Efficacy of topical cannabinoids in the management of pain: a systematic review and meta-analysis of animal studies

Lukas D Linde ,[1,2] Carey M Ogryzlo,[1] Cassandra M Choles,[1] Brian E Cairns,[3] John L K Kramer[1,2]

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[1]International Collaboration on Repair Discoveries (ICORD), Faculty of Medicine, The University of British Columbia, Vancouver, British Columbia, Canada
[2]Department of Anesthesiology, Pharmacology & Therapeutics, The University of British Columbia, Vancouver, British Columbia, Canada
[3]Faculty of Pharmaceutical Sciences, The University of British Columbia, Vancouver, British Columbia, Canada

Correspondence to
Dr Lukas D Linde, The University of British Columbia International Collaboration on Repair Discoveries, 818 W 10th Ave, Vancouver, BC V5Z 1M9, Canada; lukas.linde@ubc.ca

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ABSTRACT

Background/importance Cannabinoids are emerging as an alternative pain management option, preliminarily supported by preclinical and clinical studies. Unwanted side effects from oral or inhaled cannabinoids remain, however, a major barrier to widespread use. Peripherally acting cannabinoids (eg, topically applied) may circumvent these side effects while providing localized pain management.

Objective Our purpose was to systematically review the literature on the effectiveness of peripherally acting cannabinoids for pain management.

Evidence review We searched MEDLINE, EMBASE, CENTRAL, CINAHL, and PubMed databases. Included studies examined the effect of topical/peripherally administered cannabinoids on pain ratings in humans, as well as pain-related outcomes in animals (eg, paw withdrawal). Due to a lack of trials, human studies were summarized in a narrative synthesis. Separate meta-analyses were performed for animal studies using radiant tail flick or paw withdrawal outcomes.

Findings Our search yielded 1182 studies following removal of duplicates, with 46 studies (6 human, 40 animal) included. Human studies (one randomized controlled trial and five case studies/series) reported no adverse events to topical cannabinoids and preliminary evidence of decreased pain ratings. Animal studies reporting tail flick (5) (2.81, 95% CI 1.93 to 3.69, p<0.001) and mechanical withdrawal (11) (2.74, 95% CI 1.82 to 3.67, p<0.001) reported prolonged responses (analgesia) in peripheral cannabinoid groups compared with controls.

Conclusions Preclinical animal studies provided low-quality evidence for peripherally administered cannabinoids to provide regional, antinociceptive effects. The scarcity of high-quality human studies underscores the need to translate preclinical evidence into well-controlled human trials.

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INTRODUCTION

More than 20% of people living throughout Europe and North America suffer from chronic pain.[1–3] Among the most prominent and alarming features of chronic pain is a general refractoriness to commonly used analgesics. Decades of research have proposed a prominent role for cannabis-based interventions as an alternative pain management option, summarized in numerous recent reviews.[4–6] So far, these have largely focused on products that contain Δ9-tetrahydrocannabinol (THC),[7] the principal psychoactive component of cannabis and potent agonist of CB1 and CB2 receptors.[8]

A major barrier towards adoption of cannabinoids in patients is their negative side effects, typically observed after common forms of administration, such as oral consumption or inhalation. A concern regarding adverse side effects was raised in a recent Cochrane review, which concluded that the 'potential benefits of cannabis-based medicine in chronic pain might be outweighed by their potential harms'.[6] The problem this creates was evidenced in one notably large trial, where 18% of subjects withdrew from treatment (compared with 3% in the placebo group) due to adverse events in response to THC.[9] The perceived unpleasantness associated with the psychoactive effects of cannabinoids may also, in some individuals, increase levels of pain.[10 11] For a significant proportion of the population, high-dose orally consumed or inhaled cannabinoids will never represent a viable pain management option.

One alternative approach is localized pain therapy with cannabinoids applied in the periphery via topical and transdermal applications. In general, topical analgesics only penetrate the first layer of skin, avoiding widespread systemic effects. In comparison, transdermal applications can enter the blood stream and provide more widespread effects.[12] From a pharmacodynamic and safety perspective, the advantage of a topical application is that a high concentration of cannabinoids can be delivered locally without a substantial concentration entering the blood stream. For both topical and transdermal delivery methods, targeted analgesic therapy avoids the first pass metabolism effect associated with oral routes,[13] as well as gastrointestinal tract side effects.[12] Owing to high fat solubility, topically applied cannabinoids are readily absorbed in the skin,[14] where cannabinoids bind to peripheral receptors to exert biological effects on primary cutaneous afferent fibers.[15]

Recent legislative changes in Canada, the USA, and numerous European countries have increased the availability of cannabis-containing products for both medical and recreational uses[16–18]—among them are topicals. A consensus that topical cannabinoids should be considered as an over-the-counter or prescribed intervention to manage symptoms of chronic pain is, however, currently lacking. To this end, the primary aims of our systematic review and meta-analysis were to examine: (1) the use of

peripheral cannabinoids to influence pain/nociception in animal studies; and (2) the safety and efficacy of topical cannabinoids products for the management of pain in humans.

