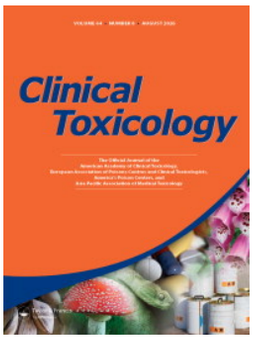

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: www.tandfonline.com/journals/ictx20

Serum cannabinoid profiles of emergency department patients presenting with cannabinoid hyperemesis syndrome and acute cannabis intoxication

David Toomey, Kian Merchant-Borna, Alex J. Krotulski, Savannah Baker, Victoria Zhang & Nicholas Nacca

To cite this article: David Toomey, Kian Merchant-Borna, Alex J. Krotulski, Savannah Baker, Victoria Zhang & Nicholas Nacca (27 Jul 2026): Serum cannabinoid profiles of emergency department patients presenting with cannabinoid hyperemesis syndrome and acute cannabis intoxication, Clinical Toxicology, DOI: 10.1080/15563650.2026.2703873

To link to this article: https://doi.org/10.1080/15563650.2026.2703873

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2026.2703873

Taylor & Francis
by informa

CLINICAL RESEARCH

Serum cannabinoid profiles of emergency department patients presenting with cannabinoid hyperemesis syndrome and acute cannabis intoxication

David Toomey[a], Kian Merchant-Borna[a], Alex J. Krotulski[b], Savannah Baker[b], Victoria Zhang[a] and Nicholas Nacca[a]

[a]University of Rochester Medical Center, Rochester, NY, USA; [b]Center for Forensic Science Research and Education, Fredric Rieders Family Foundation, Horsham, PA, USA

ABSTRACT

Introduction: The underlying pathophysiology of cannabinoid hyperemesis syndrome remains poorly understood. Proposed mechanisms include "hyperintoxication" with delta-9-tetrahydrocannabinol, accumulation of delta-9-tetrahydrocannabinol metabolites, and differential exposure to non-psychotropic phytocannabinoids. This study sought to examine quantitative differences in serum concentrations of delta-9-tetrahydrocannabinol, delta-9-tetrahydrocannabinol metabolites, delta-8-tetrahydrocannabinol, and common non-psychotropic phytocannabinoids between patients presenting to the emergency department with either acute, symptomatic cannabinoid hyperemesis syndrome or acute cannabis intoxication.

Methods: This was a retrospective cohort study performed in the emergency department of a single academic medical center. Subjects were screened based on discharge diagnosis consistent with either cannabinoid hyperemesis syndrome or acute cannabis intoxication and on availability of remnant blood samples. Chart data including emergency department length of stay, disposition, treatment, and labs were abstracted, and blood samples were analyzed via liquid chromatography-triple quadrupole tandem mass spectrometry for serum concentrations of delta-9-tetrahydrocannabinol, delta-8-tetrahydrocannabinol, 11-nor-9-carboxy-delta-9-tetrahydrocannabinol, 11-hydroxy-delta-9-tetrahydrocannabinol, delta-8-carboxy-tetrahydrocannabinol, cannabidiol, cannabigerol, and cannabinol.

Results: Fifty subjects were enrolled; thirty-five presented with cannabinoid hyperemesis syndrome and 15 with acute cannabis intoxication. Groups were well matched with regard to baseline demographics, emergency department disposition, and emergency department length of stay. No significant differences were noted in serum concentrations of delta-9-tetrahydrocannabinol, delta-9-tetrahydrocannabinol metabolites, non-psychotropic phytocannabinoids, or their respective ratios

Discussion: While limited by uncontrolled host factors, the results of this study further existing literature arguing against the differential accumulation of psychoactive cannabinoids, non-psychoactive cannabinoids, or their metabolites as causative factors in the development of acute symptomatic episodes of cannabinoid hyperemesis syndrome.

Conclusion: There does not appear to be a significant difference in concentrations of psychoactive and non-psychoactive cannabinoids between emergency department patients with symptomatic cannabinoid hyperemesis syndrome and those with acute cannabis intoxication.

