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Gastroenterology & Hepatology
Advanced Practice Providers

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Chronic Nausea and Vomiting – The Challenge

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Case Study

- Jason is a 20 year old male, 10 years ago, after mild traumatic brain injury, developed worsening headaches, migraines and vomiting episodes. His vomiting episodes became more frequent and debilitating requiring prolonged hospitalizations for hydration, and electrolyte replacement. Despite multiple admissions no clear source was found to his symptoms. He is now referred to you for second opinion.

Additional History

- Since infancy, vomiting spells from age 4 to 16 lasting 2 days to 1 week-then symptoms disappear for weeks to months
- First – 'feels funny" x 1 hour, then vomiting abdominal discomfort-epigastric
- Fasting can trigger
- No clear trigger food
- Denies melena or rectal bleeding
- Reports anxiety type symptoms takes Lexapro 20 mg QHS, sleeps poorly

Previous Work Up

- EGD – multiple most recent -(11/20/18)- Changes of mild gastritis, bx negative for *H. pylori*
- CT chest, abdomen, pelvis 6/17, negative
- Normal CBC, liver enzymes, lipase
- Negative for celiac
- Normal TSH, Free T4
- Mild hypokalemia and hypomagnesia
- Positive cannabis last toxicology screen
- Negative porphyrins

Previous Treatments

- Famotidine 40 mg daily to bid
- Pantoprazole 40 mg daily to bid
- Ondansetron 4 mg, now 8 mg during vomiting episodes
- Compazine 25 mg prn vomiting episodes
- Lexapro 20 mg per mouth daily
- Hospital admission, multiple
 - IV hydration, IV antiemetics, electrolyte replacement

What Next?



Current Symptoms

- 2-5 day vomiting episodes every 2-3 months. Frequency increased over 4 years ago.
- Epigastric pain during the episodes. However, outside of these episodes, he has no abdominal pain.
- Reported 50 lb weight loss in the last year and does not know why. He thinks it may be related to the vomiting.
- Missing multiple days of work – may lose his job

Current Treatment Regimen

- Pantoprazole 40 mg during episodes
- Ondansetron 4 mg ODT prn
- Compazine 25 mg suppository prn
- Lexapro 20 mg QHS
- Ambien 10 mg prn
- Marijuana 2-3 times per week, more during acute episodes feels helps
- Hot showers alleviate symptoms as well

FRUSTRATION





What Else Want to Know?

- Previous surgeries
- Family history
- Alcohol abuse
- Over the counter treatments
- NSAID use
- Herbal supplements
- What alleviates symptoms

Evaluation



What Diagnostic Tests Would You Consider Ordering?

- EGD
- Routine labs
- Pregnancy test in women-childbearing
- Ultrasound of the abdomen
- Small bowel follow through
- Gastric emptying scan
- SMA/celiac dopplers
- MRI/CT brain

Results

- Normal CBC
- Mild leukocytosis
- Normal LFTs
- Mild hypokalemia, 3.1
- EGD, mild gastritis, healing Mallory Weiss tear
- CT chest, abdomen and pelvis negative
- Gastric emptying rapid-emptying

Differential Diagnosis



Differential Diagnosis

- Peptic or gastric ulcer
- Pyloric stenosis
- Gastroparesis
- GERD
- Gastritis
- Cholelithiasis/choledocholithiasis
- Cyclic vomiting syndrome
- Gastric outlet obstruction
- Small bowel obstruction
- Hyperemesis cannabis syndrome
- Pancreatitis

Diagnosis





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Cyclic Vomiting Syndrome (CVS)

Cyclic Vomiting Syndrome (CVS)

- First described in the late 1800s
- “Is a chronic **functional idiopathic** gastrointestinal disorder”
- It is characterized by recurrent episodes of nausea, vomiting separated by **asymptomatic periods**
- Typically starts in childhood, may occur during adulthood only
- Being recognized more frequently in adults

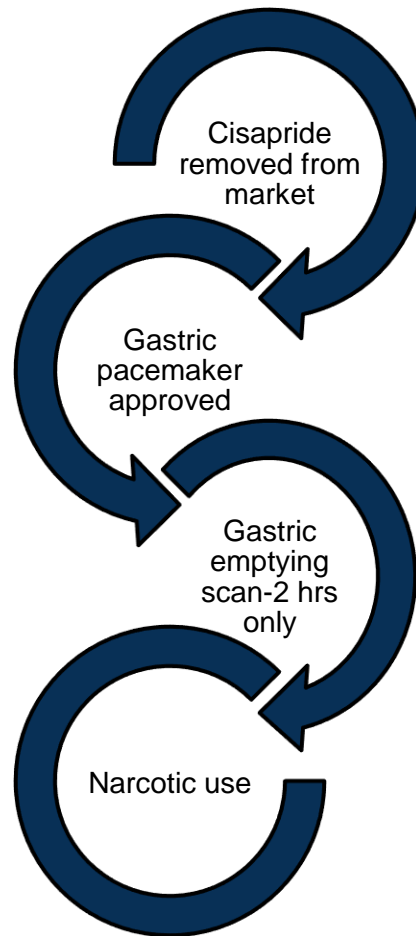
Cyclic Vomiting Syndrome (CVS) – Significant Morbidity

