2014

Cyclic vomiting syndrome: a retrospective chart review

Weber, Katharine

http://hdl.handle.net/2144/15309

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

CYCLIC VOMITING SYNDROME: A RETROSPECTIVE CHART REVIEW

by

KATHARINE WEBER
B.A., University of Rochester, 2012

Submitted in partial fulfillment of the
requirements for the degree of

Master of Science

2014
DEDICATION

This work is dedicated to my family and friends who have supported me through my education and life. Your love and tireless dedication to my goals has given me the strength and courage to follow my dreams and to always strive to be better, both personally and professionally. Also, thank you for always impressing on me a passion for learning and education. Your enthusiasm for teaching, knowledge, and the nurturing environment that allowed for the pursuit of any aspiration I had is what I hope to emulate in my career. Thank you for everything you have done and all of the sacrifices you have made for me.
ACKNOWLEDGMENTS

I would just like to thank everyone in the Kuo lab for this amazing opportunity. Working with you has been a genuine pleasure and one that I will always hold dear to me. I am truly grateful to have had the experience to learn from you and work with you. It is my aspiration to one-day work on a team that is as kind and nurturing as yours as well as to be able to give to others the outstanding mentorship I have received from you. I will carry everything I learned during this year into future research and professional endeavors. I would also like to acknowledge my advisor, Dr. Karen Symes. Thank you for all of your advice and support during my years as a graduate student at Boston University. I couldn’t have asked for a more helpful and knowledgeable mentor to guide me through my medical school applications and my coursework. I couldn’t have done it without you!
Purpose: We aim to characterize a large cohort of CVS patients seen at MGH in order to better understand this disorder. In addition, as CVS patients are known to have a higher cannabis use than those with other functional disorders, characteristics specific to CVS marijuana user patients have yet to be determined. Therefore, we aim to determine the variables that are patient specific predictors of cannabis use in CVS.

Methods: All patients with a CVS diagnosis were seen at our facility as inpatient, outpatient or in the emergency department and medical record numbers were identified via Research Patient Data Registry (RPDR) query search tool. From the medical records, we verified a diagnosis of CVS based on Rome III criteria and collected information on demographics, co-morbidities, health care utilization and substance abuse history over a 16 year time period (1997-2013). We then proposed patient specific predictor variables of marijuana use based on our experience with CVS patients and incorporated these variables into a model for predicting marijuana use. We used this model to examine the effect of patient characteristics on marijuana use via logistic regression with estimation of odds ratio and 95% confidence ratio.

Results: A total of 91 CVS patients were obtained, 67% of which were male with a mean age of 28 years old, average age of first attack of 20.2 years and employment or full time student status in 62% of patients. Psychiatric conditions were present in 73% of
individuals with anxiety present in 50% and depression in 47%. The presence of a chronic pain syndrome was found in 40%. Marijuana use was present in 76% of our cohort, daily alcohol use 53%, and narcotic use 27%. Men with CVS were at significantly greater risk for marijuana use compared to women (OR .23, 95% CI .07-.77) as well as daily alcohol use (OR 5.26, 95% CI 1.469-18.828). Individuals with a chronic pain syndrome were at significantly lower risk for cannabis use (OR .15, 95% CI .039-.575) and psychiatric illness, age and narcotic use were found not to be associated with marijuana use. On average, individuals presented to the ED 1.6 times/year with one patient having a high of 208 ED visits/year. Of those that presented more than once during the time period in study there was a median interval between visits of 103.6 days.

**Conclusion:** We found that CVS patients had significant psychiatric co-morbidities, chronic pain syndromes, and history of substance abuse. We found male gender and alcohol use to be two variables that were predictors of marijuana use in the CVS population while the presence of a chronic pain syndrome decreased the likelihood of marijuana use. The significant employment rate and full time student status of our cohort suggests a higher degree of functionality. Further prospective studies are needed to determine the role of marijuana use in the CVS population in terms of quality of life, health care utilization, and severity of disease.
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LIST OF ABBREVIATIONS

ACTH .............................................................. Adrenocorticotropic hormone
ANS .............................................................. Autonomic Nervous System
BMI .............................................................. Body Mass Index
CHS .............................................................. Cannabinoid Hyperemesis Syndrome
CVS .............................................................. Cyclic Vomiting Syndrome
ED .............................................................. Emergency Department
GE .............................................................. Gastric Emptying
GET ............................................................. Gastric Emptying Time
GI .............................................................. Gastroenterology
HPA .............................................................. Hyophyseal-Pituitary-Adrenal Axis
IBS .............................................................. Irritable Bowel Syndrome
mtDNA ........................................................ Mitochondrial DNA
NSAIDS ....................................................... Non-Steroidal Anti-Inflammatory
RPDR ........................................................... Research Patient Data Registry
SAS .............................................................. Statistical Analysis Software
SNPs ........................................................... Single Nucleotide Polymorphisms
TCAs .......................................................... Tricyclic Antidepressants
VAS ............................................................ Visual Analog Scale
INTRODUCTION

Cyclic Vomiting Syndrome

Cyclic Vomiting Syndrome (CVS) is a rare disorder characterized by episodic bouts of severe nausea and vomiting with periods of wellness between attacks (Hejazi & McCallum, 2011). In 1882, Samuel Gee first described CVS in English literature with a report of the illness in nine children (Abell et al., 2008; Hejazi & McCallum, 2011). Since the initial description, CVS is now increasingly being recognized in not only pediatric populations but in adults as well. Although the exact prevalence is not known in adults, it is estimated to effect anywhere from .04-2% of the pediatric population (Hejazi & McCallum, 2011). Information on the demographics that CVS affects is not yet definitive, however CVS has been noted in all races with whites being affected to a greater extent than other races (Pareek, Fleisher, & Abell, 2007). There appears to be a higher incidence of CVS among women than men as well (Tonore, Spree, & Abell, 2013).

Pathophysiology Theories

There have been abnormalities noted in CVS patients and theories proposed to explain the mechanisms of dysfunction, however CVS remains a disorder of unknown etiology. Hormonal abnormalities, autonomic nervous system (ANS) dysfunction, mitochondrial dysfunction, and abnormal Gastric Emptying Time (GET) have been observed in some CVS patients and theories have been proposed surrounding these findings.
**Hormonal Abnormalities**

Corticotrophin releasing factor (CRF) is hypothesized to contribute to the initiation of vomiting during a CVS episode. One of the main functions of CRF is to activate the hyophyseal-pituitary-adrenal axis (HPA) and the stress response via stimulation of adrenocorticotropic hormone (ACTH) and cortisol release (Abell et al., 2008). Supporting this is a finding from one group of elevation of ACTH, cortisol and catecholamine levels prior to the onset of a CVS episode (Pareek et al., 2007). CRF release activated by either physical or psychological stress and it’s downstream effectors also subsequently causes dysregulation of gut motility (Hejazi & McCallum, 2011). One of the effects of CRF is the inhibition of gastric motor activity, which can then help to precipitate nausea and vomiting (Pareek et al., 2007). In one study, per parent report, various types of stress such as infections, psychological stress or excitement precedes and triggers a CVS episode in up to 76% of pediatric patients (Li & Misiewicz, 2003). In this study, parents reported that the stressor was more likely to be associated with positive events such as birthdays, vacations, holidays or family gatherings rather than negative stressors (Li & Misiewicz, 2003). Furthermore, CVS episode onset often occurs late at night or in the early hours of the morning, perhaps corresponding to when the secretion of CRF takes place, between 1 AM and peaking at 6 AM (Pareek et al., 2007).

The hormone ghrelin has also been shown to be at abnormal levels in a study involving adult CVS patients. Ghrelin, released during a meal and produced by the gastric mucosa, decreases gastric emptying time (GET) (Hejazi, Lavenbarg, & McCallum, n.d.). This hormone is theorized to be involved with rapid gastric emptying.
sometimes found in CVS patients (Hejazi & McCallum, 2011). In a recent study investigating ghrelin levels in 22 adult CVS patients, it was found that the serum ghrelin levels were significantly higher than the control population (Hejazi et al., n.d.). These elevated ghrelin level findings could possibly contribute to the pathophysiology of CVS.

