Evaluation and Management of Chronic Nausea and Vomiting

Thangam Venkatesan, MD
Professor of Clinical Medicine
Director, Section of Neurogastroenterology and Motility
Division of Gastroenterology, Hepatology and Nutrition
Faculty Director, ASPIRE Medical Research Program
The Ohio State University Wexner Medical Center

MedNet21
Center for Continuing Medical Education

The Ohio State University
Wexner Medical Center

Objectives

- Define chronic nausea and vomiting and discuss etiology
- Discuss common causes of vomiting: cyclic vomiting syndrome and cannabinoid hyperemesis
- Understand the management of cyclic vomiting syndrome

Chronic nausea and vomiting

- Protective mechanisms during human evolution- to avoid food poisoning
- In the modern world- this is less relevant

Nausea

"Nausea is an aversive experience or the unpleasant sensation that precedes or accompanies emesis"

- Nausea can occur *without* vomiting
- Vomiting without nausea is less common
- Difficult to treat with standard antiemetics
- Can be more bothersome and disabling

What is vomiting?

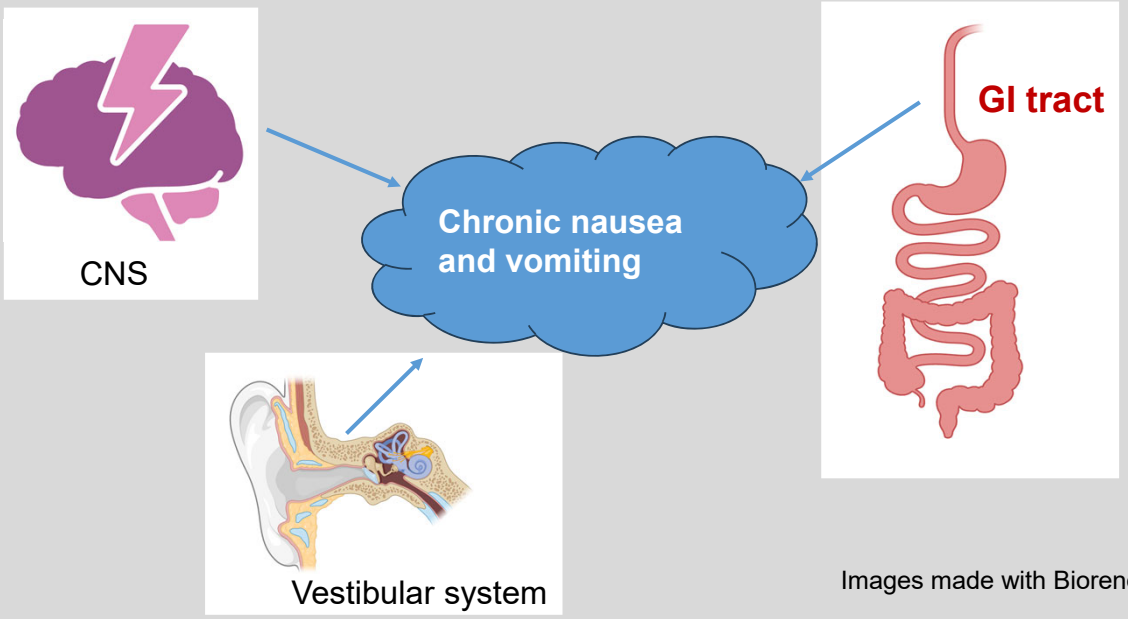
- Vomiting
  - Associated with an expulsion of gastric contents
  - ↑ Thoracic and abdominal pressure
- Retching
  - No expulsion of gastric contents
  - ↓ Thoracic pressure and ↑ abdominal pressure

Both are equally distressing to the patient and are usually lumped together

What is NOT vomiting?

