



# Evaluation and Management of Chronic Nausea and Vomiting

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## 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?

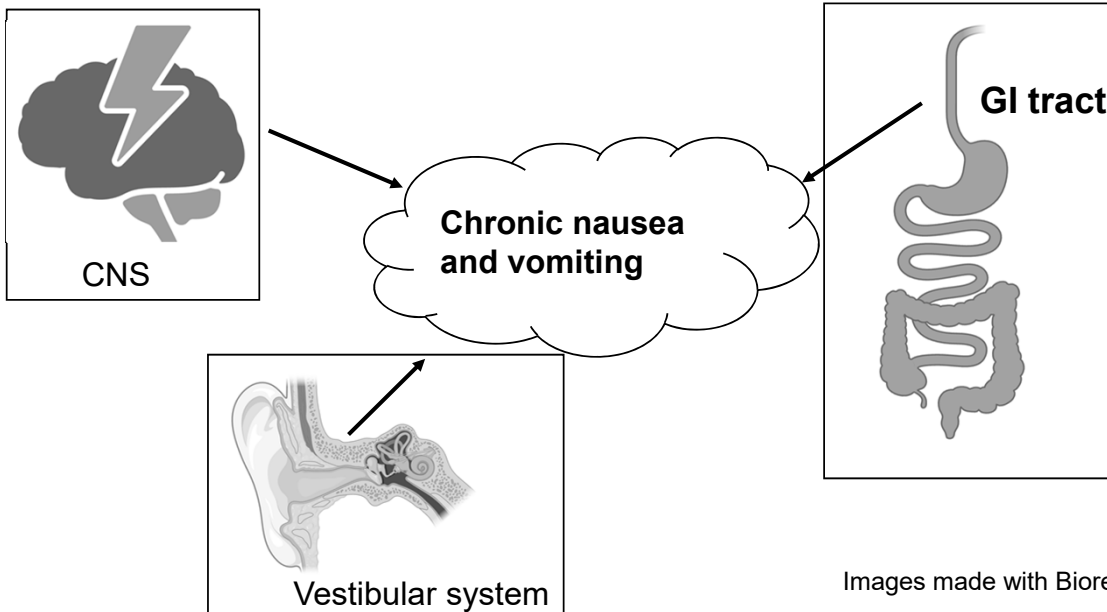
- Vomiting
  - Associated with an expulsion of gastric contents
  - ↑ Thoracic and abdominal pressure
- Retching
  - No expulsion of gastric contents
  - ↓ Thoracic pressure and ↑ abdominal pressure

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



### 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

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## What is cyclic vomiting syndrome (CVS)?

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

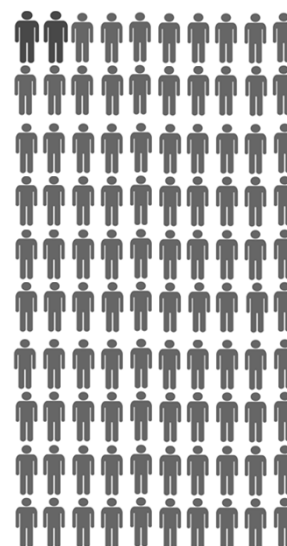
Recurrent, stereotypic episodes of nausea, vomiting and abdominal pain

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

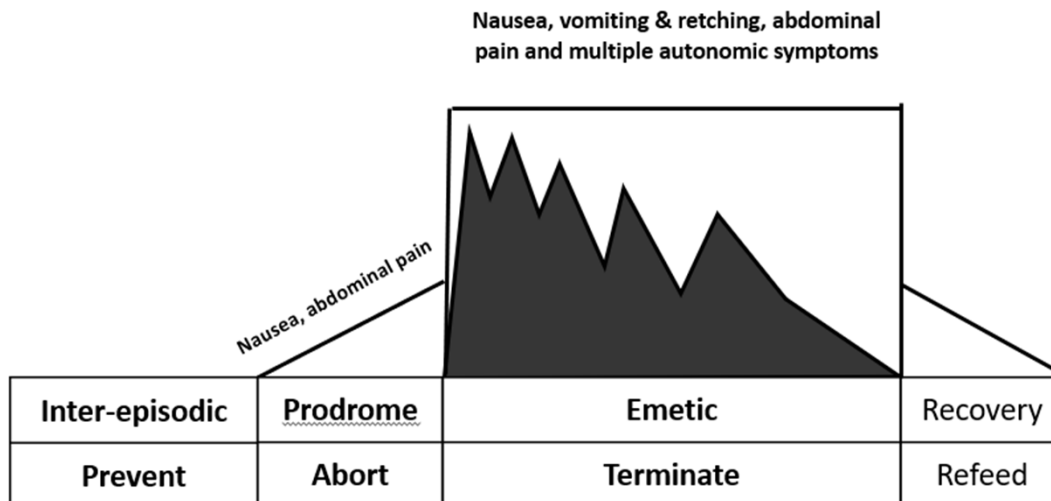
*No metabolic, gastrointestinal, central nervous system structural or biochemical disorders*



