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Cannabis-based medicines and medical cannabis for adults with cancer pain (Review)

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[Intervention Review]

Cannabis-based medicines and medical cannabis for adults with cancer pain

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ABSTRACT

Background

Pain is a common symptom in people with cancer; 30% to 50% of people with cancer will experience moderate-to-severe pain. This can have a major negative impact on their quality of life. Opioid (morphine-like) medications are commonly used to treat moderate or severe cancer pain, and are recommended for this purpose in the World Health Organization (WHO) pain treatment ladder. Pain is not sufficiently relieved by opioid medications in 10% to 15% of people with cancer. In people with insufficient relief of cancer pain, new analgesics are needed to effectively and safely supplement or replace opioids.

Objectives

To evaluate the benefits and harms of cannabis-based medicines, including medical cannabis, for treating pain and other symptoms in adults with cancer compared to placebo or any other established analgesic for cancer pain.

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 26 January 2023.

Selection criteria

We selected double-blind randomised, controlled trials (RCT) of medical cannabis, plant-derived and synthetic cannabis-based medicines against placebo or any other active treatment for cancer pain in adults, with any treatment duration and at least 10 participants per treatment arm.

Data collection and analysis

We used standard Cochrane methods. The primary outcomes were 1. proportions of participants reporting no worse than mild pain; 2. Patient Global Impression of Change (PGIC) of much improved or very much improved and 3. withdrawals due to adverse events. Secondary outcomes were 4. number of participants who reported pain relief of 30% or greater and overall opioid use reduced or stable; 5. number of participants who reported pain relief of 30% or greater, or 50% or greater; 6. pain intensity; 7. sleep problems; 8. depression and anxiety; 9. daily maintenance and breakthrough opioid dosage; 10. dropouts due to lack of efficacy; 11. all central nervous system adverse events. We used GRADE to assess certainty of evidence for each outcome.

Main results

We identified 14 studies involving 1823 participants. No study assessed the proportions of participants reporting no worse than mild pain on treatment by 14 days after start of treatment.

We found five RCTs assessing oromucosal nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) or THC alone involving 1539 participants with moderate or severe pain despite opioid therapy. The double-blind periods of the RCTs ranged between two and five weeks. Four studies with a parallel design and 1333 participants were available for meta-analysis.

There was moderate-certainty evidence that there was no clinically relevant benefit for proportions of PGIC much or very much improved (risk difference (RD) 0.06, 95% confidence interval (CI) 0.01 to 0.12; number needed to treat for an additional beneficial outcome (NNTB) 16, 95% CI 8 to 100). There was moderate-certainty evidence for no clinically relevant difference in the proportion of withdrawals due to adverse events (RD 0.04, 95% CI 0 to 0.08; number needed to treat for an additional harmful outcome (NNTH) 25, 95% CI 16 to endless). There was moderate-certainty evidence for no difference between nabiximols or THC and placebo in the frequency of serious adverse events (RD 0.02, 95% CI −0.03 to 0.07). There was moderate-certainty evidence that nabiximols and THC used as add-on treatment for opioid-refractory cancer pain did not differ from placebo in reducing mean pain intensity (standardised mean difference (SMD) −0.19, 95% CI −0.40 to 0.02).

There was low-certainty evidence that a synthetic THC analogue (nabilone) delivered over eight weeks was not superior to placebo in reducing pain associated with chemotherapy or radiochemotherapy in people with head and neck cancer and non-small cell lung cancer (2 studies, 89 participants, qualitative analysis). Analyses of tolerability and safety were not possible for these studies.

There was low-certainty evidence that synthetic THC analogues were superior to placebo (SMD −0.98, 95% CI −1.36 to −0.60), but not superior to low-dose codeine (SMD 0.03, 95% CI −0.25 to 0.32; 5 single-dose trials; 126 participants) in reducing moderate-to-severe cancer pain after cessation of previous analgesic treatment for three to four and a half hours (2 single-dose trials; 66 participants). Analyses of tolerability and safety were not possible for these studies.

There was low-certainty evidence that CBD oil did not add value to specialist palliative care alone in the reduction of pain intensity in people with advanced cancer. There was no difference in the number of dropouts due to adverse events and serious adverse events (1 study, 144 participants, qualitative analysis).

We found no studies using herbal cannabis.

Authors' conclusions

There is moderate-certainty evidence that oromucosal nabiximols and THC are ineffective in relieving moderate-to-severe opioid-refractory cancer pain. There is low-certainty evidence that nabilone is ineffective in reducing pain associated with (radio-) chemotherapy in people with head and neck cancer and non-small cell lung cancer. There is low-certainty evidence that a single dose of synthetic THC analogues is not superior to a single low-dose morphine equivalent in reducing moderate-to-severe cancer pain. There is low-certainty evidence that CBD does not add value to specialist palliative care alone in the reduction of pain in people with advanced cancer.

PLAIN LANGUAGE SUMMARY

Cannabis-based medicines for cancer pain

Do medicines based on cannabis help adults with cancer pain?

Key messages

Cannabis-based medicines (CbMs) did not relieve cancer pain that did not respond to morphine-like medicines.

The studies analysed did not allow any statement to be made on the place of these medications in the World Health Organization (WHO) analgesic ladder for cancer pain.

Trials with CbMs in cancer need to be very much better designed than those conducted so far.

Pain in cancer and its treatment

One person in two or three who gets cancer will have pain that becomes moderate or severe in intensity. The pain tends to get worse as the cancer progresses.

The WHO recommends taking morphine-like medicines for moderate-to-severe pain from cancer, but 1 in 6 to 10 people with cancer pain do not experience sufficient pain relief from morphine-like medicines. Several products based on the cannabis plant have been suggested as treatment for cancer pain. These products include inhaled or orally ingested herbal cannabis, and various oils, sprays or tablets containing active cannabis ingredients obtained from the plant, or made synthetically. Some people with cancer pain have reported that CbMs are effective for them, and that is often highlighted in the media.

What did we want to find out?

If CbMs relieved cancer pain in people living with cancer.

If CbMs were associated with any unwanted or harmful effects.

What did we do?

We searched for clinical trials that examined CbMs compared to other medications to treat cancer pain in adults.

We summarised the results of the studies and rated our confidence in the evidence, based on factors such as the methods and size of studies.

What did we find?

We found 14 studies involving 1823 people. The biggest study included 399 people and the smallest study included 10 people.

Studies were conducted in countries around the world; most (six) were based in North America.

Five studies used one dose of CbM and lasted less than one day. Other studies lasted between two and eight weeks.

Pharmaceutical companies funded seven studies.

Six studies compared a mouth spray with a plant-derived combination of tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, and cannabidiol (CBD), an anti-inflammatory ingredient of cannabis, against a fake medication (placebo). Seven studies compared an artificial cannabinoid mimicking the effects of THC against placebo. Of these seven studies, two studies compared against a morphine-like medication (codeine), too. One study compared CBD against placebo.

We did not find studies with herbal cannabis.

Main results

Mouth spray with a plant-derived combination of THC and CBD was probably not better than placebo in reducing pain in people with moderate-to-severe cancer pain despite opioid treatment. Thirty-two out of 100 people reported to be much or very much improved by cannabis-based mouth spray and 23 out of 100 people with mouth spray with placebo. A total of 19 out of 100 people withdrew early because of side effects by cannabis-based mouth spray and 16 out of 100 people by mouth spray with placebo. There was no difference in serious side effects between the cannabis-based mouth spray and a placebo mouth spray.

Artificial cannabinoid mimicking the effects of THC may not be better than a fake medication in reducing pain associated with chemotherapy or radiochemotherapy in people with head and neck cancer and a certain type of lung cancer.

A single dose of an artificial cannabinoid mimicking the effects of THC may be better than a single dose of placebo, but may not differ from a single small dose of a morphine-like medication in reducing moderate-to-severe cancer pain after cessation of previous analgesic treatment for three to four and a half hours.

CBD may not add value to specialist palliative care alone in the reduction of pain in people with advanced cancer.

We found no studies with medical cannabis.

What are the limitations of the evidence?

We are moderately confident in the evidence that a mouth spray with a plant-derived combination of THC and CBD does not reduce severe cancer pain despite opioid treatment because studies did not provide information about everything that we could have used.

We have little confidence in the evidence that an artificial cannabinoid mimicking the effects of THC (nabilone) does not reduce pain associated with chemotherapy or radiochemotherapy because the studies did not provide data about everything that we could have used, and because the studies were small.

We have little confidence in the evidence that artificial cannabinoids mimicking the effects of THC reduce cancer pain after the previous pain-relieving medication was stopped some hours before because the studies did not provide data about everything that we could have used, and because the studies were small.

We have little confidence in the evidence that CBD added to standard palliative care does not reduce cancer pain because there was only one study available.

How up to date is the evidence?

The evidence is up to date to January 2023.

SUMMARY OF FINDINGS

Summary of findings 1. Cannabis-based medicines compared with placebo medication for cancer pain

Cannabis-based medicines compared with placebo medication for cancer pain

Patient or population: adults with cancer pain

Settings: outpatient study centres and hospitals in Europe and North America

Intervention: oromucosal THC with or without CBD

Comparison: oromucosal placebo

Outcomes	Observed outcome (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Oromucosal placebo	Oromucosal THC with or without CBD				
Proportion of participants reporting no worse than mild pain by 14 days after start of treatment	No data for this outcome were reported.		—	—	—	—
PGIC of much improved or very much improved	**230 per 1000**	**320 per 1000** (95% CI 290 to 350 per 1000)	**RD 0.06** (0.01 to 0.12)	996 (3)	⊕⊕⊕⊖ **Moderate**[a]	NNTB 16 (95% CI 8 to 100)
Withdrawals due to adverse events	**160 per 1000**	**190 per 1000** (95% CI 170 to 210 per 1000)	**RD 0.04** (0.00 to 0.08)	1332 (4)	⊕⊕⊕⊖ **Moderate**[a]	NNTH 25 (95% CI 12 to endless)
Mean pain intensity (Numeric Rating Scale 0–10)	The mean pain intensity at baseline was 5.6 (SD 1.2)[b]	The mean pain intensity in the intervention group was **0.19 SDs lower** (0.40 lower to 0.02 higher)	**SMD −0.19** (−0.40 to 0.02)	1315 (4)	⊕⊕⊕⊖ **Moderate**[a]	—
Daily maintenance opioid dosage (mg morphine equivalent)	The mean dosage at baseline was 159.7 (SD 121.2) mg/day[b]	The mean dosage in the intervention group was **0.08 SDs higher** (0.10 lower to 0.27 higher)	**SMD 0.08** (−0.10 to 0.27)	970 (3)	⊕⊕⊖⊖ **Low**[c]	—
Daily breakthrough opioid dosage (mg morphine equivalent)	The mean dosage at baseline was	The mean dosage in the intervention group was **0.08 SDs lower** (0.23 lower to 0.07 higher)	**SMD −0.08** (−0.23 to 0.07)	957 (3)	⊕⊕⊕⊖ **Moderate**[a]	—

	26.4 (SD 40.4) mg/day[b]					
Participants experiencing any serious adverse event	**210 per 1000**	**240 per 1000** (95% CI 220 to 260 per 1000)	**RD** **0.02** (−0.03 to 0.07)	1330 (4)	⊕⊕⊕⊖ **Moderate**[a]	—

CBD: cannabidiol; **CI:** confidence interval;**NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **PGIC:** Patient Global Impression of Change; **RD:** risk difference; **SD:** standard deviation; **SMD:** standardised mean difference; **THC:** tetrahydrocannabinol.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to limitations of study.
[b] Lichtman 2018.
[c] Downgraded two levels due to limitations of study design and imprecision of results.

BACKGROUND

Description of the condition

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018 (WHO 2021). Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancer are the most common amongst women (WHO 2021). Pain is one of the most feared symptoms associated with cancers, and can occur at any time during the course of the disease. The frequency and intensity of pain tend to increase as the cancer advances (van den Beuken-van Everdingen 2016). One systematic review has shown that approximately 40% of people living with cancer experienced pain after curative treatment, 55% during cancer treatment, and 66% in advanced disease (van den Beuken-van Everdingen 2016). Pain may be specifically related to the cancer (direct tumour effects, systemic tumour effects), the effects of cancer treatments (e.g. radiation or chemotherapy) or due to some other comorbid disease (Swarm 2019). In this review, we defined cancer pain as pain arising as a direct consequence of the cancer or of cancer therapy (or both), and not due to another condition.

The World Health Organization (WHO) analgesic ladder advocates a stepwise approach to analgesia for cancer pain. It recommends that opioids be used as first-line treatment for moderate-to-severe cancer pain (WHO 2019). An overview of Cochrane Reviews found the quantity and quality of evidence supporting the use of opioids for cancer pain to be low (Wiffen 2017). In clinical practice, most people with cancer will achieve adequate pain relief with opioids. However, wide interpatient variability in the response to opioids has been reported and 10% to 15% of people with cancer pain are defined as opioid non-responders (Corli 2016). Therefore, there is a substantial need for new analgesics that can effectively and safely supplement or replace opioids in people with insufficient relief of cancer pain.

Description of the intervention

The cannabinoid (CB) system is ubiquitous in the animal kingdom and is said to perform multiple functions that move the organism back to equilibrium. A large body of evidence currently supports the presence of CB receptors and ligands in the peripheral and central nervous system, but also in other tissues such as bone and in the immune system (Owens 2015; Soliman 2019). The endocannabinoid system is said to have three broad and overlapping functions in mammals. The first is a stress recovery role, operating in a feedback loop in which endocannabinoid signalling is activated by stress and functions to return endocrine, nervous and behavioural systems to homeostatic balance. The second is to control energy balance through regulation of the intake, storage and utilisation of food. The third involves immune regulation; endocannabinoid signalling is activated by tissue injury and modulates immune and inflammatory responses (Hillard 2012). Thus, the endocannabinoid neuromodulatory system is assumed to be involved in multiple physiological functions, such as antinociception, cognition and memory, endocrine function, nausea and vomiting, inflammation and immune recognition (De Vries 2014; Hillard 2012).

Cannabis is a genus of the flowering plant in the family Cannabaceae. The number of species within the genus is disputed. Three species are recognised, *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. These plants, commonly known as marijuana, have been used for pain relief for millennia, and have additional effects on appetite, sleep and mood (Kalant 2001). Because of the multiple mechanisms of action of cannabis in the human organism, cannabis has the potential to modulate some of the most common and debilitating symptoms of cancer and its treatments, including nausea and vomiting, loss of appetite and pain (Kleckner 2019).

How the intervention might work

Cannabis contains over 450 compounds, with at least 120 classified as phytocannabinoids. Two are of particular medical interest. Delta 9-tetrahydrocannabinol (delta 9-THC) is the main active constituent, with psychoactive (e.g. reduction of anxiety) and pain-relieving properties. The second molecule of interest is cannabidiol (CBD), which has lower affinity for the CB receptors and the potential to counteract the negative effects of tetrahydrocannabinol (THC) on memory, mood and cognition, but may also have an effect on pain modulation due to anti-inflammatory properties. The specific roles of currently identified cannabis-based medicines (CbM) that act as ligands at CB receptors within the nervous system (primarily but not exclusively CB1 receptors) and in the periphery (primarily but not exclusively CB2 receptors) are only partially elucidated, but there are many preclinical data to support their influence on nociception (Owens 2015; Soliman 2019). It is also hypothesised that cannabis reduces alterations in cognitive and autonomic processing in chronic pain states. The frontal-limbic distribution of CB receptors in the brain suggests that cannabis may preferentially target the affective qualities of pain (Lee 2013).

Terminology and definitions of CbMs vary in the literature. A terminology based on the proposals of the task forces of the European Pain Federation (EFIC) (Häuser 2018), and the International Association for the Study of Pain (IASP) (Soliman 2019) is listed in Appendix 1.

CbMs are available in different forms.

Licenced medical drugs or products currently being tested for medical use are as follows.

- Plant-derived CBs: oromucosal THC and CBD (nabiximols; Sativex) or oral CBD (Epidiolex). Nabiximols is approved in some countries for the treatment of refractory spasticity in people with multiple sclerosis (Krcevski-Skvarc 2018). Oral CBD is approved by the European Medicines Agency for the management of Dravet syndrome and Lennox-Gastaut syndrome, two rare forms of epilepsy in children (European Medicines Agency 2019).
- Synthetic CBs: nabilone (Cesamet or Canemes), a synthetic THC, is approved in some countries for the management of refractory nausea/emesis in people with cancer (Abuhasira 2018; Krcevski-Skvarc 2018). Dronabinol (Marinol or Syndros), a synthetic THC, is approved for similar therapeutic use in some countries (Abuhasira 2018; Krcevski-Skvarc 2018). Levonantradol, a potent synthetic THC is used in research, but is not available as a licensed therapeutic drug in any country.

Magistral preparations (i.e. any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient) of cannabis plant derivatives as follows.

- Defined CBs such as plant-derived dronabinol (THC) or plant-derived CBD
- Herbal cannabis, resins and extracts, such as oil or tinctures with defined content of THC or CBD (or both), together with other active ingredients (phytocannabinoids other than CBD/THC, such as terpenes and flavonoids)

The main forms of administration are as follows.

- Oromucosal: spray (nabiximols)
- Oral: capsules (dronabinol, nabilone), oil (CBD), extracts (dronabinol, herbal cannabis)
- Smoke or vapour inhalation: CBD, dronabinol, herbal cannabis, resins
- Topical or rectal: CBD, herbal cannabis, resins, extracts

There is a great variability in European countries with regard to the availability of the different CbMs and medical cannabis and their reimbursement by health statutory companies (Krcevski-Skvarc 2018).

In addition, CBD and extracts of cannabis flowers (THC content less than 0.2%) are available in many countries as nutritional supplements (Radbruch 2020).

CB receptor antagonists and negative allosteric modulators (e.g. rimonabant (SR141716A)) and modulators that increase or enhance endocannabinoid system activity (e.g. fatty acid amide hydrolase inhibitors) are experimental medications which have been not yet been approved for use in pain therapy outside clinical studies (Ye 2019).

Why it is important to do this review

Contrary to the usual path of drug approval, CbMs in an increasing number of European countries have bypassed traditional approval by drug agencies and have been made available by legislative bodies as therapeutic products for pain management (Krcevski-Skvarc 2018). Propelled by public advocacy and the media, medical cannabis in particular has been promoted as an effective and safe treatment for cancer pain (Blake 2017). Other benefits that are quoted include the potential reduction of harm related to opioid use, and the purported benefits for sleep disturbance as well as mood disorders (Vyas 2018). The worldwide surge in use of cannabis in the management of people with cancer is illustrated by the prevalent use of medical cannabis and illegal cannabis by up to 40% of people with cancer in Canada and Israel, countries where legal access to medical cannabis is available (Bar-Lev Schneider 2018; Martell 2018).

