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# Cyclic Vomiting Syndrome: Diagnostic Criteria and Insights into Long Term Treatment Outcomes



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## INTRODUCTION

**C**yclic vomiting syndrome (CVS) in adults is a disorder characterized by recurrent abrupt bouts of nausea, vomiting and abdominal pain separated by variable periods of normal health. This alternating pattern of disease and disease-free periods distinguishes CVS from other disorders of nausea and vomiting. This entity has been increasingly recognized in adults and has resulted in significant morbidity and poor quality of life.<sup>1</sup> Recent referral patterns suggest prevalence of up to 0.2% in the adult population and an explanation for nausea and vomiting in 12% of a referral population to a teaching academic center.<sup>2</sup>

## Diagnostic Approach

CVS is really a diagnosis of eliciting a “classic” history of this disease. Patients typically present with a variable number of episodes of nausea, vomiting and mid-epigastric abdominal pain per year. During

all presentations in adults there is accompanying severe mid-epigastric abdominal pain, with or soon after the onset of nausea and vomiting. This history of mid-epigastric abdominal pain tends to attract the need to exclude other sources since it can mimic an acute abdomen. Diagnostic Criteria of CVS is based on Rome III which includes the following list in (Table 1). These criteria were developed when CVS was predominantly only being recognized in children and abdominal pain was not a predictable concomitant feature.

The majority of CVS attacks occur without any warning although in retrospect patients report that up to 60-80% of CVS attacks can be associated with a trigger mechanism such as infection (chronic sinusitis and upper respiratory infections), psychological stress, emotional stress, physical stress (heavy exercise), lack of sleep, diet (chocolate, cheese), motion sickness and onset of menses.<sup>3-4</sup> Many patients take hot showers or baths during the vomiting episodes and report a decrease in symptoms and therefore the contact with hot water is assumed to have a “relaxation effect”.

As far as contributing factors or etiologic “subgroups” approximately 24-70% of CVS patients

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report a personal or family history of migraines.<sup>1</sup> However in adults the migraine subset is more in the range of 30-40% of the CVS population. Psychiatric disorders, such as anxiety, depression are frequent comorbid findings in CVS patients.<sup>6</sup> The anxiety present in CVS patients, including panic disorder, has been reported to trigger attacks in 66% of cases.<sup>7</sup> Anxiety can also be increased as a result of the burden of the illness, anticipation of the next vomiting episode or psychological trauma and experiences prior to the onset of CVS.<sup>3,7</sup> Sometimes psychological disorders in CVS patients including depression are so dominant that co-management with a psychiatrist may be indicated.

Another identifiable subgroup is diabetes mellitus which is increased to 15% in the CVS populations compared to approximately 8% in normal population based studies. The theory proposed here is that elevated glucose levels, usually early in the course of diabetes, in the setting of genetically predisposed CNS chemoreceptors can trigger a vomiting cycle.

On review of the current literature of cyclic vomiting syndrome in adults marijuana use is present in 42-53%.<sup>8</sup> The predictable scenario is a typical pattern of daily marijuana intake beginning in the teenage years for recreational use. The cyclic episodes of vomiting do not occur until at least 5 years of chronic daily use. A clinical entity termed cannabinoid hyperemesis syndrome has also been separately described and is actually the same clinical presentation as CVS.<sup>8</sup> Cannabinoid hyperemesis syndrome is characterized by chronic marijuana use, cyclic episodes of nausea, vomiting, abdominal pain and frequent relief with taking a hot bath.<sup>9</sup>

Not all cannabis users develop cannabinoid hyperemesis syndrome. However the cumulative dose of marijuana, genetic factors, and psychological parameters may contribute to this condition. The pathophysiology of cannabinoid hyperemesis syndrome is unknown. There are some hypotheses proposed to explain this phenomenon: (a) accumulation of cannabis derivatives in the brain based on their lipid solubility and long-term half-life, (b) degradation of the cannabis ingredients to some potential emetic metabolites or toxins, (c) delayed gastric emptying induced by cannabis and (d) down-regulation or desensitization of the cannabinoid receptors due to chronic cannabis use.<sup>8,10</sup> Another theory is that chronic cannabis is associated with inhaling toxins related to the various sources and preparation of the marijuana and over time

**Table 1. Rome III Diagnostic Criteria for Cyclic Vomiting Syndrome**

<b>Must be at least 3 months, with the onset at least 6 months previously of:</b>
1. Stereotypical episodes of vomiting regarding the acute onset and duration being < 1 week.
2. Three or more discrete episodes in the prior year.
3. Absence of nausea and vomiting between episodes
4. Absence of any organic cause of vomiting.
<b>Supportive Criteria:</b>
A prior history or family history of migraine headaches.

