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:
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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:
---
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)

25 exp migraine/ (60235)

26 migraine.mp. (66593)
27 fibromyalgia/ (19402)
28 fibromyalg*.mp. (20958)
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)

Search Name: cannabis pain
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
#11 [mh Osteoarthritis] or [mh ^"Arthritis, Rheumatoid"] or [mh Neuralgia] or [mh ^"Diabetic Neuropathies"] or [mh ^"Irritable Bowel Syndrome"] or [mh ^"Migraine Disorders"] or [mh Fibromyalgia] or [mh ^"complex regional pain syndromes"] or [mh causalgia] or [mh ^"reflex

sympathetic dystrophy"] or [mh ^"pain Intractable"] or [mh ^"Phantom Limb"] or [mh Hyperalgesia] or [mh ^"back pain"] or [mh ^"failed back surgery syndrome"] or [mh ^"low back pain"] or [mh Radiculopathy] or [mh ^"musculoskeletal pain"] or [mh headache] or [mh Arthralgia] or [mh ^"Headache Disorders"] or [mh ^"Temporomandibular Joint Dysfunction Syndrome"] or [mh ^"whiplash injury"] or [mh ^"Cumulative Trauma Disorders"] or [mh "Peripheral Nervous System Diseases"/DT] or [mh ^"Pain Measurement"/DE] 28499

#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.

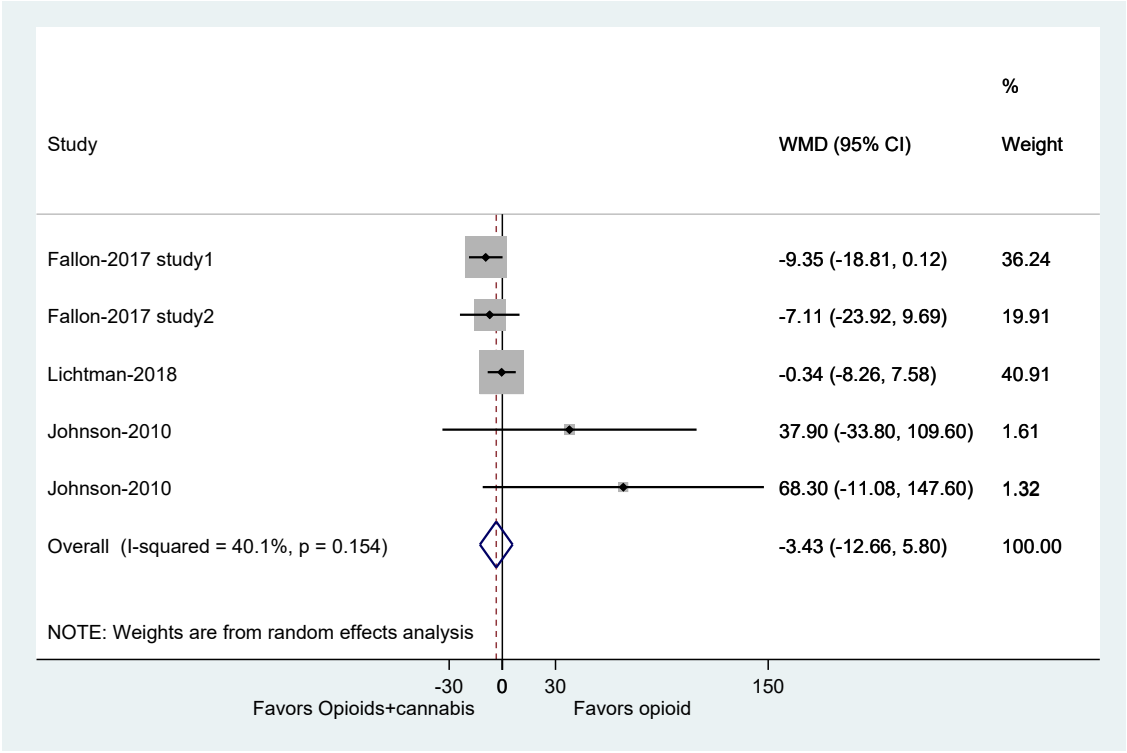
Supplement Table 11: Summary of adverse events among included observational studies*

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)