METHODS

Search strategy

Randomized controlled trials (RCTs), quasi-experimental studies, and observational studies were included in the search due to the low number of RCTs in humans available on this topic. To guide the systematic search of literature, the Problem, Intervention, Control, Outcome (PICO) design strategy was used: *Do topically applied cannabinoids (intervention) versus control affect pain perception (outcome)?* (PICO table is available in the online supplemental table 1). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[19] along with the Cochrane handbook for systematic reviews of interventions[20] were used to guide search strategy and study selection. The following databases were searched for relevant studies: MEDLINE (via Ovid 1946–2021); EMBASE (via Ovid 1974–2021); CENTRAL (via Ovid); CINAHL (via EBSCO 1982–2021); PubMed (1969–2021). The reference lists from included studies were hand-searched for further relevant studies. Gray literature searching was conducted through Google Scholar, Science Direct, and OpenGrey databases. To prevent exclusion of relevant studies, there was no language restriction. RefWorks software was initially used for storing and screening of articles, prior to a transition to Covidence for data extraction and risk of bias assessments. Our review and protocol were registered on PROSPERO (CRD42020155962). Our initial search was completed on April 20, 2020, and a follow-up search conduced on April 20, 2021.

The identification of specific descriptors (eg, MeSH terms, CINAHL headings) and their related keywords were created for each database. Search terms were combined with Boolean operators 'AND' and 'OR' appropriately. Complete search strategies for all databases are available in the online supplemental table 2. Search terminology related to cannabis and synthetic cannabis compounds (eg, cannabis, cannabinoid(s), cannabidiol (CBD), THC, WIN55-212-2) were combined with topical application (eg, skin absorption, cream, topical, transdermal) and peripheral delivery keywords (eg, peripheral, local, intramuscular injections, subcutaneous), which were both further combined with pain and analgesia terms (eg, pain, nociception, analgesia, neuropathy). Search-specific terms were modified for each database as necessary.

Study selection criteria

Studies were included provided they focused on the application of topical cannabinoids in the periphery for the management of pain. Feasibility studies without direct pain-related outcomes were initially included to provide additional narrative input. Mechanistic studies using topical or peripheral cannabinoids applied in animal models of pain were also included. Following the initial search, included articles were then categorized into human or animal studies.

To meet inclusion criteria, human studies required a focused outcome measure related to pain perception, or adverse events measures for feasibility studies. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[21] As such, pain can be assessed through numerous outcome measures.[22] The most common outcome measure used in pain studies remains the Visual Analog Scale (VAS) or the Numerical Rating Scale (NRS).[22] Briefly, these are 0–10 or 0–100 point scales, often anchored by 'no pain' and 'worst pain imaginable'. While variation exists in anchoring and certain technical elements of the tests (ie, drawn responses on a line vs verbal responses), these remain the most prominent source of quantitative pain measures. In the present review, VAS and NRS were the primary outcome measures of interest in relation to the ability of topical cannabinoid products to alter pain perception.

Beyond VAS and NRS, numerous additional outcome measures have been used to assess pain perception. Questionnaires such as the McGill Pain Questionnaire[23] have been used to better categorize pain. These questionnaires are reported as additional outcomes in this review. Further additional pain outcomes include sensory testing techniques (eg, mechanical pain threshold, pressure pain threshold, etc) and neurophysiological pain outcomes (eg, withdrawal reflexes, evoked potentials, etc). Sensory testing techniques often provide more detailed information regarding the characteristics of painful sensations,[24] while neurophysiological outcomes can provide more objective measures of nociceptive inputs that give rise to painful sensations. These additional outcomes were recorded in data extraction tables as appropriate.

Included animal studies required the application of cannabinoids in the periphery along with a measure of nociception. Behavioral pain measures such as tail flick tests or paw withdrawal latencies were included.[25] Additional measures related to pain such as change in concentrations of inflammatory cytokines were also included.

To assess safety, we examined reports of adverse events in human studies. For animal studies, we explored rotarod test performance. The rotarod test assesses coordination and locomotion in animal models, and can be used as a measure of motor impairment.

Screening and data extraction

Initial study screening based on titles and abstracts was conducted independently by two reviewers (LDL and CMO). When reviewers disagreed, the article was re-evaluated by each reviewer until consensus was reached. If no consensus was reached, a third reviewer (JLKK) was the adjudicator. Studies were categorized as either 'animal' or 'human' at this stage. Full paper screening of included studies was then fulfilled by the same researchers. Full-text articles were excluded if published in predatory journals, based on screening of journal names in https://predatoryjournalscom. RCTs were screened for registry conflicts, and excluded if registry conflicts were discovered.

A modified version of a previously published tool was used to guide data extraction,[26] which included four main domains: (1) article identification, (2) methodological characteristics (pain condition, type of topical cannabinoid product applied, dose of topical cannabinoid, region of the body applied, duration of application, outcome measures, statistical analysis), (3) main findings (effect of topical cannabinoid product on pain perception), and (4) conclusions. Follow-up on study outcomes or analysis was followed up via requests to corresponding authors as needed. Data extraction was performed in Microsoft Excel.

