Burden of Persistent Vomiting with Cannabis Use Disorder: Report from 55,549 Hospitalizations in the United States

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Abstract

Objective: We investigated the relationship between cannabis use disorder (CUD) and persistent vomiting (PV)-related hospitalization. **Methods:** Nationwide Inpatient Sample (NIS) was analyzed from 2010–2014 for patients (age 15–54) with a primary diagnosis of PV (N=55,549) and comparison was made between patients with ICD-9 classification of CUD versus non-CUD cohorts. We used logistic regression to study the odds ratio (OR) between CUD and PV. **Results:** The number of PV-related hospitalization with CUD had a significantly increasing trend ($P<.001$) with a 286% increase over five years. Higher proportion of these patients with CUD were younger (15-24 years), female and African American/Hispanic. In regression analysis, cannabis was associated with seven-fold higher odds (95% CI 6.931–7.260) of PV-related hospitalization. **Conclusions:** This study found that CUD is independently associated with a 609% increased likelihood of PV-related hospitalization and this association persists even after adjusting for known risk factors and other substances.

Keywords: cannabis use; cannabinoids; CHS; hyperemesis; persistent vomiting; hospitalization

1. Introduction

According to the National Survey on Drug Use and Health (NSDUH), an estimated 24.6 million people aged 12 or more were current users of cannabis in the US in 2016 which corresponds to 8.9% of this population group (1). From 2002 to 2014, the prevalence of cannabis use during the past month, year and almost daily had increased among adults (2). Cannabis use was higher among males and unemployed individuals (2).

Severe and/or prolonged vomiting (hyperemesis) has been linked with repeated and excessive use of cannabis and has received increased attention recently (3, 4). Cannabinoid hyperemesis syndrome (CHS) is described as the episodes of cyclical nausea and vomiting which gets relieved by hot showers or bathing behavior in the chronic cannabis users (5, 6). In the previous studies, the healthcare providers have been asked to be extra vigilant for CHS in any cannabis user who presents with excessive nausea and vomiting. However, cannabinoid (dronabinol)is also FDA approved for the use of chemotherapy-induced nausea and vomiting. Therefore, it is crucial to study these contradictory and paradoxical effects of cannabis on gastrointestinal (GI) health (4).

In a study by Al-Shammari et al., it was found that cannabinoid dependency and persistent vomiting (PV) increased by 17.9% during 2009 (the year when the medical cannabinoid legalization policy was implemented) as compared to the period of 1993-2008. They also found that the incidence rate of PV continued to rise significantly by about 8% in the post-legalization period (2010-2014) (7). This increase in cannabis use and its adverse effects on the GI system are expected to rise primarily because of recent legalization and decriminalization of recreational cannabis use in the US (6).

In our study, we evaluated the independent association between cannabis use disorder (CUD) and PV related hospitalization, and then compared the demographic characteristics and comorbid medial/psychiatric risk factors for PV in patients with CUD and without CUD.

2. Methods

2.1. Data source

The Healthcare Cost and Utilization Project (HCUP) collects inpatient data from about 4,400 US hospitals in the form of the Nationwide Inpatient Sample (NIS) to provide epidemiological assessments of disorder-related hospitalizations (8). Diagnostic information in the NIS are documented using the International Classification of Diseases, Ninth Edition (ICD-9) codes, and clinical classification software (CCS) codes (8, 9). Individual identifiers (KEY_ID variable) are used to conceal patient identification information (10). The use of publicly available anonymized and de-identified dataset like NIS under the HCUP (8) does not require approval from an Institutional Review Board.

