COLLEGE OF PHARMACY
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L. S. SKAGGS PHARMACY INSTITUTE

CANNABIS, CANNABIS-DERIVED PRODUCTS, OR CANNABINOIDS EVIDENCE REPORT:

RAPID LITERATURE REVIEW OF ACUTE PAIN

Interim report of the Drug Regimen Review Center

Reporting period: April 12, 2022 through June 1, 2022

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1.0 INTRODUCTION AND OBJECTIVE

The University of Utah Drug Regimen Review Center (DRRC) assists the Utah Center for Medical Cannabis (CMC) and Utah Cannabis Research Review Board (CRRB) in identifying medical literature on the use of medical cannabis, and cannabinoid-based products. This is an interim report of the DRRC's work during the reporting period. The interim report will summarize DRRC activities and/or evidence obtained during the reporting period.

The **objective** of this interim rapid review report is to summarize relevant clinical evidence that emerged during the reporting period. *Relevant evidence* in the current reporting period includes systematic reviews (SRs) of randomized controlled trials (RCTs) and/or RCTs examining the use of cannabis, cannabis-derived products, or cannabinoids (hereafter referred to as cannabinoid-based products [CBPs]) for the treatment of acute pain.

2.0 BACKGROUND

Pre-clinical animal studies support the potential effectiveness of CBPs for acute pain disorders.[1,2] Additionally, clinical trials using experimental pain models (eg, intradermal capsaicin, or electrical currents administered in laboratories to human volunteers) have explored the role of CBPs for acute pain. According to a recent SR, which may include only a subset of all trials evaluating analgesia due to including studies based on report of opioid-sparing outcomes, and expert opinion non-systematic review article about such studies, the anti-nociceptive activity of CBPs in clinical experimental models is *inconclusive*.[3,4] The SR authors identified 5 human experimental pain model crossover, double-blinded, trials (82 total participants, including 4 using dronabinol at doses of 2.5 mg to 20 mg, and 1 using THC [delta-9-tetrahydrocannabinol]-containing cigarettes) of moderate quality. These studies showed limited evidence of anti-nociceptive activity of CBPs relative to control in 2 studies and a reduction in affective feelings of pain ("unpleasantness") in a third. Yet, the other 2 trials support that CBPs may attenuate opioid analgesia (observed with dronabinol 2.5 mg but not 5 mg), or may induce hyperalgesia (observed with dronabinol 20 mg).[5] Similarly, the expert opinion letter describes 7 (including 6 studies not mentioned by the SR) of these experimental trials, reporting "They are mostly negative, and in 4 of them, more intense pain was reported at high doses."[4] Two recent placebo-controlled crossover experimental acute pain (intradermal electrical stimulation) trials also found a lack of benefit for a single-dose of CBD (cannabidiol) 800 mg orally on pain intensity, hyperalgesia, or allodynia[6]; and a single-dose of CBD 1600 mg orally on pain intensity, allodynia, or opioid-induced hyperalgesia.[7]

3.0 METHODS

This rapid review targeted relevant studies of CBPs for acute pain. Cannabinoids include plant-based or (semi-) synthetic cannabinoids. Acute pain was defined as pain of a duration no longer than about 1 month resulting from injury or tissue damage, consistent with general guidance.[8,9] **The primary focus was clinical trials of patients with an acute pain condition (ie, not experimental human or animal pain models).** The primary outcome of interest was any change in pain intensity; however, other outcomes were considered if reported by a SR.

Literature searches containing free-text and controlled vocabulary (eg, MESH) terms for CBPs for the treatment of acute pain were developed in Ovid-Medline and translated to Embase. A hierarchy of

evidence approach was used, meaning that the initial search queried SRs or systematic-review meta-analyses (SRMAs) of RCTs, and any subsequent searches proceeded to lower levels of evidence (ie, single RCTs) if needed. For feasibility, subsequent searches for RCTs were restricted to publication dates after the literature search date of any high-quality SRs (eg, Fisher et al. 2021), from 2020 to present.

Eligibility was assessed in title/abstract and full-text screening by a single author. Relevant evidence was extracted from SRs. Details of included RCTs and a quality-of-evidence and/or risk of bias rating from 1 or more SR were primarily extracted from SRs. Occasionally, additional detail (eg, safety outcomes) was gathered from the original RCT. A risk of bias assessment using the Cochrane Risk of Bias 2 tool[10] was performed for any RCT that was not already evaluated by a SR.

4.0 RESULTS

Our literature search strategy (reported in **Appendix A**) yielded approximately 228 potential SRs and 125 potential RCTs. After title/abstract and full-text screening, 11 SRs were identified that included at least 1 RCT of a CBP for an acute pain condition published between 2001 and 2022. We found a total of 11 relevant RCTs that were published in 1981 through 2022; of these, 10 RCTs were included among the identified SRs.

4.1 Summary of Systematic Reviews/Meta-Analyses (SRs/SRMAs)

Table B in **Appendix B** summarizes characteristics and conclusions about efficacy of CBPs for acute pain from 11 included SRs/SRMAs published between 2001 and 2022. Each review contained between 1 and 8 relevant RCTs with varying objectives and eligibility criteria. For example, some included studies on pain of any type or chronicity[3,11-13]; whereas, others focused on acute pain,[14,15] post-surgical (acute) pain,[16,17] or pain associated with specific conditions (eg, orthopedics,[18,19] or orofacial pain[20]). One SRMA evaluated the possible opioid-sparing effects of cannabinoids as a primary outcome.[3] None of the SRs included *all* RCTs identified by the overall search.

