



School of Continuous
Professional Development

EVALUATION OF NAUSEA (AND VOMITING)

ALABAMA GASTROENTEROLOGICAL SOCIETY
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DISCLOSURES

- NONE DIRECTLY RELEVANT TO THIS LECTURE
- RESEARCH FUNDING FOR GI MOTILITY DISORDERS (G-TECH)
- RESEARCH FUNDING FOR IBS (VIRTUAL REALITY – IRONWOOD/ABBVIE)
- SCIENTIFIC ADVISORY BOARDS: ARDELYX, IRONWOOD, GSK, FERRING

LEARNING OBJECTIVES

- Recognize common causes of chronic nausea and vomiting
- Appreciate the complex physiology of nausea and vomiting
- Discuss effective diagnostic strategies
- Review currently available treatment options

CASE PRESENTATION

- 37-year-old woman referred for a 5th opinion
- Intermittent severe N & V for 8 years
- Episodic, unpredictable; lasts for 2-6 days
- Multiple ER visits
- Diagnosed with idiopathic gastroparesis, CVS, CHS, abdominal migraines
- > 5 EGDs; 7 RUQ US; 8 CT scans; 3 HiDAs; 4 GES; 2 colonoscopies; 3 SBFTs; 1 mesenteric duplex – all normal
- Stable weight; labs normal; K⁺ is occasionally low

CASE PRESENTATION

- No opioids; several tox screens negative for cannabis; occasionally positive for BNZ – she has an Rx for prn use (no lost Rx; no early refills)
- Medication trials: metoclopramide, ondansetron, scopolamine, meclizine, phenothiazines, benadryl, ginger – none have helped
- Psychiatry consult – mild anxiety (no panic attacks)
- PE: BMI = 27kg/m²; mild epigastric tenderness, otherwise normal
- She is frustrated and discouraged
- What to do?

NAUSEA AND VOMITING DEFINED

- Nausea – (*Gr: nautia*) A vague, unpleasant or uneasy feeling in the epigastric area; usually accompanied by the sensation that vomiting might occur. Typically preceded by anorexia
- Objectively, nausea is associated with a reduction in gastric tone and gastric peristalsis; small bowel tone is increased



NAUSEA AND VOMITING DEFINED

- Vomiting – (Latin: *vomere*) Typically preceded by anorexia and nausea. Autonomic symptoms are usually present (hypersalivation, tachycardia, pallor, diaphoresis)



WHAT'S NOT NAUSEA AND VOMITING

- **Regurgitation**

- The effortless movement of gastric liquids or solids up into the mouth or throat; abdominal contractions are not present¹
- A classic symptom of GERD
- Nausea is typically absent; autonomic symptoms are not present

- **Rumination**

- Gastric material is voluntarily brought up into the mouth, chewed and re-swallowed²
- Nausea is typically absent; autonomic symptoms are not present
- Key diagnostic question: when food comes up, what do you do with it?

¹Lacy et al Am J Med 2010; ²Absah et al NGM 2017

WHY IS THIS IMPORTANT?

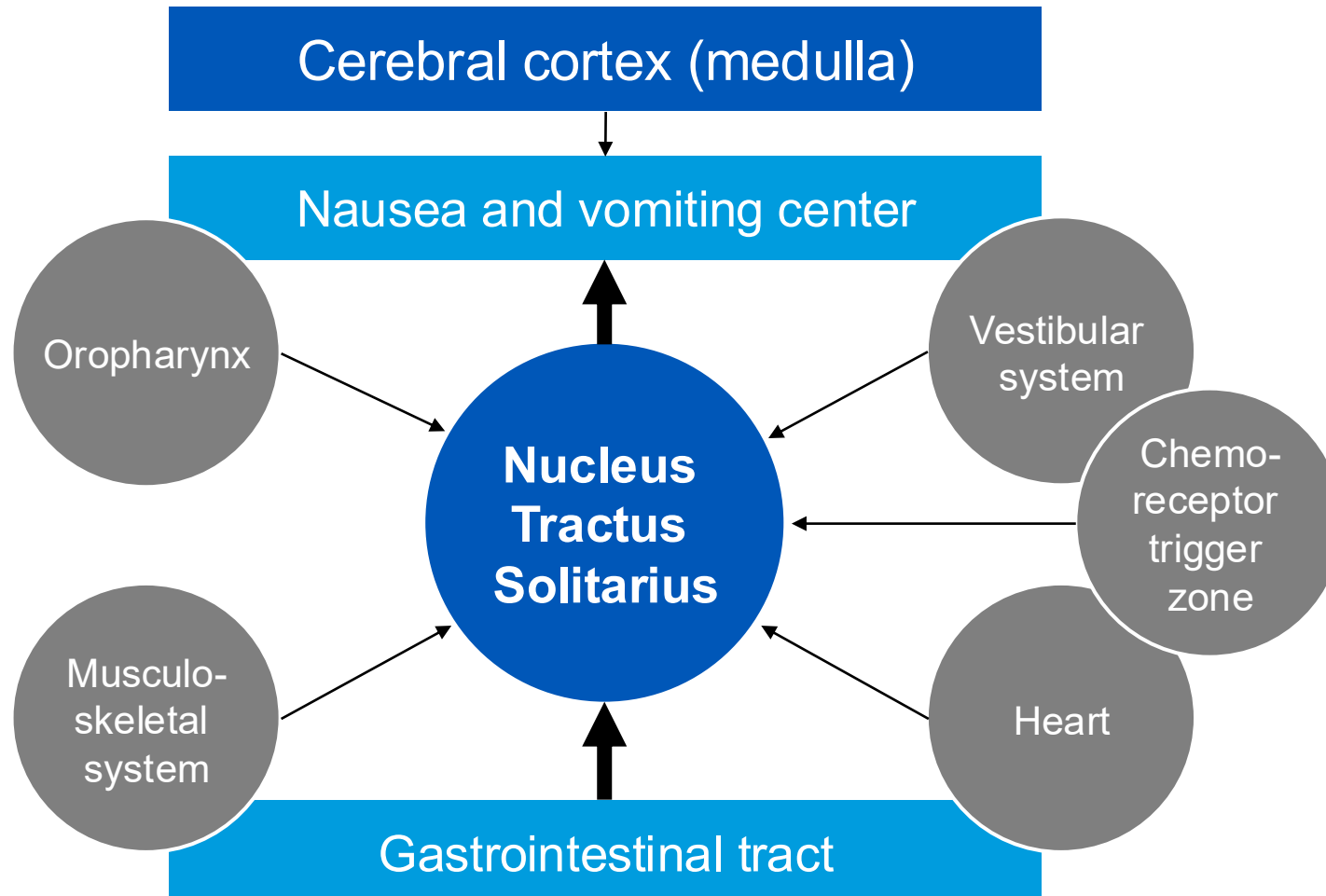
- Common
 - 1 phone survey of 21,128 adults – 7% reported nausea/vomiting in last 30 days¹
 - 50-75% of women during pregnancy
 - A common source of ER visits and out-patient referrals
 - Side effect of chemotherapy (CINV) and surgeries/procedures (PONV)
- Expensive
 - ER and clinic visits, tests, medications, lost work
 - Second most common GI reason for an ER visit²
- Reduces quality of life

