American Journal of Emergency Medicine 43 (2021) 35–40

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Topical capsaicin for the treatment of cannabinoid hyperemesis syndrome, a systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 26 December 2020
Received in revised form 3 January 2021
Accepted 3 January 2021

Keywords:
Capsaicin
Cannabinoid hyperemesis syndrome
Emergency department
Length of stay

ABSTRACT

Introduction: Cannabinoid hyperemesis syndrome (CHS) is a condition that is being recognized and treated more frequently in emergency departments (EDs) across the United States. Currently, ED providers rely on antiemetics, antipsychotics and benzodiazepines to alleviate the symptoms. Topical capsaicin, a transient receptor potential vanilloid 1 (TRPV1) agonist, has been proposed in recent years as a low-cost and effective alternative to the traditional antiemetic regimen when treating CHS. The aim of this systematic review and meta-analysis is to demonstrate the reliability and the gaps of what is known about this treatment modality.
Methods: Articles were extracted from PubMed, SCOPUS, and Google Scholar databases. Publication dates ranged from the inception of the databases to October 2020. Initial searches found 328 studies. After careful review and screening by two investigators, 7 studies met the inclusion criteria and were included for our meta-analysis. Variables that were evaluated included the prevalence of hospital admissions for patients treated with capsaicin, time to relief of symptoms after capsaicin administration, and ED length of stay (LOS). I-square and Q-statistic values were used to assess heterogeneity.
Results: Among the 7 studies, there was a total of 106 patients. Two studies reported time to resolution of symptoms following capsaicin administration and ED LOS. Means for these outcomes were 325 (95% CI 234–787) and 379 (95% CI 10–747) minutes respectively. I-square was 44%, and Q-statistic was 11 with 6 degrees of freedom, with a p-value of 0.1.
Discussion: With acceptable time to resolution of symptoms after topical administration and ED LOS, capsaicin appears to be an effective treatment option for symptomatic relief of CHS. Further randomized controlled trials should be conducted to examine if it is the more efficacious and efficient treatment for CHS across various care settings.

1. Introduction

Cannabis is considered the second most commonly used drug after alcohol in the United States [1]. As more states continue to legalize cannabis for medicinal use and decriminalize or legalize recreational use in the US, both the acute and long term sequalae of chronic frequent cannabis use will continue to manifest in a variety of ways, such as chronic bronchitis and respiratory infections [2]. Cannabis use is also associated with increased predicted risk of ischemic cerebrovascular accidents and heart failure [3]. Furthermore, psychological impacts associated with chronic usage include decreased motivation, psychotic disorders such as schizophrenia, and dependence with subsequent cannabis withdrawal syndrome [2]. In fact, 9% of cannabis users will go on to develop dependence [4].

In 2011, 456,000 visits to the emergency department (ED) were related to cannabis use in the United States [5]. In Colorado, a state that legalized recreational cannabis in 2014, one urban academic hospital noted a 3 fold increase in cannabis-related visits to the ED from 2012 to 2016 [6]. A consequence of prolonged cannabis usage, cannabinoid hyperemesis syndrome (CHS) is an emerging condition that ED's across the US are currently facing. Although the exact pathophysiology of CHS remains unclear, the condition is presumed to be a variant of cyclic vomiting syndrome [7]. It consists of the prodromal, hyperemetic, and recovery phases [7]. Prodromal symptoms include abdominal pain and morning nausea. The hyperemetic phase includes multiple sudden

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https://doi.org/10.1016/j.ajem.2021.01.004
0735-6757/

bouts of profuse vomiting. In the recovery phase, patients' eating pattern and weight gain return to normal [7]. Habboushe et al. suggested that 2.1 to 3.3 million cannabis users in the US may fit the definition for CHS[8]. Another retrospective study noted a statically significant increase in hospitalizations related to CHS between the years 2010 and 2014, with the average length of stay (LOS) of 3.2 days [9]. Such a LOS may incur significant economic impacts both in terms of the costs associated with utilization of healthcare resources and the loss in productivity and missed time from work and family for patients.