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

Tack J et al, Gastroenterology, 2006  
Stanghellini et al 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

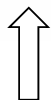
### Peripheral nervous system

- 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

Venkatesan et al. Exp Brain Res, 2014



Created by Rahmad romadoni  
from Noun Project

## 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%

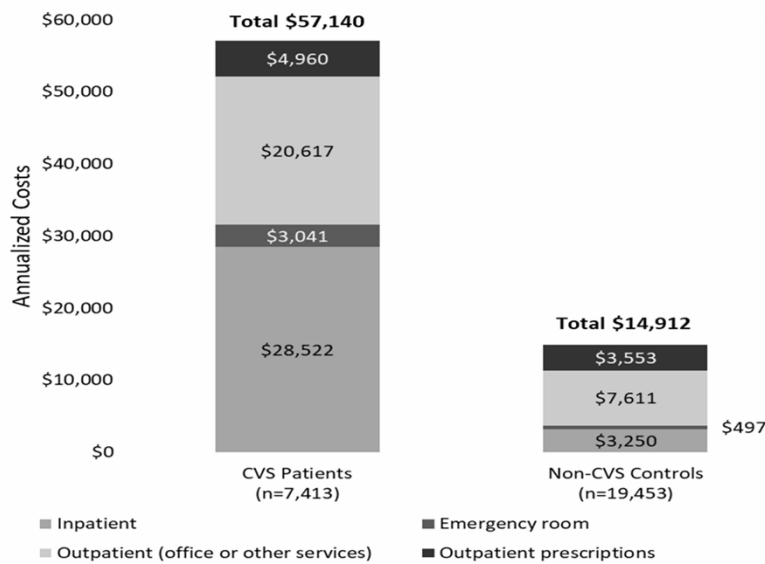
Venkatesan T et al. BMC Emerg Med. 2010

# 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

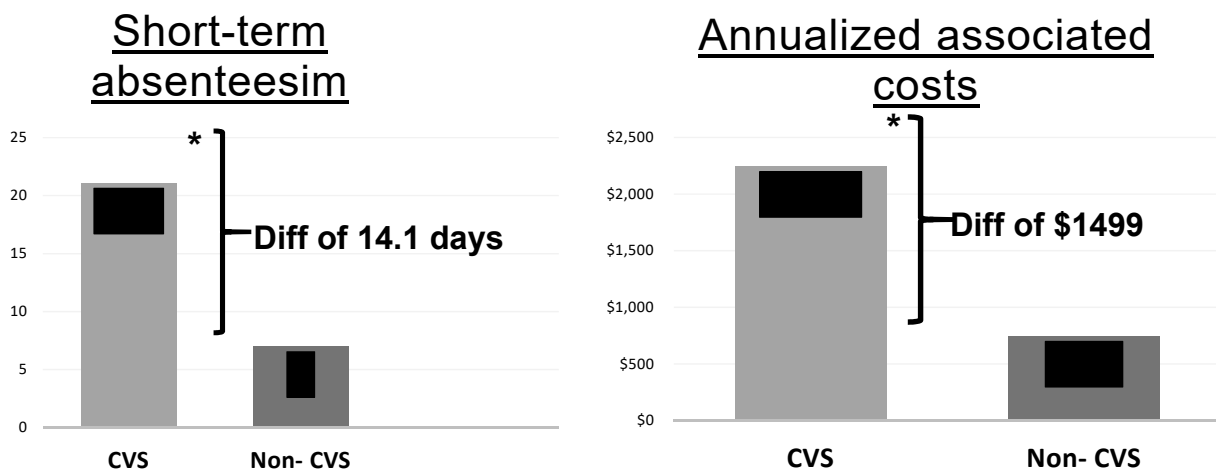
Bhandhari S, Venkatesan T, Digestive Diseases & Sciences, Jan 2017

