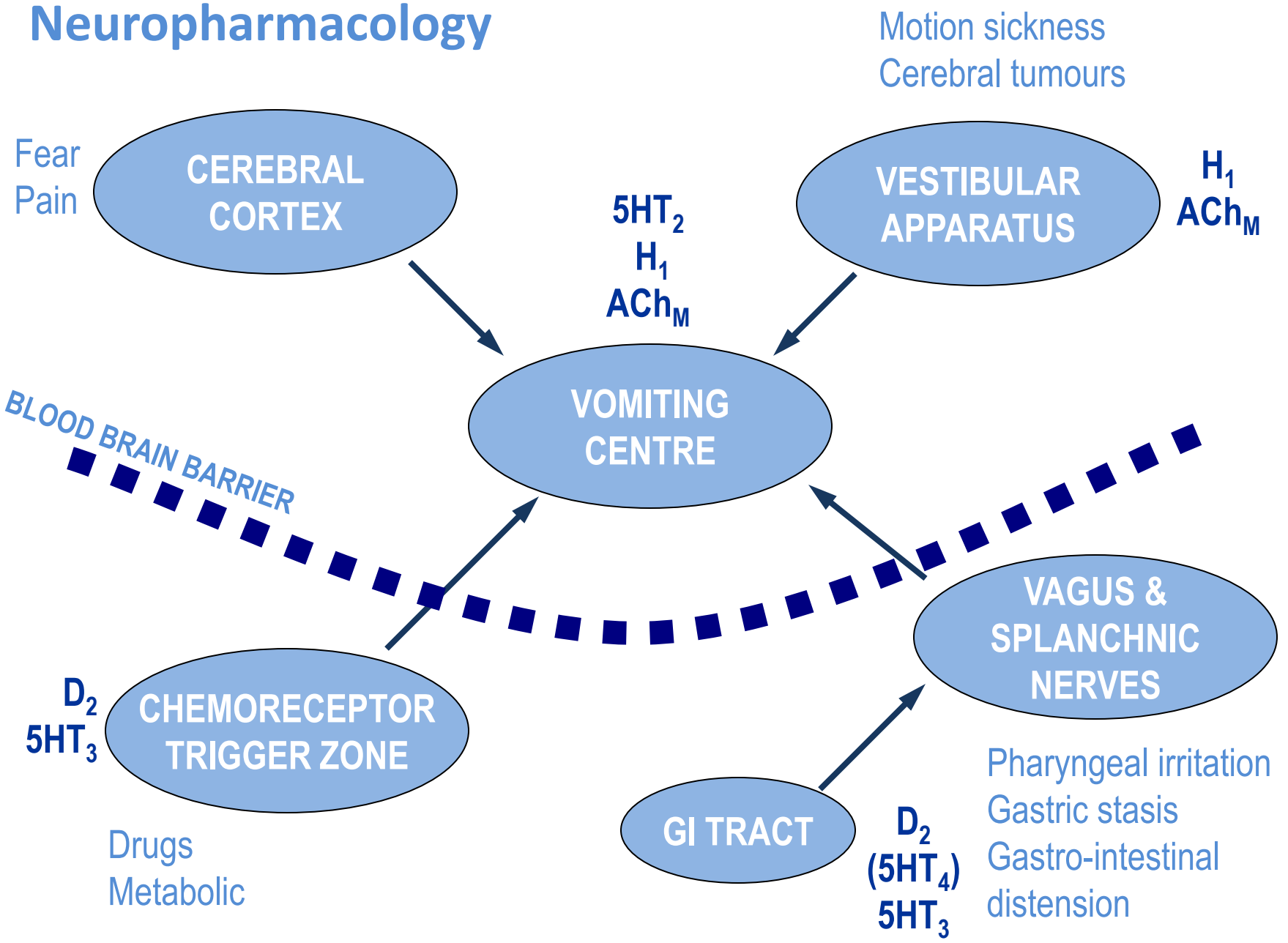
Unknown/multiple causes

- Levomepromazine

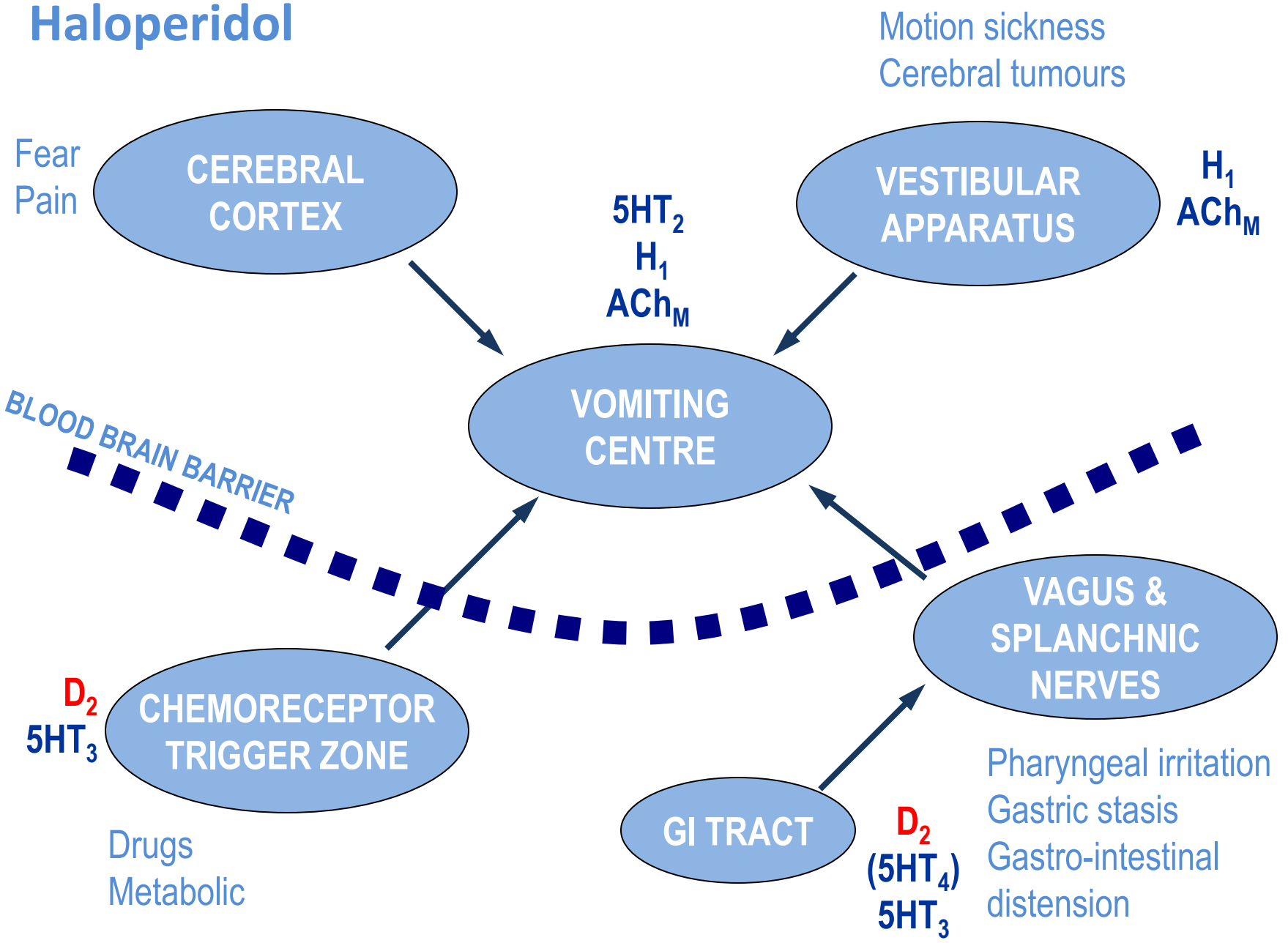
Neuroanatomy



