Opioids, Cannabis, and Cyclic Vomiting Syndrome in Adults

James R. Lathrop

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2023

Reading Committee:

Margaret M. Heitkemper, Chair

Diana T. Buchanan

Kendra Kamp

Program Authorized to Offer Degree:

Nursing

University of Washington

Abstract

Opioids, Cannabis, and Cyclic Vomiting Syndrome in Adults

James R. Lathrop

Chair of the Supervisory Committee:

Margaret M. Heitkemper

Department of Biobehavioral Nursing & Health Informatics

Cyclic vomiting syndrome is a rare debilitating illness which is stereotypical to the patient, has an unclear etiology, no biomarkers for diagnosis, and a varied course of illness. The syndrome was first recognized in pediatric patients, and in that population the symptoms generally resolve in puberty, or in a sub-set of those patients continue on into adulthood as a migraine syndrome. Over the past few decades, however, adult cyclic vomiting syndrome has become increasingly recognized with an established set of diagnostic criteria and guidelines for treatment. However, these guidelines and treatment recommendations are based primarily on published case series data and expert opinions, with a very limited number of randomized clinical trials, as well as a correspondingly few systemic reviews or metanalysis of those trials. There have been no prospective longitudinal studies of adult cyclic vomiting patients, and only a few retrospective chart reviews. Overall, however, the gastroenterological literature has been successfully accumulating data around adult cyclic vomiting syndrome as something similar, but distinct from pediatric cyclic vomiting. Then, in 2004, a research group out of South Australia published a case series of 9 patients with chronic daily cannabis use and a relatively classic cyclic vomiting syndrome. They initially identified 19 similar cases, but 5 refused consent, and 5 were excluded

on the basis confounders. Of the remaining 9 patients, 8 displayed an affinity for hot water bathing during episodes of active illness, and 2 were able to remain illness free by abstaining from cannabis. They called their newly identified syndrome 'cannabinoid hyperemesis,' and the subsequent two decades the literature witnessed a significant publication interest in the syndrome. Cannabinoid hyperemesis coincided temporally with the decriminalization and legalization of recreational cannabis use in Europe and the Americas. Several elements around this first publication of cannabinoid hyperemesis are particularly interesting. First, the syndrome is counter-intuitive, as delta-9-tetrahydrocannabinol (the primary psychoactive molecule of the cannabis plant) has been a U.S. FDA approved pharmaceutical as an antiemetic and an appetite stimulant since 1985. Second, there was the peculiar behavior of hot water bathing reported in 90% of the sample. Third, the syndrome seemed to mimic cyclic vomiting syndrome. Finally, despite the severity and chronicity of illness expressed by these individuals with cannabinoid hyperemesis, only 2 out of 9 (22%) were able to successfully abstain from cannabis, the causative agent of their illness. Yet this is supported by the literature on cannabis use disorders which is replete with the difficulties in maintaining cannabis abstinence in patients who have fallen into problematic use. Significantly more information is needed on cannabinoid hyperemesis, cannabis use, and cyclic vomiting syndrome. This 2-paper dissertation moves the field of adult cyclic vomiting syndrome and cannabinoid hyperemesis (herein referred to as cannabis hyperemesis syndrome) forward. Presented first is an in-depth narrative review of literature involving both adult cyclic vomiting syndrome and cannabis hyperemesis syndrome. Second is a retrospective chart review (original research) describing the clinical characteristics of 130 cyclic vomiting patients seen at a specialty center within a tertiary care facility in the Pacific Northwest of the United States.

ACKNOWLEDGEMENTS

I would like to express my sincerest gratitude to my primary advisor and dissertation committee chairperson, Dr. Diana Buchanan for all of her constant guidance, immense support, and editorial skill as I pursued this doctoral work, and in particular for sticking with me over the several years this project lagged through the world-wide healthcare pandemic of COVID-19. In particular, a special note of thanks for helping me pull this final paper together even though she is no longer employed at the University due to an out-of-State move – Diana I have really enjoyed writing with you, and I hope, as we had discussed, that we might write together again on future work. Along with that I wish to deeply thank Dr. Margaret Heitkemper who provided the support, encouragement, and simple belief in me – at many times when I could not see myself finishing, she could see a finish for me and her belief in me kept me going. And, when it became necessary, Dr. Heitkemper picked up as my chair, like a final-quarter superstar, she was there to bring this across the goal line. Peg – thank you. You will never know the level of appreciation I have for the support you have provided me for many years now, going back to your employment of me as a research assistant in the mid 1990's, to this final graduation moment. These have been interesting times. A deep level of appreciation is also extended to Ken Pike for his statistical advice and guidance. And the same level of appreciation is poured on to both past and current committee members: Dr. Sheldon Rosen, Dr. Maria Pettinato, Dr. Gail Anderson, Dr. Kendra Kamp, and Dr. Megan Moore. Dr. Maria Pettinato, as a friend of mine from the early years of medicinal cannabis in Washington State, always planned join me in a paper. I'm saddened that it took me so long to finish that she moved away long before the writing of even the first manuscript of this project. Likewise, Dr. Gail Anderson agreed to be my GSR for so many years, and yet once I was actually moving forward it was time for her to retire as well. So, Dr. Megan

Moore graciously stepped in to give me the committee structure needed to finish. And, too, Dr. Kendra Kamp stepped in when I needed a new committee member and provided both the statistical guidance that I needed right at the end, as well as exceptional editorial support. And here I take pause and take a sincere moment to thank Dr. Shelly Rosen for bringing this project to me and for allowing me to critically investigate many years of his patient care at the UW Digestive Health Center. There is a particular confidence, and a vulnerability, to allow a PhD student unfettered access to your clinic notes and records. But more than that, Shelly, you also stood by me (albeit sometimes with personal frustration at my pace!) for the far too many years that this project took. I hope you are proud of the work I've put together, and I hope you find it to be an accurate representation of your unique and interesting cohort of CVS patients.

DEDICATION

I dedicate this work to the members of my personal life and academic circle who made the completion of this work possible. I love you **Christina Lathrop**, and thanks for being such an incredible mother to our wonderful kids: **Rachel**, **Rosa**, **Trinity**, and **Fox**. And a shout out and thank you to my very good friend, **Dr. Tom Wilkinson**, who has been one of the greatest cheerleaders in my life, like **Dr. Peg Heitkemper** and **Dr. Diana Buchanan**, his belief in me has given me that push and lift that I've needed during the toughest of moments.

Thank you all.

Table of Contents

CHAPTER 1: INTRODUCTION

This two-paper dissertation provides a snapshot in time of the current knowledge and treatment guidelines for adults with cyclic vomiting syndromes, including adult cyclic vomiting syndrome and cannabis hyperemesis syndrome, while also providing new information to the field.

Chapter two (manuscript one) provides a narrative review of the current state of the science for both cyclic vomiting syndrome (CVS) and cannabis hyperemesis syndrome (CHS) and is based on a thorough review of the literature citing 161 references (with 169 references in its published form, doi: 10.1097/SGA.0000000000000730) (Lathrop et al., 2023). This manuscript offers a few corrections to the literature as well as presents the first English translation of the earliest medical accounting of pediatric cyclic vomiting syndrome by Dr. H. CL. Lombard (Lombard, 1861). The world prevalence of CVS is explored within publication of The Global Epidemiology Study of Functional Gastrointestinal Disorders and appears to be approximately 1.2% world-wide (Sperber et al., 2021). Diagnostic criteria and current treatment options for CVS as well as CHS are presented, including experimental treatments (Carpenter et al., 2021; Valdovinos et al., 2020). Within the cannabis hyperemesis syndrome section, a table of the 125 known cannabinoids is provided, as well an overview of the cannabis plant and a brief evolutionary history of the mammalian endocannabinoid system is provided. A discussion of the major endocannabinoid ligands and receptors in humans is included. A hypothesis that the lack of CBD in modern high-potency THC cannabis may be contributory to the development of CHS in some individuals is proposed. In patients who are unwilling or unable to stop the consumption of cannabis (proposed within this manuscript as 'intractable CHS'), then the addition of CBD or changing the consumption from high potency THC products to a high CBD product has theoretical promise.

Chapter three (manuscript two) presents data from an original research study. This is a comprehensive retrospective chart review of 130 patients with an ICD-10 code of cyclic vomiting syndrome and a referral generated to Sheldon Rosen, MD. Since the beginning of his clinical tenure at the University of Washington Digestive Health Center (UW DHS) in early 2014, Dr. S. Rosen took a particular interest in CVS patients. Due to his willingness to take on this very challenging group of patients, he become the primary referral provider at the UW DHS for both new and ongoing patients during that time period (Rosen, 2019). Additionally, the UW Medical Center is the first hospital in the United States to receive seven consecutive magnet hospital designations in nursing (Donohue, 2022) while also earning a #1 hospital ranking in Washington State from U.S. News and World Report (Clements, 2018). Therefore, the UW DHS became a regional receiving clinic for challenging CVS patients, and these referral patients were scheduled with Dr. Rosen. This provided for a unique dataset of potentially complex CVS patients who were seen and treated in a consistent manner, and with a uniformity of documentation by a single provider between 2014 -2020. The primary aim of this study was to describe the characteristics and self-care behaviors, including cannabis and prescribed opioid use of an adult patient cohort with cyclic vomiting syndrome. Secondary aims were to examine cannabis and opioid use in relation to healthcare utilization, to explore the relationship of cannabis use with a morphine equivalent standardized dosing used by these patients, and to probe symptom coalescence as a potential component of adult cyclic vomiting syndrome. In addition to the gathering of demographic and medical history data, study variables were compared by four groups: 1) non-users, 2) cannabis-only users, 3) opioid-only users, and 4) patients who use both cannabis and opioids. The cohort included 31% men and 69% women with

a mean age of 41.6 years (SD = 15.6, range 19 – 84). Onset of symptoms ranged from early childhood to the later decades of life, while the mean time from onset of symptoms to diagnosis was 8.9 years (SD = 9.6). Partial relief of symptoms with hot water bathing was reported by 45% of the cohort, while 35% mentioned that sleep could terminate an episode. Comparison by opioid and cannabis use revealed a number of differences between the 4 groups. The cannabis-only consumers were 8 years younger than the other three groups (37.5 vs. 45.6, $p = 0.047$). There were more women in both opioid groups, with more men in the cannabis-only group ($p = 0.026$). A self-report of early-age cannabis use was more common in the cannabis-only group ($p = 0.003$), while history of opioid use disorder was more common in both opioid groups ($p = < 0.001$). A reported history of past abdominal surgery was reported in 21% of the sample, and this group was more represented in the opioids-only group ($p = 0.003$). A coalescent pattern was noted in 22% of the cohort, and this group was more likely to be not-employed ($p = 0.024$) and to have a reported history of opioid use disorder ($p = 0.028$). Among the coalescence group, 48% were prescribed routine opioids plus other medications, while 45% were using cannabis for their symptoms plus other non-opioid prescriptions. Supplemental material for this manuscript includes the data collection form (Appendix A), which has also been uploaded and made available for use within the REDCap consortium (Lathrop, 2023). Additionally, Appendix B provides a list of the excluded patients from the dataset, and Appendix C is a case series presentation of possible patients exhibiting possible coalescent CVS.

References

Carpenter, A., Levinthal, D. J., Binion, D. G., & Emerick, T. (2021). Improvement of Cyclic Vomiting Syndrome with Outpatient Ketamine Infusions. *Case Rep Gastroenterol*, *15*(1), 9-16. https://doi.org/10.1159/000510933

Clements, B. (2018). *U.S. News ranks UW Medical Center as best hospital in state*. UW Medicine | Newsroom. Retrieved Nov. 16, 2019 from https://newsroom.uw.edu/news/us-news-ranks-uw-medical-center-best-hospital-washington

Donohue, B. (2022). *UW Medical Center is 1st in the U.S. to earn nursing distinction*. UW Medicine | Newsroom. Retrieved May 30, 2023 from https://newsroom.uw.edu/news/uw-medical-center-1st-us-earn-nursing-distinction

Lathrop, J. R. (2023). *Cyclic Vomiting Syndrome (CVS) - Demographics - Patient Visit Record - Healthcare Utilization Data*. REDCap. Retrieved May 20, 2023 from https://redcap.vanderbilt.edu/consortium/library/search.php

Lathrop, J. R., Rosen, S. N., Heitkempter, M. M., & Buchanan, D. T. (2023). Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome, the State of the Science. *Gastroenterological Nursing*, *Preprint*.

Lombard, H. C. (1861). Description d'une névrose de la digestion, caratérisée par des crises périodiques de vommissements et une profonde modification de l'assimilation. *Gazette Médicale de Paris*, *20*, 312-314.

Rosen, S. (2019). Personal communication: Discussion of CVS patients available for study. In.

Sperber, A. D., Bangdiwala, S. I., Drossman, D. A., Ghoshal, U. C., Simren, M., Tack, J., . . . Palsson, O. S. (2021). Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology*, *160*(1), 99-114.e113. https://doi.org/10.1053/j.gastro.2020.04.014

Valdovinos, E. M., Frazee, B. W., Hailozian, C., Haro, D. A., & Herring, A. A. (2020). A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department. *J Clin Gastroenterol*, *54*(4), 327-332. https://doi.org/10.1097/MCG.0000000000001258

CHAPTER 2

Manuscript One

This manuscript has been published. Received August 8, 2022; accepted October 10, 2022.

This preprint paper is formatted is in style of Gastroenterological Nursing for peer review. The final print version of the paper is not submitted with this dissertation as it on copywrite embargo for one year from the date of publication: April 19, 2023 – April 19, 2024, online ahead of print.

"*Preprints of articles can be posted anytime and anywhere, including on scholarly collaboration networks (SCNs). If the article is accepted, to ensure that readers can find and cite the final published version, Wolters Kluwer encourages researchers to add the Digital Object Identifier (DOI) to the posted preprint version*"

doi: 10.1097/SGA.0000000000000730

Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome:

The State of the Science

[Preprint Version of doi: 10.1097/SGA.0000000000000730]

James R. Lathrop, DNP, FNP, PhD Candidate, School of Nursing, University of Washington, Seattle, WA

Sheldon N. Rosen, M.D., Clinical Associate Professor, Division of Gastroenterology, School of Medicine, University of Washington, Seattle, WA

Margaret M. Heitkemper, PhD, RN, FAAN, Professor and Elizabeth Sterling Soule Endowed Chair in Nursing, Department of Biobehavioral Nursing & Health Informatics, School of Nursing, University of Washington, Seattle, WA

Diana Taibi Buchanan, PhD, RN, Associate Professor and Mary S. Tschudin Endowed Professor of Nursing Education, Department of Biobehavioral Nursing & Health Informatics, School of Nursing, University of Washington, Seattle, WA

Mailing Address and Phone/Fax:
c/o Diana Buchanan, PhD, RN
Associate Professor, UW SoN
Box 357266, University of Washington
Seattle, WA 98195
Office: 206-818-5527
Fax: 206-543-3624

Conflicts of interest and source of funding: This work was performed for scholastic credit towards the completion of a PhD dissertation at the University of Washington, School of Nursing. The principal author reports current ownership of a cannabis retail business and reports previous ownership of a health clinic with a primary focus in providing medicinal cannabis authorizations. There have not been any grants or sources of funding for this project.

Abstract

This paper provides a narrative review of the state of the science for both cyclic vomiting syndrome and cannabis hyperemesis syndrome along with a discussion of the relationship between these two conditions. The scope of this review includes the historical context of these conditions as well as the prevalence, diagnostic criteria, pathogenesis, and treatment strategies for both conditions. A synopsis of the endocannabinoid system provides a basis for the hypothesis that a lack of cannabidiol in modern high-potency Δ^9-tetrahydrocannabinol cannabis may be contributory to cannabis hyperemesis syndrome and possibly other cannabis use disorders. In concluding assessment, though the publications addressing both adult cyclic vomiting syndrome and cannabis hyperemesis syndrome are steadily increasing overall, the state of the science supporting the treatments, prognosis, etiology, and confounding factors (including cannabis use) are of moderate quality. Much of the literature portrays these conditions separately and as such sometimes fails to account for the confounding of adult cyclic vomiting syndrome with cannabis hyperemesis syndrome. The diagnostic and therapeutic approaches are, at present, based generally on case-series publications and expert opinion, with a very limited number randomized control trials and a complete absence of Level 1 evidence within the cyclic vomiting literature overall as well as for cannabis hyperemesis syndrome specifically.

Introduction

Despite a century and a half of clinical advancement in gastroenterological care since cyclic vomiting syndrome (CVS) was first identified within the literature, this rare yet debilitating condition remains an enigma in both etiology and cure (Hasler et al., 2019; Lombard, 1861). CVS is an uncommon condition with an onset either in childhood or adulthood and, when children are affected, the syndrome classically resolves around puberty. With adult-onset CVS, the broad differential of nausea, vomiting, and abdominal pain is a complex presentation which contributes to a delay in diagnosis (often years). This diagnostic delay creates a significant healthcare burden for the patient and society and may lead to unnecessary surgical referrals (Fleisher et al., 2005; T. Venkatesan et al., 2014). Furthermore, this syndrome is commonly associated with anxiety and depression as well as opioid and cannabis / marijuana use (Bhandari & Venkatesan, 2017b). A high percentage of cyclic vomiting patients use cannabis for their symptoms regardless of its legality, and yet a nearly identical syndrome, termed cannabis hyperemesis syndrome (CHS), is associated with long-term cannabis use (though the specific pathogenesis is unclear) (Venkatesan, Levinthal, Li, et al., 2019). This paper provides a narrative review of the state of the science for both CVS and CHS, including a discussion of the relationship between these two conditions. A brief overview of the endocannabinoid system is provided along with a hypothesis that the lack of cannabidiol (one of the two primary cannabinoids of the cannabis plant) within modern high-potency cannabis may be contributory to CHS, as well as other cannabis use disorders.

Historical Context

CVS has a long history of etiological debate within the medical literature, with most observations occurring in pediatric patients. The earliest publication originated over 150 years

ago with Dr. H. CL. Lombard's reading to the Medical Society of Geneva (Lombard, 1861). The primary author (JRL) translated this French-language paper into English, which is available as Supplemental Digital Content. Dr. Lombard described his then unidentified pediatric syndrome as "a neurosis of digestion" (as translated) which he admitted was a somewhat vague diagnostic description. His presentation was a call for additional study among colleagues with the hope of identifying both a cause and cure, as well as perhaps a more appropriate name. At that time, he described several features now known to be pathognomonic of pediatric cyclic vomiting syndrome including 1) a stereotypical yet recurrent cycle of symptoms, 2) the observance of well health between episodes, 3) the absence of organic pathology by autopsy, and 4) a tendency for resolution after puberty.

Many authors have referenced a later paper by Dr. Samuel Gee as the earliest publication of CVS (Bhandari, Jha, Thakur, et al., 2018; CVSA, 2019; Fleisher et al., 2005; Hejazi & McCallum, 2011, 2014; Issenman, 2017; Kovacic et al., 2018). In that 1882 publication, Dr. Gee described a case series of nine children with "fitful or recurrent vomiting." The publication of case studies over the more recent decades has established both an adult-onset variation of CVS (Abell et al., 1988; Hermus et al., 2016; Keller et al., 2015; Prakash & Clouse, 1999; Shearer et al., 2018) as well as a probable toxicity-induced variant described as CHS (Allen et al., 2004; Schreck et al., 2018; Sontineni et al., 2009). The classic pediatric variety, with typical resolution in puberty and associations with migraine and anxiety, has been well characterized within the gastrointestinal (GI), neurological, and pediatric literature (Boronat et al., 2017; Irwin et al., 2017; Li et al., 2008; Li et al., 1998; Rashid et al., 2016; Romano et al., 2018; Zeevenhooven et al., 2017). Therefore, this paper adds to the discussion by providing an evaluation of adult CVS and its potential relationship to CHS in the context of endocannabinoid dysregulation.

Cyclic Vomiting Syndrome, Adult-Onset

Prevalence

Similar to pediatric CVS, adult-onset CVS is a condition of stereotypical emetic episodes that tend to be predictable for the patient in duration and symptomatology over a long period of time (Aziz et al., 2019; Evans & Whyte, 2013; Kumar et al., 2012). Both adult and pediatric CVS are rare conditions (Bhandari, Jha, Thakur, et al., 2018; Issenman, 2017) and until recently population-based epidemiological data for adult CVS were absent (Hasler et al., 2019; Rosen & Singla, 2019). The Global Epidemiology Study of Functional Gastrointestinal Disorders (FGID) surveyed 73,076 adults from 33 countries to identify the prevalence of meeting criteria for at least one of 22 functional GI disorders, including CVS (Sperber et al., 2021). The study used an anonymous internet survey in 26 countries (n = 54,127) and conducted face-to-face household surveys in 9 additional countries that tended to be more rural and with less access to communication technology (n = 18,949). From the internet-based portion of the survey, the overall prevalence of adult CVS was 1.2% with a slightly higher rates in women versus men (1.2% vs 1.1%) and decline in incidence with age. The interview method revealed a much smaller CVS prevalence at 0.3%, yet a consistent slightly higher prevalence in women compared to men (0.5% vs 0.2%) and conversely a small increase in the incidence of CVS with age (see Table 1). The authors conjectured that "cultural sensitivities around reporting of FGID symptoms may have led to the large differences in prevalence rates observed between the 2 survey methods" (Sperber et al., 2021, p. 111). Therefore, the true prevalence of CVS in adults remains unclear but appears to be low.

Diagnostic Criteria

The syndrome of adult CVS is without measurable biomarkers, and as such the diagnostic criteria continue to be its unique symptom pattern; ultimately CVS is a diagnosis of exclusion (Kovacic et al., 2018). A careful history along with a generally normal physical exam may eventually lead the astute clinician to the diagnosis. A hallmark of the disease is its repetitive and cyclical nature over time, so by definition the syndrome cannot be diagnosed with the initial onset of symptoms. Furthermore, nausea, vomiting, and abdominal pain are non-specific symptoms with a broad differential. Indeed, the mean time to diagnosis from the onset of symptoms for an adult CVS patient is 7.3 ± 6.9 years (T. Venkatesan et al., 2014). Patients may suffer an extended period without a clear diagnosis, and these episodes can lead to multiple emergency department (ED) visits, hospitalizations, and surgical referrals. In a survey of 41 CVS patients, 16 of them underwent a combined total of 17 surgical attempts to cure their recurrent vomiting, yet none resulted in improvement (Fleisher et al., 2005). An internet survey questionnaire of 437 patients reported 20% (n = 88) of responders as having a cholecystectomy for symptoms which were ultimately attributed to a diagnosis of CVS (T. Venkatesan et al., 2014). In short, CVS often involves a high level of health care utilization along with unnecessary suffering, including surgery without benefit, and typically a long delay between symptom onset and diagnosis of the condition.

Key features of CVS include a rapid onset of intense nausea, vomiting, and crampy abdominal pain. The episodes will last from a few hours to a week or more, interspersed with wellness periods from weeks to months. Attacks may be without trigger, yet provoking factors are common and similar to persons with migraines: Food sensitivities such as chocolate, alcohol, cheeses, and monosodium glutamate; health conditions such as motion sickness, sleep

deprivation, and infection; and emotional stressors including both unpleasant events (e.g., exams or the loss of a loved one) as well as pleasant, yet stressful events (e.g., weddings, parties, and vacations) (Abell et al., 2008; Kovacic et al., 2018). When the recurrence pattern is associated with a menstrual cycle, it is termed catamenial CVS. The Rome Foundation (Rome IV) criteria are considered the standard for CVS diagnosis (Drossman & Hasler, 2016; Rosen, 2019; Stanghellini et al., 2016), see Box 1. The International Classification of Diseases, version 10 (ICD-10) billing codes for CVS are R11.15, *cyclical vomiting syndrome unrelated to migraine*, G43.A0, *cyclical vomiting, in migraine, not intractable* and G43.A1, *cyclical vomiting in migraine, intractable*.

The cycle of illness for CVS is divided into four phases, and a careful history should focus on identifying not only a recurrent pattern for the patient, but the relative consistency of each of these phases:

- The inter-episodic *wellness period* during which time the patient is generally symptom free, typically for a span of weeks to months.
- A *prodromal phase* which lasts anywhere from a few hours to a day; this phase has similarities to the migraine prodrome with symptoms such as nausea, pallor, sensitivity to light, sound, smell, pressure, and temperature; as well as the possibility for fatigue, myalgias, and abdominal pain.
- The *emetic phase* of sudden onset with severe vomiting even continuing after an evacuated stomach; there is a significant intolerance to the consumption of any food or drink, and emesis may occur with or without nausea. This phase will last from a few hours to a few days, with retching multiple times an hour, and may be accompanied by pallor, dizziness, flushing, drooling, listlessness, diaphoresis,

abdominal pain, as well as other symptoms such as diarrhea and core temperature variations including low-grade fever or hypothermia.

- Finally, the *recovery phase,* which is marked with the easing of nausea, retching, and other symptoms, until the intake of food can be tolerated, which marks the beginning of the wellness phase once again.

Pathogenesis

Current theories of CVS pathogenesis include autonomic dysfunction (Hejazi et al., 2011; Venkatesan, Prieto, et al., 2010), dysregulation of the brain-gut axis (Drossman & Hasler, 2016; Levinthal & Bielefeldt, 2014), stress-mediated activation of the corticotrophin-releasing factor signaling system (Adamiak & Jensen, 2015; Venkatesan, Prieto, et al., 2010), dysfunction of the hypothalamic-pituitary-adrenal axis (Bhandari, Jha, Thakur, et al., 2018; Donnet & Redon, 2018; Richards, 2017), altered genetic factors in children such as mitochondrial DNA mutations (Boles et al., 2009; Gelfand & Gallagher, 2016; Zaki et al., 2009) or polymorphisms involving the cannabinoid receptor type-1 and mu-opioid receptor genes (Wasilewski et al., 2017), and a dysfunction or dysregulation of the endocannabinoid system (Venkatesan et al., 2016). No single etiological hypothesis is dominant at this point. Furthermore, a complicating factor for both adult and pediatric CVS is the common coexistence of psychiatric comorbidities such as depression, and anxiety. Additional associations include migraine, syncope, chronic fatigue, irritable bowel syndrome, as well as alcohol, tobacco, and cannabis use (Koloski et al., 2012; Sagar et al., 2018). A US nationwide analysis of 20,952 hospitalized CVS patients in comparison to a random sampling of 44,262 hospitalized non-CVS patients found significant correlations with younger age, white race, marijuana use, tobacco smoking, irritable bowel syndrome, gastroparesis, migraine, anxiety, and gastro-esophageal reflux disease (Bhandari & Venkatesan, 2017a, p. 6).

Other studies highlight the psychiatric comorbidities as an important feature of CVS and patients should be screened for these as a routine component of CVS workup (Sagar & Ford, 2017; Thavamani et al., 2022).

Treatment of CVS

Though the publication of CVS-related literature is steadily increasing, the state of the science supporting adult CVS incidence, symptoms, treatments, prognosis, etiology, confounding factors (including cannabis use) are primarily based on case-series publications and retrospective chart review studies[1]. Within the existent literature there are very few randomized controlled trials (RCTs) and zero publications meeting level 1 evidence criteria within the CVS literature for either children or adults (Hasler et al., 2019; Issenman, 2017; Lee et al., 2012; Levinthal, 2016; Shearer et al., 2018). For this review we identified only two small RCTs evaluating CVS pharmacological treatments, and both were pediatric studies. The first was a single-blind RCT aimed to investigate the difference between amitriptyline* (tricyclic antidepressant) or cyproheptadine* (antihistamine) in the prevention of future attacks and involved 64 children between the ages of 3 and 15 years (Badihian et al., 2018); no statistical significance in effect was found between the two groups. The second RCT compared amitriptyline* (n = 34) with topiramate* (anticonvulsant) (n = 36) in prophylactic treatment of pediatric CVS patients 4-13 years of age (Bagherian et al., 2019). After three months of therapy, 79.4% (n = 27) of the amitriptyline* group achieved a ≥ 50% reduction in either frequency or duration of attacks over baseline compared to 44.4% (n = 16) of the topiramate* group (p = .003).

