Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis

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ABSTRACT

BACKGROUND: For patients with chronic, non-cancer pain, traditional pain-relieving medications include opioids, which have shown benefits but are associated with increased risks of addiction and adverse effects. Medical cannabis has emerged as a treatment alternative for managing these patients and there has been a rise in the number of randomized clinical trials in recent years; therefore, a systematic review of the evidence was warranted.

OBJECTIVE: To analyze the evidence surrounding the benefits and harms of medical cannabinoids in the treatment of chronic, non-cancer-related pain.

DESIGN: Systematic review with meta-analysis.

DATA SOURCES: Medline, Embase, CINAHL, SCOPUS, Google Scholar, and Cochrane Databases.

ELIGIBILITY CRITERIA: English language randomized clinical trials of cannabinoids for the treatment of chronic, non-cancer-related 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 6 reviewers. Data were pooled through meta-analysis with different durations of treatment (2 weeks, 2 months, 6 months) and stratified by route of administration (smoked, oromucosal, oral), conditions, and type of cannabinoids.

MAIN OUTCOMES AND MEASURES: Patient-reported pain and adverse events (AEs).

RESULTS: Thirty-six trials (4006 participants) were included, examining smoked cannabis (4 trials), oromucosal cannabis sprays (14 trials), and oral cannabinoids (18 trials). Compared with placebo, cannabinoids showed a significant reduction in pain which was greatest with treatment duration of 2 to 8 weeks (weighted mean difference on a 0-10 pain visual analogue scale −0.68, 95% confidence interval [CI], −0.96 to −0.40, $I^2 = 8\%$, $P < .00001$; n = 16 trials). When stratified by route of administration, pain condition, and type of cannabinoids, oral cannabinoids had a larger reduction in pain compared with placebo relative to oromucosal and smoked formulations but the difference was not significant (P[interaction] > .05 in all the 3 durations of treatment); cannabinoids had a smaller reduction in pain due to multiple sclerosis compared with placebo relative to other neuropathic pain (P[interaction] = .05) within 2 weeks and the difference was not significant relative to pain due to rheumatic arthritis; nabilone had a greater reduction in pain compared with placebo relative to other types of cannabinoids longer than 2 weeks of treatment but the difference was not significant (P[interaction] > .05). Serious AEs were rare, and similar across the cannabinoid (74 out of 2176, 3.4%) and placebo groups (53 out of 1640, 3.2%). There was an increased risk of non-serious AEs with cannabinoids compared with placebo.

CONCLUSIONS: There was moderate evidence to support cannabinoids in treating chronic, non-cancer pain at 2 weeks. Similar results were observed at later time points, but the confidence in effect is low. There is little evidence that cannabinoids increase the risk of experiencing serious AEs, although non-serious AEs may be common in the short-term period following use.

KEYWORDS: Cannabinoids, chronic pain, multiple sclerosis

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Introduction

The opioid epidemic is arguably the greatest public health challenge currently facing health providers, policy makers, and most importantly, patients. This epidemic continues to dominate headlines as opioid-related hospitalizations and emergency department visits in Canada have ballooned by more than 50% during the last decade, most of which occurred over the last 3 years.[1] Even more staggering is the 500% increase seen in opioid-related deaths across North America over the last year, with more than 50 000 reported fatalities, over a third of which were related to prescription medications.[2,3]

Acute and chronic musculoskeletal pain remains one of the leading reasons for opioid prescribing in North America. While the initiation of this class of analgesics may often be done to treat severe injuries or intractable pain, the highly addictive potential and narrow toxic range make it a high-risk medication. Canadian and American recommendations that are responsible for opiate prescribing discourage use of opioids for chronic, non-cancer pain.[4-6] However, opiates remain the default choice for most orthopedic providers across North America, with deeply ingrained practice patterns leading to routine prescription of opioids following a fracture, surgery, or worsening degenerative bone and joint disease.[7-9]

On October 17, 2018, Canada became the second country to legalize both recreational and medical use of Cannabis. Surrounding this decision, the spotlight was on the evidence for efficacy and harms associated with use of cannabinoids across an array of medical indications. Chronic musculoskeletal pain may be a key driver of use; 65% of Canadians authorized to possess medicinal cannabis use it for "severe arthritis," and in 1 US pain clinic up to 80% of cannabis users report myofascial pain as their primary diagnosis.[10]

Limited clinical evidence supports the use of cannabinoids for chronic, non-cancer-related pain; however studies continue to emerge at a rapid pace. Several systematic reviews have examined the role of cannabinoids across multiple indications. Two reviews presented an overall summary of the evidence using scoping or qualitative methods, and indicated that cannabinoids may be comparable with currently used analgesics[11,12] Martin-Sanchez et al[13] went on to perform a meta-analysis of 18 trials looking at the use of cannabinoids in chronic pain. They found cannabinoids to be moderately efficacious; however any benefits were offset by reported harms.[13] Conversely, Whiting et al[14] analyzed 8 trials in patients with chronic pain, and Lynch and Campbell[15] analyzed 15 trials in patients with non-cancer pain, each finding it to be safe and effective. Given the contradictory findings among reviews over the last decade, as well as the large number of recently available trials, a thorough updated meta-analysis in this area was urgently required. The aim of this systematic review was therefore to analyze the best evidence surrounding the benefits and harms of medical cannabinoids in the treatment of chronic, non-cancer-related pain.

Method

In accordance with the PRISMA guidelines for reviews of health care interventions,[16] we conducted a systematic review on the efficacy and adverse events (AEs) associated with using cannabinoids for the treatment of chronic, non-cancer-related pain.

