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Cannabinoids in the Management of Acute Pain: A Systematic Review and Meta-analysis

Aaron Gazendam,[1] Nicholas Nucci,[2] Kyle Gouveia,[3] Hassaan Abdel Khalik,[3] Luc Rubinger,[1] and Herman Johal[1,4,*]

Abstract

Objective: To synthesize the best evidence surrounding the efficacy of cannabinoids for acute pain in the clinical setting based on subjective pain scores and observed adverse effects.

Design: Systematic review with meta-analysis.

Data Sources: PubMed, Embase, Cochrane Databases, and Google Scholar.

Eligibility Criteria: English-language randomized-controlled clinical trials comparing cannabinoids with placebo in patients with acute pain.

Data Extraction and Synthesis: Study quality was assessed using the Cochrane risk of bias tool. All stages were conducted independently by a team of three reviewers. Data were pooled through meta-analysis and stratified by route of administration.

Primary Outcomes and Measures: Patient-reported pain and adverse events (AEs).

Results: Six trials (678 participants) were included examining oral (5 trials) and intramuscular (1 trial) cannabinoids. Overall, there was a small but statistically significant treatment effect favoring the use of cannabinoids over placebo (–0.90, 95% confidence interval [CI] –1.69 to –0.1, $i^2 = 65\%$, $p = 0.03$). When stratified by route of administration, intramuscular cannabinoids were found to have a significant reduction in pain relative to placebo (–2.98, 95% CI –4.09 to –1.87, $i^2 = 0\%$, $p < 0.0001$). No difference in effect was observed between oral cannabinoids and placebo (–0.21, 95% CI –0.64 to 0.22, $i^2 = 3\%$, $p = 0.34$). Serious AEs were rare, and similar across the cannabinoid (14/374, 3.7%) and placebo groups (8/304, 2.6%).

Conclusions: There is low-quality evidence indicating that cannabinoids may be a safe alternative for a small but significant reduction in subjective pain score when treating acute pain, with intramuscular administration resulting in a greater reduction relative to oral. Higher quality, long-term randomized-controlled trials examining whether there may be a role for cannabinoids in treating acute pain are required.

Keywords: acute pain; cannabinoids; meta-analysis; systematic review; surgical pain

Introduction

With the recent legalization of cannabis in Canada, cannabinoids have been gaining mainstream acceptance for potential efficacy in pain management. Typically, the term "cannabinoids" refers to a heterogeneous group of chemicals that are both naturally occurring and can be synthetically derived. There has been a growing dialogue about cannabinoids and their role as an effective tool in the management of pain.[1–4] Based on self-reported data by cannabis users, cannabinoids provide relief similar to opioids and decrease opioid consumption.[5] Furthermore, there is a growing body of evidence demonstrating the efficacy of cannabinoids for chronic pain conditions.[6]

There is a paucity of evidence from the scientific literature to support the efficacy of cannabinoid medications in treating acute pain in the clinical setting. To our knowledge, there is only one systematic review

[1]Center for Evidence-Based Orthopaedics, Division of Orthopaedic Surgery, Department of Surgery, McMaster University, Hamilton, Canada.
[2]Northern Ontario School of Medicine, Lakehead University, Thunder Bay, Canada.
[3]Michael G. DeGroote School of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Canada.
[4]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Canada.

*Address correspondence to: Herman Johal, MD, MPH, PhD(c), FRCSC, Center for Evidence-Based Orthopaedics, Division of Orthopaedic Surgery, Department of Surgery, McMaster University, 293 Wellington Street North, Suite 110, Hamilton, ON L8L 8E7, Canada, E-mail: johalh3@mcmaster.ca

and no meta-analyses investigating the effects of cannabinoids in the clinical setting for acute pain.[7] Stevens and Higgins concluded that, "on the basis of the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain." However, it seems that the conclusions may have been overstated given the limited number of studies included in their review and lack of meta-analysis performed. A meta-analysis offers a consolidated and quantitative review, allowing for a more precise estimate of the effect of the treatment. With that said, our goal was to reassess this subject using systematic review and meta-analysis methodology.

The aim of this systematic review and meta-analysis was to synthesize the best evidence surrounding the efficacy of cannabinoids for acute pain using subjective pain scores, and observed adverse effects.

