

THIRD ANNUAL

# GI ReConnect

**June 1-3, 2023**

**Hyatt Regency Huntington Beach Resort  
Huntington Beach, California**

Provided by:



# CVS and CHS

Lin Chang, M.D.

G Oppenheimer Center for Neurobiology of Stress and Resilience  
Vatche and Tamar Manoukian Division of Digestive Diseases  
David Geffen School of Medicine at UCLA

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# Objectives

- To discuss the diagnosis, pathophysiology and treatment of cyclic vomiting syndrome (CVS) and cannabinoid hyperemesis syndrome (CHS)
- To use a case-based presentation to discuss the management of CVS

# Cyclic Vomiting Syndrome (CVS)

# Case Presentation: Nausea and Vomiting

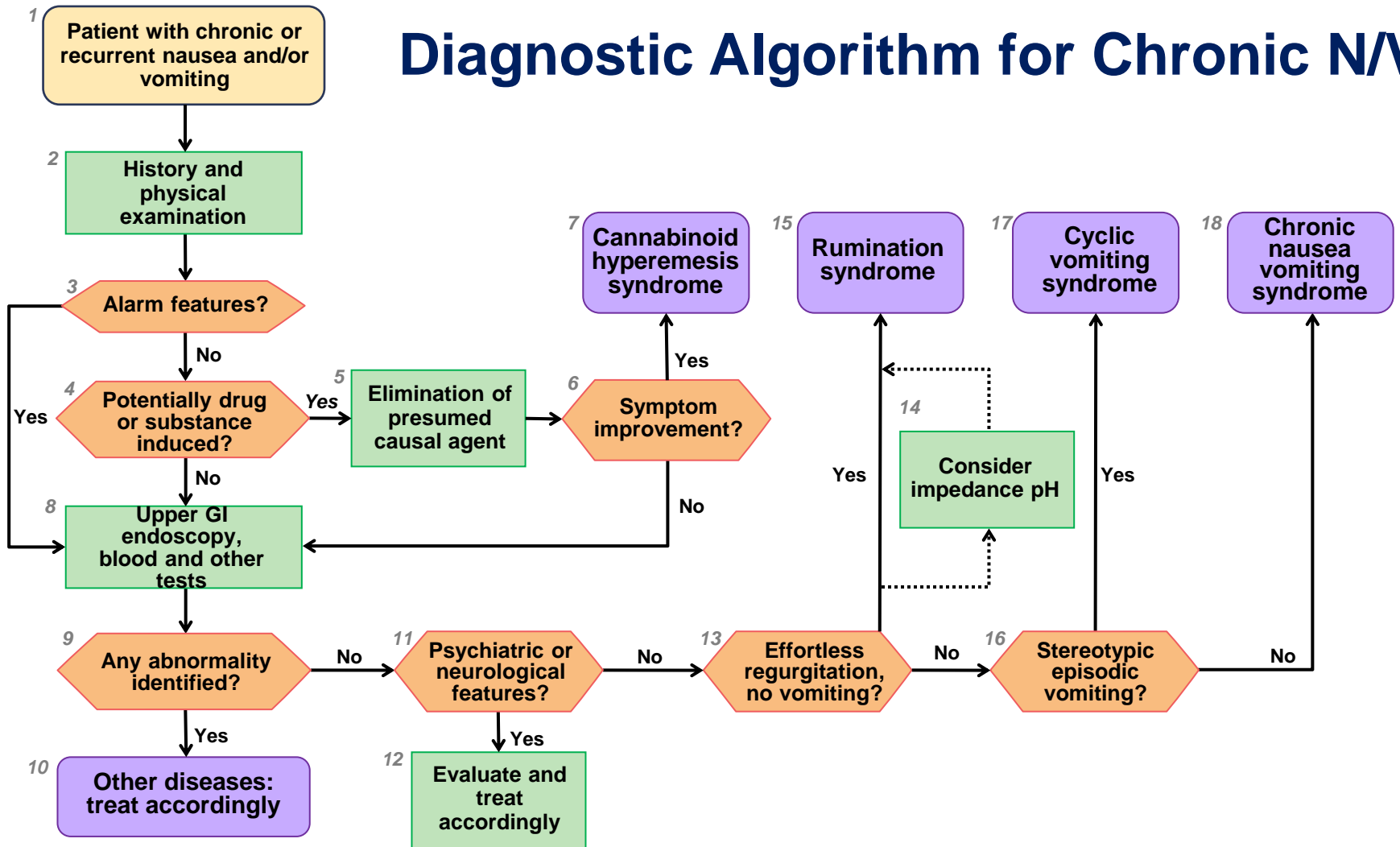
A 28 year old female lawyer in training describes **intermittent bouts of uncontrollable repeated vomiting lasting up to 48 hours**, beginning about 5 years ago. She has had **numerous hospital admissions** for several days at a time with vomiting and abdominal pain where she has received intravenous rehydration, and opiate analgesia. During these events blood biochemistry and hematology screens, urine culture, 2 gastroscopies, duodenal biopsy, an abdominal ultrasound, CT scan and MRI small bowel studies, have been **reported as normal**. She has **not lost weight and between attacks she has minimal symptoms of heartburn and occasional nausea**. Her primary care physician has prescribed a proton pump inhibitor which abolished the heartburn but had no effect on the frequency of attacks. There is a **family history of migraine** but the patient describes no migraine attacks. There is **no history of cannabis abuse**. **Physical examination is normal**. A psychiatric