At the time of writing this review, the amount and quality of evidence for CbMs for chronic pain has been low, with the evidence compromised by studies of short duration and small numbers of participants (Fisher 2021; Stockings 2018). In addition, a systematic overview of systematic reviews has pointed out that non-Cochrane systematic reviews of CBs for pain are of overwhelmingly low or very low quality (Moore 2021). A 2020 systematic review of randomised controlled trials (RCTs) of CbMs for chronic pain concluded that studies in this field have unclear or high risk of bias, and outcomes had GRADE ratings of low- or very low-certainty evidence, with little confidence in the estimates of effect (Fisher 2021). The systematic review found no benefit of nabiximols compared to placebo, for at least 30% pain relief (two RCTs delivering treatment of two to five weeks) and mean change of pain from baseline (four RCTs delivering treatment of two to five weeks). Another systematic review analysed the same RCTs as Fisher 2021 and found no benefit of nabiximols when compared to placebo for reducing pain and sleep problems (Häuser 2019). However, this review found patient impression of change to be much or very much improved in the group receiving nabiximols (Häuser 2019).

Additional outcomes have gained importance to assess the efficacy and safety of CbMs for cancer pain. The US Food and Drug Administration (FDA) has suggested new combined responder outcomes for cancer pain trials: participants are only considered responders if they experience a clinically significant decrease in pain intensity compared with baseline at the primary analysis time point, and overall analgesic use is either decreased or stable compared with baseline (Basch 2014). Moreover, Cochrane Reviews of the use of opioids for cancer pain have favoured the primary outcome of mild or no pain at 14 days (Wiffen 2017). Our review will look for that outcome to allow comparability with opioids for cancer pain, as it was not an outcome reported in Fisher 2021.

Potential positive effects of CbMs for people with cancer have to be balanced against potential adverse effects. One systematic review with pooled analysis of studies of CbMs for chronic pain emphasised the high rate of adverse effects with low (unfavourable) numbers needed to harm for central nervous system and psychiatric adverse effects (Stockings 2018). Fisher 2021 has combined all adverse effects in one analysis.

In view of these considerable uncertainties, we have seen the need to update the literature and to assess the efficacy, tolerability and safety of CbMs compared to placebo or conventional medications for cancer pain. We concentrated on:

- additional participant-reported outcomes beyond pain, such as sleep problems and mood;
- opioid-sparing effects;
- central nervous system and psychiatric adverse effects.

OBJECTIVES

To evaluate the benefits and harms of cannabis-based medicines, including medical cannabis, for treating pain and other symptoms in adults with cancer compared to placebo or any other established analgesic for cancer pain.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs are the best design to minimise bias when evaluating the effectiveness of an intervention. We considered randomised, double-blind (participants and physicians), controlled trials comparing CbMs and medical cannabis with placebo or any other established analgesic for cancer pain, according to the ladder scheme of the WHO (WHO 2019). Trials must have included participant-reported pain outcomes. We included RCTs of any duration. The emphasis of the review was studies of two weeks or longer to try to obtain the efficacy outcome used in a previous overview of Cochrane Reviews on opioids for cancer pain (Wiffen 2017). The clinical importance of experimental studies (one to three days' duration) and very short-term studies (four to 13 days'

duration) in chronic pain is limited. In addition, we considered studies in which CbMs are used as add-on therapy to established analgesics, compared to these established analgesics without CbMs, and with participant-reported pain outcomes. Studies had to include at least 10 participants per treatment arm (we made an ad hoc decision to change the method described in our protocol, which required 20 participants per treatment arm; Differences between protocol and review; Häuser 2022). We included RCTs reporting at least one of our primary outcomes.

Types of participants

Eligible studies included men and women (aged 18 years or older) of any race with cancer-related pain (cancer pain or cancer therapy-related pain, or both). We included all types and stages of cancer, in all settings, and receiving any type of cancer therapy. We included studies with mixed pain conditions, if the results for people with cancer-related pain were reported separately.

Types of interventions

We included CbMs (plant-based CBs (CBD, dronabinol, nabiximols)), or synthetic CBs (nabilone) or medical cannabis (cannabis flowers or full spectrum cannabis extracts) at any dose or by any route that were administered for the relief of cancer pain.

The comparison groups received placebo or other established analgesic medication for cancer pain.

We did not consider experimental and non-registered drugs such as CB receptor antagonists and negative allosteric modulators (e.g. rimonabant (SR141716A)) and modulators that increase or enhance endocannabinoid system activity (e.g. fatty acid amide hydrolase inhibitors) or synthetic CBs (e.g. levonantradol).

Types of outcome measures

Primary outcomes

The proposed primary outcomes are the same as those used by Wiffen 2017 in the overview review of opioids for cancer pain.

- Proportion of participants reporting no worse than mild pain by 14 days after start of treatment (typically below 30/100 mm on a 100-mm Visual Analogue Scale (VAS) or below 3 on an 11-point Numeric Rating Scale (NRS)) as an acceptable outcome when their pain was moderate or severe (Moore 2013).
- Patient Global Impression of Change (PGIC) of much improved or very much improved.
- Withdrawals due to adverse events.

Secondary outcomes

- Combined responder: number of participants who reported pain relief of 30% or greater and overall opioid use reduced or stable compared to baseline for parallel and cross-over design studies and loss of this therapeutic response for studies with an enriched enrolment randomised withdrawal (EERW) design.
- Number of participants who reported pain relief of 30% or greater.
- Number of participants who reported pain relief of 50% or greater.
- Mean pain intensity: we preferentially extracted outcomes of numeric over visual pain scales.
- Sleep problems: we preferentially extracted outcomes of multidimensional questionnaires over single-item questionnaires.
- Depression: we preferentially extracted outcomes of multidimensional questionnaires over single-item questionnaires.
- Anxiety: we preferentially extracted outcomes of multidimensional questionnaires over single-item questionnaires.
- Daily maintenance opioid dosage (mg morphine equivalent).
- Daily breakthrough opioid dosage (mg morphine equivalent).
- Number of participants dropping out due to lack of efficacy.
- All central nervous system adverse events according to the Medical Dictionary for Regulatory Activities (International Council for Harmonisation 2020).
- All psychiatric adverse events according to the Medical Dictionary for Regulatory Activities (International Council for Harmonisation 2020).
- Participants experiencing any serious adverse event.

Search methods for identification of studies

Electronic searches

We searched the following databases originally on 3 March 2022 and performed an updated search on 26 January 2023, without language or date restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, Issue 1, 2023.
- MEDLINE (via Ovid) (1946 to 25 January 2023).
- Embase (via Ovid) (1974 to 25 January 2023).

The search strategies used are outlined in Appendix 2. The MEDLINE search strategy was independently peer-reviewed when it was developed. We checked for retractions of included studies using the Retraction Watch database (retractiondatabase.org/).

Searching other resources

We reviewed the bibliographies of any RCTs identified. We searched the following clinical trials databases to identify additional published or unpublished data (all to 3 March 2022 and updated 27 January 2023).

- US National Institutes of Health ClinicalTrials.gov (www.ClinicalTrials.gov)
- EU Clinical Trials Register (www.clinicaltrialsregister.eu)
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform)

In addition, we searched grey literature, checked reference lists of reviews and retrieved articles for additional studies, and performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials. We did not contact study authors for additional information.

Data collection and analysis

Selection of studies

Three review authors (EF, LR, WH) independently determined eligibility by reading the abstract and title of each study identified

by the search. They eliminated studies that clearly did not satisfy the inclusion criteria, and obtained full copies of the remaining studies. Two review authors (RFB, WH) independently read these studies and reached agreement by discussion. Consulting a third review author (PW) was not necessary because there was no disagreement on the inclusion and exclusion of studies. We did not anonymise the studies before assessment. We created a PRISMA flow chart (Moher 2009).

Data extraction and management

Two review authors (PW, WH) independently extracted data using a prepiloted standard form and checked for agreement before entering data into Review Manager 5 (Review Manager 2020). Three review authors (PW, RFB, WH) independently extracted information about the study funding sources and study author conflicts of interest, the cancer condition, number of participants treated, study setting, inclusion and exclusion criteria, demographic and clinical characteristics of the study samples (age, gender, race, pain baseline), prior recreational cannabis use, drug and dosing regimen, cotherapies allowed, rescue medication, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals, and adverse events (participants experiencing any adverse event or serious adverse effect). We analysed the nature of all serious adverse events. We analysed the nature of all adverse events, but concentrated on those that are regarded to be most relevant adverse events of CbMs and MC, namely central nervous system and psychiatric adverse events.

Assessment of risk of bias in included studies

Two review authors (RFB, WH) independently assessed risk of bias for each study using the Cochrane RoB 1 tool, using the criteria outlined in the 2011 edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We also used criteria adapted from those used by the Pain, Palliative and Supportive Care Review Group (group was closed in 2023) for reviews on medication therapy for cancer pain, with any disagreements resolved by discussion. Consulting a third review author (PW) was not necessary because there was no disagreement on the risk of bias assessment.

We assessed the following risks of bias for each study as follows.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (i.e. any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (when the method used to generate the sequence was not clearly stated); high risk of bias (studies used a non-random process (e.g. odd or even date of birth; hospital or clinic record number)).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (when method was not clearly stated). We excluded studies that did not conceal allocation and were, therefore, at high risk of bias (e.g. open list).
- Blinding of participants and personnel/treatment providers (systematic performance bias). We assessed the methods used to blind participants and personnel/treatment providers from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved); high risk of bias (blinding of participants was not ensured, e.g. tablets different in form or taste).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that outcome assessors were blinded to the intervention or exposure status of participants); unclear risk of bias (study stated that the outcome assessors were blinded but did not provide an adequate description of how it was achieved); high risk of bias (outcome assessors knew the intervention or exposure status of participants).
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (i.e. less than 10% participant dropout or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' (LOCF) analysis); or high risk of bias (used 'completer' analysis).
- Reporting bias due to selective outcome reporting (reporting bias). We checked if a study protocol before the start of the study was available and if all outcomes of the study protocol were reported in the publications of the study. There was low risk of reporting bias if the study protocol was available and all the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported in the prespecified way, or if the study protocol was not available, but it was clear that the published reports included all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon). We judged high risk of reporting bias if not all the study's prespecified primary outcomes were reported; one or more primary outcomes was reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the review were reported incompletely so that they could not be entered in a meta-analysis; the study report did not include results for a key outcome that would be expected to have been reported for such a study. We judged unclear risk of bias if there was insufficient information to permit judgement of 'low risk' or 'high risk'.
- In addition to the original risk of bias criteria outlined in the 2011 edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we assessed 'Group similarity at baseline' (selection bias) as another risk of bias. We assessed similarity of the study groups at baseline for the most important prognostic clinical and demographic indicators. We judged low risk of bias if groups were similar at baseline for demographic factors, value of main outcome measure(s)

and important prognostic factors. We judged unclear risk of bias if important prognostic clinical and demographic indicators were not reported. We judged high risk of bias if groups were not similar at baseline for demographic factors, value of main outcome measure(s) and important prognostic factors.

We also assessed overall risk of bias in each trial according to guidance in the current edition of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

- **Low risk of bias:** the trial was judged to be at low risk of bias for all domains for this result.
- **Some concerns:** the trial was judged to raise some concerns in at least one domain for this result, but not to be at high risk for any domain for this result.
- **High risk of bias:** the trial was judged to be at high risk of bias in at least one domain for this result or the judged to raise some concerns in multiple domains for this result in a way that substantially lowers confidence in the result.

Measures of treatment effect

We calculated numbers needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR) (McQuay 1998). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We used dichotomous data to calculate risk differences (RD) with 95% confidence intervals (CIs) using a fixed-effect model unless we found significant statistical or clinical heterogeneity (see below). We set the threshold for a clinically relevant benefit or a clinically relevant harm for categorical variables by an NNTB or NNTH less than 10 (Moore 2008).

We calculated standardised mean differences (SMD) with 95% CIs for continuous variables, using a random-effects model. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' g value of 0.2 = small, 0.5 = medium and 0.8 = large (Cohen 1988). We labelled a g value less than 0.2 to be a 'not substantial' effect size. We assumed a minimally important difference if the Hedges' g value was 0.2 or greater (Fayers 2014). To increase interpretability, we analysed the mean difference of mean pain intensity. If needed, we converted 0 to 10 and 0 to 100 NRS or VAS to a single scale.

Unit of analysis issues

For studies with more than two arms, we split the control treatment arm between active treatment arms in a single study if the active treatment arms could not to be combined for analysis. We included studies with a cross-over design where separate data from the two periods were reported, data were presented that excluded a significant carry-over effect or statistical adjustments were carried out in case of a significant carry-over effect. We did not anticipate cluster trials for this intervention.

Dealing with missing data

We used intention-to-treat (ITT) analysis where the ITT population consisted of participants who were randomised, took at least one dose of the assigned study medication and provided at least one postbaseline assessment. Where means or standard deviations (SDs) were missing, we attempted to obtain these data through contacting trial authors. Where SDs were not available from trial authors, we calculated them from t-values, P values, CIs or standard errors, where reported by the studies (Higgins 2020a). Where rates of pain relief of 30% or greater and of 50% or greater were not reported or provided on request, we calculated them from means and SDs using a validated imputation method (Furukawa 2005).

Assessment of heterogeneity

We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity using the I^2 statistic. Where the I^2 value was greater than 50%, we considered possible reasons for this.

Assessment of reporting biases

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNTB of 10 or higher) (Moore 2008).

Data synthesis

We used a random-effects model, using the inverse variance method in Review Manager 5 for meta-analysis, because we expected clinical heterogeneity due to the different types of cancer pain conditions (Review Manager 2020).

Subgroup analysis and investigation of heterogeneity

We intended to perform subgroup analyses for the primary outcomes according to the following, where there were at least two studies available.

- Different types of CbMs.
- Different dosages of the same CbM and study duration. We distinguished between short-term (four to 12 weeks), intermediate-term (13 to 26 weeks) and long-term (more than 26 weeks) studies (Chaparro 2013), as well as experimental studies (one to three days) and very short-term (three to 13 days) studies.
- Types of controls (placebo; established analgesic).
- Types of cancer-related pain (pain directly caused by cancer, e.g. by bone metastases versus pain caused by cancer treatment, e.g. chemotherapy-induced polyneuropathy).

These subgroup analyses were predefined due to the many uncertainties about CbMs for chronic pain, such as the selection of the type of CbM (cannabis flowers versus CBs), optimal dosage for efficacy, duration of efficacy, and comparative efficacy and safety to established medications (Fisher 2021; Häuser 2018).

Because of the relevant differences of study designs and purposes of the studies, we decided not to pool all studies. Instead, we conducted four separate analyses.

Sensitivity analysis

We performed a sensitivity analysis by excluding studies with imputed rates of pain relief of 30% or greater. We did not conduct the planned sensitivity analysis by excluding studies with imputed rates of pain relief of 50% or greater because all rates of pain relief of 50% or greater had to be calculated by an imputation method. The planned sensitivity analysis excluding studies with less than 14 days' duration was not necessary because we did not pool studies with a duration of less and of more than 14 days.

Summary of findings and assessment of the certainty of the evidence

Two review authors (EF, WH) independently rated the certainty of the body of evidence for the outcomes. We resolved discrepancies by consulting a third review author (RAM). We used the GRADE system to rank the certainty of the evidence using the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020) and the GRADE Handbook (Schünemann 2013).

The GRADE system considers study design as a marker of quality. It uses the following criteria for assigning a certainty level to the body of evidence for a given outcome.

- **High:** randomised trials without downgrading or double-upgraded observational studies
- **Moderate:** downgraded randomised trials or upgraded observational studies
- **Low:** double-downgraded randomised trials or observational studies without downgrading
- **Very low:** triple-downgraded randomised trials, downgraded observational studies or case series/case reports

Factors that may decrease the certainty level of a body of evidence are as follows.

- Limitations in the design and implementation of available studies, suggesting high likelihood of bias. We assumed that there were limitations in study design if more than 50% of participants were from studies with high risk of bias, as defined by the Cochrane RoB 1 tool (Higgins 2011).
- Indirectness of evidence (indirect population, intervention, control, outcomes). We assessed if the study population was different from the population in routine clinical care by assessing if studies excluded participants with relevant medical conditions (cardiovascular, hepatic, renal and endocrine system). If exclusion of participants with clinically relevant medical conditions resulted in 50% or more of the total number of participants, we decreased the certainty of evidence.
- Unexplained heterogeneity (I^2 greater than 50%) or inconsistency of results.
- Imprecision of results (wide CIs; low number of events).
- High probability of publication bias. We assumed a potential publication bias if all studies were initiated and funded by the manufacturer of the drug tested in the trial.

We used the GRADE system criteria for assigning the grade of evidence (Schünemann 2013).

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- **Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- **Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

We created one summary of findings table to present in a transparent and simple tabular format the main findings for comparisons of CbMs and medical cannabis with placebo or any established analgesic. In particular, we included key information concerning the certainty of evidence, the magnitude of effect of the interventions examined and the sum of available data on these outcomes:

- proportion of participants reporting no worse than mild pain by 14 days after start of treatment;
- PGIC of much improved or very much improved;
- withdrawals due to adverse events;
- mean pain intensity;
- daily maintenance opioid dosage (mg morphine equivalent);
- daily breakthrough opioid dosage (mg morphine equivalent);
- participants experiencing any serious adverse event.