- 1/3 adults become disabled
- 39.7%-41% of adults with CVS have underlying psychiatric disorders (anxiety, depression)



Year 2000, CVS Emerging Adult Diagnosis

Early 2000, rise in admissions for nausea and vomiting



CVS was main causes of admissions

Epidemiology – Children

- Prevalence 1.9-2.3%
- Incidence 3.2 per 100,000
- Predominately Caucasian
- Average age of diagnosis 9.6, onset 5.3 years
- Girls 86% cases



Epidemiology – Adults

- Suspected adults > children
- 3-14% cause of unknown N/V etiology in adults
- 10.8% adult functional disorders
- Mean age of diagnosis 32
- Female: male predominance equal

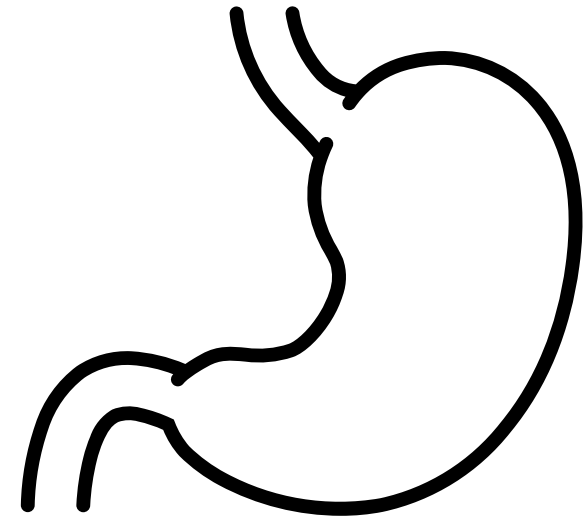


Pathogenesis

- Unknown – appears-multifactorial
- Association between CVS and migraine headaches
- CVS linked to autonomic abnormalities (elevated sympathetic tone and impaired parasympathetic regulation), hypothalamic-pituitary-adrenal activation (Sato variant), mitochondrial dysfunction-peds, CRF, menses (estrogen sensitivity)
- Food allergy, and cannabis use

Gastric Emptying in CVS

- Study 92 pts with CVS –
59% rapid gastric emptying,
27% normal, 14% slow
- Rapid GE during remission
phase-exaggerated
gastro-colic reflex – “mild
dumping syndrome”
- Critical distinction between
CVS and gastroparesis



