Cyclic Vomiting Syndrome: Diagnosis and Management

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Overview

- **Definitions**
  - **CVS vs. CHS**
  - **Epidemiology / Clinical Features / Health Care Utilization**

- **What *is* Cyclic Vomiting Syndrome (CVS)?**
  - Clues from subtypes and triggers
  - A neural model of CVS and the “CVS Threshold” concept

- **Guidance on Diagnosis and Treatment**
  - ANMS / CVSA Clinical Guideline for CVS in Adults

- **Future for next-generation CVS therapy**
  - Basis for personalized medicine approaches?
  - Newer therapeutic targets

Cyclic Vomiting Syndrome (CVS)

CVS is defined by <u>symptoms</u> (ROME IV):

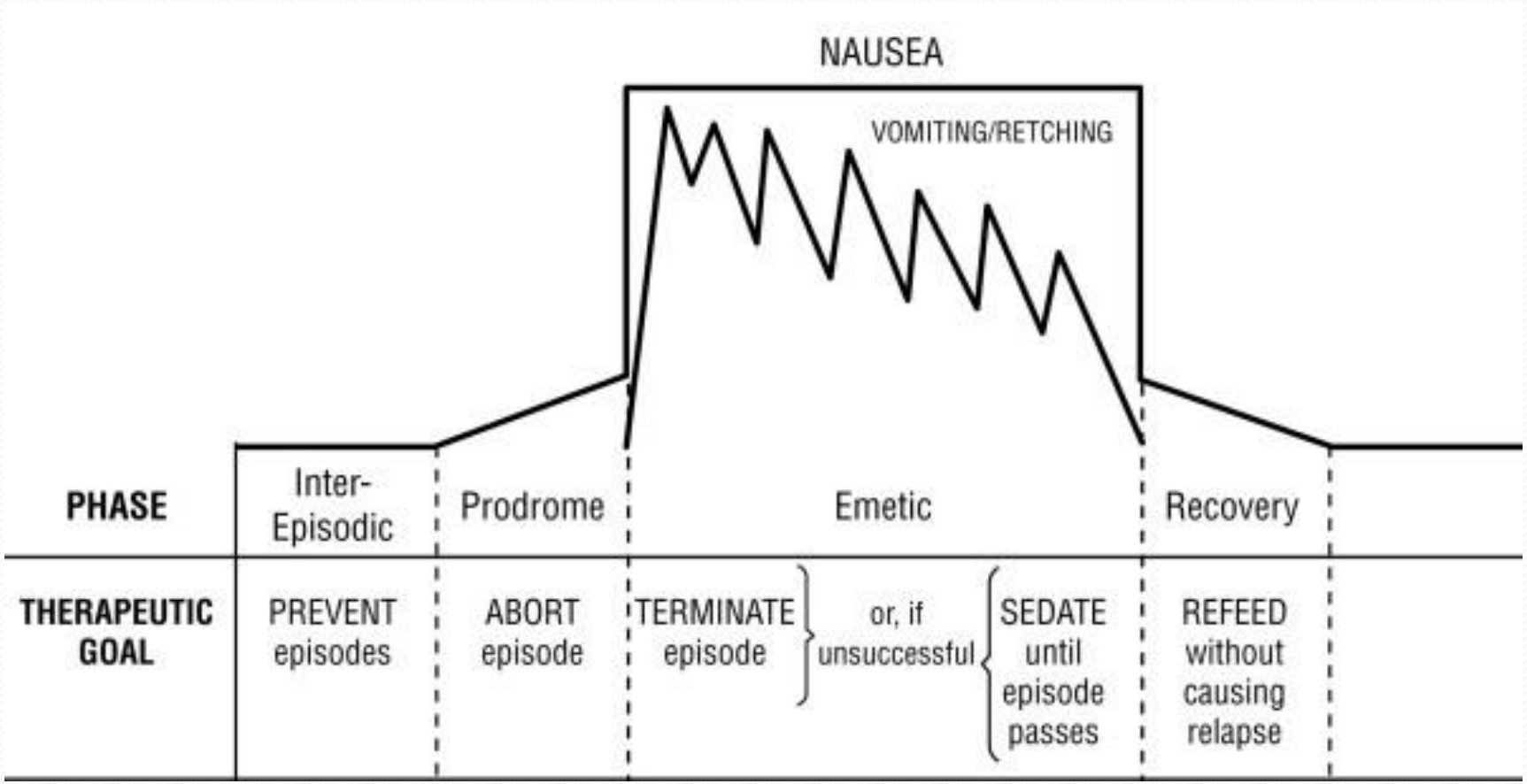
1) Stereotypical episodes of repetitive vomiting with acute onset and <1 week duration

2) **Three or more** discrete episodes in the **prior year,** with 2 episodes in the past 6 months

3) Absence of vomiting between episodes, but other milder symptoms can be present between cycles

4) *Supportive:* History or family history of migraines

CVS is an *Episodic Disorder*



Fleisher et al. BMC Med. 2005

Cannabinoid Hyperemesis Syndrome (CHS)

- **Meet criteria for CVS**, only in the context of “prolonged, excessive cannabis use”
- Relief of vomiting episodes by sustained cessation of cannabis use
- Classic CHS association: Hot water bathing during attacks

Problems with the CHS / CVS dichotomy

- Problems with the definition:
  - What is “excessive” or “prolonged” cannabis use?
  - Relief of vomiting after cannabis cessation… how long do we wait?

- Lack of specificity of hot showers/baths association
  - ~50% of CVS patients *also* take hot showers/baths Exp Brain Res. 2014 Aug;232(8):2563-70
  - **Not so “pathognomonic”**

- CVS patients often use cannabis (even therapeutically), well *after* onset of symptoms

- Evidence that same CVS treatments can be used (and successfully) for “CHS”

- **Stigmatizing patients – particularly in the ED**

CHS – a newer, “better” definition?

Proposed diagnostic criteria
Clinical features: stereotypical episodic vomiting resembling CVS in terms of onset, with a frequency of 3 or more times annually
Cannabis use patterns: duration of use in year before symptom onset; frequency greater than 4 times per week, on average
Cannabis cessation: resolution of symptoms after a period of abstinence (at least 6 months, or at least equal to the total duration of 3 typical vomiting cycles in that patient)

Maselli DB, Camilleri M. Clin Gastroenterol Hepatol. 2021 Sep;19(9):1748-1758.e2.
Venkatesan T, Levinthal DJ, Li BUK et al. Neurogastroenterol Motil. 2019 Jun;31 Suppl 2(Suppl 2):e13606.

CVS Epidemiology: How common is this condition?