2.2. Selection criteria

We analyzed the NIS data from January 2010 to December 2014 to include emergency or non-elective based hospital admissions of patients (age 15–54 years) with a principal diagnosis for PV (ICD-9 code 536.2). Current cannabis use was identified using the ICD-9-CM codes 304.30 (cannabis dependence, unspecified), 304.31 (cannabis dependence, continuous), 304.32 (cannabis dependence, episodic), 305.20 (nondependent cannabis abuse, unspecified), 305.21 (nondependent cannabis abuse, continuous), and 305.22 (nondependent cannabis abuse, episodic). Patients younger than 15 years of age or older than 54 years of age, and those with code for cannabis abuse/dependence, in remission were excluded to restrict our analysis to the middle 90^{th} percentile of the cannabis users (11).

2.3. Variables

Various demographic variables such as age, gender, and race were examined in the analysis (10). The known possible risk factors for PV were identified by using ICD-9 and CCS diagnosis codes (Appendix A). These included medical (abdominal pain, esophageal disorders,

other GI disorders, electrolyte disorders, pregnancy or related complications, maintenance chemo or radiotherapy, renal failure and liver diseases) and psychiatric (anxiety and mood disorders) comorbidities and comorbid substance use disorders (alcohol, opioid, cocaine and amphetamine) (12).

2.4. Statistical analysis

We compared non-PV and PV inpatient cohorts using bivariate analysis, and the binomial logistic regression model after adjusting for demographics and risk factors (medical and psychiatric comorbidities, and other substance use disorders) measured the odds ratio (OR) for independent association between CUD and PV-related hospitalization. Next, PV inpatient cohort was grouped by co-diagnoses of CUD to compare and analyze the OR using logistic regression model for demographic characteristics and comorbidities including other substance use disorders. Statistical analyses were conducted on SPSS version 25 (IBM Corp., Armonk, NY) with significance set a priori at <.01 for all analyses.

3. Results

The PV (N = 31,272) and non-PV (N = 68,201,366) inpatient cohorts were analyzed in the NIS (2010 to 2014) for evaluating suspected risk factors for PV and odds of associations of various substance use disorders (SUD) with PV related hospitalization. The prevalence of PV was 0.12% (31,272 out of 68,232,638) of the total non-elective hospital admissions.

When comparing with the non-PV cohort, the association of PV was higher in young inpatients (15-24 years), Whites and females. Among the medical comorbidities, abdominal pain (increased by eleven times), electrolyte disorder (increased by four times), and maintenance chemo/radiotherapy (increased by three times) were associated with higher the odds for PV hospitalizations. The predisposing psychiatric comorbidities for PV-related hospitalizations were anxiety disorder (increased by 1.7 times) and mood disorders (increased risk by 1.2 times) as shown in Table 1. As per the regression model analysis, CUD was the only significant

independent comorbid SUD associated with seven times higher odds (95% CI 6.931 – 7.260) for PV-related hospitalization after adjusting for demographics and other confounding comorbidities.

PV-related hospitalizations were grouped as CUD (N = 11,554) and non-CUD (N = 43,996) cohorts for further comparisons as shown in Table 2. Higher proportion of inpatients with CUD were young (54.2%, 15-24 years), female (61.8%). PV-related hospitalization was prevalent in Caucasian, and African American and Hispanic had 1.5 to 1.8 times higher risk of comorbid CUD. Patients with comorbid CUD had 1.3 times higher odds of association for electrolyte disorders and anxiety disorders compared to non-CUD patients in PV hospitalization cohort as shown in Table 2. CUD cohort patients were more likely to abuse or depend on other substances, namely cocaine (increased by 7.8 times), alcohol (increased by 1.7 times), opioid (increased by 1.6 times) and amphetamine (increased by 1.2 times).

