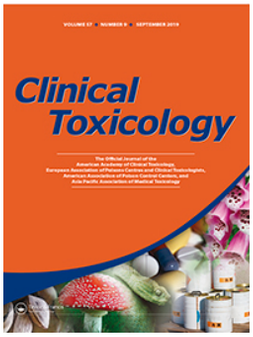

Clinical Toxicology

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

The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome

Carl Lee, Shaun L. Greene & Anselm Wong

To cite this article: Carl Lee, Shaun L. Greene & Anselm Wong (2019) The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome, Clinical Toxicology, 57:9, 773-777, DOI: 10.1080/15563650.2018.1564324

To link to this article: https://doi.org/10.1080/15563650.2018.1564324

Published online: 07 Feb 2019.

Submit your article to this journal

Article views: 474

View related articles

View Crossmark data

Citing articles: 2 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=ictx20

CLINICAL TOXICOLOGY
2019, VOL. 57, NO. 9, 773–777
https://doi.org/10.1080/15563650.2018.1564324

Taylor & Francis
Taylor & Francis Group

CLINICAL RESEARCH

Check for updates

The utility of droperidol in the treatment of cannabinoid hyperemesis syndrome

Carl Lee[a], Shaun L. Greene[a,b] and Anselm Wong[a,b,c]

[a]Austin Clinical School, University of Melbourne, Melbourne, Australia; [b]Austin Health, Austin Toxicology Unit and Victorian Poisons Information Centre, Heidelberg, Australia; [c]Department of Medicine, School of Clinical Sciences, Monash University, Melbourne, Australia

ABSTRACT

Introduction: Cannabinoid hyperemesis syndrome (CHS) can be characterized by recurrent paroxysmal episodes of intractable nausea and vomiting, abdominal pain, and compulsive hot showers/baths with symptom relief, on the background of chronic cannabis use. We reported the use of droperidol in the management of CHS.

Methods: We performed a retrospective review of electronic medical records of Emergency Department presentations to a single tertiary level metropolitan hospital between January 2006 and December 2016 using search keywords: "cannabis", "cannabinoid", "cannabis", "hyperemesis", and "droperidol". A secondary search of pharmacy droperidol dispensing records was cross matched with electronic medical record data. We reviewed each record to determine if the presentation met previously published diagnostic criteria for CHS. Data were dichotomised into presentations with droperidol administered or not administered. The primary outcome was defined as the total length of hospital stay. Secondary outcomes measures included time until discharge following last drug administration, and the total number of antiemetic dosages administered.

Results: Six-hundred and eighty-nine records were identified and 76 met CHS diagnostic criteria. Thirty-seven presentations were treated with droperidol and 39 were not. Droperidol treatment group median length of stay was significantly lower compared to the no droperidol treatment group (6.7 vs. 13.9 hours, $p = .014$). Median time to discharge after final drug administration in the droperidol treatment group was 137 minutes (IQR 65, 203) vs. the no droperidol treatment group of 185 minutes (IQR 149, 403). The most frequent dosage of droperidol used was 0.625mg intravenously. The frequency of ondansetron ($n = 100$) and metoclopramide ($n = 27$) in the no droperidol treatment group was double that of the droperidol group.

Conclusions: Use of droperidol to treat CHS associated nausea and vomiting resulted in less overall use of antiemetics and reduced length of stay.

ARTICLE HISTORY
Received 16 September 2018
Revised 16 December 2018
Accepted 25 December 2018
Published online 25 January 2019

KEYWORDS
Marijuana; cannabis; nausea; vomiting; cyclical

Introduction

Cannabinoid hyperemesis syndrome (CHS) has been increasingly recognised over the last two decades [1]. It should be suspected when there are symptoms and signs including recurrent paroxysmal episodes of cyclical nausea and intractable vomiting, abdominal pain, and compulsive hot showers/baths with symptom relief, on the background of chronic cannabis use [2]. CHS can be overlooked and underdiagnosed because of overlapping symptoms with other diagnoses [3]. Patients often present to the Emergency Department (ED) for analgesia, rehydration therapy and anti-emetics.

