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GUIDELINE OPEN ACCESS

European Guideline on Chronic Nausea and Vomiting—A UEG and ESNM Consensus for Clinical Management

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Abbreviations: CBT, cognitive behavioural therapy; CHS, cannabinoid hyperemesis syndrome; CIPO, chronic intestinal pseudo-obstruction; CNVS, chronic nausea and vomiting syndrome; CT, computed tomography; CVS, cyclic vomiting syndrome; EGG, electrogastrography; EMG, electromyography; ENS, enteric nervous system; FLIP, functional luminal imaging probe; GERD, gastroesophageal reflux disease; GES, gastric electrical stimulation; GI, gastrointestinal; HRIM, high-resolution manometry with impedance; HRQOL, health-related quality of life; IBS, irritable bowel syndrome; ICCs, interstitial cells of Cajal; LOS, lower oesophageal sphincter; MRI, magnetic resonance imaging; N&V, nausea and vomiting; NK-1, neurokinin-1; POTS, postural orthostatic tachycardia syndrome; PPI, proton pump inhibitors; R1, first voting round; R2, second voting round; SBO, small bowel obstruction; TCA, tricyclic antidepressant; THC, tetrahydrocannabinol.

The full list of members and affiliations of the Working Group is provided the Supplementary Material.

For a complete list of the International Working Group for the European Guideline on Chronic Nausea and Vomiting, see the Acknowledgments section.

[Correction added on 10 January 2025, after first online publication: The author name 'Luis Gerardo Alcalá-González' has been corrected.]

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ABSTRACT

Introduction: Chronic nausea and vomiting are symptoms of a wide range of gastrointestinal and non-gastrointestinal conditions. Diagnosis can be challenging and requires a systematic and well-structured approach. If the initial investigation for structural, toxic and metabolic disorders is negative, digestive motility and gut-brain interaction disorders should be assessed. United European Gastroenterology (UEG) and the European Society for Neurogastroenterology and Motility (ESNM) identified the need for an updated, evidence-based clinical guideline for the management of chronic nausea and vomiting.

Methods: A multidisciplinary team of experts in the field, including European specialists and national societies, participated in the development of the guideline. Relevant questions were addressed through a literature review and statements were developed and voted on according to a Delphi process.

Results: Ninety-eight statements were identified and voted following the Delphi process. Overall agreement was high, although the grade of scientific evidence was low in many areas. Disagreement was more evident for some pharmacological treatment options. A diagnostic algorithm was developed, focussing on the differentiating features between gastrointestinal motility and gut-brain interaction disorders with predominant nausea and vomiting.

Conclusion: These guidelines provide an evidence-based framework for the evaluation and treatment of patients with chronic nausea and vomiting.

1 | Introduction

Nausea and vomiting are symptoms that commonly prompt visits to the gastrointestinal (GI) specialist and general practitioner [1, 2]. They are generally transient conditions that rapidly subside; however, in a minority of patients, persist more than 4 weeks and become a chronic disorder. The differential diagnosis of chronic nausea and vomiting is broad, and can range from organic and functional GI disorders to non-digestive aetiologies. United European Gastroenterology (UEG) and the European Society for Neurogastroenterology and Motility (ESNM) identified the need to develop an updated, comprehensive clinical guideline on chronic nausea and vomiting, motivated by recent advances in the scientific knowledge of specific causes of nausea and vomiting such as cyclic vomiting syndrome, rumination syndrome, and chronic nausea and vomiting syndrome.

This European Guideline aims to provide a well-structured approach to harmonizing the diagnosis and management of chronic nausea and vomiting. It has been developed through the concerted effort of gastroenterologists, surgeons and primary care physicians from the ESNM and three other member societies: EAGEN (European Association for Gastroenterology, Endoscopy and Nutrition), EDS (European Digestive Surgery) and ESCPG (European Society for Primary Care Gastroenterology).

2 | Methods

The UEG/ESNM began a Delphi process to develop consensus statements on chronic nausea and vomiting in collaboration with other European societies, applying the adapted RAND/UCLA modified Delphi panel method [3, 4], which is a modification of the Delphi procedure combined with the "nominal group" technique [5, 6]. This method is based on current scientific evidence and the collective judgement of a panel of experts and aims to determine a consensus for complex conditions for which evidence from controlled trials is scarce [7]. The main steps in the process were: (1) the selection of a working group of five UEG/ESNM members with expertise in nausea and vomiting disorders and the Delphi consensus process; (2) the development of 54 clinically relevant questions for our target population, that is, gastroenterology patients and healthcare providers [8]; (3) the selection of a European Working Group consisting of experts in chronic nausea and vomiting from different European countries; (4) a literature review to answer each question and drafting of statements summarizing the evidence; (5) two rounds of blinded voting of the statements and (6) grading of strength using accepted criteria. For the working group, UEG/ESNM board members nominated experts from their respective specialist and national societies for participation: EAGEN (European Association for Gastroenterology, Endoscopy and Nutrition), EDS (European Digestive Surgery), ESCPG (European Society for Primary Care Gastroenterology), the Polish National Society, the Romanian National Society, SEPD and AEG (Spanish National GI societies), and the Croatian National Society. A total of 35 experts from 13 European countries agreed to participate (Supplementary Table S1). All members had outstanding experience and expertise in general clinical practice, gastroenterology, and GI motility. All experts submitted a conflict-of-interest statement by November 2022. Using the PICO process, the six members of the Core Group identified 54 clinical questions (Supplementary Table S2) that were distributed among the Working Group. Each expert carried out a structured review of the literature based on specific search terms to answer each question using MEDLINE (accessed via PubMed), EMBASE, and the Cochrane Database of Systematic Reviews (Cochrane Library) until 16 November 2022. The type of studies included were systematic reviews with/without meta-analysis, randomized/non-randomized clinical trials, cohort studies and observational studies. Low quality

of evidence documents were excluded, such as expert opinion articles, case reports or preclinical studies. Based on the evidence in the literature, each expert formulated statements related to the assigned questions, which were then reviewed and validated by the Core Group. To assess the quality of the evidence used to formulate the statements, the grading of recommendations, assessment, development, and evaluation (GRADE) methodology was applied [9] (Supplementary Table S3). The final list of 94 statements was evaluated in a first voting round by all members in March 2023, where each member indicated their level of agreement with the statement using a 5-point Likert scale (1: totally disagree, 2: partially disagree, 3: neither agree nor disagree, 4: partially agree, 5: totally agree). The degree of agreement for each statement was measured using the following criteria [3–6]. Agreement: when more than two-thirds of the panellists voted in the same range (either lower [1-2] or upper range [4-5]). Disagreement: when the median was in the lower (1–2) or upper range (4–5), but one-third or more of the panel voted in the opposite range; or if the median was 3 but one third or more of the panel voted in the lower (1-2) or upper range (4–5). Neutral: when the median was 3 and less than one third of the panel voted in the lower (1–2) or upper range (4–5). Statements that reached agreement were considered appropriate for clinical management when the median was in the upper range (4–5) and inappropriate when the median was in the lower range (1–2). If agreement was not reached, appropriateness was considered uncertain. Participants were blinded to the votes of other participants and made suggestions to improve the clarity of the statements. After the first round of voting, the statements and recommendations were revised by the Core Group. Nine statements were subjected to a second round of blinded voting due to lack of agreement. A Delphi analysis report was then generated. Finally, a manuscript was drafted and reviewed by the Core Group for final approval.

The manuscript is divided in three sections. The first section includes statements on the most common secondary causes of chronic nausea and vomiting that should be evaluated at the beginning of diagnostic process (Table 1). The second section comprises statements on nausea and vomiting related to oesophageal, gastric, and intestinal motility disorders, while the third is dedicated to disorders of gut-brain interaction associated with nausea and vomiting including cyclic vomiting syndrome, cannabinoid hyperemesis syndrome, chronic nausea and vomiting syndrome, and rumination syndrome (Figure 1). These motility and gut-brain interaction disorders often involve referral and management at specialized gastroenterological centres.

3 | Summary of Recommendations

	Level of evidence	Level of agreement*	Agreement achieved
Section 1. Secondary chronic nausea and vomiting			
Statement 1. In the evaluation of patients with chronic nausea and vomiting, endocrine and metabolic causes should be excluded.	Low	94%	Yes
Statement 2. Chronic nausea and vomiting may be caused by gastrointestinal mucosal inflammation due to pharmacological toxicity, immune-mediated disorders, or infectious diseases.	Moderate	91%	Yes
Statement 3. Gastrointestinal obstruction should be excluded in patients with chronic nausea and vomiting.	Low	85%	Yes
Statement 4. In patients with chronic nausea and vomiting, current medications should be reviewed to exclude pharmacological causes.	Moderate	94%	Yes
Statement 5. Injuries to the vagal nerve may cause chronic nausea and vomiting following cardiac, thoracic, or abdominal interventions.	Low	85%	Yes
Statement 6. Autonomic dysfunction should be considered in patients with chronic nausea and vomiting. Other symptoms that may suggest dysautonomia include orthostatic hypotension and sweating abnormalities.	Low	79%	Yes
Statement 7. Vestibular disorders may be a cause of chronic nausea and vomiting.	Low	94%	Yes
Statement 8. Vestibular disorders should be considered if chronic nausea and vomiting are accompanied by dizziness and/or vertigo, headache, hearing loss, tinnitus, impaired vision, focal weakness, and difficulty walking.	Low	91%	Yes
Statement 9. Intracranial hypertension can cause chronic nausea and vomiting.	Low	91%	Yes
Statement 10. Signs and symptoms that suggest intracranial hypertension as the cause of chronic nausea and vomiting are headache, visual disorders, vertigo, tinnitus, stiff neck, and/or focal neurologic deficits.	Low	94%	Yes
Statement 11. Patients with anxiety and depression may manifest nausea and vomiting as somatic symptoms of psychological dysfunction.	Moderate	85%	Yes

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	Level of evidence	Level of agreement*	Agreement achieved
Statement 12. Nausea and vomiting are symptoms of eating disorders and may be self-induced or occur as a manifestation of an associated gastrointestinal functional or motility disorder.	Moderate	91%	Yes
Statement 13. In patients with advanced cancer, chronic nausea and vomiting may be caused by antineoplastic agents and radiation therapy; biochemical abnormalities; impaired gastric emptying; visceral and serosal causes of delayed gastrointestinal transit; cranial, vestibular, and cortical causes.	Very low	91%	Yes
Section 2. Motility disorders			
Statement 14. Chronic nausea and vomiting are not characteristic clinical features of primary oesophageal motility disorders. Regurgitation should be differentiated from vomiting.	Very low	91%	Yes
Statement 15. In patients consulting for chronic nausea and vomiting, testing for oesophageal motility disorders (manometry) is recommended only if oesophageal symptoms (regurgitation, dysphagia) are present and structural disease has been ruled out.	Low	88%	Yes
Statement 16. When an oesophageal motility disorder is suspected in patients with regurgitation, and/or vomiting, high-resolution manometry should be performed after ruling out mechanical obstruction. Complementary tests, as high-resolution impedance manometry, barium oesophagogram or endoscopic impedance planimetry FLIP may be useful in complex cases.	High	94%	Yes
Statement 17. Chronic nausea and vomiting are frequent symptoms in patients with gastric motility disorders, but pain, early satiety, postprandial fullness and bloating may dominate the clinical picture in many patients.	Moderate	85%	Yes
Statement 18. In patients with chronic nausea and vomiting, a gastric motility disorder may be suspected, especially when associated with diseases or medications that are associated with abnormal gastric emptying.	Moderate	76%	Yes
Statement 19. A gastric emptying test is necessary to establish a diagnosis of gastroparesis in patients with unexplained chronic nausea and vomiting.	Moderate	91%	Yes
Statement 20. Valid methods to measure solid gastric emptying in patients with unexplained chronic nausea and vomiting are scintigraphy and octanoic acid breath tests.	Moderate	94%	Yes
Statement 21. Chronic nausea and vomiting may be characteristic clinical features of intestinal motility disorders, particularly when in presence of concomitant gastric and/or lower GI tract motility disorders.	Low	88%	Yes
Statement 22. Dilated small bowel loops suggest an intestinal motor disorder in patients with chronic nausea and vomiting.	Low	85%	Yes
Statement 23. Patients with confirmed intestinal motility disorders without bowel dilatation may be characterised by chronic abdominal pain.	Low	76%	Yes
Statement 24. Intestinal motility tests (i.e., scintigraphy, stable isotope breath tests, wireless motility capsule, intestinal manometry, abdominal MRI) may be advised in patients with signs of intestinal dysmotility without obstructive or mucosal disorders.	Very low	79%	Yes
Section 3. Disorders of gut-brain interaction			
Cyclic vomiting syndrome			
Statement 25. Cyclic vomiting syndrome (CVS) refers to recurrent, regular, and stereotypical episodes of nausea and severe vomiting separated by symptom-free intervals. CVS can be diagnosed only in the absence of other causes (organic or metabolic) that can explain the symptoms.	Moderate	88%	Yes
Statement 26. CVS (defined according to Rome IV) affects about 0.1%-2% of the adult population.	Low	88%	Yes

