Upper GI Symptoms in CKD

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Palliative Medicine AT

IPOS-Renal

IPOS-Renal Patient Version

www.pos-pal.org

Patient name : .....

Date (dd/mm/yyyy) : .....

Patient number : ..... *(for staff use)*

Q1. What have been your main problems or concerns over the past week??

1. .....
2. .....
3. .....

Q2. Below is a list of symptoms, which you may or may not have experienced. For each symptom, please tick the box that best describes how it has affected you over the past week?

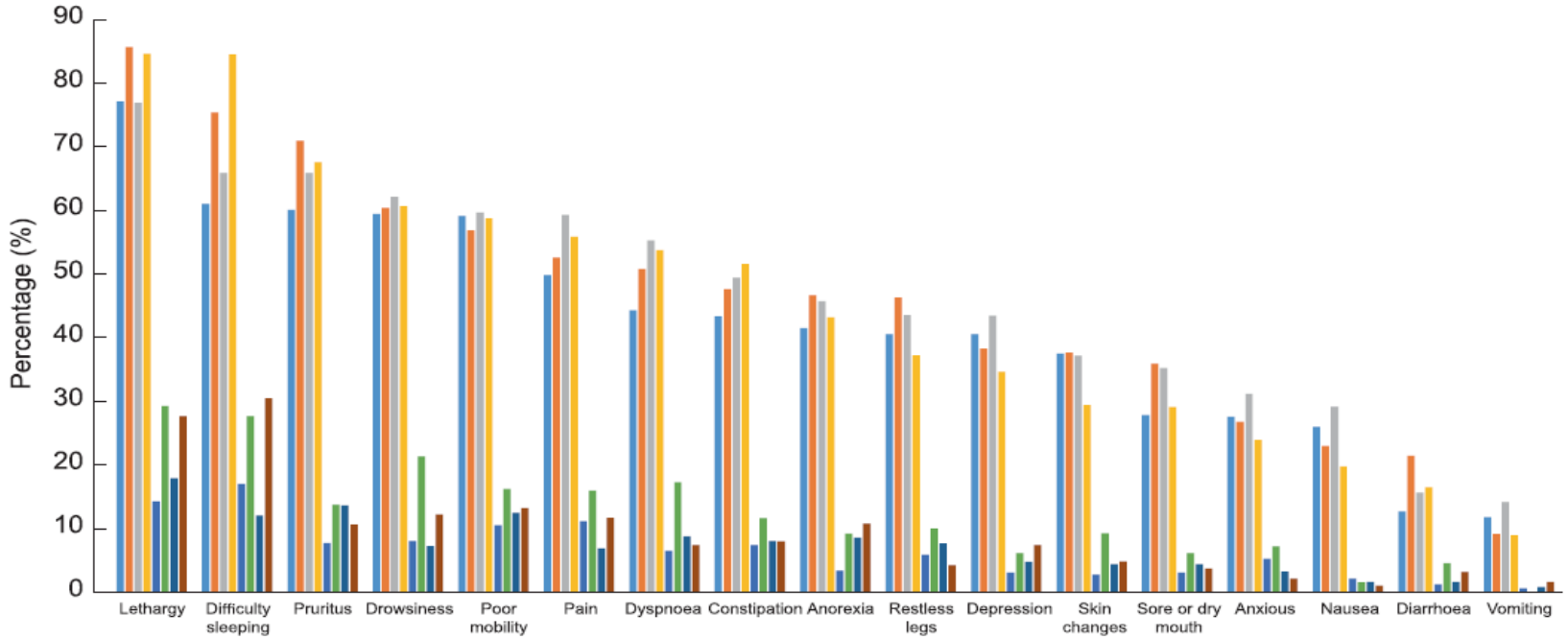
	Not at all	Slightly	Moderately	Severely	Overwhelmingly
Pain	0☐	1☐	2☐	3☐	4☐
Shortness of breath	0☐	1☐	2☐	3☐	4☐
Weakness or lack of energy	0☐	1☐	2☐	3☐	4☐
Nausea (feeling like you are going to be sick)	0☐	1☐	2☐	3☐	4☐
Vomiting (being sick)	0☐	1☐	2☐	3☐	4☐
Poor appetite	0☐	1☐	2☐	3☐	4☐
Constipation	0☐	1☐	2☐	3☐	4☐
Sore or dry mouth	0☐	1☐	2☐	3☐	4☐
Drowsiness	0☐	1☐	2☐	3☐	4☐
Poor mobility	0☐	1☐	2☐	3☐	4☐
Itching	0☐	1☐	2☐	3☐	4☐
Difficulty Sleeping	0☐	1☐	2☐	3☐	4☐
Restless legs or difficulty keeping legs still	0☐	1☐	2☐	3☐	4☐
Changes in skin	0☐	1☐	2☐	3☐	4☐
Diarrhoea	0☐	1☐	2☐	3☐	4☐

Please list any other symptoms not mentioned above, and tick the box to show how they have affected you over the past week?

1._____	0☐	1☐	2☐	3☐	4☐
2._____	0☐	1☐	2☐	3☐	4☐
3._____	0☐	1☐	2☐	3☐	4☐

Are they common?