[1] This paper discusses the off-label use of FDA-approved drugs as the only drugs approved for CVS specifically are the symptomatic agents, such as antiemetics for nausea and vomiting. Off-label use of FDA-approved drugs is designated with a superscript *.

Current guidelines for the management of CVS are published as a collaborative effort between the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association (Venkatesan, Levinthal, Tarbell, et al., 2019). For prevention and treatment considerations one therapeutic approach is to consider CVS a migraine variant (Hayes et al., 2018; Irwin et al., 2017; LenglarT et al., 2021; Yu et al., 2018). The CVS guidelines recommend that mild cases with quick recovery periods can be treated with abortive medications only (defined as < 4 episodes / year and episodes lasting < 2 days). Moderate to severe cases of CVS (defined as ≥ 4 episodes / year, episodes ≥ 2 days, prolonged recovery, or ED visits and / or hospitalizations) may need prophylactic treatment in addition to abortive therapy (Venkatesan, Levinthal, Tarbell, et al., 2019).

Symptomatic and Supportive Treatment during the Acute Phase and Recovery

During the acute phase (prodrome to emetic), evidence indicates that some medications used for acute migraine may be abortive in CVS. The basic abortive treatments include intra-nasal or subcutaneous sumatriptan* (selective serotonin receptor agonist) along with ondansetron sublingually and / or oral aprepitant (antiemetics). Once the emetic phase has started, IV treatments, usually given in the ED setting, are often necessitated, with an emphasis on the use of IV benzodiazepines plus fluid hydration. Because of the complexity in treating these patients, and the surprising failure of standard antiemetics in this population, having a written treatment plan can be facilitative for both the patient and the ED clinician (Issenman, 2017; Venkatesan, Levinthal, Tarbell, et al., 2019). Other IV agents which may be helpful include promethazine (antiemetic) diphenhydramine* (antihistamine), and proton pump inhibitors (Bhandari & Venkatesan, 2016; Calhoun & Pruitt, 2014; Mooers et al., 2021). Clinicians assessing for cannabis use in CVS patients (in attempts to differentiate CHS) should note that proton pump

inhibitors (IV pantoprazole* in particular) may result in a false positive cannabis toxicology screen during the ED or inpatient workup (Felton et al., 2015; Gomila et al., 2017). Fosaprepitant*, an IV anti-emetic approved for chemotherapy induced nausea and vomiting should be considered if available (Bhandari & Venkatesan, 2016; Hermus et al., 2016; Venkatesan, Levinthal, Tarbell, et al., 2019). Limited amounts of narcotics may be provided as needed for moderate to severe abdominal pain (Venkatesan, Tarbell, et al., 2010b). As the patient moves into the recovery phase, one key element is to limit the oral intake of fluids. Rapid oral fluid replacement can send a recovery phase patient back to the emetic phase; offer ice chips initially, continue IV fluids if available, and progress with small volume clear liquids until the patient begins to feel well once again.

Preventive Treatment during the Wellness Phase

A daily tricyclic antidepressant (amitriptyline* or nortriptyline*) is the first line choice for decreasing CVS frequency and severity over time, with alternate agents to include topiramate* (anticonvulsant), aprepitant* (antiemetic), as well as zonisamide* or levetiracetam* (anticonvulsants) (Venkatesan, Levinthal, Tarbell, et al., 2019). Mitochondrial dysfunction has also been implicated in both CVS and migraine, and the use of mitochondrial supplements[2] such as co-enzyme Q10 and riboflavin may reduce the incidence of CVS episodes in some patients (Kovacic et al., 2018; Thangam Venkatesan et al., 2014). Lifestyle modifications including stress-reducing measures, the practice of good sleep hygiene, the identification and avoidance of triggers (a lifestyle diary can be helpful in the identification of triggers), and the implementation of an exercise program may all be helpful in decreasing CVS episodes (Bhandari, Jha, Thakur, et al., 2018). And as a final consideration, although use of opioids for abdominal pain is often

[2] Supplements are not FDA-approved to treat any medical condition.

indicated during the acute emetic phase, outpatient narcotics should be minimized in this group overall. Opioids decrease gastric motility and are known to cause GI side effects including nausea and vomiting (Farmer et al., 2018; Smith & Laufer, 2014). Chronic narcotic exposure may set the patient up for narcotic bowel syndrome, which can mimic a coalescence of CVS symptoms (a shortening of the wellness phase) (Camilleri et al., 2017; Drossman, 2016). Finally, the CVS guidelines recommend screening and treatment for comorbid conditions which are common in this population (esp. anxiety, depression, migraines, sleep disorders, and substance use) with referral to the appropriate allied health services.

Considerations for Ketamine in Refractory CVS

Many CVS patients are slow to break the emetic phase and often will have prolonged hospitalizations despite appropriate management. Evolving evidence supports the potential use of IV ketamine* (general anesthetic) for treatment of resistant depression and intractable pain, and recently two small pilot studies have evaluated ketamine* for CVS abortive therapy (Ahuja et al., 2018; Valdovinos et al., 2020). A retrospective chart review of ED patients with intractable nausea and vomiting examined discharge to home or hospital admission by ketamine* dose in patients who received the drug at least once. The sample experienced a total of 108 ketamine* exposures, with 40 hospitals admissions (a 37% admission rate) and the mean index ketamine* dose was 24.4 mg. Response to ketamine* was dose dependent with < 15 mg resulting in 100% hospital admissions while > 15 mg resulted in a 31.2% admission rate (Ahuja et al., 2018). The second study was a non-blinded open-label design in which a convenience-sample of ED patients (n = 28) with nausea and vomiting and a history of CVS were given 15 mg of ketamine* by slow IV push plus 12.5 mg of chlorpromazine IV drip (phenothiazine antiemetic). After 120 minutes post-medication, the median number of observed episodes of emesis was 0 (IQR: 0 to1) as

compared to a median of 7 episodes reported by subjects in the 2-hours prior to treatment. Subject-rated nausea and pain scores decreased by a mean of 4.9 (95% CI 3.2 - 5.0) and 4.1 (95% CI 4.0 - 5.8) points, respectively, on a 0-10 numeric rating scale at 120 minutes post-treatment. Patient satisfaction was high with 100% of the study subjects reporting they would like this therapy in the future. Finally, the team performed an electronic query of the ED visits in the 24 months before the index visit for each patient and determined that "opioids were used less frequently [during the study visit] than during prior visits for the same complaint" though no specific analysis or numbers were provided (Valdovinos et al., 2020, p. 330). These two pilot studies provide direction for further study, including the consideration for using ketamine* plus chlorpromazine in acute CVS (or CHS) not otherwise responding guideline recommended agents.

Cannabis Hyperemesis Syndrome

The clinical picture of CVS is complicated by a prevalence of cannabis use in this population, coupled with the potential for cannabis to cause a cycling emesis very similar to idiopathic CVS. In 2004, a group from Australia proposed the new syndrome of CHS with the presentation of a case series of nine individuals with new adult-onset cyclic vomiting (Allen et al., 2004). The pattern described in these cases was cyclic vomiting associated with a history of daily cannabis use, and the resolution of symptoms in all patients who were able to abstain from cannabis (seven out of nine), as well as a return of symptoms rapidly with a re-introduction of cannabis even after an extended period of abstinence. The team described CHS as having a near-typical CVS presentation, but with a prodromal phase of early morning nausea and occasional vomiting for months or years prior to the first hyper-emetic phase. The emesis would then come on suddenly, last 24-48 hours, and then resolve back into a baseline morning nausea prodrome.

The key to these cases was that the initial cannabis use was not for the self-treatment of symptomatic nausea and vomiting, but rather that the cannabis use which predated the onset of cyclic vomiting symptoms.

The possibility that some CVS cases may have been CHS is concerning given reports that large proportions of CVS patients use cannabis, presumably for the long-recognized anti-emetic effects of the substance.[3] In a large anonymous internet survey, 81% of CVS patients reported the use of cannabis to assist with their symptoms including nausea and pain (T. Venkatesan et al., 2014). A hospital-based survey in Milwaukee, Wisconsin, found that 14% of their CVS patients reported the use of cannabis to alleviate symptoms, versus 3% of non-CVS patients (Bhandari & Venkatesan, 2017a). A retrospective chart review from the Mayo Clinic in Rochester, New York, from 1993 – 2006 found cannabis to be more significantly associated with CVS than with functional vomiting (OR 2.9, 95% CI), and that 79% of their adult CVS patients reported cannabis use (Choung et al., 2012). More recently, a population of CVS patients from a specialized CVS clinic in Milwaukee, Wisconsin, was administered a cannabis use survey, with 140 patients completing the questionnaire (23% of those invited to participate). Within the sample, 41% (n = 57) reported using cannabis in the prior 6 months. Among the cannabis users, 53% (n = 30) were regular cannabis users of > 4 times / week and 50% of that group (n = 15 of 30) reported using cannabis on a regular basis before they developed CVS (Venkatesan et al., 2020).

The consideration of cannabis as a potential causative agent is often not mentioned in published cases of adult-onset CVS, and it is likely that the syndrome of CHS continues to be under-recognized and underdiagnosed (Attout et al., 2020; Lua et al., 2019; Sagar et al., 2018). A

[3] The FDA has not approved the marketing of cannabis for the treatment of any disease or condition.

large global market survey of 6,300 individuals in 2015 identified the overall prevalence of CHS at 0.1% (Aziz et al., 2018) while the more recent Global Epidemiology Survey of FGID noted an even smaller prevalence at 0.01% – 0.05% (Table 1) (Sperber et al., 2021). However, each of these global surveys need to be considered with local increases in cannabis use (and cannabis potency) in the newly legalized areas as well as traditionally heavy use areas such as Western Europe, Canada, the United States, Latin America, and the Caribbean Islands. Furthermore, many CVS case studies either do not mention cannabis use at all or list it as a recreational or therapeutic measure without specific consideration as a possible cause of the symptomology (Al-Mahrouqi et al., 2020; Hejazi & McCallum, 2011; Sagar et al., 2018).

Another intermixing point between the conditions of CVS and CHS is compulsive hot water bathing, often to the point of using near scalding hot water, which provides the patient with transient relief from nausea and vomiting. Hot water bathing is associated with both conditions, though it is more strongly associated with CHS in particular. For eight of the nine patients in the Australian case series (Allen et al., 2004), relief from the acute emetic phase and abdominal pain was gained through hot showers. The first case of CHS was published in the U.S. several years later (Chang & Windish, 2009). That same year Sontineni *et al.* released a case report along with an initial listing of diagnostic criteria that included compulsive hot bathing for symptom relief as supportive, but not essential, for CHS diagnosis (Sontineni et al., 2009), see Box 2. Yet other authors have noted a pattern of hot-water bathing for relief of symptoms in CVS patients who deny cannabis use (Aziz et al., 2018). An internet survey of marijuana and hot shower use in adults reported that 72.2% of CVS patients with a history of marijuana use describe relief with hot showers or baths, while 47.5% of CVS patients with no history of marijuana use also report relief with hot showers or baths (T. Venkatesan et al., 2014). Ultimately, the key diagnostic

element of CHS is a history of cannabis use that predates the onset of symptoms, and the resolution of symptoms with cessation of cannabis use (Schreck et al., 2018; Venkatesan et al., 2020). So although the unique behavior of symptom relief with hot bathing is strongly associated with CHS, it is not specific enough to CHS alone as it occurs in up to 50% of non-marijuana consuming CVS patients as well (Rosen et al., 2021).

The CHS variant of CVS likely has been present among all cohorts of adult CVS patients (Venkatesan et al., 2020). For example, an earlier case report of recurrent vomiting marked by the "use of marijuana and the taking of several showers and baths each day" (de Moore et al., 1996, p. 291) did not consider the patient's cannabis use as a potential causative agent. Indeed, the syndrome of CHS was somewhat difficult for the clinical GI community to recognize because 1) cannabis became an illegal substance in most parts of the world during the last century, so patients tended to deny or minimize reporting of its use; 2) the anti-nausea and anti-emetic properties of Δ^9-tetrahydrocannabinol (THC) have been well recognized by both patients and clinicians, and as such a cannabis-related CVS is counterintuitive; 3) CVS patients do use cannabis for symptom alleviation without having CHS; and 4) the continued U.S. Drug Enforcement Agency (DEA) Schedule I classification of marijuana is a formidable barrier to research through common funding mechanisms. This final point creates an atmosphere of illegitimacy hovering over most discussions of cannabis and has a dampening effect on research design, even unintentionally. For example, in 2017 a group from St. James's University Hospital in Leeds, UK (where cannabis continues to be illegal in all forms) published original research from a survey study involving 920 patients who were recruited over a 2-year period from six medical GI outpatient clinics and 10.8% of respondents met diagnostic criteria for CVS (n = 99). Although in their survey they found CVS to be associated with younger age, never married social

status, psychiatric diagnoses, and cigarette smoking, ($p \leq 0.01$), they did not collect any data on cannabis use (Sagar & Ford, 2017).

Still, there has been a marked increase in the number of published cases of CHS since it was first identified in 2004, including fatal cases (Nourbakhsh et al., 2018; Sorensen et al., 2017; von Both & Santos, 2021) and associations with synthetic cannabis use (Argamany et al., 2016; Hopkins & Gilchrist, 2013; Liu et al., 2017). Many authors attribute the rise in cases directly to the increase of cannabis availability by U.S. state-level legalization and / or to the increased percentage of THC (the main intoxicating component in cannabis) within the cannabis products (Al-Shammari et al., 2017; Bhandari, Jha, Lisdahl, et al., 2018; Gubatan et al., 2016). However increased recognition of CHS cases may correlate with cannabis use and disclosure of such in the age of legalization, in combination with an increased provider recognition of the syndrome and a publication bias for a newly recognized syndrome (Hermus et al., 2016; Sontineni et al., 2009; Soriano-Co et al., 2010). Whatever the cause for the increase of this syndrome within the case literature, the Rome IV standards designate CHS as a unique nausea and vomiting disorder with a diagnosis separate from, but in the same category as, CVS (Schmulson & Drossman, 2017). Yet other authors continue to describe CHS as a CVS variant (Aziz et al., 2018). Taking this latter approach, CHS may be considered an induced or toxin-related CVS variant in which the symptoms are attributed to chronic (most often daily) long-term cannabis consumption (often 2 years or more), which resolve with abstinence, and tend to re-occur quickly with relapse of use (Aziz et al., 2018). The level of evidence for this designation is low, however, relying entirely on case reports, retrospective chart review studies, and expert opinion. Further study is needed, including longitudinal studies of cannabis users, combined with the continued advancement of

our understanding on how the consumption of exogenous cannabinoids interact with human physiology in both acute and chronic exposure.

Treatment of CHS

The only RCTs for CHS treatment identified in the literature with this review are the Haloperidol Versus Ondansetron for CHS (HaVOC) trial (Ruberto et al., 2020) and a small pilot trial of topical capsaicin cream for CHS (Dean et al., 2020). The HaVOC trial was a randomized triple-blind clinical trial comparing the effect of IV haloperidol* (n = 13) to IV ondansetron (n = 17). Inclusion criteria were >18 years old, a working diagnosis of CHS, and a presentation to one of two academic emergency departments in Ontario Canada. The primary outcome measure was the average of abdominal pain and nausea scores as measured on a 10 cm visual analog scale at 2 hours versus baseline; the mean difference between the ondansetron and haloperidol* groups was 2.3 cm favoring haloperidol* (95% CI = 06 - 4.0; p = 0.1). Secondary measures including overall treatment success, reduced use of rescue antiemetics, and shorter time to discharge were also favorable to haloperidol* (2.5-hour difference [95% CI 0.1-5.0], p = 0.03). In the discussion the authors concluded that "this randomized controlled trial demonstrates the superiority of intravenous haloperidol over ondansetron, especially at a low, one-time dose of 0.05 mg / kg, for the common symptoms of nausea, vomiting, and abdominal pain" in the treatment of acute phase CHS (Ruberto et al., 2020, p. 618).

Considerations for Capsaicin

The common behavior of using very hot water for self-management of CHS led some clinicians to try the application of over-the-counter capsaicin cream[4] (0.025%, 0.075%, or 0.1%) to the abdomen (or other regions such as the back and arms) in an attempt to abort acute cyclic

[4] OTC capsaicin cream has not been found by the FDA to be safe and effective for any condition.

vomiting in patients with emetic-phase CHS (Lee & Coralic, 2021; Richards et al., 2018). These creams were initially developed for arthritic pain syndromes and the mechanism of action is hypothesized to be both a down-regulation of cutaneous nociceptor fibers and, separately, a depressed expression of the capsaicin receptor, transient receptor potential vanilloid-1 ($TRPV_1$), a receptor responsible for the sensation of heat (Anand & Bley, 2011; Lo Vecchio et al., 2021). When applied to the skin, capsaicin, a neuropeptide-active agent derived from *Capsicum* sp. (hot chili peppers), strongly engages with $TRPV_1$ and, through activation and subsequent desensitization, decreases its activity (Geraghty et al., 2011; Sharkey et al., 2007). Similarly, noxious heat (~ 43° C) decreases $TRPV_1$ activity. (Joseph et al., 2013; Richards et al., 2018). The overall evidence for using topical capsaicin in acute CHS as a clinical recommendation is low, relying generally on a small number of published case reports (McConachie et al., 2019).

There are, however, three retrospective studies and a singular small RCT to be considered. The first is a retrospective cohort series (n = 22) that reported no significant effects of capsaicin on CHS symptoms (McCloskey et al., 2017). Second, a retrospective cohort analysis of 43 patients demonstrated support for lower anti-emetic doses needed to achieve symptomatic relief when capsaicin was used concurrently (4 vs. 2 doses, $p = 0.015$) (Wagner et al., 2020). Third, a retrospective cohort study (capsaicin n = 149; no capsaicin n = 52) showed a greater effect in total symptomatic relief (55% of the capsaicin group vs 21% of the no capsaicin group, $p < 0.001$) as well as a shorter average time to discharge from the ED in the capsaicin group (2.72 vs. 6.11 hours, $p = 0.001$) (Kum et al., 2021). However, the imbalance between the treatment group and the control, combined with the unblinded treatment and retrospective design leaves the study's conclusions as highly speculative. Finally, the singular published RCT is a pilot-level trial that enrolled 30 convivence-sample ED patients with CHS who presented to a

large-volume urban academic trauma center between December 2017 and July 2019 (treatment n = 17; placebo n = 13). Patients were treated with either 5 g of topical 0.1% capsaicin cream or an identical-appearing moisturizing cream (blinded placebo control). An ED nurse applied the cream once to the abdomen in a uniform manner, and otherwise patients received conventional therapy per the ED physician independent of study enrollment. A visual analog scale (VAS) was used to measure the subjective intensity of the patient's nausea at 30 and 60 minutes after application of the cream. The study did not meet its primary endpoint of nausea reduction by VAS at 30-minutes (4.1 cm [95% CI 2.8-5.4] vs 6.1 cm [95% CI 4.1-8.1] p = 0.075), and one patient in the treatment group experienced an adverse event consisting of skin irritation requiring immediate removal of the cream. However, the study did meet its secondary endpoint of decreased nausea by VAS at 60 minutes (3.2 [95% CI 1.6-4.8] vs 6.4 [95% CI 4.7-8.1] p = 0.007) and a higher proportion of the capsaicin group patients also reported a complete resolution of nausea at discharge (29.4% vs. 0%, relative risk = 3.4, 95% CI = 1.6 – 7.1). These results are weakened, however, by the capsaicin group randomly having a lower mean nausea VAS at baseline compared to the placebo control group (6 ± 2.9 cm vs 8.5 ± 2.0 cm) (Dean et al., 2020).

Taken together, these small capsaicin studies describe a potential effect with probable CHS cases, yet as previously noted, around 50% of non-cannabis using CVS patients may also gain relief from hot water bathing; therefore, classical CVS patients could be considered for capsaicin therapy studies as well. For example, in the Dean et al. RCT described above, 17.6 % of the capsaicin group (n=3) reported less than weekly cannabis use, and 1 patient (5.9%) denied any cannabis use, so up to ¼ of the treatment group may have been CVS vs. CHS. Furthermore, an additional research consideration is the availability of a high-potency 8.0% capsaicin patch* approved for the management neuropathic pain (Abrams et al., 2021; Anand & Bley, 2011;

Bonezzi et al., 2020), and yet there are no published reports of it being trialed in any acute CHS or CVS case. The improvement described in some of these capsaicin studies, combined with the mechanistically related behavior of gaining relief from hot water, suggests the need for more RCT's evaluating the efficacy of topical capsaicin for acute cyclic vomiting episodes in known CHS patients, and also in CVS patients, possibly focusing on those who report a positive response to hot bathing. Yet the low cost, ready availability, and benign safety profile for topical capsaicin use in this population overall has led some authors to support the routine consideration of this therapy even prior to the completion of more rigorous studies (Lapoint et al., 2018; Lee & Coralic, 2021; Stumpf & Williams, 2020).

Considerations for Cannabidiol (CBD)

Cannabis (C. *sativa sp.*) represents a highly variable, primarily dioecious (having male and female forms), singular plant species which produces cannabinoid molecules (the phytocannabinoids) primarily within the flower of the female plant. Phytocannabinoids are a class of closely related molecules (the natural cannabinoids) which are isolated from the various strains of the cannabis plant (Radwan et al., 2021). The 125 known phytocannabinoids can be grouped into three broad categories: The CBD-type, the THC-type, and a miscellaneous class (see Table 2). When cannabinoid molecules are consumed, some of them modulate the activity of the mammalian endocannabinoid system, first described in the early 1990's (Devane et al., 1992). Despite its relatively recent addition to human physiology studies, the endocannabinoid system is evolutionarily ancient originating from a common bilaterian ancestor around 500 million years ago and receptors are found within the entire animal kingdom (though with a secondary evolutionary loss of cannabinoid receptors in insects and some nematodes) (McPartland et al., 2006).

In mammals, the primary endocannabinoid receptors are the G-protein coupled receptors cannabinoid 1 (CB_1) and cannabinoid 2 (CB_2) along with six transient receptor potential (TRP) ion channel receptors (specifically $TRPV_{1-4}$, $TRPA_4$, and $TRPM_8$) (Muller et al., 2018). Two primary activating ligands, the endocannabinoids, engage with these receptors: *N*-arachidonoyl ethanolamine (anandamide or AEA) and 2-arachidonyl glycerol (2-AG). For nervous tissue, the activating ligands are produced on demand at the postsynaptic terminal and undergo retrograde travel to activate CB_1 at the presynaptic terminal. This typically results in an inhibition of neurotransmitter release at that neuron. AEA and 2-AG also activate the postsynaptic receptor $TRPV_1$ leading to an increase in the postsynaptic ion current (Yin et al., 2019). CB_1 is concentrated in the basal ganglia, hippocampus, and cerebellum, but with a notable absence in the lower brainstem sparing cardiac and respiratory depression effects (Hanus, 2009; Katona, 2009). Additionally, skeletal and cardiac muscle tissue express CB_1 along with adipose tissue and cells of the hepatic, pancreatic, and reproductive systems (Peng et al., 2022). The second primary cannabinoid receptor, CB_2, is located on the brain microglial cells and other cells of the immune system including the spleen, tonsils, thymus, T-cells, B-cells, natural killer cells, and macrophages (Cabral & Griffin-Thomas, 2009). Exogenous CB_2 activation primarily has anti-inflammatory effects including the downregulation of cytokine release, decreased nitric oxide and reactive oxygen production, and decreased cellular migration (Turcotte et al., 2016).

The cannabinoid receptors have a complex molecular structure which allows for a single receptor to recognize multiple classes of compounds producing a variety outcome effects. The phytocannabinoids are chemically quite distinct from the endocannabinoids AEA and 2-AG (which are eicosanoids) and yet they engage with CB_1 and CB_2, as well as several of the TRP channels (Console-Bram et al., 2012). The phytocannabinoid THC operates as a CB1 receptor

agonist when consumed, yet THC does not have any known action on $TRPV_1$ (Darmani et al., 2014; Muller et al., 2018). Conversely, the second most common cannabinoid of the cannabis plant, cannabidiol (CBD), is a negative allosteric modulator of CB_1 and as such CBD consumption can attenuate THC-related agonist effects including euphoria, tachycardia, anxiety, paranoia, hunger, and sedation (Boggs et al., 2018; Chung et al., 2019; Laprairie et al., 2015; Morgan et al., 2010). At the CB_2 receptor, CBD operates as an inverse agonist leading to muted immune cell migration and anti-inflammatory effects (Pertwee, 2008). Finally, CBD is a capsaicin-analog with direct agonist activity on $TRPV_1$ (Izzo & Sharkey, 2010; Pisanti et al., 2017). Because of its lack of agonism of CB_1 in particular, CBD is non-psychoactive when consumed, and originally the molecule was considered an inert cannabinoid (Mechoulam & Shvo, 1963). Yet subsequent studies have demonstrated CBD consumption to correlate with neuroprotective, antiemetic, anti-inflammatory, and anti-anxiety effects (Pisanti et al., 2017). Further evidence suggests that CBD has a potential therapeutic role in the treatment of cannabis use disorders by decreasing THC cravings and dependence use patterns (Babalonis et al., 2017; Crippa et al., 2013; Freeman et al., 2020; Russo & Guy, 2006; Shannon & Opila-Lehman, 2015; Zuardi et al., 2012).

Due to biological limitations within the cannabis plant, very high THC plant strains are unable to simultaneously produce significant amounts of CBD or any of the other minor cannabinoids to a measurable amount (Clarke & Watson, 2002). This is because both THC and CBD are produced through enzymatic synthase from a single precursor, cannabigerolic acid (CBG-A). Therefore, as the ratio of THC goes up then percentage of CBD-type cannabinoids are pushed downward (de Meijer et al., 2003). In the past four decades, through specialized cultivation intent on meeting market demands for increasing potency, the THC percentages of

cannabis have doubled in both the United States and Europe with plant THC concentrations increasing by an average of 0.29% each year between 1970 and 2017 (Cascini et al., 2012; ElSohly et al., 2016; Freeman et al., 2021). Retail cannabis stores commonly display flower THC percentages between 8 – 24% THC, with 28-35% THC by dry weight representing the upper biological limit of the cannabis flower (Roberts, 2020; Weiblen et al., 2015). In further illustration of this trend, a recent Canadian study looked at hair samples from suspected CHS patients presenting to the ED and found high levels of THC and cannabinol (CBN – which is a degradation product of THC), but only trace to undetectable amounts of CBD, further confirming a paucity of CBD within the popular products of the recreational cannabis industry (Albert et al., 2019). The notable absence of CBD in popular recreational cannabis products may explain, at least in speculation, an increased frequency of cannabis use disorders such as CHS. The specific mechanism of action for potential protective effects of CBD against the development of cannabis use disorders, including CHS, is unclear as the consumption of exogenous cannabinoids involves multiple receptor/ligand systems. These include the dopamine system, the opioid system, the endocannabinoid system, as well as serotonergic pathways, the TRP receptors of the neuro and somatosensory systems, and the process of hippocampal neurogenesis (Navarrete et al., 2021; Straiker et al., 2018; Černe, 2020).