4.1.1 Analgesic effects of CBPs for acute pain

The majority of SRs addressing acute pain concluded that CBPs are <u>not</u> better than control for analgesia; these conclusions are primarily based on short-term patient-reported pain scores in a post-operative setting.[12,15,16,20] However, 2 SRs (Gazendam et al. 2020 and Campbell et al. 2001) did report a *possible benefit* of CBP for acute pain; both of them included an RCT by Jain et al (1981) that showed a significant reduction in pain for intramuscular levonantradol compared to placebo.[11,21] The pooled synthesis of 6 trials by Gazendam et al. showed a small, but significant reduction in patient-reported pain scores for CBPs versus control (mean difference [95% confidence interval]: –0.90 [–1.69 to –0.10], I^2 = 65%).[14] In contrast, the pooled analysis of 3-7 RCTs by Abdallah et al. 2020 found potentially *increased* post-operative pain at rest at 12 hours, but not 1-6 hours, for CBP versus control (weighted mean difference in pain score at 12 hours [95% confidence interval]: 0.83 [0.04 to 1.63], I^2 = 72%). These conclusions should be interpreted in the context of the substantial heterogeneity observed in the 2 SRMA pooled syntheses (ie, the reports by Gazendam et al. and Abdallah et al.), and the fact that these 2 SRMAs lacked a robust assessment of the causes of the heterogeneity, which is a best practice for SRMAs.[22] A subgroup analysis in one (ie, Gazendam et al.) did show that route of administration could be one

potential source of heterogeneity; that is, observed analgesia versus control might be present with intramuscular levonantradol, but not oral CBPs.[14]

4.1.2 Opioid-sparing effects of CBPs

Only limited evidence was found in SRs for opioid consumption reduction (in terms of morphine equivalents when used concurrently with a CBP); this evidence does not support a reduction in opioid use when used concurrently with CBPs.[3,16,18]

4.1.3 Safety of CBPs

One SRMA summarized findings from 8 RCTs in the post-operative setting and found no significant differences between control and CBP for some AEs;[16] however, a higher odds of dizziness[14] and hypotension[14,16] for CBPs versus control was observed.

4.1.4 Risk-of-bias assessment in SRs/SRMAs

Few SRs designated a risk of bias/quality rating for the *overall body of evidence*. One SRMA (Gazendam et al.) rated the overall evidence from 6 included RCTs for acute pain to be low-quality due to a serious risk of bias and inconsistency.[14] Another (Neilsen et al.), which contained 3 RCTs not included by Gazendam et al., considered the quality of evidence for possible opioid-sparing effects to be high.[3] A third (Abdallah et al.) evaluated the quality of evidence for the few secondary outcomes where it was possible to perform a meta-analysis (ie, data from a subset of 8 RCTs they included); they found the evidence to be of moderate quality for interim (1-12 hours post-operatively) resting analgesia, and high quality for adverse events.[16]

4.2 Summary of Randomized Controlled Trials (RCTs)

Table C in **Appendix C** contains evidence tables from 11 randomized, placebo-controlled trials that examined CBPs for acute pain. The majority examined post-operative pain after a variety major surgical interventions (n = 8),[5,21,23-28] 2 assessed pain after a tooth extraction,[29,30] and 1 included emergency room patients with acute, non-traumatic, low-back pain.[31] One postoperative trial (knee arthroplasty) was conducted in patients with baseline chronic pain (ie, those with knee osteoarthritis).[25] One other included pain as a secondary outcome; the primary outcome was post-operative nausea and vomiting (the primary outcome).[27] The sample sizes of the individual trials ranged between 20 and 340 participants.[5,21,23-31]

The CBP intervention was a single cannabinoid in all trials, including 3 that used intramuscular levonantradol (a THC analog that is not approved by the U.S. Food and Drug Administration),[24,26] 2 that used THC or dronabinol 5 mg orally,[23,28] and 2 that used nabilone 0.5 to 2 mg orally.[5] Two other trials used CBD; one at a dose of 400 mg orally,[31] and the other applied CBD topically using an unknown total dose.[25] Other experimental cannabinoids were used in the remaining trials, including GW842166, a selective cannabinoid type 2 (CB2) receptor agonist,[29] and AZD1940, a peripherally selective cannabinoid type 1 (CB1) and CB2 receptor agonist.[30]

A majority administered only one dose of the cannabinoid,[21,23,24,26,27] and the timing of dose administration relative to surgery varied. For example, one trial administered the dose on post-operative day 2 (Buggy et al.),[23] and another administered the dose pre-operatively (Levin et al.).[27]

Two other studies administered repeated oral doses in the acute post-operative period (approximately 3 to 8 doses).[5,28] The longest duration of use was 2 weeks, with topical CBD applied three times daily.[25]

All trials included a placebo comparator arm,[5,21,23-31] **often given with other analgesic medications** (ie, co-occurring medications for all trial participants).[5,23,25,28-31] However, surgical analgesia characteristics[16] and/or whether participants received other postoperative analgesia was not reported for all post-operative pain trials.[21,26,27] An active comparator arm, including meperidine (an opioid)[24] and/or a non-steroidal anti-inflammatory drug (ketoprofen, ibuprofen, naproxen),[5,29,30] was also included in some trials.

4.2.1 Analgesic effects of CBPs in RCTs

Only 2 trials showed some degree of analgesic activity of the CBP relative to placebo; these were both trials of a single dose of intramuscular levonantradol, with one trial reporting statistically significant pain reduction,[21] and the other reporting numerical decreases in pain compared to placebo of unknown statistical significance.[26] Both of these trials both were rated as having an unclear risk of bias for all bias measures.[21,26] Limited information about the effects of levonantradol compared to placebo were available for the final levonantradol trial[15]; however, the active comparator meperidine significantly outperformed levonantradol and placebo for reducing pain in the acute post-operative period.[15,24]

The remaining trials generally did not find significant differences in analgesia for CBPs versus placebo, primarily based on subjective, pain measures.[23,25,27-31] One trial of patients that received various major surgeries found significant *increases* in patient-reported pain scores relative to placebo and active comparator with the highest dose of nabilone (2 mg) at later time periods (9-24 hours post-operative) at rest and with movement.[5] After tooth extraction, patients receiving an NSAID exhibited statistically reduced pain compared to placebo, but a difference compared to placebo was not observed for the experimental cannabinoids.[29,30]

4.2.2 Safety findings in RCTs

In some trials, the overall rate of adverse events (AEs) was similar between the CBP and comparator arms.[5,24,25,27,31] Numerically, more AEs were reported with levonantradol compared to placebo in one trial, a difference of unknown statistical significance.[21] Some AEs with a numerically higher rate for the CBP versus placebo included a heightened surrounding awareness for THC;[23] increased euphoria,[5] sedation,[5] and lack of post-operative muscle coordination[27] with nabilone; and increased postural dizziness, nausea, hypotension, and headache with AZD1940.[30]

4.2.3 RCT risk-of-bias assessment (within-study limitations)

Some selected notes about the limitations of available RCT evidence, based on quality or risk of bias (ROB) assessments by SR(s), are given below:

- Limited information on ROB was available for some trials (eg, Kantor et al. that is only published as an abstract, Jain et al., and Guillard et al.) as evidenced by having an unclear ROB for all Cochrane bias indicators.[15,16,19]
- Only 1 trial was rated as having high-quality evidence using GRADE criteria (Bebee et al.).[3]
- One trial was considered to be low-risk for all Cochrane ROB indicators except for selective reporting bias (Levin et al.).[16]
- Several trials were rated as having an unclear ROB for 2 or more evaluated bias domains (see **Appendix C** for details).
- One trial (Haffar et al. 2022) that was not included in any SRs required a separate ROB assessment, summarized in **Table 1**.