Symptom prevalence and severity

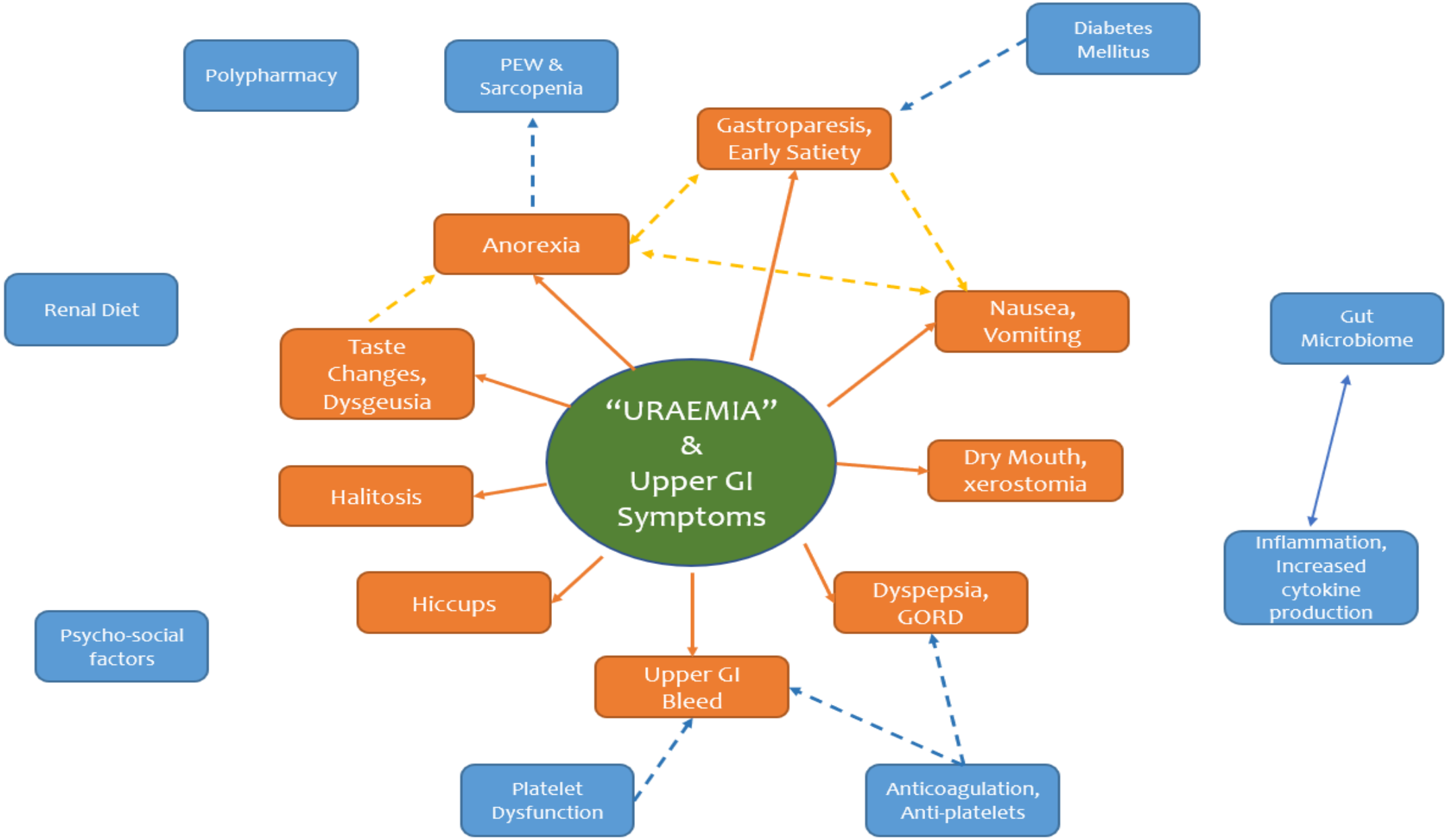


	Lethargy	Difficulty sleeping	Pruritus	Drowsiness	Poor mobility	Pain	Dyspnoea	Constipation	Anorexia	Restless legs	Depression	Skin changes	Sore or dry mouth	Anxious	Nausea	Diarrhoea	Vomiting
Prevalence baseline dialysis	77%	61%	60%	59%	59%	50%	44%	43%	41%	41%	41%	37%	28%	28%	26%	13%	12%
Prevalence baseline CKM	86%	75%	71%	60%	57%	53%	51%	48%	47%	46%	38%	38%	36%	27%	23%	21%	9%
Prevalence 12 months dialysis	77%	66%	66%	62%	60%	59%	55%	49%	46%	44%	43%	37%	35%	31%	29%	16%	14%
Prevalence 12 months CKM	85%	84%	68%	61%	59%	56%	54%	52%	43%	37%	35%	29%	29%	24%	20%	16%	9%
Severe baseline dialysis	14%	17%	8%	8%	11%	11%	7%	7%	3%	6%	3%	3%	3%	5%	2%	1%	1%
Severe baseline CKM	29%	28%	14%	21%	16%	16%	17%	12%	9%	10%	6%	9%	6%	7%	2%	5%	0%
Severe 12 months dialysis	18%	12%	14%	7%	13%	7%	9%	8%	9%	8%	5%	4%	4%	3%	2%	2%	1%
Severe 12 months CKM	28%	30%	11%	12%	13%	12%	7%	8%	11%	4%	7%	5%	4%	2%	1%	3%	2%

FIGURE 3: Symptom prevalence and severity at baseline and over 12 months in CKM and dialysis patients.

Chou A et al. Survival, symptoms and hospitalisation of older patients with advanced CKD managed without dialysis. NDT 2023.

Interconnecting symptoms; the ‘uraemic milieu’



Upper GI symptoms

- Prevalence of GI symptoms in CKD may be as high as 79% (studies range; 32-79%)
    - no clear difference between HD, PD or CKD patients.
    - dyspepsia may be higher in PD.
    - conflicting results regarding whether these symptoms improve with KRT.
    - negative impact on QoL and psychological wellbeing.

Karahan D et al. Comparison of gastrointestinal symptoms and findings in RRT modalities. BMC nephrology 2022.
Cano AE et al. Gastrointestinal symptoms in patients with ESRD undergoing treatment with HD or PD. Am J Gastroenterology 2007.
Hans Strid et al. The prevalence of gastrointestinal symptoms in patients with chronic renal failure is increased and associated with impaired psychological general well-being, NDT 2002.
Zuvela, J. Gastrointestinal symptoms in patients receiving dialysis: A systematic review. Nephrology. 2018

