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Opioid-Sparing effects of medical cannabis for chronic pain: A systematic review and meta-analysis of randomized and observational studies

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Strengths and limitations of this study

- This is the first systematic review of randomized controlled trials and observational studies exploring the impact of medical cannabis on prescription opioid use among people living with chronic pain.
- We conducted a comprehensive search for eligible studies, without language restrictions, and evaluated the certainty of evidence using the GRADE approach.
- All eligible randomized trials enrolled patients with chronic cancer-related pain, and the generalizability of their results to non-cancer chronic pain is uncertain.
- Most observational studies incorporated inadequate adjustment for confounding, and all randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use.

ABSTRACT

Objective: To assess the efficacy and harms of adding medical cannabis to prescription opioids among people living with chronic pain.

Design: Systematic review and meta-analysis.

Data sources: CENTRAL, EMBASE, and MEDLINE, from inception to March 2020, with no language restrictions.

Main outcomes and measures: Opioid dose reduction, pain relief, sleep disturbance, physical and emotional functioning, and three adverse events.

Study selection criteria and methods: We included randomized trials and observational studies that enrolled patients with chronic pain receiving prescription opioids and explored the impact of adding medical cannabis. Pairs of trained reviewers independently screened studies for eligibility, extracted data, and assessed risk of bias. We performed random-effects meta-analyses and used GRADE to assess the certainty of evidence for each outcome.

Results: Eligible studies included five randomized trials (all enrolling chronic cancer-pain patients) and 12 observational studies. All randomized trials instructed participants to maintain their opioid dose, which resulted in a very low certainty evidence that adding cannabis has little or no impact on opioid use (weighted mean difference [WMD] -3.4 milligram morphine equivalent [MME]; 95% confidence interval [CI] -12.7 to 5.8). Randomized trials provided high certainty evidence that cannabis addition had little or no effect on pain relief (WMD -0.18cm; 95%CI -0.38 to 0.02; on a 10 cm visual analogue scale [VAS] for pain) or sleep disturbance (WMD -0.22 cm; 95%CI -0.4 to -0.06; on a 10 cm VAS for sleep disturbance; minimally important difference [MID] is 1 cm) among chronic cancer-pain patients. Addition of cannabis likely increases nausea (relative risk [RR] 1.43; 95%CI 1.04 to 1.96; risk difference [RD] 4%,

95%CI 0% to 7%) and vomiting (RR 1.5; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%) (both moderate certainty), and may have little or no effect on constipation (RR 0.85; 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%) (low certainty). Eight observational studies provided very-low certainty evidence that adding cannabis reduced opioid use (WMD -22.5 MME; 95%CI -43.06 to -1.97; 8 studies).

Conclusion: Opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to very-low certainty evidence. Based on moderate-to-high certainty evidence, adding medical cannabis to opioid therapy, among chronic cancer-pain patients, influences neither pain relief nor sleep disturbance and increases the risk of nausea and vomiting.

Keywords: chronic pain; opioids; cannabis; cannabinoids; drug substitution; sparing effect; tapering

Systematic review registration PROSPERO CRD42018091098

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Introduction

Chronic pain affects approximately one in five adults and is a common reason for seeking medical care.[1, 2] Opioids are commonly prescribed for this condition, particularly in North America;[3] however, they are associated with harms such as overdose and death,[4, 5] which are dose-dependent.[6-9] As a result, there is considerable interest in therapies that may allow patients with chronic pain using opioid therapy to reduce their opioid intake.

One promising approach is adding cannabis therapy. Experimental studies have shown that opioids and cannabis have similar signal transduction systems,[10] and observational studies in the US demonstrated that the rates of opioid-related mortality reduced after cannabis was legalized.[11-13] Between 64% and 77% of patients with chronic pain responding to cross-sectional surveys reported a reduction in long-term opioid use after adding medical cannabis to their treatment.[14, 15] A 2017 systematic review concluded that pre-clinical studies provided robust evidence for the opioid-sparing effects of cannabis.[16] To clarify the issue, we undertook a systematic review of randomized controlled trials and observational studies to explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes, and related harms in patients with chronic pain using prescribed opioid therapy.

This systematic review is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation(www.magicevidnece.org) and BMJ. This systematic review informed a parallel guideline published on BMJ.com[17] and MAGICapp (https://app.magicapp.org/#/guideline/jMMYPj).

METHOD

We followed standards for meta-analysis of observational studies in epidemiology (MOOSE)[18] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[19] and registered our review (PROSPERO Identifier: CRD42018091098).

Eligibility criteria

We included randomized controlled trials (RCTs), observational studies, including cohort studies and case-control studies, in any language, that explored the impact of adding medicinal cannabis (i.e. phytocannabinoids, endocannabinoids, or synthetic cannabinoids) on the use of prescription opioids among people living with chronic pain. We defined pain as chronic if patients reported that symptoms had persisted for ≥3 months.[20] We excluded editorials, letters to the editor, pre-clinical studies, conference abstracts, case reports, case series, cross-sectional studies, studies with less than 2-weeks follow-up, and studies of recreational cannabis use. We classified observational study designs according to recommendations by the Cochrane Observational Studies Methods Group.[21]

Literature search and study selection

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and MEDLINE from inception to March 2020 with no restriction on language of publication. An experienced medical librarian (RC) developed our database-specific search strategies (Appendix A). We also searched the ClinicalTrials.gov registry to identify ongoing trials, and reference lists of all eligible studies and related systematic reviews for additional eligible studies. Two teams of paired reviewers independently screened titles, abstracts and full-text studies for eligibility using

online systematic review software (Rayyan QCRI, Qatar Computing Research Institute). Reviewers resolved disagreements through discussion.

Data collection

Using standardized forms and a detailed instruction manual, pairs of reviewers independently abstracted data from each eligible study, including study and patient characteristics, and details of treatment (e.g. dose, formulation, and duration of cannabis add-on therapy). Our primary outcome was opioid dose. We also captured patient-important outcomes, as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,[22] including pain relief, sleep disturbance, physical and emotional functioning. Regarding adverse events, we focused on vomiting, nausea, and constipation as a systematic review of values and preferences[23] demonstrated that patients living with chronic pain experience gastrointestinal complaints as the most important opioid-induced adverse events. We contacted authors to obtain unpublished data.

Risk of bias assessment

Following training and calibration exercises two independent reviewers used a modified Cochrane risk of bias tool[24, 25] to assess the risk of bias among eligible RCTs according to the following domains: allocation concealment, blinding of participants, study personnel, outcome assessors and data analyst, and loss to follow-up (≥20% missing data was assigned high risk of bias). Response options for each item were 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias). (Supplement Table 1) We used criteria suggested by the CLARITY group [26] to assess the risk of bias of observational studies including selection bias, confidence that all patients had the condition of interest, control for

confounding variables, validity of outcome assessment(s), and infrequent missing data (<20%) (details available at www.evidencepartners.com/resources/methodological-resources/). (Supplement Tables 2-3).

Data analysis

We calculated inter-rater agreement regarding the eligibility of full-text studies using an adjusted κ statistic.[27] We conducted separate analyses for randomized controlled trials and observational studies. All continuous measures for pain intensity and sleep disturbance were converted to a 10 cm visual analogue scale (VAS); the minimally important difference (MID) for both was 1 cm.[28, 29] All continuous outcomes that were reported by more than one study were pooled to derive the weighted mean difference (WMD) and associated 95% confidence interval (95% CI). We pooled binary outcomes (adverse events) as relative risks (RRs) and risk differences (RDs) and their associated 95% CIs. We conducted all meta-analyses with random-effects models and the DerSimonian-Laird method.[30]

When studies reported effects on continuous outcomes as the median and interquartile range, we derived the mean and SD using the method presented by Wan *et al.* [31] We also converted medians to means using the approach recommended by the Cochrane Handbook as a sensitivity analysis. When authors failed to report a measure of precision associated with mean differences, we imputed the SD from eligible studies that reported these measures (Technical appendix).[32] We included each comparison reported by multi-arm studies and calculated a correction factor to account for the unit of analysis error (i.e. when information from a treatment arm is used more than once in the same meta-analysis).[33] We explored the consistency of the association between our pooled results and studies reporting the same outcome domains that

were not possible to pool. We used Stata (StataCorp, Release 15.1, College Station, Texas) for all analyses. Comparisons were 2-tailed using a threshold of $p \leq 0.05$.

Subgroup analyses and meta-regression

We examined heterogeneity among pooled RCTs using the I^2 statistic, and through visual inspection of forest plots for pooled observational data, because statistical tests of heterogeneity can be misleading when sample sizes are large and associated confidence intervals, are therefore narrow.[34] When we had at least two studies in each subgroup, we explored sources of heterogeneity with five pre-specified subgroup hypotheses, assuming greater benefits with (1) shorter vs. longer duration of follow-up; (2) higher vs. lower risk of bias; (3) enriched vs non-enriched study design; (4) chronic non-cancer vs. chronic cancer-related pain; and (5) higher vs lower tetrahydrocannabinol [THC] content. We assumed similar directions of subgroup effects for harms, except for study design and THC content in which we expected greater harms with non-enriched trials and higher THC content. However, apart from item two (risk of bias), studies did not report sufficient data to undertake subgroup analyses.

The certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence on an outcome-by-outcome basis as high, moderate, low or very low.[35] With GRADE, RCTs begin as high-certainty evidence, but can be rated down because of risk of bias, imprecision, inconsistency, indirectness, or publication bias. We rated down for imprecision if the 95% CI associated with a pooled continuous outcome included ½ the

MID, or if the estimate of precision associated with the RR for binary outcomes included no effect.

Using GRADE, observational studies begin as low certainty evidence, and while they can be rated down further for the same reasons as RCTs, they can also be rated up in the presence of a large magnitude of the effect, a dose-response gradient, or presence of plausible confounders or other biases that increase confidence in the estimated effect.[36] We only reported the pooling results of observational studies when they resulted in the same or higher certainty of evidence than evidence from RCTs. When there were at least 10 studies for meta-analysis, we explored for small-study effects by visual assessment of funnel plot asymmetry and Egger's statistical test.[37]

RESULTS

Of 5133 records identified, we reviewed 133 articles in full text, and 18 studies reported in 17 publications proved eligible (Figure 1); five RCTs in four publications[38-41] and 13 observational studies.[42-54] One study enrolled a mixed group of opioid and non-opioid users;[45] however, our attempts to contact the authors to acquire pain intensity data for the sub-group of patients prescribed opioids proved unsuccessful. All five RCTs[38-41] and three observational studies[46, 49, 50] enrolled patients with chronic cancer-related pain; the remaining 9 observational studies explored adding cannabis to opioids for patients with chronic non-cancer pain,[43, 47, 48, 51-53] or a mix of cancer and non-cancer pain (Table 1).[42, 44, 45, 54]

Among the 18 included studies, the percentage of female participants was 48% (median of individual trials 48.3%, interquartile range [IQR] 42.7% to 58.4%), and the median of the mean age was 56.3 (IQR 51.2 to 59.9). Follow-up ranged from 2 to 5 weeks among RCTs, and from 4 weeks to 6.4 years for observational studies. Only 1 RCT[38] used an enrichment design (following the open-label phase, patients with at least 15% improvement in pain were randomized to the intervention and control groups) and all RCTs advised patients to maintain stable doses of all other prescribed pain medications, including opioids, during the study period (Table 1). All included RCTs, and three of the observational studies[42, 46, 47] administered synthetic cannabis products (i.e. nabilone, dronabinol, and nabiximole), five observational studies[44, 45, 52-54] reported different combinations of THC: CBD products, and 5 other observational studies[43, 48-51] did not provide details of cannabis type (Table1, Supplement Table 4). 10 studies reported receiving industry funding,[38-41, 44, 46, 47, 51, 52] five studies[45, 48-50, 54] reported no-industry funding, and three studies[42, 43, 53] did not report funding information (Table 1).

Risk of bias of included studies

All included RCTs reported adequate allocation concealment and blinding of patients and health-care providers; however, three trials[38, 40, 41] were at risk of bias due to high loss to follow up (Supplement Table 5). All observational studies were at high risk of bias, typically due to lack of confidence in the assessment of exposure, non-representative samples, and insufficient control for confounding (Supplement Tables 6-7).

Outcomes for medical cannabis add-on therapy

Opioid dose reduction

The primary limitation of RCTs was that all investigators instructed patients to not alter their dose of opioids. This represents a very serious indirectness of the findings regarding the research question, warranting rating down two levels, and was the primary reason for very low certainty evidence from the 1176 patients.[38-40] Their results raised the possibility that adding medical cannabis may not be associated with a reduction in opioid use (WMD -3.4 MME; 95%CI -12.7 to 5.9; table 2; Supplement Figure 1). There were no differences in effect based on the loss to follow-up (Supplement Figure 2; test of interaction *P*=0.79).

Very-low certainty evidence from 8 observational studies[42, 43, 45, 46, 48-50, 52] raised the possibility that adding medical cannabis may reduce the use of opioids among patients with chronic pain (WMD -22.5 MME; 95%CI -43.06 to -1.97; Table 2; Supplement Figure 3). Three observational studies that could not be pooled reported consistent results. The first study assessed the impact of providing medical cannabis to 61 patients with chronic low back pain who were prescribed opioid therapy (median opioid dose was 21 mg MME/day) and reported that 52% of patients (32 of 61) stopped all use of opioids at a median follow-up of 6.4 years.[51] The second

study [44] reported that of 94 patients with chronic pain (both cancer and non-cancer pain) who began using CBD hemp extract, 53.2% were able to decrease their use of prescription opioids at 8 weeks. An additional study [54] included 600 patients with chronic pain who all were indicated willingness to taper their opioid dose and were administered 0.5g daily of medicinal cannabis for each 10% reduction in opioid dose. After 6 months' follow-up, 55% of patients reported a 30% reduction in opioid dose on average and 26% of them discontinued opioid use.

Pain relief

High-certainty evidence from 5 RCTs[38-41] demonstrated that adding medical cannabis to opioid therapy resulted in trivial or no difference in pain (WMD -0.18 cm; 95%CI -0.38 to 0.02 on the 10 cm VAS for pain; MID 1cm; Table 2; Supplement Figure 4). Results did not differ depending on loss to follow-up (Supplement Figure 5, a test of interaction *P*=0.44).

Sleep disturbance

Five RCTs[38-41] provided high certainty evidence that adding medical cannabis to prescription opioids results in a trivial improvement in sleep disturbance (WMD -0.22 cm; 95%CI -0.4 to -0.06 on the 10 cm VAS for sleep disturbance; MID 1cm; Table 2; Supplement Figure 7). Results did not differ between trials reporting the low and high loss to follow-up (Supplement Figure 8, a test of interaction *P* =0.82).

Other reported outcomes

A single RCT[39] reported moderate certainty evidence that adding cannabis likely has little or no effect on emotional and physical functioning (Supplement Tables 8-9).

Adverse events

Nausea, vomiting, or constipation

4 RCTs[38-41] provided moderate certainty evidence that adding medical cannabis to opioid therapy likely increases the incidence of nausea (RR 1.43, 95%CI 1.04 to 1.96; RD 4%, 95%CI 0% to 7%; Supplement Figure 9-10) and vomiting (RR 1.50; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%; Supplement Figure 11-12) in patients with cancer-related chronic pain prescribed opioid therapy. 3 RCTs[38, 40, 41] provided low certainty evidence that adding medical cannabis to opioid therapy may not increase constipation (RR 0.85, 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%; Supplement Figure 13-14).

DISCUSSION

Very-low certainty evidence from randomized trials and observational studies was conflicting and leaves uncertain whether the addition of medical cannabis affects the use of prescribed opioids among patients living with chronic pain. Compared with long-term opioid therapy for chronic pain without medical cannabis, high certainty evidence showed that adding medical cannabis did not reduce pain or sleep disturbance. Results provided moderate certainty evidence that adding cannabis therapy to opioids likely increases both nausea (RR 1.43, 95%CI 1.04 to 1.96) and vomiting (RR 1.50; 95%CI 1.01 to 2.24), and low certainty evidence suggested that it may have no effect on constipation (RR 0.85, 95%CI 0.54 to 1.35).

Strengths of our review include a comprehensive search for eligible randomized and observational studies, appraisal of the risk of bias among individual studies, and use of the GRADE approach to rate the certainty of evidence. Our review has limitations, primarily due to features of primary studies eligible for review. All eligible RCTs enrolled patients with chronic cancer-related pain, and the generalizability to non-cancer chronic pain is uncertain. Most observational studies incorporated inadequate adjustment for confounding, and all randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use.

A meta-analysis of pre-clinical studies,[16] a narrative systematic review,[55] and several cross-sectional and case studies have reported an apparent reduction in opioid use with addition of cannabis therapy.[8, 9, 56-60] In a national US population-based survey[61] of 2,774 cannabis users (both medical and non-medical use) 36% of respondents reported substituting cannabis for prescription opioids (discontinued opioid use). In this survey, 60% of participants who identified as medical cannabis users were much more likely to substitute cannabis for prescription drugs

than recreational users (OR 4.59; 95%CI 3.87 to 5.43). Another US survey[62] that included 841 patients prescribed long-term opioid therapy for chronic pain reported that 61% used medical cannabis, and 97% of this subgroup reported coincident reduction of their opioid use.

Consistent with these findings, very low certainty evidence from observational studies in our review also suggests that adding medical cannabis allows patients with chronic pain to reduce their use of opioids. Although RCT results do not support reduction in opioid dose by adding medical cannabis for opioids, the evidence is also very low certainty, primarily because investigators instructed patients to maintain their current opioid dose. One could argue that this limitation makes the evidence irrelevant to the issue of opioid reduction with cannabis use. Results showed that, among patients with chronic cancer pain prescribed opioid therapy, the addition of medical cannabis does not result in important reductions in pain, and likely does not improve sleep quality.

Conclusion

The opioid-sparing effects of medical cannabis for chronic pain remain uncertain. Based on moderate-to-high certainty evidence, adding medical cannabis to opioid therapy among chronic cancer pain patients influences neither pain relief nor sleep disturbance and increases the risk of nausea and vomiting. The accompanying BMJ Rapid Recommendation[17] provides contextualized guidance based on this evidence, as well as three other systematic reviews on benefits,[63] harms[64] and patients' values and preferences.[65]

Disclosures/Conflicts of Interest: All authors have no financial relationships with any organizations that might have an interest in the submitted work.

Role of the Funding Source: This review received no external funding or other support.

Ethical approval: ethical approval is not required because this study retrieved and synthesised data from already published studies.

Data: Details of the characteristics of the included studies were shared in the supplementary materials. Data will be made available upon publication and can be obtained from the corresponding author at bussejw@mcmaster.ca.

Disclaimers: None.

Transparency: All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Patients and public involvement: Patients and public were not involved in this research.

Contribution: JWB, AN, GG, conceived and designed the study. RC performed the literature search. AN, AM, YSh, VA, YR selected the studies, extracted the relevant information, and assessed the risk of bias of selected studies. AN synthesised the data. AN wrote the first draft of the paper. AN, JWB, GG, and TA critically revised the manuscript for important intellectual content. JWB, LT, GG, MB, and NB interpreted the findings. JWB, LT, and GG provided methodological support. All authors reviewed the paper and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Figure 1: Study selection process in review of opioid-sparing effects of cannabis in chronic pain

Table 1: Characteristics of included studies (n=18)

Author-year (country)	Study design	Participants # (opioid user %)	Pain classification (specific condition)	Age mean (SD)	Female (%)	Opioid regimen (baseline dose in MME mean ± SD)	FU duration	Daily dose of medical cannabis	Co-intervention	Funding source
Bellnier et al-2018 (US)[42]	One-arm observational study	n= 29 (100%)	90% CNCP; 10% cancer pain	61 (10)	65%	Different opioids (79.94; ranged 0 to 450)	13 weeks	10mg capsules of THC/ CBD in a 1:1 ratio 3-times daily	NR	NR
Barlow et al-2019 (US)[43]	Retrospective chart-review	Enrolled in MCP=34; not enrolled in MCP=19 (100%)	100% CNCP (chronic painful pancreatitis)	49.9 (10.5)	45%	Different opioids (not enrolled in MCP 183±284; enrolled in MCP 190±273)	Ranged :34 to 297 weeks	NR	NR	NR
Capano et al-2020 (US)[44]	One-arm observational study	n= 131 (100%)	Chronic pain (mixed of cancer and non-cancer)	56.1 (range: 39 to 70)	68%	On a stable opioid for at least 1 year (defined as less than 10% change in its severity)	8 weeks	30mg CBD/1mg THC	NR	Funded by Ananda Professional.
Fallon et al-2017-study I (multicenter trial£)[38]	Parallel arm RCT	n=399; Nabiximols =20 placebo=199 (100%)	100% chronic cancer pain	59.8 (10.9)	43%	On a stable maintenance opioid therapy with <500mg MME/day (Nabiximols: 199±131;	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage	Patients allowed to take not more than one type of breakthrough	Otsuka Pharmaceutical Development & Commercialization, Inc.,

						placebo: 207±135)		of 10 sprays)	medications/other intervention that could affect pain were restricted	Rockville, MD, USA
Fallon et al-2017- study II (multicenter trial£)[38]	Parallel arm RCT	n=206; Nabiximols=103, placebo=103 (100%)	100% chronic cancer pain	61.5 (11.3)	49%	Same as above (Nabiximols: 212±136; placebo: 209±121)	5 weeks	Same as above. Patients with 15% improvement in pain entered into the double-blinded phase	Same as above	Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD, USA
Haroutounian et al-2016 (Israel)[45]	One-arm observational study	n=73 (35%)	93.2% CNCP; 6.8% chronic cancer pain	51.2 (15.4)¥	38%¥	Oxycodone-Paracetamol, Morphine, Methadone, Buprenorphine, Fentanyl (median 60; ranged 45, 90)	26 weeks	Cigarettes: 6% to 14% THC, 0.2% to 3.8% CBD; Oral: 11% to 19% THC, 0.5% to 5.5% CBD	On a stable medication however, patients were encouraged to discontinue or decrease using of other pain killers	No-external funding
Johnson et al-2010 (multicenter trial£)[39]	Parallel arm RCT	n=177; THC: CBD extract=60, THC	100% chronic cancer pain	60.2 (12.3)	46%	On a stable maintenance strong opioid therapy	2 weeks	One spray: 2.7mg THC/2.5mg CBD.	Intervention that could affect	GW Pharma Ltd

		extract=58, placebo=59 (100%)				for at least one-week before included into the study (THC:CBD: 258±789; THC: 188±234; placebo: 367±886)		The maximum permitted dose: 8 actuations in any 3-hour and 48 actuations in any 24-hour	participants with 2 weeks of screening were restricted	
Lichtman et al-2018 (multicenter£)[40]	Parallel arm RCT	n=398; Nabiximols =199 Placebo=198 (100%)	100% chronic cancer pain	60 (11.5)	46%	On a stable maintenance opioid therapy with <500 MME/day (nabiximols: 193±130; placebo: 186±131)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Patients allowed to take not more than one type of breakthrough medications/other intervention that could affect pain were restricted	Otsuka Pharmaceutical Development & Commercialization, Inc., Rockville, MD, USA
Maida et al-2008 (Canada)[46]	Prospective cohort	Enrolled in MCP=47 not enrolled in MCP=65 (100%)	100% Chronic cancer pain	69.7 (10.1)	42%	Different opioids (nabilone treated:60±64; untreated: 67±101)	4 weeks	On average 1.79 mg twice daily nabilone	Patients were permitted to use concomitant medications	Valeant Pharma-ceuticals Canada Ltd
Narang et al-2008 (US)[47]	One-arm observational study	n=30 (100%)	100% CNCP	Median=43.5	53%	Methadone, Morphine, Oxycodone,	Phase 2: open	Flexible dose schedule,	NR	Solvay Pharmaceuticals,

				(range=21-67)		Hydrocodone, Hydromorphone (68±57)	label for 4 weeks.	dronabinol 5mg to 20mg 3 times daily		Inc.
O'Connell et al-2019 (US)[48]	One-arm observational study	n=77 (100%)	100% CNCP (mixed conditions)	54.1 (range=26-76)	58%	Different opioids (140±184)	26 weeks	NR	Patients were permitted to use concomitant medication	No-industry funding
Portenoy et al-2012 (multicenter£)[41]	Parallel arm RCT	n=360; nabiximols low-dose=91, medium-dose=88, high-dose=90, placebo=91 (100%)	100% chronic cancer pain	58 (12.2)	48%	On a stable maintenance opioid therapy with <500 MME/day (median MME of 120 mg ranged 3 to 16660)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Concomitant use of medications was restricted	Supported by GW Pharmaceuticals and Otsuka
Pritchard-2020 (US)[49]	Retrospective cohort	cannabis and opioids co-use=22 Opioids only=61 (100%)	100% chronic cancer pain	53.1 (11.7)	23%	Different opioids (MCP enrolled=144±129; MCP not enrolled=119±100)	26 weeks	NR	NR	No-industry funding
Pawasarat-2020 (US)[50]	Retrospective chart review	Enrolled in MCP=137, not enrolled in MCP=95 (100%)	100% chronic cancer pain	58 (IQR: 14.7)	56%	Different opioids (MCP enrolled=median 45 IQR=135; MCP not enrolled=97,150)	Between 39 and 52 weeks for MCP enrolled; <26 weeks for not	NR	NR	No-industry funding

							enrolled			
Rod-2019 (Canada)[54]	One-arm observational study	n=600	Chronic pain (not specified type of pain)	NR	NR	Different opioids ranging from 90 to 240mg MME (average 120mg MME)	6 months	CBD and THC ranged between 4% to 6%. Doses related directly to the opioid taper.	All participants indicated ready to reduce opioid dose and also received psychological supports (e.g. CBT, mindfulness relaxation	No-external funding
Takakuwa et al-2020 (US)[51]	One-arm observational study	n=61 (100%)	100% CNCP (back pain)	50 (11.4)	38%	Different opioids divided into intermittent users and short intermittent users (median 21 ranged 1.1, 500)	Median of 6.4 years among patients who ceased opioids completely	NR	NR	The Society of Cannabis Clinicians paid for the IRB review and statistical analysis
Vigil et al-2017 (US)[52]	Retrospective chart review	Enrolled in MCP *=37 not enrolled=29 (100%)	100% CNCP	56.3 (11.8)	36%	Different opioids with maximum daily dosages of less than 200 (enrolled in MCP: 24±23;	52 weeks	Varied in individuals based on their selection	NR	the University of New Mexico Medical Cannabis Research Fund

						not enrolled: 16±14)				
Yassin et al-2019 (Israel)[53]	One-arm observational study	n=31 (100%)	100% CNCP (fibromyalgia)	33.4 (12.3)	90%	Oxycodone 5 mg three times/daily (not reported)	26 weeks	THC to CBD ratio: ¼, 20 g/month for 3 months, increased up to 30 g/month at the end of 6 months	Patients were allowed to use concomitant pain therapy in stable dose	NR

*CNCP: Chronic non-cancer pain; MCP: Medical Cannabis Program; MME: milligram morphine equivalent; FU: follow-up; NR: not reported

¥ Based on the whole population including opioid users and non-users

£In Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States

Table 2: GRADE Evidence Profile of cannabis for patients with chronic pain prescribed long-term opioid therapy

# of studies	# of Patients	FU Duration (Weeks)	Risk of bias[a]	Inconsistency (I^2, P-value)[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)	Overall certainty of evidence
Opioid dose reduction: morphine milligram equivalents (MME) per day									
4 RCTs[38-40]	1,176	2 to 5	No serious risk of bias [e]	No serious inconsistency [40.4%, *P*=0.15]	Very serious indirectness [f]	Serious imprecision [g]	Not detected	WMD -3.4MME (-12.7 to 5.9)	Very Low
8 Observational studies[42, 43, 45, 46, 48-50, 52]	453	4 to 297	Serious risk of bias [h]	Serious inconsistency [visual inspection]	No serious indirectness	No serious imprecision	Not detected	WMD -22.5MME (-43.06 to -1.97)	Very low
Pain: 10 cm VAS for pain; lower is better; the MID = 1 cm									
5 RCTs[38-41]	1,536	2 to 5	No serious risk of bias[e]	No serious inconsistency [28%, *P*=0.20]	No serious indirectness	No serious imprecision	Not detected	WMD -0.18 (-0.38 to 0.02)	High
Sleep disturbance: 10 cm VAS for sleep disturbance; lower is better; the MID= 1 cm									
5 RCTs[38-41]	1,536	2 to 5	No serious risk of bias[e]	No serious inconsistency [0%, *P*=0.45]	No serious indirectness	No serious imprecision	Not detected	WMD -0.22 (-0.39 to -0.06)	High
Nausea									
4 RCTs*[38-41]	1330	2 to 5	Serious risk of bias[i]	No serious inconsistency [0%, *P*=0.88]	No serious indirectness	No serious imprecision	Not detected	RR 1.43 (1.04 to 1.96)	Moderate
Vomiting									
4 RCTs*[38-41]	1330	2 to 5	Serious risk of bias[i]	No serious inconsistency [0%, *P*=0.50]	No serious indirectness	No serious imprecision	Not detected	RR 1.5 (1.01 to 2.24)	Moderate

Constipation									
3 RCTs*[38, 40, 41]	1153	5	Serious risk of bias [i]	No serious inconsistency [0%, *P*=0.92]	No serious indirectness	Serious imprecision [g]	Not detected	RR 0.85 (0.54 to 1.35)	Low

WMD: weighted mean difference; RR: relative risk; 95% CI: 95% confidence interval; VAS: visual analogue scale; MID: minimally important difference; FU: follow-up

[a] We assessed risk of bias using a modified Cochrane risk of bias instrument;

[b] Inconsistency refers to unexplained heterogeneity of results. For RCTs an I^2 of 75-100% indicates that heterogeneity may be considerable. We assessed heterogeneity of pooled observational studies through visual inspection of forest plots.