¹Camilleri et al, Clin Gastroenterol Hepatol 2005; 3:543-552; ²Myer et al, Am J Gastroenterol 2013; 108:1496-1507

PATHOPHYSIOLOGY OF NAUSEA AND VOMITING



AFFERENT PATHWAYS AND NTS INVOLVED IN NAUSEA AND VOMITING



Neurotransmitters

- Acetylcholine
- Beta-endorphin
- Cortisol
- Dopamine
- Histamine
- Norepinephrine
- Serotonin
- Substance P
- Vasopressin

VOMITING: A COMPLICATED EVENT

- Antral contractions stop; stomach relaxes
- Retrograde small intestine contractions
- Pyloric tone increases
- LES relaxes; UES relaxes
- Abdominal wall contracts; diaphragm contracts
- Respiration briefly ceases; glottis and vocal cords close
- Soft palate rises
- Voila – vomere



NAUSEA AND VOMITING: ACUTE VS CHRONIC

- **Acute:** <7 days in duration
 - Viral
 - Bacterial (E. Coli, Listeria, Salmonella, Campylobacter, Vibrio, Staph)
 - Medications (e.g., chemotherapy, anesthetics, GLP-1-agonists)
 - Toxins (mushrooms, seafood (scombroid), lead, mercury)
 - Somatic disorder (e.g., migraines, MI, musculoskeletal trauma)
- **Chronic:** >4 weeks in duration

COMMON GI CAUSES OF CHRONIC NAUSEA AND VOMITING

- Gastroparesis
- Functional dyspepsia
- Cyclic Vomiting Syndrome (CVS)
- Cannabinoid Hyperemesis Syndrome (CHS)*
- Chronic nausea and vomiting syndrome
- Anatomic causes (GOO, gastritis, PUD, partial SBO, compression)
- Chronic pancreatitis
- Hepatobiliary disorders (acute and chronic hepatitis, infiltrative)

*medical marijuana is now legal in 40 states and the District of Columbia; marijuana is legal in 24 states and the District of Columbia

CAUSES OF CHRONIC NAUSEA AND VOMITING

- Metabolic and endocrine disorders (pregnancy, diabetes, hyperglycemia)
- Chronic intestinal pseudo-obstruction (CIPO)
- Vascular disorders (MALs, SMA syndrome, ischemia)
- CTD (scleroderma, SLE)
- Renal insufficiency
- Vestibular, CNS and neurologic disorders (POTS, dysautonomia, Parkinson's, intracranial hypertension)
- Cardiac
- Eating disorders; psychogenic causes
- Medications and miscellaneous (alcohol, post-vagotomy, post-infectious*)
- Malignancy related (chemotherapy, radiotherapy, disease-related)