CHS is often a diagnosis of exclusion in which patients have extensive workups prior to proper diagnosis. Once diagnosed, the treatment of CHS is complex and may require multiple agents. The most effective treatment for CHS is cessation of cannabis; however, because of the long half-life, symptoms may persist for weeks after, and many patients do not want to discontinue using the drug. Although traditional antiemetics, such as ondansetron and prochlorperazine have shown effectiveness for treating emesis in general, these therapies have only shown limited success for CHS, especially when used alone [10]. A number of other agents, such as haloperidol and benzodiazepines, have shown to provide some benefit for CHS, as well [11]. Interestingly, hot showers or baths have also been noted to relieve symptoms of CHS by potentially counteracting transient receptor potential vanilloid 1 (TRPV1) desensitization and the hypothermic effect of cannabis on cannabinoid type 1 (CB1) receptors in the hypothalamus [12].

An alternative treatment modality to these agents includes topical capsaicin. Capsaicin is a TRPV1 agonist that has historically been indicated for neuropathic pain, such as postherpetic neuralgia and diabetic neuropathy [13]. Prior studies have shown cannabinoid induced desensitization of TRPV1 receptors [14]. Moreover, a large concentration of TRPV1 receptors are found in the area postrema, which is part of the chemoreceptor trigger zone of the central nervous system [15]. It is theorized that chronic cannabinoid usage may lead to emetogenic effects through the desensitization of these TRPV1 receptors [15]. As a result, TRPV1 agonists such as capsaicin may ameliorate the desensitization effects of cannabis on TRPV1 receptors, leading to its antiemetic properties in treating CHS. Furthermore, capsaicin's topical route of administration appears to be promising in treating patients with CHS, who may not tolerate oral formulations due to hyperemesis.

Prior case series and systematic reviews have examined the efficacy of capsaicin for treating CHS [16,17]. To date, however, no meta-analysis has been conducted to provide a comprehensive evaluation of the literature relating to the agent's effectiveness for CHS. This study aims to provide the most up-to-date meta-analysis on the subject, particularly pertaining to capsaicin's efficacy in the treatment of CHS and its impact on the utilization of hospital resources and CHS patients' length of stay.

2. Methods

2.1. Search strategy and selection criteria

We followed the 2015 Preferred Reporting Items for Systemic Review and Meta-analyses statement (PRISMA-P) [18]. We searched PubMed, SCOPUS, and Google Scholar databases from their conception up to October 2020. The search terms in PubMed are as following: ("Cannabis"[Mesh] OR "cannabis"[all fields] OR "Cannabinoids"[Mesh] OR "cannabinoids"[all fields] OR "Medical Marijuana"[Mesh] OR "Marijuana"[all fields] OR "Dronabinol"[Mesh] OR "Dronabinol"[all fields] OR "tetrahydrocannabinol"[all fields]) AND ("Capsaicin"[Mesh] OR "capsaicin"[all fields]) AND ("Vomiting"[Mesh] OR "Nausea"[Mesh] OR "vomiting"[all fields] OR "cyclic vomiting"[all fields] OR "emesis"[all fields]).

We included any studies involving adults who were diagnosed with CHS and were treated with any topical formulation of capsaicin. We included all prospective randomized control trials, quasi-randomized control trials, observational studies, and case series. We excluded non-English language studies, commentary, editorial or expert opinions. Two investigators reviewed each title and abstract before advancing the study to full text review. A third investigator adjudicated any disagreements. Similarly, each study needed 2 investigators' agreements during full text review to be included in the final analysis.

2.2. Outcome measures

Our primary outcome was the prevalence of hospital admissions among patients who were treated with capsaicin. Secondary outcomes included the time intervals from capsaicin administration and symptom relief and length of stay in the ED (ED LOS).