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	Level of evidence	Level of agreement*	Agreement achieved
Statement 27. Incidence and prevalence of CVS decrease with age. Accordingly, the prevalence of CVS is higher in children than in adults. Prevalence in children reaches 0.2%-6.2% (also including studies using Rome III for definition).	Moderate	79%	Yes
Statement 28. Typical characteristics suggesting CVS are the onset of episodes early in the morning, episodes lasting at least 48 h, and occurring two or fewer times per month.	Moderate	76%	Yes
Statement 29. A CVS episode typically has four phases: The prodromal phase, the vomiting phase, the recovery phase, and the inter-episodic or asymptomatic phase.	Moderate	91%	Yes
Statement 30. During the prodromal phase of a CVS episode, patients often experience nausea, sweating, irritability, abdominal pain, fatigue, temperature changes, or insomnia.	Moderate	82%	Yes
Statement 31. The vomiting phase of a CVS episode is characterized by intense vomiting, often bilious, and accompanied by disabling nausea and retching. Abdominal pain is often present and may be severe. Accompanying symptoms may include pallor, listlessness, anorexia, headache, photophobia, low-grade fever, or hypothermia.	Moderate	94%	Yes
Statement 32. Symptoms resolve during the recovery phase of a CVS episode.	Moderate	88%	Yes
Statement 33. No vomiting is present during the inter-episodic phase of a CVS episode, patients may be completely asymptomatic with regard to the GI system or may have milder GI symptoms.	Moderate	91%	Yes
Statement 34. Symptoms can be triggered by psychological and physical stress.	Moderate	91%	Yes
Statement 35. Pathogenesis of CVS is multifactorial.	High	91%	Yes
Statement 36. Psychosocial factors are involved in the pathogenesis of CVS.	High	88%	Yes
Statement 37. Gastric emptying is accelerated in the majority of patients with CVS, most of the other patients have normal gastric emptying. In a minority gastric emptying may be (intermittently) delayed. In these, gastroparesis is an important differential diagnosis.	Moderate	74%	Yes
Statement 38. Genetic factors may be involved in CVS.	Moderate	74%	Yes
Statement 39. Neurohormonal factors are involved in the pathogenesis of CVS.	Moderate	79%	Yes
Statement 40. The prevalence of migraine in paediatric and adult CVS patients ranges from about 40% to 70%. About the same percentage of CVS patients have a family history of migraine.	Moderate-low	91%	Yes
Statement 41. Both, unique and potentially shared, pathophysiologic mechanisms have been observed for CVS and migraine (e.g., regarding genetic background, brain morphology, and function). Therefore, they are considered associated comorbidities but separate entities.	Moderate-low	88%	Yes
Statement 42. There is an overlap between CVS, functional dyspepsia, and irritable bowel syndrome.	Moderate-low	87%	Yes
Statement 43. Very little is known about the specific impact of CVS on adults' and children's psychosocial function.	Low	75%	Yes
Statement 44. We recommend that the diagnosis of CVS is based on clinical presentation and relies on the criteria presented in statements 1 and 4-9 of the CVS section (in analogy to Rome IV criteria).	High	70%	Yes
Statement 45. We recommend that patients with CVS are treated holistically, taking into account lifestyle changes, psychological support, and avoidance of trigger factors.	Very low	79%	Yes
Statement 46. Pharmacological treatment of CVS can be categorized into three groups: Abortive, supportive, and prophylactic therapy.	Moderate	82%	Yes

(Continues)

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	Level of evidence	Level of agreement*	Agreement achieved
Statement 47. We recommend that benzodiazepines and antiemetics, including ondansetron, triptans, and aprepitant are used during the prodromal phase to stop an episode of CVS and prevent vomiting.	Moderate	91%	Yes
Statement 48. We recommend that during the vomiting phase energy, fluid, and electrolyte deficits are substituted intravenously.	Moderate	82%	Yes
Statement 49. We recommend that antiemetics, antianxiety medications, and analgesics should be used as needed during the vomiting phase to ameliorate symptoms.	Moderate	94%	Yes
Statement 50. We suggest that opioids are avoided because they may have a sensitizing effect in migraine analgesia.	Moderate	94%	Yes
Statement 51. We suggest that tricyclic antidepressants are used as first-line therapy for prophylaxis of CVS episodes.	Moderate	85%	Yes
Statement 52. We suggest that as second-line therapy for prophylaxis of CVS episodes the following substances are used: zonisamide/levetiracetam, L-Carnitine, coenzyme Q10 and aprepitant.	Moderate	76%	Yes
Statement 53. We suggest that in patients with slow recovery from CVS attacks with symptoms preventing oral food intake for several days enteral or parenteral nutrition is initiated.	Very low	79%	Yes
Statement 54. Cannabinoid hyperemesis syndrome is a cyclic vomiting syndrome induced by high-dose, prolonged cannabis use. Cannabinoid hyperemesis syndrome and cyclic vomiting syndrome are two distinct entities.	Low	88%	Yes
Statement 55. We recommend that in all patients with suspected cyclic vomiting syndrome, a complete history of cannabis use is performed.	Low	94%	Yes
Statement 56. Cannabinoid hyperemesis syndrome is typically characterized by severe, cyclic episodes ($\geq$ 3/year) of nausea and vomiting with acute onset, and duration of less than a week, in patients with prolonged regular cannabis use (over 2 years).	Low	85%	Yes
Statement 57. We recommend that patients with cannabinoid hyperemesis syndrome undergo withdrawal of cannabis. This is the most effective treatment.	Low	94%	Yes
Statement 58. We suggest that in acute phases, patients are treated with benzodiazepines, haloperidol, and/or topical administration of capsaicin.	Low	82%	Yes
Rumination syndrome			
Statement 59. Rumination is a voluntary but unconscious process in which patients effortlessly bring up recently ingested food from the stomach into the mouth, where it is often then chewed again and re-swallowed.	Moderate	91%	Yes
Statement 60. The prevalence of rumination syndrome in the adult general population is likely between 0.5%-5.8% depending on the study population. It is higher in selected populations such as therapy refractory GERD, children, and adolescents.	Moderate	91%	Yes
Statement 61. Dyspeptic symptoms and minor weight loss are common in patients with rumination syndrome.	Very low	70%	Yes
Statement 62. Enhanced visceral pain perception and poor postprandial accommodation of the stomach have been proposed as the mechanisms for epigastric pain and the feeling of "bloating" in patients with rumination syndrome.	Very low	70%	Yes
Statement 63. The mechanism of rumination syndrome is a voluntary but unconscious process that generates a coordinated abdomino-thoracic muscle response consisting of increased intrabdominal pressure associated to low LOS and intrathoracic pressures.	Low	85%	Yes

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	Level of evidence	Level of agreement*	Agreement achieved
Statement 64. The triggering of rumination events is not completely clear but they may be secondary to dyspeptic symptoms as subject seek relief through regurgitation and/or venting.	Low	76%	Yes
Statement 65. Functional dyspepsia, gastroparesis, cyclic vomiting, and other disorders of gut-brain interaction can overlap and increase the likelihood of rumination syndrome.	Low	88%	Yes
Statement 66. Gastro-oesophageal reflux disease and pathological supragastric belching can be mechanisms that provoke and/or aggravate rumination syndrome. In cases of non-responsive gastroesophageal reflux disease, consideration should be given to rumination syndrome.	Low	85%	Yes
Statement 67. Rumination syndrome is independently associated with depression and anxiety. Patients with rumination syndrome have a lower physical and mental quality of life and increased somatic symptom reporting (somatization).	Moderate	88%	Yes
Statement 68. In patients with rumination syndrome, a current or previous associated eating or psychiatric disorder should be considered.	Low	88%	Yes
Statement 69. Combined clinical and objective assessment using high-resolution manometry impedance is recommended to confirm the diagnosis of rumination.	Low	76%	Yes
Statement 70. Diaphragmatic breathing with or without biofeedback (visual or verbal feedback on abdominal, intercostal, or diaphragm muscle activity using either electromyography or oesophageal impedance manometry) is the first-line therapy for rumination syndrome.	Moderate	85%	Yes
Statement 71. In patients with rumination syndrome pharmacological treatment with baclofen or tricyclic antidepressants can be used if diaphragmatic breathing/ biofeedback are not available or patient does not respond.	Low	85%	Yes
Statement 72. In patients with secondary rumination syndrome, it is necessary to treat underlying gastroesophageal reflux with PPI.	Low	82%	Yes
Statement 73. Although most patients with rumination syndrome have only modest weight loss, patient-tailored dietetic assessment for severe cases of rumination is indicated.	Low	85%	Yes
Chronic nausea and vomiting syndrome			
Statement 74. Chronic unexplained nausea is defined by the presence of bothersome nausea, at least twice per week on average, in the absence of abnormalities at upper endoscopy or other disease that explains nausea, with symptoms present the last 3 months and started at least 6 months ago.	High	88%	Yes
Statement 75. Chronic unexplained vomiting is diagnosed in patients who had on average at least one episode of vomiting per week, in the absence of an eating disorder, rumination, or major psychiatric disease, in absence of self-induced induced vomiting, chronic cannabinoid use, or abnormalities in the central nervous system or metabolic diseases likely to explain the recurrent vomiting, with symptoms present the last 3 months and started at least 6 months ago.	High	88%	Yes
Statement 76. Chronic nausea and vomiting syndrome, as defined according to the Rome IV criteria, has an estimated prevalence of 1%.	Low	94%	Yes
Statement 77. Chronic nausea and vomiting syndrome is characterized by continuous, non-episodic, symptoms of unexplained nausea and vomiting.	Moderate	85%	Yes
Statement 78. The development and maintenance of chronic nausea and vomiting syndrome is best explained by the biopsychosocial model of disease encompassing biological, psychological, and social aspects.	Moderate	88%	Yes
Statement 79. Independent factors associated with chronic nausea and vomiting syndrome are younger age, presence of IBS, and functional dyspepsia.	Moderate-low	91%	Yes

(Continues)

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	Level of evidence	Level of agreement*	Agreement achieved
Statement 80. Psychological distress with mood disorders, anxiety disorders, somatization disorders, and catastrophizing may be associated with chronic unexplained nausea and vomiting.	Low	91%	Yes
Statement 81. Chronic nausea and vomiting syndrome is diagnosed based on clinical criteria after previous exclusion of systemic, organic, or metabolic diseases by objective testing.	Low	88%	Yes
Statement 82. In refractory cases of chronic nausea and vomiting syndrome, gastric electrical stimulation can be considered.	Moderate	81%	Yes
Statement 83. Histamine H1 antagonists (e.g., meclizine, promethazine) are effective for the treatment of chronic nausea and vomiting.	Low	58%	No
Statement 84. Muscarinic M1 antagonists (e.g., scopolamine) are effective for the treatment of chronic nausea and vomiting.	Low	42%	No
Statement 85. Dopamine-2 antagonists are effective for the treatment of chronic nausea and vomiting.	Low	73%	Yes
Statement 86. 5-HT3 antagonists are effective for the treatment of chronic nausea and vomiting.	Low	70%	Yes
Statement 87. Tricyclic antidepressants are effective for the treatment of chronic nausea and vomiting.	Low	70%	Yes
Statement 88. Mirtazapine is effective for the treatment of chronic nausea and vomiting.	Low	76%	Yes
Statement 89. Gabapentin is effective for the treatment of chronic nausea and vomiting.	Low	35%	No
Statement 90. Olanzapine is effective for the treatment of chronic nausea and vomiting.	Low	61%	No
Statement 91. Cannabinoids are effective for the treatment of chronic nausea and vomiting.	Low	29%	No
Statement 92. NK-1 antagonists are effective for the treatment of chronic nausea and vomiting.	Low	70%	Yes
Statement 93. In patients with chronic nausea and vomiting syndrome, attention must be given to adequate nutrition, including vitamins and minerals.	Very low	94%	Yes
Statement 94. Nutritional deficits shall be corrected by dietary modifications and oral supplementation, if possible.	Very low	91%	Yes

*Proportion of panellists with level of agreement of 4 or 5 on the 5-point Likert scale (1: totally disagree, 2: partially disagree, 3: neither agree nor disagree, 4: partially agree, 5: totally agree).

4 | Results

4.1 | Section 1. Secondary Chronic Nausea and Vomiting

4.1.1 | Metabolic and Endocrine Disorders

Statement 1. In the evaluation of patients with chronic nausea and vomiting, endocrine and metabolic causes should be excluded.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Pregnancy is the most common endocrinologic cause of nausea and vomiting and must be considered in any woman of childbearing age. Other endocrine or metabolic aetiologies encompass diabetic ketoacidosis, uremia, hyperthyroidism, adrenal disorders, parathyroid disorders and paraneoplastic syndromes [1, 10–12]. Evaluation of endocrine/metabolic causes imply a blood test that will include thyroid assessment (TSH and T4), and other biochemical parameters: glucose, creatinine, calcium and phosphate, parathyroid hormone and blood urea nitrogen.

4.1.2 | Gastrointestinal Mucosal Inflammation

Statement 2. Chronic nausea and vomiting may be caused by gastrointestinal mucosal inflammation due to pharmacological toxicity, immune-mediated disorders, or infectious diseases.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

TABLE 1 | Causes of secondary chronic nausea and vomiting.

Endocrine/ metabolic	Pregnancy
	Metabolic acidosis
	Uraemia
	Hypercalcaemia
	Hyperthyroidism
	Adrenal disorders
	Parathyroid disorders
GI inflammation	Infectious
	Autoimmune
	Mucositis
Dysautonomia	Postural orthostatic tachycardia syndrome (POTS)
	Autoimmune dysautonomia
	Neurological disorders (Parkinson's disease, multiple system atrophy)
Pharmacological	Opioids
	GLP-1 agonists
	Dopaminergics
Low-grade GI obstruction	Radiation enteritis
	Adhesions
	Intestinal strictures
CNS disorders	Intracranial hypertension
	Migraine
	Hydrocephalus
Vestibular	Labyrinthine lesions
	Meniere's disease
Vagal nerve injury	Post-surgical
Psychiatric	Anxiety
	Depression
	Eating disorders
Malignancy-related	Chemotherapy
	Radiotherapy
	Disease-related complications

Abbreviations: CNS, central nervous system; GI, gastrointestinal.

Quality of evidence: moderate

Gastrointestinal mucosal inflammation is sometimes responsible for nausea and vomiting. Antigen presentation to the mucosa (e.g. microbial antigens) induces intestinal immune activation with low grade inflammatory changes which subsequently causes neuronal functional and structural alterations, local intestinal hypersensitivity or motor dysfunction [2]. About 9% Covid-19 patients experience nausea or vomiting [13], sometimes in extended time. Putative direct effect of the virus on enteric nerves, inflammatory and immune activation in the intestine may cause alterations in the ENS enteroglial cells and intestinal smooth muscle [13]. Inflammation caused by the presence of the virus in the dorsal vagal complex and in the area postrema may elicit N&V [14].

Immune activation and subtle intestinal pathologies are involved in the pathogenesis of chronic N&V [15]. Many patients with gastroparesis symptoms have elevated inflammatory markers such as TNFα, IL-6 and interstitial cells of Cajal count abnormalities [16]. N&V related to gastroparesis appears to be a multifactorial process with inflammation playing a key role in symptom development [16].

The vast majority of the literature in this area concerns the prevalence of chronic N&V in relation to mucositis caused by chemotherapy [17–20], radiation therapy [17–19] and immunotherapy in oncologic patients [17]. However, it is difficult to establish a direct association of mucositis with N&V. It is a complex process potentially involving injury of the mucosa, leading to inflammatory or ulcerative lesions [17].