*approximately 9% of patients have nausea after covid-19 for up to 6 months

Uncommon Causes of Chronic Nausea and Vomiting

1. Endocrine disorders (hyperthyroidism, Addison's disease, hyponatremia, hyperparathyroidism, hypercalcemia)
2. Paraneoplastic syndromes
3. Radiation-induced
4. CNS disorders (aneurysm, tumor, hydrocephalus, meningitis, pseudotumor cerebri)
5. Nervous system disorders (severe neuropathy, demyelinating disorders, autonomic nervous system disorders)
6. Renal and urologic disorders (nephrolithiasis, obstruction)
7. Severe constipation
8. Retroperitoneal and mesenteric pathology
9. Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
10. Miscellaneous (acute intermittent porphyria, Familial Mediterranean Fever, angioedema, glaucoma, toxins/poisons, mitochondrial disorders, ion channel disorders, food allergies, and intolerances)

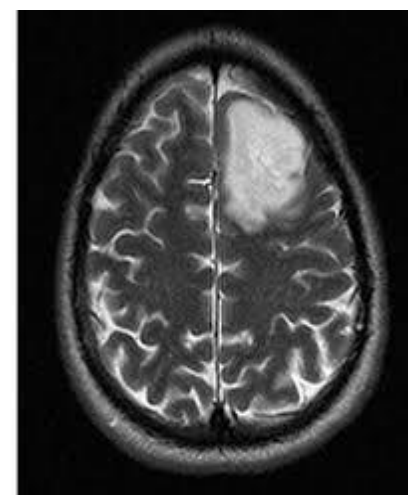
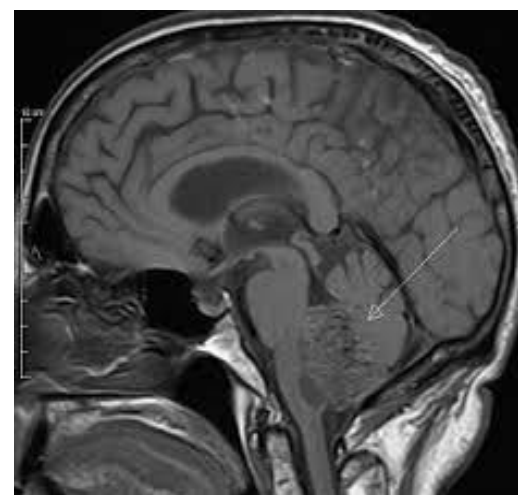
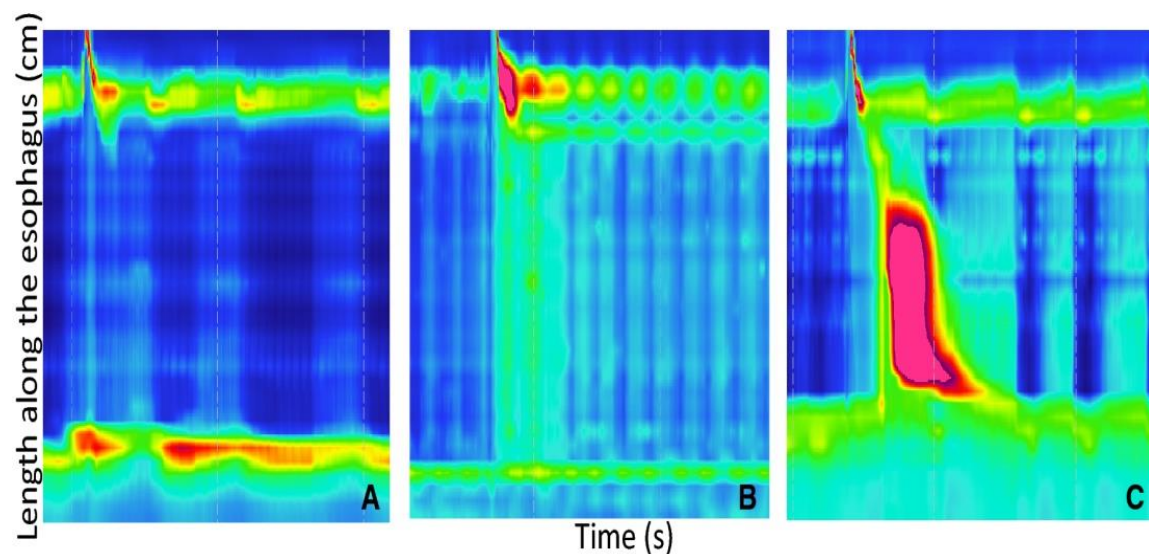
CHRONIC NAUSEA AND VOMITING: IDENTIFYING THE CAUSE

- History
- Physical examination
- Diagnostic tests



TAKING A GOOD HISTORY: POINTS TO PONDER

- Are symptoms acute or chronic in nature?
- Is this really vomiting? (could it be GERD, rumination, achalasia)
 - Forceful vomiting or passive regurgitation?
- Are symptoms GI in nature or outside of the GI tract?
 - Headaches, vertigo, focal neurologic deficits, visual or skin changes



TAKING A GOOD HISTORY

- Medications (including OTC, herbals, supplements, opioids and cannabis)
- Co-morbid conditions (migraines, anxiety, dizziness)
- Prior/recent surgeries
- Warning signs (weight loss, anemia, dysphagia, jaundice)
- Is there associated pain? (biliary, pancreatic, obstruction)
- How frequent are the symptoms?
- Is there concern about the symptoms?
 - Anorexia nervosa, bulimia
- Is there any gain to having these symptoms?