2.3. Quality assessment/heterogeneity

Two investigators assessed each study for their qualities. When there were disagreements, the investigators discussed among themselves to resolve the conflicts. We used the Newcastle-Ottawa Scale (NOS) for observational studies [19]. We used the modified NOS for case series [20] and the Cochrane's Risk of Bias Tools for any randomized controlled trials [21]. The NOS, which awards up to 9 points, assesses 3 domains in each study: (1) selection of the cohort, (2) comparability of the groups, and (3) quality of outcome. High-quality studies have a score ≥ 7, whereas moderate- and low-quality studies have scores of 4–6 and ≤ 3, respectively. Due to case series' limitation, the modified NOS only awards up to 5 points for the same domains. As a result, case series can only be of moderate quality. (Appendix 1A, 1B, 1C).

We used both I-square and Q-statistic values to assess heterogeneity. The I-square statistic provides information about the percentage of variance as difference in effect between studies. The Q-statistic tests the null hypothesis that all included studies would have similar effect size.

2.4. Data extraction

We extracted data into a standardized Excel spreadsheet (Microsoft Corp, Redmond, Washington, USA). The investigators collected the following: year of publication, study design (retrospective vs. prospective), study types (case series, cohort study), age, gender, number of patients receiving capsaicin, total dosage of capsaicin, number of patients being admitted to the hospital, time from capsaicin to symptom relief, ED LOS. For studies that did not explicitly report the time from capsaicin to resolution of symptoms, we substituted this missing time variable with the intervals from capsaicin administration to discharge from ED.

2.5. Statistical analysis

We used random-effects meta-analysis to measure the prevalence of hospital admission among patients who were treated with capsaicin for cannabinoid hyperemesis. Any two studies reporting similar outcomes were eligible to be included in the meta-analysis. To evaluate potential source of heterogeneity, we also performed subgroup analyses using moderator analyses. We defined the categorical variables for subgroups as: year of publication, study design (prospective vs retrospective), study type (case series vs cohort studies). Similarly, we performed univariate meta-regression to assess heterogeneity and potential association between independent variables and rates of hospital admissions. For these univariate meta-regressions, we used continuous moderator variables: percentage of male patients, patients' ages, percentage of patients who reported symptom relief by hot baths, percentage of patients who were given any antiemetic prior to capsaicin administration. Meta-analysis was performed with the software Comprehensive Meta-Analysis (CMA) (www.meta-analysis.com; Englewood, New Jersey, USA).

3. Results

Our electronic search identified 328 studies. We included seven studies in our final analysis after reviewing 32 full text articles (Fig. 1). Three of the studies were cohort studies while four were case series. Five studies were retrospective and two were prospective. There was a total of 106 patients being included in our patient population.

3.1. Study quality

Most of the studies included in our meta-analysis were of low quality. (Table 1).

3.2. Study outcome

3.2.1. Primary outcome: prevalence of hospital admission

The overall rate of admission in the pooled patient population was 0.15 (15%, 95% CI 6%–32%). (Fig. 2) The I-square statistic was 44%, which suggested that only 44% of the observed effect size was due to variance in true effects across studies. Similarly, the Q-statistic was 11 with 6 degrees of freedom, the *p*-value was 0.1, which suggested that the true effect sizes were not different across the studies in our meta-analysis. In other words, the level of heterogeneity regarding hospital admission in our pooled population was low.

3.2.2. Subgroup analyses

Moderator analyses with categorical variables suggested that studies that were published before 2015 had small I-square statistic. (Table 2) Additionally, prospective studies also had low I-square statistic. Univariate meta-regression suggested that higher percentage of male patients was negatively correlated with being admitted to the hospital (Correlation Coefficient − 4.04, *p*-value = 0.01). (Table 3) In other words, male patients were less likely to be admitted to hospital. Similarly, a higher percentage of patients receiving anti-emetic before capsaicin administration was negatively correlated with rates of hospital admission (Correlation Coefficient − 2.7, p-value 0.03). On the other hand, increasing age or the higher percentage of patients reporting symptom relief with hot bath, which is a hallmark diagnosis for cannabinoid hyperemesis, were not correlated with higher rate of hospital admission.

