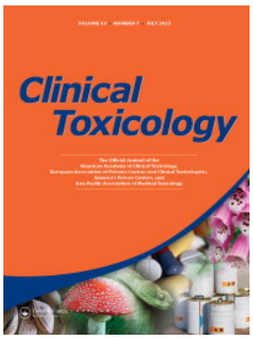

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CLINICAL RESEARCH

Droperidol is associated with reduced length of stay in the treatment of cannabinoid hyperemesis syndrome

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ABSTRACT

Introduction: Droperidol is a butyrophenone-class drug with potent antiemetic properties that may be useful for treating the acute symptoms of cannabinoid hyperemesis syndrome. We evaluated the effectiveness of droperidol in emergency department patients with cannabinoid hyperemesis syndrome.

Methods: This was a retrospective study of encounters that occurred between March 1, 2024 and August 31, 2024 at two tertiary academic emergency departments in Atlanta, Georgia. We identified cases of cannabinoid hyperemesis syndrome via diagnosis codes and manual review of relevant non-specific diagnoses codes. We stratified patients by use of droperidol in the emergency department. The primary outcome was length of stay and secondary outcomes were total medication use, use of opioids, disposition, and key safety outcomes (medication adverse events, dysrhythmias).

Results: There were 211 encounters among 158 unique patients included in the study. Droperidol was used in 77 (36.5%) of encounters at a median dose of 1.25 mg. The length of stay was significantly reduced in the droperidol group (409 min versus 641 min). After adjustments, droperidol use was associated with a reduced length of stay (mean ratio 0.76; 95% CI: 0.62 0.94; $P=0.01$), decreased total medication administration (OR 0.34; 95% CI: 0.20–0.58; $P<0.001$) and decreased usage of opioids (OR 0.16; 95% CI: 0.07–0.39; $P<0.001$). Discharge dispositions were non-significant (OR 1.19; 95% CI: 0.57–2.48; $P=0.64$). There were two mild adverse drug reactions in the droperidol group.

Discussion: Several drug classes with plausible mechanisms are used to treat the symptoms of cannabinoid hyperemesis syndrome. Droperidol use was associated with several favorable outcomes including decreased length of stay, total medication use, and opioid use.

Conclusions: We believe that droperidol may be considered as a first line treatment in patients with cannabinoid hyperemesis syndrome. Future studies should identify optimal dosing regimens using a randomized controlled trial design.

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Cannabinoid hyperemesis syndrome; CHS; droperidol; length of stay; treatment

Introduction

Cannabinoid hyperemesis syndrome is a condition characterized by episodic abdominal pain, nausea, and vomiting that affects a subset of patients who use cannabinoids over long periods of time [1]. In the United States (US), cannabis use, as well as cannabis-related emergency department visits, are increasing owing to broad cultural and legal trends towards acceptance of the drug and its derivatives [2,3]. When treating the acute symptoms of patients with cannabinoid hyperemesis syndrome, there is emerging evidence that dopamine antagonists (e.g., droperidol and haloperidol) may be superior to other classes of medications [4,5].

Droperidol is a butyrophenone-class drug that has been used since the 1970s for its favorable antiemetic and tranquilizing properties. Droperidol use in US emergency departments decreased precipitously in the 2000s subsequent to a US Food and Drug Administration publication of a black-box warning regarding a possible link between droperidol and cardiovascular complications. Numerous large studies have reaffirmed the safety and efficacy of droperidol since this warning [6–8]. In our local hospitals, an institutional restriction

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on droperidol use in the emergency department was rescinded in 2023 after a successful petition for its reinstatement.

Droperidol may be beneficial in the treatment of the symptoms of cannabinoid hyperemesis syndrome, but evidence for its use is sparse compared to other medications [9]. To date, the largest study investigating the effectiveness of droperidol in patients with cannabinoid hyperemesis syndrome comes from Lee and colleagues [4], in which droperidol use was associated with substantially decreased emergency department length of stay, a decreased need for opioids, and a good safety profile. The purpose of this present study is to describe our experience with using droperidol and to evaluate its effectiveness in the treatment of the patient with cannabinoid hyperemesis syndrome.