Table 1. Risk of Bias Assessment for Haffar et al. 2022[25] not Included in any Systematic Review[a]

Randomization process	Deviations from assigned intervention	Incomplete outcome data	Outcome Measurement	Selective reporting	Other potential bias
Random Sequence Generation	**Blinding – participants/ personnel**	Low risk[b]	Low risk[c]	Some concerns (insufficient details)	• Funded by supplier of CBD stick; unable to access COI statement • Adherence to multimodal pain regimen, and study interventions not assessed
Low risk	Low risk				
Concealment of Allocation	**Analysis in assigned groups**				
Some concerns (insufficient details)	Low risk				

Abbreviations: CBD, cannabidiol; COI, conflict of interest; Post-op, post-operative; RCT, randomized controlled trial
Key:
[a] *Risk of bias assessment for any trial not included by a systematic review (assessing quality/bias) was performed using the Cochrane Risk of Bias 2 tool[10]*
[b] *Analysis was only performed for patients with complete outcome data (80/89 participants). Reasons for incomplete data were reported (ie, lack of receipt of the intervention [n=2], discontinuation of the intervention [n=5], lost to follow-up [n=1], and co-use of post-op cannabis [n=1]). Despite this, rated as low risk because most stated reasons for the incomplete data seem unlikely to be related to the value of the missing data.*
[c] *Although criteria led to low risk of bias assessment, it was noted that the author's provided little detail of how outcomes were analyzed (eg, a mean visual analog score was reported on certain days; it is not known when during the day this was calculated for each person, and how these measures were combined).*

4.2.4 Between-study limitations of RCTs

Conclusions about the body of evidence are limited by heterogeneity related to population, intervention, or comparators. Several key differences in their research question limit the utility of findings for pooling data. Selected notes about the between-study limitations are given below:

- The majority of trials examined acute post-operative pain[5,21,23-28] after major surgery; however, the type of surgery was variable (see **Appendix C**).
- Most trials gave no information about participants' CBP use history (based on the abstract or full-text, or details published in an SR for 2 non-English language studies). Some trials mentioned

CBP-use related eligibility exclusions: Buggy et al. excluded patients with any prior use of cannabis,[23] Beaulieu et al. excluded patients with current cannabis use,[5] Haffar et al. allowed prior but not active cannabinoid use at the time of the trial,[25] and Bebee et al. excluded patients reporting CBD or cannabis use in the 7 days preceding trial entry.[31]

- It is possible that the dose-response relationship for the studied cannabinoid and acute pain analgesia is not well-characterized in many trials. Additionally, since the majority of studies administered a single CBP dose, there is limited information about the use of repeated doses.
- CBP interventions were limited to experimental single cannabinoids (ie, levonantradol, GW842166, AZD1940) or other single cannabinoids (THC, THC analog, or CBD).
- The majority of studies administered a single CBP dose and observed patients for only a short duration of follow-up.
- In many cases, the CBP was added to other analgesics (and compared to placebo with the other analgesics), and those analgesics may have impacted the patient-reported pain scores.
- In some cases, there was insufficient information to assess concurrent use of medications (eg, in Kantor et al., Jain et al., and Levin et al.), including for the 2 trials that demonstrated acute analgesia for levonantradol versus placebo.[21,26]
- Limited outcomes were assessed. For example, there was a lack of information on patient-reported outcomes such as satisfaction or quality of life.

5.0 Summary

This rapid literature review identified 11 SRs, and 11 RCTs (10 that were included among the 11 SRs) including between 20 and 340 participants that evaluated the use of a CBP for acute pain. Most studies were conducted in the acute post-operative period after various major surgeries; other settings include 2 trials of patients undergoing tooth extraction, and a single trial of patients presenting to the emergency room with non-traumatic acute lower back pain.

There is uncertainty about the risk of bias for the majority of RCTs. SR authors rated the majority of trials as having at least 2 Cochrane bias domains with unclear risk; only 2 trials were considered as either high quality by GRADE criteria, or low risk for nearly all Cochrane bias domains. Definitive conclusions about acute analgesic efficacy are hampered by between-study variability (ie, heterogeneity) in the studied population, CBP intervention, co-analgesic medications, and comparators. Of importance, the RCTs only studied a single cannabinoid, and many of the trials administered only a single dose.

Overall, the limited evidence from RCTs of patients with acute pain conditions is *inconclusive* regarding the anti-nociceptive effects of CBPs for acute pain. The majority of trials did not demonstrate significant differences in analgesia for single cannabinoids (including oral THC or nabilone, oral experimental cannabinoids that are CB1 and/or CB2 agonists, or CBD topically or orally) versus placebo; however, 2 trials of intramuscular levonantradol demonstrated numerically[26] or statistically[21] reduced pain relative to placebo.

The CRRB may review this information to assist with formulating recommendations/considerations for use of CBPs for acute pain.

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APPENDIX A: LITERATURE SEARCH

Table A1. Ovid-Medline Search for Cannabis Acute Pain Systematic Reviews (performed 4-29-22)

#	Search	Results
1	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	34755
2	(mari?uana or pot or hashish* or bhang* or ganja* or weed* or hemp*).ti,ab,kw,kf.	62598
3	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	59015
4	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	586
5	(cannabi* and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	1893
6	(nabilone or dronabinol or marinol or syndros or cesamet or epidiolex or nabiximol* or Sativex).ti,ab,kw,kf.	1094
7	2 or 3 or 4 or 5 or 6	115370
8	1 or 7	118908
9	exp acute pain/ or exp Pain, postoperative/	49117
10	(pain* adj6 (acute or short-term or postop* or post-op* or postsurg* or post-surg* or postproc* or post-proc*)).ti,ab,kw,kf.	87077
11	9 or 10	110239
12	meta-analysis/ or (metaanaly$ or meta-analy$).ti,ab,kw,kf. or "Systematic Review"/ or ((systematic* adj3 review*) or (systematic* adj2 search*) or cochrane$ or (overview adj4 review)).ti,ab,kw,kf. or (cochrane$ or systematic review?).jw.	452278
13	(MEDLINE or Embase or PubMed or systematic review).tw. or meta analysis.pt.	422536
14	12 or 13	527904
15	8 and 11 and 14	39

