Updates in Nausea and Vomiting Disorders

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Indiana University School of Medicine

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Objectives

- Neurobiology of nausea and vomiting
- Diagnostic Criteria of Nausea and Vomiting Disorders→ Rome IV
- Epidemiology
- Pathophysiology
- Clinical Evaluation and Diagnostics
- Treatment

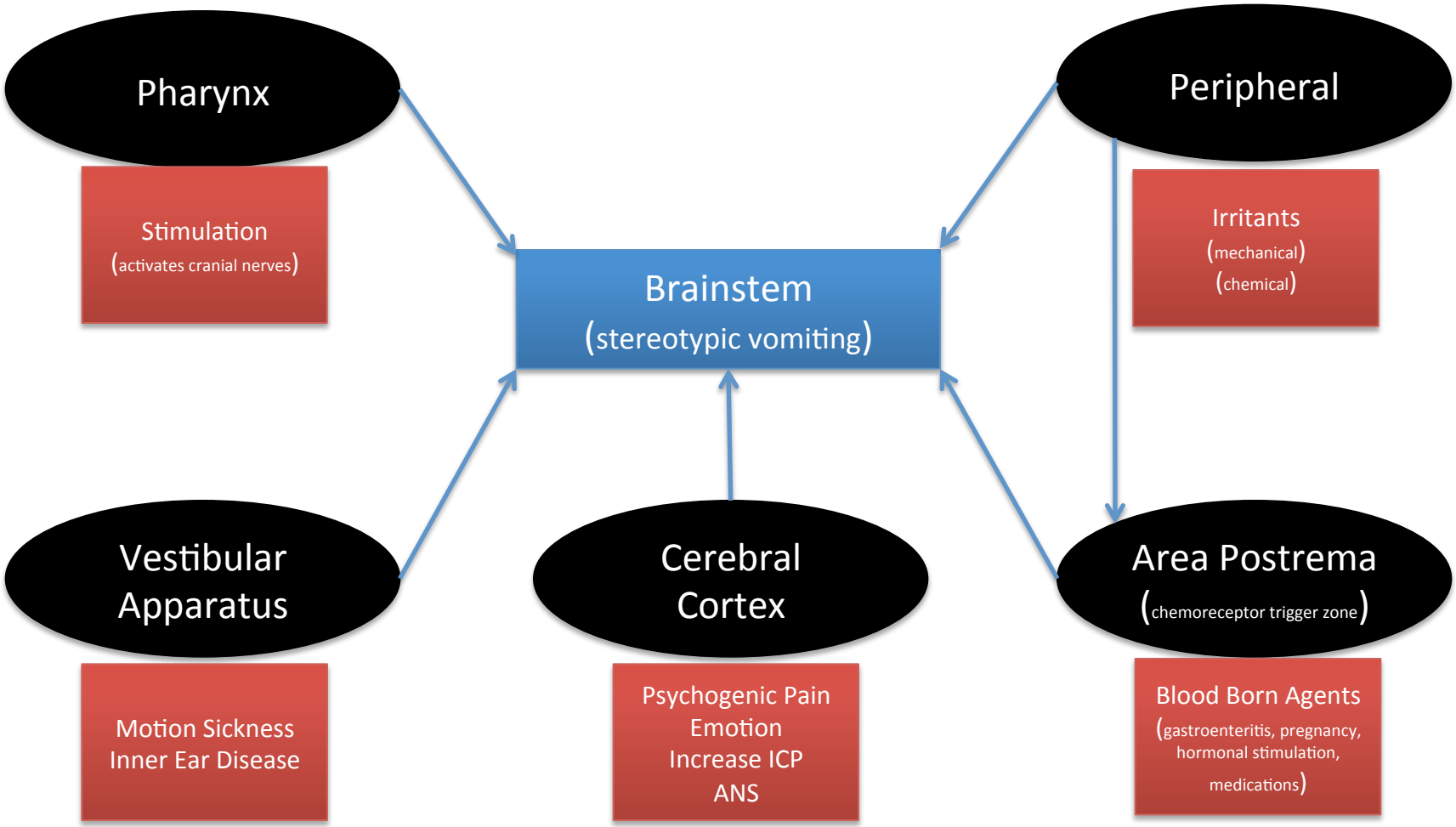
Nausea and Vomiting Disorders

- **Nausea**
  - Subjective symptom
  - Unpleasant sensation of the imminent need to vomit
  - Typically experienced in the epigastrium or throat
- **Retching**
  - Rhythmic spasmodic movements without expulsion of GI contents
- **Vomiting**
  - Forceful oral expulsion of GI contents
  - Associated with contraction of the abdominal and chest wall muscles

