Exp Brain Res (2014) 232:2563–2570
DOI 10.1007/s00221-014-3967-0

RESEARCH ARTICLE

An Internet survey of marijuana and hot shower use in adults with cyclic vomiting syndrome (CVS)

Thangam Venkatesan · Jyotirmoy Sengupta · Atena Lodhi · Abigail Schroeder · Kathleen Adams · Walter J. Hogan · Yanzhi Wang · Christopher Andrews · Martin Storr

Received: 17 October 2013 / Accepted: 15 April 2014 / Published online: 4 May 2014

Abstract Cyclic vomiting syndrome (CVS) is a chronic disorder characterized by episodic nausea and vomiting. A large proportion of patients use marijuana to control their symptoms. Several case reports implicate marijuana as a cause of intractable vomiting with compulsive hot water bathing considered pathognomonic of "cannabinoid hyperemesis." We sought to examine the relationship between marijuana use and CVS. Patients >18 years of age diagnosed by a health care provider were invited to participate in an anonymous internet-based survey. A total of 514 patients participated and 437 completed questions about marijuana use. Mean age was 34 ± 12 years with patients being predominantly female (63 %), Caucasian (92 %) and from the USA (82 %). Nineteen percent never used marijuana and 81 % did. Fifty-four percent used marijuana for health issues and 43 % for recreational purposes. Users stated that it improved nausea, appetite, general well-being, stress levels and vomiting. Users were more likely to be male and have an associated anxiety disorder. Sixty-seven percent of patients reported taking hot showers/baths for symptom relief, and this was associated with marijuana use. (OR 2.54, CI 1.50–4.31, $P = 0.0006$). Eighty-one percent of patients with CVS who completed an internet survey reported frequent use of marijuana. With marijuana use, patients noted the greatest improvement with stress levels, appetite and nausea. Marijuana users were more likely to be male and have associated anxiety. Hot showers were not pathognomonic of marijuana use though they were more likely to be associated with its use.

Keywords Vomiting · Marijuana · Hot showers · Functional gastroenterology · Clinical pharmacology

T. Venkatesan (✉) · J. Sengupta · A. Schroeder · W. J. Hogan
Division of Gastroenterology and Hepatology, Department of Medicine, Medical College of Wisconsin, 9200, W. Wisconsin Ave., Milwaukee, WI 53226, USA
e-mail: tvenkate@mcw.edu

A. Lodhi
Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

K. Adams
Cyclic Vomiting Syndrome Association (CVSA), Milwaukee, WI, USA

Y. Wang
Division of Biostatistics, Medical College of Wisconsin, Milwaukee, WI, USA

C. Andrews
Gastrointestinal Research Group, Division of Gastroenterology, Department of Medicine, University of Calgary, Calgary, AB, Canada

M. Storr
Division of Gastroenterology, Department of Medicine, Ludwig Maximilian University of Munich, Munich, Germany

Introduction

Cyclic vomiting syndrome (CVS) is a chronic disorder that is characterized by recurrent episodes of nausea and vomiting with varying intervals of normal health. It was first described in the pediatric literature by Samuel Gee in 1882 when he described "fitful or recurrent vomiting" in children but is recognized increasingly in adults as well. (Gee 1882) CVS consists of four main phases: the inter-episodic phase, the prodromal phase, the emetic phase and the recovery phase. (Fleisher and Matar 1993) Patients describe multiple symptoms including nausea, vomiting, abdominal pain, chills and hot flashes during an episode. Patients often lie

in a dark room and report that sleep is beneficial in ameliorating symptoms. Many patients with CVS also report taking hot showers/baths that seem to alleviate their symptoms at least temporarily, and this has been described as "compulsive hot water bathing" (Chepyala and Olden 2008). Some patients with CVS can deteriorate over time and develop persistent symptoms for weeks or even months without any return to normalcy. This is referred to as coalescent CVS. The current medical treatment of CVS consists of using preventive medications in the inter-episodic phase such as tricyclic antidepressants, antiepileptics such as topiramate and mitochondrial therapy such as coenzyme Q 10, carnitine and riboflavin. During the episode, management remains largely supportive with the use of IV fluids, antiemetics and sedatives as needed (Abell et al. 2008). Given the relative paucity of data in the treatment of CVS and the lack of consistent treatment protocols, these patients are frequently frustrated and resort to using marijuana. Up to 38 % of patients with CVS, use marijuana on a chronic basis with young age and male gender being a significant risk factor for use (Choung et al. 2012). However, chronic marijuana use has been identified as a potential risk factor for nonresponse to treatment in CVS (Hejazi and McCallum 2011).