4.1.3 | Gastrointestinal Obstruction

Statement 3. Gastrointestinal obstruction should be excluded in patients with chronic nausea and vomiting,

Statement endorsed in R1, median panel: 5—Appropriate/ agreement

Quality of evidence: low

Patients with chronic N&V should be ruled out for gastrointestinal obstruction. This may be especially challenging in patients with low-grade intestinal occlusion without proximal intestinal dilatation. Suspicion of chronic obstruction must be high in patients with inflammatory bowel disease, previous history of abdominal/pelvic surgeries, or radiation of the abdominopelvic region. In these cases, the diagnostic work-up should be exhaustive to rule out small bowel sub-occlusion caused by adhesions, radiation enteritis or strictures [21, 22]. In addition to chronic N&V, other clinical symptoms of obstruction include colicky abdominal pain and visible abdominal distension. Vomiting in patients with intestinal obstruction typically ceases when the patient fasts. In severe, long-standing small bowel obstruction, vomited content may be dark and malodorous or even fecaloid [23, 24].

Objective radiological signs of obstruction such as intestinal dilatation with a visible transition point between dilated and non-dilated bowel are not always evident, especially in patients with low-grade chronic obstruction. It may be helpful to perform specific imaging techniques to distend the small bowel with oral contrast, such as MRI or CT enterography, to detect an intermittent or mild obstruction. However, some forms of low-grade obstruction, particularly when caused by adhesions, are not detectable by radiology and may require an exploratory laparoscopy or laparotomy to be diagnosed. Other radiological signs that suggest intestinal obstruction include the "faeces sign" (particulate-type material in the small bowel above the point of obstruction), the "beak sign" (a sharp narrowing of the small bowel at the point of obstruction) or anterior parietal

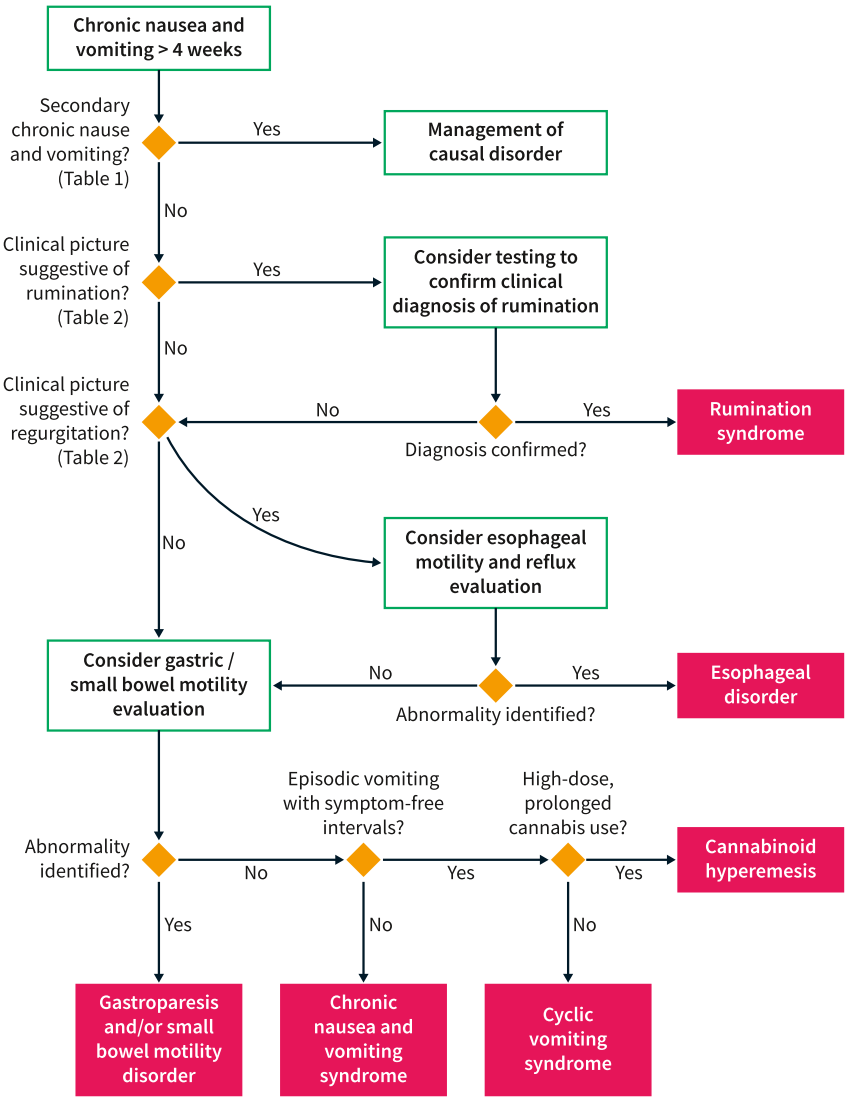

FIGURE 1 | Diagnostic algorithm for chronic nausea and vomiting. Target patients are those with chronic (> 4 weeks) chronic nausea and vomiting. The consensus recommends an initial assessment of secondary forms of chronic nausea and vomiting, summarized in Table 1. If the evaluation for secondary forms is negative, a potential motility or functional digestive disorder should be considered. At this point, it is crucial to differentiate regurgitation and rumination from vomiting (Table 2). Vomiting typically involves retching, whereas regurgitation and rumination are effortless. Rumination syndrome may be diagnosed based on the characteristic features without further testing. However, confirmation, especially in less clear cases, may be obtained using oesophageal impedance manometry. If the clinical picture suggests regurgitation, objective testing for gastroesophageal reflux disease and oesophageal motility disorders is recommended. Patients with persistent unexplained nausea and vomiting, in whom rumination and regurgitation have been excluded, should be evaluated for a gastric or intestinal motility disorder. If there is no objective evidence of an underlying gastrointestinal motility disorder, the most likely diagnosis is a gut-brain interaction disorder, either cyclic vomiting syndrome or chronic nausea and vomiting syndrome. These disorders are clinically discriminated by the vomiting pattern. When the patient presents vomiting episodes, separated by paucisymptomatic periods, the most likely diagnosis will be cyclic vomiting syndrome. If the patient with episodic vomiting is a regular cannabis user, cannabinoid hyperemesis should be considered. In patients with continuous, non-episodic nausea and vomiting, the most likely diagnosis will be chronic nausea and vomiting syndrome.

adhesion of the small bowel in patients with intestinal adhesions [25, 26].

4.1.4 | Pharmacological Agents and Toxins

Statement 4. In patients with chronic nausea and vomiting, current medications should be reviewed to exclude pharmacological causes.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Although nausea is one of the most commonly reported side effects of medications, there is a general lack of high-quality studies investigating medication-induced chronic N&V. Pharmacological agents produce N&V through direct and indirect

mechanisms. The most important are direct stimulation of the chemoreceptor trigger zone, inhibition of gastrointestinal motility, especially delaying gastric emptying, and stimulation of the vestibular apparatus. Any given medication may have more than one mechanism associated. Common medications associated with elevated rates of chronic N&V are dopamine receptor agonists, opioids and glucagon like peptide-1 (GLP-1) receptor agonists.

In patients treated with dopamine receptor agonists, the mechanism of emesis seems to be centrally mediated through activation of dopaminergic D2/3 receptors [27]. Two meta-analyses of randomized controlled trials have shown that dopamine agonists use is associated with a higher risk of N&V compared to placebo in patients with Parkinson's disease [28] and in patients with restless leg syndrome [29]. Indeed, N&V accounted for 50% of all adverse events reported with the use of ropinirole [29].

N&V are common side effects in patients that start opioid treatment, although there seems to be a tolerance phenomenon and developing chronic opioid-induced N&V is rare [30]. Opioids have a central mechanism for inducing nausea, which is associated with delayed gastric emptying and intestinal hypomotility. Moore et al. performed a systematic review of oral opioids for chronic non-cancer pain, which revealed that 21% of patients developed chronic nausea [31]. Laugsand et al. performed a systematic review of 50 studies evaluating the management of opioid-induced N&V in cancer patients. Based on the analysis of the existing evidence, it has been suggested that changing the opioid type or administration route from oral to parenteral may be beneficial [32].

GLP-1 receptor agonists are novel drugs used to treat diabetes mellitus and obesity, and their beneficial effects are mediated, at least in part, by retardation of gastric emptying [33, 34]. The main reported side effect of GLP-1-based agents are nausea and vomiting [35]. Bettge et al. performed a systemic analysis of gastrointestinal adverse events reported in clinical trials studying GLP-1 receptor agonists. They found that gastrointestinal adverse effect are dose-dependent and that long-acting GLP-1 receptor agonists were associated with less nausea and vomiting but more diarrhoea than short-acting agents [36].

4.1.5 | Vagal Nerve Injury

Statement 5. Injuries to the vagal nerve may cause chronic nausea and vomiting following cardiac, thoracic, or abdominal interventions.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

A clinically relevant vagal nerve injury has been reported in patients undergoing repeated carotid endarterectomies, coronary artery bypass surgery, pneumonectomy, heart-lung transplantation, oesophageal, gastric and bariatric surgery after fundoplication for GERD or hiatal hernia and partial gastrectomy, especially with concomitant Roux-en-Y anastomosis [37–53]. Vagal dysfunction has also been described after ablation therapy for cardiac arrhythmia [54–60].

Truncal vagotomy may result in loss of fundic and pyloric relaxation and reduced antral contractions [61]. More selective vagotomy procedures (parietal cell vagotomy or proximal gastric myotomy) may spare antral innervation and are generally associated with milder and more subtle changes in gastric function [61, 62].

Patients with vagal nerve injury after thoracic or abdominal interventions exhibit acute onset nausea, vomiting, postprandial fullness, bloating, constipation or epigastric pain, and gastric content retention [38, 43, 44, 46–48, 51, 57, 63]. The prevalence of gastric hypomotility is significantly higher in the early postoperative period and most patients recover completely with conservative treatment [44, 48, 51, 57, 63].

In thoracic surgery, symptomatic delays in gastric emptying have been reported in up to 25% of patients after single-lung transplantation and 50% of patients after combined heart-lung transplantation [38–44]. Gastroparesis after heart and lung transplantation may have serious implications because it predisposes to gastroesophageal reflux, microaspiration, subsequent pulmonary infection and risk of graft rejection [43, 44]. In abdominal surgery, inadvertent vagotomy has been estimated to occur in about 3%–5% of open surgeries. Specifically, the reported prevalence of unintended vagal nerve injury after anti-reflux surgery ranges from 10% to 42% and may be more frequent with laparoscopic anti-reflux surgery [45–52].

4.1.6 | Dysautonomia

Statement 6. Autonomic dysfunction should be considered in patients with chronic nausea and vomiting. Other symptoms that may suggest dysautonomia include orthostatic hypotension and sweating abnormalities.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

GI symptoms are among the most common complaints in patients with autonomic dysfunction. Upper GI symptoms, specifically chronic N&V are among the most frequently reported. In a systemic review of gastrointestinal symptoms in patients with postural orthostatic tachycardia syndrome (POTS), Mehr S. E. et al. [64] reported a prevalence of chronic nausea between 21% and 81% and, for chronic vomiting, between 10% and 70% of patients. In patients with suspected dysautonomia diagnosed with POTS, there is evidence of abnormal gastric motility in a subgroup of patients evaluated with gastric emptying studies, either rapid gastric emptying or delayed gastric emptying [64]. Yamakawa M. et al. [65] evaluated the clinical features of 200 patients with autoimmune dysautonomia and positive

ganglionic nicotinic acetylcholine receptor antibodies in Japan. In their study, chronic nausea and vomiting were common in children/adolescents and adults (60% and 21% of patients, respectively). On the other hand, there is evidence of autonomic dysfunction in patients with chronic N&V syndromes. There is an association of several autonomic features such as antecedent aura, associated headaches, photophobia, and phonophobia in patients with CVS [66]. Adrenergic autonomic dysfunction has been described in adults and children with CVS, which is similar to the autonomic dysfunction seen in patients with migraine headaches [67, 68]. GI dysmotility also plays a role in chronic nausea and vomiting in patients with dysautonomia. Nguyen et al. evaluated the autonomic function in 242 patients with chronic N&V, 72% of them had evidence of delayed gastric emptying. They found that parasympathetic dysfunction was associated with more severe symptoms and with delayed gastric empyting [69].

4.1.7 | Vestibular Disorders

Statement 7. Vestibular disorders may be a cause of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 8. Vestibular disorders should be considered if chronic nausea and vomiting are accompanied by dizziness and/or vertigo, headache, hearing loss, tinnitus, impaired vision, focal weakness, and difficulty walking.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

N&V are common complaints in vestibular disorders, generally as an accompanying symptom of vertigo and dizziness [70–75]. The occurrence of N&V largely depends on the type and duration of the vestibular disorder. If the vestibular disorder persists for more than 4 weeks, N&V may become chronic.

4.1.8 | Intracranial Hypertension

Statement 9. Intracranial hypertension can cause chronic nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 10. Signs and symptoms that suggest intracranial hypertension as the cause of chronic nausea and vomiting are headache, visual disorders, vertigo, tinnitus, stiff neck, and/or focal neurologic deficits.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Cranial hypertension can cause chronic vomiting, with or without nausea [10, 76–80]. Signs and symptoms that suggest cranial hypertension include non-specific headaches, various visual abnormalities (diplopia, transient visual abnormalities, peripheral visual loss, alterations in visual acuity with blurring, loss of colour distinction, sudden visual loss), vertigo, tinnitus, stiff neck and focal neurologic deficits.

4.1.9 | Psychiatric Disorders

Statement 11. Patients with anxiety and depression may manifest nausea and vomiting as somatic symptoms of psychological dysfunction.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 12. Nausea and vomiting are symptoms of eating disorders and may be self-induced or occur as a manifestation of an associated gastrointestinal functional or motility disorder.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

N&V are prevalent somatic symptoms of depression and anxiety, generally in association with other somatic symptoms such as fatigue, trouble sleeping, headache and pain in arms, legs, or joints [81]. A large population study in Norway found a strong association between reporting somatic symptoms and the presence of anxiety and depression [82]. Nausea was specifically detected in 12.5% of the community and presence of anxiety disorders carried the highest risk for nausea (OR 3.42) [83].