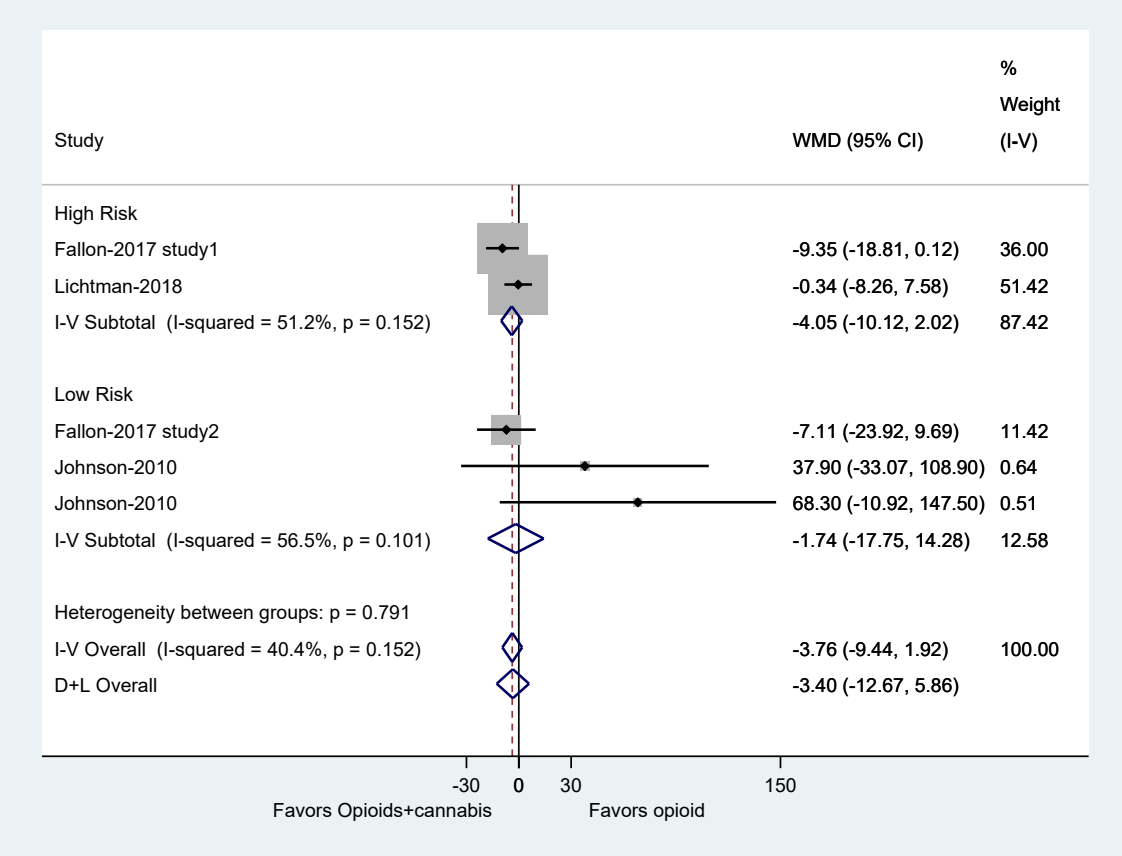
Vigil et al[12]	Self-reported.	No respondents reported any serious side effects from cannabis use (only 9% of patients reported cannabis affected negatively their concentration).
Yassin et al[13]	Self-reported	Mostly mild adverse events were reported (e.g. red eye, sore throat, increase appetite); only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