Marijuana consists of several phytocannabinoids and has been used as a herbal remedy for centuries for various maladies (Mechoulam 2005). The major psychoactive ingredient in marijuana is 9-tetrahydrocannabinol (THC); this activates a G protein-coupled receptor, called the CB1 receptor (CB1R). This receptor is a part of the endocannabinoid system (ECS), which consists of the two endogenous ligands, anandamide and 2-arachidonylglycerol (2-AG), the CB1 and CB2 receptors and enzymes that are involved in the biosynthesis and degradation of these ligands (Di Marzo and Fontana 1995). THC and other cannabinoid agonists when administered acutely in animal models have been shown to have an antiemetic effect (Van Sickle et al. 2001). It is used in treating nausea and vomiting in patients who undergo chemotherapy and also for treatment of pain and as an appetite stimulant (Thaler and Gupta 2011; Kirkham 2005). This is contrary to reports that marijuana may cause cyclic vomiting. There have been multiple case reports recently of cyclic nausea and vomiting associated with cannabis use and hot showers. A recent review by Friedenberg et al. suggested that marijuana is associated with "cyclic vomiting" contrary to evidence that marijuana has antiemetic properties in both humans and animals. In addition, they also imply that this may cause vomiting though there is insufficient data to support this given the lack of follow-up data on cases of cannabinoid hyperemesis reported in the literature. Given these observations, we sought to examine the use of marijuana and hot showers in adult patients with CVS (Galli et al. 2011).

Materials and methods

We conducted a large, internet-based, anonymous, cross-sectional study of marijuana use in patients with CVS. Patients >18 years of age who were seen at the CVS clinic at the Medical College of Wisconsin (MCW) and those who visited the Cyclic Vomiting Syndrome Association (CVSA) website were invited to participate. The clinic at MCW serves as a tertiary referral center for patients with CVS. All patients diagnosed by a physician/allied health provider were invited to participate, and subjects were required to complete a detailed questionnaire. The first section consisted of questions regarding demographics and clinical characteristics of CVS, while the second part addressed use of marijuana and its perceived benefits and side effects. Most of the questions on demographics, past medical history and features of CVS were close-ended, forced-choice questions using radio buttons, drop down menus and matrices. Many of the questions on marijuana use were not mandatory in order to give respondents the option of not answering sensitive questions. The options for response to marijuana use were based on a Likert scale with responses ranging from "Made a lot better," "No difference" and "Made a lot worse." Patients were also queried about the presence of various comorbid conditions such as anxiety and depression, which is quite prevalent in this cohort of patients (Namin et al. 2007). However, they were not asked to differentiate whether a health care provider made the diagnosis or whether they simply endorsed symptoms of these disorders. There was no financial compensation for completing the survey.

Statistical analysis

Data were analyzed using SAS on Demand Enterprises, version 4.2 (SAS Institute, Cary, NC). Continuous variables were summarized using means and standard deviations and analyzed using a two-tailed unpaired t test. Univariate analysis was carried out on categorical variables using the chi-square test or the Fisher's exact test when indicated, and a P value of <0.01 was considered statistically significant. A multivariate logistic regression analysis was also carried out to adjust for confounding variables, and odds ratios with confidence intervals are reported.

Results

Study population: demographics and disease characteristics

A total of 514 patients participated and 437 completed questions about marijuana use. Mean age was 34 ± 12 years with patients being predominantly female

(274, 63 %), Caucasian (402, 92 %) and from the USA (422, 82 %). Eighty-four (19 %) never used marijuana and 353 (81 %) reported current or previous marijuana use. In addition to nausea and vomiting, patients also experienced abdominal pain (76 %), cold sweats (76 %), hot flashes (68 %), diarrhea (52 %), headaches (49 %), photosensitivity (68 %), sensitivity to sound (58 %), excessive salivation (57 %) and vertigo (36 %). Most patients (335, 77 %) had periods of normal health in between episodes, while almost a fourth (102, 23 %) reported a pattern of coalescence with inter-episodic nausea and dyspepsia. Many of these patients had multiple comorbid conditions including anxiety (248, 57 %), depression (208, 48 %,) or bipolar disorder (32, 7 %). A personal history of migraine was present in 180 (41 %), and a matrilineal history of migraine was elicited in 198 (45 %) patients.