**Gastric Emptying Time**

Abnormal gastric emptying time has been observed in CVS patients and is theorized to play a role in the pathophysiology. The group that investigated ghrelin levels in CVS, Hejazi et al. looked at GET in adult CVS patients. Of 92 adults, they found 59% of subjects had rapid GET, 27% normal and 14% delayed during the inter-episodic period when they were asymptomatic (Hejazi, Lavenbarg, & Mccallum, 2010). They proposed that the abnormal hormonal finding suggests a possible mechanism of ghrelin facilitating the rapid GET they found in the majority of CVS patients. Furthermore, in the few studies that could be performed during the vomiting phase, there was a delay in GET (Hejazi, Lavenbarg, & Mccallum, 2010). An explanation for this may lie in CRF and it’s downstream effectors, cortisol and prostaglandin E2 being inhibitors of gastric emptying (GE) (Hejazi & McCallum, 2011). These abnormal findings in GE could possibly point to an underlying autonomic dysfunction in CVS patients (Hejazi, Lavenbarg, & Mccallum, 2010).

**Autonomic Nervous System Dysfunction**

The autonomic nervous system is involved with the generation of the emetic response. Via vagal and sympathetic afferent nerves, the brainstem nuclei receives the emetic signal and efferent responses are generated which subsequently causes the muscle
coordination involved with vomiting (Abell et al., 2008). Testing done on the autonomic nervous system (ANS) in CVS patients have revealed dysautonomia. In a study of 22 adults, 9 patients had autonomic nerve abnormalities with a dominance of sympathetic dysfunction over parasympathetic (Hejazi et al., 2011). This finding is consistent with three reports of increases in sympathetic tone in pediatric CVS patients (Hejazi & McCallum, 2011). CVS patients with these abnormalities maybe vulnerable to an over response to emetic signaling (Abell et al., 2008).

**Mitochondrial DNA Polymorphisms**

Studies that have looked at family medical history and co-morbid conditions in CVS patients have alluded to mitochondrial DNA (mtDNA) defects contributing to the disorder. mtDNA is inherited exclusively from the maternal line and the 37 genes are involved in energy metabolism (Abell et al., 2008). It is theorized that dysfunction of the mitochondria may contribute to autonomic nervous system dysfunction in CVS patients and render individuals susceptible to vomiting episodes during periods of high energy demands such as periods of stress and illness (Abell et al., 2008). Supporting this theory is the observation in families where more than one member has been affected by CVS, that there is a predominantly maternal inheritance pattern (Pareek et al., 2007).

Furthermore, dysautonomic and functional disorders often found co-morbid in CVS patients, specifically migraine, show a maternal inheritance pattern as well (Abell et al., 2008). A group that sequenced the entire mtDNA genome in 20 CVS patients as well as 10 subjects selected for specific mtDNA polymorphisms found the single nucleotide polymorphisms (SNPs) 16519T and 3010A strongly associated with both CVS and
migraine without aura and were likely to render individuals susceptible to these diseases (Zaki et al., 2009). Another study found that adult onset CVS was not correlated with the SNPs 16519T and 3010A and these polymorphisms were restricted to pediatric onset CVS only (Boles et al., 2009). This suggest that while these two migraine mtDNA polymorphisms may play a role in the development of CVS in children, there maybe other defects in energy metabolisms in adult onset CVS that render adult and pediatric CVS genetically distinct, however further investigation is needed into this matter (Boles et al., 2009).

**Associated Conditions**

Migraines, psychiatric illnesses, chronic marijuana use, gastro-esophageal reflux disease, irritable bowel syndrome (IBS) and diabetes mellitus are all conditions found to be associated with CVS (Hejazi & McCallum, 2011). The association between migraine and CVS has been noted in the literature for some time. It is estimated that migraines are found in or there is a family history of migraines in 39-82% of children and 24-70% of adults with CVS (Hejazi & McCallum, 2011). This association maybe due to more generalized abnormalities of the central nervous system (Abell et al., 2008). Diabetes is also noted at higher prevalence in CVS syndrome than the general population. One study found that in their cohort of patients, 13% had diabetes mellitus (Hejazi, Lavenbarg, & McCallum, 2010). In addition, IBS was noted in up to 67% of CVS patients and seizure disorder in up to 5.6% of patients as compared with 10-20% and .5-1% respectively of the general population (Pareek et al., 2007).
Psychiatric illness has also been well documented in patients with a high preponderance of anxiety and depression disorders. In a study of pediatric CVS patients, one group found that 15% of preschoolers, 59% of school children and 54% of adolescents met the criteria for an anxiety disorder (Tarbell & Li, 2008). In adults, Fleisher et al. found anxiety, mood disorder, alcohol and/or drug abuse in 70% of patients (Fleisher, Gornowicz, Adams, Burch, & Feldman, 2005). Namin et al. reported up to 84% of adult patients suffering from an anxiety disorder and 78% from depression (Namin et al., 2007). It is unclear if depression and anxiety contribute to the onset of CVS or if they are manifestations of the nature of the disorder itself. However half of patients reported mental stress as contributory to the onset of an episode (Namin et al., 2007). In addition, Fleisher et al. also found 17% of adult patients attributing anticipatory anxiety as a trigger to episode onset and 68% of patients noted panic attack symptoms when the felt an episode coming on and during the vomiting phase (Fleisher et al., 2005).

**CVS Phases**

The nature of CVS is such that it can be divided up into 4 stereotypic phases.

1. **Prodromal:** This phase is usually of sudden onset and the patient senses the episode coming on. This phase usually lasts anywhere from 1-2 hours and the patient may have abdominal pain, pallor, lethargy, and anorexia (Tonore et al., 2013).

2. **Emetic phase:** The patient is actively vomiting, is persistently nauseous and is unable to keep down fluids or medication. Abdominal pain, listlessness and
dehydration is frequent and this phase can last anywhere from hours to days (Abell et al., 2008).

3. Recovery phase: This phase begins when nausea and vomiting have ceased and the patient is able to resume oral intake (Abell et al., 2008).

4. Inter-episodic period: This phase can last anywhere from weeks to months and is a period of wellness where the patient does not experience nausea or vomiting (Abell et al., 2008)

The age of onset of the first episode has been reported to be anywhere from 6 days to 73 years old (Tonore et al., 2013). Additionally patients have reported that there will be events that trigger episode onset. Most common triggers include illness, physical and psychological stress including birthdays, vacations, lack of sleep, change of season, certain foods, and in females the onset of a period (Pareek et al., 2007). Often, during the prodromal phase, patients seek out dark and quiet rooms void of stimulation (Pareek et al., 2007). Episode onset frequently begins for many patients between the hours of 2:00 am and 7:00 am (Tonore et al., 2013). Once an episode has begun patients have been known to seek relief in unusual ways. Taking long hot showers or baths as well as a “guzzle and vomit” action where the patient ingests large amounts of liquid to induce vomiting has been noted (Pareek et al., 2007).

**CVS adult vs. child**

Age of symptom onset in adults is reported to be on average 35 years with diagnosis at 41 years (Tonore et al., 2013). In children symptom onset is on average 5.3 years old and diagnosis 9.6 years (Tonore et al., 2013). Adult patients on average had a
frequency of episodes similar to childhood onset with 1.2 episodes/month and .8 episodes/month respectively, however adults experienced a longer duration of episodes, 5.9 days compared to pediatric patients, 3.4 days (L. Y. W. Lee, Abbott, Mahlangu, Moodie, & Anderson, 2012). Although it has been suggested that adult CVS is more severe, studies between pediatric and adult cohorts have shown to be variable throughout the literature. Lee et al. showed that in the study’s cohort of patients, childhood onset was more severe with 15 more attacks/year than children (25/year vs. 10/year) (L. Y. Lee, Abbott, Moodie, & Anderson, 2012). Another group, found that pediatric patients had a higher incidence of CVS plus a neurocognitive disorder and a longer delay in diagnosis as compared to adults (Kumar et al., 2012). In contrast to this Boles et al. found that adult onset was more strongly associated with functional disorders and dysautonomous conditions such as migraine (Boles et al., 2009). It is thought that migraine headaches occur more frequently in adult patients with CVS, with a prevalence of 24-70% in adults and 39-82% in children (Abell et al., 2008). In addition, in some children there maybe the loss of CVS vomiting features and the development of migraines when the child reaches adolescents (Abell et al., 2008). The variability of characteristics in CVS patients both adult and pediatric provides the necessity for further investigation into patient profiles.