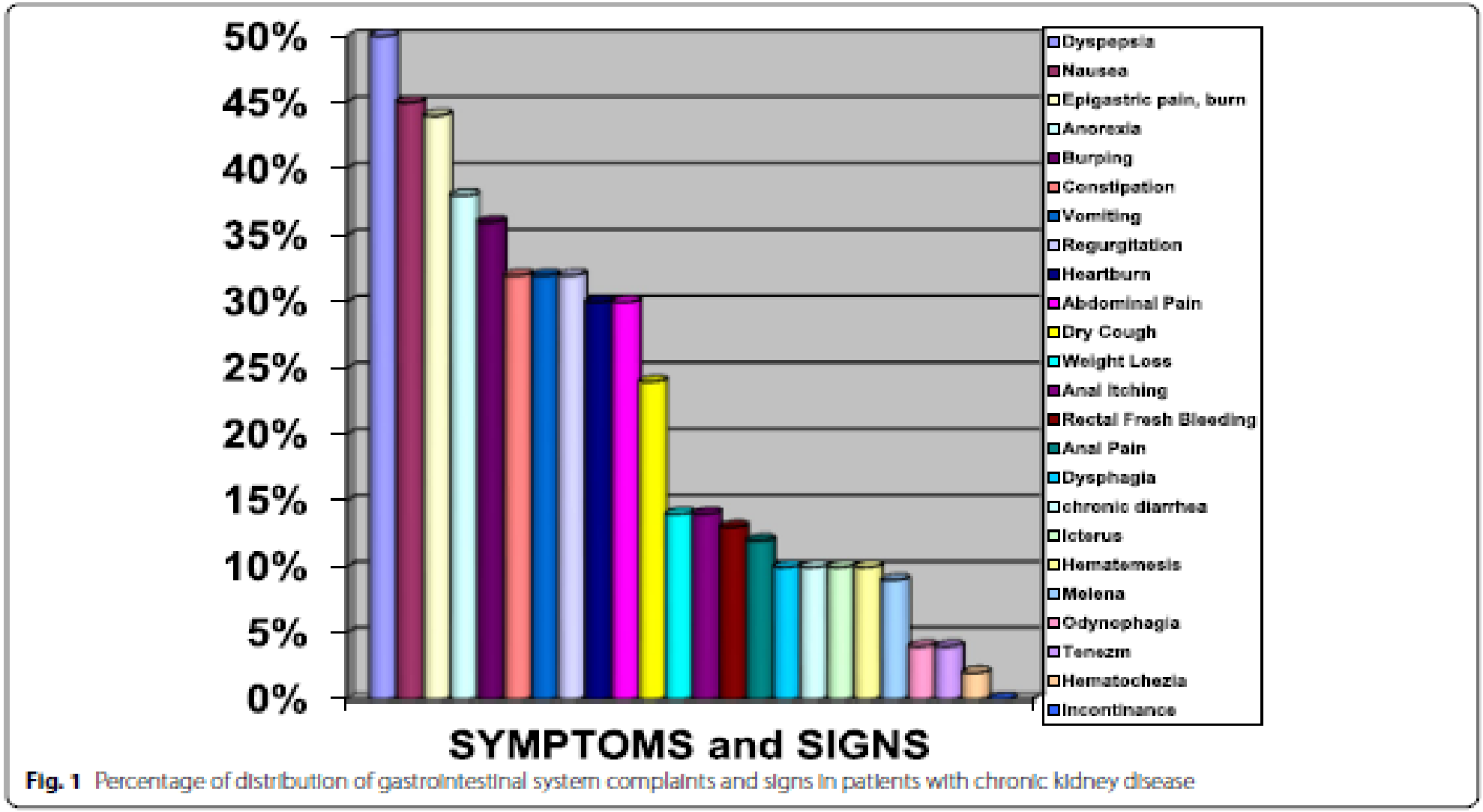
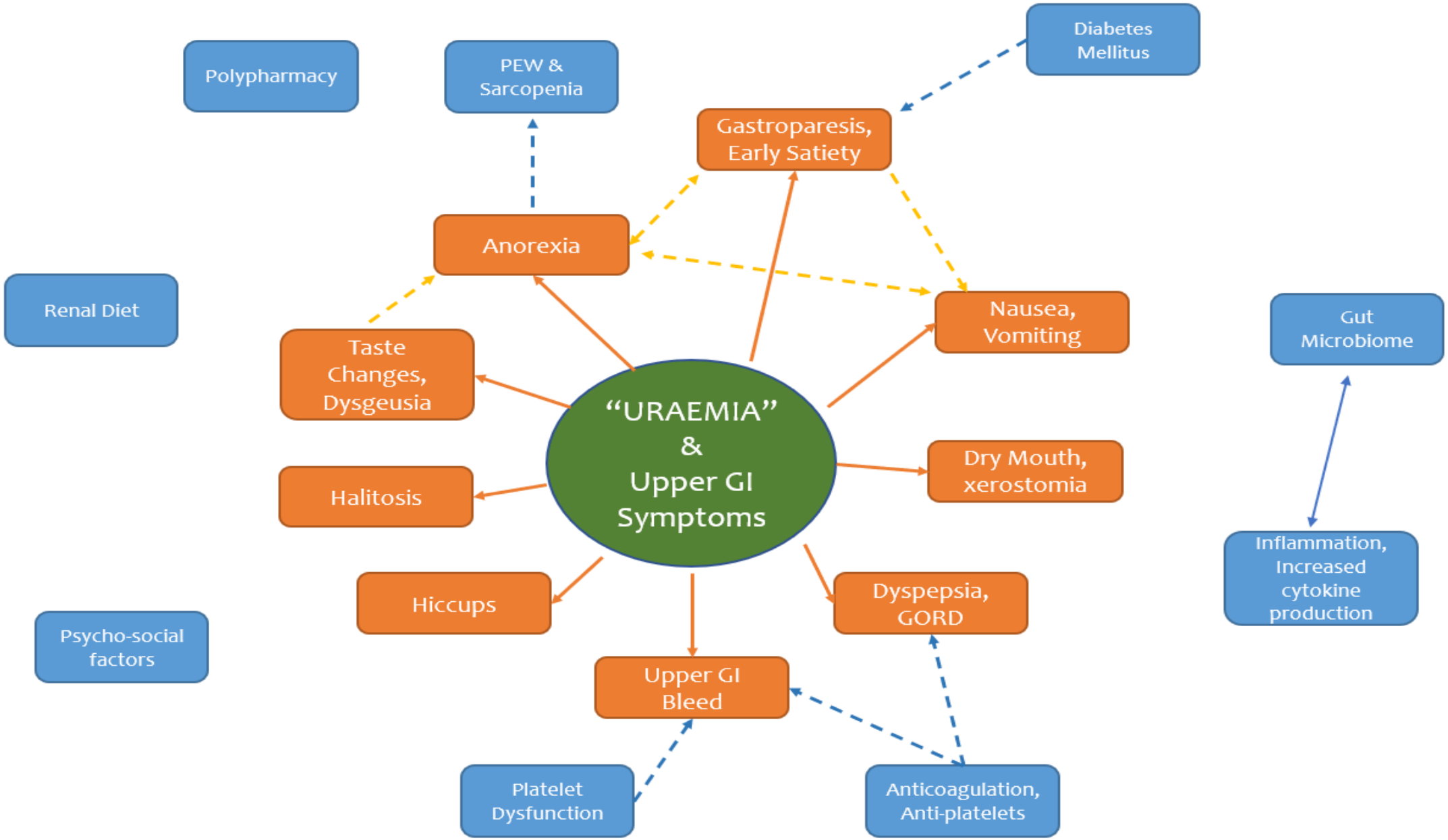