The presence of a large number of unexplained somatic symptoms, including N&V, is associated with more severe depression and higher rates of misdiagnosis [84, 85]. A study evaluating the course of somatic symptoms of anxiety and depression, including N&V, found that these symptoms were more prevalent in females and tended to persist from childhood to adulthood [86].

GI symptoms are present in most patients with eating disorders. In a systematic literature examining the prevalence of GI symptoms in eating disorders, N&V were reported by approximately 30% of patients [87]. Therefore, eating disorders should be ruled out in patients with chronic N&V. This may be challenging, but identifying an eating disorder is imperative to correctly guide therapy [88, 89]. The aetiology of N&V in eating disorders is diverse. The main cause is self-induced vomiting as a purgative mechanism used by patients with both bulimia nervosa and anorexia nervosa. N&V in patients with eating

disorders may also be a symptom of an associated functional or motility disorder. Dyspeptic symptoms are reported by almost all patients with eating disorders [90] and delayed gastric emptying has been shown to occur in up to 40% [91, 92]. In the majority of cases, functional symptoms develop concomitantly with the eating disorder and improve with weight restoration [93].

4.1.10 | Malignancy-Related

Statement 13. In patients with advanced cancer, chronic nausea and vomiting may be caused by antineoplastic agents and radiation therapy, biochemical abnormalities, impaired gastric emptying, visceral and serosal causes of delayed gastrointestinal transit, cranial, vestibular, and cortical causes.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: very low

The prevalence of N&V in patients with advanced cancer amounts to 70% [94–97]. Patients may report isolated nausea, isolated vomiting (e.g., in case of increased intracranial pressure) or a combination of both symptoms [97]. Available data reflect a very complex and multifactorial nature of N&V occurring in patients with cancer [95, 96]. More than one possible aetiology is detected in around 25% of patients with malignancy [94, 97]. In general, malignancy-related factors producing chronic N&V may be divided into those associated with cancer treatment or those associated with the disease and its complications [98, 99]. N&V secondary to antineoplastic agents and radiation therapy should be anticipated and managed according to clinical practice guidelines [100]. Other most common underlying causes of N&V in patients with cancer include chemical abnormalities (drugs, such as opioids, antidepressants, or antibiotics; toxins, derived from bowel ischemia or infection; metabolic disorders caused by renal or liver failure, hyponatremia, hypercalcemia); impaired gastric emptying (drugs, ascites, hepatomegaly, autonomic dysfunction, tumour infiltration); visceral and serosal causes of delayed gastrointestinal transit (bowel obstruction, enteritis, constipation); cranial causes (tumour or intracranial bleed, meningeal infiltration); and vestibular causes [98, 101, 102]. Given the role of anxiety and other psychological factors in patients with cancer, these causes should be also considered [95, 97]. Anticipatory N&V may occur in 25%–30% of patients by their forth chemotherapy cycle [103]. In case of N&V unrelated to antineoplastic treatment, an empirical or etiology-based approach is recommended [95, 104].

4.2 | Section 2. Motility Disorders

4.2.1 | Oesophageal Motility Disorders

Statement 14. Chronic nausea and vomiting are not characteristic clinical features of primary oesophageal motility disorders. Regurgitation should be differentiated from vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: very low

No specific data has been found in the literature, but based on clinical experience, nausea and vomiting are not considered as characteristic clinical features of primary oesophageal disorders such as achalasia, diffuse oesophageal spasms, or hypercontractile oesophagus, in which typical symptoms are dysphagia, regurgitation and chest pain [105]. Both patients and physicians often confuse "vomiting" and regurgitation. It is important to emphasize that an adequate clinical history should make the difference between vomiting, that is an active gastroduodenal process often preceded or accompanied by nausea, and regurgitation, which is passive and describes the retrograde flow of oesophageal or gastric contents into the mouth.

In patients with functional dyspepsia who often experience nausea and vomiting, nonspecific oesophageal motor disorders may be observed, mainly related to gastroesophageal reflux disease (GERD) and oesophagitis. One recent study suggests that abnormal motility of the proximal oesophagus is more often associated with symptoms of nausea and vomiting [106].

Statement 15. In patients consulting for chronic nausea and vomiting, testing for oesophageal motility disorders (manometry) is recommended only if oesophageal symptoms (regurgitation, dysphagia) are present and structural disease has been ruled out.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Data in the literature is scarce about the prevalence of oesophageal motility disorders in patients with nausea and vomiting. The relationship between oesophageal dysmotility and gastric disorders, such as gastroparesis and functional dyspepsia, remains unclear. In patients with functional dyspepsia who often present with nausea and vomiting as predominant symptoms, nonspecific oesophageal motor disorders may be observed, mainly related to GERD and oesophagitis [107]. We could find only one retrospective study which specifically investigated the prevalence of oesophageal motor disorders in patients with functional dyspepsia [108]. They observed a prevalence of 7%, 32% and 13% of achalasia, diffuse oesophageal spams/hypercontractile oesophagus, and esophagogastric junction outflow obstruction, respectively. Most patients had acid regurgitation and/or dysphagia though not presenting as the predominant symptom. The prevalence of achalasia and oesophageal spasms was higher in patients with delayed gastric emptying at scintigraphy. Though retrospective and probably biased, this study suggests that oesophageal motor disorder may coexist in patients with functional dyspepsia, especially when oesophageal symptoms such as acid regurgitation and dysphagia are present.

Statement 16. When an oesophageal motility disorder is suspected in patients with regurgitation, and/or vomiting, high-resolution manometry should be performed after ruling out mechanical obstruction. Complementary tests, as high-resolution

impedance manometry, barium oesophagogram or endoscopic impedance planimetry FLIP may be useful in complex cases.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: high

The analysis of suspected oesophageal motility disorder (OMD) should start with an esophagogastroduodenoscopy, to exclude benign or malignant conditions that can mimic a primary EMD. In cases with non-conclusive endoscopic exploration and high suspicion of a structural disorder other tests like CT-scan can be performed [109]. High-resolution manometry (HRM) is the gold standard to assess EMD [110]. The Chicago 4.0 Classification [111] provides a classification of oesophageal motility disorders based on HRM. There are no studies evaluating the added value of high resolution impedance manometry in OMD diagnosis, only case series reporting its benefits in deciding OMD management [112], however it is recommended if rumination syndrome is suspected [113]. Chicago 4.0[111] suggests that other tests can be added to the HRM to investigate OMD when equivocal results are identified using the HRM protocol or/and there is suspicion for EGJOO that do not fulfil achalasia criteria. These additional tests are timed barium esophagogram (if it is possible with a barium tablet swallow) and/or endoluminal functional lumen imaging probe (FLIP).

4.2.2 | Gastric Motility Disorders

Statement 17. Chronic nausea and vomiting are frequent symptoms in patients with gastric motility disorders, but pain, early satiety, postprandial fullness and bloating may dominate the clinical picture in many patients.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

The cardinal symptoms of gastric motility disorders include nausea (present in about 90%) and vomiting (present in about 75%), but patients may also complain of early satiety, postprandial fullness, bloating, belching, and upper abdominal discomfort [114–116]. Although pain was previously considered suggestive of functional dyspepsia rather than gastroparesis [117, 118], one study showed that pain occurs up to 90% of patients [115, 119, 120], and it is increasingly recognized as one of the most common symptoms of gastroparesis [121]. Evaluation of specific symptoms is complicated, since gastric motility disorders do not typically present in isolation, but may include the involvement of other organs. In diabetes, structural changes of the brain affecting the vomiting centre in the medulla, may cause nausea [122]. Pilot studies have also shown changes in brain networks in patients with gastroparesis [123, 124]. As motility disorders are not restricted to specific organs but affect several segments of the GI tract [125], symptoms may overlap between conditions. For example, many patients with gastroparesis have gastro-oesophageal reflux, which in turn may impair oesophageal motility. In healthy subjects, in whom confounding factors such as concomitant medication and the involvement of many other organs can be controlled, the cardinal symptoms of induced gastroparesis were nausea and vomiting [126–128]. Gastrointestinal tract symptoms do, however, overlap partly due to the diffuse termination of visceral afferents in the spinal cord rendering them less specific as compared with somatic system symptoms [129, 130], and this also adds to the complexity of subjective complaints.

Statement 18. In patients with chronic nausea and vomiting, a gastric motility disorder may be suspected, especially when associated with diseases or medications that are associated with abnormal gastric emptying.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Gastric motility disorders are often associated with nausea and vomiting, but patients typically also complain of other symptoms such as early satiety, postprandial fullness, bloating and upper abdominal discomfort [114]. The clustering of such symptoms will therefore suggest a gastric motility disorder per se. Nausea and vomiting in gastroparetic patients, particularly those with diabetes, may follow a cyclical pattern, similar to cyclic vomiting syndrome [131, 132]. Suspicion that gastroparesis is the cause of nausea and vomiting should be increased in diseases associated with motility disorders, for example, diabetes and neurological disorders like Parkinson's disease. Gastroparesis should also be considered in patients with symptoms relating to previous surgery, infections, rheumatological and endocrine diseases [133]. As mentioned in statement 17, pain is frequent in patients with gastroparesis, especially in those with concomitant bowel disturbances and greater impairment in quality of life [121].

One important limitation when correlating symptoms with gastric motility is the poor association between the presence and intensity of symptoms and the degree of delayed gastric emptying [115, 134, 135]. This can be related to poor scintigraphy reporting [136], but also to the pathophysiology of gastroparesis, which encompasses several components (such as abnormal accommodation, gastric hypomotility and dysrhythmias, visceral hypersensitivity or psychological disturbances) that are not measured with standard methods such as scintigraphy [115]. However, recent data suggest that when “optimal” test methods are used, significant associations with symptoms are observed [137]. Newer techniques such as the wireless motility capsule, three-dimensional transit or methods based on magnetic resonance imaging, where the transit time and motility of the whole GI tract are taken into consideration, may overcome these obstacles [138, 139] and offer the potential to better characterize patients with gastric motility disorders and identify their symptoms [140].

Statement 19. A gastric emptying test is necessary to establish a diagnosis of gastroparesis in patients with unexplained chronic nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 20. Valid methods to measure solid gastric emptying in patients with unexplained chronic nausea and vomiting are scintigraphy and octanoic acid breath tests.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

A gastric motility disorder may be considered in patients with unexplained chronic nausea and vomiting after excluding mechanical cause. The United European Gastroenterology and European Society for Neurogastroenterology and Motility consensus on gastroparesis recently acknowledged that both endoscopy and gastric emptying test were mandatory for establishing a diagnosis of gastroparesis [133]. Most studies, but not all [141–144], found a correlation between nausea and vomiting severity and the delay of gastric emptying [137, 145–150], although this correlation was weak. Most of therapeutic trials failed to demonstrate correlation between acceleration of gastric emptying and nausea and vomiting alleviation [151–154]. Valid methods to measure solid gastric emptying include scintigraphy or C13 octanoic acid breath test [133, 155]. Appropriate methodology of gastric emptying studies includes an accurate 4-h measurement and at best the absence of medications that impact on gastric motility (e.g., prokinetics or opioids) [133, 141, 155, 156]. A recent study showed that only 1/3 of patients with symptoms evocative of gastroparesis accessed to gastric emptying studies, likely due to the limited availability of tests [157]. Alternatives include wireless motility capsule test and gastric ultrasonography, but both techniques cannot be considered as first line tests. Indeed, gastric expulsion of the wireless motility capsule relies on gastric phase III activity rather than overall gastric emptying. Likewise, the main pitfall with ultrasonography is that this technique is not able to distinguish between solid and liquid emptying [133, 155]. An indirect method to assess gastric emptying relies on pressure, diameter and distensibility measurement of the pylorus using the endoFLIP system. This may represent an alternative to gastric emptying test in situations where there are no gastric emptying normal values reported (e.g., sleeve gastrectomy or esophagectomy) or in patients unable to tolerate the test meal. Pyloric pressure or distensibility alteration correlates with gastric emptying [158, 159] whereas correlation with nausea and vomiting severity remains discrepant [158–160]. EndoFLIP measurement has also been suggested to predict therapeutic response to pyloric directed therapies, including endoscopic pyloromyotomy, although this requires to be confirmed with larger trials [161–163]. Other gastric motility alterations, involving impaired fundic relaxation and/or visceral hypersensitivity poorly correlate with nausea and vomiting [164–168].

4.2.3 | Intestinal Motility Disorders

Statement 21. Chronic nausea and vomiting may be characteristic clinical features of intestinal motility disorders, particularly when in presence of concomitant gastric and/or lower GI tract motility disorders.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Chronic nausea and vomiting are considered clinical features of motility disorders and, in particular, stomach and/or bowel motility disorders such as gastroparesis and chronic intestinal pseudo-obstruction (CIPO) [169]. However, past studies evaluating the correlation between the presence of delayed gastric emptying and symptoms of nausea and/or vomiting have generally found little correlation between these symptoms and altered motility [170]. The same applies to studies evaluating small bowel motility [171].

More recent studies suggest that nausea and vomiting are less likely to correlate with the presence of a motility disturbance in a single segment of the GI tract. Nausea was reported in patients with concomitant gastroparesis and impaired small bowel motility measured by manometry in a single-centre retrospective study [125]. A prospective single-centre study using a wireless capsule demonstrated a moderate correlation between the presence of nausea and concomitant altered motility of the stomach, small intestine, and colon [172]. In a retrospective study conducted at a single centre, concomitant complaints of delayed colonic transit or rectal evacuation were reported in a large proportion of patients referred to a tertiary referral centre with chronic nausea and vomiting [173].

Statement 22. Dilated small bowel loops suggest an intestinal motor disorder in patients with chronic nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 23. Patients with confirmed intestinal motility disorders without bowel dilatation may be characterised by chronic abdominal pain.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Very few studies have compared the clinical presentation of patients referred for suspected intestinal dysmotility with those

without [174, 175]. In these studies, the number of patients with predominant nausea and/or vomiting is very small to allow a comparison [174, 175]. In the largest retrospective study in the literature, patients who underwent 24-h small bowel manometry and were found to have normal motility had mainly unexplained abdominal pain or constipation [174]. In this study, excluding patients with previous surgery, patients presenting with symptoms/signs of sub-occlusion were all found to have abnormal small bowel manometry [174].