Diagnosis

Historically, vomiting that was of unknown causes was frequently labeled as psychogenic (Talley, 2007). Now, diagnosis of CVS is based on Rome III Criteria for Functional Gastrointestinal Disorders and is in the same category as similar vomiting disorders such as chronic idiopathic nausea, functional vomiting and rumination
syndrome (Drossman). In order for a patient to receive a diagnosis of CVS all of the following conditions must be met.

1. Acute vomiting onset lasting less than one week.
2. Three or more episodes in the last year
3. Wellness between episodes (no nausea or vomiting).

Criteria supporting a diagnosis are a family history or patient history of migraines (Drossman). As there are several disorders that show similarities to CVS, it is important to rule out others before arriving at a diagnosis.

**Table 1: Differential Diagnosis**

| Non-surgical Gastrointestinal Disorders | Peptic ulcer disease, hepatitis, pancreatitis with or without pseudo cyst, motility disorders, inflammatory bowel disease, infections |
| Surgical Gastrointestinal Disorders      | Pancreatic pseudo cyst, recurrent sub acute appendicitis, bowel obstruction, intermittent duodenal intussusception, duodenal web/atrophia/diverticulum, adhesions, choledochal cyst, cholelithiasis/gallbladder dyskinesia, gastrointestinal malignancies |
| Urologic/Renal/Gynecologic Disorders    | Urolithiasis, reteropelvic junction obstruction, ovarian cyst, pregnancy, premenstrual syndrome |
| Neurological Disorders                  | Hydrocephalus/slit ventricle syndrome, brain tumors, budd chiari malformations, epilepsy, subdural hematomas or effusions, familial dysautonomia |
| Endocrinologic disorders                | Diabetes mellitus, adrenal insufficiency, pheochromocytoma |
| Miscellaneous disorders                 | Abdominal migraines/epilepsy, hypothalamic surge, asthma, chronic sinusitis, benign positional vertigo, psychiatric disorders |

(Modified from Pareek et al., 2007)
**Diagnostic Tests**

Although there are no tests specifically for CVS, there are several exams to run in order to exclude other causes of nausea and vomiting (Hejazi & McCallum, 2011). Upper endoscopy, small bowel X-ray, CT scan, gastric emptying time study, biochemical analysis for electrolyte imbalances, liver chemistry, pregnancy tests, pancreatic enzyme testing and hormonal testing maybe helpful when deciding upon a CVS diagnosis (Hejazi & McCallum, 2011; Talley, 2007)

**Difficulties in Diagnosis and Recognition**

Lack of recognition of CVS by physicians often leads to misdiagnosis and suboptimal care in patients, affecting an individual’s quality of life and ability to manage the disease. There is typically a delay of 3-8 years in the adult population and a 2.5 year delay in the pediatric population (Venkatesan et al., 2010). As patients often utilize the emergency department (ED) during attacks it is important that emergency physicians recognize the disorder and the patient receives a diagnosis if they have not already had one. However, in the ED it is not uncommon for patients to receive a diagnosis of viral gastroenteritis or food poisoning (Abell et al., 2008). Based on a survey of CVS patients, it was found that in 80% of CVS patients, the disorder was not recognized both before and after diagnosis (Venkatesan et al., 2010). The majority of patients in this study were not recommended to be seen by a gastroenterologist as well (Venkatesan et al., 2010).

Physicians’ inability to diagnosis CVS results in unnecessary procedures and tests performed on patients as well. In a study of 41 patients, it was found that 16 patients underwent surgical attempts to correct CVS with none finding improvement in their
symptoms (Fleisher et al., 2005). Lack of recognition and referral to specialists greatly impacts a patient’s ability to receive appropriate prophylactic care. This can result in financial burdens and a poor quality of life as employment, education, family and social environment are all affected by this disorder.

**Treatments**

To treat CVS, physicians have typically recommended both pharmacological interventions and lifestyle changes. Figure 1 represents the treatment goals of each phase. There are measures that can be taken as prophylactic therapy to prevent episodes, abortive therapy during the prodromal phases, and treatment to keep the patient hydrated and lessen the severity of the emetic phase and recovery phase.

![Cyclic Vomiting Syndrome Phases and Treatments Goals](image)

**Figure 1. Cyclic Vomiting Syndrome Phases and Treatments Goals.** CVS phases and treatment goals schematic (Figure taken from Fleisher et al., 2005)
**Inter-episodic Period Therapy**

Important lifestyle changes should be implemented with CVS patients. Patients should learn to recognize triggers and if possible avoid them as well as get adequate amounts of sleep. In addition, behavioral therapy and biofeedback may prove beneficial to some patients. In a case report of a 13 year old boy with CVS the psychotherapist aimed to reduce anticipatory anxiety and to address the theory of underlying autonomic nervous system dysfunction in CVS patients through biofeedback (Slutsker, Konichezky, & Gothelf, 2010). Gaining insight into his trigger factors, learning stress reduction, relaxation and biofeedback techniques the patient remained symptom free throughout the 4 month treatment and at a 4 month follow-up (Slutsker et al., 2010).

Pharmacologically, several studies have proven tricyclic anti-depressants (TCAs) to be an effective treatment option. It is theorized that TCAs could possibly be affecting the central nervous system, modifying the brain-gut axis and underlying autonomic dysfunction found in some patients (Hejazi, Reddymasu, et al., 2010). As TCAs have also been shown to inhibit the CRF gene promoter region, it is possible that TCAs are alleviating symptoms through down-regulation of CRF (Hejazi & McCallum, 2011). In a two-year study with 46 patients, 88% of patients saw a significant reduction in the frequency and duration of episodes, as well as the number of ED visits and hospitalizations as compared to baseline status (Hejazi, Reddymasu, et al., 2010). In addition, 3 patients in the study had complete resolution of symptoms (Hejazi, Reddymasu, et al., 2010).
Non-steroidal anti-inflammatory (NSAID) proved effective for one adult male in a case report study. The patient, diagnosed with CVS and experiencing symptoms on a weekly basis was prescribed meloxicam, an NSAID for his back pain. When on a full dose of meloxicam (15 mg) and a small dose of a TCA, the patient experienced full resolution of CVS symptoms (Vidula, Wadhwani, Roberts, & Berkowitz, 2013). The authors of this paper proposed that CVS episodes were terminated in this patient through the known mechanism of NSAIDs inhibition prostaglandin synthesis, which normally stimulates ACTH release and initiates vomiting (Vidula et al., 2013). This inhibition maybe the cause of the cessation of vomiting the patient experienced and could serve as a useful treatment regime along with TCAs for other CVS patients.

