



# Management of Nausea and Vomiting in patients with chronic kidney disease

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## Nausea and Vomiting



### Terms for Nausea

#### Pre-ejection phase

- Sickness
- Queasiness
- Retching
- Gagging

Associated anorexia, salivation, vasomotor changes over minutes to days

Highly prevalent – 70% in Advanced Cancer  
- 50% in Advanced non-cancer conditions

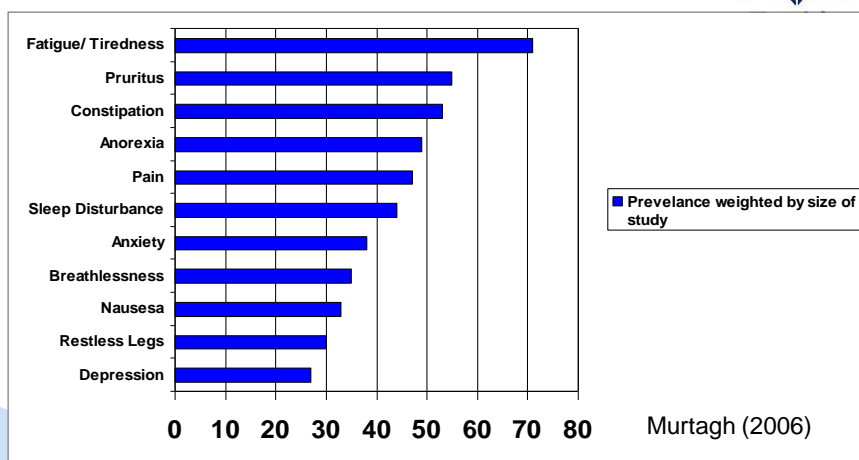
### Terms for vomiting

#### Forceful expulsion of gastric contents

- Be sick
- Retch (up)
- Fetch up
- Heave
- Spew
- The Boak
- The Dry Boak

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## Weighted mean Prevalence of Symptoms (%) in CKD stage 5 (dialysis patients)



Prevalence of vomiting in HD patients – 11% (Asgari, 2017)

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## Session Aims

- General principles
- Physiology of nausea and vomiting (N&V)
- Management of N&V

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## Introduction and general principles



- N+V are related but separate symptoms
- Undermine quality of life
- Fully assess...
  - Regurgitation
  - Reflux
  - Expectoration
  - Vomiting
  - Nausea without vomiting
- Identify the likely cause(s)
- Systematic approach favoured with targeted therapies
- Consider route of administration
  - Oral/IV/SC bolus/CSCI

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## Case 1



- 45 yr old male, Type 1 diabetes since 17yrs old
- Small vessel disease
- Partially blind, autonomic neuropathy, peripheral neuropathy, CKD stage 5
- No known cardiac disease
- Commenced dialysis 2 years ago x3 weekly

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## Case 1



### Symptoms

- Reflux, Nausea and recurrent vomiting – especially after meals
  - Constipated
  - Barium swallow – delayed gastric emptying
- What is your antiemetic of choice?
- A. Cyclizine
  - B. Haloperidol
  - C. Metoclopramide
  - D. Ondansetron

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## Case 1

- Answer:
- Metoclopramide

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## Case 2

What is your antiemetic of choice?

- 89yr old lady
- CKD stage 5 – conservatively managed
- CCF and AF

- A. Haloperidol
- B. Cyclizine
- C. Metoclopramide
- D. Levomepromazine

- Urea 22
- Cr – 240
- eGFR 11mL/min

- Continuous nausea – occasionally vomiting

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## Case 2

- Answer:
- Haloperidol

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## Case 3

- 56 yr female on HD
- Recent stroke
- Anxiety ++
- Significant N+V on movement since stroke, affecting her ability to dialyse and to travel for dialysis

What is your antiemetic of choice?