RESULTS

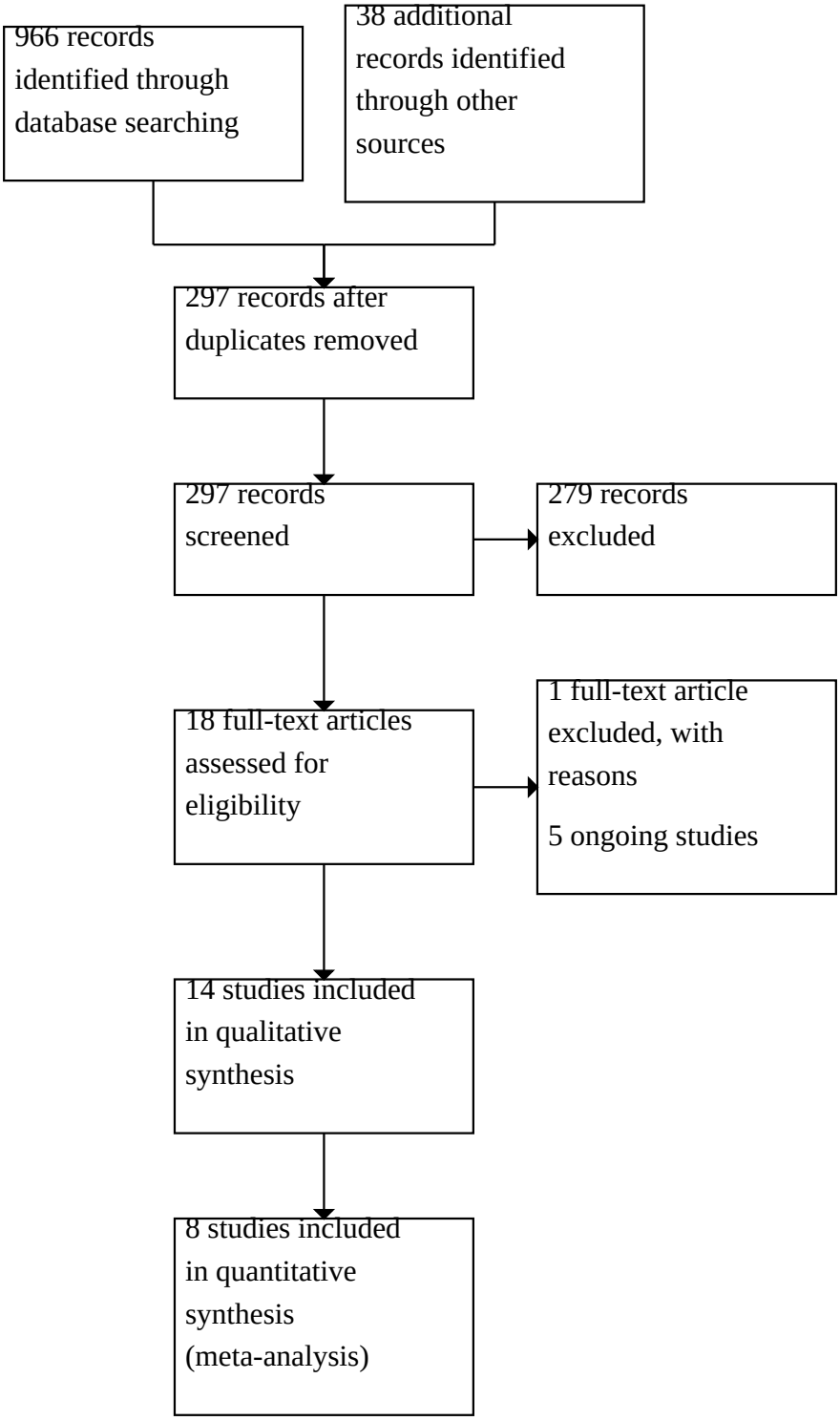
Description of studies

See Characteristics of included studies; Characteristics of excluded studies; and Characteristics of ongoing studies tables.

Results of the search

The searches (performed 3 March 2022, updated 26 January 2023) produced 966 records We identified 145 potentially relevant studies in CENTRAL, 433 in MEDLINE, 246 in Embase, 121 in the ClinicalTrials.gov, nine in the EU Clinical Trials Register and 12 in the WHO ICTRP. A search for studies in the International Association for Cannabinoid Medicines (IACM) databank was not possible because the database was no longer available. We identified 38 additional records through other sources. After removing duplicates, we read the titles and abstracts of 297 articles and excluded studies that were clearly irrelevant. We read the full text of 18 potentially eligible articles and included 14 studies in the review (Côté 2016; Fallon 2017a; Fallon 2017b; Hardy 2023; Jochimsen 1978; Johnson 2010; Lichtman 2018; Lynch 2014; Noyes 1975a; Noyes 1975b; Portenoy 2012; Staquet 1978a; Staquet 1978b; Turcott 2018) (see Figure 1). We excluded one study with reasons (see Characteristics of excluded studies table) and identified five ongoing studies (see Characteristics of ongoing studies table). No studies are awaiting classification.

Figure 1. Study flow diagram.



Four studies with nabiximols for opioid refractory cancer pain (Fallon 2017a; Johnson 2010; Lichtman 2018; Portenoy 2012), and four experimental studies with a synthetic THC analogue (Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b), were suited for quantitative analysis. Six studies were included only in qualitative analysis: one study employed a withdrawal design (Fallon 2017b). The heterogeneity of the aims of four studies (reducing chemotherapy induced neuropathic pain (Lynch 2014), improving health-related quality of life (Côté 2016), reducing cachexia (Turcott 2018), and total symptom burden (Hardy 2023)), and the different medications used prohibited quantitative synthesis (Lynch 2014: nabiximols; Côté 2016; Turcott 2018: synthetic THC analogue (nabilone); Hardy 2023: CBD). The reported outcomes of one experimental study with synthetic THC analogue was not suited for quantitative analysis (Jochimsen 1978).

Included studies

Characteristics of the studies

We included 14 studies with 20 treatment arms involving 1823 participants into the analysis. The studies of Noyes 1975a and Noyes 1975b involved different populations. Four studies involving different participants were reported in two publications (Fallon 2017a; Fallon 2017b; Staquet 1978a; Staquet 1978b).

Aims of the studies

Five studies tested if nabiximols was effective as an add-on therapy for people with cancer pain not adequately relieved by opioids (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Portenoy 2012). Five studies tested if a single dose of synthetic THC analogue relieved moderate-to-severe cancer pain after stopping other analgesics four hours before the intake of synthetic THC analogue (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). One study tested nabiximols for chemotherapy-induced neuropathic pain (Lynch 2014). Two studies tested a synthetic THC analogue (nabilone) to reduce cancer and radiochemotherapy-related symptoms (Côté 2016; Turcott 2018). One study tested CBD to reduce total symptom burden in advanced cancer (Hardy 2023). Thus, the aim of one study was to reduce cancer therapy-related pain (Lynch 2014), of two studies to reduce cancer-related and cancer therapy-related pain (Côté 2016; Turcott 2018), and of the remaining studies to reduce cancer-related pain.

Study setting

We found eight studies used a single-centre recruitment strategy (Côté 2016; Jochimsen 1978; Lynch 2014; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b; Turcott 2018), the remaining studies were multicentre. The number of study centres ranged between 20 and 114. Six studies were conducted in North America (Côté 2016; Jochimsen 1978; Lynch 2014; Noyes 1975a; Noyes 1975b; Portenoy 2012), two in Belgium (Staquet 1978a; Staquet 1978b), one in Australia (Hardy 2023), and one in Mexico (Turcott 2018). The remaining studies were conducted across two continents: Fallon 2017a; Johnson 2010; and Lichtman 2018 included participants from North America and Europe and Fallon 2017b from Europe and Asia.

Study design

Seven studies used a parallel design (Côté 2016; Fallon 2017a; Hardy 2023; Johnson 2010; Lichtman 2018; Portenoy 2012; Turcott 2018), six studies had a cross-over design (Jochimsen 1978; Lynch 2014; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b), and one study had a withdrawal design (Fallon 2017b). The one-day studies tested two and three dosages of a synthetic THC analogue (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). One study had one THC and one THC/CBD arm (Johnson 2010). One study had three THC/CBD arms with different dosages (Portenoy 2012).

Study duration

We found five experimental studies with one dose lasting less than one day (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). The double-blind period was two weeks in one study (Johnson 2010), five weeks in four studies (Fallon 2017a; Fallon 2017b; Lichtman 2018; Portenoy 2012), and eight weeks in three studies (Côté 2016; Lynch 2014; Turcott 2018).

Sample sizes

The sample sizes ranged between 10 and 399. Eight studies had treatment group sizes below 50 participants (Côté 2016; Jochimsen 1978; Lynch 2014; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b; Turcott 2018). The remaining six were between 50 and 200 participants in each treatment group (Fallon 2017a; Fallon 2017b; Hardy 2023; Johnson 2010; Lichtman 2018; Portenoy 2012). Treatment group sizes were of the order of 200 participants or more in two studies (Fallon 2017a; Lichtman 2018).

Study period

Two studies reported the study period which was 2005 to 2007 (Côté 2016) and 2017 to 2019 (Hardy 2023).

Study funding

Four studies received public funding (Côté 2016; Hardy 2023; Noyes 1975a; Noyes 1975b). Pharmaceutical companies funded four studies (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018). Two studies received public and pharmaceutical company funding (Jochimsen 1978; Portenoy 2012). Two studies received no funding (Lynch 2014; Turcott 2018). Two studies did not report on funding (Staquet 1978a; Staquet 1978b).

Conflicts of interest

Authors of seven studies reported that they had no conflicts of interest (Côté 2016; Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Lynch 2014; Turcott 2018). Authors of six studies did not report on conflicts of interest (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Portenoy 2012; Staquet 1978a; Staquet 1978b). Authors of one study reported on conflicts of interest (Hardy 2023).

Characteristics of participants

Age

The mean age of the participants was between 55 and 60 years. Two studies reported the range of age which was 21 to 75 years (Staquet 1978a; Staquet 1978b).

Gender

The percentage of men was between 17% and 93%. Two studies did not report gender (Staquet 1978a; Staquet 1978b).

Types of cancer and of cancer pain

The studies included mainly participants with carcinoma. One study included participants with squamous cell carcinoma of the head and neck (Côté 2016), and one study included participants with non-small cell lung cancer (Turcott 2018). Four studies reported the percentage of participants with different types of cancer pain (e.g. nociceptive, neuropathic, visceral) (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018). One study included participants with chemotherapy-induced neuropathic pain (Lynch 2014).

Inclusion criteria

One study did not report on a required pain intensity for inclusion (Jochimsen 1978). The inclusion criteria of three studies were not based on pain intensity. Of these, one study did not report baseline pain values (Côté 2016). Two studies indicated a moderate pain intensity with a large SD and thus included some participants with a lower pain intensity (Hardy 2023; Turcott 2018). The remaining studies required at least moderate pain intensity for inclusion, of which four studies required moderate pain intensity despite opioid therapy (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018).

Exclusion criteria

Eight studies excluded people with major internal diseases (e.g. of the heart, liver) (Côté 2016; Fallon 2017a; Fallon 2017b; Jochimsen 1978; Johnson 2010; Lichtman 2018; Lynch 2014; Portenoy 2012). Five studies excluded people with major psychiatric disorders (e.g. psychosis, substance-use disorder) (Côté 2016; Hardy 2023; Jochimsen 1978; Johnson 2010; Portenoy 2012). Five studies excluded people with cannabis use (Fallon 2017a; Fallon 2017b; Lichtman 2018; Portenoy 2012; Turcott 2018). Five studies excluded people with "large dosages of narcotics" without defining the type of narcotic and the threshold of a large dosage (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b).

Previous experience of participants with herbal cannabis

Two studies reported on previous cannabis experience (12% of participants in both studies) without making a distinction between recreational and medical use (Johnson 2010; Portenoy 2012).

Characteristics of the treatment delivered

Types and doses of cannabis-based medicines and comparators

Five studies used flexible oromucosal nabiximols with 'medium' dosages (THC/CBD up to 27/24 mg/day) (Fallon 2017a; Fallon 2017b; Lichtman 2018; Lynch 2014; Portenoy 2012). One study included a treatment arm with 'low-dose' THC/CBD (up to 10.8/10 mg/day). One study included an arm with 'high-dose' THC/CBD (up to 42.2/40 mg/day) (Portenoy 2012). One study arm used a 'medium' dosage of THC (up to 27 mg/day) (Johnson 2010). The experimental studies tested different fixed dosages of synthetic THC analogue orally (4 mg/day, 5 mg/day, 10 mg/day and 20 mg/day) (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). The fixed dosages of nabilone orally were within the recommended range with 1 mg/day (Côté 2016), and 2 mg/day (Turcott 2018). The median daily dose in the study with oral CBD oil was 400 mg/day. All studies compared CbMs to placebo. The experimental studies also compared CbMs to codeine 50 mg/day, 60 mg/day and 120 mg/day (Noyes 1975a; Noyes 1975b; Staquet 1978a).

Rescue medication

Three studies used opioids as rescue medication. The study authors did not report the dosages of rescue medication used in the study groups (Fallon 2017a; Fallon 2017b; Lichtman 2018). The single dosage studies did not use rescue medication (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). The remaining studies did not report on the type of rescue medication (Côté 2016; Hardy 2023; Johnson 2010; Portenoy 2012; Turcott 2018).

Excluded studies

We excluded one study after full-text review because it did not include a study arm as required by our inclusion criteria (placebo or other active medication) (Zylla 2021).

Ongoing studies

We identified five ongoing studies with unpublished results; two studies used medical cannabis, either by oral liquid (ACTRN12619001534178) or by inhalation (NCT04042545) application, and three studies used THC/CBD, either by orobuccal (ACTRN12621001302842) or oral liquid application (EudraCT 001382-32; Hardy 2020).

Risk of bias in included studies

We judged risk of bias across most domains as unclear (Figure 2; Figure 3; see Characteristics of included studies table for detailed information regarding risk of bias assessments of each study). We rated the overall risk of bias according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). Five studies were at unclear overall risk of bias (Côté 2016; Fallon 2017a; Fallon 2017b; Lichtman 2018; Lynch 2014), and the overall risk of bias was high in the remaining studies (Hardy 2023; Jochimsen 1978; Johnson 2010; Noyes 1975a; Noyes 1975b; Portenoy 2012; Staquet 1978a; Staquet 1978b; Turcott 2018). No trial was at low risk of bias for all categories examined.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

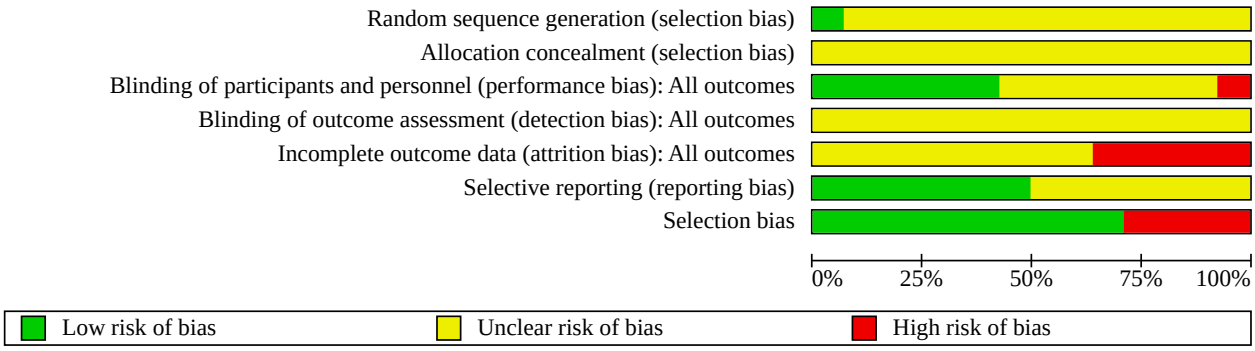
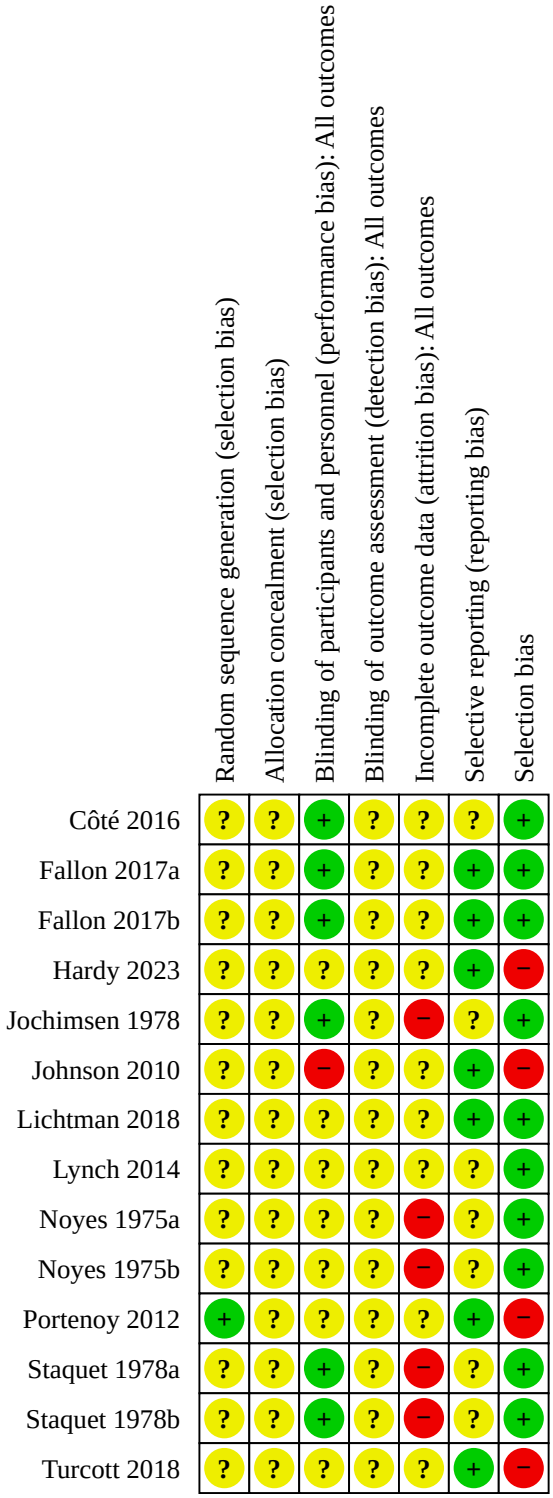


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation (selection bias)

We judged one study at low risk of random sequence generation (Portenoy 2012). There were concerns for the remaining studies, which did not report the details of random sequence generation (unclear risk).

Allocation concealment (selection bias)

No studies described allocation concealment adequately. Therefore, we judged all studies at unclear risk of bias.

Blinding

We judged blinding of participants and personnel as low risk of bias in six studies (Côté 2016; Fallon 2017a; Fallon 2017b; Jochimsen 1978; Staquet 1978a; Staquet 1978b). There were some concerns for the studies for seven studies, which reported no details of the blinding of participants and personnel; we judged these at unclear risk of bias (Hardy 2023; Lichtman 2018; Lynch 2014; Noyes 1975a; Noyes 1975b; Portenoy 2012; Turcott 2018). One study was at high risk of bias, as it did not report if nabiximols and placebo were identical in taste (Johnson 2010).

No study reported on details of the blinding of the outcome assessor and therefore we judged all studies at unclear risk of detection bias.

Incomplete outcome data

Five studies had high risk of attrition bias, which used completer analysis (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). There were some concerns for the remaining studies, which used ITT analysis by LOCF. We judged these studies at unclear risk of bias.