[c] Indirectness results if the intervention, control, patients or outcomes are different from the research question under investigation.

[d] Serious imprecision refers to situations in which the confidence interval includes both benefit and harm (the 95%CI includes 1 MID).

[e] Some of the included RCTs were at high risk of bias, due to loss to follow-up (>20%); however, we did not rate down for risk of bias as subgroup analysis showed no difference in treatment effect between trials at high and low risk of bias for missing outcome data (test of interaction p= 0.791).

[f] downgraded twice due to indirectness since all trials instructed participants to maintain their opioid dose during the study period.

[g] The 95%CI around the WMD includes no effect.

[h] Studies are based on non-representative samples.

[i] Most of the included RCTs were at high risk of bias due to loss to follow-up (>20%).

*Fallon et al-2017 (the results of two separate RCTs reported in this publication): only study number 1 reported these outcomes and subsequently included in the meta-analysis.

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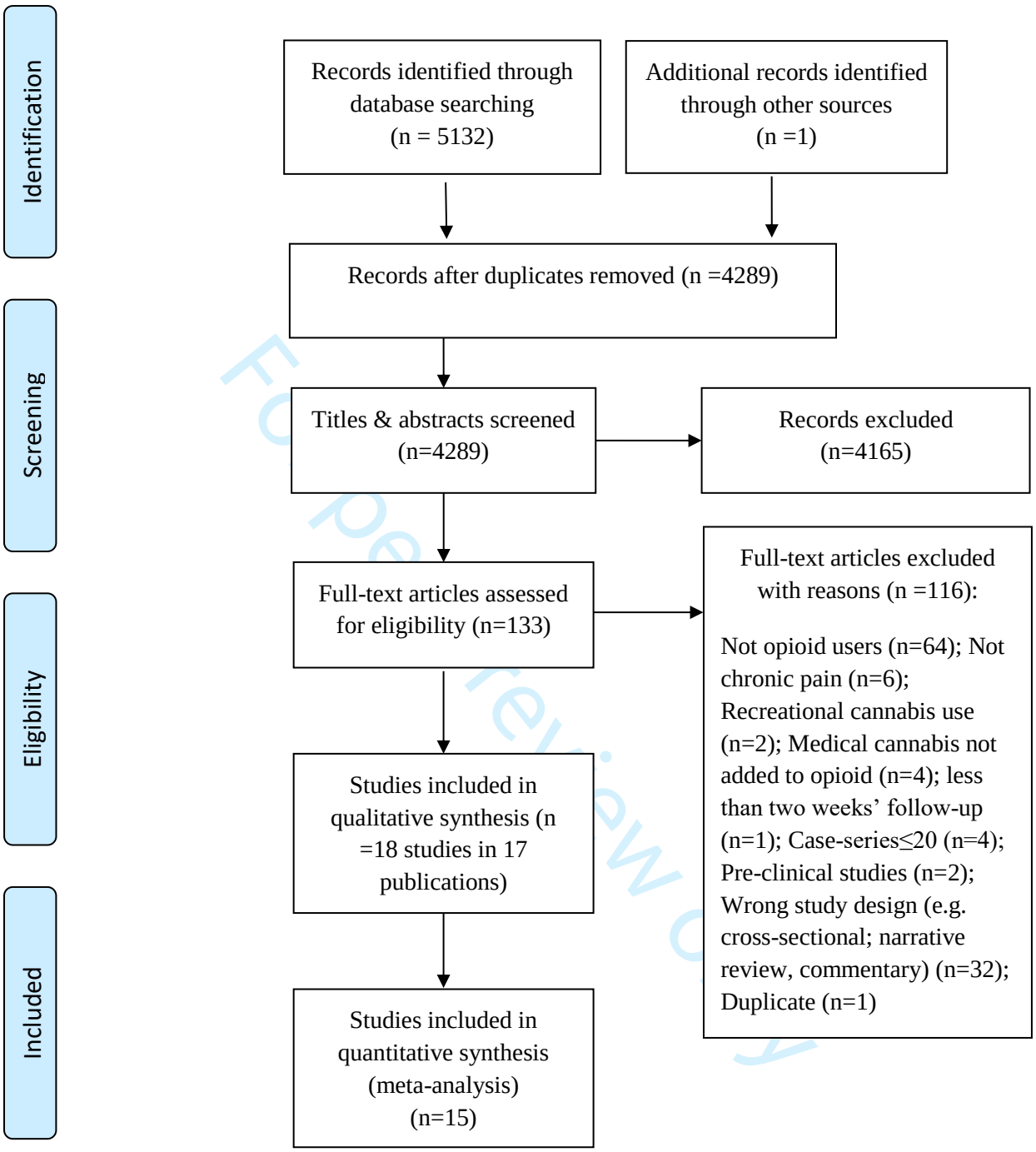

Figure 1: Study selection process in review of opioid-sparing effects of cannabis in chronic pain

Supplementary Material

Opioid-sparing effects of cannabis for chronic pain: A systematic review and meta-analysis of randomized and observational studies

Contents

Appendix A: Literature Search Strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.

The search terminology included all types of chronic pain AND any kinds of cannabinoids:

……

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

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1 exp Analgesics, Opioid/ (111496)
2 opioid*.mp. (112576)
3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (150565)
4 or/1-3 (207118)
5 exp Narcotics/ (119511)
6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism

supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10373)
7 or/1-6 (213683)
Annotation: opioid block
8 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (52087)
9 Cannabis/ (8573)
10 exp CANNABINOIDS/ (13258)
11 8 or 9 or 10 (52087)
Annotation: cannabis block
12 7 and 11 (6089)
Annotation: opioid and cannabis
13 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (65717)
14 Chronic Pain/ (12620)
15 exp Osteoarthritis/ (59676)
16 osteoarthrit*.mp. (84419)
17 osteo-arthritis.mp. (375)
18 exp Arthritis, Rheumatoid/ (109607)
19 exp Neuralgia/ (19415)
20 Diabetic Neuropathies/ (14247)
21 (neuropath* adj5 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23043)
22 neuralg*.mp. (26154)
23 zoster.mp. (20386)
24 Irritable Bowel Syndrome/ (6748)
25 IBS.mp. (8435)
26 Migraine Disorders/ (24388)
27 migraine.mp. (37040)
28 Fibromyalgia/ (8088)
29 fibromyalg*.mp. (11178)
30 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5426)
31 Pain, Intractable/ (6126)
32 Phantom Limb/ (1816)
33 Hyperalgesia/ (11136)

34 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (37369)
35 radiculopathy.mp. (8722)
36 musculoskeletal pain/ or headache/ (29687)
37 exp Headache Disorders/ (33178)
38 headache*.mp. (89612)
39 exp Temporomandibular Joint Disorders/ (16711)
40 whiplash.mp. or exp whiplash injury/ (3896)
41 exp Cumulative Trauma Disorders/ (13326)
42 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (14079)
43 Pain Measurement/de [Drug Effects] (6594)
44 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (43072)
45 ((noncancer* or non-cancer* or back or discogen* or chronic* or recurrent or persist* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or non-malign* or shoulder* or knee* or hip or hips) adj3 pain).mp. (206944)
46 exp Pain/ (379991)
47 pain*.mp. (745044)
48 or/13-47 (1122771)
49 12 and 48 (1034)

Database: Embase <1974 to 2019 September 04>
Search Strategy:
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1 exp narcotic analgesic agent/ (317763)
2 (opioid* or opiate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (188237)
3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (278150)
4 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-

dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (50642)

5 or/1-4 (403926)

6 exp cannabis/ (32390)

7 cannabinoid/ or cannabidiol/ or cannabinoid derivative/ or cannabinol/ or cannabinol derivative/ or cannabis derivative/ or delta8 tetrahydrocannabinol/ or delta8 tetrahydrocannabinol derivative/ or "delta9(11) tetrahydrocannabinol"/ or dronabinol/ or medical cannabis/ or nabiximols/ or tetrahydrocannabinol/ or tetrahydrocannabinol derivative/ or tetrahydrocannabinolic acid/ (26180)

8 (Cannabis or cannabinol or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (69860)

9 6 or 7 or 8 (75281)

10 5 and 9 (16412)

11 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (109897)

12 chronic pain/ (57642)

13 exp osteoarthritis/ (122475)

14 osteoarthrit*.mp. (136019)

15 osteo-arthritis.mp. (424)

16 degenerative arthrit*.mp. (1563)

17 exp rheumatoid arthritis/ (194747)

18 exp neuralgia/ (99958)

19 diabetic neuropathy/ (22699)

20 (neuropath* adj5 (pain* or diabet*)).mp. (71799)

21 neuralg*.mp. (29200)

22 zoster.mp. (36684)

23 irritable colon/ (24792)

24 (Irritable Bowel Syndrome or IBS).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (24025)

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26 migraine.mp. (66593)
27 fibromyalgia/ (19402)
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29 reflex sympathetic dystrophy.mp. (2356)
30 (complex regional pain syndromes or causalgia).mp. (1275)
31 intractable pain/ (4701)
32 phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (7388)
33 hyperalgesia/ (18711)
34 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (27031)
35 exp backache/ (104042)
36 radiculopathy.mp. or exp radiculopathy/ (37176)
37 musculoskeletal pain/ (10292)
38 exp arthralgia/ (58208)
39 headache/ (204055)
40 headache*.mp. (264831)
41 temporomandibular joint disorder/ (13308)
42 ((TMJ or TMJD) and pain*).mp. (3648)
43 whiplash.mp. or whiplash injury/ (4815)
44 exp cumulative trauma disorder/ (20089)
45 exp pain/ (1249315)
46 pain*.mp. (1280762)
47 or/11-46 (1963522)
48 10 and 47 (3115)

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Date Run: 05/09/2019 16:12:03
Comment:

ID Search Hits
#1 MeSH descriptor: [Cannabis] explode all trees 293
#2 MeSH descriptor: [Cannabinoids] explode all trees 743
#3 MeSH descriptor: [Endocannabinoids] explode all trees 46
#4 MeSH descriptor: [Endocannabinoids] explode all trees 46
#5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 4215
#6 #1 or #2 or #3 or #4 or #5 4215
#7 MeSH descriptor: [Pain] explode all trees 45094
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#9 #7 or #8 169846
#10 #6 and #9 578
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#12 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyni* or ischialgi* or crps or rachialgi*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*) 104465

#13 (irrita* or inflam*) near/4 (bowel or colon) 7249

#14 #11 or #12 or #13 113256

#15 #6 and #14 in Trials 353

Characteristics of eligible studies and Risk of Bias Assessment

Supplement Table 1: Detailed guidance for risk of bias assessment RCTs

Domain	Judgment
Random allocation concealment	**Definitely yes (low risk):** used central allocations (e.g. computer, telephone) **Probably yes (low risk):** sequentially numbered, opaque, sealed envelopes; studies did not provide enough information about concealment approach; however, it was placebo-control trial with double blinded design. **Probably no (high risk):** not enough information was provided and study was not blinded. **Definitely no (high risk):** used any unconcealed approach of allocation (e.g. case record number, day of week, health-care decision).
Blinding of patients	**Definitely yes (low risk):** explicitly mentioned that patients were blinded **Probably yes (low risk):** a placebo-controlled double-blinded trial. **Probably no (high risk):** no explicit statement about blinding status and not double-blinded placebo-controlled trial. **Definitely no (high risk):** explicitly mentioned that patients were not blinded.

Blinding of health care providers	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of data collector	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of outcome assessor	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Blinding data analyst	**Definitely yes (low risk):** explicitly mentioned that this group were blinded

	Probably yes (low risk): **Probably no (high risk):** no explicit statement about blinding and only mentioned double-blinded. **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Loss to follow-up	**Definitely yes:** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome, or missing outcome data were balanced across groups. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. **Definitely no (high risk):** the retention rate was less than 80%.
Sample size	We also considered the sample size lower than 250 per arm as high risk of bias and rated down on the basis of imprecision in GRADE assessment.

Supplement Table2: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with control group

Domain	Judgment
1) **Did the study match participants for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?** (This item queries how confident we are that the reported association or lack thereof is not due to confounding).	**Definitely yes (low risk):** studies that adjusted based on all important covariates including age, sex, baseline pain, baseline opioid dose, and other disabilities. **Probably yes (low risk):** studies that adjusted at a minimum for baseline pain and baseline opioid dose. **Probably no (high risk):** studies that did not provide any details about analysis method. **Definitely no (high risk):** Studies that did not adjust based on baseline opioid dose or baseline pain.
2) **Was selection of exposed and non-exposed cohorts drawn from the same population?** (this item queries whether participants who co-used cannabis and opioids or used opioids alone were drawn from the same population)	**Definitely yes (low risk):** Studies in which selection for participation is not dependent on exposure status (cannabis and opioid co-use). **Probably yes (low risk):** studies that did not provide enough information about recruitment to judge whether recruitment into the study was dependent on exposure status or not. **Probably no (high risk): NA**

	Definitely no (high risk): studies that compared cannabis and opioid co-users and non-users from different cohort.
3) Can we be confident in the assessment of exposure? (this item queries how confident we are about the quantification of cannabis and opioids co-use).	**Definitely yes (low risk):** if study reported some ascertainment methods for cannabis use (e.g. urine analysis), or study prescribed the specific dose of medical cannabis to the participants. **Probably yes (low risk):** self-report of cannabis use. **Probably no (high risk):** when study did not provide any details about assessing exposure status. **Definitely no (high risk):** participants self-reported cannabis usage only at baseline, or exposure status not assessed during the 4-weeks follow-up at least one time, or level of cannabis usage was not similar among participants. For example, some studies allowed patients to select the type or dose of cannabis themselves.
4) Can we be confident in the assessment of the presence or absence of prognostic factors?	**Definitely yes (low risk):** when patients self-reported the prognostic factors. **Probably yes (low risk):** when the method of assessment was not reported, it was considered as probably yes. *Note that for this item, we are only concerned with the measurement of the prognostic

	factors that mentioned in item number 1 as minimum adjusted variables (baseline pain intensity and opioid dose).
5) **Were co-interventions similar between groups?** (this item queries how similar are the use of other pain killers (e.g. NSAIDs) between cannabis users and non-users.	**Definitely yes (low risk):** study reported that co-intervention other than study intervention were limited during the study period. **Probably yes (low risk):** when co-intervention usage was approximately balanced between both intervention and control groups. **Probably no (high risk):** when study did not provide enough information about other drugs that participants may use. **Definitely no (high risk):** when participants were allowed to use all other co-interventions that could affect the outcome of the study.
6) **Was the follow up of cohorts adequate?** (This item queries the risk of bias associated with loss to follow-up and missing outcome data).	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance, if patients were required to come to clinic for

	outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.
7) Can we be confident in the assessment of outcome? (This item queries our confidence in the accuracy of the measurement of the outcome).	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** study used non-validated/reliable instrument.

Supplement Table 3: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with no control group

Domain	Judgment
Is the source population (sampling frame) representative of the general population?	**Definitely yes (low risk):** participants were selected from a representative sample (e.g. national population registry) **Probably yes (low risk):** single community center, however the center was the only referral center that provided cannabis legally to participants. **Probably no (high risk):** based on the provided information source population could not be defined. **Definitely no (high risk):** sampling from one center or clinic or hospital or patients selected through using convenience sampling.
Is the assessment of the outcome accurate both at baseline and at follow-up?	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** used of different instruments at different follow-up intervals with concern of

	accuracy of responses, or used invalidated/reliable instruments.
Is there little missing data?	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance, if patients were required to come to clinic for outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.

Supplement Table 4: Characteristics of Eligible studies

Barlowe et al-2019[1]

Study design	Retrospective chart review.
Participants	34 chronic painful pancreatitis patients with chronic use of opioids enrolled in a state therapeutic cannabis program were compared to 19 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	Cohort of patients who enrolled into the program had received cannabis therapy with a range from 34 to 297 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Bellnier et al-2018[2]

Study design	One-arm observational study (before/after).
Participants	29 patients with chronic pain who used opioids enrolled in a state therapeutic cannabis program.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	3 months
Funding source	Not reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain Quality Assessment Scale (PQAS) paroxysmal domain

Capano et al-2020[3]

Study design	One-arm observational study (before/after).
Participants	131 patients with chronic pain who used opioids enrolled in a pain clinic cannabis therapy.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	8 weeks
Funding source	Industry fund reported.
Outcome	- Pain disability index

	- Pittsburgh Sleep Quality Index - Pain intensity and interference index

Haroutounian et al-2016 [4]

Study design	One-arm observational study (before/after).
Participants	Chronic non-cancer pain (14 individuals had pain due to cancer) with a duration of 3 months or longer, and a lack of satisfactory analgesic response or intolerable adverse effects with at least 2 analgesics from 2 different drug classes at full dose (Opioid user: N=73; 35%).
Intervention (comparison)	The initial recommended medical cannabis dose was 20 g/mo added to opioids, which could be obtained as smoked cannabis, baked cookies or oil taking from cannabis dispensary centers. Cannabis could be titrated up to 3 times a day until satisfactory pain relief was gained (before using cannabis).
Follow-up	6 months.
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily intravenous [IV] morphine equivalence dosages among opioid users).

Maida et al-2008[5]

Study design	Prospective cohort study.
Participants	47 patients with chronic cancer pain who were opioid user and treated with nabilone were compared to 65 non-treated patients.
Intervention (comparison)	nabilone added to opioids (no nabilone).
Follow-up	30 days.
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily morphine equivalence dosages);

	-Pain reduction (Edmonton Symptom Assessment System 0: no pain-10: most severe pain); -anxiety, nausea, depression.

Narange et al-2008[6]

Study design	Phase II: One-arm observational study (before/after).
Participants	30 patients with chronic non-cancer pain who were taking opioids for a long time.
Intervention (comparison)	The starting dose was 5mg of dronabinol twice daily and titrated up to 20 mg 3 times a day added to opioids (before using dronabinol).
Follow-up	4 weeks
Funding source	Industry funding reported.
Outcome	-Pain reduction (VAS 0: no pain-10: most severe pain); -patients' satisfaction -pain interfere with sleep (Brief pain inventory) -social functioning -sleep disturbance -adverse events including anxiety, dizziness, and inability to concentrate.

O'Connell et al-2019[7]

Study design	One-arm observational study (before/after).
Participants	77 mixed type of chronic non-cancer pain patients who used opioids (96%) or benzodiazepines.
Intervention (comparison)	Medical cannabis including THC, CBD products added to opioid (before using cannabis)
Follow-up	6 months
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages among opioid users).

	-pain reduction (VAS 0: no pain-10: most severe pain).

Pritchard-2019[8]

Study design	Retrospective chart review.
Participants	22 patients who had chronic cancer-related pain and used opioids with the presence of THC in their urine drug screening were compared to 61 patients with opioid use only.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	26 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Pawasarat-2020[9]

Study design	Retrospective chart review.
Participants	137 chronic cancer-related pain patients with chronic use of opioids enrolled in a State of New Jersey Medicinal Marijuana Program Registry were compared to 95 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	Between 36 and 52 weeks for enrolled patients and 24 weeks for non-enrolled patients.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain reduction.

Rod-2019[10]

Study design	One-arm observational study (before/after).
Participants	600 of chronic pain patients who used opioids and indicated they were prepared to reduce their opioid dose.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	6 months
Funding source	No industry funding reported.
Outcome	- Reduction or cease of opioid use (reported as percentage of patients who ceased or reduced their opioid use after 6 months).

Takakuwa et al-2020[11]

Study design	One-arm observational study (before/after).
Participants	61 of chronic non-cancer pain patients (low-back pain) who used opioids.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	Median of 6.4 years among patients who ceased opioids completely
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily morphine equivalence dosages among chronic and intermittent opioid users).

Vigil et al-2017 [12]

Study design	Retrospective chart review.
Participants	37 habitual opioid using, severe CNCP patients enrolled in the Medical Cannabis Program were compared to 29 non-enrolled patients.
Intervention (comparison)	Medical cannabis added to opioids (no cannabis).
Follow-up	1 year.

Funding source	No industry funding reported.
Outcome	-Cessation of opioid (defined as the absence of opioid prescriptions activity during the last three months of observation) -Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages); -Pain reduction only among cannabis users; -Quality of life (no effect; good benefit; great benefit; negative effect; and extremely negative effect of co-prescription of cannabis on quality of life).

Yassin et al-2019[13]

Study design	One-arm observational study (before/after).
Participants	31 patients with fibromyalgia were treated for at least 12 months with 5 mg of oxycodone hydrochloride equivalent to 4.5 mg oxycodone and 2.5 mg naloxone hydrochloride twice a day and duloxetine 30 mg once a day.
Intervention (comparison)	20 grams of smoked medical cannabis added to opioids (before cannabis inhalation).
Follow-up	6 months
Funding source	No industry funding reported.
Outcome	-Pain reduction -Change in pain medication use in 5 categories: 1- increased doses, 2- stable dose through medical cannabis therapy duration, 3- less than half reduction in medication consumption, 4- more than half reduction in analgesic consumption, 5-deceased analgesic consumption. - Owestry Disability Index reduction (scale 0: no disability, 100: total disability)

Johnson et al-2010[14]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	177 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	tetrahydrocannabinol: cannabidiol (THC:CBD) extract added to opioids (placebo)
Follow-up	2 weeks
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Physical, emotional, role, and social functioning (QLQ-C30) -Nausea, vomiting, constipation.

Portenoy et al-2012[15]

Study design	Parallel, randomized double-blinded, placebo-controlled trial.
Participants	360 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Nabiximols at a low dose (1–4 sprays/day), medium dose (6–10 sprays/day), or high dose (11–16 sprays/day) added to opioids-(placebo)
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Pain interference-BPI-SF

	- Patient Assessment of Constipation Quality of Life (PAC-QoL) - Montgomery-Asberg Depression Rating Scale -Opioid composite score - Nausea, vomiting, constipation.

Fallon et al-2017-Study 1[16]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	399 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL) added to opioids (placebo)
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Mean constipation (NRS 0: no constipation-10: most severe constipation) -Global Impression of Change (SGIC), Patient Satisfaction - Nausea, vomiting, constipation.