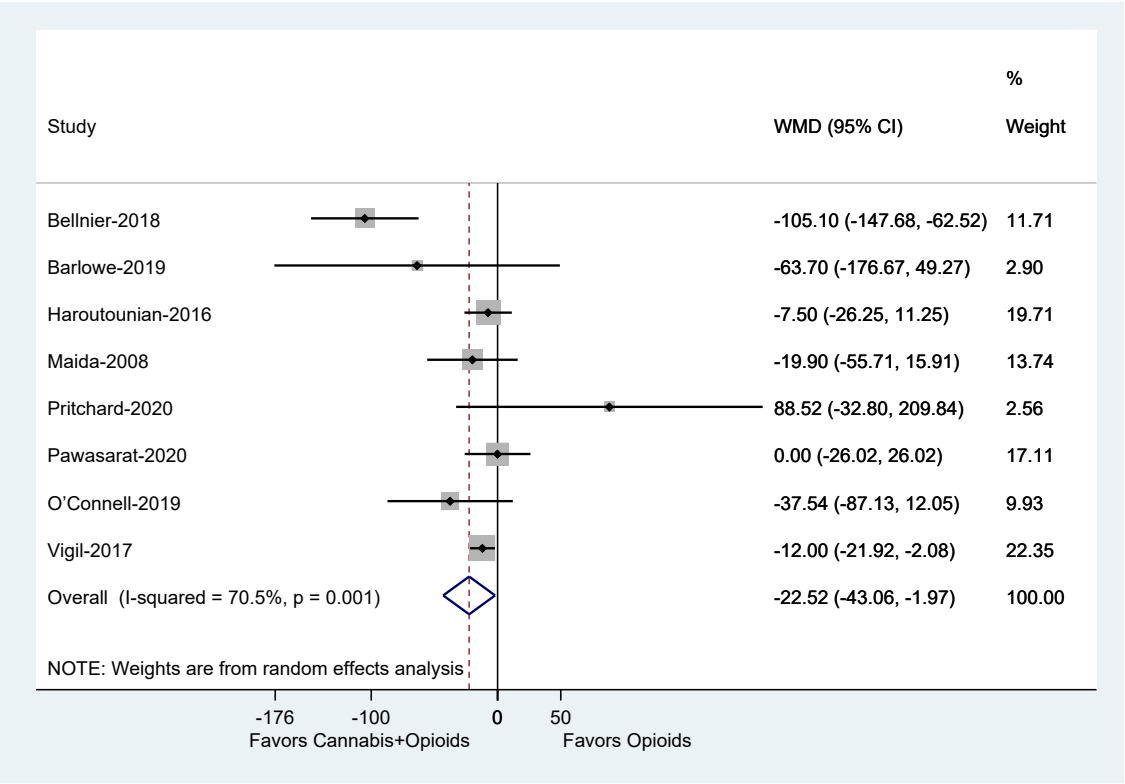
Additional results tables and figures



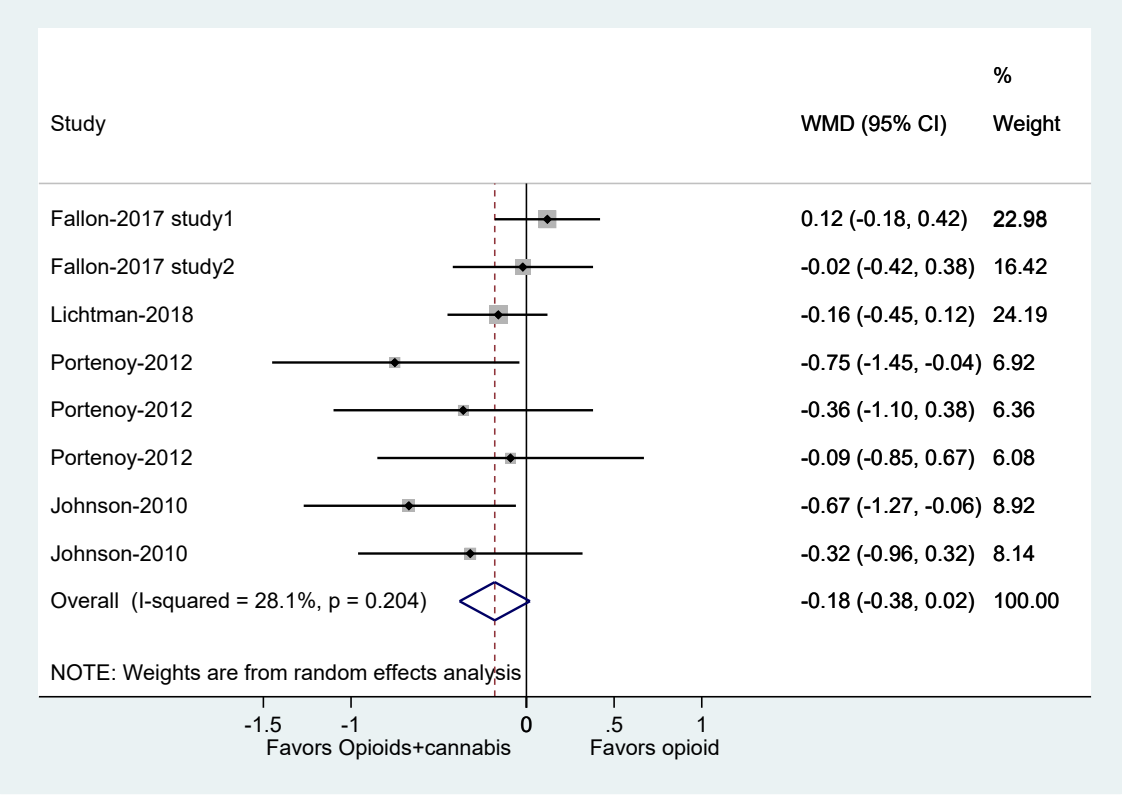
Supplement Figure 1: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