Neuropharmacology



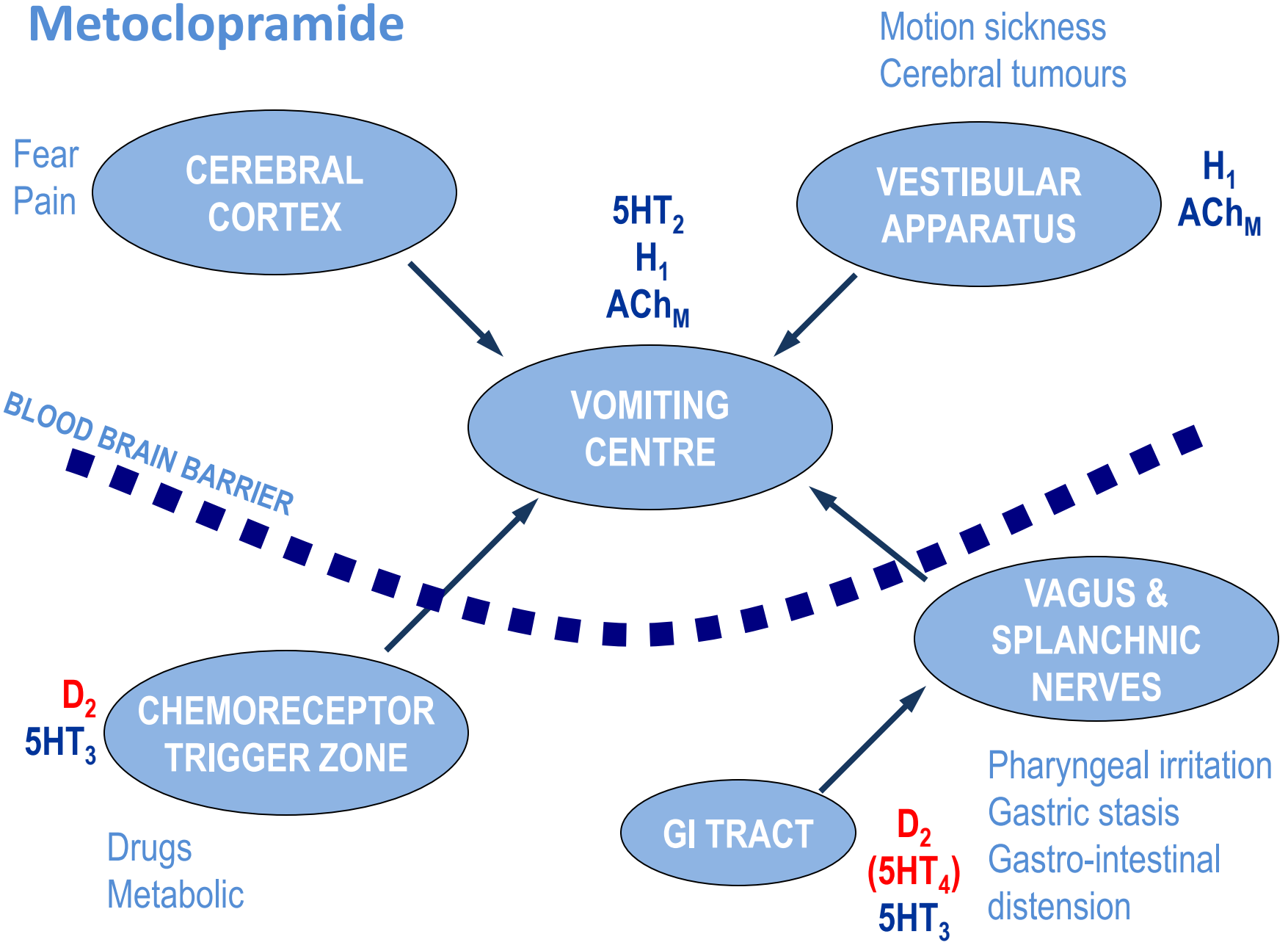
Haloperidol



Haloperidol (Contra-indications PD, LBD, MI and Decompensated Heart Failure)