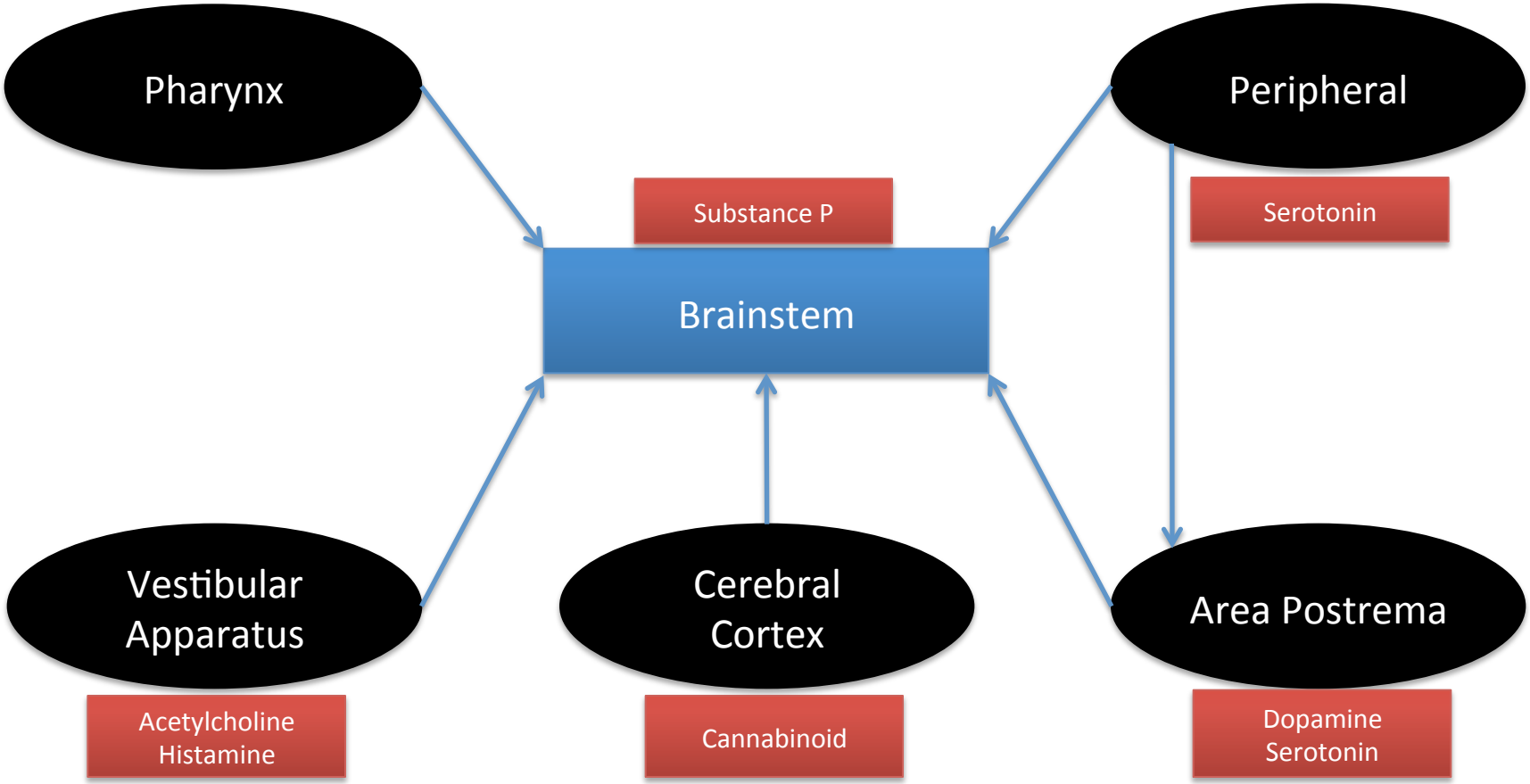
Pathophysiologic Principles

- **Stimuli**
  - Multiple (clinical & experimental studies)
- **Emetic Receptor Sites**
  - Stimuli act on peripheral and central nervous system structures
- **Initiation of Vomiting Program**
  - Brainstem nuclei stimulate motor events of vomiting → stereotypic
- **Nausea**
  - Unknown pathways – requires conscious perception (i.e. higher function)

Neural Pathways Mediating Vomiting

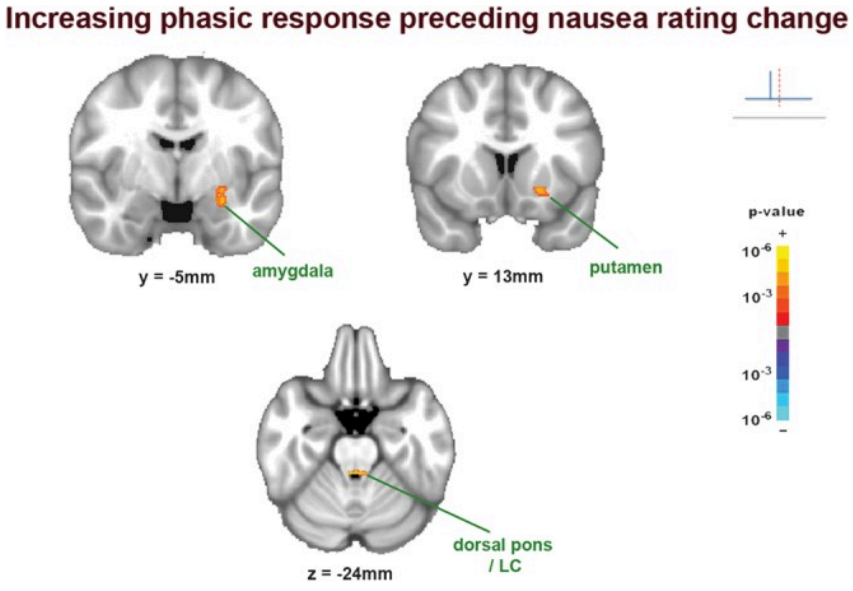


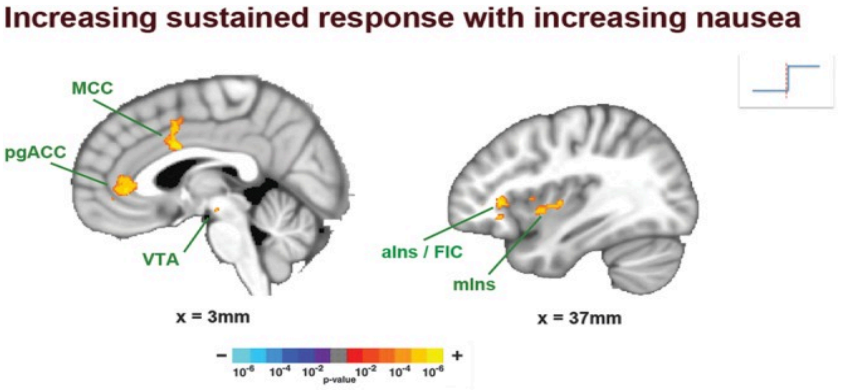
Neurotransmitter Receptor Control of Vomiting



CNS Activation Patterns During Experimental Nauea

- fMRI (BOLD) activation in 28 healthy controls during experimental motion sickness
- Phasic activation in fear conditioning and noradrenergic brainstem regions precipitates transition to strong nausea
- Sustained activation following this transition occurs in a broader interoceptive, limbic, somatosensory, and cognitive network → *multiple dimensions to nausea*





Napadow *et al*. (2012). Cerebral Cortex.

Rome III : Nausea and Vomiting Disorders

- **Functional Vomiting**
  - At least 1 vomiting episode per week
  - Absence of eating disorder, self-induced vomiting, rumination, major psychiatric disease
  - No CNS or metabolic cause of symptoms
- **Chronic Idiopathic Nausea**
  - Bothersome nausea several times weekly
  - Not usually associated with vomiting
  - Absence of organic or metabolic disease
- **Cyclic Vomiting Syndrome**
  - Stereotypic acute vomiting episodes with duration < 1 week
  - ≥ 3 episodes in the past year
  - Absence of nausea and vomiting between episodes
    - may have subtle/mild dyspeptic symptoms in between episodes
  - Symptom onset ≥ 6 months ago

Tack *et al*. (2006). Gastroenterology.