ARTICLE HISTORY
Received 27 May 2025
Revised 16 June 2026
Accepted 2 July 2026

KEYWORDS
Acute cannabis intoxication; cannabinoid hyperemesis syndrome; cannabis; tetrahydrocannabinol; marijuana; THC

Introduction

The association between chronic, heavy cannabis use and a syndrome of periodic cyclic vomiting and abdominal pain has been described since 2004[1]. While previously controversial, this clinical phenomenon (now termed "cannabinoid hyperemesis syndrome (CHS)") is now broadly recognized as an increasingly common cause for presentation to emergency departments (EDs) in the United States and Canada [2–4]. Despite this, the lack of a commonly accepted definition of CHS as well as a generally poor understanding of the underlying pathophysiology continue to make CHS a diagnostic and therapeutic challenge for bedside clinicians.

CONTACT David Toomey David_toomey@urmc.rochester.edu University of Rochester Medical Center, Department of Emergency Medicine, Division of Medical Toxicology, 265 Crittenden Blvd, Rochester, NY, 14642, USA.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/15563650.2026.2703873.

Current theoretical framework regarding the underlying pathophysiology of CHS can be divided into two categories. The first body of research has focused on the known role of the cannabinoid receptor type 1 (CB1), which serves as the primary modulator of the endocannabinoid system in the central nervous system and typically demonstrates anti-emetic effects when agonized by endogenous or exogenous cannabinoids [5–7]. Theories based on the role of the CB1 receptor include dysregulation of interplay between the endocannabinoid and hypothalamic-pituitary-adrenal (HPA) axes, selective down-regulation of CB1 receptors in regions of the brain typically associated with suppression of vomiting, and paradoxical pro-emetic activity of CB1 when exposed to high concentrations of exogenous agonists[8]. The second broad category of research has focused on epidemiologic trends of CHS as access to cannabis products has become more widespread in the wake of liberalized cannabis policy in the United States. This research has almost universally demonstrated increased rates of CHS in the US following legalization, suggesting that frequency and chronicity of cannabis use may play a role in the development of CHS [2,9,10]. Further research has focused on a general trend of increased potency of licit and illicit cannabis products over time, suggesting a potential dose-response effect when considering the underlying mechanism of CHS [11,12].

Prior literature has demonstrated that ED patients with CHS have generally similar concentrations of delta-9-tetrahydrocannabinol (delta-9-THC) but different concentrations of downstream metabolites between symptomatic periods of CHS and during asymptomatic periods on outpatient follow-up [13]. Despite this, there remains a dearth of literature regarding the correlation of symptomatic CHS with concentrations of psychoactive and non-psychoactive cannabinoids and their corresponding metabolites. Furthermore, there remains a lack of clarity regarding whether patients presenting to EDs with CHS demonstrate different profiles of delta-9-THC parent compound and metabolites compared to patients with acute cannabis intoxication (ACI) who are not experiencing gastrointestinal symptoms. The aim of this study is to assess the serum cannabinoid profiles of ED patients with clinically distinct presentations of CHS and ACI. In comparing patients with CHS to those with ACI, we sought to address theories related to "threshold" concentrations of delta-9-THC as well as those related to differential accumulation of THC metabolites in the pathogenesis of CHS.

Methods

This was a retrospective cohort study based on a convenience sample of patients presenting to a level 1 trauma ED at a single academic medical center. This study was approved by the Institutional Review Board and deemed eligible for a waiver of informed consent. The authors report there are no competing interests to declare.

Initial screening for study subjects was performed by generating a query using a search function of the electronic medical record system that identified patients who had been given a primary ED clinical impression consistent with either CHS or ACI. This query identified subjects who had presented to the ED and been provided with a diagnosis consistent with either CHS or ACI and who had bloodwork drawn as part of routine clinical care. Queries were performed in an overlapping fashion by two trained research personnel every five days to ensure capture of all potentially eligible research subjects prior to disposal of remnant blood samples (below). Once identified, subject charts were individually reviewed by a medical toxicologist to ensure appropriateness of diagnosis. Subjects in the CHS cohort were excluded if they were ultimately admitted and found to have an alternate cause for their symptoms. Subjects in the ACI cohort were excluded if their presentation was deemed to be the result of an alternative ingestion, the result of an alternative medical cause, or the result of long-term cannabis abuse without documented concern for concomitant acute THC intoxication. Data were collected over a ten-month timeframe.

