Children's Hospital and Health System™

**HUMAN RESEARCH REVIEW BOARD**
**SUMMARY**

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**STUDY TITLE: Efficacy of Auricular Neurostimulation for Children and Adults with Cyclic Vomiting Syndrome: a Pilot Study**

## A. PURPOSE OF THE STUDY

Functional gastrointestinal disorders (FGIDs) affect a large percentage of children and negatively impact quality of life.[1] Cyclic vomiting syndrome (CVS) is an FGID characterized by relentless episodes of vomiting followed by return to baseline health.[2] Majority (80%) of children and adults with CVS have concurrent severe abdominal pain and migraine-features, rendering them incapacitated throughout the emetic cycle.[3,4] In many children, CVS evolves into migraine headaches during teenage years or adulthood. Although the etiology is still obscure, CVS is considered a migraine-equivalent disorder.

There are very few targeted treatment options for FGIDs including CVS. Empiric therapy with tricyclic antidepressants is standard[3] and fraught with side effects. The frequency of emergency department use for patients with CVS is extremely high and the syndrome has an immense impact on health-related quality of life.[5] Therapies for FGIDs represent a considerable unmet need in modern gastroenterology (GI) practice and a recent systematic review concluded that there is no evidence to support pharmacologic therapy for FGIDs due to lack of high quality studies.[6]

Nausea, vomiting and gastrointestinal pain is modulated by the vagus nerve.[7] The vagus nerve is an important regulator of the autonomic nervous system (ANS) and conveys visceral sensory information about the GI tract to the central nervous system (CNS). The major role of the vagal neurocircuitry in the generation of nausea and vomiting is well established.[7,8] Many studies indicate that vagal nerve stimulation (VNS) activates CNS pain modulation mechanisms and provides analgesia.[9,10] There is emerging consensus that CVS involves dysregulated central neural pathways and neuro-endocrine mediators involving the pathways for nausea and vomiting. Transcutaneous VNS of the auricular branch of the vagal nerve in the ear has emerged as a non-invasive alternative to implantable VNS. We have recently demonstrated safety and efficacy of a newly developed *percutaneous* auricular neurostimulation device in children with pain-associated FGIDs compared to a sham device (randomized, controlled trial; manuscript accepted for publication). Notably, vagal tone as measured by heart rate variability testing increased significantly in the treatment group compared to sham. Many patients had concurrent improvement in nausea and migraine symptoms. The aim of this project is to investigate the role of non-invasive neurostimulation in CVS with concurrent abdominal pain. This study may provide a potential novel and non-invasive therapy for a debilitating and prevalent disorder with few established treatment options. It may also further our understanding of the mechanisms involved in auricular neurostimulation therapy.

## B. SPECIFIC AIMS / HYPOTHESIS

**Specific aim #1:** Demonstrate that auricular neurostimulation prevents cyclic vomiting/abdominal migraine episodes when applied in the prodromal phase.

**Hypothesis**: Auricular neurostimulation will result in a reduction in the frequency of emesis and severity of abdominal pain and nausea during episodes compared to baseline and sham therapy.

**Specific aim #2:** Compare measures of functional disability, quality of life and psychological health in children and adults with cyclic vomiting syndrome before and after auricular neurostimulation therapy.
**Hypothesis:** Auricular neurostimulation will improve overall functional disability, anxiety and quality of life by reducing emesis and pain episodes compared to baseline and sham therapy.

**Specific aim #3:** Compare heart rate variability measures as surrogate of vagal tone before and after auricular neurostimulation therapy.
**Hypothesis:** Auricular neurostimulation will improve vagal tone compared to baseline and sham therapy.

## C. BACKGROUND, SIGNIFICANCE, AND RATIONALE

Cyclic vomiting syndrome is a functional GI disorder characterized by severe, stereotypical and disabling episodes of intense nausea and vomiting, lasting anywhere from 1 to 10 days.[3] The disorder is more prevalent than commonly recognized, estimated to occur in 1.9% of children.[11,12] While initially thought to be a pediatric disorder, it is as common in adults. This is more common than the prevalence of celiac disease and comparable to the prevalence of pediatric inflammatory bowel disease in the state of Wisconsin. The medical costs for the diagnosis and treatment of CVS are immense. In 1999, the costs of care for children with CVS was and estimated $17, 035 annually per child.[4] The costs of just hospitalizations due to CVS in adults is staggering and a total of $400 million over 2 years was incurred due to hospitalizations alone.[13] This did not include the cost of investigations and indirect costs from work days lost. Quality of life is markedly affected and worse in children and adults with CVS compared to those with IBS and healthy controls.[14] In adulthood, one third are disabled by the disorder and suffer significant psychosocial problems including job loss and divorce.[15]

About 80% of patients with CVS suffer from concurrent migraine headaches or abdominal migraines during the episodes.[3] In fact, abdominal pain is a prominent feature of CVS episodes and precipitates vomiting in many cases. Therapies are therefore targeted both towards nausea and vomiting as well as aggressive pain control. Safe and effective treatments for children and with CVS are needed. Currently, there are no FDA approved drugs for the treatment of CVS in children and little evidence of success for any medication. Therapies are empiric and response is often variable with numerous patients still requiring emergency room visits or hospital admissions.[5] One of the most commonly used treatments in the clinical setting is amitriptyline, a tricyclic antidepressant (TCA) that is used “off-label” similar to all other drugs used for CVS.[3] Most patients receive a daily prophylactic medication such as a TCA but still require frequent hospital admits for severe and drug-refractory episodes. These patients receive high doses of intravenous anti-emetics along with anxiolytics, sedatives and pain-control including opiates while in the hospital. Chronic or frequent opiate use is seen in a subset of adults with CVS and is associated with non-response to therapy along with risks of dependence and even addiction in some patients. Some even require anesthesia in the intensive care unit for drug-refractory CVS.[16] Many of these therapies may involve serious side effects with TCAs being discontinued in 25% of adults due to intolerable side effects.

Strong migraine features, including headaches, pallor, photophobia and nausea are characteristic of CVS episodes. CVS is considered a migraine related or migraine-equivalent disorder based on clinical similarities, a high family prevalence of migraines, effectiveness of anti-migraine therapy and the recent discovery of mitochondrial DNA polymorphisms in CVS and migraine

patients.[3,17,18] Therapies for CVS such as amitriptyline is also a standard migraine prophylaxis therapy.[19] The etiology of CVS is yet unclear but there is emerging consensus of altered brain-gut neurocircuitry and autonomic imbalance.[20] There is some evidence for an altered brain response to visceral and emotional stimuli.[20,21] An altered hypothalamic-pituitary-adrenal (HPA) axis is one proposed mechanism based on a few studies.[22,23] Typical CVS episodes are often triggered by stress states, whether physical or psychological. Stress may thus initiate the vomiting cascade in susceptible individuals (perhaps with underlying migraines, autonomic imbalance or mitochondrial defect). Similar triggers initiate migraine headaches and the pathophysiology of migraines is also not completely understood. The trigemino-cervical system, brainstem nuclei and pain modulation pathways are thought to play a key roles.[24-26] Autonomic abnormalities are documented in both children and adults with CVS and migraines alike.[20, 27-29] These features suggest that central mechanisms are key in CVS patients with migraine features.