Additional medications addressing conditions associated with CVS maybe beneficial to patients. For those patients who experience migraines it is recommend that in children β-receptor antagonists and histamine (H1)/serotonin receptor antagonists such as propranolol and cyproheptadine be added to a TCA regime (Hejazi & McCallum, 2011). In adults, TCAs and topiramate is recommended for those who experience migraine (Hejazi & McCallum, 2011). In addition, benzodiazepines for anxiety disorders, antispasmodic agents for IBS, anti-emetic agents for nausea that may occur between episodes, proton-pump inhibitors for gastro-esophageal reflux, and non-narcotic pain relievers for those that experience significant abdominal pain as well as seeking out treatment from a pain specialist should be incorporated into a CVS regime for those affected by additional conditions (Abell et al., 2008).
**Abortive and Acute Phase Treatments**

During the prodromal phase, some physicians have recommended NSAIDs, drinking sweet caffeinated drinks, intravenous or oral dexteroous and the use of antimi grated agents such as 5HT_{1B/1D} receptor agonists (Abell et al., 2008). The hope of administration of these agents is to either abort or lessen the severity of the episode through very early treatment. During the vomiting phase, patients often find that they require hospitalization or treatment in the ED for dehydration. It is recommended that patients receive a 5-10% dextrose solution for intravenous fluid replacement as this hydration regime appears to be of greater therapeutic efficacy in CVS patients (Abell et al., 2008; Hejazi & McCallum, 2011). Intravenous anti-emetic agents administered at high doses, sedatives, and narcotics are all useful in helping patients experience symptom relief (Hejazi & McCallum, 2011). Additionally, as CVS is often not recognized in the ED, where patients receive emetic phase relief it can be helpful for patients to carry a protocol of treatment. It was found that of those patients that who had protocols, 80% had their protocol followed by ED physicians (Venkatesan et al., 2010).

**CVS and Marijuana**

**Cannabinoid Hyperemesis Syndrome**

Cannabis use has often been found at higher frequency of usage among Cyclic Vomiting Syndrome patients. The role of cannabis as a contributory or ameliorating factor to CVS has yet to be determined. However, when diagnosing and treating CVS patients who engage in cannabis use, it important to distinguish CVS from another disorder that shows striking similarities, Cannabinoid Hyperemesis Syndrome (CHS).
According to case reports, patients with CHS tend to be heavy cannabis users with daily use often reported, their vomiting begins after engaging in marijuana use, they frequently take hot showers to alleviate symptoms, abdominal pain accompanies episodes, and cessation of vomiting is observed after discontinuation of marijuana use (Donnino, Cocchi, Miller, & Fisher, 2011; Sontineni, 2009). In addition, many patients have been heavy cannabis users for years before episodic vomiting begins (Sullivan, 2010). Like CVS, there are three stereotypical phases to the disorder. The prodromal phase starts with nausea and stomach pain in the early morning however, the patient can still engage in oral intake of food and liquids (Galli, Sawaya, & Friedenberg, 2011). The vomiting phase of CHS is very much like CVS in that vomiting is profuse and frequent. During the recovery phase, oral intake is able to be resumed and normal health is returned however this may take days, weeks or months (Galli et al., 2011). Often, confusion exists in diagnosing patients who use cannabis and have CVS and those whose cannabis use are causing CHS. Similarities between the two syndromes include the presence of a stereotypical prodromal, vomiting and recovery phase as well as a hot shower or bathing phenomenon to alleviate symptoms. In addition, there is often a high prevalence of marijuana use in the CVS population to alleviate inter-episodic nausea and vomiting. However, there are several important distinguishing factors between the two syndromes that should be taken into account when diagnosing and differentiating the two vomiting disorders. Table 2 helps to differentiate CVS vs. CHS and highlights important differences. Important characteristics to note are the presence of occasional to frequent cannabis use in CVS patients but not universal use in CVS patients where as all CHS
patients use cannabis. The cessation of cannabis use may help to ameliorate frequency of symptom development in some CVS patients but not necessarily all CVS patients as some have noted marijuana to help their nausea and vomiting. In the case of CHS, cessation of cannabis completely stops symptom development where as CVS patient’s still experience symptoms even with cannabis cessation. There is often a strong family or personal history of migraine in CVS patients with a migraine like aura sometimes accompanying vomiting episodes where no migraine exists in CHS patients. Gastric emptying time in CVS patients often tends to be accelerated where in CHS patients, GET is delayed due to the effect of cannabis on the gastrointestinal system.
Table 2. Cyclic Vomiting Syndrome vs. Cannabinoid Hyperemesis Syndrome. A table highlighting the differences between CVS and CHS (Figure adapted from Galli et al.)

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<td>Age of Diagnosis (y)</td>
<td>34.8</td>
<td>29.3</td>
</tr>
<tr>
<td>Delay in Diagnosis (y)</td>
<td>7.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Duration of episodes (days)</td>
<td>3.8</td>
<td>N/A</td>
</tr>
<tr>
<td>Cannabis Use</td>
<td>Occasionally to Frequent</td>
<td>Universal</td>
</tr>
<tr>
<td>Triggers</td>
<td>Frequent</td>
<td>Absent</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Universal</td>
<td>Universal</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>Compulsive Bathing/Showering</td>
<td>Occasional</td>
<td>Occasional</td>
</tr>
<tr>
<td>GET</td>
<td>Accelerated</td>
<td>Delayed</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Common</td>
<td>Not common</td>
</tr>
<tr>
<td>Psychiatric Conditions</td>
<td>Common (24-70%)</td>
<td>Not common</td>
</tr>
<tr>
<td>Migraine Headaches</td>
<td>Common</td>
<td>Not common</td>
</tr>
<tr>
<td>Treatment</td>
<td>Anti-migraine agents, TCA, trigger avoidance</td>
<td>Cannabis cessation</td>
</tr>
</tbody>
</table>
Cannabis and CVS

Studies that have taken note of cannabis use in CVS patients have yet to elicit a relationship between use and symptoms. However, a high prevalence of marijuana use in CVS patients has led to some investigators reporting on descriptive characteristics of CVS patients who use marijuana. In a literature review of CVS adults, it was found that 42-53% of CVS patients used marijuana and that substance use often predated CVS episodes by 5-10 years (Pattathan, Hejazi, & McCallum, 2012). Furthermore, one group found that cannabinoid use in specifically the male gender was more strongly associated with CVS as compared with functional vomiting (Choung et al., 2012). When looking at treatments typically recommended for CVS patients, Hejazi et al. found that those patients with chronic marijuana use, migraine headaches, psychological illnesses or dependence on narcotics for pain control were more likely to not respond to TCA treatment (Hejazi, Lavenbarg, Foran, & McCallum, 2010). However, patients that were chronic marijuana users viewed marijuana as a beneficial agent initially in their treatment regime but some individuals saw a lessening of therapeutic effect after years of use (Hejazi, Lavenbarg, Foran, et al., 2010).

In studies on GET in CVS patients, there have been mixed reports on the effect of marijuana use on GET as well. In one study conducted by Hejazi et al. they found that there was a slow GE in observed in 14% of CVS patients studied and of those, there was more likely to be chronic marijuana and chronic narcotic use (Hejazi, Lavenbarg, & McCallum, 2010). The same group in the study looking at non-responders to TCAs however observed that there was no difference in GET among those that responded to
treatment and the non-responders (marijuana and narcotic users, psychiatric disorders, migraine headaches) (Hejazi, Lavenbarg, Foran, et al., 2010).

Recording patient views on their own marijuana use, Kumar et al. observed that a third of their CVS patients used marijuana as a remedy for nausea and to stimulate appetite and the authors believed that there was no connection between marijuana use and symptom onset (Kumar et al., 2012). In another study, Namin et al. found 13 (42%) patients in his study group used marijuana daily to weekly and out of the 13, 7 viewed marijuana as beneficial to their symptoms, 4 with no regards to marijuana use and their symptoms and 2 with observed symptom improvement upon cessation of use (Namin et al., 2007).