these toxins could accumulate in the CNS.<sup>11</sup> However, the major message is chronicity of >5 years with daily use leading to increasing storage in fat tissue in the brain and in those genetically susceptible individuals nausea receptors are activated. This setting is to be distinguished from the “legal use” of marijuana for cancer and pain related indications. In addition cannabis has been shown to acutely delay gastric emptying and this can also contribute to inducing a vomiting cycle.<sup>9,11</sup>

In our experience at an academic gastrointestinal motility referral center, we recently reviewed a total of 48 patients diagnosed with CVS, 37 females and 11 males with a mean age of 34.8 year old. The majority of the patients reported cyclic episodes occurring approximately every 2-3 months. Five (10%) patients had relief of symptoms with hot baths or showers and 11 (23%) had worsening of symptoms with stress, menses or sleep deprivation. Comorbidities included diabetes mellitus (31%), hypertension (23%), hyperlipidemia (15%), anxiety (48%), depression (25%), migraines (40%), family history of headaches/migraines (31%), panic disorder (11%), and chronic daily marijuana use (23%) for more than 5 years. Eleven (23%) patients were smokers, 7 (15%) had a history of alcohol use and 15 (33.3%) were given narcotics acutely at some time throughout the course of their disease during ED visits. Six (20%) of patients reported a significant disruption in their professional and/or personal social life. Fifteen (19%) patients had a cholecystectomy. Twenty-five

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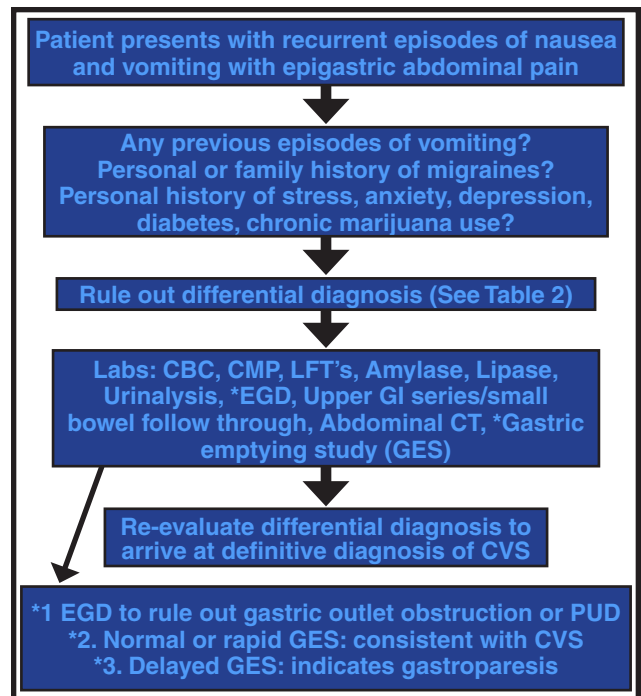
(52%) had frequent ED visits before being diagnosed and treated.

Adult patients typically have been symptomatic for a long time before diagnosis. Patients often remain undiagnosed for some time due to lack of recognition of this clinical entity with reports suggesting a delay in diagnosis for as long as 8-21 years following onset of the symptoms.<sup>6,12</sup> Over time without appropriate specific treatment, CVS cycles slowly begin to “coalesce” and become closer together and this can confuse the presentation and suggest more of a “chronic” entity such as gastroparesis. CVS results in a significant morbidity for patients with loss of time at work or school, a significant disruption in professional and personal life as well as an economic burden.<sup>9,12-13</sup> CVS in adults can range from mild disease with infrequent episodes to severe debilitating disease requiring multiple emergency department (ED) visits and frequent hospitalizations.<sup>12</sup> These patients often undergo multiple unnecessary diagnostic tests and procedures without any apparent clinical benefit. Abdominal pain and mild leukocytosis have prompted unnecessary cholecystectomies and other abdominal surgeries because CVS was mistaken for an acute abdomen.