Fig. 1 Percentage of distribution of gastrointestinal system complaints and signs in patients with chronic kidney disease

Karahan D et al. Comparison of gastrointestinal symptoms and findings in renal replacement therapy modalities. BMC nephrology 2022.

How do we treat?...taking the pragmatic approach

- Management strategies depend on:
  - severity of symptoms
  - level of distress to patient
  - what is reversible?
  - does the potential treatment align with patient goals of care?


Polypharmacy
PEW & Sarcopenia
Diabetes Mellitus
Gastroparesis, Early Satiety
Anorexia
Renal Diet
Nausea, Vomiting
Gut Microbiome
Taste Changes, Dysgeusia
"URAEMIA" & Upper GI Symptoms
Dry Mouth, xerostomia
Halitosis
Inflammation, Increased cytokine production
Hiccups
Dyspepsia, GORD
Psycho-social factors
Upper GI Bleed
Platelet Dysfunction
Anticoagulation, Anti-platelets

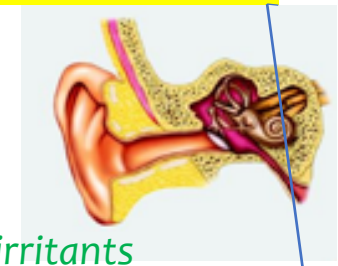
Nausea and Vomiting

What does the patient mean?

H1, ACh

Motion, opioids, base of skull tumours

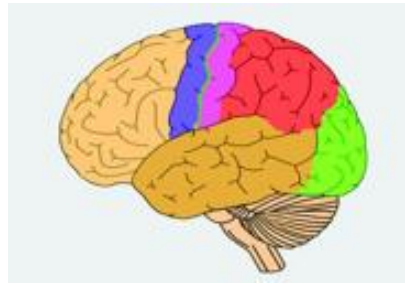
Vestibular system



GABA, H1, 5HT, NK1

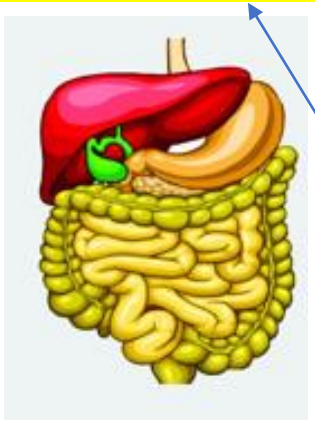
Pain, fear, raised ICP

Cerebral Cortex



Gastric stasis, visceral/serosal stretch, irritants

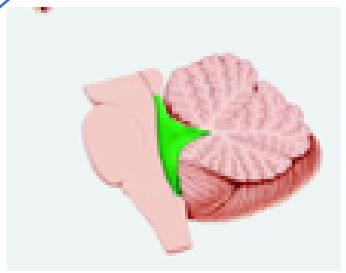
GI Tract



Vagus nerve

***Uraemia,** drugs, metabolic changes*

Chemoreceptor Trigger zone (CTZ)



D2, 5HT3, NK1, a2

5HT4, D2, 5HT3, ACh

Vomiting Centre

Raised ICP, meningeal irritation

H1, ACh, 5HT2, NK1, mu

Management summary

1) Non-pharmacological strategies
    - Small frequent meals, bland food, ginger, liberalise diet if possible, regular sodium bicarbonate mouthwash, review medications, head of bed elevated, relaxation techniques

2) Pharmacotherapy
    - **Start low and go slow**
    - Consider the aetiology; although often multi-factorial
    - Think about drug interactions and patient co-morbidities
    - Think about associated symptoms e.g. GORD/dyspepsia

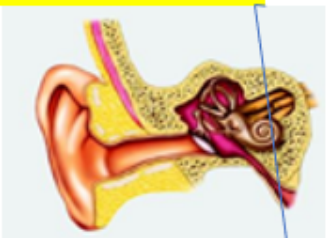
Hardy, *J et al.* A randomized open-label study of guideline-driven antiemetic therapy versus single agent antiemetic therapy in patients with advanced cancer and nausea not related to anticancer treatment. BMC cancer 2018.
Ljutić D et al. Comparison of ondansetron with metoclopramide in the symptomatic relief of uremia-induced nausea and vomiting. *Kidney Blood Press Res*. 2002;25(1):61-64.