In contradiction to the hypothesis that the absence of protective effects from CBD may be significant to the development of CHS, several authors have proposed that high-dose CBD may actually cause CHS citing a 2004 study by Parker et al. (Allen et al., 2004; Darmani, 2010; Galli et al., 2011; Rajaram Manoharan et al., 2018; Venkatesan et al., 2020). These claims primarily stem from a partial misinterpretation of Parker and colleagues' animal study that tested the effects of THC or CBD on lithium chloride (LiCl) induced vomiting in the house musk shrew

(*Suncus murinus*). In the CBD arm of the study, 45 subjects were separated into 5 groups evaluating a range of CBD pretreatment doses on LiCl-induced vomiting. The CBD solution (dose range 2.5 mg / kg – 40 mg / kg) was provided by intraperitoneal injection 10 minutes prior to the injection of LiCl toxin, plus one group to determine the emetic effects of high-dose CBD alone at 40 mg / kg (n = 7). CBD had a biphasic therapeutic effect on induced vomiting where it suppressed vomiting at low doses and enhanced vomiting at high doses, but when the maximal dose of 40 mg / kg CBD was injected alone they concluded that "this dose of CBD does not produce vomiting in the shrew" (Parker et al., 2004, p. 158). So, in that study, high-dose CBD was less effective than THC in preventing lithium-induced vomiting and may have contributed to lithium-induced vomiting in a dose-dependent manner, but high dose CBD did not cause vomiting by itself. Finally, in 2018, the FDA approved Epidiolex® (cannabidiol) oral solution for the treatment of Lennox-Gastaut syndrome and Dravet syndrome, the first FDA-approved drug containing purified CBD from cannabis. The most common CBD adverse effects as listed in the Epidiolex® prescription information include somnolence, decreased appetite, diarrhea, liver transaminase elevations, fatigue, malaise, asthenia, rash, insomnia, sleep disorders, and infections ("Epidiolex, full prescribing information," 2018), but not nausea and vomiting.

The treatment protocols for cannabis use disorders, such as cannabis dependency, are without effective pharmacological agents, and relapses after attempts at abstinence are high (Budney et al., 2019). Therefore, in cannabis-dependent individuals who have developed cyclic vomiting and are unwilling to or fail in efforts to abstain from cannabis (which may be termed intractable CHS), transitioning from a THC-dominant to a CBD-dominant strain has theoretical promise, as does a consideration for the off-label administration of cannabidiol* solution. This is supported by 1) reports of CHS caused from the use of synthetic cannabis that mimics THC, but

not CBD, 2) increased incidence of CHS corresponding to increased market availability of very high THC strains which are generally lacking in CBD, 3) mounting research that demonstrates CBD to be antiemetic, anti-anxiety, anti-inflammatory, and neuroprotective, and 4) evidence that CBD exhibits an action on $TRPV_1$ similar to capsaicin both in vitro and in animal models (Pisanti et al., 2017). Presently, no clinical studies have examined switching CHS patients to CBD-dominant strains of cannabis in those individuals unwilling or unable to cease their cannabis use (recognizing abstinence as gold standard treatment) (Rong et al., 2017). However, a recent survey evaluating a cohort of CVS patients from a specialty GI clinic did identify one patient with complete resolution of CVS symptoms after an abstinence from cannabis and a prior history of heavy cannabis use. The authors report, "This was the only cannabis-using patient in our study who could be reclassified as having CHS based on Rome IV criteria. This patient subsequently resumed using cannabis with a higher proportion of cannabidiol vs THC and reportedly remains episode-free." (Venkatesan et al., 2020, pp. 1087-1089).

Conclusion

Cyclic vomiting syndrome is a rare yet disabling syndrome with a long history within the GI literature. This syndrome afflicts both children and adults and may present either as an idiopathic (as in CVS) or an induced variation (with CHS), yet our understanding of the physiology for these two conditions, and the levels of evidence supporting present treatment considerations are based primarily on case studies, retrospective review studies, and expert opinion collaborations. Future treatment RCTs as well as additional population-based epidemiological, longitudinal, and cohort studies are needed to advance our understanding of these two enigmatic and often severely disabling disorders. Further pathophysiologic and mechanistic studies involving the endocannabinoid system and its relationship to the capsaicin-

receptor $TRPV_1$ are also needed, as well as evidenced-based clinician understanding of the short-term and long-term effects of consuming phytocannabinoids, both positive and negative. Although the present-day U.S. state-level legalization of cannabis has brought the discussion of cannabis and the endocannabinoid system into serious medical discussion, as well as public health consideration, healthcare providers still cannot make true evidence-based recommendations for, or against, cannabis use for their patients in many instances (such as using cannabis for CVS vs. cannabidiol* for CHS, for example). Significant regulatory barriers continue to preclude high-quality research involving cannabis, and healthcare organizations are hesitant, and often prohibited (due to receiving Medicare funding), from stepping beyond the U.S. federal stance of strict prohibition. Changes to the present regulatory status of cannabis would provide opportunities for high-quality adequately funded research. These studies are needed for providers and patients to arrive at well-informed decisions concerning cannabis as a therapeutic, as well as to further develop best practice recommendations for treating GI classical conditions like CVS and its affiliated cannabis use disorder, CHS.

Supplemental Digital Content. English translation of the earliest known medical description of pediatric cyclic vomiting, an oral reading by Dr. H. Lombard in Geneva, France, 1861. pdf

Table 1. Prevalence Rates of CVS and CHS.

Internet Survey n = 54,127		Sex		Age Group (years old)		
		Female	Male	18-39	40-64	65+
CVS	1.2 (1.1-1.2)	1.2 (1.1–1.3)	1.1 (1.0–1.2)	1.6 (1.4–1.8)	0.9 (0.8–1.0)	0.6 (0.5–0.8)
CHS	0.05 (0.03-0.07)	0.02 (0.01–0.04)	0.08 (0.05–0.11)	0.11 (0.07–15)	0.01 (0.00–0.02)	0.01 (0.00–0.03)
Household Interview n = 18,949						
CVS	0.3 (0.3–0.4)	0.5 (0.3–0.6)	0.2 (0.1–0.3)	0.3 (0.2–0.4)	0.4 (0.2–0.5)	0.5 (0.2–0.7)
CHS	2.01 (0.00–0.02)	0.00	2.01 (0.00–0.03)	2.01 (0.00–0.04)	0.00	0.00

Note. Pooled prevalence rates by percentage (95% CI) for CVS and CHS from a population-based internet survey sample in 26 countries and from a household interview survey sample involving 9 countries (Sperber et al., 2021, pp. 103-104).

Box 1: Rome IV Criteria to Diagnose CVS.

- ✓ Onset of symptoms > than 6 months prior to diagnosis (essential criteria)
- ✓ Abrupt onset of vomiting stereotypical to the patient with a duration of < 1 week
- ✓ Three or more discrete episodes in the past 1 year, with cycles > 1 week apart, or
- ✓ Two or more discrete episodes in the past 6 months, with cycles > 1 week apart
- ✓ Absence of vomiting between episodes, however other mild symptoms may be present during the wellness phase
- ✓ Organic causes have been reasonably excluded
- ✓ Personal or familial history of migraine is supportive

Note. Adapted from (Aziz et al., 2018).

Box 2: Clinical Diagnosis of CHS.

Essential Criteria:

- ✓ Long term cannabis use (months to years); shorter phase with synthetic cannabis use
- ✓ Resolution of symptoms with abstinence from cannabis and / or synthetic cannabis

Major Features:

- ✓ Cannabis use pattern is at least weekly, often daily
- ✓ Abrupt onset of nausea and vomiting with a duration of < 72 hours
- ✓ Relief of symptoms with hot showers or bathing
- ✓ Epigastric or periumbilical abdominal pain

Supportive Criteria:

- ✓ Inter-episodic symptoms of morning nausea and occasional vomiting
- ✓ First cannabis use in teenage years with onset of symptoms at age = 20's
- ✓ Male gender and no particular association with migraine history

Note. Adapted from (Simonetto et al., 2012; Sontineni et al., 2009; Sorensen et al., 2017).

Table 2. The Natural Cannabinoids.

Compound Name	Variations	First Reported
Cannabin-Type Cannabinoids (65)		
cannabinol (CBN)	11	Wood, Spivey & Easterfield, 1899
cannabidiol (CBD)	8	Adams, Hunt, & Clark, 1940
cannabidiolic acid (CBD-A)	1	Krejci & Santavy, 1955
cannabigerol (CBG)	16	Goani & Mecholum, 1964
cannabichromene (CBC)	9	Goani & Mecholum, 1966
cannabitriol (CBT)	9	Obata & Yagi, 1966
cannabicyclol (CBL)	3	Mecholum & Goani, 1967
cannabinodiol (CBND)	2	Van Ginneken & Vree, 1972
cannabielsoin (CBE)	5	Bercht, Lousberg & Küppers, et al., 1973
cannabidivarin (CBDV)	1	Shoyama, Hirano & Umekita, et al., 1977
THC-Type Cannabinoids (30)		
Δ^9tetrahydrocannabinol (Δ^9-THC)	23	Goani & Mecholum, 1964
tetrahydrocannabinolic acid (THC-A)	1	Yamauchi, Shoyama, & Aramaki, et al., 1967
tetrahydrocannabivarin (THCV)	1	Gill, 1971; & Merkus, 1971
Δ^8tetrahydrocannabinol (Δ^8-THC)	5	Krejcí & Šantavy´, 1975
Miscellaneous-Type Cannabinoids (30)		
CBCN, CBF, CBR, DCBF, OTHC, etc.	30	Various authors, 1974 - 2015
Total Known Cannabinoids = 125		

Note. CBCN = Cannabichromanone; CBF = Cannabifuran; CBR = Cannabiripsol; DCBF = Dehydrocannabifuran; OTHC = 10-oxo-Δ6a(10a)-tetrahydrocannabinol.

Adapted from (Andre et al., 2016; Appendino, 2020; Elsohly & Slade, 2005; Radwan et al., 2021; Rock & Parker, 2021).

References

Abell, T. L., Adams, K. A., Boles, R. G., Bousvaros, A., Chong, S. K., Fleisher, D. R., . . . Vakil, N. (2008). Cyclic vomiting syndrome in adults. *Neurogastroenterol Motil*, *20*(4), 269-284. https://doi.org/10.1111/j.1365-2982.2008.01113.x

Abell, T. L., Kim, C. H., & Malagelada, J. R. (1988). Idiopathic cyclic nausea and vomiting - a disorder of gastrointestinal motility? *Mayo Clin Proc*, *63*(12), 1169-1175.

Abrams, R. M. C., Pedowitz, E. J., & Simpson, D. M. (2021). A critical review of the capsaicin 8% patch for the treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet in adults. *Expert Rev Neurother*, *21*(3), 259-266. https://doi.org/10.1080/14737175.2021.1874920

Adamiak, T. R., & Jensen, M. J. (2015). Cyclic vomiting syndrome. *S D Med*, *68*(1), 9-11, 13.

Ahuja, A., Kingsley MJ, Diable C, Binion DG, & DJ, L. (2018). Sul1641-ketamine as a novel abortive therapy for cyclic vomiting syndrome attacks. *Gastroenterology*, *154*(6), S558-S559. https://doi.org/10.1016/s0016-5085(18)32063-8

Al-Mahrouqi, T., Al Busaidi, S. A., & Al Alawi, A. M. (2020). Cyclic Vomiting Syndrome: A Case Report and Mini Literature Review. *Cureus*, *12*(11), e11695. https://doi.org/10.7759/cureus.11695

Al-Shammari, M., Maklad, M. A., Yoo, J. W., & Makar, R. (2017). U.S. national trend analysis of cyclic vomiting incidence with liberalization of cannabis use [Conference Abstract]. *Gastroenterology*, *152*(5), S941-S942.

Albert, K., Sivilotti, M. L. A., Gareri, J., Day, A., Ruberto, A. J., & Hookey, L. C. (2019). Hair cannabinoid concentrations in emergency patients with cannabis hyperemesis syndrome. *CJEM*, *21*(4), 477-481. https://doi.org/10.1017/cem.2018.479

Allen, J. H., de Moore, G. M., Heddle, R., & Twartz, J. C. (2004). Cannabinoid hyperemesis: Cyclical hyperemesis in association with chronic cannabis abuse. *Gut*, *53*(11), 1566-1570. https://doi.org/10.1136/gut.2003.036350

Anand, P., & Bley, K. (2011). Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *Br J Anaesth*, *107*(4), 490-502. https://doi.org/10.1093/bja/aer260

Andre, C. M., Hausman, J. F., & Guerriero, G. (2016). Cannabis sativa: The Plant of the Thousand and One Molecules. *Front Plant Sci*, *7*, 19. https://doi.org/10.3389/fpls.2016.00019

Appendino, G. (2020). The early history of cannabinoid research. *Rendiconti Lincei. Scienze Fisiche e Naturali 31*, 919-929. https://doi.org/https://doi.org/10.1007/s12210-020-00956-0

Argamany, J. R., Reveles, K. R., & Duhon, B. (2016). Synthetic cannabinoid hyperemesis resulting in rhabdomyolysis and acute renal failure. *Am J Emerg Med*, *34*(4), 765.e761-762. https://doi.org/10.1016/j.ajem.2015.08.051

Attout, H., Amichi, S., Josse, F., Appavoupoule, V., Randriajohany, A., & Thirapathi, Y. (2020). Cannabis Hyperemesis Syndrome: A Still Under-Recognized Syndrome. *Eur J Case Rep Intern Med*, *7*(5), 001588. https://doi.org/10.12890/2020_001588

Aziz, I., Palsson, O. S., Whitehead, W. E., Sperber, A. D., Simrén, M., & Törnblom, H. (2018). Epidemiology, clinical characteristics, and associations for Rome IV functional nausea and vomiting disorders in adults. *Clin Gastroenterol Hepatol*. https://doi.org/10.1016/j.cgh.2018.05.020

Aziz, I., Palsson, O. S., Whitehead, W. E., Sperber, A. D., Simrén, M., & Törnblom, H. (2019). Epidemiology, clinical characteristics, and associations for Rome IV functional nausea and vomiting disorders in adults. *Clin Gastroenterol Hepatol*, *17*, 878-886. https://doi.org/10.1016/j.cgh.2018.05.020

Babalonis, S., Haney, M., Malcolm, R. J., Lofwall, M. R., Votaw, V. R., Sparenborg, S., & Walsh, S. L. (2017). Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Drug Alcohol Depend*, *172*, 9-13. https://doi.org/10.1016/j.drugalcdep.2016.11.030

Badihian, N., Saneian, H., Badihian, S., & Yaghini, O. (2018). Prophylactic therapy of cyclic vomiting syndrome in children: Comparison of amitriptyline and cyproheptadine, a randomized clinical trial. *Am J Gastroenterol*, *113*(1), 135-140. https://doi.org/10.1038/ajg.2017.194

Bagherian, Z., Yaghini, O., Saneian, H., & Badihian, S. (2019). Comparison of the Efficacy of Amitriptyline and Topiramate in Prophylaxis of Cyclic Vomiting Syndrome. *Iran J Child Neurol*, *13*(1), 37-44.

Bhandari, S., Jha, P., Lisdahl, K. M., Hillard, C. J., & Venkatesan, T. (2018). Recent trends in cyclic vomiting syndrome - associated hospitalizations with liberalization of cannabis use in the state of Colorado. *Intern Med J*. https://doi.org/10.1111/imj.14164

Bhandari, S., Jha, P., Thakur, A., Kar, A., Gerdes, H., & Venkatesan, T. (2018). Cyclic vomiting syndrome: Epidemiology, diagnosis, and treatment. *Clin Auton Res*, *28*(2), 203-209. https://doi.org/10.1007/s10286-018-0506-2

Bhandari, S., & Venkatesan, T. (2016). Novel treatments for cyclic vomiting syndrome: Beyond ondansetron and amitriptyline. *Curr Treat Options Gastroenterol*, *14*(4), 495-506. https://doi.org/10.1007/s11938-016-0114-y

Bhandari, S., & Venkatesan, T. (2017a). Clinical characteristics, comorbidities and hospital outcomes in hospitalizations with cyclic vomiting syndrome: A nationwide analysis. *Digestive Diseases & Sciences*, *62*(8), 2035-2044. https://doi.org/10.1007/s10620-016-4432-7

Bhandari, S., & Venkatesan, T. (2017b). Clinical Characteristics, Comorbidities and Hospital Outcomes in Hospitalizations with Cyclic Vomiting Syndrome: A Nationwide Analysis. *Dig Dis Sci*, *62*(8), 2035-2044. https://doi.org/10.1007/s10620-016-4432-7

Boggs, D. L., Nguyen, J. D., Morgenson, D., Taffe, M. A., & Ranganathan, M. (2018). Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Clinical Δ9 -Tetrahydrocannabinol. *Neuropsychopharmacology*, *43*(1), 142-154. https://doi.org/10.1038/npp.2017.209

Boles, R. G., Zaki, E. A., Lavenbarg, T., Hejazi, R., Foran, P., Freeborn, J., . . . McCallum, R. (2009). Are pediatric and adult-onset cyclic vomiting syndrome (CVS) biologically different conditions? Relationship of adult-onset CVS with the migraine and pediatric CVS-associated common mtDNA polymorphisms 16519T and 3010A. *Neurogastroenterol Motil*, *21*(9), 936-e972. https://doi.org/10.1111/j.1365-2982.2009.01305.x

Bonezzi, C., Costantini, A., Cruccu, G., Fornasari, D. M. M., Guardamagna, V., Palmieri, V., . . . Dickenson, A. H. (2020). Capsaicin 8% dermal patch in clinical practice: an expert opinion. *Expert Opin Pharmacother*, *21*(11), 1377-1387. https://doi.org/10.1080/14656566.2020.1759550

Boronat, A. C., Ferreira-Maia, A. P., Matijasevich, A., & Wang, Y. P. (2017). Epidemiology of functional gastrointestinal disorders in children and adolescents: A systematic review. *World J Gastroenterol*, *23*(21), 3915-3927. https://doi.org/10.3748/wjg.v23.i21.3915

Budney, A. J., Sofis, M. J., & Borodovsky, J. T. (2019). An update on cannabis use disorder with comment on the impact of policy related to therapeutic and recreational cannabis use. *Eur Arch Psychiatry Clin Neurosci*. https://doi.org/10.1007/s00406-018-0976-1

Cabral, G. A., & Griffin-Thomas, L. (2009). Emerging role of the cannabinoid receptor CB2 in immune regulation: Therapeutic prospects for neuroinflammation. *Expert Rev Mol Med*, *11*, e3. https://doi.org/10.1017/S1462399409000957

Calhoun, A. H., & Pruitt, A. P. (2014). Injectable sumatriptan for cyclic vomiting syndrome in adults: A case series. *Headache: The Journal of Head & Face Pain*, *54*(9), 1526-1530. https://doi.org/10.1111/head.12444

Camilleri, M., Lembo, A., & Katzka, D. A. (2017). Opioids in gastroenterology: Treating adverse effects and creating therapeutic benefits. *Clin Gastroenterol Hepatol*, *15*(9), 1338-1349. https://doi.org/10.1016/j.cgh.2017.05.014

Cascini, F., Aiello, C., & Di Tanna, G. (2012). Increasing delta-9-tetrahydrocannabinol (Δ-9-THC) content in herbal cannabis over time: Systematic review and meta-analysis. *Curr Drug Abuse Rev*, *5*(1), 32-40.

Chang, Y. H., & Windish, D. M. (2009). Cannabinoid hyperemesis relieved by compulsive bathing. *Mayo Clin Proc*, *84*(1), 76-78. https://doi.org/10.1016/s0025-6196(11)60811-2

Choung, R. S., Locke, G. R., Lee, R. M., Schleck, C. D., Zinsmeister, A. R., & Talley, N. J. (2012). Cyclic vomiting syndrome and functional vomiting in adults: Association with cannabinoid use in males [Article]. *Neurogastroenterology and Motility*, *24*(1), 20-e21. https://doi.org/10.1111/j.1365-2982.2011.01791.x

Chung, H., Fierro, A., & Pessoa-Mahana, C. D. (2019). Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study. *PLoS One*, *14*(7), e0220025. https://doi.org/10.1371/journal.pone.0220025

Clarke, R. C., & Watson, P. D. (2002). Chapter 1: Botany of natural cannabis medicines. In F. Grotenhermen & E. Russo (Eds.), *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential* (pp. 3-12).

Console-Bram, L., Marcu, J., & Abood, M. E. (2012). Cannabinoid receptors: nomenclature and pharmacological principles. *Prog Neuropsychopharmacol Biol Psychiatry*, *38*(1), 4-15. https://doi.org/10.1016/j.pnpbp.2012.02.009

Crippa, J. A., Hallak, J. E., Machado-de-Sousa, J. P., Queiroz, R. H., Bergamaschi, M., Chagas, M. H., & Zuardi, A. W. (2013). Cannabidiol for the treatment of cannabis withdrawal syndrome: a case report. *J Clin Pharm Ther*, *38*(2), 162-164. https://doi.org/10.1111/jcpt.12018

CVSA. (2019). *What is Cyclic Vomiting Syndrome (CVS)?* Cyclic Vomiting Syndrome Association (CVSA). Retrieved May 16, 2021 from https://www.cvsaonline.org/what-is-cvs/

Darmani, N. A. (2010). Cannabinoid-induced hyperemesis: A conundrum-from clinical recognition to basic science mechanisms [Review]. *Pharmaceuticals*, *3*(7), 2163-2177. https://doi.org/10.3390/ph3072163

Darmani, N. A., Chebolu, S., Zhong, W., Trinh, C., McClanahan, B., & Brar, R. S. (2014). Additive antiemetic efficacy of low-doses of the cannabinoid CB(1/2) receptor agonist Δ(9)-THC with ultralow-doses of the vanilloid TRPV1 receptor agonist resiniferatoxin in the least shrew (Cryptotis parva). *Eur J Pharmacol*, *722*, 147-155. https://doi.org/10.1016/j.ejphar.2013.08.051

de Meijer, E. P., Bagatta, M., Carboni, A., Crucitti, P., Moliterni, V. M., Ranalli, P., & Mandolino, G. (2003). The inheritance of chemical phenotype in Cannabis sativa L. *Genetics*, *163*(1), 335-346. https://doi.org/10.1093/genetics/163.1.335

de Moore, G. M., Baker, J., & Bui, T. (1996). Psychogenic vomiting complicated by marijuana abuse and spontaneous pneumomediastinum. *Aust N Z J Psychiatry*, *30*(2), 290-294. https://doi.org/10.3109/00048679609076108

Dean, D. J., Sabagha, N., Rose, K., Weiss, A., France, J., Asmar, T., . . . Miller, J. (2020). A Pilot Trial of Topical Capsaicin Cream for Treatment of Cannabinoid Hyperemesis Syndrome. *Acad Emerg Med*, *27*(11), 1166-1172. https://doi.org/10.1111/acem.14062

Devane, W. A., Hanus, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., . . . Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, *258*(5090), 1946-1949.

Donnet, A., & Redon, S. (2018). Cyclic vomiting syndrome in children [Review]. *Current Pain and Headache Reports*, *22*(4), Article 30. https://doi.org/10.1007/s11916-018-0684-6

Drossman, D. A. (2016). Functional gastrointestinal disorders: History, pathophysiology, clinical features and Rome IV. *Gastroenterology*. https://doi.org/10.1053/j.gastro.2016.02.032

Drossman, D. A., & Hasler, W. L. (2016). Rome IV - Functional GI disorders: Disorders of gut-brain interaction. *Gastroenterology*, *150*(6), 1257-1261. https://doi.org/10.1053/j.gastro.2016.03.035

ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S., & Church, J. C. (2016). Changes in cannabis potency over the last 2 decades (1995-2014): Analysis of current data in the United States. *Biol Psychiatry*, *79*(7), 613-619. https://doi.org/10.1016/j.biopsych.2016.01.004

Elsohly, M. A., & Slade, D. (2005). Chemical constituents of marijuana: the complex mixture of natural cannabinoids. *Life Sci*, *78*(5), 539-548. https://doi.org/10.1016/j.lfs.2005.09.011

Evans, R. W., & Whyte, C. (2013). Cyclic vomiting syndrome and abdominal migraine in adults and children. *Headache: The Journal of Head & Face Pain*, *53*(6), 984-993. https://doi.org/10.1111/head.12124

Farmer, A. D., Holt, C. B., Downes, T. J., Ruggeri, E., Del Vecchio, S., & De Giorgio, R. (2018). Pathophysiology, diagnosis, and management of opioid-induced constipation. *Lancet Gastroenterol Hepatol*, *3*(3), 203-212. https://doi.org/10.1016/S2468-1253(18)30008-6

Felton, D., Zitomersky, N., Manzi, S., & Lightdale, J. R. (2015). 13-Year-Old Girl With Recurrent, Episodic, Persistent Vomiting: Out of the Pot and Into the Fire. *Pediatrics*, *135*(4), e1060-1063. https://doi.org/10.1542/peds.2014-2116

Fleisher, D. R., Gornowicz, B., Adams, K., Burch, R., & Feldman, E. J. (2005). Cyclical vomiting syndrome in 41 adults: The illness, the patients, and problems of management [Article]. *BMC Medicine*, *3*(20). https://doi.org/10.1186/1741-7015-3-20

Freeman, T. P., Craft, S., Wilson, J., Stylianou, S., ElSohly, M., Di Forti, M., & Lynskey, M. T. (2021). Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction*, *116*(5), 1000-1010. https://doi.org/10.1111/add.15253

Freeman, T. P., Hindocha, C., Baio, G., Shaban, N. D. C., Thomas, E. M., Astbury, D., . . . Curran, H. V. (2020). Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry*, *7*(10), 865-874. https://doi.org/10.1016/S2215-0366(20)30290-X

Galli, J. A., Sawaya, R. A., & Friedenberg, F. K. (2011). Cannabinoid hyperemesis syndrome. *Curr Drug Abuse Rev*, *4*(4), 241-249.

