ACUTE AND LONG-TERM EFFECTS OF APP-DELIVERED HEARTFULNESS MEDITATION ON PSYCHOLOGICAL OUTCOMES AND THE ENDOCANNABINOID SIGNALING SYSTEM IN CYCLIC VOMITING SYNDROME

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Introduction

Cyclic vomiting syndrome (CVS) is a disorder of gut-brain interaction (DGBI) characterized by episodes of intense vomiting that are often triggered by stress. CVS affects 2% of the population and negatively impacts patients. Although gastrointestinal symptoms are prominent, most patients have comorbid anxiety, depression, and high degrees of psychological distress that adversely affect health-related quality of life (HRQoL) and patient outcomes. Further, stress is known to trigger episodes of CVS in ~ 80% of patients.(9) The exact mechanism of how stress influences the gut-brain axis in CVS is not clear. It is hypothesized that CVS is a disorder of allostatic dysregulation whereby multiple biopsychosocial factors including chronic stress, sleep deprivation, mood disorders and early life adversity can disrupt normal allostatic regulation and result in CVS episodes. CVS is likely multifactorial with a combination of genetic, environmental and neurohormonal factors that result in symptoms.

Nonetheless, it is crucial to address underlying stress and other psychological comorbidities that can drive symptoms and negatively impact influence overall HRQoL of these patients irrespective of typical measures of disease severity in CVS.(8) Recent guidelines recommend a biopsychosocial model of care incorporating techniques like meditation to mitigate stress and improve outcomes in CVS, but there are limited data to support this recommendation.

One such approach is Heartfulness meditation (HFM), which includes progressive relaxation with a concentrated focus on the heart to increase awareness of the present moment, reduce stress, and promote relaxation. HFM is a secular, guided meditation technique that is safe and offered free-of-charge. HFM has been shown to reduce perceived stress, and anxiety and improve well-being in normal subjects. Our overall objective was to determine the efficacy of HFM deliver via an app. The specific aims of our study are listed below.

Specific Aim 1a: Conduct a prospective study to elucidate the *acute effects* of HFN meditation on the ECSS in CVS. We will measure circulating endocannabinoids and related lipids immediately before and after HFN meditation.

1b: Correlate indices of ECSS with state anxiety and mood pre-and post-HFN meditation. We will measure state anxiety and mood with validated tools including the State Trait Anxiety Inventory (STAI) and Profile of Mood States (POMS) which evaluates tension, depression, anger, vigor, fatigue, and confusion.

Hypothesis: HFN meditation will acutely increase circulating endocannabinoids which will be correlated with a reduction in state anxiety and improvement in mood.

Specific Aim 2: Determine the *long-term effects* of a 6-week HFN meditation program on ECSS and correlate with psychological outcomes including psychological distress, STAI scores, sleep quality, and HRQoL. We will measure these outcomes with validated tools including the Brief Symptom Inventory (BSI), STAI, Pittsburgh Sleep Quality Index (PSQI), and PROMIS quality of life questionnaires.

Hypothesis: A regular HFN meditation practice over 6 weeks will further augment ECSS, and this will be result in an improvement in psychological outcomes such as psychological distress, sleep, mood and HRQoL.

Study protocol

This study was approved by the Institutional Review Board at the Ohio State University and registered with clinicaltrials.gov (Registration number: NCT05961995). All participants signed an informed consent prior to this 6-week single-arm study.

Development of the Heartfulness meditation app and meditation protocol.
We developed a HIPAA complaint smartphone application (app) for delivering HFM that was self-paced and convenient for patients to use. The meditation app was developed in conjunction with the Heartfulness Institute, a non-profit global organization that offers HFM free-of-charge and has certified instructors. A standard script was used for the instructional video and recorded with the help of a certified experienced Heartfulness instructor. App users were encouraged to complete a half-hour meditation session three times weekly throughout the six-week intervention period. he app is HIPAA compliant, collecting no personal identifying information, and monitored compliance by recording the number of sessions completed.