Literature search

We performed a systematic search of the Medline, Embase, CINAHL, SCOPUS, Google Scholar, and Cochrane databases from inception to December 15, 2018. Structured search strategies were developed using keywords related to "cannabis," "marijuana," or "cannabinoids" AND "chronic, non-cancer pain," using Medical Subject Heading (MeSH) terms wherever possible. We did not restrict our search by date of publication. Database-specific search strategies were developed and an example can be found in e-Table 1. Recently completed or ongoing studies were identified using online trial registries (clinicaltrials.gov, TrialsCentral.org). We further searched the references lists of included studies and previously performed related reviews for additional eligible articles.

Study eligibility

Randomized controlled trials (RCTs) comparing cannabinoids with placebo for patients with chronic, non-cancer pain were eligible for inclusion. We defined chronic pain as persistent or recurrent pain lasting beyond 3 months. If duration of pain was not stated, the article was still considered for inclusion if the study population had an established diagnosis for a chronic condition associated with pain (ie, multiple sclerosis, Parkinson disease, rheumatoid arthritis). Pain outcomes of interest included any validated scale dedicated to measuring pain, such as the visual analogue scale (VAS), numeric rating scale (NRS), neuropathic pain scale (NPS), or McGill pain questionnaire. We excluded (1) non-human or preclinical trials; (2) non-English language trials; (3) trials reporting on acute or cancer-related pain; (4) trials with less than 24-hours follow-up; (5) trials only reported as abstracts or posters, with no available full-text article; (6) pilot trials where patients overlapped with those in a subsequent full trial report; and (7) trials with incomplete pain outcome and AE reporting for analysis. Two authors independently screened search results in duplicate, with disagreements resulting in automatic inclusion at the title and abstract stage, and resolution through discussion with involvement of a third reviewer as necessary at the full-text stage. For full-text articles deemed ineligible, the reason(s) for exclusion were recorded.

Data extraction

Data were abstracted independently by a team of 6 reviewers using the OrthoEvidence (OE) online platform. Data extraction forms were pilot-tested across the reviewers, and all abstracted data were confirmed in duplicate. Any discrepancies were resolved through discussion. We collected study and patient demographic information (author, year of publication, country, funding, study design, length of follow-up, sample size, patient population, condition(s) studied), as well as information regarding each of the treatment arms (type of cannabinoid/control, dose, route of administration). The outcomes of interest were pain and AEs. The type of pain scale used was recorded, as well as the mean score and standard deviation (SD) at baseline, follow-up, and/or change from baseline. Results from the between-group analyses reported by each

Table 1. Summary of interventions (43 cannabinoid arms) by included studies (36 trials).

INTERVENTION	ROUTE	DOSE/SPECIFIC PREPARATION STUDIED	INDICATION STUDIED	# OF STUDIES
Cannabis (flower)	Inhaled (smoked)	Cannabis (3.56% THC)	HIV sensory neuropathy	1[22]
		Cannabis (4.0% THC)	Multiple sclerosis (spasticity)	1[28]
		Cannabis (1%-8% THC)	HIV sensory neuropathy	1[30]
		Cannabis (9.4% THC)	Postsurgical/posttraumatic neuropathic pain	1[52]
Cannabis extract	Oral (capsule)	THC 2.5 mg/capsule, 5-25 mg THC/d	Multiple sclerosis (muscle stiffness, spasticity)	3[33,56,57]
			Parkinson dyskinesia	1[26]
THC/CBD spray	Oromucosal	Nabiximols/THC 27 mg/mL: CBD 25 mg/mL (~0.1 mL/spray)	Neuropathic pain ± allodynia (general; diabetic; secondary to brachial plexus avulsion)	5[24,40,43,44,50]
			Rheumatoid arthritis	1[25]
			Multiple sclerosis (spasticity, central neuropathic pain)	7[27,34,35,37,39,41,51]
			Chronic pain	1[38]
THC only spray	Oromucosal	THC 27 mg/mL (~0.1 mL/spray)	Neuropathic pain (general; secondary to brachial plexus avulsion)	2[24,50]
			Chronic pain	1[38]
CBD only spray	Oromucosal	CBD 2.5 mg (~0.1 mL/spray)	Neuropathic pain	1[50]
			Chronic pain	1[38]
Synthetic THC (delta-9 THC)	Oral	Dronabinol/marinol (2.5-15 mg/d)	Functional chest pain	1[36]
			Multiple sclerosis (spasticity, central neuropathic pain)	5[23,33,42,46,56]
			Amyotropic lateral sclerosis (cramps)	1[53]
			Idiopathic cervical dystonia	1[55]
			Spinal cord injury	1[31]
		Nabilone (0.5-4 mg/d)	Fibromyalgia	1[45]
			Neuropathic pain (diabetic)	1[47]
			Multiple sclerosis (spasticity, central neuropathic pain)	2[48,54]
		Namisol (9-24 mg/d)	Postsurgical/pancreatitis-related abdominal pain	1[29]
			Multiple sclerosis (spasticity)	1[49]
Synthetic THC (THC-11)	Oral	Ajulemic acid/CT3 (40-80 mg/d)	Neuropathic pain (with hyperalgesia/allodynia)	1[32]

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

study (mean difference, 95% confidence intervals [CIs], and *P* values) were also extracted. Adverse events were recorded by overall incidence for each study, and classified as serious or non-serious if reported, or by applying accepted criteria.[17]

Study appraisal

Methodological quality for each of the included RCTs was assessed in duplicate by a team of 6 independent reviewers for each outcome using a modified Cochrane Risk of Bias tool[18] through the OE online platform. The following items were assessed: sequence generation; allocation sequence concealment; blinding of participants, providers, and outcome assessors; incomplete outcome data (loss to follow-up); selective outcome reporting; and other biases. Risk of bias for each item was determined to be "low risk" (+), "high risk" (-), or "unclear risk" (?). If all domains were judged as low, the trial was considered at low risk of bias. If 2 or more of the domains were rated

as high or unclear, the trial was considered at high risk of bias. Otherwise, the trial was considered as having moderate risk of bias. Any discrepancies were resolved through discussion between the reviewers. No studies were excluded from the analysis due to high risk of bias.