## 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

## Impact of CVS

**Job loss**

**Disability 30%**

**Delay in higher education**

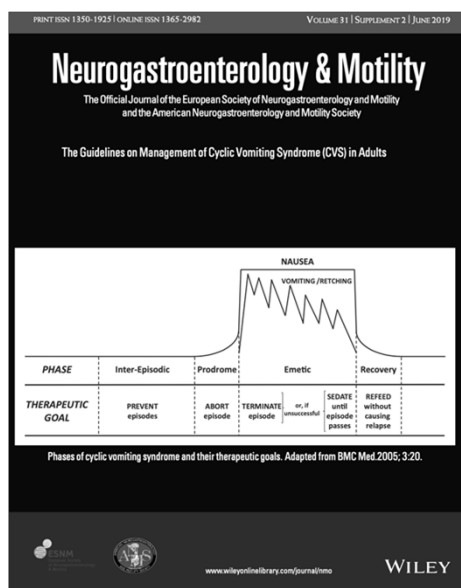
**Divorce**

**Medical bills**

Mrs. M

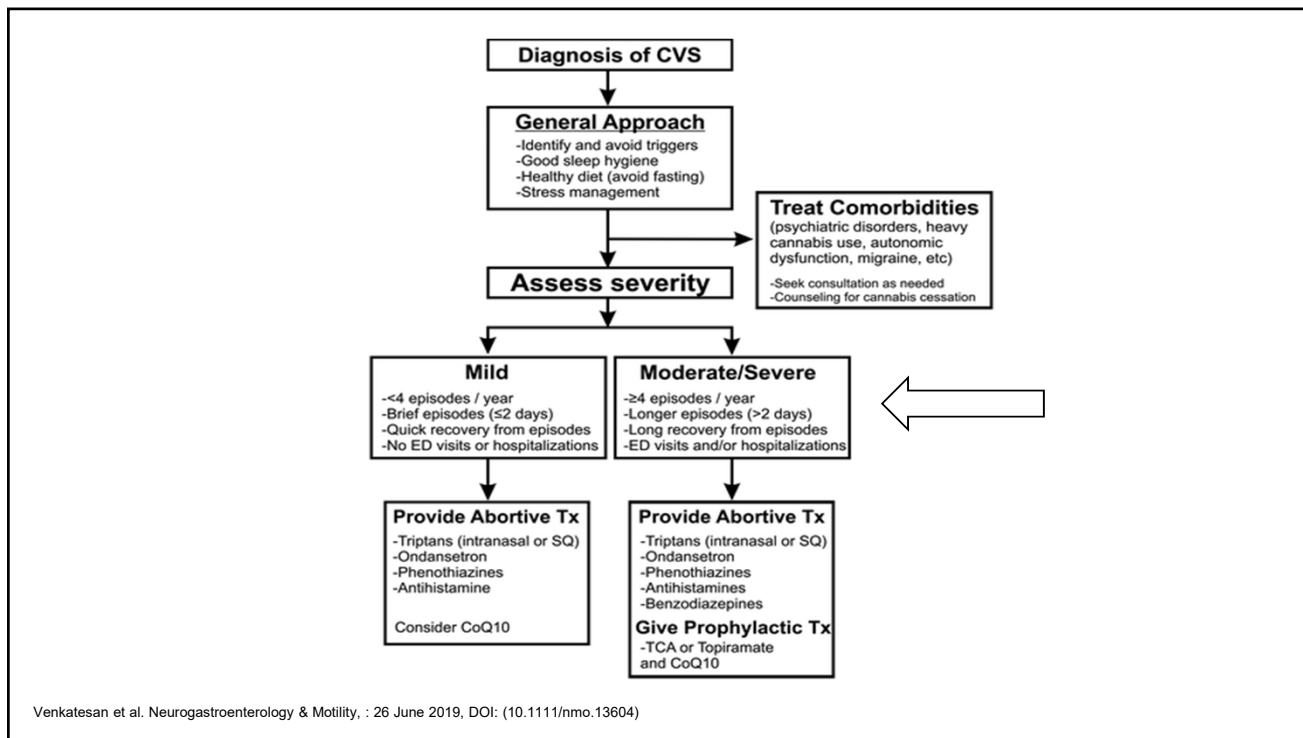
How do we manage Mrs. M?