- Also useful in hiccup, delirium and in agitated, imminently dying patients
- Sedation is the most common undesirable side-effect
- Bioavailability ~60%, Onset of action 15min sc and ~1hour PO, long t1/2 and long duration of action
- Cautions in dementia (associated with increased mortality and stroke risk), epilepsy (lowers seizure threshold) and can prolong QT interval
- CYP3A4 inducers (Carbamazepine, Rifampicin and Phenytoin) will reduce haloperidol levels
- CYP3A4 inhibitors (Itraconazole) can increase plasma haloperidol levels
- CYP2D6 inhibitor (Fluoxetine) can increase plasma haloperidol levels (Fluvoxamine and Venlafaxine can do the same but mechanism unknown)
- Start with a low dose for nausea and vomiting and titrate up…. If no response by 5mg try something else

Metoclopramide



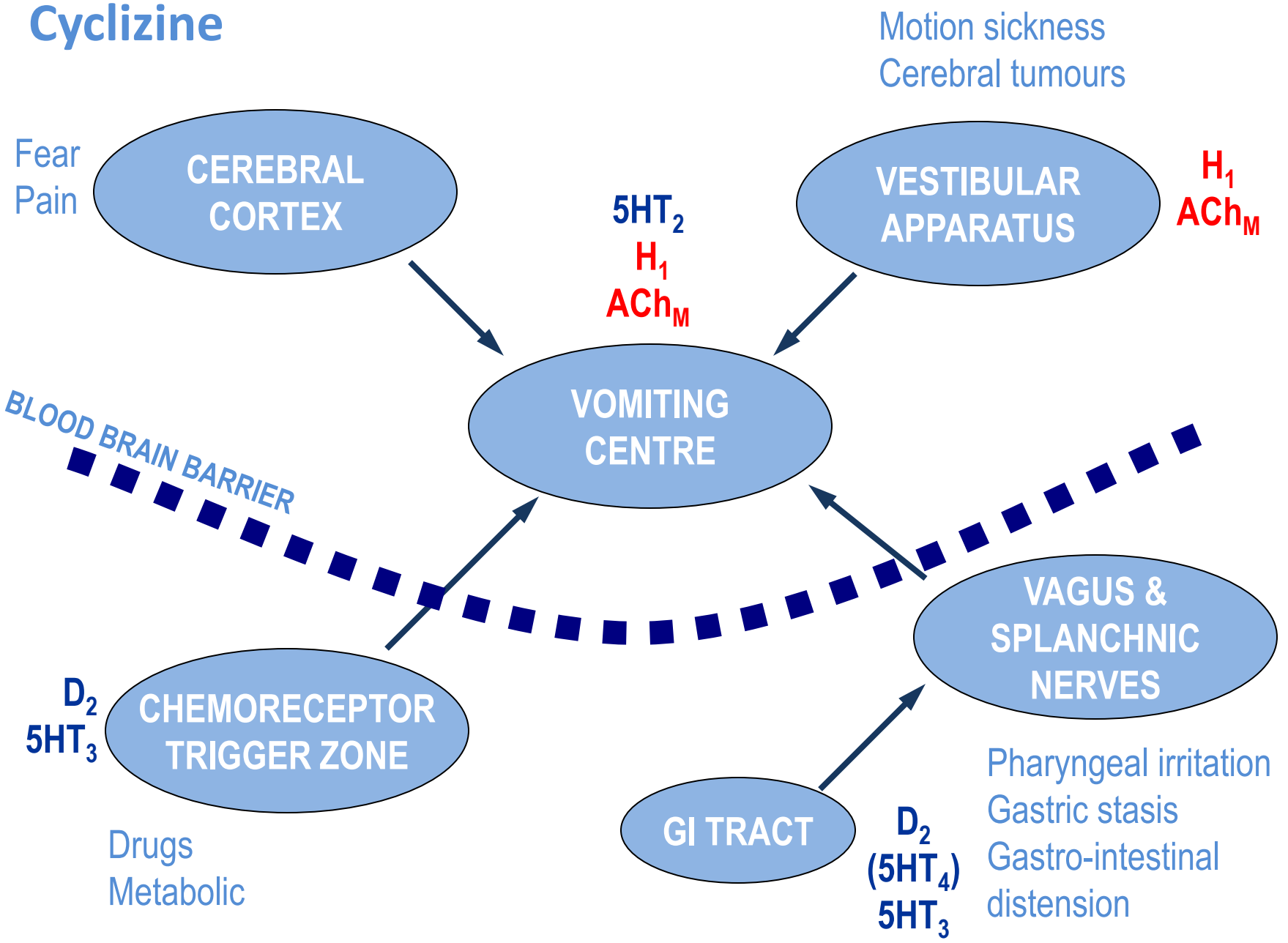
Metoclopramide (Contra-indications Children, Young women under 20, Phaeos (hypertensive crisis), GI haemorrhage or perforation or within 4 days of GI surgery), anyone who has had extra-pyramidal side effects with it)

- Major use is a prokinetic (NB opioids cause gastric stasis and constipation)
- Peripheral and central action; GI tract and area postrema
- Antiemetic of choice in cirrhosis and useful in renal impairment at lower doses
- Bioavailability 50-80%, works quickly and has a short t1/2
- Significant drug interractions- particularly when given with IV Metoclopramide (arrhythmias) and risk of serotonin toxicity when given with other serotinergic drugs
- Start oral tds and try to give 30minutes before meals for maximum effect; check for colic