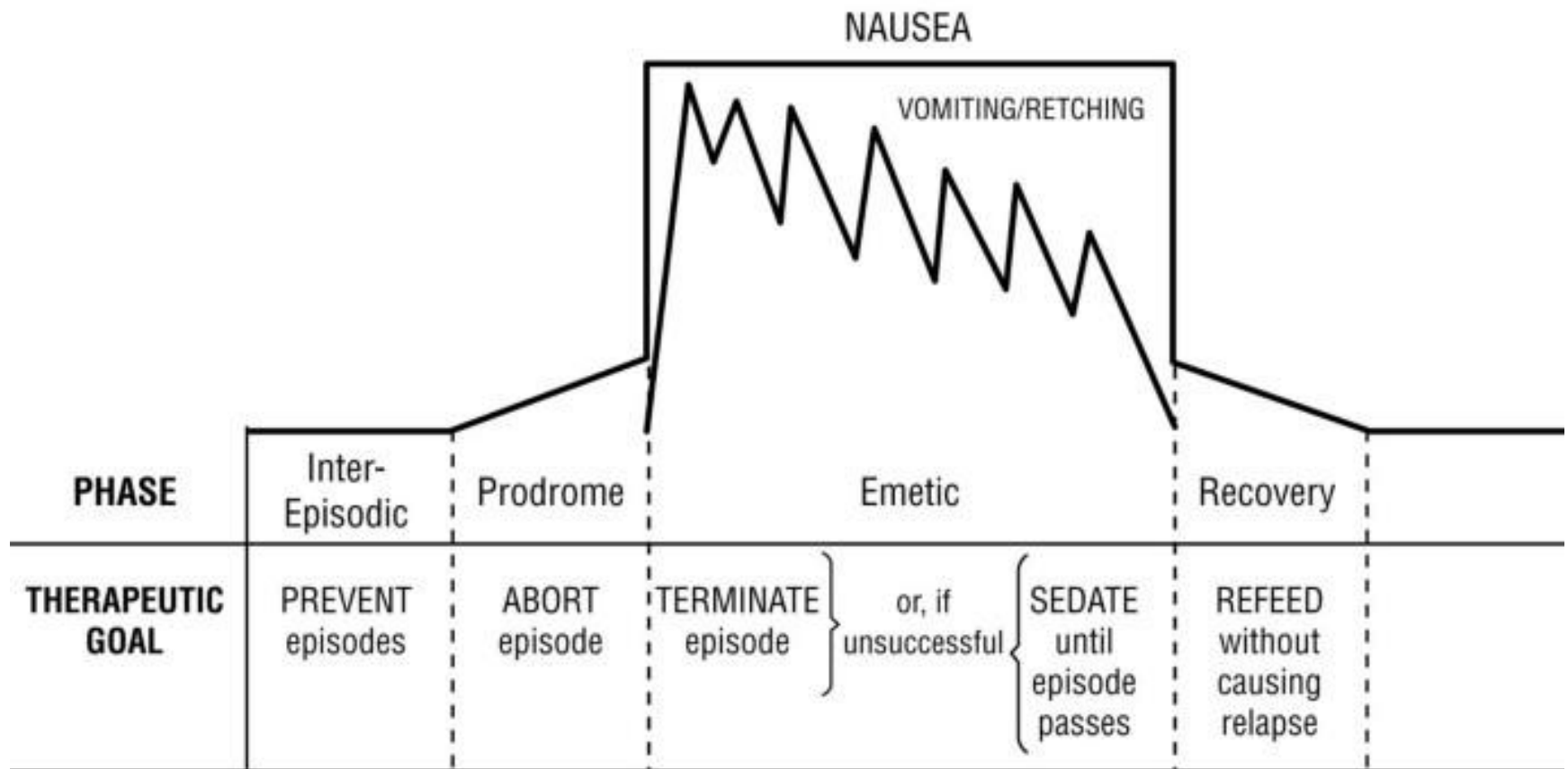
Etiology of Rapid Gastric Emptying

	Female	Male	Total (%)
Number of patients	28	20	48
CVS	9	8	17 (35%)
N/V-non-ulcer	8	4	12 (25%)
Diabetes	3	3	6 (13%)
Fundoplication/ Vagotomy	2	3	5 (11%)
Diarrhea/abdominal pain unknown source	4	1	5 (11%)
Gastric bypass	3	0	3 (6%)

Rome Criteria (2016)

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

Phases of CVS



Prodromal

- 93% of adults reports a prodromal phase
- Nausea, epigastric pain, or headache
- Early morning onset; abdominal pain during episodes; and a high peak rate of vomiting of eight emesis per hour during the emetic phase
- Reports worse with menstrual cycles or pregnancy
- 1/3 report orthostatic tachycardia – POTs or hypotension

Symptoms

- Vomiting 1-6 times per hour – occurs out of the blue
- Abdominal pain-epigastric – 70% adults
- Restlessness
- Excessive thirst – “guzzling behavior” – vomiting
- Migraine headache – not required
- Photosensitivity
- Difficult articulation

CVS vs HCS

Cyclic vomiting syndrome	Hyperemesis cannabis syndrome
Acute vomiting < 1 week	Episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration, and frequency
≥ three discrete episodes in past year and two episodes in the past 6 months, occurring at least 1 week apart	Occurs after prolonged use of cannabis
Absence of vomiting between episodes, can have milder symptoms between cycles	Relief of vomiting episodes by sustained cessation of cannabis use

CVS Triggers

- Stress
- Poor sleep
- Motion sickness
- Excitement
- Infection
- Food
 - Chocolate, cheese, red wine, MSG
- Menses
- Medications – Cannabis





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Associated Conditions

Associated Migraine



- 13-70% CVS has associated migraines
- 57%-CVS pts- 1st or 2nd degree relative with migraine (mother)
- Unclear if treating migraines improves CVS
- Many abortive therapies TCA, anti-seizure, or abortive therapy work for both conditions

Autonomic Function

- Study 35% had postural tachycardia
- Additional study 23% postural tachycardia or orthostatic hypotension
- Abnormalities in skin sympathetic responses



Psychiatric Disorders

- Associated anxiety and depression
- Panic attacks can precipitate
- 44% of adults with CVS – physical, emotional, or sexual abuse childhood