Gelfand, A. A., & Gallagher, R. C. (2016). Cyclic vomiting syndrome versus inborn errors of metabolism: A review with clinical recommendations. *Headache*, *56*(1), 215-221. https://doi.org/10.1111/head.12749

Geraghty, D. P., Mazzone, S. B., Carter, C., & Kunde, D. A. (2011). Effects of systemic capsaicin treatment on TRPV1 and Tachykinin NK(1) receptor distribution and function in the nucleus of the solitary tract of the adult rat. *Pharmacology*, *87*(3-4), 214-223. https://doi.org/10.1159/000324530

Gomila, I., Barceló, B., Rosell, A., Avella, S., Sahuquillo, L., & Dastis, M. (2017). Cross-Reactivity of Pantoprazole with Three Commercial Cannabinoids Immunoassays in Urine. *J Anal Toxicol*, *41*(9), 760-764. https://doi.org/10.1093/jat/bkx047

Gubatan, J., Staller, K., Barshop, K., & Kuo, B. (2016). Cannabis abuse is increasing and associated with increased emergency department utilization in gastroenterology patients. *Dig Dis Sci*, *61*(7), 1844-1852. https://doi.org/10.1007/s10620-016-4090-9

Hanus, L. O. (2009). Pharmacological and therapeutic secrets of plant and brain (endo)cannabinoids. *Med Res Rev*, *29*(2), 213-271. https://doi.org/10.1002/med.20135

Hasler, W. L., Levinthal, D. J., Tarbell, S. E., Adams, K. A., Li, B. U. K., Issenman, R. M., . . . Venkatesan, T. (2019). Cyclic vomiting syndrome: Pathophysiology, comorbidities, and future research directions. *Neurogastroenterol Motil*, *31 Suppl 2*, e13607. https://doi.org/10.1111/nmo.13607

Hayes, W. J., VanGilder, D., Berendse, J., Lemon, M. D., & Kappes, J. A. (2018). Cyclic vomiting syndrome: Diagnostic approach and current management strategies. *Clin Exp Gastroenterol*, *11*, 77-84. https://doi.org/10.2147/ceg.s136420

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. *Neurogastroenterol Motil*, *23*(5), 439-443. https://doi.org/10.1111/j.1365-2982.2011.01679.x

Hejazi, R. A., & McCallum, R. W. (2011). Review article: Cyclic vomiting syndrome in adults - rediscovering and redefining an old entity [Review]. *Alimentary Pharmacology and Therapeutics*, *34*(3), 263-273. https://doi.org/10.1111/j.1365-2036.2011.04721.x

Hejazi, R. A., & McCallum, R. W. (2014). Cyclic vomiting syndrome: Treatment options. *Exp Brain Res*, *232*(8), 2549-2552. https://doi.org/10.1007/s00221-014-3989-7

Hermus, I. P., Willems, S. J., Bogman, A. C., Janssen, P. K., Brabers, L., & Schieveld, J. N. (2016). Cyclic vomiting syndrome: An update illustrated by a case report. *Prim Care Companion CNS Disord*, *18*(3). https://doi.org/10.4088/PCC.15br01912

Hopkins, C. Y., & Gilchrist, B. L. (2013). A case of cannabinoid hyperemesis syndrome caused by synthetic cannabinoids. *J Emerg Med*, *45*(4), 544-546. https://doi.org/10.1016/j.jemermed.2012.11.034

Irwin, S., Barmherzig, R., & Gelfand, A. (2017). Recurrent gastrointestinal disturbance: Abdominal migraine and cyclic vomiting syndrome. *Curr Neurol Neurosci Rep*, *17*(3), 21. https://doi.org/10.1007/s11910-017-0731-4

Issenman, R. (2017). A recurrent theme: A nationwide analysis of hospitalization for cyclic vomiting syndrome [Editorial]. *Digestive Diseases and Sciences*, *62*(8), 1844-1846. https://doi.org/10.1007/s10620-017-4485-2

Izzo, A. A., & Sharkey, K. A. (2010). Cannabinoids and the gut: New developments and emerging concepts [Review]. *Pharmacology and Therapeutics*, *126*(1), 21-38. https://doi.org/10.1016/j.pharmthera.2009.12.005

Joseph, J., Wang, S., Lee, J., Ro, J. Y., & Chung, M. K. (2013). Carboxyl-terminal domain of transient receptor potential vanilloid 1 contains distinct segments differentially involved in capsaicin- and heat-induced desensitization. *J Biol Chem*, *288*(50), 35690-35702. https://doi.org/10.1074/jbc.M113.513374

Katona, I. (2009). Endocannabinoid receptors: CNS localization of the CB_1 cannabinoid receptor. *Curr Top Behav Neurosci*, *1*, 65-86. https://doi.org/10.1007/978-3-540-88955-7_3

Keller, K., Desuki, A., Hobohm, L., Münzel, T., & Ostad, M. A. (2015). Acute episode of cyclic vomiting syndrome preceded by arterial hypertension – case presentation and review [Article]. *Netherlands Journal of Medicine*, *73*(8), 379-382.

Koloski, N. A., Jones, M., Kalantar, J., Weltman, M., Zaguirre, J., & Talley, N. J. (2012). The brain-gut pathway in functional gastrointestinal disorders is bidirectional: A 12-year prospective population-based study. *Gut*, *61*(9), 1284-1290. https://doi.org/10.1136/gutjnl-2011-300474

Kovacic, K., Sood, M., & Venkatesan, T. (2018). Cyclic vomiting syndrome in children and adults: What is new in 2018? *Curr Gastroenterol Rep*, *20*(10), 46. https://doi.org/10.1007/s11894-018-0654-5

Kum, V., Bell, A., Fang, W., & VanWert, E. (2021). Efficacy of topical capsaicin for cannabinoid hyperemesis syndrome in a pediatric and adult emergency department. *Am J Emerg Med*, *49*, 343-351. https://doi.org/10.1016/j.ajem.2021.06.049

Kumar, N., Bashar, Q., Reddy, N., Sengupta, J., Ananthakrishnan, A., Schroeder, A., . . . Venkatesan, T. (2012). Cyclic Vomiting Syndrome (CVS): Is there a difference based on onset of symptoms - pediatric versus adult? *BMC Gastroenterology*, *12*(1), 52-52. https://doi.org/10.1186/1471-230X-12-52

Lapoint, J., Meyer, S., Yu, C. K., Koenig, K. L., Lev, R., Thihalolipavan, S., . . . Kahn, C. A. (2018). Cannabinoid hyperemesis syndrome: Public health implications and a novel

model treatment guideline [Article]. *Western Journal of Emergency Medicine*, *19*(2), 380-386. https://doi.org/10.5811/westjem.2017.11.36368

Laprairie, R. B., Bagher, A. M., Kelly, M. E., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol*, *172*(20), 4790-4805. https://doi.org/10.1111/bph.13250

Lee, A., & Coralic, Z. (2021). Use of Capsaicin Cream in Cannabinoid Hyperemesis Syndrome in Patients Presenting to the Emergency Department. *Ann Pharmacother*, 10600280211018516. https://doi.org/10.1177/10600280211018516

Lee, L. Y., Abbott, L., Mahlangu, B., Moodie, S. J., & Anderson, S. (2012). The management of cyclic vomiting syndrome: a systematic review. *Eur J Gastroenterol Hepatol*, *24*(9), 1001-1006. https://doi.org/10.1097/MEG.0b013e328355638f

LenglarT, L., Caula, C., Moulding, T., Lyles, A., Wohrer, D., & Titomanlio, L. (2021). Brain to Belly: Abdominal Variants of Migraine and Functional Abdominal Pain Disorders Associated With Migraine. *J Neurogastroenterol Motil*, *27*(4), 482-494. https://doi.org/10.5056/jnm20290

Levinthal, D. J. (2016). The cyclic vomiting syndrome threshold: A framework for understanding pathogenesis and predicting successful treatments. *Clin Transl Gastroenterol*, *7*(10), e198. https://doi.org/10.1038/ctg.2016.55

Levinthal, D. J., & Bielefeldt, K. (2014). Adult cyclical vomiting syndrome: A disorder of allostatic regulation? *Exp Brain Res*, *232*(8), 2541-2547. https://doi.org/10.1007/s00221-014-3939-4

Li, B. U. K., Lefevre, F., Chelimsky, G. G., Boles, R. G., Nelson, S. P., Lewis, D. W., . . . Rudolph, C. D. (2008). North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*, *47*(3), 379-393. https://doi.org/10.1097/MPG.0b013e318173ed39

Li, B. U. K., Murray, R. D., Heitlinger, L. A., Robbins, J. L., & Hayes, J. R. (1998). Heterogeneity of diagnoses presenting as cyclic vomiting. *Pediatrics*, *102*(3 Pt 1), 583-587.

Liu, X., Villamagna, A., & Yoo, J. (2017). The importance of recognizing cannabinoid hyperemesis syndrome from synthetic marijuana use [Letter]. *Journal of Medical Toxicology*, *13*(2), 199-200. https://doi.org/10.1007/s13181-017-0612-x

Lo Vecchio, S., Andersen, H. H., Elberling, J., & Arendt-Nielsen, L. (2021). Sensory defunctionalization induced by 8% topical capsaicin treatment in a model of ultraviolet-B-induced cutaneous hyperalgesia. *Exp Brain Res*. https://doi.org/10.1007/s00221-021-06170-0

Lombard, H. C. (1861). Description d'une névrose de la digestion, caratérisée par des crises périodiques de vommissements et une profonde modification de l'assimilation. *Gazette Médicale de Paris*, *20*, 312-314.

Lua, J., Olney, L., & Isles, C. (2019). Cannabis hyperemesis syndrome: still under recognised after all these years. *J R Coll Physicians Edinb*, *49*(2), 132-134. https://doi.org/10.4997/JRCPE.2019.210

McCloskey, K., Goldberger, D., Rajasimhan, S., McKeever, R., & Vearrier, D. (2017). Use of topical capsaicin cream for the treatment of cannabinoid hyperemesis syndrome [Conference Abstract]. *Clinical Toxicology*, *55*(7), 828-829. https://doi.org/10.1080/15563650.2017.1348043

McConachie, S. M., Caputo, R. A., Wilhelm, S. M., & Kale-Pradhan, P. B. (2019). Efficacy of Capsaicin for the Treatment of Cannabinoid Hyperemesis Syndrome: A Systematic Review. *Ann Pharmacother*, *53*(11), 1145-1152. https://doi.org/10.1177/1060028019852601

McPartland, J. M., Agraval, J., Gleeson, D., Heasman, K., & Glass, M. (2006). Cannabinoid receptors in invertebrates. *J Evol Biol*, *19*(2), 366-373. https://doi.org/10.1111/j.1420-9101.2005.01028.x

Mechoulam, R., & Shvo, Y. (1963). Hashish. I. The structure of cannabidiol. *Tetrahedron*, *19*(12), 2073-2078.

Mooers, H., Srivastava, S., Garacci, E., & Venkatesan, T. (2021). Retrospective review of patients treated for cyclic vomiting syndrome with topiramate. *Aliment Pharmacol Ther*, *54*(2), 153-159. https://doi.org/10.1111/apt.16457

Morgan, C. J., Freeman, T. P., Schafer, G. L., & Curran, H. V. (2010). Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. *Neuropsychopharmacology*, *35*(9), 1879-1885. https://doi.org/10.1038/npp.2010.58

Muller, C., Morales, P., & Reggio, P. H. (2018). Cannabinoid Ligands Targeting TRP Channels. *Front Mol Neurosci*, *11*, 487. https://doi.org/10.3389/fnmol.2018.00487

Navarrete, F., García-Gutiérrez, M. S., Gasparyan, A., Austrich-Olivares, A., & Manzanares, J. (2021). Role of Cannabidiol in the Therapeutic Intervention for Substance Use Disorders. *Front Pharmacol*, *12*, 626010. https://doi.org/10.3389/fphar.2021.626010

Nourbakhsh, M., Miller, A., Gofton, J., Jones, G., & Adeagbo, B. (2018). Cannabinoid hyperemesis syndrome: Reports of fatal cases. *J Forensic Sci*. https://doi.org/10.1111/1556-4029.13819

Parker, L. A., Kwiatkowska, M., Burton, P., & Mechoulam, R. (2004). Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew).

Psychopharmacology (Berl), *171*(2), 156-161. https://doi.org/10.1007/s00213-003-1571-2

Peng, J., Fan, M., An, C., Ni, F., Huang, W., & Luo, J. (2022). A narrative review of molecular mechanism and therapeutic effect of cannabidiol (CBD). *Basic Clin Pharmacol Toxicol*, *130*(4), 439-456. https://doi.org/10.1111/bcpt.13710

Pergolizzi, J. V., LeQuang, J. A., & Bisney, J. F. (2019). Cannabinoid Hyperemesis. *Med Cannabis Cannabinoids*, *1*(2), 73-95. https://doi.org/10.1159/000494992

Pertwee, R. G. (2008). The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*, *153*(2), 199-215. https://doi.org/10.1038/sj.bjp.0707442

Pisanti, S., Malfitano, A. M., Ciaglia, E., Lamberti, A., Ranieri, R., Cuomo, G., . . . Bifulco, M. (2017). Cannabidiol: State of the art and new challenges for therapeutic applications. *Pharmacol Ther*, *175*, 133-150. https://doi.org/10.1016/j.pharmthera.2017.02.041

Prakash, C., & Clouse, R. E. (1999). Cyclic vomiting syndrome in adults: Clinical features and response to tricyclic antidepressants. *Am J Gastroenterol*, *94*(10), 2855-2860. https://doi.org/10.1111/j.1572-0241.1999.01428.x

Radwan, M. M., Chandra, S., Gul, S., & ElSohly, M. A. (2021). Cannabinoids, Phenolics, Terpenes and Alkaloids of. *Molecules*, *26*(9). https://doi.org/10.3390/molecules26092774

Rajaram Manoharan, S. V. R., Aggarwal, R., & Taneli, T. (2018). Cannabinoid hyperemesis syndrome: A case report [Letter]. *Asian Journal of Psychiatry*, *34*, 64. https://doi.org/10.1016/j.ajp.2018.04.013

Rashid, A. N.-S., Taminiau, J. A., Benninga, M. A., Saps, M., Tabbers, M. M., & Nassar-Sheikh Rashid, A. (2016). Definitions and outcome measures in pediatric functional upper gastrointestinal tract disorders: A systematic review. *Journal of Pediatric Gastroenterology & Nutrition*, *62*(4), 581-587. https://doi.org/10.1097/MPG.0000000000000973

Richards, J. R. (2017). Cannabinoid hyperemesis syndrome: A disorder of the HPA axis and sympathetic nervous system? *Med Hypotheses*, *103*, 90-95. https://doi.org/10.1016/j.mehy.2017.04.018

Richards, J. R., Lapoint, J. M., & Burillo-Putze, G. (2018). Cannabinoid hyperemesis syndrome: Potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment [Review]. *Clinical Toxicology*, *56*(1), 15-24. https://doi.org/10.1080/15563650.2017.1349910

Roberts, C. (2020). Science reveals the cannabis industry's greatest lie: You're buying weed wrong (and so is everyone else). *Forbes*. Retrieved October 24, 2021, from https://www.forbes.com/sites/chrisroberts/2020/06/16/science-reveals-the-cannabis-

industrys-greatest-lie-youre-buying-weed-wrong-and-so-is-everyone-else/?sh=4f48282a2ee3

Rock, E. M., Goodwin, J. M., Limebeer, C. L., Breuer, A., Pertwee, R. G., Mechoulam, R., & Parker, L. A. (2011). Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews. *Psychopharmacology (Berl)*, *215*(3), 505-512. https://doi.org/10.1007/s00213-010-2157-4

Rock, E. M., & Parker, L. A. (2021). Constituents of Cannabis Sativa. *Adv Exp Med Biol*, *1264*, 1-13. https://doi.org/10.1007/978-3-030-57369-0_1

Romano, C., Dipasquale, V., Rybak, A., Comito, D., & Borrelli, O. (2018). An overview of clinical management of cyclic vomiting syndrome in childhood [Article in Press]. *Current Medical Research and Opinion*. https://doi.org/10.1080/03007995.2018.1445983

Rong, C., Lee, Y., Carmona, N. E., Cha, D. S., Ragguett, R. M., Rosenblat, J. D., . . . McIntyre, R. S. (2017). Cannabidiol in medical marijuana: Research vistas and potential opportunities. *Pharmacol Res*, *121*, 213-218. https://doi.org/10.1016/j.phrs.2017.05.005

Rosen, S. (2019). Personal communication: Discussion of CVS patients available for study. In.

Rosen, S., Diaz, R., Garacci, Z., Kumar, V. C. S., Thyarala, S. R., Hillard, C. J., & Venkatesan, T. (2021). Hot-Water Bathing Improves Symptoms in Patients with Cyclic Vomiting Syndrome and Is Modulated by Chronic Cannabis Use. *Dig Dis Sci*, *66*(4), 1153-1161. https://doi.org/10.1007/s10620-020-06343-x

Rosen, S., & Singla, A. (2019). Personal Communication: Email discussion regarding specific sources on the epidemiology of CVS. In.

Ruberto, A. J., Sivilotti, M. L. A., Forrester, S., Hall, A. K., Crawford, F. M., & Day, A. G. (2020). Intravenous Haloperidol Versus Ondansetron for Cannabis Hyperemesis Syndrome (HaVOC): A Randomized, Controlled Trial. *Ann Emerg Med*. https://doi.org/10.1016/j.annemergmed.2020.08.021

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*, *66*(2), 234-246. https://doi.org/10.1016/j.mehy.2005.08.026

Sagar, R. C., & Ford, A. C. (2017). Cyclic vomiting syndrome: Randomized controlled trials are also needed in adults. *Am J Gastroenterol*, *112*(11), 1752-1753. https://doi.org/10.1038/ajg.2017.293

Sagar, R. C., Sood, R., Gracie, D. J., Gold, M. J., To, N., Law, G. R., & Ford, A. C. (2018). Cyclic vomiting syndrome is a prevalent and under-recognized condition in the gastroenterology outpatient clinic. *Neurogastroenterol Motil*, *30*(1). https://doi.org/10.1111/nmo.13174

Schmulson, M. J., & Drossman, D. A. (2017). What is new in Rome IV [Review]. *Journal of Neurogastroenterology and Motility*, *23*(2), 151-163. https://doi.org/10.5056/jnm16214

Schreck, B., Wagneur, N., Caillet, P., Gerardin, M., Cholet, J., Spadari, M., . . . Victorri-Vigneau, C. (2018). Cannabinoid hyperemesis syndrome: Review of the literature and of cases reported to the French addictovigilance network. *Drug Alcohol Depend*, *182*, 27-32. https://doi.org/10.1016/j.drugalcdep.2017.09.038

Shannon, S., & Opila-Lehman, J. (2015). Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integr Med (Encinitas)*, *14*(6), 31-35.

Sharkey, K. A., Cristino, L., Oland, L. D., Van Sickle, M. D., Starowicz, K., Pittman, Q. J., . . . Di Marzo, V. (2007). Arvanil, anandamide and N-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB1 and vanilloid TRPV1 receptors in the ferret. *Eur J Neurosci*, *25*(9), 2773-2782. https://doi.org/10.1111/j.1460-9568.2007.05521.x

Shearer, J., Luthra, P., & Ford, A. C. (2018). Cyclic vomiting syndrome: A case series and review of the literature. *Frontline Gastroenterol*, *9*(1), 2-9. https://doi.org/10.1136/flgastro-2016-100705

Simonetto, D. A., Oxentenko, A. S., Herman, M. L., & Szostek, J. H. (2012). Cannabinoid hyperemesis: A case series of 98 patients. *Mayo Clin Proc*, *87*(2), 114-119. https://doi.org/10.1016/j.mayocp.2011.10.005

Smith, H. S., & Laufer, A. (2014). Opioid induced nausea and vomiting. *Eur J Pharmacol*, *722*, 67-78. https://doi.org/10.1016/j.ejphar.2013.09.074

Sontineni, S. P., Chaudhary, S., Sontineni, V., & Lanspa, S. J. (2009). Cannabinoid hyperemesis syndrome: Clinical diagnosis of an underrecognised manifestation of chronic cannabis abuse. *World J Gastroenterol*, *15*(10), 1264-1266.

Sorensen, C. J., DeSanto, K., Borgelt, L., Phillips, K. T., & Monte, A. A. (2017). Cannabinoid hyperemesis syndrome: Diagnosis, pathophysiology, and treatment - a systematic review [Review]. *Journal of Medical Toxicology*, *13*(1), 71-87. https://doi.org/10.1007/s13181-016-0595-z

Soriano-Co, M., Batke, M., & Cappell, M. S. (2010). The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: A report of eight cases in the United States. *Dig Dis Sci*, *55*(11), 3113-3119. https://doi.org/10.1007/s10620-010-1131-7

Sperber, A. D., Bangdiwala, S. I., Drossman, D. A., Ghoshal, U. C., Simren, M., Tack, J., . . . Palsson, O. S. (2021). Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology*, *160*(1), 99-114.e113. https://doi.org/10.1053/j.gastro.2020.04.014

Stanghellini, V., Chan, F. K. L., Hasler, W. L., Malagelada, J. R., Suzuki, H., Tack, J., & Talley, N. J. (2016). Gastroduodenal disorders [Article]. *Gastroenterology*, *150*(6), 1380-1392. https://doi.org/10.1053/j.gastro.2016.02.011

Straiker, A., Dvorakova, M., Zimmowitch, A., & Mackie, K. (2018). Cannabidiol Inhibits Endocannabinoid Signaling in Autaptic Hippocampal Neurons. *Mol Pharmacol*, *94*(1), 743-748. https://doi.org/10.1124/mol.118.111864

Stumpf, J. L., & Williams, L. D. (2020). Management of Cannabinoid Hyperemesis Syndrome: Focus on Capsaicin. *J Pharm Pract*, 897190020934289. https://doi.org/10.1177/0897190020934289

Thavamani, A., Umapathi, K. K., Velayuthan, S., & Sankararaman, S. (2022). Burden of psychiatric disorders in patients with cyclic vomiting syndrome - Need for aggressive screening and early intervention. *Dig Liver Dis*, *54*(2), 287-289. https://doi.org/10.1016/j.dld.2021.11.020

Turcotte, C., Blanchet, M. R., Laviolette, M., & Flamand, N. (2016). The CB2 receptor and its role as a regular of inflammation. *Cell Mol Life Sci*, *73*(23), 4449-4470. https://doi.org/10.1007/s00018-016-2300-4

Valdovinos, E. M., Frazee, B. W., Hailozian, C., Haro, D. A., & Herring, A. A. (2020). A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department. *J Clin Gastroenterol*, *54*(4), 327-332. https://doi.org/10.1097/MCG.0000000000001258

Venkatesan, T., Hillard, C. J., Rein, L., Banerjee, A., & Lisdahl, K. (2020). Patterns of Cannabis Use in Patients With Cyclic Vomiting Syndrome. *Clin Gastroenterol Hepatol*, *18*(5), 1082-1090.e1082. https://doi.org/10.1016/j.cgh.2019.07.039

Venkatesan, T., Levinthal, D. J., Li, B. U. K., Tarbell, S. E., Adams, K. A., Issenman, R. M., . . . Hasler, W. L. (2019). Role of chronic cannabis use: Cyclic vomiting syndrome vs cannabinoid hyperemesis syndrome. *Neurogastroenterol Motil*, *31 Suppl 2*, e13606. https://doi.org/10.1111/nmo.13606

Venkatesan, T., Levinthal, D. J., Tarbell, S. E., Jaradeh, S. S., Hasler, W. L., Issenman, R. M., . . . Li, B. U. K. (2019). Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association. *Neurogastroenterol Motil*, *31 Suppl 2*, e13604. https://doi.org/10.1111/nmo.13604

Venkatesan, T., Prieto, T., Barboi, A., Li, B., Schroeder, A., Hogan, W., . . . Jaradeh, S. (2010). Autonomic nerve function in adults with cyclic vomiting syndrome: A prospective study. *Neurogastroenterol Motil*, *22*(12), 1303-1307, e1339. https://doi.org/10.1111/j.1365-2982.2010.01577.x

Venkatesan, T., Sengupta, J., Lodhi, A., Schroeder, A., Adams, K., Hogan, W. J., . . . Storr, M. (2014). An Internet survey of marijuana and hot shower use in adults with cyclic

vomiting syndrome (CVS). *Exp Brain Res*, *232*(8), 2563-2570. https://doi.org/10.1007/s00221-014-3967-0

Venkatesan, T., Tarbell, S., Adams, K., McKanry, J., Barribeau, T., Beckmann, K., . . . Li, B. U. (2010). A survey of emergency department use in patients with cyclic vomiting syndrome. *BMC Emerg Med*, *10*, 4. https://doi.org/10.1186/1471-227x-10-4

Venkatesan, T., Zadvornova, Y., Raff, H., & Hillard, C. J. (2016). Endocannabinoid-related lipids are increased during an episode of cyclic vomiting syndrome. *Neurogastroenterol Motil*, *28*(9), 1409-1418. https://doi.org/10.1111/nmo.12843

Venkatesan, T., Zaki, E. A., Kumar, N., Sengupta, J., Ali, M., Malik, B., . . . Boles, R. G. (2014). Quantitative pedigree analysis and mitochondrial DNA sequence variants in adults with cyclic vomiting syndrome. *BMC Gastroenterology*, *14*(1), 181-181. https://doi.org/10.1186/1471-230X-14-181

von Both, I., & Santos, B. (2021). Death of a young woman with cyclic vomiting: a case report. *Forensic Sci Med Pathol*. https://doi.org/10.1007/s12024-021-00410-z

Wagner, S., Hoppe, J., Zuckerman, M., Schwarz, K., & McLaughlin, J. (2020). Efficacy and safety of topical capsaicin for cannabinoid hyperemesis syndrome in the emergency department. *Clin Toxicol (Phila)*, *58*(6), 471-475. https://doi.org/10.1080/15563650.2019.1660783

Wasilewski, A., Lewandowska, U., Mosinska, P., Watala, C., Storr, M., Fichna, J., & Venkatesan, T. (2017). Cannabinoid Receptor Type 1 and mu-Opioid Receptor Polymorphisms Are Associated With Cyclic Vomiting Syndrome. *Am J Gastroenterol*, *112*(6), 933-939. https://doi.org/10.1038/ajg.2017.73

Weiblen, G. D., Wenger, J. P., Craft, K. J., ElSohly, M. A., Mehmedic, Z., Treiber, E. L., & Marks, M. D. (2015). Gene duplication and divergence affecting drug content in Cannabis sativa. *New Phytol*, *208*(4), 1241-1250. https://doi.org/10.1111/nph.13562

Yin, A. Q., Wang, F., & Zhang, X. (2019). Integrating endocannabinoid signaling in the regulation of anxiety and depression. *Acta Pharmacol Sin*, *40*(3), 336-341. https://doi.org/10.1038/s41401-018-0051-5

Yu, E. S., Priyadharsini S S, Y., & Venkatesan, T. (2018). Migraine, cyclic vomiting syndrome, and other gastrointestinal disorders. *Curr Treat Options Gastroenterol*, *16*(4), 511-527. https://doi.org/10.1007/s11938-018-0202-2

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

Zeevenhooven, J., Koppen, I. J. N., & Benninga, M. A. (2017). The new Rome IV criteria for functional gastrointestinal disorders in infants and toddlers [Review]. *Pediatric*

Gastroenterology, Hepatology and Nutrition, *20*(1), 1-13. https://doi.org/10.5223/pghn.2017.20.1.1

Zuardi, A. W., Crippa, J. A., Hallak, J. E., Bhattacharyya, S., Atakan, Z., Martin-Santos, R., . . . Guimarães, F. S. (2012). A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. *Curr Pharm Des*, *18*(32), 5131-5140.

Černe, K. (2020). Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol. *Arh Hig Rada Toksikol*, *71*(1), 1-11. https://doi.org/10.2478/aiht-2020-71-3301

Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome: The State of the Science

Supplemental Content

English translation by James R. Lathrop, DNP, PhDc of the earliest known medical description of pediatric cyclic vomiting (Gazette_Medicale_de_Paris, 1861; Google; Lombard, 1861; Springer, personal communication, February 2019).

MEDICAL CORRESPONDENCE.

CHILDREN'S DISEASES: Notes read to the Medical Society of Geneva,

by Dr. H. CL. LOMBARD (from Geneva).

I. — DESCRIPTION OF A NEUROSIS OF DIGESTION, CHARACTERIZED BY PERIODIC CRISES OF VOMITING AND A DEEP MODIFICATION OF ASSIMILATION.

Dear colleagues,

I wish to speak to you today of a disease which I do not know how to designate and on to which I come to call your attention, hoping that you will help me solve the physiological and pathological problems of this study, to which I invite you to do.