Once identified, subjects were further screened for inclusion based on the availability of remnant blood samples. For the purpose of this investigation, remnant blood samples were defined as samples of serum that were obtained as part of the subject's ED evaluation, per the discretion of the subject's ED provider, that were not ultimately used for clinical analysis. These samples are typically "held" for a period of 72 h after being obtained in the event additional clinical testing was requested by the patient's ED/Inpatient team(s). If additional testing is not requested, these samples are typically discarded. During the holding period, samples are stored at 2–4 degrees C in a temperature controlled, secured clinical laboratory. Samples were considered adequate for analysis if they had a serum volume ≥500 µL following clinical analyses. If subjects screened via the search criteria above were not deemed to have adequate remnant samples for analysis, they were excluded from further study. Remnant samples from subjects who met inclusion criteria were obtained from the clinical laboratory by research staff for storage at −80 degrees C until batch sample analysis. Remnant samples were assayed for quantitative serum concentrations of delta-9-THC, delta-8-tetrahydrocannabinol (delta-8-THC), 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (delta-9-COOH), 11-hydroxy-delta-9-tetrahydrocannabinol (delta-9-OH), delta-8-carboxy tetrahydrocannabinol

(delta-8-COOH), cannabidiol (CBD), cannabigerol (CBG), and cannabinol (CBN). Charts were de-identified and retroactively reviewed by research staff. Demographic data abstracted for review included subject age, gender, and race. Clinical data abstracted for review included primary ED diagnosis, vital signs at presentation, results of laboratory testing, whether or not imaging studies were performed, the results of imaging studies (if performed), and treatment modalities employed while receiving care. Data related to ED length of stay (LOS) and disposition were also obtained and recorded.

Quantitative analysis was performed via liquid chromatography-triple quadrupole tandem mass spectrometry (LC-QQQ-MS) using an Agilent Technologies 1290 ultra-high performance liquid chromatography coupled to a 6495 triple quadrupole mass spectrometer (Santa Clara, CA, USA). Chromatographic separation was achieved using an Agilent Poroshell EC C-18 column (2.1 mm x 150 mm, 2.7 µm) heated to 40 °C with a flow rate of 0.5 mL/min. A mobile phase gradient was employed using 5 mM ammonium formate in water (pH 3) (A) and 0.1% formic acid in 50:50 methanol: acetonitrile (B). The total assay run time was 30 min (to allow for isomer resolution). The instrument operated using Agilent Jet Strem positive ion electrospray. The desolvation gas temperature was 400 °C at 12 L/min with a source temperature of 250 °C. The voltage for the capillary was 3000 V. Multiple reaction monitoring (MRM) was employed using a quantifier and qualifier ion for each analyte.

Serum specimens were prepared for quantitation and extracted using a previously published methodology described by Krotulski et al. [14,15]. Calibrator and control specimens were prepared by aliquoting 0.2 mL of drug-free serum and fortifying with varying amounts of drug standard. Internal standard was added at a final concentration of 25 ng/mL. Samples were extracted following a liquid-liquid extraction protocol using 0.5 mL of phosphoric acid in water (5%, v/v) and 1.5 mL of 80:10:10, hexane/ethyl acetate/MTBE, v/v). Samples were capped and rotated for 15 min and then centrifuged at 4200 RPM for 10 min Samples were then frozen to collect the organic layer, which was subsequently evaporated to dryness under nitrogen at a temperature of 40 °C. Samples were reconstituted in 100 µL of initial chromatographic conditions (30 A:70B).

The method was validated following in-house procedures for quantitation based on guidance issued by the American Academy of Forensic Science (AAFS) Standards Board 036: Standard Practices for Method Validation in Forensic Toxicology with a modified three-day validation [16]. The validation was performed specifically for delta-9-THC, delta-8-THC, delta-9-COOH, delta-9-OH, delta-8-COOH, CBD, CBG, and CBN. The following experiments were assessed during this validation protocol: linearity over the target range (0.5-100 ng/mL); determination of limit of detection (LOD) and limit of quantitation (LOQ); evaluation of recovery (50 ng/mL); dilution integrity; carryover; and determination of interferences from matrix, analyte, internal standard, and commonly encountered drugs.

Descriptive statistics and statistical analyses were performed using SAS Software Version 9.4 (SAS Institute Inc.; Cary, NC, USA). Continuous data are presented as medians and interquartile ranges, and categorical data are presented as proportions. Hypothesis testing involving quantitative variables was performed using Mann-Whitney U testing. Figures 1 and 2 were produced using SAS Software Version 9.4 (SAS Institute Inc.; Cary, NC, USA). Tables 1–3 and Supplemental Figures 1 and 2 were produced using Chat GPT version 4.1 for the purpose of improved data visualization. Supplemental Tables 1 and 2 were produced using Microsoft Word 2024 (Microsoft inc.; Redmond, WA) and Microsoft Excel 2024 (Microsoft inc.; Redmond, WA, USA).