In another large retrospective study, patients with chronic CIPO and severe functional disorders, mostly with abnormal small bowel manometry, were compared with IBS patients without abnormal motility. In this study, patients with CIPO were defined according to the presence of radiologically confirmed bowel dilatation compared to those with severe functional disorders. Patients with severe functional disorders presented higher epigastric pain and burning scores than those with CIPO and IBS [175]. They also had higher scores and frequency of vomiting and fullness than patients with CIPO [175]. No differences in the frequency of altered bowel habits were reported between these two groups [175].

Considering studies that only included patients with altered bowel motility, in patients diagnosed with chronic bowel dysmotility in the absence of radiological bowel dilatation, the most frequently reported symptoms were abdominal pain, abdominal distension and bloating [176, 177]. In patients with CIPO and radiologically confirmed bowel dilatation, the presence of symptoms/signs of sub-occlusion were the main clinical presentation [178].

Statement 24. Intestinal motility tests (i.e., scintigraphy, stable isotope breath tests, wireless motility capsule, intestinal manometry, abdominal MRI) may be advised in patients with signs of intestinal dysmotility without obstructive or mucosal disorders.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: very low

Plain abdominal x-ray film has low sensitivity and specificity in detecting small bowel obstruction (SBO) [179], whereas abdominal CT scan can adequately identify patients with SBO who should be referred to surgery and determine the location of obstruction [180] with higher sensitivity than other imaging tests (i.e., plain radiography [181, 182], abdominal ultrasound [182] and small bowel follow through [183]). The current gold-standard test to evaluate small intestinal motility is intestinal manometry. Other tests including scintigraphy and abdominal MRI are alternatives that have shown to be helpful to detect intestinal dysmotility [184–190]. Features of abnormal standard radiography and small bowel manometry may show similar findings in patients with mechanical obstruction to those with 'functional' obstruction (neuro-muscular, hence CIPO) [191, 192]. Wireless capsule technology may help to evaluate small bowel dysmotility, thus aiding in recognizing possible causes of chronic nausea and vomiting [193, 194].

4.3 | Section 3. Disorders of Gut-Brain Interaction

4.3.1 | Cyclic Vomiting Syndrome

4.3.1.1 | Definition

Statement 25. Cyclic vomiting syndrome (CVS) refers to recurrent, regular, and stereotypical episodes of nausea and severe vomiting separated by symptom-free intervals. CVS can be diagnosed only in the absence of other causes (organic or metabolic) that can explain the symptoms.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

4.3.1.2 | Epidemiology

Statement 26. CVS (defined according to Rome IV) affects about 0.1%–2% of the adult population.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 27. Incidence and prevalence of CVS decrease with age. Accordingly, the prevalence of CVS is higher in children than in adults. Prevalence in children reaches 0.2%–6.2% (also including studies using Rome III for definition).

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Cyclic vomiting syndrome (CVS) was first described in 1888 by Samuel Gee as episodes of nausea and vomiting separated by symptom-free intervals [195, 196]. The term "cyclic" implies regularity and predictability of attacks [195, 196]. The length of symptom-free intervals is patient specific and can last from weeks to months. Each episode can last from hours to days. CVS is a chronic entity that can persist for years [195, 196].

The syndrome was first described in children and therefore most of the criteria are based on studies and epidemiology in this population. One of the first epidemiologic studies in Aberdeen, Scotland, showed that the syndrome is not as rare as it was thought (1.9% of school-going children) with similar prevalence in girls and boys [197, 198]. CVS is heterogeneous and the lack of definitive laboratory markers is well recognized [199]. A study in more than 200 children highlighted that, in 49% of patients diagnosed with CVS, an additional disorder can be identified that probably causes or could contribute to the vomiting [200]. For this reason, systematic diagnostic testing is recommended to look for these underlying disorders [200]; and the diagnosis of CVS is thus based upon the fulfilment of the criteria (described below) in the absence of another explanation for the symptoms [199, 201].

A larger study tried to make a distinction between cyclic nausea and chronic nausea, two frequently observed temporal patterns in children [202]. The threshold of cyclic vomiting was then defined in those patients having a high intensity (12.6 peak emeses/hour), low frequency (1.5 episodes/month) pattern, whereas the chronic group had a low intensity, high frequency, daily pattern (1.9 peak emeses/hour with 36.6 episodes/month) [203]. The cutoff of at least 4 emeses per hour and up to 2 episodes per month for the cyclic pattern was 92% sensitive and 100% specific for the final diagnosis of cyclic vomiting syndrome following negative exclusionary testing [203].

A population-based study [204] showed an incidence of 3.15/100,000 children per year. The median age at diagnosis of CVS was 7.42 years (range 1.8–15 years). The median number of episodes of CVS per child per year was eight (range 3–52); the median duration of an episode was 24 h (range 1 h–5 days).

The Rome criteria and the task force of the international Scientific Symposium on CVS defined CVS with the following criteria [201, 205]: (1) at least 5 attacks in any interval, or a minimum of 3 attacks during a 6-month period; (2) episodic attacks of intense nausea and vomiting lasting 1 h–10 days and occurring at least 1 week apart; (3) stereotypical pattern and symptoms in the individual patient: vomiting during attacks occurs at least 4 times/h for at least 1 h with return to baseline health between episodes; (4) Not attributed to another disorder.

However, the CVS board acknowledged the lack of evidence at the time. The criteria were defined by a combination of expert opinion, available literature, and the clinical and research experience of the task force. Some task force members recognized that atypical CVS may exist with less frequent vomiting.

CVS in adults was later recognized in 17 patients [206]. Subjects were diagnosed with CVS and considered for inclusion in the study using the following criteria: three or more discrete, stereotypic episodes of nausea and vomiting, each lasting > 12 h; > 7 days between episodes; complete resolution of nausea and vomiting between episodes; and no structural or metabolic explanation for the symptoms [206]. The results showed that an average episode of nausea and vomiting lasted 6 days (range 1–21 days), and the symptom-free interval averaged 3.1 (0.5) months (range 0.5–6.0 months). The most uniform aspect in adult patients with CVS was the stereotypical nature of the vomiting episodes and the distinct lack of intercurrent symptoms, although it has been suggested that milder gastrointestinal symptoms may persist. In another study comparing adults and children [207], vomiting attacks occurred on average 10 times a year with a mean duration of 55.3 h in adults. In children, vomiting attacks occurred on average 25.5 times a year with a mean duration of 54.5 h [207].

4.3.2 | Signs and Symptoms

Statement 28. Typical characteristics suggesting CVS are the onset of episodes early in the morning, episodes lasting at least 48 h, and occurring two or fewer times per month.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Statement 29. A CVS episode typically has four phases: the prodromal phase, the vomiting phase, the recovery phase, and the inter-episodic or asymptomatic phase.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 30. During the prodromal phase of a CVS episode, patients often experience nausea, sweating, irritability, abdominal pain, fatigue, temperature changes, or insomnia.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 31. The vomiting phase of a CVS episode is characterized by intense vomiting, often bilious, and accompanied by disabling nausea and retching. Abdominal pain is often present and may be severe. Accompanying symptoms may include pallor, listlessness, anorexia, headache, photophobia, low-grade fever, or hypothermia.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 32. Symptoms resolve during the recovery phase of a CVS episode.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 33. No vomiting is present during the inter-episodic phase of a CVS episode, patients may be completely asymptomatic with regard to the GI system or may have milder GI symptoms.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 34. Symptoms can be triggered by psychological and physical stress.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

The duration of episodes progressively increases as infants/toddlers pass through childhood and adolescence and into adulthood [208]. The delay in diagnosis is greater in adult-onset CVS patients than in children, and they are typically misdiagnosed for years [207–211]. Many other characteristics of CVS, including clinical features and response to standard therapy, are similar irrespective of age at onset, suggesting a uniform pathogenesis [208, 210]. Over time, patients usually show a gradual improvement in symptoms and complete resolution in some cases [207].

CVS typically presents in four phases: prodrome phase, vomiting phase, recovery phase and asymptomatic phase until the next episode [203, 211]. Some patients experience recognizable prodromal symptoms (e.g. nausea, sweating, irritability, abdominal pain, fatigue, temperature changes, insomnia) that provide opportunities for treatment that might provide some relief [209, 212–214]. In paediatric patients, behavioural states during episodes seem to be of three types: (1) subdued but responsive; (2) an immobile, unresponsive state referred to as "conscious coma"; and (3) writhing and moaning [212].

The vomiting is intense, accompanied by disabling nausea, and frequently bilious [201, 209]. The nausea, emesis, and retching persist even when the gastric contents consist of only mucus and bile [215]. The accompanying symptoms include pallor, listlessness, anorexia, retching, abdominal pain, headache, and photophobia, and some children have fever or diarrhoea [209, 215]. Episodes often start in the morning and are frequently triggered by psychological and physical stress, including anticipatory anxiety, infection, exercise, trauma, menstruation, and foods [206, 209, 215–217].

CVS is linked to some neurological disorders (migraine in particular) and gut-brain interaction disorders (involving autonomic function) [197, 199, 211, 215, 216, 218]. Moreover, compared to chronic nausea and vomiting syndrome, CVS has been associated with a higher prevalence of metabolic-endocrine disorders and genetic mitochondrial mutations and polymorphisms [215, 218, 219], the latter being more frequent in paediatric CVS compared to adult CVS [219]. In a multivariate analysis, CVS was significantly associated with comorbidities including dysautonomia, migraine, anxiety, marijuana use, irritable bowel syndrome, gastroparesis, gastroesophageal reflux disease, asthma, cigarette smoking, and hypertension [211, 220].

4.3.3 | Pathophysiological Mechanisms

Statement 35. Pathogenesis of CVS is multifactorial.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: high

Statement 36. Psychosocial factors are involved in the pathogenesis of CVS.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: high

Statement 37. Gastric emptying is accelerated in the majority of patients with CVS, most of the other patients have normal gastric emptying. In a minority gastric emptying may be (intermittently) delayed. In these, gastroparesis is an important differential diagnosis.

Statement endorsed in R2, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Statement 38. Genetic factors may be involved in CVS.

Statement endorsed in R2, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Statement 39. Neurohormonal factors are involved in the pathogenesis of CVS.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Although several factors have been implicated in the pathogenesis of CVS, the majority of studies investigating these factors are in small series, retrospective or not replicated [221–225]. Psychosocial factors, such as anxiety or depression, have been reported in most patients with CVS [226]. High levels of stress have also been reported [227]. Gastric motility changes, primarily accelerated gastric emptying, have been observed [226, 228]. The presence of migraine in some patients with CVS [229] has been explained by genetical abnormalities related to mitochondrial DNA polymorphisms [219, 229]. Neurohormonal regulation has also been studied [230, 231]. Older studies identified the role of autonomic nervous dysfunction, with more frequent sympathetic abnormalities [230]. CVS patients may also have elevated levels of ghrelin and corticotrophin-releasing factor (CRF) [231]. The gene RYR2, encoding a stress-induced calcium channel occurring in many neurons, presents polymorphisms associated with CVS [231].

The endocannabinoid system may also play a role in CVS [232], which could explain why CVS has similar manifestations to cannabinoid hyperemesis syndrome (CHS). Furthermore, many CVS patients use cannabinoids, increasing the risk of confusion with CHS [233]. The involvement of other neurotransmitters (such as dopamine, serotonin, histamine, GABA) has not been sufficiently demonstrated [234], despite the positive effects of drugs acting on their receptors in the therapy of CVS. Other suggested factors are urea cycle disorders, hypoglycaemia, sleep

disorders, or cranial hypertension. In sum, the complexity of the pathophysiology of CVS explains the comorbidities observed [218].

4.3.4 | Relation With Migraine

Statement 40. The prevalence of migraine in paediatric and adult CVS patients ranges from about 40% to 70%. About the same percentage of CVS patients have a family history of migraine.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate-C

Statement 41. Both, unique and potentially shared, pathophysiologic mechanisms have been observed for CVS and migraine (e.g., regarding genetic background, brain morphology, and function). Therefore, they are considered associated comorbidities but separate entities.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate-C

Migraine is a frequent comorbidity in individuals with CVS, affecting both adults and children. In a systematic review by Lee et al. including both populations, 40% of patients had headaches or migraines [235]. There was a family history of headaches/migraines in 38.9%, and this association was much stronger in the adult CVS cohort compared with the paediatric cohort [235]. Li et al. reported a series of 214 children with idiopathic CVS of whom 82% had migraine-associated CVS. This subgroup had, or subsequently developed, migraine/headaches and/or had family histories of migraine [236]. In a recent retrospective analysis of data from 57 children, 47% had a family history of migraine [237].

With respect to adults, Fleisher et al. published a retrospective analysis of 40 adult patients with CVS [213]. Of these, 28 (70%) experienced migraine headaches during or between CVS episodes. Twenty-three (57%) of the patients had first and/or second-degree relatives with migraine headache or its variants [213]. Partovi et al. conducted a retrospective review of patients using the clinical CVS patient registry which includes prospectively collected data of patients from 49 states in the US. Out of 455 patients with complete data, 217 (48%) also had migraine and 53% had a family history of migraine. So far, these data have been published in abstract form only [238].

The mitochondrial DNA single nucleotide polymorphisms (SNPs) 16519C_T and 3010G_A are associated with migraine and childhood cyclic vomiting syndrome [239]. Other mitochondrial DNA variants may also play a role [240]. Overall, CVS and migraine both share some form of mitochondrial dysfunction. CVS is characterized by altered insular cortex function. Migraine shows some similar alterations but also has distinct brain function characteristics [241]. Using brain MRIs, Rashid et al. demonstrated migraine-like white matter hyperintensities in a subgroup of children with CVS and migraine, not in children with CVS who did not simultaneously suffer from migraine [242].

4.3.5 | Associations

Statement 42. There is an overlap between CVS, functional dyspepsia, and irritable bowel syndrome.

Statement endorsed in R2, median panel: 4—Appropriate/agreement

Quality of evidence: moderate-C

Patients with CVS frequently report inter-episodic digestive symptoms. A study applying standardized Rome III questionnaires to collect GI symptoms in patients with CVS found 51% fulfiled criteria for irritable bowel syndrome and 66% for functional dyspepsia [243]. Other disorders of gut-brain interaction, such as functional belching and functional heartburn, were also likely (39% and 38% respectively). Dyspeptic symptoms are higher in patients with migraine [213] and predict psychological distress in patients with CVS [244].

Epidemiological data from Canada, USA and UK show no difference in the prevalence of cannabis use among subjects fulfiling criteria for CVS and those with chronic nausea and vomiting syndrome, indicating an overlap between diagnoses dominated by nausea and vomiting that are included among the nausea and vomiting disorders [245].