There are multiple retrospective case studies looking at the use of pharmaceuticals for the treatment of CHS related nausea and vomiting, including haloperidol, topical capsaicin, benzodiazepines, propranolol and tricyclic anti-depressants (TCAs) [4–8]. Clinicians often use commonly prescribed antiemetics, such as metoclopramide and ondansetron; however, they are largely ineffective [9]. A recent systematic review reported benefit from the use of haloperidol and capsaicin; however, these conclusions are drawn from small case series [4].

Droperidol is an antipsychotic belonging to the butyrophenone class which also includes haloperidol. It is effective when used to treat nausea and vomiting in the ED [10]. In addition, droperidol is often used for postoperative nausea and vomiting with proven efficacy [11]. Droperidol is commonly used in Australia and other parts of the world for acute psychosis, agitation, and as an anti-emetic [12,13]. In December 2001, the United States Food and Drug Administration (FDA) issued a black box warning for droperidol due to the increased risk of QT prolongation and potential dysrhythmia which has limited its use by clinicians in the US [12]. However, larger studies [13,14] demonstrated that droperidol is safe and effective for the treatment of agitation in ED patients. Doses used in these studies (10–20 mg) are much larger than commonly used antiemetic doses. In addition, the development of Torsades des Pointes from prolonged QT is multifactorial.

CONTACT Anselm Wong anselm.wong@austin.org.au Emergency Department, Austin Health, Heidelberg, Victoria, Australia
© 2019 Informa UK Limited, trading as Taylor & Francis Group

The utility of droperidol in the treatment of CHS needs further definition and may have similar utility as reported with haloperidol previously. In this study, we aimed to evaluate the utility of droperidol in the treatment of CHS.

Materials and methods

We conducted the study at a major metropolitan tertiary referral hospital with a toxicology service and an annual ED volume of 90,000 patients. We performed a retrospective review of the medical records from presentations between January 2006 and December 2016. We searched electronic (PowerChart™, V 2012.01, 2013, CERNER, North Kansas City, MO) records for keywords including "cannabis", "cannabinoid", "cannabis", "hyperemesis" and "droperidol". A secondary search of pharmacy data for records of droperidol dispensing was cross-referenced with cannabis use documented in the electronic medical records. Two investigators reviewed each record to determine if that presentation met criteria for CHS. We defined CHS using the criteria set out by Simonetto et al. [15]: (1) a history of long-term cannabis use, (2) symptoms of recurrent vomiting, and (3) absence of illness that could otherwise explain symptoms. Presentations not fitting this description were excluded.

The primary outcome was defined as the total length of hospital stay. Secondary outcome measures included time until discharge following last antiemetic administration and number of antiemetics used before and after intravenous (IV) droperidol administration. Adverse reactions were noted including dystonia, arrhythmias and drowsiness. The qualitative responses to antiemetics gathered from nursing staff documentation were grouped as no, transient/partial or complete symptom relief. Qualitative statements from notes were also noted regarding the perceived effect of droperidol, e.g., improvement in nausea or ability to eat and drink.

Data collected included age, gender, admission dates, cannabis use frequency, co-morbidities, symptomology, treatment, adverse reactions onto an electronic spreadsheet and devised *a priori*. Data were analysed and separated into two groups: presentations receiving droperidol and presentations that did not. Data were collected and analysed using Excel 2016 (Microsoft Office 365 ProPlus, 2016, Redmond, WA).

Statistical analysis was performed using Minitab (Minitab® 18.1, 2017, State College, PA). All data were analysed descriptively using medians, percentages, standard deviation and interquartile ranges as appropriate. Non-parametric continuous variables were compared using the Mann–Whitney *U*-test. Ethics approval for the study was obtained from the Austin Health Ethics Committee.

Results

Six-hundred and eighty-nine records were identified as potentially fulfilling the study inclusion criteria, and 76 met criteria for CHS (Figure 1). The demographics of each group are shown in Table 1.

Clinical characteristics of patients fulfilling the diagnostic criteria for CHS are shown in Table 2. Thirteen presentations (35%) in the droperidol treatment group and 14 presentations (36%) in the no droperidol treatment group documented symptomatic relief with hot baths/showers. Twenty-two presentations (60%) in the droperidol treatment group reported daily cannabis use and seven (19%) presentations reported weekly use. Thirty presentations (77%) in the no droperidol treatment reported daily cannabis use and six (15%) presentations reported weekly cannabis use.