Data analysis

For pain, we reported the mean difference in change from baseline, along with 95% CIs. We transformed all scores to the scale of an index instrument, the VAS, which resulted in scores that could range from 0 to 10, where higher scores reflect a worse outcome (more pain). If missing, SDs were calculated from other reported data (standard error, CIs, *P* values) or imputed using median values across similar study characteristics (intervention, population, follow-up duration). For AE data, we summarized number of patients and calculated proportions of specific AEs. To avoid double counting for studies with more than 2 treatment arms, we divided the control arms by the number of comparator arms for the meta-analysis. Similarly, for crossover studies, the overall sample size was divided by the number of treatment arms. For the analysis of harms, data regarding any Severe AE reported was summarized and pooled for analysis.

Heterogeneity was investigated visually through inspection of the forest plots, and objectively with the I^2 statistic ($I^2 < 40\%$, low heterogeneity; $I^2 \geqslant 75\%$, substantial heterogeneity). We present pooled results of pain reduction with 3 durations of treatment and follow-up (1-14 days, 2-8 weeks, and 2-6 months). We conducted 3 stratified analyses independently, to investigate whether effects varied by route of administration (oral, oromucosal, or inhaled), by patients' conditions (pain other than multiple sclerosis, multiple sclerosis pain, or rheumatoid arthritis pain), and by types of cannabinoids (Ajulemic acid, tetrahydrocannabinol [THC], cannabidiol [CBD], combination of THC and CBD, nabilone, or dronabinol). All analyses were performed using STATA 14.0 (STATA Corporation, College Station, TX, USA) and Review Manager 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014, Copenhagen, Denmark).

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach was used to evaluate confidence in the pooled effect estimates.[19,20] According to GRADE, data from RCTs are considered high-quality evidence but can be rated down due to risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect.[20] The quality of the evidence was graded as high, moderate, low, or very low, and applied to each outcome of interest separately.[21]

Results

Following the removal of duplicates, we identified 1664 potential eligible studies for review through our database and gray literature searches. Of these, 111 were considered potentially relevant based on title and abstract screening, and full-text articles were reviewed. A total of 36 studies published between 2002 and 2018 (4006 participants) were eligible for final inclusion for both pain and AE outcomes (Figure 1).[22-57]

Study characteristics

Most of the trials included in the meta-analysis were conducted in the United Kingdom (16 out of 36, 44%),[23-27,34,38-41,43,44,50,51,56,57] followed by Canada (7 out of 36, 19%),[34,44,45,47,48,52,55] the Czech Republic (5 out of 36, 14%),[27,34,37,39,44] the United States (4 out of 36, 11%),[22,28,30,36] the Netherlands (3 out of 36, 8%),[29,33,49] Austria (2 out of 36, 6%),[37,54] Belgium (2 out of 36, 6%),[30,44] Spain (2 out of 36, 6%),[34,39] Switzerland (2 out of 36, 6%),[31,53] Italy (2 out of 36, 6%),[35,39] and Germany (2 out of 36, 6%),[32,42] with the remaining countries (Denmark,[46] France,[34] Poland,[39] and Romania)[44] contributing participants to 1 study each. Of the included studies, 6 trials recruited patients from more than 1 country (range: 2-5 countries).[27,34,37,39,40,44]

Twenty-two of the included studies were parallel-group trials (3633 participants),[22,23,25,27,29,31,34,36,37,39-45,47-49,51,56,57] and 14 were crossover trials (373 participants).[24,26,28,30,32,33,35,38,46,50,52-55] All the studies compared a variety of cannabinoid-based interventions with a placebo control (Table 1), with 5 studies having more than 1 cannabinoid treatment arm.[24,33,38,50,56] This led to 43 direct comparisons of a cannabinoid with a placebo control across the individual 36 trials, the details of which can be found in e-Table 2.

Synthetic THC capsules were the most frequently studied cannabinoid intervention (16 trials). Fifteen of these trials examined synthetic Δ9-tetrahydrocannabinol (THC) capsules known as Dronabinol,[23,31,33,36,42,46,53,55,56] Nabilone,[45,47,48,54] or Namisol,[29,49] and a single study assessed ajuvenic acid capsules (THC-11, CT3).[32] The next most commonly studied cannabinoids were in the form of oromucosal sprays (14 trials).[24,25,27,34,35,37-41,43,44,50,51] The oromucosal sprays typically deliver 0.1 mL per spray, and were either a THC (27 mg/mL): CBD (25 mg/mL) formulation known as nabiximols, a THC only (27 mg/mL), or CBD only (25 mg/mL) spray. Four of the studies evaluated smoked, rolled cannabis (flower), from plants of varying THC potency (1%-9% THC),[22,28,30,52] compared with identical placebos where the active THC components had been extracted out. There were also 4 studies that analyzed an herbal cannabis extract oil, containing THC (2.5 mg/mL) and CBD (1.25 mg/mL), which was administered orally as a capsule.[26,32,56,57] The medical conditions associated with the chronic pain varied between studies and are summarized in Table 1, along with a breakdown of the interventional arms across all studies.