3.2.3. Other outcomes

Only two studies reported intervals from capsaicin to symptom relief. These studies also explicitly reported ED LOS. In the pooled meta-analysis of 2 studies, the mean intervals from capsaicin administration and symptom relief was 325 min (95% CI 234–787). The mean ED LOS (minutes) was 379 (95% CI 10–747). (Table 4).

4. Discussion

Our meta-analysis of prevalence of hospital admission showed a moderate level of heterogeneity (I-square = 44%). We further identified

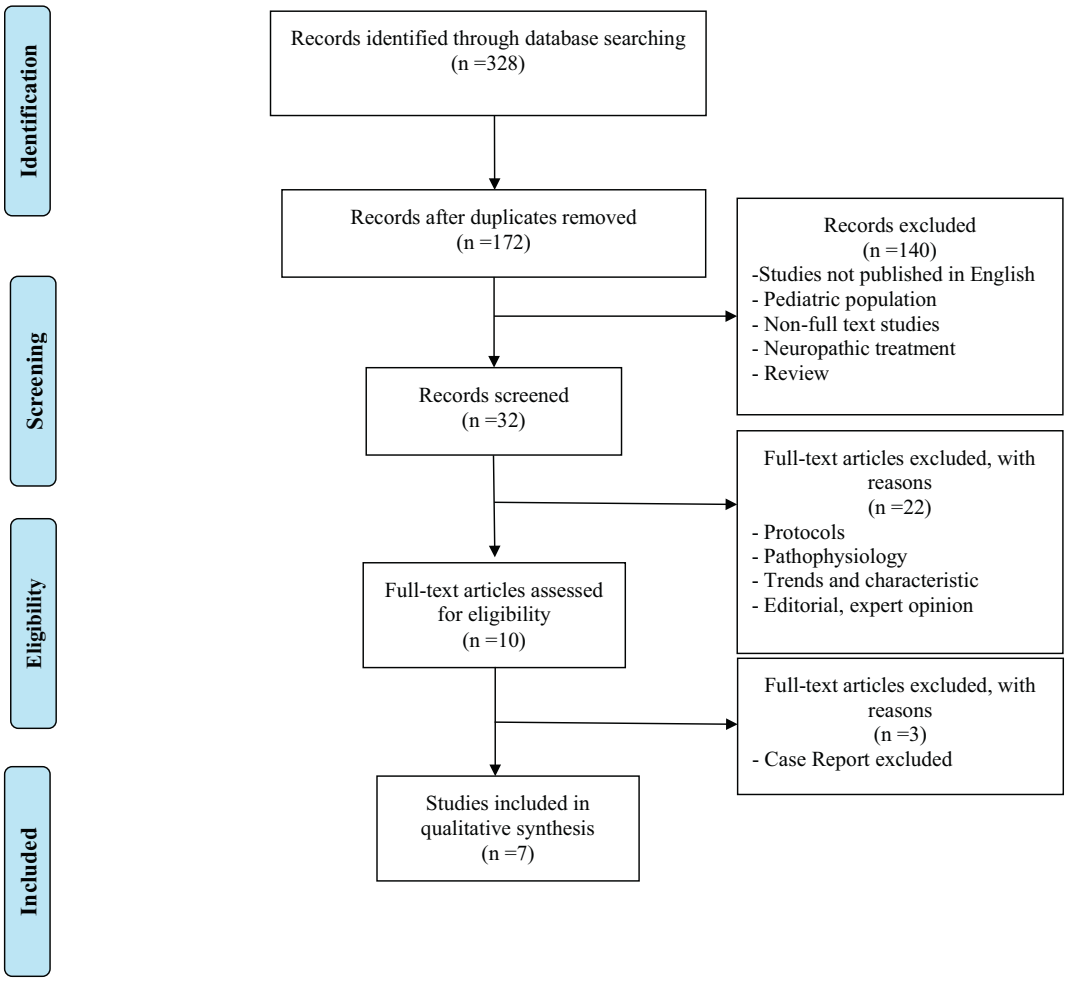

Fig. 1. PRISMA flow chart.