Fallon et al-2017-Study 2[16]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	206 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL)) added to opioids (placebo)-patients who tolerated titrated dose of cannabis and showed an

	improvement of at least 15% on pain NRS score randomized into this study (randomized withdrawal design).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) - Global Impression of Change (SGIC), Patient Satisfaction - mean constipation (NRS 0: no constipation-10: most severe constipation)

Lichtman et al-2017[17]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	397 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Nabiximols was added to opioids and was titrated the maximum allowed daily dosage of 10 sprays per day (placebo).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (NRS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Mean constipation (NRS 0: no constipation-10: most severe constipation) -Global Impression of Change (SGIC), Patient Satisfaction

Supplement Table 5: Risk of bias assessment for RCTs

Study (author-year)	Allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of Data analyst	Loss to follow-up (≤20%)
Johnson et al-2010	PY	PY	PY	PY	PY	PN	PY€
Portenoy et al-2012	DY	DY	PY	PY	PY	PN	DN£
Fallon et al-2017 Study 1	PY	PY	PY	PY	PY	PN	DN¥
Fallon et al-2017 Study 2	PY	PY	PY	PY	PY	PN	PY€
Lichtman et al-2017	PY	PY	PY	PY	PY	PN	DN¥

***definitely/probably yes= low risk of bias; definitely//probably no=high risk of bias.**

£ The rate of loss to follow-up was more than 27%.
¥The rate of loss to follow-up was approximately 26%.
€The rate of loss to follow-up was approximately less than 20%

Supplement Table 6: Risk of bias assessments for chart reviews with control group

Study	Were the exposed and unexposed drawn from same	Are we confident in the assessment of exposure?	Can we be confident in the assessment of the presence or absence of prognostic	Can we be confident in the outcome assessment?	Was there adequate follow-up?	Were the co-interventions similar?	Did the authors adjust for different confounders?	Overall risk of bias
Vigil 2017	DY	DN	PY	PN	PY	PN	PY	High
Maida 2008	DY	DY	PY	DY	PN	PN	PY	High
Barlowe 2019	DY	DN	PY	DY	PN	PN	PN	High
Pritchard-2020	DY	DY	PY	DY	DN	PN	PN	High
Pawasarat-2020	DY	DN	PY	DY	DY	PN	PN	High

***DY: definitely yes; DN: definitely no; PY: probably yes; PN: probably no; DY/PY= low risk of bias; DN/PN=high risk of bias.**

Supplement Table 7: Risk of bias assessments for one-arm studies with no control group

Study	Is the source population (sampling frame) representative of the general population?	Is the assessment of the outcome accurate both at baseline and at follow-up?	Is there little missing data?	Overall risk of bias
Haroutounian et al-2016	DN	DY	PN	High
Narang et al-2008	DN	DY	PY	High
Yassin et al-2019	DN	DY	PY	High
O'Connell et al-2019	DN	DY	PY	High
Takakuwa et al-2020	DN	DY	PY	High
Vigil et al-2017	DN	PN	PY	High
Bellnier-2018	DN	DY	DY	High
Capano et al-2020	DN	DY	PN	High
Rod-2019	DN	PN	PN	High

***definitely/probably yes= low risk of bias; definitely//probably no=high risk of bias.**

Supplement Table 8: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for physical function among patients with chronic pain from 1 RCT[14]

Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Physical functioning	Cannabis=118, placebo=59 (1 RCT[14])	Two weeks	THC: CBD vs. placebo: -4.23 (*P*=0.108) THC vs. placebo: -1.25 (*P*=0.631)	Moderate [b]	Adding cannabis to opioids probably does not improve physical functioning.

[a] In favor of placebo; [b] Due to imprecision.

Supplement Table 9: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for emotional function among patients with chronic pain from 1 RCT[14]

Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Emotional functioning	Cannabis=118, placebo=59 (1 RCT[14])	Two weeks	THC: CBD vs. placebo: 6.73 (*P*=0.084) THC vs. placebo: 5.22 (*P*=0.174)	Moderate[b]	Adding cannabis to opioids probably does not improve emotional functioning.

[a] In favor of cannabis; [b] Due to imprecision.

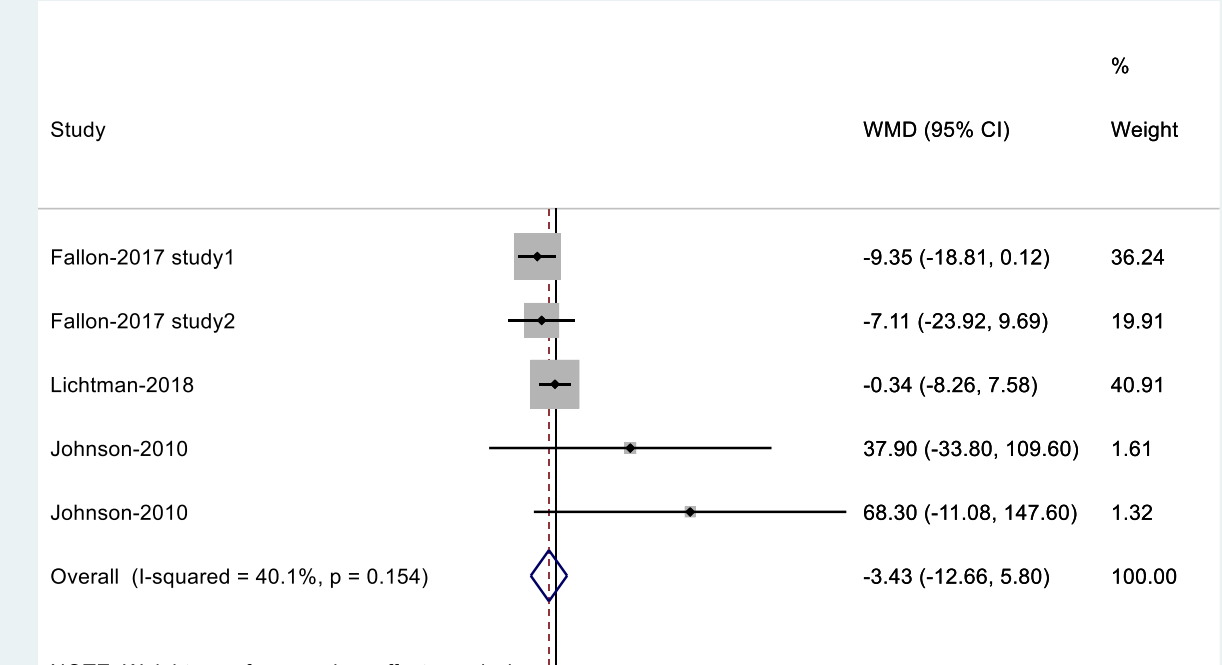
Supplement Table 10: Summary of adverse events among included observational studies*

Study	Method of assessment	Adverse events reported
Haroutounian et al[4]	Self-reported.	Two participants discontinued treatment due to serious side effects.
Maida et al[5]	Self-reported	Anxiety (P=0.028), nausea (P<0.001), and distress (P=0.021) were decreased significantly among patients who used nabilone in comparison to patients who did not use it.
Narang et al[6]	Self-reported (29-item symptom Side Effect Checklist).	*Phase II:* Dry mouth, tiredness (both P<0.0001), abnormal thinking, anxiety, facial flushing, eye irritation, headache, and ringing in the ears, and drowsiness (P< 0.05) showed a significantly higher occurrence at the 20 mg dronabinol dose compared with placebo. -Dry mouth, difficulty speaking, forgetfulness, confusion, dizziness, and euphoria were more occurred in both treatment group versus placebo (P= 0.01)

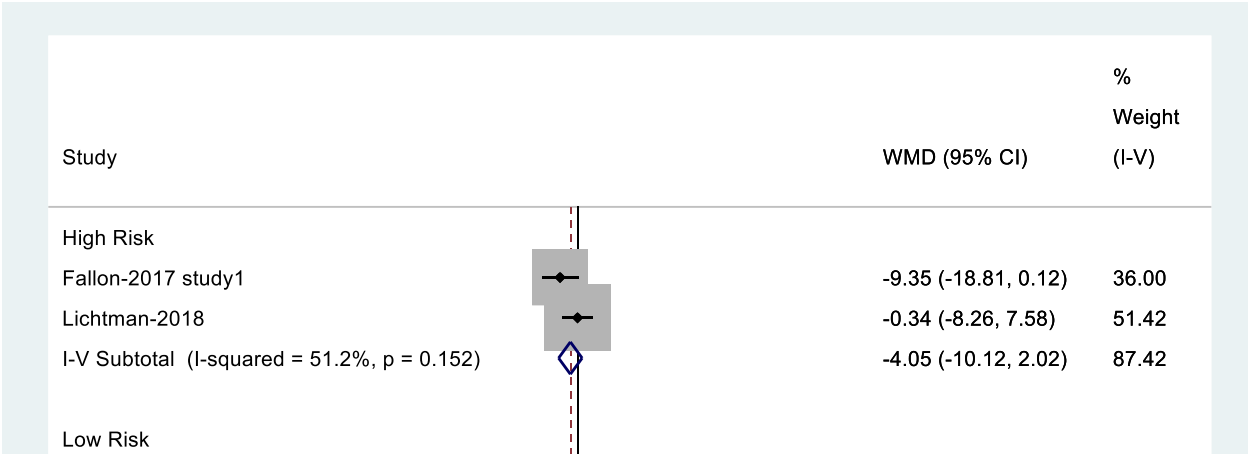
Vigil et al[12]	Self-reported.	No respondents reported any serious side effects from cannabis use (only 9% of patients reported cannabis affected negatively their concentration).
Yassin et al[13]	Self-reported	Mostly mild adverse events were reported (e.g. red eye, sore throat, increase appetite); only 6 patients out of withdrew due to the side effects in non-cannabis group.

*O'Connell et al[7], Barlowe et al[1], Rod 2019, and Takakuwa et al[11] did not report adverse events.

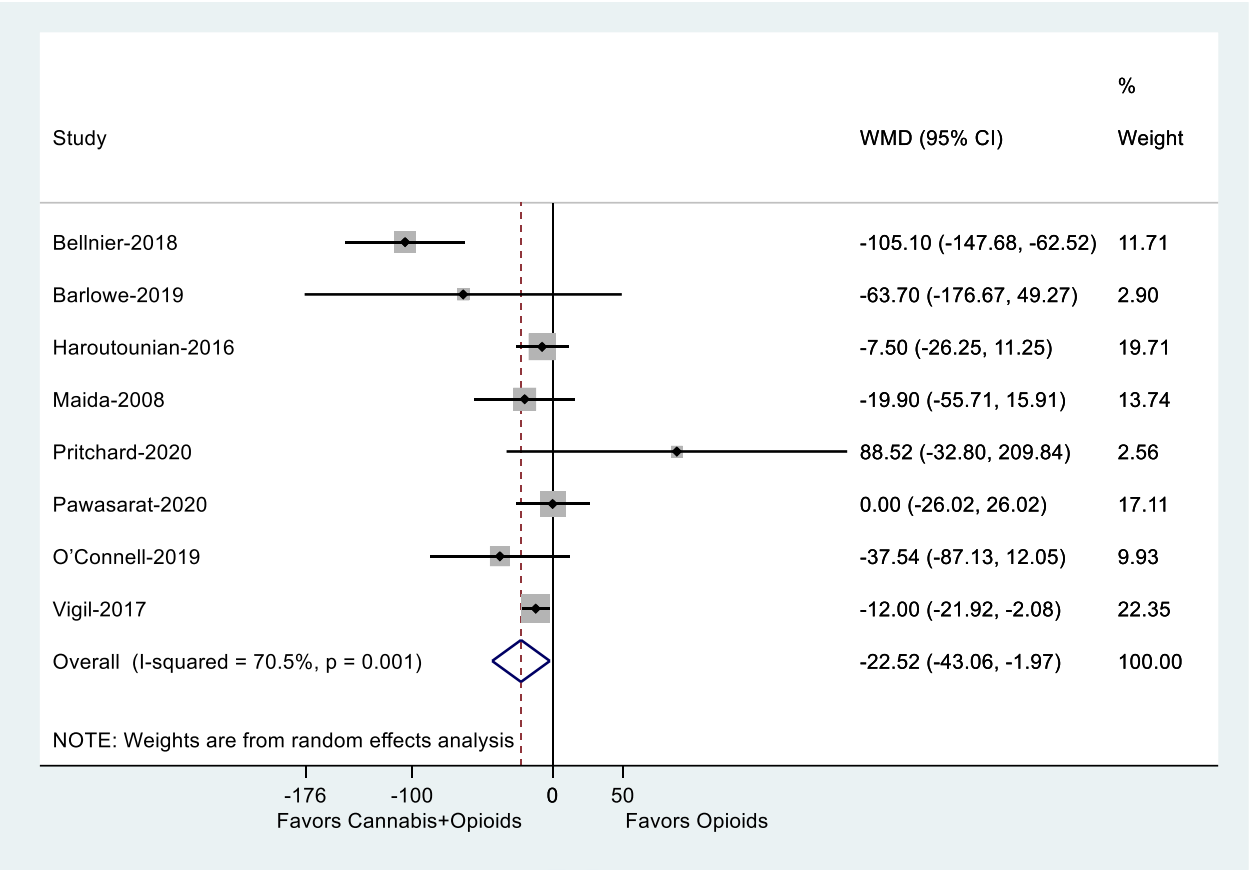
Additional results tables and figures



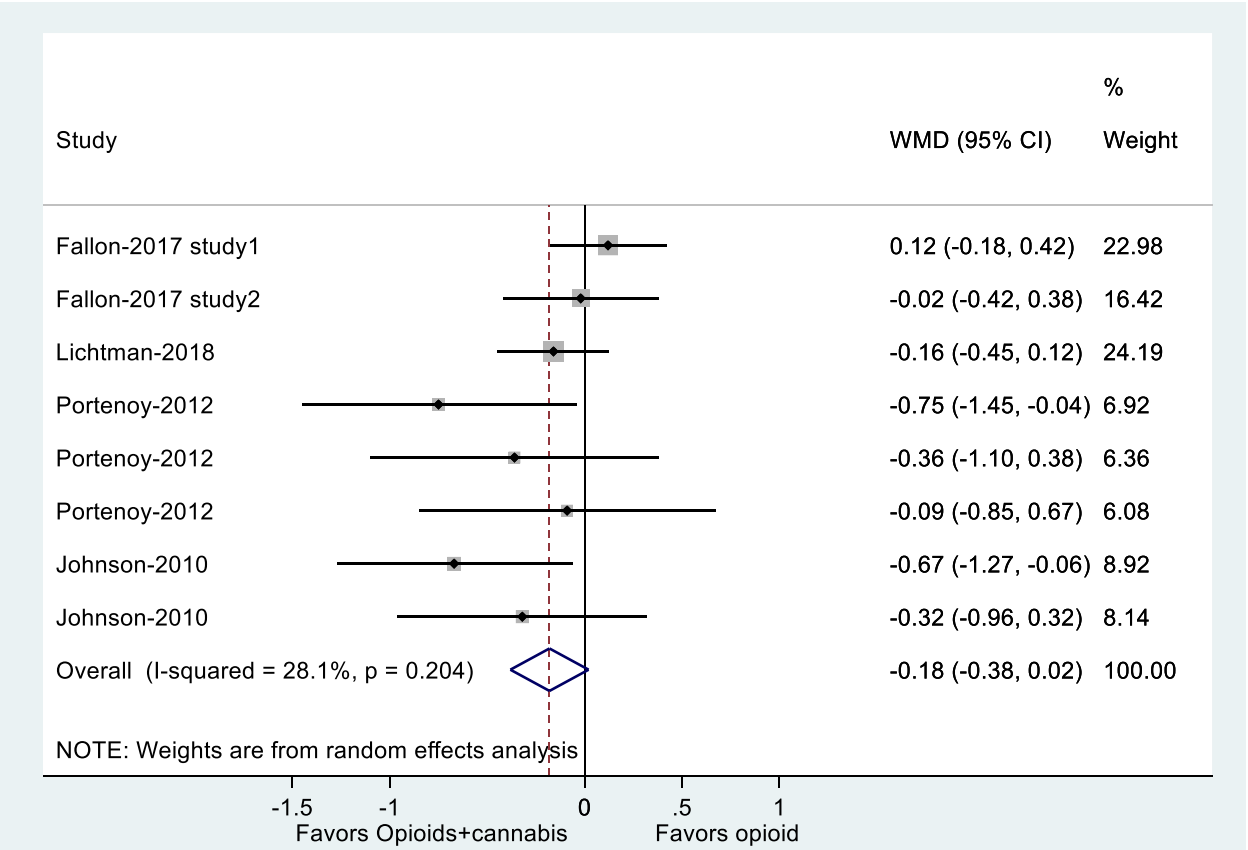
Supplement Figure 1: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



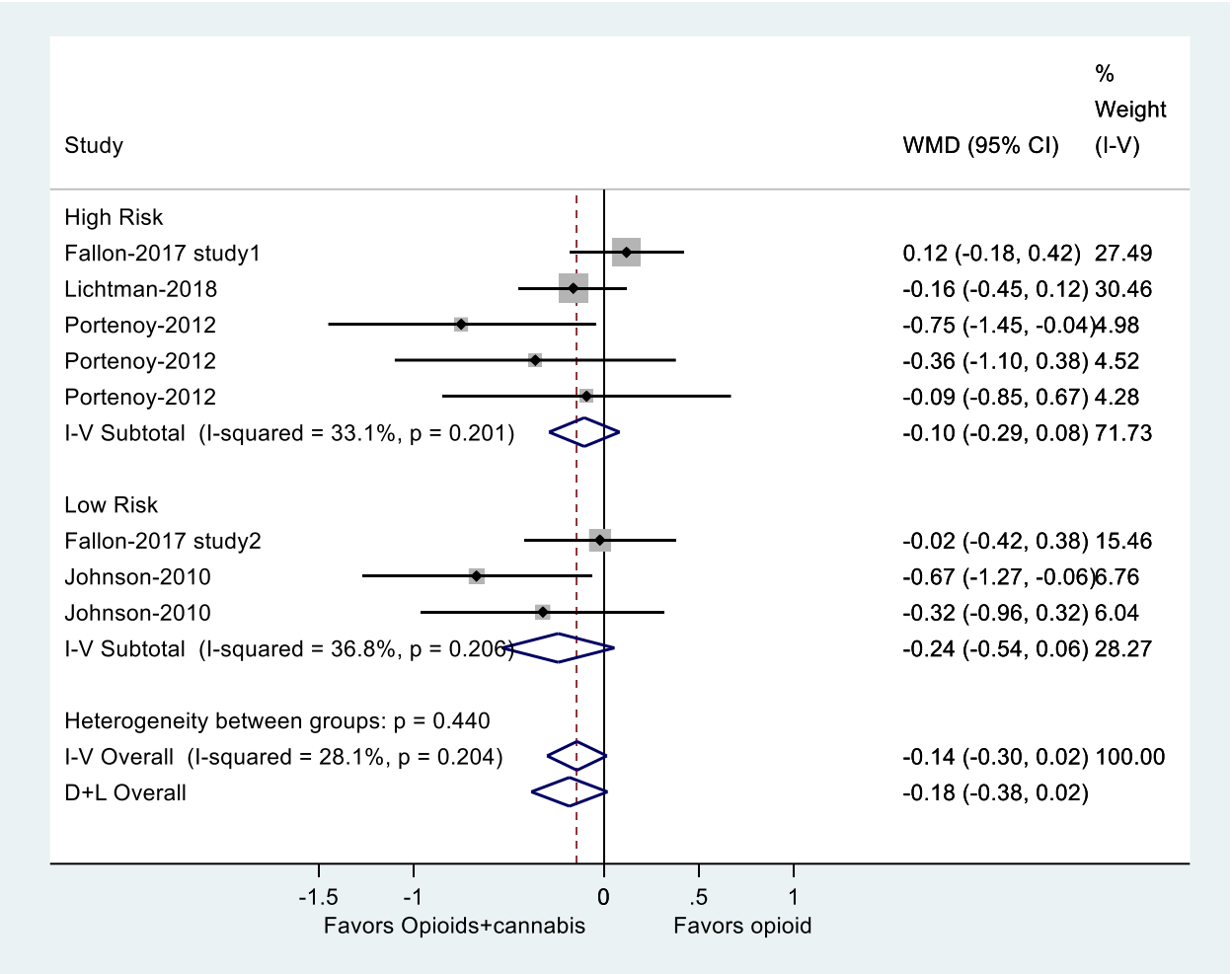
Supplement Figure 2: Subgroup analysis for opioid dose reduction and risk of bias (high risk vs. low risk) from 4 RCTs of Cannabis+opioids vs. placebo



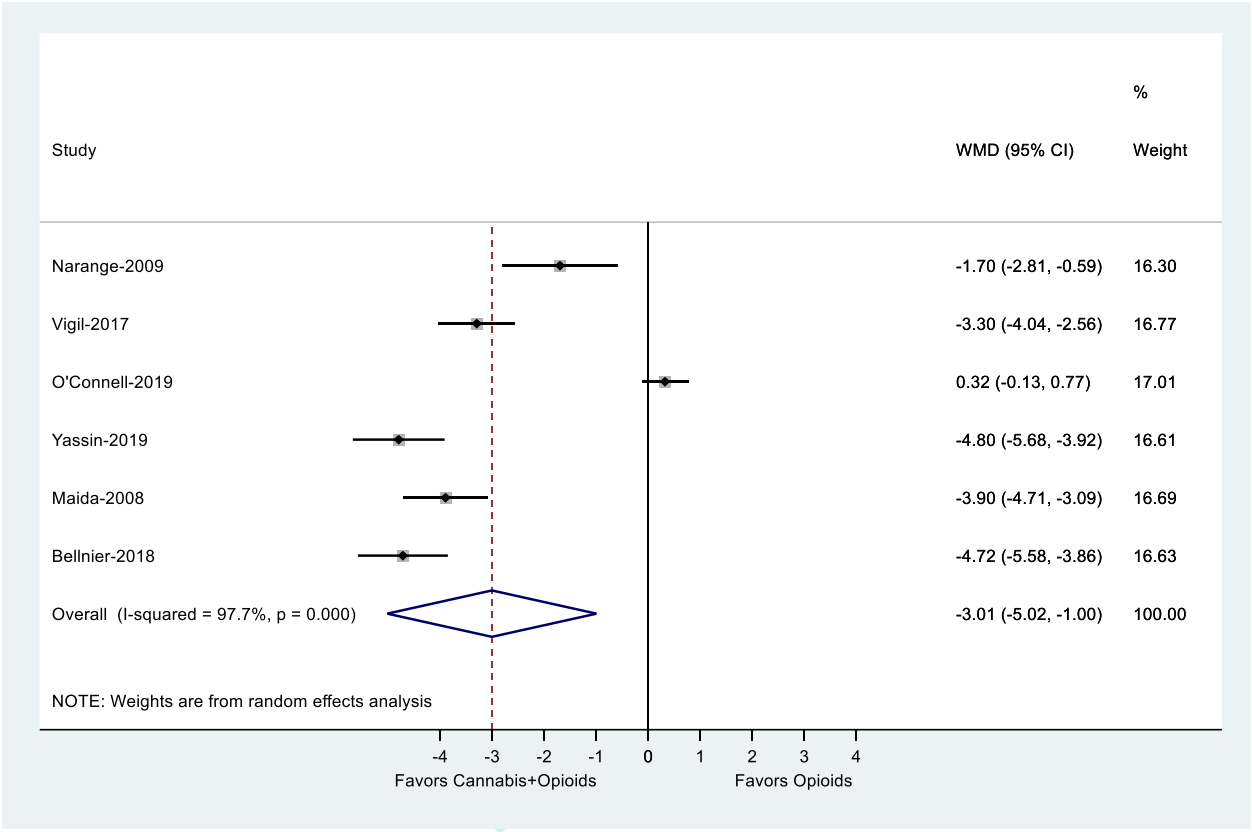
Supplement Figure 3: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies



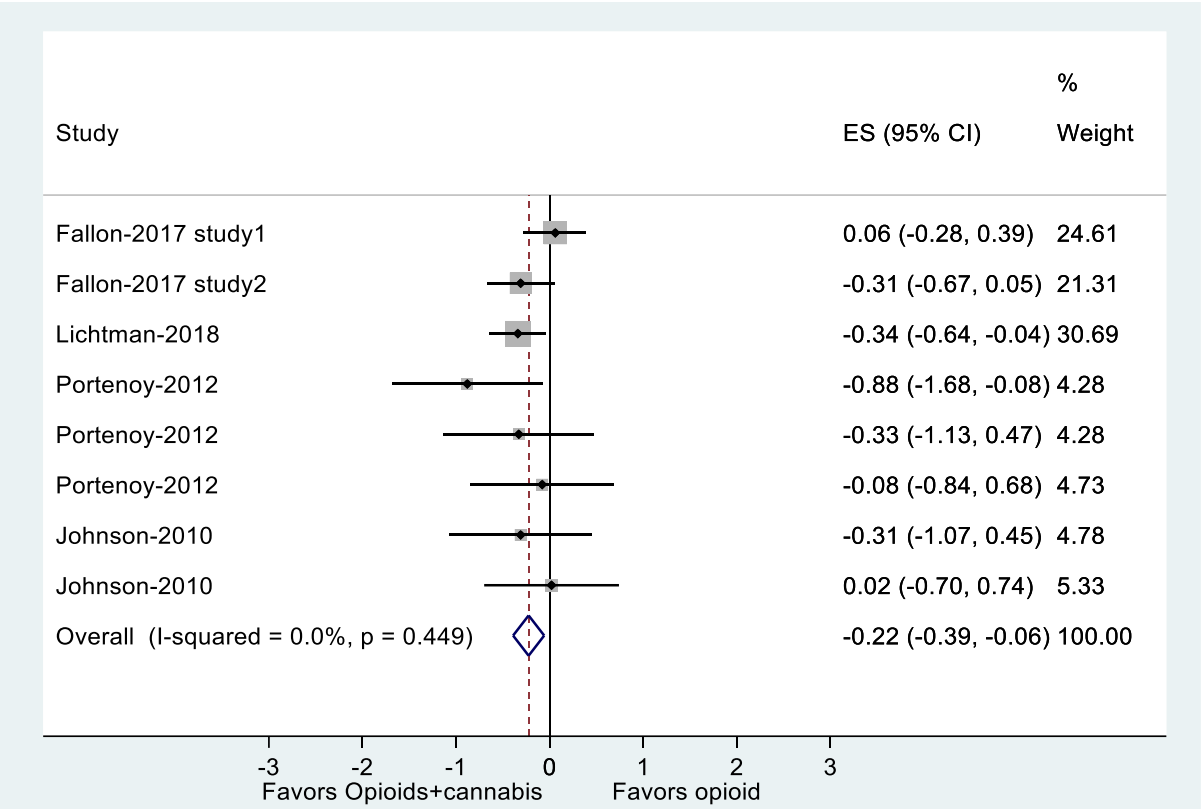
Supplement Figure 4: forest plot for pain relief on a 10-cm Visual Analog Scale (VAS) among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