Results

A total of 52 subjects met initial screening criteria, of which two were excluded based on insufficient volume of remnant blood samples. There were 35 subjects with presentations consistent with CHS, and 15

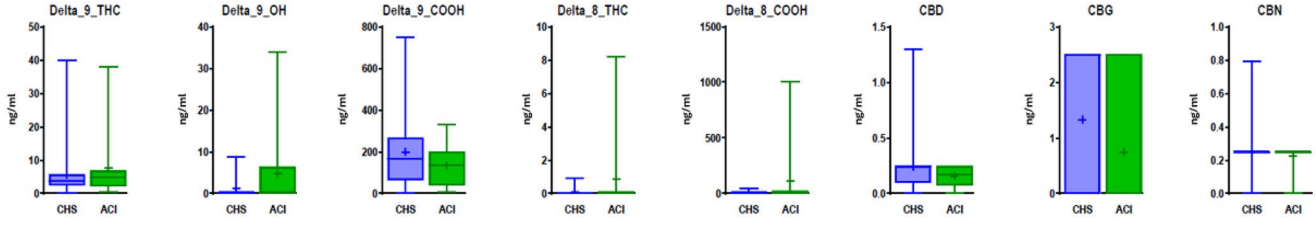

Figure 1. Serum concentrations of cannabinoids and metabolites between emergency department patients with cannabinoid hyperemesis syndrome (CHS) and acute THC intoxication (ACI).
Legend: Delta-9-THC (Delta-9-Tetrahydrocannabinol); Delta-9-OH (11-hydroxy-delta-9-tetrahydrocannabinol); Delta-9-COOH (11-nor-9-carboxy-tetrahydrocannabinol); Delta-8-THC (delta-8-tetrohydrocannabinol); Delta-8-COOH (delta-8-carboxy tetrahydrocannabinol), CBD (cannabidiol); CBG (cannabigerol), CBN (cannabinol)

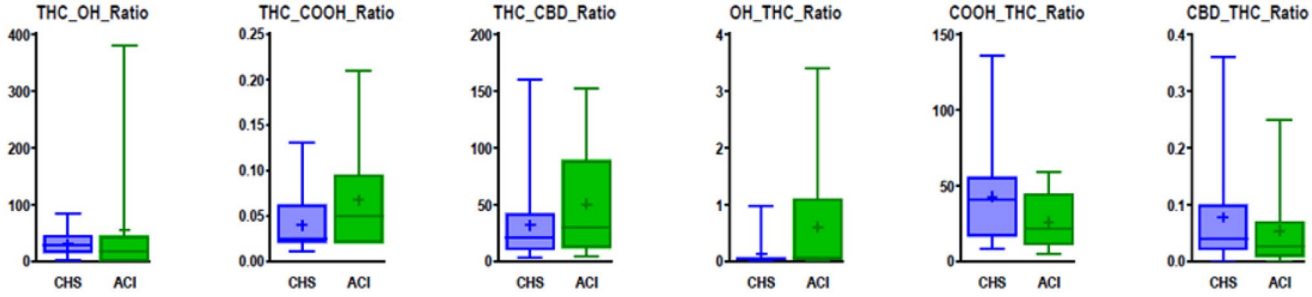

Figure 2. Ratios of delta-9-THC metabolites and CBD to delta-9-THC in emergency department patients with cannabinoid hyperemesis syndrome (CHS) and acute cannabis intoxication (ACI).
Legend: THC:OH ratio (delta-9-tetrahydrocannabinol: 11-hydroxy-delta-9-tetrahydrocannabinol); THC:COOH ratio (delta-9-tetrahydrocannabinol: 11-nor-9-carboxy-tetrahydrocannabinol); THC:CBD ratio ((delta-9-tetrahydrocannabinol: cannabidiol); OH-THC ratio (11-hydroxy-delta-9-tetrahydrocannabinol: delta-9-tetrahydrocannabinol), COOH:THC ratio (11-hydroxy-delta-9-tetrahydrocannabinol: delta-9-tetrahydrocannabinol); CBD:THC ratio (cannabidiol: delta-9-tetrahydrocannabinol)

Table 1. Demographic characteristics of cannabinoid hyperemesis syndrome (CHS) and acute cannabis intoxication (ACI) groups.