Quality assessment

The quality of RCTs was assessed using the risk of bias RoB 2 tool,[27] in accordance with the Cochrane handbook for systematic reviews of interventions.[20] Non-randomized studies were assessed using the ROBINS-I tool, when appropriate.[28] For animal studies, the SYRCLE risk of bias assessment tool was used, which is modified from the RoB 2 tool for use in animal

studies.[29] The SYRCLE tool does not provide an overall quality score. Instead, 10 aspects of study quality are individually reported as either low, high, or unclear risk. We determined our own criteria to rank overall quality. If more than two aspects were ranked high risk, the overall risk was classified as high risk. If only one aspect was ranked high risk, the overall risk was classified as some concerns. If no aspects were high risk, and seven or more aspects were low risk, the overall risk was classified low. All other combinations would involved four or more aspects ranked as unclear, with no aspects ranked high, in which case overall risk was classified as unclear. Two independent reviewers (LDL and CMC) appraised all eligible studies and provided scores, respectively. Disagreements were mediated by a third reviewer (JLKK). Risk of bias assessments are summarized in the online supplemental figures 1 and 2.

Meta-analysis

To quantify the effect of topical cannabinoid products on pain perception in humans and animals, we planned to conduct meta-analyses on commonly occurring outcomes among included studies. For humans, RCTs and cohort-controlled studies with low risk of bias were planned to be included in a meta-analysis with pain perception (NRS or VAS) as a primary outcome measure. However, during screening, we observed insufficient data for a human meta-analysis. Consequently, findings from human studies were presented as a narrative synthesis.

For animal studies, the two most common outcome measures observed during final screening were tail flick tests and paw withdrawal tests. Paw withdrawal tests were further divided based on test stimuli (heat and mechanical). Meta-analyses were conducted for each outcome (tail flick tests, mechanical withdrawal, and heat withdrawal).

All statistical tests were completed in R (V.4.0.2, R Core Team). We calculated standardized mean differences between control and cannabinoid groups[30] along with 95% CIs, and performed tests of heterogeneity. Data were pooled using a random-effects model to account for interstudy variability. We plotted standardized differences versus SEs and assessed symmetry of the funnel plot visually. Funnel plots were only generated when more than 10 studies were included in a meta-analysis, as per Cochrane guidelines.

Quality of evidence for primary outcomes (meta-analyses) from animal studies was assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[31] GRADE offers specific criteria for rating the quality of evidence, including study design, risk of bias, imprecision, inconsistency, indirectness and magnitude of effect. Five categories may lead to downgrading of evidence, while three categories may lead to upgrading. This results in quality of evidence for each outcome being categorized from high to very low. GRADE appraisal was carried out by two reviewers (LDL and CMC), and consensus was reached on all decisions regarding downgrading and upgrading quality of evidence.

RESULTS

Study screening is outlined in the PRISMA flow diagram (figure 1). After the removal of duplicates, our initial search produced a total of 1182 articles. Initial screening resulted in the exclusion of 1079 articles (742 human, 337 animal), leaving 103 articles (42 human, 61 animal) for full-text screening. Additional 57 articles (36 human, 21 animal) were removed during full-text screening (reasons listed in figure 1), resulting in 46 (6 human, 40 animal) included articles. No full-text studies were excluded for publication in predatory journals. Full-text studies were further assessed for eligibility for quantitative analysis. Only one human study would have been eligible for meta-analysis. As such, meta-analysis was not undertaken for human studies. Five animal studies were included in a meta-analysis with tail flicks as the primary outcome, while 16 studies were included in a meta-analysis with paw withdrawal as the primary outcome. These studies were further divided into heat (6) and mechanical (11) withdrawal, with one study investigating both heat and mechanical withdrawal.

Peripheral cannabinoid safety

None of the human studies reported any adverse events in response to peripheral cannabinoid exposure. However, only one trial explicitly reported examining adverse effects, observing none.[32] The remaining studies made no mention to adverse events.

For animal studies, seven (7) studies included rotarod tests to assess locomotion/balance following cannabinoid exposure.[33–39] Five of these studies reported animals in both cannabinoid and control groups 'maxed out' the time of the rotarod test, indicating no motor deficits in either group.[34–36 38 39] Another study reported no significant difference between groups.[33] A significant reduction in rotarod test performance following exposure to cannabinoids was also reported.[37] In addition, multiple studies reported the effects of peripheral cannabinoid activation to be limited only to the application site.[40–42] For example, when cannabinoids were peripherally injected into masseter muscles of rats, analgesic effects were observed in the nerve growth factor muscle pain model.[40 41] However, no effects were observed for contralateral muscle mechanical withdrawal threshold, suggesting the effects remained isolated to the cannabinoid application site.[40 41]

Human studies: narrative synthesis

The six (6) human studies that were eligible for inclusion all showed that topical cannabinoids were efficacious at reducing pain. They were, however, limited in size and quality. The six human studies were comprised of four case reports,[43–46] one case series,[47] and one voluntary RCT.[32] As such, the case reports and case series were classified as high risk of bias, while the RoB 2 tool was used to characterize the voluntary RCT as some concerns (online supplemental figure 1). In the voluntary RCT, Rukwied *et al* applied an HU210 patch (synthetic cannabinoid agonist) as pretreatment in an experimental capsaicin pain model. Patches were randomly applied, such that participants were likely unaware of which were placebo versus cannabinoid treatments. However, blinding of experimenters was not reported, resulting in elevated risk of bias. Rukwied *et al* observed that heat hyperalgesia was eliminated and touch-evoked hyperalgesia reduced compared with control.[32] In a case series, Phan *et al* applied N-palmitoylethanolamine, a putative cannabinoid receptor agonist, in a cream to treat eight patients with facial postherpetic neuralgia.[47] A significant reduction in pain ratings was reported in five of eight patients following the intervention 2–4 weeks.