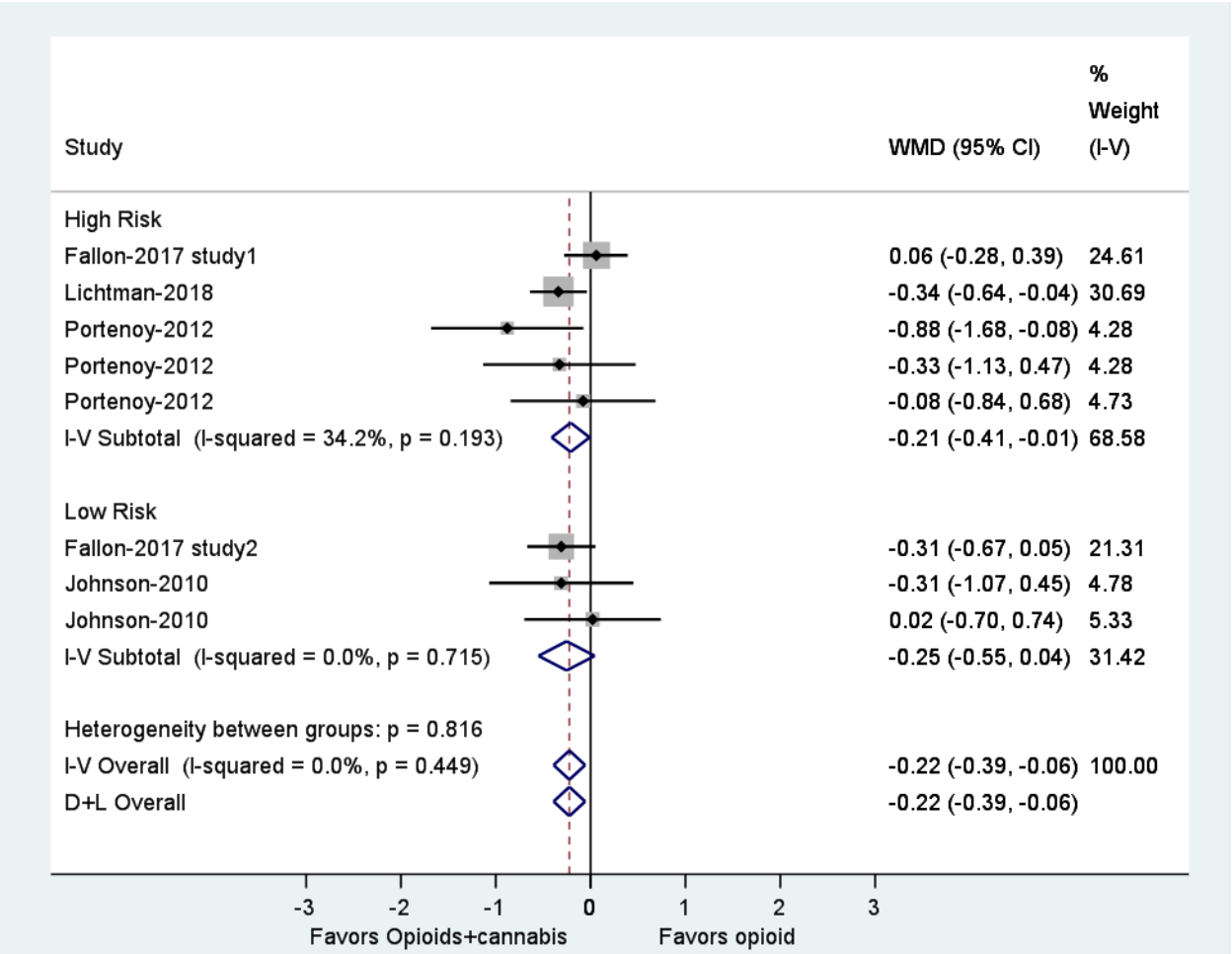
Supplement Figure 5: Subgroup analysis for pain relief on a 10-cm VAS and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



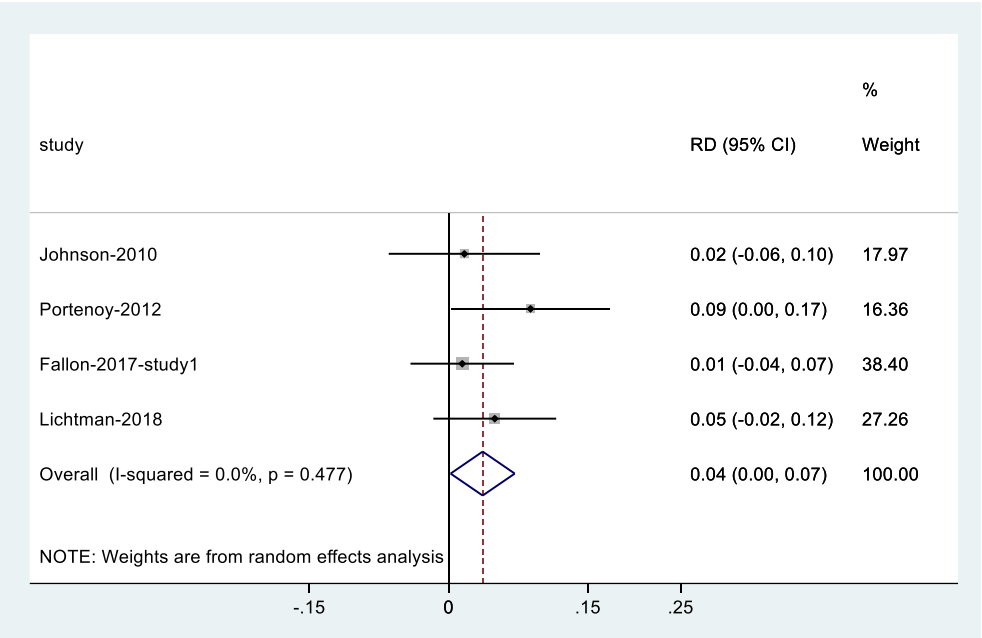
Supplement Figure 6: forest plot for pain relief on a 10-cm VAS among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies with no control group



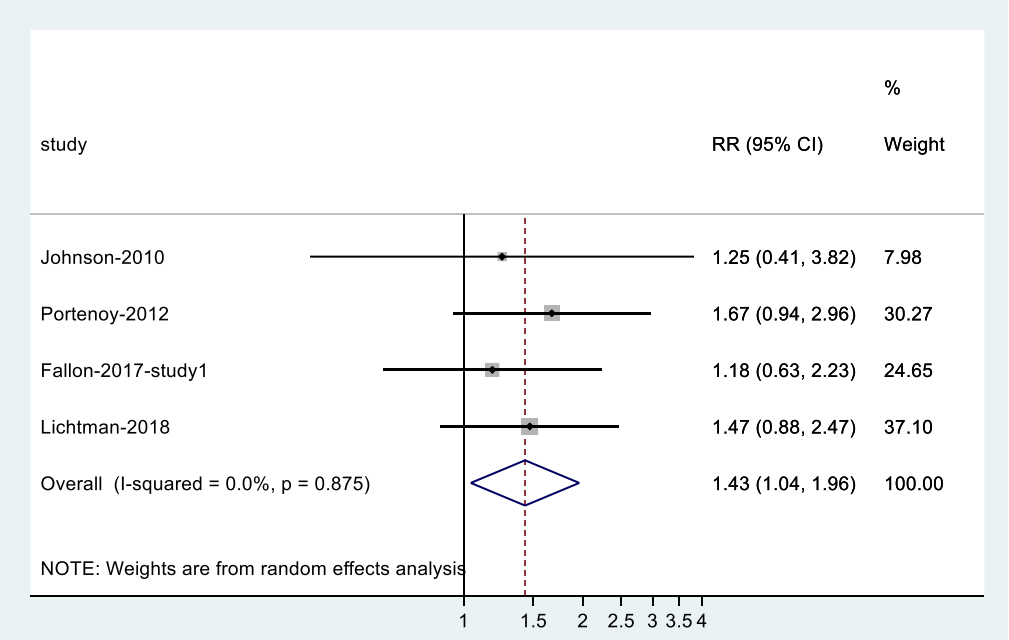
Supplement Figure 7: forest plot for sleep disturbance on a 10 cm VAS for sleep disturbance among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



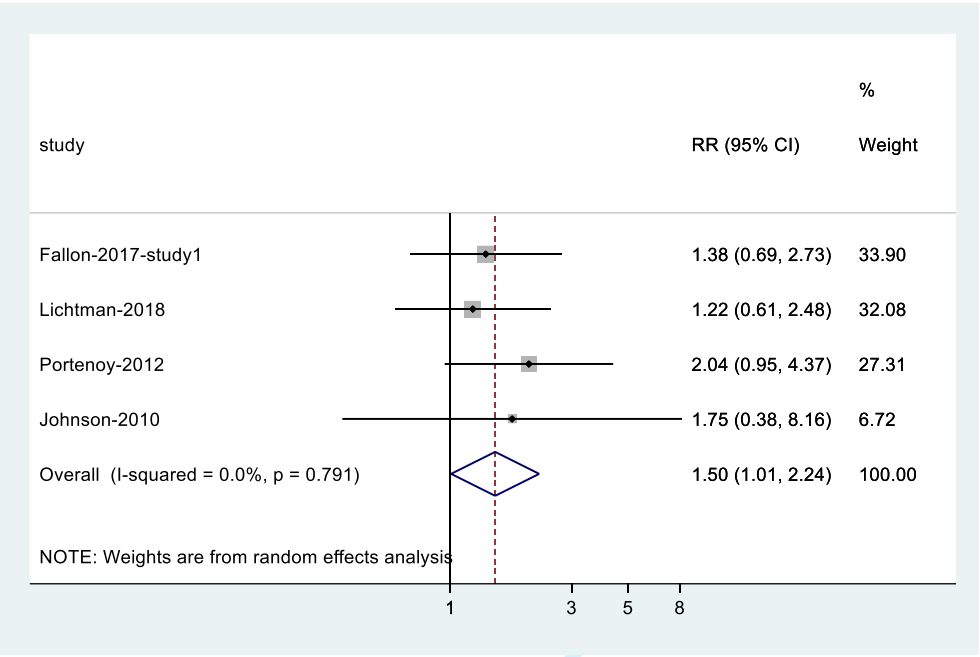
Supplement Figure 8: Subgroup analysis for sleep disturbance a 10-cm VAS for sleep disturbance and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



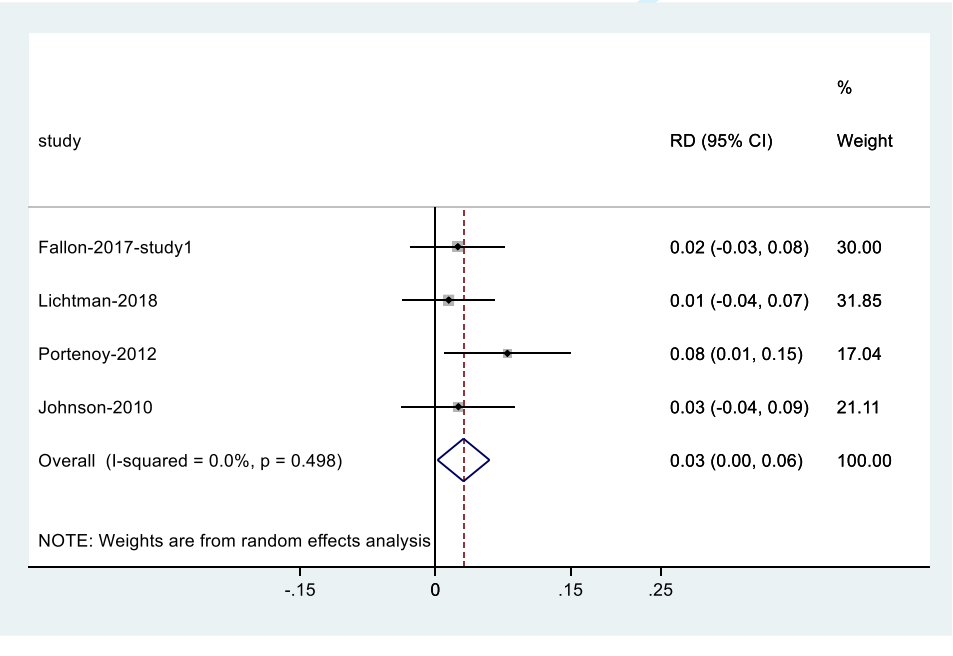
Supplement Figure 9: Risk difference of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



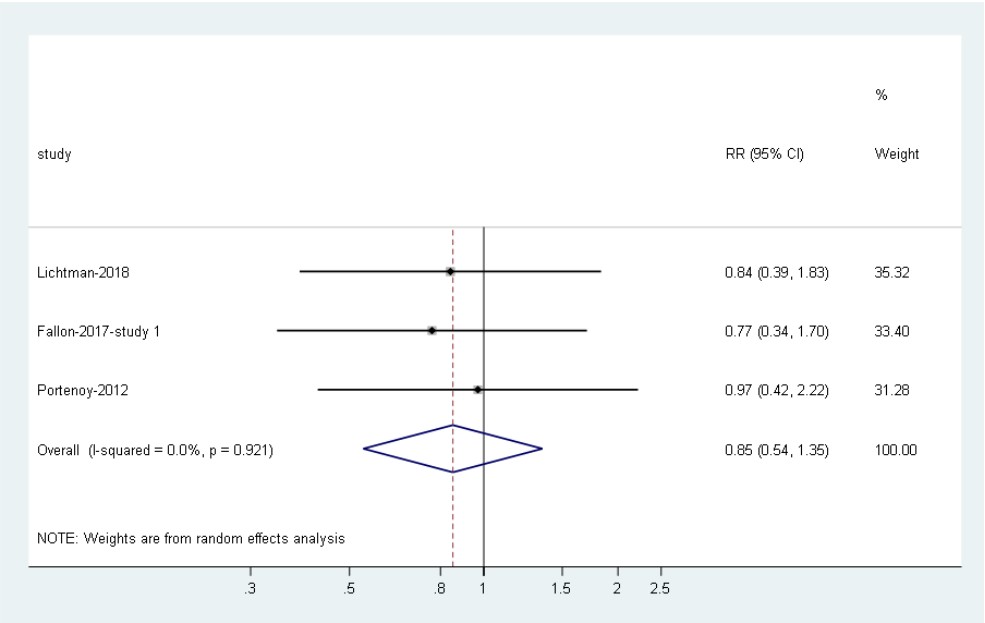
Supplement Figure 10: Relative Risk of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



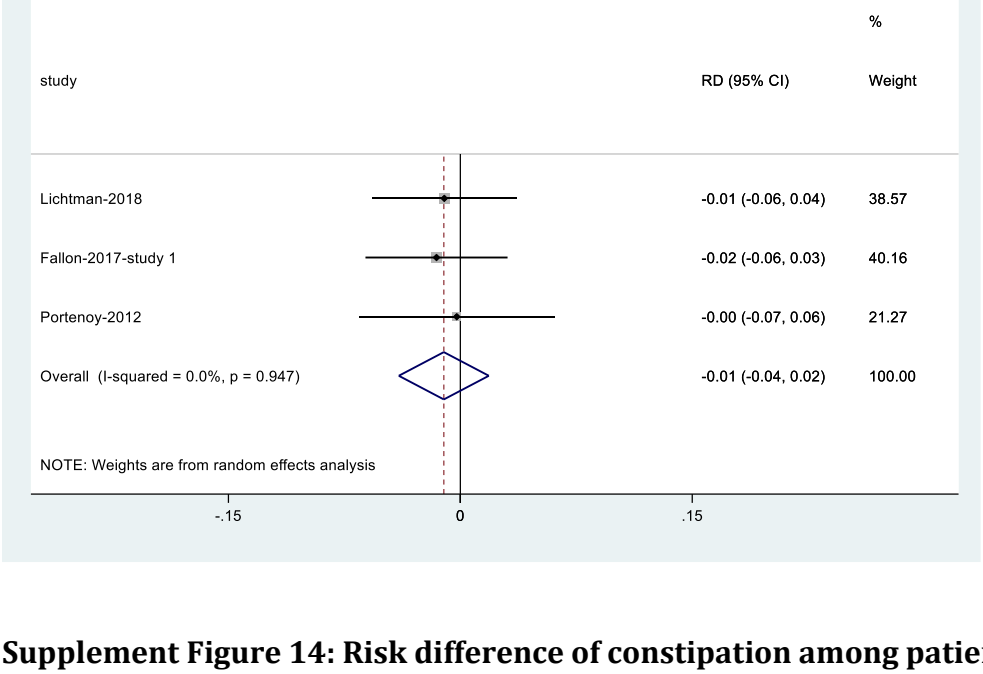
Supplement Figure 11: Relative Risk of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 12: Risk Difference of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 13: Relative Risk of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 14: Risk difference of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs

Appendix B: Reference List of Eligible studies

1. Barlowe TS, Koliani-Pace JL, Smith KD, Gordon SR, Gardner TB. Effects of medical cannabis on use of opioids and hospital visits by patients with painful chronic pancreatitis. *Clinical Gastroenterology and Hepatology* 2019.
2. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. *Mental Health Clinician* 2018;8(3):110-5.
3. Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med* 2020;132(1):56-61. doi:10.1080/00325481.2019.1685298.
4. Haroutounian S, Ratz Y, Ginosar Y, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain* 2016;32(12):1036-43. doi:10.1097/ajp.0000000000000364.
5. Maida V, Ennis M, Irani S, Corbo M, Dolzhykov M. Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring. *The journal of supportive oncology* 2008;6(3):119-24.
6. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9(3):254-64. doi:10.1016/j.jpain.2007.10.018.
7. O'Connell M, Sandgren M, Frantzen L, Bower E, Erickson B. Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control. *Annals of Pharmacotherapy* 2019:1060028019854221.
8. Pritchard ER, Dayer L, Belz J, et al. Effect of cannabis on opioid use in patients with cancer receiving palliative care. *J Am Pharm Assoc (2003)* 2020;60(1):244-7. doi:10.1016/j.japh.2019.10.013.
9. Pawasarat IM, Schultz EM, Frisby JC, et al. The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain. *J Palliat Med* 2020;23(6):809-16. doi:10.1089/jpm.2019.0374.
10. Rod K. A Pilot Study of a Medical Cannabis - Opioid Reduction Program. *American Journal of Psychiatry and Neuroscience* 2019;7(3):74-7. doi:10.11648/j.ajpn.20190703.14
11. Takakuwa KM, Hergenrather JY, Shofer FS, Schears RM. The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage. *Cannabis and Cannabinoid Research* 2020.
12. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS One* 2017;12(11):e0187795. doi:10.1371/journal.pone.0187795.
13. Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. *Clin Exp Rheumatol* 2019;37(Suppl 116):S13-S20.
14. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. *Journal of pain and symptom management* 2010;39(2):167-79.
15. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *The Journal of Pain* 2012;13(5):438-49.
16. Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *British journal of pain* 2017;11(3):119-33.
17. Lichtman AH, Lux EA, McQuade R, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as an adjunctive therapy in advanced cancer

patients with chronic uncontrolled pain. *Journal of pain and symptom management* 2018;55(2):179-88. e1.

Technical Appendix

This appendix provides additional details on two different methods of estimation, including 1) estimating the mean and standard deviation (SD) from sample size, median, and interquartile range (IQR); 2) estimating missing SD (for two non-randomized studies [5,7]) using the available SD from other included studies.

1) Estimating the mean and standard deviation (SD) from sample size, median, and IQR:

1) Pawasarat et al 2020 original reported data: median total morphine equivalent=45, n=137, and IQR=135.

-Using Wan et al method[1] produced: mean=60, SD=101

-Method recommended by Cochrane as *sensitivity analysis*:

$$S \approx \frac{q_3 - q_1}{1.35}.$$

q3-q1=IQR. This method produced SD=100.

2) Bellnier et al 2018 original reported data: median total morphine equivalent (before adding cannabis) =79.94, range=0 to 450, median (after adding cannabis) =19.65; range =0 to 150, n=29.

-Using Wan et al method produced: mean (before)=152.4, SD=111; mean (after)=47.3, SD=37.0

-Using Cochrane approach (Hozo et al[3]): Mean (before)= 152.4, SD= 112.5; mean (after)= 47.3, SD= 37.5

We finally included estimation by Wan et al method. The excel sheet including all formula was provided by Wan et al in supplementary file of their article[1].

2) Estimating missing SD using the available SD from other included studies:

1) Maida et al 2008 did not report SD around the mean at the end of follow-up for pain intensity. Original reported data: mean (SD) before adding cannabis= 7.1(2.4); after adding cannabis mean=3 (missing)
2) Connell et al 2019 original reported data: mean (SD) before adding cannabis=6.25 (missing); mean after adding cannabis=6.57 (missing)

We imputed missing SDs for these two studies from the given SDs related to other five included studies using prognostic method that presented by Ma et al[2]:

$$SEM_j^* = \frac{\sum_{i=1}^{k} SEM_i \sqrt{n_i}}{k\sqrt{n_j^*}}.$$

Assume there are k + l trials altogether where k trials are with full given information

SEM: value for trial *j (missing)* with sample size:

n_j: sample size for study with missing information.

SD (imputed) for first study= 1.51

SDs (imputed) for second study=1.76, 1.20

[1] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;**14**(1):135.

[2] Ma J, Liu W, Hunter A, et al. Performing meta-analysis with incomplete statistical information in clinical trials. BMC medical research methodology 2008;8(1):56.

[3] Hozo, S.P., Djulbegovic, B. & Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5, 13 (2005). https://doi.org/10.1186/1471-2288-5-13

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic # Checklist item Reported on page #

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

BMJ Open

Opioid-Sparing effects of medical cannabis or cannabinoids for chronic pain: A systematic review and meta-analysis of randomized and observational studies

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Anaesthesia
Keywords:	PAIN MANAGEMENT, Cancer pain < ONCOLOGY, GENERAL MEDICINE (see Internal Medicine)

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Opioid-Sparing effects of medical cannabis or cannabinoids for chronic pain: A systematic review and meta-analysis of randomized and observational studies

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ABSTRACT

Objective: To assess the efficacy and harms of adding medical cannabis to prescription opioids among people living with chronic pain.

Design: Systematic review.

Data sources: CENTRAL, EMBASE, and MEDLINE.

Main outcomes and measures: Opioid dose reduction, pain relief, sleep disturbance, physical and emotional functioning, and adverse events.

Study selection criteria and methods: We included studies that enrolled patients with chronic pain receiving prescription opioids and explored the impact of adding medical cannabis. We used GRADE to assess the certainty of evidence for each outcome.

Results: Eligible studies included five randomized trials (all enrolling chronic cancer-pain patients) and 12 observational studies. All randomized trials instructed participants to maintain their opioid dose, which resulted in a very low certainty evidence that adding cannabis has little or no impact on opioid use (weighted mean difference [WMD] -3.4 milligram morphine equivalent [MME]; 95% confidence interval [CI] -12.7 to 5.8). Randomized trials provided high certainty evidence that cannabis addition had little or no effect on pain relief (WMD -0.18cm; 95%CI -0.38 to 0.02; on a 10 cm VAS for pain) or sleep disturbance (WMD -0.22 cm; 95%CI -0.4 to -0.06; on a 10 cm VAS for sleep disturbance; minimally important difference [MID] is 1 cm) among chronic cancer-pain patients. Addition of cannabis likely increases nausea (relative risk [RR] 1.43; 95%CI 1.04 to 1.96; risk difference [RD] 4%, 95%CI 0% to 7%) and vomiting (RR 1.5; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%) (both moderate certainty) and may have no effect on constipation (RR 0.85; 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%) (low

certainty). Eight observational studies provided very-low certainty evidence that adding cannabis reduced opioid use (WMD -22.5 MME; 95%CI -43.06 to -1.97).

Conclusion: Opioid-sparing effects of medical cannabis for chronic pain remain uncertain due to very-low certainty evidence.

Systematic review registration PROSPERO CRD42018091098

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Keywords: chronic pain; opioids; cannabis; cannabinoids; drug substitution; sparing effect; tapering

Strengths and limitations of this study

- This is the first meta-analysis to pool the results of randomized controlled trials (RCTs) and observational studies exploring the opioid-sparing effects of medical cannabis among people living with chronic pain.
- We conducted a comprehensive search for eligible studies, appraised the risk of bias of included studies, and evaluated the certainty of evidence using the GRADE approach.
- Most observational studies incorporated inadequate adjustment for confounding, and all randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use.

Introduction

Chronic pain affects approximately one in five adults and is a common reason for seeking medical care.[1, 2] Opioids are commonly prescribed for this condition, particularly in North America;[3] however, they only provide benefit to a minority of patients. A 2018 systematic review of 96 trials found high certainty evidence that, versus placebo, opioids provide important pain relief (≥1cm improvement on a 10-cm visual analog scale for pain) to 12% of patients for whom they are prescribed.[4] Moreover, opioids are associated with harms such as overdose and death,[5, 6] which are dose-dependent.[7-10] As a result, there is considerable interest in therapies that may allow patients with chronic pain using opioid therapy to reduce their opioid intake.

One promising approach is adding cannabis therapy, which low certainty evidence suggests may be similarly effective to opioids for reducing pain and improving physical functioning among people living with chronic pain.[4] Experimental studies have shown that opioids and cannabis have similar signal transduction systems,[11] and observational studies in the US demonstrated that the rates of opioid-related mortality reduced after cannabis was legalized.[12-14] Between 64% and 77% of patients with chronic pain responding to cross-sectional surveys reported a reduction in long-term opioid use after adding medical cannabis to their treatment.[15, 16] A 2017 systematic review concluded that pre-clinical studies provided robust evidence for the opioid-sparing effects of cannabis.[17] To clarify the issue, we undertook a systematic review of randomized controlled trials and observational studies to explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes, and related harms in patients with chronic pain using prescribed opioid therapy.

This systematic review is part of the BMJ Rapid Recommendations project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation

(www.magicevidnece.org) and BMJ. This systematic review informed a parallel guideline published on BMJ.com[18] and MAGICapp (https://app.magicapp.org/#/guideline/jMMYPj).

METHODS

We followed standards for meta-analysis of observational studies in epidemiology (MOOSE)[19] and preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[20] and registered our review (PROSPERO Identifier: CRD42018091098).