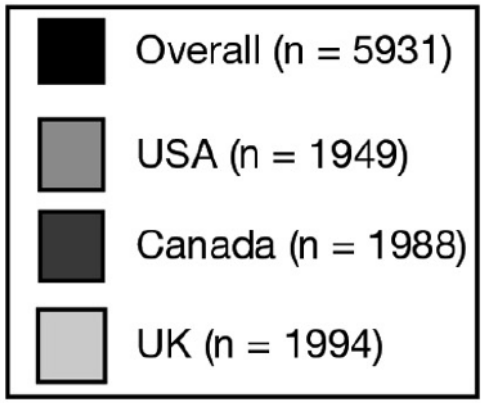
Symptom Surveys in General Population
(sampling errors, response bias)

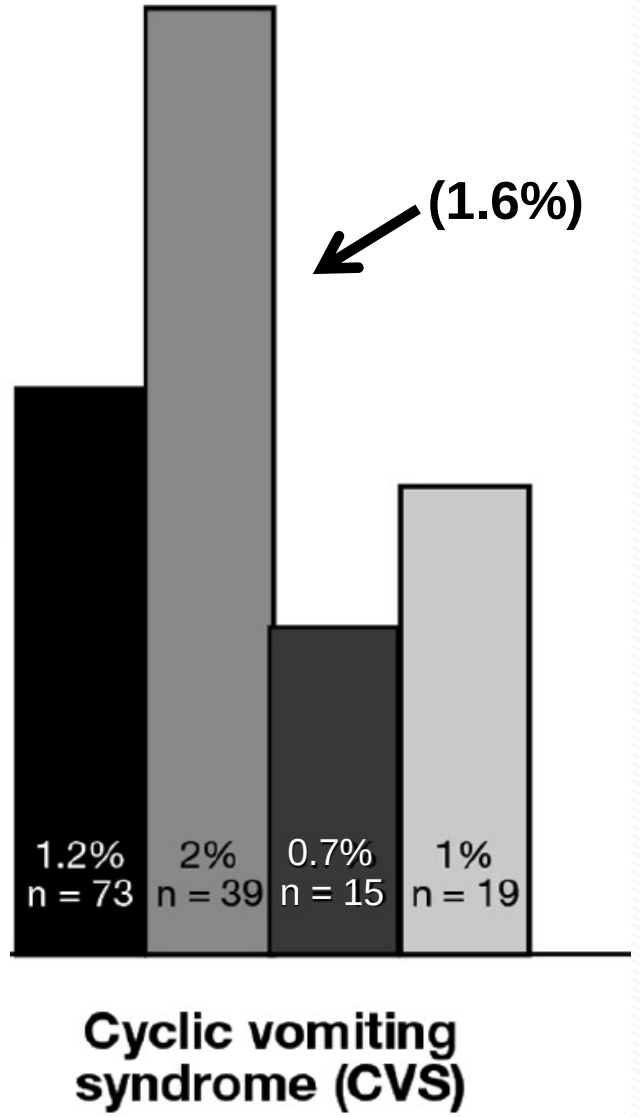
Aziz et al. CGH 2019; 17:878-886

Nearly 6000 surveys; Rome IV questionnaire
Total of *73 individuals* met CVS criteria (7 w/ "CHS" in US cohort)

Average Age = 37.3 years old
% Female = 65.8%

Prevalence of CVS in Adults?
– *Maybe ~1%*
(*Really? 2.55 million US adults with CVS?)*





CVS Epidemiology: How common is this condition?

Diagnostic Code Prevalence in a National Sample

(underestimate; lower bound)

Kosinski E, Levinthal DJ Gastroenterology 2019; 156(6):S-780

Study Population:
Accrual to **C**linical **T**rials **Network** (**ACT Network**)

Pt's 18 or older, seen *at least once* in any encounter between 2016-2018

N=37,581,995 patients across **25 CTSIs** nationwide.

Adult CVS Population: **42,049 adults**, ICD10 code G43.A0

CVS Prevalence (Under)Estimate = 0.11%
(~280,000 US adults diagnosed with CVS)

	Weighted mean % (SD)
Adult CVS prevalence	0.11% (0.06)
Demographics	
Gender	
Male	29.2 (4.1)
Female	70.8 (4.1)
Age	
18-34	29.9 (3.6)
35-44	18.1 (4.4)
45-54	17.3 (4.5)
55-64	16.2 (4.7)
>/=65	18.5 (4.3)

CVS Epidemiology: How common is this condition?

- **Summary: We don't really know**

- **Likely ~0.5% in Adults (my best guess)**

CVS Epidemiology: Common comorbid conditions

Migraine - ~35% (range 13%-70%)

Epilepsy?

ACT Network search: ~6%
IBM MarketScan Study: ~3%

Mood Disorders - ~40-70%

Depression – 27%
Anxiety / Panic – 38.2%
Bipolar Disorder – 6%

Image Source: iStock

Image Source: Freepik

Venkatesan et al. NGM 2019; 31(Suppl 2):e13604.
Kosinski E, Levinthal DJ Gastroenterology 2019; 156(6):S-780
Chen et al. Gastro Hep Advances 2022; 1:963-973.

CVS Epidemiology: Clinical Features

What proportion of CVS patients have:

1) A prodrome? – 60-70% have a distinct prodrome before emetic phase
- Median ~55 minutes[1]

2) Attacks >3x per year?[1]

4-9	(22%)
10-14	(14%)
15+	(38%)

3) Symptom Free between CVS attacks: ~70%[1]

Duration Suffered *prior to CVS Diagnosis*: ~4-8 years

[1] Levinthal et al. Neurogastro Motil. 2021 Dec;33(12):e14159.

CVS Epidemiology: Medical Utilization

~50% of CVS patients visit the ED

1-3x / year (28%)

4x + / year (23%)