The four case studies all reported a reduction in pain ratings after using topical cannabinoids.[43–46] Case studies reported reductions in pain ratings in three cases of epidermolysis bullosa,[44] two cases of low back pain,[45] three cases of pyoderma gangrenosum,[43] and two cases of non-puremic calciphylaxis ulcers.[46] The non-randomized and non-controlled methodologies of case reports were subject to high risk of bias. All studies varied in their dosages and compounds of cannabinoids (see online

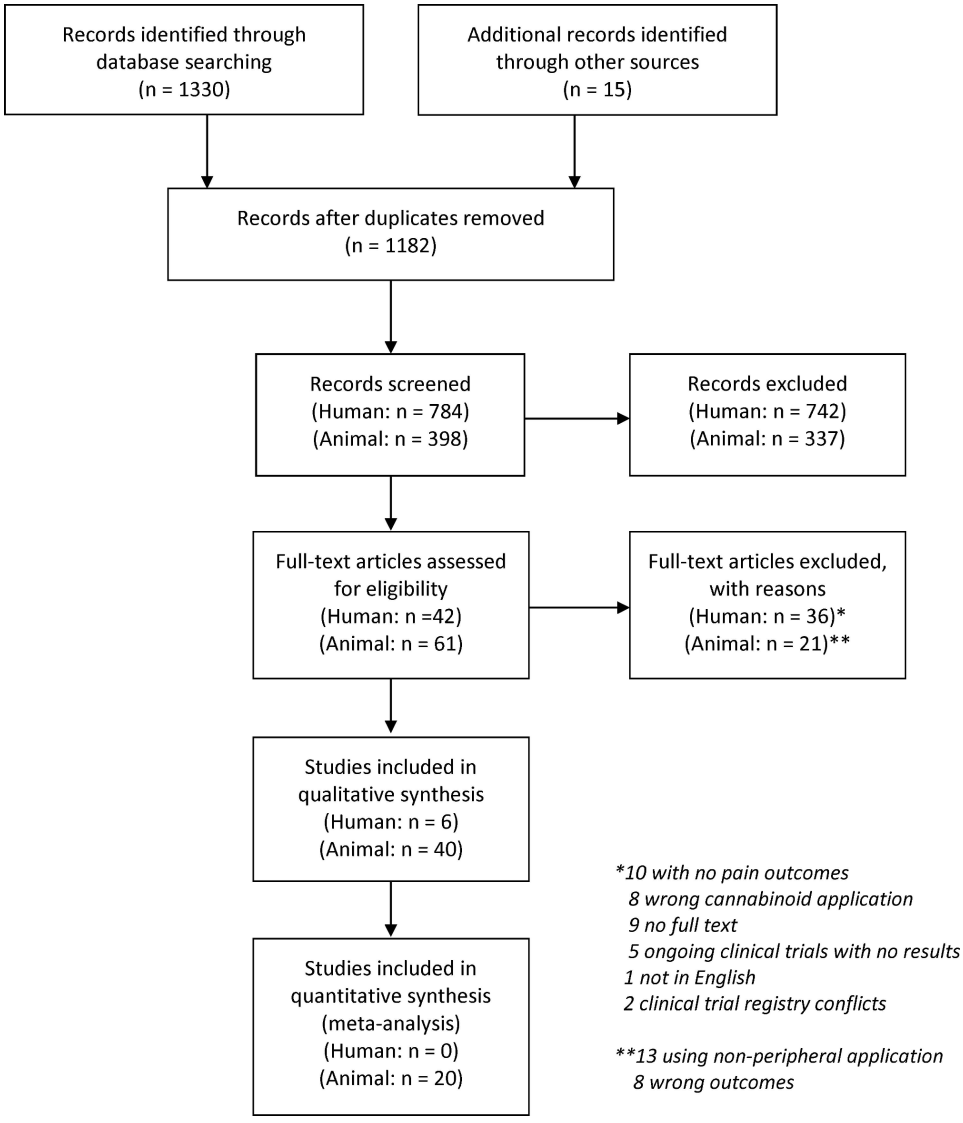

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

supplemental table 3). Finally, two recently published RCTs showed promising results,[48 49] however, these were excluded due to registry conflicts (figure 1).

Animal meta-analysis

For animal studies, separate meta-analyses were completed for paw withdrawal and tail flick outcome measures. An overall summary of findings is presented in table 1. For tail flick, five included studies revealed a significant pooled standardized mean difference between peripheral cannabinoid product and control (2.81, 95% CI 1.93 to 3.69, p<0.001) (figure 2). Heterogeneity tests were not significant (I^2=42%, tau^2=0.42, Q=7.04, df=4, p=0.13). The GRADE quality of evidence for the effect of cannabinoids on tail flick outcomes was low (table 2).

For mechanical withdrawal, 11 included studies revealed a significant pooled standardized mean difference between peripheral cannabinoid product and control (2.74, 95% CI 1.82 to 3.67, p<0.001) (figure 3). There was a high level of heterogeneity in the pooled estimate (I^2=79%, tau^2=1.85, Q=39.68, df=10, p<0.001), with the funnel plot displaying asymmetry among included studies (online supplemental figure 3). The GRADE quality of evidence for the effect of cannabinoids on mechanical withdrawal outcomes was very low (table 2).