The sympathetic and parasympathetic (vagus) branches of the autonomic nervous system (ANS) connect with the enteric nervous system to modulate GI function and sensation.[30] The ANS plays an important role in the responses to various emetic stimuli. It is well known that a series of brainstem nuclei receive vagal and sympathetic afferent input during emesis.[7,20] Output neurons then signal the stereotypical vomiting response. A central emetic relay station is the brainstem nucleus tractus solitarius (NTS). The NTS integrates afferent inputs from the vagus and project to higher brain regions such as limbic regions (amygdala, hypothalamus) involved in arousal and *central autonomic control* (Fig 1). These regions also control the behavioral and emotional response to visceral sensations. Autonomic imbalance in adolescents is linked to reduced vagal baroreflex response and heart rate variability (HRV).[31] HRV is a measure of cardiac autonomic outflow via baroreceptors.[31] A study of adolescent FGID with nausea showed decreased HRV, suggesting low vagal modulation of the heart.[32] Low vagal (parasympathetic) tone is also demonstrated in several FGIDs including CVS.[33-35] Cranial nerves IX and X may link ANS dysregulation with nausea and vomiting and the involvement of higher brain regions. The ANS hence plays a key role in both central afferent input and likely the output signals for vomiting through vagal and sympathetic signals. There is ample data that anxiety is highly prevalent in CVS and a known trigger of episode.[3,36,37] Stress and sympathetic nervous system activity may thus contribute to initiation of vomiting in CVS patients and therapy via vagal modulation may alter these signals and prevent episodes.

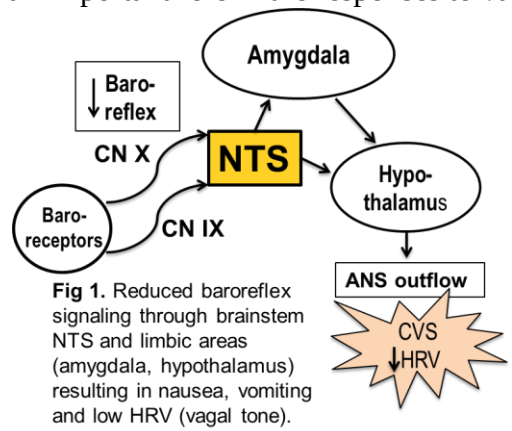



**Fig 1.** Reduced baroreflex signaling through brainstem NTS and limbic areas (amygdala, hypothalamus) resulting in nausea, vomiting and low HRV (vagal tone).

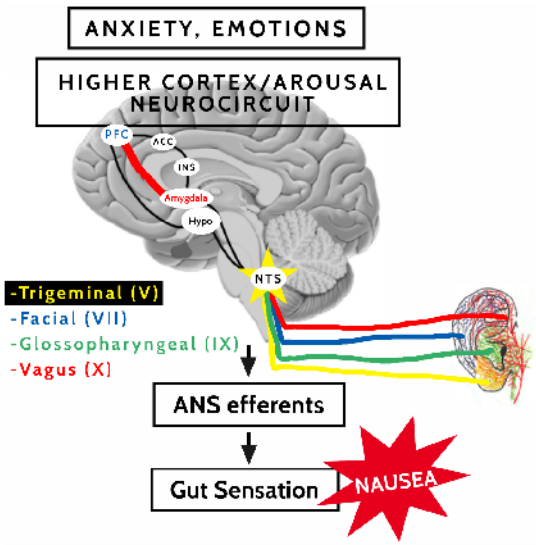



**Fig 2.** Central projections of 4 cranial nerves converging in brainstem NTS and modulated by auricular stimulation. *Hypo=Hypothalamus; INS=Insula; ACC=Anterior Cingulate Cortex; PFC=PreFrontal Cortex*

The implantable vagal nerve stimulator (VNS) is approved for epilepsy and depression. It also has demonstrated anti-nociceptive effects by inhibition of sensory neurons in the brainstem based on animal models.[38,39] In humans, VNS also reduces anxiety, improves pain and migraine headaches and has mood and memory-enhancing properties.[40-44] Unfortunately, the implantable VNS is highly invasive. Our group has recently demonstrated efficacy of percutaneous auricular neurostimulation with a novel, non-invasive device [Electroauricular device (EAD), Innovative Health Solutions, IN, USA] in adolescent FGIDs. This

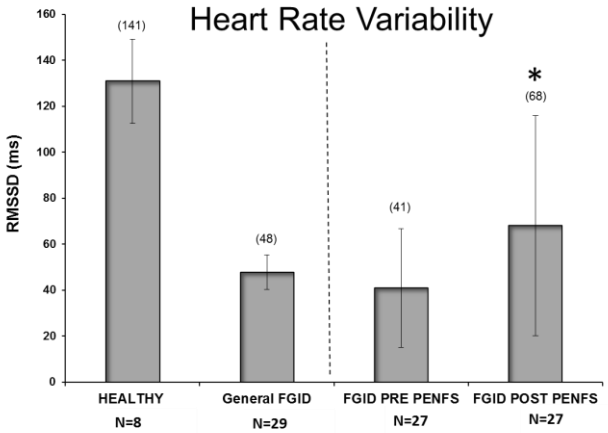



**Fig 3.** Left: RMSSD (vagal tone) value in healthy control vs general FGIDs. Right: PENFS (percutaneous electrical nerve field stimulation) therapy in FGID subset shows increase in vagal tone from baseline (pre) after only 3 weeks of therapy (post) ($p \leq 0.0001$).

randomized, double blind, sham-controlled trial of 115 adolescents with FGIDs showed significant reduction in weekly pain scores ($p=0.003$), global symptoms ($p \leq 0.001$) and disability ($p=0.01$) compared to sham after only three weeks of therapy with sustained effects several months later ($p=0.018$) (manuscript accepted for publication). Effects are likely improved by a field stimulation effects (aka percutaneous electrical nerve field stimulator=PENFS) of the entire ear with resulting stimulation of several cranial nerves (V, VII, IX) in addition to the vagus (X). The cymba concha region of the external ear receives 100% of the afferent auricular vagal nerve distribution.[45] HRV measures showed improvement in vagal tone as measured by RMSSD (root mean square of successive differences) (mean ± SD) from pre (40.9 ± 25.9) to post (68.1 ± 47.9) in standing position ($p<0.0001$) with no change in sham (Fig 3). The standing heart rate in the treatment group was also significantly reduced from pre (83 ± 15) to post (76 ± 13) ($p=0.011$) in the treatment group which was not seen in sham. This suggests strengthening of the baroreceptor stress response and vagal nerve stimulation effects with this therapy. Many had improvement in concurrent nausea, vomiting and migraine symptoms but their exact phenotype is unclear. In a small subset with improved nausea, three weeks of therapy increased vagal tone compared to baseline ($p \leq 0.01$). Further, in a rat model of post-inflammatory hyperalgesia our group has shown that the this device reduces firing of amygdala and spinal neurons by approximately 50% and attenuates visceral hyperalgesia.[46] A recent study also demonstrated that the same device reduces symptoms of opioid withdrawal up to 97% after only 5 days of therapy.[47] Alterations in limbic pathways and ANS balance appears to be a common link between the state of chronic pain and opioid dependence and could explain these effects.[48] Auricular neurostimulation may thus modulate ANS balance and improve symptoms in CVS and abdominal migraines by strengthening vagal tone.

The ear is an ideal target for non-invasive vagal neurostimulation for patients with centrally mediated nausea, vomiting and pain due to the presumed sympathovagal imbalance. **We therefore propose a pilot study to investigate the effects of auricular neurostimulation in children and adults with cyclic vomiting syndrome and abdominal pain/abdominal migraines.** We will investigate the effects of auricular neurostimulation on emesis frequency, pain, functioning and quality of life in patients migraine-associated CVS.