4.3.6 | Psychosocial Factors

Statement 43. Very little is known about the specific impact of CVS on adults' and children's psychosocial function.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

There is a limited number of studies on psychosocial function/dysfunction specifically associated with CVS in adults. In a population based survey on adults, somatic symptom severity, physical and mental health-related quality of life (HRQOL), and health care utilization was higher in the chronic nausea and vomiting disorders in general, and higher somatic symptom severity was reported to be associated specifically with CVS [245]. Almost half of CVS patients in a recent study demonstrate poor patient engagement as measured by a validated questionnaire, which was reported to be associated with poor outcomes [246]. Low patient engagement was associated with an increased number of hospitalizations and lower mental HRQOL scores.

Children with CVS reported lower HRQOL compared with those with irritable bowel syndrome (IBS), and both parents and

children reported lower HRQOL compared with healthy controls [247]. This has been reported as associated with anxiety symptoms to a greater extent than the disease characteristics. Screening for anxiety symptoms and improved recognition of CVS and school support is suggested to reduce the impact of CVS on HRQOL [248].

4.3.7 | Diagnosis

Statement 44. We recommend that the diagnosis of CVS is based on clinical presentation and relies on the criteria presented in statements 1 and 4-9 of the CVS section (in analogy to Rome IV criteria).

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: high

The diagnosis of CVS is based on, but should not rely only on clinical presentation, at least for the first episodes of CVS. Diagnostic tests are necessary to rule out confounding conditions, assess the impact of repeating vomitus on body homeostasis, and reassure the patient or the relatives. The diagnostic work-up is addressed to clinical presentation. Upper digestive endoscopy, small bowel X-Ray, abdominal CT or MRI, brain imaging [249], motility studies (antroduodenal manometry, gastric emptying) [228] should be considered. In difficult cases, other rare conditions should be explored [250]. Psychological assessment should complete the work-up [251]. In order to assess the effect of severe vomiting on the homeostasis of each patient, biochemical tests addressed to dyselectrolytemia, acid-base balance, should be performed [250]. At present, genetic studies should be reserved for research.

4.3.8 | Non-Pharmacological Treatment Options

Statement 45. We recommend that patients with CVS are treated holistically, taking into account lifestyle changes, psychological support, and avoidance of trigger factors.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: very low

Long-term management of CVS includes education on trigger avoidance (foods such as chocolate, cheese, monosodium glutamate and red wine), regulating caffeine consumption, and fasting. Diabetes needs to be aggressively managed with a goal of blood glucose levels < 160 mg/dL [252, 253]. Episodes of hypoglycaemia must also be avoided as this may also trigger episodes. During the emetic phase, the patient's room should be kept dark, interruptions during sleep should be minimized, and the use of electronics and noise should be avoided. Moreover, avoidance of excessive emotional excitement, illness, and sleep disorders can effectively reduce the frequency of episodes in some patients. One study found that episodes of CVS fell in frequency by 70% when lifestyle changes were initiated [243]. Since chronic cannabis intake is associated with a lack of response to therapy and hyperemesis, patients should be encouraged to abstain from its use [254]. Treatment of CVS should also include strategies to address underlying psychological comorbidities, such as anxiety and depression which are common. Although data is scarce, alternative therapies such as acupressure or acupuncture could be considered for CVS prevention [254, 255].

4.3.9 | Pharmacological Treatment Options

Statement 46. Pharmacological treatment of CVS can be categorized into three groups: abortive, supportive, and prophylactic therapy.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 47. We recommend that benzodiazepines and antiemetics, including ondansetron, triptans, and aprepitant are used during the prodromal phase to stop an episode of CVS and prevent vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 48. We recommend that during the vomiting phase energy, fluid, and electrolyte deficits are substituted intravenously.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 49. We recommend that antiemetics, antianxiety medications, and analgesics should be used as needed during the vomiting phase to ameliorate symptoms.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 50. We suggest that opioids are avoided because they may have a sensitizing effect in migraine analgesia.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 51. We suggest that tricyclic antidepressants are used as first-line therapy for prophylaxis of CVS episodes.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Statement 52. We suggest that as second-line therapy for prophylaxis of CVS episodes the following substances are used: zonisamide/levetiracetam, L-Carnitine, coenzyme Q10 and aprepitant.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Pharmacological treatment of CVS can be categorized into three groups: abortive, supportive and prophylactic therapy. The therapeutic goal of abortive (prodromal) therapy is to stop an episode of CVS and prevent vomiting. Antiemetics and benzodiazepines are routinely used. In a recent survey [256], ondansetron was the most prescribed medication during this phase. Other effective medications are triptans, for example sumatriptan, a 5-hydroxytryptamine-1 receptor 1B/1D agonist, as demonstrated in a study in which 83% of episodes were aborted [210]. Moreover, the NK-1 receptor antagonist aprepitant appears to be a potent therapy (80–125 mg on the first day followed by 40–80 mg on the second and third days) [257].

During the vomiting phase, treatment consists of hydration to correct energy, fluid, and electrolyte deficits. Other rescue therapy consists of antiemetics, antianxiety medications, and analgesics. Additionally, a randomized controlled trial in a paediatric population showed that amitriptyline outperformed topiramate in reducing the severity of CVS attacks in a short-term assessment [258].

During remission, treatment focuses on preventing further episodes. First-line therapy for CVS prophylaxis are tricyclic antidepressants (TCAs). Amitriptyline is the preferred TCA to treat adults and is prescribed using the step-up approach, starting with low initial doses (e.g., 10 mg at night) that are gradually increased (in some cases to 100 mg daily). At higher TCA doses (e.g. amitriptyline at 1 mg/kg/per day), 93% of patients experienced a decreased frequency and severity of attacks [226]. In addition, a randomized controlled trial conducted in Iran compared amitriptyline and cyproheptadine and revealed that both have similar positive effects on the prophylaxis of CVS [259]. Second-line approaches include antiepileptic medications zonisamide/levetiracetam [235], L-carnitine, and coenzyme Q10 [260, 261]. Nutritional supplements such as carnitine and coenzyme Q10 have shown some efficacy and high tolerability in small studies. The threshold for initiation of supplements should therefore be low for patients who do not achieve disease control with first-line prophylaxis [260, 262, 263]. Aprepitant is also effective as a prophylactic treatment (40–125 mg orally twice a week) [257] (Table 3).

4.3.10 | Nutritional Support

Statement 53. We suggest that in patients with slow recovery from CVS attacks with symptoms preventing oral food intake for several days enteral or parenteral nutrition is initiated.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: very low

According to expert opinion, temporary nasojejunal feedings (or exceptionally, parenteral nutrition) can hasten recovery and only should be considered if the lack of nutrition due to prolonged symptoms exceeds 5 days [264].

4.3.11 | Cannabinoid Hyperemesis Syndrome

Statement 54. Cannabinoid hyperemesis syndrome is a cyclic vomiting syndrome induced by high-dose, prolonged cannabis use. Cannabinoid hyperemesis syndrome and cyclic vomiting syndrome are two distinct entities.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 55. We recommend that in all patients with suspected cyclic vomiting syndrome, a complete history of cannabis use is performed.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 56. Cannabinoid hyperemesis syndrome is typically characterized by severe, cyclic episodes (≥ 3/year) of nausea and vomiting with acute onset, and duration of less than a week, in patients with prolonged regular cannabis use (over 2 years).

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Cannabinoid hyperemesis syndrome (CHS) is cyclic vomiting secondary to prolonged high-dose cannabis use [265, 266]. Retrospective series of patients with CHS have shown that most patients had been consuming cannabis for more than 2 years, and at high-doses, defined as daily or nearly daily (at least 4 days a week). However, a safe threshold below which the syndrome is less likely to develop has not been defined. In 2020, 209 million individuals were using cannabis worldwide, either as a recreational drug or for treatment [267, 268]. The prevalence of CHS is unknown. One study in subjects from a drug dependent unit reported a prevalence of 18% [269].

CHS should be considered before diagnosing a patient of CVS, however differentiating these entities may be challenging since 41% of CVS patients report at least occasional cannabis use [270]. If vomiting episodes precede cannabis use, or if consumption is not high-dose, CHS is unlikely, so

CVS should be the most probable diagnosis and the aim of treatment [271]. Ultimately, the only reliable criterion to distinguish CHS from CVS is complete and persistent resolution of all symptoms of the disease following cannabis cessation [271].

The human body has two types of cannabinoid receptors, CB1 and CB2, that bind to endogenous cannabinoids [272]. CB1 receptors are in the brain, the enteric nervous system and other organs. They modulate gastric secretion, motility, inflammation, and sensation. The cannabis plant contains 3 cannabinoids: tetrahydrocannabinol (THC), cannabidiol, and cannabigerol. Exogenous cannabinoids bind to CB1 and CB2 receptors, determine psychic effects, and interestingly, some have antiemetic effects, while others at high doses cause emesis. In addition, THC accumulates in body fat and has a prolonged half-life, leading to a large reservoir of stored THC in chronic cannabis users. These particularities might explain CHS during periods of stress [272, 273].

CHS is defined by the following characteristics: (1) severe nausea and vomiting, with a cyclic pattern (≥ 3 cycles/year), with similar onset, duration, and frequency to CVS; (2) a history of regular cannabis use for over 2 years (daily use is frequent); (3) the symptoms disappear after prolonged cannabis cessation. The third criterion is very important for the diagnosis of CHS. Patients who present ≥ 3 cycles/year, should be followed in the first year of abstinence to establish the diagnosis of CHS [266]. Similarly to CVS, CHS has 3 phases: prodromal (can last for month or years, characterized by nausea, abdominal discomfort), hyperemetic (< 1 week) and recovery phase (lasts for days-months) [272]. Typically, patients are young (< 50 years) and use compulsive hot baths/showers to relieve symptoms, but this habit was also reported in other CVS patients. Associated symptoms are abdominal pain and weight loss [233, 274–277]. Most patients start using cannabis in their teenage years, and CHS appears after prolonged, high-dose use in the third decade of life [265]. Most patients with CHS attend the emergency department several times before diagnosis. An initial work-up including biochemical testing, upper gastrointestinal endoscopy and CT scan are commonly performed to exclude organic causes for hyperemesis, but a complete history of cannabis use should always be performed [265].

Statement 57. We recommend that patients with cannabinoid hyperemesis syndrome undergo withdrawal of cannabis. This is the most effective treatment.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 58. We suggest that in acute phases, patients are treated with benzodiazepines, haloperidol, and/or topical administration of capsaicin.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

No high-quality evidence is available on the pharmacological treatment of CHS. Several systematic reviews [265, 278] have been published on data gathered from prospective or retrospective studies, case reports and case series. Based on these reports, the only effective treatment for CHS is abstinence that achieves resolution of symptoms in 96% of cases [265]. Unfortunately, many patients are unwilling to follow this advice [270], or resume cannabis usage with the consequent relapse of CHS. It is unclear how long patients must be abstinent for their symptoms to start improving. This can vary and may take several months because of the cyclical nature of the attacks and because of the accumulation of THC in body fat.

Patients with severe dehydration and acute renal failure need fluid replacement [265]. Benzodiazepines, haloperidol [278, 279] and topical administration of capsaicin [280–282] were reported as useful in acute phases. Some reports showed that topical capsaicin decreased the total medications administered [283], while other studies did not find this association [284]. Ondansetron, the first drug used as antiemetic in the emergency department, was ineffective for CHS treatment [279]. A recent prospective observational study reported good results in patients with presumed CHS in acute phase, with intravenous ketamine and chlorpromazine [285]. Opioid analgesics should be avoided, as they can determine bowel dysfunction and emesis, and thus can worsen symptoms [265, 271]. There are limited data from case reports or small observational studies on the efficacy of prophylactic (i.e., tricyclic antidepressants, propranolol) or abortive treatments (i.e., aprepitant) in CHS [266, 278, 286, 287].

4.4 | Rumination Syndrome

4.4.1 | Definition

Statement 59. Rumination is a voluntary but unconscious process in which patients effortlessly bring up recently ingested food from the stomach into the mouth, where it is often then chewed again and re-swallowed.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Rumination is characterized by an abrupt and simultaneous increase in activity of the intercostal and muscles of the anterior abdominal wall, which brings up recently ingested food. Ruminated content may be reswallowed or spat out [288]. Rumination may be accompanied by weight loss and may be easily confused with vomiting [289–291].

Rumination should be differentiated from regurgitation, as a symptom of gastroesophageal reflux and oesophageal motility disorders, which is characterized by the effortless and

TABLE 2 | Differential features of vomiting, rumination and regurgitation.

		Vomiting	Rumination	Regurgitation
General features	Source	Stomach	Stomach	Oesophagus/stomach
	Content	Food or secretions	Food	Food or secretions
Associated symptoms	Nausea	Yes	No	No
	Retching	Yes	No	No
	Re-swallowing	No	Frequent	Rare
Mechanism	Relation to meals	Fasting or postprandial	Postprandial	Fasting or postprandial
	Abdominal wall contraction	Yes, forceful	Yes, inadvertent	No
	Mediation	Reflex	Behavioural	Passive

involuntary movement of gastric or oesophageal content to the mouth without abdominal wall contractions, not preceded by nausea, and is not accompanied by the various physical phenomena associated with vomiting [1, 288, 289] (Table 2).

4.4.2 | Epidemiology

Statement 60. The prevalence of rumination syndrome in the adult general population is likely between 0.5% and 5.8% depending on the study population. It is higher in selected populations such as therapy refractory GERD, children, and adolescents.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

There are several studies among adults in the general population which have reported prevalence rates of 0.8% in Mexico [292, 293] as well as Canada [294], and 0.5%–0.9% in Australia [295, 296]. A higher prevalence rate was demonstrated in the United States of residents in Olmstead County, Minnesota, which found a 5.8% [297]. The larges study to date with 54,127 participants from 26 countries showed a prevalence of 3.1% [298]. However, studies on selected populations have reported a higher prevalence of rumination syndrome, such as patients with eating disorders (7%) or fibromyalgia (8%) [299, 300]. Several studies have also suggested that the syndrome is more common in children, adolescents (0%–7%), and patients with developmental, or psychiatric disorders [301–305]. The prevalence has also been suggested to be higher than the general population in patients with therapy refractory gastroesophageal reflux disease (GERD, up to 20%–46%) [306]. The prevalence of rumination syndrome also differs depending on which threshold of the frequency of rumination episodes is chosen. Patients with several episodes a day constitute a minority of the rumination syndrome population but are likely more common among patients seeking health care [298, 307].