Selective reporting

We judged reporting bias as low in the nabiximols studies because there was a study protocol (Fallon 2017a; Fallon 2017b; Hardy 2023; Johnson 2010; Lichtman 2018; Portenoy 2012). The risk of bias was unclear for the remaining studies because they did not publish a study protocol.

Other potential sources of bias

Four studies were at high risk of other bias due to significant differences in demographic or clinical variables (or both) at baseline between the study groups (Hardy 2023; Johnson 2010; Portenoy 2012; Turcott 2018). We found group similarity at baseline in the remaining studies, which were at low risk of other bias.

Effects of interventions

See: **Summary of findings 1** Cannabis-based medicines compared with placebo medication for cancer pain

In total, we analysed 14 studies with 20 treatment arms involving 1823 participants. See Summary of findings 1 for the main comparison.

Cannabis-based medicines as add-on for opioid refractory cancer pain

Studies with a parallel design

We found four studies with seven study arms including 1334 participants that used a parallel design for nabiximols in participants with opioid-refractory cancer pain. We report the meta-analyses below.

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

No study assessed this outcome.

Patient Global Impression of Change of much improved or very much improved

We analysed three studies with five treatment arms. A total of 179/561 (31.9%) participants in the nabiximols and 100/434 (23.0%) participants in the placebo group reported being much or very much improved (RD 0.06, 95% CI 0.01 to 0.12; P = 0.03; I^2 = 0%; NNTB 16, 95% CI 8 to 100; Analysis 1.1). According to the predefined categories, there was no clinically relevant benefit by nabiximols. We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (one study was at high risk of bias).

Withdrawals due to adverse events

We analysed four studies with seven treatment arms and 1332 participants. We found 148/785 (18.6%) participants in the nabiximols and 85/547 (15.5%) participants in the placebo group dropped out due to adverse events (RD 0.04, 95% CI 0 to 0.08; P = 0.04; I^2 = 0%; NNTH 25, 95% CI 12 to indefinite; Analysis 1.2). According to the predefined categories, there was no clinically relevant harm. We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies were at high risk of bias).

Secondary outcomes

Combined responder

No study assessed this outcome.

Number of participants who reported pain relief of 30% or greater

We analysed four studies with seven treatment arms and 1332 participants. We found 217/785 (26.8%) participants receiving nabiximols and 145/547 (26.5%) participants in the placebo group reported pain relief of 30% or greater (RD 0.02, 95% CI −0.03 to 0.07; P = 0.51; I^2 = 0%; Analysis 1.3). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Number of participants who reported pain relief of 50% or greater

We analysed four studies with seven treatment arms and 1333 participants. We found 104/786 (13.2%) participants receiving nabiximols and 50/547 (9.1%) participants in the placebo group reported pain relief of 50% or greater (RD 0.01, 95% CI −0.02 to 0.05; P = 0.38; I^2 = 1%; Analysis 1.4). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Mean pain intensity

We analysed four studies with seven treatment arms and 1315 participants. There was no evidence of a difference in mean pain intensity on a 0 to 10 scale (MD −0.19, 95% CI −0.40 to 0.02; P = 0.08, I^2 = 21%; Analysis 1.5). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Sleep problems

We analysed four studies with seven treatment arms and 1314 participants. We found no benefit of nabiximols for improving sleep (SMD −0.06, 95% CI −0.19 to 0.06; P = 0.31, I^2 = 11%; Analysis 1.6). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Depression

In one study including 360 participants, we found no difference between placebo and the low-dose THC/CBD group (P = 0.48), the medium-dose THC/CBD group (P = 0.08) and the high-dose THC/CBD group (P = 0.15) on the Montgomery Åsberg Depression Rating Scale (Portenoy 2012). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (two studies at high risk of bias), and imprecision of results (only one study analysed).

Anxiety

No studies assessed anxiety.

Daily maintenance opioid dosage (mg morphine equivalent)

We analysed three studies with four treatment arms and 970 participants. We found no difference in opioid dose between groups (SMD 0.08, 95% CI −0.10 to 0.27; P = 0.38, I^2 = 43%; Analysis 1.7). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (two studies at high risk of bias), and imprecision of results (CIs included zero). Portenoy 2012 reported that there were no differences between the three dosages arms of THC and CBD (P values not reported).

Daily breakthrough opioid dosage (mg morphine equivalent)

We analysed three studies with four treatment arms and 957 participants. We found no difference between groups (SMD −0.08, 95% CI −0.23 to 0.07; P = 0.29, I^2 = 19%; Analysis 1.8). Portenoy 2012 reported that there was no difference between the three dosages arms of THC and CBD (P values not reported). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Number of participants dropping out due to lack of efficacy

No study assessed this outcome.

All central nervous system adverse events

We analysed four studies with seven treatment arms and 1331 participants. We found 202/785 (25.7%) participants receiving nabiximols and 57/546 (10.4%) participants in the placebo group reported nervous system disorders adverse events (RD 0.11, 95% CI 0.05 to 0.17; P < 0.001; I^2 = 43%; NNTH 9, 95% CI 6 to 25; Analysis 1.9). According to the predefined categories there was a clinically relevant harm by nabiximols. We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

All psychiatric adverse events

We analysed four studies with seven treatment arms and 1331 participants. We found 75/785 (9.6%) participants receiving nabiximols and 17/546 (3.1%) participants in the placebo group reported psychiatric disorders adverse events (RD 0.01, 95% CI −0.01 to 0.04; P = 0.24; I^2 = 35%; Analysis 1.10). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Participants experiencing any serious adverse event

We analysed four studies with seven treatment arms and 1330 participants. We found 187/784 (23.9%) participants receiving nabiximols and 116/546 (21.2%) participants in the placebo group reported serious adverse events (RD 0.02, 95% CI −0.03 to 0.07; P = 0.43; I^2 = 9%; Analysis 1.11). We judged the certainty of evidence as moderate, downgraded one level due to limitations of study design (two studies at high risk of bias).

Studies with a withdrawal design

We found one study with 206 participants that used a withdrawal design (Fallon 2017b). We could not meta-analyse the results, so we describe the double-blind period only below.

Primary outcomes

Proportion of participants reporting no worse than mild pain 14 days after start of treatment

The study did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

There was no evidence of a difference on the mean PGIC (0.33, 95% CI −0.35 to 0.41; P = 0.41). We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (only one study available).

Withdrawals due to adverse event

We found 21/103 of participants receiving nabiximols and 13/103 in placebo group withdrew due to adverse events (P = 0.05). We judged the certainty of evidence as low, downgraded one level to low due to imprecision of results (only one study available).

Secondary outcomes

Combined responder

The study did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

The study did not assess this outcome.

Number of participants who reported pain relief of 50% or greater

The study did not assess this outcome.

Mean pain intensity

There was no evidence of a difference in mean pain intensity (MD −0.02, 95% CI −0.42 to 0.38; P = 0.92). We judged the certainty of evidence as moderate, downgraded one level due to and imprecision of results (only one study available).

Sleep problems

There was no evidence of a difference in sleep problems (MD 0.06, 95 CI −0.28 to 0.39; P = 0.73). We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (only one study available).

Depression

The study did not assess this outcome.

Anxiety

The study did not assess this outcome.

Daily maintenance opioid dosage (mg morphine equivalent)

There was no evidence of a difference in daily maintenance opioid dosage (MD −8.93, 95% CI −19.69 to 1.84; P = 0.10). We judged the certainty of evidence as low, downgraded one level due to imprecision of results (only one study available).

Daily breakthrough opioid dosage (mg morphine equivalent)

There was no evidence of a difference in daily breakthrough opioid dosage (MD 1.81, 95% CI −10.34 to 13.69; P = 0.77). We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (only one study available).

Number of participants dropping out due to lack of efficacy

One participant in each group withdraw due to lack of efficacy. We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (low number of events).

All central nervous system adverse events

Six participants in the nabiximols and one in the placebo group reported dizziness or somnolence. We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (only one study available).

All psychiatric adverse events

There were no treatment-emergent suicidal ideations or behaviour in either group. We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (low number of events).

Participants experiencing any serious adverse event

There were treatment-related serious adverse events in 33/103 of nabiximols-treated and 16/103 of placebo-treated participants (P = 0.13). We judged the certainty of evidence as moderate, downgraded one level due to imprecision of results (low number of events).

Nabiximols for cancer therapy-induced neuropathic pain

We found one study with 16 participants that delivered nabiximols for cancer therapy-induced neuropathic pain (Lynch 2014). This could not be meta-analysed, so we described the results below.

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

The study did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

The study did not assess this outcome.

Withdrawals due to adverse event

The study did not report why two participants dropped out.

Secondary outcomes

Combined responder

The study did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

We found 5/18 participants with nabiximols and 3/18 participants with placebo reported pain relief of 30% or greater (P = 0.16). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (study with high risk of bias) and imprecision of results (only one study with low number of participants available).

Number of participants who reported pain relief of 50% or greater

We found 2/18 participants with nabiximols and 3/18 participants with placebo reported pain relief of 50% or greater (P = 0.47). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (study with high risk of bias) and imprecision of results (only one study with low number of participants available).

Main pain intensity

The mean pretreatment score was 6.75 and was 6.00 in the nabiximols and 6.38 in the placebo group. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (study with high risk of bias) and imprecision of results (only one study with low number of participants available).

Sleep problems

The study did not assess this outcome.

Depression

The study did not assess this outcome.

Anxiety

The study did not assess this outcome.

Daily maintenance opioid dosage (mg morphine equivalent)

The study did not assess this outcome.

Daily breakthrough opioid dosage (mg morphine equivalent)

The study did not assess this outcome.

Number of participants dropping out due to lack of efficacy

The study did not assess this outcome.

All central nervous system adverse events

Nine participants with nabiximols (six dizziness, one confusion, two "foggy brain") and none with placebo reported nervous system adverse events (P = 0.02). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design

(study with high risk of bias) and imprecision of results (only one study with low number of participants available).

All psychiatric adverse events

Three participants with nabiximols and none with placebo reported on psychiatric disorders adverse events (feeling "stoned", anxiety and panic attack, one each) (P = 0.23). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (study with high risk of bias) and imprecision of results (only one study with low number of participants available).

Participants experiencing any serious adverse event

The study reported "There were no serious medication-related events."

Studies with synthetic tetrahydrocannabinol analogue (nabilone) compared to placebo to improve health-related quality of life of people undergoing radiation or radiochemotherapy

We found two studies with 89 participants that delivered nabilone to improve health-related quality of life of people undergoing radiation or radiochemotherapy (Côté 2016; Turcott 2018). The presentation of the outcomes did not allow quantitative synthesis, so we described the results below.

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

The studies did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

The studies did not assess this outcome.

Withdrawals due to adverse events

Neither study reported withdrawal due to adverse effects in detail. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (study with high risk of bias) and imprecision of results (low number of participants).

Secondary outcomes

Combined responder

The studies did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

Neither study reported this outcome. We could not use the imputation method because Côté 2016 did not report baseline pain intensity. By imputation, Turcott 2018 reported 7/14 participants in the nabilone and 7/19 participants in the placebo group experienced pain relief of 30% or greater (P = 0.45). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

Number of participants who reported pain relief of 50% or greater

Neither study reported this outcome. We could not use the imputation method because Côté 2016 did not report baseline pain intensity. By imputation, Turcott 2018 reported 5/14 participants in the nabilone and 5/19 participants in the placebo group experienced pain relief of 50% or greater (P = 0.56). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

Mean pain intensity

Côté 2016 reported no difference between nabilone and placebo in mean pain intensity (P = 0.61). Turcott 2018 reported the change in mean pain intensity score in the nabilone group from baseline to the end of treatment was 13 in the nabilone group and 6.6 in the control group on a 0 to 100 scale. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

Sleep problems

Côté 2016 reported no difference between nabilone and placebo in sleep problems (P = 0.44). Turcott 2018 reported change in mean insomnia score in the nabilone group from baseline to the end of treatment was −40.7 in the nabilone group and −9.9 in the control group on a 0 to 100 scale. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

Depression

Côté 2016 reported no difference between nabilone and placebo on mood (P = 0.32). Turcott 2018 did not assess this outcome. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

Anxiety

The studies did not assess this outcome.

Daily maintenance opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Daily breakthrough opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Number of participants dropping out due to lack of efficacy

Neither study reported withdrawals due to lack of efficacy in detail. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

All central nervous system adverse events

Côté 2016 reported that there was no difference between nabilone and placebo in the prevalence of drowsiness (P = 0.32). Turcott 2018 did not assess this outcome. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one study with high risk of bias) and imprecision of results (low number of participants).

All psychiatric adverse events

Côté 2016 reported that there was no difference between nabilone and placebo in the prevalence of anxiety (P = 0.91). Turcott 2018 did not assess this outcome. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (one

study with high risk of bias) and imprecision of results (low number of participants).

Participants experiencing any serious adverse event

Neither study explicitly mentioned serious adverse events.

Experimental (single dosage) studies to reduce cancer pain: synthetic THC analogue versus placebo

We found five studies with 126 participants that delivered a single dosage of a synthetic THC analogue (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b).

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

The studies did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

The studies did not assess this outcome.

Withdrawals due to adverse events

The studies did not assess this outcome.

Secondary outcomes

Combined responder

The studies did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

The studies did not assess this outcome.

Number of participants who reported pain relief of 50% or greater

Jochimsen 1978 reported that 23% of participants with 4 mg of a synthetic THC analogue, 40% of participants with 2 mg of a synthetic THC analogue and 43% of participants with placebo reported pain relief of 50% or greater. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

Mean pain intensity

We analysed three studies with four treatment arms and 301 participants. There was a difference in mean pain intensity in favour of THC analogue (SMD of pain reduction −0.98, 95% CI −1.36 to −0.60; P < 0.001, I^2 = 54%; Analysis 2.1). The effect size was large according to Cohen's categories. The criterion of a clinically relevant effect was met. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and inconsistency (high heterogeneity). Jochimsen 1978 stated that "reductions of pain intensity occurred in a larger proportion of patients than pain relief, but the reductions were small and clearly without clinical significance." A total of 19/35 participants with 2 mg synthetic THC analogue, 20/35 participants with 4 mg synthetic THC analogue and 25/35 participants with placebo reported a pain reduction.

Sleep problems

The studies did not assess this outcome.

Depression

The studies did not assess this outcome.

Anxiety

The studies did not assess this outcome.

Daily maintenance opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Daily breakthrough opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Number of participants dropping out due to lack of efficacy

The studies did not assess this outcome.

All central nervous system adverse events

Jochimsen 1978 did not report nervous system adverse events in the placebo group. Noyes 1975a reported 94% of participants with THC 20 mg, 71% of participants with THC 10 mg and 29% of participants with placebo reported sedation. Noyes 1975b reported 14 nervous system adverse events (drowsiness, dizziness) with 5 mg, 19 with 10 mg, 26 with 15 mg, and 36 with 20 mg synthetic THC analogue, and 21 with placebo. Staquet 1978b and Staquet 1978a pooled the data of both studies and reported that 40% of participants reported drowsiness with synthetic THC analogue and 21% of participants reported drowsiness with placebo. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

All psychiatric adverse events

Jochimsen 1978 reported that "psychiatric interview, failed to reveal any consistent changes which could be ascribed to any drug or to the test period as a whole." Noyes 1975a reported 62 psychiatric adverse events (mental clouding, disorientation thought, slurred speech) in the 20 mg synthetic THC analogue group, 32 in the 10 mg synthetic THC analogue group and 15 in the placebo group. Noyes 1975b reported 17 psychiatric adverse events (slurred speech, blurred vision, mental clouding, dreaminess, disconnected thought, euphoria, visual hallucinations) in the 5 mg, 19 in the 10 mg, 33 in the 15 mg and 37 in the 20 mg synthetic THC analogue groups and five in the placebo group. Staquet 1978b and Staquet 1978a pooled the data of both studies and reported there was no euphoria reported by participants with synthetic THC analogue and placebo. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

Participants experiencing any serious adverse event

The studies did not assess this outcome.

Experimental (single dosage) studies to reduce cancer pain: synthetic THC analogue versus codeine

We found four studies with 116 participants which compared a single dose of a synthetic THC analogue with a single dose of codeine.

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

The studies did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

The studies did not assess this outcome.

Withdrawals due to adverse events

The studies did not assess this outcome.

Secondary outcomes

Combined responder

The studies did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

The studies did not assess this outcome.

Number of participants who reported pain relief of 50% or greater

Jochimsen 1978 reported that 23% of participants with 4 mg of a synthetic THC analogue, 40% of participants with 2 mg of a synthetic THC analogue, 57% of participants with codeine 120 mg and 49% of participants with codeine 60 mg reported pain relief of 50% or greater. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

Mean pain intensity

We analysed two studies with three treatment arms and 194 participants. There was no evidence of a difference in pain intensity (SMD 0.03, 95% CI −0.25 to 0.32; P = 0.82, I^2 = 0%; Analysis 3.1). We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (both studies with high risk of bias) and imprecision of results (CIs included zero). In Jochimsen 1978, we found 19/35 participants receiving synthetic THC analogue 2 mg, 20/35 participants receiving synthetic THC analogue 4 mg, 25/35 participants receiving codeine 60 mg and 31/35 participants receiving codeine 120 mg reported a pain reduction.

Sleep problems

The studies did not assess this outcome.

Depression

The studies did not assess this outcome.

Anxiety

The studies did not assess this outcome.

Daily maintenance opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Daily breakthrough opioid dosage (mg morphine equivalent)

The studies did not assess this outcome.

Number of participants dropping out due to lack of efficacy

The studies did not assess this outcome.

All central nervous system adverse events

Jochimsen 1978 reported that the sedation induced by synthetic THC analogue in doses of 2 mg and 4 mg was of the same order as that induced by the two doses of codeine, "although this was not marked for either drug." Noyes 1975a reported that 94% of participants with THC 20 mg, 71% of participants with THC 10 mg, 47% of participants with codeine 60 mg and 50% of participants with codeine 120 mg reported sedation. Staquet 1978b and Staquet 1978a pooled the data of both studies and reported that 40% of participants with synthetic THC analogue and 44% of participants treated with codeine reported drowsiness. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

All psychiatric adverse events

Jochimsen 1978 reported that "psychiatric interview, failed to reveal any consistent changes which could be ascribed to any drug or to the test period as a whole". Noyes 1975a reported 62 psychiatric adverse events (mental clouding, disorientation thought, slurred speech) in the 20 mg, 32 in the 10 mg, 11 in the codeine 60 mg and seven in the codeine 120 mg group. Staquet 1978b and Staquet 1978a pooled the data of both studies; participants reported no euphoria with synthetic THC analogue. We judged the certainty of evidence as low, downgraded two levels due to limitations of study design (all studies with high risk of bias) and imprecision of results (low number of participants).