Domperidone (Contra-indications Prolactinoma, prolonged QT, GI haemorrhage and within 4days of GI surgery)

- Useful in Parkinson's disease as no central action
- No parenteral formulation
- I only really see it used as prophylaxis in chemotherapy regimes

Cyclizine


Motion sickness
Cerebral tumours
Fear
Pain
CEREBRAL CORTEX
5HT2
H1
AChM
VESTIBULAR APPARATUS
H1
AChM
VOMITING CENTRE
BLOOD BRAIN BARRIER
D2
5HT3
CHEMORECEPTOR TRIGGER ZONE
Drugs
Metabolic
VAGUS & SPLANCHNIC NERVES
GI TRACT
D2
(5HT4)
5HT3
Pharyngeal irritation
Gastric stasis
Gastro-intestinal distension

Cyclizine (no significant contra-indications)

- Useful in nausea and vomiting from central/cerebral causes and in motion sickness, vertigo and labrynthine disorders
- Bioavailability 50% (beware the “high” from IV Cyclizine), onset of action 30-60 minutes and t1/2 20h
- Watch out for anticholinergic toxicity….
- MUST be diluted with WFI
- Start low- 25mg tds prn and 75mg/24hour via CSCI

First line antiemetics

Metoclopramide 10mg tds po/sc or 30mg/24hrs CSCI (lower in hepatic impairment)

Indication: GI obstruction without colic (functional/partial mechanical)

Mechanism: D_2 antagonist, $5HT_4$ agonist

Adverse effects: colic, diarrhoea, extra-pyramidal symptoms

Haloperidol 0.5 - 1.5mg od/bd po/sc or 1-3mg/24hrs CSCI

Indications: chemical causes including opioids, renal failure

Mechanism: D_2 antagonist

Adverse effects: drowsiness, extra-pyramidal symptoms

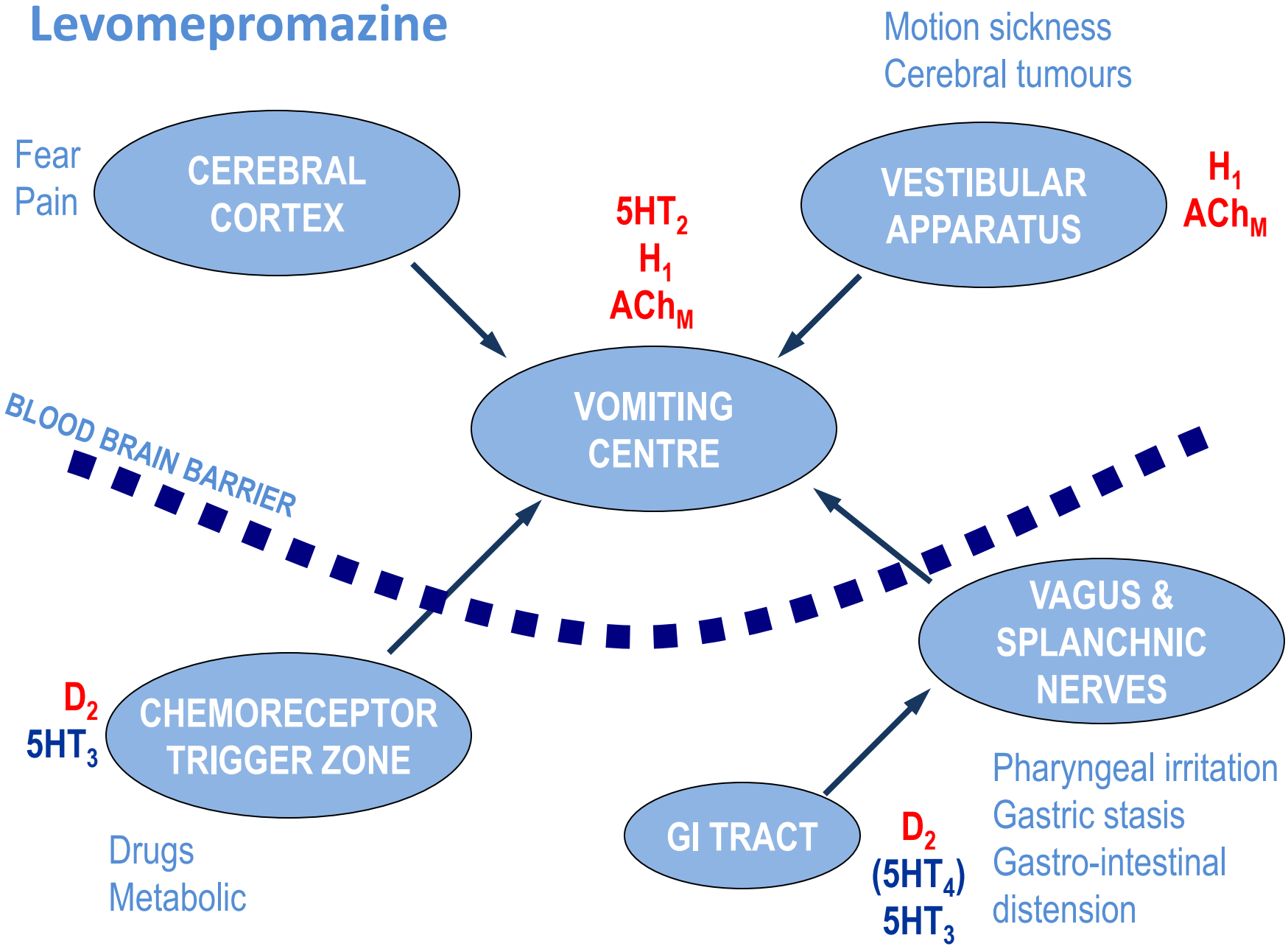
Cyclizine 25mg tds po/sc or 75-150/24hrs CSCI