4.4.3 | Signs and Symptoms

Statement 61. Dyspeptic symptoms and minor weight loss are common in patients with rumination syndrome.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: very low

Statement 62. Enhanced visceral pain perception and poor postprandial accommodation of the stomach have been proposed as the mechanisms for epigastric pain and the feeling of "bloating" in patients with rumination syndrome.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: very low

Research into the association of epigastric symptoms and rumination syndrome in the medical literature is scarce. Up to 38% of patients complained of abdominal pain in a study involving children and adolescents [308].

The pathophysiology of epigastric symptoms in patients with rumination syndrome is poorly understood. Enhanced visceral pain perception and poor postprandial accommodation of the stomach have been proposed as mechanisms for epigastric pain and the feeling of "bloating" [309]. Rumination may well be an effort to reduce/relieve abdominal pain and/or bloating by "tensing the anterior abdominal wall muscles" which may then become a subconscious, maladaptive behaviour [113].

4.4.4 | Pathophysiological Mechanisms

Statement 63. The mechanism of rumination syndrome is a voluntary but unconscious process that generates a coordinated abdomino-thoracic muscle response consisting of increased intrabdominal pressure associated to low LOS and intrathoracic pressures.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 64. The triggering of rumination events is not completely clear but they may be secondary to dyspeptic symptoms as subject seek relief through regurgitation and/or venting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

The proposed mechanism of rumination syndrome is an increase in intra-abdominal pressure, due to straining of the abdominal wall muscles, usually not intentionally, and simultaneous expansion of the chest along with diaphragm relaxation, which overcomes the pressure at the lower oesophageal sphincter (LOS), leading to ascent of gastric content due to the lower intrathoracic pressure [289, 291]. The upper oesophageal sphincter also relaxes with a forward motion of the head, allowing the contents of the oesophagus to enter the mouth and be re-masticated or spat out.

The process is usually started by the stimulus of a food bolus, and three different types of rumination have been described [310, 311]. First, a primary form of rumination with no specific cause has been identified. Second, where GERD can initiate a rumination event, and third, supragastric belching which also can initiate a rumination event. Rumination syndrome can also be misinterpreted as therapy refractory GERD, with or without associated supragastric belching [306, 312, 313].

Several diagnoses and conditions associated with rumination syndrome have been identified but no causative factor has been conclusively recognized. Studies have demonstrated an overlap with functional dyspepsia, and it has been suggested that rumination syndrome may be triggered by dyspeptic symptoms, as subjects seek relief through venting [297, 314]. Gastric accommodation and emptying in rumination syndrome is probably not of key importance, but gastric sensation may be higher, so less pressure is needed to induce LOS relaxation, which predisposes for rumination episodes [290, 309, 315]. Psychiatric comorbidities such as depression, anxiety, and eating disorders are more common in subjects with rumination syndrome [295, 298, 316].

4.4.5 | Associations

Statement 65. Functional dyspepsia, gastroparesis, cyclic vomiting, and other disorders of gut-brain interaction can overlap and increase the likelihood of rumination syndrome.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 66. Gastro-oesophageal reflux disease and pathological supragastric belching can be mechanisms that provoke and/or aggravate rumination syndrome. In cases of non-responsive gastroesophageal reflux disease, consideration should be given to rumination syndrome.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Rumination syndrome is categorized as primary or idiopathic and secondary when associated with gastroesophageal reflux and/or supragastric belching [310, 317, 318]. Rumination syndrome is a cause of persistent, non-responding gastroesophageal reflux disease in both adults [306, 318] and paediatrics [306]. Supragastric belching can elicit regurgitation episodes in patients with rumination syndrome and also aggravate oesophageal acid exposure [306, 319, 320]. There is emerging evidence that a subset of patients with rumination syndrome have duodenal eosinophilic inflammation [321, 322], supporting an overlap with functional dyspepsia [297]. Rumination syndrome can overlap with gastroparesis [150, 323], but patients with rumination syndrome can demonstrate either a delay or an acceleration in gastric emptying [315]. Rumination syndrome can also overlap with cyclical vomiting syndrome [298], and the presence of gut-brain interaction disorders generally increases the likelihood of rumination syndrome [298].

4.4.6 | Psychosocial Factors

Statement 67. Rumination syndrome is independently associated with depression and anxiety. Patients with rumination syndrome have a lower physical and mental quality of life and increased somatic symptom reporting (somatization).

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Statement 68. In patients with rumination syndrome, a current or previous associated eating or psychiatric disorder should be considered.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

A cross-sectional observational study of adults in the United States found rumination syndrome to be independently associated with depression (OR 1.10, 95% CI 1.05–1.16) [297]. A large global epidemiology study of gut-brain interaction disorders found rumination syndrome to be independently associated with anxiety (OR 1.8, 95% CI 1.6–2.1) and depression (1.5, 95% CI 1.3–1.7) [298]. Subjects fulfiling the criteria for rumination syndrome had lower physical and mental quality of life, and increased somatic symptom reporting compared with controls. Moreover, increasing frequency of rumination episodes was associated with a clear trend to lower physical and mental quality of life, and greater severity of somatization [298]. In a case-control study of 72 patients (24 with rumination syndrome and 48 controls), those with rumination syndrome had a significantly higher prevalence of eating disorders (37.5% vs. 4.2%, OR 16.4) and psychiatric disorders (83% vs. 50%, OR 4.5) compared with controls [324]. Specifically, the

risks of both anorexia nervosa (16.7% vs. 0%) and bulimia nervosa (21.1% vs. 0%) were increased in patients with rumination syndrome [324].

4.4.7 | Diagnosis

Statement 69. Combined clinical and objective assessment using high-resolution manometry impedance is recommended to confirm the diagnosis of rumination.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Rumination syndrome is a global clinical entity [298] and is described as a mental disorder in DSM-5 and ICD-11 [325], but as a functional gastrointestinal disorder called rumination syndrome in the Rome classification system [326]. Rome IV includes six diagnostic criteria for rumination syndrome in adults [326]. Although the clinical presentation of rumination syndrome shares some symptoms with other gastrointestinal disorders [113, 288, 321, 327–333], a large proportion of patients can be identified based on the clinical features of rumination [113, 321, 334]. Surprisingly, no validated screening instruments or questionnaires are available for rumination disorder. Single-item screening for regurgitation or re-swallowing of food are included in several questionnaires [335], for instance, the STEP [335, 336]. In terms of rumination diagnostic interviews, the EDA-5 [337] and the PARDI [338] include questions related to rumination syndrome, but validation studies are required to determine the utility and accuracy of these tests [335].

In contrast, the objective testing of rumination has received a lot of attention in the literature during the last decade. The diagnosis of rumination has been studied using postprandial high-resolution oesophageal manometry [312, 323, 339, 340], pH-impedance studies [306] or high-resolution impedance manometry [318, 341]. High-resolution manometry (HRM), manometric findings in patients with rumination syndrome show an increase in intragastric pressure of > 30 mm Hg associated with oesophageal pressurization and a clinically recognized rumination episode [310]. There is proximal movement of the gastroesophageal junction from the intra-abdominal cavity into the thorax due to increased intra-abdominal pressure at the onset of rumination episodes [311, 342–345]. In case of diagnostic uncertainty [323], manometric evaluation combined with pH-impedance monitoring may confirm the diagnosis [306, 312, 346]. Whether HRM is superior to conventional manometry in the diagnostic work-up of the rumination syndrome needs to be determined in future studies [347]. A large proportion of regurgitation episodes in patients with rumination syndrome are weakly acidic, so pH-impedance monitoring is superior to pH-metry for the detection of regurgitation episodes in rumination patients [306, 346, 348]. However, rumination episodes could not be distinguished from GERD on pH-impedance studies using standard reflux metrics [349]. More "reflux" episodes are noted to extend to the proximal oesophagus in rumination [349]. Baseline impedance values are similar in rumination and GERD, and are not useful for discriminating between these conditions [350]. Combined ambulatory high-resolution manometry and pH-impedance had an 86% sensitivity for identification of rumination episodes in a small case series, but this technique is not universally available for clinical use [306, 312, 346]. When rumination is suspected in patients with refractory postprandial regurgitation, high-resolution manometry with impedance (HRIM) (stationary, postprandial [351]) is indicated to distinguish rumination from GERD [312, 318, 352–354]. HRIM allows combined evaluation of oesophageal function, bolus transit and clearance [354]. When performed during postprandial periods or following test meals, HRIM can be used to diagnose rumination [354], as it allows detection of increased gastric pressure as well as retrograde bolus flow. This use of postprandial HRIM to document rumination may help indicate behavioural therapies amongst patients with ongoing symptoms despite PPI therapy [318]. This is crucial, considering that rumination can benefit more from behavioural interventions than from medical therapy or surgery [318, 354, 355].

4.4.8 | Non-Pharmacological Treatment Options

Statement 70. Diaphragmatic breathing with or without biofeedback (visual or verbal feedback on abdominal, intercostal, or diaphragm muscle activity using either electromyography or oesophageal impedance manometry) is the first-line therapy for rumination syndrome.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Medical treatments for rumination syndrome are limited [356]. The most studied and effective therapy for rumination syndrome is diaphragmatic breathing with or without a biofeedback component. Biofeedback means that patients receive visual or verbal feedback on abdominal, intercostal or diaphragm muscle activity using either electromyography or oesophageal high-resolution impedance manometry.

Diaphragmatic breathing without biofeedback can be taught to patients and is effective, but rumination episodes restart promptly when patients resume their normal breathing pattern [357]. This was evaluated in a study of 16 patients who were instructed in diaphragmatic breathing during a postprandial HRIM: the technique led to decreased gastric pressure and increased esophago-gastric junction pressure [357]. The strongest evidence of benefit of diaphragmatic breathing with biofeedback comes from two single randomized trials. In the first, patients with rumination syndrome learnt the biofeedback technique based on electromyography (EMG)-guided control of abdomino-thoracic muscular activity. In three biofeedback sessions, patients were instructed to voluntarily reduce the activity of intercostal and anterior abdominal muscles and to increase the activity of the diaphragm and were given visual feedback on muscle activity shown on a monitor, after each biofeedback session. Patients were instructed to perform the same exercises daily at home for 5 min before and after meals. With this

TABLE 3 | First- and second-line pharmacological and behavioural therapeutic options for gut-brain interaction disorders with predominant rumination/nausea/vomiting.

	1st line	2nd line
Cyclic nausea and vomiting (prophylaxis)	Tricyclic antidepressants	Zonisamide, levetiracetam, L-carnitine, coenzyme Q10, aprepitant
Cannabinoid hyperemesis	Quitting use of cannabinoids Acute vomiting phase: Benzodiazepines, haloperidol	Acute vomiting phase: Topical administration of capsaicin
Rumination syndrome	Diaphragmatic breathing (+/− biofeedback)	Baclofen, tricyclic antidepressants
Nausea and vomiting syndrome	Tricyclic antidepressants, mirtazapine, dopamine D2 antagonists, 5-HT3 antagonists	Gabapentin, olanzapine, NK-1 antagonists

technique, regurgitation episodes decreased significantly from 27 ± 1 regurgitation episodes/day at baseline to 8 ± 2 episodes/day immediately after treatment [291]. Applying the same methodology in a second study, 24 patients were randomized to either diaphragmatic breathing with biofeedback or placebo. Only patients receiving biofeedback treatment reduced rumination activity [358]. In rumination syndrome psychological interventions (e.g., cognitive behavioural therapy (CBT), hypnosis) have been used but there are no randomized studies to demonstrate the objective response [359].

4.4.9 | Pharmacological Treatment Options

Statement 71. In patients with rumination syndrome pharmacological treatment with baclofen or tricyclic antidepressants can be used if diaphragmatic breathing/biofeedback are not available or patient does not respond.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Statement 72. In patients with secondary rumination syndrome, it is necessary to treat underlying gastroesophageal reflux with PPI.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Baclofen has been proposed as a pharmacological agent for rumination syndrome because it increases the pressure and reduces transient relaxations of the lower oesophageal sphincter. An initial open-label study found that baclofen decreased the number of rumination episodes by 68% [360]. A subsequent randomized, placebo-controlled study confirmed this finding to a milder degree [356]. This later study also found that some patients taking baclofen experienced notable side effects, including sleepiness, dizziness, and acral paraesthesia, but these resolved in less than 2 days in all cases.

A single open-label study evaluated the effect of combining diaphragmatic breathing with low-dose tricyclic antidepressants, with the objective of reducing the associated gastric visceral hypersensitivity and anxiety, and found that 91% of patients with rumination syndrome reported an improvement in their symptoms [361] (Table 3).

4.4.10 | Nutritional Support

Statement 73. Although most patients with rumination syndrome have only modest weight loss, patient-tailored dietetic assessment for severe cases of rumination is indicated.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Although patients with rumination syndrome have only modest weight loss [308, 334, 362], some case reports describe severe malnutrition and need for nutritional support [363–365]. To date, no data on specific macro-/micro-nutrient deficiencies in patients with rumination have been reported in the literature. However, a dietetic assessment performed as part of a multidisciplinary team approach is considered appropriate for the most severe cases [364].

4.5 | Chronic Nausea and Vomiting Syndrome

4.5.1 | Definition

Statement 74. Chronic Unexplained Nausea is defined by the presence of bothersome nausea, at least twice per week on average, in the absence of abnormalities at upper endoscopy or other disease that explains nausea, with symptoms present the last 3 months and started at least 6 months ago.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: high

Statement 75. Chronic Unexplained Vomiting is diagnosed in patients who had on average at least one episode of vomiting per week, in the absence of an eating disorder, rumination, or major psychiatric disease, in absence of self-induced induced vomiting,

chronic cannabinoid use, or abnormalities in the central nervous system or metabolic diseases likely to explain the recurrent vomiting, with symptoms present the last 3 months and started at least 6 months ago.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

While the sensation of "nausea" is readily expressed by chronic nausea and vomiting syndrome (CNVS) patients, its meaning is not uniform across subjects and cultures, and to some patients it represents a generalized sense of malaise and even fatigue [366]. The Rome consensus defined nausea in the classical medical symptom sense, as a sick sensation that precedes the need or desire to vomit, and which may be felt predominantly in the epigastrium or the throat [314]. Vomiting is defined as the forceful oral expulsion of gastric contents associated with contraction of the muscles of the abdominal and chest wall.