Risk of bias

Across all outcomes, 3 (8%) of the trials were judged to be at low risk of bias,[23,41,49] 5 (14%) were judged at moderate risk of

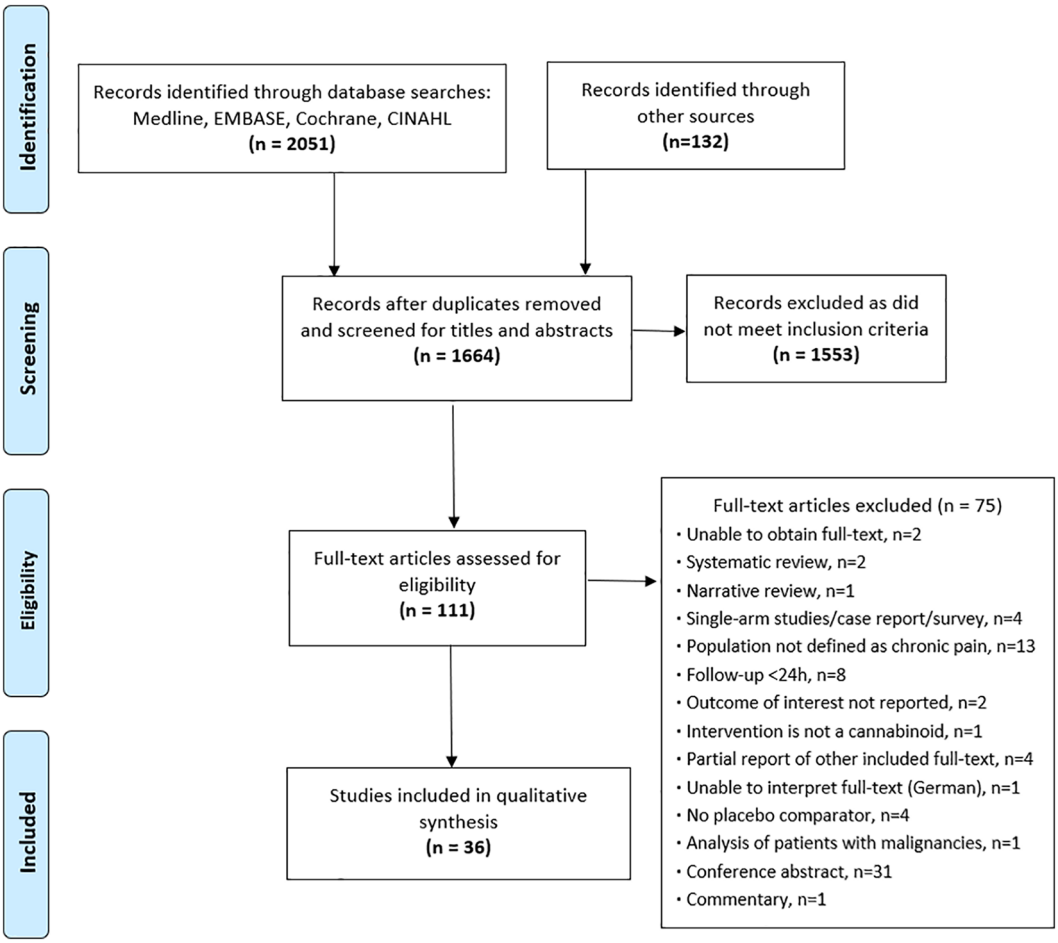

Figure 1. Study flow diagram—Depiction of the number of studies at each stage of the review, and reasons for exclusion for full texts.

bias,[24,34,40,44,57] and 28 (77.8%) at high risk of bias (Figure 2A and B).[22,25-33,35-39,42,43,45-48,50-56] The major sources of bias in the trials were inadequate sample size to determine efficacy (mean of 50 patients per study arm) and selective outcome reporting; the latter requiring imputation and additional calculations in 21 out of 34 (61.7%) of pain outcome comparisons for meta-analysis. As each of the studies had a placebo control, patients were adequately blinded in all 36 of the included studies, decreasing bias for each of the outcomes reviewed.

Pain

Across the 29 trials (34 comparisons) that had reported on pain outcomes, there was a significant treatment effect favoring the use of cannabinoids over placebo (−0.63, 95% CI, −0.85 to −0.42, $I^2 = 16\%$, $P < .00001$; low-quality evidence). When stratified by follow-up period, we found that within the first 2 weeks, cannabinoids had a greater reduction in pain compared with placebo (−0.54, 95% CI, −0.76 to −0.31, $I^2 = 0\%$; n = 13 trials; moderate-quality evidence). This difference remained at 2 months (−0.68, 95% CI, −0.96 to −0.40, $I^2 = 8\%$; n = 13 trials; low-quality evidence), however decreased by 6 months (−0.43, 95% CI, −0.75 to −0.10, $I^2 = 30\%$; n = 8 trials; low-quality evidence), yet still remained significant (Table 2, e-Figures 1-4).

Across all time points, oral formulations demonstrated a superior effect compared with oromucosal and inhaled routes of administration. Results regarding pain outcomes are summarized in Tables 2 and 3, with additional forest and funnel plots available in the online supplementary materials (e-Figures 5-10).

Small effects of cannabinoids in pain reduction were found in patients with neuropathic pain related to multiple sclerosis and those with other chronic neuropathic pain conditions, including HIV sensory neuropathy, postsurgical or posttraumatic pain, diabetes, functional chest pain, pancreatitis-related abdominal pain, amyotrophic lateral sclerosis, fibromyalgia, hyperalgesia, allodynia, and cervical dystonia. No statistically significant difference was found for patients with rheumatoid arthritis, which had only available data from 1 trial (Table 4, e-Figures 11-16).

Greater than 1 point differences favoring cannabinoids over placebo were found with ajulemic acid within 2 weeks and with nabilone beyond 2 weeks. Mild differences were found at shorter durations with the combination of THC and CBD, THC alone and dronabinol. No statistically significant differences were found for combination of THC and CBD after 2 weeks or for CBD alone within 2 weeks (Table 5, e-Figures 17-22).

Table 2. GRADE evidence profile summary table for pain.