Indications: raised ICP, motion-induced

Mechanism: antihistaminic, antimuscarinic

Adverse effects: constipation, dry mouth, confusion

Levomepromazine



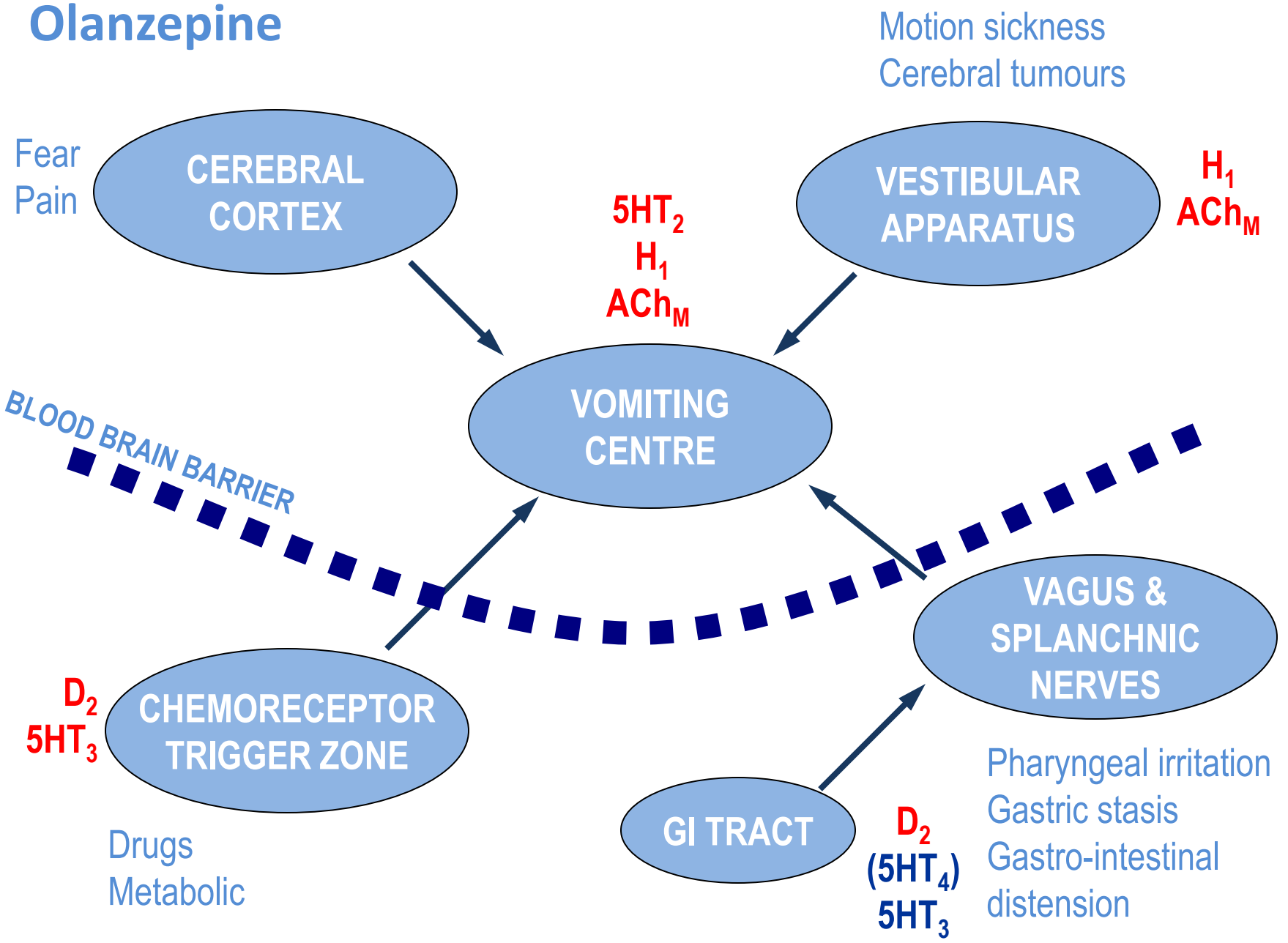
Levomepromazine

- Useful in low dose for nausea and vomiting and in higher doses for agitation in the imminently dying patient
- Cautions include Parkinsonism, Epilepsy and Dementia
- Bioavailability 20-50%, t ½ 15-30h and duration of action 12-24h
- Main side effects- dry mouth and sedation, can also cause QT prolongation
- Dose 3-6mg (3.125-6.25) once daily or 12-25mg/24h via CSCI

Olanzepine (Contra-indication narrow angle glaucoma)

- Most evidence is in RCTs alongside Dexamethasone and Ondansetron where it has been found to increase the likelihood of symptom control by between 30-100% (no head to head comparisons of Haloperidol and Levomepromazine)
- Also used in psychosis and mania and in paraneoplastic sweating
- Tolerability is pretty good- less movement disorders but similar drowsiness and weight gain
- Excellent bioavailability 80% (2.5mg oral at night usual starting dose)