Rome IV : Nausea and Vomiting Disorders

- **Chronic Nausea and Vomiting Syndrome (CNVS)**
  - Bothersome (i.e. severe enough to impact on usual activities) nausea, occurring at least 1 day per week and/or 1 or more vomiting episodes per week
  - Exclusion of self-induced vomiting, eating disorders, regurgitation, or rumination
  - No evidence of organic, systemic, or metabolic diseases that is likely to explain the symptom on routine investigations (including at upper endoscopy

- **Cyclic Vomiting Syndrome (CVS)**
  - Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
  - At least 3 discrete episodes in the prior year and 2 episodes in the past 6 months, occurring at least 1 week apart
  - Absence of vomiting between episodes, but other milder symptoms can be present between cycles
  - Supportive criteria : personal or family history of migraine headaches

- **Cannabinoid Hyperemesis Syndrome (CHS)**
  - 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 criteria: may be associated with pathologic bathing behavior (prolonged hot baths or showers)

Stanghellini V. *et al*. (2016). Gastroenterology.

Epidemiology

Epidemiology : CNVS

- Nausea is less prevalent than epigastric pain or meal-related symptoms in the community
- Unexplained chronic nausea is often associated with other gastroduodenal symptoms
- Unexplained vomiting occurring at least once monthly is distinct from occasional vomiting reported with functional dyspeptsia
  - Believed to be rare
  - Occurring in approximately 2% women and 3% men
- Overall prevalence of CNVS remains unknown

Talley NJ *et al*. (2008). Digestive Diseases and Sciences.

Epidemiology : CVS

- Estimated to cause symptoms in 3-14% of adults referred for unexplained nausea and vomiting
- Presents in young adults across all races and in both sexes
- Adult patients present to ED a median of 15 times before diagnosis 5-6 years after symptom onset
- Linked to menses (catemenial CVS), precipitated by pregnancy, or associated with diabetes mellitus
- Common precipitants
  - Stress, sleep deprivation, infections, foods (e.g. MSG), motion sickness
- Most patients show gradual symptom reduction over time but some progress to daily nausea and vomiting without asymptomatic intervals (coalescent CVS)

Hejazi RA and McCallum RW. (2011). Alimentary Pharmacology and Therapeutics.

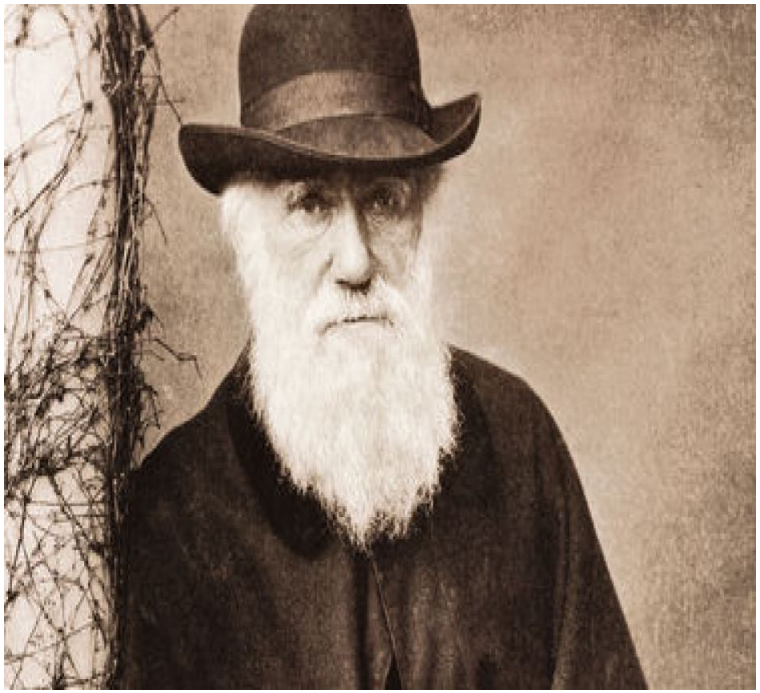
Brief History of CVS

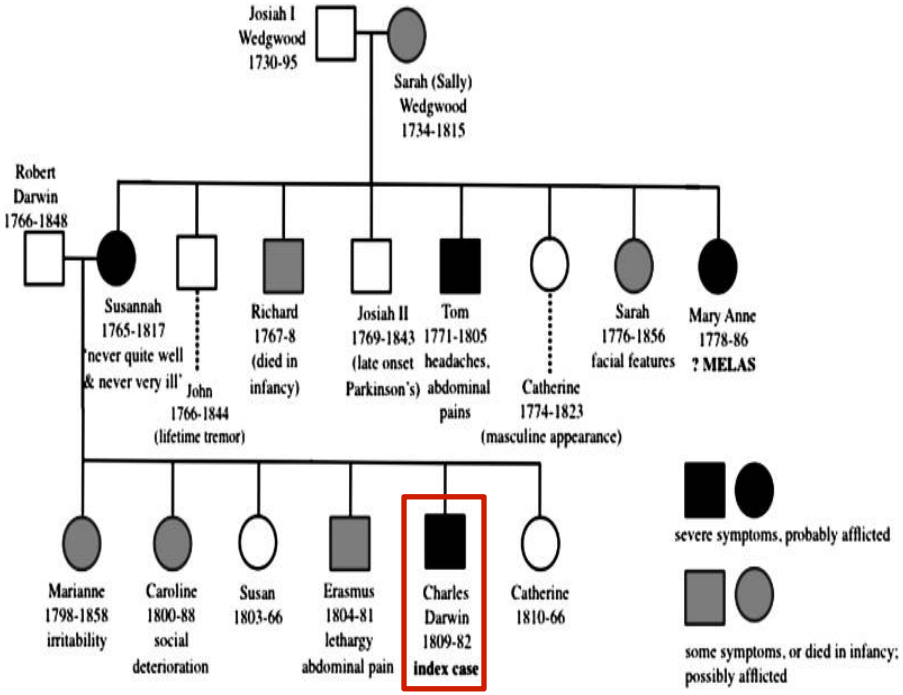
- Samuel Jones Gee
- First described in the English literature in 1882 by an English physician and pediatrician
- He reported a series of 9 children ranging in age from 4-8 years

"These cases all seem to be of the same kind, their characteristic being fits of vomiting that recur after intervals of uncertain length. The intervals themselves are free from signs of disease. The vomiting continues for a few hours or days. When it has been severe the patients are left much exhausted."