Participants experiencing any serious adverse event

The studies did not assess this outcome.

Cannabidiol added to specialist palliative care to reduce pain in advanced cancer

We found one study with 142 participants (Hardy 2023). We report the outcomes at day 28.

Primary outcomes

Proportion of participants reporting no worse than mild pain by 14 days after start of treatment

The study did not assess this outcome.

Patient Global Impression of Change of much improved or very much improved

About 70% of participants in the CBD group and 64% in the placebo group reported feeling better or much better.

Withdrawals due to adverse events

A total of 10/70 participants withdrew with CBD and 8/72 participants withdrew with placebo.

Secondary outcomes

Combined responder

The study did not assess this outcome.

Number of participants who reported pain relief of 30% or greater

A total of 26/70 in the CBD group and 29/72 in the placebo group reported pain relief of 30% or greater (calculated by imputation method).

Number of participants who reported pain relief of 50% or greater

A total of 19/70 in the CBD group and 20/72 in the placebo group reported pain relief of 50% or greater (calculated by imputation method).

Mean pain intensity

In the CBD group, baseline pain score (VAS 0 to 100) was 40.34 (SD 26.26) and at 28 days was 37.80 (SD 28.14). In the placebo group, baseline pain score (VAS 0 to 100) was 50.94 (SD 30.20) and at 28 days was 43.56 (SD 30.54).

Sleep problems

The study did not assess this outcome.

Depression

The mean change in depression in the CBD group was −0.50 (SD 0.46) and in the placebo group was −0.63 (SD 0.405).

Anxiety

The mean change in the CBD group was −1.10 (SD 0.44) and in the placebo group was −0.79 (SD 0.43).

Daily opioid dosage (mg morphine equivalent)

The study did not make a distinction between maintenance and breakthrough opioid doses. At day 28, 3/42 (7.1%) participants in the CBD group and 6/4 (13.6%) participants in the placebo group had a morphine dose reduction from baseline; 20/42 (47.6%) participants in the CBD group and 21/42 (50%) participants in the placebo group had no change; and 18/42 (42.9%) participants in the CBD group and 16/42 (38.1%) participants in the placebo group had an increase in total opioid dose.

Number of participants dropping out due to lack of efficacy

The study did not assess this outcome.

All central nervous system adverse events

A total of 30/66 (45%) participants in the CBD group and 21/68 (31%) participants in the placebo group reported new or worse days with somnolence; 16/66 (24%) participants in the CBD group and 14/68 (11%) participants in the placebo group reported new or worse days with dizziness; and 9/70 (12.8%) participants in the CBD group and 7/72 (9.7%) participants in the placebo group reported new or worse days with fatigue.

All psychiatric adverse events

A total of 3/70 (4.3%) participants in the CBD group and 1/72 (1.4%) participants in the placebo group reported new or worse days with anxiety.

Participants experiencing any serious adverse event

There were eight serious adverse events resulting in hospitalisations (five in the CBD group and three in the placebo group).

Subgroup analysis

We conducted a subgroup analysis comparing the effects of lower dosages of synthetic THC analogue (5 mg or 10 mg) versus placebo (four studies with 193 participants) compared to higher dosages of synthetic THC analogue (15 mg or 20 mg) versus placebo (two studies with 108 participants) on mean pain intensity. The P value for the subgroup comparison was 0.16 (see Analysis 2.1).

We conducted a subgroup analysis comparing the effects of lower dosages of synthetic THC analogue (4 mg or 10 mg) versus codeine 50 mg or 60 mg (two studies with 126 participants) compared to higher dosages of synthetic THC analogue (20 mg) versus codeine 120 mg. The P value of subgroup comparison was 0.51 (see Analysis 3.1).

We did not perform the other predefined subgroup analyses because most subgroups included only one study or treatment arm.

Sensitivity analysis

By removing one study with one treatment arm with imputed rates for pain relief of 30% or greater, the RD of the remaining study with two study arms was 0.03 (95% CI −0.03 to 0.09; P = 0.31).

Publication bias

Analysis 1.1 for PGIC much or very much improved had an NNTB of 16. This precluded any sensitivity analysis for publication bias as the NNTB of 16 was already higher than the preset utility boundary of an NNTB of 10. Increasing the preset boundary to an NNTB of 20 would mean that results from 249 participants in zero treatment effect trials would be required to that higher level. That is about the size of one of the larger trials included in the analysis.

DISCUSSION

Summary of main results

We identified five RCTs delivering oromucosal nabiximols or THC to 1539 participants with moderate and severe pain despite opioid therapy (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Portenoy 2012). The double-blind periods of the RCTs ranged between two and five weeks. We found four studies that used a parallel design and included 1333 participants that could be included in a meta-analysis (Fallon 2017a; Johnson 2010; Lichtman 2018; Portenoy 2012). The certainty of evidence was moderate for all comparisons except one, which was low. Nabiximols and THC did not differ from placebo in reducing pain, sleep problems, and opioid maintenance and breakthrough dosages. There was no clinically relevant benefit of nabiximols for the number of participants who reported that they were much or very much improved (NNTB 16, 95% CI 6 to 100). There was no difference between nabiximols and THC versus placebo with regards to the dropout rates due to adverse events and to the frequency of psychiatric disorders as adverse events. There was a clinically relevant harm by nabiximols and THC in the frequency of nervous system adverse events compared to placebo (NNTH 9, 95% CI 6 to 20).

We found low-certainty evidence for two RCTs of eight weeks' duration that delivered nabilone (compared to placebo) in 89 participants (Côté 2016; Turcott 2018). We found that nabilone did not reduce pain associated with chemotherapy or radiochemotherapy in people with head and neck cancer and non-small cell lung cancer.

We found low-certainty evidence across five single-dose RCTs with 126 participants that synthetic THC analogue was superior to placebo and not superior to codeine in reducing moderate-to-

severe cancer pain after cessation of previous analgesic treatment for three to 4.5 hours (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b).

Overall completeness and applicability of evidence

The evidence for all types of CbMs and medical cannabis is not complete because we did not analyse studies with medical cannabis only. The ongoing studies might change the findings and conclusions of our review (ACTRN12619001534178; ACTRN12621001302842; EudraCT 001382-32; Hardy 2020; NCT04042545). The usefulness of the available evidence is limited because the quality of studies was overall poor by current standards. The results of the studies analysed can be mainly applied to routine clinical care because the participants included in the clinical studies were largely representative for people with cancer in routine clinical care. However, the studies with nabiximols excluded studies with advanced hepatic and renal failure (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Portenoy 2012).

Quality of the evidence

We found the evidence for the outcomes of the studies with synthetic THC analogues to be low quality because of limitations of study design and imprecision (Côté 2016; Jochimsen 1978; Johnson 2010; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b; Turcott 2018), and the outcomes of the studies with nabiximols to be moderate quality because of limitations of study design (Fallon 2017a; Johnson 2010; Lichtman 2018; Portenoy 2012). Our confidence in the effect estimates is limited; the true effect may be substantially different from the estimate of the effect.

In addition, the studies with synthetic THC analogues might have overestimated the effect size due to their small sample size (Côté 2016; Jochimsen 1978; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b; Turcott 2018).

Six studies used a cross-over design (Jochimsen 1978; Lynch 2014; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b), which has methodological issues that could lead to bias (Elbourne 2002).

The experimental studies with synthetic THC analogue were single-dose studies (Jochimsen 1978; Noyes 1975a; Noyes 1975b; Portenoy 2012; Staquet 1978a; Staquet 1978b). We do not know if the effects on pain relief can be maintained. Another concern is the short study duration of the nabiximols and dronabinol studies (Côté 2016; Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Lynch 2014; Portenoy 2012; Turcott 2018) and CBD study (Hardy 2023), with no intermediate (12 to 26 weeks) or long-term (greater than 26 weeks) randomised study. However, long-term studies are difficult to conduct in people with advanced cancer because of the limited life expectancy.

There are different types of cancer pain (bone, neuropathic, visceral, somatic). Although the nabiximols studies reported the percentages of these categories of cancer pain in the baseline characteristics (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Portenoy 2012), no study has conducted subgroup analyses according to these cancer pain characteristics.

Potential biases in the review process

We conducted a broad search for studies and believe that it is unlikely that significant amounts of relevant data have been overlooked. We cannot exclude the possibility that early studies including synthetic THC analogues have not been published before registration of a study protocol was required for approval by ethical committees or drug agencies.

We did not analyse other relevant symptoms associated with cancer pain such as fatigue and did not analyse other relevant adverse effects of CbMs such as gastrointestinal disorders.

We had to estimate some missing SDs from P values. We calculated most 50% responder rates of the nabiximols studies using imputation methods.

All studies used statistical methods (LOCF, completer analysis) that bias results towards exaggerating the efficacy of the medication.

The influence of allowed co-interventions (e.g. rescue medication) on positive effects and adverse events was unclear because type and dosage of co-interventions were neither clearly reported nor controlled.

Adverse events were not systematically assessed or reported (or both) by most studies. Therefore, we may have underestimated the prevalence of adverse events.

It is possible that we have overestimated risk of bias for studies that failed to report some details of methodology (e.g. randomisation and treatment allocation).

The negative results of the nabiximols trials could be due to a relatively high number of patient withdrawals and high mortality rate (Boland 2020). The intensity of cancer pain can increase in the end stage of the disease and might have counterbalanced the positive effects of nabiximols. In addition, there is a high degree of variability in pharmacokinetic parameters between participants as well as within participants following single and repeat dosing of oromucosal nabiximols. When nabiximols is administered oromucosally, plasma levels of THC and other CBs are lower compared with the levels achieved following inhalation of CBs at a similar dose (GW Pharmaceuticals 2020). Insufficient plasma concentrations of nabiximols might be a potential cause of therapeutic failure in some participants of the studies analysed.

However, analyses for CbMs as add-on for opioid refractory cancer pain were dominated (70% or greater weighting) by two large trials that each had about 200 participants in the treatment and placebo groups. The results were negative, and while there was some uncertainty, we have considered that this constitutes no lower than moderate confidence. This is especially the case when the effects of poor quality are almost universally to inflate treatment effect. So the lack of effect in large, reasonably well-designed studies leads to a conclusion that benefits of CBs tested to date for opioid refractory cancer pain is unlikely.

Finally, this systematic review included 1823 participants. To capture rare and potentially severe adverse events a much larger data set is necessary. For example, to capture an adverse event with a frequency of 1 in 100,000 population, 300,000 participants' observations would be required (Andersohn 2008). We did not look at other data from observational studies for safety evaluations within the scope of our review.

Agreements and disagreements with other studies or reviews

There are numerous reviews available on the efficacy and safety of CbMs and medical cannabis for chronic pain in general. Here, we compare our results only to systematic reviews that included separate analyses for studies on cancer pain. The results and conclusions of our review are not in line with the ones of Aviram 2017 and Wang 2021. Aviram 2017 analysed three RCTs with 10 arms that were also included into our analyses and found an SMD for a fixed-effect model of −0.62 Hedge's g (95% CI −0.80 to −0.44) for mean pain reduction (Johnson 2010; Noyes 1975a; Noyes 1975b; Staquet 1978a; Staquet 1978b). The divergent results can be explained as follows: Aviram 2017 pooled experimental studies with only one of the studies with negative results with nabiximols in opioid-refractory cancer pain (Johnson 2010). Wang 2021 concluded that moderate to high certainty evidence showed that, compared with placebo, non-inhaled medical cannabis or CBs results in a very small to small increase in the proportion of people living with chronic pain. The authors pooled studies with cancer and non-cancer pain. They included only one study with cancer pain in their analysis of mean pain reduction, which was also included into our review (Portenoy 2012).

The findings on nabiximols for opioid-refractory cancer pain are in line with two systematic reviews (Boland 2020; Häuser 2019), which included the same studies as we did (Fallon 2017a; Fallon 2017b; Johnson 2010; Lichtman 2018; Portenoy 2012). Nabiximols was not effective in relieving opioid-refractory cancer and did not reduce maintenance and breakthrough opioid medication. In addition, the use of CbMs was associated with a higher frequency of nervous system and psychiatric disorders compared to placebo. However, serious adverse events did not differ from placebo. These findings were supported by a subgroup analyses of the systematic review of Fisher 2021 on participants with cancer pain. It found no superiority of nabiximols over placebo in the two studies that reported the number of participants with pain relief of 30% or greater (Johnson 2010; Portenoy 2012). In addition, Fisher 2021 did not find a benefit of nabiximols compared to placebo for mean pain intensity as reported by four studies (MD on a 0 to 10 scale 0.22, 95% CI −0.49 to 0.06) as we did.

AUTHORS' CONCLUSIONS

Implications for practice

The potential importance of cannabis-based medicines (CbMs) and medical cannabis in the management of the different types and stages of cancer pain cannot be defined by our review because of the lack of any good evidence of efficacy or harm. The studies analysed do not allow any statement to be made on the place of these medications in the World Health Organization (WHO) analgesic ladder for cancer pain (e.g. if they can be used first, second or third line or as an adjunct). We do not know if the efficacy of single-dose synthetic tetrahydrocannabinol (THC) analogue in analgesic-naive people can be maintained. In addition, synthetic THC analogue was not superior to codeine 50 mg to 120 mg which corresponds to 7 mg, 5 mg and 18 mg morphine equivalent (Oregon Health Authority 2022). There was moderate-certainty evidence against the use of oromucosal nabiximols for cancer pain that is not sufficiently relieved by strong opioids and low-certainty evidence against the use of nabilone to improve health-related quality of life in people undergoing (radio-)chemotherapy. In consideration of adverse effects, CbMs are not as well tolerated as is often claimed by some authors. Nervous system and psychiatric adverse events are prevalent and may limit the clinical usefulness of CbMs.

Of note, we did not find a randomised controlled trial that could confirm the positive effects of medical cannabis on multiple symptoms of people with cancer (pain, sleep problems, psychological distress) described by Israeli observational studies (Aviram 2020; Bar-Lev Schneider 2018). We hope that the ongoing trials with THC and cannabidiol (CBD)-rich medical cannabis will provide high-certainty evidence of medical cannabis in the treatment of cancer pain, as currently the certainty is low (ACTRN12619001534178; ACTRN12621001302842; EudraCT 001382-32; Hardy 2020; NCT04042545). Currently, the European Pain Federation recommends clinicians should consider the use of CbMs only on a case-to-case basis. Taking patient preferences into consideration, an individual therapeutic trial in opioid-naive people with cancer can be considered. An individual therapeutic trial may also be considered in people with moderate-to-severe cancer pain despite optimised pharmacological therapy including co-analgesics (Häuser 2018). Smoking of herbal cannabis is not recommended for people with cancer-related pain as there is no easily defined dosage of cannabis ingredients and smoking presents dangers for physical health. In the event that a person insists on the use of cannabis flowers used for medical reasons, it is prudent for the healthcare professional to recommend inhalation using a vaporiser and oral intake as cannabis oil extract (Fitzcharles 2019).

Implications for research

- Studies should clearly define if the medication aims to relieve pain arising as a direct consequence of the cancer or of cancer therapy, or both.
- Pain mechanisms underlying the cancer pain (e.g. nociceptive, neuropathic) should be reported to enable subgroup analyses of efficacy according to pain mechanisms.
- Placebo-controlled studies without absence of any established analgesic for cancer pain are unlikely to be ethically feasible. WHO analgesic ladder-recommended medication as comparator would allow the assessment of comparative efficacy and safety.
- Studies with different CbMs arms (e.g. THC-rich, CBD-rich, balanced THC/CBD ratio) are necessary to define the optimal ratio of THC and CBD for cancer pain.
- Many of the studies were very small, and, combined with cross-over design and consequent attrition, resulted in reporting on very few participants. Much larger studies of at least several hundred participants are needed.
- Prospective cohort studies incorporating initial randomisation but a pragmatic design in order to provide immediately relevant information on effectiveness and costs should complement randomised controlled trials.
- It is preferable that study protocols define that treating people with CbMs who do not have pain relief is unacceptable, so that there would be built-in stopping rules linked to pain relief after an adequate trial of therapy.
- Reporting the details of the assessment of adverse events (spontaneous reports, open questions, symptom questionnaires) is mandatory because the type and frequency of adverse events is influenced by the modes of assessment.

- Reporting of mean pain changes should be complemented using responder analyses (pain relief of 50% or greater or participants experiencing mild or no pain).
- Imputation method are to be abandoned, as the outcome desired is that of adequate pain relief in the longer term, and for that people have to continue on therapy. Withdrawal for any reason has to be classified as treatment failure.
- Study data have to be made available to review authors for individual participant data analyses.
- Systematic reviews should not pool experimental and clinical studies, or studies aimed to relieve pain arising as a direct consequence of the cancer with studies aimed to relieve cancer therapy-related pain.

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Dr Neil O'Connell, PaPaS Co-ordinating Editor, and Reader at Brunel University London.
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Thomas (review), Anna Erskine (protocol and review), Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford, UK.
- Contact Editor (editorial and methods input): Prof McKenzie Ferguson PharmD, BCPS, Southern Illinois University Edwardsville, USA.
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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Côté 2016

Study characteristics	
Methods	**Purpose of the study:** improving quality of life, especially pain, appetite and nausea, of people treated by radiotherapy or radiochemotherapy for head and neck squamous cell carcinomas **Study setting:** 1 university centre in Canada **Study period:** May 2005 to August 2007 **Study design:** double-blind, randomised, placebo-controlled, parallel-group design **Study duration:** 8 weeks (no data on washout period reported); 4 weeks' double-blind individually titrated dose, 4 weeks' follow-up
Participants	**Type of cancer:** head and neck squamous cell carcinoma **Inclusion criteria:** histological diagnosis of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or a combination of these; treated by radiotherapy alone, postoperative radiotherapy, radiochemotherapy alone, or postoperative radiochemotherapy; aged 18–80 years; no other cancer diagnosis in past 5 years, except for basal cell and squamous cell carcinoma of the skin **Exclusion criteria:** metastatic disease; history of radiotherapy in the head and neck region; Karnofsky score < 60; cognitive impairment; hepatic insufficiency; pregnant or breastfeeding woman; history of hypersensitivity or adverse reactions to marijuana or other CBs; history of schizophrenia or any other form of psychosis **Nabilone:** 28 participants; 93% men; mean age 63.5 years; race: not reported; type of cancer pain: not reported; previous cannabis use: not reported **Placebo:** 28 participants; 71% mean; mean age 63.8 years; race: not reported; type of cancer pain: not reported; previous cannabis use: not reported
Interventions	**Nabilone, PO, flexible dosage up to 2 mg/day:** administration began the day before the first radiotherapy treatment, with 1 tablet (0.5 mg PO at bedtime). The same dose was maintained for the entire first week (0.5 mg). For the second week, the dose was increased to 2 tablets a day (0.5 mg PO twice daily). From the third week until the end of radiotherapy treatments, the dose was adjusted by the radio-oncologist to a maximum of 4 tablets a day. **Placebo** **Rescue medication:** not reported

Côté 2016 *(Continued)*

	Allowed cotherapies: antiemetics (metoclopramide only) and analgesics (only paracetamol/codeine, hydromorphone or transdermal fentanyl) allowed. Dosages not reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Participant impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** VAS 0–10, time frame not reported. Imputation method could not be used because baseline values were not reported. **Pain relief ≥ 50%:** VAS 0–10, time frame not reported. Imputation method could not be used because baseline values were not reported. **Mean pain intensity:** VAS 0–10, time frame not reported. No means and SDs reported. **Sleep problems:** EORTC QLQ-C30 subscale sleep. No means and SDs reported. **Depression:** EORTC QLQ-C30 subscale mood. No means and SDs reported. **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported in detail **Nervous system disorders adverse effects:** no details of assessment reported **Psychiatric disorders adverse effects:** no details of assessment reported **Any serious adverse event:** no details of assessment reported
Notes	**Funding:** research grants from the Canadian Institutes of Health Research and the Fonds de Recherche en Santé du Québec. ICN Valeant Pharmaceuticals provided the nabilone and the placebo tablets during the trial. **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	Quote: "The physicians, nurse, and subjects were blinded: the hospital pharmacist was the only one who knew patients' grouping." Comment: no details of blinding reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Nabilone and placebo "both look identical."
Blinding of outcome assessment (detection bias)	Unclear risk	No details reported.