Variable	CHS ($n=35$)	ACI ($n=15$)	*P*-value
Age (median ± SD)	25 ± 9.7	17 ± 18.0	0.052
Gender			0.785
Female	17 (49%)	7 (47%)	
Male	17 (49%)	8 (53%)	
Nonbinary	1 (3%)	0 (0%)	
Race			0.040
Black	14 (40%)	6 (40%)	
Caucasian/White	13 (37%)	7 (47%)	
Hispanic	8 (23%)	0 (0%)	
Not Listed	0 (0%)	2 (13%)	

Table 2. Emergency department vital signs, length of stay (LOS), and disposition between cannabinoid hyperemesis syndrome (CHS) and acute cannabis intoxication (ACI) groups.

Variable	CHS ($n=35$)	ACI ($n=15$)	*P*-value
Temp (°C) mean ± standard deviation	36.5 ± 0.5	36.5 ± 0.8	0.889
Heart rate (bpm) mean ± standard deviation	78.9 ± 18.4	104.7 ± 24.9	0.002
Systolic blood pressure (mmHg) mean ± standard deviation	137.7 ± 19.9	115.6 ± 25.8	0.009
Diastolic blood pressure (mmHg) mean ± standard deviation	83.6 ± 13.4	64.7 ± 18.1	0.002
Respiratory rate (rpm) mean ± standard deviation	17.8 ± 3.5	19.9 ± 3.9	0.085
Oxygen saturation (%) mean ± standard deviation	98.8 ± 1.2	98.2 ± 2.1	0.302
ED length of stay (hrs) mean ± standard deviation	9.1 ± 7.1	6.1 ± 2.7	0.034
Disposition			
Discharged	26 (74%)	11 (73%)	
Admitted	9 (26%)	4 (27%)	1.000
If Admitted (Setting)			0.043
ED Observation	6 (67%)	0 (0%)	
Inpatient Floor	2 (22%)	1 (25%)	
Inpatient ICU/PICU	0 (0%)	2 (50%)	
Inpatient psychiatry	0 (0%)	1 (25%)	

Table 3. Laboratory comparison between cannabinoid hyperemesis syndrome (CHS) and acute cannabis intoxication (ACI) groups.

Lab variable	CHS	ACI	*P*-value
CBC obtained	Yes: 34 (97%) | No: 1 (3%)	Yes: 11 (73%) | No: 4 (27%)	0.040
WBC ($\times10^3$/μL [$\times10^9$/L])	10.8 ± 3.2	9.4 ± 3.1	0.211
Hemoglobin (g/dL [g/L])	14.5 ± 1.7 [145 ± 17]	12.2 ± 2.6 [122 ± 26]	0.018
Hematocrit (%)	42.6 ± 4.4	36.6 ± 7.0	0.019
Platelets ($\times10^3$/μL [$\times10^9$/L])	268.6 ± 57.7	273.7 ± 69.5	0.828
% Eosinophils	0.3 ± 0.4	0.8 ± 1.8	0.454
Basic metabolic panel obtained	Yes: 34 (97%) | No: 1 (3%)	Yes: 12 (80%) | No: 3 (20%)	0.139
Glucose (mg/dL [mmol/L])	120.2 ± 22.8 [6.7 ± 1.3]	129.7 ± 46.4 [7.2 ± 2.6]	0.508
Sodium (mmol/L)	139.3 ± 2.6	138.8 ± 2.6	0.582
Potassium (mmol/L)	3.9 ± 0.4	4.1 ± 0.4	0.335
Chloride (mmol/L)	101.9 ± 3.6	103.9 ± 2.7	0.049
Bicarbonate (mmol/L)	21.3 ± 2.7	22.8 ± 2.1	0.058
Anion Gap	16.0 ± 3.5	12.2 ± 3.3	0.003
BUN (mg/dL [mmol/L])	13.4 ± 5.1 [4.8 ± 1.8]	11.9 ± 3.5 [4.2 ± 1.2]	0.282
Creatinine (mg/dL [μmol/L])	0.9 ± 0.2 [80 ± 18]	0.7 ± 0.3 [62 ± 27]	0.114
Calcium (mg/dL [mmol/L])	9.8 ± 0.6 [2.45 ± 0.15]	9.3 ± 0.6 [2.33 ± 0.15]	0.026
Hepatic function panel obtained	Yes: 31 (91%) | No: 3 (9%)	Yes: 10 (67%) | No: 5 (33%)	0.085
Amylase (IU/L)	90.1 ± 37.4	65.9 ± 27.4	0.074
Lipase (IU/L)	34.2 ± 30.6	18.1 ± 3.3	0.009
Total bilirubin (mg/dL [μmol/L])	0.7 ± 0.5 [12.0 ± 8.6]	0.7 ± 0.4 [12.0 ± 6.8]	0.952
Direct bilirubin (mg/dL [μmol/L])	0.2 ± 0.1 [3.4 ± 1.7]	0.2 ± 0.0 [3.4 ± 0.0]	0.560
Alkaline phosphatase (IU/L)	77.3 ± 22.8	111.5 ± 59.6	0.107
AST (IU/L)	26.5 ± 12.0	25.3 ± 10.8	0.797
ALT (IU/L)	26.2 ± 17.9	18.4 ± 7.1	0.058