# Case Presentation: Nausea and Vomiting

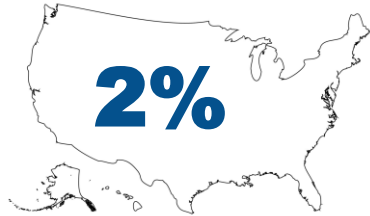
consultation during one hospitalization found her to be anxious but otherwise revealed no significant abnormality and **no evidence of an eating disorder**. **Gastric emptying studies showed an initial rapid gastric emptying slowing to normal** in the later phases. The hospitalizations have increased, now up to **3 times per month** and are disrupting her studies. She asks for a letter to her supervisors to explain why she is behind in her course work as she is at risk of being denied the chance to complete her final qualifying exams.



# Diagnostic Algorithm for Chronic N/V



# Epidemiology of CVS



PREVALENCE IN US



CVS OCCURS IN CHILDREN AND ADULTS, ACROSS ALL RACES AND BOTH SEXES

**3-14%**

CVS CAUSE OF UNEXPLAINED NAUSEA AND VOMITING

Adults & Peds



MEAN AGE OF CVS ONSET: 5 YRS IN CHILDREN & 37 YRS IN ADULTS

**15**

MEDIAN NUMBER OF ED VISITS



**5-6 YR**

AVERAGE PERIOD OF SYMPTOMS BEFORE DIAGNOSIS OF CVS

Sperber AD et al. Gastroenterology. 2021;160(1):99-114

Aziz I et al. Clin Gastroenterol Hepatol 2018

Frazier R et al. American Journal of Gastroenterology 2023

# CVS: Symptoms

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- Onset: often early morning
- Duration: hours or days
- CVS attacks are longer and more frequent in adults than in children
- 1/3 have migraine headaches and psychological symptoms
- FH of migraines (typically mother)
- Symptoms are triggered by stress (negative or excitatory), sleep deprivation, infection

# Management of Cyclic Vomiting Syndrome

## Diagnosis

- Rome IV criteria
- Investigations
- EGD and imaging studies of the abdomen and pelvis