The median length of stay in the droperidol treatment group was 6.7 hours (IQR 4.7, 11.9) vs. 13.9 hours (IQR 5.2, 57.3) in the no droperidol treatment group ($p = .014$). The median length of time to discharge after final drug administration, in the droperidol treatment group was 137 minutes

Table 1. Demographics of patients with cannabinoid hyperemesis syndrome.

	Droperidol	No droperidol
Median age, years (IQR)	29 (21, 36)	34 (27, 40)
Gender		
Male, *n* (%)	28 (76)	23 (59)
Female, *n* (%)	9 (24)	16 (41)
Ethnicity		
Caucasian, *n* (%)	35 (95)	37 (95)
Other, *n* (%)	2 (5)	2 (5)

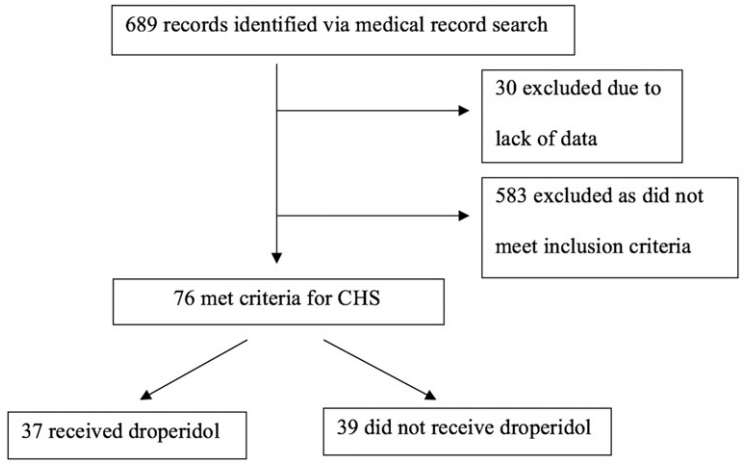

Figure 1. Study recruitment. CHS: cannabinoid hyperemesis syndrome.

Table 2. Characteristics of patients presenting with cannabinoid hyperemesis syndrome.

	No. of patients (%) Droperidol ($n = 37$)	No. of patients (%) No droperidol ($n = 39$)
History of cannabis use	37 (100)	39 (100)
Nausea and vomiting	37 (100)	39 (100)
Hot baths/showers-symptom relief	13 (35)	14 (36)
Not reported (%)	24 (65)	25 (64)
Abdominal pain	37 (100)	35 (90)
Cyclical pattern	36 (97)	39 (100)
Resolution of symptoms post cessation cannabis	3 (8)	4 (10)
Return of symptoms with resumption of cannabis use	7 (19)	6 (15)
Reported daily cannabis use	22 (60)	30 (77)
Reported weekly cannabis use	7 (19)	6 (15)
Frequency of use not recorded	8 (21)	3 (8)
Age < 50 at onset of illness	37 (100)	39 (100)

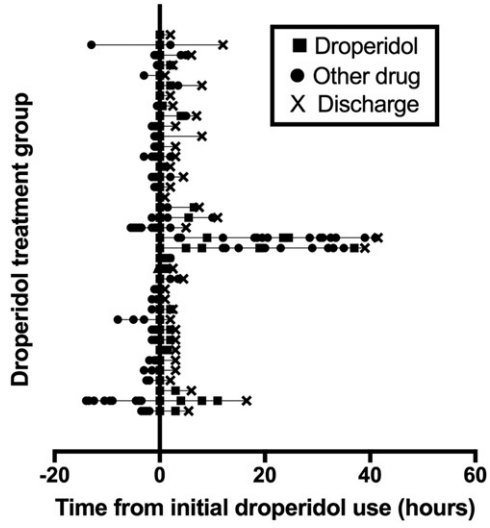

Figure 2. Clinical course of droperidol treatment group.

(IQR 65, 203) vs. 185 minutes (IQR 149, 403) in the no droperidol treatment group ($p = .002$).

The median number of anti-emetics used before IV droperidol ($n = 1$, IQR 0, 1.5) compared to number of anti-emetics used after droperidol ($n = 0$, IQR 0, 1) was higher ($p = .02$). In the droperidol treatment group, 54% (20 of 37 presentations) used droperidol as the last drug prior to discharge (Figure 2). Other antiemetic and medication use is documented in Table 3. Ondansetron IV was given a total of 47 times (1.27 per person) in the droperidol treatment group compared to 100 times (2.56 per person) in the no droperidol treatment group. Morphine IV use was also higher in the no droperidol treatment group (median of 1.10 administrations per person) compared to the droperidol treatment group (median of 0.41 per person per person).