The mean duration of CVS was 10.6 ± 7.7 years with an average delay in diagnosis of 7.3 ± 6.9 years. Median number of episodes was 10 (range 0–200), ED visits were 3 (range 0–99), and hospitalizations were 1 (range 0–60) in the past year. Most patients (251, 57 %,) did not use conventional medications used in CVS treatment such as amitriptyline, topiramate, zonisamide, levetiracetam and mitochondrial supplements such as coenzyme Q 10 and L-carnitine. In contrast, almost two-thirds of patients (285,65 %,) used alternative therapies such as massage, meditation, naturopathy, probiotics, flax, salmon oil/fish oil, dietary modification and chiropractic treatment.

Patients had undergone extensive investigations for their symptoms, and there were a total of 825 EGD's (mean ± SD, 2.1 ± 2.3,), 487 colonoscopies (mean ± SD, 1.3 ± 1.8), 1,360 CT scans of the abdomen (mean ± SD, 3.6 ± 7.2), 1,534 ultrasounds of the abdomen (mean ± SD, 3.9 ± 7.4), 454 CT scans of the head (mean ± SD, 1.3 ± 2.1) and 427 gastric emptying studies (mean ± SD, 1.2 ± 1.7). Several patients (88, 20 %) reported having a cholecystectomy for treatment of symptoms attributable to CVS.

Characteristics of CVS patients with and without marijuana use

Of 437 patients who completed the questionnaire, 353 (81 %) reported any use of marijuana and 84 (19 %) had never used marijuana. Table 1 depicts the demographics and clinical characteristics of patients with and without marijuana use. On univariate analysis, patients with CVS who used marijuana were more likely to be male (41 vs. 20 %, $P < 0.001$). Users were also more likely to have comorbid conditions such as anxiety (62 %, $P < 0.0001$) and depression (52 %, $P < 0.001$). Hot showers/compulsive hot water bathing was significantly associated with marijuana use ($P < 0.0001$). However, this was not pathognomonic of marijuana use and almost half the patients without marijuana use (48 %) reported hot showers during episodes versus 72 % of marijuana users.

Most patients in both groups were Caucasian, and there were no differences in age, educational status, employment status, coalescence of symptoms, health care utilization (ED visits and hospitalizations for CVS) and use of conventional medications for CVS between the two groups On multivariate regression analysis, male gender (OR 2.88; CI 1.50–5.38), anxiety (OR 4.33; CI 2.48–7.55) and use of hot showers/baths (OR 2.54; CI (1.50–4.31) continued to be significantly associated with marijuana use in patients with cyclic vomiting syndrome (Table 2).

Perceived benefits and side effects of marijuana use in CVS

Of 353 (81 %) patients who used marijuana, 190 (54 %) used marijuana for health issues and 152 (43 %) for recreational purposes. Most patients (185, 59 %,) used 1–7 g of marijuana/week, 69 (22 %) used <1 g/week, 37 (12 %) used 7–14 g/week, and 25 (8 %) used >14 g/week. Most patients (90 %) stated that marijuana improved stress levels, and 89 % had an improvement in appetite. About 80 % noted an improvement in nausea, and 59 % had an improvement in general well-being, and surprisingly only 18 % stated that it improved vomiting. There was no improvement in vertigo in most patients from marijuana use (Fig. 1). Ninety-two (26 %) patients were able to decrease the use of conventional medications (reduction in dose of medication), and 29 (8 %) were able to stop regular medications after using marijuana. Many patients (53 %) also stated that this helped to reduce the number of ED visits, and 48 % had a reduction in hospitalizations due to CVS. Almost a third (34 %) reported being able to maintain employment status. Side effects were reported in 7.3 % of patients and included dry mouth, palpitations, paranoia, memory loss, increased anxiety and increase in nausea and vomiting.