The lack of consensus on the role of marijuana in the CVS population calls for additional investigation into the possible benefits and harmful outcomes of cannabis use among CVS patients. However, the historically and generally conservative views among physicians towards marijuana’s therapeutic effects may hinder or bias investigation. In a study done looking into physician views of medical marijuana among a study cohort of Colorado based physicians, more than 60% of participants thought there were significant risks both mentally and physically to marijuana use with only 27% viewing marijuana as having significant therapeutic value (Peckham, Stetka, & Vega, n.d.). The role of marijuana use in the CVS population needs to be further examined as well as additional characterization of both the disease and patients suffering from this poorly understood disorder.
In summary, due to the nature and rarity of CVS, this disease is difficult to investigate and remains poorly understood. We have reviewed the literature and have identified several gaps requiring further investigation. Additional insight is needed into what population is affected in terms of age, race and gender; the health care utilization by CVS patients; a deeper characterization of the patient profile in terms of associated conditions and the prevalence of substance abuse; and patients treatment regimes both traditional pharmacological methods as well as non-traditional methods patients may use to self medicated such as marijuana. Of possible areas, we specifically aim to characterize patient’s demographics, disease co-morbidities, ED utilization, predictors of marijuana use in CVS patients, and effect of marijuana in determining health care utilization in order to further contribute insight into the syndrome.
METHODS

We chose to further describe CVS patients and predictors of marijuana use through a retrospective patient chart review of individuals seen at Massachusetts General Hospital (MGH). Using a Partners Health Care System/MGH specific research tool, Research Patient Data Registry (RPDR), we used a query search to obtain a total of 640 patients. We then carefully analyzed the electronic medical records of the 640 patients excluding those patients with a history of hyperemesis gravidarum, chronic idiopathic nausea and vomiting, eating disorders, and CVS mentioned only in the differential diagnosis. We were able to obtain a total of 91 patients who received a diagnosis of CVS in their medical record, whose diagnosis was further verified based on the clinical expertise of one of the authors and through meeting Rome III criteria. Additionally, those selected were seen as either an inpatient, outpatient or in the ED at MGH over a 16 year period (1997-2013). Initially, of these 91 CVS patients, we collected data on the variables in Table 3
Table 3: Variables collected on 86 CVS patients seen at MGH between 1997-2013

| Demographics:                      | • Sex  
|                                   | • Race  
|                                   | • Ethnicity  
|                                   | • Employment status  
|                                   | • Education level  
|                                   | • Zip code  
| Patient Medical History:          | • Height  
|                                   | • Weight  
|                                   | • Body Mass Index (BMI)  
|                                   | • Age of First CVS attack  
|                                   | • Presence of diabetes and mitochondrial disease  
|                                   | • Gastroenterology (GI), psychiatric and neurological diagnoses.  
| Health Care Utilization:          | • Number of ED visits  
|                                   | • ED chief complaint  
|                                   | • Number of admissions  
|                                   | • Presence of a GI or Psychiatric consult upon admission  
|                                   | • Length of stay upon admission  
|                                   | • Number of outpatient visits for a GI doctor  
|                                   | • Time span going to a GI doctor  
|                                   | • Number of outpatient for primary care doctor, psychiatric, pain management specialist, neurology, immunology and urgent care  
|                                   | • Their total time span of contact at MGH  
| Substance abuse history and frequency of use: | • Alcohol  
|                                   | • Tobacco  
|                                   | • Marijuana  
|                                   | • Narcotics  
|                                   | • Cocaine  
|                                   | • Heroine  
|                                   | • Benzodiazepines  
|                                   | • Ecstasy  
| Prescription Medication:          | • Presence of a dronabinol prescription  
|                                   | • Purpose of dronabinol prescription  
|                                   | • Self reported dronabinol efficacy  
|                                   | • Length of dronabinol prescription  
|                                   | • Number of ED visits 6 months before and after dronabinol  
|                                   | • Active and Inactive medications  


Of these variables, we used descriptive statistics to describe our cohort’s gender, employment, age of first attack, psychiatric conditions, marijuana use, alcohol use, narcotic use, chronic pain syndromes, and ED usage. Using Statistical Analysis Software (SAS) we first performed univariate analysis to examine differences in CVS patient marijuana users vs. CVS patients non-marijuana users. Fichers exact test was used for dichotomous variables and T-test was used for continuous variables. In addition we used SAS multivariate analysis logistic regression controlling for the variables alcohol use, age, sex, psychological diagnosis, narcotic use and chronic pain to determine the variables that were predictors of marijuana use in our CVS population. Of the categories, we chose to exclude the data with incomplete information from our descriptive, univariate and multivariate analysis.
RESULTS

Characterization of Cohort

As seen in Table 4 which highlights our results on the descriptive statistics of our cohort, of the 91 patients, there were 57 males (67%) with a mean age of 28 years, average age of first attack of 20.2 years and an employment rate of 62% of our cohort being either employed or full time students.

73% of the cohort had a psychiatric condition with anxiety (50%) predominating followed closely by depression (47%). The other co-morbid condition we analyzed was the presence of a chronic pain syndrome, which we defined as lower back pain, migraine headaches and fibromyalgia. A chronic pain syndrome was found in 40% of our cohort. History of substance use or abuse was found in a significant number of patients. 76% of our cohort had a history of THC exposure, which we defined as marijuana use or dronabinol prescription. In addition 51% used alcohol daily, and 28% were found to be regular users of narcotics, both heroine and pill form.

ED usage by patients was found to have an occurrence on average of 1.6 times per year. In our cohort, all patients were found to have presented to the ED at least once a year with one patient having a very high 208 ED visits in one year. Of patients who presented more than once during the total duration of the years in study (1997-2013), there was a median interval between ED visits of 103.6 days. ED chief complaint included abdominal pain, nausea and vomiting which was present in 82% of patients.
**Univariate Results**

We first used univariate analysis to screen for significant variables associated with marijuana use in our CVS population. Table 5 highlights our findings. Of interest, sex (p-value .0246), chronic pain (p-value .0351), and education level (p-value .0328) were found to be variables of significance.

**Multivariate Results**

From univariate analysis, we used multivariate logistic regression analysis in SAS and found daily alcohol use to be associated significantly with marijuana use in our CVS population (OR 5.26, 95% CI 1.469-18.828). Men were also significantly more likely to use marijuana than females (OR .23, 95% CI .07-.77). Interestingly, the presence of a chronic pain syndrome significantly lowered the risk for cannabis use (OR .15, 95% CI .039-.575). Of the other variables we examined in the multivariate logistic regression, the presence of a psychiatric illness, patient age and narcotic use were not significantly associated with marijuana use.
### Table 4: Results Summary

<table>
<thead>
<tr>
<th>Gender:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:</td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td>Female:</td>
<td></td>
<td>33%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>28</td>
<td>years</td>
</tr>
<tr>
<td>Age of first attack</td>
<td>20.2</td>
<td>years</td>
</tr>
</tbody>
</table>

| Employment:       |       | 67%   |

<table>
<thead>
<tr>
<th>Psychiatric Illness:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

| Chronic Pain Syndrome: |       | 40%  |

<table>
<thead>
<tr>
<th>Substance Abuse:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana:</td>
<td>67%</td>
<td></td>
</tr>
<tr>
<td>Alcohol:</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Narcotics:</td>
<td>28%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ED Use:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>1.6</td>
<td>time/year</td>
</tr>
<tr>
<td>Interval between visits</td>
<td>103.6</td>
<td>days</td>
</tr>
</tbody>
</table>