Eligibility criteria

We included randomized controlled trials (RCTs) and observational studies, including cohort studies and case-control studies, in any language, that explored the impact of adding medical cannabis (i.e. phytocannabinoids, endocannabinoids, or synthetic cannabinoids) on the use of prescription opioids among people living with chronic pain. We defined pain as chronic if patients reported that symptoms had persisted for ≥3 months.[21] We excluded editorials, letters to the editor, pre-clinical studies, conference abstracts, case reports, case series, cross-sectional studies, and studies with less than 2-weeks follow-up. We also excluded studies of recreational cannabis use as these products typically contain much higher amounts of the psychotropic cannabinoid tetrahydrocannabinol (THC) than would be administered for therapeutic purposes.[22, 23] We classified observational study designs according to recommendations by the Cochrane Observational Studies Methods Group.[24]

Literature search and study selection

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and MEDLINE from inception to March 2020 with no restriction on language of publication. An experienced medical librarian (RC) developed our database-specific search strategies (Appendix A). We also searched the ClinicalTrials.gov registry to identify ongoing trials, and reference lists of all eligible studies and related systematic reviews for additional eligible studies. Two teams of

paired reviewers independently screened titles, abstracts and full-text studies for eligibility using online systematic review software (Rayyan QCRI, Qatar Computing Research Institute). Reviewers resolved disagreements through discussion.

Data collection

Using standardized forms and a detailed instruction manual, pairs of reviewers independently abstracted data from each eligible study, including study and patient characteristics, and details of treatment (e.g. dose, formulation, and duration of cannabis add-on therapy). Our primary outcome was opioid dose. We also captured all patient-important outcomes, as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials,[25] including pain relief, sleep disturbance, physical and emotional functioning. Regarding adverse events, we focused on vomiting, nausea, and constipation as a systematic review of values and preferences[26] demonstrated that patients living with chronic pain experience gastrointestinal complaints as the most important opioid-induced adverse events. We contacted authors to obtain unpublished data.

Risk of bias assessment

Following training and calibration exercises two independent reviewers used a modified Cochrane risk of bias tool[27, 28] to assess the risk of bias among eligible RCTs according to the following domains: allocation concealment, blinding of participants, study personnel, outcome assessors and data analyst, and loss to follow-up (≥20% missing data was assigned high risk of bias). Response options for each item were 'definitely or probably yes' (assigned a low risk of bias) and 'definitely or probably no' (assigned a high risk of bias). (Supplement Table 1) We used criteria suggested by the CLARITY group [29] to assess the risk of bias of observational studies

including selection bias, confidence that all patients had the condition of interest, control for confounding variables, validity of outcome assessment(s), and infrequent missing data (<20%) (details available at www.evidencepartners.com/resources/methodological-resources/). (Supplement Tables 2-3).

Data analysis

We calculated inter-rater agreement regarding the eligibility of full-text studies using an adjusted kappa (κ) statistic.[30] We conducted separate analyses for randomized controlled trials and observational studies. All continuous measures for pain intensity and sleep disturbance were converted to a 10 cm visual analogue scale (VAS); the minimally important difference (MID) for both was 1 cm.[31, 32] All continuous outcomes that were reported by more than one study were pooled to derive the weighted mean difference (WMD) and associated 95% confidence interval (95% CI). We pooled binary outcomes (adverse events) as relative risks (RRs) and risk differences (RDs) and their associated 95% CIs. We conducted all meta-analyses with random-effects models and the DerSimonian-Laird method.[33]

When studies reported effects on continuous outcomes as the median and interquartile range, we derived the mean and SD using the method presented by Wan *et al.* [34] We also converted medians to means using the approach recommended by the Cochrane Handbook as a sensitivity analysis. When authors failed to report a measure of precision associated with mean differences, we imputed the SD from eligible studies that reported these measures (Technical appendix).[35] We included each comparison reported by multi-arm studies and calculated a correction factor to account for the unit of analysis error (i.e. when information from a treatment arm is used more than once in the same meta-analysis).[36] We explored the consistency of

association between our pooled results and studies reporting the same outcome domains that were not possible to pool. We used Stata (StataCorp, Release 15.1, College Station, Texas) for all analyses. Comparisons were 2-tailed using a threshold of $p \leq 0.05$.

Subgroup analyses and meta-regression

We examined heterogeneity among pooled RCTs using the I^2 statistic, and through visual inspection of forest plots for pooled observational data, because statistical tests of heterogeneity can be misleading when sample sizes are large and associated confidence intervals are therefore narrow.[37] When we had at least two studies in each subgroup, we explored sources of heterogeneity with five pre-specified subgroup hypotheses, assuming greater benefits with: (1) shorter vs. longer duration of follow-up; (2) higher vs. lower risk of bias; (3) enriched vs non-enriched study design; (4) chronic non-cancer vs. chronic cancer-related pain; and (5) higher vs lower tetrahydrocannabinol [THC] content. We assumed similar directions of subgroup effects for harms, except for study design and THC content in which we expected greater harms with non-enriched trials and higher THC content. However, apart from item two (risk of bias), studies did not report sufficient data to undertake subgroup analyses.

The certainty of the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence on an outcome-by-outcome basis as high, moderate, low or very low.[38] With GRADE, RCTs begin as high-certainty evidence, but can be rated down because of risk of bias, imprecision, inconsistency, indirectness, or publication bias. We rated down for imprecision if the 95% CI associated with a pooled continuous outcome included ½ the

MID, or if the estimate of precision associated with the RR for binary outcomes included no effect. We considered an I^2 value between 75% and 100% to represent considerable inconsistency.[39] We rated down the certainty of evidence for indirectness if there were important differences between our research question and the patients enrolled, intervention tested, or outcomes reported among studies contributing to our meta-analyses.[40]

Using GRADE, observational studies begin as low certainty evidence, and while they can be rated down further for the same reasons as RCTs, they can also be rated up in the presence of a large magnitude of the effect, a dose-response gradient, or consideration of plausible confounders or other biases that increase confidence in the estimated effect.[41] We only reported the pooling results of observational studies when they resulted in the same or higher certainty of evidence than evidence from RCTs. When there were at least 10 studies for meta-analysis, we explored for small-study effects by visual assessment of funnel plot asymmetry and Egger's statistical test.[42]

Patients and public involvement

Patients and public were not involved in this research.

RESULTS

Of 5133 records identified, we reviewed 133 articles in full text, and 18 studies reported in 17 publications proved eligible (Figure 1, Appendix B); five RCTs in four publications[43-46] and 13 observational studies.[47-59] One study enrolled a mixed group of opioid and non-opioid users;[50] however, our attempts to contact the authors to acquire pain intensity data for the sub-group of patients prescribed opioids proved unsuccessful. All five RCTs[43-46] and three observational studies[51, 54, 55] enrolled patients with chronic cancer-related pain; the remaining 10 observational studies explored adding cannabis to opioids for patients with chronic non-cancer pain (e.g. chronic low back pain, fibromyalgia, painful chronic pancreatitis),[47, 52, 53, 57-59] or a mix of cancer and non-cancer pain (Table 1).[48-50, 56]

Among the 18 included studies, the percentage of female participants was 48% (median of individual trials 48%, interquartile range [IQR] 43% to 58%), and the median of the mean age was 56.3 (IQR 51.2 to 59.9). Follow-up ranged from 2 to 5 weeks among RCTs, and from 4 weeks to 6.4 years for observational studies. Only 1 RCT[43] used an enrichment design (following the open-label phase, patients with at least 15% improvement in pain were randomized to the intervention and control groups) and all RCTs advised patients to maintain stable doses of all other prescribed pain medications, including opioids, during the study period (Table 1). All included RCTs, and three of the observational studies[48, 51, 52] administered synthetic cannabis products (i.e. nabilone, dronabinol, and nabiximole), five observational studies[49, 50, 56, 58, 59] reported different combinations of THC: CBD products, and 6 other observational studies[47, 53-55, 57] did not provide details on the type of cannabis or cannabinoids provided (Table 1, Supplement Table 4). Ten studies reported receiving industry funding,[43-46, 49, 51, 52, 57, 58] five studies[50, 53-56]

reported no-industry funding, and three studies[47, 48, 59] did not report funding information (Table 1).

Risk of bias of included studies

All included RCTs reported adequate allocation concealment and blinding of patients and health-care providers; however, three trials[43, 45, 46] were at risk of bias due to high loss to follow up (Supplement Table 5). Each RCT specified that they employed an intention-to-treat analysis. All observational studies were at high risk of bias, typically due to lack of confidence in the assessment of exposure, non-representative samples, and insufficient control for confounding (Supplement Tables 6-7).

Outcomes for medical cannabis add-on therapy

Opioid dose reduction

The primary limitation of RCTs was that all investigators instructed patients to not alter their dose of opioids. This represents a very serious indirectness of the findings regarding the research question, warranting rating down two levels, and was the primary reason for very low certainty evidence from the 1176 patients.[43-45] Their results raised the possibility that adding medical cannabis may not be associated with a reduction in opioid use among patients living with chronic cancer pain (WMD -3.4 MME; 95%CI -12.7 to 5.9; table 2; Supplement Figure 1). There were no differences in effect based on the loss to follow-up (Supplement Figure 2; test of interaction P=0.758).

Very-low certainty evidence from 8 observational studies (7 of which enrolled people with chronic non-cancer pain)[47, 48, 50, 51, 53-55, 58] raised the possibility that adding medical cannabis

may reduce the use of opioids among patients with predominantly chronic non-cancer pain (WMD -22.5 MME; 95%CI -43.06 to -1.97; Table 2; Supplement Figure 3). Three observational studies that could not be pooled, as they only reported opioid reduction as a percentage, also found that providing medical cannabis allowed patients to decrease their opioid dose. The first study assessed the impact of providing medical cannabis to 61 patients with chronic low back pain who were prescribed opioid therapy (median opioid dose was 21 mg MME/day) and reported that 52% of patients (32 of 61) stopped all use of opioids at a median follow-up of 6.4 years.[57] The second study [49] reported that of 94 patients with chronic pain (both cancer and non-cancer pain) who began using CBD hemp extract, 53% were able to decrease their use of prescription opioids at 8 weeks. A third study[56] included 600 patients with chronic pain who indicated willingness to taper their opioid dose and were administered 0.5g daily of medicinal cannabis for each 10% reduction in opioid dose. After 6 months' follow-up, 55% of patients reported a 30% reduction in opioid dose on average and 26% of them discontinued opioid use.

Pain relief

High-certainty evidence from 5 RCTs[43-46] demonstrated that adding medical cannabis to opioid therapy resulted in trivial or no difference in cancer related pain (WMD -0.18 cm; 95%CI -0.38 to 0.02 on the 10 cm VAS for pain; MID 1cm; Table 2; Supplement Figure 4). Results did not differ depending on loss to follow-up (Supplement Figure 5, a test of interaction P=0.623). Very low certainty evidence from observational studies suggested a large decrease in pain when medical cannabis was added to opioids (Supplement Figure 6).

Sleep disturbance

Five RCTs[43-46] provided high certainty evidence that adding medical cannabis to prescription opioids results in a trivial improvement in sleep disturbance in people living with cancer-related chronic pain (WMD -0.22 cm; 95%CI -0.4 to -0.06 on the 10 cm VAS for sleep disturbance; MID 1cm; Table 2; Supplement Figure 7). Results did not differ between trials reporting the low and high loss to follow-up (Supplement Figure 8, a test of interaction P =0.93). Very low certainty evidence from observational studies suggested an improvement in sleep disturbance when medical cannabis was added to opioids (Supplement Table 8).

Other reported outcomes

A single RCT[44] reported moderate certainty evidence that adding cannabis likely has little or no effect on emotional and physical functioning (Supplement Tables 9-10).

Adverse events

Nausea, vomiting, or constipation

4 RCTs[43-46] provided moderate certainty evidence that adding medical cannabis to opioid therapy likely increases the incidence of nausea (RR 1.43, 95%CI 1.04 to 1.96; RD 4%, 95%CI 0% to 7%; Supplement Figure 9-10) and vomiting (RR 1.50; 95%CI 1.01 to 2.24; RD 3%; 95%CI 0% to 6%; Supplement Figure 11-12) in patients with cancer-related chronic pain prescribed opioid therapy. Three RCTs[43, 45, 46] provided low certainty evidence that adding medical cannabis to opioid therapy may not increase constipation (RR 0.85, 95%CI 0.54 to 1.35; RD -1%; 95%CI -4% to 2%; Supplement Figure 13-14). Supplement Table 11 summarizes adverse events reported in observational studies.

DISCUSSION

Very-low certainty evidence from randomized trials and observational studies was conflicting and leaves uncertain whether the addition of medical cannabis affects the use of prescribed opioids among people living with chronic pain. Compared with long-term opioid therapy for chronic cancer pain without medical cannabis, high certainty evidence showed that adding medical cannabis had little to no effect on pain or sleep disturbance. Results provided moderate certainty evidence that adding cannabis therapy to opioids likely increases both nausea (RR 1.43, 95%CI 1.04 to 1.96) and vomiting (RR 1.50; 95%CI 1.01 to 2.24), and low certainty evidence suggested no effect on constipation (RR 0.85, 95%CI 0.54 to 1.35).

Strengths of our review include a comprehensive search for eligible randomized and observational studies, appraisal of the risk of bias among individual studies, and use of the GRADE approach to rate the certainty of evidence. Our review has limitations, primarily due to features of primary studies eligible for review, which failed to report all recommended outcomes that have been established as important for people living with chronic pain. Most observational studies incorporated inadequate adjustment for confounding. All randomized trials, despite reporting this outcome, were not designed to address the effect of medical cannabis on opioid use. All eligible RCTs enrolled patients with chronic cancer-related pain, and the generalizability to non-cancer chronic pain is uncertain. Specifically, substitution effects of medical cannabis for prescription opioids may also differ between chronic cancer and non-cancer pain; however, lack of variability among studies eligible for our review precluded exploration of this subgroup effect. Studies included in our review administered different formulations of cannabis and cannabinoid products; however, pooled effects of outcomes reported in RCTs showed no important heterogeneity.

A meta-analysis of pre-clinical studies,[17] a narrative systematic review,[60] and several cross-sectional and case studies have reported an apparent reduction in opioid use with addition of cannabis therapy.[9, 10, 61-65] In a national US population-based survey[66] of 2,774 cannabis users (both medical and non-medical use) 36% of respondents reported substituting cannabis for prescription opioids (discontinued opioid use). In this survey, the 60% of participants who identified as medical cannabis users were much more likely to substitute cannabis for prescription drugs than recreational users (OR 4.59; 95%CI 3.87 to 5.43). Another US survey[67] that included 841 patients prescribed long-term opioid therapy for chronic pain reported that 61% used medical cannabis, and 97% of this subgroup reported coincident reduction of their opioid use. Consistent with these findings, very low certainty evidence from observational studies in our review also suggests that adding medical cannabis allows patients predominantly with chronic non-cancer pain to reduce their use of opioids. Although RCT results do not support reduction in opioid dose by adding medical cannabis for opioids, the evidence is also very low certainty, primarily because investigators instructed patients to maintain their current opioid dose. This is a critical limitation, despite the 2019 NICE guideline having concluded that providing medical cannabis for chronic pain does not reduce opioid use on the basis of these trials.[68] Future trials should randomize chronic pain patients who voluntarily agree to engage in a trial of opioid tapering to receive medical cannabis or placebo and report all patient-important outcomes.[69] Forced opioid tapering is ineffective[70] and may cause harm.[71]

Conclusion

The opioid-sparing effects of medical cannabis for chronic pain remain uncertain. Based on moderate-to-high certainty evidence, adding medical cannabis to opioid therapy among chronic cancer pain patients had little or no effect on neither pain relief nor sleep disturbance and likely increases the risk of nausea and vomiting. The accompanying BMJ Rapid Recommendation[18] provides contextualized guidance based on this evidence, as well as three other systematic reviews on benefits,[72] harms[73] and patients' values and preferences[74].

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Role of the Funding Source: This review received no external funding or other support.

Ethical approval: ethical approval was not required because this study retrieved and synthesized data from already published studies.

Data: Details of the characteristics of the included studies were shared in the supplementary materials. Data will be made available upon publication and can be obtained from the corresponding author at bussejw@mcmaster.ca.

Disclaimers: None.

Transparency: All authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Contribution: JWB, AN and GHG conceived and designed the study. RC performed the literature search. AN, AM, YS, VA and YR selected the studies, extracted the relevant information, and assessed the risk of bias of selected studies. AN synthesised the data. AN wrote the first draft of the paper. AN, JWB, GHG and TA critically revised the manuscript for important intellectual content. AN, JWB, LT, GHG, MB and NB interpreted the findings. JWB, LT and GHG provided methodological support. All authors reviewed the paper and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Figure Legends

Figure 1: Study selection process in review of opioid-sparing effects of cannabis in chronic pain

Table 1: Characteristics of included studies (n=18)

Author-year (country)	Study design	No. of participants (% prescribed opioids)	Type of chronic pain (specific condition)	Age mean (SD)	% Female	Baseline opioid dose	Follow-up duration	Medical cannabis dose	Analgesic Co-intervention	Funding source
Fallon et al., 2017 study I (multicenter trial£)[43]	Parallel arm RCT	n=399; nabiximols [n =20], placebo [n=199] (100%)	100% chronic cancer pain	59.8 (10.9)	43%	Receiving opioid therapy of <500 MME/day (Nabiximols group: 199MME/day± 131; placebo group: 207MME/day± 135)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Fallon et al., 2017 study II (multicenter trial£)[43]	Parallel arm RCT	n=206; nabiximols [n=103], placebo=103 (100%)	100% chronic cancer pain	61.5 (11.3)	49%	Receiving opioid therapy of <500 MME/day (Nabiximols: 212MME/day± 136; placebo: 209MME/day± 121)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Johnson et al., 2010 (multicenter trial£)[44]	Parallel arm RCT	n=177; THC: CBD extract [n= 60], THC extract [n=58], placebo [n=59] (100%)	100% chronic cancer pain	60.2 (12.3)	46%	Receiving opioid therapy for at least one-week before enrollment (THC:CBD: 258MME/day± 789; THC: 188MME±234;	2 weeks	One spray: 2.7mg THC/2.5mg CBD. The maximum permitted dose: 8 actuations over 3-hours and	Patients were excluded if they planned to undergo clinical interventions that would affect pain	GW Pharmaceuticals

						placebo: 367±886)		48 actuations over 24-hours		
Lichtman et al., 2018 (multicenter£)[45]	Parallel arm RCT	n=398; nabiximol [n=199], placebo [n=198] (100%)	100% chronic cancer pain	60 (11.5)	46%	Receiving opioid therapy of <500 MME/day (nabiximols: 193MME/day± 130; placebo: 186MME/day± 131)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Patients were excluded if they planned to undergo clinical interventions that would affect pain	Otsuka Pharmaceutical Co., Ltd.
Portenoy et al., 2012 (multicenter£)[46]	Parallel arm RCT	n=360; nabiximols low dose (1-4 sprays/day) [n=91], medium dose (6-10 sprays/day) [n=88], high dose (11-16 sprays/day) [n=90], placebo [n=91] (100%)	100% chronic cancer pain	58 (12.2)	48%	Receiving opioid therapy of <500 MME/day (median was 120MME/day; range 3 to 16,660)	5 weeks	THC 27 mg/mL; CBD 25 mg/mL (maximum allowed daily dosage of 10 sprays per day)	Patients were allowed to use breakthrough opioid analgesic as required	GW Pharmaceuticals; Otsuka Pharmaceutical Co., Ltd.
Barlow et al., 2019 (US)[47]	Retrospective chart-review	Enrolled in MCP [n=34], not enrolled in MCP [n=19] (100%)	100% CNCP (chronic painful pancreatitis)	49.9 (10.5)	45%	Not enrolled in MCP 183MME/day± 284; enrolled in MCP 190MME/day± 273	Range 4 to 297 weeks	NR	NR	NR
Bellnier et al., 2018 (US)[48]	One-arm observational study	n= 29 (100%)	90% CNCP; 10% cancer pain	61 (10)	65%	Patients were receiving a median opioid dose of 79.94MME/day	13 weeks	10mg capsules of THC/ CBD in a 1:1 ratio 3-times daily	NR	NR

Capano et al., 2020 (US)[49]	One-arm observational study	n= 131 (100%)	100% chronic pain (cancer and non-cancer)	56.1 (range: 39 to 70)	68%	Receiving at least 50MME/day	8 weeks	30mg CBD/1mg THC	NR	Ananda Professional.
Haroutounian et al., 2016 (Israel)[50]	One-arm observational study	n=73 (35%)	93.2% CNCP; 6.8% chronic cancer pain	51.2 (15.4)¥	38%¥	Receiving a median opioid dose of 60MME/day (range 45 - 90)	26 weeks	Cigarettes: 6% to 14% THC, 0.2% to 3.8% CBD; Oral: 11% to 19% THC, 0.5% to 5.5% CBD	All participants were encouraged to attempt gradual dose reduction and possible discontinuation of other analgesics	No-external funding
Maida et al., 2008 (Canada)[51]	Prospective cohort	Enrolled in MCP [n=47], not enrolled in MCP [n=65] (100%)	100% chronic cancer pain	69.7 (10.1)	42%	nabilone treated:60MME/day±64; nabilone untreated: 67MME/day±101	4 weeks	On average 1.79 mg twice daily nabilone	Patients were permitted to use concomitant analgesics	Valeant Pharma-ceuticals Canada Ltd
Narang et al., 2008 (US)[52]	One-arm observational study	n=30 (100%)	100% CNCP	Median=43.5 (range=21-67)	53%	Receiving an average opioid dose of 68MME/day±57	4 weeks	Flexible dose schedule, dronabinol 5mg to 20mg 3 times daily	NR	Solvay Pharmaceuticals, Inc.
O'Connell et al., 2019 (US)[53]	One-arm observational study	n=77 (100%)	100% CNCP	54.1 (range=26-76)	58%	Receiving a mean opioid dose of 140MME/day±184	26 weeks	NR	NR	No industry funding
Pritchard et al.,2020 (US)[54]	Retrospective cohort	cannabis and opioids co-use [n=22], opioids only [n=61] (100%)	100% chronic cancer pain	53.1 (11.7)	23%	MCP enrolled: 144MME/day±129; MCP not enrolled: 119MME/day ±100	26 weeks	NR	NR	No industry funding

Pawasarat et al., 2020 (US)[55]	Retrospective chart review	Enrolled in MCP [n=137], not enrolled in MCP [n=95] (100%)	100% chronic cancer pain	58 (IQR: 14.7)	56%	MCP enrolled: median 45MME/day, IQR=135; MCP not enrolled: median 97.5MME/day, IQR=150	Between 39 and 52 weeks for MCP enrolled; <26 weeks for not enrolled	NR	NR	No industry funding
Rod et al., 2019 (Canada)[56]	One-arm observational study	n=600	100% chronic pain (cancer and non-cancer)	NR	NR	Receiving a mean opioid dose of 120 MME/day (range 90 to 240MME/day)	26 weeks	CBD and THC ranged between 4% to 6%. Doses related directly to the opioid taper.	All participants indicated ready to reduce opioid dose and also received psychological supports (e.g. CBT, mindfulness, relaxation)	No external funding
Takakuwa et al., 2020 (US)[57]	One-arm observational study	n=61 (100%)	100% CNCP (back pain)	50 (11.4)	38%	Receiving a median opioid dose of 21MME/day	Median of 6.4 years among patients who ceased opioids completely	NR	NR	The Society of Cannabis Clinicians
Vigil et al., 2017 (US)[58]	Retrospective chart review	Enrolled in MCP [n=37], not enrolled [n=29] (100%)	100% CNCP (90% back pain)	56.3 (11.8)	36%	Maximum daily dosage of < 200MME/day (enrolled in MCP: mean 24MME/day±23; not enrolled	52 weeks	NR	NR	University of New Mexico Medical Cannabis Research Fund

						in MCP: mean 16MME/day±14)				
Yassin et al., 2019 (Israel)[59]	One-arm observational study	n=31 (100%)	100% CNCP (fibromyalgia)	33.4 (12.3)	90%	Receiving Oxycodone 5 mg three times/day	26 weeks	THC to CBD ratio was 1:4; 20 g/month for 3 months, increased up to 30 g/month at the end of 6 months	Patients were permitted to use standardized analgesic therapy (duloxetine 30 mg once daily and Targin 5/2.5 mg twice a day)	NR

*CNCP: Chronic non-cancer pain; MCP: Medical Cannabis Program; MME: milligram morphine equivalent; FU: follow-up; NR: not reported

¥ Based on the whole population including opioid users and non-users

£In Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, the United Kingdom and the United States

Table 2: GRADE Evidence Profile of medical cannabis or cannabinoids for patients with chronic pain prescribed long-term opioid therapy

# of studies	# of Patients	FU Duration (Weeks)	Risk of bias[a]	Inconsistency (I^2, P-value)[b]	Indirectness[c]	Imprecision[d]	Publication bias	Treatment association (95% CI)	Overall certainty of evidence
Opioid dose: morphine milligram equivalents (MME) per day									
4 RCTs[43-45]	1,176	2 to 5	No serious risk of bias [e]	No serious inconsistency [40%, *P*=0.15]	Very serious indirectness [f]	Serious imprecision [g]	Not detected	WMD -3.4MME (-12.7 to 5.8)	Very Low
8 Observational studies[47, 48, 50, 51, 53-55, 58]	453	4 to 297	Serious risk of bias [h]	Serious inconsistency [visual inspection]	No serious indirectness	No serious imprecision	Not detected	WMD -22.5MME (-43.06 to -1.97)	Very low
Pain: 10 cm VAS for pain; lower is better; the MID = 1 cm									
5 RCTs[43-46]	1,536	2 to 5	No serious risk of bias	No serious inconsistency [28%, *P*=0.20]	No serious indirectness	No serious imprecision	Not detected	WMD -0.18 (-0.38 to 0.02)	High
Sleep disturbance: 10 cm VAS for sleep disturbance; lower is better; the MID= 1 cm									
5 RCTs[43-46]	1,536	2 to 5	No serious risk of bias	No serious inconsistency [0%, *P*=0.45]	No serious indirectness	No serious imprecision	Not detected	WMD -0.22 (-0.39 to -0.06)	High
Nausea									
4 RCTs[43-46]	1330	2 to 5	Serious risk of bias	No serious inconsistency [0%, *P*=0.88]	No serious indirectness	No serious imprecision	Not detected	RR 1.43 (1.04 to 1.96)	Moderate
Vomiting									

4 RCTs[43-46]	1330	2 to 5	Serious risk of bias	No serious inconsistency [0%, *P*=0.50]	No serious indirectness	No serious imprecision	Not detected	RR 1.5 (1.01 to 2.24)	Moderate
Constipation									
3 RCTs[43, 45, 46]	1153	5	Serious risk of bias [i]	No serious inconsistency [0%, *P*=0.92]	No serious indirectness	Serious imprecision [g]	Not detected	RR 0.85 (0.54 to 1.35)	Low

WMD: weighted mean difference; RR: relative risk; 95% CI: 95% confidence interval; VAS: visual analogue scale; MID: minimally important difference; FU: follow-up.