Discussion

A majority of adult patients with CVS (81 %) completing an anonymous internet survey reported use of marijuana. On univariate analysis, male gender, hot showers/baths and presence of comorbid conditions such as anxiety and depression were associated with marijuana use. There were no significant differences in race, educational status and prevalence of coalescent symptoms or severity of disease as measured by number of episodes, hospitalizations and ED visits between users and nonusers. On multivariate analysis, only male gender, hot showers/baths and anxiety were associated with marijuana use. These findings are consistent with a previous study by Choung et al.

Table 1 Univariate analysis of demographics and clinical characteristics of CVS patients with and without marijuana use

Patients with CVS	History of marijuana use $n = 353$	History of no marijuana use $n = 84$	Fisher's exact P value
Age group			0.0270
25 and below	83 (23.5 %)	29 (34.5 %)	
25–40	162 (45.9 %)	30 (35.7 %)	
40–60	101 (28.6 %)	20 (23.8 %)	
60 and above	7 (2.0 %)	5 (6.0 %)	
Gender			0.0003
Female	209 (59.4 %)	65 (80.2 %)	
Male	143 (40.6 %)	16 (19.8 %)	
Race			0.2695
Nonwhite	31 (8.8 %)	4 (4.8 %)	
White	322 (91.2 %)	80 (95.2 %)	
Education			0.2350
Less than 11 years of school	28 (7.9 %)	8 (9.5 %)	
High school graduate	59 (16.7 %)	20 (23.8 %)	
Some college/university	133 (37.7 %)	23 (27.4 %)	
College/university graduate	97 (27.5 %)	21 (25.0 %)	
Professional training beyond college/university	36 (10.2 %)	12 (14.3 %)	
Employment			0.0349
Disabled	64 (18.1 %)	12 (14.3 %)	
Employed	214 (60.6 %)	63 (75.0 %)	
Unemployed	75 (21.2 %)	9 (10.7 %)	
Coalescence			
No	270 (76.5 %)	65 (77.4 %)	1.0000
Yes	83 (23.5 %)	19 (22.6 %)	
Use of conventional CVS medications			0.0495
No	211 (59.8 %)	40 (47.6 %)	
Yes	142 (40.2 %)	44 (52.4 %)	
Hot showers/baths			0.0000
No	98 (27.8 %)	44 (52.4 %)	
Yes	255 (72.2 %)	40 (47.6 %)	
Comorbid conditions			
Anxiety			0.0000
No	109 (30.9 %)	52 (61.9 %)	
Not sure	25 (7.1 %)	3 (3.6 %)	
Yes	219 (62.0 %)	29 (34.5 %)	
Depression			0.0003
No	149 (42.2 %)	56 (66.7 %)	
Not sure	21 (5.9 %)	3 (3.6 %)	
Yes	183 (51.8 %)	25 (29.8 %)	
Bipolar disorder			0.0196
No	302 (85.6 %)	81 (96.4 %)	
Not sure	21 (5.9 %)	1 (1.2 %)	
Yes	30 (8.5 %)	2 (2.4 %)	

showing that young males with CVS were more likely to use marijuana. This is also true of young males who are predominant users of medical marijuana regardless of medical condition (Pujazon-Zazik and Park 2009). Age was not significant in our study and reasons for this are unclear. Our results showing that anxiety was associated with marijuana use is supported by epidemiological data where Cheung et al. showed a strong association between

Table 2 Variables associated with marijuana use on multiple regression analysis

Variable	Group	*N*	Odds ratio (95 % CI)	*P* value
Anxiety	Yes	248	4.33 (2.48–7.55)	<0.0001
Gender	Female	274	1.00	0.0009
	Male	159	2.88 (1.54–5.38)	
Showers/baths	Yes	295	2.54 (1.50–4.31)	0.0006
Use of conventional CVS medications	Yes	186	0.53 (0.31–0.91)	0.0208

mood disorders and heavy marijuana use (Cheung et al. 2010).