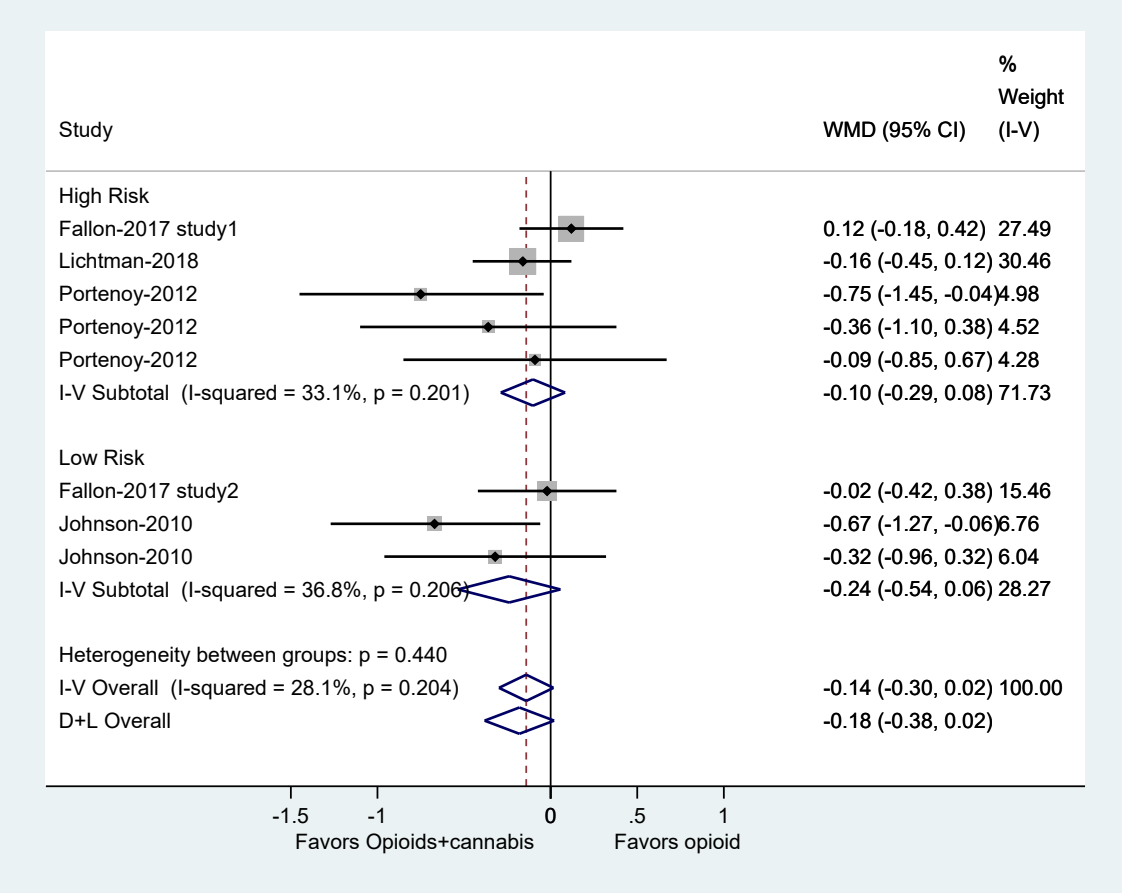
Supplement Figure 2: Subgroup analysis for opioid dose reduction and risk of bias (high risk vs. low risk) from 4 RCTs of Cannabis+opioids vs. placebo



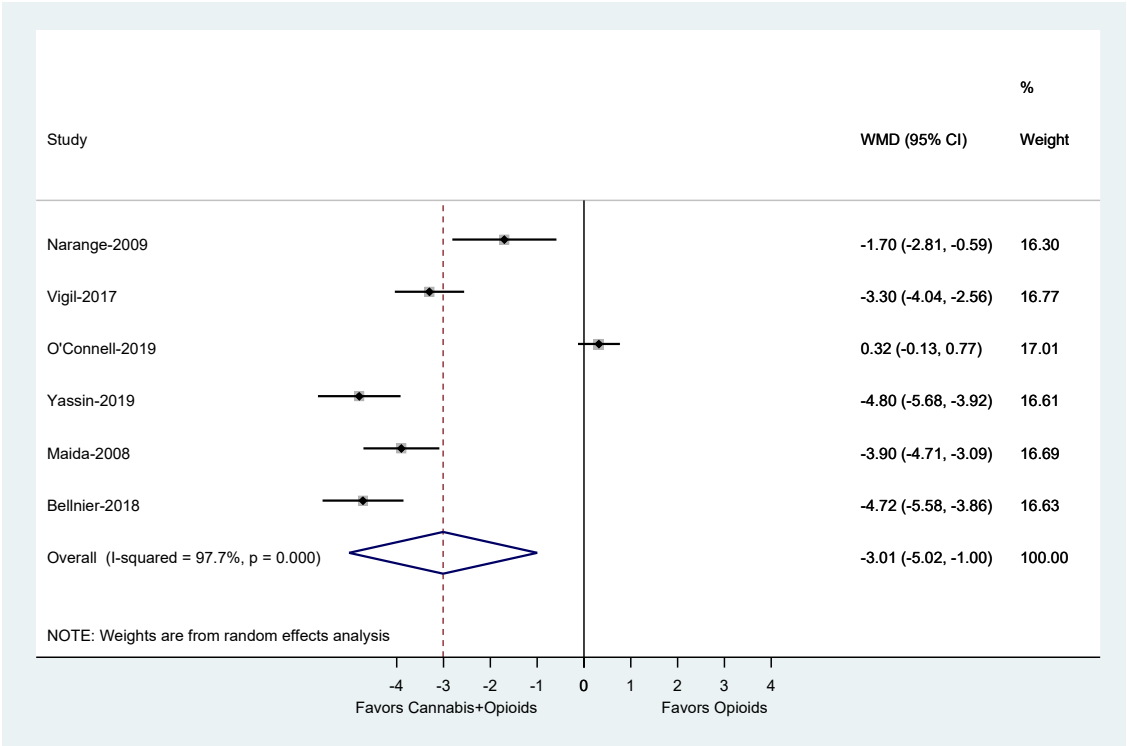
Supplement Figure 3: forest plot for oral morphine equivalence dose reduction among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies



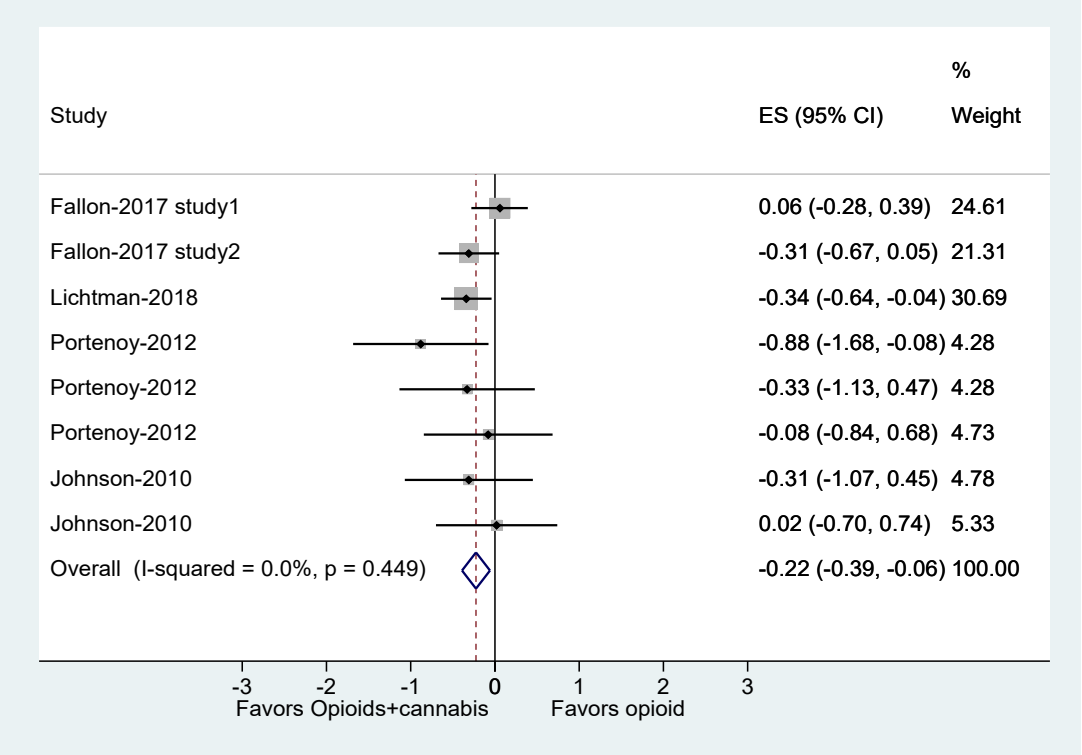
Supplement Figure 4: forest plot for pain relief on a 10-cm Visual Analog Scale (VAS) among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