Table A2. Embase Search for Cannabis Acute Pain Systematic Reviews (performed 4-29-22)

#	Search	Results
#1	'pain'/exp AND (acute:ti,ab,kw OR postsurg*:ti,ab,kw OR 'post surg*':ti,ab,kw OR postproc*:ti,ab,kw OR 'post proc*':ti,ab,kw OR postop*:ti,ab,kw OR 'post op':ti,ab,kw)	311,874
#2	'postoperative pain'/exp OR 'postprocedural pain'/exp	80,428
#3	'pain'/exp	1,528,215
#4	#1 OR #2	333,869
#5	#2 OR #3	1,528,217
#6	(pain* NEAR/6 (acute OR 'short term' OR postop* OR 'post op*' OR postsurg* OR 'post surg*' OR postproc* OR 'post proc*')):ti,ab,kw	126,747
#7	#4 OR #6	362,869
#8	#5 OR #6	1,554,988

#	Search	Results
#9	('cannabinoid'/exp OR 'cannabis use'/exp OR 'cannabis smoking'/exp) AND 'cannabis addiction'/exp[1]	6,940
#10	mari?uana:ti,ab,kw OR pot:ti,ab,kw OR hashish*:ti,ab,kw OR bhang*:ti,ab,kw OR ganja*:ti,ab,kw OR weed*:ti,ab,kw OR hemp*:ti,ab,kw	78,868
#11	tetrahydrocannab*:ti,ab,kw OR cannabi*:ti,ab,kw OR thc:ti,ab,kw OR cbd:ti,ab,kw OR cbn:ti,ab,kw OR cbg:ti,ab,kw OR cbc,:ti,ab,kw OR thcv:ti,ab,kw OR cbdv:ti,ab,kw OR cbcv:ti,ab,kw OR cbgv:ti,ab,kw OR thca:ti,ab,kw OR cbda:ti,ab,kw OR cbga:ti,ab,kw OR cbna:ti,ab,kw	89,913
#12	thc:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	763
#13	cannabi*:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	2,404
#14	nabilone:ti,ab,kw OR dronabinol:ti,ab,kw OR marinol:ti,ab,kw OR syndros:ti,ab,kw OR cesamet:ti,ab,kw OR epidiolex:ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw	1,640
#15	#9 OR #10 OR #11 OR #12 OR #13 OR #14	161,207
#16	(cochrane*:jt OR 'systematic review*':jt OR 'meta analysis'/exp OR 'systematic review'/exp OR ((systematic* NEAR/3 review*):ti,ab,kw) OR ((systematic* NEAR/2 search*):ti,ab,kw) OR 'meta analys*':ti,ab,kw OR metaanalys*:ti,ab,kw OR ((overview NEAR/4 (review OR reviews)):ti)) NOT ('conference abstract'/it OR 'conference review'/it)	502,429
#17	#7 AND #15 AND #16	73
#18	#8 AND #15 AND #16	374
#19	#8 AND #15 AND #16 AND [2020-2022]/py	141
#20	#17 OR #19	189

Table A3. Ovid-Medline Search for Cannabis Acute Pain RCTs 2020-2022 (performed 5-13-22) Database(s): Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to May 11, 2022 Search Strategy:

#	Searches	Results
1	exp Cannabis/ or exp cannabinoids/ or exp Medical Marijuana/ or exp "Marijuana Use"/ or exp Marijuana Abuse/	34887
2	(mari?uana or pot or hashish* or bhang* or ganja* or weed* or hemp*).ti,ab,kw,kf.	63145
3	(Tetrahydrocannab* or cannabi* or THC or CBD or CBN or CBG or CBC, or THCV or CBDV or CBCV or CBGV or THCA or CBDA or CBGA or CBNA).ti,ab,kw,kf.	59188
4	(THC and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	588
5	(cannabi* and (analog* or enantiomer* or isomer*)).ti,ab,kw,kf.	1897
6	(nabilone or dronabinol or marinol or syndros or cesamet or epidiolex or nabiximol* or Sativex).ti,ab,kw,kf.	1097
7	1 or 2 or 3 or 4 or 5 or 6	119604

[1] Note: an error occurred on this line. It should be OR 'cannabis addiction'/exp. The author of this summary updated the query and screened any differences in the relevant results, not finding any.

8	exp acute pain/ or exp Pain, postoperative/	49268
9	(pain* adj10 (acute or short-term or postop* or post-op* or postsurg* or post-surg* or postproc* or post-proc* or arthroplast* or joint* or surg*)).ti,ab,kw,kf.	160681
10	8 or 9	179422
11	((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.)	1370299
12	7 and 10 and 11	95
13	limit 12 to yr="2020 -Current"	28

Table A4. Embase Search for Cannabis Acute Pain RCTs 2020-2022 (performed 5-13-22)

#	Search	Results
#1	'pain'/exp AND (acute:ti,ab,kw OR postsurg*:ti,ab,kw OR 'post surg*':ti,ab,kw OR postproc*:ti,ab,kw OR 'post proc*':ti,ab,kw OR	312,676
#2	'postoperative pain'/exp OR 'postprocedural pain'/exp	80,650
#3	#1 OR #2	334,729
#4	(pain* NEAR/10 (acute OR 'short term' OR postop* OR 'post op*' OR postsurg* OR 'post surg*' OR postproc* OR 'post proc*' OR arthroplast* OR joint* OR surg*)):ti,ab,kw	235,181
#5	#3 OR #4	446,236
#6	'cannabinoid'/exp OR 'cannabis use'/exp OR 'cannabis smoking'/exp OR 'cannabis addiction'/exp	91,715
#7	mari?uana:ti,ab,kw OR pot:ti,ab,kw OR hashish*:ti,ab,kw OR bhang*:ti,ab,kw OR ganja*:ti,ab,kw OR weed*:ti,ab,kw OR hemp*:ti,ab,kw	79,083
#8	tetrahydrocannab*:ti,ab,kw OR cannabi*:ti,ab,kw OR thc:ti,ab,kw OR cbd:ti,ab,kw OR cbn:ti,ab,kw OR cbg:ti,ab,kw OR cbc,:ti,ab,kw OR thcv:ti,ab,kw OR cbdv:ti,ab,kw OR cbcv:ti,ab,kw OR cbgv:ti,ab,kw OR thca:ti,ab,kw OR cbda:ti,ab,kw OR cbga:ti,ab,kw OR cbna:ti,ab,kw	90,246
#9	thc:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	765
#10	cannabi*:ti,ab,kw AND (analog*:ti,ab,kw OR enantiomer*:ti,ab,kw OR isomer*:ti,ab,kw)	2,410
#11	nabilone:ti,ab,kw OR dronabinol:ti,ab,kw OR marinol:ti,ab,kw OR syndros:ti,ab,kw OR cesamet:ti,ab,kw OR epidiolex:ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw	1,646
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	187,585
#13	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti	2,931,511
#14	#5 AND #12 AND #13 AND [2020-2022]/py	97