- **Regurgitation**
  - Passive reflux of esophageal content, usually associated with gastroesophageal reflux disease (GERD)
- **Rumination**
  - Persistent or recurrent regurgitation of recently ingested food into the mouth with subsequent spitting or remastication and swallowing
  - Regurgitation is not preceded by retching or nausea

Causes of chronic nausea and vomiting



Images made with Biorender

Case: Mrs. M

Mrs. M: 35-year old female

- 5 years of episodic nausea, vomiting and abdominal pain, every 3 months, lasts about 5 days
- Triggers: include stress and travel
- Symptoms relieved by sleep, hot showers and cannabis
- Cannabis use – once a week and started about 4 years ago
- Anxiety - attributes to the illness

Case: Mrs. M

- At least 3 hospitalizations over the past 12 months
  - Treated with IV fluids and antiemetics
  - Improved in 3 days and was told to quit marijuana
  - Patient quit marijuana x 6 months, but continued to have symptoms and resumed use

Case: Mrs. M

- Saw three gastroenterologists
  - EGD x 3 , colonoscopy x1, CT scan of the abdomen and pelvis X 4 (all negative)
  - 4-hour gastric emptying study was mildly delayed
- Treatment
  - Trial of reglan was not helpful
  - Asked to quit marijuana again
- Lost her job as she was constantly sick

Question

What is the diagnosis?

A. Gastroparesis
B. Cannabinoid Hyperemesis Syndrome
C. Cyclic Vomiting Syndrome
D. Psychogenic vomiting

Question

What is the diagnosis?

A. Gastroparesis
B. Cannabinoid Hyperemesis Syndrome
C. Cyclic Vomiting Syndrome
D. Psychogenic vomiting

What is cyclic vomiting syndrome (CVS)?

CVS is a disorder of gut-brain interaction (DGBI)

Recurrent, stereotypic episodes of nausea, vomiting and abdominal pain

Patients return to normal or baseline in between episodes

CVS is common

- Prevalence in adults
  - U.S. - 2%
- Prevalence in children
  - Scotland 1.9%
  - Western Australia 2.3%

Similar to celiac disease and ~10 times higher than gastroparesis

Abu-Arafeh et al, J Pediatr Gastroenterol Nutr,1995
Fitzpatrick E et al, J Gastroenterol. 2008
Aziz et al., Clin Gastro and Hep, 2018
Jung HK et al. Gastroenterology. 2009

Diagnosis: Rome IV criteria

Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)

- Abrupt in onset
- Lasting less than 1 week
- Occurring at least 1 week apart

Three or more discrete episodes in the prior year

- 2 episodes in the past 6 months

Absence of nausea and vomiting between episodes

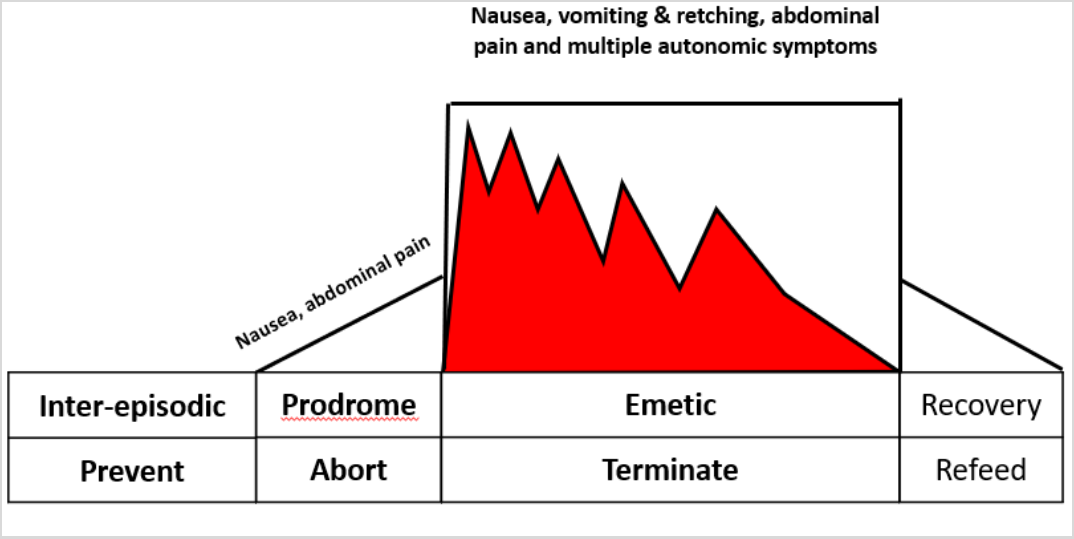
- But other milder symptoms can be present between episodes

No metabolic, gastrointestinal, central nervous system structural or biochemical disorders

Criteria fulfilled for the last 12 months with symptom onset at least 6 months before diagnosis