OUTCOME TIME FRAME	NUMBER OF STUDIES (NUMBER OF PATIENTS)	RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	OTHER CONSIDERATIONS	MAGNITUDE OF EFFECT (95% CI)	OVERALL QUALITY
Pain (1 day to 6 months)	Data from 2345 patients in 29 studies, 34 comparisons	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Serious (publication bias)	Mean difference 0.63 less (0.85 less to 0.42 less)	Low
Pain (1 day to 2 weeks)	Data from 1252 patients in 13 studies, 18 comparisons	Serious[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Mean difference 0.54 less (0.76 less to 0.31 less)	Moderate
Pain (2-8 weeks)	Data from 1362 patients in 16 studies, 16 comparisons	Serious[c]	No serious inconsistency	No serious indirectness	No serious imprecision	Serious (publication bias)	Mean difference 0.68 less (0.96 less to 0.40 less)	Low
Pain (2-6 months)	Data from 1399 patients in 9 studies, 9 comparisons	Serious[d]	Serious[e]	No serious indirectness	No serious imprecision	None	Mean difference 0.43 less (0.75 less to 0.10 less)	Low

Abbreviations: CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.
[a]Of the 29 trials, 8 had moderate risk of bias for randomization sequence generation, 16 had moderate risk of bias for allocation concealment, 10 had moderate risk of bias for blinding of outcome assessment, 5 had high risk of bias for incomplete outcome data, 6 had high risk of bias for selective reporting, and 12 had moderate risk of bias for selective reporting.
[b]Of the 13 trials, 2 had moderate risk of bias for randomization sequence generation, 4 had moderate risk of bias for allocation concealment, 2 had moderate risk of bias for blinding of outcome assessment, 2 had high risk of bias for incomplete outcome data, 2 had high risk of bias for selective reporting, and 4 had moderate risk of bias for selective reporting.
[c]Of the 16 trials, 2 had moderate risk of bias for randomization sequence generation, 8 had moderate risk of bias for allocation concealment, 2 had moderate risk of bias for blinding of outcome assessment, 2 had high risk of bias for incomplete outcome data, 2 had high risk of bias for selective reporting, and 5 had moderate risk of bias for selective reporting.
[d]Of the 9 trials, 5 had moderate risk of bias for randomization sequence generation, 5 had moderate risk of bias for allocation concealment, 4 had moderate risk of bias for blinding of outcome assessment, 4 had high risk of bias for incomplete outcome data, 3 had high risk of bias for selective reporting and 2 had moderate risk of bias for selective reporting.
[e]Heterogeneity $I^2 = 30\%$.

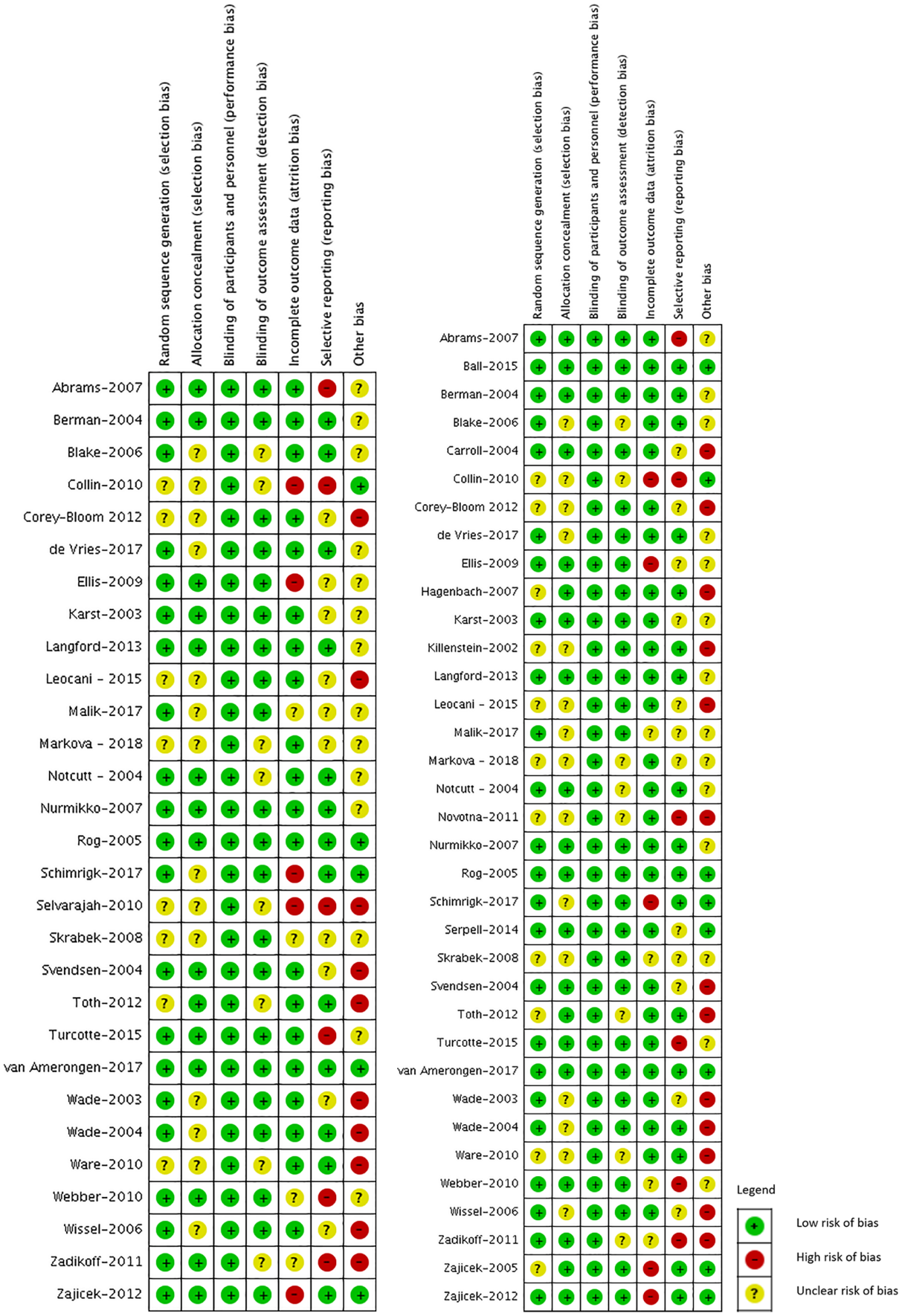

Figure 2. Risk of bias summary—Review authors' judgments about each risk of bias item for each outcome: (A) pain, 29 trials and (B) adverse events, 35 trials.