After thirty-one years of practicing medicine, I have, seven to eight times, the opportunity to meet, in children aged 5 to 12, a very singular disease, the apparent gravity of which has always given me much anxiety. Fortunately, my fears of a fatal outcome have only occurred once, but this fatal case was enough to show that my concerns were not completely unfounded.

Let us first study the symptoms of the malady that I wish to make known; we will then go to the treatment and finally to the diagnosis, to consider causes to which this morbid condition may be attributed to.

Symptoms. The characteristic feature of this disease is incessant vomiting which occurs without any determinative cause, in the middle of the best health, and by repeated spasms

every quarter of an hour or every half hour. The expelled liquid is purely aqueous, with some glairy filaments, without a mixture of bile, blood, or food. The quantity becomes less and less significant as we move away from the onset, until finally after the vomiting has continued on for several hours there is only an evacuation of just a few small phlegm after great effort.

Intense thirst, retraction of the belly, considerable febrile movement and stubborn constipation accompany and follow the attacks of vomiting. Their duration is quite variable, but seldom exceeds forty-eight hours; they yield most often within eighteen or twenty-four hours. These vomitus spams are usually accompanied by pallor, weight loss, and facies quite similar to that observed in patients with cholera.

I could not recognize any atmospheric cause for the development of this disease that has presented itself to me in all seasons. As for the age at which it began most frequently, it is between five and seven years, and it has rarely been prolonged beyond twelve or fourteen, appearing to diminish with age and to lose in intensity what it acquires in duration; and this points out one of the most striking characters of this morbid affection: its frequent recurrences. Indeed, all the patients that I treated have presented, some weeks apart for several years; one of them, whose crises have always been very intense, continued for ten or twelve years, and even beyond, for, quite recently, at the age of eighteen, although completely free for a long time he incessantly vomited at the beginning and during the first period of a measles infection; which demonstrated to me the imprint of the disease had been deep enough for this certain disorder in his physiology to have a recurrence of symptoms which, for quite some time, were without persistence and without gravity.

This same patient presented to me another phenomenon no less remarkable, on which I desire to bring your attention. In this young man the vomiting attacks were accompanied by a very notable loss of weight; I had been in the habit of weighing him every month, so I could

see his return to health, observing nutrition repair the losses of the disease. But what was very peculiar about this patient was that every time he approached a certain weight (about 25 kilograms), he had a new crisis which made him lose weight again by 2 or 3 kilograms; then he had scarcely gone up the hill, when a new invasion of vomiting made him come down again. Several times I verified this singular phenomenon and could see it reproduce identically in the same circumstances. Subsequently, after a number of years my young friend had, in a certain way, doubled the interval between the storms, and was able to resume the growth and weight that the disease had so long suppressed.

For the rest, it is not only in this case that I have observed the profound modification made to nutrition by these attacks of vomiting which I describe. Most of my patients have remained lean, pale, and defeated for a great many years, without being able to assign any other cause than the frequent repetition of crises which prevent assimilation and may compromise their existence. Two girls, whom I followed during the long years in which they suffered from these vomiting episodes, went through very difficult times and presented all the phases of the most advanced marasmus: their anemia was pushed so far that an anasarca had invaded not only the extremities, but even the trunk and the face. And yet there was no diarrhea, nor albuminuria, nor cough, and the most scrupulous examination of all the organs could not recognize any organic lesion; which, moreover, has been satisfactorily demonstrated by the restoration of health, as soon as the attacks of vomiting had disappeared.

Pathological anatomy. The only mortal case that came to my attention is that of a girl aged 7 to 8, who had been suffering from spasmodic vomiting for several years, and that I had treated frequently during these crises. She had one during her stay in the country, and the disease could not be stopped. She succumbed despite the most varied treatments and the

most assiduous of care. The autopsy showed no lesions of the gastric mucosa, which was perfectly healthy, without redness or softening, and without ulceration or erosion; the intestines, peritoneum and mesenteric glands were also found to be intact, as well as the other abdominal organs; in the end, we must recognize the disease that I now describe as vigorous but without identifiable organic cause. I insist all the more on this result due to the cadaverous examination that this young patient exhibited, yet who has succumbed as a result of a well-marked attack of the morbid affection for which I am trying to describe.

Treatment. If the therapeutic axiom is: *Naturam Morborum Ostendit Curatio*[*] and we could throw some light on the nature of this disease, it would undoubtedly be to a great advantage; but I am afraid that the result of my research in this respect is just as unsatisfactory as that of the unremarkable anatomical investigations.

I have struggled for many years, against all odds, for the treatment of the disease which occupies us, often succeeding in stopping the vomiting, and having had no fatal accident to occur, but without ever having been able to prevent its return and therefore truly establish a rational treatment.

During the crisis I have tried almost all medications. Those that usually succeed in stopping the contractions are: The opiates, bismuth sub-nitrate, and nux-vomica, along with an ice made from milk and water, while at the same time the application of a dressing of opiate poultice to the abdominal walls.

But, in the end, what has been the most successful for me is, without a doubt, the total abstinence from either beverages or medicines. If I resisted the ardent desires of patients devoured by thirst, it is because experience has shown me that the best way to stop the

[*] Nature shows the treatment of diseases

vomiting is to not introduce anything into the stomach. It is true that, as soon as there is a little calm, we may first give a teaspoon of ice water at rare intervals, and then a tablespoonful; finally, when eight to twelve hours have elapsed relentlessly, we may start a chicken broth or cold milk, also by spoonful. Nothing is more important than to police these first feeding trials, because relapses easily occur under the influence of too hasty of drink or of too much food.

It is rare that in convalescence the intestinal functions are restored by themselves, and if an enema fails, then it is necessary to have remedy of some evacuator which is of the least irritating type, such as castor oil or the dried sap of manna.

Nature and designation of the disease. And now that I have brought to you these elements, describing the symptoms, the progress, and the termination of this disease, we now move on to the etiological and pathological problems.

What is this morbid condition that is characterized by periodic vomiting attacks for many years, profoundly affecting nutrition, and capable of causing death, either in an acute manner under the influence of a violent crisis of vomiting, or in a chronic manner by bringing about anemia and severe wasting?

It seems obvious to me that it is not a disease of gastric inflammation, because in that case the symptoms would be continuous, or if they took an intermittent form, they would not disappear completely and would not allow the patients to resume a certain degree of strength and weight gain in the interval between crises. Moreover, the total absence of inflammatory lesions in the autopsy mentioned above seems to me to contradict this supposition more formally.

This is certainly not what Messrs. Rilliet and Barthez have referred to as chronic catarrh of the stomach, whose mild form, according to these authors, is characterized by bloating of the abdomen with alternating diarrhea and constipation, symptoms that are absolutely missing in

this disease. Furthermore, even in its severe form, fever is generally lacking, and, in the majority of the cases under my observation, while the stomach cannot support any food, digestion itself was only a little disturbed during the period of the crises. Besides, what is known as the catarrhal element, with or without localization, also seemed to be absent from the syndrome we are discussing. I have never observed any diarrhea or bronchial complication, let alone continuous febrile movement or a persistence of the or a persistence of the symptoms beyond the second or third day. Fever, when present, has always ceased at the same time or soon after the vomiting period, and thus catarrhs does not seem to be a significant component of the disease that I now describe, however modified of a catarrhal form it may be.

The vomiting I speak of also cannot be better regarded as purely spasmodic; for it is not natural to suppose that a simple cramp of the gastric muscles, though frequently recurring, may bring about such a pronounced period of vomiting, and lead to such marked changes of digestive assimilation.

Is this possibly a gastralgia, a kind of stomach neuralgia that causes the symptoms we have just listed? I do not think so either, because the pain appears with the efforts of the vomiting and disappears with them, so that one cannot say anything except that the persistence of the efforts makes them painful, exactly as in any other disease which causes incessant vomiting, and besides, I have never seen them alternate with any other pain, nor present those transformations so frequent in neural or rheumatic diseases, often under the influence of seasonal changes.

What, then, ultimately is the anatomy of this nefarious condition that I have described? It seems to me to reside entirely in some essential and primitive modification of the nutritive functions, which are sometimes suspended by gastric spasms, and sometimes deeply modified

by a temporary arrest of nutritive assimilation. All of this is very vague, I agree, but it seems to me difficult to specify in a more complete manner a disease which can lead to death without appreciable lesion in its sense, and which must therefore return to the class so elastic and obsessed with neuroses. So that in the end I think I have described a *neurosis of digestion*, characterized by more or less periodic crises of vomiting and by a profound modification of the digestive and assimilative forces.

To those who may consider themselves more knowledgeable and who may seek to find a better description, I would be the first to rejoice, especially if such study gives rise to some satisfactory therapeutic indication and that a new method of treatment does not simply relieve the symptoms but manages to fight victoriously over the cause of this illness itself.

References

Gazette_Medicale_de_Paris. (1861). Digitized by the University of Michigan and Published Online by the Hathi Trust Digital Library (original pages 312-314; digital document pages 360-362). Accessed January 2019 from: https://babel.hathitrust.org/cgi/pt?id=mdp.39015023983078&view=1up&seq=360

Google. *Google Translate*. Accessed February 2019 from: https://translate.google.com/
Lombard, H. C. (1861). Description d'une névrose de la digestion, caratérisée par des crises

Périodiques de vommissements et une profonde modification de l'assimilation. *Gazette Médicale de Paris*, *20*, 312-314.

Springer, E. (personal communication, February 2019). Proofreading and correcting Google Translate erros.

CHAPTER 3

Manuscript Two

Paper formatting is in style of Digestive Diseases and Sciences (including an abstract with the maximum allowed length of 250 words, no abbreviations in the abstract, and a listing of up to 8 keywords).

Original research study.

Planned submission for publication once all authors have signed off on the final draft.

Cannabis, Opioids and the Clinical Characteristics of Adult Cyclic Vomiting Syndrome

[Original Research Study]

James R. Lathrop, DNP, FNP, ARNP School of Nursing, University of Washington, Seattle, WA

Margaret M. Heitkemper, PhD, RN, Professor, Department of Biobehavioral Nursing & Health Informatics, School of Nursing, University of Washington, Seattle, WA

Sheldon N. Rosen, MD, Clinical Associate Professor, Division of Gastroenterology, School of Medicine, University of Washington, Seattle, WA

Kendra Kamp PhD, MS, RN, Assistant Professor in the Department of Biobehavioral Nursing & Health Informatics, School of Nursing, University of Washington, Seattle, WA

Diana Taibi Buchanan, PhD, RN, Affiliate Associate Professor, Department of Biobehavioral Nursing & Health Informatics, School of Nursing, University of Washington, Seattle, WA

Mailing Address and Phone/Fax:
c/o Margaret M. Heitkemper, PhD, RN, FAAN, Professor,
School of Nursing, Department of Biobehavioral Nursing and Health Informatics
Box 357266, University of Washington, Seattle, WA 98195
Office: 206-818-5527 Fax: 206-543-3624

Conflicts of interest and source of funding: This work was performed for scholastic credit towards the completion of a PhD dissertation at the University of Washington, School of Nursing. The principal author reports current ownership of a cannabis retail business. The University of Washington provides hosting to the REDCap system with support of an NIH to NCATS grant, UL1 TR002319.

Abstract

Background. Patients with cyclic vomiting syndrome often use cannabis for their symptoms, while opioids may be prescribed for abdominal pain. However, cannabis can cause a cyclic vomiting illness, cannabis hyperemesis syndrome, while opioid-related complications can develop as abdominal pain.

Aims. The primary aim of this study was to describe the characteristics of adult patients with cyclic vomiting syndrome. Secondary aims were to examine cannabis and opioid use in relation to healthcare utilization, to explore the relationship of cannabis use with opioid dosing, and to explore the potential of coalescence.

Methods. A chart review of 130 adults seen between 2014-2020 with a diagnosis of cyclic vomiting syndrome was performed. Demographic and medical history data was collected, and study variables were compared by four groups: Non-users, cannabis-only, opioids-only, and patients who use both cannabis and opioids.

Results. The cohort included 69% women, 31% men, with a mean age of 41.6 years. Onset of symptoms ranged from early childhood to the later decades of life, while the mean time from onset of symptoms to diagnosis was 8.9 years. Relief of symptoms with hot water bathing was reported by 45% of the cohort, while 35% mentioned that sleep could terminate an episode. A coalescent pattern was noted in 22% of the cohort.

Conclusions. This study describes adults with cyclic vomiting syndrome, provides insight on the use of cannabis and prescribed opiates within in this population and offers sleep as a new variable to consider with future treatments. The potential phenomenon of coalescence is explored.

Keywords: Cannabis Hyperemesis Syndrome, Coalescence, Cyclic vomiting syndrome, Disorder of Gut-Brain Interaction, Hot-water bathing, Narcotic effect.

Introduction

Adult Cyclic Vomiting Syndrome (CVS) is a rare chronic condition with no specific cure, an unclear etiology, and a varied course of illness [1, 2]. Pediatric CVS (with its classic resolution around puberty) was first described by Dr. H. CL. Lombard at a conference with the Medical Society of Geneva, France in 1861 [3, 4]. Yet adult CVS has only been recognized more recently with the first diagnostic criteria published in the Rome III consensus statement in 2006 [5]. An International Classification of Diseases (ICD) code for CVS in migraine was established in 2015, with an updated code specific to CVS unrelated to migraine in 2019 [6]. There are no diagnostic biomarkers for CVS, and the syndrome is described both as a Functional Gastrointestinal Disorder as well as a Disorder of Gut-Brain Interaction within the Rome IV framework [7, 8]. The cyclic nature of the illness is a defining characteristic and therefore the condition cannot be diagnosed at the outset [9]. The broad differential of nausea and vomiting leaves CVS a diagnosis of exclusion, and the delay from symptom onset to diagnosis can be in the order of years [10]. A unique behavior of seeking relief through prolonged hot shower bathing may be supportive of the diagnosis, but this is only reported in approximately 50% of CVS cases, and the amount of relief achieved with this is highly variable [10-12].

The acute phase of CVS is characterized by a rapid onset of intense vomiting, with or without nausea, and is often associated with crampy abdominal pain. The episodes may last from a few hours to several days interspersed with a wellness period of weeks to months [13]. The condition may range from stable recurrence to a progression of symptom frequency and a shortening of the wellness phase, described as coalescence [14, 15]. Treatment guidelines, drawn almost entirely from case reports and expert opinion, are based on the recommendations from two professional organizations working in concert: The American Neurogastroenterology and

Motility Society and the Cyclic Vomiting Syndrome Association [16]. These guidelines are supported by a low number of randomized controlled trials [17, 18].

Patients with CVS have a limited set of management options, both pharmacological and non-pharmacological, which are used with varying degrees of success. Medications used to prevent or abort emetic episodes include the benzodiazepines, antihistamines, phenothiazines, other anti-emetics, tricyclic antidepressants, the triptans and antiepileptic drugs, as well as supplements such as mitochondrial supplements and cannabis [17, 19]. Patients with CVS may also be treated with opioids for abdominal pain and cramping [20]. However, the use of cannabis or opioids can create additional problems. Specifically, heavy and long-term cannabis consumption can lead to a similar cyclic vomiting illness, known as cannabis hyperemesis syndrome (CHS) [21-23] while frequent use of opioids can result in abdominal pain through several different mechanisms [24-33]. Overall, the use of cannabis and/or opioids has not been systematically studied in patients with CVS, and recommendations for either cannabis or opioid use in this group of patients is an area that needs further investigation [15, 34, 35].

The primary purpose of this study was to describe the demographics and clinical characteristics of a cohort of patients with CVS seen at a specialty clinic. The second aim of this study was to examine the individual and joint effects of cannabis use and opioid use in relation to healthcare utilization in these patients, including number of hospitalization days, number of clinic visits, and number of emergency department (ED) visits over a two-year period. A third aim was to determine if there was a difference in prescribed opioid dosing (as calculated by milligram equivalent dose of morphine) between the patients using cannabis and opioids for their symptoms vs. the patients not using cannabis but were using opioids. Last, as an exploratory aim, we describe a subgroup of patients who may be experiencing CVS coalescence.

Methods

Design, Study Population, Human Subjects

The first author (J.R.L.) conducted a retrospective chart review of 164 adult patients with a diagnosis code of CVS seen between 2014-2020 at the University of Washington (UW) Digestive Health Center in Seattle, Washington. The study procedures were approved by the UW Institutional Review Board. Data collection occurred through a secure remote server into the Digestive Health Center's electronic medical record (EMR) system, Epic [36]. The cases were identified by three ICD-10 billing codes G43.A0, G43.A1, and R11.15. The data collection form was developed for this study using the Research Electronic Data Capture (REDCap) system hosted by the UW Institute of Translational Health Sciences [37, 38]. Appendix A provides the contents of the data collection tool, and these tools are available for download through the REDCap consortium [39]. All patients were either evaluated by, or referred to, a co-author (S.N.R.), who is a board-certified gastroenterologist, and the visit used for data collection was the most recent CVS visit identified in the patient chart. Exclusion criteria included prisoner status, age < 18 at the time of the most recent CVS-related visit, and patients with no diagnosis of CVS. After chart review of the initial 164 cases, 34 cases were excluded. Three cases were excluded due to age < 18 at the time of the most recent CVS visit, and 31 cases did not meet diagnostic criteria for CVS as determined by the treating physician, leaving 130 cases for final data analysis (see Appendix B for a listing of the excluded cases).

Study Variables

Demographics, Clinical Characteristics, and Cannabis Use. Demographic variables included age, self-reported gender and ethnicity, partner status, as well as disability status and comorbid conditions. CVS history was characterized by length of time with CVS diagnosis, age

at onset of first symptoms, frequency of episodes, and change in frequency over time. Comorbid psychiatric diagnoses included conditions such as depression, anxiety, suicide ideation, and possible addiction (identified by self-report of early-age cannabis use, concurrent tobacco use, heavy alcohol use, and other drug use). Past medical history included migraine, CVS history as a child, previous surgeries, other functional bowel disorders such as irritable bowel syndrome, and any temporal relationship with menstruation (catamenial CVS). Cannabis use was based on the patient's self-report. Information such as amount, route of administration, and frequency of use was collected during chart review, but for statistical analysis the variable was reduced to yes or no. Non-pharmacological symptom management including the use of hot water bathing behaviors or the use of sleep to abort an episode were set as dichotomous yes or no variables. Possible CHS and possible CVS coalescence were determined by the physician notes in the EMR and noted as yes or no.

Opioid Dose and Frequency. Opioid use was determined by whether the patient had an active prescription for opiates in the UW EMR system within the previous 30 days of the most recent CVS-related healthcare visit, or evidence of administration of opiates either during a hospital inpatient stay or ED visit within that same 30-day period. Opioid dosing was standardized between patients using a Morphine Equivalent Dose (MED)/day, calculated by the Washington State Agency Medical Directors' Group online calculator [40]. The MED value was calculated as a daily average for the 30-day period prior to the reviewed CVS visit. Additionally, an equivalent variable, the Morphine Milligram Equivalent dose (MME)/day was also gathered from the Washington State Prescription Monitoring Program for the same 30-day period [41].

Healthcare Utilization. Measures for healthcare utilization were collected in a subgroup of 51 patients with two years or more of CVS-related healthcare data retrievable from the EMR.

For this variable, clinic visits, ED presentations, and a sum of hospital days, were gathered using EMR data from the two years immediately prior to the most recent CVS visit.

Statistical Analysis

The data analysis was conducted in IBM® SPSS® Statistics version 27. Demographic and descriptive data were quantified by mean and standard deviation for continuous variables, and number and percentage for categorical variables. Statistical significance was set at $p < 0.05$. To answer the primary aim of describing the cohort in relation to cannabis and opioid use, 4 groups 1) non-users, 2) cannabis-only users, 3) opioid-only users, and 4) cannabis plus opioid users were compared using one-way ANOVA for continuous variables and Fisher's exact test for categorical variables. For the second aim evaluating if cannabis or opioid use impacts healthcare utilization, a count of clinic days, emergency department (ED) visits, and number of hospital days over a two-year period was compared against the 4 user groups. To explore the third aim evaluating if opioid use by morphine equivalence differed between cannabis-using and non-cannabis-using groups, the cannabis + opioids and the opioids-only groups were compared against the Prescription Monitoring Program MME values. For the exploratory aim of coalescence, the subset of variables with statistical significance from the demographic and clinical characteristic section were compared for differences between the coalescence group and the non-coalescence group, as well as a narrative case series was generated.

Results

Demographic and Clinical Characteristics. Cohort demographics are shown in Table 1. The sample had a mean age of 41.6 ± 15.6 years with a range of 19-84 and 69% were women. Ethnicity was self-reported as White in 60% of the sample, with only 10% reporting other ethnicities while 30% did not disclose an ethnicity. Employment status was reported as 44%

unemployed, 25% employed, and 32% unknown. For clinical characteristics, the mean time from onset of symptoms to diagnosis was 8.9 years (SD = 9.6) with a mean duration of CVS symptoms overall of 14.5 ± 12.6 years. A majority of the cohort (65%) developed their first CVS symptoms during adulthood with no childhood history of CVS. Nearly half of the cohort (49%) had an onset of symptoms in their 2nd or 3rd decade of life. For the later decades, 8.5% reported an onset in the 40's, 7% reported an onset in their 50's, 2% reported an onset in 60's, and 2% had an onset at age 70 or greater. Conversely, 30% reported continuous symptoms since either childhood or teenage years, and 7% patients reported an onset of symptoms in childhood or teenage years that resolved and then returned with a renewed onset later in life. Prescribed opioid use was noted in 35% of the cohort (as determined by an active prescription or the administration of opioids within 30 days prior to the CVS visit), while concurrent cannabis use was self-reported by 67%. A determination of possible CHS was present in 11% of the sample and early-age cannabis use was noted in 13%. Abdominal pain was a prominent symptom in 68% of all cases. A personal history of migraine was reported in 48%, with 45% reporting a positive family history of migraine. Two cases (1.5%) reported a past family history of CVS. Of the 90 women, 17% noted an association with menses, however this did not account for the percentage of post-menopausal women within the cohort.

Cannabis – Opioid Groups. Demographic characteristics were examined across four groups: *non-users*, *cannabis-only*, *opioids-only*, and *opioids + cannabis*. Fisher's exact calculation of age by the user groups demonstrated a difference between groups with a mean age of the *cannabis-only* consumers 8-years younger than the average of the other three groups (37.5 vs. 45.6, $p = 0.047$). There was also a significant effect of gender across the groups with more women in the *opioid + cannabis* group than men, and more men in the *cannabis-only* group vs.

women ($p = 0.026$). Among those reporting an ethnic identification there was no difference between groups. A difference across groups was noted for the partner status with 69% of *cannabis-only* reporting no partner and 73% of *opioids-only* reporting married or partnered status ($p = 0.020$). Employment status differed with more employed in the *non-user* group and more unemployed in the *cannabis + opioids* group ($p = 0.013$). Self-report of disability status was 17% for the total cohort and was highest in the *cannabis + opioids* group ($p = 0.003$).

Clinical characteristics were also examined across the 4 user groups. Differences were noted within the three CVS symptom frequency categories. Those experiencing the highest CVS symptom frequency (weekly or constant) were more represented in the *cannabis + opioids group*, whereas those with the lowest symptom frequency (yearly or > yearly) were more represented in the *non-users group* ($p = 0.005$). For symptom management, 45% of the cohort reported at least partial relief with hot water bathing with no significant difference across the 4 groups. Sleep was reported to improve symptoms or terminate a cycle in 35% of the sample, with no difference across the 4 groups. In the total sample, comorbid psychiatric disorders including depression (25%) and anxiety disorder (35%) did not differ across the 4 groups. Tobacco smoking was noted in 18.5% of the sample with a higher grouping in the *cannabis + opioid* group ($p = 0.017$). A possible history of opioid use disorder was noted in 14% of the sample and was highest in the 2 opioid groups ($p < 0.001$).

Healthcare Utilization. Fifty-one patients (39% of the sample) had two years or more of EMR data available immediately prior to the most recent CVS-related encounter. For those hospitalized with CVS symptoms, a 3-day length of stay represented 25% of the sample ($n = 16$, mean 21.4, median 8, mode 3, range 2 – 175 days). The mean number of Digestive Health Center clinic visits was 4.3 ± 2.8 over 2 years with CVS-related ED-discharge-to-home at approximately

1 visit / year (m 1.7, SD = 3.8, range 0 - 23). When compared across the four groups, there initially appeared to be a group difference in number of all-cause hospital days (and the subgroup of CVS – only hospital days) within the opioids-only column. However, this significance was due to an outlier case with 210 hospital days (for all cause) and 177 days (for CVS-related hospitalization) representing 5 standard deviations above the next highest value at 46 days. A sensitivity analysis removing the outlier from the relevant column resulted in no statistical significance across the groups (see Table 2).

Cannabis Opioid Interaction. Within the cohort, 46 (35.4%) participants had morphine equivalent data available for consideration of inclusion in the cannabis – opioid interaction analysis. Correlation between the chart review MED values and the prescription monitoring program MME numbers demonstrated a significant linear relationship (R^2 Linear = 0.405, see Figure 1), between daily MED (n = 21, m = 53.04 mg, SD = 72.43 mg) and daily MME for the same review period (n = 34, m = 34.15 mg, SD = 38.18 mg), $r(53) = 0.637$, $p = 0.008$. As the prescription monitoring program provided the highest number of participants with data, the MME values used for the interaction analysis evaluating for group difference between the *opioids only* and the *cannabis + opioids* group. There was no significant difference between the *opioids only* (n = 5, m = 35.7 mg, SD = 37.7 mg, range 2.5 mg – 100.0 mg) and *cannabis + opioids* groups (n = 29, m = 33.9 mg, SD = 40.1 mg, range 1.3 mg – 172.5 mg) ($p = 0.925$).

Coalescence. A coalescent pattern was reported in the physician narrative in 22% of the sample (see Table 3). Group comparison was performed between the coalescent group (n = 29) and the non-coalescent group (n = 101) across the variables previously noted as significant from Table 1. As this was an exploratory aim, no correction was made for multiple comparisons. There were no differences in groups with probable CHS, early-age cannabis use, or nicotine use, but

those with coalescence had a significant history of opioid use ($p = 0.028$) and were more likely to be not employed ($p = 0.024$). Among the opioid users of the coalescence group, the mean MME was 28.2 mg / day ($n = 13$, 44.8%, SD = 24.6 mg, range 2.3 mg – 80.0 mg). Of the 29 cases considered to be exhibiting coalescent CVS, 8 of the cases were seen most recently in the ED or by one of the other providers in the clinic, while 4 cases were possible or likely CVS but still undergoing workup. The remaining 17 cases (59%) were most recently seen by the same physician (SNR), and a case series description of these cases is provided in Appendix C.

Discussion

This study represents a comprehensive retrospective chart review of a set of patients with CVS seen at one specialty GI referral center over a 6-year period between 2014 and 2020. On examining the characteristics of this sample of persons with CVS, we found that this group was mostly female, White, middle aged, and not employed. Consistent with other studies of adult CVS patients, we found a prolonged length of time from onset of symptoms to diagnosis [10, 42], a reported past medical history of abdominal surgeries [10, 14] and migraine headache, including a family history of migraine [43, 44], as well as anxiety, depression and substance use [45-47]. With respect to CVS onset, this study identified three subtypes (adult onset, childhood onset, reemergence of childhood CVS as adults). We examined whether or not CVS characteristics and symptoms varied by opioid and/or cannabis use and found that those who were younger in age and not partnered were more represented in the *cannabis-only* group, while current disability and unemployment status were more common in the *cannabis + opioids* group. We found no differences in health care utilization between the opioid/cannabis use groups, and there was no morphine equivalent dosing difference between the *cannabis + opioids* group and the *opioids-only* group.