Tack J et al, Gastroenterology, 2006
Stanghellini et an Gastroenterology, 2016

Phases of CVS

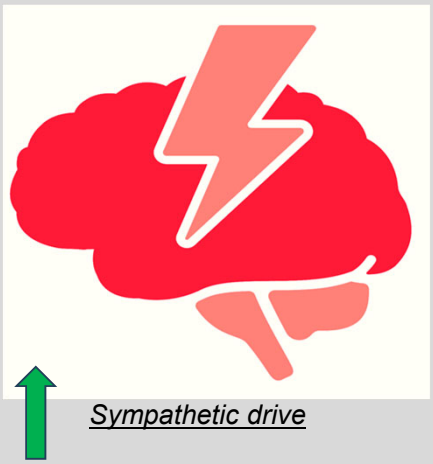


Fleisher et al, BMC Medicine, 2005

Other symptoms in CVS

Autonomic nervous system	• Tachycardia, hypertension, pallor, diarrhea, sweating, feeling hot and cold
Peripheral nervous system	• Muscle weakness/aching, numbness, tingling
Central nervous system	• Confusion, anxiety, “conscious coma”

Autonomic symptoms during an acute CVS flare



Sympathetic drive

Nausea

Sweating

Diarrhea

Photosensitivity

Vomiting

Abdominal pain

Feeling hot

Headache

Hot-water bathing

- Not pathognomonic for CVS
- Significant association with cannabis use
- Seen in 48% of CVS *without cannabis use* vs. 74% with cannabis use

Created by Rahmad romadoni from Noun Project

Venkatesan et al. Exp Brain Res,2014

Investigations:

- Upper endoscopy
- CT imaging of the abdomen and pelvis

Avoid repeated and unnecessary testing

What about a gastric emptying test?

Gastric emptying patterns in CVS

- Either rapid or normal (59% and 27% respectively)
- Small subset of CVS patients had slow emptying (14%) explained by narcotics and/or cannabis
- Rapid emptying – surrogate marker for autonomic dysfunction

A gastric emptying test is not recommended as part of the work-up

Hejazi et al, Neurogastroenterol Motil ,2010
Venkatesan et al. Neurogastroenterology & Motility, 2019

Subset of CVS patients have high healthcare utilization

Variable	Adults n=104
Total number of ED visits (median, range)	15 (1-200)
Number of ED visits prior to diagnosis of CVS (median, range)	7 (1-150)
Diagnosis NOT made in the ED	94.5%
Diagnosis NOT recognized by the ED in patients with an established diagnosis of CVS	96.3%

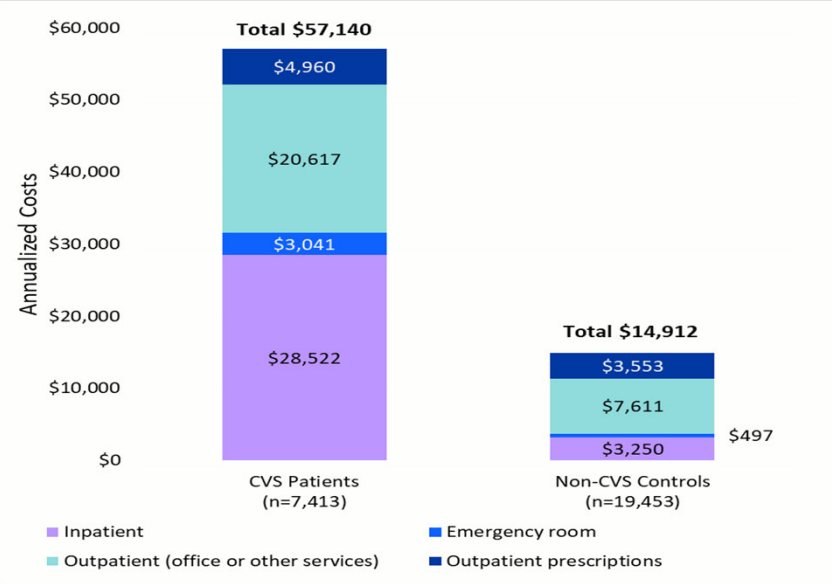
Venkatesan T et al. BMC Emerg Med. 2010

CVS is expensive!