Diabetes

**Diabetes 13% of
CVS patients**



Drugs Associated With CVS

Cannabis

- CVS symptoms ↑
- CHS (cannabinoid hyperemesis syndrome)
- Hot showers to relieve
- 37-81% pts with CVS use
- Internet study 81% pts with CVS use Cannabis
- Colorado study after medical marijuana legalized – 46% in CVS hospitalizations ↑



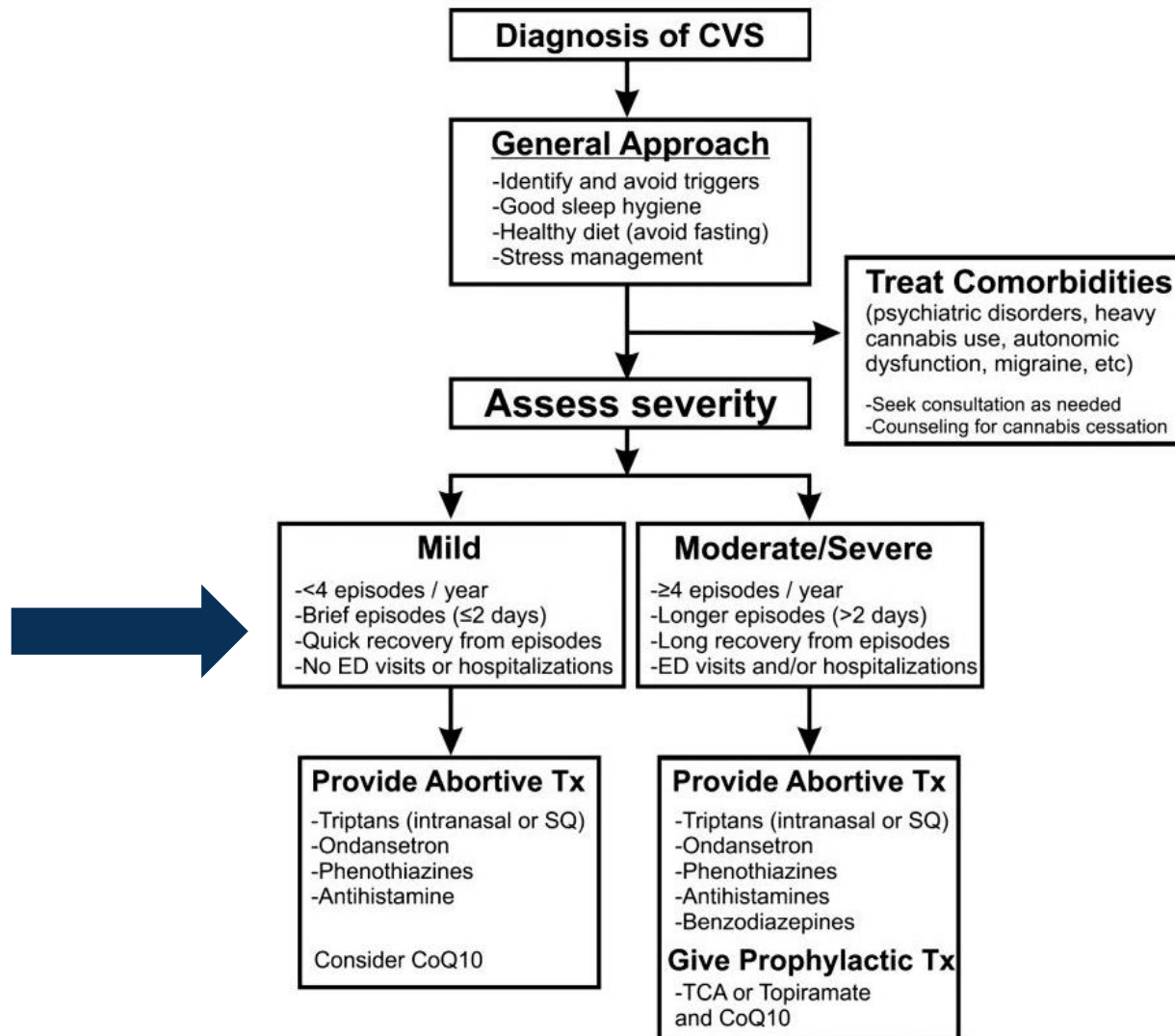
Treatment of Mild CVS



Treatment

- Based on guidelines in adults by the American Neurogastroenterology and Motility Society (2019)
- Treatment is based on a biophysical care model integrating:
 - Lifestyle modification
 - Prophylactic and/or abortive medications
 - Evidenced based psychotherapy