H1, ACh

Motion, opioids, base of skull tumours

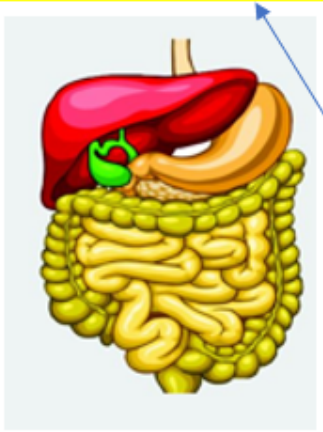
Vestibular system

cyclizine



Gastric stasis, visceral/serosal stretch, irritants

GI Tract



Vagus nerve

5HT4, D2, 5HT3, ACh

domperidone, metoclopramide, Cyclizine, ondansetron

Vomiting Centre

Raised ICP, meningeal irritation

H1, ACh, 5HT2, NK1, mu

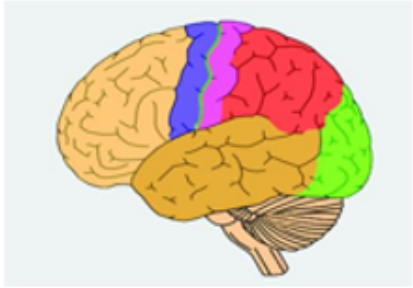
cyclizine, levomepromazine

GABA, H1, 5HT, NK1

Pain, fear, raised ICP

Cerebral Cortex

cyclizine



Uraemia, drugs, metabolic changes

Chemoreceptor Trigger zone (CTZ)

D2, 5HT3, NK1, a2

domperidone, metoclopramide, Aprepitant, ondansetron

Pharmacotherapy

Drug	Main Actions	Cautions
Domperidone	CTZ and peripheral D2 antagonist, 5HT4 agonist *10 mg tds*	QTc, avoid in BO
Metoclopramide	CTZ and peripheral D2 antagonist, 5HT4 agonist, 5HT3 antagonist as dose increased *5-10 mg tds*	QTc, Avoid in Parkinson's disease, EPS
Haloperidol	Highly potent D2 antagonist at CTZ, lesser peripheral effects *0.5 mg bd*	QTc, EPS
Cyclizine	H1 and Ach antagonist, slows gut transit (reduces colic) 12.5/25/50 mg tds	Sedation, dry mouth
Ondansetron	5-HT3 antagonists	Constipating

BO=bowel obstruction

Polypharmacy

What can we safely stop?

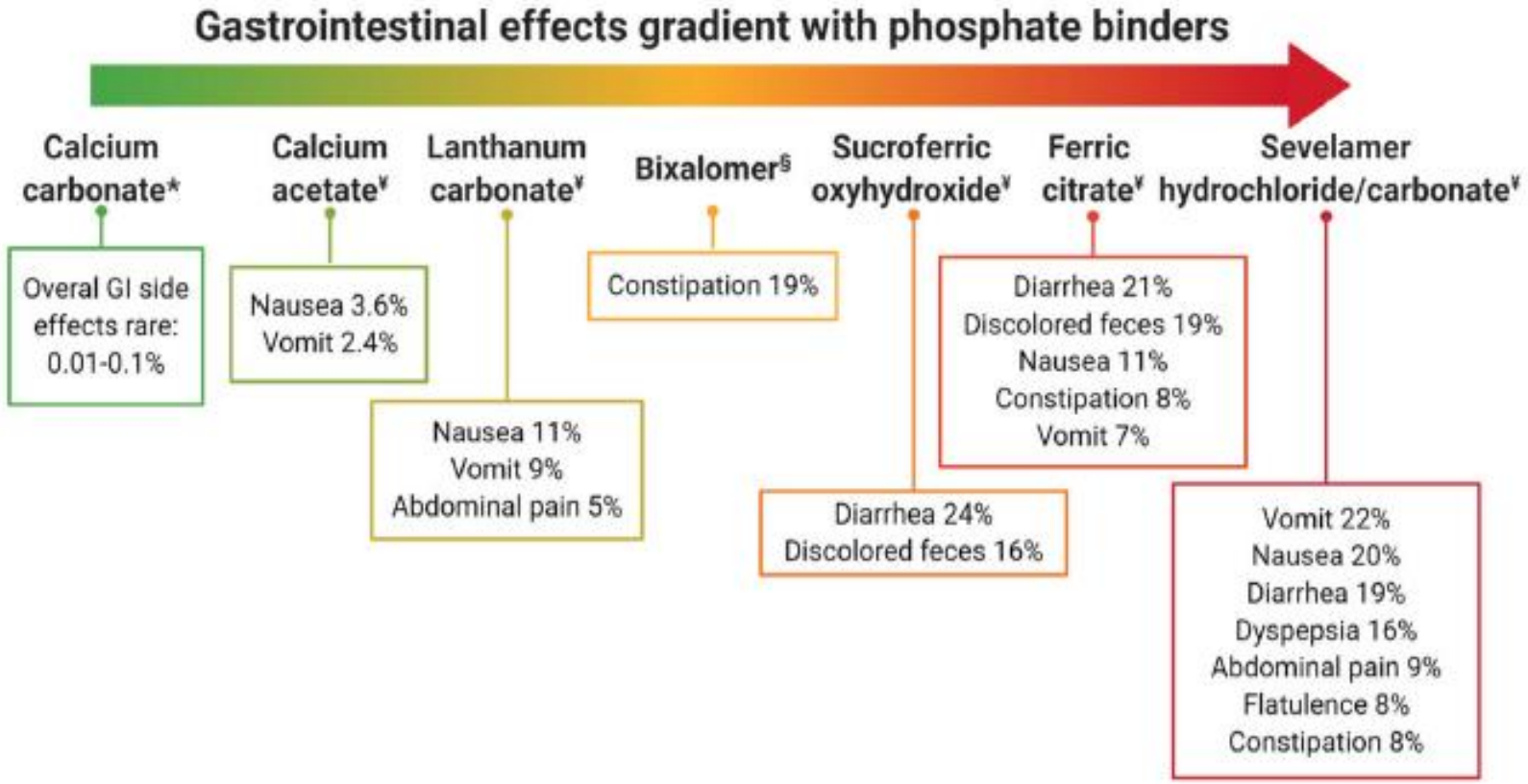
Roux-Marson et al. Medication burden and inappropriate prescription risk among elderly with advanced CKD. BMC Geriatrics 2020.
Schmidt et al. Patterns of medication use and the burden of polypharmacy in patients with CKD: the German Chronic Kidney Disease study. CKJ 2019.