The demographic findings of adults with CVS are consistent with previous CVS studies. In 2019, Siddiqui and colleagues performed an analysis of data from the United States National Inpatient Sample database pulling data from 129,090 hospitalizations between 2005 – 2014 with a primary diagnosis of CVS [35]. They reported a mean age of 49.0 years (SD = 18.5) for non-cannabis users, and a lower average age of 32.4 years for CVS patients who use cannabis. They also found overall a higher percentage of patients with CVS as female (65.7) with a trend for cannabis use to be males with CVS (54.7%) and White (59.5%), which are consistent with our results. In evaluation of cannabis use, Siddiqui *et. al* noted an overall national cannabis use in CVS patients at 10.4%, with an upward trend in reported cannabis use in patients with CVS from 2.5% in 2005 and increasing to 21.2% in 2014. A similar study by Bhandari and colleagues using hospital admission data from 2010 – 2014 in Colorado reported an overall cannabis use by diagnosis in hospitalized CVS patients between 13-17% [48]. However, these numbers may not fully capture cannabis use among CVS patients. In these two studies cannabis use was determined from inpatient data of cannabis a diagnosis and may be more reflective of heavy or problematic use. It is also important to note that prior to 2014 there were zero states with legalized recreational cannabis stores, and only a handful with medicinal cannabis options. In our Washington State cohort fear of reporting cannabis use may have been low as cannabis use by adults has been legal[1] with retail sales of cannabis to the public since 2014. This may partially explain the higher reported rate of cannabis use (67%) among CVS patients in our study. Other studies have noted that 37-38 % of patients with CVS use cannabis [42, 49]. In the current study it was not possible to determine why patients used cannabis, however an anonymous survey of

[1] US Federal law supersedes US State law where there is a conflict, and at present cannabis use, possession, cultivation, and trade, continues to be prohibited for any use at the federal level.

437 patients with CVS noted that 54% of the respondents reported using cannabis "for health issues" [10][p. 2563].

Among the women in our study, nearly 17% (n = 15) reported an association of their CVS symptoms with their menstrual cycle. There was not sufficient data in the medical record to separate out menopausal women, though of the 90 women in the sample, 25 were of the age 51 or greater. Therefore, using age 51 as the average age for menopause in the United States [50] and subtracting them from the total, nearly a quarter (23%) of pre-menopausal women in our sample reported some element of menstrual-related CVS. In 2005 Fleisher and colleagues performed a retrospective chart review of 41 adults with CVS with an age range of 20 – 64 years, 24 men and 17 women. Seven of the women (41%) reported menstrual periods as trigger for CVS [14]. In 2019 Hassani and colleagues provided a case report of successfully treating a 16-year-old girl with severe, recurrent catamenial CVS with estrogen therapy [51]. Therefore, given that 20-25% or more of female patients with CVS might have components of catamenial CVS (although this needs further validation), hormonal therapy for CVS in pre-menopausal women warrants further study.

Two previous studies illustrated the use of hot water bathing as a self-management strategy is highly correlated with cannabis use but is not unique to cannabis use [10, 11]. In our study, 44.6 % of the cohort reported some relief with hot water bathing activities with no differences across the four user groups (i.e non-users, cannabis-only, opioids-only, cannabis plus opioids). Similarly, via anonymous survey, Venkatesan *et. al* reported hot bathing activity in 72.2% of CVS patients who report a history of cannabis use, and 47.6% in patients with no history of cannabis use [10]. This data was subsequently confirmed in a survey by Rosen *et. al* which reported 85.7% of regular cannabis users with CVS taking hot showers during prodrome

to relieve symptoms, while 62.7% of non-users plus occasional cannabis users, also reported the positive utility of hot shower bathing [11].

In describing the clinical characteristics of adults with CVS this study found several variables not previously reported in the literature. First, approximately one-third of CVS patients in this review used sleep as a method to abort an acute CVS cycle. The induction of sleep may partially explain the effectiveness of benzodiazepines, phenothiazines, and antihistamines within this population, as well as the success of the recent trials of ketamine as an abortive measure [52, 53]. Second, this study found an extended wellness phase between episodes in a small number of adult patients with CVS (n = 11, 8.5%). Authors consistently describe adult CVS as having cyclical periods of weeks to months [1, 2, 8, 9, 16, 17, 44], however this study found evidence for yearly or greater than yearly cycles in some patients. Further study is warranted to determine if this type of intermittent CVS is the same as the 'weeks to months' type of CVS as typically reported in the literature. Third, while prior studies note symptomatic patients in all decades of life [10, 35, 54], to our knowledge ours is the first study to specifically identify that first symptoms of CVS can occur across the adult lifespan.

We examined whether opioids and/or cannabis use groups differed on healthcare utilization in order to provide recommendations for use of these substances within the CVS population. Analyzing chart data from the National Inpatient Sample database, Siddiqui and colleges noted an overall decreased mean length of stay in cannabis users as compared to those who did not use cannabis (2.6 days vs. 3.6 days) and correspondingly a lower mean hospitalization cost ($4,832 vs. $5,813). After performing multivariate analysis and adjusting for confounders, however, these differences were not significant [35]. Similar to the Siddiqui study, we found no differences in health care utilization as measured by hospitalization days, ED

presentations, and clinic visits over a 2-year period. We believe the absence of significance between the four user groups and healthcare utilization highlights the symptom burden of patients with CVS is unrelated to their use of cannabis or opioids, though further study in this area is warranted.

One hypothesis of this study was that the use of cannabis would reduce the amount of opioids consumed by individuals with CVS who used both agents. However, contrary to our hypothesis there was no difference in MME values between the *opioid-only* group and the *opioid + cannabis* group in our study. This conclusion is limited by the small number of patients available for the interaction analysis, and further study of this variable is needed. Kienzl and colleagues published a 2020 review considering cannabinoids and opioids in the treatment of inflammatory bowel diseases (IBD). They reviewed 6 survey studies, 4 prospective clinical studies, and 1 retrospective observational study. They concluded that the evidence supported the use of cannabis in relieving the symptoms of patients IBD, while prolonged opioid treatment in IBD should be avoided.

An exploratory aim of this study looked at the characteristics of a small group of patients who once had recognizable CVS symptoms of episodic illness but progressed to a nearly constant state of symptoms, described as coalescent CVS. To date, there has been only two previous studies evaluating possible coalescence in a cohort of CVS patients [14, 15]. Fleisher *et al*., performed an interview and exam of 41 adult patients along with a retrospective chart review of those patients and follow-up data by telephone and mailed questionnaire. In their cohort of patients, they noted that 63% had a pattern of nausea and vomiting that was both cyclic and chronic, with a low intensity nausea and abdominal discomfort between episodes. Their study was published in 2005, and it was only in 2004 that the proposal of cannabis hyperemesis

syndrome was first revealed [21]. Thus, some of the patients in Dr. Fleisher's group may have actually had unidentified CHS. This possibility is illustrated by an even earlier case report from 1996 of a patient with coalescing-type CVS, cannabis use, and hot water bathing [55]. Fleisher's group did not explore either cannabis or narcotic use in their study design, rather they proposed a hypothesis for the pathogenesis of coalescence as a heightened level of autonomic activity due to a sensation of anxiety and dread towards the next potential CVS event. They proposed this heightened autonomic nervous state would then bring on the next CVS episode more quickly than before. In 2010, Saligram and Bielfeldt conducted a retrospective chart review of 41 patients with CVS seen by a singular physician over a 14-month period, and 23 patients had 6 months or more of longitudinal data which was used for analysis (mean 12.3 ± 1.7 months). They reported an apparent coalescence in 11 of the total sample (27%). In comparison to the non-coalescent CVS group, the prescribed opioids (by morphine equivalent dose) was significantly higher in the coalescent group (278.0 ± 145.0 mg / day vs. 36.8 ± 9.9 mg / day, $p = < 0.01$). Furthermore, they noted that 21% of their patients, all of whom were on daily opioids, were responsible for 88% of the hospitalization days [15]. In our study the current use of cannabis and/or opioids, and well as a past history of addiction to opioids, were higher in the possible coalescent group in comparison to non-coalescent patients, yet two patients (6% of the coalescent group) were not using cannabis or opioids for their symptoms. These patients did, however, have multiple other comorbid conditions which may have contributed to their state of coalescence. It cannot be discounted that that use of opioids and cannabis may indicate the utility of these substances for a patient who is exhibiting significant and frequent CVS symptoms, yet this present study, combined with previous data, suggests that some cases of coalescence (but not

all) may be related to cannabis use and/or opioid dosing which, if positively identified, may give direction for treatment.

Strengths and Limitations

While the current study provides novel information regarding characteristics of those with CVS who also use cannabis and opioids, the results must be interpreted cautiously. Limitations of the study include the first author serving as the chart reviewer and all cases were seen by one medical provider in a tertiary care center thereby limiting the generalizability of this study. In particular the designations of possible coalescence and diagnosis of possible CHS were not validated by a second provider. Currently there is no accepted definition or diagnostic parameters for coalescence and none of the cases in the study met diagnostic criteria for CHS (i.e., the resolution of symptoms following complete cessation of cannabis). Additional limitations include lack of sample diversity and the small number of cases with 2 years or more of health record available for review. As the UW Digestive Health Center is a specialty clinic often receiving patients by referral from throughout the State of Washington, the majority of the sample had a limited number of consultation visits before returning to primary care in their area or otherwise being lost to follow up. And finally, there were difficulties in determining an accurate morphine daily equivalent dosing in this population. Of the cases where either the patient reported taking outpatient opioids or there was evidence for the administration of opioids during a recent ED presentation or during a hospital stay, an actual MED value was only able to be calculated in 46% of those cases. Conversely, the Washington State prescription monitoring program provided opioid dosing data on a few more cases (72%) but not the whole positive-for-opioids subgroup as that system is specific to outpatient prescriptions only. The system did not

register opioids provided in the ED or hospital setting, and outpatient methadone as well as buprenorphine-naloxone prescriptions were also not available data within the program.

Conclusions

This study identified several elements that have not been previously reported in the literature, while verifying the known characteristics unique to the CVS population. This study is the first to identify sleep as a strategy to reduce or abort symptoms in acute phase CVS. The majority of CVS cases seen at this tertiary care center in the Pacific Northwest received their first diagnosis as across the lifespan, while a few cases were identified with symptoms that began in childhood, resolved, and then returned later in life. This study also found a small subgroup of adults whose episodes occurred yearly or more. Building on previous literature, this project provided confirmation that the behavior hot water bathing is common in the CVS population and is not exclusive to cannabis use. Additionally, this study confirmed a prolonged time of years from onset of symptoms to CVS diagnosis, highlighting the complexity of diagnosing this syndrome based on symptomatic presentation alone. Finally, as part of an exploratory aim, we found that those who experienced coalescent CVS were likely to use both cannabis and opioids and may have complex presentations with multiple other confounding illnesses. Prospective studies are needed for cause-and-effect conclusions and future research is needed to determine if coalescence, as an independent variable, is part of the trajectory for some adults with CVS. A centralized national database of CVS patients, both adult and pediatric, with longitudinal monitoring could be very useful in establishing best practice standards for these complex, and yet fairly rare, patients.

Table 1. Comparison of Demographic and Clinical Characteristics by Cannabis Use, Opioid Use, Cannabis plus Opioid Use, and Non-Users.

Sample N = 130		Opioids and Cannabis: Comparison by Groups				*p* value
		Non-users n = 32	Cannabis only n = 52	Opioids only n = 11	Cannabis + Opioids n = 35	
Demographic Variables						
Age, m(SD), range	41.6 (15.6), 19 – 84	42.7 (17.6), 19 – 78	37.5 (15.5), 19 – 84	49.6 (16.0), 28 – 73	44.4 (12.0), 23 – 66	0.047
Gender[1], n(%)						
Male	40 (30.8)	9 (28.1)	23 (44.2)	3 (27.3)	5 (14.3)	0.026
Female	90 (69.2)	23 (71.9)	29 (55.8)	8 (72.7)	30 (85.7)	
Ethnicity, n(%)						
Caucasian / white	78 (60.0)	20 (62.5)	31 (59.6)	8 (72.7)	19 (54.3)	0.298
Other ethnicities	13 (10)	3 (9.4)	2 (3.8)	1 (9.1)	7 (20.0)	
Ethnicity not disclosed	39 (30.0)	9 (28.1)	19 (35.5)	2 (18.2)	9 (25.7)	
Partner Status, n(%)						
Married / partnered	58 (44.6)	14 (43.8)	16 (30.8)	8 (72.7)	20 (57.1)	0.020
No partner reported	72 (55.4)	18 (56.3)	36 (69.2)	3 (27.3)	15 (42.9)	
Employment Status n(%)						
Employed	32 (24.6)	15 (46.9)	8 (15.4)	3 (27.3)	6 (17.1)	0.013
Not employed	57 (43.8)	7 (21.9)	24 (46.2)	5 (45.5)	21 (60.0)	
Unknown or not reported	41 (31.5)	10 (31.3)	20 (38.5)	3 (27.3)	8 (22.9)	
Disability[2]	22 (16.9)	2 (6.3)	7 (13.5)	0 (0.00)	13 (37.1)	0.003
Clinical Characteristics						
Symptom length, years, m(SD)	14.5 (12.6)	12.4 (10.6)	13.1 (8.4)	20.0 (21.1)	16.9 (15.4)	0.178
Time to diagnosis, years, m(SD)	8.9 (9.6)	9.2 (11.3)	8.07 (6.7)	12.3 (15.0)	8.4 (9.0)	0.585
CVS Frequency, n(%)						
Weekly / constant	30 (23.1)	3 (9.4)	11 (21.2)	1 (9.1)	15 (42.9)	0.005
> Weekly & < yearly	89 (68.5)	23 (71.9)	39 (75.0)	8 (72.7)	19 (54.3)	
Yearly or > yearly	11 (8.5)	6 (18.8)	2 (3.8)	2 (18.2)	1 (2.9)	

		Non-users n = 32	Cannabis only n = 52	Opioids only n = 11	Cannabis + Opioids n = 35	
Possible CHS, n(%)	14 (10.8)	0 (0.00)	9 (17.3)	0 (0.00)	5 (14.3)	0.035
Possible coalescence, n(%)	29 (21.5)	2 (6.3)	13 (25.0)	2 (18.2)	12 (34.3)	0.032
Catamenial CVS, *n*(% women)	*n* = 90 15 (16.7)	*n* = 23 3 (13)	*n* = 29 7 (24.1)	*n* = 8 2 (25)	*n* = 30 3 (10)	0.396
Abdominal Pain, n(%)	88 (67.7)	16 (50.0)	35 (67.3)	10 (90.9)	27 (77.1)	0.039
Age of Symptom Onset, n(%)						
Childhood	23 (17.7)	5 (15.6)	11 (21.2)	2 (18.2)	5 (14.3)	0.273
Teen years	23 (17.7)	5 (15.6)	14 (26.9)	2 (18.2)	2 (5.7)	
20-30 years old	32 (24.6)	8 (25.0)	13 (25.0)	2 (18.2)	9 (25.7)	
30-years and over	52 (40.0)	14 (43.8)	14 (26.9)	5 (45.5)	19 (54.3)	
Behavioral Management, n(%)						
Hot bathing	58 (44.6)	11 (34.3)	27 (51.9)	2 (18.2)	18 (51.4)	0.104
Sleep	46 (35.4)	13 (40.6)	19 (36.5)	2 (18.2)	12 (34.2)	0.632
Other[3]	2 (1.5)	0 (0.00)	0 (0.00)	0 (0.00)	2 (5.7)	0.293
Past Medical History, n(%)						
CVS symptoms as a child	25 (19.2)	5 (15.6)	11 (21.2)	3 (27.3)	6 (17.1)	0.785
Migraine	62 (47.7)	19 (59.4)	19 (36.5)	4 (36.4)	20 (57.1)	0.104
IBS	3 (2.3)	1 (3.1)	0 (0.00)	0 (0.00)	2 (5.7)	0.313
Abdominal surgery	27 (20.8)	5 (15.6)	6 (11.5)	7 (63.6)	9 (25.7)	0.003
Psychiatric History, n(%)						
Depression	32 (24.6)	7 (21.9)	14 (26.9)	6 (54.5)	5 (14.3)	0.064
Anxiety disorder	45 (34.6)	8 (25.0)	18 (34.6)	3 (27.3)	16 (45.7)	0.347
Suicide ideation or attempt	3 (2.3)	1 (3.1)	1 (1.9)	0 (0.00)	1 (2.9)	1.000
PTSD	8 (6.2)	0 (0.00)	3 (5.8)	1 (9.1)	4 (11.4)	0.190
ADHD	4 (3.1)	0 (0.00)	0 (0.00)	1 (9.1)	3 (8.6)	0.031
OCD	2 (1.5)	1 (3.1)	0 (0.00)	0 (0.00)	1 (2.9)	0.426
Addiction History, n(%)						
Early-age cannabis use	17 (13.1)	0 (0.00)	13 (25%)	0 (0.00)	4 (11.4)	0.003

		Non-users n = 32	Cannabis only n = 52	Opioids only n = 11	Cannabis + Opioids n = 35	
Possible alcoholism	7 (5.4)	1 (3.1)	2 (3.8)	1 (9.1)	3 (8.6)	0.531
Nicotine	24 (18.5)	1 (3.1)	10 (19.2)	2 (18.2)	11 (31.4)	0.017
Opioids	18 (13.8)	1 (3.1)	3 (5.8)	4 (36.4)	10 (28.6)	< 0.001
Simulants	7 (5.4)	0 (0.00)	5 (9.6)	0 (0.00)	2 (5.7)	0.316

[1] There were no non-binary gender or trans-gender cases identified in the data set.

[2] Disability variable represents the patient's self-report of receiving state or federal funded disability-related financial support.

[3] One case reported partial relief when using a heated abdominal pad, and another reported some relief with mindfulness meditation.

Table 2. Healthcare Utilization of CVS Patients by History of Cannabis Use, Opioid Use, Cannabis plus Opioid Use and Non-Users.

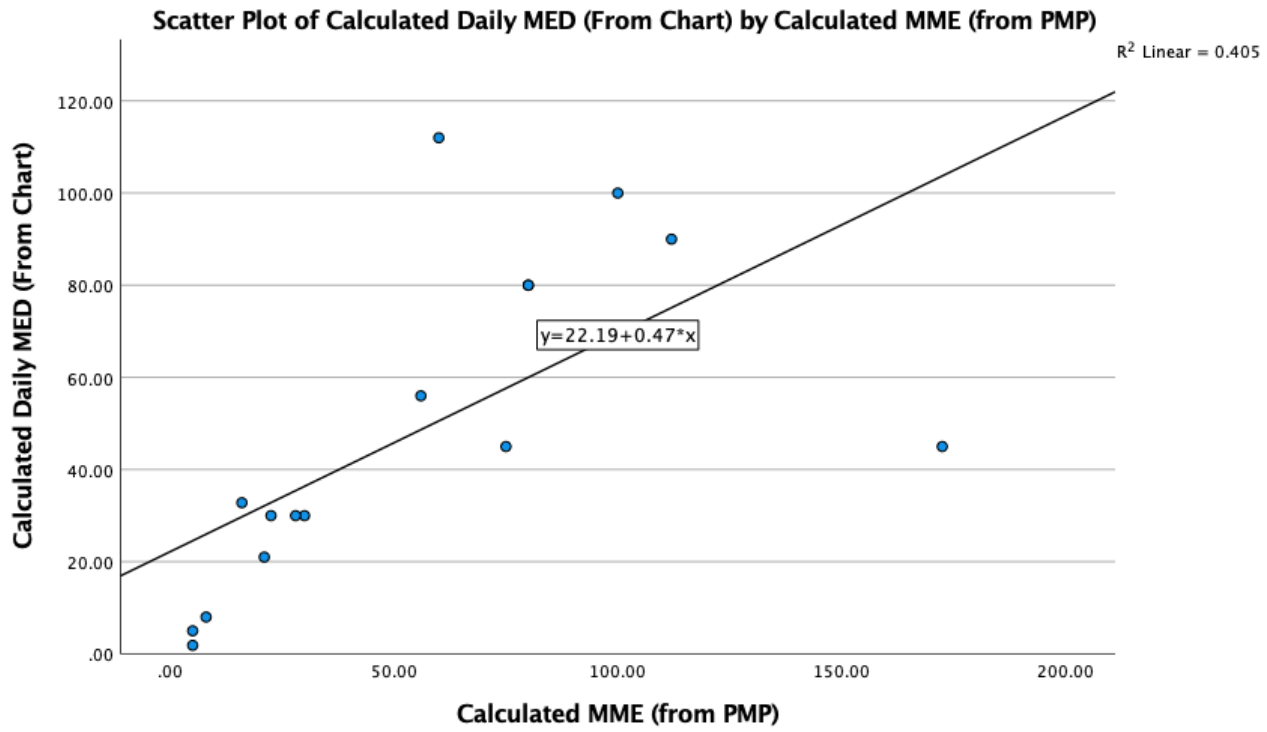
Subgroup *N* = 51		Opioids and Cannabis: Comparison by Groups				*p* value
		Non-users *n* = 11	Cannabis only *n* = 18	Opioids only *n* = 6	Cannabis + Opioids *n* = 16	
Subgroup Demographics						
Age, range, m (SD)	19 – 84, 46.4 (16.4)	19 – 78, 37.7 (17.1)	23 – 84, 47.9 (17.1)	41 – 73, 56.6 (13.9)	28 – 66, 46.8 (14.1)	0.129
Gender, *n* (%)						
Male	13 (25.5%)	2 (18.2)	8 (44.4)	2 (33.3)	1 (6.3)	0.058
Female	38 (74.5%)	9 (81.8)	10 (55.6)	4 (66.7)	15 (93.8)	
Healthcare Days, range, m (SD)						
All-Cause Clinic Visits	1 – 43, 10.8 (10.6)	3 – 25, 10.7 (9.9)	1 – 43, 7.4 (9.9)	4 – 32, 11.3 (10.4)	2 – 35, 14.6 (11.5)	0.283
GI-only Clinic Visits	1 – 14, 4.3 (2.8)	1 – 14, 4.6 (3.8)	1 – 9, 3.2 (2.1)	3 – 5, 4.3 (0.8)	2 – 11, 5.4 (2.9)	0.162
All-Cause Hospital Days	0 – 210, [1] 8.6 (30.7)	0 – 8, 1.0 (2.5)	0 – 21, 2.2 (5.2)	0 – 28, [1] 6.4 (12.2)	0 – 46, 9.2 (14.8)	0.115
CVS-only Hospital Days	0 – 177, [1] 6.9 (25.9)	0 – 8, 1.0 (2.5)	0 – 21, 2.0 (5.3)	0 – 28 [1] 5.6 (12.5)	0 – 46, 6.1 (11.7)	0.353
All-Cause ER Visits	0 – 23, 3.0 (5.2)	0 – 4, 0.9 (1.5)	0 – 8, 1.7 (2.3)	0 – 22, 5.7 (9.1)	0 – 23, 5.4 (6.8)	0.062
CVS-only ER to Home	0 – 23, 1.7 (3.8)	0 – 4, 0.5 (1.2)	0 – 8, 1.3 (2.3)	0 – 4, 1.0 (1.6)	0 – 23, 3.6 (6.4)	0.187

[1] One influential outlier was removed from the opioids-only column for the comparison by groups analysis.

Table 3. Patients in Coalescence vs. Non-coalescent CVS.

Sample N = 130	Coalescence - Yes n = 29	Coalescence - No n = 101	*p* value
Demographic Variables			
Age, m(SD), range	43.7 (15.9), 20 – 76	41.0 (15.5), 19 – 84	0.432
Gender, n(%)			
Male	9 (31.0)	31 (30.7)	1.000
Female	20 (69.0)	70 (69.3)	
Partner Status, n(%)			
Married / partnered	13 (44.8)	56 (55.4)	1.000
No partner reported	16 (55.2)	45 (44.6)	
Employment Status n(%)			
Employed	3 (10.3)	29 (28.7)	0.024
Not employed	19 (65.5)	38 (37.6)	
Unknown or not reported	7 (24.1)	34 (37.6)	
Disability	8 (27.6)	14 (13.9)	0.096
Clinical Characteristics n(%)			
No-cannabis or opioids n(%)	2 (6.9)	30 (29.7)	0.032
Cannabis only n(%)	13 (44.8)	39 (38.6)	
Opioids only n(%)	2 (6.9)	9 (8.9)	
Cannabis + opioids n(%)	12 (41.4)	23 (22.8)	
CVS Frequency, n(%)			
Weekly to Constant	19 (65.5)	11 (10.9)	< 0.001
> Weekly & < Yearly	10 (34.5)	79 (78.2)	
Yearly or > Yearly	0 (0.00)	11 (10.9)	
Possible CHS, n(%)	4 (13.8)	10 (9.9)	0.513
Abdominal pain, n(%)	24 (82.8)	64 (63.4)	0.060
Past Medical History, n(%)			
Abdominal Surgery	9 (31.0)	18 (17.8)	0.192
Addiction History, n(%)			
Early-age cannabis use	4 (13.8)	13 (12.9)	1.000
Nicotine	6 (20.7)	18 (17.8)	0.787
Opioids	8 (27.6)	10 (9.9)	0.028

Figure 1: Correlations Between Calculated MED from the Chart and Calculated MME from the Washington State Prescription Monitoring Program (PMP).



References

1. Kovacic, K. and B.U.K. Li, *Cyclic vomiting syndrome: A narrative review and guide to management.* Headache, 2021. **61**(2): p. 231-243.

2. Frazier, R. and T. Venkatesan, *Current understanding of the etiology of cyclic vomiting syndrome and therapeutic strategies in its management.* Expert Rev Clin Pharmacol, 2022. **15**(11): p. 1305-1316.

3. Lombard, H.C., *Description d'une névrose de la digestion, caratérisée par des crises périodiques de vommissements et une profonde modification de l'assimilation.* Gazette Médicale de Paris, 1861. **20**: p. 312-14.

4. Lathrop, J.R. *Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome: The State of the Science Supplemental Digital Content*. Description of a Neurosis of Digestion, Characterized by Periodic Crises of Vomiting and a Deep Modification of Assimilation [cited 2023; English Translation of the Earliest Publication of Pediatric CVS]. Available from: http://links.lww.com/GNJ/A89.

5. Drossman, D.A., *Rome III: the new criteria.* Chin J Dig Dis, 2006. **7**(4): p. 181-5.

6. Medicare. *Billing and Coding: Upper Gastrointestinal Endoscopy (Diagnostic and Therapeutic). Article ID A57414.* 10/01/2019 [cited May 13, 2023]; Available from: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleID=57414.

7. Drossman, D.A., *Functional gastrointestinal disorders: History, pathophysiology, clinical features and Rome IV.* Gastroenterology, 2016.

8. *Rome IV Functional Gastrointestinal Disorders - Disorders of Gut-Brain Interaction*. 4th ed. Vol. 1 & 2. 2016, Raleigh, NC: The Rome Foundation.

9. Lin, L.D. and L. Chang, *How to Diagnose and Manage Cyclic Vomiting Syndrome?* Am J Gastroenterol, 2023. **118**(4): p. 579-584.

10. Venkatesan, T., et al., *An Internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS).* Exp Brain Res, 2014. **232**(8): p. 2563-70.