[a] We assessed risk of bias using a modified Cochrane risk of bias instrument.

[b] Inconsistency refers to unexplained heterogeneity of results. For RCTs an I^2 of 75-100% indicates that heterogeneity may be considerable. We assessed heterogeneity of pooled observational studies through visual inspection of forest plots.

[c] Indirectness results if the intervention, control, patients or outcomes are different from the research question under investigation.

[d] Serious imprecision refers to situations in which the confidence interval includes both benefit and harm (the 95%CI includes 1 MID).

[e] Some of the included RCTs were at high risk of bias, due to loss to follow-up (>20%); however, we did not rate down for risk of bias as subgroup analysis showed no difference in treatment effect between trials at high and low risk of bias for missing outcome data (test of interaction p= 0.758 and p=0.623 for opioid dose reduction and pain respectively).

[f] Downgraded twice due to indirectness since all trials instructed participants to maintain their opioid dose during the study period.

[g] The 95%CI around the WMD includes no effect.

[h] Studies are based on non-representative samples.

[i] Most RCTs were at high risk of bias due to loss to follow-up (>20%).

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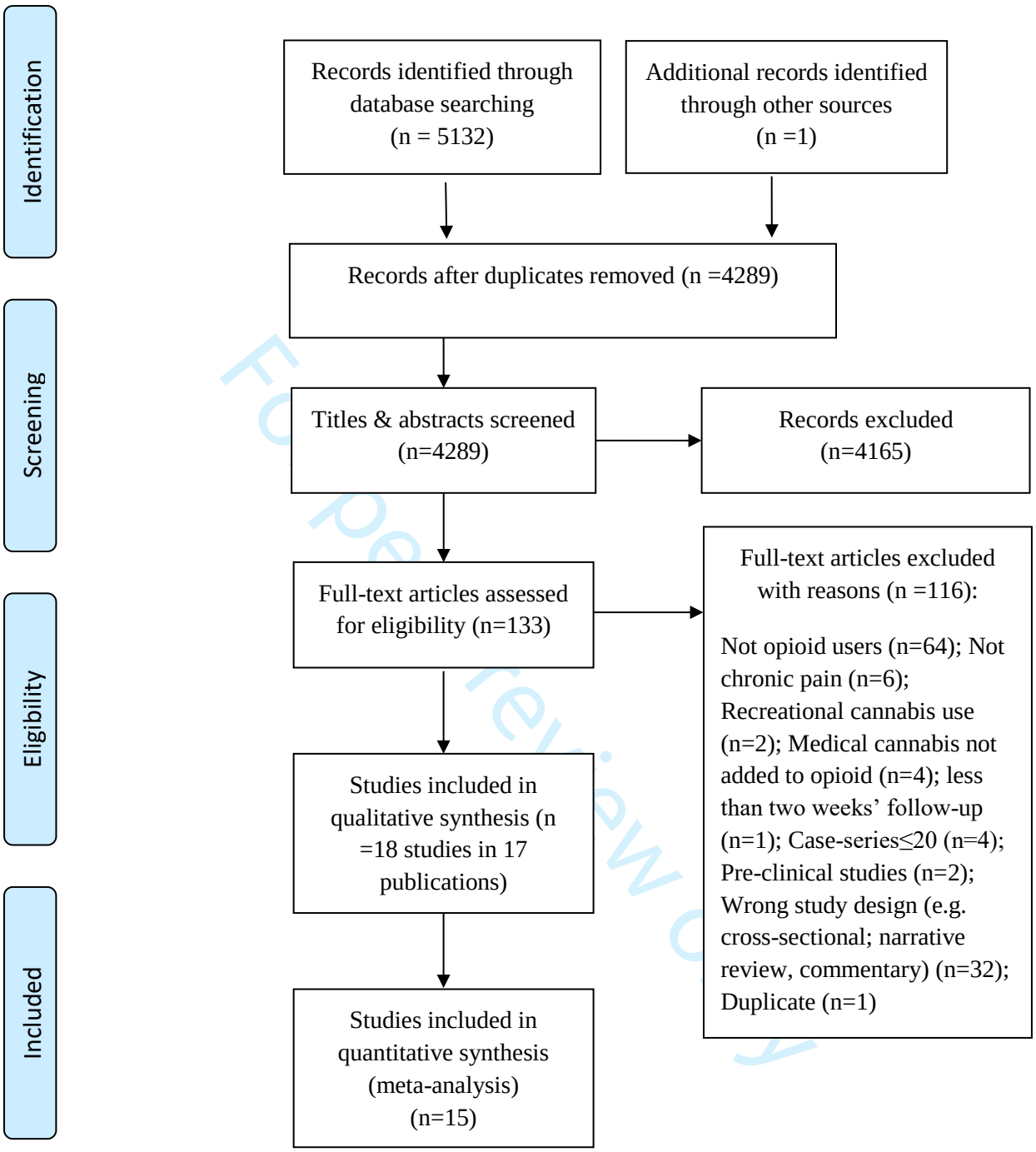

Figure 1: Study selection process in review of opioid-sparing effects of cannabis in chronic pain

Supplementary Material

Opioid-sparing effects of cannabis for chronic pain: A systematic review and meta-analysis of randomized and observational studies

Contents

Appendix A: Literature Search Strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.

The search terminology included all types of chronic pain AND any kinds of cannabinoids:

……

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:

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1 exp Analgesics, Opioid/ (111496)
2 opioid*.mp. (112576)
3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (150565)
4 or/1-3 (207118)
5 exp Narcotics/ (119511)
6 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism

supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10373)
7 or/1-6 (213683)
Annotation: opioid block
8 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (52087)
9 Cannabis/ (8573)
10 exp CANNABINOIDS/ (13258)
11 8 or 9 or 10 (52087)
Annotation: cannabis block
12 7 and 11 (6089)
Annotation: opioid and cannabis
13 (chronic adj4 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (65717)
14 Chronic Pain/ (12620)
15 exp Osteoarthritis/ (59676)
16 osteoarthrit*.mp. (84419)
17 osteo-arthritis.mp. (375)
18 exp Arthritis, Rheumatoid/ (109607)
19 exp Neuralgia/ (19415)
20 Diabetic Neuropathies/ (14247)
21 (neuropath* adj5 pain*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (23043)
22 neuralg*.mp. (26154)
23 zoster.mp. (20386)
24 Irritable Bowel Syndrome/ (6748)
25 IBS.mp. (8435)
26 Migraine Disorders/ (24388)
27 migraine.mp. (37040)
28 Fibromyalgia/ (8088)
29 fibromyalg*.mp. (11178)
30 complex regional pain syndromes/ or exp causalgia/ or exp reflex sympathetic dystrophy/ (5426)
31 Pain, Intractable/ (6126)
32 Phantom Limb/ (1816)
33 Hyperalgesia/ (11136)

34 exp back pain/ or exp failed back surgery syndrome/ or exp low back pain/ (37369)
35 radiculopathy.mp. (8722)
36 musculoskeletal pain/ or headache/ (29687)
37 exp Headache Disorders/ (33178)
38 headache*.mp. (89612)
39 exp Temporomandibular Joint Disorders/ (16711)
40 whiplash.mp. or exp whiplash injury/ (3896)
41 exp Cumulative Trauma Disorders/ (13326)
42 exp Peripheral Nervous System Diseases/dt [Drug Therapy] (14079)
43 Pain Measurement/de [Drug Effects] (6594)
44 (backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or fibromyalgi* or myodyni* or neuralgi* or ischialgi* or crps or rachialgi*).ab,ti. (43072)
45 ((noncancer* or non-cancer* or back or discogen* or chronic* or recurrent or persist* or bone or musculoskelet* or muscle* or skelet* or spinal or spine or vertebra* or joint* or arthritis or Intestin* or neuropath* or neck or cervical* or head or facial* or complex or radicular or cervicobrachi* or orofacial or somatic or non-malign* or shoulder* or knee* or hip or hips) adj3 pain).mp. (206944)
46 exp Pain/ (379991)
47 pain*.mp. (745044)
48 or/13-47 (1122771)
49 12 and 48 (1034)

Database: Embase <1974 to 2019 September 04>
Search Strategy:
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1 exp narcotic analgesic agent/ (317763)
2 (opioid* or opiate*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (188237)
3 (alfentanil or alphaprodine or beta-casomorphin$ or buprenorphine or carfentanil or codeine or deltorphin or dextromethorphan or dezocine or dihydrocodeine or dihydromorphine or enkephalin$ or ethylketocyclazocine or ethylmorphine or etorphine or fentanyl or heroin or hydrocodone or hydromorphone or ketobemidone or levorphanol or lofentanil or meperidine or meptazinol or methadone or methadyl acetate or morphine or nalbuphine or opium or oxycodone or oxymorphone or pentazocine or phenazocine or phenoperidine or pirinitramide or promedol or propoxyphene or remifentanil or sufentanil or tilidine or tapentadol).mp. (278150)
4 (adolonta or Anpec or Ardinex or Asimadoline or Alvimopam or amadol or biodalgic or biokanol or Codinovo or contramal or Demerol or Dicodid or Dihydrocodeinone or dihydromorphinone or dihydrohydroxycodeinone or dihydrone or dilaudid or dinarkon or dolsin or dolosal or dolin or dolantin or dolargan or dolcontral or duramorph or duromorph or duragesic or durogesic or eucodal or Fedotzine or Fentanest or Fentora or Fortral or Hycodan or Hycon or Hydrocodone or Hydrocodeinonebitartrate or hydromorphon or hydroxycodeinon or isocodeine or isonipecain or jutadol or laudacon or l dromoran or levodroman or levorphan or levo-

dromoran or levodromoran or lexir or lidol or lydol or morfin or morfine or morphia or morphin or morphinium or morphinene or morphium or ms contin or n-methylmorphine or n methylmorphine or nobligan or numorphan or oramorph or oxycodeinon or oxiconum or oxycone or oxycontin or palladone or pancodine or pethidine or phentanyl or prontofort or robidone or skenan or sublimaze or sulfentanyl or sulfentanil or sufenta or takadol or talwin or theocodin or tramadol or tramadolhameln or tramadolor or tramadura or tramagetic or tramagit or tramake or tramal or tramex or tramundin or trasedal or theradol or tiral or topalgic or tradol or tradolpuren or tradonal or tralgiol or tramadorsch or tramadin or tramadoc or ultram or zamudol or zumalgic or zydol or zytram).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (50642)

5 or/1-4 (403926)

6 exp cannabis/ (32390)

7 cannabinoid/ or cannabidiol/ or cannabinoid derivative/ or cannabinol/ or cannabinol derivative/ or cannabis derivative/ or delta8 tetrahydrocannabinol/ or delta8 tetrahydrocannabinol derivative/ or "delta9(11) tetrahydrocannabinol"/ or dronabinol/ or medical cannabis/ or nabiximols/ or tetrahydrocannabinol/ or tetrahydrocannabinol derivative/ or tetrahydrocannabinolic acid/ (26180)

8 (Cannabis or cannabinol or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (69860)

9 6 or 7 or 8 (75281)

10 5 and 9 (16412)

11 (chronic adj4 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (109897)

12 chronic pain/ (57642)

13 exp osteoarthritis/ (122475)

14 osteoarthrit*.mp. (136019)

15 osteo-arthritis.mp. (424)

16 degenerative arthrit*.mp. (1563)

17 exp rheumatoid arthritis/ (194747)

18 exp neuralgia/ (99958)

19 diabetic neuropathy/ (22699)

20 (neuropath* adj5 (pain* or diabet*)).mp. (71799)

21 neuralg*.mp. (29200)

22 zoster.mp. (36684)

23 irritable colon/ (24792)

24 (Irritable Bowel Syndrome or IBS).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (24025)

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27 fibromyalgia/ (19402)
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29 reflex sympathetic dystrophy.mp. (2356)
30 (complex regional pain syndromes or causalgia).mp. (1275)
31 intractable pain/ (4701)
32 phantom limb.mp. or agnosia/ or phantom pain/ or amputation stump/ (7388)
33 hyperalgesia/ (18711)
34 ((noncancer* or non-cancer*or chronic* or recurrent or persist* or non-malign*) adj3 pain).mp. (27031)
35 exp backache/ (104042)
36 radiculopathy.mp. or exp radiculopathy/ (37176)
37 musculoskeletal pain/ (10292)
38 exp arthralgia/ (58208)
39 headache/ (204055)
40 headache*.mp. (264831)
41 temporomandibular joint disorder/ (13308)
42 ((TMJ or TMJD) and pain*).mp. (3648)
43 whiplash.mp. or whiplash injury/ (4815)
44 exp cumulative trauma disorder/ (20089)
45 exp pain/ (1249315)
46 pain*.mp. (1280762)
47 or/11-46 (1963522)
48 10 and 47 (3115)

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Date Run: 05/09/2019 16:12:03
Comment:

ID Search Hits
#1 MeSH descriptor: [Cannabis] explode all trees 293
#2 MeSH descriptor: [Cannabinoids] explode all trees 743
#3 MeSH descriptor: [Endocannabinoids] explode all trees 46
#4 MeSH descriptor: [Endocannabinoids] explode all trees 46
#5 (Cannabis or cannabinol or cannabinoid* or cannabidiol or bhang or cannador or charas or ganja or ganjah or hashish or hemp or marihuana or marijuana or nabilone or cesamet or cesametic or ajulemic acid or cannabichromene or cannabielsoin or cannabigerol or tetrahydrocannabinol or dronabinol or levonantradol or nabiximols or palmidrol or tetrahydrocannabinolic acid or tetrahydro cannabinol or marinol or tetranabinex or sativex or endocannabinoid*):ti,ab,kw (Word variations have been searched) 4215
#6 #1 or #2 or #3 or #4 or #5 4215
#7 MeSH descriptor: [Pain] explode all trees 45094
#8 (pain*):ti,ab,kw (Word variations have been searched) 164064
#9 #7 or #8 169846
#10 #6 and #9 578
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#12 (osteoarthrit* or osteo-arthritis or arthrit* or neuropath* or neuralgi* or zoster* or migraine* or headache* or fibromyalgi* or causalgia or radiculopathy* or whiplash or backache* or backpain* or dorsalgi* or arthralgi* or polyarthralgi* or arthrodyni* or myalgi* or myodyni* or ischialgi* or crps or rachialgi*or TMJ or TMJD or IBS or crohn* or colitis* or enteritis* or ileitis*) 104465

#13 (irrita* or inflam*) near/4 (bowel or colon) 7249

#14 #11 or #12 or #13 113256

#15 #6 and #14 in Trials 353

Characteristics of eligible studies and Risk of Bias Assessment

Supplement Table 1: Detailed guidance for risk of bias assessment RCTs

Domain	Judgment
Random allocation concealment	**Definitely yes (low risk):** used central allocations (e.g. computer, telephone) **Probably yes (low risk):** sequentially numbered, opaque, sealed envelopes; studies did not provide enough information about concealment approach; however, it was placebo-control trial with double blinded design. **Probably no (high risk):** not enough information was provided and study was not blinded. **Definitely no (high risk):** used any unconcealed approach of allocation (e.g. case record number, day of week, health-care decision).
Blinding of patients	**Definitely yes (low risk):** explicitly mentioned that patients were blinded **Probably yes (low risk):** a placebo-controlled double-blinded trial. **Probably no (high risk):** no explicit statement about blinding status and not double-blinded placebo-controlled trial. **Definitely no (high risk):** explicitly mentioned that patients were not blinded.

Blinding of health care providers	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of data collector	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study; mentioned investigator were blinded. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded.
Blinding of outcome assessor	**Definitely yes (low risk):** explicitly mentioned that this group was blinded. **Probably yes (low risk):** mentioned that it was a double-blinded study. **Probably no (high risk)** **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Blinding data analyst	**Definitely yes (low risk):** explicitly mentioned that this group were blinded

	Probably yes (low risk): **Probably no (high risk):** no explicit statement about blinding and only mentioned double-blinded. **Definitely no (high risk):** explicitly mentioned that this group was not blinded; open-blinded or unblended trial.
Loss to follow-up	**Definitely yes:** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome, or missing outcome data were balanced across groups. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. **Definitely no (high risk):** the retention rate was less than 80%.
Sample size	We also considered the sample size lower than 300 for continuous as high risk of bias and rated down on the basis of imprecision in GRADE assessment.

Supplement Table 2: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with control group

Domain	Judgment
1) **Did the study match participants for all variables that are associated with the outcome of interest or did the statistical analysis adjust for these prognostic variables?** (This item queries how confident we are that the reported association or lack thereof is not due to confounding).	**Definitely yes (low risk):** studies that adjusted based on all important covariates including age, sex, baseline pain, baseline opioid dose, and other disabilities. **Probably yes (low risk):** studies that adjusted at a minimum for baseline pain and baseline opioid dose. **Probably no (high risk):** studies that did not provide any details about analysis method. **Definitely no (high risk):** Studies that did not adjust based on baseline opioid dose or baseline pain.
2) **Was selection of exposed and non-exposed cohorts drawn from the same population?** (this item queries whether participants who co-used cannabis and opioids or used opioids alone were drawn from the same population)	**Definitely yes (low risk):** Studies in which selection for participation is not dependent on exposure status (cannabis and opioid co-use). **Probably yes (low risk):** studies that did not provide enough information about recruitment to judge whether recruitment into the study was dependent on exposure status or not. **Probably no (high risk): NA**

	Definitely no (high risk): studies that compared cannabis and opioid co-users and non-users from different cohort.
3) Can we be confident in the assessment of exposure? (this item queries how confident we are about the quantification of cannabis and opioids co-use).	**Definitely yes (low risk):** if study reported some ascertainment methods for cannabis use (e.g. urine analysis), or study prescribed the specific dose of medical cannabis to the participants. **Probably yes (low risk):** self-report of cannabis use. **Probably no (high risk):** when study did not provide any details about assessing exposure status. **Definitely no (high risk):** participants self-reported cannabis usage only at baseline, or exposure status not assessed during the 4-weeks follow-up at least one time, or level of cannabis usage was not similar among participants. For example, some studies allowed patients to select the type or dose of cannabis themselves.
4) Can we be confident in the assessment of the presence or absence of prognostic factors?	**Definitely yes (low risk):** when patients self-reported the prognostic factors. **Probably yes (low risk):** when the method of assessment was not reported, it was considered as probably yes. *Note that for this item, we are only concerned with the measurement of the prognostic

	factors that mentioned in item number 1 as minimum adjusted variables (baseline pain intensity and opioid dose).
5) **Were co-interventions similar between groups?** (this item queries how similar are the use of other pain killers (e.g. NSAIDs) between cannabis users and non-users.	**Definitely yes (low risk):** study reported that co-intervention other than study intervention were limited during the study period. **Probably yes (low risk):** when co-intervention usage was approximately balanced between both intervention and control groups. **Probably no (high risk):** when study did not provide enough information about other drugs that participants may use. **Definitely no (high risk):** when participants were allowed to use all other co-interventions that could affect the outcome of the study.
6) **Was the follow up of cohorts adequate?** (This item queries the risk of bias associated with loss to follow-up and missing outcome data).	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance, if patients were required to come to clinic for

	outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.
7) **Can we be confident in the assessment of outcome?** (This item queries our confidence in the accuracy of the measurement of the outcome).	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** study used non-validated/reliable instrument.

Supplement Table 3: Detailed guidance for risk of bias assessment retrospective or prospective chart-reviews with no control group

Domain	Judgment
Is the source population (sampling frame) representative of the general population?	**Definitely yes (low risk):** participants were selected from a representative sample (e.g. national population registry) **Probably yes (low risk):** single community center, however the center was the only referral center that provided cannabis legally to participants. **Probably no (high risk):** based on the provided information source population could not be defined. **Definitely no (high risk):** sampling from one center or clinic or hospital or patients selected through using convenience sampling.
Is the assessment of the outcome accurate both at baseline and at follow-up?	**Definitely yes (low risk):** study used a validated/reliable measurement for pain assessment (e.g. VAS, NRS); reported opioid dose in a morphine equivalence dose by assessing patients' medical or prescription records. **Probably yes (low risk):** NA **Probably no (high risk):** when study did not provide enough information about the outcome measurement. **Definitely no (high risk):** used of different instruments at different follow-up intervals with concern of

	accuracy of responses, or used invalidated/reliable instruments.
Is there little missing data?	**Definitely yes (low risk):** the retention rate was at least 90% through the study. **Probably yes (low risk):** the retention rate approximately 80-89% and loss to follow-up unlikely to be related to the outcome. **Probably no (high risk):** the retention rate approximately 80-89%, however its rate likely to be related to the loss to follow-up. For instance, if patients were required to come to clinic for outcome measurement, patients who had poorer outcomes, or on the other hand, patients who were feeling better, may be less likely to attend the clinic. Loss to follow-up did not report or could not estimate. **Definitely no (high risk):** loss to follow-up more than 20%.

Supplement Table 4: Characteristics of Eligible studies

Barlowe et al-2019[1]

Study design	Retrospective chart review.
Participants	34 chronic painful pancreatitis patients with chronic use of opioids enrolled in a state therapeutic cannabis program were compared to 19 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	Cohort of patients who enrolled into the program had received cannabis therapy with a range from 34 to 297 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Bellnier et al-2018[2]

Study design	One-arm observational study (before/after).
Participants	29 patients with chronic pain who used opioids enrolled in a state therapeutic cannabis program.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	13 weeks
Funding source	Not reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain Quality Assessment Scale (PQAS) paroxysmal domain

Capano et al-2020[3]

Study design	One-arm observational study (before/after).
Participants	131 patients with chronic pain who used opioids enrolled in a pain clinic cannabis therapy.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	8 weeks
Funding source	Industry fund reported.

Outcome	- Reduction of opioid use (reported as percentage of patients who reduced their opioid use after 8 weeks). - Pain disability index - Pittsburgh Sleep Quality Index - Pain intensity and interference index (PEG)

Haroutounian et al-2016 [4]

Study design	One-arm observational study (before/after).
Participants	Chronic non-cancer pain (14 individuals had pain due to cancer) with a duration of 3 months or longer, and a lack of satisfactory analgesic response or intolerable adverse effects with at least 2 analgesics from 2 different drug classes at full dose (Opioid user: N=73; 35%).
Intervention (comparison)	The initial recommended medical cannabis dose was 20 g/mo added to opioids, which could be obtained as smoked cannabis, baked cookies or oil taking from cannabis dispensary centers. Cannabis could be titrated up to 3 times a day until satisfactory pain relief was gained (before using cannabis).
Follow-up	26 weeks.
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily intravenous [IV] morphine equivalence dosages among opioid users).

Maida et al-2008[5]

Study design	Prospective cohort study.
Participants	47 patients with chronic cancer pain who were opioid user and treated with nabilone were compared to 65 non-treated patients.
Intervention (comparison)	nabilone added to opioids (no nabilone).
Follow-up	4 weeks.
Funding source	Industry funding reported.

Outcome	-Reduction of opioid (calculated in average daily morphine equivalence dosages); -Pain reduction (Edmonton Symptom Assessment System 0: no pain-10: most severe pain); -anxiety, nausea, depression.

Narange et al-2008[6]

Study design	Phase II: One-arm observational study (before/after).
Participants	30 patients with chronic non-cancer pain who were taking opioids for a long time.
Intervention (comparison)	The starting dose was 5mg of dronabinol twice daily and titrated up to 20 mg 3 times a day added to opioids (before using dronabinol).
Follow-up	4 weeks
Funding source	Industry funding reported.
Outcome	-Pain reduction (VAS 0: no pain-10: most severe pain); -pain interfere with sleep (Brief pain inventory) -sleep disturbance -adverse events including anxiety, dizziness, and inability to concentrate.

O'Connell et al-2019[7]

Study design	One-arm observational study (before/after).
Participants	77 mixed type of chronic non-cancer pain patients who used opioids (96%) or benzodiazepines.
Intervention (comparison)	Medical cannabis including THC, CBD products added to opioid (before using cannabis)
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages among opioid users).

	-pain reduction (VAS 0: no pain-10: most severe pain).

Pritchard-2019[8]

Study design	Retrospective chart review.
Participants	22 patients who had chronic cancer-related pain and used opioids with the presence of THC in their urine drug screening were compared to 61 patients with opioid use only.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	26 weeks.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages)

Pawasarat-2020[9]

Study design	Retrospective chart review.
Participants	137 chronic cancer-related pain patients with chronic use of opioids enrolled in a State of New Jersey Medicinal Marijuana Program Registry were compared to 95 non-enrolled patients.
Intervention (comparison)	medical cannabis added to opioids (no cannabis).
Follow-up	Between 36 and 52 weeks for enrolled patients and 24 weeks for non-enrolled patients.
Funding source	No industry funding reported.
Outcome	-Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain).

Rod-2019[10]

Study design	One-arm observational study (before/after).
Participants	600 of chronic pain patients who used opioids and indicated they were prepared to reduce their opioid dose.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	- Reduction or cease of opioid use (reported as percentage of patients who ceased or reduced their opioid use after 6 months).

Takakuwa et al-2020[11]

Study design	One-arm observational study (before/after).
Participants	61 of chronic non-cancer pain patients (low-back pain) who used opioids.
Intervention (comparison)	Medical cannabis added to opioid (before using cannabis)
Follow-up	Median of 6.4 years among patients who ceased opioids completely
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in median daily morphine equivalence dosages among chronic and intermittent opioid users).

Vigil et al-2017 [12]

Study design	Retrospective chart review.
Participants	37 habitual opioid using, severe CNCP patients enrolled in the Medical Cannabis Program were compared to 29 non-enrolled patients.
Intervention (comparison)	Medical cannabis added to opioids (no cannabis).
Follow-up	52 weeks

Funding source	No industry funding reported.
Outcome	-Cessation of opioid (defined as the absence of opioid prescriptions activity during the last three months of observation) -Reduction of opioid (calculated in average daily intravenous [IV] morphine equivalence dosages); -Pain reduction only among cannabis users (VAS 0: no pain-10: most severe pain); -Quality of life (no effect; good benefit; great benefit; negative effect; and extremely negative effect of co-prescription of cannabis on quality of life).