### Gastric Emptying Studies in CVS

Even though CVS has been increasingly recognized in the adult population, there is a lack of data as to the gastric emptying (GE) pattern. Using a standardized 4 hour egg beater scintigraphic method a normal GE is defined as < 90% retention at 1 h, < 60% at 2 h, and < 10% at 4 h. Rapid GE is defined as < 35% isotope retention at 1st hour and/or < 20% at 2nd hour.<sup>14</sup> Delayed gastric retention is defined as a delay of greater than 90% at 1 h, 60% at 2 h, and 10% at 4 h based on normal data established for this standardized GES.<sup>14</sup> Employing these criteria for rapid GES we found that 30% met these criteria while 70% had a normal GES. The GE test was performed during the remission phase of CVS. Delayed gastric emptying was not identified. Our group also published criteria for rapid gastric emptying as being <50% isotope retention at 1 hour and the majority of our adult patients (65%) with CVS had a rapid GE and 35% had a normal GE.<sup>15</sup>

A rapid or normal GE can therefore be used as confirmatory evidence of CVS so that clinicians can confidently exclude gastroparesis from the differential. Gastric emptying studies should be performed during



**Figure 1.** Cyclic Vomiting Syndrome: Proposed Algorithm for Making the Diagnosis

the remission phase when there are minimal or no symptoms and no narcotic medications are being received.<sup>16-17</sup> Gastric emptying studies while patients are in the hospital receiving narcotics are discouraged. Narcotics inhibit GE thus producing a slow gastric emptying result leading to a mislabeling of these patients as having gastroparesis. In addition, the preceding use of marijuana can delay GE. Explaining the role of a rapid GE during a vomiting free period has led to speculation and support for an underlying autonomic dysfunction in these patients as well as evidence for increased serum ghrelin as another factor in speeding up the GE.<sup>11</sup>

### Diagnostic Evaluation

The diagnosis of CVS requires that other known and treatable disorders be excluded. The differential diagnosis for patients with CVS that should be ruled out includes those listed in Table 2. We recommended a diagnostic algorithm (Figure 1) through which a patient presenting with an acute episode of nausea, vomiting, epigastric abdominal pain should be evaluated so that other diagnoses can be excluded by history, physical examination, and basic laboratory studies including a complete blood count (CBC), complete metabolic panel (CMP) with liver function tests, amylase, and lipase, a urinalysis as well as an upper GI series/small

bowel follow through.<sup>6</sup> An abdominal ultrasound may help in evaluation of possible gallstones, pancreatitis and ureteropelvic junction obstruction. An esophagogastroduodenoscopy (EGD) should be performed in patients with acute vomiting with or without hematemesis to exclude gastric outlet obstruction or peptic ulcer disease as well as *H. pylori*. Imaging studies such as an abdominal CT should be considered to exclude structural lesions.

The decision as to which diagnostic tests to perform should be tailored to the clinical presentation of the patient. In adults, much consideration must be used to differentiate CVS from gastroparesis. A subset of patients with idiopathic or diabetic gastroparesis

presents with cyclic emetic episodes similar to CVS.<sup>7</sup> Patients with gastroparesis exhibit more chronic daily symptom severity and a delayed gastric emptying on scintigraphic study. In contrast, gastric emptying is often accelerated or normal and not delayed in patients with CVS during the asymptomatic period when vomiting is absent.<sup>7</sup>

### Management

Once a cyclic vomiting episode is in progress, supportive measures are at the forefront of management. Intravenous fluids should be given to prevent dehydration and electrolyte imbalance. The approach to treatment in the ED setting is inducing sedation, sleep and relaxation

**Table 2. Differential Diagnosis for Cyclic Vomiting Syndrome**

Disorder	Appropriate Test to Evaluate for this Disorder
<b>Gastrointestinal Disorders</b>	
<b>Gastric Disorders</b>	
Peptic ulcer disease	Upper Endoscopy
Gastroparesis	Gastric Emptying Study
<b>Gallbladder Disorders</b>	
Cholecystitis	Abdominal Ultrasound
Biliary tract dysmotility	HIDA scintigraphic imaging
<b>Small Bowel Disorders</b>	
Intermittent small bowel obstruction	Abdominal CT scan
Chronic intestinal pseudo-obstruction	Abdominal obstruction radiographic series
Malrotation with volvulus	Upper gastrointestinal series with small bowel follow through
<b>Extra-intestinal Disorders</b>	
<b>Central nervous system abnormalities</b>	
Mass	Brain MRI
Hydrocephalus	Brain CT or MRI
<b>Renal Disorders</b>	
Nephrolithiasis	Urinalysis, Abdominal CT
Ureteropelvic junction obstruction	Renal ultrasound
<b>Hormonal and Metabolic Disorders</b>	
Adrenocorticoid insufficiency	Plasma cortisol
Acute intermittent porphyria	Urinary porphyrins

mainly through IV lorazepam (1-2mg every 4 hours) with support from narcotics, anti-histamines and antiemetics to terminate the emetic phase although hospitalization is often required to achieve this goal. Family involvement is a crucial part of management in order to cope with an unpredictable, disruptive, unexplained illness that is commonly misdiagnosed.