Côté 2016 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details reported if ITT was applied.
Selective reporting (reporting bias)	Unclear risk	No study protocol available.
Selection bias	Low risk	No differences in demographic and clinical parameters between the study groups at baseline.

Fallon 2017a

Study characteristics	
Methods	**Purpose of the study:** reducing cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy **Study setting:** 101 centres in Belgium, Bulgaria, Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, UK and US **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, parallel-group design **Study duration:** 6 weeks (2 weeks' double-blind individual titration, 3 weeks' double-blind stable individual dose, 1-week follow-up)
Participants	**Type of cancer:** not reported **Inclusion criteria:** aged ≥ 18 years; cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimised if 1. a dose increase was clinically inappropriate due to opioid-related adverse effects or 2. further efficacy benefit was not expected at higher doses (for the second definition, participants had to be receiving ≥ 90 mg morphine equivalents/day, inclusive of maintenance and breakthrough opioids). ≤ 4 opioid breakthrough analgesic episodes per day (mean over the 3 days), a stable maintenance opioid therapy dose, mean pain ≥ 4 and ≤ 8 on a 0–10 NRS and mean pain scores on the NRS that did not change by > 2 points from the beginning to end of screening (i.e. no more than a 2-point difference between the highest and lowest scores, with all scores remaining between 4 and 8). **Exclusion criteria:** baseline use of morphine at > 500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids), current use of > 1 type of breakthrough opioid analgesic, planned clinical interventions that would affect pain, and history of schizophrenia or substance abuse including recreational use of cannabis product. Any planned clinical interventions that would have affected their pain (e.g. chemotherapy or radiotherapy where, in the clinical judgement of the investigator, these would be expected to affect pain). The participant was using or had used cannabis or CB-based medications within 30 days of study entry and was unwilling to abstain for the duration of the study. The participant had experienced myocardial infarction or clinically significant cardiac dysfunction within the last 12 months or had a cardiac disorder that, in the opinion of the investigator, would have put the participant at risk of a clinically significant arrhythmia or myocardial infarction. Impaired renal or hepatic function. **THC/CBD:** 200 participants; 53% men; mean age 60.0 (SD 11.0) years; Caucasian 97%; type of cancer pain: neuropathic (13.5%), somatic (4.5%), visceral (10.5%), mixed (55.5%), bone (16.0%), other (0%); mean pain baseline 5.7 (SD 1.2); daily morphine equivalent maintenance 170.4 (SD 118.7) mg/day; daily breakthrough morphine equivalent 28.8 (SD 40.2) mg/day; previous cannabis use: not reported

Fallon 2017a *(Continued)*

	Placebo: 199 participants; 49% men; mean age 59.6 (SD 11.0) years; Caucasian 91%; type of cancer pain: neuropathic (11.6%), somatic (8.5%), visceral (11.1%), mixed (58.3%), bone (10.6%), other (0%); mean pain 5.8 (SD 1.1); daily morphine equivalent maintenance 182.4 (SD 124.3) mg/day; daily breakthrough morphine equivalent 25.3 (SD 38.1) mg/day; previous cannabis use: not reported
Interventions	**THC/CBD extract, oromucosal spray; flexible dosage:** THC 2.7 mg and CBD 2.5 mg, both per 100 µL (which equalled 1 pump action). Treatment was initiated as a single spray in the evening of the first day of treatment and was gradually increased by 1 additional spray/day (15 minutes apart) according to a prespecified dose escalation protocol until participants experienced/ unacceptable adverse effects, received acceptable pain relief or reached the maximum allowed daily dosage of 10 sprays/day (participants were advised to reach ≥ 3 sprays/day). Mean 6.3 sprays/day **Placebo, oromucosal spray:** mean 7.4 sprays/day **Rescue medication:** opioids **Allowed cotherapies:** not reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Participant impression to be much or very much improved:** Subject Global Impression of Change **Withdrawal due to adverse events:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Combined responder:** not assessed **Pain relief ≥ 30%:** NRS 0–10, last 24 hours. Calculated by imputation method **Pain relief ≥ 50%:** NRS 0–10, last 24 hours. Calculated by imputation method **Mean pain intensity:** NRS 0–10, last 24 hours **Sleep problems:** sleep disruption score 0–10, last 24 hours **Depression:** not assessed **Anxiety:** not assessed **Maintenance opioid therapy dose:** – **Breakthrough opioid therapy dose:** – **Withdrawals due to lack of efficacy:** not reported in detail **Nervous system disorders adverse effects:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Psychiatric disorders adverse effects:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Any serious adverse event:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit.
Notes	**Funding:** Otsuka Pharmaceutical Development & Commercialisation, Inc, Rockville, Maryland, USA **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Fallon 2017a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active product peppermint flavoured, placebo coloured and peppermint flavoured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis; no details reported.
Selective reporting (reporting bias)	Low risk	Data reported as outlined in NCT01361607.
Selection bias	Low risk	No differences in demographic and clinical variables between the study groups at baseline.

Fallon 2017b

Study characteristics	
Methods	**Purpose of the study:** reducing cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy **Study setting:** 65 centres in Australia, Bulgaria, Germany, Hungary, India, Israel, Italy, Lithuania, Poland, Romania, Spain, Taiwan and UK **Study period:** not reported **Study design:** double-blind, placebo-controlled, enriched enrolment randomised withdrawal design **Study duration:** 7 weeks (2 weeks' single-blind individual titration, 5 weeks' randomised withdrawal, 2 weeks' follow-up for safety evaluation)
Participants	**Type of cancer:** not reported **Inclusion criteria:** aged ≥ 18 years; cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimised if 1. a dose increase was clinically inappropriate due to opioid-related adverse effects or 2. further efficacy benefit was not expected at higher doses (for the second definition, participants had to be receiving ≥ 90 mg morphine equivalent/day, inclusive of maintenance and breakthrough opioids). ≤ 4 opioid breakthrough analgesic episodes/day (mean of the 3 days), a stable maintenance opioid therapy dose, mean pain ≥ 4 and ≤ 8 on a 0–10 NRS and mean pain scores on the NRS that did not change by > 2 points from the beginning to end of screening (i.e. ≤ 2-point difference between the highest and lowest scores, with all scores remaining between 4 and 8). **Exclusion criteria:** baseline use of morphine at > 500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids), current use of > 1 type of breakthrough opioid analgesic, planned

Fallon 2017b *(Continued)*

	clinical interventions that would affect pain and any history of schizophrenia or substance abuse including recreational use of cannabis product. Any planned clinical interventions that would have affected their pain (e.g. chemotherapy or radiotherapy where, in the clinical judgement of the investigator, these would be expected to affect pain). The participant was using or had used cannabis or CB-based medications within 30 days of study entry and was unwilling to abstain for the duration of the study. The participant had experienced myocardial infarction or clinically significant cardiac dysfunction within the last 12 months or had a cardiac disorder that, in the opinion of the investigator, would have put the participant at risk of a clinically significant arrhythmia or myocardial infarction. Impaired renal or hepatic function. **THC/CBD:** 103 participants; 61.2% men; mean age 61.4 (SD 10.9) years; Caucasian 99.1%; type of cancer pain: neuropathic (10.7%), somatic (8.7%), visceral (11.7%), mixed (54.4%), bone (13.6%), other (1.0%); mean pain baseline 5.6 (SD 1.1); daily morphine equivalent maintenance 185.5 (SD 123.7) mg/day; daily breakthrough morphine equivalent 26.8 (SD 36.1) mg/day; previous cannabis use: not reported **Placebo:** 103 participants; 53.4% men; mean age 61.6 (SD 11.8) years; Caucasian 98.1%; type of cancer pain: neuropathic (11.7%), somatic (5.8%), visceral (7.8%), mixed (52.4%), bone (19.4%), other (2.9%); mean pain 5.6 (SD 1.2); daily morphine equivalent maintenance 175.3 (SD 106.5) mg/day; daily breakthrough morphine equivalent 34.0 (SD 48.5) mg/day; previous cannabis use: not reported
Interventions	**THC/CBD extract, oromucosal spray; flexible dosage:** THC 2.7 mg and CBD 2.5 mg, both per 100 µL (which equalled 2 pump action). Treatment was initiated as a single spray in the evening of the first day of treatment and was gradually increased by 1 additional spray/day (15 minutes apart) according to a prespecified dose escalation protocol until participants experienced unacceptable adverse effects, received acceptable pain relief or reached the maximum allowed daily dosage of 10 sprays/day (participants were advised to reach ≥ 3 sprays/day). Mean 6.5 sprays/day in double-blind phase **Placebo, oromucosal spray:** mean 6.3 sprays/day in double-blind period **Rescue medication:** opioids **Allowed cotherapies:** not reported
Outcomes	**Loss of proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Loss of therapeutic response of patient impression to be much or very much improved:** authors reported mean Subject Global Impression of Change scores. Not suited for meta-analysis. **Withdrawal due to adverse events:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Combined responder:** not assessed **Loss of pain relief ≥ 30%:** not assessed **Pain relief ≥ 50%:** not assessed **Mean pain intensity:** NRS 0–10, last 24 hours **Sleep problems:** Sleep Disruption Score 0–10, last 24 hours **Depression:** not assessed **Anxiety:** not assessed **Maintenance opioid therapy dose:** reported **Breakthrough opioid therapy dose:** reported **Withdrawals due to lack of efficacy:** not reported in detail

Fallon 2017b *(Continued)*

	Nervous system disorders adverse effects: no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Psychiatric disorders adverse effects:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Any serious adverse event:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit.
Notes	**Funding:** Otsuka Pharmaceutical Development & Commercialisation, Inc, Rockville, Maryland, USA **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active product peppermint flavoured, placebo coloured and peppermint flavoured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis; no details reported.
Selective reporting (reporting bias)	Low risk	Data reported as outlined in NCT01424566.
Selection bias	Low risk	No differences in demographic and clinical variables between the study groups at baseline.

Hardy 2023

Study characteristics

Methods	**Purpose of the study:** to determine whether CBD oil can improve symptom distress in people with advanced cancer receiving palliative care. **Study setting:** 5 tertiary medical centres within south-east Queensland, Australia **Study period:** February 2019 to November 2021 **Study design:** double-blind, randomised, placebo-controlled, parallel-group design

Hardy 2023 *(Continued)*

	Study duration: no information on baseline period reported, 4 weeks' double-blind
Participants	**Type of cancer:** prostate 21%, breast 16%, colorectal 15%, gynaecological 13%, lung 9%, haematological 5%, others 22% **Inclusion criteria:** aged > 18 years, with advanced cancer who had a TSDS as measured using an ESAS 8 of ≥ 10/90 (with ≥ 1 score ≥ 3), a negative baseline THC urine test, Australian-modified Karnofsky Performance Scale ≥ 30, adequate cognitive function (as assessed using the St Louis University Mental Status Examination) and were able to take oral medications. **Exclusion criteria:** severe hepatic or renal dysfunction, history of significant psychiatric or substance use disorder (as assessed by the Alcohol, Smoking and Substance Involvement Screening Test) and the potential for drug diversion or a new anticancer therapy or radiotherapy within 7 days. **CBD:** 70 participants; 56% men; mean age 63.6 (SD 14.0) years; race not reported; type of cancer pain: not reported; pain medication: background opioid dose 45 mg (OMEs) median (range 0–590); previous cannabis use: not reported **Placebo:** 72 participants; 50% men; mean age 65.5 (SD 11.4) years; race not reported; type of cancer pain: not reported; pain medication: background opioid dose 40 mg (OMEs) median (range 0–555); previous cannabis use: not reported
Interventions	**CBD:** 50–600 mg/day PO, flexible dosage (median dose 400 mg/day, range 50–600 mg/day) **Placebo:** PO, flexible dosage **Rescue medication:** no details reported **Allowed cotherapies:** antipsychotics: CBD group 19%; placebo group 22%; benzodiazepines: CBD group 30%; placebo group 39%
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** EORTC QLQ-C15, score 0–100, time frame last week; calculated by imputation method **Pain relief ≥ 50%:** EORTC QLQ-C15, score 0–100, time frame last week; calculated by imputation method **Mean pain intensity:** EORTC QLQ-C15, score 0–100, time frame last week; calculated by imputation method **Sleep problems:** EORTC QLQ-C15, score 0–100, time frame last week; scores at baseline and end of treatment not reported **Depression:** Depression Anxiety Stress Scale 0–42 **Anxiety:** Depression Anxiety Stress Scale 0–42 **Daily maintenance and breakthrough opioid therapy dose combined:** assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** only somnolence and dizziness reported **Psychiatric disorders adverse effects:** not reported

Hardy 2023 *(Continued)*

	Any serious adverse event: reported
Notes	**Funding:** Commonwealth of Australia–Medical Research Future Fund Grant No. APP1152232 **Conflicts of interest:** 2 authors received funding from GD Pharma Ltd (Inst).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Any effect of dropouts was evaluated using Cox proportional hazards regression."
Selective reporting (reporting bias)	Low risk	Outcomes reported as outlined in ACTRN 126180001220257.
Selection bias	High risk	Quote: "Those randomly assigned to placebo had a higher baseline total symptom distress score than those on CBD oil."

Jochimsen 1978

Study characteristics

Methods	**Purpose of the study:** to assess the analgesic activity of a synthetic THC analogue at 2–4 mg **Study setting:** 1 university hospital in USA **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** 1 day each. Regular medication was stopped 4 hours before the intake of the medication
Participants	**Type of cancer:** no details reported **Inclusion criteria:** pain related to malignancies and history of frequent analgesic use, though 1 had received large doses of narcotics **Exclusion criteria:** conditions interfering with drug metabolism, severe organic disease other than cancer, pregnancy or major psychiatric disorders

Jochimsen 1978 *(Continued)*

	Synthetic THC analogue: 35 participants; 17% men; aged 38–77 years; race: not reported; type of cancer pain: not reported; pain medication: not reported; previous cannabis use: not reported
Interventions	**Synthetic nitrogen-containing benzopyran derivative (modification of delta-I-trans-THC):** 2 mg and 4 mg single, fixed dosage PO **Codeine:** 60 mg and 120 mg single, fixed dosage PO **Placebo:** PO **Rescue medication:** none **Allowed cotherapies:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** not reported; imputation method not applicable because baseline pain scores not reported. Number of participants with moderate pain relief reported **Pain relief ≥ 50%:** reported **Mean pain intensity:** hourly ratings of the severity of pain (0, absent; 1, mild; 2, moderate; 3, severe) were used to determine hourly pain reduction scores **Sleep problems:** not assessed **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** at hourly intervals, the participant completed an 11-item subjective effects questionnaire, designed to quantify certain psychic manifestations of the test preparations. Data provided not suited for analysis. **Psychiatric disorders adverse effects:** at hourly intervals, the participant completed an 11-item subjective effects questionnaire, designed to quantify certain psychic manifestations of the test preparations. Data provided not suited for analysis. **Any serious adverse event:** not assessed
Notes	**Funding:** grant RR-59 from the General Clinical Research Canters Program Division of Research Resources, National Institutes of Health and Abbott Laboratories. **Conflicts of interest:** not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.

Jochimsen 1978 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical appearing capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Responder analysis.
Selective reporting (reporting bias)	Unclear risk	No prepublished study protocol available.
Selection bias	Low risk	Identical baseline parameters of the study groups due to cross-over design.