**Fig 4**. Auricular neurostimulation with EAD.

## D. DESIGN AND METHODS

### Experimental design

This is a prospective trial to evaluate:

1. The efficacy of percutaneous auricular neurostimulation in reducing emesis episodes in children and adults with CVS.

2. Improvement in pain, nausea, daily functioning, anxiety and quality of life in patients with migraine-related CVS pre vs. post auricular neurostimulation.

**Equitable subject selection, inclusion and exclusion criteria**

- Children aged 10-17 years, presenting to the Pediatric Gastroenterology Clinic at the Children's Hospital of Wisconsin (CHW) and who meet criteria for CVS based on the 2016 Pediatric Rome IV Criteria for FGIDs[2]
- Adults ages 18-65, presenting to the Gastroenterology Clinic at Froedtert Hospital and who meet criteria for CVS based on adult Rome IV criteria.
- All patients will meet the following inclusion criteria: 1) suffer from concurrent episodic abdominal pain, 2) English-speaking, 3) lack other explanation for vomiting; and 4) are willing to participate and consent to this study (for children, have a parent willing to participate).
- All patients will either suffer from "calendar-timed" CVS with predictable episodes every 4 weeks (or as frequent as every 2 weeks) and/or have prodromal signs (nausea, pallor, pain, fatigue, irritability etc) for minimum 12-24 hours prior to symptom onset that is predictive of episode.

Medically complex children or those who take a medication or suffer from a disease that can explain symptoms will be excluded from participation in the study. Adult subjects, children or their parents who have significant developmental delay, will be excluded due to difficulties in accurately completing the questionnaires and assessing symptoms. By definition, all participants in this study will have no clear explanation for their symptoms after undergoing medical workup per standard of care. Patients with findings of organic disease such as intestinal malrotation, peptic ulcer disease, H.pylori gastritis, celiac disease, inflammatory bowel disease, allergic disorders, hydronephrosis, metabolic disorder or any other chronic condition or medication that may cause episodic pain and/or vomiting will be excluded from the study. Patients who are treated with a new drug affecting the central nervous system in the week prior to enrollment will also be excluded. Patients must have an intact external ear that is free of infection or severe dermatological conditions, have stable vital signs for their respective age and no currently implanted electrical device. Other exclusion criteria in adults (adolescents as applicable) will include: 1) pregnancy 2) severe cardiopulmonary diseases such as chronic obstructive pulmonary disease (COPD) or coronary artery disease and 3) current chronic marijuana use defined as marijuana use > 2 times a month over the last 6 months prior to study enrollment.

Subjects with a diagnosis of a concurrent anxiety or autonomic disorder will <u>not</u> be excluded.

**Subject recruitment and enrollment**

Subjects presenting to the GI clinics at CHW and Froedtert Hospital with complaints concerning for cyclic vomiting syndrome and concurrent abdominal pain will be identified by evaluating GI physician and will be approached for inclusion in the study if they meet criteria for CVS. The Principal investigator, a co-investigator or research coordinator will introduce the study to patients seen in the CHW or Froedtert GI Clinic during their regularly scheduled clinic visit. Research coordinators, the Principal investigator or a co-investigator will explain the details and purpose of the study during an informed consent discussion and obtain consent and assent. Once the patient and caregivers had enough time to consider participation, understand all of the risks and benefits and would like to participate, they will sign informed consent and HIPAA documents.

Subjects will undergo medical workup per standard of care. Subjects refractory to current medical therapy may be enrolled without changes to their current medical treatment within the past two weeks. No new pharmacological agents will be added during the study period unless clinically indicated and no changes in dosing or scheduling of current therapy will be allowed during the study period. Subjects will be asked to not use any as needed anti-emetic or pain medications during the study. To participate in the study, patients must be able to verbalize their condition and concerns about nausea, vomiting, pain and other symptoms. Subjects will be screened by RNs from the Pediatric Translation Unit (pTRU) at all visits for any side effects. Subjects will be asked to notify the PI or research team with any worsening in symptoms or side effects of therapy. Any subject without improvement in symptoms during the study will be able to discontinue the study. If symptoms worsen or fail to improve during the study or if their clinical presentation changes in any way, subjects will have the option to drop out any time, receive standard medical therapy and appropriate referrals. If per standard of care, a subject requires a change in one or several of their regular medications during the study, they will be asked to notify the research team. To monitor this, the subjects will be inquired about their medication list and doses at each visit. If the medication change is determined to potentially affect the study results, the subject may be excluded from further study as determined by the PI. Subjects will also be asked if they wore the device for all five days.

Subjects will undergo diagnostic testing as clinically indicated per standard of care. This may include but is not limited to upper endoscopy, upper GI contrast study, renal ultrasound, brain imaging, 4-hour solid-phase gastric emptying scan, metabolic workup, stool studies and screening blood work. Subjects with positive testing for any organic condition will be excluded from further study and treated per standard of care.

After consent and assent is obtained, the standard-of-care clinic procedures and research questionnaires will be performed. Information on demographics, medical history, symptoms, treatment and diagnostic workup will be collected by physician as part of the initial clinic visit. Participants will complete the attached baseline questionnaires (Table 1). These will take about 15 minutes to complete (see attached and explanations below). Patients will return to the pTRU on a separate day during the prodromal phase prior to episode onset or 1-3 days prior to predicted CVS episode if "calendar-timed" for placement of the ear neurostimulator (Table 1; Visit #1). Patients with "calendar-timed" CVS will be primary targets for the study as their episodes occur on same day each month (many triggered by menstrual periods).

During the first week of neurostimulation therapy (Treatment #1), subjects will complete daily vomiting, nausea and pain surveys (INVR, BARF and numeric pain scale; attached). At the end of the week (day 5 +/- 2 days due to possible coinciding with weekend), they will return to the pTRU for HRV measurement (Visit #2) and completion of questionnaires (per Table 1). When they return for the second week of therapy (Visit #3), they will complete questionnaires as outlined in Table 1. Each week, the subject will wear the neurostimulator for 5 days and then remove it in the home setting or in the pTRU if they return on day 5.

**Technical details**

Subjects will prospectively complete the following questionnaires at different time points during the study (see Table 1 for timeline):

1. Demographics: a brief demographic questionnaire will be completed by a member of the research team (see attached).
2. Rome IV Diagnostic Questionnaire on Pediatric and Adult Functional Gastrointestinal Disorders: clinical classification into Rome IV CVS criteria (pediatric and adult)[49]

3. Rhodes Index of Nausea, Vomiting and Retching (INVR): validated short, 8-item scale to assess severity of nausea, vomiting and retching symptoms daily (assessed daily during treatment).[50]
4. Baxter Retching Faces (BARF): pictorial nausea scale (0-10) validated in children (assessed daily during treatment).[51]
5. Numeric pain rating scales (0-10). Subjects will be asked to grade the severity of any abdominal and headache pain that was significant enough to distract from their usual activities (daily).
6. State-Trait Anxiety Inventory for Children (STAI-C) and Adults (STAI-AD). Subjects will be assessed for symptoms of state anxiety by this validated measure.[52] State and trait anxiety is measured with a two-page (40-item) questionnaire at baseline. Repeat measurements will assess state anxiety only. A Research Psychologist (PhD) will assist with interpretation of the psychometric data.
7. Patient Reported Outcome Measurement Information System (PROMIS): A newly developed and validated global health/quality of life outcome measure that provides an efficient (7-item) summary of a patient's physical, mental and social health.[53]
8. Functional Disability Inventory (FDI): Symptoms of disability and reduced quality of life in children will be assessed with the FDI.[54] This is a one page, self-report measure of the degree that children experience difficulty in physical and psychosocial functioning due to impaired physical health. Patients rate each of the 15-items on a five-point Likert scale indicating how much difficulty they have doing common childhood activities because of their physical health.
9. Adult subjects will complete the short, 5-item validated Sheehan Disability Scale, assessing functional impairment in work/school, social and family life.[55]
10. Subjects will also fill out a short validated overall symptom response scale.[56] Subjects will rate their symptoms as better, worse or no change based on a 15 point scale: -7 to -1= worse; 0 = no change; +1 to +7 = better). Specific symptoms that improved (or worsened) will be checked if applicable.