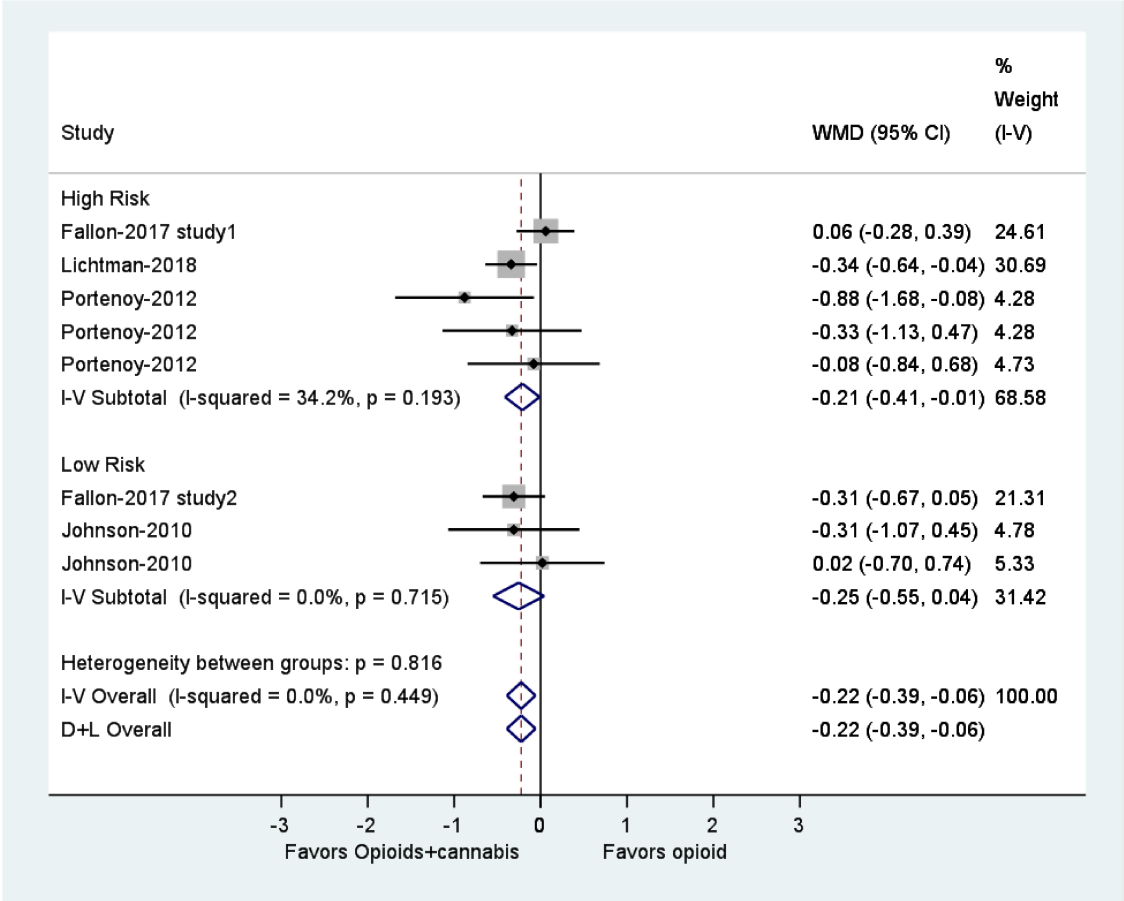
Supplement Figure 5: Subgroup analysis for pain relief on a 10-cm VAS and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



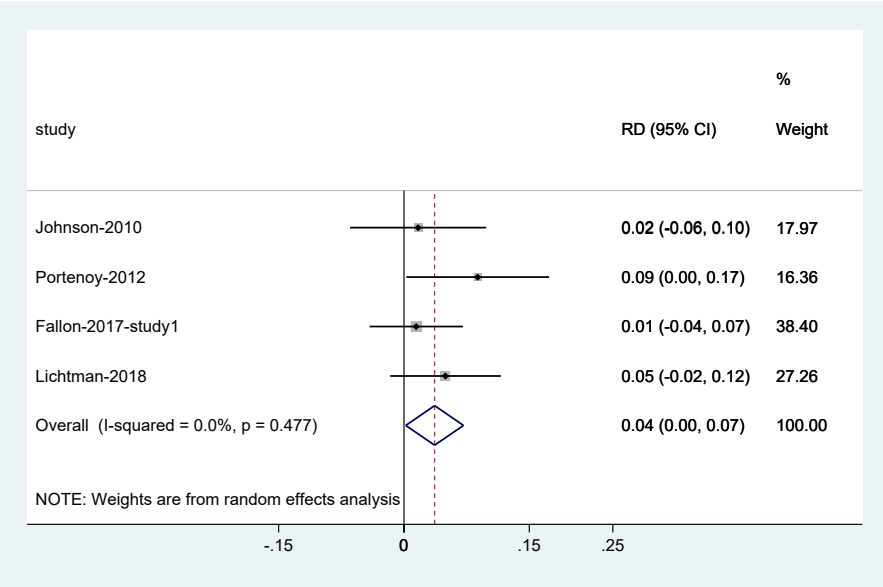
Supplement Figure 6: forest plot for pain relief on a 10-cm VAS among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in observational studies with no control group