Olanzepine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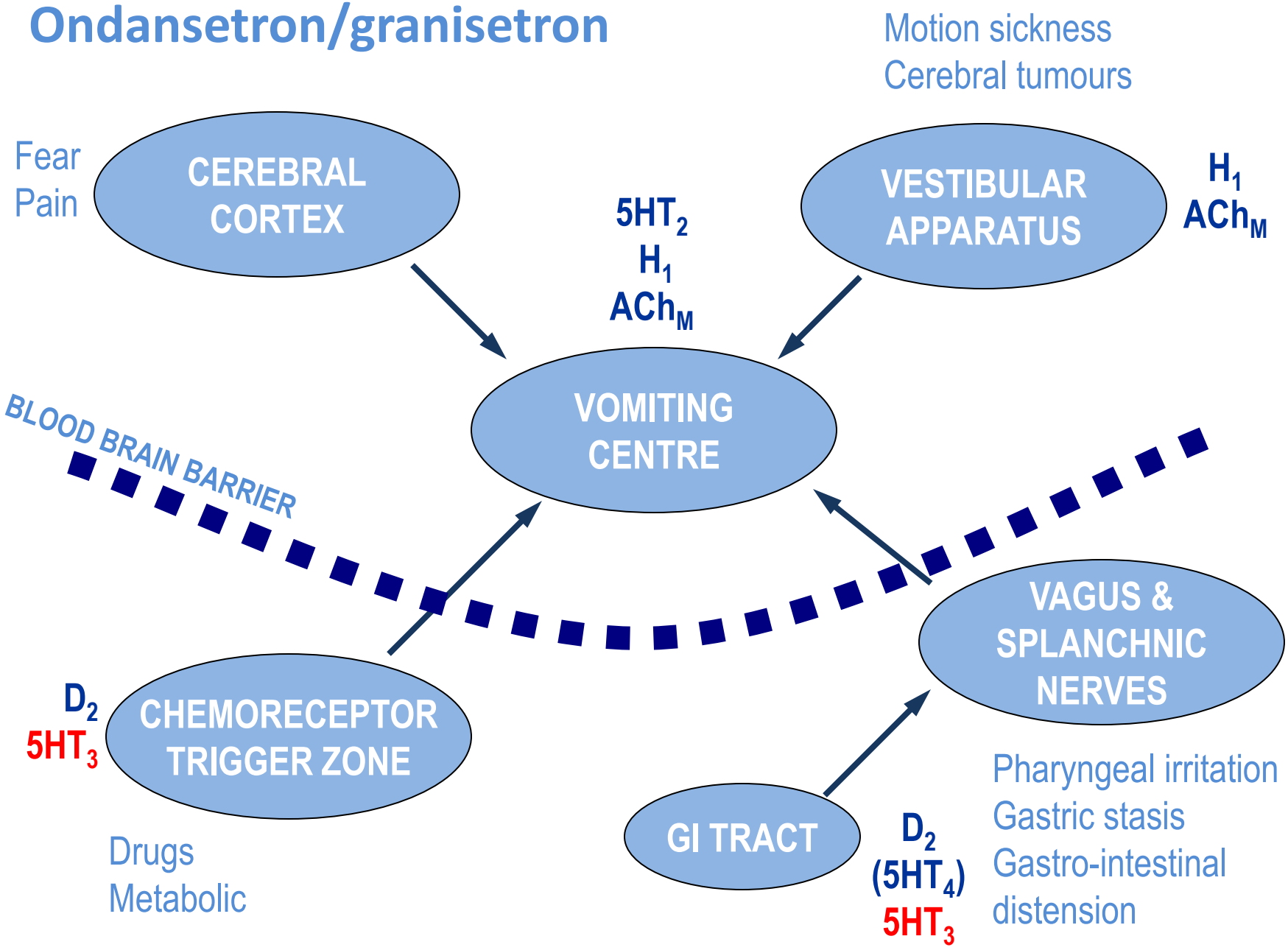
Ondansetron/granisetron



Ondansetron (Contra-indications Congential Long QT syndrome)

- Indications – nausea and vomiting after chemotherapy, surgery and radiotherapy and intractable vomiting when usual approaches have failed
- Also useful in the diarrhoea associated with carcinoid and opioid induced pruritis
- TD patches (Granisetron) only really useful for prevention
- Oral 4-8mg tds, CSCI 16-24mg/24h
- Side effects constipation and headache

Other drugs with an antiemetic action

Dexamethasone 4-8mg/day po/sc

Indications: raised intracranial pressure, GI obstruction

Mechanism: unclear, reduced inflammation

Adverse effects: hyperglycaemia, disturbed sleep, emotional lability, gastric irritation, muscle weakness, adrenal suppression…..

Antacids

Pantoprazole, Omeprazole and Lansoprazole

- Increase gastric pH which can reduce absorption of Itraconazole and Posaconazole
- Increase risk of C.diff, Hypomagnesaemia, B12 deficiency, renal toxicity and community acquired pneumonia

- Ranitidine no longer available
- Famotidine can be useful….. PO 20-40mg once daily and unauthorized use in CSCI 40mg/24hours

Drugs you know better than I do….

- Aprepitant…. Blocks the action of neurokinin on NK1 receptors a natural substance in the brain that causes nausea and vomiting

- Akynzeo (Netupitant/Palanosetron)

Prescribing points

- Prescribe regular and PRN antiemetic
- Both nausea and vomiting reduce enteral drug absorption. Use subcutaneous route (oral route only for prophylaxis)
- Use combinations with complimentary actions eg cyclizine and haloperidol. Avoid antagonistic combinations eg cyclizine and metoclopramide
- Levomepromazine can replace drug combinations

Summary

- The key to managing nausea and vomiting it to determine the cause
- A detailed description of the symptom can help identify the cause
- Always consider reversible causes
- The cause of the symptom guides the choice of antiemetic

Clinical case 1

- 73 year old man with pancreatic cancer and bone metastases
- Pain worse recently, especially on movement
- Drowsy, with nausea, anorexia and sore mouth
- Over last few days vomited twice; nausea is continual
- Only on morphine sulphate MR 30mg bd, diclofenac 50mg tds

Clinical case 2

- 68 year old woman with advanced pancreatic cancer
- Severe headaches, vomiting, unable to keep down morning medications
- Taking diclofenac 50mg tds for chronic low back pain

Clinical case 3

- A 52 year old man with pancreatic cancer has been admitted with vomiting every time he tries to eat
- The vomitus contains undigested food
- He has severe epigastric pain radiating to his back
- He has not been able to keep down his MST tablets (60mg bd) or cyclizine tablets (50mg tds)
- He is passing small pellets of hard stool infrequently

Q: How will you manage this situation?