**Table 1.**

| | Baseline | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Follow-up |
|---|---|---|---|---|---|---|
| **Screening Consent** | X | | | | | |
| **Neurostimulator (EAD)** | | x | | x | | |
| **HRV** | | x* | x** | x* | x** | x |
| **Demographics** | x | | | | | |
| **Rome IV questionnaire** | x | | | | | |
| **INVR (daily during therapy)** | x | x | | x | | x |
| **BARF (daily during therapy)** | x | x | | x | | x |
| **Pain scale (daily during therapy)** | x | x | | x | | x |
| **STAI-C/STAI** | x | x | x | x | x | x |
| **PROMIS** | x | x | x | x | x | x |
| **FDI** | x | x | x | x | x | x |
| **Sheehan Disability Scale** | x | x | x | x | x | x |
| **Symptom response scale (SRS)** | | | x | x | x | x |

**Before and after neurostimulator placement*

*** To occur 5-7 days following the nerve stimulator placement*

*STAI-C= State-Trait Anxiety Inventory for Children; PROMIS= Patient Reported Outcome Measurement Information; FDI=Functional Disability Inventory*

### *Statistical Analysis*

#### Data Management

The data gathered will be entered into REDCap data system with each ID having a unique identifier for each participant. REDCap is a secure, web-based application for building and managing online databases. All data will be de-identified and samples will only have a unique identifier that will link the unique identifier with the patient's name.

The REDCap clinical database will be maintained by the Department of Quantitative Health Sciences, at the Children's Research Institute under the direction of Pippa Simpson, PhD.

Questionnaires may be emailed to the patient when feasible, otherwise paper forms will be used in the event that the patient does not have access to a computer.

**Statistical Analysis**

**Missing Data Handling**

Every effort will be made to avoid missing data. Using logistic regression (LR), the assumption of missing at random data will be explored. If the data appear missing at random (MAR), multiple imputations for items and longitudinally random effects models will be used. If missing data appear not random, a sensitivity analysis will be employed, using clinical information and different assumptions to substitute values and see how results are affected.

***Patient Demographics and Characteristics Data***

Patient characteristics at baseline, demographic and disease characteristics will be summarized using descriptive statistics. In addition, previous and concomitant diseases and medications will be summarized. Frequencies will be presented for the categorical variables (e.g. race) and descriptive statistics will be presented for continuous variables (e.g. age).

**Efficacy Variables**

**Aim 1 (Primary):**

Primary efficacy: Change in vomiting episode frequency scores *(measured by # of emesis and pain episodes/day)*

Secondary efficacy: Change in vomiting, nausea, retching and pain severity

**Aim 2:**

Primary efficacy variable: Change in functional disability
Secondary efficacy variable: Change in anxiety, quality of life and global symptom scores

**Aim 3:**

Primary efficacy variable: Change in heart rate variability as measured by RMSSD and the high frequency domain
Secondary efficacy variable: Changes in low frequency domain, high to low frequency ratio and other HRV parameters

**Statistical Methods**

The primary model will include independent variables of the fixed, categorical effects of treatment, assessment visit, and treatment-by-assessment, interaction, along with the continuous effects of baseline and baseline-by-assessment interaction up to end of study. An unstructured variance-covariance structure will be used to model the within-patient errors and different variance-covariance structures will be tried for goodness-of-fit exploration. A treatment by-week interaction contrast will be constructed to estimate the difference between placebo dummy and the auricular stimulation arm in mean change from pre to post therapy. The 95% confidence intervals (CI) of treatment difference from placebo will be reported.

All efficacy data will be analyzed including mITT patients. Per-protocol analysis will be done only if more than 10% of the ITT patients do not qualify for the per-protocol analysis. For all efficacy variables, the baseline value will be defined as the last value taken prior to the start of randomized study.

**Continuous/ Ordinal variables**
Summary statistics such as mean, median, standard deviation, range and correlation plots and tree analysis will be used to examine distributions and interrelationships. Where necessary, for parametric assumption, we will employ appropriate transformations with justifications. If data cannot be appropriately transformed we will compare variables between the two groups using a Mann-Whitney test.

**Categorical variables**
We will compare the two groups using a chi - square or Fisher-Haltom exact test.

**Additional Analysis**
In addition to the above described primary analysis, the following analysis will be done.
1. The mean change from baseline in all efficacy variable scores will be summarized using descriptive statistics at all assessment time points.

2. To assess effects of dropouts, the dropout cohort analysis will be performed by summarizing the change of primary and secondary efficacy variables using different dropout cohorts. Dropout cohorts will be formed by patients that had their last primary efficacy measurement in the same assessment interval.

For all efficacy variables, nominal p-values will be presented without applying any adjustment for multiple comparisons.

**Safety Data**
All safety variables (e.g., adverse events will be summarized for each assessment time (including follow-up) using descriptive statistics. Incidence of adverse events will be summarized by treatment.

## E. TOTAL NUMBER OF HUMAN RESEARCH PARTICIPANTS PROPOSED FOR THIS STUDY AT THIS SITE AND GLOBALLY. WHAT ARE THESE NUMBERS BASED ON?

We expect to enroll a total of 40-50 subjects with estimated 30-40 who will complete all study-related procedures. The pediatric GI clinic evaluates at least 4-6 patients with cyclic vomiting syndrome each week. The CVS program at CHW (run by Dr. Kovacic) has several hundred established patients. The CVS program at Froedtert (run by Dr. Venkatesan), evaluates at least 12-16 per week and has > 1000 established patients enrolled in a clinical registry who receive ongoing care at the CVS clinic at Froedtert hospital.

Enrollment will be discontinued after reaching 40 subjects. If it is determined that there is enough data sooner, enrollment may cease prior to reaching the total number.

## F. DRUGS OR PROCEDURES

**Auricular Neurostimulation treatment protocol**
Subjects will enter a two-week, prospective randomized-controlled, cross-over treatment trial with the FDA-approved and commercially available device Neuro-Stim manufactured by Key Electronics (Jeffersonville, IN, USA) and distributed by Innovative Health Solutions (Versailles, IN, USA). This is an ambulatory, neurological device which consists of a battery powered, externally affixed generator with 4 wire leads attached to 3 electrode/ needle arrays and one single point needle. The device delivers low voltage (3.2V) stimulation in alternating frequencies for a total of 5 days (around the clock). The arrays are designed to produce a field effect similar to surgically implanted peripheral neurostimulators. Study Investigators (MDs) will place the

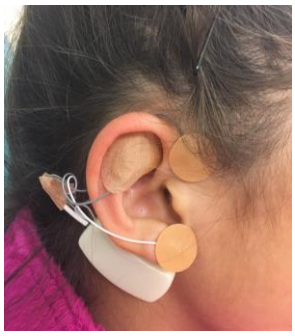
electrodes percutanesously in the external ear with the help of a transilluminator to visualize the neurovascular bundles. Three electrodes will be placed on the ventral and one on the dorsal aspect of the ear. The electrodes will be taped and secured behind the ear next to the generator itself which is secured to the skin with adhesive. The entire device may be covered by longer hair. The placement of the devices is within standard of care by properly trained medical doctors as already performed as part of separate, ongoing IRB-approved trial. Training of MDs (Dr. Kovacic and Dr. Miranda) has already been performed by Dr. Chris Brown or Dr. Brian Carrico as representatives of Innovative Health Solutions. The placement protocol is the same as prior IRB approved study (#689519) recently completed at CHW. All subjects will receive the device in their prodromal/warning phase of their cyclic vomiting cycle or in case of calendar-timed CVS, within 1-3 days prior to expected start of vomiting cycle.