Methods

This was a retrospective chart review performed at Emory University Hospital Midtown and Emory University Hospital, which are academic, tertiary care hospitals in Atlanta, Georgia. The two emergency departments are staffed by the same faculty group. The annual censuses are approximately 90,000 and 38,000, respectively.

We performed a retrospective chart review to identify cases of cannabinoid hyperemesis syndrome between March 1, 2024 and August 31, 2024. This time frame corresponds to the timing of droperidol becoming available in the emergency department and the acceptance of this protocol by the local Institutional Review Board with a waiver of informed consent (study number 00008296).

Inclusion criteria were age ≥18 years and an emergency department diagnosis of cannabinoid hyperemesis syndrome. Exclusion criteria were pregnancy, concurrent emergency department treatment for another condition, or plausible alternative diagnosis to account for symptoms (e.g., infections, ketoacidosis, diabetic gastroparesis, or other functional gastrointestinal disorders). Concurrent treatment for conditions that may naturally result from cannabinoid hyperemesis syndrome such as metabolic abnormalities or dehydration were included. The primary method of case identification was an electronic medical record search based on emergency department diagnosis codes. Data sources included clinical documentation (emergency department notes, nursing notes, admission history and physicals, and discharge summaries), medication administration records, and scanned ECG tracings.

Based on an observed local practice pattern of assigning non-specific diagnosis codes to cases of cannabinoid hyperemesis syndrome, we also sought to enrich the sample by reviewing all encounters with non-specific diagnosis codes during the study period. These included International Classification of Diseases 10th revision (ICD-10) codes for primary or secondary diagnoses of non-specific abdominal pain, nausea, vomiting, nausea and vomiting, and unspecified cyclic vomiting syndromes. To include an encounter, we required two reviewers to agree that the encounter was cannabinoid hyperemesis syndrome despite assignment of a non-specific diagnosis. To be conservative in this practice, disagreements between reviewers or uncertainty resulted in exclusion of the case rather than adjudication. For potential cases meeting inclusion criteria, the second reviewer was not blinded to first reviewer's assessment. We used criteria adapted from the previous works [4,10]: (1) stated or objective evidence of long-term cannabis use, (2) primary symptomatology of nausea, vomiting, and/or abdominal pain, and (3) absence of any other diagnosis or condition to better explain the symptoms. In addition, the narrative documentation had to explicitly mention cannabinoid hyperemesis syndrome as either the primary etiology or most likely etiology among differential considerations. Supplement 1 contains excerpts of narrative documentation from physician notes to support the assertion that physicians contemporaneously understood that they were treating patients with cannabinoid hyperemesis syndrome despite coding the encounter with a non-specific diagnosis.

Patients were stratified based on whether they received droperidol in the emergency department. The primary study outcome was length of stay inclusive of emergency department, observation unit, and hospital admission time when applicable. Secondary outcomes included: total medication use, opioid use, and disposition. We assessed safety by narrative review of physician and nursing notes for adverse medication effects or dysrhythmic events. We used a standardized data abstraction worksheet to collect the following variables: age, gender, event timings, diagnosis, QTc intervals by automated machine read, medications with total dose, morphine milligram equivalents, and disposition. The encounter reviews and data abstraction were performed by four of the study authors who are an emergency medicine physician (GSK) and clinical pharmacists with primary appointments in the emergency department (GM, BM, and VD). We adhered to STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines for cohort studies [11].

Statistical analyses

Categorical variables were described using frequencies and percentages. Continuous and scale variables were described using medians and interquartile ranges (IQR). The primary outcome, length of stay, tends to be