Marijuana users reported an improvement in general well-being, appetite, nausea, vomiting and overall symptoms in our study. A higher percentage of patients reported improvement in stress levels and appetite as opposed to vomiting. This is relevant as marijuana is often used as an anxiolytic and is consistent with data demonstrating that while marijuana has an important role in the regulation of nausea and vomiting, it also acts as a stress buffer. Preclinical data supports the role of endocannabinoid signaling in the neuromodulation of anxiety and fear (Hill et al. 2009). Inhibition of fatty acid amide hydrolase (FAAH), the enzyme that is responsible for degradation of anandamide, has been shown to reduce fear and anxiety in rodents (Haller et al. 2009). In normal subjects, THC may cause euphoria and reduction in anxiety but is dose dependent and larger doses may in fact have the reverse effect and cause dysphoria and anxiety (D'Souza et al. 2004; Wade et al. 2003). In addition to effects on stress, marijuana also plays a role in nausea and vomiting. Activation of central and peripheral CB1R by THC and other cannabinoid agonists in animal models inhibit nausea and vomiting (Parker et al. 2011). Conversely, both nausea and vomiting were frequent adverse effects of CB1R-antagonist use in humans, indicating that endocannabinoid/CB1R signaling has an important role in suppressing nausea and vomiting (Bergman et al. 2008). An interesting study in human subjects demonstrated that high concentrations of circulating anandamide and 2-AG were associated with less motion sickness in a hyperbolic plane ride. The same study also showed that individuals who developed motion sickness had higher cortisol concentrations than those who did not (Chouker et al. 2010). And so while there is ample evidence that CB1 agonists improve nausea and vomiting, there is conflicting data suggesting that marijuana may in fact be a cause of nausea and vomiting.

There has recently been increasing interest in a condition called "cannabinoid hyperemesis" where chronic marijuana use has been associated with hot showers and cyclic vomiting. While this has been touted as a new diagnosis, there is insufficient evidence to prove that marijuana causes vomiting. The duration of follow-up in most of these cases was small, and the mean duration of use prior to symptoms was 10.2 ± 7 years which would argue against this being a cause of vomiting (Wallace et al. 2011). There are several possible explanations for this apparent discrepancy. The

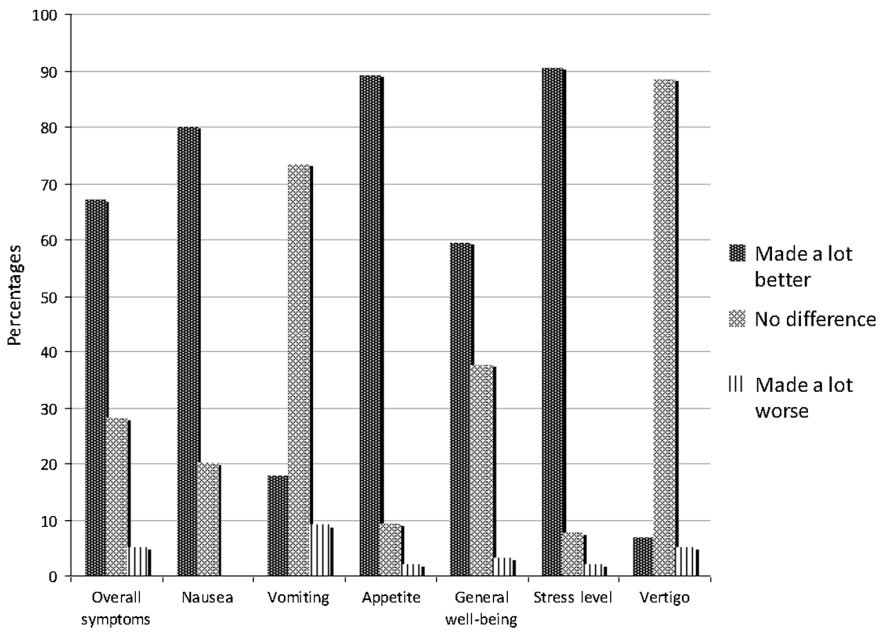

Fig. 1 Self-reported effects of marijuana in patients with CVS

primary psychoactive ingredient in marijuana has increased significantly with time, and it is unclear how this affects its actions (2004). We hypothesize that chronic use may in fact have a paradoxical effect due to downregulation of CB1 receptors. These receptors are present in the dorsal vagal complex in the brainstem, which plays a role in the emetic reflex. Future studies to explore this hypothesis are warranted.

