PROJECT TITLE: **Effectiveness of Electrical Neurostimulation as an Opioid-Sparing Alternative in the Treatment of Cyclic Vomiting Syndrome.**	
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Aims and Objectives (limit - 1 page)

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder (FGID) characterized by episodic nausea, vomiting and severe abdominal pain in majority (80%) of patients. Most patients also have a migraine headache, photophobia, phonophobia and lethargy during an episode. The pathophysiology of CVS is not known but is thought to be a migraine diathesis given the overlap between the two syndromes. Various factors such as mitochondrial DNA polymorphisms, genetic variants in the cannabinoid receptor genes and and calcitonin gene-related peptide (CGRP) are thought to play key roles.

CVS is common and affects 2% of the population in the US. The disorder is disabling, and healthcare costs associated with CVS hospitalizations in adults are staggering, amounting to $200 million dollars bi-annually. Due to sub-optimal therapies, hospitalized patients are usually treated empirically with IV fluids, anti-emetics, benzodiazepines and opioids for the intense abdominal pain. Unfortunately, opiate therapy in CVS is fraught with problems and is a risk factor for recurrent hospitalizations (preliminary data) as well as non-response to prophylactic therapy. Additionally, use of opioids is associated with dependence, withdrawal, addiction, overdose and even death. Hence, there is a critical need for safe, opiate-sparing strategies to treat pain associated with CVS episodes. Neurostimulation via a novel auricular percutaneous electrical nerve field stimulation (PENFS) device has recently emerged as a safe and non-invasive therapy for the treatment of pain, nausea and vomiting disorders. This therapy was recently FDA-approved for the symptoms of opioid withdrawal. Preliminary data indicates that PENFS modulates peripheral vagal nerve signaling, likely also modulating the trigeminal pathway from the external ear to the brainstem.

We hypothesize that 1) **PENFS is a safe, non-invasive opioid-sparing** alternative therapy **for the severe abdominal pain,** nausea and vomiting associated with CVS. We also hypothesize that 2) PENFS **reduces length of stay (LOS), and improves patient satisfaction.** ***We propose the following specific aim:***

Aim 1. Investigate the efficacy of PENFS compared to a sham in hospitalized patients with CVS

Objective 1:

a. Demonstrate reduction in abdominal pain, nausea and vomiting using validated tools.
b. Obviate or reduce the need for opioids.
c. Reduce length of hospital stay and improve patient satisfaction.

This approach will specifically **address the current opioid problem using a novel, non-invasive neurostimulation therapy with proven efficacy for opioid withdrawal. Long-term, it may** improve health care outcomes and significantly reduce overall health care costs.

(A) Significance

Cyclic vomiting syndrome (CVS) is a chronic functional gastrointestinal disorder (FGID) that is characterized by episodic nausea, vomiting and abdominal pain and is a significant health care problem.[1, 2] It affects 2% of the U.S. population and imposes an enormous burden on patients and the health care system.[3] Due to the recalcitrant nature of the disease, patients have high rates of health care utilization with multiple emergency department visits and hospitalizations. These in turn lead to school and work absenteeism, job loss, divorce, and disability.[4] The economic impact of CVS is staggering amounting to > $200 million over 2 years, based on a nationwide study.[5]

CVS is associated with multiple comorbid conditions such as migraine headaches, autonomic dysfunction, anxiety and depression, which further contribute to disease severity. A personal and family history of migraine is present in 87% of patients.[6,7] CVS is considered a migraine equivalent given the striking similarities between the two disorders such as periodicity, response to medications like amitriptyline and triptans and common symptoms such as nausea, vomiting, photo- and phono-sensivtivity[8]. Both migraine and CVS are also triggered by sleep deprivation and stress.[9] A recent brain imaging study demonstrates similarities in functional connectivity of the insular region in CVS and migraine, further solidifying the link between these disorders[10]. These data suggest that *CVS and migraine share similar pathophysiology* and potential for a common therapeutic avenue.

Opioid use in CVS and the critical need for opioid sparing therapy

Given the lack of knowledge about pathophysiology and evidence-based therapies, patients are often hospitalized to treat symptoms of CVS. During an episode, patients present with severe vomiting and abdominal pain and are treated empirically with IV fluids, antiemetics, benzodiazepines, and opioids. Estimates of opioid use range from 23%-27% in adults with CVS.[4, 11] Patients are often dissatisfied with the level of analgesia as recurrent opioid use results in tolerance and dependence. This often undermines the physician-patient relationship and patients even leave against medical advice out of frustration with what they perceive as ineffective care.[5, 12] This can lead to worse outcomes including recurrent hospitalizations, morbidity and increased health care costs.