Response to antiemetic therapy is shown in Table 4. Seven presentations (19%) reported being able to tolerate fluids and/or solids in the droperidol treatment group, with a median time of 105 minutes post droperidol administration.

The frequency of droperidol use is shown in Table 5. The most frequent dosage of droperidol used was 0.625 mg IV. The median total dose of droperidol received per presentation was 2.19 mg (IQR 1.25, 4.69) IV.

Drowsiness was reported in two cases and no cardiac adverse events were reported. One patient developed a dystonic reaction and responded immediately to 1 mg IV benztropine. There were no reported side effects to other antiemetics used.

Discussion

Cannabis is the most commonly used recreational drug worldwide, with the United Nations estimating approximately 277 million users globally [16]. In 2016, cannabis was the most commonly used illicit drug in Australia, with 34.8% of Australians having tried cannabis in their lifetime, and 10.4% having used cannabis in the last 12 months [17]. With the increasing legalisation of cannabis in different countries, there is likely to be an increase in complications associated with the usage such as CHS.

In our study, there was a statistically significant shorter length of stay in the droperidol treatment group compared to the no droperidol treatment group. More than half the presentations in the droperidol treatment group received droperidol as their last medication before discharge. Seven patients had documented improvement in fluid and/or food tolerance, with a median time of 105 minutes post droperidol administration. This suggests that droperidol may be more effective than other antiemetics in controlling nausea and vomiting associated with CHS, allowing earlier discharge. There was also a shorter time until discharge following final drug administration in the droperidol treatment group. This is particularly important with overcrowded EDs and hospital systems.

The exact pathophysiology of CHS is not well understood. There are various theories that attempt to explain the pro-emetic effect of cannabinoids in chronic users. Activation of cannabinoid 1 (CB1) receptors in the gut inhibits gastric emptying and intestinal motility, which may contribute to the nausea and hyper-emetic state seen in CHS [18]. Another suggestion is the downregulation of cannabinoid receptors due to chronic exposure to the receptor ligand. Genetic variations may also contribute to CHS [19]. A variation in hepatic metabolic enzymes (e.g., cytochrome P450 enzymes) may produce excessive metabolites of cannabinoids which could promote emesis [20].

Various medications and treatments have been used to treat CHS. A potential mechanism for the efficacy of droperidol is its high affinity for the dopamine receptor (D_2)

Table 3. Frequency of drug usage in the droperidol and no droperidol treatment groups.

	Droperidol treatment group		
	Prior to droperidol, frequency of use (*n*)	After droperidol, frequency of use (*n*)	No droperidol treatment group, frequency of use (*n*)
Metoclopramide	14	3	27
Ondansetron	45	2	100
Prochlorperazine	5	0	1
Domperidone	0	0	27
Hyoscine	7	4	16
Morphine	14	1	43
Oxycodone	7	5	34
Diazepam	2	2	36
Capsaicin cream	1	1	0
Tramadol	0	0	3

Table 4. Response to anti-emetic therapy.

	Droperidol, *n* (%)	Conventional anti-emetic, *n* (%)
No symptom relief	1 (3)	9 (23)
Transient/partial symptom relief	21 (57)	6 (15)
Complete symptom relief	2 (5)	0 (0)
Not documented	13 (35)	24 (62)

Table 5. Dose of intravenous (IV) droperidol and frequency of use in droperidol treatment group.

IV dose (mg)	Frequency of use (*n*)	Droperidol as last anti-emetic used (*n*)	Median (IQR) number of agents used after last dose of droperidol
0.625	25	7	1 (0,1.5)
1.25	20	8	0.5 (0,1.75)
2.5	17	9	0 (0,1)
5	3	0	1 (1,1)

compared to other drugs such as metoclopramide and prochlorperazine. The D_2 receptor had been implicated in the development of nausea and vomiting in humans [21]. In a rat study, it is shown that droperidol had the lowest K_i value (2.4 ± 0.6) when compared to metoclopramide (240 ± 60) and prochlorperazine (18 ± 5) [22]. K_i can be defined as the concentration required to produce half maximum inhibition; therefore, droperidol was a highly potent antagonist at the D_2 receptor. However, this study did not compare the potency of ondansetron to droperidol.