Gee S. (1882). Saint Bartholomew's Hospital Reports.

Famous Person with CVS





"Attacks of nausea and vomiting were his most distressing complaint and these were brought on by stressful events, even very minor stresses or pleasurable events such as the visits of friends…He also experienced headaches, abdominal pains, palpitations, chest pain, sweating, eczema, flushing of his face and extremities, attacks of acute anxiety, and heat and cold sensitivity"

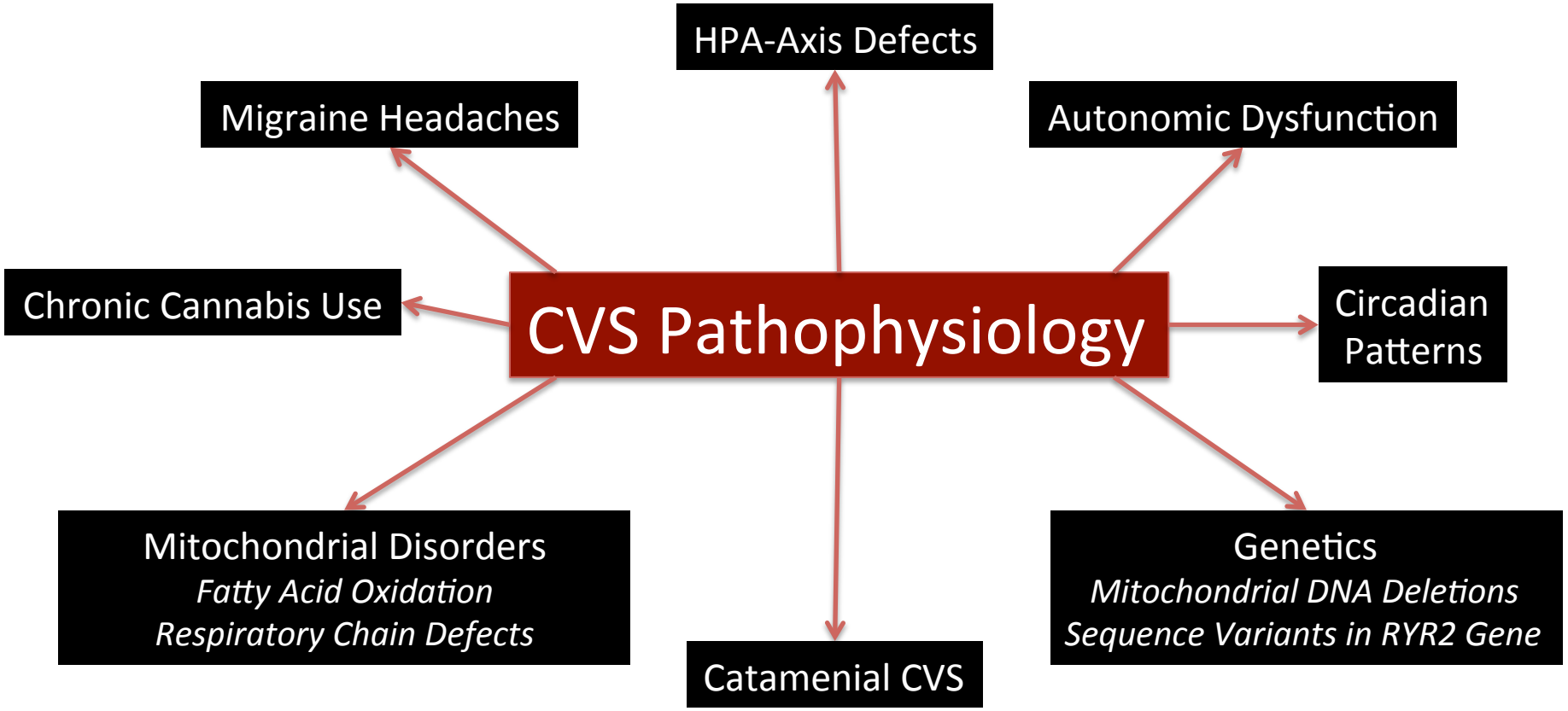
Hayman J. (2013). Genetics.

Epidemiology : CHS

- Resolves with cessation of marijuana smoking
- ⅓ of patients with presumed CVS report marijuana use
- Typically occurs in males with prolonged daily cannabis use (up to 3-5 times daily) over at least 2-3 years
- As with CVS, delays in CHS diagnosis and numerous ED visits before diagnosis are typical

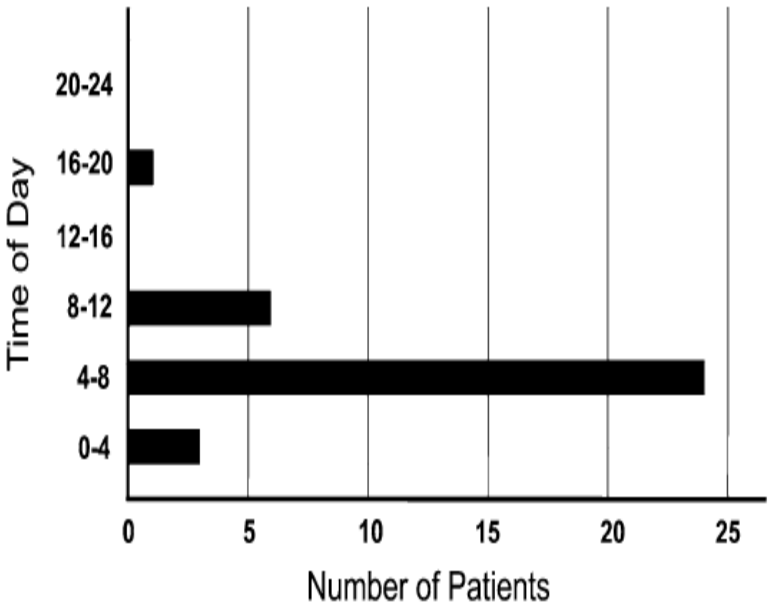
Hejazi RA and McCallum RW. (2011). Alimentary Pharmacology and Therapeutics.