positively skewed and heteroskedastic. It was evaluated using a mixed-effects Gamma regression. We present mean ratios, 95% confidence intervals (95% CI), and *P* values. The secondary outcomes, opioid use and total medication use, were evaluated using mixed-effects binary logistic and ordinal logistic regressions, respectively. Finally, we evaluated discharge status using a mixed-effects binary logistic regression. The mixed-effects models were used in order to incorporate hospital- and patient-level clustering. Adjustment for potential confounding was accomplished using a doubly-robust regression approach [12]. This approach involves a two-stage regression. In the first stage, the covariates are used to generate inverse propensity score weights for receiving droperidol. A number of weighting methods were evaluated; entropy balancing resulted in the best covariate balance [13]. In the second stage, droperidol, the covariates, and the weights were included in the regression analyses for the outcomes. Covariates were chosen a priori. All models included age, sex, chief complaint, and QTc as covariates. The model for length of stay also included haloperidol, metoclopramide, ondansetron, prochlorperazine, capsaicin, midazolam, dicyclomine, scopolamine, crystalloid, morphine, and hydromorphone. The model for opioid use included all of these covariates except for morphine and hydromorphone usage. Covariate balance before and after the weighting procedure is presented in Supplement 2. Analyses were conducted using R (v 4.4; R Core Team).

Results

There were 67,290 emergency department encounters during the study period. Seventy-eight encounters were diagnosed as cannabinoid hyperemesis syndrome. Among non-specific diagnoses, 34/8,408 abdominal pain (0.4%), 91/8,914 nausea and/or vomiting (1.0%), and 8/93 unspecified cyclic vomiting or other diagnoses (8.6%) met inclusion criteria. Of the included 133 encounters with non-specific diagnoses, 96 (72.2%) had a previous emergency department encounter with a diagnosis of cannabinoid hyperemesis syndrome (Figure 1). There was 96% concordance between reviewers for inclusion of encounters with non-specific diagnoses.

The sample consisted of 211 encounters among 158 unique patients. Patient characteristics and encounter details are presented in Table 1. Droperidol was used in 77 (36.5%) of encounters. The median dose of droperidol was 1.25 mg (IQR: 0.625–2.5 mg; range 0.625–5 mg).

Primary and secondary outcomes are presented in Table 2. Patients who received droperidol had a shorter length of stay (409 min versus 641 min). These results are shown in Figure 2. In addition, patients who received droperidol required fewer opioids (15% versus 38.8%), fewer total medication administrations (five versus six), and were discharged more frequently (83.1% versus 55.2%). Adjusted outcomes are summarized in Table 3. Droperidol use remained strongly associated with the primary outcome (mean ratio 0.76; 95% CI:

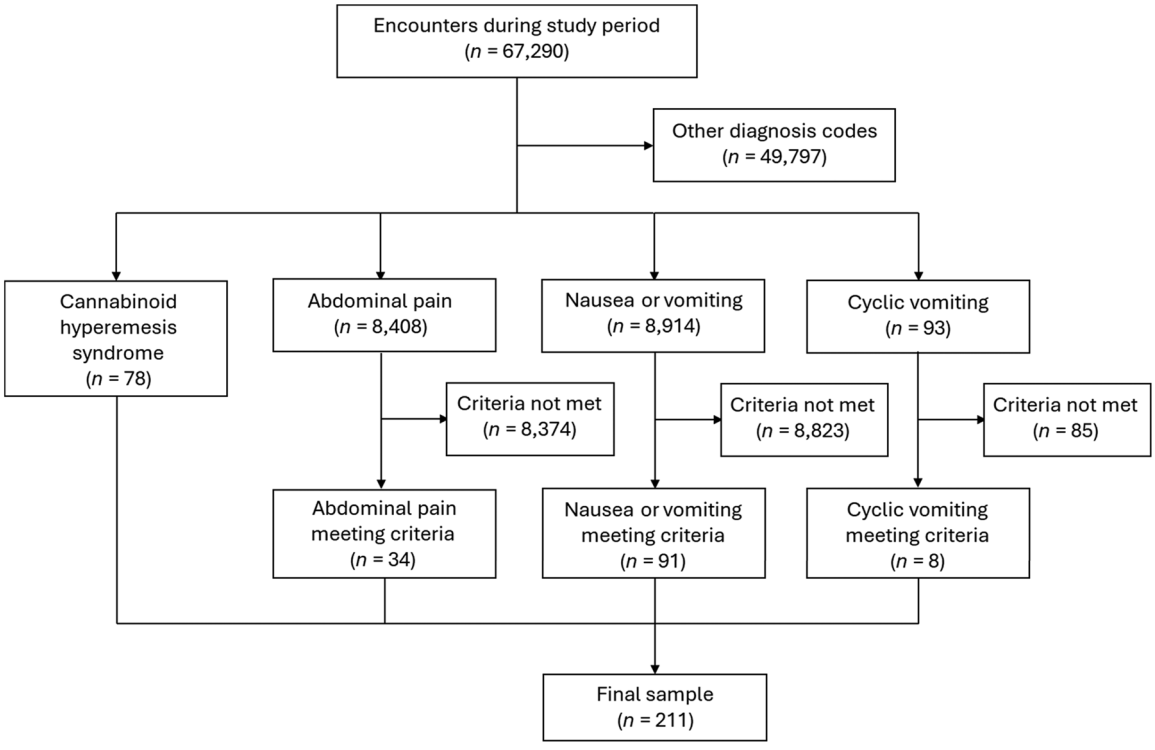

Figure 1. Flow diagram. Criteria refers to inclusion criteria described in the methods section.

Table 1. Patient characteristics stratified according to droperidol usage.

Characteristic	No droperidol (*n* = 134)	Droperidol (*n* = 77)	Full sample (*n* = 211)
Age (years), median (IQR)	29.5 (23–37)	35 (27.5–45.5)	31 (25–39)
Sex, *n* (%)			
Female	97 (72.4)	38 (49.4)	135 (64)
Male	37 (27.6)	39 (50.6)	76 (36)
Chief complaint*, *n* (%)			
Abdominal pain	66 (49.3)	37 (48.1)	103 (48.8)
Nausea	16 (11.9)	14 (18.2)	30 (14.2)
Other	3 (2.2)	5 (6.5)	8 (3.8)
Vomiting	49 (36.6)	21 (27.3)	70 (33.2)
Corrected QT interval (msec), median (IQR)	435 (415–457)	434 (416–457)	435 (415–457)
Drugs administered			
Haloperidol, *n* (%)	56 (41.8)	6 (7.8)	62 (29.4)
Metoclopramide, *n* (%)	61 (45.5)	9 (11.7)	70 (33.2)
Ondansetron, *n* (%)	89 (66.4)	32 (41.6)	121 (57.3)
Prochlorperazine, *n* (%)	7 (5.2)	2 (2.6)	9 (4.3)
Capsaicin, *n* (%)	31 (23.1)	13 (16.9)	44 (20.9)
Midazolam, *n* (%)	11 (8.2)	2 (2.6)	13 (6.2)
Dicyclomine, *n* (%)	26 (19.4)	8 (10.4)	34 (16.1)
Scopolamine, *n* (%)	5 (3.7)	1 (1.3)	6 (2.8)
Crystalloid, *n* (%)	125 (93.3)	70 (90.9)	195 (92.4)
Morphine, *n* (%)	47 (35.1)	14 (18.2)	61 (28.9)
Hydromorphone, *n* (%)	8 (6)	1 (1.3)	9 (4.3)
Disposition, *n* (%)			
Discharge	74 (55.2)	64 (83.1)	138 (65.4)
Observation	45 (33.6)	12 (15.6)	57 (27)
Admission	15 (11.2)	1 (1.3)	16 (7.6)

IQR – Interquartile range. *When multiple chief complaints were present, the first complaint was recorded.

Table 2. Unadjusted outcomes stratified by droperidol usage.

Outcome	No droperidol (*n* = 134)	Droperidol (*n* = 77)	Full sample (*n* = 211)
Length of stay, min, median (IQR)	641 (384–1,437)	409 (267.5–570)	505 (331–1,101)
Opioid use, *n* (%)	52 (38.8)	15 (19.5)	67 (31.8)
Total medications given, median (IQR)	6 (4–10.5)	5 (3–7.5)	6 (4–9)
Discharge, *n* (%)	74 (55.2)	64 (83.1)	138 (65.4)

0.62–0.94; $P = 0.01$). In addition, droperidol was associated with decreased use of opioid medications (OR 0.16; 95% CI: 0.07–0.39; $P < 0.001$) and decreased total medication use (OR 0.34; 95% CI: 0.20–0.58; $P < 0.001$) after adjusting. Finally, the association between droperidol and a discharge disposition was not significant following adjustment (OR 1.19; 95% CI: 0.57–2.48).