- A. Levomepromazine
- B. Cyclizine
- C. Ondansetron
- D. Domperidone

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## Case 3

- Answer:
- Cyclizine
- Plus lorazepam PRN

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## Physiology of Nausea and Vomiting



### Vomiting

- Primitive but complex reflex
- Triggered when a central threshold is crossed
- 2 main centres in the control of vomiting:
  - Chemoreceptor Trigger Zone (CTZ)
  - Vomiting Centre (VC)

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## Physiology of N&V



### Chemoreceptor Trigger Zone (CTZ)

- Floor of 4<sup>th</sup> ventricle
- Effectively outwith BBB
- Chemoreceptors directly exposed to blood borne chemicals
- CTZ stimulates the VC

### Vomiting Centre (VC)

- Medulla
- Diffuse interconnecting neural network
- Fully within BBB
- Integrates afferents
- Triggers vomiting reflex

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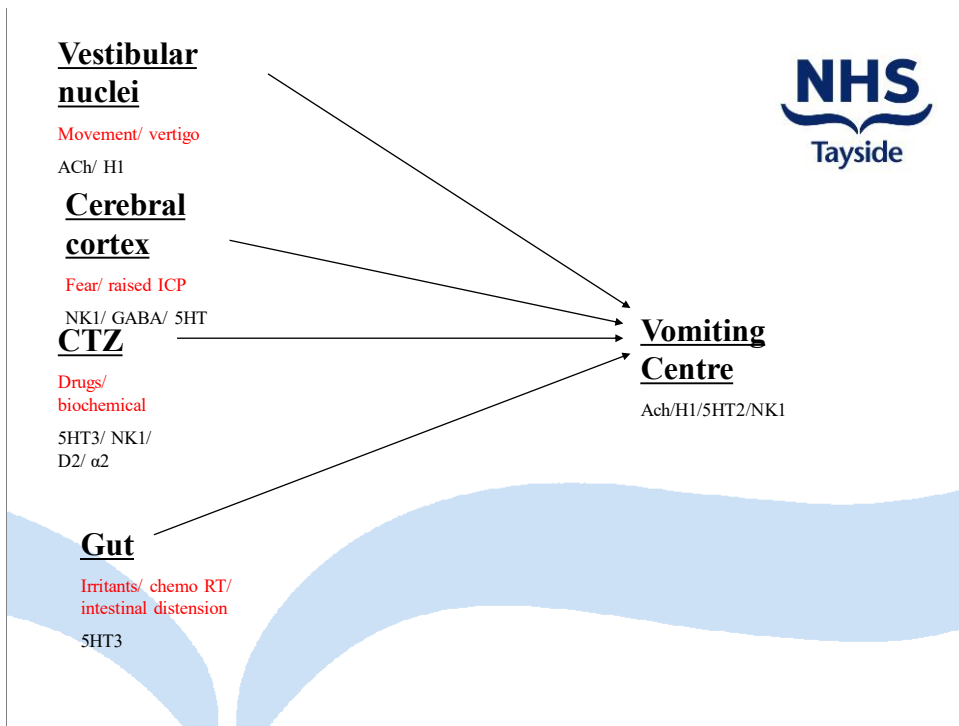
## The Vomiting Centre (VC)



- Co-ordinates the signals stimulating N+V
- Integrates afferent stimuli, (including CTZ) with parasympathetic & motor efferent activity  
→ vomiting reflex
- Reverse peristalsis in upper GIT
- Relaxation of pylorus and oesophagus
- Rhythmic contractions of the intercostal muscles
- Co-ordination of involuntary contractions of diaphragm and abdominal wall muscles

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**Nausea**

- If the stimulus is insufficient to produce vomiting it may cause nausea
- If nausea persists after vomiting it suggests a continuing stimulus

**NHS Tayside**

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## Common causes of N&V in Advanced CKD



- Chemical – drugs, uraemia, hypercalcaemia, hyponatraemia, ketoacidosis
- Gastric stasis – ascites, autonomic dysfunction, drugs
- Leaky platelets – release of 5HT3
- Other co-morbid conditions