11. Rosen, S., et al., *Hot-Water Bathing Improves Symptoms in Patients with Cyclic Vomiting Syndrome and Is Modulated by Chronic Cannabis Use.* Dig Dis Sci, 2021. **66**(4): p. 1153-1161.

12. Rangan, V. and A. Ukleja, *Treatment of Cyclic Vomiting Syndrome: Is Bathing a Panacea or Is It in Hot Water?* Dig Dis Sci, 2021. **66**(4): p. 935-937.

13. Aziz, I., et al., *Epidemiology, clinical characteristics, and associations for Rome IV functional nausea and vomiting disorders in adults.* Clin Gastroenterol Hepatol, 2019. **17**: p. 878-886.

14. Fleisher, D.R., et al., *Cyclical vomiting syndrome in 41 adults: The illness, the patients, and problems of management.* BMC Medicine, 2005. **3**(20).

15. Saligram, S. and K. Bielefeldt, *The two sides of opioids in cyclical vomiting syndrome.* North American Journal of Medical Sciences, 2014. **6**(3): p. 114-118.

16. Venkatesan, T., et al., *Guidelines on management of cyclic vomiting syndrome in adults by the American Neurogastroenterology and Motility Society and the Cyclic Vomiting Syndrome Association.* Neurogastroenterol Motil, 2019. **31 Suppl 2**: p. e13604.

17. Sharaf, R.N., et al., *Management of cyclic vomiting syndrome in adults: Evidence review.* Neurogastroenterol Motil, 2019. **31 Suppl 2**: p. e13605.

18. Lathrop, J.R., et al., *Cyclic Vomiting Syndrome and Cannabis Hyperemesis Syndrome, the State of the Science.* Gastroenterological Nursing, 2023. **Preprint**.

19. Venkatesan, T., et al., *Patterns of Cannabis Use in Patients With Cyclic Vomiting Syndrome.* Clin Gastroenterol Hepatol, 2020. **18**(5): p. 1082-1090.e2.

20. Venkatesan, T., et al., *A survey of emergency department use in patients with cyclic vomiting syndrome.* BMC Emergency Medicine, 2010. **10**: p. 4-4.

21. Allen, J.H., et al., *Cannabinoid hyperemesis: Cyclical hyperemesis in association with chronic cannabis abuse.* Gut, 2004. **53**(11): p. 1566-70.

22. Donnino, M.W., et al., *Cannabinoid hyperemesis: a case series.* J Emerg Med, 2011. **40**(4): p. e63-6.

23. Senderovich, H., et al., *A Systematic Review on Cannabis Hyperemesis Syndrome and Its Management Options.* Med Princ Pract, 2022. **31**(1): p. 29-38.

24. Bekhit, M.H., *Opioid-induced hyperalgesia and tolerance.* Am J Ther, 2010. **17**(5): p. 498-510.

25. Drossman, D. and E. Szigethy, *The narcotic bowel syndrome: a recent update.* Am J Gastroenterol Suppl, 2014. **2**(1): p. 22-30.

26. Farmer, A.D., E. Ferdinand, and Q. Aziz, *Opioids and the gastrointestinal tract - a case of narcotic bowel syndrome and literature review.* J Neurogastroenterol Motil, 2013. **19**(1): p. 94-8.

27. Jones, J.L. and E.V. Loftus, *Avoiding the vicious cycle of prolonged opioid use in Crohn's disease.* Am J Gastroenterol, 2005. **100**(10): p. 2230-2.

28. Keefer, L., et al., *Centrally Mediated Disorders of Gastrointestinal Pain.* Gastroenterology, 2016.

29. Lee, M., et al., *A comprehensive review of opioid-induced hyperalgesia.* Pain Physician, 2011. **14**(2): p. 145-61.

30. Smith, H.S. and A. Laufer, *Opioid induced nausea and vomiting.* Eur J Pharmacol, 2014. **722**: p. 67-78.

31. Farmer, A.D., et al., *Pathophysiology, diagnosis, and management of opioid-induced constipation.* Lancet Gastroenterol Hepatol, 2018. **3**(3): p. 203-212.

32. Tuteja, A.K., et al., *Opioid-induced bowel disorders and narcotic bowel syndrome in patients with chronic non-cancer pain.* Neurogastroenterol Motil, 2010. **22**(4): p. 424-30, e96.

33. Kurlander, J.E. and D.A. Drossman, *Diagnosis and treatment of narcotic bowel syndrome.* Nat Rev Gastroenterol Hepatol, 2014. **11**(7): p. 410-8.

34. Hasler, W.L., et al., *Cyclic vomiting syndrome: Pathophysiology, comorbidities, and future research directions.* Neurogastroenterol Motil, 2019. **31 Suppl 2**: p. e13607.

35. Siddiqui, M.T., et al., *Prevalence of cannabis use has significantly increased in patients with cyclic vomiting syndrome.* Neurogastroenterol Motil, 2020. **32**(4): p. e13806.

36. Balagoni, H., et al., *Abdominal epilepsy: A rare cause of paroxysmal abdominal symptoms associated with epilepsy.* American Journal of Gastroenterology, 2016. **111**: p. S809-S810.

37. Harris, P.A., et al., *Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.* J Biomed Inform, 2009. **42**(2): p. 377-81.

38. Harris, P.A., et al., *The REDCap consortium: Building an international community of software platform partners.* J Biomed Inform, 2019. **95**: p. 103208.

39. Lathrop, J.R. *Cyclic Vomiting Syndrome (CVS) - Demographics - Patient Visit Record - Healthcare Utilization Data*. 2023; Available from: https://redcap.vanderbilt.edu/consortium/library/search.php.

40. AMDG. *Opioid Dose Calculator by the Washington State Agency Medical Director's Group*. 2019 [cited 2019 February 07]; Available from: https://agencymeddirectors.wa.gov/Calculator/DoseCalculator.

41. DOH. *Prescription Monitoring Program (PMP)*. 2007 [cited May 14, 2023]; Available from: https://doh.wa.gov/public-health-healthcare-providers/healthcare-professions-and-facilities/prescription-monitoring-program-pmp.

42. Kumar, N., et al., *Cyclic vomiting syndrome (CVS): Is there a difference based on onset of symptoms - pediatric versus adult?* BMC Gastroenterology, 2012. **12**(1): p. 52-52.

43. LenglarT, L., et al., *Brain to Belly: Abdominal Variants of Migraine and Functional Abdominal Pain Disorders Associated With Migraine.* J Neurogastroenterol Motil, 2021. **27**(4): p. 482-494.

44. Herlihy, J.D., et al., *Cyclic vomiting syndrome: an overview for clinicians.* Expert Rev Gastroenterol Hepatol, 2019. **13**(12): p. 1137-1143.

45. Bhandari, S. and T. Venkatesan, *Clinical characteristics, comorbidities and hospital outcomes in hospitalizations with cyclic vomiting syndrome: A nationwide analysis.* Digestive Diseases & Sciences, 2017. **62**(8): p. 2035-2044.

46. Levinthal, D.J., et al., *Greater intolerance to uncertainty predicts poorer quality of life in adults with cyclic vomiting syndrome.* Neurogastroenterol Motil, 2021. **33**(12): p. e14159.

47. Thavamani, A., et al., *Burden of psychiatric disorders in patients with cyclic vomiting syndrome - Need for aggressive screening and early intervention.* Dig Liver Dis, 2022. **54**(2): p. 287-289.

48. Bhandari, S., C.J. Hillard, and T. Venkatesan, *Marijuana users do not have increased healthcare utilization: A National Health and Nutrition Examination Survey (NHANES) study.* European Journal of Internal Medicine, 2016. **34**: p. e9-e10.

49. Choung, R.S., et al., *Cyclic vomiting syndrome and functional vomiting in adults: Association with cannabinoid use in males.* Neurogastroenterology and Motility, 2012. **24**(1): p. 20-e1.

50. Takahashi, T.A. and K.M. Johnson, *Menopause.* Med Clin North Am, 2015. **99**(3): p. 521-34.

51. Hassani, M.E.M.E., et al., *Catamenial cyclic vomiting syndrome responding to oestrogen therapy: an adolescent case report.* Pan Afr Med J, 2019. **33**: p. 286.

52. Ahuja, A., et al., *Sul1641-ketamine as a novel abortive therapy for cyclic vomiting syndrome attacks.* Gastroenterology, 2018. **154**(6): p. S558-S559.

53. Valdovinos, E.M., et al., *A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department.* J Clin Gastroenterol, 2020. **54**(4): p. 327-332.

54. Abell, T.L., et al., *Cyclic vomiting syndrome in adults.* Neurogastroenterol Motil, 2008. **20**(4): p. 269-84.

55. de Moore, G.M., J. Baker, and T. Bui, *Psychogenic vomiting complicated by marijuana abuse and spontaneous pneumomediastinum.* Aust N Z J Psychiatry, 1996. **30**(2): p. 290-4.

Appendix B.

Excluded Cases from the Dataset.

[case number in dataset] … Description of exclusion.

[2] … Not a CVS or CHS case.

[5] … Not a CVS or CHS case.

[22] .. Epigastric pain; may have had CVS in the past.

[30] .. Consideration for resolved CHS but without mention that cannabis has been stopped.

[34] .. Dx changed from CVS to IBS over the two-year review period.

[39] .. Pt. is a minor - chart excluded.

[41] .. Crohn's and IBD, CVS ruled out.

[45] .. CVS "resolved" – lost to follow up.

[46] .. Not a confirmed CVS or CHS case; lost to follow up.

[54] .. Cyclical Pelvic Pain, not CVS.

[89] .. Uncertain for CVS; A sudden increase of GERD symptoms.

[90] .. Age 15 at the time of visit.

[93] .. Intractable vomiting with nausea, unspecified.

[95] .. Not a CVS or CHS case.

[100] . A constellation of chronic medical issues that includes chronic nausea and vomiting.

[102] . Nausea and vomiting, unspecified, intractability of vomiting not specified.

[103] . Chronic ABD pain with NV.

[104] . Intractable vomiting with nausea, unspecified vomiting type.

[105] . Not a CVS or CHS case.

[108] . Chronic NV syndrome or centrally mediated abdominal pain syndrome (CAPS).

[111] . Age < 18 at time of most recent CVS visit.

[113] . Intractable vomiting with nausea, unspecified vomiting type.

[114] . Gastroparesis (primary encounter diagnosis). No consideration for CVS.

[116] . Most likely chronic nausea and vomiting syndrome.

[128] . Non-intractable vomiting with nausea (primary encounter diagnosis).

[132] . Likely small intestinal bacterial overgrowth, prescribed ciprofloxacin and metronidazole.

[138] . Dx is N/V of unspecified type.

[139] . Functional dyspepsia.

[141] . Gastroparesis. Suspect overlapping functional dyspepsia and IBS-C.

[144] . Ileocolonic Crohn's Disease.

[155] . Chronic generalized abdominal pain; Chronic vomiting.

[159] . Not a CVS or CHS case.

[161] . Non-intractable vomiting with nausea, unspecified vomiting type.

[162] . Possible CHS. He did not show up for his clinic visit; was a scheduled visit, no encounter.

Appendix C.

Observations from one physician:

A case series of 17 patients with CVS in possible coalescence.

1) [3] [case number in dataset] ----------

67 y.o. Caucasian female, not employed, on disability, divorced, no current partner.

Age of onset of symptoms: CVS as child, resolved at puberty, return of symptoms age 40

Length of time with CVS symptoms now: 27 years

PMH: Migraines, colitis and gastric ulcers, depression, R. shoulder joint replacement, Sneddon-Wilkinson Syndrome, depression.

Cannabis: Started taking CBD pills for attacks; sometimes cannabis lotion to the neck.

Routine Opioids: None now.

Dx: CVS with history of narcotic-related coalescence.

She had "abdominal migraines" in childhood. She developed adult-onset CVS around age 40, and 5-10 years ago her spells became more frequent. She reported severe epigastric pain prior to vomiting for which she was receiving frequent opioids as well as daily pain control for chronic R. shoulder pain, which resolved after joint replacement. Now she has minor spells managed with abortive medications twice a week and with reduced narcotics, pt. is much improved and no longer in a coalescent phase.

TWO YEARS PRIOR: 30-day opioids include Demerol inj. 100mg #8, Oxycontin 15mg #120, Hydromorphone 5mg #70, Hydrocodone 5mg #5, and Oxycodone 5mg #30. MME is 147.68 / day. She has been having CVS attacks, starting at 3:30 am, 2 times a month, lasting 3-5 days. They are typical attacks for her. Sleep can terminate an episode; hot showers do not help

symptoms. The episodes used to occur 4X a year with normal intervals between. She was just in hospital 12 days and tends to have very severe episodes about twice in a month. She has "minor spells" managed with abortive medications 2 times a week. A major attack occurs 3-4 times a month. In the ER she receives IV medications that can terminate an episode, but sometimes her symptoms come back within 48 hours. For her severe migraine headaches, she injects Demerol 4 times a month.

2) [13] ----------

34 y.o. Caucasian male, unemployed, not on disability, no partner status reported.

Age of onset of symptoms: Childhood CVS with an asymptomatic period age 16-22., then was hospitalized several times for CVS. **Length of time with CVS symptoms now:** 31

PMH: GERD

2-year data: Eight ER-to-home visits for CVS, and one 21-day hospitalization for hemorrhagic CVS – Mallory Weiss tear surgically treated with upper GI endoscopy and hemostatic clips.

Cannabis: Every other day use. The importance of stopping all marijuana use has been discussed. He says he has tried stopping marijuana for up to 2-months with no change in the vomiting pattern.

Routine Opioids: None.

Dx: CVS.

Vomiting 2x/week early in the am with nausea 3-4x/week. The vomiting spells always happen upon wakening in the morning and is accompanied by stomach cramping and diarrhea. Denies abdominal pain. He can get termination of an episode with sleep; hot showering had previously helped but by the most recent visit they were not really helping.

3) [15] ----------

44 y.o. Caucasian female, married not employed, not on disability.

Age of onset of symptoms: 30. **Length of time with CVS symptoms now:** 16 years

PMH: Hx spinal fusion, chronic back pain**;** anxiety disorder.

2-year Data: 11 ED visits with 28 hospitalization days for CVS.

Cannabis: None.

Routine Opioids: Oxycodone daily for chronic back pain; frequent ER and hospitalizations with narcotic exposure.

30-day PMP MME: 30.00 mg / day

Dx: CVS.

She had been having attacks averaging about one per every 12-18 months. This past year she has had more frequent episodes requiring hospitalizations for frequent episodes of cyclic vomiting, about every 2 weeks.

Her episodes usually begin stereotypically with a prodrome of intense thirst and "insomnia" lasting up to several hours. During this time hot bathing is of no help. After the prodrome severe epigastric pain begins then nausea and vomiting that can last up to two weeks if untreated. She uses fluid therapy at home, and she takes up to 2 litters a day. She uses fluids every 4-5 days to keep up her hydration. Self-treats at home with fluids by PICC line for nausea; to ER for vomiting episodes.

4) [16] ----------

28 y.o. Caucasian female with an S.O. or domestic partner, employed part-time.

Age of onset of symptoms: Childhood (age 2-3 she would vomit when in public places), resolved in later childhood, and then return of CVS symptoms in her mid-twenties.

Length of time with CVS symptoms now: 6

PMH: GERD, Barrett's' esophagitis, anxiety disorder with PTSD and OCD. Early-age cannabis use (started at age 15), history of alcoholism and street use opioids (previous heroin addiction, now maintains on a suboxone program).

2-year data: Multiple ED and behavioral health visits for PTSD, OCS, anxiety; history of sexual and physical assault as a child, feelings of suicidality. One admission for SI. Two ED visits for CVS/CHS last year.

Cannabis: Uses a concentrate pen every night and when sick she uses it more. States it can help when she starts feeling nauseated.

Routine Opioids: buprenophine-naloxone 1.4-0.36, daily.

30-day PMP MME: MME is not calculated in the PMP for Suboxone.

Dx: CVS, possible CHS.

Previously she had symptoms once a month, however she has been vomiting daily over past 2 months, and she notes chronic morning nausea every day. Cannabinoid hyperemesis syndrome is a possibility here. She has used since age 15 and stopped for a month during her rehab period before the episodes began. She has not tried showers; she feels too sick to get in a shower.

The episodes begin in the early morning between 3:00- 5:00 am when she wakes up feeling "hot and sweaty" with her skin feeling as though it were "on fire." She is also nauseated.

Vomiting starts 10 to 120 minutes later, and then epigastric pain occurs. She describes having severe acid reflux in association with these episodes.

5) [21] ----------

66 y.o. Caucasian male, not working, not on disability, notes report a significant other.

Age of onset of symptoms: 51 **Length of time with CVS symptoms now:** 17

PMH: CAD without angina.

2-year data: Three ER treatments for CVS. However, he lives out of the area, so likely the ED visits are under-reported here.

Cannabis: He has used marijuana for years with symptomatic benefit. He reported stopping for as long as a month without benefit. However, he did have a decrease in symptom frequency when he switched from high THC cannabis to high CBD cannabis.

Dx: CVS with CHS components.

The frequency of attacks and their severity has decreased in the past 6-8 months once he switched over from "regular weed" to high CBD content cannabis. His last CVS episode was about 3 months ago. He'd been having an episode each month for 3 months prior, but they are a lot less severe than in the past. He needed intravenous treatments for each one. In the ER he notes that Toradol IV worked well. He has been trying to avoid narcotics. For the last 3-4 weeks he has a "bad" pain in central abdomen and into his lower back.

Typically, his symptoms start "out of blue" at any time. Lately, however, they are more likely to start in the early am. An episode usually begins with heavy salivation and peri-umbilical pain, like a "twisting or ripping" that radiates into his lower back, lasting about 15-20 minutes. He gets "grumpy" and his eyes change a day or so before the onset, a condition his significant other

has commented on repeatedly. He also has nausea during that period of time. When vomiting starts it occurs about 4 times an hour. Spells used to last 12-18 hours without intervention. Spells had not been associated with much abdominal pain in the past, but he started having upper peri-umbilical several years ago. It has required narcotics, both parenteral and oral to control. He is definitely well between spells.

6) [28] ----------

48 y.o. Caucasian male, not employed, not on disability, married.

Age of onset of symptoms: 38. **Length of time with CVS symptoms now:** 10

PMH: Bleeding hemorrhoids, chronic diarrhea, arthritis.

Cannabis: Early age cannabis use; started prior to high school at about age 11. He smokes between 1/4 and 1 gram a day.

Routine Opioids: None.

Dx: CVS with a strong consideration for CHS.

He is a daily marijuana user. He is currently coalescent and has daily nausea. Nausea and vomiting is much better than he was before starting nortriptyline but still has nausea every day. The "improvement" he describes is that, unlike before he started taking nortriptyline, he no longer vomits every morning. The nausea leads to vomiting a couple of times a week. He is nauseated if he can't fall asleep at night and after getting up to urinate during the night. During the night, his nausea lasts until he can fall asleep again.

He also experiences nausea during the day, mainly in the mornings or evenings. Sometimes it can last all day and usually doesn't cause vomiting. Sleep can terminate an episode. Taking a hot bath can "get rid" of the nausea. The symptoms would begin to ease within 5-10

minutes to 2 hours, depending on severity. He has fallen asleep in the bathtub. On leaving the tub the symptoms often stayed in remission until he would eat supper at night, leading to relapse of nausea and vomiting. He's never actually scalded himself. In discussing this with his wife, she says the water is never actually "very hot."

For the last year and a half, he says he's had "more sick days" than well ones. He now vomits "just about every day", so the distinct cyclical pattern has merged into one of nearly constant daily nausea with almost daily emesis. He also has some severe episodes with multiple vomiting episodes in a day. On his "best day" he can overcome the nausea and not vomit. On his worst day he vomits all day long. He never has a totally well day.

7) [33] ----------

41 y.o. Caucasian female, not employed at this time, not on disability, single.

Age of onset of symptoms: 31. **Length of time with CVS symptoms now:** 12

PMH: Roux-Y gastric bypass in 2006, cholecystectomy in 2000; iron deficiency anemia, thyroid mass.

Cannabis: She uses cannabis daily since age 27. She states she uses it for symptoms and uses a CBD-type flower. Although cannabis use pre-dates the onset of her symptoms, she states that she engaged in 4-year period of abstinence and still had the same symptoms.

Routine Opioids: None.

Dx: CVS.

Around the age of 33 she started having episodes of sudden onset, severe epigastric pain almost immediately followed by nausea and vomiting. CHS is not as likely here based on the patients' continued symptoms after a stated withdrawal. She now has been having daily

symptoms in the last 12 months. The pain has lessened somewhat in recent years; however, she seems to have entered a coalescent phase with severe daily nausea that may or may not be accompanied by vomiting. Falling asleep can also terminate attacks. She says that hot showers turn off symptoms and the relief may or may not be last after she exits the hot water. She may, at times, shower 15 times a day.

8) [50] ----------

30 y.o. male, unreported ethnicity, not employed, no reported partner, not on disability.

Age of onset of symptoms: ~ age 18. **Length of time with CVS symptoms now:** 14

PMH: Class 3 obesity, asthma, GERD, depression, PTSD.

2-year data: 5 ER visits are noted in provider notes over previous 2 years.

Cannabis: Started smoking at age 15 before the onset of CVS. He has cut down to smoking less than a gram of marijuana from 2-3 grams a day.

Dx: CVS with coalescence, consider CHS

He is having episodes about once every 2 months; very few before. Coalescence is considered. CHS is also a possibility here. After a stated withdrawal from cannabis for a period of a month he states he was worse, though an absolute minimum withdrawal period has not been established. Symptoms lasts 3 days to a week. He states he has no response to hot showers. Smoking hash puts him to sleep during an episode and he wakes up feeling well.

Typically for an episode he wakes about 6:00 am, has a BM and after that nausea starts. He then has a cold, goose-bump-like sensation, and he sweats profusely. He also has some mild RLQ discomfort. When vomiting starts, he vomits twice an hour. He can abort vomiting "about 8 times out of 10" by taking a SL Zofran and "smoking some marijuana."

9) [53] ----------

20 y.o. male, unreported ethnicity, not employed, no reported partner, not on disability.

Age of onset of symptoms: His symptoms began at about age 12 but became "bad" at about age 15. **Length of time with CVS symptoms now:** 11

PMH: Migraine, s/p appendectomy.

Cannabis: Daily use for the past two years. CHS is not likely here based on the patient-stated onset of his illness before he started using marijuana. Also, he states he has stopped 4-6 weeks at a time without benefit.

Dx: CVS.

Coalescing symptoms are considered here. He has been sick 15 times in last 30 days. The symptoms have gotten worse over time, but the pattern is the same. Typically, he has episodes first thing in the am, but recently they have also occurred later in the evening. He describes getting stomach cramps that feel as though something inside is "ripping". He also gets nausea and uncontrolled vomiting. Occasionally he becomes dizzy. He feels cold but sweats. He is not sure which symptom, pain or nausea and vomiting, is worse. He'll vomit 30+ times an hour. He describes the pain as severe and periumbilical. Sleep can terminate an episode. Some positive relief with showers ("not too hot"). Heating pad to the abdomen works as well; helps the symptoms but does not terminate an episode.

10) [67] ----------

47 y.o. female, unreported ethnicity, not employed, no reported partner, not on disability.

Age of onset of symptoms: 42 **Length of time with CVS symptoms now:** 7

PMH: Migraine, diverticulosis, fatty liver, GERD, HTN

2-year data: Frequent need for hospitalizations & IV infusions.

Cannabis: Cannabis oil under the tongue prior to onset of symptoms, 2-3 times a year.

Routine Opioids: Oxycodone and occ Hydromorphone

Calculated 30-day MME: 30

Dx: CVS.

Near constant symptoms with 10-12 spells / month. She has been getting ondansetron infusions daily. She still has daily nausea and vomiting and abdominal pain though she takes all together 30 morphine equivalents daily as oxycodone and occasional hydromorphone. Typically, she now wakes with nausea between 3:00 and 4:00 am and "fights off vomiting" for 10-15 minutes. Her abdominal pain starts with nausea. The pain is epigastric with some "wrap around" to her back. She describes it as "extremely bad gas cramps that move around." She has occasional early satiety. She has vomited food from the night before. The pain lasts through entire attack. Medicated sleep (IV Lorazepam in hospital) can terminate an episode, but she can't take enough to induce sleep at home. Symptoms do improve with hot bath or shower, but she has to lie on her stomach. Water not too hot. Heating pad works somewhat.

11) [82] ----------

59 y.o. Caucasian male, not employed, on state disability from a prior head injury; single.

Age of onset of symptoms: 52 **Length of time with CVS symptoms now:** 7

PMH: Migraine, dyslipidemia, type-2 diabetes, delayed gastric emptying, portal hypertension, GERD, gastritis, cirrhosis, chronic hepatitis C, depression, anxiety disorder, mood disorder, unspecified psychosis, insomnia, headaches after head trauma (TBI), COPD.

2-year data: Heavy healthcare utilization; however, first CVS diagnosis in 2017 and then death 4 months later in 2017 due to liver failure.

Cannabis: Smokes a gram a day. Uses marijuana for abdominal pain and headaches.

Routine Opioids: Dilauded 2 mg along with parenteral Phenergan is the usual regimen than terminates an attack (ED). He has been in ER 5 times in the past 8 days.

Calculated 30-day MME: Oxycodone #16

Dx: CVS; Multiple confounding illnesses; Terminal Hep C Liver Failure.

For the last 7 years patient says he wakes up about 4:00 to 6:00 am, immediately feels nauseated and vomits. He then develops pain starting in his right, para-umbilical area which may radiate until he feels in in most of his abdomen. He will tend to vomit 3 times in an hour along with retching. He vomits bile, never food. Once he starts vomiting it never ceases on its own and he requires treatment in an ER setting. Possible coalescing symptoms. This is unusual for him. He cannot actually tell me how often he has these episodes, but it has usually been far less frequent, probably close to once a month. His abdominal pain is very severe, "over 10 on a 1-10 scale, and can be of multiple different qualities. No response to hot bath or shower.

12) [110] ----------

24 y.o. male, married, ethnicity not reported. On partial disability due to symptoms.

Age of onset of symptoms: 19. **Length of time with CVS symptoms now:** 5

PMH: Migraine. **Chemical Dependency:** Was addicted to opiates at age 19, 20. Used cocaine, heroin, and Percocet. He quit at age 20 and has been clean.

Cannabis: Early-age cannabis use; marijuana every couple of days since 8 years old. He smokes and takes concentrate orally. He estimates he uses takes 1/4 gm q 2 days. He states he took a year off since the vomiting started and he felt his symptoms were much worse when off.

Dx: CVS, possible CHS

He has been having spells every 2 months lasting 2 weeks at a time. This is most likely CVS that is progressing to a more coalescent stage. The stereotypical onset of spells, prodrome, FH and personal history of migraine, normal intervening periods are all compatible. Abdominal pain is also a very frequent symptom in CVS. CHS is not likely here based on the patients' continued symptoms after a stated withdrawal from cannabis for a period of a year. However, as he started using it at age 8, the possibility remains of an etiological role for it. Feeling perfectly well. He has been taking 75 mg of amitriptyline q am for 2 months. He still has minor nausea episodes that last an hour at most. He has one every few weeks. Prior to taking amitriptyline the vomiting episodes typically lasted up to 2 weeks. Sleep may terminate an episode, but with variable success. Response to hot bath or shower: at first it worked. Just warm. It was variable in timing. Now it is actually a trigger.

13) [115] ----------

20 y.o. Caucasian female student, lives at home, works as an assistant manager of a shop.