Subjects will be randomized in a 1:1 ratio to either treatment or sham group for their first week of treatment. They will subsequently cross over to the other group for the second week of treatment. Randomization will be stratified by age (child vs adult) and gender and determined using a computer program based on random number generation in blocks of 10 subjects at a time and subjects will be stratified by gender and age (child vs adult). The manufacturer will provide the researchers with 2 devices per package (2 treatments per patient). Each package will have a serial number and only one research coordinator will have the key to which serial numbers represent active devices and which represent inactive ones. This research coordinator will keep the data in a secure database and will not be involved in any of the patient recruitment or study procedures. All other research coordinators, investigators, statistitian and nurses involved will be blinded to group allocation.

Devices will be delivered by Innovative Health Solutions. Research coordinators within the division of gastroenterology will store the devices as pre-packaged by manufacturer. A coded folder for each patient with all questionnaires needed for the entire study will also be kept with each subject package. The devices and folders will be stored in a locked office in the pediatricgastroenterology division, only accessible by the research team. A research coordinator will meet the patient in the TRU for device placement by one of the certified doctors.

The inactive devices will be custom made by the physical manufacturer, Key Electronics, Jeffersonville, IN. This control device will be identical in every way to the active device except it will lack the battery. The devices will be "made to order" when requested by the PI and will be shipped packaged as above. Both the subjects and the doctors placing the devices will be blinded, as the treatment and inactive devices will look identical with identical packaging and placement procedures. All patients will be told that they may or may not feel a flushing sensation after device placement. Blinding will be tested by asking the subjects and caregivers to guess their group assignment (active vs control) at the end of the study (Visit #4).

The electrode/needle arrays are placed according to the individual's arterial and cranial nerve anatomy. The exact location of the placement may vary slightly from person to person but is determined by both knowledge of auricular neuro-anatomy and visualization of the neurovascular bundles by transillumination (IHS, Versailles, IN, USA). The points will be targeted by four-point electrical stimulation using the EAD after carefully disinfecting the ear. The small device will be positioned and secured behind the ear similar to a hearing aid, which may be covered by hair. Neurostimulation will be delivered below sensation threshold for 5 consecutive days. The device will be applied by a trained MD. A second week of neurostimulation will be performed at the expected next calendar-times CVS onset unless the patient is symptom free. If so, the treatment trial but may be stopped after one week if there is complete symptom resolution. If there is



evidence of symptoms or emesis after the first 5 days of therapy, subjects may resume their usual abortive medicines as clinically indicated. They will remove the device independently at home and discard them as they are non-functioning after 5 days (5 days battery life). Each week when subjects return, they will be asked if they wore the device for the whole 5 days and this will be documented by pTRU RN. The devices are easily removed by removing the tapes and adhesives. Subjects will complete questionnaires at different time points as shown in Table 1.

The EAD Surgical kit consists of :
(1) An alcohol swab (2) prep and stay swab (3) round fixation plasters
(4) fixation plasters to fasten the generator (5) Steri-strip adhesive vial
(6) Sterile wire harness pack (7) Generator (8) Tweezers (9) Surgical marker
(10)Transilluminator

**EAD placement details:**

1. A research coordinator in the GI office will document the patient ID, name and the device serial number in the study database.
2. Patient will return to the CHW pTRU where the research coordinator will give a labeled device package (with patient ID and serial number only) to the doctor to attach to the subject.
3. The research coordinator or RN will administer the above questionnaires to the subjects and perform a medication and side effects check at all visits. At the initial visit, the baseline questionnaires will be administered by the research coordinator at the time of the clinic visit.
4. The pTRU RN will document the patient's vital signs (temperature, heart rate and blood pressure).
5. The neurostimulator placement will be performed as directed and per EAD training protocol instructions identically to per our prior IRB approved protocol (#689519).
6. Before neurostimulator placement, the subject should be advised that some discomfort is normal at first but should report if the discomfort persists or gets worse after a few minutes. The patients should be advised that they may feel a slight pulsing sensation and perhaps a warming sensation in the ear to which the electrodes are affixed. The pulsing and warming sensation may disappear after approximately 5 minutes. If the discomfort level increases the offending array can be slightly repositioned until the patient's discomfort level decreases to an acceptable level.
7. The patient will remain at rest for the next 10 minutes.
8. Subjects will be advised not to immerse the device in water as the device is water resistant but not water proof. If showering or washing their hair, place a dry wash cloth over the area to help protect the device. Subjects will be given a contact person (Principal investigator and research coordinator) to call if they are having any problems with the device or if it falls off.
9. The patient will be instructed on removing the device after 5 days. If not comfortable doing so or unable to carry out the instructions, the patient will be seen on that day for removal by one of the investigators.
10. The patient will be asked to return the used device for proper disposal when they return the following week (or to their follow-up medical appointment if last treatment week).
11. Subjects will be given a handout with short, daily symptoms surveys and reminded to complete them every night and bring them back the following week.
12. The subject will be given a handout with information (attached) on device handling, exact date and time of device removal and date and time to return.
13. The subject will be advised to refrain from using any as new or as needed anti-emetic or pain medications during the time of study period.
14. The research coordinator will ensure a follow up visit has been scheduled in GI clinic within 1-2 months of study completion.
15. The subject is dismissed.

**Heart rate variability (HRV)**
The evaluation of heart rate variability (HRV) provides a functional assessment of the relation between the sympathetic and parasympathetic tone. The high-frequency power of the heart rate variability and the root mean square of successive differences (RMSSD) reflects the vagal modulation of the heart. This can be evaluated by analyzing the HRV at rest and in standing position to assess the baroreflex response.

Subjects will undergo HRV measurements before and after each week of neurostimulation therapy (day 1 and day 5-7 of both treatment weeks). The HRV measurements will also be repeated immediately after each neurostimulator placement. After a 5-minute period of rest in supine position, the subject will lay supine for 5 minute for HRV recordings followed by 5 minute of recording while standing (total of 15 minute per session). We will use the Actiwave EKG recorder by CamNTech to measure HRV. This device is a single channel recorder, where two electrodes are placed on the patient's chest by an RN who then completes the recording according to our standard protocol. The HRV evaluation will take place before and after both neurostimulator placements (visits #1 and 3) and at the end of each therapy (day 5; visits #2 and 4) and at the post-study follow-up clinic visit. The HRV data will be analyzed using Kubios program or a similar computer program.

**Data to be collected:**
Consent from participants for use of these materials for research will be obtained.

Demographic Information
Data will be collected as part of the clinic visit and at enrollment. This includes subject's date of birth, age, sex and ethnicity. The physician assessment will also include questions about prior medical diagnoses, co-morbid symptoms and the characteristics of vomiting, pain and nausea such as timing and triggers.