APPENDIX B: EVIDENCE TABLES FOR SRS/SRMAS

Table B. Overview of Systematic Reviews with at Least 1 RCT of a CBP for Acute Pain

First author (publication year) **Study design**	**Included RCTs** (overall quality ratings if available)	**Efficacy**	**Safety**	**Notes**
Neilsen et al. (2022)[3] SRMA	3 RCTs: Bebee 2021, Levin 2017, Seeling 2006 (high quality)	"…no evidence of opioid-sparing effects of cannabinoids in acute pain"[3] (no MA of these trials)	Not reported	• Focus is co-use of opioids and cannabinoids ("opioid sparing effect") • Authors also looked at pre-clinical data, observational studies, experimental pain models, and other pain clinical trials (cancer, non-cancer chronic pain)
Vivace et al. (2021)[18] SR	3 RCTs: Beaulieu 2006, Jain 1981, Levin 2017 (rated as medium quality)	• Mixed analgesic effect: one reporting cannabinoids reduced pain, one reporting no effect, and one with increased pain • Opioid-sparing: no change in morphine equivalents used in 2 trials • Potential for gender-dependent effects of cannabinoids on analgesia (eg, Jain et al. included primarily male participants, while the other studies included all or nearly all females): "Attention to route of administration, dosage, choice of cannabinoid, and potential differences in gender response may be important considerations in designing future trials"[18]	Higher AE rate in the cannabinoid arm vs control arm	• Focus is orthopedic surgery or related orthopedic disorders • One additional trial was for post-operative pain, but was not randomized or controlled
Fisher et al. (2021)[12]	4 RCTs: Kalliomaki 2013, Levin et al 2017,	"We found no analgesic effect for CBM [cannabis-based medicines] in acute or cancer pain when treatment was delivered up to 7 days"[12]	Not reported	• Authors also looked at any type of pain and performed a MA of studies

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based products; CI, confidence interval; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MA, meta-analysis; MME, milligrams of morphine equivalents; N/S, not specified; OA, osteoarthritis; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; RCTs, randomized controlled trials; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty

Key: [a] Authors did not classify chronicity of pain among included trials. One table shows duration of pain eligibility criteria among included trials, but this does not reliably show chronicity (eg, 1 trial reporting 2 weeks duration was checked by this writer and found to study chronic pain) and many trials did not report this information. Thus, we cannot be sure that there were no other acute pain trials; this is a limitation of the screening approach.

First author (publication year) **Study design**	**Included RCTs** (overall quality ratings if available)	**Efficacy**	**Safety**	**Notes**
SRMA	Ostenfeld 2011, Seeling 2006	(no MA of these trials)		categorized by treatment length (>7 vs <7 days). • Overall conclusions: "The evidence neither supports nor refutes claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain"[12]
Grossman et al. (2021)[20] SR	2 RCTs: Kalliomaki 2013 and Ostenfeld 2011	"The studies…showed no statistically significant postoperative pain improvement following mandibular third molar surgery in comparison with ibuprofen."[20]	See Table C in Appendix C (individual RCT summary)	• Focus is orofacial pain • 1 additional RCT examined the potential myorelaxant effect of topical CBD twice daily in people with temporomandibular disorders; secondarily, they reported with-in group decreases in pain scores from baseline to 14 days in both the CBD and placebo groups
Rabgay et al.[a] (2020)[13] SRNMA	1 RCT: Buggy 2003	Authors do not report conclusions for acute pain specifically	See Table C in Appendix C (individual RCT summary)	• Focus is any type of pain; included experimental pain models • Authors classified type of pain (eg, cancer, nociceptive, neuropathic) and type of cannabinoid (with route and dose), and report effects of certain formulations on types of pain
Gazendam et al. (2020)[14]	6 RCTs: Beaulieu 2006, Buggy 2003, Jain 1981,	• MA of patient-reported pain scores (all 6 RCTs; mean difference [95%CI]): –0.90 [–1.69 to –0.10], P=0.002, I^2 = 65%	Serious AE in cannabinoid arm (3.7%) vs control arm	• Focus is acute pain • Authors note that route of administration could influence acute

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based products; CI, confidence interval; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MA, meta-analysis; MME, milligrams of morphine equivalents; N/S, not specified; OA, osteoarthritis; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; RCTs, randomized controlled trials; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty

Key: [a] Authors did not classify chronicity of pain among included trials. One table shows duration of pain eligibility criteria among included trials, but this does not reliably show chronicity (eg, 1 trial reporting 2 weeks duration was checked by this writer and found to study chronic pain) and many trials did not report this information. Thus, we cannot be sure that there were no other acute pain trials; this is a limitation of the screening approach.