- Median of 8 regular medications, range 7-11 (Roux-Marson et al)
  - Incorrect dosing and inappropriate prescribing common
  - Other studies suggest median of 12 medications for patients on dialysis

- Older patients with CKD 3-10 x more likely to experience adverse drug effects

- Avoid the **'prescribing cascade'**

Roux-Marson et al. Medication burden and inappropriate prescription risk among elderly with advanced CKD. BMC Geriatrics 2020.
Schmidt et al. Patterns of medication use and the burden of polypharmacy in patients with CKD: the German Chronic Kidney Disease study. CKJ 2019.
Qato D et al. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. JAMA. 2008.
Cardone KE, Bacchus S, Assimon MM, Pai AB, Manley HJ. Medication-related problems in CKD. Adv Chronic Kidney Dis. 2010



Biurete A et al. Feeling gutted in CKD: gastrointestinal disorders and therapies to improve gastrointestinal health in individuals CKD, including those undergoing dialysis. Semin Dial 2023.

Drug causes of nausea/vomiting

Mechanism	Drugs
Gastric Irritation	Antibiotics, steroids, Iron supplements, NSAIDs, Spironolactone, phosphate binders, sodibic, cinacalcet
Gastric Stasis	Antimuscarinics, opioids
CTZ	Antibiotics, opioids, cytotoxics, digoxin, dopamine agonists
5HT3 receptor stimulation	Antibiotics, SSRI's, cytotoxics

Douglas C. Management of nausea and vomiting in patients with CKD. NHS Tayside

Case 1

- 45-year-old man
- T1 DM since age 17
- Partially sighted, autonomic and peripheral neuropathy
- CKD stage 5 on HD

- Reflux, nausea and vomiting, especially after meals

Anti-emetic of choice?

Case 2

- 56-year-old lady on HD
- Recent CVA
- Significant nausea on movement since CVA, affecting ability to dialyse and to travel for dialysis.
- Very anxious

Anti-emetic of choice?

- Thinking outside the box…
  - If anxiety or anticipatory nausea/vomiting → consider an SSRI, prn Lorazepam
- Intractable nausea: Levomepromazine
- Dyspepsia/GORD: antacids, PPI, H2 antagonists

Anorexia

- Estimated to affect 25-60% of CKD patients.
- Altered levels of satiety hormones e.g. leptin, ghrelin
- Can contribute to protein energy wasting (PEW)
  - Associated with morbidity and mortality
  - CKD 3–5 patients showed 11–54% PEW prevalence

Stevenson J et al. Nutrition in RSC. Nephrology 2017.

Protein Energy Wasting

- *"loss of body protein mass and fuel reserves in patients with CKD and ESKD" (ISRNM, 2007)*
- Distinct but overlapping definition with disease related malnutrition
- Renal priority v Nutritional priority

Serum chemistry Serum albumin <3.8 g/dL, transthyretin (pre-albumin) <30 mg/dL (in dialysis patients)
BMI <23 kg/m^2 5% weight loss over 3 months or 10% over 6 months Total body fat percentage <10%
Muscle mass loss 5% reduction in muscle mass over 3 months or 10% over 6 months Reduced mid arm muscle circumference by 10% in relation to 50th percentile Lower than expected serum creatinine
Deficient dietary intake <0.8 g/kg/day of protein for at least 2 months in dialysis patients <25 kcal/kg/day for at least 2 months
PEW, protein-energy wasting; CKD, chronic kidney disease; BMI, body mass index.

Piccoli GB et al. Nutritional status and the risk of malnutrition in older adults with CKD – implications for low protein intake and nutritional care: A critical review endorsed by ERN-ERA and ESPEN. Clinical Nutrition 2023.
Ramy M et al. A Practical Approach to Nutrition, Protein-Energy Wasting, Sarcopenia, and Cachexia in Patients with Chronic Kidney Disease. *Blood Purif* 28 February 2020

Gastroparesis

stomach paralysis

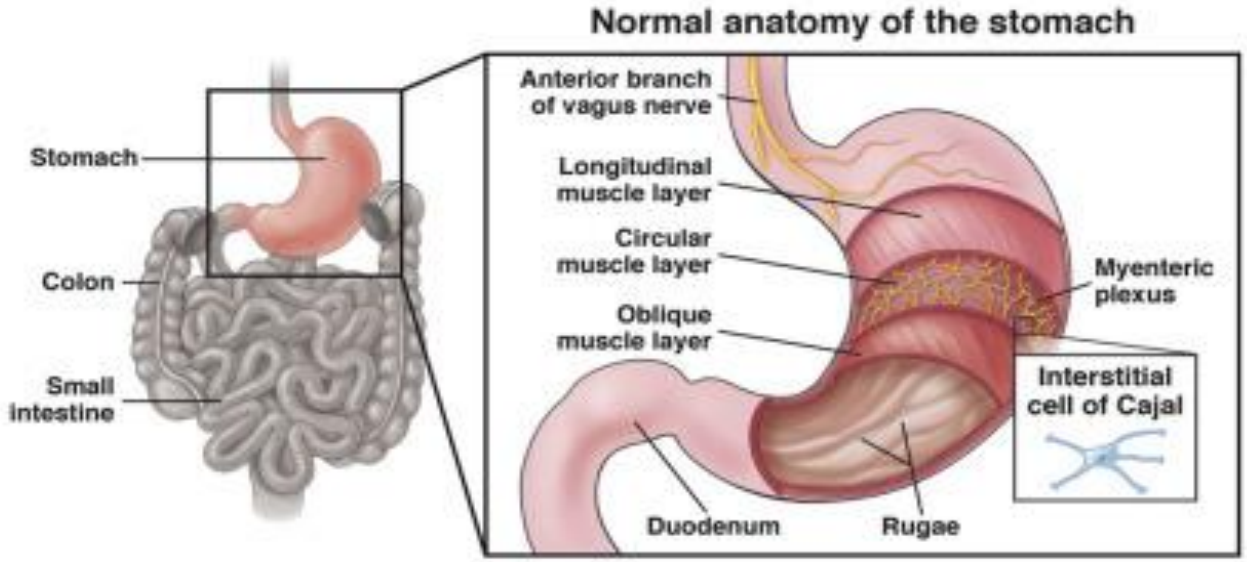
"delayed gastric emptying in the absence of a mechanical obstruction and symptoms suggestive of retained food in the stomach"