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## Causes of N&V - 'in the head'



Cause and example triggers		Features
Cranial	↑ICP, Radiotherapy, meningeal disease	Headache (am), personality change, fatigue, reduced conscious level, delirium
Cortical	Pain, anxiety	Anticipatory nausea, psychological distress
Vestibular	Base of skull tumour, Cerebellar disease, motion sickness	Symptoms often movement related, although can occur with gastric stasis

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## Causes of N&V – below the head



Cause and example triggers		Key features
Chemical	Drugs - many	Look at any new drugs
	Metabolic – renal failure, liver failure, hypercalcaemia, hyponatraemia, ketoacidosis	Electrolyte or glucose abnormalities
	Toxins – ischaemic bowel, tumour products, infection	
Impaired gastric emptying	Autonomic dysfunction, drugs, tumour, ascites	Early satiety, reflux, hiccups
Visceral or serosal	Bowels obstruction, severe constipation, ureteric distension, liver capsule stretch	Vomiting food contents (undigested or digested) Abdominal pain, change in bowel habit

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## Drug Causes of N&V



Mechanism	Drugs
Gastric irritation	Antibiotics, Steroids, Iron supplements, NSAIDs, Spironolactone
Gastric Stasis	Antimuscarinics (TCAs), Opioids
Chemoreceptor Trigger Zone	Antibiotics, Opioids, cytotoxics, Digoxin
5HT <sub>3</sub> – receptor stimulation	Antibiotics, Cytotoxics, SSRIs

Antibiotics – Macrolides (Erythromycin), Cephalosporins (Ceftriaxone), Penicillins (Amoxicillin) and Fluroquinolones (Ciprofloxacin)

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## Management – Often multifactorial Take a history



- Background co-morbidity
- Is it nausea alone or N+V
- Does the nausea improve after the vomiting
- When does it happen?
- Any changes in medication
- Any associated symptoms – headaches / vertigo / reflux / constipation / abdominal pain
- Which antiemetics have they tried and which route?

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## General principles of management of N&V in CKD



- Guidance extrapolated from evidence in post-op / chemotherapy / neuro-imaging studies and clinical experience
- All drugs should be used with caution (start low / go slow / review)
- Drugs with long half-life may show side-effects after a period of time (**cyclizine / levomepromazine / haloperidol**)
- **Drugs most likely to cause prolonged QTc – Domperidone, haloperidol, ondansetron, levomepromazine**
- No changes required in PD / HD patients

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## Biochemical / drug induced N&V

### Drug of choice – Dopamine antagonists



#### Haloperidol – 1<sup>st</sup> line

- antipsychotic
- Highly potent  $D_2$  antagonist @ CTZ, lesser peripheral effects in GI tract
- 5HT<sub>2</sub>,  $\alpha_1$ -adrenergic (VC)
- Crosses BBB
- **Accumulates in renal impairment – eGFR <30ml/min**
- Extrapyramidal, endocrine side effects, ↑[PRL], prolong QTc

Dose: 500mcg po/sc PRN

- 1.5mg nocte po / 2–5mg/24h CSCI/24h

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## Chemical N&V

### 5-HT<sub>3</sub> Antagonists – Ondansetron, Granisetron



- Developed to reduce vomiting from highly emetogenic chemotherapy – ie Cisplatin (available as a patch)
- Use if excessive 5HT<sub>3</sub> released from GI tract - chemo / XRT / gastric distension / gastroenteritis / **leaky platelets in renal failure / autonomic dysfunction**
- Also acts at CTZ – useful for head injury, brainstem abnormalities
- SE – **constipation** / headaches / caution if risk of prolonged QTc
- Useful if chemical / gut causes unresponsive to other anti-emetics (in addition)

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## Gastric stasis / visceral – Prokinetic anti-emetics (Metoclopramide / Domperidone)