Table 1
Characteristics of studies included in the meta-analysis

Study Name	Hospital Admission, N	Patients Received Capsaicin, N	Study Design	Study Type	Male (%)	Patient Age (years, mean)	Relief by Hot Bath (%)	Timing of Dose	Site of Topical Capsaicin Application	Time to Symptom Relief (minutes, SD)	ED LOS (minutes, SD)
2014 Lapoint [22]	0	2	Prospective	Case Series	0.5	24	1	QDaily	NR	NR	NR
2014 Lapoint [23]	0	5	Retrospective	Case Series	0.8	24	0.6	QDaily	Abdomen	NR	NR
2017 Dezieck [16]	0	13	Retrospective	Case Series	0.7	33	0.2	QDaily	Abdomen, Back, Chest	565 (635)	570 (295)
2017 Hafez [30]	0	4	Retrospective	Case Series	0.8	NR	NR	QDaily	Abdomen	NR	NR
2017 McCloskey [26]	8	22	Retrospective	Cohort	0.2	30	NR	NR	NR	NR	NR
2020 Dean [24]	4	17	Prospective	Cohort	0.4	35	NR	QDaily	Anterior Abdomen	NR	NR
2020 Wagner [25]	0	43	Retrospective	Cohort	0.5	32	0.4	NR	Abdomen, Chest	97 (31)	194 (38)
Total	12	106									

NR; Not reported, ED; emergency departed, LOS; length of stay.

sources of potential heterogeneity. Studies that were published before 2015 were case series with low heterogeneity. This was likely because they also reported smaller percentages of hospital admission rate. Similarly, prospective studies in our meta-analysis were associated with lower heterogeneity than retrospective studies, as prospective studies allow authors to have more control over their patient enrollment and the process of data collection. This may suggest that researchers should consider designing future studies on CHS in with a prospective design, as opposed to case studies or retrospective.

The current meta-analysis sought to evaluate capsaicin's efficacy in the treatment of CHS and its impact on the utilization of hospital resources and CHS patients' LOS in the ED. As of December 2020, there were only 7 studies that examined the use of capsaicin in the treatment of CHS. Four were case series and 3 were cohort studies. Across the 7 studies examined, there was at total population of 106 patients that were diagnosed with CHS in the ED. Of note, it appears to be a pathology targeting younger adults. Patients with CHS varied from 24 to 35 years old [16,22-26]. In addition, 4 of the 7 studies reported patients that found CHS symptom relief via hot bath [16,22,23,25]. Thus, CHS appears to be a very real diagnosis with predictable symptomologies that requires a tested and proven treatment.

Although some treatments for CHS exist, these remedies may pose risks to the patient. For example, currently used antipsychotics, such as haloperidol and droperidol may lead to excessive sedation and prolong the QT interval. Moreover, these treatments' specific mechanisms for alleviating CHS symptoms are not entirely understood. One of the benefits of capsaicin is its pharmacokinetics, well tolerated nature, topical route of administration, and low cost. Capsaicin is fat soluble, and therefore is absorbed rapidly through the skin. Its half-life is 24 h. Capsaicin is metabolized in the liver via the cytochrome *p*450 enzymes and excreted renally [27]. It has limited adverse effects including local erythema and hyperthermia [28]. Due to this limited adverse effect profile, capsaicin does not require extensive monitoring when compared to other treatment modalities for CHS such as antipsychotics, benzodiazepines, or traditional antiemetics. By managing dosages, clinicians are able to limit the potential, albeit limited, adverse effects of capsaicin. Capsaicin dosages may vary from 0.025% to 0.075%. Currently, low dose capsaicin (0.075%) is used in the management of neuropathic pain [29]. However, there is no consensus on the standard capsaicin dosage for the treatment of CHS as of yet. As a result, the various studies analyzed in the current meta-analysis varied in capsaicin dosages from 0.025% to 0.1% topical cream [16,22-24,30]. Future studies should examine various dosages of capsaicin and their efficacies on symptomatic relief of CHS. Self-administered treatment at home should also be examined in the future as a possible way to avoid visits to the ED.