Long term treatment of CVS is based on trying to identify the etiologic subgroups particularly the role of psychological stress while prescribing prophylactic drug and abortive therapy and supportive measures to ameliorate acute vomiting episodes. In relation to psychological stressors, stress management techniques as well as daily lorazepam (1mg up to every 6 hours) will help relieve anxiety. For the subset of patients with significant depression, co-management with a psychiatrist may be indicated to select antidepressant therapies with the least likelihood of exacerbating the emetic illness. It is appropriate to start anti-migraine prophylaxis in those CVS patients with a positive family history or personal migraine history. Anti-migraine drugs that are effective at reducing the number of episodes or severity of migraines include sumatriptan, propranolol and topamax. Patients with a history of chronic cannabinoid use should be counseled in regards to cessation that commonly leads to symptomatic improvement.<sup>4,11</sup> Studies from our patient population have shown a high rate of cannabis use in a subset of patients with CVS. These patients need a higher dose of amitriptyline for the control of their CVS attacks compared to non-cannabis users.<sup>18-19</sup> Therefore, it is important to identify cannabinoid hyperemesis syndrome as part of CVS, since a long term goal is decreasing and stopping cannabis use in these patients.

Long term management is focused on reducing and actually preventing future hyperemesis episodes.<sup>20-21</sup> At the forefront of CVS management, tricyclic antidepressants (TCA), especially amitriptyline, have been shown to be effective for pharmacological prophylaxis. They are well tolerated and very effective in treating adult patients with CVS in doses of 50 to 200mg as necessary and as tolerated. Tricyclic medications act by decreasing cholinergic neurotransmission and modulating alpha-2-adrenoreceptors, thereby reducing the sympathetic nervous system and brain-gut autonomic dysfunction.<sup>13,22-23</sup>

The treatment approach with tricyclic antidepressants requires beginning with a low initial dose of amitriptyline 10 mg at night with

**Table 3. Proposed Diagnostic Criteria for Adult Cyclic Vomiting Syndrome**

**Must be at least 3 months, with the onset at least 6 months previously of:**

1. Stereotypical episodes of nausea, vomiting and mid-epigastric abdominal pain with an acute onset and duration being approximately or up to < 1 week.
2. Three or more discrete episodes in the prior year.
3. Minimal or absence of nausea, vomiting and mid-epigastric abdominal pain during the remission phase.
4. Absence of any organic cause of vomiting.

**Additional Proposed Criteria:**

1. Personal history of migraine headaches, diabetes and stress.
2. Chronic marijuana use (>5 years).
3. Rapid or normal gastric emptying study during the remission phase.
4. Response to increasing doses of amitriptyline.

incremental increases in 10 mg doses every 2 to 4 weeks to titrate to the desired therapeutic effect.<sup>24-25</sup> There is no established dose to control the symptoms but prevention of the vomiting cycles is the goal. Side effects of using TCAs include dry mouth, somnolence, constipation, postural hypotension, chronic fatigue, blurred vision and mild hallucinations.<sup>24-25</sup> Side effects can be minimized by slowly increasing the dose by 10 mg every 2-4 weeks. The rationale for this approach is to identify what is the lowest dose that may be therapeutic in an individual and still limit side effects that can occur with higher doses. Tricyclic antidepressants take more than 1 month to achieve full therapeutic effect following initiation and this must be conveyed to the patient. Other TCAs such as nortriptyline and doxepin can be used as substitutes with less adverse events, but still with therapeutic benefits. More recently, the anticonvulsant agents zonisamide (100-600mg daily) and levetiracetam (500-1000 twice daily) agents have demonstrated efficacy in adult patients who are unresponsive or intolerant of TCAs, but their current role can only be considered as second line therapy.<sup>7,26</sup>

Once initial control is achieved with escalating amitriptyline dosing and concurrent lorazepam for anxiety, supportive therapy involves antiemetic agents

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include ondansetron, promethazine or prochlorperazine for breakthrough nausea. The antispasmodic (dicyclomine) is for irritable bowel syndrome (IBS) like abdominal pain, especially in patients with rapid gastric emptying and an exaggerated gastro-colic reflex. Proton pump inhibitors can be briefly used for gastroesophageal reflux symptoms in relation to excessive vomiting.