## 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)



# Prophylactic medications

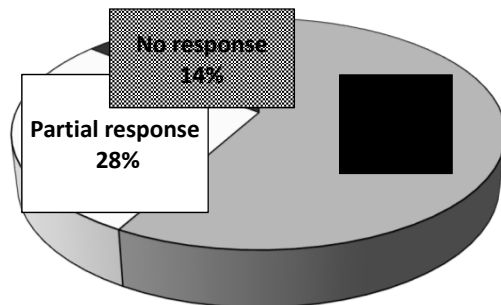
<p><b>Neuromodulators</b></p> <ul style="list-style-type: none"> <li>• Tricyclic antidepressants</li> <li>• Amitriptyline</li> <li>• Nortriptyline</li> </ul>	<p><b>Anticonvulsants</b></p> <ul style="list-style-type: none"> <li>• Topiramate</li> </ul>	<p><b>NK1 receptor antagonists</b></p> <ul style="list-style-type: none"> <li>• Aprepitant</li> <li>• Fosaprepitant</li> </ul>	<p><b>Mitochondrial supplements</b></p> <ul style="list-style-type: none"> <li>• Coenzyme Q-10 and riboflavin</li> <li>• L-carnitine</li> </ul>
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## Efficacy of tricyclic antidepressants

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

Hejazi RA et al, J Clin Gastroenterol, 2010

## Efficacy of tricyclic antidepressants



Complete response
  Partial response
  No response

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



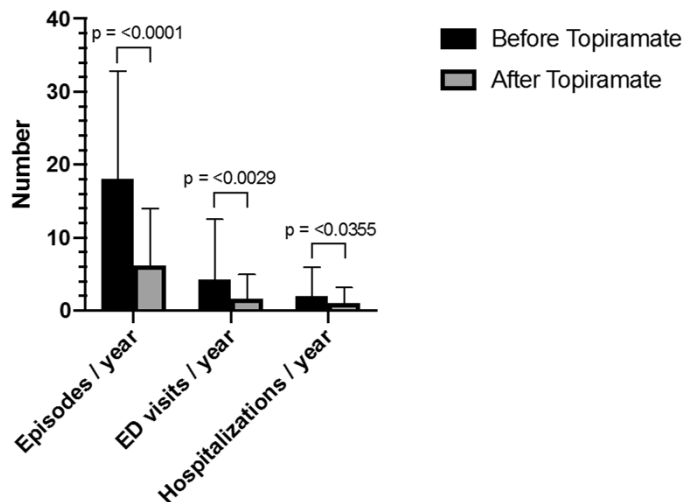
## Side effects

- 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



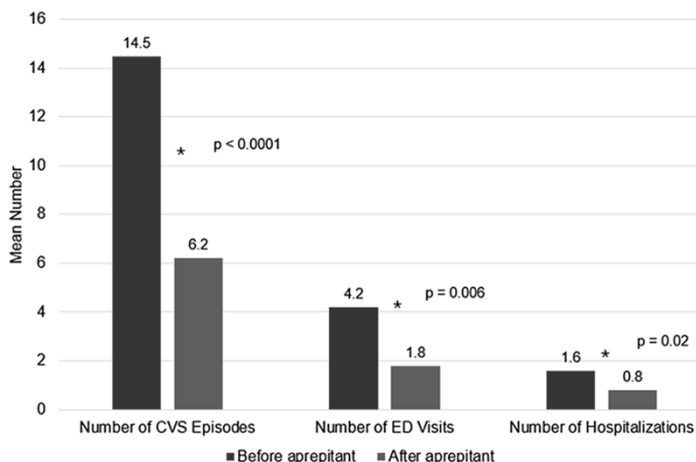
Mooers H, Srivastava S, Venkatesan T, Alimentary Pharmacology & Therapeutics, June 2021