- Based on an NIS study between 2010-2011
- Total number of CVS patients: 20,952
- **Total cost of $400 million from hospitalizations due to CVS in 2 years**
- Does not include testing and outpatient management

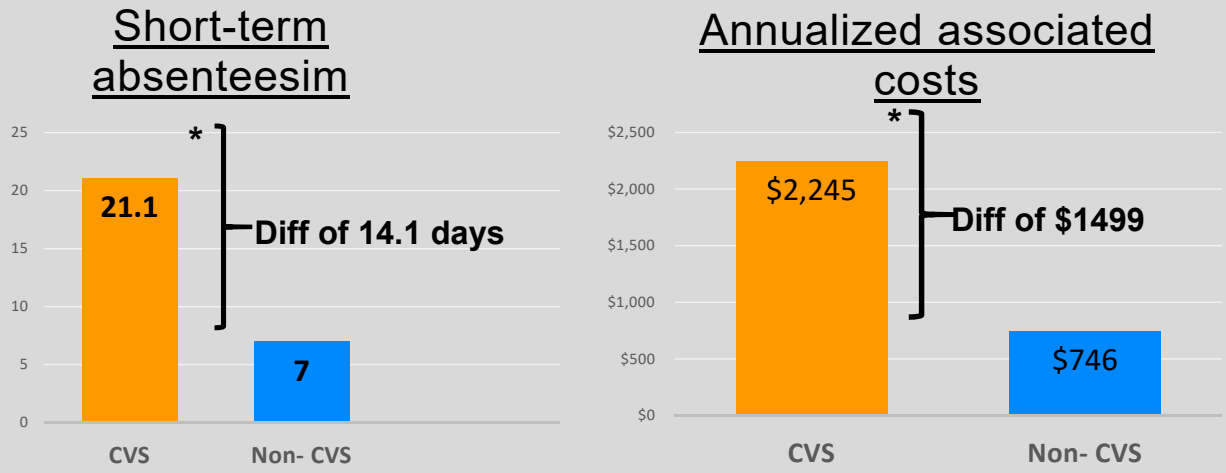
Bhandhari S, Venkatesan T, Digestive Diseases & Sciences, Jan 2017