COMMONLY USED MEDICATIONS ASSOCIATED WITH NAUSEA AND VOMITING*

- Opioids
- GLP-1 agonists
- Antibiotics (erythromycin, sulfa, TCN)
- Aspirin and NSAIDs
- Cardiovascular agents (digoxin, anti-arrhythmics, CCB)
- SSRIs (sertraline, fluoxetine)
- Others (colchicine, theophylline, iron supplements)
- Diabetes medications (metformin)
- Oral contraceptives
- Chemotherapeutic agents
- CNS medications (levodopa, anticonvulsants, anti-Parkinson's)
- Agents to treat GI conditions (sulfasalazine, azathioprine)

*3 common mechanisms: stimulation of CTZ, inhibition of gastrointestinal motility, stimulation of vestibular apparatus

TAKING A GOOD HISTORY

- Ask about the timing of vomiting
 - During the meal – likely esophageal
 - Within 1-3 hours of eating – likely gastric related (GP, FD or GOO)
 - Within 3- 6 hours of eating; possible feculent – think small bowel
- Ask about the contents
 - Food vs bile alone vs saliva
- Vomiting before breakfast
 - Consider pregnancy, uremia, alcohol, CNS

TAKING A GOOD HISTORY

- Ask about associated symptoms
 - Early satiety, post-prandial fullness – GP or FD?
 - RUQ or epigastric pain – hepatobiliary or pancreas
 - Colicky pain, distension – small intestine obstruction/compression
 - Pain with weight loss – malignancy, ischemia
 - CNS symptoms – migraines, vestibular dysfunction, tumor

LET'S RETURN TO OUR PATIENT

- Any other questions you'd like to ask?



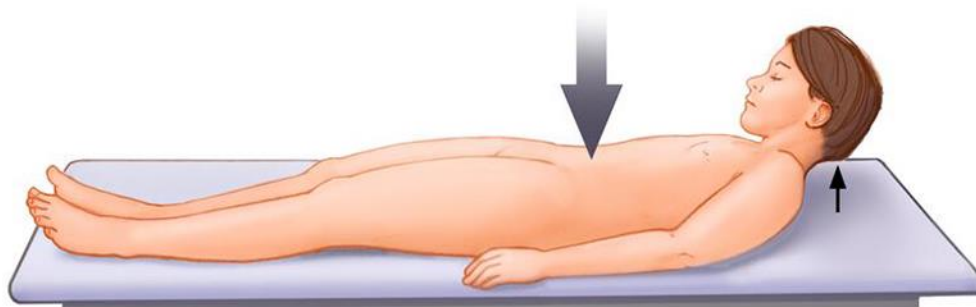
THE ROLE OF THE PHYSICAL EXAMINATION

- Vitals – consider checking orthostatics
- Overall appearance
 - Evidence of dehydration, weight loss, jaundice
- Check for loss of dental enamel; Raynaud's; fingernails, fingers
- ? Succussion splash, bruit, high pitched bowel sounds
- ? Organomegaly or lymphadenopathy
- Check cranial nerves; assess for long tract signs
- ? Carnett's sign



Russell's sign

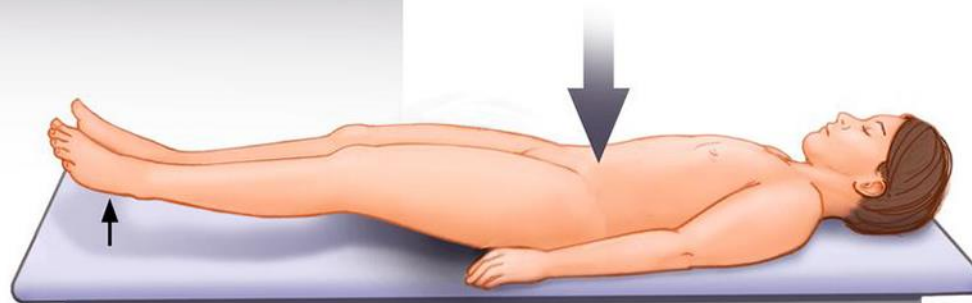
CARNETT'S SIGN



Step 1: The clinician identifies and palpates the point of maximal abdominal tenderness (resting supine position).

Step 2: The patient raises both legs off the examination table (tense position) while the clinician palpates the abdomen. Alternatively, the patient can raise their head and shoulders off the bend, tensing the abdominal wall.

Positive Carnett's sign: Palpation of abdominal muscles in the tense position elicits the same or more tenderness as the rest position → musculoskeletal source (abdominal wall pain).