The Rome IV consensus defined chronic nausea and vomiting syndrome based on the presence of chronic unexplained nausea and/or chronic unexplained nausea vomiting following the criteria stated above [314].

4.5.2 | Epidemiology

Statement 76. Chronic nausea and vomiting syndrome, as defined according to the Rome IV criteria, has an estimated prevalence of 1%.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Data on the epidemiology of CNVS in the scientific community is scarce [1]. The highest quality evidence is available from the Rome Foundation Global Epidemiology Study, in which survey data from 6300 individuals across the United States, UK and Canada was collected [245]. The prevalence of chronic nausea and vomiting syndrome according to the Rome IV criteria was ~1% (58/6300).

Jung et al. evaluated the prevalence of clinically significant chronic nausea in general population in 5096 South Korean individuals via telephone survey [367]. Cases were defined as chronic unexplained nausea after exclusion of organic causes through the meticulous medical examination and if the frequency of nausea was 'more than one day per week'. Its prevalence was 1.6% (1.4%–1.8%) and about 90% of nausea was not accompanied by vomiting. Camilleri et al. reported on results of a telephone survey of 21,128 adults in the United States [368]. Nausea and vomiting were present in 9.5% and 2.7% of individuals at least once during the past 3 months, respectively. When considering a frequency of at least once per week (considered clinically relevant), the prevalence was 2.2% and 0.4%, respectively, for nausea and vomiting.

4.5.3 | Signs and Symptoms

Statement 77. Chronic nausea and vomiting syndrome is characterized by continuous, non-episodic symptoms of unexplained nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Unlike occasional vomiting, for example, in case of functional dyspepsia with other predominant symptoms, unexplained vomiting should occur at least once per month to be considered chronic [314, 369]. Following the Rome IV criteria, CNVS presents with vomiting episodes of ≥ 1/week, with or without nausea for the past 3 months (onset ≥ 6 months before diagnosis) [314]. Vomiting in the absence of nausea may be caused by a central nervous system disease, and other systemic, organic or metabolic diseases should be excluded before considering a diagnosis of CNVS [314]. In addition, vomiting should not be self-induced (e.g., bulimia nervosa with binge episodes) and distinguished from regurgitation and rumination [1, 314].

4.5.4 | Pathophysiological Mechanisms

Statement 78. The development and maintenance of chronic nausea and vomiting syndrome is best explained by the biopsychosocial model of disease encompassing biological, psychological, and social aspects.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: moderate

Studies identified several biological, psychological and social aspects contributing to CNVS. Regarding the biological component, an overlap with migraine has been shown [196, 235, 236, 370, 371]. On a functional basis, gastric emptying may be either normal, accelerated or delayed [245, 372]. Gastric electrophysiology can be altered with abnormal frequency or uncoupling [228, 373], possibly related to histologically visible neuropathies (e.g. fewer interstitial cells of Cajal [374]) or myopathies, serum autoimmune abnormalities [373] or autonomic nerve dysfunction [67–69, 227, 230, 375]. In the brain, chronic nausea and vomiting syndrome may be related to chronic vestibular dysfunction [73].

In terms of the psychological component, an association exists between CNVS and psychological comorbidities [216, 376], symptoms, such as dizziness [377], as well as other functional disorders [229], such as IBS [196, 220] or evacuation disorders [173]. Regarding the social component, independent factors associated with CNVS include increasing somatic symptom severity and lower quality of life [245].

4.5.5 | Associations

Statement 79. Independent factors associated with chronic nausea and vomiting syndrome are younger age, presence of IBS, and functional dyspepsia.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: moderate-C

As the aetiology of CNVS is diverse and not limited to the gastrointestinal tract, it is difficult to find common predisposing factors. There is limited data in the literature about this topic, most based on expert opinions derived from review articles [1, 224, 314, 378]. Consequently, the level of evidence is low. Aziz 2019 et al. reported that independent factors associated with functional nausea and vomiting disorders are younger age, presence of IBS and functional dyspepsia [245].

4.5.6 | Psychosocial Factors

Statement 80. Psychological distress with mood disorders, anxiety disorders, somatization disorders, and catastrophizing may be associated with chronic unexplained nausea and vomiting.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

CNVS adheres to a biopsychosocial model in the field of neurogastroenterology, resulting from complex and reciprocal interactions between biological, psychological, and social factors, rather than from linear monocausal etiopathogenic processes [224, 250, 314, 379]. Indeed, symptoms are conceptually generated based on a complex interaction between factors such as gut dysbiosis, altered mucosal immune function, altered gut signalling (e.g. visceral hypersensitivity), and central nervous system dysregulation of the modulation of gut signalling and motor function. The physiologic feature of gastric emptying may be either normal, accelerated or delayed [245]. A stressful life and emotional events are associated with symptom exacerbation [376, 379, 380], and early-life adverse events, such as physical or sexual abuse, are also prevalent [379, 381]. Nausea is a common symptom in patients with pain-associated functional gastrointestinal disorders that correlates with poor school and social functioning [382] and reduces patients' quality of life [383]. A perturbation in interoception processing is probably also involved [2, 384]. Psychological distress with mood disorders, anxiety disorders, somatization disorders, and catastrophizing may also be associated.

4.5.7 | Diagnosis

Statement 81. Chronic nausea and vomiting syndrome is diagnosed based on clinical criteria after previous exclusion of systemic, organic, or metabolic diseases by objective testing.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: low

Following the Rome IV criteria, possible systemic, organic or metabolic diseases should be excluded before a diagnosis of CNVS [314]. Although the endoscopic detection of food in the stomach after an overnight fast may be indicative of gastroparesis, confirmation of delayed gastric emptying with scintigraphy or breath tests is mandatory according to the recent European consensus on gastroparesis [1, 133]. Following exclusion of a mechanical obstruction, antroduodenal manometry is useful to exclude dysmotility [1, 314]. In addition, oesophageal manometry or pH-testing is indicated when suspecting achalasia or gastro-esophageal reflux, respectively [1, 314]. Metabolic abnormalities (less common and usually presenting with CVS in childhood) require more complex plasma (ammonia, amino acids) and urine (organic acids, amino-levulinic acid and porphobilinogen levels) testing [205, 314].

Recordings of gastric myoelectrical activity by electrogastrography (EGG), may identify dysrhythmias in patients with chronic unexplained nausea and vomiting, although this technique is only available at highly specialized centres [385]. Recently, the technique has evolved to high-resolution electrogastrography mapping, and shown to detect electrophysiological patterns that correlate with specific gastroduodenal symptom profiles [386].

Histological and molecular analyses of full-thickness gastric biopsies from patients with chronic unexplained nausea and vomiting have evidenced a loss of pacemaker interstitial cells of Cajal (ICCs) and macrophage-based immune dysregulation [374, 387]. At present, gastric full-thickness biopsies are surgically obtained at specialized referral centres for comprehensive evaluation of patients with severe refractory unexplained nausea and vomiting [388].

4.5.8 | Non-Pharmacological Treatment Options

Statement 82. In refractory cases of chronic nausea and vomiting syndrome, gastric electrical stimulation can be considered.

Statement endorsed in R2, median panel: 4—Appropriate/agreement

Quality of evidence: moderate

Besides pharmacological treatments, as in irritable bowel syndrome, a non-pharmacological approach to CNVS based on the dogma of gut-brain interaction disorder is possible. However, the available data on hypnosis, cognitive behavioural therapy and others are poor or fragmented, or apply to non-functional GI disorders. Several bioelectric therapies have been advocated for CNVS. The most well studied is gastric electrical stimulation (GES). A recent meta-analysis including 730 patients concluded that GES improves gastroparesis symptoms and specifically reduces the frequency of weekly vomiting episodes [389]. GES is effective in the long-term in patients with medically refractory

nausea and vomiting, showing an efficacy of 50% at 5 years [390] and 10 years [391] in an intention-to-treat analysis. Non-invasive vagus nerve stimulation performed for 4 weeks in patients with idiopathic gastroparesis significantly improved nausea/vomiting but there was no control group [392].

Hypnotherapy (gut-directed hypnotherapy, 3-month intervention period) is more effective than standard medical treatment in reducing nausea symptoms in children with functional nausea during treatment and at the 6-month follow-up visit, but not at the 12-month follow-up evaluation [393, 394]. Hypnosis is of interest in the management of anticipatory nausea and vomiting [395] and nausea and vomiting in cancer therapy [396] or pregnancy [397] and could be extrapolated to CNVS in adults. Hypnotherapy could possibly be used to treat early-life trauma with hypno-analysis. One study suggested that acupressure wristbands were ineffective in relieving nausea and vomiting in hospice patients [398]. Most studies of complementary and alternative therapies for nausea and vomiting have been performed in the setting of chemotherapy and anticipatory nausea and vomiting. Treatments investigated have included behavioural therapies, acupuncture, and ginger, but it is unclear if such strategies can be extrapolated to patients not undergoing chemotherapy [399]. An integrative healthcare model with heartfulness meditation and care coordination improved outcome in CVS [400] but data are lacking in CNVS.

4.5.9 | Pharmacological Treatment Options

Statement 83. Histamine H1 antagonists (e.g., meclizine, promethazine) are effective for the treatment of chronic nausea and vomiting.

Statement Endorsed in R2, median panel: 4—Appropriate/neutral

Quality of evidence: low

Statement 84. Muscarinic M1 antagonists (e.g., scopolamine) are effective for the treatment of chronic nausea and vomiting.

Statement Endorsed in R2, median panel: 3—Uncertain/disagreement

Quality of evidence: low

Statement 85. Dopamine-2 antagonists are effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Statement 86. 5-HT3 antagonists are effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Statement 87. Tricyclic antidepressants are effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Statement 88. Mirtazapine is effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

Statement 89. Gabapentin is effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R2, median panel: 3—Uncertain/disagreement

Quality of evidence: low

Statement 90. Olanzapine is effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R2, median panel: 4—Appropriate/neutral

Quality of evidence: low

Statement 91. Cannabinoids are effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R2, median panel: 3—Uncertain/neutral

Quality of evidence: low

Statement 92. NK-1 antagonists are effective for the treatment of chronic nausea and vomiting.

Statement endorsed in R1, median panel: 4—Appropriate/agreement

Quality of evidence: low

The pharmacological treatment of CNVS has been addressed in only a relatively small number of studies. Several classes of drugs with antiemetic capabilities have been developed, including histamine H1 antagonists (e.g. meclizine, promethazine), muscarinic M1 antagonists (e.g. scopolamine), dopamine D2 antagonists (e.g. prochlorperazine), serotonin 5-HT3 antagonists (e.g. ondansetron, granisetron), neurokinin NK1 antagonists (e.g. aprepitant), and cannabinoids (e.g. dronabinol) [250, 401] (Table 3). A few case series of 5-HT3 antagonists, approved in the setting of cancer chemotherapy, report efficacy in nausea and vomiting, mostly in patients with gastroparesis [402–404].

Tricyclic antidepressant agents (e.g. amitriptyline, nortriptyline, desipramine) have been reported as beneficial in uncontrolled series of patients with functional vomiting, while in one controlled trial in functional dyspepsia, amitriptyline improved nausea [405, 406]. In a retrospective report of 94 patients fulfiling Rome III criteria for chronic idiopathic nausea or functional vomiting, 72% experienced at least moderate symptomatic improvement and 22% noted symptom remission with neuromodulators—primarily tricyclic agents (66 patients), but also norepinephrine dopamine reuptake inhibitors (10 patients), selective serotonin reuptake inhibitors (5 patients), serotonin norepinephrine reuptake inhibitors (5 patients), and other agents (9 patients) [405]. An open-label series and several case reports suggest efficacy with mirtazapine, an antidepressant that has nausea-suppressive properties probably due to histamine-1 receptor antagonism [407, 408]. In a controlled trial in functional dyspepsia, mirtazapine improved nausea [409].

Emerging data from other indications support potential efficacy with other neuromodulators, such as the delta ligand gabapentin, the atypical antipsychotic agent olanzapine, and cannabinoids, but evidence on these agents in the treatment of chronic nausea and vomiting syndrome remains scant [408]. While cannabinoids may have some efficacy in chemotherapy-induced nausea and vomiting, studies in CNVS are lacking [410]. The NK1 antagonist aprepitant improved nausea and vomiting symptoms in a controlled trial in patients with symptoms suggestive of gastroparesis, but a large subset of this series had a normal gastric emptying rate [411].

The identification of serum autoantibodies again various channelopathies has led to the use of intravenous immunoglobulin in patients with severe refractory nausea and vomiting [412, 413].

4.5.10 | Nutritional support

Statement 93. In patients with chronic nausea and vomiting syndrome, attention must be given to adequate nutrition, including vitamins and minerals.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: very low

Statement 94. Nutritional deficits shall be corrected by dietary modifications and oral supplementation, if possible.

Statement endorsed in R1, median panel: 5—Appropriate/agreement

Quality of evidence: very low

There are no relevant scientific studies that have investigated the role of nutritional support for patients with CNVS. However, there is literature on nutritional management of gastroparesis which may have clinical implications for the treatment of patients with CNVS.

In a study on 305 patients with gastroparesis the BlockBrief 2000 food frequency questionnaire was used to estimate caloric, vitamin and mineral intake [414]. They observed that mean caloric intake was reduced to 58% of daily energy requirements and that 64% of patients reported caloric-deficient diets, defined as less than 60% of estimated energy requirements. Deficiencies were also shown for several vitamins and minerals.

Published reviews and guidelines [12, 62, 114, 117, 133, 415] generally suggest that dietary modifications represent the first line of treatment for gastroparesis, regardless of disease severity. As patients often have early satiety, they are recommended to eat small meals and to avoid foods high in fat and indigestible fibres because they delay gastric emptying [62, 416]. When small meals are eaten, more frequent meals may be required to maintain caloric intake. Patients are advised to consume liquids as the gastric emptying of caloric liquids or homogenized solids is often preserved in patients with gastroparesis [62, 417]. A high-fat diet with solid meals increases the severity and frequency of symptoms among patients with gastroparesis [416], whereas a small-particle-size diet reduces upper GI symptoms in patients with diabetic gastroparesis [418].

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.