Methods

We conducted a systematic review and meta-analysis on the efficacy and adverse events (AEs) associated with using cannabinoids for the treatment of acute pain. This review adhered to the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Cochrane Collaboration guidelines for the performance and reporting of systematic reviews and meta-analysis.[8,9]

Literature search

A systematic literature search of PubMed, Embase, Cochrane Databases, and Google Scholar from inception to January 21, 2019, was performed. We utilized a structured search strategy with keywords related to "cannabinoids," "cannabis" or "marijuana" AND "acute pain" or "postoperative pain," utilizing MeSH terms where possible. A manual search of related citations was also performed.

Study eligibility

Peer-reviewed randomized-controlled clinical trials comparing cannabinoids with placebo in patients with acute pain were eligible for inclusion. We defined acute pain as a distressing experience secondary to actual or potential tissue damage lasting <3 months. We excluded any studies where the duration of pain was >3 months, or the condition being studied was associated with chronic pain (i.e., diabetic neuropathy, multiple sclerosis). Although there are a number of human experimental acute pain studies, we excluded them for several reasons.[10–24] First, there are significant differences in trial design and patient population compared with clinical trials. As well, cannabinoid impact on experimental acute pain was recently explored as the primary topic of a well-done systematic review and meta-analysis.[25] Pain outcomes of interest consisted of validated subjective pain scores, including the visual analog scale (VAS), McGill Pain Questionnaire, or the numeric rating scale (NRS).

Exclusion criteria included the following: (1) trials focusing on chronic pain or conditions associated with chronic pain; (2) nonhuman trials or nonclinical trials; (3) abstracts or posters from conferences; and (4) trials with incomplete or absent pain outcome data. Titles and abstracts were then screened for eligibility by two independent reviewers (N.N., K.G.) utilizing the Rayyan QCRI software.[26] Any disagreements on eligibility led to inclusion of the study for full-text review by the primary author (A.G.).

Data extraction

Two investigators (N.N., K.G.) collected all relevant information regarding study and patient population, including the study design, patient demographic information, and sample size. Intervention details abstracted included the type, dosage, and route of cannabinoid utilized. Outcomes collected included the type of pain scale used, as well as the mean score and standard deviation (SD) at baseline, and change from baseline or postoperative pain score and SD when available. The following decisions were made regarding the calculation of effect size for the data. When studies utilized multiple pain scores (i.e., on movement vs. rest), a mean pooled effect size was computed for the overall meta-analysis. When multiple cannabinoid types or doses were examined within a single study, these were handled as individual comparisons and the placebo group was divided by the number of comparators. When pain measurements were taken at multiple time points following the pain stimulus, the raw pain score from the largest single time point contrast between the active and placebo conditions was taken (peak effect). If raw pain scores at specific time points were unavailable, we utilized the average pain scores over the study duration, if provided. Pain scores were recorded as mean and SD when available. When not reported, SD was calculated from the other available data in the article. For data presented exclusively in graph format, we utilized a validated data extraction software (WebPlotDigitizer, version 4.1; Ankit Rohatgi) to

record outcomes. AEs were recorded by type and overall incidence for each study and classified as serious or nonserious if reported.

Study appraisal

Three independent reviewers (A.G., N.N., K.G.) assessed the methodological quality and study validity utilizing the Cochrane risk of bias tool through Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark) software.[27] Bias was assessed utilizing the following domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Risk of bias for each of these domains was determined to be low risk, high risk, or unclear risk. The included studies were then given a grade of high risk, moderate risk, or low risk.

The quality of the evidence and the confidence in the estimate of the effect across outcomes were assessed utilizing the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[28,29] Accordingly, data from randomized-controlled trials are considered high-quality evidence, but the quality can be rated down due to risk of bias, imprecision, indirectness, imprecision, and publication bias.[29]

Data analysis

Pain scores were reported as the mean pain scores following the pain stimulus along with 95% confidence intervals (CIs). Our index instrument of choice was the VAS, which utilizes a scale from 0 to 10, with higher scores representing increased pain. All subjective pain scores were transformed to match our index instrument leading to mean pain scores between 0 and 10. The mean pain scores were analyzed through a random effects model based on the inverse variance method. Total and serious AEs were pooled and odds ratios (ORs) were calculated between the two groups.

Heterogeneity was quantified utilizing the I^2 statistic, which estimates the proportion of total variability among studies due to heterogeneity as opposed to chance alone.[30,31] The I^2 values were then interpreted according to the Cochrane Handbook; I^2 0–40% representing low heterogeneity, I^2 30–60% representing moderate heterogeneity, I^2 50–90% representing substantial heterogeneity, and I^2 75–100% representing considerable heterogeneity.[27] We planned to stratify our analysis by type of cannabinoid and route of administration to explore results with moderate or substantial heterogeneity. Forest plots were visually inspected to assess for publication bias.