Symptom Information
Patients will complete the questionnaires as outlined above before application of the neurostimulator, after the first week of therapy and at the follow up clinic visit. They will also complete daily surveys. These instruments have demonstrated reliability and validity and have been used for both clinical and research purposes in both adult and pediatric populations. Up to one year after study completion, the investigators my conduct brief follow-up phone calls to subjects to assess long-term effects.

Medical Information
Information recorded for patients is part of clinical care and includes weight, height, vital signs, medications, gastrointestinal symptoms, early life events, family history, surgeries and other medical co-morbidities.

## G. RISK CATEGORY:

(2) 45 CFR 46.405 - Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child subjects involved in the research.

Overall risks/ discomforts involved are very minimal – Rare (event rate 1% - < 5%)

Possible risks/discomforts may involve:
a. Discomfort upon insertion of the electrodes for < 5 minutes - Rare (event rate 1% - < 5%)
b. Discomfort at the lead placement site > 5 minutes – Rare (1 % - < 5%)

c. Bleeding at the electrode site if the neurovascular bundle is penetrated - Rare (event rate 1% - < 5%)
d. Localized discomfort if the electrodes should become dislodged during the wearing of the device - Rare (event rate 1% - < 5%)
e. Localized dermatitis - Rare (event rate 1% - < 5%)
f. Drop in blood pressure - Rare (event rate 1% - < 5%)
g. Syncope (fainting) - Rare (event rate 1% - < 5%)

Adverse effects to supporting personnel
a. Skin piercing with percutaneous needles - Rare (event rate 1 % - < 5%)

Of note, in the recently completed neurostimulation trial for functional abdominal pain disorders, there were no serious adverse events. The rate of reported side effects were no different between the treatment and placebo groups. Of 115 subjects, n=10 (9%) reported the following side effects: ear discomfort (n=6; three treatment/three placebo), adhesive allergy (n=3; one treatment/two placebo) and syncope due to needle phobia (n=1; placebo).

## H. RISKS AND THE PRECAUTIONS WHICH WILL BE TAKEN TO MINIMIZE RISK EXPOSURE

**Safety Monitoring Plan**
All procedures will be performed by trained professionals within the standard of care under continuous medical supervision in the hospital setting (research unit). Side effects will be inquired about and documented every week during the study and at the post-study follow-up visit. Daily vomiting, pain and nausea ratings will be filled out by patients so this will be carefully monitored. If any serious harm or discomfort is identified by the subjects or the study personnel, the treatment will be discontinued. Any patient with worsening or no improvement in symptoms during the study will be able to drop out at any time and receive standard of care medical therapy. The skin of the external ear will be carefully disinfected to avoid any infection risks.

**Safety Analysis Plan**
There are no dangerous interventions related to this study, and the short study timeline allows for discontinuation of treatment when it is proven to be ineffective. Completion of psychometric questionnaires may be associated with mild distress in some participants. Because the questionnaires include assessment of patient psychosocial functioning, clinically significant symptoms that the patient or parent were unaware of may be brought to light.

Patient distress during questionnaire completion: If children/adults become distressed during completion of study questionnaires, they are instructed in the consent and assent forms to inform the researchers or nurse. The researchers/nurse will then contact the primary investigator who will place a referral to a psychologist.as necessary and as dictated by law (e.g., suspected child abuse/neglect) to ensure patient and family safety and to address psychosocial needs.

Patient/Parent report of clinically significant psychosocial or safety issues: Any child endorsing clinically significant psychological distress on questionnaire-reported screening measures will be referred to a psychologist. Regarding psychological screeners, research assistants will score the STAI-C questionnaires within a week of completion. Based on the normalized T-scores for the STAI-C S-anxiety scores (Table 2 in State-Trait Anxiety Inventory for Children Sampler Set Manual, Test Booklet and Scoring Key), any scores 2 or more standard deviations above 50[51] will be reported to the PI. In turn, the PI will discuss the results with the family and provide them with a referral to a licensed clinical psychologist as necessary.

## I. PROVISION FOR THE PROTECTION OF PRIVACY OF SUBJECTS AND TO MAINTAIN THE CONFIDENTIALITY OF DATA

Each subject will be assigned a unique identifying number which will be the only identifier listed on the questionnaires, neurostimulator kits and data collection forms. Each subject's identifying number and related electronic data will be kept on a secured, MCW password-protected database that provides access only to the PI and research staff. Only authorized research personnel will have access to the database. A separate secure database will have the subject identification number linked to the patient's name. The neurostimulator devices will be shipped directly from the manufacturer (Key Electronics) to the GI office research coordinator who will store the randomization scheme on a secure computer and label each package of 2 devices with a patient ID and serial number with a prepared sticker label. A subject folder will also be prepared and labeled with the same ID and kept together with the device package. The devices will be stored in a locked room in the division of gastroenterology. Only one kit at a time will be transported by a research coordinator to the pTRU. The remaining kits will be stored in the same locked room, labeled with the patient's ID. Only research coordinators within the division of gastroenterology will have access to the storage room. To track use and proper disposal of the devices, subjects will be asked to return the used device the following week (at time of the next stimulator placement or follow-up clinic visit). The RN or research coordinator will record that device was returned and dispose it properly.

## J. PROVISIONS FOR MONITORING DATA TO ENSURE THE SAFETY OF SUBJECTS; AND ADDITIONAL SAFEGUARDS TO PROTECT THE RIGHTS AND WELFARE OF SUBJECTS WHO ARE LIKELY TO BE VULNERABLE

The PI will monitor the health of all patients in the study per standard clinical practice. Dr. Kovacic will monitor protocol adherence and supervise data collection, entry, and analysis.

## K. ANTICIPATED BENEFITS ASSOCIATED WITH THE PROTOCOL TO HUMAN RESEARCH PARTICIPANTS AND SOCIETY

There are numerous, possible direct and long-term benefits to the subjects in this study. Our preliminary data on the EAD in adolescents with functional GI disorders is showing safety and high efficacy over placebo. For the first time, adolescents suffering from CVS have the opportunity to benefit from a non-pharmacological and non-invasive therapy without the adverse effects of multiple pharmacological agents that CVS patients depend on. The results of this study may provide important insights to the medical field regarding a poorly characterized group of patients and the underlying mechanisms. Most importantly, this study may shed light on a new, non-pharmacologic therapy that could improve quality of life for patients suffering from a debilitating condition with very few treatment options.

## L. STOPPING POINTS THAT WOULD NOT ALLOW THE STUDY TO CONTINUE AS PROPOSED

Stopping points for the study include achieving adequate information on enough of the goal subjects, unanticipated adverse events, inability to obtain enough data or patients/caregivers electing to discontinue the study.

**Reporting Adverse Events and Unanticipated Problems**

Expected adverse events that are not serious will be reported on the Continuing Review Progress Report. Continuing Review will be performed on a 12-month cycle, starting at time of protocol's initial approval. More frequent progress reports will be submitted at the request of the IRB.

Serious Adverse Events: The PI, within 24 hours, will report all serious adverse events occurring in any enrolled subjects to the IRB. Unexpected (but not serious) adverse events occurring in enrolled subjects which, in the opinion of the PI, are possibly related to participation in the protocol will be reported by the PI within 5 working days to the IRB.

Unanticipated problems involving risks to subjects or others will be reported to the IRB within 24 hours.