For heat withdrawal, six included studies revealed a significant pooled standardized mean difference between peripheral cannabinoid product and control (3.66, 95% CI 2.15 to 5.17, p<0.001) (figure 3). There was a high level of heterogeneity in the pooled estimate (I^2=76%, tau^2=2.58, Q=22.40, df=5, p<0.001). The GRADE quality of evidence for the effect of cannabinoids on heat withdrawal outcomes was very low (table 2).

Animal studies: narrative synthesis

Animal studies presented with low and some concerns risk of bias (online supplemental figure 2). The most common pain-related outcome measures in animal models were the tail flick test and mechanical/heat withdrawal reflexes. Five studies showed increased withdrawal latencies in the tail flick test following the peripheral application of cannabinoids, indicative of an analgesic effect. Three studies made use of WIN55-212-2,[34 38 50] a commonly employed synthetic cannabinoid receptor agonist compound. One study used THC,[42] while another used a

Table 1 Summary of findings

Outcomes	Cannabinoids mean (SD)	Control mean (SD)	Standardized mean difference (95% CI)	Number of participants (studies)	Quality or certainty of the evidence (GRADE)	Comments
Tail flick test in animal models Assessed by time to withdrawal tail (longer time favors cannabinoid treatment)	2.6 (2.0)	33.0 (17.7)	2.81 (1.93 to 3.69)	76 (5 studies)	⊕⊕◯◯ LOW	Risk of bias concerns regarding blinding of outcome assessors and randomization. Animal studies provide indirect estimate of human models. Very large effect size.
Mechanical paw withdrawal test in animal models Assessed by weight required to elicit withdrawal (higher weight favors cannabinoid treatment)	14.6 (17.6)	27.8 (29.6)	2.74 (1.82 to 3.67)	180 (11 studies)	⊕◯◯◯ VERY LOW	Risk of bias concerns regarding blinding of outcome assessors and randomization. Animal studies provide indirect estimate of human models. Non-overlapping CIs; I^2 test for heterogeneity 79% and p<0.001. Very large effect size.
Heat paw withdrawal test in animal models Assessed by time required to withdrawal paw (longer time favors cannabinoid treatment)	8.9 (7.0)	27.8 (36.6)	3.66 (2.15 to 5.17)	86 (6 studies)	⊕◯◯◯ VERY LOW	Risk of bias concerns regarding blinding of outcome assessors and randomization. Animal studies provide indirect estimate of human models. Non-overlapping CIs; I^2 test for heterogeneity 76% and p<0.001. Very large effect size.

Population: animal models of nociception; Intervention: topical/peripherally applied cannabinoids; Comparator: control/sham animals.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.
GRADE, Grading of Recommendations Assessment, Development and Evaluation.

different synthetic cannabinoid compound.[51] Similar findings were observed for paw withdrawal. For the 11 included studies that examined mechanical withdrawal, there was an increased force (g) required for paw withdrawal in cannabinoid groups, indicative of an analgesic effect. Similarly, for the six studies that examined heat withdrawal, cannabinoid groups reported longer time to withdrawal, indicative of an analgesic effect. These 16 included studies used formulations of CBD,[33 41 52] WIN55-212-2,[53–56] and several others including but not limited to THC, anandamide, and AM1241.[35 36 40 51 57–61] An additional animal model finding that was not included in the meta-analyses was from a study on hairless guinea pigs using a topical THC patch in a neuropathic pain model, which showed an enhancement of opioid potency and consequent antinociception when administered together.[62] This finding is of significance as it suggests peripherally applied cannabinoids could be a possible synergistic agent that could allow for reduced opioid usage to achieve similar antinociceptive effects.

DISCUSSION

The findings of this systematic review and meta-analysis suggest that topically or peripherally administered cannabinoid products may be effective in the management of pain. This is largely