There were two adverse medication events recorded. The first was akathisia in a patient who received droperidol 2.5 mg and a second patient who developed a dystonic reaction after droperidol 2.5 mg. Both were treated with diphenhydramine 25 mg intravenously and the adverse events did not affect the dispositions. There were no reported dysrhythmic events.

Finally, we conducted two sets of additional exploratory analyses. First, because patients with non-specific diagnosis codes were also included, we tested whether the effect of droperidol differed between those with and those without a specific cannabinoid hyperemesis syndrome diagnosis. Second, because droperidol and haloperidol are pharmacologically similar, we tested whether the effect of droperidol differed between patients who had and had not also received haloperidol. For both analyses, this was accomplished by including interaction terms with droperidol in the regression models described above. For cannabinoid hyperemesis syndrome diagnoses, these terms were non-significant for length of stay ($P = 0.99$), opioid use

Table 3. Adjusted outcomes, reported as mean ratio and odds ratios.

Outcome	Effect	95% CI	*P* value
Length of stay, mean ratio	0.76	0.62–0.94	0.01
Opioid use, odds ratio	0.16	0.07–0.39	<0.001
Total medications given, odds ratio	0.34	0.20–0.58	<0.001
Discharge, odds ratio	1.19	0.57–2.48	0.64

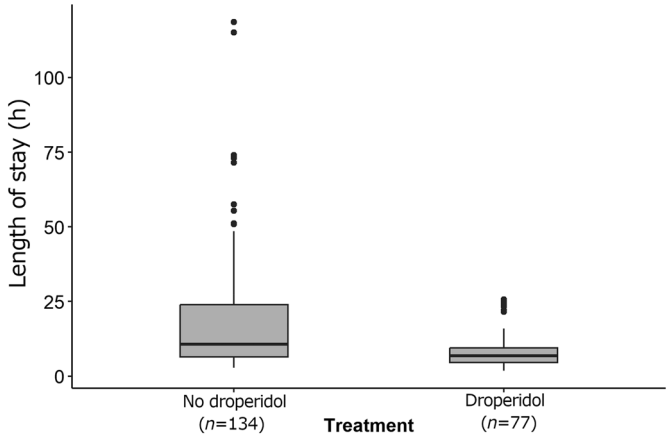

Figure 2. Length of stay stratified by droperidol usage. Shaded areas represent the IQR, bolded lines are medians, and whiskers are 1.5 times the IQR.

($P = 0.51$), and total medication use ($P = 0.74$). For concurrent usage of haloperidol, these terms were also non-significant: length of stay ($P = 0.26$), opioid use ($P = 0.99$), and total medication use ($P = 0.38$). Thus, we do not find evidence that the effect of droperidol differed as a function of either having a specific cannabinoid hyperemesis syndrome diagnosis or having concurrent received haloperidol.

Discussion

In this retrospective study comparing outcomes of droperidol use versus non-use in the treatment of patients with cannabinoid hyperemesis syndrome, droperidol use was associated with significantly reduced length of stay, decreased use of total medications, and decreased use of opioids. These results remained significant when controlling multiple covariates including use of antiemetics and adjunctive treatments. These results support the use of droperidol as an effective treatment for the acute symptoms of cannabinoid hyperemesis syndrome.