### Table 5: Univariate Analysis of Predictors of Marijuana Use

*Denotes variables of significance

<table>
<thead>
<tr>
<th>Variables</th>
<th>Non-Marijuana Users</th>
<th>Marijuana Users</th>
<th>Fischer’s Exact Two sided P value</th>
<th>Relative Risk Value</th>
<th>95% confidence interval</th>
<th>T value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex*</td>
<td></td>
<td></td>
<td>.0246</td>
<td>.4540</td>
<td>.2366, .8710</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12 (13.19%)</td>
<td>49 (53.85%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (14.29%)</td>
<td>17 (18.68%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td>.1220</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>20 (22.73%)</td>
<td>54 (61.36%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>1 (1.14%)</td>
<td>2 (2.27%)</td>
<td></td>
<td></td>
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<tr>
<td>Hispanic</td>
<td>0</td>
<td>6 (6.82%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (3.41%)</td>
<td>1 (1.14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 (1.14%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----</td>
<td>-----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>x=24.0818</td>
<td>x=25.5315</td>
<td>.1286</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age of first attack</td>
<td>x=19.2528</td>
<td>x=20.5215</td>
<td>.5705</td>
<td></td>
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<td>Marital Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Single</td>
<td>20 (22.22%)</td>
<td>54 (60%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>4 (4.44%)</td>
<td>23 (13.33%)</td>
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<td></td>
<td></td>
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<tr>
<td>Employment</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Unemployed</td>
<td>12 (14.12%)</td>
<td>33 (38.82%)</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Employed</td>
<td>10 (11.76%)</td>
<td>30 (35.29%)</td>
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<tr>
<td><strong>Education</strong></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>Level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nothing</td>
<td>8 (10.38%)</td>
<td>14 (18.18%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High School</td>
<td>5 (6.49%)</td>
<td>8 (10.39%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College</td>
<td>5 (6.49%)</td>
<td>37 (48.05%)</td>
<td></td>
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</tr>
<tr>
<td>TCA prescriptions</td>
<td>.4360</td>
<td>1.4545</td>
<td>.6146, 3.4423</td>
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</tr>
<tr>
<td>No TCA</td>
<td>20 (22.22%)</td>
<td>46 (51.11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TCA</td>
<td>5 (5.56%)</td>
<td>19 (21.11%)</td>
<td></td>
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<tr>
<td>Psych Diagnosis</td>
<td></td>
<td>.6030</td>
<td>1.2424</td>
<td>.6151, 2.5094</td>
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</tr>
<tr>
<td>No Diagnosis</td>
<td>8 (8.79%)</td>
<td>17 (18.68%)</td>
<td></td>
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</tr>
<tr>
<td>Diagnosis</td>
<td>17 (18.68%)</td>
<td>49 (53.85%)</td>
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<td></td>
</tr>
<tr>
<td><strong>Chronic Pain</strong></td>
<td></td>
<td>.0351</td>
<td>.4780</td>
<td>2.414, .9465</td>
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</tr>
<tr>
<td>No Pain</td>
<td>10 (10.99%)</td>
<td>43 (47.25%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>15 (16.48%)</td>
<td>23 (25.27%)</td>
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</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td>.1658</td>
<td>1.6643</td>
<td>.8218, 3.3703</td>
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</tr>
<tr>
<td>No Anxiety</td>
<td>16 (17.58%)</td>
<td>31 (34.07%)</td>
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</tr>
<tr>
<td>Anxiety</td>
<td>9 (9.89%)</td>
<td>35 (38.46%)</td>
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</tr>
<tr>
<td>Depression</td>
<td>.8147</td>
<td>.8642</td>
<td>.4430, 1.6858</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No Depression</td>
<td>12 (13.19%)</td>
<td>35 (38.46%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>13 (14.29%)</td>
<td>31 (34.07%)</td>
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<tr>
<td>Narcotic Use</td>
<td></td>
<td>.1047</td>
<td>2.4804</td>
<td>.8176, 7.5247</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Count</td>
<td>Percentage</td>
<td></td>
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<tr>
<td>----------------</td>
<td>-------</td>
<td>------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Narcotics</td>
<td>22</td>
<td>24.18%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcotics</td>
<td>3</td>
<td>3.30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>50.55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>21.98%</td>
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</tr>
</tbody>
</table>
DISCUSSION

Our study compiled the experience of CVS patients seen at a tertiary care center over the span of 13 years. Through retrospective patient chart review we described our cohort based on demographics, co-morbidities, substance abuse history, and ED usage. In univariate analysis sex, educational level and chronic pain were shown to be variables that showed a statistical difference between CVS marijuana users and non-users. Upon multivariate analysis controlling for the variables of alcohol use, age, sex, psychological diagnosis, narcotic use and chronic pain, we found sex, alcohol use and chronic pain to be predictors of marijuana use in CVS patients. Our sample size of 91 patients is fairly large in comparison to other CVS studies and our result differ from the literature in terms of employment status, presence of chronic pain, emergency department use, and substance abuse.

As CVS has been historically thought of as a disorder of pediatric patients, there now is an increasing investigation into adult CVS. The higher average age of our CVS population and age of first attack in our CVS cohort represents an older demographic of CVS patients rather than the traditional study of a pediatric group. As seen in Table 6, our average age and age of first attack is comparable to other recent studies but appears to be a bit more male skewed than other groups.
Table 6: A Comparison of Demographics

<table>
<thead>
<tr>
<th></th>
<th>Choung et al.</th>
<th>Namin et al.</th>
<th>Lee et al.</th>
<th>Hejazi et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>91</td>
<td>30</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Average Age</td>
<td>28 years</td>
<td>30 years</td>
<td>29 years</td>
<td>28 years</td>
</tr>
<tr>
<td>Age of First Attack</td>
<td>20.2 years</td>
<td>-</td>
<td>30 years</td>
<td>21.1 years</td>
</tr>
<tr>
<td>Gender Breakdown</td>
<td>67% male</td>
<td>67% male</td>
<td>58% male</td>
<td>35.7% male</td>
</tr>
</tbody>
</table>

The high employment and full time student status of our cohort represents perhaps a higher degree of functionality within our population. This is perhaps due to the location of our center. Boston has many medical resources in comparison to other areas of the country. The ease of availability and accessibility to centers that have much experience with more rare and difficult to treat disorders like CVS could explain why our population enjoys a higher employment and full time student status. This finding is unique in that it has been frequently observed that individuals affected with CVS have significant impairments to employment and ability to attend school. One report found that 57% of non-responders to TCA treatment experienced both disability and loss of job and 20% of responders experienced disability and 31% loss of job (Kumar et al., 2012). In addition Fleisher et al. found that out of 39 patients, 17 (43.5%) had moderate CVS characterized as work or educational status being in jeopardy and 19 (48.7%) had severe CVS defined as the duration of time ill equaled or exceeded their duration of periods of wellness (Fleisher et al., 2005).
Although there are no specific prevalence rates documented for the co-morbidities we chose to analyze in CVS patients, the higher incidences of depression and anxiety found in our cohort is consistent with many studies findings of a mental illness diagnosis within the CVS population. A high incidence of psychiatric illnesses is not uncommon in CVS due to the nature of the disorder. Many patients experience anxiety and depression relating to their symptoms and the affect it has on their life. Anxiety is sometimes noted by patients as a precipitating factor to symptom development and many patients experience anxiety when thinking about their illness or events that commonly trigger an episode. Kumar et al. found a similar rate of anxiety and depression (47% and 49% respectively) in his population of adult CVS patients along with Boles et al. who found both anxiety and depression in 55% his CVS cohort (Boles et al., 2009; Kumar et al., 2012). Other studies have found depression to range anywhere from 6%-78% and anxiety from 8%-84% (Hejazi & McCallum, 2011).

CVS is a chronic condition that often has pain associate with it. Inter-episodic abdominal pain is sometimes noted in patients and many experience abdominal pain during episodes. In our cohort, 82% of patients experienced abdominal pain that accompanied nausea and vomiting. In addition to abdominal pain, 40% of our cohort was found to have a chronic pain syndrome. In the literature, pain is often recorded in the CVS population through the incidence of migraines and/or family history of migraines as the association of CVS and migraines has been well known for some time. One study done by Namin et al. even went so far as to specifically assess for pain using a visual analog scale (VAS) at baseline and after starting a treatment regime of amitriptyline
(Namin et al., 2007). However, we chose not to focus only on migraine in our analysis but more broadly the presence of a chronic pain syndrome due to the observation that individuals with functional disorders such as CVS often have other co-morbid functional pain disorders. In patients with IBS, a study found that there was a high prevalence of other functional pain disorders such as temporomandibular joint disorder and fibromyalgia (Kim & Chang, 2012). Furthermore, individuals with many co-morbid functional disorders have found to have central sensitization correlated with heightened pain perception (Kim & Chang, 2012). As pain syndromes have been analyzed in other functional GI disorders such as IBS, our documentation of the prevalence of chronic pain syndromes specific to the CVS population is the first.