**M. IS THERE A DATA SAFETY MONITORING BOARD IN PLACE? WHO ARE IT'S MEMBERS? HOW OFTEN DO THEY MEET?**

As this is a low risk protocol, no data safety monitoring board will be appointed unless requested.

**N. DESCRIBE HOW THE CONSENT PROCESS WILL TAKE PLACE. INCLUDE A LIST OF APPROPRIATELY TRAINED PERSONNEL WHO WILL BE INVOLVED.**

Written informed consent for participation will be obtained from the adult subjects and from parents and children for their child's participation. Written assent will be obtained from youth between 10 and 13 years of age using the CHW assent form. Patients ages 14 and above will sign the assent line on the consent form per CHW policy. Consent will be obtained by a study investigator or member of the research team at the patients' appointment in the GI Clinic. Volunteers' consent will allow for accessing information collected for program evaluation/clinical purposes. Participating children and parents will have the option of having the consent/assent document read aloud to them to facilitate understanding. Copies of signed consent/assent documents will be given to participants.

Patients who turn 18 years of age while participating in this study will be re-consented. The consenting process will be conducted by the PI or a member of the research team.

**O. PROCEDURES TO BE EMPLOYED IN ANALYZING DATA AND THE ANTICIPATED SIGNIFICANCE OF THE PROPOSED STUDY**

Analyses will be conducted with SPSS and SAS software programs. Probability levels of $< .05$ will be used as cut offs for statistical significance.

The key significance of this study is the identification of a successful, non-invasive therapy for pain-related CVS that can give clues to underlying physiology and individual physiological and susceptibility factors, making the enrollment of appropriate study participants critical. We expect to be able to show if neurostimulation is effective for CVS. With this study, we hope to lay the foundation for the application of auricular neurostimulation for CVS. This is an innovative and novel treatment approach, which will enhance our knowledge on the brain-gut neural connectivity underlying functional disorders and ultimately improve patient care.

**P. FINANCIAL RELATIONSHIPS**

The EAD devices will be purchased by the distributing company (IHS) at the manufacture rate.

**Q. ADVERTISEMENTS / FLIERS**

N/A

**R. BIBLIOGRAPHY**

1. Youssef NN, Murphy TG, Langseder AL, Rosh JR. Quality of life for children with functional abdominal pain: a comparison study of patients“ and parents” perceptions. *Pediatrics*. 2006;117(1):54–59.

2. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. *Gastroenterology*. 2016;150(6):1456-1468.

3 Li, B., Lefevre, F., & Chelimsky, G. G. (2008). North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *Journal of Pediatric …*.

4. Li BU, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. *Adv Pediatr*. 2000;47:117–160.

5. Venkatesan, T., Tarbell, S., Adams, K., McKanry, J., Barribeau, T., Beckmann, K., et al. (2010). A survey of emergency department use in patients with cyclic vomiting syndrome. *BMC Emergency Medicine*, *10*, 4. http://doi.org/10.1186/1471-227X-10-4

6. Korterink, J. J., Rutten, J. M. T. M., Venmans, L., Benninga, M. A., & Tabbers, M. M. (2015). Pharmacologic treatment in pediatric functional abdominal pain disorders: a systematic review. *The Journal of Pediatrics*, *166*(2), 424–31.e6. http://doi.org/10.1016/j.jpeds.2014.09.067

7. Andrews PL, Davis CJ, Bingham S, Davidson HI, Hawthorn J, Maskell L. The abdominal visceral innervation and the emetic reflex: pathways, pharmacology, and plasticity. *Can J Physiol Pharmacol*. 1990;68(2):325–345.

8. Babic T, Browning KN. The role of vagal neurocircuits in the regulation of nausea and vomiting. *Eur J Pharmacol*. 2014;722:38–47.

9. Multon S, Schoenen J. Pain control by vagus nerve stimulation: from animal to man...and back. *Acta Neurol Belg*. 2005;105(2):62–67.

10. Zurowski D, Nowak Ł, Wordliczek J, Dobrogowski J, Thor PJ. Effects of vagus nerve stimulation in visceral pain model. *Folia Med Cracov*. 2012;52(1-2):57–69.

11. Abu-Arafeh I, Russell G. Cyclical vomiting syndrome in children: a population-based study. Journal of Pediatric Gastroenterology and Nutrition. 1995 Nov.;21(4):454–458.

12. Ertekin V, Selimo lu MAE, Altnkaynak S. Prevalence of Cyclic Vomiting Syndrome in a Sample of Turkish School Children in an Urban Area. Journal of Clinical Gastroenterology. 2006 Nov.;40(10):896–898.

13. Bhandari, S. and T. Venkatesan (2017). "Clinical Characteristics, Comorbidities and Hospital Outcomes in Hospitalizations with Cyclic Vomiting Syndrome: A Nationwide Analysis." Digestive Disease Science. 2017; 62 (8): 2035-2044.

14. Tarbell, S. E., & Li, B. U. K. (2013). Health-related quality of life in children and adolescents with cyclic vomiting syndrome: a comparison with published data on youth with irritable bowel syndrome and organic gastrointestinal disorders. *The Journal of Pediatrics*, *163*(2), 493–497.

15. Fleisher DR, Gornowicz B, Adams K, Burch R, Feldman EJ. Cyclic Vomiting Syndrome in 41 adults: the illness, the patients, and problems of management. *BMC Med*. 2005;3:20.

16. Khasawinah, T. A., Ramirez, A., Berkenbosch, J. W., & Tobias, J. D. (2003). Preliminary Experience With Dexmedetomidine in the Treatment of Cyclic Vomiting Syndrome. *American Journal of Therapeutics*, *10*(4), 303.

17. Symon, D. N. K., & Russell, G. (1995). The Relationship Between Cyclic Vomiting Syndrome and Abdominal Migraine. *Journal of Pediatric Gastroenterology and Nutrition*, *21*, S42.

18. Zaki, E. A., Freilinger, T., Klopstock, T., Baldwin, E. E., Heisner, K., Adams, K., et al. (2009). Two common mitochondrial DNA polymorphisms are highly associated with migraine headache and cyclic vomiting syndrome. *Cephalalgia*, *29*(7), 719–728. http://doi.org/10.1111/j.1468-2982.2008.01793.

19. Silberstein, S. D. (2015). Preventive Migraine Treatment. *Continuum (Minneapolis, Minn.)*, *21*(4 Headache), 973–989.

20. Hejazi, R. A., Lavenbarg, T. H., Pasnoor, M., Dimachkie, M., Foran, P., Herbelin, L., & McCallum, R. W. (2011). Autonomic nerve function in adult patients with cyclic vomiting syndrome. *Neurogastroenterology & Motility*, *23*(5), 439–443. http://doi.org/10.1111/j.1365-2982.2011.01679.x

21. Abell TL, Adams KA, Boles RG *et al.* Cyclic vomiting syndrome in adults. *Neurogastroenterol Motil* 2008; **20**: 269–84.

22. TachéY(1999) Cyclic vomiting syndrome: the corticotropin-releasing-factor hypothesis. *Dig Dis Sci* 44 (Suppl 8): 79S–86S

23. Marcus S, Agjabe-Williams M, Grigoriadis DE, Chatzaki E, Malany S, Tache Y, Zimmerman D and BUK Li. Corticotropin-releasing factor, adrenocorticotropin hormone and cortisol levels are elevated during episodes of cyclic vomiting syndrome. Gastroenterology 2006;43:A4.