Age of onset of symptoms: 5 **Length of time with CVS symptoms now:** 19

PMH: Migraine, GERD, obesity, depression, anxiety

Chemical Dependency: ½ ppd cigarette smoker; cocaine use by history.

Cannabis: Daily use of marijuana concentrate; 1/2-2 grams a day for the past 4 years. Marijuana is helpful and a period of 8 weeks abstinence was of no benefit. Her episodes also started long before she began to use marijuana.

Dx: CVS.

Episodic "uncontrolled nausea, vomiting and abdominal pain" starting at age 5. Between episodes she felt normal. Her symptoms disappeared for several years then reappeared when she entered puberty at about age 10. She was originally thought to bulimic in her teenage years. She was 14 she first saw a GI specialist. The episodes are stereotypical, and she did have normal intervals between them at first but now has episodes more frequently, 2-3 times a month.

She does describe very poor sleep habits with difficulty getting enough sleep so that she is often sleepy during the day. The most common time of an episode is at the end of the day. They always begin with cramps located just below her umbilicus with a gradual spread more widely through her abdomen. Then "acid comes up" and she develops nausea. After about 15 minutes vomiting starts, and she will tend to vomit about three times an hour, with spells lasting 25 minutes to an hour. Her longest episode was about 90 minutes. She now tends to have low-grade nausea most of the time. Moderate epigastric and RUQ pain prior to vomiting. She does not respond to hot bathing.

14) [123] ----------

28 y.o. married Caucasian female, on disability for CVS symptoms, not working.

Age of onset of symptoms: 21 **Length of time with CVS symptoms now:** 7

PMH: Migraine, GERD. Past surgeries: C-section, laparoscopy for endometriosis, appendectomy, elbow surgery, knee surgery, anxiety disorder, ADHD, schizoaffective disorder, bipolar. **2-year data:** 11 all cause clinic visits, with 5 of them for CVS type symptoms. 1 ER to home for CVS, no hospitalization days. CVS complicated by severe GERD symptoms and complicated psych history. 6 clinic visits for consideration of surgical intervention for severe GERD. Outpatient procedures: Endoscopy, upper GI manometry.

Cannabis: Uses marijuana products every other week or when the nausea is bad. States has stopped for 2-month without improvement in CVS symptoms.

Routine Opioids: Tramadol 50 mg #8 and Hydrocodone 5 mg #34

Calculated 30-day MME: 2.32

Dx: CVS.

She now vomits at least twice a day. Also, her migraines have been bad and occurring daily. She also complains of recurring "insatiable thirst." Progression from once a month to daily symptoms. Vomiting again every am and she now vomits at least twice a day. She was not stressed during the summer. She says that most of her morning vomiting is acid and again ascribes most of that symptom to reflux. Severe epigastric pain with vomiting. No symptom improvement with hot showers.

TWO YEARS PRIOR: They happen about every month. Early am onset, lasting a couple of days. Recurrent spells are the same. They happen now about every month. She is basically well between spells though now she has nausea in between spells in the am for which she takes PRN promethazine 25 mg orally. She has epigastric pain and into chest with vomiting. The pain starts right with vomiting. It is sharp, occasionally radiates into her shoulders and rises to 10 on a 1-

10 scale. It lasts as long as the vomiting. Interval abdominal pain: Yes, but mild. Pot takes it away. No response to hot bath or shower.

15) [135] ----------

39 y.o. married Caucasian female, no partner status reported, not working, not on disability.

Age of onset of symptoms: 28. **Length of time with CVS symptoms now:** 11

PMH: Migraine, IBS, gastroparesis, joint hypermobility, asthma.

2-year data: She goes to an ER for treatment about every 3-4 months.

Cannabis: Reports rare use 'Every now and then'; helps with retching.

Routine Opioids: Hydrocodone-Acet 7.5mg-325 #90 / month

Calculated 30-day MME: 22.5

Dx: CVS.

Vomits 5 days a week. Bad spells weekly. Now she can vomit up to 5 days a week but says that actual severe spells still occur on average weekly. She stresses that she didn't start taking hydrocodone until 3 years ago long after the problem developed. Sometimes she wakes at midnight and vomits undigested food up to 12 hours afterwards. She usually vomits 3-4 times an hour or non-stop. Occasionally she sees red blood but only after she has vomited multiple times. A vomiting spell can last for a day. Sleep can help symptoms somewhat.

16) [142] ----------

49 y.o. married Caucasian female, not employed, on State disability.

Age of onset of symptoms: 25 **Length of time with CVS symptoms now:** 24

PMH: Migraine, unspecified hypothyroidism, low back pain, insomnia, laparoscopic fundoplication for GERD in 2014: Within days after the fundoplication surgery her spells became much more frequent. After 2 days she was in hospital for 19 days because of vomiting and pain. She had a G tube after surgery that couldn't be used because of vomiting. More recently she has been in the ER every 2 weeks and is hospitalized monthly. She gets daily injections of hydromorphone or Toradol in her PCP's office because of persistent nausea vomiting and pain in addition to the periodic ER visits and hospitalizations. **Psych Dx:** Single Episode of Major Depressive Disorder.

Chemical Dependency: 1 ppd cigarettes, 8-10 marijuana joints a day, frequent opioid prescriptions.

Cannabis: Daily marijuana use, up to 8-10 joints per day; Currently she admits to using about 3 bowls a day. She's emphatic that she's gone up to 6-9 months off marijuana without benefit, however she also says that when she is actually vomiting, she can't use it because the smoke actually makes her feel worse.

Routine Opioids: ER Meds (1x): 1 mg IM dilaudid, 1 mg Im ativan, and 25 mg PO benadryl

Calculated 30-day MME: 0.13

2-year data: She had 32 clinic visits and 6 hospitalizations and ER visits in the past 90 days.

Dx: CVS, consideration for CHS, symptoms are also possibly a complication of a 2014 lap. fundoplication surgery.

10 vomiting spells / month. She may have begun her problem with a fairly typical adult CVS presentation that has evolved, perhaps triggered by upper abdominal surgery, into a coalescent phase wherein the characteristic episodic nature of symptoms is submerged in a more chronic symptom constellation. Possible roles for narcotic bowel syndrome and cannabis

hyperemesis syndrome in her symptom complex are also considerations. Typically, the symptoms start in the middle of night with vomiting and there was no pain. She would vomit 3-4 times an hour for up to 3.5 days until going to the ER for treatment. She had these about 3 x a year. Hot showers help relieve the nausea while she's taking them.

She gets daily injections of hydromorphone or Toradol in her PCP's office because of persistent nausea vomiting and pain in addition to the periodic ER visits and hospitalizations. Another potential confounder is her chronic marijuana use for about 20 years at a reasonably high dose. However, she is adamant that long periods of abstinence of up to 9 months had no effect on her symptoms. Also, she states that during a vomiting spell, rather than relieving her symptoms marijuana use makes her feel worse.

17) [160] ----------

25 y.o. Caucasian female; no reported partner; no reported employment; not on disability.

Age of onset of symptoms: 19 **Length of time with CVS symptoms now:** 6 years

PMH: Migraines, no CVS symptoms as child.

Cannabis: Smokes “two times every few weeks” and uses a cannabis lotion.

Routine Opioids: None outpatient; however near-monthly opioids through the ED.

Dx: Catamenial CVS, possible coalescence.

8 ED visits for nausea and vomiting over a 6-month period. Reports daily symptoms of nausea and epigastric pain that gradually fades away by noon; unable to eat until symptoms subsided. Once she starts to vomit, she can have 4-5 emesis per hour. The pain is sharp, stabbing spasm-like and achy. It occasionally radiates to her back and down to her pelvis and can rise to an 8-10:10 in severity. Her abdominal pain is typically treated with either oxycodone or

hydromorphone in the ED setting. She tends to go to the ED for more than ½ of these episodes. She does report some or partial relief with hot showers but were generally not abortive. CHS is not strongly considered given her self-report of very light use. She may well have entered a coalescent period with her daily am nausea, however she is now greatly improved on amitriptyline.

CHAPTER 4

CONCLUSION

The combined elements of this dissertation, including the summary of history, analysis, theories, tables, and conclusions is a significant addition to the existing literature regarding cyclic vomiting syndrome. Manuscript One provides a comprehensive narrative review of the state of the science regarding CVS and CHS. In exploration of the historical context of CVS, this dissertation identified H. CL. Lombard as the earliest medical description of pediatric cyclic vomiting syndrome (a 'neurosis of digestion,' as translated) (Lombard, 1861). Dr. Lombard's historic reading to the medical society of Geneva was gradually overshadowed by Dr. Samuel Gee's later English-language publication of a case series of nine children with 'fitful or recurrent vomiting' (Gee, 1882). In the early 1900's authors would credit Dr. Gee's publication as the first English-language case series of pediatric cyclic vomiting while also mentioning Dr. Lombard as an earlier discussion. At that time in the literature there were also references of an 1840's potential pediatric cyclic vomiting case by Dr. Gruère (Dods, 1935; Marfan, 1921). During the 20th Century, however, English surpassed both French and German as the dominant language of science and medicine (Porzucki, 2014). As English-language publications cited previous English-language publications, Dr. Lombard's article was lost from citations and most experts in the field (including the current website of the Cyclic Vomiting Syndrome Association) confidently purport this syndrome to be first described by Dr. Samuel Gee (Bhandari et al., 2018; CVSA, 2019; Fleisher et al., 2005; Issenman, 2017; Kovacic et al., 2018). To correct the historical record, as a component of this dissertation Manuscript One, Dr. Lombard's French-language manuscript was translated into English and is now available as public record. The earliest known mention of pediatric cyclic vomiting within the modern medical record does appear to possibly be from Dr.

Gruère, however, describing a singular case (Gruère, 1843). Yet in translation of that work, it is more of a presentation of treatment modalities for vomiting at that time, and it does not consider any proposal of a new syndrome. In particular, although he notes the curiosity of this periodic vomiting without any apparent cause, in closing statements Dr. Gruère highlights the efficacy of quinine sulfate in treating the vomiting in this particular case, even in absence of typical symptoms such as fever (see Appendix A). This dissertation work therefore decided to highlight Dr. Lombard's 1861 contestation as the first description of pediatric cyclic vomiting syndrome within the literature of modern medicine (Lathrop, 2023).

With the initial proposal for this project (2018) the incidence of CVS was not known but was considered to be low (Rosen & Singla, 2019). However, at that time the Global Epidemiology Study of Functional Gastrointestinal Disorders was underway, and the report was published during the writing of this Manuscript One. The data was incorporated into the prevalence section of the paper (Sperber et al., 2021). Current theories of CVS pathogenesis were reviewed and listed, and treatment parameters, including recently published experimental data around ketamine was incorporated (Carpenter et al., 2021; Valdovinos et al., 2020). Cannabis hyperemesis syndrome is thoroughly discussed, compared, and contrasted to cyclic vomiting syndrome. Treatment strategies are listed, including recently published experimental data around capsaicin, with the mention of a potential consideration for the trial of the high-potency 8% capsaicin patch (Abrams et al., 2021). Finally, this manuscript takes the symptomatic improvement with capsaicin as a correlation with the action of CBD (a 'capsaicin analog') on the endocannabinoid receptor, $TRPV_1$ (Muller et al., 2018). With this Manuscript One of the dissertation, is the proposal of both an etiology for CHS as a syndrome of endocannabinoid dysregulation due to long term THC toxicity effects, and a potential treatment

consideration for CHS with CBD as a recognized modulator of THC effects (Chung et al., 2019; Laprairie et al., 2015; Russo & Guy, 2006; Černe, 2020).

Subsequent to the narrative review of Manuscript One, Manuscript Two provides a detailed original research description of a cohort of adult patients with CVS. This retrospective chart review of 130 patients with CVS provides a wealth of both confirmatory, as well as new data to the field. As a novel approach to this group, and not previously presented in the literature, the primary variables of the study were compared across four groups: Cannabis users, opioid users, cannabis and opioid users, and non-users of either substance. The characteristics and behaviors of adults with cyclic vomiting syndrome are described and additional insight on the use of cannabis and prescribed opiates are provided through the data analysis. This study adds to the literature by both confirming existing parameters in adult CVS, such as a higher ratio of female to men (Siddiqui et al., 2020), as well as a prolonged time from onset of symptoms to diagnosis (Venkatesan et al., 2014), and the self-care behavior of hot water bathing with no significance across cannabis or opioid use within adult CVS (Rosen et al., 2021; Venkatesan et al., 2014). Menstrual-related symptoms are identified as a potential direction for treatment in some pre-menopausal women (Fleisher et al., 2005; Hassani et al., 2019). The design of the study offers a robust and repeatable measure of healthcare utilization: A sum of hospitalization days, plus number of emergency department presentations, plus number of primary and specialty clinic visits over a set time period (for this study, a 2-year review period was used). Additionally, in meeting a goal of promoting translational science, the chart review instruments used for this study have been uploaded to the REDCap consortium for unrestricted use by future researchers (Lathrop, 2023).

FUTURE RESEARCH

While Manuscript One serves as a summary of the existing knowledge around adult CVS and CHS, Manuscript Two is a retrospective chart review describing the clinical characteristics of a cohort of adult cyclic vomiting patients seen at a specialty treatment center. The next step, then, is to establish randomized clinical trials based on potential treatments identified within those two manuscripts. Within Manuscript One an 8% capsaicin patch was identified as a potential treatment option given the partial success of lower potency capsaicin creams. Additionally, capsaicin has only been trialed in CHS cases, but both previous literature as well as the case series of Manuscript Two suggests that up to 50% of CVS patients gain some relief response with hot water bathing. Thus, use of both the lower potency creams, as well as the 8% capsaicin patch, could be trialed in patients with CVS as well as CHS. Manuscript One also identified CBD as an organic capsaicin-analog with a high affinity for the endocannabinoid receptor $TRPV_1$ (Louis-Gray et al., 2022; Peng et al., 2022). Therefore, not only does CBD have theoretical promise as a modulator of THC toxicity and have potential to be used as a THC substitute in the treatment of cannabis use disorders (including CHS), but it also has the potential for direct symptom relief through the dermal activation of $TRPV_1$ (and without the hot-pepper side effects). So, a high-potency topical CBD skin cream or patch should be trialed both against placebo as well as various strengths of topical capsaicin, in both CHS as well as CVS cases to evaluate for a potential therapeutic effect with acute emetic CVS.

Within the chart review of Manuscript Two, several future areas of research are identified. Not previously mentioned elsewhere the literature is the notion that sleep, if it can be achieved, may improve or abort an acute phase CVS in up to one-third of patients with CVS. One question that should be explored further is if this variable is identified in patients with CHS

as well. The noted improvement with sleep offers a likely explanation for the successes of the sedating pharmaceuticals which are already the mainstay treatment of both acute phase CVS and CHS. The involvement of sleep researchers in a prospective cohort study of adult CVS (and CHS), measuring brain-wave activity as they progress through the four phases (wellness – prodrome – acute phase – recovery), may bring additional insights onto this variable. Another treatment direction identified in this cohort review was the element of catamenial CVS in pre-menopausal women, and trials of hormone therapy in both prevention of attacks, as well as potentially aborting attacks in the prodromal phase. Finally, the retrospective review identified several new clinical descriptions of adults with CVS that needs further verification through additional chart reviews and / or prospective longitudinal cohort studies. These include the notion that some pediatric CVS cases do not resolve in puberty but continue on into adulthood as ongoing CVS. Additionally, there appears to be an even smaller number of pediatric CVS cases that do resolve in puberty, but then re-emerge later in life as adult CVS. For the majority of adults with CVS in our cohort, however, the symptoms began in adulthood without any history of pediatric symptoms, and this review identified new-onset cases presenting for the first time within all decades of life. Finally, this review identified a few individuals with cycles of once a year, or even longer. Are these cases resolved CVS? Or is there an intermittent type of CVS that does not fit into the classic weeks-to-months cyclical pattern? Future studies of cohorts of adult CVS could provide further validation of these data points. And then there is the question of coalescence. Is this a natural course of CVS in some individuals? Or is it secondary to cannabis use, opioid use, or other unrealized variables or co-morbid conditions? A large longitudinal prospective cohort study of adults with CVS would best answer this question.

References

Abrams, R. M. C., Pedowitz, E. J., & Simpson, D. M. (2021). A critical review of the capsaicin 8% patch for the treatment of neuropathic pain associated with diabetic peripheral neuropathy of the feet in adults. *Expert Rev Neurother*, *21*(3), 259-266. https://doi.org/10.1080/14737175.2021.1874920

Bhandari, S., Jha, P., Thakur, A., Kar, A., Gerdes, H., & Venkatesan, T. (2018). Cyclic vomiting syndrome: Epidemiology, diagnosis, and treatment. *Clin Auton Res*, *28*(2), 203-209. https://doi.org/10.1007/s10286-018-0506-2

Carpenter, A., Levinthal, D. J., Binion, D. G., & Emerick, T. (2021). Improvement of Cyclic Vomiting Syndrome with Outpatient Ketamine Infusions. *Case Rep Gastroenterol*, *15*(1), 9-16. https://doi.org/10.1159/000510933

Chung, H., Fierro, A., & Pessoa-Mahana, C. D. (2019). Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study. *PLoS One*, *14*(7), e0220025. https://doi.org/10.1371/journal.pone.0220025

CVSA. (2019). *What is Cyclic Vomiting Syndrome (CVS)?* Cyclic Vomiting Syndrome Association (CVSA). Retrieved May 16, 2021 from https://www.cvsaonline.org/what-is-cvs/

Dods, L. (1935). Observations on Certain Aspects of the Cyclic Vomiting Syndrome. *The Medical Journal of Australia*, *II*(8), 231-260.

Fleisher, D. R., Gornowicz, B., Adams, K., Burch, R., & Feldman, E. J. (2005). Cyclical vomiting syndrome in 41 adults: The illness, the patients, and problems of management [Article]. *BMC Medicine*, *3*(20). https://doi.org/10.1186/1741-7015-3-20

Gee, S. (1882). On Fitful or Recurrent Vomiting. *Saint Bartholomew's Hospital Reports*, *18*, 1-6.

Gruère, N. (1843). Observation des Vomissements Périodiques, sans Signes D'Inflammation ni de Lésion Organique. *Précis Analytique des Travaux de la Société Médicale de Dijon*, *41*, 71-74.

Hassani, M. E. M. E., Saad, B., Mounir, M., Kouach, J., & Rahali, D. M. (2019). Catamenial cyclic vomiting syndrome responding to oestrogen therapy: an adolescent case report. *Pan Afr Med J*, *33*, 286. https://doi.org/10.11604/pamj.2019.33.286.17978

Issenman, R. (2017). A recurrent theme: A nationwide analysis of hospitalization for cyclic vomiting syndrome [Editorial]. *Digestive Diseases and Sciences*, *62*(8), 1844-1846. https://doi.org/10.1007/s10620-017-4485-2

Kovacic, K., Sood, M., & Venkatesan, T. (2018). Cyclic vomiting syndrome in children and adults: What is new in 2018? *Curr Gastroenterol Rep*, *20*(10), 46. https://doi.org/10.1007/s11894-018-0654-5

Laprairie, R. B., Bagher, A. M., Kelly, M. E., & Denovan-Wright, E. M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *Br J Pharmacol*, *172*(20), 4790-4805. https://doi.org/10.1111/bph.13250

Lathrop, J. R. (2023). *Cyclic Vomiting Syndrome (CVS) - Demographics - Patient Visit Record - Healthcare Utilization Data*. REDCap. Retrieved May 20, 2023 from https://redcap.vanderbilt.edu/consortium/library/search.php

Lombard, H. C. (1861). Description d'une névrose de la digestion, caratérisée par des crises périodiques de vommissements et une profonde modification de l'assimilation. *Gazette Médicale de Paris*, *20*, 312-314.

Louis-Gray, K., Tupal, S., & Premkumar, L. S. (2022). TRPV1: A Common Denominator Mediating Antinociceptive and Antiemetic Effects of Cannabinoids. *Int J Mol Sci*, *23*(17). https://doi.org/10.3390/ijms231710016

Marfan, A. B. (1921). Les Vomissemfnts Périodiques Avec Acétonémie. *Archives de Médecine des Enfants*, *I*(01), 5-28.

Muller, C., Morales, P., & Reggio, P. H. (2018). Cannabinoid Ligands Targeting TRP Channels. *Front Mol Neurosci*, *11*, 487. https://doi.org/10.3389/fnmol.2018.00487

Peng, J., Fan, M., An, C., Ni, F., Huang, W., & Luo, J. (2022). A narrative review of molecular mechanism and therapeutic effect of cannabidiol (CBD). *Basic Clin Pharmacol Toxicol*, *130*(4), 439-456. https://doi.org/10.1111/bcpt.13710

Porzucki, N. (2014). *How did English become the language of science?* TheWorld. Retrieved March 30, 2023 from https://theworld.org/stories/2014-10-06/how-did-english-become-language-science

Rosen, S., Diaz, R., Garacci, Z., Kumar, V. C. S., Thyarala, S. R., Hillard, C. J., & Venkatesan, T. (2021). Hot-Water Bathing Improves Symptoms in Patients with Cyclic Vomiting Syndrome and Is Modulated by Chronic Cannabis Use. *Dig Dis Sci*, *66*(4), 1153-1161. https://doi.org/10.1007/s10620-020-06343-x

Rosen, S., & Singla, A. (2019). Personal Communication: Email discussion regarding specific sources on the epidemiology of CVS. In.

Russo, E., & Guy, G. W. (2006). A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*, *66*(2), 234-246. https://doi.org/10.1016/j.mehy.2005.08.026

Saligram, S., & Bielefeldt, K. (2014). The two sides of opioids in cyclical vomiting syndrome [Article]. *North American Journal of Medical Sciences*, *6*(3), 114-118. https://doi.org/10.4103/1947-2714.128472

Siddiqui, M. T., Bilal, M., Singh, A., Olivier-Cabrera, S., Lebovics, E., Schorr-Lesnick, B., . . . Kirby, D. F. (2020). Prevalence of cannabis use has significantly increased in patients

with cyclic vomiting syndrome. *Neurogastroenterol Motil*, *32*(4), e13806. https://doi.org/10.1111/nmo.13806

Sperber, A. D., Bangdiwala, S. I., Drossman, D. A., Ghoshal, U. C., Simren, M., Tack, J., . . . Palsson, O. S. (2021). Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology*, *160*(1), 99-114.e113. https://doi.org/10.1053/j.gastro.2020.04.014

Valdovinos, E. M., Frazee, B. W., Hailozian, C., Haro, D. A., & Herring, A. A. (2020). A Nonopioid, Nonbenzodiazepine Treatment Approach for Intractable Nausea and Vomiting in the Emergency Department. *J Clin Gastroenterol*, *54*(4), 327-332. https://doi.org/10.1097/MCG.0000000000001258

Venkatesan, T., Sengupta, J., Lodhi, A., Schroeder, A., Adams, K., Hogan, W. J., . . . Storr, M. (2014). An Internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS). *Exp Brain Res*, *232*(8), 2563-2570. https://doi.org/10.1007/s00221-014-3967-0

Černe, K. (2020). Toxicological properties of Δ9-tetrahydrocannabinol and cannabidiol. *Arh Hig Rada Toksikol*, *71*(1), 1-11. https://doi.org/10.2478/aiht-2020-71-3301

Chapter 4 - Appendix A

Dr. N. Guère's "Observation de Vomissements Périodiques"

as Translated by

James R. Lathrop, DNP FNP ARNP in 2023.

OBSERVATION (1843)

PERIODIC VOMITING,

NO SIGNS OF INFLAMMATION OR ORGANIC LESIONS.

BY MISUSER DOCTOR GRUÈRE.

Periodic conditions sometimes present themselves in such insidious forms and with such varied symptoms that practitioners often cannot, in the interest of science, record the facts of this kind that are submitted to their observation too frequently. Therefore, your Secretary hastened to communicate the following case to you, which he encountered in his practice.

L***, 11 years old, of a lymphatic-sanguine temperament, with a strong constitution, usually having a fresh and rosy complexion, despite having lived in a low, humid, and poorly ventilated room since birth, had always been in fairly good health. However, he was suddenly afflicted with vomiting without any apparent cause, which caused him to indiscriminately reject, without any warning signs, the food he consumed shortly after ingestion. The usual symptoms of nausea, discomfort, syncope, and other accompanying signs that typically precede or accompany this phenomenon were absent. The vomiting occurred abruptly, and the child did not feel better or worse afterward. His father attributed this condition to the presence of worms and

administered semen contra (Artemisia cina), without success for two or three days, followed by a purgative of castor oil, but the vomiting persisted. Eight days after the onset of this condition, the patient was presented to the consultation of Mr. Gruére, who noted that the child had maintained his usual robustness, with no noticeable changes in his facial features. There was no pain or discomfort in the head, and his sleep was calm and deep. The tongue appeared normal, and both the epigastrium and the abdomen, when palpated in all areas, were soft and insensitive. Bowel movements occurred as usual, the skin temperature was normal, and the organs of circulation showed no abnormalities. In short, apart from the vomiting, this individual enjoyed excellent health. (Prescription: eight leeches on the epigastrium, emollient and laudanum poultices applied to this area, a glass of carbonated Seltzer water after each meal, liquid animists prepared with butter or milk.)

From the implementation of this prescription, vomiting no longer occurred immediately after food ingestion; however, they became regular and consistently appeared around five o'clock in the evening, regardless of the time of day the food had been consumed. This pattern continued for three days, but on the fourth day, the vomiting was accompanied by syncope with loss of consciousness and convulsive movements that ceased only when the patient fell into a comatose state that lasted until the next morning. It was at this time that your colleague was called in; he prescribed carbonated lemonade as a beverage, eight leeches to be applied to the temples and behind the ears, which bled for a long time, gradually dissipating the comatose state. However, in the evening of the same day, at five o'clock, the vomiting recurred, accompanied only by syncope, which was promptly alleviated by applying mustard plasters to the thighs. Noting the regular recurrence of the vomiting, Mr. Gruére did not hesitate to combat it with antiperiodic measures, even though it did not exhibit any characteristic symptoms of intermittent fever such

as chills, fever, or sweating. Therefore, he prescribed four decigrams of quinine sulfate to be taken in divided doses the following day, with the last dose to be administered approximately half an hour before the presumed time of the vomiting's return. The vomiting reappeared that day, but in a weaker form, meaning with a smaller quantity of ingested substances and with less effort. The same prescription was given for the next day: the stomach tolerated the medication perfectly, and the vomiting did not recur. The same approach was continued for a few more days; the child resumed their regular diet and lifestyle without the aforementioned symptoms reoccurring.

In the case that has just been presented to you, it may have been more rational to administer quinine sulfate through a route other than oral ingestion. However, the fact remains that, despite the pathological condition of the stomach, there was no need to fear administering a medication that it might not have tolerated if one had been guided solely by the pre-existing symptoms. The author of this observation has frequently seen, in cases of intermittent fevers, the digestive organs showing all the signs of heightened excitation, yet still tolerating quinine sulfate. In several of these cases, not only was it well tolerated, but it also acted vigorously: while ceasing the periodicity, it simultaneously alleviated the symptoms of gastric inflammation that seemed to contradict its use.

References

Gruère, N. (1843). Observation des Vomissements Périodiques, sans Signes D'Inflammation ni de Lésion Organique. *Précis Analytique des Travaux de la Société Médicale de Dijon*, *41*, 71-74.

Open AI. *Chat GPT*. Accessed May 2023 from: https://chat.openai.com/