As seen in Table 7, the frequency of emergency department usage by our patients of 1.6 times per year with a median interval of 103.5 days between visits is lower than other reports. In Kumar et al. study cohort, they recorded 3.4±9 ED visits/year of individuals who responded to TCA treatment and 15.8±9.2 of individuals who didn’t respond to TCA treatment (Kumar et al., 2012). Our ED visits per year is also lower than Hejazi et al. baseline measure of 15.8±13.4 visits per year before TCA treatment was initiated as well as the first and second years after TCA treatment (4.2±5 and 3.3±3.6 visit per year respectively) (Hejazi, Lavenbarg, Foran, et al., 2010).
Table 7: Comparison of ED Usage

<table>
<thead>
<tr>
<th></th>
<th>Kumar et al.</th>
<th>Hejazi et al.</th>
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<tbody>
<tr>
<td>ED usage/year</td>
<td>1.6</td>
<td>Before TCA initiation: 4.2±5</td>
</tr>
<tr>
<td></td>
<td>TCA responders: 3.4±9</td>
<td>After TCA initiation: 3.3±3.6</td>
</tr>
<tr>
<td></td>
<td>TCA non-responders: 15.8±9.2</td>
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There are several reasons why our patients ED utilization maybe lower than others. It perhaps could represent a higher functionality by our patients where they have less health care utilization. This would coincide with our finding of a higher employment and full time student status in our cohort. In addition, over the past 5 years there have been an increasing number of patients with CVS being treated at MGH. Subsequently, the ED at MGH has become very knowledgeable about treating patients and giving patients protocols to control their symptoms to decrease hospitalizations. However, this finding was most likely due to our method of data collection. With retrospective data collection, we were only able to see patients that were seen at MGH without the ability to account for other visits at other health care facilities. It is however interesting that our ED utilization is lower than Kumar et al., who also gathered data through retrospective chart review of patients seen at their institution.

On a national level, the therapeutic use of marijuana for various disorders is increasingly being investigated. Since 1986, THC has been in use as an alternative to antiemetic drugs for individuals undergoing chemotherapy and as an agent to increase weight and appetite in those with conditions that cause cachexia such as HIV/AIDS and cancer (Peckham et al., n.d.). We chose to examine THC use in our cohort to further shed
light on marijuana use in the CVS population and to provide direction for additional studies as marijuana may prove to be a beneficial prophylactic treatment option for inter-episodic nausea, appetite stimulant and perhaps method to reduce episode frequency and enhance quality of life. As shown in Table 8, our cohort has a very high marijuana prevalence rate in comparison to other groups.

**Table 8: Comparison of Substance Abuse**

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<tr>
<td>n</td>
<td>86</td>
<td>92</td>
<td>29</td>
<td>82</td>
<td>31</td>
</tr>
<tr>
<td>Marijuana use</td>
<td>76%</td>
<td>32%</td>
<td>17.4%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Narcotic use</td>
<td>28%</td>
<td>19%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>51%</td>
<td>-</td>
<td>-</td>
<td>28%</td>
<td>-</td>
</tr>
</tbody>
</table>

The very high marijuana use rate, low ED usage rate and high employment status may point to higher functionality and quality of life in our cohort due to marijuana use. Through multivariable regression we were not able to find a relationship between these variables due to small sample size and retrospective study design. Data on current and past marijuana use was often missing or difficult to determine in the medical history and an accurate capture of health care utilization was impossible as we could only see visits to our institution. Further investigation through prospective data collection would be a better tool to determine the role of significant marijuana use in a patient’s functionality and quality of life.
Before multivariate analysis, univariate analysis was performed to see if there were any differences between non-marijuana users and marijuana users in terms of the variables collected in Table 4. We found sex, education level and chronic pain to be statistically significant differences between the two groups. There were more males in the marijuana user group, individuals with a college education were found at higher frequency in the marijuana users group and those with a chronic pain syndrome were less likely to use marijuana. The finding of more males using marijuana in comparison to females with CVS also proved to be true upon multivariate logistical regression and is consistent with prior literature. Generally, illicit drug use, including marijuana is more common in males than females (11.2% vs. 6.8%) for those age 12 and older (“Results from the 2010 NSDUH,” 2010). Specifically looking at CVS, it was found in a literature review that males were more likely to be marijuana users. A retrospective patient chart review study also revealed that cannabinoid use in males increased the odds for CVS (OR 2.9, 95% CI 1.2, 7.2) (Choung et al., 2012; Pattathan et al., 2012).

Education level and risk of marijuana use showed a surprising outcome in our cohort. It is generally presumed that a higher education level decreases risk of substance abuse. However, there seems to be a complex relationship between education level and substance abuse. According to a 2010 National Survey on Drug Use from the Department of Health and Human Services, there was an inverse correlation for the rate of illicit drug use and educational achievement with individuals not completing high school having the highest level of drug use and college graduates having the lowest risk of drug use (“Results from the 2010 NSDUH,” 2010). When looking at lifetime rates of drug use
though, the opposite was found in that those with the lowest educational attainment had the lowest lifetime rate of drug use and those with the highest level of educational achievement had the highest rate (“Results from the 2010 NSDUH,” 2010).

Looking specifically at marijuana use and education level, a twin study of Vietnam era veteran twins revealed that there were no differences in level of educational attainment in terms of marijuana use, early marijuana initiation and marijuana dependence (Grant et al., 2012). In addition, some studies have found that those with a higher education were more disposed to use marijuana throughout the course of their life (Galea, et al., 2007). The more educated population having a higher risk of marijuana use in our cohort could reflect a higher level of disposable income that generally follows a greater educational attainment. In addition, marijuana maybe allowing the more educated CVS population to function better with their symptoms in comparison to the less educated CVS population.

Our findings of the presence of a chronic pain syndrome lowering the risk of cannabis use in CVS patients in univariate analysis also proved to be of significance in multivariate logistical regression controlling for the variables of alcohol use, age, sex, psychological diagnosis, narcotic use and chronic pain. This goes against other findings of cannabis use in pain syndromes. Cannabis has been noted as treatment for chronic pain for thousands of years including neuropathic pain and fibromyalgia (Peckham et al., n.d.). A systematic review analyzing randomized controlled trials for the treatment of chronic pain with cannabis revealed cannabis had a modest effect on the treatment of chronic non-cancer pain with minimal to no side effects and should be consider a safe treatment
option for pain, particularly neuropathic pain (Lynch & Campbell, 2011). Given what is
known about the use of marijuana in those with a chronic pain condition, it is surprising
that individuals with CVS and a co-morbid pain condition were less likely to use
marijuana. It maybe that individuals with a chronic pain condition in our cohort were
abusing other, more dangerous forms of substances such as opioids. However we were
unable to examine this due to difficulties in data collection.

**Limitations**

There are several limitations to our study. Being a retrospective design, we were
only able to collect data that was present in the patient’s medical record and often had
data that was not available. The variables that were particularly affected and difficult to
collect were most recent height and weight, age of first CVS attack, education level,
number of ED visits and admissions, the presence and type of a consult upon admission,
type and frequency of outpatient admissions and substance abuse history. There was an
average frequency of 7 individuals per variable with missing data in the univariate
analysis with a range of 1-20 individuals. The variable with the lowest amount of missing
data was BMI, the highest was education level and the second highest with a frequency of
12, employment level. Many of these variables with data missing were key variable
outcomes, which could have significantly affected our results and ability to achieve our
initial objectives. To deal with this problem, we chose not to include individuals in
analysis if there data was missing which could have biased analysis. In addition
information on total frequency and type of health care utilization was difficult to gather
due to only MGH records being available to our group. Some individuals only had one or
no recordings of ED visits at MGH with no mention of frequency of hospitalizations at other institutions in the medical record by physicians. Therefore our information was not an accurate reflection of our patient’s total medical usage and experience in every patient. Information such as the age of first CVS attack, most recent height, weight and substance abuse history was sometimes not documented as well. The lack of complete and accurate documentation on substance abuse history as well as the inability to see health care utilization at other institutions affected our ability to measure health care utilization frequency as an outcome of marijuana use to the point that we decided to only measure predictors of marijuana use in CVS patients.