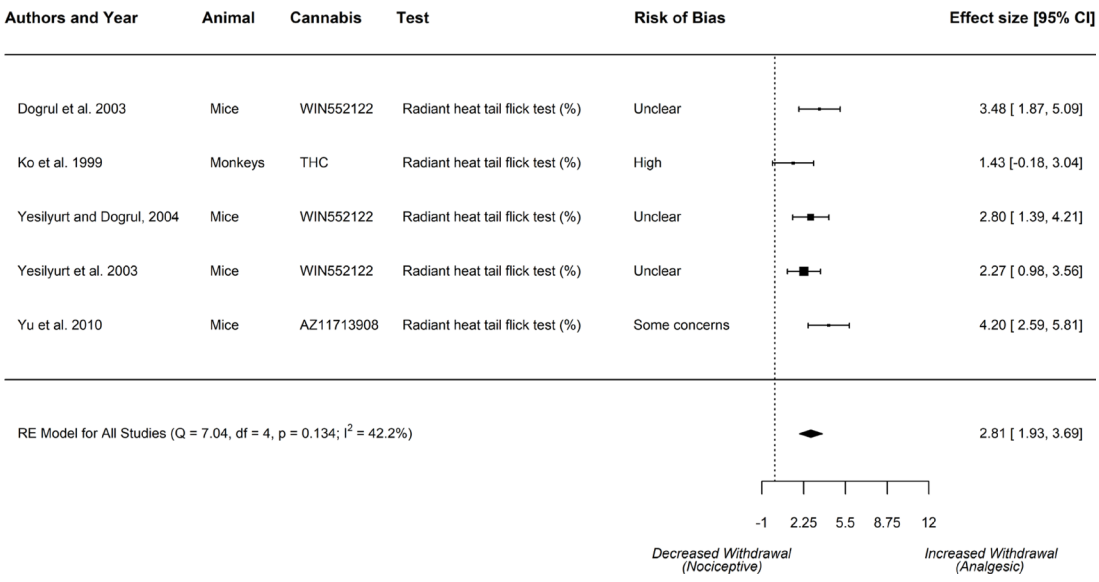

Figure 2 Forest plot for animal studies that examined radiant heat tail flick tests. THC, Δ9-.tetrahydrocannabinol.

Table 2 Evidence profile for the effect of topical cannabinoids on animal outcomes of nociception

Outcomes	Limitations	Inconsistency/ heterogeneity	Indirectness	Imprecision	Publication bias	Mean difference or OR (95% CI)	Number of participants (studies)	Quality or certainty of the evidence (GRADE)
Tail flick test in animal models Assessed by time to withdrawal tail (longer time favors cannabinoid treatment)	Randomization and blinding of outcome assessors were inconsistently reported among included studies.	Not serious	Serious*	Serious†	Not detected	SMD 2.81 (1.93 to 3.69) higher‡	76 (5 studies)	⊕⊕◯◯ LOW
Mechanical paw withdrawal test in animal models Assessed by weight required to elicit withdrawal (higher weight favors cannabinoid treatment)	Randomization and blinding of outcome assessors were inconsistently reported among included studies.	Non-overlapping CIs; I^2 test for heterogeneity 79% and p<0.001	Serious*	Serious†	Not detected	SMD 2.74 (1.82 to 3.67) higher‡	180 (11 studies)	⊕◯◯◯ VERY LOW
Heat paw withdrawal test in animal models Assessed by time required to withdrawal paw (longer time favors cannabinoid treatment)	Randomization and blinding of outcome assessors were inconsistently reported among included studies.	Non-overlapping CIs; I^2 test for heterogeneity 76% and p<0.001	Serious*	Serious†	Not detected	SMD 3.66 (2.15 to 5.17) higher‡	86 (6 studies)	⊕◯◯◯ VERY LOW

*Direct evidence consists of research that directly compares the interventions which we are interested in, delivered to the populations in which we are interested, and measures outcomes important to patients. Indirectness was likely present as animal models provide indirect estimates of human effects.
†Overall sample size of less than 400.
‡Large effect sizes.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; SMD, standardized mean difference.

based on observations in preclinical animal models, displaying large standardized pooled effects for both the tail flick test and paw withdrawal (heat and mechanical). These preclinical animal models did, however, provide very low to low-quality evidence following GRADE downgrading due to indirectness (animal models are downgraded due to indirectness compared with humans[31]), concerns regarding risk of bias, and heterogeneity. These observations of preclinical efficacy, some of which are over 20 years old, are in the early phases of translation into humans. Our review only identified a total of six eligible human studies. These human studies echoed the findings of the animal studies, suggesting that topical cannabinoid products may also be beneficial for the management of pain. However, human studies were primarily case reports, with only one voluntary RCT. Overall, our findings generally support that topical cannabinoids can reduce pain behavior in animal models, however, there is an urgent need for high-quality RCTs in humans.

To address safety of peripheral cannabinoid exposure, a subset (seven) of animal studies reported rotarod performance.[33–39] Deficits in rotarod test performance are indicative of reductions in coordination or locomotion in animals, and have been reported following oral/systemic use of cannabinoids in animal models.[63 64] Six studies reported no significant differences between peripheral cannabinoid and control groups,[33–36 38 39] while one study reported report deficits in rotarod test performance following exposure to HU210.[37] These findings suggest that, with the exception of HU210, the majority of peripheral cannabinoids do not result in measurable differences in locomotor function in animal models, and provide some preclinical evidence for safe, non-intoxicating use. As for humans, only one study reported adverse events (reporting none),[32] while the remaining studies made no mention of safety metrics. There remains a need for sufficiently sized studies to properly assess the safety of the various topical cannabinoid compounds available for current use in humans. Further, with the development of new topical cannabinoid compounds, continued exploration into potential skin allergic reactions is also of note.[65] For example, a recent study reported 53.2% (74 of 140) of patients with asthma demonstrated allergic skin reactions to a cannabis leaf pinprick test.[66] While the general idea of topical cannabinoid applications is to avoid unwanted side effects of inhalation/oral consumption, the potential for allergic skin reactions needs to be considered in the development of topical cannabinoid products.