Results

Our search identified 1257 citations after exclusion of duplicates. Twenty-five articles underwent full-text review, and six articles were assessed to be eligible after reviewing the inclusion and exclusion criteria (Fig. 1).[32–37] Publication years ranged from 1981 to 2017.

Study characteristics

Relevant study characteristics and treatment information are provided in Table 1. The study sample ranged from 30 to 340 participants, for a total of 678 participants. Of the six studies included, two were conducted in the United States, two in Canada, one in the United Kingdom, and one multinational trial completed in the United Kingdom, Italy, and Germany.

The six included studies were randomized, placebo-controlled, parallel-group trials ($n = 678$). Three studies examined multiple cannabinoid doses, leading to a total of 11 cannabinoid intervention versus placebo comparisons.[32–37]

Table 2 summarizes the route of administration utilized for the included studies. Oral cannabinoids were examined in 5/6 (83%) of the included studies. Three of these trials examined synthetic Δ^9-tetrahydrocannabinol (THC) in the form of nabilone (2) and AZD1940 (1).[32,35,36] One study examined the effects of a synthetic CB2-selective agonist, GW842166.[37] One study examined a plant-based cannabis oil extract in capsule form.[33] Finally, one study analyzed the effects of levonantradol, a synthetic liquid THC, administered intramuscularly.[34]

Risk of bias

Reviewers assessed the risk of bias utilizing the Cochrane risk of bias tool for all included studies (Fig. 2). Two studies were found to be at a low risk of bias, three studies were found to be at moderate risk of bias, and one was found to be at high risk of bias.

Reviewers also rated the quality of evidence for included trials utilizing the GRADE approach. The evidence for pain reduction in the included trials was downgraded to "low" given the serious risk of bias and inconsistency noted (Table 3).

Pain outcomes

Meta-analysis results for pain scores are summarized in Table 4. When reviewing all 11 comparisons (678 participants) of the included studies (6), there was a statistically significant treatment effect for the use of cannabinoids (–0.90, 95% CI –1.69 to –0.10, $i^2 = 65\%$,