- Diabetes, one of the most common causes.
  - reduced smooth muscle contractility secondary to autonomic dysfunction

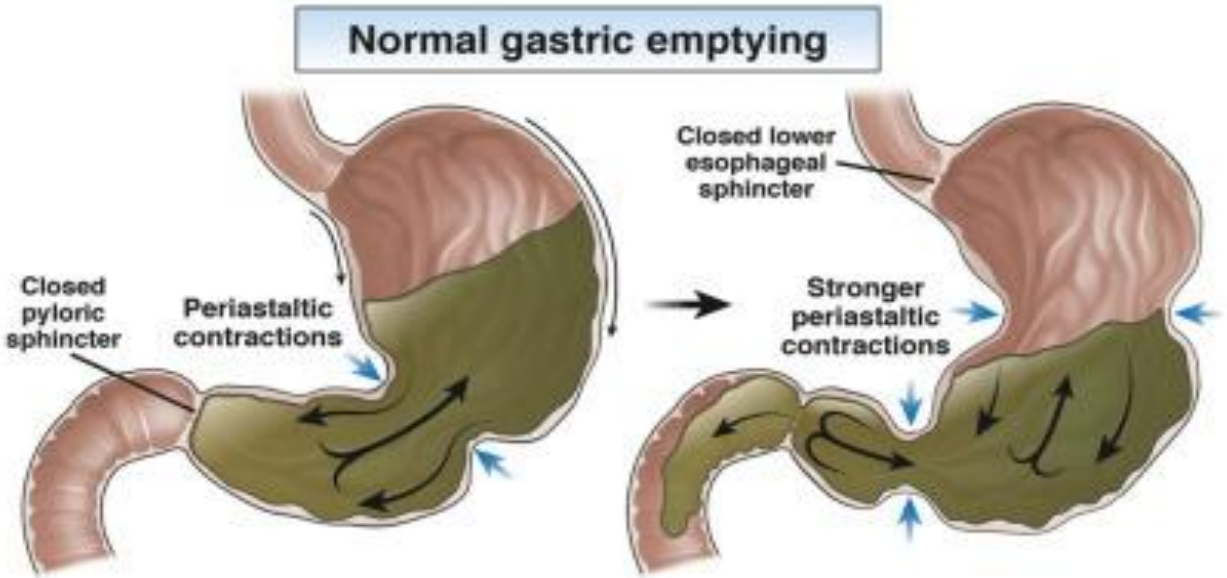
Causes of gastroparesis

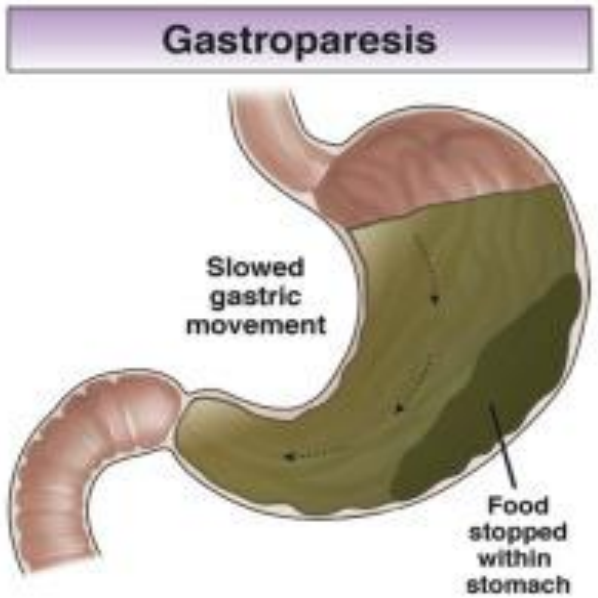
Causes	Details
Idiopathic	Most common cause
Diabetes Mellitus	Most common and severe in type 1
Rheumatological disease	Amyloidosis, Scleroderma
Autoimmune	Autoimmune gastrointestinal dysmotility
Neurological	Parkinson's disease, MS, brainstem CVA or tumour, autonomic neuropathy
Trauma	Spinal cord injury
Viral infections	e.g. Rotavirus
Medications	e.g. opiates, cyclosporine, dopamine agonists, phenothiazines, octreotide, a2-agonists, TCA's, ca-channel blockers, GLP-1 agonists, Li, progesterone

Reddivari AKR, Mehta P. Gastroparesis. [Updated 2022 Sep 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023