Q: In the second week of admission his wife asks to see you. She is angry his symptoms are no better and is asking for him to be artificially fed (TPN). What will you do now?

Clinical Case 4

- Patient with pancreatic cancer on treatment
- Difficulties with bloating, crampy abdominal pain, diarrhoea and loose, greasy stools
- Losing weight

Latest info on Pancreatic Enzyme replacement therapy

- https://www.psgbi.org/position-statement-pert-shortage/

Clinical case 5

- 71 year old lady with pancreatic cancer BMI 16
- Admitted with vomiting
- Still nauseated after successful intervention, with ongoing anorexia and weight loss
- Her daughter is very distressed and continually encouraging her to eat

Don’t forget

- Serotinergic syndrome; symptoms can develop rapidly or over a few weeks

  Autonomic hyperactivity; sweating, fever, tachycardia and hypertension

  Neuromuscular hyperactivity; tremor, hyperreflexia, hypertonia, myoclonus and clonus

  Altered mental status; agitation, altered consciousness and coma

Drug combinations to look out for- anti-depressants and opioids, metoclopramide, ondansetron and triptans

Don’t forget

- Anticholinergic syndrome
- Results from competitive antagonism of acetylcholine at central and peripheral muscarinic receptors
- Leads to an agitated delirium including confusion, restlessness and picking at imaginary objects
- Patients look hot, have dry skin, a flushed appearance, tachycardia and often urinary retention
- All the a’s – anti-histamines, tussives, depressants, psychotics, convulsants, emetics and plants lupins and deadly nightshade

A plea from the Palliative Care Team

Let’s talk about your bowels…..

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely Liquid

How should we define constipation?

Clinical case A

- A 72 year old lady has advanced pancreatic cancer which has progressed despite chemotherapy
- Her abdominal pain is well controlled with MST 20mg bd
- She has been constipated for months, and opens her bowels twice weekly if she takes lactulose
- For the last 3 days she has vomited several times daily with little nausea; she has severe episodic abdominal pain
- She has not defaecated for 5 days, but is passing flatus
- This morning she had a large volume vomit

How will you differentiate between the two main differential diagnoses?


R

Scenario A: constipation

- Impact?
- Causes?
- Management?

Scenario A: constipation

- Management
  1. Find causes
  2. Treat reversible causes
  3. Non pharmacological
  4. Pharmacological

  Simple approaches make a difference:
  - Increase fluids
  - Mobilise
  - Toilet (privacy, raised seat)
  - Fibre in diet

Laxatives

- Faecal Softeners
  - Surface wetting agents — Docussate
  - Surface wetting agents — Poloxamer (in co-d)
  - Osmotic laxatives — lactulose, milpar, movicol
- Stimulant laxatives — bisacodyl, dantron, senna, sodium picosulphate
- Lubricants — liquid paraffin
- Bulk-forming — Fybogel, Normacol

New options

- Methylnaltrexone – peripherally acting opioid antagonist

- Naloxegol

Principles of laxative use

Oral laxatives should be used more than rectal measures

Oral

- Patient preference often dictates choice
- Usually use a softener with a stimulant eg docusate with senna
- Osmotic laxatives effective in impaction but large volume eg Movicol
- Avoid bulking agents as can obstruct without adequate fluid
- Methylnaltrexone and naloxegol are novel agents for opioid-induced constipation

Rectal

- Bisacodyl suppositories, stimulant (insert in contact with bowel wall)
- Glycerine suppositories, softener (insert into stool)