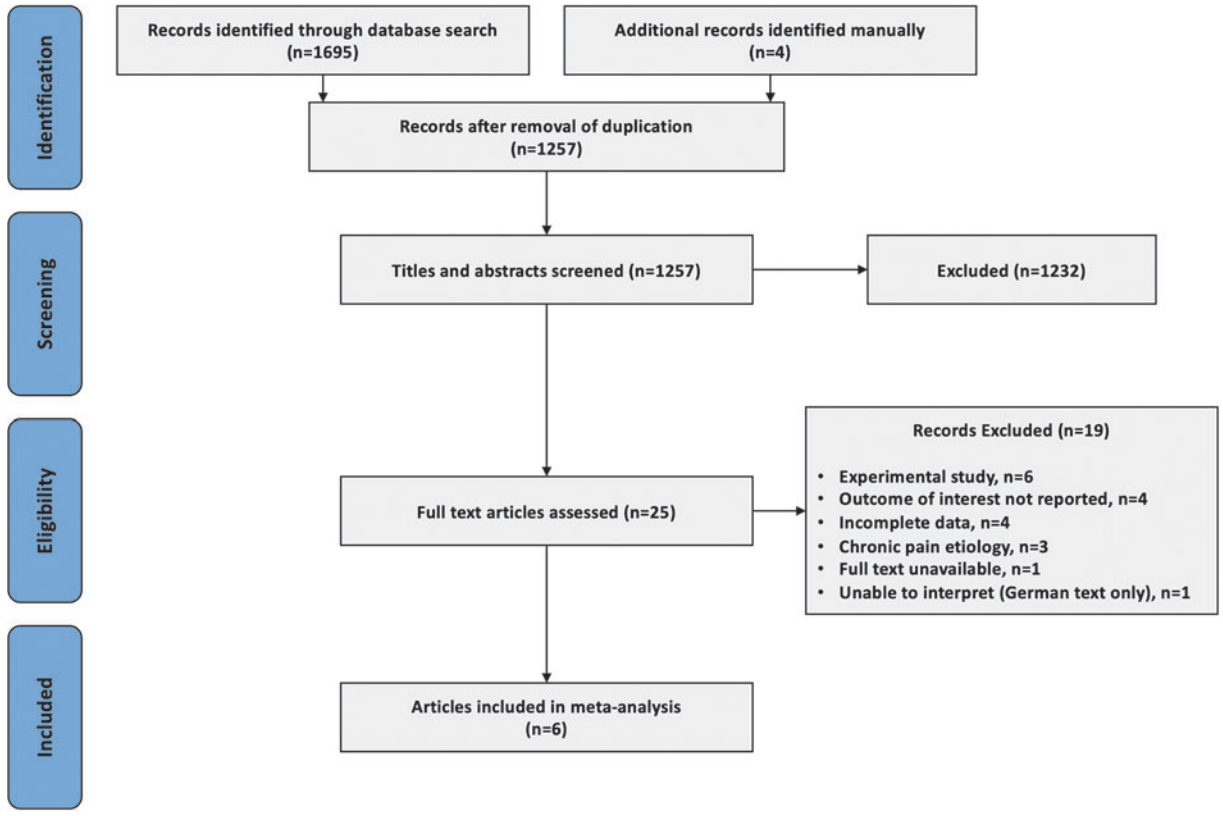

FIG. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

$p = 0.002$). There was significant heterogeneity within this analysis due to one study with a large treatment effect, which utilized a different route of administration (intramuscular vs. oral) when compared with the rest of the clinical trials included.[34]

Given this marked difference, we stratified results based on route of administration. There were five studies (7 comparisons and 622 patients) that reported on oral cannabinoids and found no significant treatment effect when compared with placebo (–0.21, 95% CI –0.64 to 0.22, $i^2 = 3\%$, $p = 0.41$. There was one trial (4 comparisons, 56 participants) that evaluated intramuscular administration of cannabinoids and found a significant treatment effect favoring the use of cannabinoids over placebo (–2.98, 95% CI –4.09 to –1.87, $i^2 = 39\%$, $p < 0.0001$).

Table 1. Studies Included in the Meta-Analysis

Study	Total no. of patients (males)	Pain stimulus	Type and dosage of cannabinoid used	Route of administration	Length of follow-up
Beaulieu[32]	30 (3)	Surgery (gynecologic [46%], orthopedic [44%], other [10%])	Nabilone (1 or 2 mg)	Oral	24 h
Buggy et al.[33]	40 (0)	Surgery (elective total abdominal hysterectomy)	THC (5 mg)	Oral	6 h
Jain et al.[34]	56 (51)	Acute postoperative, trauma, or fracture pain	Levonantradol (1.5, 2, 2.5, or 3 mg)	Intramuscular	6 h
Kalliomaki et al.[35]	120 (120)	Lower third molar surgical removal	AZD1940 (800 μg)	Oral	8 h
Levin et al.[36]	340 (0)	Elective surgery	Nabilone (0.5 mg)	Oral	120 min
Ostenfeld et al.[37]	92 (49)	Third molar tooth extraction	GW842166 (100 or 800 mg)	Oral	10 h

THC, Δ^9-tetrahydrocannabinol.

Table 2. Route of Cannabinoid Administration

Cannabinoid	No. of studies
Oral synthetic THC	3 (Refs.[32,35,36])
Nabilone	2 (Refs.[32,36])
AZD1940	1 (Ref.[35])
Oral synthetic CB2-selective agonist (GW842166)	1 (Ref.[37])
Oral cannabis oil extract in capsule	1 (Ref.[33])
Intramuscular synthetic THC (levonantradol)	1 (Ref.[34])

Adverse events

All six studies reported AEs experienced in both the placebo and cannabinoid arms. Examining these studies, there was a total of 437 events in 374 patients (1.17 AE/patient) in the cannabinoid group and 309 side effects in 304 patients in the control group (1.02 AE/patient). In the cannabinoid group, there was a significantly higher incidence of dizziness and hypotension (Table 5).

There was no significant difference in serious adverse effects (OR 1.44 [0.60–3.48]).