Pathophysiology


HPA-Axis Defects
Migraine Headaches
Autonomic Dysfunction
Chronic Cannabis Use
CVS Pathophysiology
Circadian Patterns
Mitochondrial Disorders
Fatty Acid Oxidation
Respiratory Chain Defects
Catamenial CVS
Genetics
Mitochondrial DNA Deletions
Sequence Variants in RYR2 Gene

CVS and Circadian Patterns

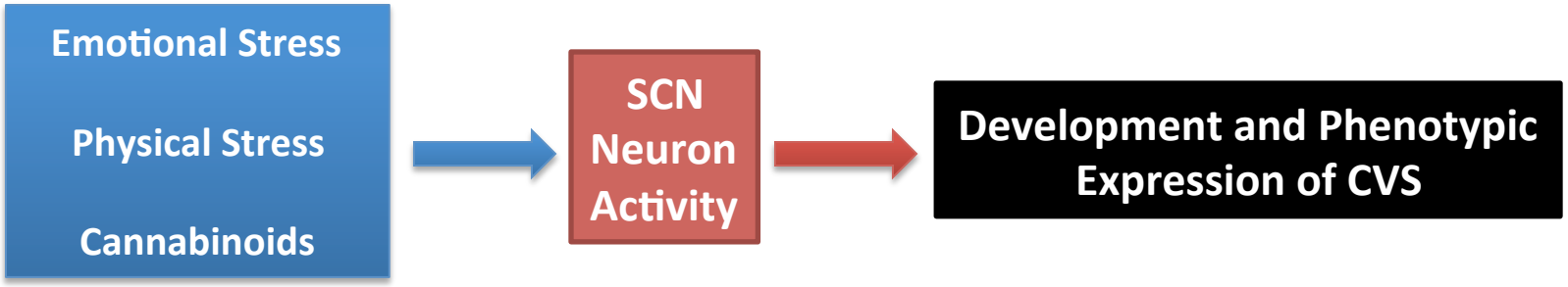
- **Normal physiologic diurnal patterns**
  - ↑ CRF production by neurons within the paraventricular nucleus (PVN) of the hypothalamus in early AM hours
  - increased peripheral CRF levels have inhibitory effects on gastric motility, which may lower threshold to develop vomiting during the day
- **Distinct circadian pattern in CVS attacks**
  - majority of patients experience onset of symptoms in early morning hours
  - physiologically associated with CRF levels, ↑ cortisol production, and ↑ SNS activity



Kalsbeek A *et al*. (2012). Molecular & Cellular Endocrinology.
Tache Y, Perdue MH. (2004). Neurogastroenterology & Motility.
Tache Y. (1999). Digestives Diseases and Sciences.

Circadian Patterns and HPA Axis

- Basic circadian rhythms and subsequent impact on HPA axis and autonomic function are ultimately driven by the **suprachiasmatic nucleus (SCN)**
- Animal Experiments → changes in motor behavior and mild stressors significantly influence SCN neuronal activity
- Acute administration of cannabinoids impacts SCN function



Webb I *et al*. (2010). Neuroscience.
Van Oosterhout F *et al.* (2012). PLoS ONE.
Acuna-Goycolea C *et al*. (2006). Journal of Neuroscience.

CVS and Autonomic Function

- Several of the clinical associations and manifestations of CVS implicate an essential role for aberrant SNS activity in disease pathogenesis
- Circadian pattern of early morning hour attacks suggests an important role for increased sympathetic tone

Potential Triggers
acute stress
sleep deprivation
prolonged fasting

Associated Symptoms
tachycardia
elevated blood pressure
significant sweating

Abell TL *et al*. (2008). Neurogastroenterology & Motility.
Fleisher DR *et al.* (2005). BMC Medicine.
Zhong X *et al*. (2005). Journal of Applied Physiology.

Abnormal Autonomic Function Testing in Patients with CVS

	CVS subjects (n = 19)	Controls (n = 19)	P-value
Thermoregulatory sweat test	17 (85.0%)	2 (10.5.0%)	<0.001
Percentage area of anhidrosis	15%	6.68%	0.003
Heart rate response to deep breathing	1 (5%)	1 (5%)	1.00
Postural tachycardia	7 (35.0%)	1 (5%)	0.04
Heart increase by (20–30) on standing	5 (25.0%)	4 (20%)	1.00

Majority of adults with CVS had evidence of sympathethic dysfunction (sudomotor and vasomotor dysfunction) but no evidence of parasympathetic dysfunction when compared to healthy controls

Venkatesan T *et al*. (2010). Neurogastroenterology & Motility.

Autonomic Nerve Dysfunction is Common in Adults with CVS

			Orthostatic test		Parasympathetic function			
Case #	Age	Gender	BP change	HR change	Deep breathing (E/I index)	Valsalva index	Posture index	Sympathic skin response
1	21	F	↓2/7 mmHg	↑**42 beats min^{-1}**	1.37	1.67	1.32	Present
2	44	F	↓**31/9 mmHg**	↑15 beats min^{-1}	**1.14**	1.23	1.07	Absent
3	24	M	↑**13/10 mmHg**	↑12 beats min^{-1}	**1.18**	1.93	1.41	Absent
4	44	F	↓**28/18 mmHg**	No change	**1.07**	1.51	1.07	Absent
5	43	F	↑7/5 mmHg	↑14 beats min^{-1}	**1.10**	1.86	1.17	Present
6	50	F	↓11/2 mmHg	↑15 beats min^{-1}	**1.04**	**1.18**	**1.01**	Absent
7	50	F	↓5/2 mmHg	↑24 beats min^{-1}	**1.21**	1.70	**1.02**	Absent
8	27	F	↑11/8 mmHg	↑**35 beats min^{-1}**	1.58	1.59	1.38	Absent
9	19	F	↑15/7 mmHg	↑16 beats min^{-1}	1.43	1.73	1.50	Absent