## Treatment



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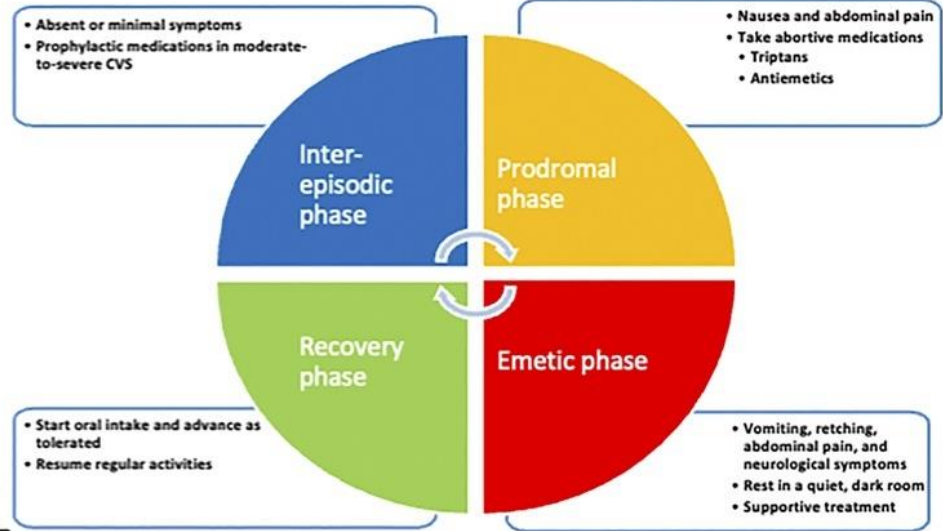


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Medications    Complementary Rx    Emergency room plan

## Phases of CVS



# CVS: Diagnostic Testing

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- Dictated by clinical presentation
- More aggressive testing if bilious vomiting, abdominal tenderness, abnormal neurologic findings, or a worsening pattern of vomiting
- Complete blood count, serum electrolytes, glucose, liver panel, lipase
- Testing for hypercalcemia, hypothyroidism, and Addison's disease
- Consider drug screening if CHS is a possibility but is denied
- Upper endoscopy, small bowel imaging, or CT or US can evaluate for gastroduodenal disease and SBO
- Brain imaging if focal neuro signs or symptoms
- Gastric emptying test not recommended (can be normal, rapid or delayed)

# Rome IV Diagnostic Criteria\* for Cyclic Vomiting Syndrome (CVS)

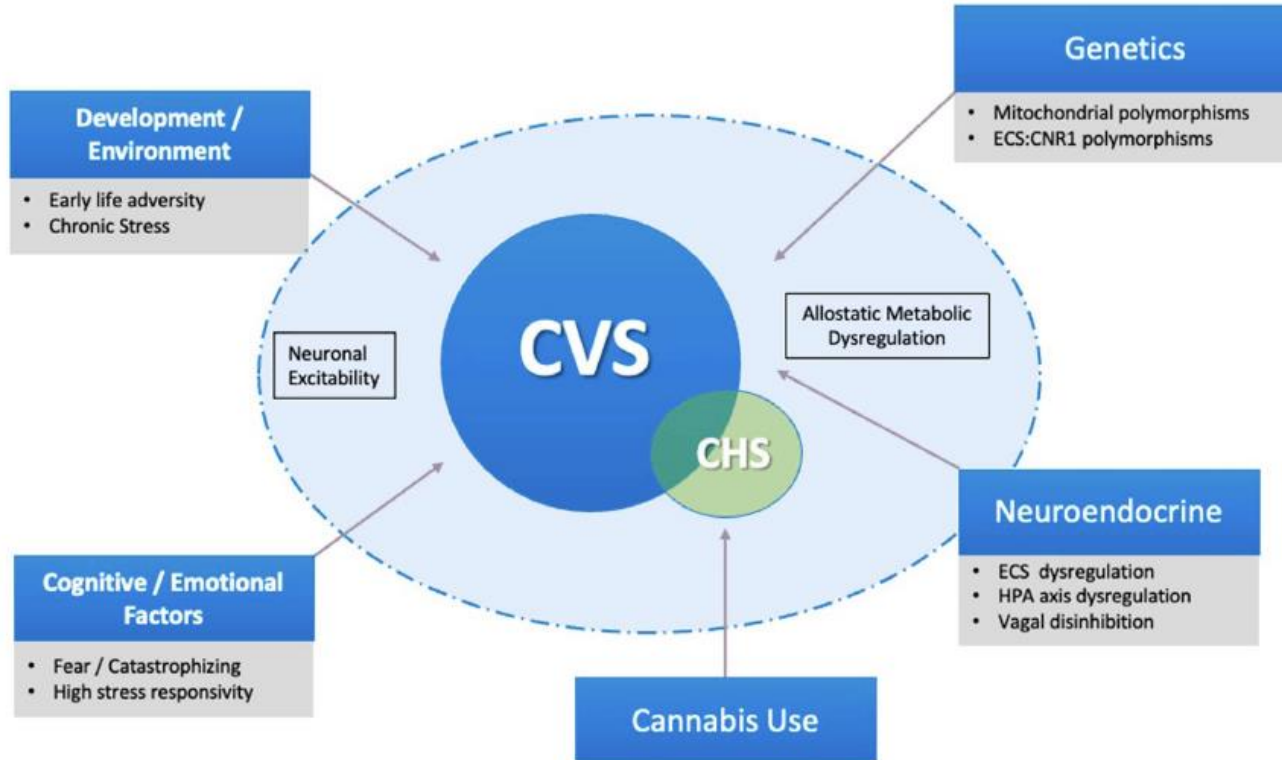
Must include **all** of the following:

- 1. Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)**
- 2. At least three discrete episodes in the prior year and two episodes in the past 6 months, occurring at least 1 week apart**
- 3. Absence of vomiting between episodes, but other milder symptoms can be present between cycles**

\* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

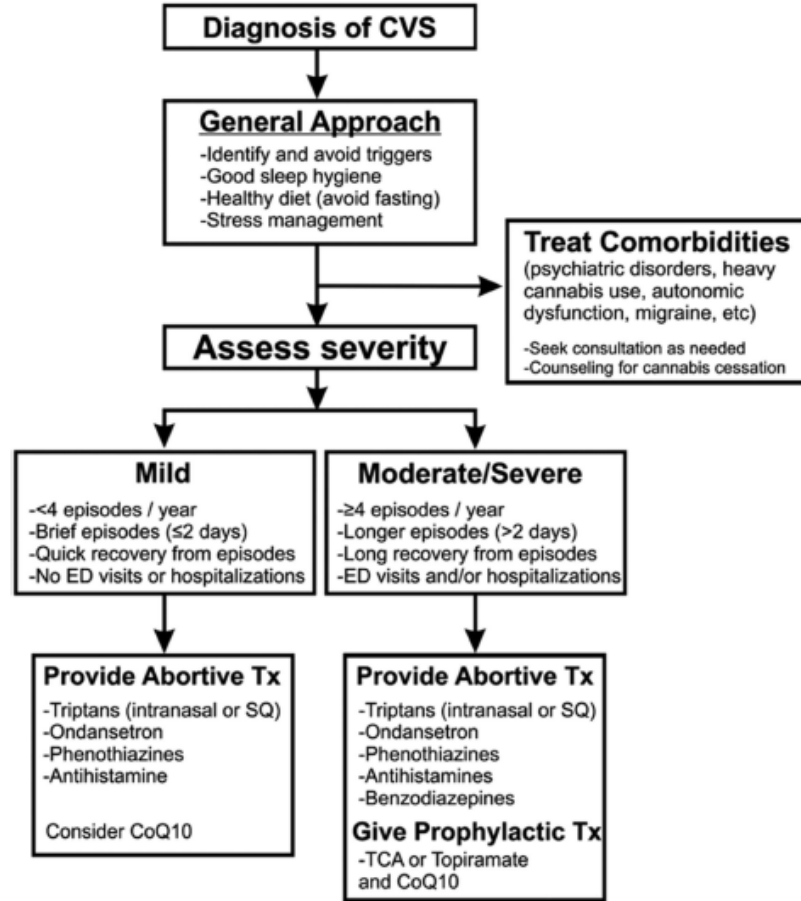
**Supportive remark: History or family history of migraine headaches**