In our experience at a gastrointestinal motility referral center, we found that 83.3% of our patients who began on a low dose (10mg) of amitriptyline before bedtime were able to gradually escalate using an approach of 10mg increments every 2-4 weeks as tolerated and achieve symptom control as evidenced by preventing relapses and ED visits. This titration approach to the dosing of amitriptyline achieved symptomatic relief in 8% patients at a dose of 50-75mg; 50% at 100mg; 21% at 150mg and 8% at 200mg. Nonresponse to standard therapy in adult cyclic vomiting syndrome patients occurs in approximately 13% and is not explained by under dosing with TCA therapy.<sup>24</sup> The main risk factors for nonresponse to amitriptyline are: co-existing poorly controlled migraine headaches, psychiatric disorder, chronic narcotic and ongoing marijuana use, which should be addressed aggressively when symptom exacerbations continue during attempts to induce remission in cyclic vomiting syndrome with high-dose TCA therapy.<sup>24</sup>

Long term outcomes are now becoming apparent as treatment patterns become recognized. One pattern requires further increasing the maintenance dose overtime due to some dose tolerance slowly occurring with breakthrough vomiting cycles. Another group in whom symptoms were controlled for at least one year with no ED visits were able to be successfully tapered to a lower dose with no ED visits. The amitriptyline dose is slowly tapered or even stopped over time, usually at least 1 year. Twenty-one percent of our patients were able to reduce their dose to 10-20mg per day. One additional incentive we witnessed was a pregnancy goal in females since amitriptyline is listed as a category C by the FDA and therefore is not recommended during pregnancy.

In Summary, treatment with TCA is an effective strategy in 87% of patients and significantly decreases the frequency of attacks, number of emergency room visits and hospitalizations. Once symptoms are controlled for at least 12 months the dose of TCA can slowly be tapered to reach very low doses or even be stopped

while maintaining symptomatic control. This has been a new observation, namely that effective tapering over 6 to 12 months can be achieved. The theory to explain this observation is that the CNS receptor hypersensitivity initially present in CVS patients has been successfully blocked during treatment with amitriptyline providing a time frame where the recognized risk factors of migraine, stress, diabetes, marijuana can be addressed and better controlled. Hence, the environment affecting CNS nausea receptor sensitivity has now changed so that the protective role of amitriptyline is no longer required.

## CONCLUSIONS

The intent of this article was to further characterize the clinical presentation and propose new diagnostic criteria for CVS in the adult population (Table 3). CVS is not a rare condition in adults as it was once thought to be and is essentially a bedside diagnosis based on the “classic” stereotypical cycles of the vomiting episodes and discrete symptom-free intervals. It is now more common in adults than children and is diagnosed in up to 12% of patients being referred for evaluation of nausea and vomiting. As cyclic vomiting episodes coalesce, usually because no specific therapy has been given, patient symptoms can begin to resemble gastroparesis, a disorder presenting with more continuous chronic nausea and vomiting but typically much less abdominal pain. However, subsets of diabetic gastroparesis patients can have relapsing “cycles” superimposed on this chronicity and this is an example where the distinction from CVS becomes very difficult. Overall the epigastric abdominal pain is a more dominant complaint among CVS patients which is not the usual case in gastroparesis. However, rapid or normal gastric emptying in CVS may be a final “tie-breaker” in distinguishing it from the slow gastric emptying of gastroparesis.

The important message for our clinicians is that CVS can be presented to the patient as a potentially reversible disease: Following initial intensive treatment to achieve remission and after effectively addressing comorbidities, the dose of amitriptyline can be slowly tapered and even stopped over time.

## Take Home Message

CVS in adults is under diagnosed and improved awareness and recognition of disease characteristics can help reduce invasive and costly diagnostic workups

that have a negative effect on patient economics. This is particularly so for physicians in the Emergency Department who should have a high clinical index when a pattern of unexplained episodes of acute nausea, vomiting and abdominal pain, are observed with frequent ED visits and hospitalizations. This is the CVS “blue print” and epigastric abdominal pain should be added to the Rome criteria for adult CVS patients. Further key clinical clues for CVS lie in appreciating the comorbidities of anxiety, depression, migraine headaches and diabetics. Chronic marijuana has now become a new and very prevalent etiology and should be added as supplementary criteria. Finally, CVS patients have either a rapid or normal GE. This is a “signature” finding separating CVS from gastroparesis and we strongly recommend that GE status be added as one of the major criteria for the diagnosis of CVS. ■

List of Abbreviations: CVS: Cyclic vomiting syndrome; GES: Gastric emptying study; GE: Gastric emptying; ED: Emergency department; TCA: tricyclic antidepressants; PPI: proton pump inhibitors

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Answers to this month’s crossword puzzle:

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18	C	H	Y	M	E			20	E	R	C	P			22	U	R	E	A			
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41	R	A	Y	S						42	A	S	C	I	T	E					S	N