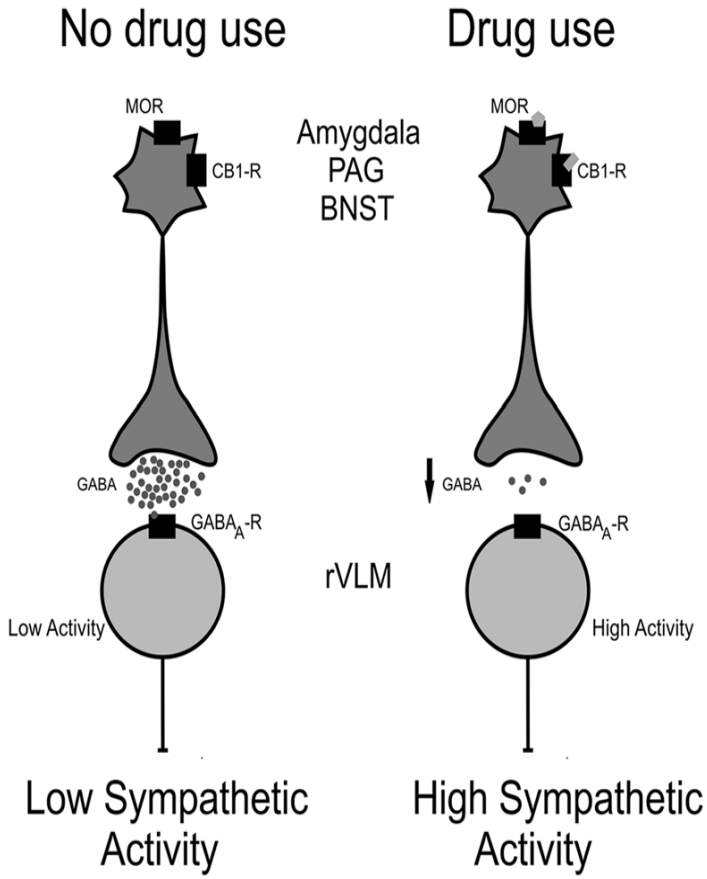
Note: abnormal findings are in bold.
BP, blood pressure; HR, heart rate; E/I index, expiration/inspiration index; ↑, increase; ↓, decrease.

43% of CVS patients had autonomic nerve dysfunction – sympathetic abnormalities predominated. Rapid gastric emptying, present in 57% of patients, did not correlate with autonomic testing results.

Hejazi RA *et al*. (2011). Neurogastroenterology & Motility.

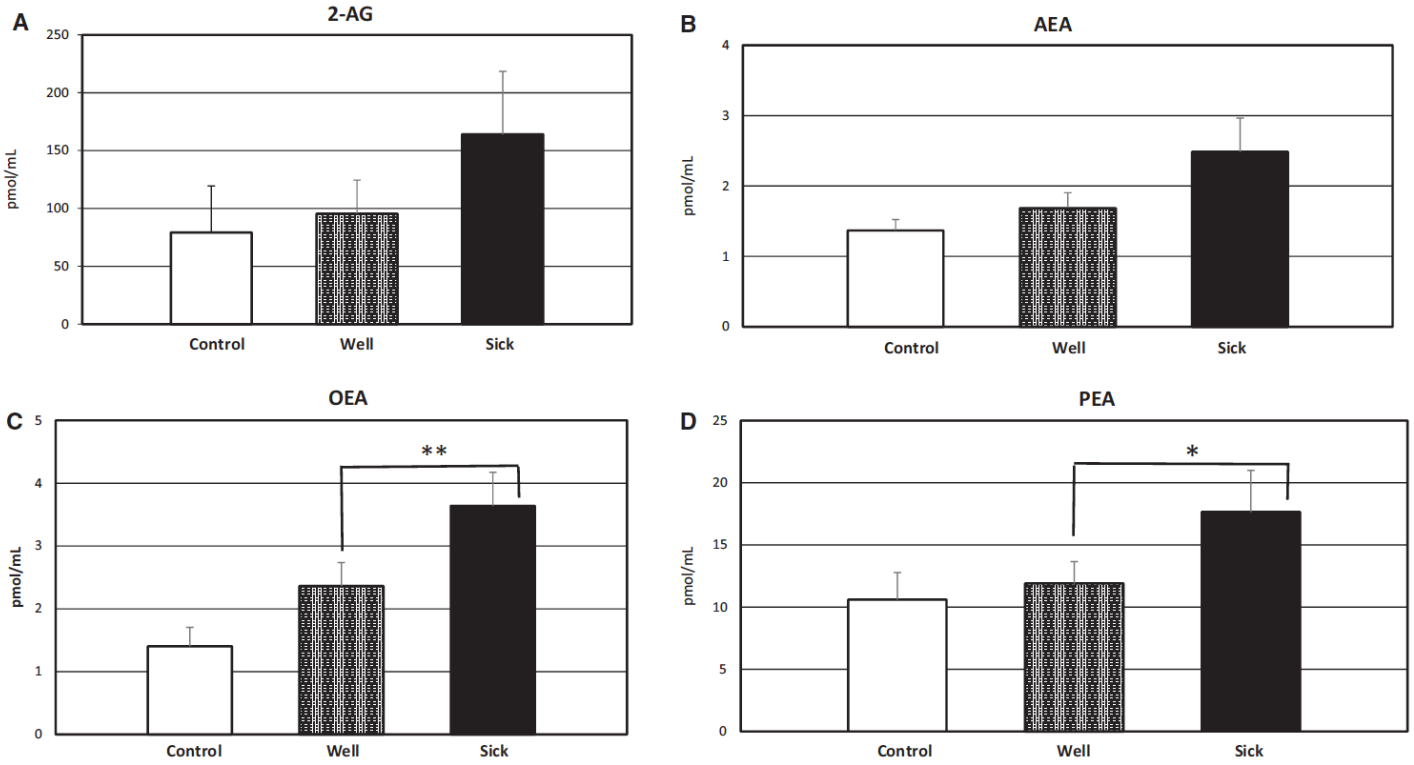
Impact of Cannabis and Opiates on Regulation of Sympathetic Neural Activity

- CB1 receptors and MOR are expressed on GABAergic neurons within several brain regions
- Cannabinoids and opiates may have a broad influence on autonomic activity
  - ↓ GABAergic input to the rVLM and NTS could lower the threshold to vomit
- Chronic exposure can ultimately increased basal sympathetic activity and sensitize central neural systems for vomiting, predisposing to more frequent CVS attacks → coalescent and/or refractory CVS



Yan J *et al*. (2013). Neuroscience.
Wilson-Poe AR *et al*. (2012). Neuroscience.
Hejazi R *et al*. (2010). Alimentary Pharmacology & Therapeutics.

Endocannabinoid-Related Lipids are Increased During an Episodes of CVS



Serum concentrations of 2-arachidonoylglycerol (**A**), *N*-arachidonylethanolamine (**B**), *N*-oleoylethanolamine (**C**), and palmitoylethanolamide (**D**) (pmol/mL) in 12 controls and 22 CVS patients during the well and sick phase are shown.