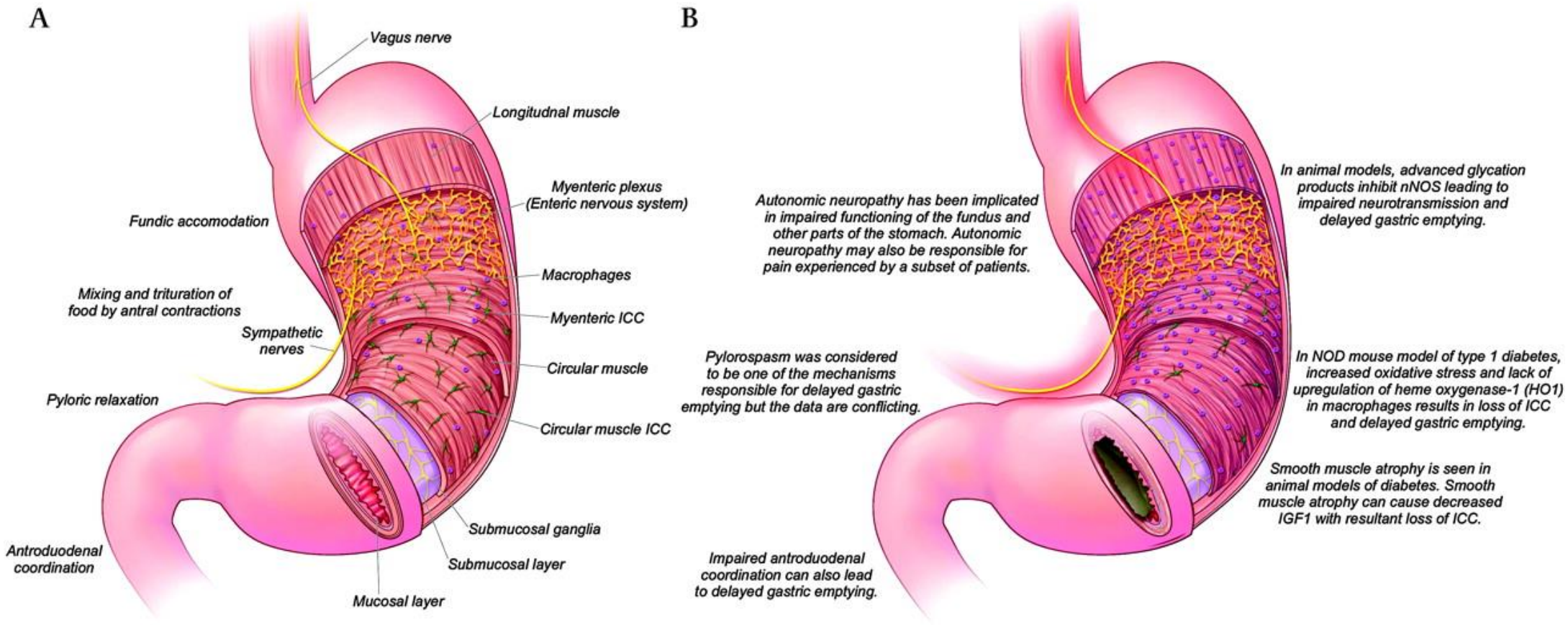
- nausea, vomiting
- early satiety
- weight loss
- post prandial fullness
- epigastric tenderness
- bloating
- anorexia
- GORD





https://patient.gastro.org/gastroparesis

Pathophysiology, diabetic gastroparesis



Kashyap P, Farrugia G. Diabetic gastroparesis: what we have learned and had to unlearn in the past 5 years. *Gut* 2010

CKD and gastroparesis

- Multiple studies have shown abnormal UGI motility in patients with CKD

- SR in 2022 – looking at CKD and gastroparesis
  - delayed gastric emptying common
  - pathophysiological mechanisms – electrolyte imbalance, direct toxicity of uremic retention molecules, altered levels of hormones including **gastrin**, **cholecystokinin** which modulate GI motility and glucagon which helps regulate satiety

Guelli, et al MO558: Chronic Kidney Disease and Gastroparesis: What is the Association?, *Nephrology Dialysis Transplantation*, Volume 37, Issue Supplement_3, May 2022.
Grant C et al. Patients with CKD have abnormal upper GIT digestive function: A study of uremic enteropathy. Gastroenterology and Hepatology 2017.
De Schoenmakere G et al. Relationship between gastric emptying and clinical and biochemical factors in chronic HD patients. NDT 2001.

What can be done?

- Optimise BSL control
- Small regular meals
- Avoid foods that take longer to digest e.g. fatty foods, high protein
- Consume drinks away from meals

- Domperidone, Metoclopramide, Nizatidine
  - macrolides

- Newer drugs
  - Aprepitant, Relamorelin – ghelin receptor agonist, trazpiroben – dopamine D2/D3 receptor antagonist

Zheng T et al. A Randomized, Controlled Trial of Efficacy and Safety of Cannabidiol in Idiopathic and Diabetic Gastroparesis. Clin Gastroenterol Hepatol. 2023.
Camilleri M, Zheng T. Cannabinoids and the Gastrointestinal Tract. Clin Gastroenterol Hepatol. 2023.
Zheng et al. Management of gastroparesis. Gastroenterology and Hepatology 2021.

Is there a role for cannabis?

- Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and well-described phytocannabinoids.

- G-protein coupled cannabinoid CB1 and CB2 receptors
- Abundant throughout the body

    - THC is the primary psychoactive component of cannabis and is a partial agonist to CB1 and CB2 receptors
    - CBD is non-intoxicating. Little affinity for these receptors, acts as a negative allosteric modulator of CB1 with pharmacological effects on other receptor systems including GPR55, TRPV1, 5HT1A

Worth H et al. Cannabinoids for symptom management in patients with kidney failure. A narrative review. CJASN 2022
Kliuk-Ben Bassat O et al. Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study. *Clin Kidney J*. 2022;16(4):701-710
Rein JL. The nephrologist's guide to cannabis and cannabinoids. Curr Opin Nephrol Hypertens. 2020 Mar;29(2):248-257
Ho C, Martinusen D, Lo C. A Review of Cannabis in Chronic Kidney Disease Symptom Management. Can J Kidney Health Dis. 2019
Zheng T et al. A Randomized, Controlled Trial of Efficacy and Safety of Cannabidiol in Idiopathic and Diabetic Gastroparesis. Clin Gastroenterol Hepatol. 2023.

Clinical Kidney Journal, 2023, vol. 16, no. 4, 701–710

https://doi.org/10.1093/ckj/sfac275
Advance Access Publication Date: 23 December 2022
Original Article

ORIGINAL ARTICLE

Medical cannabis for pain management in patients undergoing chronic hemodialysis: randomized, double-blind, cross-over, feasibility study

Orit Kliuk-Ben Bassat[1,2], Meir Schechter[3,4], Natalia Ashtamker[5], Ilan Yanuv[3,4], Aliza Rozenberg[3,4], Boaz Hirshberg[5], Ayelet Grupper[1,2], Nachum Vaisman[2,6], Silviu Brill[2,7,*] and Ofri Mosenzon[3,4,*]

- No difference in adverse effects between groups
- Study not powered to assess efficacy

Szepietowski JC, Szepietowski T, Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. Acta Dermatovenerol Croat. 2005

Systematic **E**valuation of **I**nterventions for **S**ymptom **M**anagement **I**n **C**hronic kidney disease: **C**anna**B**i**Diol** (SEISMIC: CBD)

- A prospective, single-arm, open-label, dose titration and safety study.
- The study consists of a 6-week treatment period with CBD (given as oral, fast dissolving wafers).
- The dosing will slowly increase until the participant finds the amount that best helps their symptoms.

Thank you