Substantial heterogeneity was observed in animal studies with regard to the effect of topical cannabinoids on mechanical and heat withdrawals. Several factors likely contribute to heterogeneity, including the type of topical cannabinoid compounds employed (we observed upwards of 15 different cannabinoids or phytocannabinoids) and the respective dose (eg, WIN55-212-2 intraplantar/subcutaneous doses ranged from 0.1 mg/kg to 10 mg/kg, with dose frequency ranging from a single dose up to 13 daily doses[33 54] (online supplemental table 4)). Furthermore, studies incorporated different methods of application, including topical application, transdermal application, and peripheral muscle injections (online supplemental table 4). Transdermal applications, such as an HU210 patch, may contain delivery system enhancers that facilitate faster absorption than more 'traditional' topical applications, such as the direct application of CBD oil to the skin.[13] Differences between transdermal[32 47] and topical[44 45] applications add further complexity when trying to reconcile comparative treatment effects between studies. Another potential source of heterogeneity was differences in methodology in measuring paw withdrawal outcomes. For example, differences between findings of Johanek and Simone

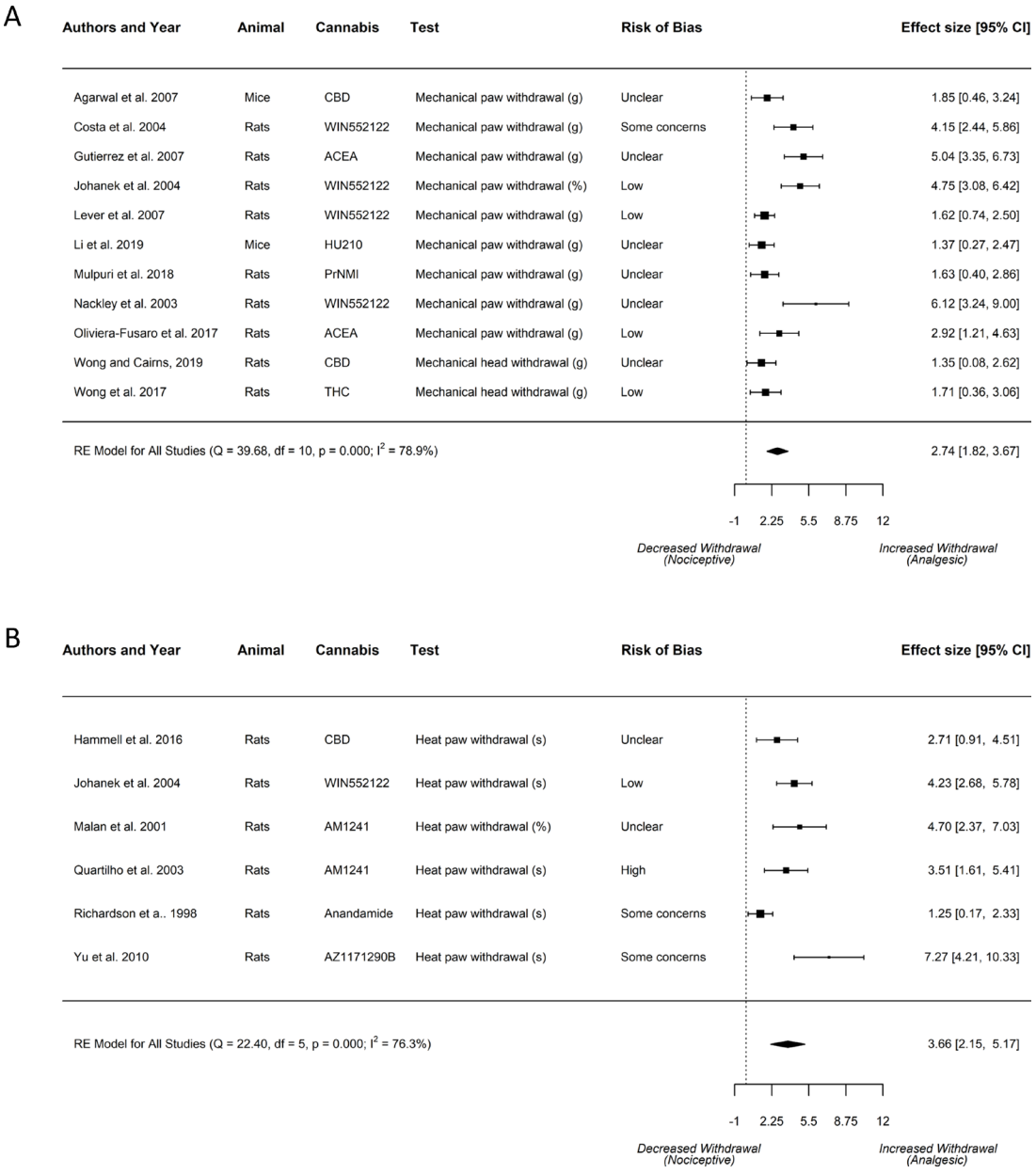

Figure 3 Forest plots for animal studies that examined (A) mechanical withdrawal and (B) heat withdrawal. ACEA, arachidonyl-2′-chloroethylamide; CBD, cannabidiol; THC, Δ9-tetrahydrocannabinol.

(4.75 (3.08 to 6.42)) and Nackley *et al* (6.12 (3.24 to 9.00)) may be partially attributable to the reporting of mechanical paw withdrawal in percentage of withdrawal versus force required to elicit withdrawal, respectively (online supplemental table 4).[53 56]

SYRCLE risk of bias assessments revealed wide variation across included studies in terms of quality (online supplemental figure 2). Of note, studies were sporadic in their reporting of randomization and blinding (for caregivers and/or experimenters) procedures, which led to numerous studies with 'unclear' scores for multiple sections. This is common when evaluating animal studies, as despite the adjusted SYRCLE tool, reporting of aspects such as randomization and blinding is often not to the same standards of RCTs in humans. As such, GRADE scores for all animal meta-analyses were downgraded as appropriate.