Case reports have demonstrated that treatment with haloperidol another high potency D2 receptor antagonist may be effective in controlling symptoms of CHS [5,23,24]. These presentations showed that after refractory treatment with conventional anti-emetics, haloperidol was used and showed symptom improvement. One case series showed a temporal relationship where four patients were discharged within eight hours of admission [5]. For the indication of sedation of agitated patients, haloperidol and droperidol have been shown to be both efficacious and safe therapeutic options [25]. However, there have been no studies comparing the use of droperidol vs. haloperidol for treatment of CHS.

The evidence behind the efficacy of anti-emetics in CHS such as ondansetron and metoclopramide is weak [26]. Given the various phenotypes of presentations, variable response and the intrinsic low data quality of case reports, it is difficult to conclude whether ondansetron and/or metoclopramide is efficacious in treating CHS. In our study, we found mixed responses to ondansetron and metoclopramide, and more use of analgesics such as morphine and oxycodone in the no droperidol treatment group.

Topical capsaicin has been reported to be beneficial in the relief of symptoms [27]. Capsaicin acts on transient receptor potential cation channel subfamily V member 1 (TRPV1) in the brainstem to reduce emesis. The exact mechanism is unknown, but it is proposed that capsaicin depletes substance P at a critical site, the nucleus tractus solitarius in the central emetic pathway, therefore, reducing stimulation of the chemoreceptor trigger zone, and ultimately reducing nausea/emesis [7]. The TRPV1 channel is activated at temperatures higher than 43 °C, which may also explain the symptom relief experienced with hot showers.

Other therapeutics that have shown utility include benzodiazepines and TCAs as short- and long-term treatments, respectively [8,26,28]. Cessation of cannabis use appears to be an effective long-term treatment for CHS [2,3].

There are several limitations of this retrospective case series. There were potentially missed presentations as CHS may have been undiagnosed or cannabis use may not have been recorded in the medical records. Patients often received various supportive and antiemetic treatments which were not standardised. The efficacy of one treatment compared to another would be better investigated in larger prospective trials. ECGs were not routinely obtained; however, there were no cardiac events reported. Clinical details pertinent to CHS were frequently omitted, including length, amount and onset of cannabis use. In addition, symptom response to antiemetic agents was not recorded in all cases or as part of a

formal rating scale. However, we were able to determine a shorter length of stay and number of antiemetics used in those patients treated with droperidol.

Droperidol should be considered part of antiemetic treatment for CHS. From the limited data in our retrospective study, we suggest an initial dose of 1.25mg with further doses as required. This is a substantially lower dose used than in chemical sedation of agitated patients [13,14]. Clinician assessment of risk of QT prolongation, and a medication review is suggested prior to administration.

Conclusions

Use of droperidol for the management of CHS resulted in less use of antiemetics and reduced length of stay. Droperidol should be considered in the treatment of CHS. Further prospective studies should be undertaken to assess the efficacy of this intervention.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

AW has received a National Health and Medical Research Council Early Career Fellowship ID 1159907.