Annualized health care costs due to CVS

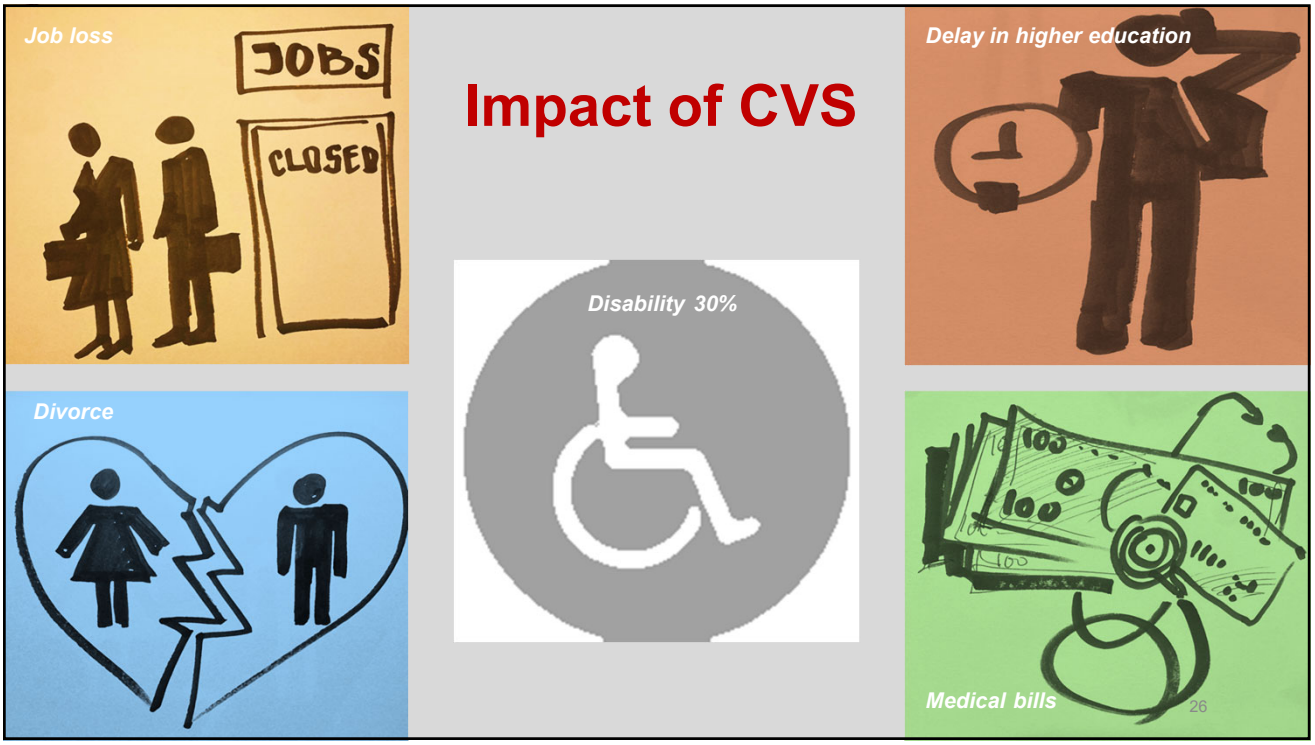


Song X et al., Venkatesan T, Levinthal DJ et al. Gastro Hep Advances, 2022

Indirect costs and impact due to CVS



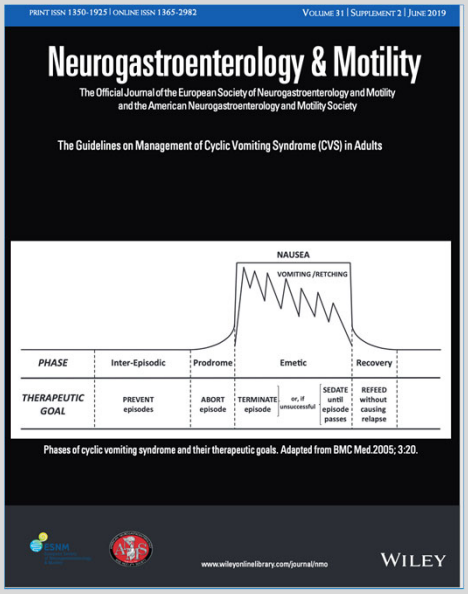
Chen YJ et al. Venkatesan T et al. Gastro Hep Advances,2022



Mrs. M

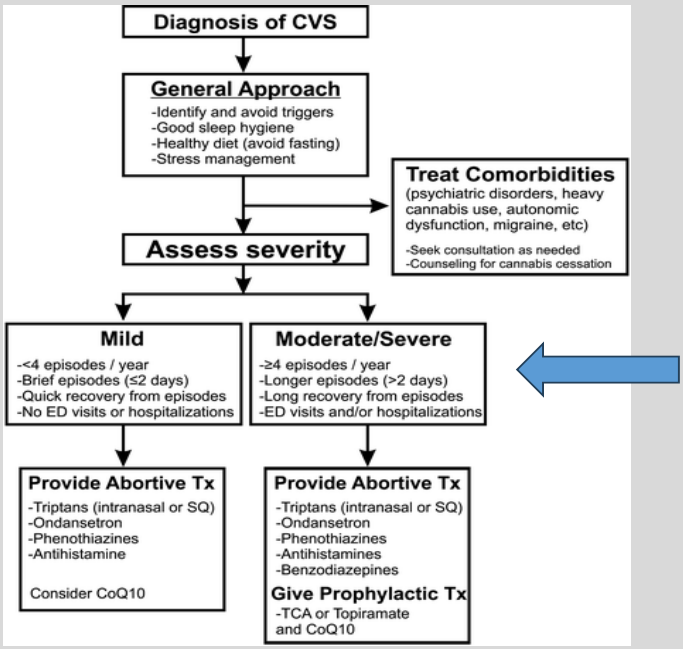
How do we manage Mrs. M?

Guidelines on management of CVS in adults



Kathleen Adams & Thangam, Milwaukee 2019

Venkatesan et al. Neurogastroenterology & Motility, : 26 June 2019, DOI: (10.1111/nmo.13604)



Venkatesan et al. Neurogastroenterology & Motility, : 26 June 2019, DOI: (10.1111/nmo.13604)

Prophylactic medications

Neuromodulators	Anticonvulsants	NK1 receptor antagonists	Mitochondrial supplements

• Tricyclic antidepressants
  • Amitriptyline
  • Nortriptyline
	• Topiramate	• Aprepitant
		• Fosaprepitant
			• Coenzyme Q-10 and riboflavin
			• L-carnitine