Treatment Algorithm



General Approach

- Trigger identification
- Good sleep pattern
- Healthy diet
 - Avoid fasting
- Stress management
- Treat comorbidities
 - Psychiatric disorders, migraines, cannabis usage
 - Drug usage, smoking
 - Narcotics, limit



How Severe Is It? Case Study



Mild-CVS

- < 4 episodes a year
- Brief, lasts < 2 days
- Quick recovery
- Does not require ER or hospitalization



Treatment of Mild CVS

- Focus on abortive treatments
 - Triptans
 - Ondansetron
 - Phenothiazines
 - Antihistamine
 - Consider CoQ10



Triptans

- Sumatriptan-serotonin agonist – migraine
- CVS subgroup of periodic syndromes including migraines
- Nasal spray – 20 mg initially or 6 mg subcutaneous
- May be repeated every 2 hours
- Maximum 6 doses per week
- Proper administration – “head forward” improves delivery

Triptan

- Study with 11 children with CVS – efficacy high in patients with family history of migraine vs no migraine (82% vs 50%)
- Works best – acute within 30-45 minutes of prodrome
- Nasal and injectable better absorption
- Limit to max 6 doses per week
- Avoid in CAD, PVD, HTN, CVA

Ondansetron

- Ondansetron 4-8 mg ODT every 6-8 hrs scheduled-maximum total dose of 32 mg/24 hours
- Decreases serotonin circulation at CTZ level
- There has been overall lack of clinical trials, although for many overall effective
- Recommended as first line agent in aborting CVS
- May be used in conjunction other medications
- Monitor QTc interval

Phenothiazines and antihistamines

- Compazine 2.5 to 10 mg every 3 to 4 hours as needed IV – hospital
 - 25 mg suppository every 12 hours prn
- Phenergan 12.5 to 25 mg IM or IV every 4 to 6 hours
- Benadryl 25-50 mg every 6 hours prn – sleep helps