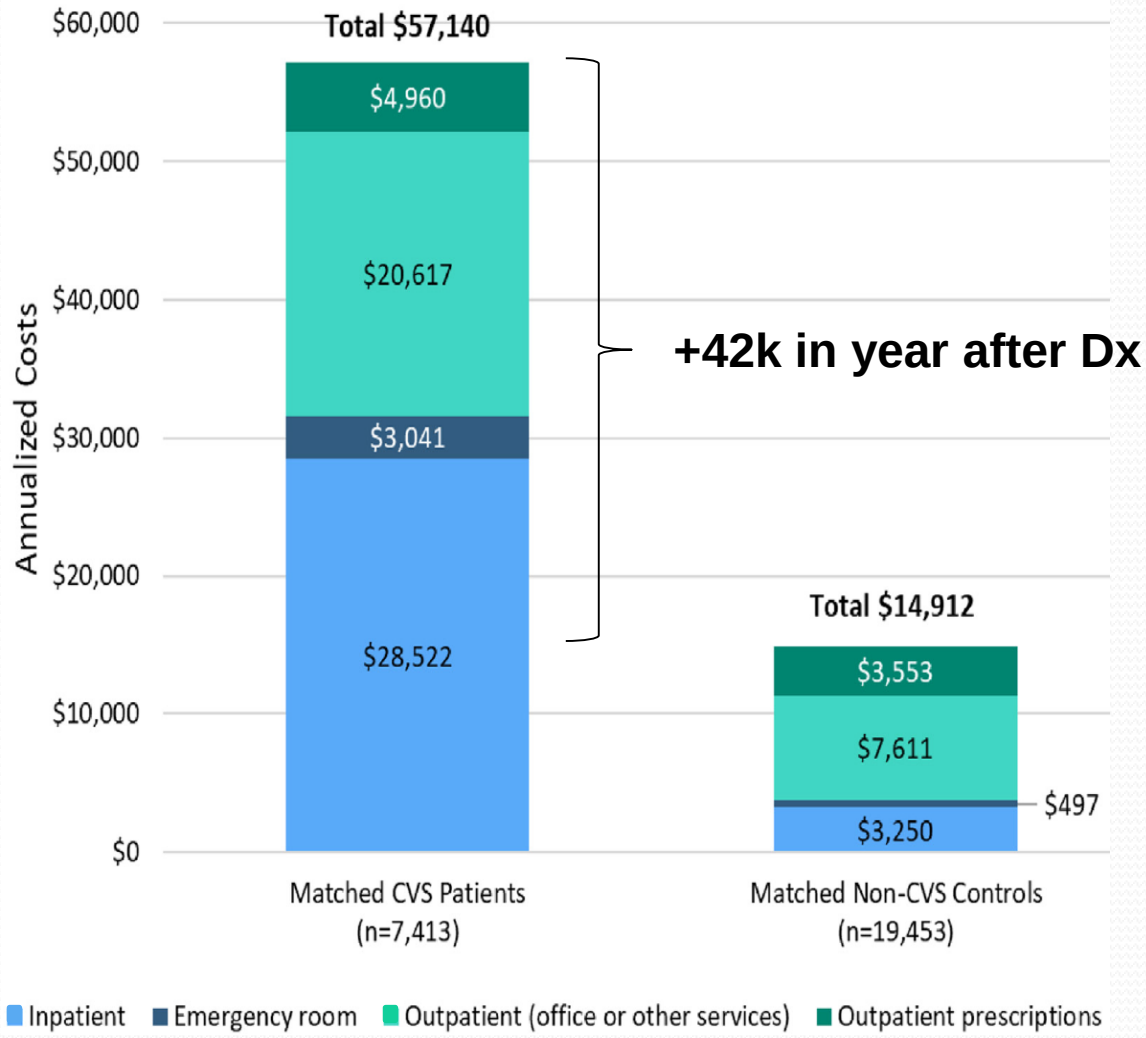
UPMC CVS Experience (2014-2015):

787 patients → 1200 ED visits

388 (49%) – no ED visits

330 (42%) – 1-3 ED visits / yr

69 (~9%) – 4+ ED visits/ yr (avg ~8; **46% of all ED visits!**)



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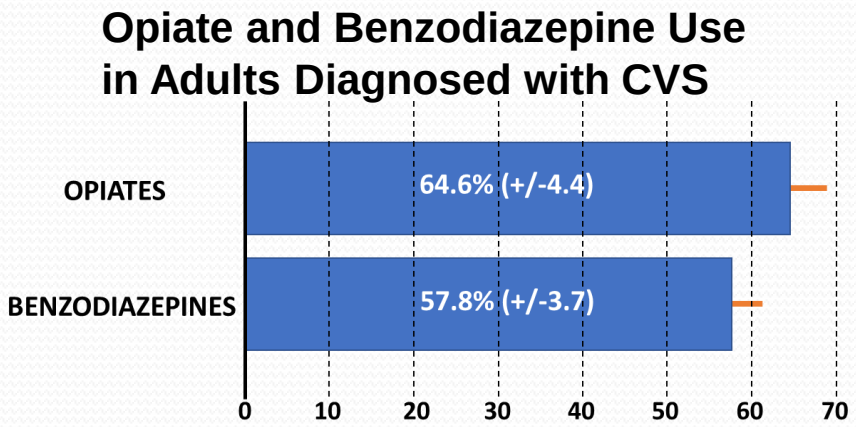
Chen et al. Gastro Hep Advances 2022; 1:963-973

CVS Natural History: What's going to happen next?

Poor prognostic signs:

1) Chronic Opiate / Benzo use
2) Severe mental illness
3) Escalating freq. and severity of attacks
   - Increasing medical utilization
4) *** "Coalescent CVS" ***