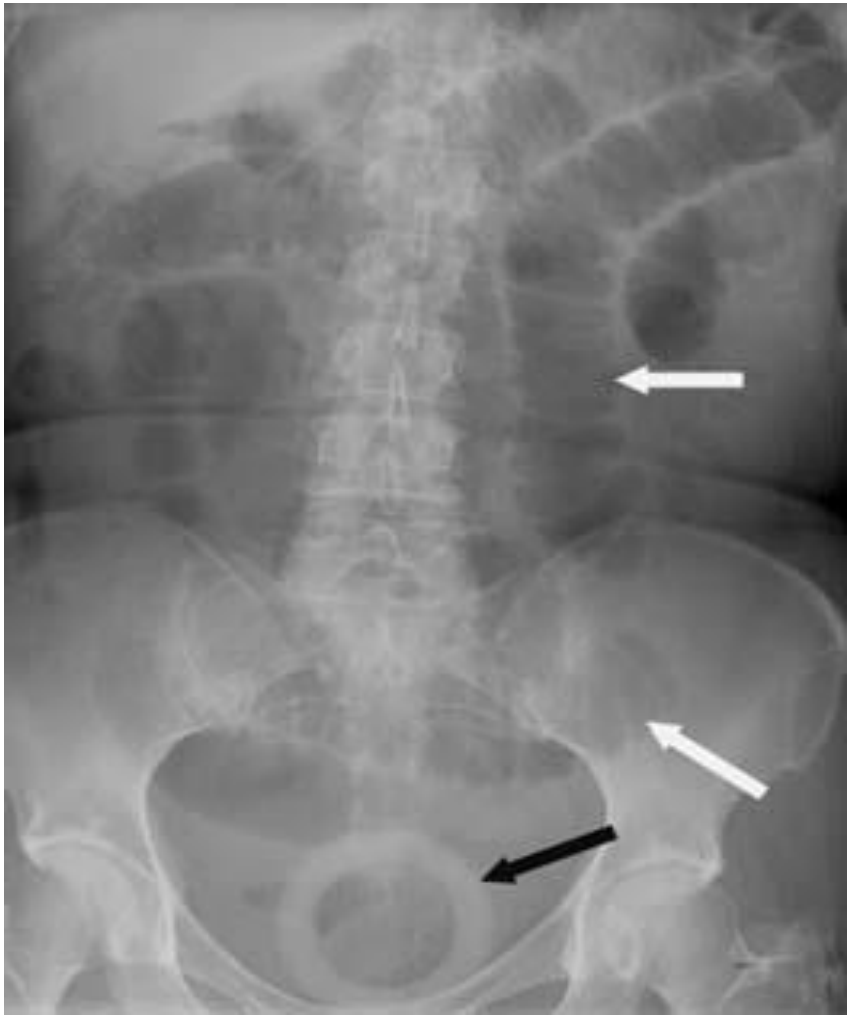
Scenario B: malignant bowel obstruction

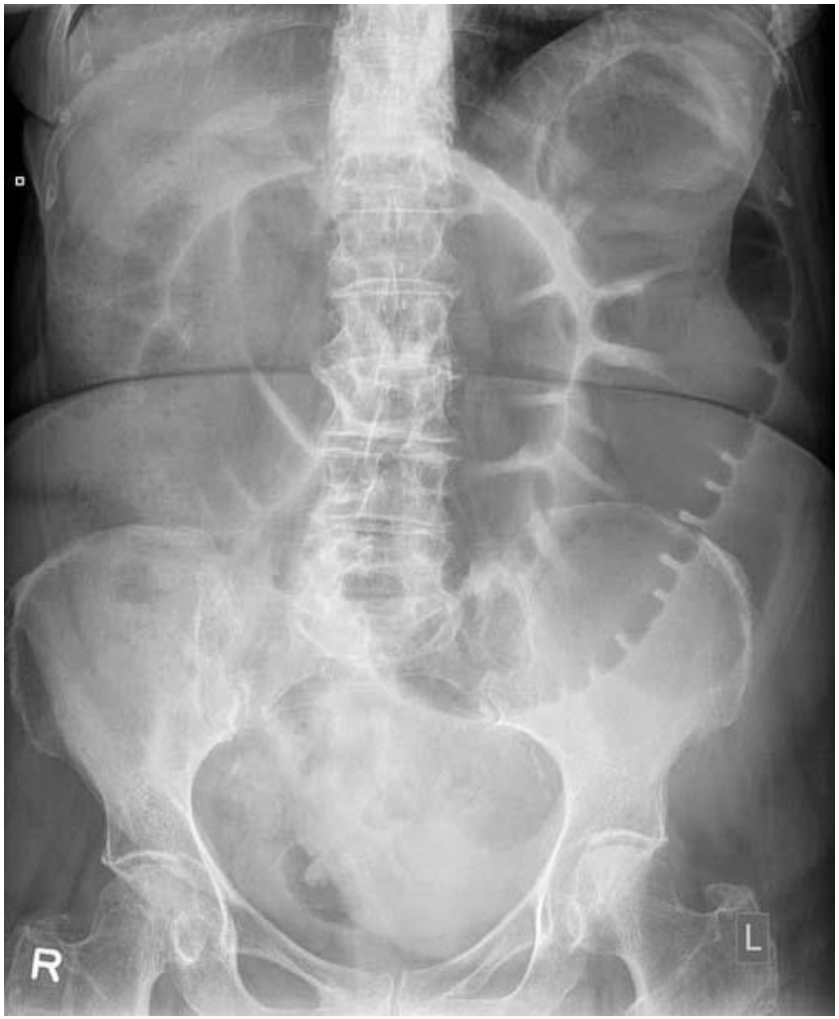
- Prevalence: 5-50% ovarian cancer, 10-30% bowel cancer
- Prognosis: 30-90 day median survival
- Symptoms: pain (constant and colic), vomiting, constipation, distension
- Describe in terms of four features:
  1. Upper or lower GI (small/large bowel)
  2. Single or multiple sites
  3. Partial or complete
  4. Mechanical or functional

Mechanical versus functional

- Mechanical
  - Extrinsic occlusion, eg adhesions, post RT fibrosis
  - Intraluminal eg polyp
  - Intramural occlusion eg linitis plastica
  - Colic, high pitched bowel sounds
- Functional
  - Mesenteric infiltration
  - Coeliac plexus involvement
  - Drug-induced (antikinetic)
  - Post-operative
  - No colic, quiet bowel sounds

Small versus large bowel obstruction





Management of malignant bowel obstruction (MBO)

- Surgery
  - Only if mechanical, single site, no ascites, good PS, chance response to further chemo/radiotherapy (mortality 10-40%)

- Endoscopic
  - Stent: only single site, oesophageal/duodenal/rectal
  - Venting gastrostomy: for intractable symptoms

- ‘Medical management’

‘Medical management’

Depends if mechanical/functional, partial/complete, colic/no colic

Either

a) Functional MBO or b) partial mechanical without colic

- Metoclopramide (with care...)
- Stool softeners (consider stimulants in functional MBO)

Or

a) Complete mechanical MBO or b) partial mechanical with colic

- Morphine sulphate
- Hyoscine butylbromide and/or octreotide
- Dexamethasone
- Stool softeners

Clinical case

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- Her abdominal pain is well controlled with MST 20mg bd
- She has been constipated for months, and opens her bowels twice weekly if she takes lactulose
- For the last 3 days she has vomited several times daily with little nausea; she has severe episodic abdominal pain
- She has not defaecated for 5 days, but is passing flatus
- This morning she had a large volume vomit
- Her abdominal CT shows multiple sites of small bowel obstruction

Q: How will you manage this situation?

Summary

- Take constipation seriously, and usually combine a stool softener with a stimulant laxative
- Medical management of malignant bowel obstruction requires either a prokinetic approach or an antisecretory approach
- Specialist support from a palliative care team or ‘feeding issues MDT’ may be needed