References

[1] Allen JH, de Moore GM, Heddle R, et al. Cannabinoid hyperemesis: cyclical hyperemesis in association with chronic cannabis abuse. Gut. 2004;53:1566–1570.
[2] Sorensen CJ, DeSanto K, Borgelt L, et al. Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment—a systematic review. J Med Toxicol. 2017;13:71–87.
[3] Blumentrath CG, Dohrmann B, Ewald N. Cannabinoid hyperemesis and the cyclic vomiting syndrome in adults: recognition, diagnosis, acute and long-term treatment. Ger Med Sci. 2017;15:Doc06.
[4] Richards JR, Gordon BK, Danielson AR, et al. Pharmacologic treatment of cannabinoid hyperemesis syndrome: a systematic review. Pharmacotherapy. 2017;37:725–734.
[5] Witsil JC, Mycyk MB. Haloperidol, a novel treatment for cannabinoid hyperemesis syndrome. Am J Ther. 2017;24:e64–e67.
[6] Richards JR, Lapoint JM, Burillo-Putze G. Cannabinoid hyperemesis syndrome: potential mechanisms for the benefit of capsaicin and hot water hydrotherapy in treatment. Clin Toxicol. 2018;56(1):15-24.
[7] Moon AM, Buckley SA, Mark NM. Successful Treatment of Cannabinoid Hyperemesis Syndrome with Topical Capsaicin. ACG Case Rep. 2018;5:e3.
[8] Hejazi RA, Reddymasu SC, Namin F, et al. Efficacy of tricyclic antidepressant therapy in adults with cyclic vomiting syndrome: a two-year follow-up study. J Clin Gastroenterol. 2010;44:18–21.
[9] Chang YH, Windish DM. Cannabinoid hyperemesis relieved by compulsive bathing. Mayo Clin Proc. 2009;84:76–78.
[10] Meltzer AC, Mazer-Amirshahi M. For adults with nausea and vomiting in the emergency department, what medications provide rapid relief? Ann Emerg Med. 2016;68:717–718.
[11] Apfel CC, Cakmakkaya OS, Frings G, et al. Droperidol has comparable clinical efficacy against both nausea and vomiting. Br J Anaesth. 2009;103:359–363.
[12] Richards JR, Schneir AB. Droperidol in the emergency department: is it safe? J Emerg Med. 2003;24:441–447.
[13] Calver L, Isbister GK. High dose droperidol and QT prolongation: analysis of continuous 12-lead recordings. Br J Clin Pharmacol. 2014;77:880–886.
[14] Calver L, Page CB, Downes MA, et al. The safety and effectiveness of droperidol for sedation of acute behavioral disturbance in the emergency department. Ann Emerg Med. 2015;66:230–238.e1.
[15] Simonetto DA, Oxentenko AS, Herman ML, et al. Cannabinoid hyperemesis: a case series of 98 patients. Mayo Clin Proc. 2012;87:114–119.
[16] United Nations Office on Drugs and Crime. World Drug Report 2016. New York; 2016.
[17] Australian Institute of Health and Welfare. National Drug Strategy Household Survey (NDSHS) 2016. In: Welfare AIoHa, editor. 2017.
[18] Iacopetti CL, Packer CD. Cannabinoid hyperemesis syndrome: a case report and review of pathophysiology. Clin Med Res. 2014;12:65–67.
[19] Sharkey KA, Wiley JW. The role of the endocannabinoid system in the brain–gut axis. Gastroenterology. 2016;151:252–266.
[20] Darmani NA. Cannabinoid-induced hyperemesis: a conundrum-from clinical recognition to basic science mechanisms. Pharmaceuticals (Basel). 2010;3:2163–2177.
[21] Smith HS, Cox LR, Smith BR. Dopamine receptor antagonists. Ann Palliat Med. 2012;1:137–142.
[22] Hamik A, Peroutka SJ. Differential interactions of traditional and novel antiemetics with dopamine D2 and 5-hydroxytryptamine3 receptors. Cancer Chemother Pharmacol. 1989;24:307–310.
[23] Hickey JL, Witsil JC, Mycyk MB. Haloperidol for treatment of cannabinoid hyperemesis syndrome. Am J Emerg Med. 2013;31:1003.e5–1003.e6.
[24] Jones JL, Abernathy KE. Successful treatment of suspected cannabinoid hyperemesis syndrome using haloperidol in the outpatient setting. Case Rep. 2016;2016:3614053.
[25] Calver L, Drinkwater V, Gupta R, et al. Droperidol v. haloperidol for sedation of aggressive behaviour in acute mental health: randomised controlled trial. Br J Psychiatry. 2015;206:223–228.
[26] Richards JR, Dutczak O. Propranolol treatment of cannabinoid hyperemesis syndrome: a case report. J Clin Psychopharmacol. 2017;37:482–484.
[27] Dezieck L, Hafez Z, Conicella A, et al. Resolution of cannabis hyperemesis syndrome with topical capsaicin in the emergency department: a case series. Clin Toxicol. 2017;55(8):908-913.
[28] Namin F, Patel J, Lin Z, et al. Clinical, psychiatric and manometric profile of cyclic vomiting syndrome in adults and response to tricyclic therapy. Neurogastroenterol Motil. 2007;19:196–202.
[29] Malik Z, Baik D, Schey R. The role of cannabinoids in regulation of nausea and vomiting, and visceral pain. Curr Gastroenterol Rep. 2015;17:429.