4. Discussion

Using the nationwide database from the US hospitals we found that there are a significant number of inpatients with the primary discharge diagnosis of PV and comorbid CUD, and this increased from 2010 to 2014. Our results are similar to a study conducted by Bollom et al. from the national emergency department sample (NEDS) which showed that the rates of emergency visits in patients with vomiting and CUD increased from 2.3 to 13.3 per 100,000 with 68.5% increase in the inflation-adjusted associated cost (13). This increase could be due to number of reasons, namely 1. increase in the use of cannabis in the younger population; 2. increased awareness of cannabinoid hyperemesis syndrome (CHS) among healthcare providers; and 3. recent legalization and decriminalization of recreational cannabis use in the US (7). A study in Colorado was conducted during the post-cannabis legalization (2009) had similar result to our

study as they found that the prevalence of cyclic vomiting visits increased from 41 per 113,262 emergency visits to 87 per 125,095, corresponding to a prevalence ratio of 1.92 (95% CI 1.33 – 2.79) (14). Patients with cyclic vomiting in the post- legalization period were more likely to have cannabis use than the patients in the pre-legalization period (OR 3.59, 95% CI 1.44 – 9.00) (14).

In our analysis, a higher proportion of PV-related hospitalization were seen in young adults (25-34 years, 29.7%), females (61.8%) and Whites (65.5%) which is supportive of the Colorado study (14). PV-related hospitalization with comorbid CUD was seen in young adults (15-24 years, 54.2%) as per our data analysis, and also as per a trend study conducted from 2006-2013 by Bollom et al., adults (20- 29 years) had the highest rate of emergency visits for vomiting with CUD (39 per 100,000 emergency visits in 2013) (13). Though, prevalence of PV-related hospitalization with CUD was higher in Caucasians (57.2%), but African American and Hispanic had 1.5 to 1.8 times higher likelihood of comorbid CUD when compared with the non-CUD cohort. In a case series of 98 patients with CHS, 66 patients (80%) were White (15). However, the information on demographic-wise distribution of PV with CUD or CHS is not much explored.

Among the medical comorbidities the odds of association for PV-related hospitalization was higher with abdominal pain, maintenance chemotherapy or radiotherapy, and esophageal or GI disorders which was not seen in PV with CUD cohort. Among psychiatric comorbidities, anxiety disorders and CUD were significantly associated with PV-related hospitalization (16).

After controlling for demographic confounders, and other possible risk factors of PV, including SUD, we found that CUD increases the likelihood for PV-related hospitalization by seven times. Further, by comparing the CUD and non-CUD cohort, we found that PV inpatients with CUD had higher likelihood of co-diagnoses of cocaine (increased by 7.8 times), alcohol

(increased by 1.7 times), opioid (increased by 1.6 times) and amphetamine (increased by 1.2 times) use disorders. This could be a reason for higher chances of hospitalization as a study showed that individuals with cannabis, alcohol, opioid, cocaine and amphetamine use have higher risk of emergency admission and inpatient hospitalization compared to those with only CUD (17).

Many theories as per the existing literature have explained the underlying pathophysiology of CHS. CHS is caused by dysregulation of the endocannabinoid system, a group of endogenous cannabinoid receptors (CB-1 and CB-2) located in the brain, gastrointestinal tract, peripheral nervous system, and immune system of mammals. The endocannabinoid system is thought to play a role in gastrointestinal motility, appetite, nausea/vomiting, inflammation, mood, sleep, pain, and more (18). GI actions of cannabinoids are mediated chiefly by CB_1 receptors. Activation of CB_1 receptors result in inhibition of gastric acid secretion, lower esophageal sphincter relaxation, altered intestinal motility, visceral pain, and inflammation (19). CB_1 receptor activation reduces gastric motility and results in delayed gastric emptying, which may promote nausea and vomiting (19). In addition, it is also believed that the buildup of lipophilic THC in cerebral fat may manifest itself as toxic in some individuals which can lead to PV (13). Also, genetic variations in hepatic drug transforming enzymes in susceptible individuals may cause high levels of cannabis metabolites thereby promoting the development of vomiting (13).