- **Metoclopramide**
  - CTZ & peripheral  $D_2$  antagonist /  $5HT_4$  agonist - prokinetic
  - $5HT_3$  antagonist as  $\uparrow$  dose
  - Crosses BBB / **Accumulates in renal impairment**
  - EP side effects – tardive dyskinesia
  - Cardiac conduction disturbance (rare)
  - Avoid in complete bowel obstruction / PD
- Use low dose / for as short a time as possible
- PO/IV/SC route
- 10mg tds po/sc
- 30mg/24h CSCI

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## Gastric stasis / visceral – Prokinetic anti-emetics



### Domperidone

- CTZ & peripheral  $D_2$  antagonist
- $5HT_4$  agonist - Prokinetic
- **Doesn't** cross BBB – safe in PD
- Colic if bowel obstruction
- Cardiac conduction defects (QTc)
- Accumulates in renal impairment
- Use for as short a time as possible
- Oral route / PR
- 10-20mg 3-4x/24h

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## Cranial / Vestibular cause



## Visceral cause (if prokinetic contraindicated)

### Cyclizine

H<sub>1</sub> and Ach antagonist in vestibular system / cortex / gut

- Slows gut transit (reduces colic)
- Good for motion sickness / brain stem related nausea / cerebral causes of nausea
- Side-effects – sedation / dry mouth / dizziness
- Can cause cardiac arrhythmias
- Avoid in cardiac failure
- Blocks prokinetic effect of metoclopramide
- Add **haloperidol** as 2<sup>nd</sup> line if ineffective in cranial

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## Cortical cause



- Anxiety  
anticipatory N & V
- Consider Lorazepam  
0.5mg SL PRN
- Consider SSRI  
Mirtazepine
- Consider non-pharmacological support – CBT, relaxation, etc



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## Refractory N&V



- Consider change of route – CSCI, IV, patch
- Broad spectrum anti-emetics

### Levomepromazine

- Broad spectrum phenothiazine antipsychotic
- D<sub>2</sub>, H<sub>1</sub>, 5HT<sub>2</sub>, ACh<sub>m</sub>, α<sub>1</sub>-Ad antagonist
- Does not act at 5HT<sub>3</sub>
- Useful in dying phase
- Dose: 2mg SC PRN, 5mg–25 mg/24h via CSCI
- *Levinan* scored 6mg tablets available
  - 3-6mg bd orally

Side effects of sedation, postural hypotension, prolonged QTc, may be dose-limiting

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## Newer anti-emetics – used in chemotherapy induced N&V



- Aprepitant – NK1 antagonist
- Nabilone – CBD
- Used in refractory N&V secondary to chemotherapy
- No evidence yet of use in CKD

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## Case 1

45 yr old man, DM, autonomic neuropathy



What is your antiemetic of choice?

### Symptoms

Reflux, Nausea and recurrent vomiting – especially after meals

- Constipated
- Barium swallow – delayed gastric emptying

Delayed gastric emptying  
Uraemic

Needs a prokinetic  
Laxatives

C. Metoclopramide

Added Granisetron patch  
and regular laxatives

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## Case 2



What is your antiemetic of choice?

- 89yr old lady
- CKD stage 5 – conservatively managed
- Arthritis – on codeine

Biochemical cause of  
nausea

- U – 22, Cr 240
- eGFR 11mL/min

- Continuous nausea – occasionally vomiting

Haloperidol  
Stopped codeine (converted to Buprenorphine patch)

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## Case 3



- 56 yr female on HD
  - Recent stroke
  - Anxiety
  - Significant N+V on movement since stroke, affecting her ability to dialyse and to travel for dialysis
- What is your antiemetic of choice?
- Vestibular and cortical cause of N&V
- Cyclizine, Lorazepam PRN and Mirtazepine

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## Summary of N&V

- Consider underlying cause (s)
- Correct reversible factors
- Systematic approach to drug selection
- Give regularly +/- parenterally for persistent symptoms
- Review effectiveness
- CSCI not just for the dying

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