# Potential Pathophysiology of CVS



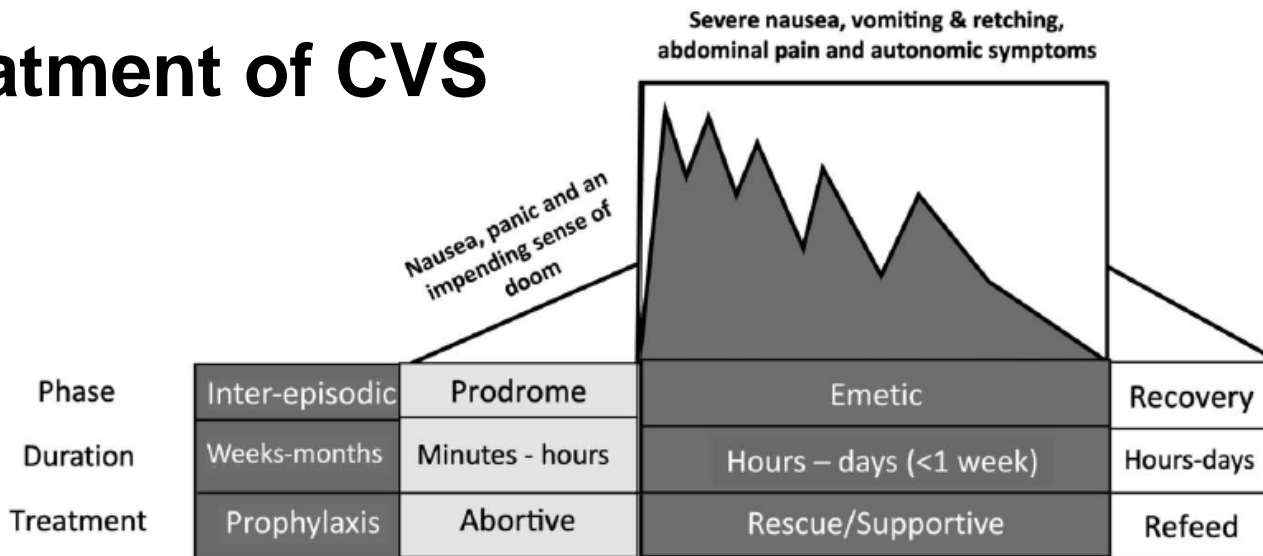
# Management Algorithm

## Cyclic Vomiting Syndrome (CVS)





# Treatment of CVS



**Tricyclic agent 25-75 mg qhs**  
**Mitochondrial supplements (Co-Q10, Riboflavin, L-carnitine)**  
**Cyproheptadine 2-4 mg qhs**  
**Propranolol 20 mg tid**  
**Clonazepam 0.25 mg bid**  
**Sumatriptan**  
**NK1 antagonist (Aprepitant)**  
**Anti-epileptics (Toprimate, Zonisamide, Levetiracetam)**

**Clonazepam 0.5-1.0 mg sublingually at earliest prodromal symptoms**  
**Sumatriptan**  
**Ondansetron**  
**Aprepitant**  
**Hot shower**  
**Abdominal breathing**

**IV fluids**  
**Promethazine, Prochlorperazine**  
**Diphenhydramine**  
**Ondansetron**  
**Sumatriptan**  
**NK1 antagonist (Aprepitant)**  
**Benzodiazepines**  
**May need narcotics but avoid if possible**

# Back to Patient Case: Nausea and Vomiting Disorders

## Cyclic Vomiting Syndrome – Severe

A 28 year old women with intermittent repeated vomiting, abdominal pain x 48 hours for past 5 yrs and many hospital admissions. Normal diagnostic workup and PE except GE scan with rapid emptying. Denies weight loss, migraines, cannabis use. PPI relieved heartburn only.

- A. Categorical Diagnosis: **Cyclic Vomiting Syndrome**
- B. Clinical Modifier: **Gastroesophageal reflux**
- C. Impact on Daily Activities: **Severe**
- D. Psychosocial Modifier: **Anxiety**
- E. Physiological Features and Biomarkers: **Initial rapid gastric emptying**