Besides retrospective study design inherently limiting the information we could gather, MGH is a tertiary care center so patients seen here may not reflect the average CVS patient or the average CVS patient’s experience. We also did not have quality of life measures such as patient surveys to give patients to determine how marijuana use affected quality of life. The lack of control group also was a severe limitation on our study design.

**Future Directions**

Future directions for our group would be to prospectively gather patient data through sending out quality of life surveys and surveys designed to record an individuals health care utilization to the patient’s home or e-mail address as well as collecting information on site through giving surveys to those our group personally treats at MGH. We will also have to select a control group to make future results more statistically sound and accurate description of CVS patients. In selection of a control group for the future,
we would try to select another functional disorder such as IBS, gastroparesis, or migraine and match them to our CVS cohort in terms of age, sex, and disease severity.

**Conclusion**

We chose to examine a cohort of CVS patients at a tertiary care center in order to further describe this disorder and patient characteristics. In addition to analyzing patient demographics, co-morbidities and health care utilization, we originally hoped to see how marijuana use affected quality of life through the end point of ED usage. Due to the limitations of retrospective data collection, MGH being a tertiary care center and therefore not accurately reflecting the average CVS patient’s experience, lack of control group and lack of quality of life measures we instead described our cohort in terms of demographics, co-morbidities, ED utilization, substance abuse and variables that predicted marijuana use. We found a significant number of our patients had psychiatric conditions, chronic pain syndrome, and a history of substance abuse. In addition alcohol use and being male were two variables that predicted marijuana use in the CVS population while the presence of a chronic pain syndrome lowered the risk of marijuana use. The high employment status and marijuana use along with lower than average ED usage may point to a better quality of life due to marijuana use however further investigation is needed into this hypothesis. Future directions aim to conduct prospective trials including patient surveys, interviews and questionnaires conducted both in clinic and through mail measuring quality of life, health care utilization at MGH and outside hospitals, history of marijuana or dronabinol, and perceived patient benefit or detriment of marijuana to symptoms.
REFERENCES


CURRICULUM VITAE

KATHERINE WEBER

(716) 512-0436 • katharine.weber2@gmail • D.O.B : 1990
Permanent address: 181 Hillside Dr. Elma, NY 14059
Local Address: 260 Columbia St. Cambridge, Ma, 02139

GRADUATE STUDIES
BOSTON UNIVERSITY SCHOOL OF MEDICINE BOSTON, MA
Bachelor of Arts in Biology Anticipated September 2014
• Cumulative GPA 3.79/4.0

SELECTED GRADUATE SCHOOL COURSEWORK
Medical School Physiology with lab, Cellular Organization of Tissues with Lab, Biochemistry
• **Physiology with Lab:** Studied membrane transport, neurophysiology, blood and muscle, the cardiovascular system and gastrointestinal system. Participated in small group labs and discussions of physiological problems and clinical cases.
• **Cellular Organization of Tissues with Lab:** Studied the organization of the body at the cellular and tissue level. Analyzed and interpreted medically related histological slides and the cellular appearance of pathological conditions.
• **Biochemistry:** Studied the molecular basis of cellular functions including topics on proteins and enzyme kinetics, heme biosynthesis, bilirubin metabolism and porphyria, connective tissue, carbohydrate and energy metabolism, urea cycle and amino acid metabolism, lipids and hormone action and signaling, nucleotide metabolism, transcription and translation and regulation of processes in prokaryotes and eukaryotes, RNA processing and protein synthesis

UNDERGRADUATE BIOLOGY AND PRE-MEDICAL STUDIES AND HONORS
UNIVERSITY OF ROCHESTER ROCHESTER, NY
Bachelor of Arts in Biology May 2012
• Cumulative GPA 3.4/4.0  Biology GPA 3.49/4.0
• Recipient of Kodak Leadership Scholarship for leadership at school and within the community
• Barbara Finch Scholarship awarded for involvement and leadership in the University community
SELECTED BIOLOGY AND PRE-MEDICAL COURSEWORK, CONCEPTS AND LABS

Biology I and II with Lab, Genetics with Lab, Biochemistry, Evolution, Environmental Animal Physiology, Mammalian Anatomy with Lab, Biology of Aging, Psychology, Behavioral Medicine, Topics in Drug Development, General Chemistry II with Lab, Organic Chemistry I and II with Lab, Physics I and II with Lab, Calculus I, II & III, Statistics, Multidimensional Calculus, Linear Algebra, Spanish

- Mammalian Anatomy with Lab: Studied the structural and systematic anatomy of humans. Performed dissections of various organisms for the purpose of analyzing and identifying systems and structures.
- Biology of Aging: Discussed the molecular mechanisms of aging with emphasis on current theories and research in the aging field. Studied abnormalities in aging including progeroid syndromes, relationship between cancer and aging, and model organisms used in research.
- Evolution: Evolutionary biology topics included study of population genetics, molecular evolution, human evolution, and speciation.
- Organic Chemistry Lab I and II: Studied chemical bonding, stereochemistry, and reaction mechanisms reactivity of functional groups, organic synthesis, and lab analysis of compounds using NMR.

CLINICAL AND BIOLOGY RESEARCH AND LABORATORY EXPERIENCE

UNIVERSITY COLLEGE LONDON LONDON, ENGLAND
Student Intern, Anesthesiology Department Summer 2011
- Interviewed and photographed female patients prior to scheduled cesarean sections to be used in educational pamphlet from patient perspective
- Talked to patients in clinics about concerns/thoughts about cesarean section
- Requested consent from two selected patients prior to surgery
- Collaborated with midwives, obstetricians, and anesthetists about content and wording of pamphlet
- Photographed women during cesarean section
- Attended and assisted at international medical conferences

HARVARD UNIVERSITY BOSTON, MA
Research Assistant Summer 2009
Principal Investigator, Dr. Charles Dimitroff, Ph.D.
- Completed biochemical analyses of galectin-1 to be used in treatment of inflammatory cells in synovial fluid of rheumatoid arthritis patients
- Required in-depth knowledge of glycobiology, biochemistry, immunology, cell biology and tumor biology
- Skilled in performance of western blotting techniques, protein identification, isolation and purification, maintenance of cell lines, and protein binding assays
• Attended weekly group meetings to discuss research and data collected
• Culmination presentation for the Department of Immunology on summer research findings

**MEDICAL AND VOLUNTEER EXPERIENCE**

**ELLIS HOSPITAL**
**Schenectady, NY**

Shadowing Opportunity 
Fall 2011

• Shadowed Emergency Room Pharmacist for one day
• Learned how to and practiced mixing medications
• Observed Pharmacist reading patient charts, questioning patients on medical history and medications used, and consulting with physicians on plan-of-care
• Witnessed spinal-tap procedure and setting of dislocated forearm

**STRONG MEMORIAL HOSPITAL**
**Rochester, NY**

Emergency Room Volunteer 
Summer 2010

• Escorted patients from the waiting room to hospital beds
• Provided assistance to patients in need and responded to requests for linens, food, etc.
• Responded to patients calls and relayed messages and requests to attending nurses and other medical staff

**WORK AND LEADERSHIP EXPERIENCE AND OTHER ACTIVITIES**

**UNIVERSITY OF ROCHESTER**
**Rochester, NY**

University IT Help Desk 
Fall 2011-present

• Assist University-affiliated students, faculty and staff with computer-related issues
• Cover overnight shifts once a week and various shifts during weekdays
• Answer phone calls, assisting as needed, or forwarding issues on to appropriate personnel

President, Vice President, Women’s Club Squash 
2010-present

• Arranged practices and matches with Varsity teams across the East Coast
• Fundraised for events by soliciting donations from parents and alumni, selling university apparel and arranging Rochester-community tournaments
• Maintained records of club expenses and finances
• Recruited players

**EASTMAN SCHOOL OF MUSIC**
**Rochester, NY**

Violin Lessons 
2008-present

• Participate in weekly violin lessons
• Culminating performances each academic year for jury composed of Eastman faculty and graduate students
• Member of University of Rochester Symphony and Chamber Orchestra (2008-2009)
• Chile Exchange Program: performed with local chamber orchestras throughout Chile (Winter 2009)