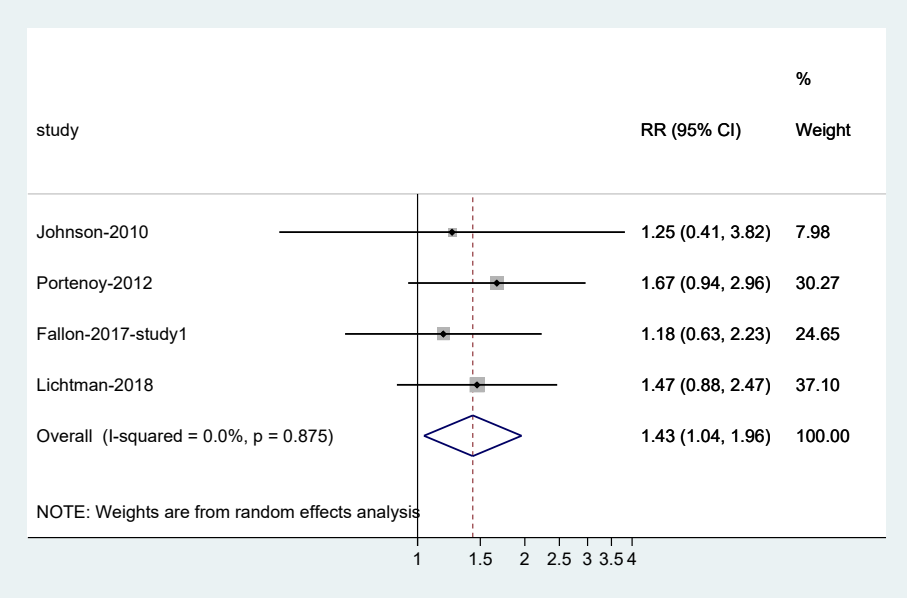
Supplement Figure 7: forest plot for sleep disturbance on a 10 cm VAS for sleep disturbance among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



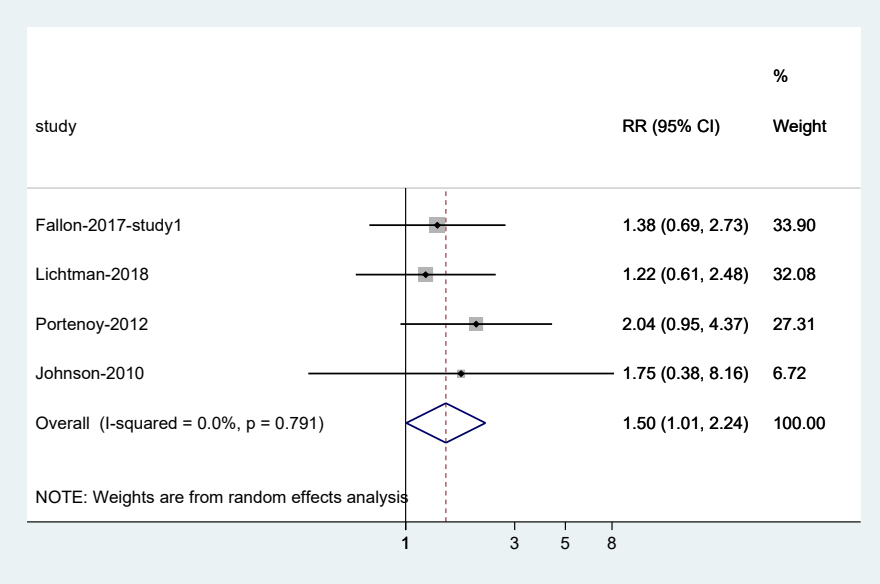
Supplement Figure 8: Subgroup analysis for sleep disturbance a 10-cm VAS for sleep disturbance and risk of bias (high risk vs. low risk) from 5 RCTs of Cannabis+opioids vs. placebo