Our study also showed that marijuana use is associated with hot showers though this phenomenon of "compulsive hot water bathing" was also seen in CVS patients who denied any use of marijuana. Hot showers improved symptoms during an episode, but the pathophysiological mechanism underlying this is unclear. The incidence of marijuana use in our study (81 %) was much higher than previously reported in the literature. This may reflect a selection bias as this was an internet-based survey and patients who are more refractory to therapy, and thus use the CVSA Web site may be more motivated to complete these studies. Previous studies have noted that 37–38 % of patients with CVS use marijuana (Choung et al. 2012; Kumar et al. 2012). These observations may be limited by significant reporting bias in a clinic setting where marijuana use is illegal in many states in the USA, and patients may be reluctant to admit to illicit drug use. In contrast, our study was anonymous and patients may have been more likely to report marijuana use as they would not be subject to the legal ramifications associated with its use. There are studies that have shown that the quality of data is enhanced using anonymous versus confidential surveys when assessing sensitive health behaviors such as illicit drug use (Bjarnason and Adalbjarnardottir 2000; Durant et al. 2002). The use of marijuana in the USA tends to peak in adolescence and young adulthood up to 30 years of age and is associated with disorders such as major depression, bipolar disorder, dysthymia and increased rates of suicide (Loga et al. 2010). It has also been associated with various anxiety disorders such as panic, social phobias and multiple personality disorders (Van Ours et al. 2013).

Another factor to consider in the interpretation of these data is that while the majority of respondents (99 %) had seen a physician for evaluation of nausea and vomiting, less than half were on any standard therapy for CVS. This poses important questions about whether these respondents had given up on the medical profession due to poor recognition of this disorder, or did not respond to prior medical treatments, which may have led them to try alternative therapies. Amitriptyline has been associated with side effects resulting in discontinuation of the drug in up to 21 % of patients, which may have also limited its use (Boles et al. 2009). Our questionnaire asked respondents about whether they used marijuana for health or recreational purposes but did not go into further details as to the exact motive behind marijuana use. We speculate that this may have been due to a knowledge gap in CVS among the medical community. There are very few centers in the USA that manage patients with CVS and many physicians do not recognize the symptom pattern (Venkatesan et al. 2010). Use of marijuana in CVS is a very complex issue, and there could be several factors, both environmental and genetic that could predispose to marijuana use/dependence in this patient cohort. For instance, there are certain single nucleotide polymorphisms (SNP's) in the gene encoding fatty acid amide hydrolase (FAAH) and the CB1 receptor called CNR1 that have been associated with cannabis dependence. FAAH is responsible for the degradation of anandamide, which is a cannabinoid agonist, and heterogeneity in these genes can affect an individual's susceptibility for cannabis and substance abuse (Chiang et al. 2004; Tyndale et al. 2007). We propose to examine these complex interactions between genetic and environmental factors in the future.

The use of marijuana in CVS also poses several important questions about the role of endocannabinoid signaling in CVS and warrants further investigation. While marijuana-based drugs are used in cancer chemotherapy-induced nausea and vomiting and cancer-related pain, the potential for abuse is of concern. Indeed, as previously reported, chronic marijuana use can result in a variety of mood disorders including early-onset psychosis and cognitive and learning impairment (Loga et al. 2010). Marijuana use has also been cited as a risk factor for nonresponse to conventional therapy in CVS (Hejazi et al. 2010). Drugs that can more selectively target cannabinoid receptors or inhibitors of the enzyme FAAH and monoacylglycerol lipase (MAGL) which degrade endocannabinoids without causing psychotropic side effects hold promise in the treatment of this disorder. Marijuana use in CVS cannot be endorsed based on this study given the high and variable concentration of THC in marijuana, the unwanted psychoactive effects and association with psychosis and learning impairment. This study, however, provides a framework for future studies in this area and presents opportunities for the development of novel therapeutic agents in the treatment of nausea and vomiting. Other findings in our study that merit further investigation include the high use of unnecessary diagnostic and therapeutic procedures. The diagnostic procedures are probably due to a lack of recognition of CVS among the medical community, and surgeries such as cholecystectomies are not only futile but can be potentially harmful. In the future, education about CVS and developing guidelines for the diagnosis and management of CVS in adults may be helpful in addressing this knowledge gap.