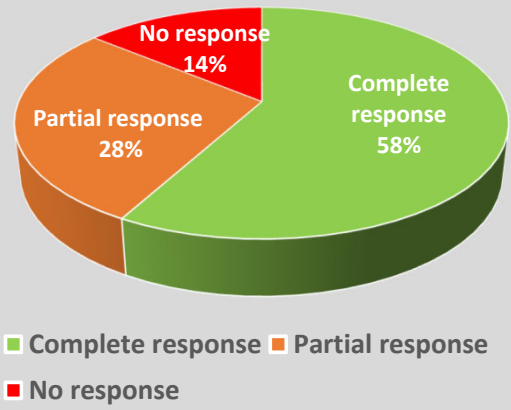
30

Efficacy of tricyclic antidepressants

Outcome measures	Baseline Mean ± SD (95% CI)	After 1 year of follow up Mean ± SD (95% CI)	After 2 years of follow up Mean ±S D (95% CI)	P value (at 1 year)	P value (at 2 years)
Frequency of CVS episodes/year	17.8±8.3 (4.5-180)	5.4±3.8 (1-54)	3.3±2.8 (1-42)	0.003	0.002
Duration of CVS episodes (days)	6.7±6.1 (0.2-30)	2.5±2.7 (0-14)	2.2±2.4 (0-10)	0.0009	0.0008
No. of ED visits and hospitalizations/year	15±13.4 (1-27)	4.2±5 (0-20)	3.3±3.6 (0-14)	0.009	0.007

Hejazi RA et al, J Clin Gastroenterol, 2010

Efficacy of tricyclic antidepressants



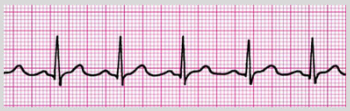
Kumar N, Venkatesan et al, BMC Gastroenterology, 2012

Amitriptyline

Neuromodulators:

Amitriptyline (Elavil) or Nortriptyline (Pamelor)

- **Onset of action – 6-8 weeks**
- Dose: start at 25 mg
  - titrate in increments of 10 mg/week
  - target dose of 75-100 mg at night in adults
- **EKG at baseline and during titration recommended**
- Effective in ~ 70- 80% of patients
  - Reduces frequency and severity of CVS episodes



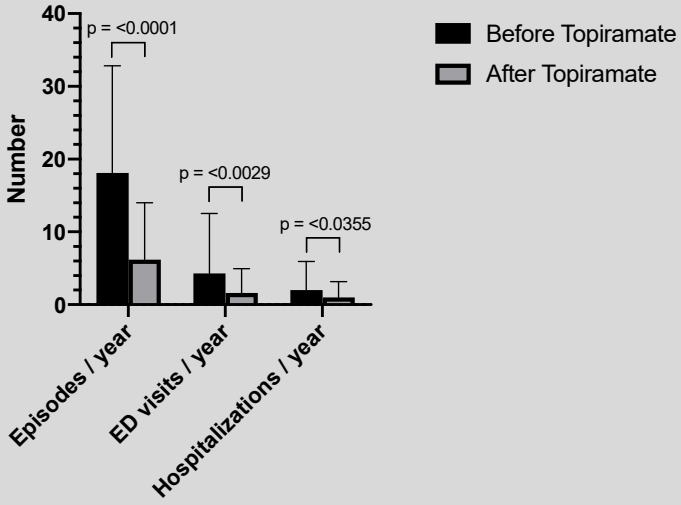
Side effects

- Occurs in approximately 25% of patients
- Common side effects
  - **Daytime sedation (improves over 12 weeks)**
  - Promotes sleep
  - Dryness of mouth
  - Constipation
  - Weight gain

Remember – side effects occur before you see it beginning to take effect!

Effectiveness of topiramate

- Retrospective study of 141 patients
- Overall response rate of 65%
- Refractory group of patients
- Side effects in 55% with 32% discontinuing Rx
- Major side effects
  - Cognitive dysfunction
  - Fatigue
  - Paresthesia



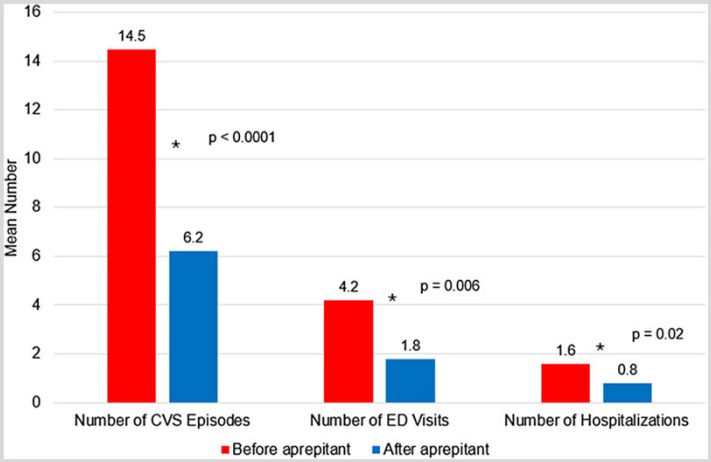
Mooers H, Srivastava S, Venkatesan T, Alimentary Pharmacology & Therapeutics, June 2021