Inclusion and exclusion criteria
Patients aged 18-80 years diagnosed with CVS based on Rome criteria were eligible to participate. Exclusion criteria included: (1) Major psychiatric illness such as schizophrenia, bipolar disease, and major depression or anxiety that was *not* controlled with medication or requiring inpatient care within the past year; (diagnosis was made by the patient's primary care provider or psychiatrist) (2) history of suicidal attempt/ideation in the past year; (3) cognitive impairment that precluded the ability to meditate; (4) inability to sit for at least 30 minutes; (5) severe cardiopulmonary diseases, malignancy, or renal failure on dialysis; (6) organic gastrointestinal diseases or systemic diseases including but not limited to inflammatory bowel disease and chronic liver diseases; (7) pregnancy at the time of enrolment; (8) BMI < 18 or >35; (9) current regular cannabis use defined as use $\geq$ 4 times a week; and (10) significant prior meditation experience that included mindfulness, heartfulness, music therapy, and other forms of meditative movement practices like yoga and qi gong (continuous meditation practice for $\geq$ 3 months within the previous year).

Study outcomes
Primary outcomes
The primary outcomes were state and trait anxiety and mood states, measured using the State-Trait-Anxiety Inventory (STAI)(26) and Profile of Mood States (POMS) respectively.(27) The STAI has two 20-item subscales that measure the temporary emotional condition of "state anxiety" (STAI-S) and the long-standing personal characteristic of "trait anxiety" (STAI-T), respectively. The STAI-S evaluates amount of current feelings of apprehension, tension, nervousness, and worry. The POMS is a 35-item validated questionnaire that assesses mood across the 6 mood states of tension, depression, anger,

vigor, fatigue and confusion. These outcomes were measured immediately before and after a meditation session at baseline, at 3 weeks, and at the end of study (6 weeks).

Secondary outcomes

Psychological distress was measured using the Brief Symptom Inventory (BSI)(28). Health-related quality of life (PROMIS)(29), sleep quality (Pittsburgh Sleep Quality Index)(30) and coping (COPE)(31) were also measured with validated tools. These outcomes were all measured at baseline, weeks 3 and 6. Perceived intervention effectiveness was assessed with a visual analog scale (VAS) (from 0 = “not effective at all” to 10 = “most effective imaginable”) after intervention sessions at baseline and at end of study. All questionnaires were completed on REDCap, a secure online platform for conducting research.

Endocannabinoid concentrations and related lipids

Blood was collected for measurement of circulating endocannabinoid concentrations before and immediately after meditation sessions at baseline and at week 6 (first and last mediation sessions during the study). Serum concentrations of endocannabinoids *N*-arachidonylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) and related lipids *N*-oleoylethanolamine (OEA) and palmitoylethanolamide (PEA) were quantified by isotope dilution following measurement using atmospheric pressure, chemical ionization liquid chromatography/mass spectrometry (LC-APCI-MS).

Subjects completed the first and last meditation sessions at the clinical translational unit. These sessions were scheduled between 8 AM and 1 PM given diurnal variation in endocannabinoid concentrations. The remainder of the session were completed at home by subjects. All study questionnaires were completed at the beginning of the study (baseline), week 6 and 12.

Statistical analysis

Patient characteristics were summarized using means and standard deviations or medians and interquartile ranges for continuous variables, depending on the distribution of the data. Frequencies and relative frequencies were used to describe categorical patient characteristics. Changes in means for state and trait anxiety, mood states, health-related quality of life, daytime sleepiness, subscale scores and index scores of the BSI, and subscales scores of the COPE were examined over time (baseline, week 3, and week 6) using repeated measures ANOVA. Paired t-tests were used to compare means of state anxiety, total mood disturbance, visual analog scale scores, and levels of serum endocannabinoids and related lipids before and after HFM at baseline and before and after HFM at 6 weeks. Analyses were performed using SPSS version 28.0 (IBM SPSS, Armonk, NY). The level of significance for all analyses was $\alpha=0.05$.