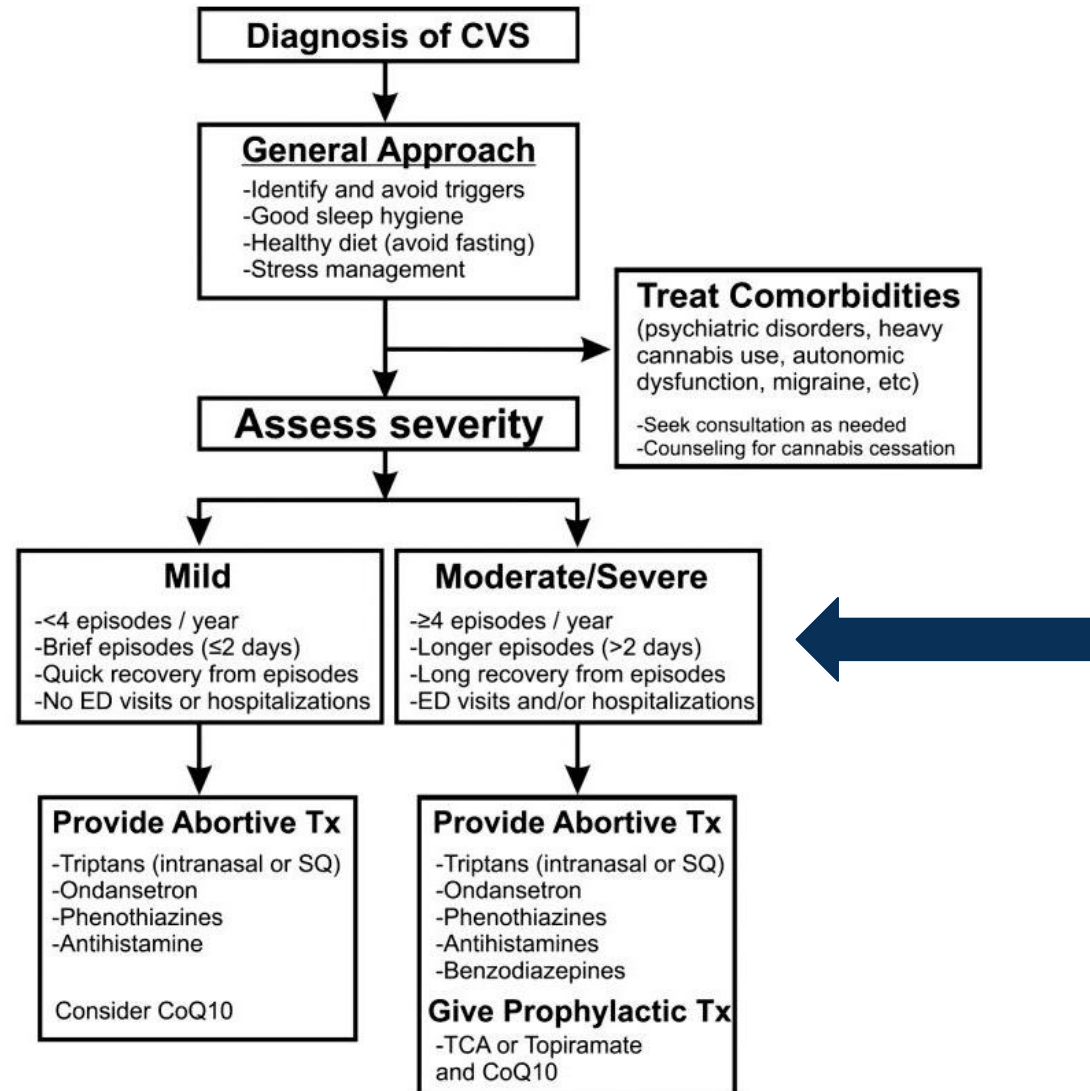
Case Study

- 1 month follow up from initial consultation
- 2 hospital admissions since consultation – 5 days both admissions
- IV hydration, antiemetics
- Pantoprazole IV
- Discharged home on previous regimen + Sumatriptan 20 mg nasal spray-at prodrome + Scopolamine patch
- Stopped Marijuana
- Despite the above changes nausea and vomiting episodes every 1-2 weeks lasting 3-4 days

Treatment of Moderate to Severe CVS



Treatment Algorithm



Treatment Prophylactic + Abortive

- Triptans – nasal or subcutaneous
- Ondansetron
- Phenothiazines
- Antihistamines
- Benzodiazepines
 - Prophylactic
- Tricyclic antidepressants
- Anti-seizure
- Aprepitant

Tricyclic Antidepressant (TCA)

- Amitriptyline start 10-25 mg QHS or 1-1.5 mg/kg daily-titrate in 10-25 mg increments-every 2-3 weeks
- 15-35% poor responders to TCA – predictable profile – co-existing disorders
 - Psychological disorders
 - Marijuana use
 - Chronic narcotics
 - Uncontrolled migraines

Tricyclic Antidepressants

- Should be considered patients moderate to severe CVS that:
 - ≥ 4 episodes per year
 - Episodes > 2 days
 - Severe episodes requiring ER visits or hospitalizations
 - Or significantly interfere with ADLs

Studies Supporting TCA for CVS

- Retrospective review
- 14 studies -600 adults and pediatrics with CVS
 - 413/600(70%)-reported complete or partial improvement in frequency, duration, and severity of CVS symptoms
- Kumar et al retrospective study 86% patients responded to Amitriptyline
 - Some patients were treated with Topiramate, Co-Q10, L-carntine

TCA Considerations

- Dosage individualized
- Daytime sedation
- Night administration better tolerated
- Baseline EKG
 - At start, during titration and after target dose reached
 - QTc < 470 msec-women, <450 msec men



Benzodiazepines

- Lorazepam 0.5-1 mg prn (max every 6 hours prn) – rare occasions!
- Limited to acute care/emergency room
- May help decrease anxiety-acute CVS
- Short term only
- Study 2011-2016
Benzodiazepines – 10 most frequently drugs in overdoses and death