with presentations consistent with ACI. Within the CHS group, there were foiur subjects who were enrolled on two separate presentations. A statistically significant difference was found between groups with regard to race, with 8 (23%) patients identifying as Hispanic in the CHS group and 0 identifying as Hispanic in the ACI group (Table 1).

There were no statistically significant differences between groups with regard to triage temperature, respiratory rate, or oxygen saturation (Table 2). Statistically significant differences were noted in triage heart rate ($P=0.002$) as well as systolic and diastolic blood pressure ($P=0.002$ and 0.009, respectively), with CHS patients demonstrating higher values compared to patients with ACI. There was a statistically significant difference noted ($P=0.03$) regarding ED LOS, with increased ED LOS in CHS patients compared to patients with ACI. The two groups had similar rates of inpatient admission from the ED, though patients in the ACI group were less likely to be admitted to an ED Observation setting and more likely to be admitted to a critical care setting (which occurred in only two instances, both of which involved large cannabinoid ingestions in pediatric patients).

Most patients in either group were assessed with bloodwork while in the ED, though patients presenting with concern for ACI were less likely to be assessed with labs compared to patients presenting with concern for CHS (Table 3). For patients who were assessed with a complete blood count (34 in the CHS group, 11 in the ACI group)), statistically significant differences were seen with respect to both Hemoglobin and Hematocrit ($P=0.018$ and 0.019, respectively), which were higher in the CHS group. For patients who were assessed with a basic metabolic panel (34 in the CHS group, 12 in the ACI group)), statistically significant differences were seen with respect to anion gap ($P=0.003$), serum chloride ($P=0.049$), and serum calcium ($P=0.026$). The serum anion gap and serum calcium were higher in the CHS group, and the serum chloride was higher in the ACI group. For patients assessed with a right upper quadrant panel (31 in the CHS group, 10 in the ACI group), serum lipase was significantly elevated ($p=0.009$) in the CHS group compared to the ACI group.

In patients who presented to the ED that were ultimately assigned a clinical impression consistent with CHS, most patients were treated with traditional antiemetics (ondansetron, metoclopramide, prochlorperazine) and/or butyrophenone antipsychotics (74% for either category) (supplemental Table 1). A minority of patients (14%) were treated with benzodiazepines, and only a single patient was treated with opioids. Four patients (11%) were treated with topical capsaicin. Use of butyrophenone antipsychotics was associated with a statistically significant increase in ED LOS ($P=0.046$), and while the non-butyrophenone group was approximately 3.6 times more likely to be admitted this difference was not noted to be statistically significant ($P=0.192$ via Fisher's Exact Test) (Supplemental Figures 1 & 2).

No statistically significant differences were noted in serum concentrations of delta-9-THC, delta-8-THC, delta-9-COOH, delta-9-OH, delta-8-COOH, CBD, CBG, and CBN between groups (Figure 1, Supplemental Table 2). There were also no significant differences noted in ratios of psychoactive cannabinoids to their respective metabolites, or in the ratio(s) of THC to CBD (Figure 2, Supplemental Table 2).

Discussion

In general, interpretation of serum cannabinoid concentrations remains a challenge due to uncontrollable variables including dose, formulation, route of use, chronicity/frequency of use, and host factors. In a study by Kramer et al. (2021), serum cannabinoid concentrations were obtained in 56 patients who reported cannabis use within the last 24 h. Serum delta-9-tetrahydrocannabinol concentrations ranged between 0 and 30 ng/ml, serum 11-hydroxy-delta-9-tetrahydrocannabinol concentrations ranged between 0 and 17 ng/ml, and serum 11-nor-9-carboxy-delta-9-tetrahydrocannabinol ranged between 0.8 and 648 ng/ml [17].