24. Goadsby, PJ, Lipton RB, Ferrari, MD. Migraine. Current Understanding and Treatment. *N Engl J Med* 2002;346:257- 270.

25. Goadsby PJ, Zagami AS, Lambert GA. Neural processing of craniovascular pain: a synthesis of the central structures involved in migraine. *Headache*. 1991;31(6):365-371.

26. Weiller C, May A, Limmroth V, et al. Brainstem activation in spontaneous human migraine attacks. *Nat Med*. 1995;1(7):658-660.

27. Chelimsky, T. C., & Chelimsky, G. G. (2007). Autonomic Abnormalities in Cyclic Vomiting Syndrome. *Journal of Pediatric Gastroenterology and Nutrition*, *44*(3), 326–330. http://doi.org/10.1097/MPG.0b013e31802bddb7

28. Venkatesan, T., Prieto, T., Barboi, A., Li, B., Schroeder, A., Hogan, W., et al. (2010). Autonomic nerve function in adults with cyclic vomiting syndrome: a prospective study. *Neurogastroenterology & Motility*, *22*(12), 1303–e339. http://doi.org/10.1111/j.1365-2982.2010.01577.x

29. H, R., TL, A., BO, F., & S, C. (1999). Autonomic function in cyclic vomiting syndrome and classic migraine. *Digestive Diseases and Sciences*, *44*(8 Suppl), 74S–78S.

30. Cheng P, Shih W, Alberto M, Presson AP, Licudine A, Mayer EA, Naliboff BD, Chang L. Autonomic response to a visceral stressor is dysregulated in irritable bowel syndrome and correlates

with duration of disease. Neurogastroenterology & Motility. 2013;25(10):e650–e659.

31. Stewart JM. Autonomic Nervous System Dysfunction in Adolescents with Postural Orthostatic Tachycardia Syndrome and Chronic Fatigue Syndrome Is Characterized by Attenuated Vagal Baroreflex and Potentiated Sympathetic Vasomotion. Pediatric Research. 2000;48(2):218–226.

32. Tarbell SE, Shaltout HA, Wagoner AL, Diz DI, Fortunato JE. Relationship among nausea, anxiety, and orthostatic symptoms in pediatric patients with chronic unexplained nausea. Experimental Brain Research. 2014:232(8):2645-50.

33. Chelimsky G, Madan S, Alshekhlee A, Heller E, McNeeley K, Chelimsky T. A comparison of dysautonomias comorbid with cyclic vomiting syndrome and with migraine. Gastroenterology Research and Practice. 2009;2009:1-6.

34. Sullivan SD, Hanauer J, Rowe PC, Barron DF, Darbari A, Oliva-Hemker M. Gastrointestinal symptoms associated with orthostatic intolerance. Journal of Pediatric Gastroenterology and Nutrition. 2005;40(4):425–428.

35. Manabe N, Tanaka T, Hata J, Kusunoki H, Haruma K. Pathophysiology underlying irritable bowel syndrome--from the viewpoint of dysfunction of autonomic nervous system activity. Journal of Smooth Muscle Research. 2009;45(1):15–23.

36. Tarbell, S., & Li, B. U. K. (2008). Psychiatric symptoms in children and adolescents with cyclic vomiting syndrome and their parents. *Headache*, *48*(2), 259–266. http://doi.org/10.1111/j.1526-4610.2007.00997.x

37. Tarbell, S. E., & Li, B. U. K. (2015). Anxiety Measures Predict Health-Related Quality of Life in Children and Adolescents with Cyclic Vomiting Syndrome. *The Journal of Pediatrics*, *167*(3), 633–8.e1. http://doi.org/10.1016/j.jpeds.2015.05.032

38. Bohotin C, Scholsem M, Multon S, Martin D, Bohotin V, Schoenen J. Vagus nerve stimulation in awake rats reduces formalin-induced nociceptive behaviour and fos-immunoreactivity in trigeminal nucleus caudalis. *Pain*. 101(1–2):3–12.

39. Multon S, Schoenen J. Pain control by vagus nerve stimulation: from animal to man...and back. *Acta Neurol Belg*. 2005;105(2):62–67.

40. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biological Psychiatry*. 47(4):276–286.

41. Hord ED, Evans MS, Mueed S, Adamolekun B, Naritoku DK. The effect of vagus nerve stimulation on migraines. *J Pain*. 2003;4(9):530–534.

42. Sedan, O., Sprecher, E., & Yarnitsky, D. (2005). Vagal stomach afferents inhibit somatic pain perception. *Pain*, *113*(3), 354–359. http://doi.org/10.1016/j.pain.2004.11.012

43. Jensen, R. A., Clark, K. B., Naritoku, D. K., Smith, D. C., & Browning, R. A. (1999). Enhanced recognition memory following vagus nerve stimulation in human subjects. *Nature Neuroscience*, *2*(1), 94–98. http://doi.org/10.1038/4600

44. Therapeutic mechanisms of vagus nerve stimulation. (2002). Therapeutic mechanisms of vagus nerve stimulation.

45. Peuker ET, Filler TJ. The nerve supply of the human auricle. Clin Anat. 2002;15(1):35–37.

doi:10.1002/ca.1089.

46. Babygirija R, Sood M, Kannampalli P, Sengupta J, Miranda A. Percutaneous Electrical Nerve Field Stimulation Modulates Central Pain Pathways and Attenuates Post-Inflammatory Visceral and Somatic Hyperalgesia in Rats. Neuroscience 2017; 356: 11–21.

47. Miranda A, Taca A. Neuromodulation with percutaneous electrical nerve field stimulation is associated with reduction in signs and symptoms of opioid withdrawal: a multisite, retrospective assessment. The American Journal of Drug and Alcohol Abuse. 2017;39(2):1–8.

48. Nestler EJ. Is there a common molecular pathway for addiction? Nature Neuroscience. 2005;8(11):1445–1449.

49. Palsson OS, Whitehead WE, van Tilburg MAL, Chang L, Chey W, Crowell MD, Keefer L, Lembo S, Rao S, Parkman H, Sperber A, Spiegel B, Tack J, Vanner S, Walker L, Whorwell P, Yang Y. Rome IV Diagnostic Questionnaires and Tables for Investigators and Clinicians. *Gastroenterology*. 2016;150(6):1481-1491.

50. Rhodes VA, McDaniel RW. The Index of Nausea, Vomiting, and Retching: a new format of the lndex of nausea and vomiting. *Oncol Nurs Forum* 1999; 26:889-93.

51. Baxter AL, Watcha MF, Baxter WV, Leong T, Wyatt MM. Development and validation of a pictorial nausea rating scale for children. *Pediatrics*. 2011;127(6):e1542–e1549.

52. Spielberger CD. *State Trait Anxiety Inventory for Children*. 1973.

53. Kashikar-Zuck, S., Carle, A., Barnett, K., Goldschneider, K. R., Sherry, D. D., Mara, C. A., DeWitt, E. M. (2015). Longitudinal evaluation of Patient Reported Outcomes Measurement Information Systems (PROMIS) measures in pediatric chronic pain. Pain, 157(2), 339-347.

54. Walker LS, Greene JW. The Functional Disability Inventory: Measuring a Neglected Dimension of Child Health Status. *J Pediatr Psychol*. 1991;16(1):39–58.

55. http://www.medical-outcomes.com/index/sds56.

56. Juniper E, Guyatt G, Willan A, Griffith L. Determining a minimal important change in a disease-specific quality of life questionnaire. *Journal of Clinical Epidemiology*. 1994;47(1):81–87.