Aprepitant in the prophylaxis of CVS

Very effective in ~ 70% refractory cases

No lag time – within a week or two to assess response

Expensive, may need prior authorization



Venkatesan et al. Neurogastroenterology and Motility, 2023

Triggers

- Stress - both positive and negative
  - Stress management
  - Therapy
  - Other techniques
    - Meditation
- Sleep deprivation
- Starvation
- Chronic cannabis use

Abortive therapy

Triptans (sumatriptan)

- 20 mg intranasally
- may repeat in 2 hours

Antiemetics

- 5-HT3 antagonists
  - Ondansetron SL
- NKI receptor antagonists
  - Aprepitant
- Sedatives
  - Diphenhydramine

Take abortive agents as early as possible during the prodrome to abort symptoms

The Mind-Body (Gut) Connection

- Treatment of comorbid anxiety and depression
  - Cognitive behavioral therapy
  - Heartfulness meditation

Summary

- CVS is common
  - Prevalence of 2%
- CVS is a disorder of gut-brain interaction
  - Diagnosed by Rome criteria
- Testing
  - EGD and imaging (CT scan) usually performed
- High health care utilization
- Can be debilitating
  - Especially if not treated adequately
- Poor quality of life

Best managed by a team of CVS specialist + local team

Other diagnosis to consider

- Cannabinoid hyperemesis syndrome
- Gastroparesis

Cannabinoid Hyperemesis Syndrome

- Stereotypical episodic vomiting resembling (CVS) in terms of onset, duration, and frequency
- Presentation after *prolonged, excessive* cannabis use
- Relief of vomiting episodes by sustained cessation of cannabis use

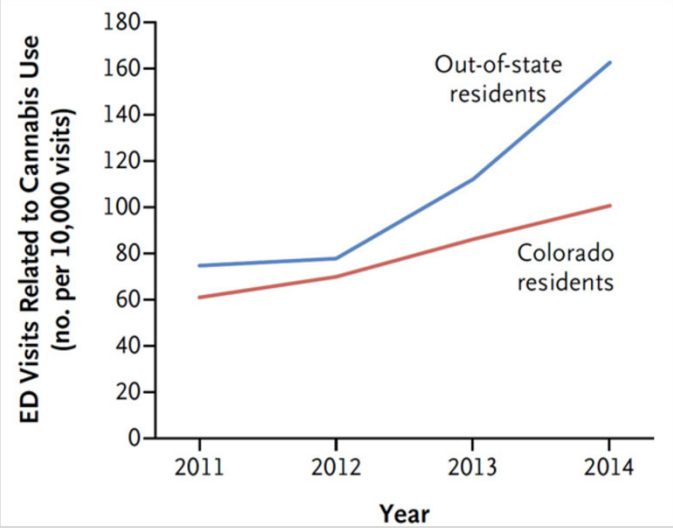
Supportive remarks

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

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

Stanghellini et al. Gastroenterology, 2016

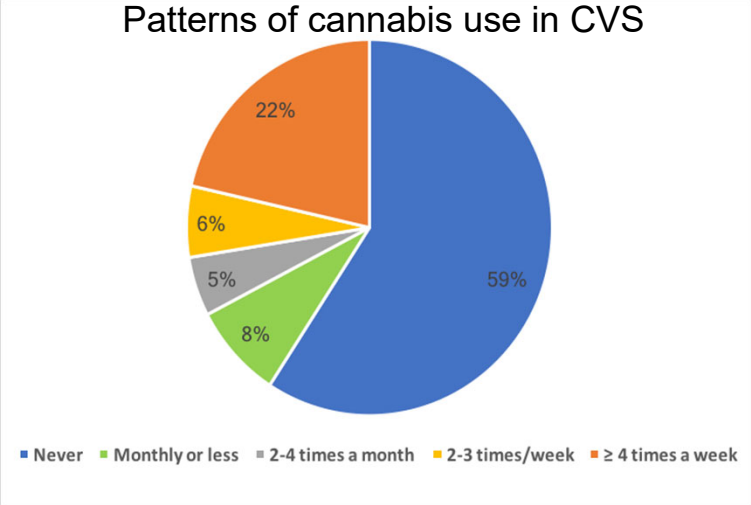
ED visits related to marijuana tourism in Colorado