As the current pathophysiology of CHS is still being understood, symptomatic treatment of the syndrome without causing additional harm is the primary goal of emergency care. Once symptoms are managed, patients are able to leave the ED, creating space for other patients with various conditions to be treated. A forest plot compiled for the seven studies' incidence of hospital admissions among CHS patients treated with capsaicin found favorable outcomes with values to the

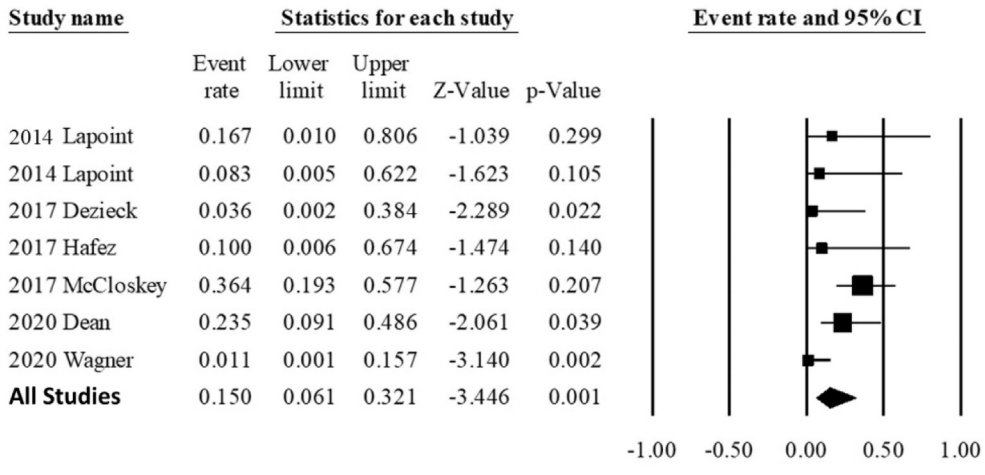

Fig. 2. Forest plot for incidence of hospital admission.

Table 2
Summary of moderator analyses by subgroups

Moderator Category	Moderator Variables	Study Number	Hospital Admission	95%CI	*P*	Q-value	df (Q)	*P*	I^2	Between group comparison
Year of publication	<2015	2	0.12	0.01–0.7	0.15	0.14	1	0.71	0	0.89
	2015–2017	3	0.16	0.03–0.6	0.09	4.1	2	0.13	51	
	2018–2020	2	0.09	0.01–0.47	0.04	4.5	1	0.032	78	
Study Design	Prospective	2	0.21	0.03–0.7	0.23	0.07	1	0.79	0	0.5
	Retrospective	5	0.1	0.02–0.3	0.004	11	4	0.032	62	
Study Type	Case Series	4	0.09	0.02–0.3	0.003	0.7	3	0.89	0	0.26
	Cohort	3	0.2	0.08–0.5	0.02	7	2	0.03	72	

Table 3
Meta-regression, using continuous variables, for incidence of hospital admissions among patients who were diagnosed with cannabinoid hyperemesis and was treated with capsaicin

Covariate	NO. of Study	Corr. Coeff	95%CI	*P*	R^2	I^2
Percentage of male patients	7	−4.04	−7.2, −0.9	0.01	0.9	44
Age - each year	6	−0.01	−0.33, 0.31	0.97	0	51
Percentage of relief by hot bath	4	2.8	−2.2, 7.8	0.27	0	0
Percentage of patients receiving antiemetic prior to capsaicin	4	−2.7	−5.1, −0.23	0.03	0.9	48

Table 4
Results from random-effects meta-analysis estimating ED length of stay (LOS) and time to symptoms relief from capsaicin administration

Variables	Study Name	Mean (minutes)	Standard Error	95% CI	Q-value	df(Q)	P-value	I-squared
Symptom Relief					7	1	0.008	85
	2017 Dezieck [16]	565	176	219–910				
	2020 Wagner [25]	97	5	87–106				
Pooled Results 325, 234, 130-787								
ED LOS					4.5	1	0.03	78
	2017 Dezieck [16]	570	176	225–915				
	2020 Wagner [25]	194	5	184–204				
	Pooled Results	379	187	10–747				