Johnson 2010

Study characteristics	
Methods	**Purpose of the study:** reducing moderate-to-severe cancer-related pain despite therapy with strong opioids **Study setting:** 20 study centres in UK and Romania **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, parallel-group design **Study duration:** 2 days' baseline, 2 weeks' double-blind
Participants	**Type of cancer:** breast, prostate, lung **Inclusion criteria:** adults using strong opioids ≥ 1 week to relieve pain associated with incurable malignancy, pain severity score ≥ 4 on a 0–10 NRS on both days of the baseline period **Exclusion criteria:** cancers affecting the oral cavity; radiotherapy to the floor of the mouth; major psychiatric or cardiovascular disorders; epilepsy; renal or hepatic impairment; or pregnant, lactating or not using adequate contraception. Participants who received therapies expected to confound the study outcome (epidural analgesia within 48 hours of screening; palliative radio-, chemo-, or hormonal therapy within 2 weeks of screening; or CBs within 7 days of randomisation). Participants taking levodopa, sildenafil or fentanyl, or participants with a hypersensitivity to CBs **THC/CBD:** 60 participants; 55% men; mean age 59.4 (SD 12.1) years; Caucasian 98%; type of cancer pain: neuropathic (18%), somatic (11%), visceral (23%), mixed (52%), bone (27%), other (0%): mean pain 5.7 (SD 1.2); daily morphine equivalent maintenance 258 (789) mg/day; daily breakthrough morphine equivalent: not reported; previous cannabis use: 10% **THC:** 58 participants; 52% men; mean age 61.3 (SD 12.5) years; Caucasian 98%; type of cancer pain: neuropathic (19%), somatic (9%), visceral (21%), mixed (48%), bone (41%), other (0%): mean pain 5.6 (SD 1.2); daily morphine equivalent maintenance 188.2 (243.5) mg/day; daily breakthrough morphine equivalent: not reported; previous cannabis use: 10%

Johnson 2010 *(Continued)*

	Placebo: 59 participants; 54% men; mean age 60.1 (SD 12.3) years; Caucasian 98%; type of cancer pain: neuropathic (29%), somatic (10%), visceral (19%), mixed (51%), bone (42%), other (0%): mean pain 5.6 (SD 1.2); daily morphine equivalent maintenance 367 (886.4) mg/day; daily breakthrough morphine equivalent: not reported; previous cannabis use: 12%
Interventions	**THC/CBD extract; oromucosal spray; flexible dosage:** THC 2.7 mg and CBD 2.5 mg, both per 100 µL (which equalled 1 pump action). Mean 8.8 sprays/day **THC extract (plant-based), oromucosal spray flexible dosage:** THC 2.7 mg/100 µL. Mean 8.4 sprays/day **Placebo, oromucosal spray:** mean 9.1 sprays/day **Rescue medication:** no details reported **Allowed cotherapies:** usual breakthrough analgesia as required (recorded) maintained background medication as necessary
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** adverse events as reported by the participant **Combined responder:** not assessed **Pain relief ≥ 30%:** NRS 0–10, last 24 hours (mean of 3 ratings). **Pain relief ≥ 30%:** NRS 0–10, last 24 hours. Extracted from figure **Mean pain intensity:** NRS 0–10, last 24 hours (mean of 3 ratings) **Sleep problems:** Sleep Disruption Score 0–10, last 24 hours **Depression:** not assessed **Anxiety:** not assessed **Maintenance opioid therapy dose:** mean change from baseline **Breakthrough opioid therapy dose:** baseline to end of week 2 (last 3 days of treatment) **Withdrawals due to lack of efficacy:** not reported in detail **Nervous system disorders adverse effects:** participant-reported adverse events **Psychiatric disorders adverse effects:** participant-reported adverse events **Any serious adverse event:** participant-reported adverse events. Study physicians determined the intensity of adverse events
Notes	**Funding:** Otsuka Pharmaceutical Development & Commercialisation, Inc, Rockville, Maryland, USA **Conflicts of interest:** study authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.

Johnson 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo was only coloured, no taste blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis; no details reported.
Selective reporting (reporting bias)	Low risk	Data reported as outlined in NCT00674609.
Selection bias	High risk	Higher morphine dose in THC and placebo compared to THC/CBD group at baseline.

Lichtman 2018

Study characteristics	
Methods	**Purpose of the study:** reducing cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy **Study setting:** 114 centres in the Czech Republic, Estonia, Germany, Hungary, Latvia, Lithuania, Poland, Romania, UK, and US **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, parallel-group design **Study duration:** 5–14 days' screening, 4 weeks' double-blind (2 weeks' titration, 3 weeks' stable dosage)
Participants	**Type of cancer:** not reported **Inclusion criteria:** advanced cancer, aged ≥ 18 years, clinical diagnosis of cancer-related pain that was unalleviated by an optimised maintenance dose of Step 3 opioid therapy. Opioid therapy was considered optimised if: 1. a dose increase was clinically inappropriate due to opioid-related adverse effects or 2. further efficacy benefit was not expected at higher doses (for the second definition, participants had to be receiving ≥ 90 mg morphine equivalents/day, inclusive of maintenance and breakthrough opioids). The maintenance opioid was preferably a sustained-release formulation, but a 24-hour immediate-release formulation was acceptable. To be eligible, participants also had to fulfil the following criteria on each of 13 consecutive days during the screening period: ≤ 4 opioid breakthrough analgesic episodes/day (mean over 3 days); a stable maintenance opioid therapy dose; mean pain ≥ 4 and ≤ 8 on a 0–10 NRS; and mean pain scores on the NRS that did not change by > 2 points (i.e. ≤ 2-point difference between the highest and lowest scores), with all scores remaining between 4 and 8. **Exclusion criteria:** baseline use of morphine at > 500 mg morphine equivalents/day (inclusive of maintenance and breakthrough opioids), current use of > 1 type of breakthrough opioid analgesic, planned clinical interventions that would affect pain, and any history of schizophrenia or substance abuse. Any planned clinical interventions that would have affected their pain (e.g. chemotherapy or radiotherapy) where, in the clinical judgement of the investigator, these would be expected to affect pain. The

Lichtman 2018 *(Continued)*

	participant was using or had used cannabis or CB-based medications within 30 days of study entry and was unwilling to abstain for the duration of the study. The participant had experienced myocardial infarction or clinically significant cardiac dysfunction within the last 12 months or had a cardiac disorder that, in the opinion of the investigator, would have put the participant at risk of a clinically significant arrhythmia or myocardial infarction, impaired renal or hepatic function. **THC/CBD:** 199 participants; 55.8% men; mean age 59.2 (SD 12.0) years; Caucasian 93.0%; type of cancer pain: neuropathic (13.1%), somatic (5.0%), visceral (13.1%), mixed (48.2%), bone (19.6%), other (1.0%); mean pain 5.6 (SD 1.2); daily morphine equivalent maintenance 167.5 (SD 118.8) mg/day; daily breakthrough morphine equivalent 25.4 (SD 38.3); previous cannabis use: not reported **Placebo:** 198 participants; 52.0% men; mean age 60.7 (SD 11.1) years; Caucasian 93.4%; type of cancer pain: neuropathic (12.6%), somatic (3.0%), visceral (14.1%), mixed (54.0%), bone (16.2%), other (0%): mean pain 5.6 (SD 1.2); daily morphine equivalent maintenance 159.7 (SD 121.2) mg/day; daily breakthrough morphine equivalent 26.4 (SD 40.4); previous cannabis use: not reported
Interventions	**THC/CBD extract, oromucosal spray, flexible dosage:** THC 2.7 mg and CBD 2.5 mg, both per 100 µL (which equalled 1 pump action). Mean spray in nabiximols group: 6.4 sprays/day **Placebo, oromucosal spray:** mean spray in nabiximols group: 7.3 sprays/day **Rescue medication:** opioids **Allowed cotherapies:** (quote) "Whenever possible, stable doses of other prescribed pain medications were continued during the study period."
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** PGIC **Withdrawal due to adverse events:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Combined responder:** not assessed **Pain relief ≥ 30%:** NRS 0–10, last 24 hours **Pain relief ≥ 30%:** NRS 0–10, last 24 hours. Calculated by imputation method **Mean pain intensity:** NRS 0–10, last 24 hours **Sleep problems:** Sleep Disruption Score 0–10, last 24 hours **Depression:** not assessed **Anxiety:** not assessed **Maintenance opioid therapy dose:** mg/day **Breakthrough opioid therapy dose:** mg/day. SD calculated from P value **Withdrawals due to lack of efficacy:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Nervous system disorders adverse effects:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit. **Psychiatric disorders adverse effects:** no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit.

Lichtman 2018 *(Continued)*

	Any serious adverse event: no details of assessment reported except that participants completed the Columbia Suicide Severity Rating Scale at every visit and that laboratory tests and vital signs reading were performed at every study visit.
Notes	**Sponsor:** Otsuka Pharmaceutical Development & Commercialisation, Inc, Rockville, Maryland, USA. The efforts of AH Lichtman were supported by the Virginia Commonwealth University School of Pharmacy start-up funds. **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis by last observation carried forward method.
Selective reporting (reporting bias)	Low risk	All outcomes reported as outlined in NCT01262651.
Selection bias	Low risk	No differences in demographic and clinical variables between the study groups at baseline.

Lynch 2014

Study characteristics

Methods	**Purpose of the study:** reducing chemotherapy-induced neuropathic pain **Study setting:** participants were recruited through advertisements in the local paper and posters in oncology clinics at the university teaching hospital (Capital District Health Authority, Halifax, Nova Scotia, Canada) **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** no information on baseline period reported, 4 weeks each study period separated by a 2-week wash-out period
Participants	**Type of cancer:** ovary cancer (27.8%), uterus cancer (16.7%), lung cancer (16.7%), cervix cancer (11.1%), breast cancer (11.1%), blood/lymphoma (5.6%), lung cancer (5.6%), testicle cancer (5.6%)

Lynch 2014 *(Continued)*

	Inclusion criteria: neuropathic pain based on history and general physical examination along with specific quantitative sensory testing of the painful area; neuropathic pain persisting for 3 months after completing chemotherapy with paclitaxel, vincristine or cisplatin; mean 7-day intensity of pain had to be ≥ 4 on an 11-point NRS; concurrent analgesics had to be stable for 14 days before entry into the trial. **Exclusion criteria:** ischaemic heart disease, ongoing epilepsy, a personal or family history of schizophrenia, or psychotic disorder or substance abuse or dependency within the previous 2 years, pregnancy or other medical condition that might compromise safety in the trial. **Nabiximols and placebo:** 18 participants; 17% men; mean age 55 years; race not reported; type of cancer pain: neuropathic pain induced by chemotherapy; co-medication: antidepressants (5.6%), NSAIDs (11.1%), opioids (11.1%); previous cannabis use: 27.8%
Interventions	**Oromucosal spray THC/CBD extract, flexible dosage:** THC 2.7 mg and CBD 2.5 mg, both per 100 µL (which equalled 1 pump action). Individually titration, maximum 12 pumps/day; mean 8 sprays/day (range 8–12) **Oromucosal placebo spray, flexible dosage:** individual titration, maximum 12 pumps/ day; mean 11 sprays/day **Rescue medication:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** neuropathic pain score 7-day mean; calculated by imputation method **Pain relief ≥ 50%:** neuropathic pain score 7-day mean; calculated by imputation method **Mean pain intensity:** neuropathic pain score 7-day mean **Sleep problems:** not assessed **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** no details of assessment reported **Psychiatric disorders adverse effects:** no details of assessment reported **Any serious adverse event:** no details of assessment reported
Notes	**Funding:** none **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement

Lynch 2014 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Last observation carried forward analysis.
Selective reporting (reporting bias)	Unclear risk	No study protocol reported.
Selection bias	Low risk	Identical baseline data of the study groups due to cross-over design.

Noyes 1975a

Study characteristics	
Methods	**Purpose of the study:** reducing moderate-to-severe cancer pain **Study setting:** 1 university hospital in USA **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** 1 day each. Regular medication was stopped 4.5 hours before the intake of the medication
Participants	**Type of cancer:** 13 breast, 7 non-Hodgkin's lymphoma, 3 Hodgkin's disease, 2 each lung, colon, prostate and malignant melanoma, and 1 each cervix, carcinoid, leiomyosarcoma, parotid gland and anaplastic carcinoma of unknown origin **Inclusion criteria:** continuous pain of moderate severity **Exclusion criteria:** none **Synthetic THC:** 36 participants; 28% men; mean age 51 years; race: not reported; type of cancer pain: not reported; pain medication: (quote) "None were receiving large doses of narcotics;" previous cannabis use: not reported
Interventions	**Synthetic THC, fixed dosage:** 10 mg and 20 mg single dosage PO **Codeine, fixed dosage:** 120 mg single dosage PO **Placebo** **Rescue medication:** none

Noyes 1975a *(Continued)*

	Allowed cotherapies: no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** not reported; imputation method not applicable because baseline pain scores not reported **Pain relief ≥ 50%:** not reported; imputation method not applicable because baseline pain scores not reported. Number of participants with substantial pain relief reported **Mean pain intensity:** hourly ratings of the severity of pain (0, absent; 1, mild; 2, moderate; 3, severe) were used to arrive at hourly pain reduction scores. The sum of hourly pain reduction or relief scores for a given 7-hour observation period (total reduction or relief scores) was used as a basis for statistical analysis. **Sleep problems:** not assessed **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** the nurse's observations, including evident or reported adverse effects, were recorded on a pain chart designed for that purpose. The same observer also administered an 11-item subjective effects questionnaire hourly and an adverse effects inventory at the end of each 7-hour observation period. **Psychiatric disorders adverse effects:** the nurse's observations, including evident or reported adverse effects, were recorded on a pain chart designed for that purpose. The same observer also administered an 11-item subjective effects questionnaire hourly and an adverse effects inventory at the end of each 7-hour observation period. **Any serious adverse event:** not reported
Notes	**Funding:** grant RR-59 from the General Clinical Research Canters Program Division of Research Resources. National Institute of Health. **Conflicts of interest:** not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.

Noyes 1975a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis.
Selective reporting (reporting bias)	Unclear risk	No pre-published protocol available.
Selection bias	Low risk	Identical baseline data of the study groups due to cross-over design.

Noyes 1975b

Study characteristics	
Methods	**Purpose of the study:** reducing moderate-to-severe cancer pain **Study setting:** 1 university hospital in USA **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** 1 day each. Regular medication was stopped 4.5 hours before the intake of the medication
Participants	**Type of cancer:** 5 breast, 2 malignant lymphoma, 1 cervix, 1 colon and 1 lymphoepithelioma **Inclusion criteria:** continuous pain of moderate severity **Exclusion criteria:** participants receiving large doses of narcotics **Synthetic THC analogue:** 10 participants; 20% men; mean age 51 years; race not reported; type of cancer pain: not reported; pain medication: (quote) "None were receiving large doses of narcotics." 7 participants had received methadone as part of their regular analgesic regimen. Previous cannabis use: not reported
Interventions	**Synthetic THC analogue, fixed dosage:** 5 mg, 10 mg, 15 mg and 20 mg single dosage PO **Placebo:** single dose, PO **Rescue medication:** none **Allowed cotherapies:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported

Noyes 1975b *(Continued)*

Combined responder: not assessed

Pain relief ≥ 30%: not reported; imputation method not applicable because baseline pain scores not reported

Pain relief ≥ 50%: not reported; imputation method not applicable because baseline pain scores not reported. Number of participants with substantial pain relief reported

Mean pain intensity: hourly ratings of the severity of pain (0, absent; 1, mild; 2, moderate and 3, severe) were used to arrive at hourly pain reduction scores. The sum of hourly pain reduction or relief scores for a given 7-hour observation period (total reduction or relief scores) was used as a basis for statistical analysis.

Sleep problems: not assessed

Depression: not assessed

Anxiety: not assessed

Daily maintenance opioid therapy dose: not assessed

Daily breakthrough opioid therapy dose: not assessed

Withdrawals due to lack of efficacy: not reported

Nervous system disorders adverse effects: the nurse's observations, including evident or reported adverse effects, were recorded on a pain chart designed for that purpose. The same observer also administered an 11-item subjective effects questionnaire hourly and an adverse effects inventory at the end of each 7-hour observation period.

Psychiatric disorders adverse effects: the nurse's observations, including evident or reported adverse effects, were recorded on a pain chart designed for that purpose. The same observer also administered an 11-item subjective effects questionnaire hourly and an adverse effects inventory at the end of each 7-hour observation period.

Any serious adverse event: not reported

Notes

Funding: grant RR-59 from the General Clinical Research Canters Program Division of Research Resources. National Institutes of Health

Conflicts of interest: not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.

Noyes 1975b *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis.
Selective reporting (reporting bias)	Unclear risk	No prepublished protocol available.
Selection bias	Low risk	Identical baseline data of the study groups due to cross-over design.

Portenoy 2012

Study characteristics	
Methods	**Purpose of the study:** to reduce moderate-to-severe cancer pain despite stable opioid regimen **Study setting:** USA, number of study centres not reported **Study period:** not reported **Study design:** randomised, double-blind, placebo-controlled, parallel group, graded-dose design **Study duration:** 5- to 14-day baseline period, a 5-week double-blind titration and treatment period, and a poststudy visit after 2 weeks. Maximum duration 9 weeks
Participants	**Inclusion criteria:** active cancer and chronic pain that was moderate or severe despite a stable opioid regimen that could not be made more effective by further opioid dose titration **Type of cancer:** breast, gastrointestinal, lung, prostate, other **Exclusion criteria:** receiving long-term methadone therapy for pain, major psychiatric or cardiovascular disorder, epilepsy, or significant renal or hepatic impairment, pregnancy, lactating or not using adequate contraception, had received or were to receive radiotherapy, chemotherapy or hormonal therapy, usage of marijuana, CB-based medications or rimonabant within 30 days of study entry unwilling to abstain for the duration of the study **Oromucosal spray; THC:CBD extract:** THC 2.7 mg and CBD 2.5 mg **Low-dose group:** 91 participants; 49.4% men; mean age 59 (SD 12.3) years; Caucasian 73.6%, Black 12.1%, Hispanic 11.0%, Asian 0%, other 3.3%; type of cancer pain: neuropathic (8.8%), somatic (1.1%), visceral (22.0%), mixed (46.2%), bone (22.0%), other (0%); mean pain 5.8 (SD 1.3); daily morphine equivalent maintenance 120 mg/day; daily breakthrough morphine equivalent not reported; previous cannabis use: 12.1% **Medium-dose group:** 88 participants; 55.7% men; mean age 59 (SD 13,1) years; Caucasian 84.1%, Black 6.8%, Hispanic 8.0%, Asian 1.1%, other 0%. Type of cancer pain: neuropathic (13.6%), somatic (14.8%), visceral (12.5%), mixed (42.0%), bone (17.0%), other (0%); mean pain 5.8 (SD 1.2); daily morphine equivalent maintenance 120 mg/day; daily breakthrough morphine equivalent not reported; previous cannabis use 12.5% **High-dose group:** 90 participants; 53.3% men; mean age 58 (SD 11.2) years; Caucasian 75.6%, Black 11.1%, Hispanic 7.8%, Asian 1.1%, Other 4.4%; type of cancer pain: neuropathic (7.8%), somatic (7.8%), visceral (11.1%), mixed (35.6%), bone (37.8%), other (0%); mean pain 5.8 (SD 1.2); daily morphine equivalent maintenance 180 mg/day; daily breakthrough morphine equivalent not reported; previous cannabis use: 11.1% **Placebo:** 91 participants, 48.3% men; mean age 56 (SD 12.2) years; Caucasian 75.8%, Black 6.6%, Hispanic 13.2%, Asian 0%, Other 4.4%; type of cancer pain: neuropathic (12.1%), somatic (12.1%), visceral (14.3%), mixed (42.9%), bone (18.7%), other (0%); mean pain 5.7 (SD 1.2); daily morphine equivalent

Portenoy 2012 *(Continued)*

	maintenance 120 mg/day; daily breakthrough morphine equivalent not reported; previous cannabis use: 6.6%
Interventions	**THC/CBD extract 2.7 mg/2.5 mg, oromucosal spray, flexible dosage:** low-dose group: 1–4 actuations/day; medium-dose group: 6–10 actuations/day, high-dose group: 11–16 actuations/day **Placebo, oromucosal spray:** 1–16 actuations/day; flexible dosage **Rescue medication:** not reported **Allowed cotherapies:** all opioids typically used for severe cancer pain except for methadone were allowed.
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** PGIC **Withdrawal due to adverse events:** adverse events as reported by the participant **Combined responder:** not assessed **Pain relief ≥ 30%:** BPI-SF NRS 0–10, daily **Pain relief ≥ 50%:** BPI-SF NRS 0–10, daily. Calculated by imputation method. **Mean pain intensity:** BPI-SF NRS 0–10, daily **Sleep problems:** Sleep Disruption Score 0–10, last 24 hours **Depression:** Montgomery Åsberg Depression Rating Scale **Anxiety:** not assessed **Maintenance opioid therapy dose:** assessed, but not reported in detail. Data not suited for meta-analysis **Breakthrough opioid therapy dose:** assessed, but not reported in detail. Data not suited for meta-analysis **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** participant-reported adverse events **Psychiatric disorders adverse effects:** participant-reported adverse events **Any serious adverse event:** participant-reported serious adverse events
Notes	**Funding:** in part by the Huntsman Cancer Foundation (S.W.). GW Pharmaceuticals produces nabiximols, which is licenced in Canada as an adjunctive analgesic treatment in adults with advanced cancer. GW Pharmaceuticals and Otsuka funded the study. **Conflicts of interest:** not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by computer using a block approach.
Allocation concealment (selection bias)	Unclear risk	No details provided.