Yassin et al-2019[13]

Study design	One-arm observational study (before/after).
Participants	31 patients with fibromyalgia were treated for at least 12 months with 5 mg of oxycodone hydrochloride equivalent to 4.5 mg oxycodone and 2.5 mg naloxone hydrochloride twice a day and duloxetine 30 mg once a day.
Intervention (comparison)	20 grams of smoked medical cannabis added to opioids (before cannabis inhalation).
Follow-up	26 weeks
Funding source	No industry funding reported.
Outcome	-Pain reduction (VAS 0: no pain-10: most severe pain) -Change in pain medication use in 5 categories: 1) increased doses, 2) stable dose through medical cannabis therapy duration, 3) less than half reduction in medication consumption, 4) more than half reduction in analgesic consumption, 5) deceased analgesic consumption. - Owestry Disability Index reduction (scale 0: no disability, 100: total disability)

Johnson et al-2010[14]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	177 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	tetrahydrocannabinol: cannabidiol (THC:CBD) extract added to opioids (placebo)
Follow-up	2 weeks
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) -Physical, emotional, role, and social functioning (QLQ-C30) -Nausea, vomiting, constipation.

Portenoy et al-2012[15]

Study design	Parallel, randomized double-blinded, placebo-controlled trial.
Participants	360 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Nabiximols at a low dose (1–4 sprays/day), medium dose (6–10 sprays/day), or high dose (11–16 sprays/day) added to opioids-(placebo)
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	- Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) - Nausea, vomiting, constipation.

Fallon et al-2017-Study 1[16]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	399 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ 9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL) added to opioids (placebo)
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance) - Nausea, vomiting, constipation.

Fallon et al-2017-Study 2[16]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	206 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Sativex (Δ 9-tetrahydrocannabinol (27 mg/mL): cannabidiol (25 mg/mL)) added to opioids (placebo)-patients who tolerated titrated dose of cannabis and showed an improvement of at least 15% on pain NRS score randomized into this study (randomized withdrawal design).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (VAS 0: no pain-10: most severe pain)

	-Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance)

Lichtman et al-2017[17]

Study design	Parallel, multi-center randomized double-blinded, placebo-controlled trial.
Participants	397 patients with chronic cancer pain who were under treatment by opioid regimen.
Intervention (comparison)	Nabiximols was added to opioids and was titrated the maximum allowed daily dosage of 10 sprays per day (placebo).
Follow-up	5 weeks
Funding source	Industry funding reported.
Outcome	-Reduction of opioid (calculated in mean daily morphine equivalence dosages) -Pain reduction (NRS 0: no pain-10: most severe pain) -Sleep disturbance (NRS 0: no disturbance-10: most severe disturbance)

Supplement Table 5: Risk of bias assessment for RCTs

Study (author-year)	Allocation concealment	Blinding of patients	Blinding of health care providers	Blinding of data collectors	Blinding of outcome assessors	Blinding of Data analyst	Loss to follow-up (≤20%)
Johnson et al-2010	PYes	PYes	PYes	PYes	PYes	PNo	Plow-risk[€]
Portenoy et al-2012	DYes	DYes	PYes	PYes	PYes	PNo	Dhigh-risk[£]
Fallon et al-2017 Study 1	PYes	PYes	PYes	PYes	PYes	PNo	Dhigh-risk[¥]
Fallon et al-2017 Study 2	PYes	PYes	PYes	PYes	PYes	PNo	Plow-risk[€]
Lichtman et al-2017	PYes	PYes	PYes	PYes	PYes	PNo	Dhigh-risk[¥]

* DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.
[£] The rate of loss to follow-up was more than 27%.
[¥]The rate of loss to follow-up was approximately 26%.
[€]The rate of loss to follow-up was approximately less than 20%

All RCTs used intention-to-treat (ITT) analysis, which included all randomized patients who had at least one post-randomization efficacy endpoint into the analysis.

Supplement Table 6: Risk of bias assessments for chart reviews with control group

Study	Were the exposed and unexposed drawn from same	Are we confident in the assessment of exposure?	Can we be confident in the assessment of the presence or absence of prognostic	Can we be confident in the outcome assessment?	Was there adequate follow-up?	Were the co-interventions similar?	Did the authors adjust for different confounders?	Overall risk of bias
Vigil 2017	DYes	DNo	PYes	PNo	PYes	PNo	PYes	High
Maida 2008	DYes	DYes	PYes	DYes	PNo	PNo	PYes	High
Barlowe 2019	DYes	DNo	PYes	DYes	PNo	PNo	PNo	High
Pritchard-2020	DYes	DYes	PYes	DYes	DNo	PNo	PNo	High
Pawasarat-2020	DYes	DNo	PYes	DYes	DYes	PNo	PNo	High

* DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.

Supplement Table 7: Risk of bias assessments for one-arm studies with no control group

Study	Is the source population (sampling frame) representative of the general population?	Is the assessment of the outcome accurate both at baseline and at follow-up?	Is there little missing data?	Overall risk of bias
Haroutounian et al-2016	DNo	DYes	PNo	High
Narang et al-2008	DNo	DYes	PYes	High
Yassin et al-2019	DNo	DYes	PYes	High
O'Connell et al-2019	DNo	DYes	PYes	High
Takakuwa et al-2020	DNo	DYes	PYes	High
Vigil et al-2017	DNo	PNo	PYes	High
Bellnier-2018	DNo	DYes	DYes	High
Capano et al-2020	DNo	DYes	PNo	High
Rod-2019	DNo	PNo	PNo	High

* DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no
DYes/PYes= low risk of bias; DNo/PNo=high risk of bias.

Table 8: Other reported outcomes in observational studies

Sleep disturbance results from two observational studies

Capano et[3] al assessed the effect of adding CBD among patients with chronic pain who were opioid users for at least 1 year.	The mean of Pittsburgh Sleep Quality Index* decreased from 12.09±4.1 at baseline to 10.3±4.3 at the end of week 8.	Very-low certainty evidence; p value=0.03
Narang et al[6] also evaluated the impact of adding dronabinol among 30 patients taking opioids for chronic pain.	The sleep disturbance decreased significantly at the end of week 4.	Very low certainty evidence; p-value <0.01

*Ranges between 0 to 21 with the higher total score (referred to as global score) indicating worse **sleep quality**.

Other reported outcomes in one observational study

Capano et[3] al reported that pain disability index[1] did not show a significant reduction, from 38.02±15.2 at baseline to 34.1±12.4 at week 4 (P-value=0.09).
Pain intensity and inference index[2] reduced from 6.5±1.9 to 5.7±2 after 8 weeks' follow up (P-value=0.006).

[1]Ranges from 0 to 70 (The higher the index the greater the person's disability due to pain).

[2]PEG ranges from 0 to 10 (The higher the worse pain and interference).

Table 9: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for physical function among patients with chronic pain from 1 RCT

Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Physical functioning[14]	Cannabis=118, placebo=59 (1 RCT[14])	Two weeks	THC: CBD vs. placebo: -4.23 (*P*=0.108) THC vs. placebo: -1.25 (*P*=0.631)	Moderate [b]	Adding cannabis to opioids probably does not improve physical functioning.

[a] In favor of placebo; [b] Due to imprecision.

Table 10: GRADE evidence profile of cannabis adjuvant to opioids vs. opioid alone for emotional function among patients with chronic pain from 1 RCT

Outcome	n of participants (studies)	Follow-up	Mean difference	Certainty of evidence (GRADE)	Plain-language summary
Emotional functioning[14]	Cannabis=118, placebo=59 (1 RCT[14])	Two weeks	THC: CBD vs. placebo: 6.73 (*P*=0.084) THC vs. placebo: 5.22 (*P*=0.174)	Moderate[b]	Adding cannabis to opioids probably does not improve emotional functioning.

[a] In favor of cannabis; [b] Due to imprecision.

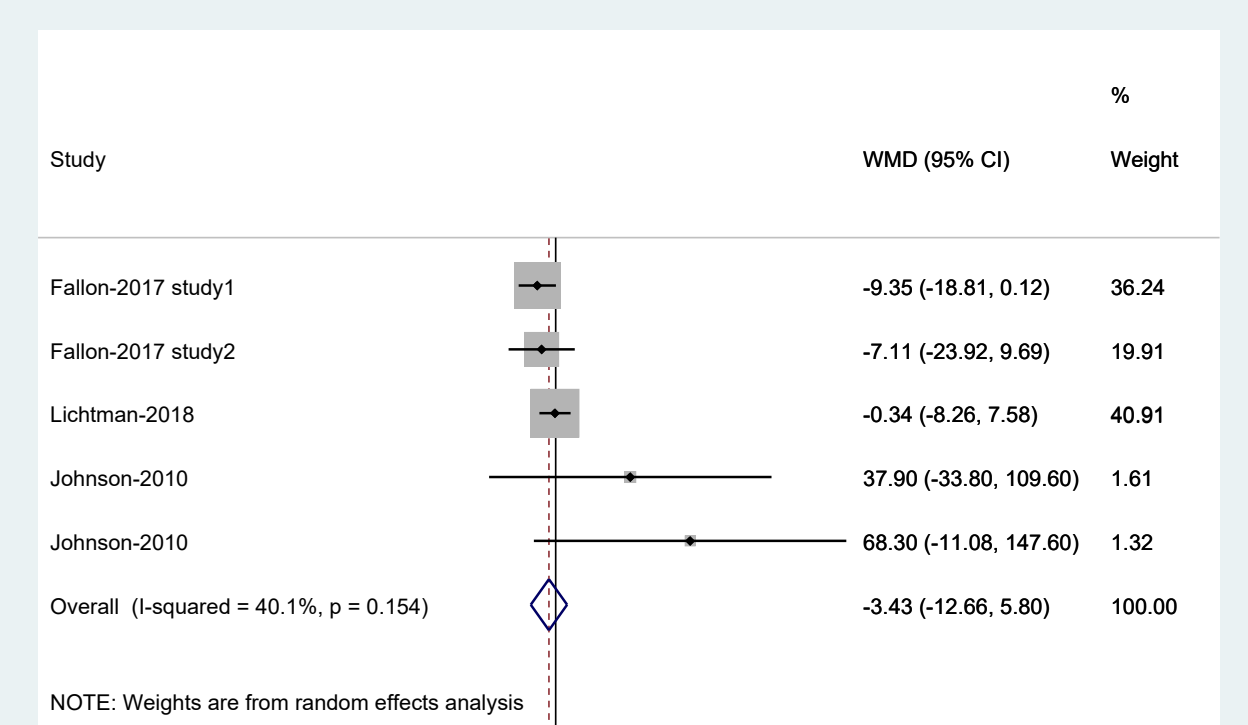
Supplement Table 11: Summary of adverse events among included observational studies*

Study	Method of assessment	Adverse events reported
Haroutounian et al[4]	Self-reported.	Two participants discontinued treatment due to serious side effects.
Maida et al[5]	Self-reported	Anxiety (P=0.028), nausea (P<0.001), and distress (P=0.021) were decreased significantly among patients who used nabilone in comparison to patients who did not use it.
Narang et al[6]	Self-reported (29-item symptom Side Effect Checklist).	*Phase II:* Dry mouth, tiredness (both P<0.0001), abnormal thinking, anxiety, facial flushing, eye irritation, headache, and ringing in the ears, and drowsiness (P< 0.05) showed a significantly higher occurrence at the 20 mg dronabinol dose compared with placebo. -Dry mouth, difficulty speaking, forgetfulness, confusion, dizziness, and euphoria were more occurred in both treatment group versus placebo (P= 0.01)

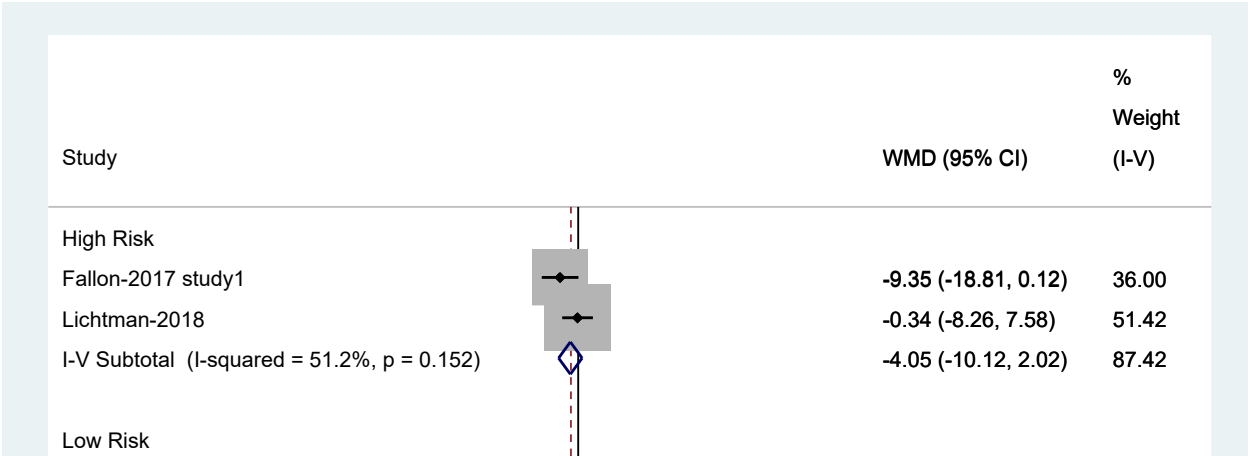
Vigil et al[12]	Self-reported.	No respondents reported any serious side effects from cannabis use (only 9% of patients reported cannabis affected negatively their concentration).
Yassin et al[13]	Self-reported	Mostly mild adverse events were reported (e.g. red eye, sore throat, increase appetite); only 6 patients out of withdrew due to the side effects in non-cannabis group.

*O'Connell et al[7], Barlowe et al[1], Rod 2019, and Takakuwa et al[11] did not report adverse events.

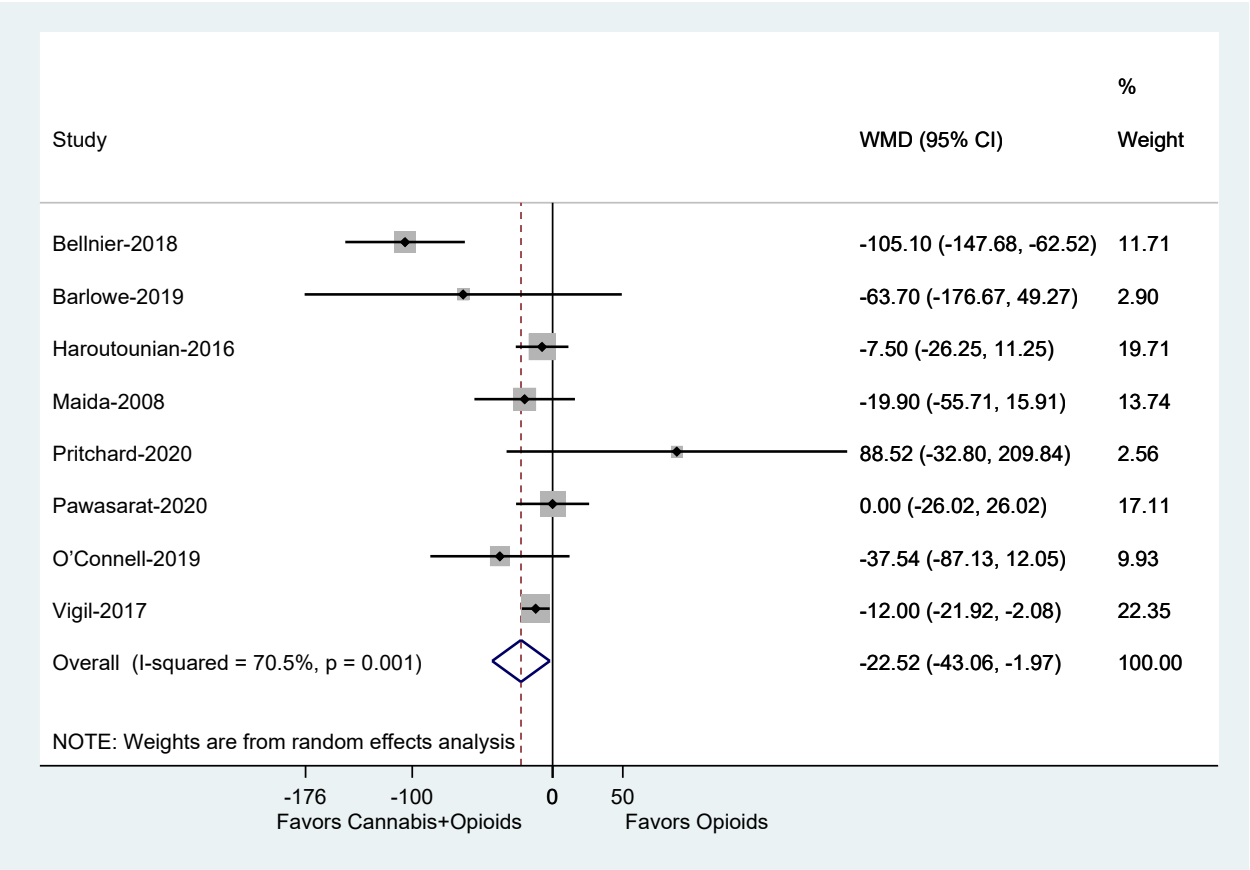
Additional results tables and figures



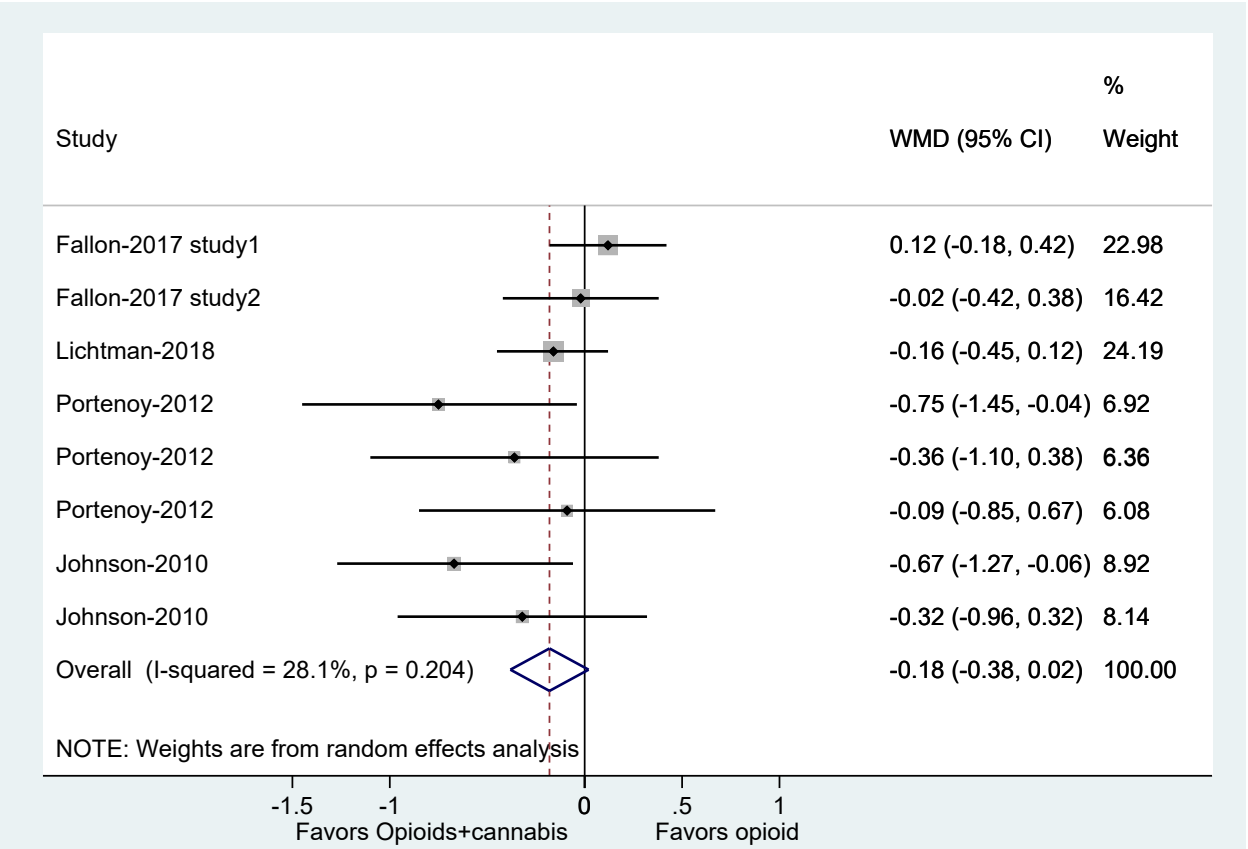
Supplement Figure 1: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



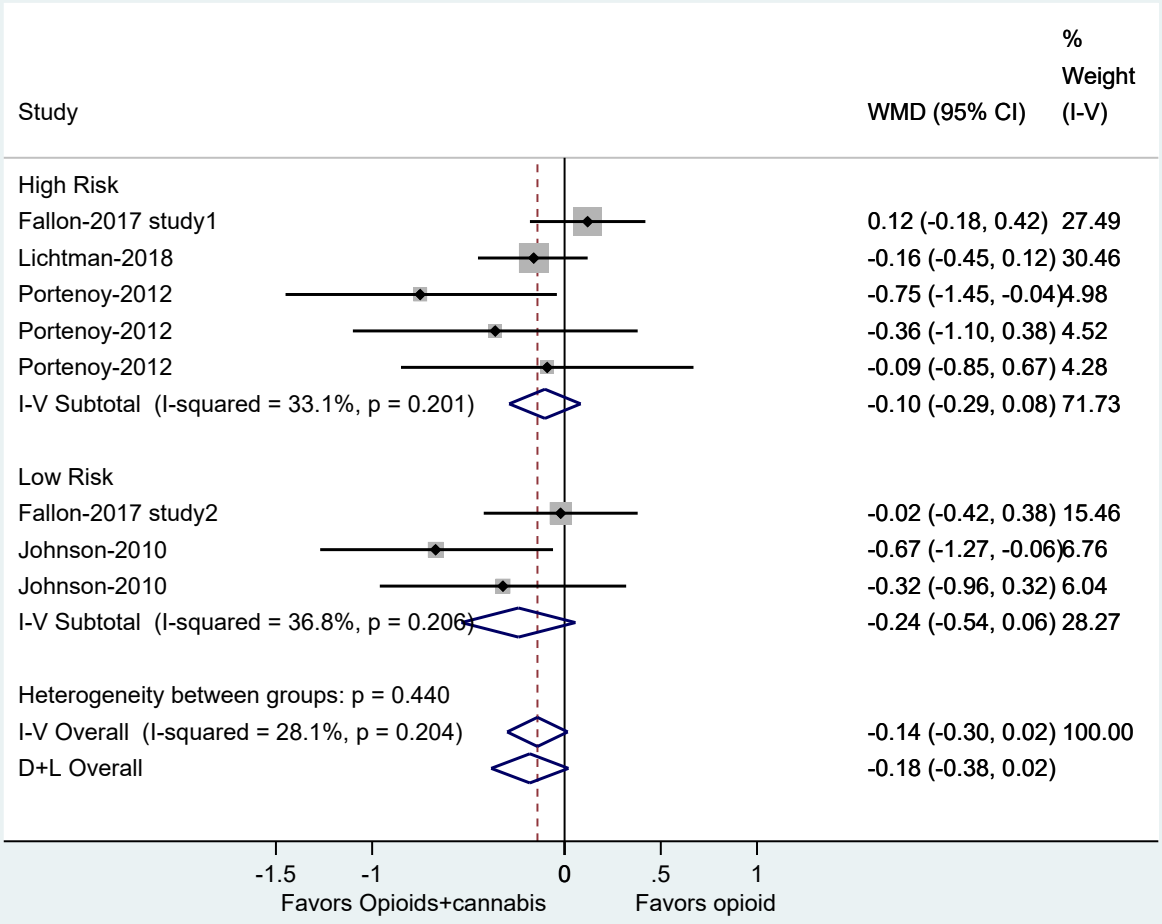
Supplement Figure 2: Subgroup analysis for opioid dose reduction and risk of bias (high risk vs. low risk) from 4 RCTs of Cannabis+opioids vs. placebo



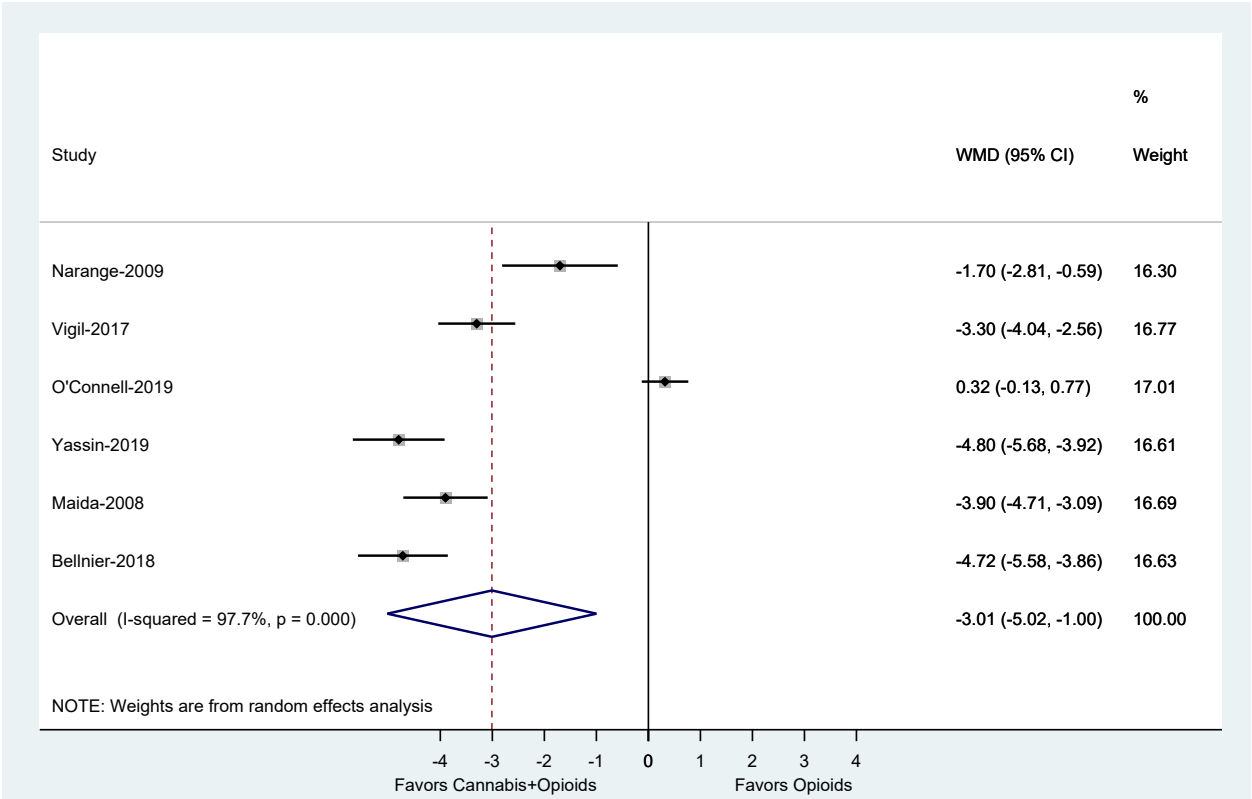
Supplement Figure 3: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies



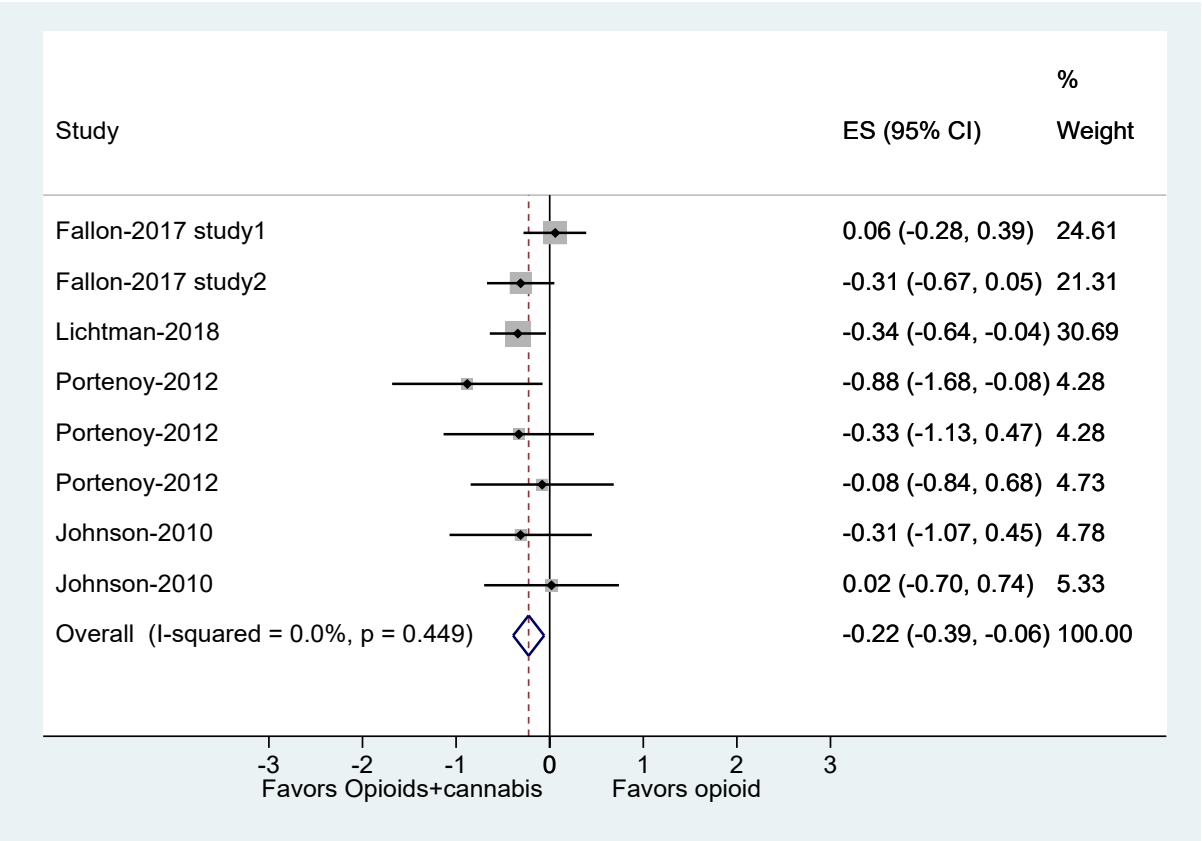
Supplement Figure 4: forest plot for pain relief on a 10-cm Visual Analog Scale (VAS) among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



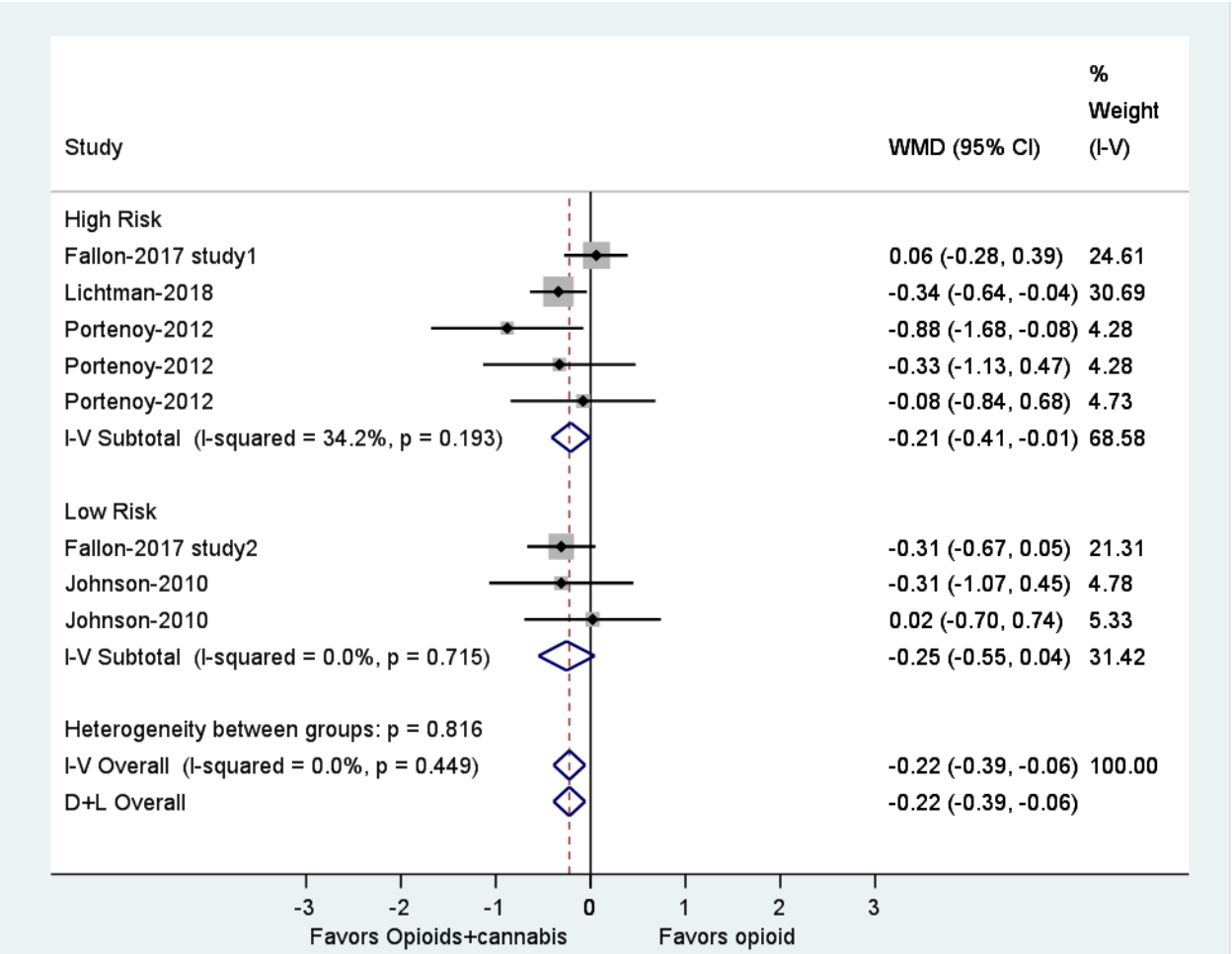
Supplement Figure 5: Subgroup analysis for pain relief on a 10-cm VAS and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



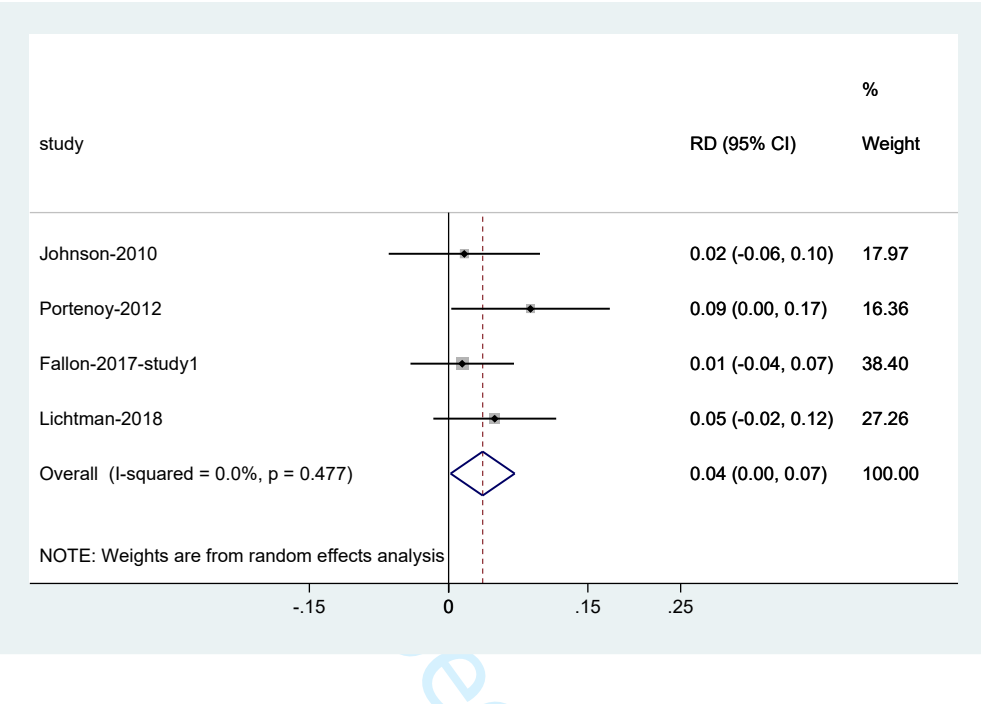
Supplement Figure 6: forest plot for pain relief on a 10-cm VAS among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies with no control group



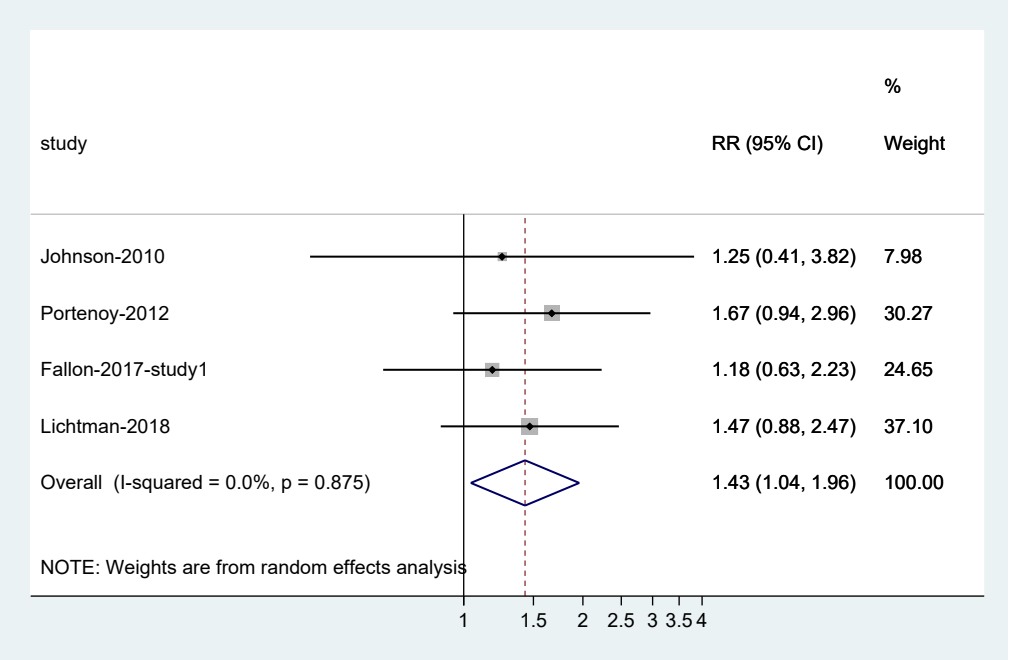
Supplement Figure 7: forest plot for sleep disturbance on a 10 cm VAS for sleep disturbance among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



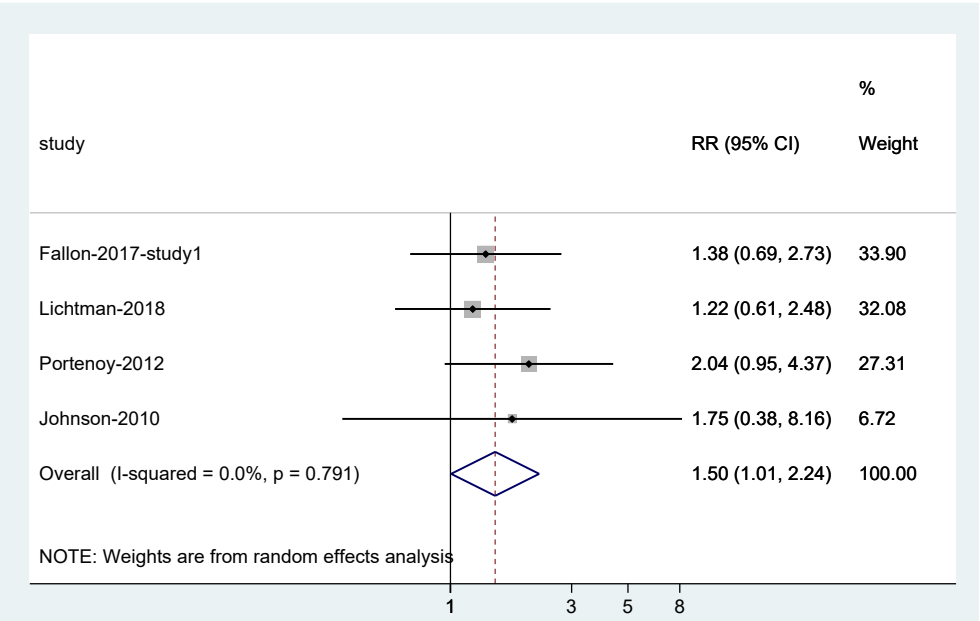
Supplement Figure 8: Subgroup analysis for sleep disturbance a 10-cm VAS for sleep disturbance and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



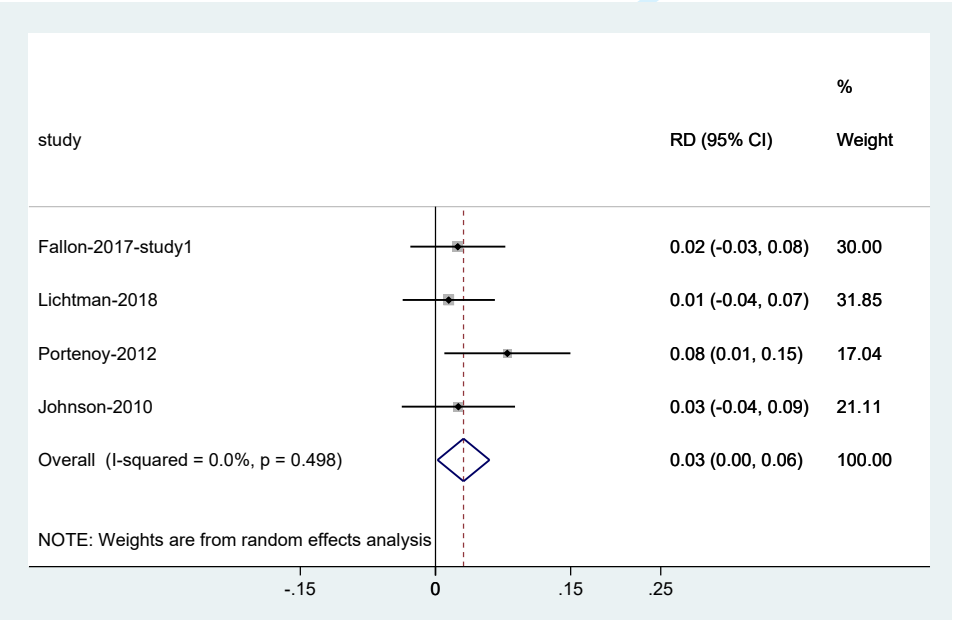
Supplement Figure 9: Risk difference of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



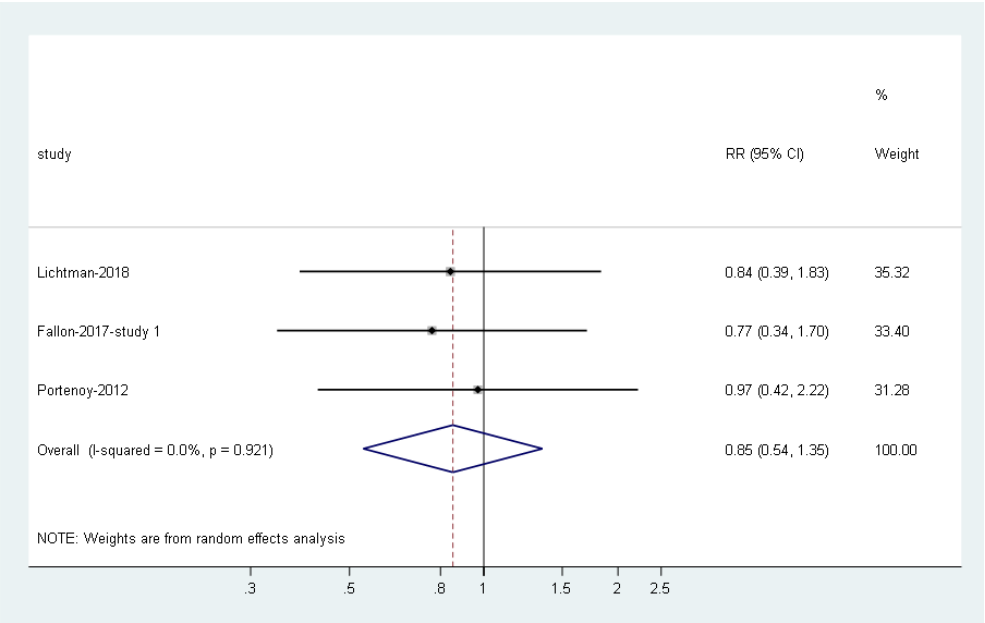
Supplement Figure 10: Relative Risk of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



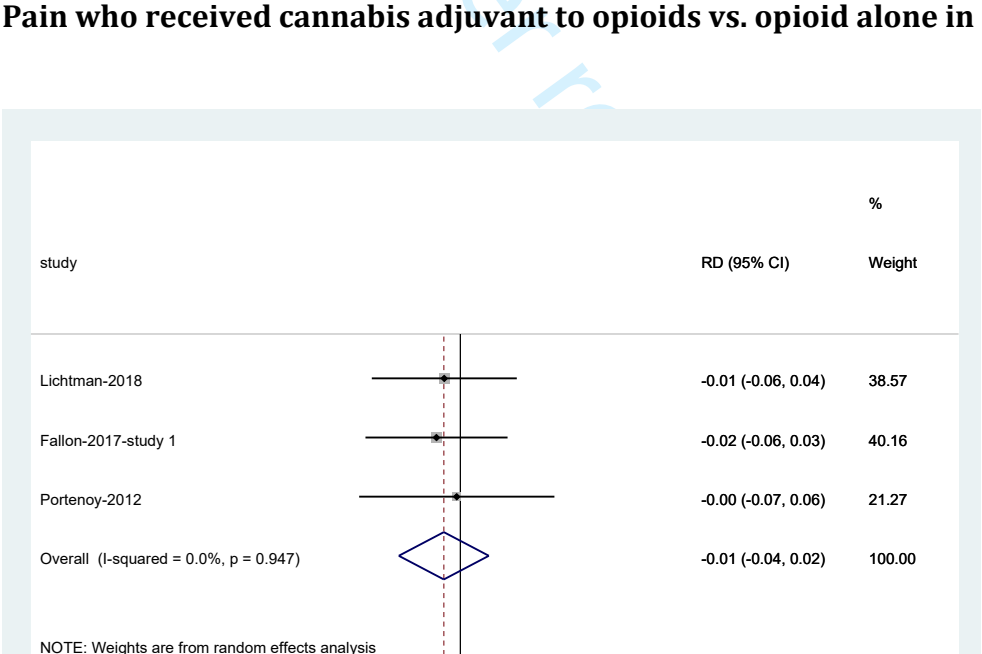
Supplement Figure 11: Relative Risk of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 12: Risk Difference of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 13: Relative Risk of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



Supplement Figure 14: Risk difference of constipation among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs

Appendix B: Reference List of Eligible studies

1. Barlowe TS, Koliani-Pace JL, Smith KD, Gordon SR, Gardner TB. Effects of Medical Cannabis on Use of Opioids and Hospital Visits by Patients With Painful Chronic Pancreatitis. *Clin Gastroenterol Hepatol* 2019;17(12):2608-9.e1. doi: 10.1016/j.cgh.2019.01.018.
2. Bellnier T, Brown GW. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. *Ment Health Clin* 2018;8(3):110-5. doi: 10.9740/mhc.2018.05.110.
3. Capano A, Weaver R, Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med* 2020;132(1):56-61. doi: 10.1080/00325481.2019.1685298.
4. Haroutounian S, Ratz Y, Ginosar Y, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. *Clin J Pain* 2016;32(12):1036-43. doi: 10.1097/ajp.0000000000000364.
5. Maida V, Ennis M, Irani S, Corbo M, Dolzhykov M. Adjunctive nabilone in cancer pain and symptom management: a prospective observational study using propensity scoring. *J Support Oncol* 2008;6(3):119-24.
6. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018.
7. O'Connell M, Sandgren M, Frantzen L, Bower E, Erickson B. Medical Cannabis: Effects on Opioid and Benzodiazepine Requirements for Pain Control. *Ann Pharmacother* 2019;53(11):1081-6. doi: 10.1177/1060028019854221.
8. Pritchard ER, Dayer L, Belz J, et al. Effect of cannabis on opioid use in patients with cancer receiving palliative care. *J Am Pharm Assoc (2003)* 2020;60(1):244-7. doi: 10.1016/j.japh.2019.10.013.
9. Pawasarat IM, Schultz EM, Frisby JC, et al. The Efficacy of Medical Marijuana in the Treatment of Cancer-Related Pain. *J Palliat Med* 2020;23(6):809-16. doi: 10.1089/jpm.2019.0374.

10. Rod K. A pilot study of a medical cannabis-opioid reduction program. *Am J Psychiatry Neurosci* 2019;7(3):74. doi: 10.11648/j.ajpn.20190703.14.

11. Takakuwa KM, Hergenrather JY, Shofer FS, Schears RM. The Impact of Medical Cannabis on Intermittent and Chronic Opioid Users with Back Pain: How Cannabis Diminished Prescription Opioid Usage. *Cannabis Cannabinoid Res* 2020;5(3):263-70. doi: 10.1089/can.2019.0039.

12. Vigil JM, Stith SS, Adams IM, Reeve AP. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. *PLoS One* 2017;12(11):e0187795. doi: 10.1371/journal.pone.0187795.

13. Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: an observational cross-over single centre study. *Clin Exp Rheumatol* 2019;37(Suppl 116):S13-S20.

14. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008.

15. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain* 2012;13(5):438-49. doi: 10.1016/j.jpain.2012.01.003.

16. Fallon MT, Albert Lux E, McQuade R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *Br J Pain* 2017;11(3):119-33. doi: 10.1177/2049463717710042.

17. Lichtman AH, Lux EA, McQuade R, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *J Pain Symptom Manage* 2018;55(2):179-88.e1. doi: 10.1016/j.jpainsymman.2017.09.001.

Technical Appendix

This appendix provides additional details on two different methods of estimation, including 1) estimating the mean and standard deviation (SD) from sample size, median, and interquartile range (IQR); 2) estimating missing SD (for two non-randomized studies [5,7]) using the available SD from other included studies.

1) Estimating the mean and standard deviation (SD) from sample size, median, and IQR:

1) Pawasarat et al 2020 original reported data: median total morphine equivalent=45, n=137, and IQR=135.

-Using Wan et al method[1] produced: mean=60, SD=101

-Method recommended by Cochrane as *sensitivity analysis*:

$$S \approx \frac{q_3 - q_1}{1.35}.$$

q3-q1=IQR. This method produced SD=100.

2) Bellnier et al 2018 original reported data: median total morphine equivalent (before adding cannabis) =79.94, range=0 to 450, median (after adding cannabis) =19.65; range =0 to 150, n=29.

-Using Wan et al method produced: mean (before)=152.4, SD=111; mean (after)=47.3, SD=37.0

-Using Cochrane approach (Hozo et al[3]): Mean (before)= 152.4, SD= 112.5; mean (after)= 47.3, SD= 37.5

We finally included estimation by Wan et al method. The excel sheet including all formula was provided by Wan et al in supplementary file of their article[1].

2) Estimating missing SD using the available SD from other included studies:

1) Maida et al 2008 did not report SD around the mean at the end of follow-up for pain intensity. Original reported data: mean (SD) before adding cannabis= 7.1(2.4); after adding cannabis mean=3 (missing)

2) Connell et al 2019 original reported data: mean (SD) before adding cannabis=6.25 (missing); mean after adding cannabis=6.57 (missing)

We imputed missing SDs for these two studies from the given SDs related to other five included studies using prognostic method that presented by Ma et al[2]:

$$SEM_j^* = \frac{\sum_{i=1}^{k} SEM_i\sqrt{n_i}}{k\sqrt{n_j^*}}.$$

Assume there are k + l trials altogether where k trials are with full given information

SEM: value for trial *j (missing)* with sample size:

n_j: sample size for study with missing information.

SD (imputed) for first study= 1.51

SDs (imputed) for second study=1.76, 1.20

[1] Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC medical research methodology 2014;**14**(1):135.

[2] Ma J, Liu W, Hunter A, et al. Performing meta-analysis with incomplete statistical information in clinical trials. BMC medical research methodology 2008;8(1):56.

[3] Hozo, S.P., Djulbegovic, B. & Hozo, I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5, 13 (2005). https://doi.org/10.1186/1471-2288-5-13

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic # Checklist item Reported on page #

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	12-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17