There are several limitations to our study, and these include the anonymous nature of the survey. We were unable to check the accuracy of patient responses; however,

anonymity was maintained due to the legal ramifications associated with marijuana use and there is evidence that data quality may in fact be enhanced by maintaining anonymity. There were a significantly higher proportion of marijuana users in this study, and this may reflect a selection bias as patients who use marijuana may be more motivated to complete such studies. More than half the patients in this study did not use any form of conventional therapy for CVS in contrast to patients seen in our center where >90 % of patients are on some form of therapy. As this was an anonymous study, we do not have information about access that these patients had to physicians with expertise in this area. The benefits of marijuana are self-reported by patients, and this is subject to bias given the psychotropic effects of THC.

In conclusion, the results of our study show that a significant proportion of patients with CVS use marijuana for perceived health benefits including reduction in stress, improvement in general well-being and appetite and reduction in nausea. While univariate analysis indicated that male gender and comorbid conditions including anxiety, depression and hot showers/baths were associated with marijuana use only male gender, presence of anxiety and hot showers/baths were associated with marijuana use on multivariate analysis. Hot showers were seen in both users and nonusers irrespective of marijuana use and should not be interpreted as being pathognomonic of marijuana use. Further studies are warranted to examine the potential role of marijuana and the ECS in CVS.

Acknowledgments Statistical analysis was supported, IN PART, by grant 1UL1RR031973 from the Clinical and Translational Science Award (CTSI) program of the National Center for Research Resources, National Institutes of Health. We would also like to gratefully acknowledge the Cyclic Vomiting Association for use of its website and input with survey design. There is no financial support for this research study.

Conflict of interest None of the authors of the above manuscript has declared any conflict of interest within the last three years which may arise from being named as an author on the manuscript.

References

Abell TL, Adams KA, Boles RG, Bousvaros A, Chong SK, Fleisher DR, Hasler WL, Hyman PE, Issenman RM, Li BU, Linder SL, Mayer EA, McCallum RW, Olden K, Parkman HP, Rudolph CD, Tache Y, Tarbell S, Vakil N (2008) Cyclic vomiting syndrome in adults. Neurogastroenterol Motil 20:269–284

Bergman J, Delatte MS, Paronis CA, Vemuri K, Thakur GA, Makriyannis A (2008) Some effects of CB1 antagonists with inverse agonist and neutral biochemical properties. Physiol Behav 93:666–670

Bjarnason T, Adalbjarnardottir S (2000) Anonymity and confidentiality in school surveys on alcohol, tobacco, and cannabis use. J Drug Issues 30:335–344

Boles RG, Zaki EA, Lavenbarg T, Hejazi R, Foran P, Freeborn J, Trilokekar S, 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:e936–e972

Chepyala P, Olden KW (2008) Cyclic vomiting and compulsive bathing with chronic cannabis abuse. Clin Gastroenterol Hepatol 6:710–712

Cheung JT, Mann RE, Lalomiteanu A, Stoduto G, Chan V, Ala-Leppilampi K, Rehn J (2010) Anxiety and mood disorders and cannabis use. Am J Drug Alcohol Abuse 36(2):118–122. doi:10.3109/00952991003713784

Chiang KP, Gerber AL, Sipe JC, Cravatt BF (2004) Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: evidence for a link between defects in the endocannabinoid system and problem drug use. Hum Mol Genet 13:2113–2119

Chouker A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D, Vogeser M, Thiel M, Schelling G (2010) Motion sickness, stress and the endocannabinoid system. PLoS ONE 5:e10752

Choung RS, Locke GR 3rd, Lee RM, Schleck CD, Zinsmeister AR, Talley NJ (2012) Cyclic vomiting syndrome and functional vomiting in adults: association with cannabinoid use in males. Neurogastroenterol Motil 24(20–26):e21

Di Marzo V, Fontana A (1995) Anandamide, an endogenous cannabinomimetic eicosanoid: 'killing tow birds with one stone'. Prostaglandins Leukot Essent Fatty Acids 53(1):1–11