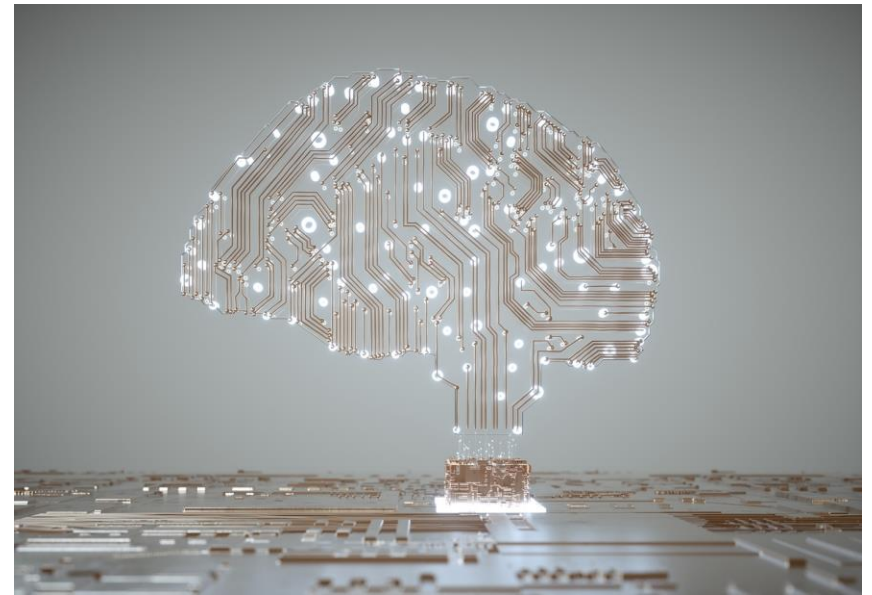


Anti-Seizure

- Topiramate 25 mg daily goal 100 mg daily
- Zonisamide 100 mg daily goal 400 mg daily
- Levetiracetam 500 mg bid goal 1000-2000 mg daily
- Retrospective case series 20 adult patients – 12 episodes per year
 - 75% moderate clinical response
 - 20% complete cessation of episodes
 - Mean follow up 9.5 months

Topiramate

- Alternative therapy
- Migraine prevention
- Retrospective study
18 adults – 72% had
 $\geq 50\%$ reduction in
frequency and
severity of CVS
- Therapeutic drug
monitoring
- Weight loss



Zonisamide and Levetiracetam

- Clouse et al (2007) Zonisamide and Levetiracetam in adults that suffered 12 or more CVS episodes per year
 - Substantial reduction mean 1.3 ± 0.3 to 0.5 ± 0.2 per year
 - 75% patients reported a moderate clinical response
 - Dosage similar to anti seizure dosing
 - Routine laboratory testing not required. Suggested in liver and renal disease to dose reduce

Aprepitant (Emend)

- Substance P neurokinin
- Chemotherapy
- Expensive-average \$120-\$230 per pill
- Trial peds/adolescents >60kg-Aprepitant 125 mg twice weekly-12 months 82% achieved complete resolution of episodes
- Adults trial for gastroparesis/related syndromes
 - 126 adults – did not significantly reduce nausea although decreased severity
- Reserved for refractory non-responders

Case Study

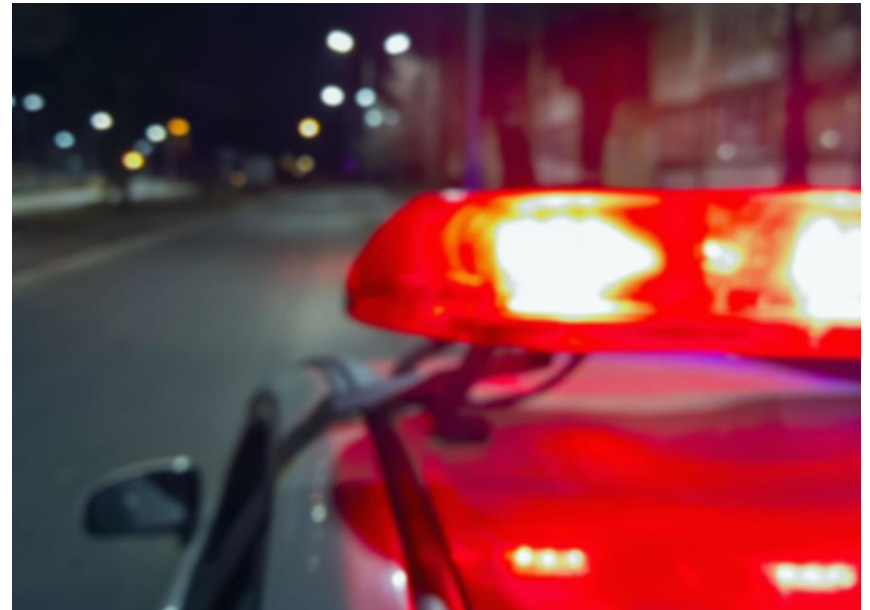
- It has been 3 months since Jason was last seen, he has been admitted to the hospital multiple times with CVS episodes, his admissions are increasing in length
- Jason was started on Amitriptyline while inpatient-he is currently on 150 mg QHS, vomiting has slightly decreased-1-2 episodes every 2 weeks he reports increasing headaches
- He has two EKGs with normal QTc interval
- What do you anticipate as the next step for him?