These results are consistent with the findings from the heretofore largest study on droperidol in cannabinoid hyperemesis syndrome by Lee and colleagues [4], in which patients who received droperidol had a decreased length of stay compared to a non-droperidol group: 6.7 h (IQR: 4.7–11.9 h) versus 13.9 h (IQR: 5.2–57.3 h). In the present study, the effect of droperidol on length of stay had a similar magnitude and direction. In an era in which emergency department overcrowding is commonplace, this finding has the potential to help individuals as well as healthcare systems. Lee and colleagues [4] reported a lower median droperidol dose than the dose used in our study (0.625 mg versus 1.25 mg). Relative to Lee and colleagues [4], we had a larger sample size with roughly double the encounters with droperidol use. In addition, we adjusted for patient characteristics and other medications. A recently published study by Chopra and colleagues [14], described a persistent decrease in symptoms of cannabinoid hyperemesis syndrome including abdominal pain, nausea, and vomiting at 30 min, 60 min, and 120 min intervals when using droperidol 2.5 mg and diphenhydramine 25 mg in a prospective, open-label study. This study further supports the efficacy of droperidol and provides guidance for its use at relatively higher doses, although generalizability is limited with an unblinded design without a comparator group.

In this study we reviewed every individual non-specific diagnosis code for abdominal pain, nausea, vomiting, and cyclic vomiting during the study period to increase the number of cases of cannabinoid hyperemesis syndrome. A possible criticism of this method may be the introduction of misclassification bias via retroactively applying diagnoses of cannabinoid hyperemesis syndrome. This method was devised after finding a lower-than-expected number of diagnoses when attempting to identify cases by solely by diagnosis codes for cannabinoid hyperemesis syndrome. There are likely several reasons for this. Symptomatic diagnosis rather than specific or pathological diagnosis is a common practice in emergency medicine. A study by Wen and colleagues [15] reported that up 57% of patients presenting with abdominal pain received a non-specific diagnosis of "abdominal pain" rather than a pathological diagnosis. Notably, abdominal pain was the most common chief complaint in our population. In addition, a well-described phenomenon that many emergency department physicians have likely encountered is the patient that is resistant to a diagnosis of cannabinoid hyperemesis syndrome or denies an association between their symptoms and cannabinoid usage [16,17]. These patients commonly assert that cannabinoid use cannot be responsible for their symptoms or believe that usage relieves their symptoms. Assignment of a non-specific diagnosis may be an attempt to avoid an adversarial patient interaction or a reluctance to assign a diagnosis that relies on context rather than an objective laboratory and imaging results. We used a systematic approach to case identification to minimize the risk of misclassification. Notably, most of the patients with non-specific diagnoses (72%) had previously been diagnosed with cannabinoid hyperemesis syndrome at the time of their index visit.

There are other limitations to our study. While we took steps to account for potential confounding, such as conducting a doubly-robust regression procedure, this study, like all observational studies, is limited by the possibility of unmeasured confounding. That is, it is possible that the observed results can be attributed to an unknown confounder. The dose of droperidol was not pre-selected in our electronic ordering system and the dose is selected at the discretion of the ordering physician. We did not include minors or pregnant patients and therefore our conclusions cannot necessarily be extended to these populations. The median dose of droperidol in our study was 1.25 mg, which demonstrated effectiveness but is lower than the dose advocated by some investigators [14]. While the optimal dose of droperidol in patients with cannabinoid hyperemesis syndrome remains incompletely characterized, our finding of effectiveness at this dose supports an assertion by Lee and colleagues [4], regarding using droperidol doses of at least 1.25 mg. We used a pragmatic definition of cannabinoid hyperemesis syndrome that aligns with prior emergency department-based studies [4,10], but differs from the Rome IV [18] and American Gastroenterology Society definitions [19]. In

particular, the diagnostic requirement that a patient's symptoms resolve after cannabis cessation is challenging to apply in an acute care setting. Finally, we relied on narrative notes to identify adverse events, which may result in underestimation of adverse events. While there may be underreporting of mild adverse events, it is unlikely that a significant event such as a dysrhythmia occurred even with this limitation.

Conclusion

We found droperidol use in patients with cannabinoid hyperemesis syndrome to be associated with shortened emergency department length of stay, decreased total medication needs, and decreased use of opioids. We believe that droperidol should be considered as an initial treatment when managing the acute symptoms of cannabinoid hyperemesis syndrome. Future studies should include randomized controlled trials and seek to determine an optimal droperidol dosing regimen, which provides symptom relief without increasing rates of adverse events.

Disclosure statement

No potential conflict of interest was reported by the authors.

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