** p value <0.01 * p value of <0.05

Venkatesan T *et al*. (2016). Neurogastroenterology & Motility.

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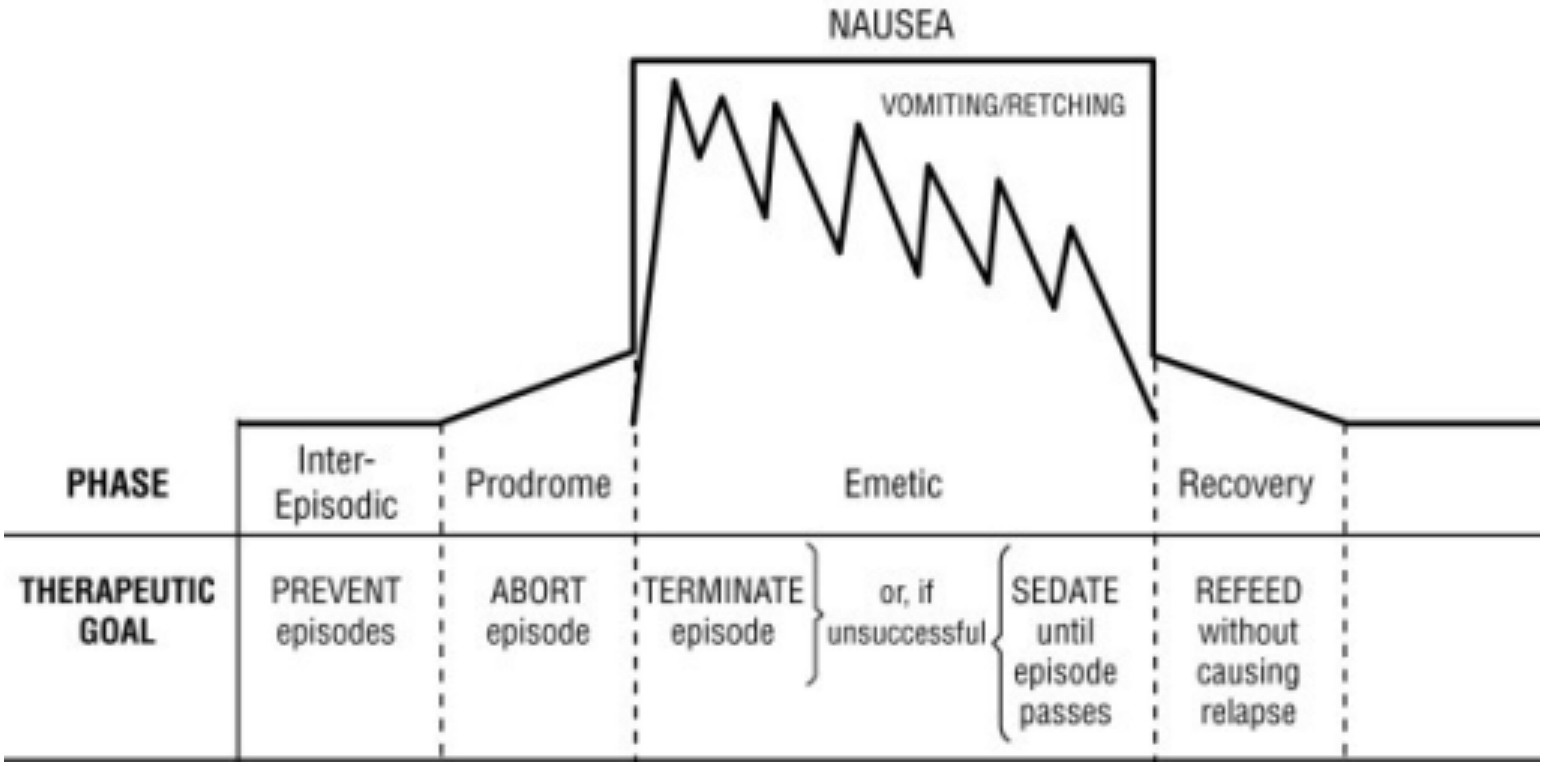
Clinical Evaluation and Diagnostics

Symptom Profile : Phases of CVS and CHS



Differential Diagnosis of Recurrent Vomiting

- Gastoparesis, CIPO, mechanical obstruction, and metabolic / CNS diseases can present with recurrent nausea and/or vomiting
- Rumination syndrome presents with effortless regurgitation of undigested food often with reswallowing or spitting within minutes of eating (can be mistaken for vomiting)
- Patients with bulimia may have self-induced vomiting associated with binge episodes
- Rare conditions have presentations that mimic CVS
  - Acute intermittent porphyria
  - Disorders of fatty acid oxidation

Diagnostic Testing

- Blood work to exclude electrolyte and acid-base abnormalities, hypercalcemia, hypothyroidism, Addison's disease
- Consider drug screening if CHS is a possibility but is denied
- Exclude gastroduodenal disease and SBO (imaging, endoscopy)
- Exclude CNS space-occupying lesions
- If above tests are negative then can consider gastric-emptying evaluation
- If severe symptoms persist, ADM can assess for enteric neuropathy or myopathy
- Consider rare conditions in some CVS patients
  - Urine measurements of aminolevulinic acid and porphobilinogen
  - Plasma amino acids
  - Urine organic acid quantification

Treatment

Treatment of CNVS

- Limited investigation has focused on treatment of what is now called CNVS
- Agents with antiemetic capabilities have been developed in several drug classes
  - Histamine (H_1) antagonists → promethazine (Phenergan)
  - Muscarinic (M_1) antagonists → scopolamine, hyoscyamine
  - Dopamine (D_2) antagonists → prochlorperazine (Compazine), trimethobenzamide (Tigan)
  - Serotonin (5-HT_3) antagonists → ondansetron, granisetron
  - Neurokinin (NK_1) antagonists → aprepitant, fosaprepitant
- 5-HT_3 antagonists exhibit superior control of vomiting compared with nausea
- Pain negatively impacts symptom reductions while gastric emptying rates do not predict responses
- Uncontrolled series of patients with presumed functional causes of nausea and vomiting report significant benefits with:
  - Tricyclic antidepressants
  - Cognitive behavioral therapy
  - Mirtazapine (noradrenergic and serotonergic antidepressant)

TCA Therapy for Functional Vomiting

- Retrospective case series (N=37)
- Amitriptyline, nortriptyline, desipramine, or imipramine (average doses 50mg/day for 5.4 ± 1.1 months)
- Moderate symptom reduction in 31/37 (84%)
- Complete symptom remission in 19/37 (51%)
- Major sites of action : sensory nerves, CNS

Prakash *et al*. (1998). Digestive Diseases and Sciences.