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DIAGNOSTIC TESTS

- Testing should be directed by the history and exam
- Order tests in a logical manner
- A “shotgun” approach is not helpful and is not reassuring

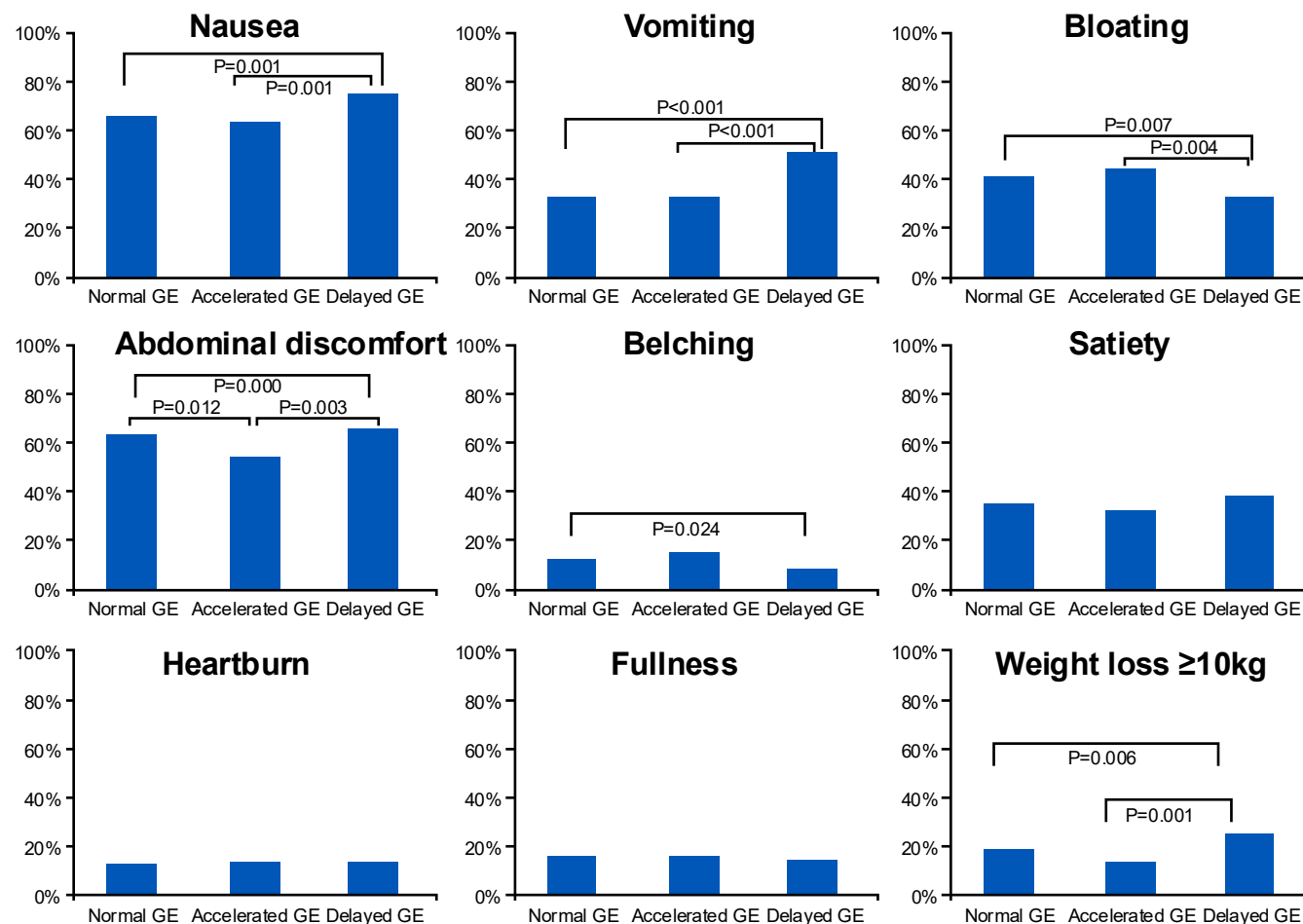
DIAGNOSTIC TESTS – ROUND 1

- Laboratory studies
 - CBC, BMP, albumin
 - Check glucose, Ca^{++} (and HgbA1c, if appropriate)
 - Check for hypokalemic metabolic acidosis
 - Assess for hyponatremia and hyperkalemia of Addison's
 - Toxicology studies (opioids, digitalis, theophylline, salicylates)
- Urine studies – pregnancy, toxicology screen
- KUB
 - ? Dilated stomach; air-fluid levels; large fecal load
- Treat and reassess

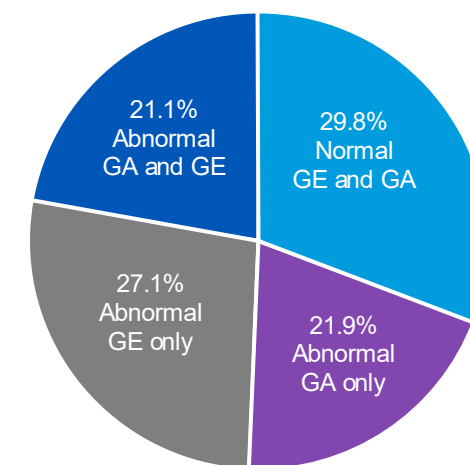
DIAGNOSTIC TESTS – ROUND 2

- Rule out obstruction
 - EGD
 - CTE or SBFT
 - CT or MRI
- Abdominal US
- Evaluate for possible motility disorders
 - 4-hour scintigraphic gastric emptying scan or Spirulina breath test
 - HREM
 - Antroduodenal manometry
 - Wireless motility capsule
- Treat and reassess

GASTRIC EMPTYING SCANS HELP IDENTIFY THE RELATIONSHIP BETWEEN GASTRIC MOTOR FUNCTION AND UGI SYMPTOMS



N (mean ± SD)	1,287
Age (years)	43.1±15.4
Female, n (%)	953 (74.0)
Height (cm)	168.4±8.8
Weight (kg)	70.3±19.3
Body mass index, kg/m ² (n=1,221)	24.7±6.2



Pie chart showing percentages of four groups of gastric motor functions in the 1,287 patients with upper functional gastrointestinal symptoms

Association of dyspeptic symptoms and gastric emptying. Patients with delayed GE had more frequent nausea, vomiting, and weight loss ≥10kg than those with accelerated or normal GE (all $P < 0.05$). Patients with delayed GE had less frequent bloating than those with normal and accelerated GE (all $P < 0.05$).