Kim et al., N Engl J Med. 2016
Venkatesan et al, BMC Gastro,2010

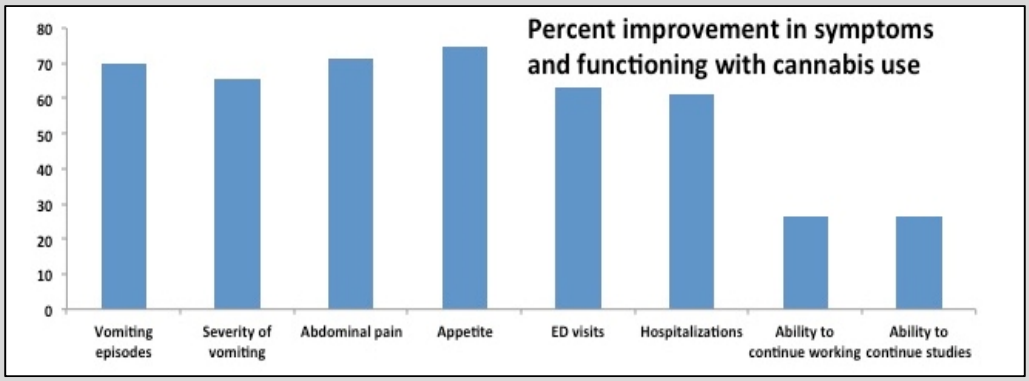
Is CHS a myth?

- Cross-sectional study of 140 patients with CVS
  - 72% female
  - mean age 37±13 years



Venkatesan, et al. Clinical Gastro and Hepatology, July 2019

Self-reported effects of cannabis use in CVS



Venkatesan, et al. Clinical Gastro and Hepatology, July 2019

Effects of cannabis abstinence

- Most cannabis users (50/57,86%) abstained from cannabis for at least a month
- **Only 1 patient reported resolution of symptoms following**

  cannabis cessation
  - Subsequently resumed cannabis (with higher CBD) and remains symptom-free
- Longer follow-up needed
- Patient perceptions and beliefs a challenge

Venkatesan, et al. Clinical Gastro and Hepatology, July 2019

Systematic review: Cannabinoid Hyperemesis Syndrome

- From January of 2000 – March of 2018
- 105 individual cases
- 25 case series (n= 271)

Venkatesan et al. Neurogastroenterology and Motility, 2019

Systematic review of CHS

Variable	Case series (25, n=271)	Case reports n=105
Age (years)	30.5 ± 7.6	29.4 ± 9.0
Gender Male	 68.6%	 72.3%
Duration of cannabis use (prior to symptom onset)	6.6 ± 4.3 years	8.0 ± 8.4
Frequency of cannabis use Daily use Weekly use Not reported	 68% 16% 16%	 69.5%
Hot-water bathing pattern	71.5%	86%
Follow up > 4 weeks following abstinence	16.2 %	25.7%
Met Rome IV criteria for CVS	14%	20%

Gastroparesis

- *Gastroparesis is defined as a delay in the emptying of ingested food in the absence of mechanical obstruction of the stomach or duodenum*
  - Idiopathic ~60%, diabetic – 30-35%, and post-surgical 5-10%
- Poor correlation between symptoms and degree of gastric emptying
- Medications that improve symptoms do not improve emptying
- Gastric emptying changes over time

Camilleri M, Parkman H, Shafi M, et al. Am J Gastroenterol 2013;108:18–37.

Overlap of functional dyspepsia and gastroparesis

Large number of patients (41% of the idiopathic and 39% of the diabetic population) can be reclassified into the alternative group after a year.

The stomach of patients with FD had the same characteristic pathology (ie, loss of ICC and CD206-expressing macrophages) similar to Gp.

Pasricha et al. Gastroenterology 2021;160:2006–2017

Case: Mrs. M

- Was treated with amitriptyline 75 mg at night
- Given ondansetron SL and sumatriptan nasal spray
- Significant improvement in 3-4 months
- Was able to work again