First author (publication year) **Study design**	**Included RCTs** (overall quality ratings if available)	**Efficacy**	**Safety**	**Notes**
SRMA	Kalliomaki 2013, Levin 2017, Ostenfeld 2011 (Overall quality rating: Low, due to serious risk of bias and serious risk of inconsistency)	• Largest and significant effect on pain intensity seen in Jain et al. study of IM levonantradol (overall benefit not observed in studies using an oral dosage form) • "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."[14]	(2.65%): OR 1.44 (0.60 to 3.48) OR [95%CI for cannabinoid vs control]: of dizziness (1.96 [1.20 to 3.20], P=0.007); hypotension (3.61 [1.02 to 12.80], P=0.047)	pain treatment effectiveness; examples of reasons they cite for this are oral doses have a slower onset of effect (relative to IM), and in general, the bioavailability of the oral dosage forms is poor
Adballah et al. (2020)[16] SRMA	8 RCTs: Jain 1981, Guillaud 1983, Buggy 2003, Beaulieu 2006, Seeling 2006, Ostenfeld 2011, Kalliomaki 2013, Levin 2017 (Overall GRADE quality rated [provided for selected outcomes]: Moderate for interim resting pain scores; high for AE)	• Morphine equivalents use within 24 h post-op: no significant difference in CBP vs control in 2 RCTs reporting this outcome • Pain scores at rest at 24 h post-op: no significant difference in pain scores vs control in 1 RCT; 2nd RCT reported higher pain scores in CBP vs control arm • Interim pain scores at rest (1-12 h post-op): Authors report a MA containing data from a variable number of RCTs. No significant differences were reported between the CBP and control arms for 1 h post-op (7 RCTs; I^2 = 86%) or 6 (6 RCTs); however, the pooled weighted mean difference at 12 h showed significantly higher pain scores in the CBP arm (0.83 [95%CI, 0.04 to 1.63]; 3 RCTs; I^2 = 71%)	Most common AE across the 8 RCTs (not necessarily reported by each RCT): "…blurred vision, hypotension, dizziness, drowsiness, dry mouth, hallucinations, headache, nausea"[16] Significantly higher odds of hypotension with CBP vs control (data from 4 RCTs; OR 3.24 [99%CI 1.12 to 9.36]; I^2 = 41%)	• Focus is post-surgical acute pain • Authors also looked at observational studies • Included studies did not report quality of recovery, patient satisfaction, or opioid-related side effect outcomes

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based products; CI, confidence interval; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MA, meta-analysis; MME, milligrams of morphine equivalents; N/S, not specified; OA, osteoarthritis; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; RCTs, randomized controlled trials; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty

Key: [a] Authors did not classify chronicity of pain among included trials. One table shows duration of pain eligibility criteria among included trials, but this does not reliably show chronicity (eg, 1 trial reporting 2 weeks duration was checked by this writer and found to study chronic pain) and many trials did not report this information. Thus, we cannot be sure that there were no other acute pain trials; this is a limitation of the screening approach.

First author (publication year) **Study design**	**Included RCTs** (overall quality ratings if available)	**Efficacy**	**Safety**	**Notes**
		• Overall conclusions: "…analgesic role of perioperative cannabinoid compounds is limited, with no clinically important benefits detected when cannabinoids are added to traditional systemic analgesics vs the traditional systematic analgesics alone." "These results do not support the routine use of cannabinoids to manage acute postoperative pain…"[16] Additional concerns noted: possibility of increases pain and hypotension with CBPs	No other significant differences in MA of AE; however, the CI for the pooled estimate was wide in many cases, suggesting imprecision	
Madden et al. (2019)[19] SR	3 RCTs: Beaulieu 2006, Kantor 1981, Levin 2017	Authors do not report conclusions for acute pain specifically	See Table C in Appendix C (individual RCT summary)	• Focus is orthopedics (not acute pain specific), and study quality • Includes many types of studies in addition to RCTs including non-randomized studies, and SRs
Rai et al. (2017)[17] SR	2 RCTs: Beaulieu 2006, Buggy 2003	Higher-dose nabilone (2mg) increased pain at rest and with movement as an adjunct to opioids post-operatively; THC 5 mg did not significantly improve pain compared to PBO on post-op day 2	Not reported	• Review of options for post-surgical multimodal pain management (includes multiple classes of agents)
Stevens et al. (2017)[15] SR	7 RCTs: Jain 1981, Beaulieu 2006, Buggy 2003, Guillaud 1983, Kalliomaki 2013,	• Differences in pain intensity: 5 RCTs reported CBPs were similar to PBO; 1 RCT reported increased pain with CBP vs control; 1 RCT found CBP superior to PBO for analgesia	See Table C in Appendix C (individual RCT summary)	• Focus is acute pain

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based products; CI, confidence interval; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MA, meta-analysis; MME, milligrams of morphine equivalents; N/S, not specified; OA, osteoarthritis; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; RCTs, randomized controlled trials; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty

Key: [a] Authors did not classify chronicity of pain among included trials. One table shows duration of pain eligibility criteria among included trials, but this does not reliably show chronicity (eg, 1 trial reporting 2 weeks duration was checked by this writer and found to study chronic pain) and many trials did not report this information. Thus, we cannot be sure that there were no other acute pain trials; this is a limitation of the screening approach.

First author (publication year) **Study design**	**Included RCTs** (overall quality ratings if available)	**Efficacy**	**Safety**	**Notes**
	Ostenfeld 2011, Seeling 2006	• Overall conclusions: "On the basis of the available randomized controlled trial evidence, cannabinoids have no role in the management of acute pain"[15]		
Campbell et al. (2001)[11] SR	1 RCT (with 2 parts): Jain 1981	Levonantradol superior to PBO for post-op analgesia; "…but no more effective than codeine. Such a level of efficacy makes cannabinoids unlikely to be useful, certainly for moderate to severe postoperative pain."[11]	See Table C in Appendix C (individual RCT summary) "Levonantradol was commonly associated with adverse effects (predominantly drowsiness or sedation, or both), of which over half were considered to be moderate or severe"[11]	• Focus is in-human pain studies, including acute, chronic, or cancer pain

Abbreviations: AE, adverse event; CBD, cannabidiol; CBP, cannabinoid-based products; CI, confidence interval; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MA, meta-analysis; MME, milligrams of morphine equivalents; N/S, not specified; OA, osteoarthritis; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; RCTs, randomized controlled trials; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty

Key: [a] Authors did not classify chronicity of pain among included trials. One table shows duration of pain eligibility criteria among included trials, but this does not reliably show chronicity (eg, 1 trial reporting 2 weeks duration was checked by this writer and found to study chronic pain) and many trials did not report this information. Thus, we cannot be sure that there were no other acute pain trials; this is a limitation of the screening approach.