As, PV associated with CUD or CHS can be fatal and lead to death in some instances (20), it is important to study these conditions in detail and develop interventional strategies as cannabis cessation is the only cure for CHS (21, 22). CHS is potentially under-recognized and underdiagnosed in the emergency department. Multidisciplinary care may be necessary for

management and diagnosis. Being a diagnosis mainly based on history and physical examination, physicians cognizant of CHS who maintain a high degree of suspicion for presentation in their patient populations, can enable considerable savings and prevent unnecessary testing. CHS should be considered in the differential diagnosis of any patient presenting with persistent nausea and vomiting. In particular, the diagnosis is suggested if the patient demonstrates regular and chronic cannabis use, intractable nausea and vomiting, cyclical vomiting, relief of symptoms with hot baths, and resolution of symptoms after cannabis cessation (23). A thorough social history is needed in all cyclic vomiting patients. Higher education is needed among clinicians in order to limit repeated "exclusionary" workups and iatrogenesis. Also, as the trend toward cannabis legalization spreads, states need to create public health messages to warn cannabis users of the possibility of developing this syndrome (18). Collaborative care is a useful model for integrating behavioral (mental) health care into emergency medical settings for effective management of CHS. It aims to improve the physical and mental health of people with mental illness associated with CHS.

The main limitation of this study is that due to the retrospective and administrative nature of the database the information about the dose, route of ingestion, and duration of cannabis use was not available to better explain the pathophysiology. Also, we conducted a cross-sectional study and were not able to find a causal association between CUD and PV. The other limitation of our study was that we might have under/over-estimated the number of PV-related hospitalization with CUD due to the nature of the NIS data i.e. based on ICD-9 codes recorded in the patient records for administrative and insurance/billing purpose. Also, our sample population may have affected due to change during this time period given increasing cannabis use and/or clinician awareness of CHS. However, the main strength of our study is a large sample size of

PV-related hospitalizations that enables us to evaluate CUD as a significant risk factor in the nationally representative population.

5. Conclusion

The use of cannabis is on the rise in the US with legalization for both medical and recreational purposes, and subsequently, it has also been increasingly seen in the inpatient population. Our study results show that the number of patients presenting to the hospitals with complaints of nausea and vomiting associated with CUD has been increasing significantly. It is sometimes difficult and time-consuming to diagnose the causes of persistent or intractable vomiting that can lead to costly, invasive procedures. So, we would like to advise that the healthcare practitioners should have a high index of suspicion for CHS in any patient who presents to them with intractable nausea and vomiting and history of chronic cannabis consumption or co-diagnosis of CUD. The results of our study add to the growing body of evidence to suggest for the need of prospective high□quality studies on cannabis consumption and health outcomes. Both the patients and healthcare practitioners will need to carefully consider the anticipated benefits in light of potentially significant health risks.

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294 **Table 1. Suspected risk factors for persistent vomiting-related ED visits**

Variables	No PV	PV	OR	95% CI	P value
Total patients	47753472	55549	-	-	-
Age groups, %					
15 – 24 years	18.2	20.5	Reference		
25 – 34 years	26.7	29.7	.941	.918 – .965	< .001
35 – 44 years	22.3	24.7	.706	.688 – .725	< .001
45 – 54 years	32.8	25.0	.445	.433 – .457	< .001
Sex, %					
Male	39.4	38.2	Reference		
Female	60.6	61.8	1.220	1.198 – 1.243	< .001
Race, %					
Caucasian	56.0	65.5	Reference		
African American	21.2	21.2	.880	.860 – .899	< .001
Hispanic	15.7	8,7	.637	.618 – .658	< .001
Other	7.1	4.6	.757	.726 – .789	< .001
Comorbid medical conditions, %					
Abdominal pain	2.0	27.2	11.129	10.904 – 11.358	< .001
Esophageal disorders	10.5	28.3	2.357	2.310 – 2.406	< .001
Other GI disorders	23.1	23.8	1.636	1.601 – 1.670	< .001
Endocrine/metabolic disorders	18.1	22.0	.817	.799 – .835	< .001
Fluid/electrolyte disorders	18.5	55.1	4.374	4.295 – 4.453	< .001
Pregnancy or related complications	10.4	0	0.001	0.001 – 0.003	< .001
Maintenance chemo/radio-therapy	0	0	2.974	1.780 – 4.970	< .001
Renal failure	4.9	4.9	1.194	1.170 – 1.219	< .001
Liver disease	3.6	3.4	0.713	0.679 – 0.748	< .001
Comorbid psychiatric conditions, %					
Mood disorders	15.3	28.1	1.194	1.170 – 1.219	< .001
Anxiety disorders	10.2	24.9	1.738	1.701– 1.776	< .001
Comorbid substance use disorder, %					
Alcohol	8.3	4.3	.346	.331 – .361	< .001
Cannabis	3.9	20.8	7.094	6.931 – 7.260	< .001
Opioid	3.1	4.5	.890	.852 – .929	< .001
Amphetamine	1.0	.3	.162	.139 – .189	< .001
Cocaine	2.4	1.0	.243	.222 – .265	< .001