Need for a "CVS" Disease Trajectory Model



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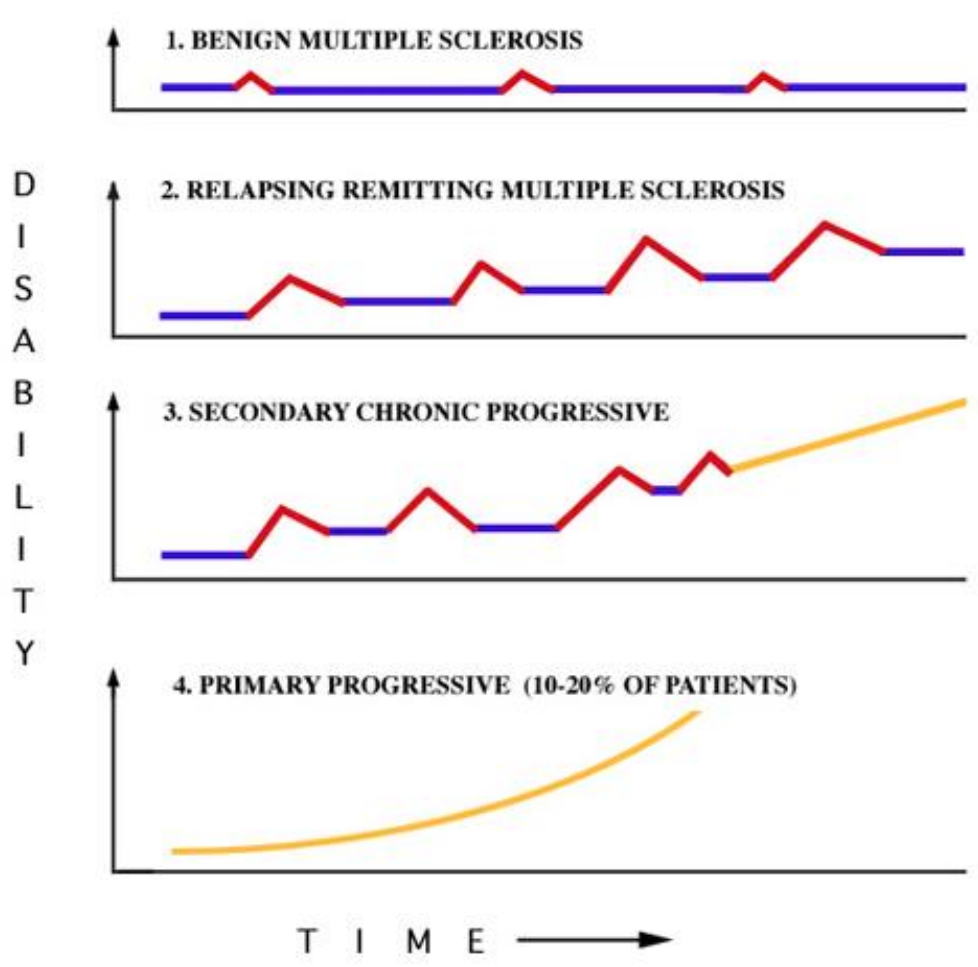
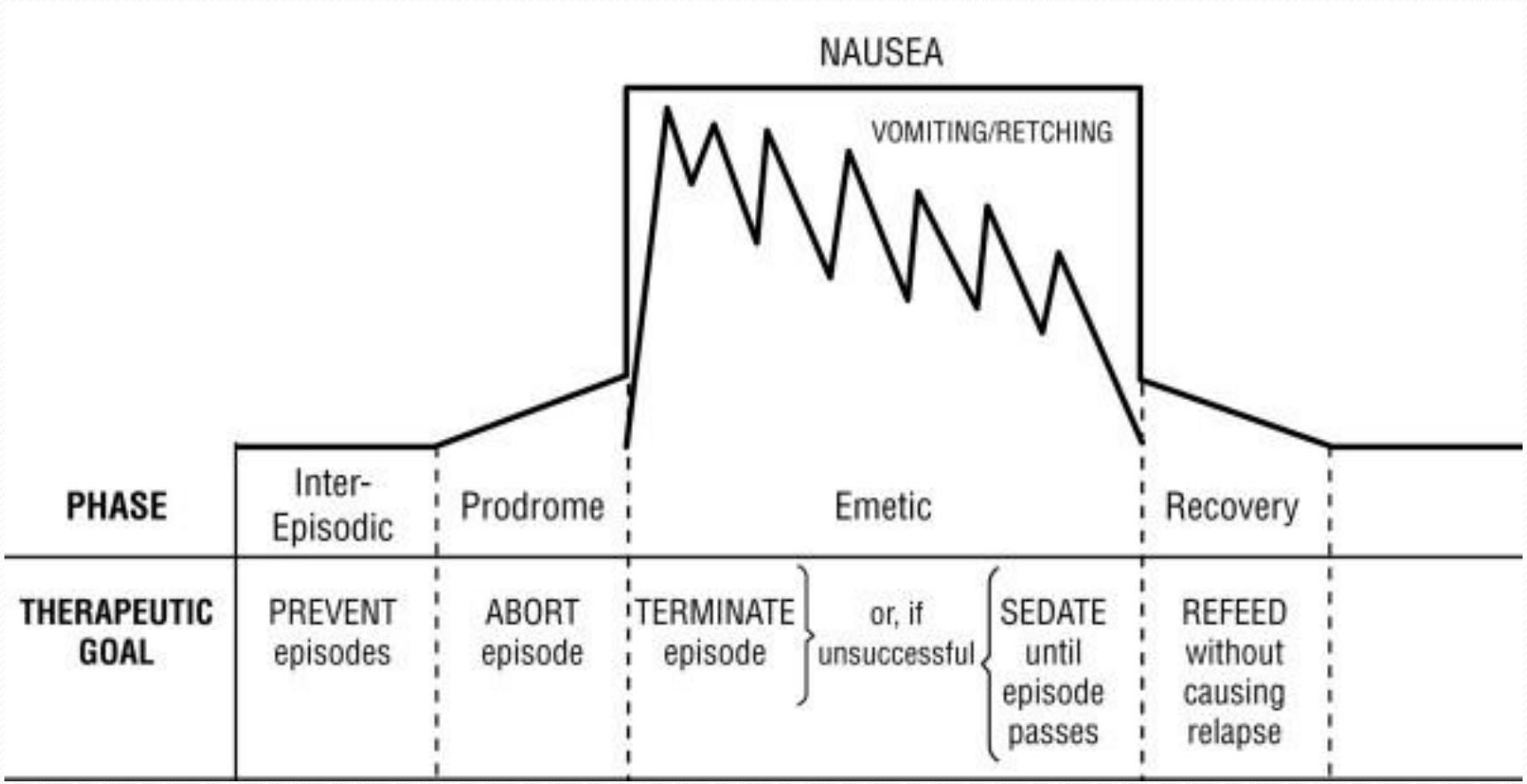


Multiple Sclerosis

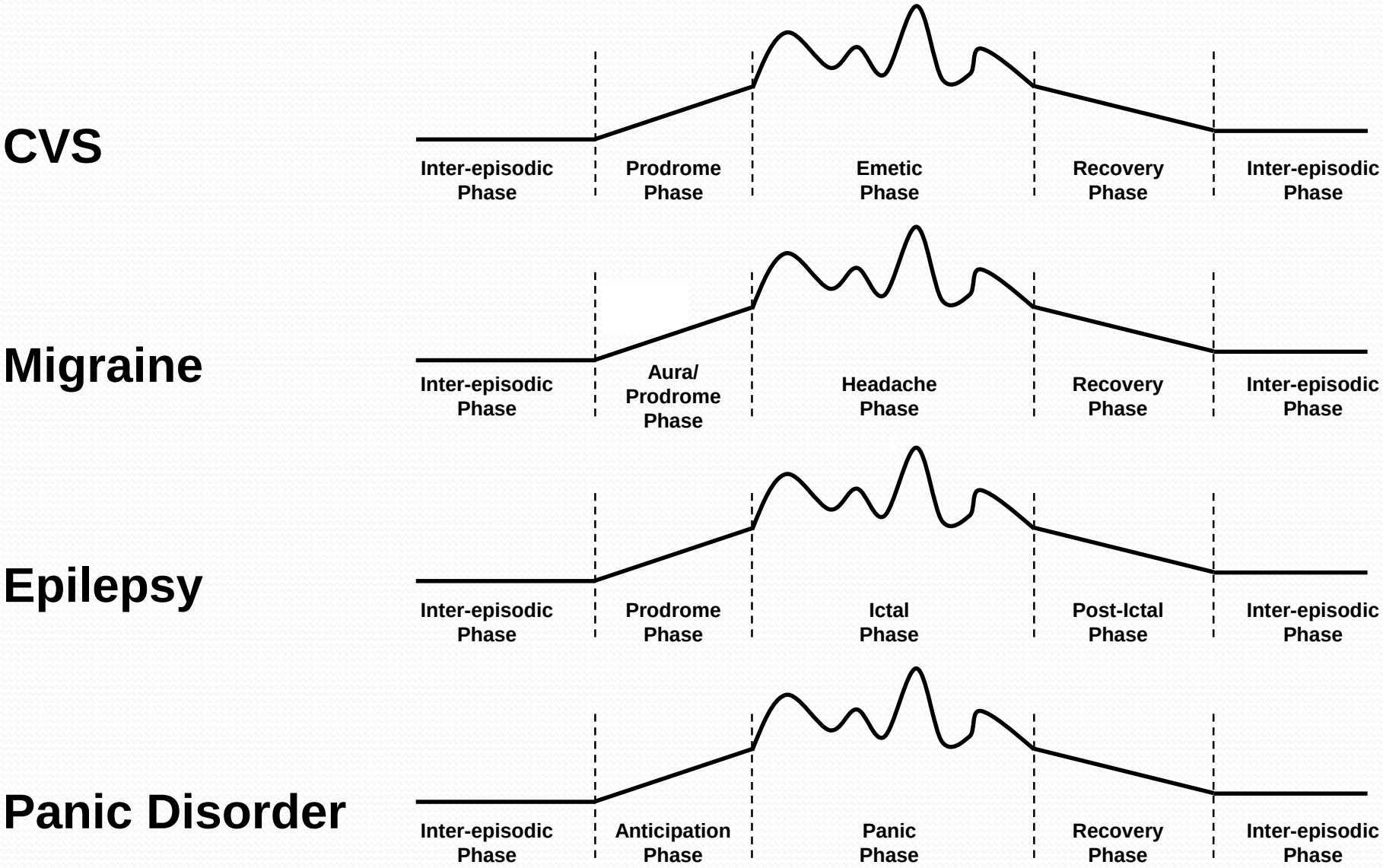
What *is* Cyclic Vomiting Syndrome (CVS)?