Redrawn from Park et al, Am J Gastro, 2017: 112

DIAGNOSTIC TESTS – ROUND 3 (RARELY NEEDED)

- Consider tests to evaluate gastric accommodation
 - Nutrient drink test
 - Gastric barostat
 - SPECT
 - MRI

DIAGNOSTIC TESTS – ROUND 4 – SPECIALIZED TESTS

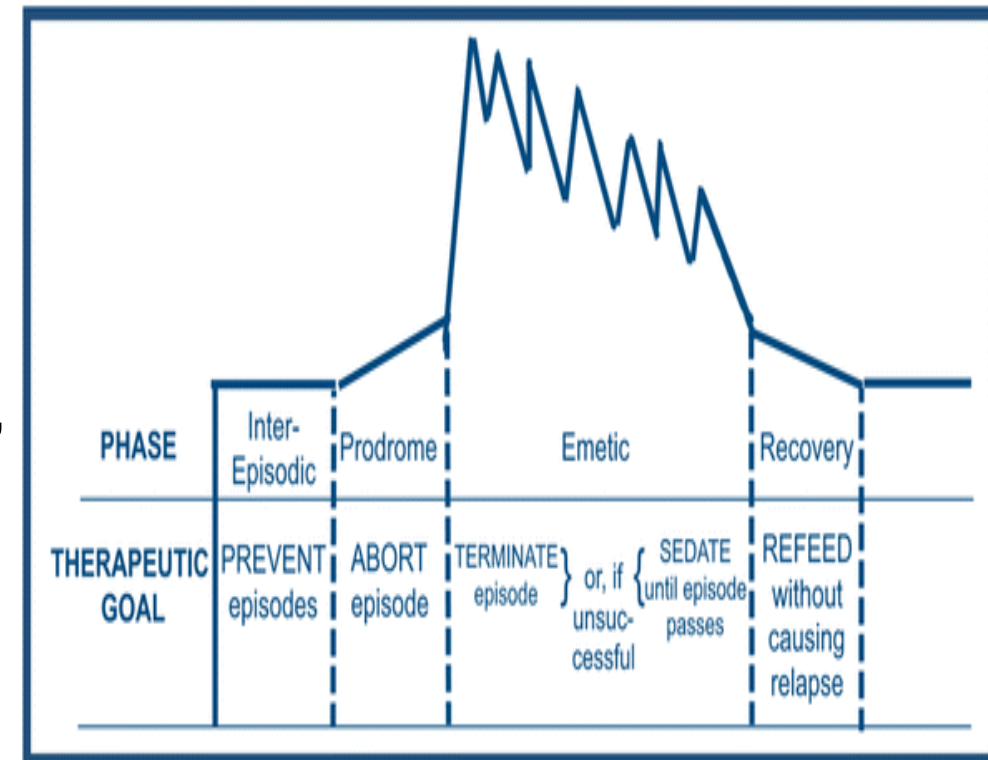
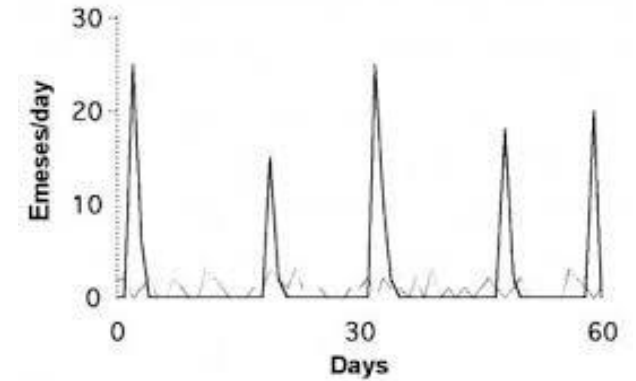
Etiology	Tests	Risk population
Hormonal	TSH, Cortisol, PTH	Weight loss, orthostasis, bowel disturbances
Autoimmune	CRP, ESR, ANA, SCL-70 etc Autonomic function testing	Raynaud's, immune diseases
Paraneoplastic	ANNA-1, Anti-Hu (others)	Old age, smokers
Amyloid	Serum light chains, fat pad bx or rectal bx	Heart problems, back pain
Vascular	CT or MRI angio, duplex US	Known vascular disease, OCP use
Post- vagotomy syndrome	Pancreatic polypeptide testing	Post-surgical patient (i.e., cholecystectomy) Suspected vagal nerve damage