# Treatment Options for CVS

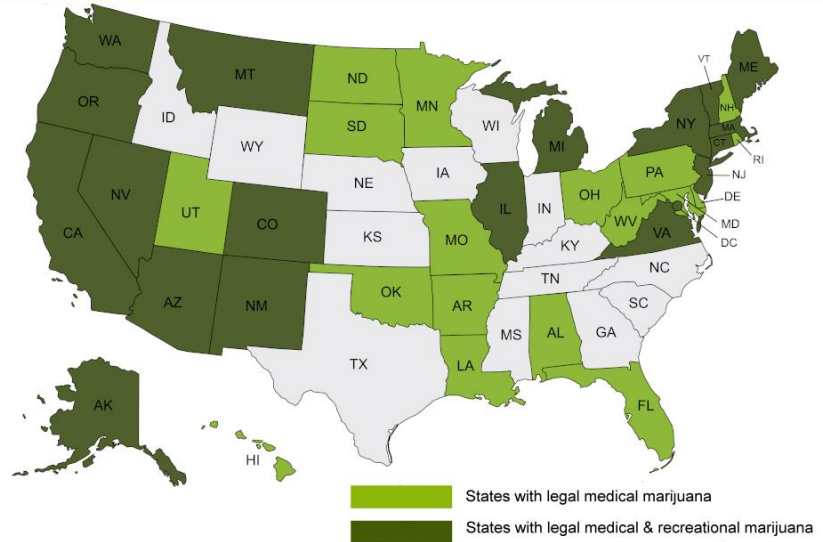
- **Tricyclic antidepressants (TCA)**
  - Start at 10-25 mg, then can increase up to 100 mg
- **Beta-blocker**
  - Propanolol at 10-40 mg bid
- Mirtazepine (in place of TCA)
  - 7.5 to 30 mg qhs
- **Histamine 1 antagonist**
  - Cyproheptadine 4 mg bid or 8 mg po qhs
- Anticonvulsants
  - Topiramate
- NK-1 receptor antagonist
  - Aprepitant 125 mg po twice weekly (40-80 mg if <60 kg)
- Mitochondrial supplements
  - L-carnitine, Coenzyme Q10, riboflavin

# Cannabinoid Hyperemesis Syndrome (CHS)

# Medical and Recreational Marijuana (MJ) Use and Laws

- Most commonly used federally illegal drug in the US; 48.2 million (18% of Americans) used it at least once in 2019
- 3 in 10 who use marijuana have marijuana use disorder
- For people who begin using marijuana before age 18, risk of developing marijuana use disorder is even greater
- Marijuana use affects parts of the brain responsible for memory, learning, attention, decision-making, coordination, emotion, and reaction time.
- Using marijuana during pregnancy may increase risk for complications. Pregnant and breastfeeding persons should avoid marijuana

## Legal Medical & Recreational Marijuana States

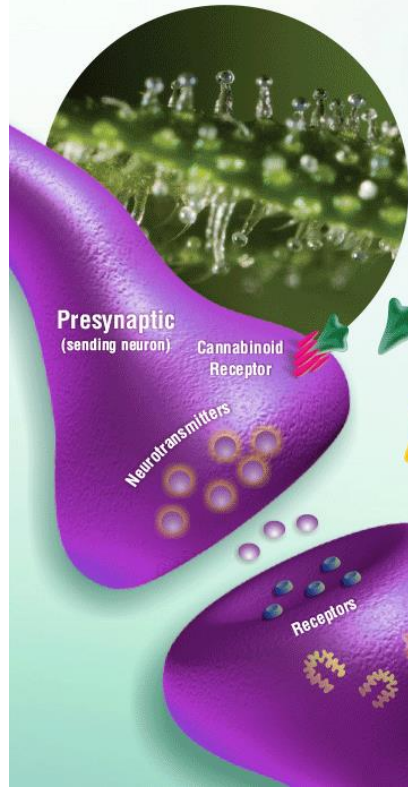


<https://www.cdc.gov/marijuana/data-statistics.htm>

<https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/>

# Endocannabinoid system: naturally occurring ligands N- arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), their biosynthetic and degradative enzymes, and CB1 and CB2 receptors

The endocannabinoid system comprises two types of receptors, CB1 and CB2, which serve distinct functions in human health and well-being.