This retrospective observational study of patients presenting to the ED with either CHS or ACI demonstrates largely similar serum profiles of delta-9-THC, THC metabolites, and non-THC phytocannabinoids between groups. These findings further existing literature arguing against either "hyperintoxication" with delta-9-THC or accumulation of THC metabolites as the etiology of acute episodes of symptomatic CHS.

Several trends were noteworthy regarding the ED course and disposition of CHS and ACI patients. Cannabinoid hyperemesis syndrome patients tended to have a longer ED LOS compared to patients with ACI, as most adult patients with ACI required only a brief period of observation prior to discharge. The two groups had similar rates of inpatient admission, though this can likely be attributed to a higher proportion of pediatric patients in the ACI group, who are more commonly admitted for observation in the setting of known or suspected high-potency THC intoxication.

The overall trends in laboratory data seen between groups was largely consistent with clinically observed rates of nausea, vomiting, and dehydration in the CHS group compared to the acute THC intoxication group. Namely, CHS patients had significantly elevated hemoglobin, hematocrit, and calcium concentrations which are likely reflective of hemoconcentration in the setting of hypovolemia from vomiting. These patients were noted to have comparatively elevated anion gaps and decreased serum chloride, which is also consistent with vomiting and volume losses. Serum lipase was significantly

elevated in the CHS group compared to the ACI group, though mean serum lipase in the CHS group (34.18 units/L) was within normal range (0–160 units/L).

For patients presenting with CHS, a majority were treated with "traditional" antiemetics, butyrophenone antipsychotics, or a combination of the two. Compared to patients who did not receive any butyrophenone antipsychotics, patients who were treated with either haloperidol or droperidol had a significantly longer average ED LOS. This would seemingly contradict existing retrospective and randomized-control studies examining the utility of butyrophenone antipsychotics in patients with CHS [18,19]. While our study was underpowered to detect differences with regard to relative rates of admission, we observed a non-statistically significant increased rate of admission in patients who were not treated with either haloperidol or droperidol compared to those who were (OR 3.6, $p = 0.192$). In addition, the study design was not able to t capture the timing of clinical interventions, and thus we could not detect a difference between patients who had been administered butyrophenones as an initial therapy versus those who had been administered butyrophenones after several rounds of alternative agents.

Limitations

The design of this study introduces several limitations. First, the study's sample size was small, limiting the ability to draw broad based conclusions based on the available data. In addition, while individual chart review was performed to ensure overall accuracy of ED diagnoses and clinical impressions, the structure of patient screening was such that individual patient factors including baseline medical comorbidities and concomitant substance use disorders could not be controlled for. However, the metabolite profiles would suggest that the screening methodology employed was adequate in terms of capturing patients with recent acute cannabis use. There were limitations in capture of data related to individual cannabis use patterns including typical dose, frequency, cannabis formulation, chronicity of use, or time of last use relative to onset of symptoms. This precludes the use of toxicokinetic modeling to estimate peak serum concentrations relative to onset of symptoms. However, it is worth noting that all patient charts individually reviewed with suspicion for CHS included at least some reference to chronic cannabis use as part of ED clinical documentation.

In addition, the generalizability of the data is limited as it pertains to ED LOS, disposition, and CHS treatment modalities. While the two groups did not demonstrate a statistically significant difference in age, several patients in the ACI group involved high dose edible THC ingestions in pediatric patients. This cohort is in general more likely to be admitted than adults for observation, with some cases requiring observation in a critical care setting. With respect to the CHS population, our study was generally underpowered to detect significant differences in rates of admission based on use of butyrophenone antipsychotics while in the ED despite the general trend of the data suggesting that this is likely the case.

Conclusion

Quantitative analysis of serum concentrations of delta-9-THC, THC metabolites, and non-psychotropic phytocannabinoids were similar between patients presenting to the ED with acute, symptomatic CHS and ACI. These findings argue against current theories regarding the underlying pathophysiology of acute, symptomatic CHS including "hyperintoxication" with delta-9-THC and differential accumulation of THC metabolites. Given the recent drastic increase in the incidence of CHS in the US population, more research is needed to elucidate an underlying disease mechanism.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

University of Rochester Medical Center, P30 ES001247.

References

[1] Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53(11):1566–1570. doi: 10.1136/gut.2003.036350.

[2] Costales B, Lu Y, Young-Wolff KC, et al. Prevalence and trends of suspected cannabinoid hyperemesis syndrome over an 11-year period in Northern California: an electronic health record study. Drug Alcohol Depend. 2024;263:112418. doi: 10.1016/j.drugalcdep.2024.112418.