CVS is an *Episodic Disorder*



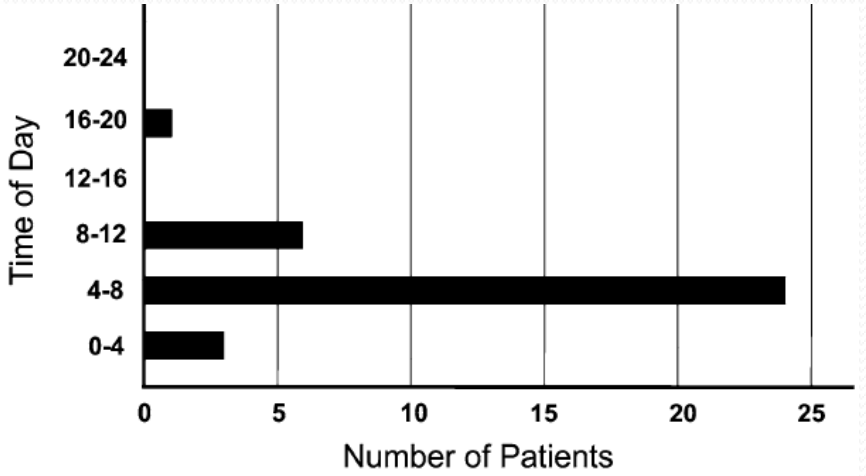
Fleisher et al. BMC Med. 2005

CVS Shares Features with Other Episodic Disorders



Other Shared Features of CVS with Panic Disorder, Migraines and/or Seizures

- CVS prodromes and attacks involve *multiple body systems*
  - **Autonomic, Affective / Cognitive, Constitutional, Skeletal motor, Sensory**
- Circadian Pattern (early AM hours)
- Similar Triggers
  - **Prolonged fasting / hypoglycemia** (energy depletion)
  - **Sleep Deprivation**
  - **Acute Physical Stressors** (surgery / infection)
  - **Menstrual Cycle**
  - **Mental triggers**
    - Surprise / Intense Emotion
    - ***Stress***
    - Acute Anxiety



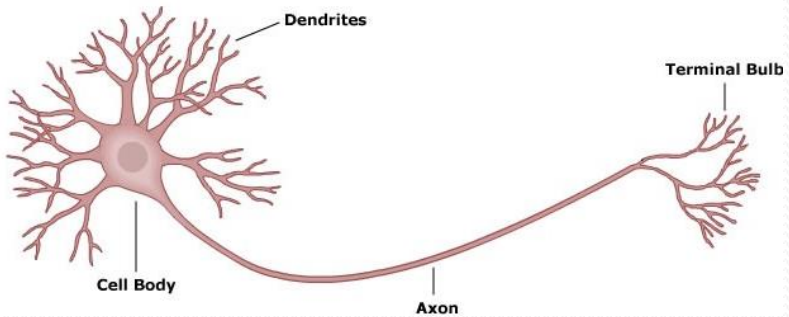
Exp Brain Res. 2014 Aug;232(8):2541-7.

A Shared Basis for Episodic Disorders?

- **Migraine and epilepsy meds are effective for CVS**
- **Migraine and epilepsy have similar subtypes and triggers**
- **Migraine and Epilepsy: Diseases of Neuronal Excitability**
  - Medications for migraines and seizures influence or directly *reduce* neuronal activity or increase excitability thresholds
  - Could CVS share a similar neurophysiologic basis?

A Concept Model for Adult CVS Pathogenesis

- CVS can be viewed as a brain-based disorder



- **Maladaptive plasticity within central neural circuits**
  - Essential Feature: *generally increased neuronal excitability*
  - Neural sensitization (“a lower threshold”) to activate neural circuits for nausea and vomiting

The “CVS Threshold”

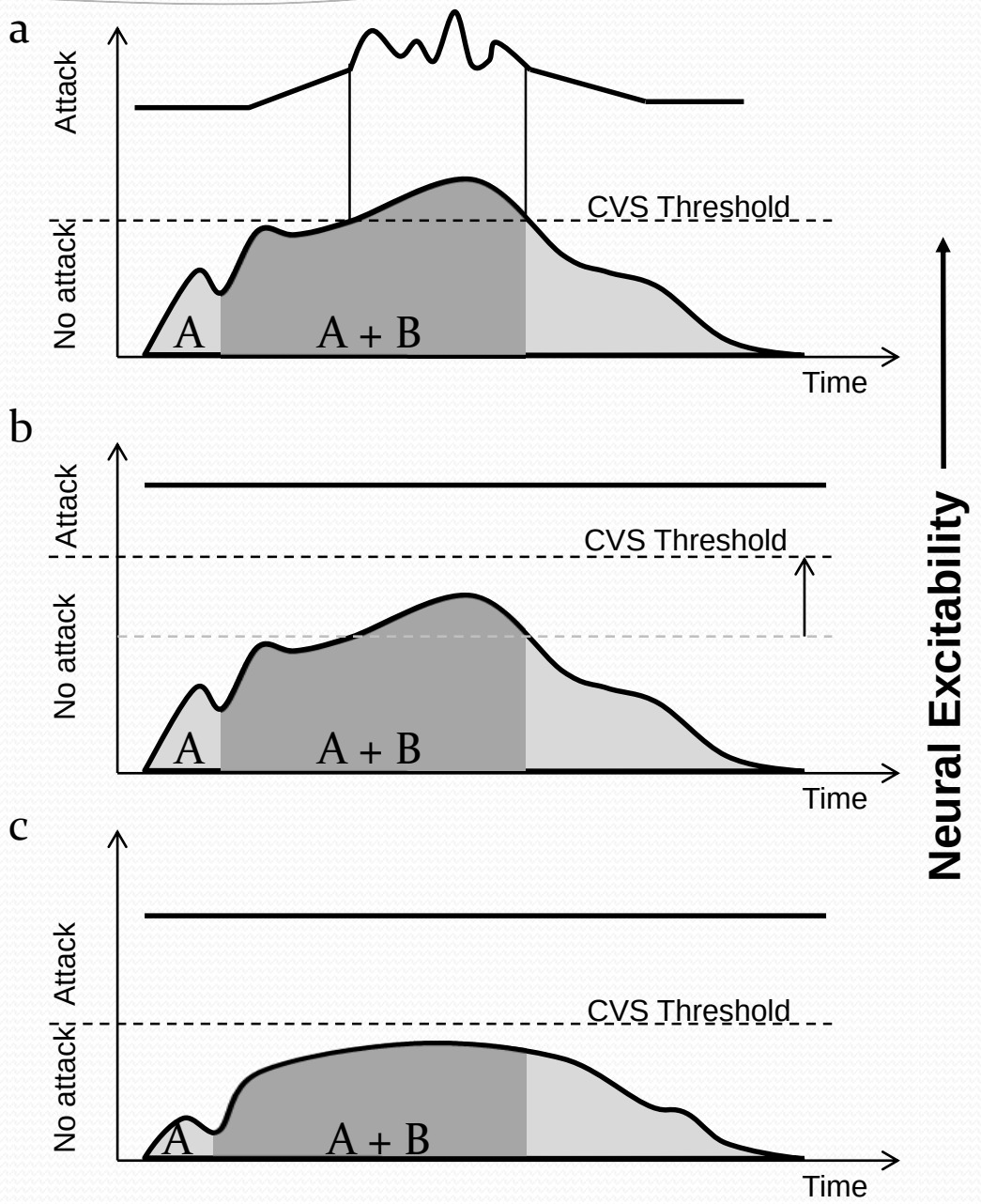
(a) A and B triggers need to be present for a CVS attack to occur