Case Study

- **Initiate anti-seizure medications**
- Seen by neurology while inpatient-underwent EEG and MRI of the brain – negative
- Plan as outpatient to trial Topiramate
- Comes back to clinic 6 weeks later two more hospital admissions, Topiramate worsened headaches and CVS
- Started on Keppra (Levetiracetam) 500 mg bid- by neurology
- Will attempt authorization of Emend prn CVS flare

Moderate to Severe CVS – Inpatient Management

- ≥ 4 episodes a year
- Longer episodes
> 2 days
- Longer recovery from episodes
- Emergency room visits or hospitalizations



Hospital/Inpatient Management – Hydration Critical



- Correct hypovolemia-bolus, isotonic saline 10 to 20 mL/kg, or 1 L in adults) as needed
- Remaining hydration
- saline (0.9% NaCl) with 5% dextrose for adults
Given at 1.5 times the maintenance rate
- Correct electrolytes (i.e. K⁺, mag, Cl⁻)

Additional Management Plans

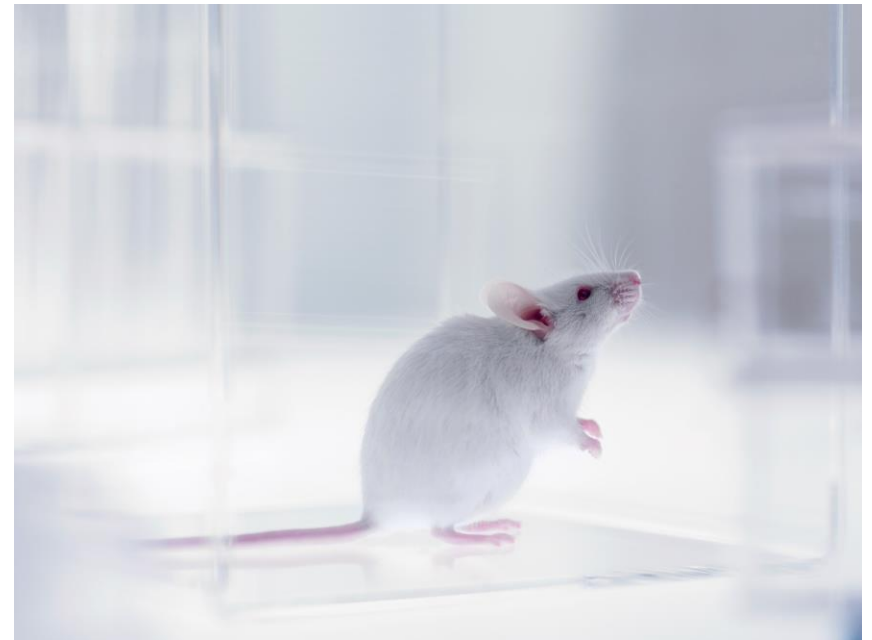
- Have a chart pop up/plan of care when patient arrives in ER
- Allows consistent care, prevents worsening symptoms/delay in care
- Prevents misconceptions – drug seeking etc.
- Consider IV port permanent access
- Dark quiet room – during flares
- NPO until can tolerate oral intake, start slow or with foods patient generally tolerates first

Case Study

- Jason is in the office for routine follow up, last seen 2 months ago, he is currently following with neurology
- He is currently on Keppra (Levetiracetam) 1000 mg bid, Pantoprazole 40 mg per mouth daily, his last CVS flare was 4 weeks ago
- He has gained 10 lbs, tolerating a regular diet and has maintained a normal work schedule

Recap Mild CVS-Regimen – Case Study

- Keppra 1000 mg per mouth bid
- Pantoprazole 40 mg per mouth daily
- Mild nausea prn
 - Ondansetron 8 mg ODT prn
 - Sumatriptan 20 mg nasal spray – at prodrome



Recap Moderate to Severe CVS-Regimen – Case Study

- IV hydration
- Electrolyte replacement
- Zofran IVP 8 mg QID
- Pantoprazole 40 mg IVP BID
- Scopolamine patch
- Ativan 1 mg TID
- Benadryl 50 mg IVP QID
- Compazine 25 mg IVP every 6 hours prn
- Emend 125 mg x 1 dose for severe emesis





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Additional Treatment Considerations

Mitochondrial Supplements

- Co-Q10-10 mg/kg
bid-68% efficacy-
reduction
- Riboflavin-200 mg bid
- Mitochondrial
dysfunction possible
contributory to
migraine and CVS



Complementary Treatments

- Functional-gut/brain interaction
- Avoid stress triggers
- Incorporate
 - Meditation
 - Yoga
 - Good sleep hygiene
 - Avoidance of fasting and dehydration



Catamenial Cyclic Vomiting Syndrome

- CVS – coincide with the onset of menses
- Treatment – oral or injectable contraceptives
- May tolerate injectable contraceptive better, due to risk of nausea



It Takes a Village

- Team approach to care
- Gastroenterology, primary medicine, neurology, psychiatry
- Medical professionals with experience improves outcomes
- Team members – need to believe in the diagnosis to have success and work together
- Have treatment plan to allow consistent care