APPENDIX C: EVIDENCE TABLES FOR RCTS

Table C. Randomized Clinical Trials of Cannabis, Cannabis-Derived Medicines, or Cannabinoids for Acute Pain

First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
Post-operative Pain					
Kantor et al.* (1981)[26,a] R, DB, PC	Unknown surgery (n = 61)	Levonantradol (0.25 mg or 0.5 mg, or 1 mg) IM x 1 dose[b] Vs PBO Other treatments: N/S	• Numerical decreases in pain relative to PBO with higher doses, but not the lowest (0.25 mg) dose Length of follow-up: N/S	Mild euphoria, drowsiness, dry mouth, and nausea	Unclear ROB for all Cochrane bias indicators[19,c]
Jain et al.* (1981)[21] R, DB, PC	Surgery for acute fracture or trauma (n = 56)	Levonantradol (1.5 mg, 2 mg, 2.5 mg, or 3 mg) IM x 1 dose Vs PBO	• Significant reduction in pain for all doses vs PBO (P<0.05) • Rapid onset of effect, peaking 2-3h post-dose	57% vs 12.5% (levonantradol vs PBO) reported AE Most common: drowsiness; other: dizziness, other CNS changes including mild	Unclear ROB for all Cochrane bias indicators[16,c]

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

Key:

**** Indicates a lack of information (due to insufficient details or inability to access text in English) about whether the study was approved by an Institutional Review Board (IRB) or similar body*** *in the country of study conduct.* Studies without an asterisk indicated the study reported that it was IRB-approved or *approved by a local ethics committee.*

[a] *Published as an abstract only; only limited information available*

[b] *Authors also report 20 patients receiving oral levonantradol (1.5 – 3 mg), possibly as part of an ongoing trial (it is unclear). They report a possible analgesic effect, and also some AEs including catatonia and paranoia.*

[c] *The Cochrane Risk of Bias tool assesses methodological rigor and other quality indicators including random sequence generation, allocation concealment, blinding of key partiers (participants, outcome assessors), the completeness of outcomes (ie, attrition), selective reporting bias, and other bias noted by the review authors*

[d] *Article is published in French; review was limited to information reported by SR*

[e] *Article is published in a non-English language and unable to access full text. Limited to information reported by SR.*

[f] *Experimental selective CB2 receptor agonist*

[g] *Experimental peripherally selective CB1/CB2 receptor agonist*

First Author (Publication year) Study Design	Population (n, total enrolled participants)	Intervention	Efficacy Result(s)	Safety	SR Quality/ ROB Rating
		Other treatments: N/S	Length of follow-up: 6 h	hallucinations; mild increases in HR and decreases in BP with levonantradol	
Guillard et al.* (1983)[15,24,d] R, PC, (blinding unknown)	Renal surgery (n = 100)	Levonantradol (1 mg, or 2 mg) IM x 1 post-op dose in recovery room Vs meperidine 1 mg/kg IM, or PBO IM Other treatments: noramidopurine, camylofine	• Meperidine superior to PBO and both levonantradol groups for verbal pain scores in first 6 h (p<0.001), VAS pain scores in first 6 h (P<0.01) and global analgesia 24 h after dose • Limited details on levonantradol vs PBO; no differences for levonantradol vs PBO for 24h global analgesic effect • Time to supplemental analgesia significantly longer	No significant differences in overall AE between arms. Levonantradol 2 mg arm: 1 patient with agitation/hallucinations requiring intervention; levonantradol 1 mg arm: 1 moderate episode of agitation	Unclear ROB for all Cochrane bias indicators[15,16,c]

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

Key:

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[f] *Experimental selective CB2 receptor agonist*

[g] *Experimental peripherally selective CB1/CB2 receptor agonist*

First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
			in meperidine arm vs other arms (P<0.05) Length of follow-up: unknown; at least 24h		
Buggy et al. (2003)[23] R, DB, PC	Hysterectomy abdominal surgery (n = 20)	THC 5 mg orally x 1 dose post-op day 2 Vs Matched PBO Other treatments: morphine PCA (prior to post-op day 2)	• No statistically significant difference in summed pain intensity difference between THC and placebo with movement or at rest Length of follow-up: 6 h	Higher proportion with heightened awareness of surroundings with THC vs PBO (40% vs 5%, P = 0.04)	Unclear ROB for sequence generation and selective reporting[16]; another SR rated blinding of outcome assessed as unclear ROB[15]; low-risk for other bias indicators[16c]

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

Key:

**** Indicates a lack of information (due to insufficient details or inability to access text in English) about whether the study was approved by an Institutional Review Board (IRB) or similar body** in the country of study conduct.* Studies without an asterisk indicated the study reported that it was IRB-approved or *approved by a local ethics committee.*

[a] *Published as an abstract only; only limited information available*

[b] *Authors also report 20 patients receiving oral levonantradol (1.5 – 3 mg), possibly as part of an ongoing trial (it is unclear). They report a possible analgesic effect, and also some AEs including catatonia and paranoia.*

[c] *The Cochrane Risk of Bias tool assesses methodological rigor and other quality indicators including random sequence generation, allocation concealment, blinding of key partiers (participants, outcome assessors), the completeness of outcomes (ie, attrition), selective reporting bias, and other bias noted by the review authors*

[d] *Article is published in French; review was limited to information reported by SR*

[e] *Article is published in a non-English language and unable to access full text. Limited to information reported by SR.*

[f] *Experimental selective CB2 receptor agonist*

[g] *Experimental peripherally selective CB1/CB2 receptor agonist*

First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
Beaulieu et al. (2006)[5] R, DB, PC	Variable major surgeries [orthopedic, gynecologic, urologic, plastic or general] (n = 41)	Nabilone (1 mg or 2 mg) orally x 3 doses/24h, dose 1 pre-op Vs Ketoprofen 50 mg, vs PBO Other treatments: morphine PCA	• No difference in 24-h total morphine use between arms • Significantly higher patient-reported pain scores in the nabilone 2 mg arm vs other arms at rest (9-16 h post-op, and 17-24 h post-op) and with movement (17-24 h, vs placebo and ketoprofen only) (primary outcome was opioid use) Length of follow-up: 24 h	No serious AE. No significant differences in AE between groups; numerically higher euphoria rates in nabilone arm vs non-nabilone arms, and sedation with nabilone 2 mg	Unclear ROB for sequence generation and selective reporting[16]; another SR rated it as high risk for incomplete outcome data[14]; low-risk for other bias indicators[16c]
Seeling et al.* (2006)[15,28,e] R, DB, PC	Radical prostatectomy, age <70 years (n = 105)	dronabinol 5 mg orally x 8 doses, 1 pre-op and 7 post-op within 48h Vs	• No significant difference in opioid consumption between arms	Not available/not reported[h]	Evidence GRADE: "high"[3] (focus on opioid use outcome);

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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[c] *The Cochrane Risk of Bias tool assesses methodological rigor and other quality indicators including random sequence generation, allocation concealment, blinding of key partiers (participants, outcome assessors), the completeness of outcomes (ie, attrition), selective reporting bias, and other bias noted by the review authors*

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[f] *Experimental selective CB2 receptor agonist*