(b) **Prophylaxis raises the CVS threshold**

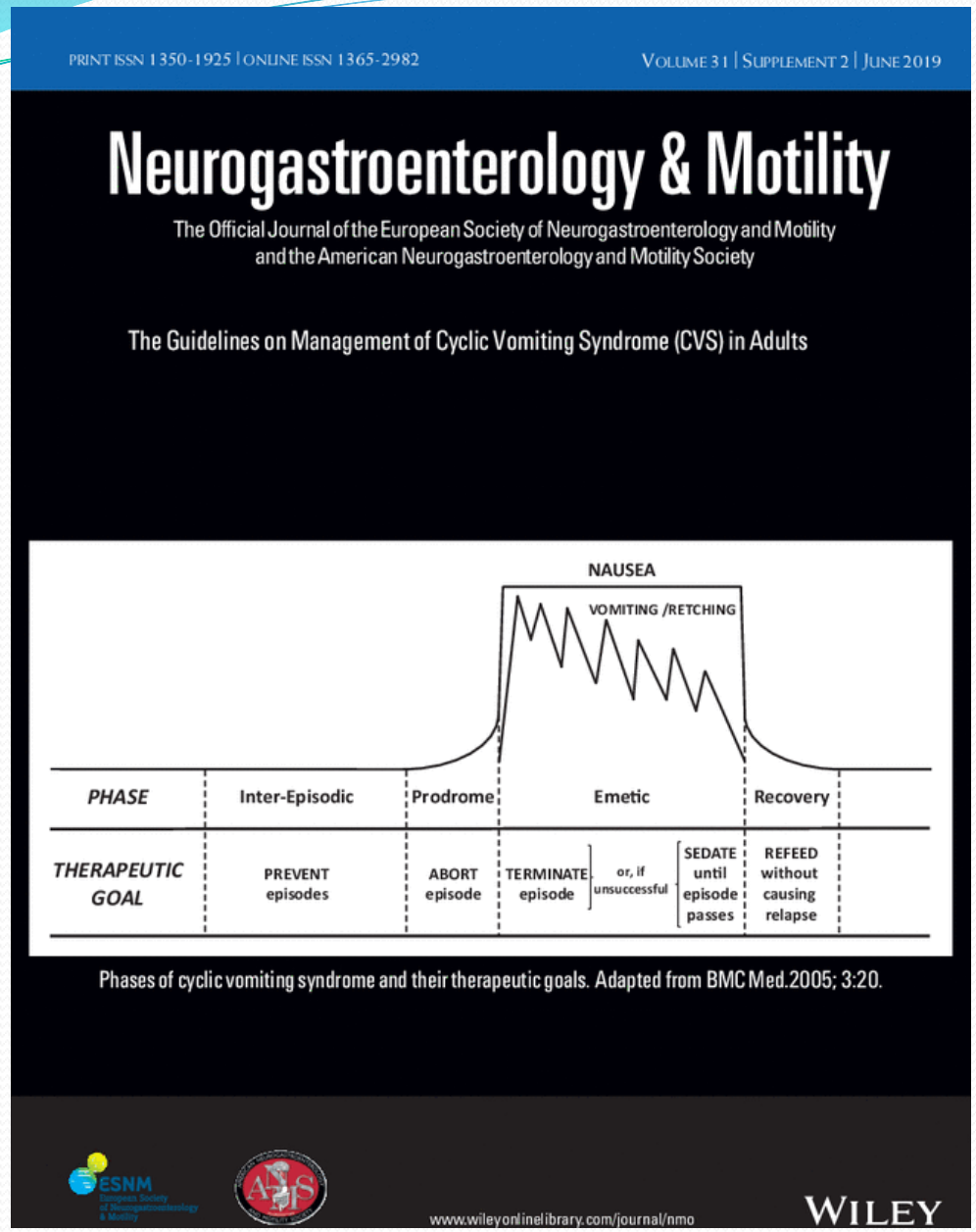
exposure to A and B triggers can occur without breaching the threshold for an attack

(c) **Impact of triggers can be blunted**

exposure to A and B triggers can occur but with a blunted response such that the effect does not breach the threshold for an attack



Levinthal DJ Clin Transl Gastroenterol. 2016 Oct 27;7(10):e198.