Table 3. Pain outcomes stratified by follow-up duration and route of administration.

CANNABIS VS PLACEBO BY ROUTE OF ADMINISTRATION	DURATION OF TREATMENT	N OF COMPARISONS	WEIGHTED MEAN DIFFERENCE ON 0-10 VAS PAIN	NOTES
Oral	1-14 days	3	−1.07 (−2.11 to −0.02)	Difference > 1 point
	2-8 weeks	10	−0.81 (−1.17 to −0.45)	Mild difference
	2-6 months	5	−0.48 (−0.91 to −0.05)	Mild difference
Oromucosal spray	1-14 days	11	−0.43 (−0.74 to −0.12)	Mild difference
	2-8 weeks	6	−0.46 (−1.04 to 0.11)	NS
	2-6 months	4	−0.39 (−0.93 to 0.15)	NS
Smoked	1-14 days	4	−0.42 (−0.92 to 0.09)	NS

Abbreviations: NS, not significant; VAS, visual analogue scale.

Table 4. Pain outcomes stratified by follow-up duration and pain condition.

CANNABIS VS PLACEBO BY ROUTE OF ADMINISTRATION	DURATION OF TREATMENT	N OF COMPARISONS	WEIGHTED MEAN DIFFERENCE ON 0-10 VAS PAIN	NOTES
Neuropathic or chronic pain other than multiple sclerosis	1-14 days	14	−0.82 (−1.18 to −0.46)	Mild difference
	2-8 weeks	5	−1.19 (−1.79 to −0.60)	Difference > 1 point
	2-6 months	3	−0.92 (−1.80 to −0.03)	Mild difference
Multiple sclerosis pain	1-14 days	4	−0.35 (−0.64 to −0.06)	Mild difference
	2-8 weeks	10	−0.57 (−0.94 to −0.19)	Mild difference
	2-6 months	6	−0.36 (−0.71 to −0.02)	Mild difference
Rheumatoid arthritis pain	2-8 weeks	1	−0.50 (−1.85 to 0.85)	NS

Abbreviations: NS, not significant; VAS, visual analogue scale.

Table 5. Pain outcomes stratified by follow-up duration and type of cannabinoids.

CANNABIS VS PLACEBO BY TYPE OF DRUGS	DURATION OF TREATMENT	N OF COMPARISONS	WEIGHTED MEAN DIFFERENCE ON 0-10 VAS PAIN	NOTES
Ajulemic acid	1-14 days	1	−1.90 (−2.78 to −1.02)	Difference > 1 point
THC and CBD	1-14 days	6	−0.40 (−0.73 to −0.07)	Mild difference
	2-8 weeks	6	−0.46 (−1.04 to 0.11)	NS
	2-6 months	4	−0.39 (−0.93 to 0.15)	NS
THC	1-14 days	7	−0.47 (−0.92 to −0.03)	Mild difference
	2-8 weeks	3	−0.65 (−1.25 to −0.05)	Mild difference
	2-6 months	1	−0.60 (−1.30 to 0.10)	NS
CBD	1-14 days	2	−0.45 (−2.79 to 1.88)	NS
Nabilone	2-8 weeks	4	−1.48 (−2.54 to −0.42)	Difference > 1 point
	2-6 months	3	−1.23 (−2.19 to −0.28)	Difference > 1 point
Dronabinol	1-14 days	2	−0.50 (−1.01 to 0.02)	NS
	2-8 weeks	4	−0.79 (−1.33 to −0.26)	Mild difference
	2-6 months	1	−0.11 (−0.61 to 0.39)	NS

Abbreviations: CBD, cannabidiol; NS, not significant; THC, tetrahydrocannabinol; VAS, visual analogue scale.

Adverse events

Data regarding AEs were reported in 35 studies, although reporting was inconsistent, precluding pooled analysis across the individual events reported. Compared with placebo, cannabinoids were associated with a similar risk of serious AE; however there were a greater number of non-serious treatment-related AEs reported for cannabinoids, due largely to events such as dizziness, throat discomfort, asthenia, fatigue, drowsiness, dry mouth, increased appetite, hallucinations, nausea, and refractory spasticity (Table 6). No studies evaluating the long-term AEs of cannabinoids were identified, even when searches were extended to lower levels of evidence, including non-randomized trials and retrospective cohort studies. Overall, 225 out of 3816 (5.9%) patients reported a serious AE, requiring either medical intervention or withdrawal from the trial. Of these, 74 out of 2176 (3.4%) occurred in patients receiving cannabinoids, and 53 out of 1640 (3.2%) occurred in patients receiving placebo, indicating little overall difference between the 2 treatment groups. All of the remaining AEs described in the included studies were classified as either moderate or minor. Among those receiving cannabinoids, 1046 out of 2176 (48%) described experiencing a moderate or minor AE, compared with 648 out of 1640 (40%) of those receiving placebo. Overall, 4561 individual AEs were reported (cannabinoid = 3280, placebo = 1281), with a further breakdown of the 20 most frequently reported events in the intervention group summarized in Table 6.

Discussion

We conducted an extensive systematic review of the benefits and harms associated with medical cannabinoids for chronic, non-cancer-related pain. We included 36 RCTs (4006 participants) and found that cannabinoids are an effective form of pain control in this patient population, with a particularly strong effect among those cannabinoids that are orally administered. Compared with the findings in a systematic review that concluded opioids were effective in chronic pain reduction versus placebo (weighted mean difference and 95% CI, −0.69 [−0.82 to −0.56]) on a 10-cm VAS between 3 and 6 months,[58] the effect of cannabinoids versus placebo between 2 and 6 months in our current study was smaller and less precise (weighted mean difference and 95% CI, −0.43 [−0.75 to −0.10]); however, their CIs overlap and without more high-quality evidence directly comparing medical cannabis with opioids, and considerations of cost and AEs, it is difficult to assess if any differences between these 2 forms of therapy are statistically significant or cost-effective relative to one another.