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH (2004) The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 29(8):1558–1572

Durant LE, Carey MP, Schroder KE (2002) Effects of anonymity, gender, and erotophilia on the quality of data obtained from self-reports of socially sensitive behaviors. J Behav Med 25:438–467

Fleisher DR, Matar M (1993) The cyclic vomiting syndrome: a report of 71 cases and literature review. J Pediatr Gastroenterol Nutr 17:361–369

Galli JA, Sawaya RA, Friedenberg FK (2011) Cannabinoid hyperemesis syndrome. Curr Drug Abuse Rev 4:241–249

Gee S (1882) On fitful or recurrent vomiting. Saint Bartholomew's Hospital Reports, pp 1–6

Haller J, Barna I, Barsvari B, Gyimesi Pelczer K, Yasar S, Panlilio LV, Goldberg S (2009) Interactions between environmental aversiveness and the anxiolytic effects of enhanced cannabinoid signaling by FAAH inhibition in rats. Psychopharmacology 204(4):607–616. doi:10.1007/s00213-009-1494-7

Hejazi RA, McCallum RW (2011) Review article: cyclic vomiting syndrome in adults–rediscovering and redefining an old entity. Aliment Pharmacol Ther 34:263–273

Hejazi RA, Lavenbarg TH, Foran P, McCallum RW (2010) Who are the nonresponders to standard treatment with tricyclic antidepressant agents for cyclic vomiting syndrome in adults? Aliment Pharmacol Ther 31:295–301

Hill MN, McLaughlin RJ, Morrish AC, Viau V, Floresco SB, Hillard CJ, Gorzalka BB (2009) Suppression of amygdalar endocannabinoid signaling by stress contributes to activation of the hypothalamic-pituitary-adrenal axis. Neuropsychopharmacology 34(13):2733–2745. doi:10.1038/npp.2009.114

Kirkham TC (2005) Endocannabinoids in the regulation of appetite and body weight. Behav Pharmacol 16:297–313

Kumar N, Bashar Q, Reddy N, Sengupta J, Ananthakrishnan A, Schroeder A, Hogan WJ, Venkatesan T (2012) Cyclic Vomiting Syndrome (CVS): is there a difference based on onset of symptoms—pediatric versus adult? BMC Gastroenterol 12:52

Loga S, Loga-Zec S, Spremo M (2010) Cannabis and psychiatric disorders. Psychiatr Danub 22:296–297

Mechoulam R (2005) Plant cannabinoids: a neglected pharmacological treasure trove. Br J Pharmacol 146:913–915

Namin F, Patel J, Lin Z, Sarosiek I, Foran P, Esmaeili P, McCallum R (2007) Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. Neurogastroenterol Motil 19:196–202

Parker LA, Rock EM, Limebeer CL (2011) Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol 163:1411–1422

Pujazon-Zazik M, Park MJ (2009) Marijuana: use among young males and health outcomes. Am J Men's Health. 3:265–274

Thaler A, Gupta A (2011) Cohen SP Cannabinoids for pain management. Adv Psychosom Med 30:125–138

Tyndale RF, Payne JI, Gerber AL, Sipe JC (2007) The fatty acid amide hydrolase C385A (P129T) missense variant in cannabis users: studies of drug use and dependence in Caucasians. Am J Med Genet B Neuropsychiatr Genet 144B:660–666

Van Ours JC, Williams J, Fergusson D, Horwood LJ (2013) Cannabis use and suicidal ideation. J Health Econ 32:524–537

Van Sickle M, Oland L, Ho W, Hillard C, Mackie K, Davison J, Sharkey K (2001) Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology 121:767–774

Venkatesan T, Tarbell S, Adams K, McKanry J, Barribeau T, Beckmann K, Hogan WJ, Kumar N, Li BU (2010) A survey of emergency department use in patients with cyclic vomiting syndrome. BMC Emerg Med 10:4

Wade DT, Robson P, House H, Makela P, Aram J (2003) A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 17(1):21–29

Wallace EA, Andrews SE, Garmany CL, Jelley MJ (2011) Cannabinoid hyperemesis syndrome: literature review and proposed diagnosis and treatment algorithm. South Med J 104:659–664