[g] *Experimental peripherally selective CB1/CB2 receptor agonist*

First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
		PBO dronabinol Other treatments: piritramide PCA	• Median resting pain scores did not significantly differ between arms Length of follow-up: 48 h		Unclear ROB for all bias indicators other than complete outcome data reported[12,C]
Levin et al. (2017)[27] R, DB, PC	Elective surgeries of many types; gynecologic most common (30-35%); 100% female (n = 340)	Nabilone 0.5 mg orally x 1 dose pre-op before general anesthesia Vs control Other treatments: N/S	• No significant analgesic benefit (NRS pain scores) vs PBO within 30 min post-op (at rest, P=0.47, with movement, P=0.70) • No significant difference in max pain score vs PBO (Difference, 95%CI at rest: –0.50, –1.78 to 0.76; P = 0.43; Difference, 95%CI with	Similar overall AE rate, and types of AE between arms. One only one AE significantly differed: lack of muscle coordination, which was higher in the PBO arm pre-op, and higher in the nabilone arm post-op	Low ROB for all bias indicators other than unclear ROB for selective reporting[16,c]

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
			movement: –0.66, –13.5 to 12.22; P=0.92) • No significant differences between arms for mean MME given in the OR (P = 0.40) or PACU (P=0.62) (*Primary outcome*: post-op nausea/vomiting; pain = secondary outcome) Length of follow-up: 2 h		
Haffer et al. (2022)[25] R, DB, PC	Primary knee OA post unilateral TKA (n = 89; 80 included in analysis)	Topical CBD stick (120 mg/oz) Vs Matched topical EO (arnica/wintergreen) stick Vs	• No differences in mean pain intensity (by VAS), other than higher pain in the CBD-only arm vs EO-only arm on post-op day 2, which did not persist at other time points	CBD-only arm: mild skin reaction (1/19) EO-only arm: mild skin reaction (1/21) PBO-arm: 1 readmission	Unclear ROB for allocation concealment and selective reporting; see Table 1

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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First Author (Publication year) Study Design	Population (n, total enrolled participants)	Intervention	Efficacy Result(s)	Safety	SR Quality/ ROB Rating
	Median age ~65 years; prior use of CDP allowed, chronic MME>20 excluded	Matched topical CBD + EO stick Vs Matched topical PBO stick All: TID from post-op day 0 to day 14 Other treatments: 1000 mg APAP QID, 300 mg gabapentin TID, 15 mg meloxicam daily; if moderate to severe pain: oxycodone 5-10 mg Q4-6h prn *or* tramadol 50 mg TID prn	• Similar mean opioid use between arms Length of follow-up: 6 weeks		
Dental Pain					

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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First Author (Publication year) **Study Design**	**Population** (n, total enrolled participants)	**Intervention**	**Efficacy Result(s)**	**Safety**	**SR Quality/ ROB Rating**
Ostenfeld et al. (2011)[29] R, DB, PC	Tooth extraction – third molar (n = 123; 121 completed the study) Moderate-severe pain after extraction	GW842166[f] (100 mg, or 800 mg) x 1 dose, pre-op + PBO post-op vs Ibuprofen 800 mg pre-op + 400 mg post-op vs PBO pre-op + post-op *All* pre-op doses given 1h before surgery Other treatments: 500 mg APAP, 15 mg codeine	• No significant difference in weighted mean pain score over 10 hours in either GW82166 group vs PBO (whereas ibuprofen was significantly better than PBO) • No significant differences in either GW82166 group vs PBO for time to rescue medication Length of follow-up: 10 hours	Similar rate of TEAE among each arm. GW842166 considered well-tolerated; most common AE: headache, nausea, pyrexia, syncope (with events only reported in the GW842166 arm)	Unclear ROB for all bias indicators except for selective outcome reporting[15]; rated as high-risk for incomplete outcome data by another SR[12,C]
Kalliomaki et al. (2013)[30] R, DB, PC	Impacted tooth extraction – third molar (n = 151)	AZD1940[g] 800 mcg orally x 1 dose + naproxen-PBO vs Dual-PBO	• No significant difference in the sum of mean pain score over 8 hours of AZD1940 vs PBO, P	No serious AE. Numerically more mild-mod AE of postural dizziness, nausea, hypotension,	Unclear ROB for all bias indicators except for incomplete outcome data (low-risk); rated as high-

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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		Vs Naproxen 500 mg + AZD1940-PBO *All* given 1.5h before surgery Other treatments: 1000 mg APAP	= 0.48 (whereas naproxen was significantly better than PBO) • No significant difference between AZD1940 vs PBO for time to rescue medication, P = 0.06 Length of follow-up: 8 hours	and headache occurred in the AZD1940 arm vs PBO Subjective CNS effects (eg, feeling "high" and "sedated") associated with cannabinoids occurred.	risk for selective outcome reporting by another SR[12]
Other Acute Pain					
Bebee et al. (2021)[31] R, DB, PC	Non-traumatic LBP <30 days (n =100) presenting to emergency department	CBD 400 mg orally x 1 dose vs Matched PBO (oil)	• Similar mean 2h pain scores (verbal, 0-10 range) in each arm • Absolute difference in mean pain score at 2h:	• Similar AE reported in both arms; most common AE = sedation	Evidence GRADE: "high"[3]

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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	About 10-11% of patients with exacerbation of chronic LBP	Other treatments: oxycodone q6h + prn as rescue analgesia; most patients also received APAP 1000 mg and ibuprofen 400 mg on presentation	–0.3 (95% CI –1.3 to 0.6 points) • Numerically similar median mg of oxycodone use before and after intervention drugs; and numerically similar median mg of APA and ibuprofen after study drugs between arms Length of follow-up: 2 h (48 h for safety follow-up)		

Abbreviations: AE, adverse event; APAP, acetaminophen; CB, cannabinoid receptor; CBD, cannabidiol; CDP, cannabis-derived products; CNS, central nervous system; DB, double-blind; h, hour; EO, essential oils; IM, intramuscularly; LBP, low back pain; LOE, level of evidence; MME, milligrams of morphine equivalents; N/S, not specified; NRS, numeric rating scale; OA, osteoarthritis; OR< operating room; PACU, post-operative care unit; PBO, placebo; PC, placebo-controlled; PCA, patient-controlled analgesia; post-op, postoperative; prn, as needed; q, every; R, randomized; ROB, risk of bias; SR, systematic review; THC, delta-9-tetrahydrocannabinol; TID, three times daily; TKA, total knee arthroplasty; VAS, visual analog scale;

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