Over the past 5 years, the political and cultural backdrop surrounding cannabis has undergone a major shift, leading to wider societal acceptance and use. Currently, the recreational and medical use of cannabis is legal across Canada and in 10 US states, with an additional 23 US states providing legal medical access only.[59] Overall, the greater access to cannabis in North America has led to rapid growth in interest around the possible benefits and harms surrounding its use. Furthermore, the movement away from opiates as an analgesic has fueled an increased interest in applications for cannabinoids in the treatment of chronic, non-cancer-related pain.

The efficacy of cannabinoids on chronic, non-cancer-related pain varied by route of administration, with cannabinoids taken orally having the largest effect size, followed by oromucosal sprays and inhaled (smoked) cannabis although the interaction effect was not significant. The differences in efficacy are likely related to differences in cannabinoid absorption, metabolism, and distribution across the routes of administration. The effects of cannabinoids occur through interactions with the endogenous cannabinoid system (ECS), a complex network of receptors and transmitters that has been implicated in a number of physiological functions, both in the central and peripheral nervous systems as well as peripheral organs.[60] The ECS is comprised of 2 main receptors (cannabinoid receptor type-1 [CB1] and type-2 [CB2]), endogenous ligands that bind to and activate these receptors (primarily *N*-arachidonylethanolamide [AEA] and 2-arachidonyl glycerol [2-AG]), and the enzymes responsible for their metabolism (fatty acid amide hydrolase and monoacyl glycerol lipase for AEA and 2-AG, respectively).[61] Although found throughout the body, including the brain, endothelium, gastrointestinal lining, lungs, bone, and muscle,[62] there is considerable variation in the expression of ECS components throughout the body.[63] The differences in ECS distribution and in the bioavailability of cannabinoids across routes of administration likely underscore variation in drug efficacy of the different cannabinoid forms. The ECS is a highly dynamic system that is substantially altered in chronic pain states.[64] Some effects of cannabinoids may be mediated through G protein-coupled receptor 55.[65] Cannabidiol may interact with the serotonin 1A receptor[66] and voltage gated sodium channels.[67]

We found statistically significant effects in favor of medical cannabis for patients with multiple sclerosis and those with neuropathic or chronic pain other than multiple sclerosis across all durations of treatment. Interestingly, of note, although medical cannabis has been prescribed for patients with arthritis, we only found 1 trial on patients with rheumatoid arthritis (over a treatment period of 2-8 weeks, which was not statistically significant) and none on patients with osteoarthritis; therefore, generalizing our results to patients with these arthritic conditions may be problematic.

We did not find a significant difference for pain reduction after stratifying by types of cannabinoids except for the analysis at 1 to 14 days duration (*P* value for interaction = .04), which was most likely due to the data from 1 study that evaluated ajulemic acid (e-Figure 17). Ajulemic acid is an orally taken cannabinoid and, when pooling the effects with the other 2 studies that evaluated oral cannabinoids (THC), the subgroup difference by route of administration was not significant

Table 6. Adverse events for cannabinoid treatment arms.

ADVERSE EVENTS	ALL CANNABINOIDS	CANNABINOID GROUP					
		INHALED	OROMUCOSAL			ORAL	
		CANNABIS (FLOWER)	THC/CBD SPRAWY (NABIXIMOLS)	THC ONLY SPRAY	CBD ONLY SPRAY	SYNTHETIC DELTA-9 THC (DRONABINOL, NABILONE, NAMISOL)	CANNABIS EXTRACT
Dizziness	356/1156 (31%)	13/80 (16%)	166/612 (27%)	12/71 (17%)	0/24 (0%)	76/225 (34%)	89/144 (62%)
Application site discomfort	24/137 (18%)	3/23 (13%)	21/114 (18%)	—	—	—	—
Asthenia	53/334 (16%)	2/23 (9%)	26/167 (16%)	—	—	—	25/144 (17%)
Fatigue	124/823 (15%)	8/53 (15%)	86/535 (16%)	0/24 (0%)	0/24 (0%)	5/43 (12%)	25/144 (17%)
Increased appetite	10/65 (15%)	2/23 (9%)	—	—	—	8/42 (19%)	—
Dry mouth	114/826 (14%)	1/23 (4%)	55/462 (12%)	—	—	24/197 (12%)	34/144 (24%)
Drowsiness	109/765 (14%)	0/23 (0%)	62/588 (11%)	6/47 (13%)	41/107 (38%)	—	—
Nausea	115/920 (13%)	5/53 (9%)	94/612 (15%)	6/71 (8%)	1/24 (4%)	9/160 (6%)	—
Hallucination	22/164 (13%)	—	—	—	—	—	22/144 (15%)
Muscle spasticity	20/179 (11%)	—	17/167 (10%)	—	—	3/12 (25%)	—
Headache	75/725 (10%)	11/53 (21%)	23/399 (6%)	3/24 (13%)	1/24 (4%)	37/225 (16%)	—
Vertigo	39/400 (10%)	—	20/247 (8%)	—	—	19/153 (12%)	—
Euphoria/ euphoric mood	11/113 (10%)	1/23 (4%)	2/34 (6%)	—	—	8/56 (14%)	—
Dysgeusia (bad taste)	25/322 (8%)	—	—	—	—	—	—
Fall	20/293 (7%)	0/23 (0%)	6/89 (7%)	1/24 (4%)	1/24 (4%)	12/133 (9%)	—
Feeling abnormal (drunk/high)	31/546 (6%)	2/53 (4%)	21/390 (5%)	4/47 (9%)	—	4/56 (7%)	—
Attention disturbance	23/458 (5%)	—	18/368 (5%)	1/24 (4%)	0/24 (0%)	4/42 (10%)	—
Vomiting	16/390 (4%)	0/23 (0%)	15/319 (5%)	1/24 (4%)	0/24 (0%)	4/42 (10%)	—
Balance disorder or difficulty	13/316 (4%)	1/23 (4%)	6/191 (3%)	1/24 (4 %)	0/24 (0%)	5/54 (9%)	—
Dysphagia/ sore throat	7/267 (3%)	4/53 (8%)	3/201 (1%)	—	—	0/13 (0%)	—

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

(e-Figure 5). Although the study on ajulemic acid has a relatively low risk of bias (Figure 2B), the sample size was small with only 19 patients in total.[32] The mechanism of a possibly larger pain reduction with ajulemic acid relative to other types of cannabinoids is not known.