Guidelines on Management of CVS in Adults

- ANMS / CVSA Co-Sponsored Guideline Committee
  - Multi-specialty physicians, psychologists, and patient advocates
  - Released in Summer 2019
  - Covers prophylaxis, abortive therapies, and ED management

- https://onlinelibrary.wiley.com/toc/13652982/2019/31/S2

Adult CVS Guidelines

- *Caveats*
  - No placebo-controlled RCTs (only a few comparative RCTs in children)
  - Low or very low quality evidence (GRADE)
  - Expert opinion…but strong consensus

Adult CVS Guidelines: DIAGNOSIS

- **Based on compatible symptom profile**

- **No need for extensive 'rule out' testing**
  - Upper GI series / SBFT or EGD (obstructive lesion; gastric volvulus)
  - Possibly RUQ U/S (biliary disease)
  - Basic labwork (CBC, Comp, Lipase)
  - Consider AM cortisol (Addison's), urine porphobilinogen (Porphyria)

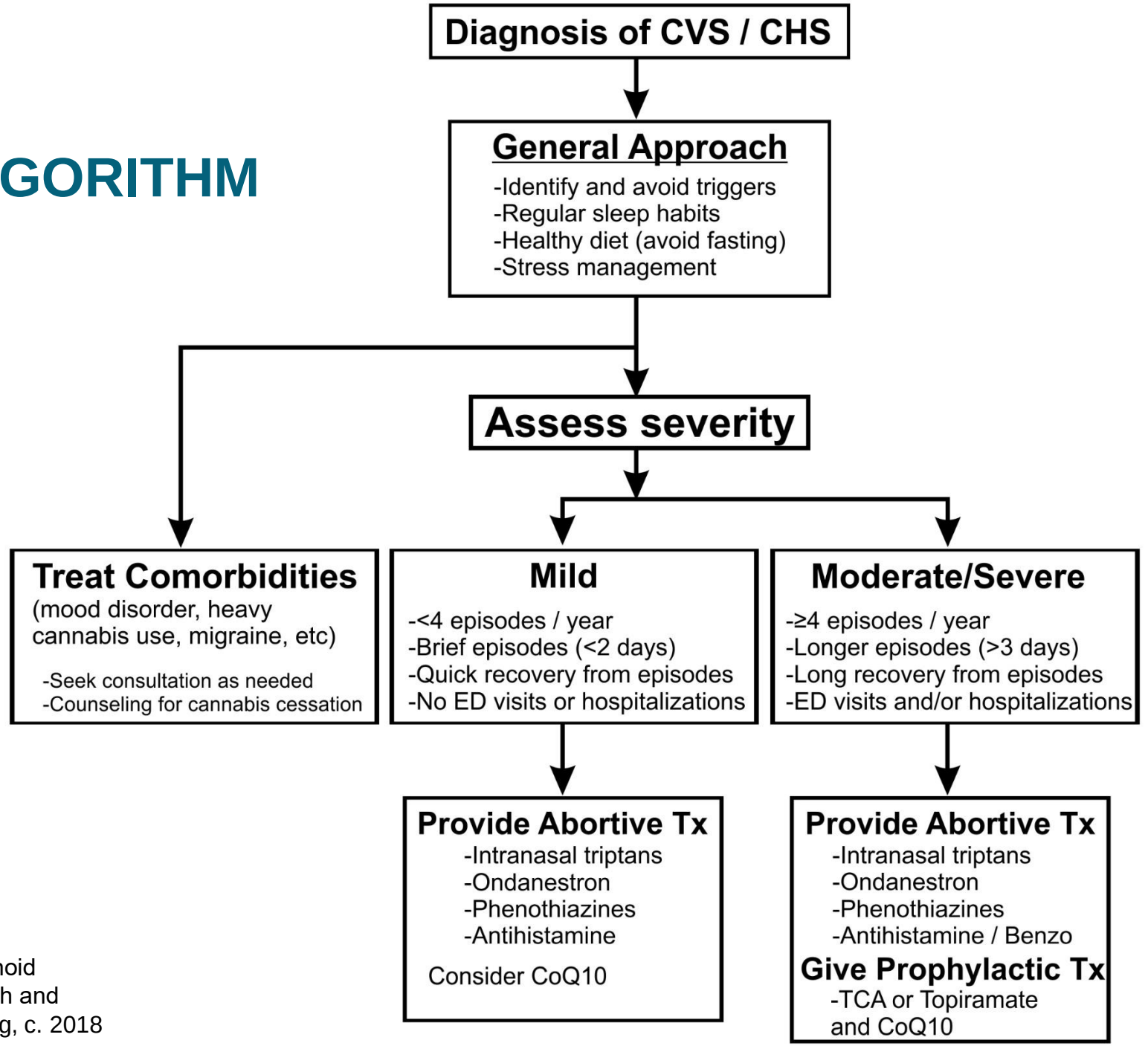
  - Gastric emptying scan -- ** controversial **

CVS / CHS TREATMENT ALGORITHM

-*Personalized approach*

-Based on <u>symptom severity</u>
- -Attack frequency
- -Length of attacks
- -Healthcare utilization

-Influenced by <u>co-morbidities</u>



Kingsley M and Levinthal DJ “Cyclic Vomiting Syndrome and Cannabinoid Hyperemesis Syndrome” in Essential Medical Disorders of the Stomach and Small Intestine; Lacy, DiBaise, Pimentel, Ford, eds. Springer Publishing, c. 2018

RECOMMENDATION #1: Prophylaxis
Conditionally recommend that adults with **moderate-to-severe CVS** receive tricyclic antidepressants, such as amitriptyline, as first-line prophylactic medication.

- Based on open-label and retrospective studies

- No comparative trials among TCAs (traditionally amitriptyline used)

- 46 adult CVS patients (mean follow-up 2 years) with marked reduction in CVS episodes (18 → 3).

- Observational study with 24 adult CVS patients: amitriptyline for at least 3 months
  - 93% had reduction in symptoms with 26% in complete remission.
  - Duration of episodes reduced from 6.7 days to 2.2 days.
  - Significant reduction in number of ED visits + hospitalizations

- **"HIGH DOSE" – goal is 1 mg/kg or ~75-100 mg daily, but up to 150 mg not unusual**
  - Best practice: Obtain an EKG at baseline, during titration, once on target dose (QTc <460 F / <440 M)

Namin et al. Neurogastroenterol Motil. 2007 Mar;19(3):196-202; Hejazi et al. J Clin Gastroenterol. 2010 Jan;44(1):18-21.

RECOMMENDATION #2: Prophylaxis
Conditionally recommend that adults with **moderate-to-severe CVS** receive topiramate as an alternate prophylactic medication.

- No large studies in adult CVS (data from pediatric/adolescent CVS)
    - Good data in adult migraine

- Start topiramate at 25 mg daily, titrate by 25 mg each week, to target **100 mg daily**.

- Higher risk of kidney stones; check serum electrolytes / renal function twice yearly

- **Weight loss as desirable side effect** in overweight / obese patients

RECOMMENDATION #3: Prophylaxis
Conditionally recommend that adults with **moderate to severe CVS** receive aprepitant as an alternate prophylactic medication.

- Evidence in children with CVS (Cristofori et al. APT 2014)
- **125 mg PO, dosed 2-3 times per week**

- Hard to get insurance coverage; emerging role in TCA / topiramate failures
- Very favorable side effect profile

RECOMMENDATION #4: Prophylaxis
Conditionally recommend that adults with **moderate to severe CVS** receive zonisamide or levetiracetam as an alternate prophylactic medication.

- Some evidence of efficacy in those ***refractory to TCA***
- Start low and increase steadily (doses mirror those used in epilepsy)

- **Zonisamide**: start 100 mg PO qd, weekly incr. of 100 mg/day, target 400 mg/day.
- **Levetiracetam**: start 500 mg PO divided BID, weekly incr. of 500 mg/day, target ~1000–2000 mg/day.