Preliminary data from a study by our group reveals that of 101 patients hospitalized with CVS at Froedtert Hospital, chronic opioid therapy is associated with a two-fold increased risk of hospitalization (RR 2.22, CI 1.1-4.4, P=0.02) and three-fold increase in hospital length of stay (LOS) (RR 3.43, CI 1.26-9.34, P=0.01).[13] In a study of 132 CVS patients, opioid use was associated with non-response to amitriptyline (53% vs 15%, $p<0.05$), a prophylactic therapy used in CVS.[14] This in turn was associated with increased frequency and duration of CVS episodes per year and increased number of hospitalizations/emergency

department (ED) visits at baseline (18% vs 15.2%, p<0.05). *Hence there is an urgent need for an opioid-sparing, non-invasive strategy to treat CVS symptoms.*

In summary, CVS is common and disabling and is associated with significant health care costs. Much of this burden can be tied to iatrogenic opioid overuse, resulting in chronic opioid use and high risk of addiction and health care utilization. Understanding the pathophysiology of CVS and development of novel therapies are urgently needed. Further, similar to other disorders with rampant opioid use, **there is a critical need for opioid-sparing therapy in CVS to negate the devastating short and long-term effects of opioid use**. Our proposed project using a novel, non-invasive device to treat CVS will also address the current opioid crisis.

Auricular neurostimulation: a novel treatment modality in CVS

The major role of the arousal neurocircuitry in nausea and vomiting is well established.[15, 16] Similar to migraines, stress and neuronal excitability may trigger CVS episodes. Various neurostimulation modalities have emerged as therapy for gastrointestinal disorders and migraines but most options are invasive.[17, 18] The effects are believed to be mediated via increased vagal afference to the brainstem nucleus tractus solitarius (NTS) and modulation of the trigemino-autonomic reflex, influencing higher cortex.[19-21] Tracing studies confirm that the ear contains branches of four cranial nerves (CN V, VII, IX, X) that project to the NTS, providing a conduit for stimulation of NTS[22, 23]. Animal and human data show that transcutaneous stimulation of the vagus nerve (CN X) in the ear transmits signals to the NTS and improves migraine, presumably via modulation of trigemino-cervical complex (TCC).[24, 25] Neuroimaging studies show that this therapy modulates brainstem and limbic brain regions such as the amygdala, a region involved in stress and fear signaling.[26, 27] This arousal network is activated by perturbation of homeostasis[28] such as in stress-triggered CVS. Auricular neurostimulation may thus alter emetic signals through NTS activation, modulating the TCC and limbic regions.

Fig 1: Bridge device

More recently, the Bridge device, a non-invasive percutaneous electrical nerve field stimulation (PENFS) applied to the external ear, has demonstrated efficacy in treating pain, nausea and vomiting in opioid addiction (Fig. 1).[29] A large, randomized sham-controlled trial also demonstrated significant improvement in abdominal pain, well-being and disability in adolescent FGIDs.[30] Based on neuronal tracing studies, PENFS likely modulates the vagus and the trigeminal nerves which project to the external ear.[22, 23] Branches of these nerves converge in the brainstem NTS and signal to higher brain regions (amygdala, hypothalamus). Recent data has also shown that PENFS modulates neurons of the central amygdala and improves visceral sensitivity in an animal model.[31] *We propose that the neurostimulation of cranial nerves through the PENFS device will alleviate*

CVS symptoms by modulating the neurocircuitry pathway involved in the pathogenesis of the disease.

B) Innovation, Novel Technology and/or Novel Approach

PENFS: a novel technology for the treatment of CVS
The Bridge device (PENFS) is a novel technology that is designed to treat pain and also improves other symptoms such as nausea and vomiting. The Bridge device has recently been approved by the FDA for treating opioid withdrawal symptoms including pain, nausea, vomiting, insomnia and agitation.[32] Most recently, it has also been shown to be a safe and effective therapeutic option for adolescents with abdominal pain-related functional gastrointestinal disorders, resulting in reduction in abdominal pain and global symptom imrovement.[30] *If our study shows the efficacy of the Bridge device compared to sham in mitigating pain, nausea and vomiting, it will have the potential to transform the clinical care of CVS patients with the advent of an innovative, opiate sparing, non-invasive technology.* Further, our purposed device through its effectiveness in resolution of symptoms will improve *patient satisfaction*, reduce hospital LOS and overall health care costs. *More importantly, it will address the current opioid crisis that affects patients with CVS and potentially can be applied to other chronic disorders associated with pain.*

In summary, our study attempts to **shift the current clinical practice paradigm** in CVS and enhance our understanding of the pathophysiology through the use of PENFS device as a novel, non-invasive **approach in mitigating the detrimental effects from opioids** in CVS. Additionally, this device can also be used in the treatment of other chronic pain disorders.