While animal studies demonstrate that peripheral administration of cannabinoids reduces nocifensive behaviors, the degree this translates to humans is unknown. In animal models, behavioral or reflexive measures in response to painful stimuli are often quantified by tail flicking and paw withdrawal responses. These pain-inducing measures provide an objective measure of nociception in animals and reflect neural encoding of the noxious stimulus, but not the perception of pain. In humans, pain is a multidimensional and subjective experience, related to nociception; however, a change in the latter may not be sufficient to reduce the former. To aid in translation from preclinical models, Rukwied *et al*[32] made use of an experimental pain model (topical capsaicin) in humans to demonstrate the effectiveness of HU210, a synthetic topical cannabinoid to reduce evidence of heat hyperalgesia and mechanical secondary hyperalgesia to touch.[32] These are important observations insofar as both indicate an effect on processes involved in central sensitization, a key neural mechanism proposed to underlie the transition from acute to chronic pain.[67 68] The prevention of mechanical secondary hyperalgesia is key preclinical finding for analgesic drug interventions, and is evidenced in other analgesics such as pregabalin.[69 70] As

such, the preclinical evidence of Rukwied *et al*[32] closely parallels the preclinical evidence of animal models, and provides a mechanistic framework for future studies to explore other topical cannabinoid compounds for their analgesic effects.

Regarding mechanisms of peripheral cannabinoid analgesia, previous animal studies have long established that cannabinoids have antinociceptive effects.[7 71] The mechanism by which peripherally administered cannabinoids exert their analgesic effect, however, differs from that of broad activating or systemically administered cannabinoids. Topical cannabinoids are readily absorbed in human skin[14] owing to their lipid solubility where they then activate peripheral cannabinoid receptors. CB1 and CB2 receptors are present on afferent fibers that also express TRPV1, indicating these fibers are nociceptive in nature.[40] Peripheral analgesic effects of THC are evidenced to be mediated by CB1 receptor activation, as analgesic effects are attenuated with CB1 antagonists, but not CB2 antagonists.[40] Furthermore, CB2 receptor activation has been shown to be anti-inflammatory in arthritis models.[72] Thus, the peripheral activation of CB1 receptors appears to mediate analgesia, while the peripheral activation of CB2 receptors appears to decrease inflammation, further contributing to analgesia. In contrast, orally consumed or smoked cannabis appears to mediate analgesia through widespread CB1 receptor activation centrally, in areas of the brain and spinal cord.[8] CBD, a cannabinoid found in cannabis products, on the other hand, whether administered orally or topically, acts as a negative allosteric modulator of CB1 receptors.[73] As a result, CBD on its own does not produce psychoactive effects, and further reduces the psychoactive effects of THC when taken in combination.[74] CBD has been found to act in other non-CB1 receptor mechanisms, as an agonist to serotonin 1A receptor (5-TH1A), vanilloid receptor 1 (TRPV1), and adenosine A2A receptors.[75–77] Despite their different mechanisms, both CBD and THC offer local analgesia without unwanted side effects in both animal and human studies, evidenced by no adverse events in humans and little influence on rotarod tests in animals. Additionally, in rat and rhesus monkey models, the effects of peripherally administered cannabinoids were limited to the area of application, with no evident central effects.[40–42]

With animal research on peripheral mechanisms of cannabinoids dating back more than 20 years, human research using topical cannabinoids has been slow to catch up. A hypothesis for the slow translation for cannabinoids into humans is the issue of legislative restrictions acting as a research barrier for cannabinoid research. The recent legalization of cannabis products in Canada[18] and select regions in the USA[16] has resulted in a notable increase in clinical trials examining the efficacy of cannabis as a treatment for various health conditions, although with remaining regulatory challenges.[78] Of course, such legislative changes also indicate that cannabinoids are available for both recreational and medicinal use, with high-quality studies urgently needed to catch up on the efficacy for pain management.[79] Our meta-analyses specific to topical cannabinoids echo many limitations of previous cannabinoid reviews, with the lumping together of multiple chronic pain pathologies, experimental pain models, and cannabinoid compounds.[79] As previously stated, while preclinical animal evidence supports the underlying mechanisms of peripheral efficacy of topical cannabinoids for pain management, there is still a need for large-scale human clinical trials, with differing topical formulations and doses.

CONCLUSION

Overall, our findings suggest that topical or peripherally applied cannabinoids may have benefits in the management of pain; however, the overwhelming majority of current knowledge stems from preclinical studies with generally unclear to concerning risk of bias, resulting in low quality of evidence. With regard to knowledge generated in the course of investigation in humans, there is preliminary evidence of efficacy in models of chronic pain (eg, capsaicin). However, studies are, overall, lacking in quantity and methodological quality. The ever-present burden of chronic pain warrants a safe, effective, alternative therapy. To that end, there is a need for high-quality RCTs in humans on cannabinoid safety and efficacy in pain management, bridging the gap between preclinical and clinical observations.

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ORCID iD

Lukas D Linde http://orcid.org/0000-0001-5180-4904

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