**THC**  
Tetrahydrocannabinol



**CBD**  
Cannabidiol



**CBN**  
Cannabinol

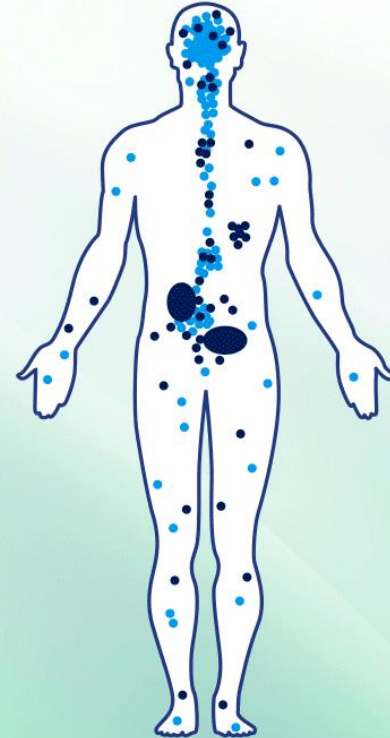
extent in other tissues.

**CB1**

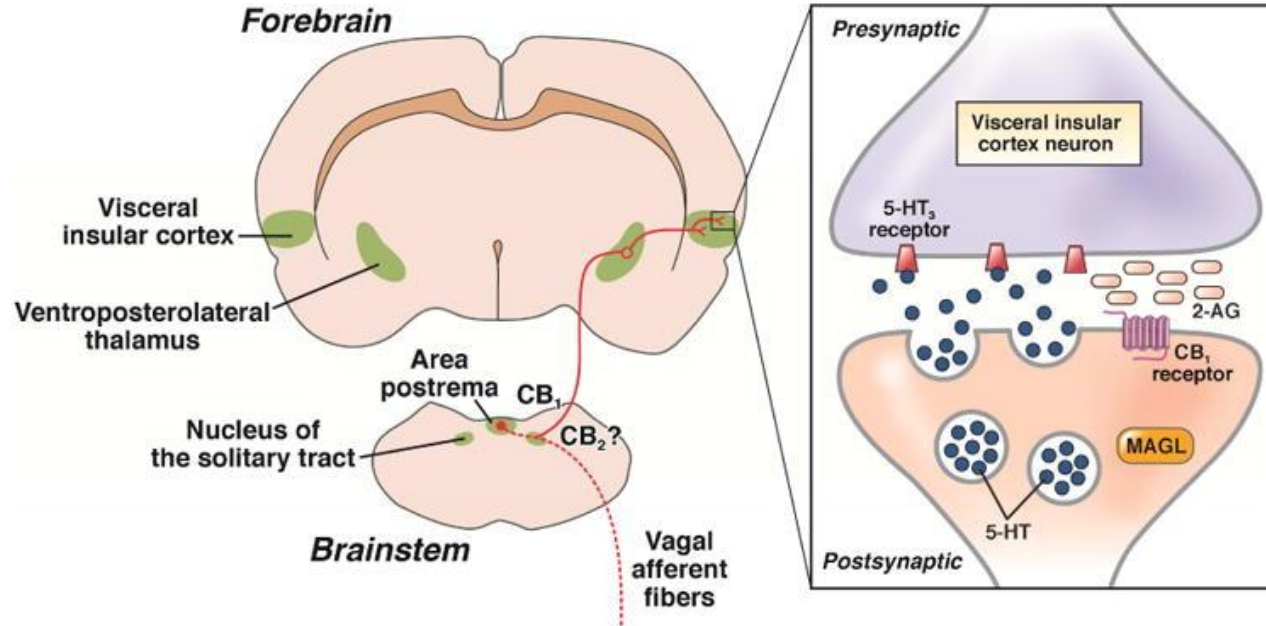
CB1 does not directly “fit”  
CB1 or CB2 receptors but  
has powerful indirect  
effects still being studied.

**CB2**

CB2 receptors are mostly in the  
peripheral organs especially cells  
associated with the immune system.