(C) Approach, Feasibility, and Environment

Aim 1: Investigate the efficacy of PENFS in adults admitted with cyclic vomiting syndrome

Methods
Inclusion/Exclusion Criteria. We will enroll 80 adults between the ages of 18-65 years with a diagnosis of CVS (based on Rome IV diagnostic criteria).[33] This study will only include patients who are admitted to Froedtert Hospital with an episode of CVS. Exclusion

criteria includes developmental delays, non-English speaking patients, pregnancy, any implanted electrical device or any significant dermatological/infectious condition of the ear.

Randomization. Subjects will be randomized to the intervention group (receiving the Bridge device) or control group (receiving an identical sham device lacking electrical charge) in 1:1 ratio. The auricular neurostimulator device will be placed on the subject's ear upon presentation to the hospital. The device delivers low voltage (3.2), continuous stimulation for 5 days (around the clock) in alternating frequencies (1-10Hz) with an impulse interval of 100ms/2 sec. The neurostimulators (for both treatment arms) will be placed by a certified MD/APP/RN inside the patient's room. All patients will be allowed to receive rescue medications after implantation of the device if the symptoms do not improve with the device or at patient's request.

We have performed a sample size calculation based on prior data. At a significance level of 0.05 and 80% power, we estimate a sample size of 40 participants per group to detect the minimum standardized effect size of 0.64 using two-sided tests, using prior data. We will compare the different variables (average daily reduction in abdominal pain, nausea/vomiting scores, average daily use/frequency/dosage of rescue medications (opiates, antiemetics and sedatives between PENFS vs sham device.

Outcomes. Primary outcome will include the change in abdominal pain and concurrent opioid use. Abdominal pain will be assessed daily through Visual Analog Scale with the score ranging from 0 to 10, with 0 being the least and 10 being the worst pain. The need for opiates will be assessed through- (a) the time taken by the subject from the time of admission to the first felt need accompanied by the actual administration of opiates (IV hydromorphone or morphine), (b) daily frequency and total dosage of opiates received. Secondary outcomes will include- (a) severity of daily nausea and vomiting assessed through the Index for Nausea, Vomiting and Retching (INVR); (b) the need for other rescue medications (which include antiemetics like ondansetron, promethazine & metoclopramide; benzodiazepines like lorazepam; antihistaminics like diphenhydramine, etc.), (c) hospital LOS and (d) survey on patient satisfaction. While all other outcomes will be assessed daily, LOS and patient satisfaction will be assessed at the time of discharge (Table 1). All variables will be compared between the subjects in intervention arm versus control arm.

We hypothesize that PENFS will effectively mitigate the abdominal pain, nausea and vomiting associated with CVS episodes, obviate or reduce the need for opiates and simultaneously improve healthcare outcomes including LOS and patient satisfaction.

Table 1. Study Protocol

	Admission (0 hours)	2 hours post - placement	24 hrs.	Daily	5 days*	Discharge
Screening & Consent	x					

Demographics	**x**					
Neurostimulator (PENFS) vs sham	**x**	**x**	**x**	**x**	**x**	
Rome IV questionnaire[33]	**x**					
INVR (vomiting scale; daily during therapy)[34]	**x**	**x**	**x**	**x**	**x**	**x**
Abdominal pain (Visual Analogue Scale)	**x**	**x**	**x**	**x**	**x**	**x**
Need for opiates and other rescue medications	**x**	**x**	**x**	**x**	**x**	**x**
Length of stay						**x**
Patient Satisfaction Survey						**x**

INVR=Rhodes Index of Nausea, Vomiting & Retching; CGRP= Calcitonin Gene-Related Peptide
** questionnaires will be completed as an outpatient if patient is already discharged*

Statistical Analysis: Summary statistics, such as mean, median, standard deviation and range will be used as a first step to examine data. To satisfy parametric assumptions, we may perform transformations with justifications if possible and otherwise use non-parametric tests. For any binary outcomes, we will use Chi-square or Fisher's exact tests to compare the proportions between the two groups. We will compare the different variables (average daily reduction in abdominal pain, nausea/vomiting scores, average daily use/frequency/dosage of rescue medications (opiates, antiemetics and sedatives) between PENFS vs sham device.
Data analyses will be performed using SAS version 9.4 (SAS institute, Cary, NC).

Potential Pitfalls: This pilot data is both safe and non-invasive and will help us better understand the pathophysiology underlying CVS symptoms. The proposed device is non-invasive and currently utilized at our institution. The PI is certified in the PENFS placement and has already used it in some of her patients with success. We thus expect no feasibility or safety issues. Potential risks generally would include bleeding or infection at the puncture site, pain at the application site, or skin irritation at the site of application.