CHRONIC NAUSEA AND VOMITING: MAJOR CAUSES

- Gastroparesis
- Functional dyspepsia
- Cyclic Vomiting Syndrome (CVS)
- Cannabinoid Hyperemesis Syndrome (CHS)
- Chronic unexplained nausea and vomiting

CYCLIC VOMITING SYNDROME

- Recurrent, stereotypical episodes of N & V
- May last hours to days
- Separated by symptom-free intervals (or nearly symptom-free)
- Prevalence in adults unknown; 0.1% in pediatric patients
- Caucasians, males appear more affected
- Average age at diagnosis in adults – 25 yrs
- Physiology unclear
- Treatment approach:
 - Preventative and abortive strategies
- Treatment: TCAs, benzodiazepines, anti-spasmodics, L-carnitine, and standard anti-emetics



B2: NAUSEA AND VOMITING DISORDERS

B2b. Diagnostic Criteria for Cyclic Vomiting Syndrome

Must include all of the following:

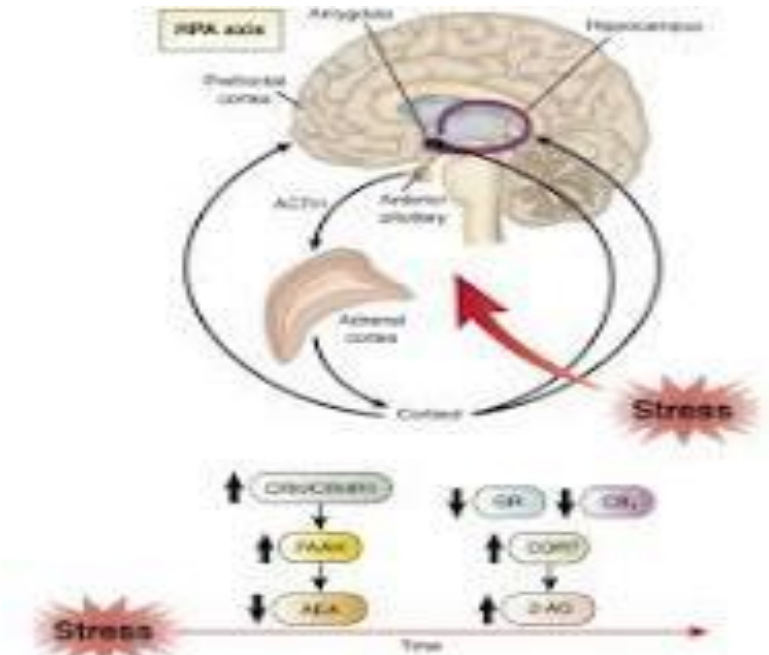
- 1. Stereotypical episodes of repetitive vomiting regarding onset (acute) and duration (up to 10 days)**
- 2. At least 3 discrete episodes in the prior year and 2 episodes in the past 6 months occurring at least 1 week apart**
- 3. Milder symptoms including nausea and isolated vomiting can be present between cycles**

Supportive remark

Personal or family history of migraine headaches

CANNABINOID HYPEREMESIS SYNDROME

- Associated with long term use
- Causes chronic nausea and vomiting
- Often confused with CVS
- Compulsive bathing is (nearly) diagnostic
- Men > women
- Normal labs, endoscopy, radiology
- Tx: stop marijuana use (minimum of 6 months)



B2: NAUSEA AND VOMITING DISORDERS

B2c. Diagnostic Criteria for Cannabinoid Hyperemesis Syndrome

Must include all of the following:

1. **Stereotypical episodic vomiting resembling cyclic vomiting syndrome** in terms of onset, duration, and frequency.
2. **Presentation after prolonged (1 year) and excessive** (≥ 4 days per week and/or ≥ 15 doses per week) cannabis use.
3. **Relief of vomiting episodes by sustained (at least 6 months** or 3 typical emetic cycles) cessation of cannabis use.

Supportive remark

May be **associated with pathologic bathing behavior** (prolonged hot baths or showers)

Prevalence – 0.4% in US

Gastroenterology 2026 1701240-1260

CANNABINOID HYPEREMESIS SYNDROME

Dear Healthcare Providers, Laboratories and Medical Examiners:

The Centers for Disease Control and Prevention (CDC) has issued an alert regarding potential life-threatening vitamin K-dependent antagonist coagulopathy associated with synthetic cannabinoids use (see alert at <https://content.govdelivery.com/accounts/USCDC/bulletins/1eb9503>). Since March 8, 2018, multiple states (IL, IN, MD, MO, WI, PA, KY, VA and FL) have identified at least 160 individuals with serious unexplained bleeding including five deaths. Laboratory testing identified at least 60 cases of vitamin K-dependent antagonist coagulopathy associated with use of synthetic cannabinoids contaminated with brodifacoum (a long-acting anticoagulant rodenticide). The presence of brodifacoum in at least seven synthetic cannabinoid product samples has also been confirmed by laboratory testing. The majority of the cases have occurred in Illinois and have reported using a synthetic cannabinoid product obtained in Illinois. Cases occurring in other locations report no exposure or association with products coming from Illinois.

As of April 30, Florida Poison Information Center Network (PFICN) in collaboration with the Florida Department of Health (the Department) have identified two cases of coagulopathy associated with synthetic marijuana use. Both patients are laboratory confirmed testing positive for brodifacoum.