[3] Hernandez JM, Paty J, Price IM. Cannabinoid hyperemesis syndrome presentation to the emergency department: a two-year multicentre retrospective chart review in a major urban area. Can J Emerg Med. 2018;20(4):550–555. doi: 10.1017/cem.2017.381.

[4] Gubatan J, Staller K, Barshop K, et al. Cannabis abuse is increasing and associated with increased emergency department utilization in gastroenterology patients. Dig

Dis Sci. 2016;61(7):1844–1852. doi: 10.1007/s10620-016-4090-9.

[5] Darmani N. Δ9-Tetrahydrocannabinol and synthetic cannabinoids prevent emesis produced by the cannabinoid cb1 receptor antagonist/inverse agonist SR 141716A. Neuropsychopharmacology. 2001;24(2):198–203. doi: 10.1016/S0893-133X(00)00197-4.

[6] Darmani NA. The cannabinoid CB1 receptor antagonist SR 141716A reverses the antiemetic and motor depressant actions of WIN 55, 212-2. Eur J Pharmacol. 2001;430(1):49–58. doi: 10.1016/S0014-2999(01)01355-3.

[7] Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 2011; 163(7):1411–1422. doi: 10.1111/j.1476-5381.2010.01176.x.

[8] Perisetti A. Cannabis hyperemesis syndrome: an update on the pathophysiology and management. aog. 2020;33(6):571–578. doi: 10.20524/aog.2020.0528.

[9] Wang GS, Buttorff C, Wilks A, et al. Changes in emergency department encounters for vomiting after cannabis legalization in Colorado. JAMA Netw Open. 2021;4(9):e2125063. doi: 10.1001/jamanetworkopen.2021.25063.

[10] Khattar N, Routsolias JC. Emergency department treatment of cannabinoid hyperemesis syndrome: a review. Am J Ther. 2018;25(3):e357–e361. doi: 10.1097/MJT.0000000000000655.

[11] Chandra S, Radwan MM, Majumdar CG, et al. New trends in cannabis potency in USA and Europe during the last decade (2008–2017). Eur Arch Psychiatry Clin Neurosci. 2019;269(1):5–15. doi: 10.1007/s00406-019-00983-5.

[12] Freeman TP, Winstock AR. Examining the profile of high-potency cannabis and its association with severity of cannabis dependence. Psychol Med. 2015;45(15):3181–3189. doi: 10.1017/S0033291715001178.

[13] Wightman RS, Metrik J, Lin TR, et al. Cannabis use patterns and whole-blood cannabinoid profiles of emergency department patients with suspected cannabinoid hyperemesis syndrome. Ann Emerg Med. 2023;82(2):121–130. doi: 10.1016/j.annemergmed.2023.03.005.

[14] Krotulski AJ, Bishop-Freeman SC, Mohr ALA, et al. Evaluation of synthetic cannabinoid metabolites in human blood in the absence of parent compounds: a stability assessment. J. Anal. Toxicol. 2021;45(1):60–68. doi: 10.1093/jat/bkaa054.

[15] Krotulski AJ, Mohr ALA, Friscia M, et al. Field detection of drugs of abuse in oral fluid using the Alere™ DDS®2 mobile test system with confirmation by liquid chromatography tandem mass spectrometry (LC–MS/MS). J. Anal. Toxicol. 2018;42(3):170–176. doi: 10.1093/jat/bkx105.

[16] American Academy of Forensic Sciences Standards Board. ANSI/ASB Standard 036, 1st Ed. 2019: standard Practices for Method Validation in Forensic Toxicology. Colorado Springs, CO: AAFS Standards Board. Retrieved from ; 2019. www.asbstandardsboard.org

[17] Krämer M, Schäper M, Dücker K, et al. Detectability of cannabinoids in the serum samples of cannabis users: indicators of recent cannabis use? A follow-up study. Drug Test Anal. 2021;13(9):1614–1626. doi: 10.1002/dta.3110.

[18] Braude D, Soliz T, Crandall C, et al. Antiemetics in the ED: a randomized controlled trial comparing 3 common agents. Am. J. Emerg. Med. 2006;24(2):177–182. PMID: 16490647. doi: 10.1016/j.ajem.2005.08.017.

[19] Lee C, Greene SL, Wong A. The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome. Clin. Toxicol. 2019;57(9):773–777. doi: 10.1080/15563650.2018.1564324.