# Role of Endocannabinoids in Control of N/V



**Endocannabinoid system:** naturally occurring ligands N- arachidonylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), their biosynthetic and degradative enzymes, and CB1 and CB2 receptors

# Systemic review of CVS and CHS

- Limited studies with incompletely characterized case series and individual cases
- Prevalence of CHS in adults is uncertain
- Minimum of cannabis use of >4 times/week for at least 1-year preceding onset of cyclic vomiting for CHS
- Most cases of CHS associated with daily, high dose use
- Abstinence from cannabis for at least 3-episode cycles prior to making a diagnosis of CHS
- Compulsive hot “water bathing” pattern associated with CHS is also seen in CVS w/o cannabis use and chronic N/V



# CHS: Pathophysiology

- Mechanism of CHS is unclear
- Paradoxical emetic effects of chronic cannabis use may be due to increasing potency of cannabis (with higher ratios of THC to cannabidiol) and prolonged duration of use
- Biphasic mechanism of action: Anti-emetic effects at lower or less frequent dosing but is pro-emetic at higher or more sustained doses.
- May involve toxic metabolite(s) from the cannabis plant
- Progressive high exposure to ligand may lead to down-regulation of cannabinoid (CB1) receptors and loss of the endocannabinoid anti-emetic pathway
- Genetic factors— presence of genetic variation in hepatic drug-transforming enzymes results in excessive levels of cannabis metabolites that promote emesis
- Stress increases release of THC from adipocytes via ACTH; alterations in HPA axis and sympathetic system trigger emesis, CRH1 reduces endocannabinoid ligands and increase degradation, decreased CB1

# Rome IV and CVS Guidelines Committee Diagnostic Criteria\* for Cannabinoid Hyperemesis Syndrome (CHS)

## Rome IV Diagnostic Criteria<sup>1</sup>

**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 use of cannabis**
- 3. Relief of vomiting episodes by sustained cessation of cannabis use**

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Supportive remark: May be associated with pathologic bathing behavior (prolonged hot baths or showers)

\*Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

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## CVS Guidelines Committee Diagnostic Criteria<sup>2</sup>

**Must include all of the following:**

- 1. Stereotypical episodic vomiting resembling cyclic vomiting syndrome in terms of onset and frequency  $\geq 3$  episodes a year**
- 2. Duration of cannabis use  $>1$  year preceding onset of symptoms**
- 3. Frequency of cannabis use  $>4$  times a week on average**
- 4. \*Resolution of symptom should follow a period of cessation from cannabis for a minimum of 6 months or at least equal to a duration that spans three typical cycles in an individual patient**

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**\*Patients unwilling or unable to abstain from heavy cannabis use pose a diagnostic challenge and may be considered to have presumed cannabinoid hyperemesis syndrome**

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<sup>1</sup>Talley NJ, et al. Disorders of Brain-Gut Interaction, 4<sup>th</sup> ed. Rome Foundation, 2016; pp. 903-966

<sup>2</sup>Venkatesan, T., et al. Neurogastroenterol Motil, 2019. 31 Suppl 2(Suppl 2): p. e13606

# Pharmacologic Agents for Treatment of CHS

Drug	Number of patients in published reports	Number of patients with response (%)
Haloperidol	11	9 (81.8%)
Capsaicin	94	58 (80.6%) <sup>a</sup>
Lorazepam	36	21 (58.3%)
Morphine	20	3 (15.0%)
Metoclopramide	46	4 (8.7%)
Promethazine	24	2 (8.3%)
Diphenhydramine	13	1 (7.7%)
Ondansetron	64	4 (6.3%)
Olanzapine	42	1 (2.4%)

Abbreviation: CHS, cannabinoid hyperemesis syndrome.

Adapted from Reference 3.

<sup>a</sup>Data on efficacy available for 72 patients.

# Treatment of CVS & CHS

Treatment of CVS

Psychological Treatment

Yes

Psychological Factors

The only effective treatment of CHS is a drug holiday—cessation of cannabis use to allow clearance of putative toxic metabolites and/or normalization of CB receptor levels and function

↓

Abuse of cannabis?

No

Yes

Treatment options complete

Effective

Treatment Options:  
Tricyclic antidepressants  
Anti-convulsants

Add or switch

Treatment Options:  
Stop use of cannabis

Effective

Treatment options complete



# Summary

- **CVS**

- A brain-gut, multifactorial disorder with overlap with abdominal migraine and migraine headache
- A distinctive (stereotypical) temporal pattern and should be treated with preventive and acute care measures

- **CHS**

- Typically occurs with long history with heavy use of cannabis
- Due to downregulation of cannabinoid receptors and loss of anti-emetic pathway
- Sustained cessation of cannabis is required for diagnosis and relief of vomiting