295 The proportion of hospitalization with/without persistent vomiting were obtained using cross tabulation and the Pearson Chi-Square ($\chi 2$) test.
296 Significant P values $\leq .01$ at 95% Confidence Interval. Odds ratio generated by binomial logistic regression model. PV: persistent vomiting; GI:
297 gastrointestinal; OR: odds ratio; CI: confidence interval.

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300 **Table 2. Characteristics of persistent vomiting-related ED visits by cannabis use disorder.**

Variables	CUD (–)	CUD (+)	OR	95% CI	P value
Total patients	43996	11554	-	-	-
Age groups, %					
15 – 24 years	34.1	54.2	Reference		
25 – 34 years	65.9	45.8	.884	.835 – .936	< .001
35 – 44 years	26.3	18.7	.455	.426 – .486	< .001
45 – 54 years	28.3	12.7	.290	.270 – .312	< .001
Sex, %					
Male	39.4	38.2	Reference		
Female	60.6	61.8	.422	.403 – .441	< .001
Race, %					
Caucasian	67.6	57.2	Reference		
African American	19.7	26.9	1.844	1.746 – 1.948	< .001
Hispanic	8.1	10.8	1.550	1.435 – 1.673	< .001
Other	4.5	5.0	1.283	1.156 – 1.424	< .001
Comorbid medical conditions, %					
Abdominal pain	26.9	28.1	1.018	.968 – 1.070	< .001
Esophageal disorders	27.6	30.6	1.227	1.167 – 1.290	< .001
Other GI disorders	26.3	18.1	.723	.684 – .765	< .001
Endocrine/metabolic disorders	22.7	19.5	.942	.890 – .998	.041
Fluid/electrolyte disorders	54.2	58.2	1.249	1.193 – 1.307	< .001
Pregnancy or related complications	0	0	<.001	–	.999
Maintenance chemo/radio-therapy	0	0	<.001	–	.999
Renal failure	5.6	2.0	.321	.277 – .373	< .001
Liver disease	3.6	2.6	1.072	1.016 – 1.130	< .001
Comorbid psychiatric conditions, %					
Mood disorders	28.4	27.0	1.072	1.016 – 1.130	< .001
Anxiety disorders	24.0	28.1	1.311	1.243– 1.382	< .001
Comorbid substance use disorder, %					
Alcohol	3.6	7.2	1.733	1.569 – 1.914	< .001
Opioid	4.0	6.1	1.633	1.478 – 1.804	< .001
Amphetamine	0.2	0.6	1.244	.866 – 1.788	.237
Cocaine	0.4	3.3	7.788	6.377 – 9.512	< .001

301 The proportion of persistent vomiting hospitalization with/without cannabis use disorder were obtained using cross tabulation and the Pearson
302 Chi-Square ($\chi 2$) test. Significant P values $\leq .01$ at 95% Confidence Interval. Odds ratio generated by binomial logistic regression model. PV:
303 persistent vomiting; GI: gastrointestinal; CUD: cannabis use disorder; OR: odds ratio; CI: confidence interval.

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