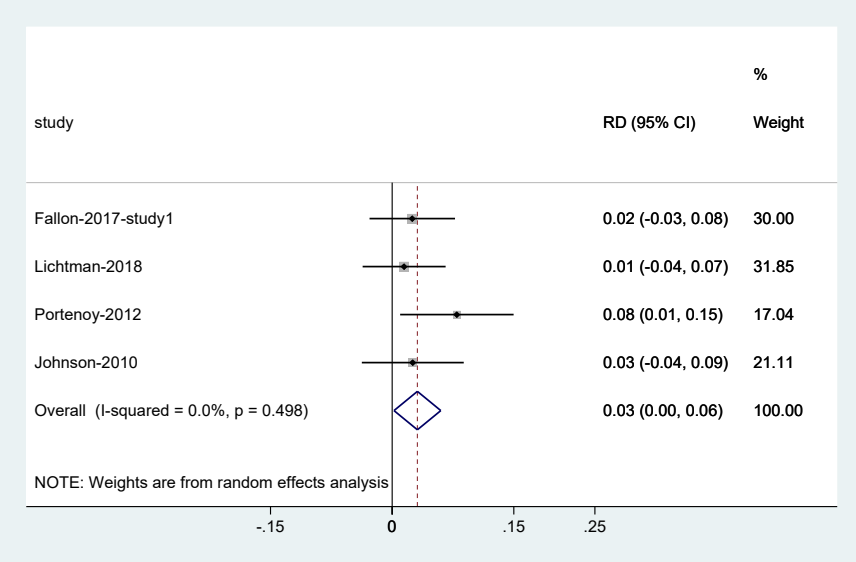
Supplement Figure 9: Risk difference of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



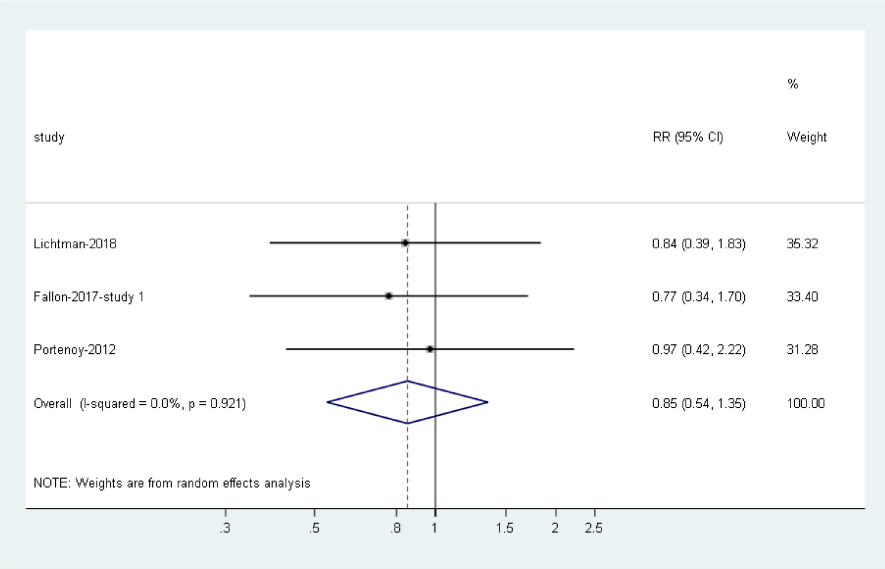
Supplement Figure 10: Relative Risk of nausea among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



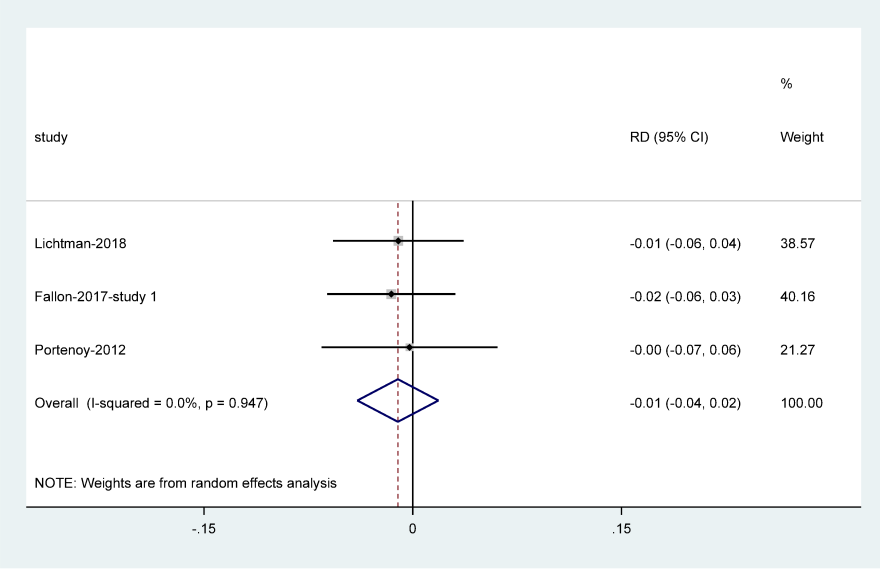
Supplement Figure 11: Relative Risk of vomiting among patients with Chronic Pain who received cannabis adjuvant to opioids vs. opioid alone in RCTs



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