All identified cases have reported using synthetic marijuana prior to illness. The effects of synthetic marijuana (commonly known as fake pot, fake weed, legal weed, spice, K2, KO, Mind Trip, OMG, Black Giant, Matrix, Scooby Snacks, AK-47, Genie, Sexy Monkey, and others) can be dangerous and sometimes life-threatening.



B2: NAUSEA AND VOMITING DISORDERS

B2a. Diagnostic Criteria* for Chronic Nausea Vomiting Syndrome

Must include all of the following:

1. **Bothersome (i.e. severe enough to affect usual activities)** nausea occurring at least 2 days per week with or without 1 or more vomiting episodes per week.
2. Self-induced vomiting, eating disorders, regurgitation, or rumination are excluded as a cause of vomiting.
3. **No evidence of structural, systemic, or metabolic diseases that is likely to explain the symptoms** on routine investigations.
4. Symptoms predominantly due to postprandial distress syndrome exclude the diagnosis.
5. Predominant nausea and/or persistent vomiting associated with delayed gastric emptying should prompt a diagnosis of gastroparesis.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis

WHICH MEDICATION IS FDA APPROVED FOR CHRONIC NAUSEA AND VOMITING?

- A. Metoclopramide
- B. Scopolamine
- C. Aprepitant
- D. Ondansetron
- E. All of the above
- F. None of the above

ANTIEMETIC THERAPIES

- Over the counter agents
 - Antihistamines
 - Diphenhydramine (Benadryl) – 12.5-25mg bid or tid prn
 - Dimenhydrinate (Dramamine) – 50mg bid or tid prn
 - Meclizine (Bonine) – 12.5-25mg bid or tid prn
 - Phosphorated dextrose/fructose (Emetrol) – 15-30ml q 15-30 mins
 - Pressure bands (P-6; Neiguan)
 - Ginger
 - Iberogast
 - Cannabis*
- Prescription medications
- Devices – gastric electrical stimulation

*40 states and DC have legalized medical cannabis; 24 states and DC have legalized marijuana for adults ≥21

RX ANTIEMETIC THERAPIES

- Phenothiazines (prochlorperazine, promethazine)
- Anticholinergics (scopolamine, TCAs)
- DA antagonists (metoclopramide, domperidone)
- 5-HT₃ antagonists (ondansetron, granisetron, palonosetron*)
- NK-1 antagonist (aprepitant, tradipitant, rolapitant, netupitant)
- Combination NK-1 antagonist- 5-HT₃ antagonist (netupitant-palonosetron)
- Butyrophenones (haloperidol, droperidol)
- Benzodiazepines (lorazepam)
- Cannabinoids (dronabinol)
- Others: prednisone, trimethobenzamide, mirtazapine, olanzapine

*30x more potent than other 5-HT₃ antagonists

MEDICATIONS AND DOSES USED FOR GASTROPARESIS

Medications	Oral Dose
Metoclopramide	5-10 mg tid-qid
Domperidone*	10 mg tid-qid
Ondansetron	8 mg tid
Prochlorperazine	5-10 mg qid
Chlorpromazine	10-25 mg qid
Scopolamine	1.5 mg patch every 3 days
Aprepitant	80 mg qd
Dronabinol	5-10 mg tid
TCA's	25-100 mg/day
Tradipitant	85 mg bid

*Requires IND

RECENT FDA APPROVED MEDICATIONS: POTPOURRI

- N & V in pregnancy: doxylamine succinate and pyridoxine HCl (Diclegis; previously called bendectin; removed from market in 1983)
- PONV: amisulpiride (Barhemsys)
- Chemotherapy associated N & V: rolapitant (Varubi) & aprepitant (Emend)

COMMON ANTI-EMETIC SIDE EFFECTS

- Sedation – most except 5-HT₃ antagonists and NK-1 antagonists
- Anxiety/agitation – metoclopramide
- Depression – dronabinol, promethazine
- Menstrual irregularities – metoclopramide, domperidone
- EKG changes – metoclopramide, domperidone, 5-HT₃ antagonists, droperidol
- Tardive dyskinesia – metoclopramide, prochlorperazine, chlorpromazine
- Constipation - 5-HT₃ antagonists, high dose TCAs, scopolamine, mirtazapine
- Visual changes – scopolamine, prochlorperazine
- Headaches - 5-HT₃ antagonists, NK-1 antagonists

DO I NEED TO CHECK ANYTHING?

- EKG – prior to domperidone; consider prior to using 5-HT₃ antagonist



FUN BOARD QUESTION

- Which medication is considered the best first choice to help prevent/minimize chemotherapy induced nausea and vomiting?
- A. scopolamine
- B. metoclopramide
- C. olanzapine
- D. ondansetron
- E. aprepitant

LET'S RETURN TO OUR PATIENT

What was the intervention?

- A diary



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FINAL DIAGNOSIS

- Psychogenic vomiting
- Likely a conditioned response in this patient
- Tx: Unlisted phone number; referral for counseling
- Outcome: symptom resolution

**THANK YOU VERY MUCH
FOR ASKING ME TO JOIN
YOU HERE TODAY**

QUESTIONS?