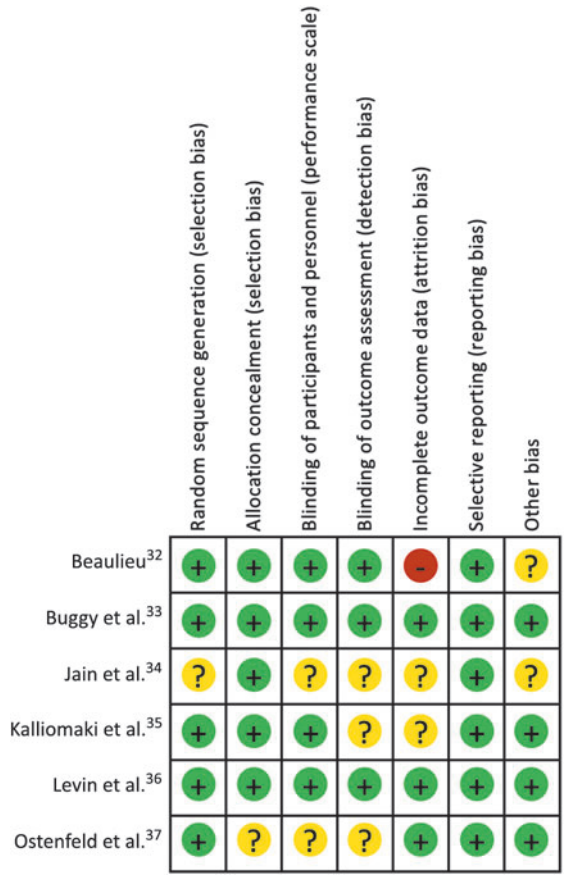

FIG. 2. Risk of bias summary.

Overall, 22/678 (3.2%) of the patient encounters included in the meta-analysis had serious adverse effects. There were 14/374 (3.7%) serious AEs in the cannabinoid arms and 8/304 (2.6%) in the control group. Serious adverse effects in the treatment groups consisted of nausea (5), headache (4), sedation (3), dysphagia (1), and pharyngolaryngeal pain (1). Side effects in the placebo group consisted of headache (3), nausea (2), myalgia (1), pain (1), and swelling (1).

Discussion

Systematic review and meta-analysis of the available literature revealed that there was a small but significant reduction in subjective pain scores when compared with placebo in patients experiencing acute pain.

There was a significant difference in the effect size between oral and nonoral routes of administration. This indicated that there may be differences in efficacy for acute pain based on route of administration. Varying results based on route of administration have been well documented in the chronic pain population.[3] These differences are not surprising given that pharmacokinetics varies as a function of the route of absorption.[38] Specifically, oral absorption of cannabinoids is slow and variable with maximal plasma concentrations occurring 60–120 min postingestion but can be delayed upward of 6 h.[38] Cannabinoids are subjective to significant first-pass liver metabolism, which further reduces the bioavailability.[39] Utilizing transdermal, inhaled, or oral transmucosal formulations allows for direct plasma uptake and avoidance of the first-pass effect. Inhaled cannabinoids reach peak effect in 10 min and plasma levels are maintained for several hours.[40]

There was a high rate of AEs in both groups. This is not surprising given that all subjects involved underwent a pain stimulus making it difficult to attribute side effects to the cannabinoids versus the pain stimulus or a combination of the two. However, there was a significant increase in nonserious AEs in the cannabinoid group. There was no evidence of increase in serious AEs, suggesting an overall favorable safety profile for cannabinoids in this population.

Given the well-documented harms of prescribing opioids, patients and providers alike are searching for safer nonopioid analgesics for acute pain.[41] With the recent legalization of recreational cannabis in Canada and the legalization of medical cannabis in 33 U.S. states and Washington, District of Columbia, as of January 2020, there is significant interest surrounding the potential benefits and harms of cannabinoids as

Table 3. Grade Evidence

Subjects (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Quality
678 (6)	Serious	Serious	No serious indirectness	No serious imprecision	None	Low

an analgesic agent. A recently published retrospective analysis of postoperative cannabinoid use supports our data suggesting that there may be a role for cannabinoids in the management of acute pain.[42] Hickernell et al. found that postoperative dronabinol led to significantly reduced length of stay and trended toward lower opioid consumption in primary total joint arthroplasty patients.[42] Interestingly, they found that VAS pain scores remained the same between the two groups, indicating that we may need different outcome measures to better understand how cannabinoids effect acute pain. Holdcroft et al. utilized a dose-escalation protocol for postoperative oral THC, and demonstrated significantly improved subjective pain scores and a reduced need for rescue analgesia in postoperative patients.[43] However, other level III evidence suggested that utilization of cannabinoids perioperatively leads to worse pain scores postoperatively. Prabhu performed a retrospective review of patients undergoing major orthopedic surgery[44] and found that patients on preoperative cannabinoids had higher postoperative pain scores when compared with a propensity-matched cohort that did not utilize cannabinoids.