Feasibility: Recruitment should not pose a problem as the PI (Dr. Venkatesan) has the largest cohort of patients with CVS in the nation. Further in our experience, CVS sufferers are also highly motivated to enroll in studies and trial new therapies The PI also works closely with the Cyclic Vomiting Syndrome Association, who will advertise the study on their website and

through email and supports this project. Co-PI (Dr. Bhandari) and Dr. Kovacic have worked extensively with the PI and published collaboratively in the field. Dr. Segon, the Section Chief, along with Dr. Bhandari, both hospitalists, are aware and will oversee all the logistics regarding the admissions and the study, as CVS patients are typically admitted under Hospitalist service. In a recent neurostimulation trial conducted by Dr. Kovacic, a high degree of compliance and a low dropout rate (12%) was observed despite a sham-controlled study design. Patient satisfaction with this non-pharmacological therapy was extremely high.

In summary, this proposal will evaluate a novel, safe and non-invasive therapy for a debilitating and prevalent disorder with few established treatment options. Demonstrating that this therapy is effective in treating and preventing CVS via neuromodulation will allow us to apply for extramural funding and expand our studies to a larger number of CVS patients and possibly other conditions.

(D) Special Emphasis

Patients who are admitted to the hospital with a CVS episode typically suffer from intense abdominal pain.[35] Opiates with anxiolytic properties are therefore particularly effective in controlling symptoms in patients with CVS. Consequently, patients admitted with a CVS episode frequently require treatment with intravenous opioids. The addictive potential of narcotic pain medications is well known. As with other acute painful conditions, the use of opioids during a CVS episode may be followed by ongoing use of opioids. Also, withdrawal from opiates may be equivalent to a panic trigger for another exacerbation for a CVS episode. Therefore, patients are often reluctant to give up using opiates on an ongoing basis. Ongoing use of opioids in turn leads to disease coalescence with opioid dependence and withdrawal leading to recurrent episodes of CVS exacerbation.[11] Escalating use of opiates can also lead to narcotic bowel syndrome which is characterized by worsening bouts of abdominal pain induced by opioid-induced bowel dysfunction.[36]

The *main focus of our study is to replace the need for intravenous opiates during a CVS episode with a non-invasive and safe device* that can be placed with ease and does not require specific expertise.

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CTSI Support

The CTSI's infrastructure provides an optimal framework for accomplishing the aims of our study. This study will utilize number of CTSI research support services.

Our project involves collaboration between different CTSI member organizations, including the Medical College of Wisconsin ((PIs-Dr. Venkatesan, Dr. Bhandari) and Co-I-Dr. Segon), and Children's Hospital of Wisconsin (Dr. Kovacic). Through this unique consortium of CTSI member institutions, we will have the ability to share research resources, technology, knowledge, and expertise to achieve our project's goals.

The IRB reviewer of the CTSI will be consulted to assist in fulfilling the appropriate research regulatory requirements in order to accomplish the study in a safe and ethical manner. We will also utilize the services of the translational research unit (TRU) and the Clinical Trials Office (CTO) for sample collection and storage and assistance with coordination of various study related activities. These CTSI services, along with the inter-institutional collaboration fostered by the CTSI, are critical for the success of this project.

Project Timeline and Future Plans

Timeline – Provide a detailed timeline/project plan for the project. Project must demonstrate its ability to be completed in 12 months.

Dates	**Plan**	**Feasibility**
Feb-2019	Obtain IRB approval Working on logistics such as training personnel in placement of the device, communicating with/aligning hospitalists/ nurses regarding project	IRB submission in progress Dr. Ankur Segon is Chief of the Hospitalist Section and will assist with the logistics of conducting the study.
March 2019	Enroll 12 patients/month in the study (allowing for attrition rates)	Approximately 180 patients with CVS get admitted each year Dr Bhandari and Dr Segon including Hospitalist fellows will conduct the study
April 2019	Enroll 12 patients/month in the study (allowing for attrition rates)	Approximately 180 patients with CVS get admitted each year Dr Bhandari and Dr Segon including Hospitalist fellows will conduct the study
May-June 2019-	Analysis and data reporting	Statistician (Rebekah Walker) from DOM will provide statistical support.

Future Plans – Explain how pilot funding will be used for conducting research activities that will lead to future extramural grant funding (i.e. NIH, NSF) and ultimately to tangible clinical improvements.

This study will enable us to collect preliminary data to study the efficacy of this non-invasive device to treat pain and other symptoms in CVS and understand the underlying pathophysiology. We intend to submit **an R01 proposal for a larger multi-center to the NIH.** The PI, Dr. Venkatesan is currently chairing the committee that has been charged with developing guidelines for the management of CVS in adults in collaboration with the American Neurogastroenterology and Motility Society (ANMS), which is slated for

publication this year. As such, she has collaborative relationships with multiple faculty from various centers in the US and this will provide the framework for such multicenter trials.

This project aims to study the effectiveness of a safe and novel therapy and elucidate the pathophysiology of CVS will change the treatment paradigm from one of trial and error to an evidence-based approach. This will significantly improve the lives of many patients who suffer from this debilitating illness.