Treatment of CVS

TREAT ACUTE ATTACKS

- **Supportive Care**
  - IV fluids, electrolytes
- **Antiemetics**
  - 5-HT_3 antagonists
  - Aprepitant
- **Anti-migraine treatments**
  - Sumatriptan (nasal)
- **Analgesics**
- **Sedation**
  - Benzodiazepines
  - Diphenhydramine

PREVENT FUTURE ATTACKS

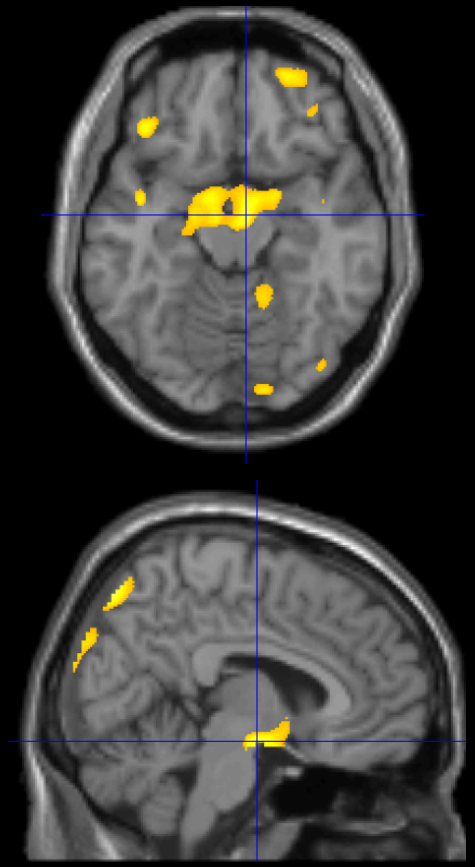
- **Tricyclic Antidepressants**
- **Anti-epileptics**
  - Topiramate (Topamax)
  - Zonisamide (Zonegran)
  - Levetiracetam (Keppra)
  - Valproate
- **Anti-migraine Treatments**
  - Beta blockers
  - Cyproheptidine
- **Mitochondrial Co-factors**
  - L-carnitine
  - Coenzyme Q-10

Sensory Modulators for Chronic or Recurrent Vomiting

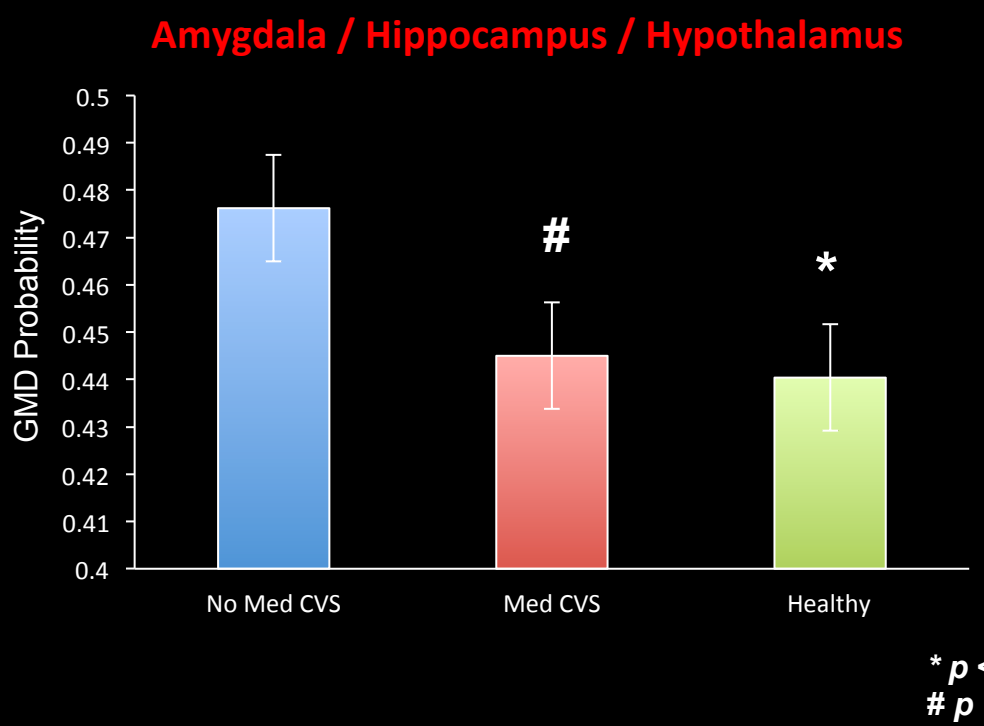
- **Cyclic Vomiting Syndrome**
  - Prophylactic efficacy of TCAs – 68% adults, 76% children
  - TCAs reduce attack frequency and duration and number of ED visits
- **Functional Vomiting**
  - 2 case series : moderate or greater responses to TCAs in ~75% at 50mg/day
  - Pain negatively affects responses; responses unrelated to emptying
  - Also reported benefits of mirtazapine and olanzapine

Prakash *et al*. (1998). Digestive Diseases and Sciences.
Prakash and Clouse. (1999). American Journal of Gastroenterology.
Lee *et al*. (2012). European Journal of Gastroenterology and Hepatology.
Hejazi *et al*. (2010). Journal of Clinical Gastroenterology.
Boles *et al*. (2011). BMC Neurology.

Maintenance Medications for Cyclic Vomiting Syndrome Affect Gray Matter Density in Brain Areas Serving HPA/Autonomic Function



(x,y,z = 7, -9, -15)
K = 4415 voxels



Siwiec *et al*. (2015). Gastroenterology.

Antiepileptic Drugs for Adult CVS

- 18 CVS patients (mean age 39) given Zonegran (15 patients) or Keppra (3 patients) for 10 ± 2 months after TCA failure (13 patients) or intolerance (5 patients)
  - Moderate response (decrease score ≥ 2) in 72%
  - Near resolution in 44%
  - Episode rate decrease from 1.1 ± 0.3 to 0.5 ± 0.2/month

Clouse *et al*. (2007). Clinical Gastroenterology and Hepatology.