The rate of absorption and rapidity of effects of cannabinoids on the endocannabinoid system will be largely influenced by the route of administration and specific drug formulation. Smoking, the traditional method of cannabis administration, provides rapid cannabinoid delivery, with THC being detectable in the blood immediately after the first puff of a cannabis cigarette, and reaching peak blood concentrations within 10 min, at a bioavailability of nearly 30%.[68,69] However, large inter-subject differences have been shown in controlled laboratory and clinical experiments due to variability in number of puffs, length of inhalation, hold time, time between puffs, and depth of inhalation, despite using formulations with similar THC concentrations.[68] In addition, the speed of delivery and ability to titrate dosing is offset by the substantial short- and long-term harmful effects of smoking, making it a non-preferred route for medical applications. Among the AEs recorded in the included studies, smoking appeared to have higher rates of dysphagia and sore throat, as well as headache over the study follow-up periods, with long-term risk of cancers and interstitial lung disease remaining unknown. To avoid many of the negative side effects of smoking, oral cannabinoids emerged as a therapeutic delivery alternative. Absorption is slower when cannabinoids are ingested orally compared with inhalation, with a more delayed time to reach peak THC blood concentrations that are typically lower.[69,70] Dose and vehicle of delivery also play a role in circulating cannabinoid concentrations, along with other patient-related factors such as gastrointestinal content and motility.[68,71] In addition, degradation of cannabinoids in the stomach and substantial first-pass metabolism lead to the oral bioavailability of cannabinoids only ranging from 4% to 20%, and reaching peak blood concentrations over 1 to 5 hours.[71,72] Furthermore, first-pass hepatic metabolism of cannabis and cannabinoids results in the conversion of Δ9-THC to 11-OH-THC, a potent psychoactive metabolite that readily crosses the blood-brain-barrier, and thus likely contributes to the effects observed after oral ingestion.[73] Oromucosal administration, on the contrary, uses absorption via the mucous membranes, avoiding the first-pass effect, yet still exhibiting bioavailability and pharmacodynamics similar to that of oral dosing, as demonstrated in an investigation of 10 patients by Karschner et al,[74] where both formulations were administered. In a similar study where 17 volunteers had blood-concentration volumes measured after taking a single synthetic Δ9-THC capsule (10 mg), initial peak cannabinoid concentrations were reached within 1 to 2 hours of ingestion, with a second peak frequently being observed several hours later due to enterohepatic circulation, which was not present in those using oromucosal dosing.[74] Overall, delayed absorption after oral ingestion leads to an extended period over which the effects were experienced, and a prolonged time to return to baseline concentrations.[68] Thus, differences in cannabinoid absorption, metabolism, and interactions with the ECS across the different routes of administration may explain why those studies examining oral cannabinoid formulations demonstrated a greater improvement in pain over placebo, relative to both smoked and oromucosal formulations in our meta-analysis.

Strengths and limitations

Our article followed recommendations for systematic reviews, using a standardized, structured and extensive search strategy and multiple independent reviewers for study selection, data abstraction, and risk of bias evaluation.[16,18] This strategy allowed us to complete a rigorous review and meta-analysis of the highest level of evidence available, including recent RCTs not previously assessed, supplemented by interpretation following the guidelines laid out by the GRADE working group.[19-21] Potential heterogeneity through the inclusion of multiple different cannabinoids assessed over varying durations of follow-up was addressed through the use of stratified analysis. Additional methodological steps were taken to avoid double counting of studies with multiple treatment arms, and to limit the impact of missing data through the use of imputation. Despite these strengths, we were limited by the overall quality of the trials available, which were largely underpowered and selective and inconsistent in their reporting. These limitations affect our ability to collect and examine AE outcomes through meta-analysis, allowing us only to pool and present the data across those studies that had reported similar individual events by each treatment arm. Furthermore, a recent review suggested that elderly patients, who have a high prevalence of arthritis, which is a chronic non-cancer pain (CNCP) condition, may experience greater and more serious neuropsychiatric AEs (eg, dizziness, cognitive dysfunction, etc) associated with cannabinoid uptake.[75] It would be valuable if we had sufficient evidence to determine whether or not the rate of neuropsychiatric AEs among seniors is indeed higher than in younger individuals; however, no data from the included trials in our study were available for such an analysis.

Conclusions

There was a moderate-quality evidence of small effect for the use of cannabinoids in treating chronic, non-cancer-related pain at all time points studied up to 6 months. There is little evidence that cannabinoids increase the risk of experiencing serious AEs, although mild and moderate AEs may be common in the short-term period following use. Of note, many conditions can be classified as "chronic, non-cancer pain" and the evidence base on this topic is represented by certain conditions more so than others. For example, there was very limited evidence on non-neuropathic chronic pain conditions. As such,

large, high-quality clinical trials examining oral cannabinoids would help better establish the efficacy among this patient population, with particular attention to the reporting of AEs to better characterize the safety profile of this emerging analgesic class of medications.

Author Contributions

TD and MB contributed to the design of the study. HJ, TD, YC, and CV contributed to the acquisition and interpretation of data. HJ drafted the manuscript. All the other authors reviewed and revised the manuscript prior to submission. All authors approved the final version of the manuscript.

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Supplemental material

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