- Both agents are now available as generic medications (not particularly expensive)
- Neither agent requires routine serum monitoring of liver or renal function

Recommendation 6: Abortive

We conditionally recommend using **triptans** like sumatriptan to abort symptoms of a CVS episode

Useful to administer via NASAL SPRAY

-20 mg sumatriptan, 1 spray in one nostril; can repeat once 2 hours later

Recommendation 7: Abortive

We conditionally recommend using **serotonin antagonists** such as ondansetron to abort symptoms of a CVS episode

Useful to administer via sublingual dissolvable tablet (8 mg ondansetron)

Sedation as Useful abortive therapy: Benzodiazepines

- Not in the clinical guideline!

- My favored approach – SL alprazolam 1-2 mg

- Thus, a common ‘abortive regimen’ could be:

Delivered at earliest recognized prodrome onset

- **Zofran 8 mg SL**
- **Sumatriptan nasal spray x 1**
- **+/- Alprazolam 1 mg SL**

CVS management in the ED

Do's

Everyone should be treated (CHS vs. CVS should not matter!)

A) Patients without signs of dehydration and/or observed vomiting in the ED:
- Anti-emetics, then enteral hydration
- Diphenhydramine +/- Ondansetron

B) Patients obviously retching/vomiting and potentially dehydrated:
- **Rehydration**: IV fluids (dextrose containing)
- **IV Ondansetron** 8 mg x 1 - May repeat q 4-6 hrs
- **IV Ativan** 1-2 mg and/or IV Diphenhydramine (Benadryl) 50 mg for additional sedation
  * *If ondansetron ineffective, consider IV fosaprepitant 150 mg if available*
- **For Pain**: IV Ketoralac 30 mg if > 60 minutes from onset; may repeat 15 mg q6hr x 2 (maximum 60 mg/day)

Goal: SEDATION (A sleeping CVS patient is undergoing "active therapy"!)

CVS management in the ED

Don’ts

Opioid medications (especially IV) should be avoided (if possible)

-Opioids don’t improve long term outcomes and can perpetuate or exacerbate patients’ symptoms

-Non-opioid analgesics are recommended when needed for pain

Avoid diphenhydramine IV push

-If needed, consider oral route or slow IV infusion, especially if combined with opioid medications (to avoid addiction)

CVS management in the hospitalized patient

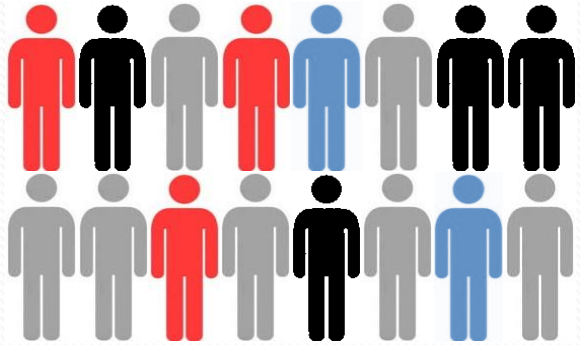
- **We just don’t know.**

- **Sedation likely is key**
  - Benzo’s +/- opiates (everyone’s nightmare).
  - Aprepritant (PO) / Fosaprepitant (IV)
  - Ketamine?
  - Development of a WAS-like protocol?

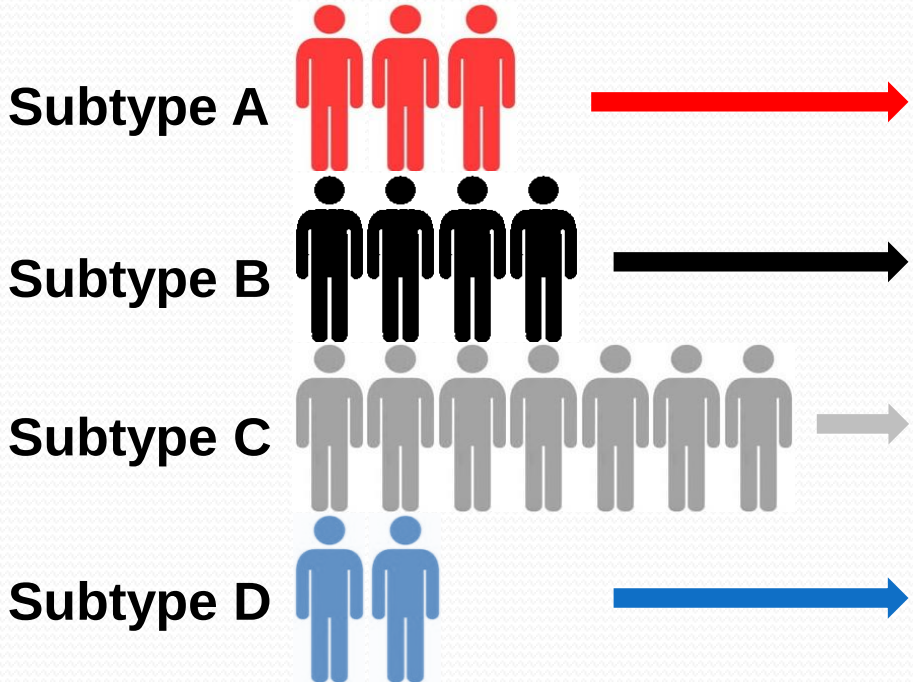
Personalized Medicine in CVS?

- Mechanisms for neural hyperexcitability = specific targets for treatment

- Subtypes/triggers give clues to some mechanisms
  - Behavioral medicine for anxiety/stress subtype?
  - Mitochondrial cocktail for fasting or exercise-triggered CVS?
  - Difference in prophylactic therapy for CVS patient with migraines?

	CVS Patients (Mixture of Subtypes/Mechanisms)	Treatment	Outcomes
Current Model of CVS Care		Generic Rx for all CVS patients	*Fair*

Future Model of CVS Care



Excellent

Prophylactic strategies in migraine and epilepsy with *potential utility* in CVS

Treatment Strategy	Pharmacological Target	Potential Medications
Glutamate receptor system	NMDA receptors	Ketamine Memantine
Calcium channels	A2-delta subunits R-type channels T-type channels	Gabapentin / Pregabalin Lamotrigine, Zonisamide Valproate
Serotonin System	Mixed channels	Mirtazapine
CGRP system	CGRP receptors or CGRP ligand	Monoclonal antibodies: erenumab,eptinezumab, galcanezumab, fremanezumab CGRP receptor antagonists: rimegepant, ubrogepant

Levinthal DJ Clin Transl Gastroenterol. 2016 Oct 27;7(10):e198.

Questions, please!

Patient Resources:

1) Cyclic Vomiting Syndrome Association

-- www.cvsaonline.org

2) American Neurogastroenterology and Motility Society

-- https://motilitysociety.org

3) International Foundation for Gastrointestinal Disorders

-- https://iffgd.org/