Shi[45] evaluated the State Inpatient Databases for both cannabis- and opioid-related hospitalizations before and after legalization of medical cannabis. Regardless of legalization status, hospitalizations related to both cannabis and opioids increased significantly over the time period analyzed (1997–2004). However, states with legalization demonstrated that in the years following legalization there was a 23% reduction in hospitalizations related to opioid dependence and a 13% reduction in opioid-related overdoses.[45] Legalization had no association with cannabis-related hospitalizations.

Our understanding of the antinociceptive effects of cannabinoids is evolving with the rapidly growing body of preclinical and clinical data. THC acts on various components of the endogenous cannabinoid system (ECS) to exert anti-inflammatory and antinociceptive effects.[46–48] THC interacts with the CB1 and CB2 receptors in the ECS and has been found to downregulate proinflammatory markers in preclinical trials.[49,50] Several animal model trials have found that both agonists of the CB1 and CB2 receptors play a role in acute antinociception.[51] Cannabidiol (CBD), the major nonpsychoactive cannabis compound, may elicit analgesic effects through different cellular pathways.[52,53] CBD has been found to be an agonist to several cell surface receptors associated with anti-inflammatory and analgesic pathways.[53–55]

Interestingly, of the studies included in this review, all of them examined the effects of *trans*-THC predominately or exclusively. However, there is a growing body of literature that suggests that CBD has analgesic and anti-inflammatory pathways with a more favorable side effect profile.[56] There have been several animal studies showing reductions in pain and inflammation in osteoarthritis and neuropathic pain models.[53,57,58] Given the promising animal studies and favorable safety profile, further human trials examining the efficacy of CBD for the management of acute pain and inflammation are warranted.

Strengths and limitations

This study was an exhaustive review of the literature and includes recent studies that have not previously

Table 4. Pain Scores

Route	No. of Studies	No. of Patients	Mean difference [95% CI]
All	6	678	−0.90 [−1.69, −0.10]
Oral	5	622	−0.21 [−0.64, 0.22]
Intramuscular	1	56	−2.98 [−4.09, −1.87]

CI, confidence interval; IV, inverse variance.

Table 5. Common and Serious Adverse Events

Event	Cannabis	Placebo	OR (CI)	*p*
Nausea	102	80	1.05 (0.75–1.48)	0.78
Sedation	66	61	0.85 (0.58–1.26)	0.42
Dizziness	58	26	1.96 (1.20–3.20)	0.007*
Dry mouth	49	49	0.78 (0.51–1.20)	0.27
Headache	41	31	1.08 (0.66–1.78)	0.75
Increased awareness/ psychological high	9	2	3.72 (0.80–17.40)	0.09
Hypotension	13	3	3.61 (1.02–12.80)	0.047*
Red eyes	1	0	2.44 (0.10–60.10)	0.59
Malaise/fatigue	10	8	1.02 (0.40–2.60)	0.97
Vomiting	9	3	2.47 (0.66–9.22)	0.17
Serious adverse reaction	14	8	1.44 (0.60–3.48)	0.42

*Indicates statistical significance between groups ($p < 0.05$).

been assessed and represents the most current literature on the evidence for use of cannabinoids for acute pain. We followed conduct and reporting guidelines for the systematic reviews and meta-analysis, including duplicate assessment of study eligibility and a risk of bias evaluation. To our knowledge, this is the first study to perform a meta-analysis on cannabinoids in acute pain in clinical trials.

This study has several limitations. Our review was limited by the overall quality and quantity of the available trials, as well as inconsistency in the reporting of outcome and AE reporting. The majority of studies included in this review were of relatively small sample size and largely underpowered. There was significant heterogeneity in the studies included. Variation existed in the type, dosage, timing, duration, and route of cannabinoid used.

Given the current available evidence, there is low-quality evidence that cannabinoids have a small, but statistically significant reduction in acute pain in the clinical setting. At the time of this publication, there remain few randomized-controlled trials for the use of cannabinoids for acute pain. Our review highlights the need for further research to investigate the optimal route and composition of cannabinoids in the acute pain setting, including large, high-quality randomized clinical trials to better understand the risks and benefits of cannabinoids in this patient population.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AEs = adverse events
CBD = cannabidiol
CI = confidence interval
ECS = endogenous cannabinoid system
GRADE = Grading of Recommendations Assessment, Development and Evaluation
IV = inverse variance
NRS = numeric rating scale
ORs = odds ratios
SD = standard deviation
THC = Δ^9-tetrahydrocannabinol
VAS = visual analog scale