ED: emergency department; LOS: length of stay.

right of the line of null effect. In addition, two of the studies included in the meta-analysis examined time to resolution of symptoms after the application of capsaicin. The mean time to resolution of symptoms was acceptable at 325 min and the mean ED LOS was 379 min, which may be attributed to the drug's rapid onset of action [16,25,30]. If patients' symptoms are managed and resolved appropriately in the ED, they may be able to be discharged in an acceptable time frame. It is important that EDs ensure capsaicin is properly stocked and available to avoid delays.

Despite the availability of various treatment modalities, the most effective treatment for CHS is still the cessation of cannabis use, and this should be reiterated to patients accordingly. Given capsaicin's long half-life in peripheral tissues, resolution to symptom relief still takes time after application. Thus, capsaicin could possibly be used as a bridge therapy for cannabis cessation. As overcrowding in the ED continues to be an ongoing challenge, the previous findings still highlight that prompt symptomatic treatment with capsaicin and subsequent discharge of patients with CHS may help alleviate the strain on hospital beds and ED resources.

4.1. Limitations

The current meta-analysis examined a small number of studies. Only 7 studies were analyzed, which led to a small sample size of 106 patients. In addition, no large randomized controlled trials were available and included. Among the 7 studies, there were no standardized dosages of capsaicin. Moreover, the site of topical capsaicin application and ribbon size were not completely uniform across the 7 studies. Lastly, only Dezieck 2017, mentioned exact antiemetic regiments and IV hydration therapy, with dosages, used other than capsaicin. As a result, we were unable to run an analysis comparing capsaicin to other antiemetic treatment modalities. Future studies should include blinded randomized controlled trials with larger sample sizes to further analyze the effect of capsaicin when compared to standard doses of specific antiemetics for the treatment of CHS.

5. Conclusion

As more states in the US legalize or decriminalize the public's use of cannabis (medical or recreational), ED's will be faced with treating the effects of chronic cannabis use such as CHS. Current treatments with various side effect profiles exist for CHS, but their mechanisms of alleviating CHS symptoms are not well understood. An emerging treatment for CHS with low adverse effects, topical capsaicin appears to be an effective alternative treatment for CHS with acceptable time to symptom relief and ED LOS. Further studies should be conducted to examine whether capsaicin may be the more advantageous treatment for CHS in the ED and possibly other care settings.

Funding

This is a non-funded study, with no compensation or honoraria for conducting the study.

Declaration of Competing Interest

The authors do not have a financial interest or relationship to disclose regarding this research project.

Appendix A. Appendix 1A. Study quality assessment of observational studies included in the meta-analysis using the Newcastle-Ottawa scale

Study (Year)	Newcastle-Ottawa Quality Assessment Scale				
	Selection (4)	Comparability (2)	Outcome (3)	Total	Grade
2017 McCloskey	3	1	3	7	High
2020 Wagner	3	1	3	7	High

Appendix B. Appendix 1B. Study quality assessment of observational studies included in the meta-analysis using the modified Newcastle-Ottawa scale (modified NOS)

Study (Year)	Newcastle-Ottawa Quality Assessment Scale					
	Selection (1)	Comparability (3)		Outcome (1)	Total	Grade
		Ascertainment (2)	Causality (1)	Reporting (1)		
2014 Lapoint	0	2	1	0	3	Low
2014 Lapoint	0	2	1	1	4	Moderate
2017 Dezieck	0	2	1	1	5	Moderate
2017 Hafez	0	2	0	1	3	Low

Appendix C. Appendix 1C. Study quality assessment of randomized trial using the cochrane collaboration's risk of bias tool 2

Study (year)	Risk of bias arising from the randomization process	Risk of bias due to deviations from the intended interventions	Missing outcome data	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result
2020 Dean	Some concern	Some concern	Low	Some concern	Low

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