## 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-HT<sub>3</sub> antagonists
  - Ondansetron SL
- NK<sub>1</sub> 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

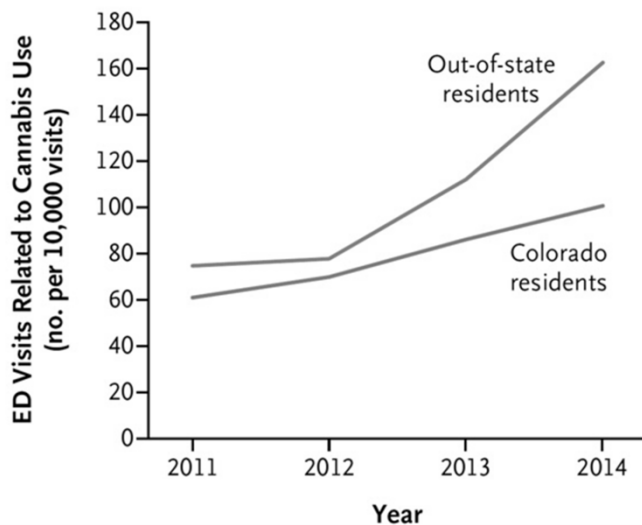
Supportive remarks

- 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

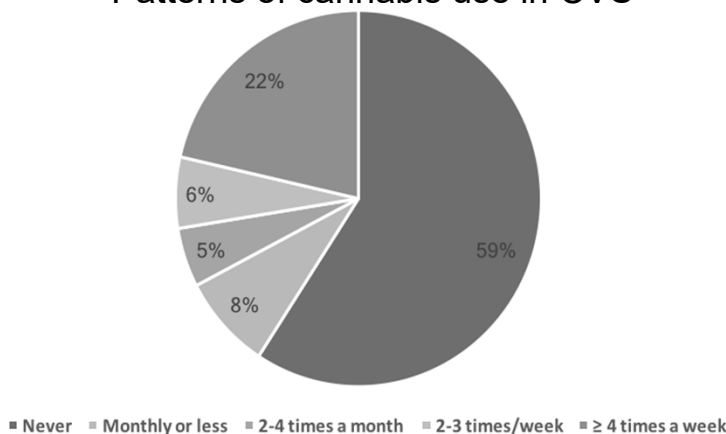


Kim et al., N Engl J Med. 2016  
Venkatesan et al, BMC Gastro, 2010

## Is CHS a myth?

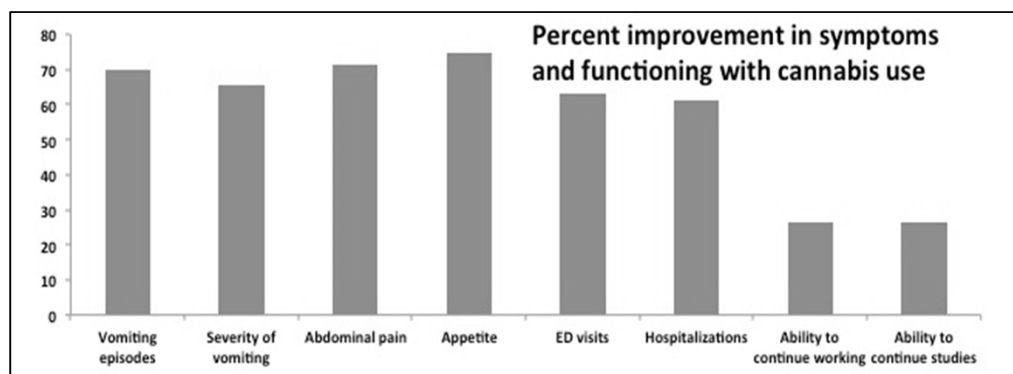
- Cross-sectional study of 140 patients with CVS
  - 72% female
  - mean age  $37 \pm 13$  years

Patterns of cannabis use in CVS



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	68%	69.5%
Weekly use	16%	
Not reported	16%	
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