Portenoy 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo was similar colour, no adjustment for taste described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis by last observation carried forward.
Selective reporting (reporting bias)	Low risk	NCT00530764.
Selection bias	High risk	Number of participants with previous cannabis use double in all nabiximols groups as in placebo groups.

Staquet 1978a

Study characteristics	
Methods	**Purpose of the study:** reducing moderate-to-severe cancer pain **Study setting:** 1 university hospital in Belgium **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** 1 day each. Regular medication was stopped 3 hours before the intake of the medication
Participants	**Type of cancer:** no details reported **Inclusion criteria:** continuous moderate-to-severe pain for ≥ 3 days at time of admission to study **Exclusion criteria:** receiving large doses of narcotics, insufficient mental clarity to judge discomfort or relief, serious gastrointestinal pathology, renal and hepatic diseases susceptible to interfere with drug metabolism or excretion **Synthetic THC:** 30 participants; gender not reported; aged 21–75 years; race not reported; type of cancer pain: not reported; pain medication: not reported; previous cannabis use: not reported
Interventions	**Synthetic nitrogen-containing benzopyran derivative (which is a modification of delta-I-trans-THC):** 4 mg single dose, fixed dosage PO **Codeine:** 50 mg single dose, fixed dosage **Placebo** **Rescue medication:** none **Allowed cotherapies:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed

Staquet 1978a *(Continued)*

	Patient impression to be much or very much improved: not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** not reported; imputation method not applicable because baseline pain scores not reported **Pain relief ≥ 50%:** not reported; imputation method not applicable because baseline pain scores not reported **Mean pain intensity:** hourly ratings of the severity of pain (0, absent; 1, mild; 2, moderate; 3, severe) were used to arrive at hourly pain reduction scores. The sum of hourly pain reduction or relief scores for a given 6-hour observation period (total reduction or relief scores) was used as a basis for statistical analysis. **Sleep problems:** not assessed **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** reports on drowsiness without providing information how the symptoms were assessed **Psychiatric disorders adverse effects:** not assessed **Any serious adverse event:** not assessed
Notes	**Funding:** not reported **Conflicts of interest:** not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis.

Staquet 1978a *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No prepublished study protocol available.
Selection bias	Low risk	Identical baseline data of the study groups due to cross-over design.

Staquet 1978b

Study characteristics	
Methods	**Purpose of the study:** reducing moderate-to-severe cancer pain **Study setting:** 1 university hospital in Belgium **Study period:** not reported **Study design:** double-blind, randomised, placebo-controlled, cross-over design **Study duration:** 1 day each. Regular medication was stopped 3 hours before the intake of the medication
Participants	**Type of cancer:** no details reported **Inclusion criteria:** continuous moderate-to-severe pain for ≥ 3 days at time of admission to study **Exclusion criteria:** receiving large doses of narcotics, insufficient mental clarity to judge discomfort or relief, serious gastrointestinal pathology, renal and hepatic diseases susceptible to interfere with drug metabolism or excretion **Synthetic THC:** 15 participants; gender not reported; aged 21–75 years; race not reported; type of cancer pain: not reported; pain medication: not reported; previous cannabis use: not reported
Interventions	**Synthetic nitrogen-containing benzopyran derivative (modification of delta-I-trans-THC):** 4 mg single dose, fixed dosage PO **Secobarbital:** 50 mg single dose, fixed dosage (not used for comparison, because secobarbital is not used for cancer pain treatment) **Placebo** **Rescue medication:** none **Allowed cotherapies:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** not reported; imputation method not applicable because baseline pain scores not reported **Pain relief ≥ 50%:** not reported; imputation method not applicable because baseline pain scores not reported **Mean pain intensity:** hourly ratings of the severity of pain (0, absent; 1, mild; 2, moderate; 3, severe) were used to arrive at hourly pain reduction scores. The sum of hourly pain reduction or relief scores

Staquet 1978b *(Continued)*

	for a given 6-hour observation period (total reduction or relief scores) was used as a basis for statistical analysis **Sleep problems:** not assessed **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** reports on drowsiness without information how the symptoms were assessed **Psychiatric disorders adverse effects:** not assessed **Serious adverse events:** not reported
Notes	**Funding:** not reported **Conflicts of interest:** not declared

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Identical capsules."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Completer analysis.
Selective reporting (reporting bias)	Unclear risk	No prepublished study protocol available.
Selection bias	Low risk	Identical baseline data of the study groups due to cross-over design.

Turcott 2018

Study characteristics

Turcott 2018 *(Continued)*

Methods	**Purpose of the study:** improvement of appetite, nutritional status and quality of life in people with lung cancer undergoing chemotherapy or targeted therapy **Study setting:** 1 outpatient clinic at the National Institute of Cancer Mexico **Study period:** December 2013 to December 2015 **Study design:** double-blind, randomised, placebo-controlled, parallel-group design **Study duration:** no information on baseline period reported, 8 weeks' double-blind
Participants	**Type of cancer:** histologically confirmed advanced NSCLC **Inclusion criteria:** adults with histologically confirmed advanced NSCLC, regardless of current therapeutic scheme, with a good performance status (ECOG 0–2), diagnosed with anorexia **Exclusion criteria:** known allergy or contraindication for receiving CBs, previously received treatment with CBs, and previously received any other pharmacological treatment for anorexia **Nabilone:** 14 participants; 21% men; mean age 61.1 (SD 10.6) years; race not reported; type of cancer pain: not reported; pain medication: not reported; previous cannabis use: not reported **Placebo:** 19 participants; 21% men; mean age 52.6 (SD 11.8) years; race not reported; type of cancer pain: not reported; pain medication: not reported; previous cannabis use: not reported
Interventions	**Nabilone:** 1.0 mg/day PO, fixed dosage **Placebo:** PO, fixed dosage **Rescue medication:** no details reported **Allowed cotherapies:** no details reported
Outcomes	**Proportion of participants reporting no worse than mild pain on treatment at 14 days after start of treatment (typically < 30/100 mm on a 100-mm VAS or < 3 on an 11-point NRS):** not assessed **Patient impression to be much or very much improved:** not assessed **Withdrawal due to adverse events:** no details of assessment reported **Combined responder:** not assessed **Pain relief ≥ 30%:** VAS 0–100, time frame not reported; calculated by imputation method **Pain relief ≥ 50%:** VAS 0–100, time frame not reported; calculated by imputation method **Mean pain intensity:** VAS 0–100, time frame not reported **Sleep problems:** EORTC-QLQ-C30 and EORTC-QLQ-LC13. Scores for the multi-item functional, symptom scales and the single-item scales were calculated using a linear transformation of raw scores to produce a range from 0 to 100, as described by EORTC. Subscale Insomnia **Depression:** not assessed **Anxiety:** not assessed **Daily maintenance opioid therapy dose:** not assessed **Daily breakthrough opioid therapy dose:** not assessed **Withdrawals due to lack of efficacy:** not reported **Nervous system disorders adverse effects:** not assessed **Psychiatric disorders adverse effects:** not assessed

Turcott 2018 *(Continued)*

	Any serious adverse event: not reported
Notes	**Funding:** nabilone and placebo were donated by Valeant pharmaceutical without any further participation in the trial. **Conflicts of interest:** authors declared no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported.
Allocation concealment (selection bias)	Unclear risk	No details reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details reported.
Selective reporting (reporting bias)	Low risk	All outcomes reported as outlined in NCT02802540
Selection bias	High risk	Significant differences between nabilone and control group with regard to ECOG status and age at baseline,

BPI-SF: Brief Pain Inventory – Short Form; CB: cannabinoid; CBD: cannabidiol; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires – Cancer; EORTC-QLQ-LC: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires – Lung Cancer; ESAS: Edmonton Symptom Assessment Scale; ITT: intention to treat; NRS: Numeric Rating Scale; NSAID: non-steroidal anti-inflammatory drug; NSCLC: non-small cell lung cancer; PGIC: Patient Global Impression of Change; PO: oral; SD: standard deviation; THC: tetrahydrocannabinol; TSDS: Total Symptom Distress Score; VAS: Visual Analogue Scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Zylla 2021	30 participants with stage IV cancer requiring opioid randomised 1:1 to early cannabis (15 participants) vs delayed start cannabis (15 participants) for 12 weeks. No control group with placebo or other non-cannabis based medication.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12619001534178

Study name	A phase I/II double-blind, randomised controlled trial assessing effect of medicinal cannabis on quality of life and symptom control in advanced cancer
Methods	Phase 1/2 Purpose: treatment Allocation: randomised controlled trial Blinding: yes Assignment: parallel Type of endpoint: safety/efficacy
Participants	People with incurable advanced cancer, of any histological subtype; target sample size: 116
Interventions	CGL002 (medicinal cannabis) vs placebo CGL002 2.5–30 mg administered 1–3 times a day, oral liquid administered via syringe, daily for a maximum of 168 days/6 months.

Outcomes	**Primary outcomes**
	Phase 1 (composite)
	• To determine the safety, tolerability and dose range of CGL002 by evaluating and characterising the pharmacokinetic profile of medicinal cannabis and active metabolites, analysis of dose-limiting toxicities and adverse events. Pharmacokinetic parameters include serum concentration of CBD002 and metabolites. Dose-limiting toxicities and adverse events measured by CTCAE criteria, which can be classified by clinical examination, laboratory findings or participant reported symptoms (baseline (predose), and 1, 2, 4, and 8 hours postadministration of study drug, on days 1, 8, 15 and 29 postinitiation of medicinal cannabis/placebo).
	Phase 2
	• To determine the impact of medicinal cannabis on global quality of life, as measured by change in EORTC QLQ PAL-Q30 from baseline (day 29 postinitiation of medicinal cannabis/placebo).
	Secondary outcome
	Phase 1
	• To undertake exploratory pharmacokinetics studies profiling the medicinal cannabis and active metabolites. Pharmacokinetic parameters assessed include serum concentration of CBD002 and metabolites (day 29 postinitiation of medicinal cannabis or placebo)
	• To test the feasibility of the objectives proposed in the Phase 2 study. This includes the impact of medicinal cannabis on global quality of life, pain, insomnia, nausea, anxiety and treatment satisfaction. Feasibility will be assessed by questionnaires understandable and acceptable to all participants, dosing uptitration schedule able to be followed by all participants and feasibility of self-administration (day 29 postinitiation of medicinal cannabis or placebo)
	Phase 2
	• To evaluate impact of medicinal cannabis on (at days 56, 84, 112, 140 and 168 postinitiation of medicinal cannabis/placebo):
	  • anxiety (measured using Hospital Anxiety and Depression Scale)
	  • sleep (measured using Insomnia Severity Index), nausea (measured using NRS)
	  • pain (measured using change in Brief Pain Inventory – Short Form)
	  • anorexia (measured using Functional Assessment of Anorexia/Cachexia and weight)
	  • global quality of life (measured using EORTC QLQ PAL-Q30)

ACTRN12619001534178 *(Continued)*

	• caregiver burden measured using Caregiver Quality of Life Index – Cancer • treatment satisfaction measured using Treatment Satisfaction Questionnaire for Medication • To determine the safety and optimal Phase 2 dose range of medicinal cannabis measured by occurrence of dose-limiting toxicities and adverse events, clinically meaningful changes from baseline in clinical laboratory parameters using standard CTCAE criteria (composite outcome at days 56, 84, 112, 140 and 168 postinitiation of medicinal cannabis/placebo)
Starting date	25 September 2020
Contact information	Name: Dr Jodie Palmer Address: Olivia Newton-John Cancer Research Institute Level 5, ONJWRC 145 Studley Road Heidelberg VIC 3084 Australia Telephone: +61 3 9496 3573 E-mail: trials@onjcri.org.au
Notes	Funding: Victorian Cancer Agency

ACTRN12621001302842

Study name	NanaBis™ an oro-buccal administered delta9-tetrahydrocannabinol (d9-THC) and cannabidiol (CBD) medicine for the management of chronic pain from metastatic bone cancer
Methods	Phase 3 Purpose: treatment Allocation: randomised controlled trial Blinding: yes Assignment: parallel Type of endpoint: safety/efficacy
Participants	Metastatic bone pain from a cancer diagnosis as the only major cause of pain Target sample size: 360
Interventions	NanaBis vs placebo or oxycodone NanaBis: a nanoparticle water soluble equimolar solution of delta 9-THC and CBD administered through the oro-buccal membrane. 1 dose is equivalent to 2 actuations of the pump delivering 280 µL volume containing delta 9-THC 2.5 mg and CBD 2.5 mg. The dose administered will be 2 to 3.5 doses (2–7 sprays) per 4 hours unless asleep.
Outcomes	**Primary outcome** • Proportion of participants who respond to study treatment at the end of the 6-week study period. 'Responder' defined as a participant who completes the maintenance phase with an acceptable level of pain (NPRS 5) and without requiring excessive amounts of rescue (breakthrough analgesia) medication. Unlimited breakthrough analgesia (oxycodone) is allowed throughout the study; however, excessive use will result in discontinuation. Participants who discontinue due to excessive oxycodone use will be classified as 'non-responders'. The NPRS is completed twice daily by the participant throughout the entire 18 weeks of the study. **Secondary outcomes**

ACTRN12621001302842 *(Continued)*

	• Proportion of participants in the NanaBis group who prefer further treatment with NanaBis in the open-label extension phase assessed by audit of signed consent forms from participants (at the end of the 6-week study period). • Proportion of responders in the NanaBis group compared to the oxycodone CR group determined by pain levels recorded using NPRS. • Proportion of responders in the oxycodone CR group compared to the placebo group determined by pain levels recorded using NPRS. A responder is defined as a participant who completes the maintenance phase with an acceptable level of pain (NPRS 5) and without requiring excessive amounts of rescue (breakthrough analgesia) medication. • Quality of life assessed using EORTC-QLQ-C30 validated questionnaire. • Safety and tolerability will be assessed via standardised adverse events, serious adverse events, deaths, UKU Scale, Local Adverse Events Charts and patient medical records. • Adverse events, serious adverse events and deaths will be summarised by treatment arm (monitored continuously for the duration of the 18-week study).
Starting date	1 October 2021
Contact information	Name: Mrs Larah Hall Address: Medlab Clinical Ltd, Unit 5-6/11 Lord St, Botany, NSW Australia 2019 Australia Telephone: +61 02 8188 0311 Email: larah_hall@medlab.co
Notes	Funding: Medlab Clinical Ltd

EudraCT 001382-32

Study name	A double-blind, randomized phase 1/2 study to assess the efficacy and safety of BCT-521 versus placebo for pain associated with cancer in patients already receiving standard of care treatment with opioids
Methods	Phase 1/2 Purpose: treatment Allocation: randomised controlled trial Blinding: yes Assignment: parallel Type of endpoint: safety/efficacy
Participants	Any type of active cancer at any stage; cancer-related pain that is not wholly alleviated with their current opioid treatment and whose mean pain NRS score over 24 hours is ≥ 4 but < 8 during the last 3 days of screening, with ≤ 2-point difference between the highest and lowest scores, with all scores remaining between 4 and 8; target sample size 173
Interventions	CBD 3.5 mg/THC 2.5 mg soft capsules twice a day vs placebo up to 5 weeks
Outcomes	**Primary outcomes** • Mean change in pain score from baseline to end of treatment • Adverse events and laboratory changes **Secondary outcomes**

EudraCT 001382-32 *(Continued)*

	• 30% reduction in pain using Total Brief Pain Inventory, which includes all the pain and interference items • Mean change from baseline on BPI for worst pain in last 24 hours • Mean change from baseline on the BPI interference items • Mean change from baseline on the Total BPI • Percent change from baseline for mean pain NRS score • Percent change from baseline for Total BPI score • Mean change in opioid consumption
Starting date	26 November 2019
Contact information	Beckley Canopy Therapeutics Ltd; Head of Clinical Operations Address: Beckley Park, Oxford, UK Telephone: +44 7545 923519 E-mail: kalpana@beckley-canopy.com
Notes	Funding: Beckley Canopy Therapeutics Ltd

Hardy 2020

Study name	Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo-controlled, randomised clinical trial of efficacy and safety of 1:1 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
Methods	Phase 2 Purpose: treatment Allocation: randomised controlled trial Blinding: yes Assignment: parallel Type of endpoint: safety/efficacy
Participants	People with advanced histologically confirmed cancer (metastatic or locally advanced) known to the palliative care team of the recruiting centre; target sample size 144 participants
Interventions	THC/CBD 10 mg/mL oral oily liquid (dose range 2.5 mg/2.5 mg–30 mg/30 mg/day) vs placebo
Outcomes	**Primary outcome** Change from baseline of total ESAS TSDS (assessed at baseline and day 14) **Secondary outcomes** • Adverse events using CTCAE v4.0 recorded at baseline to day 28. Particular attention will be given to: mood change, dizziness, somnolence, confusion, concentration, feeling "high" warm/tingle feeling, exaggerated sense of well-being, anxiety, headache, insomnia, clumsiness, lack of co-ordination, weakness, unsteadiness, red eyes, dry mouth, nausea, vomiting, diarrhoea, stomach/abdominal pain, personality change, paranoia, psychosis, hypertension, tachycardia, sweating (assessed at baseline and compared at days 2, 4, 7, 9, 11, 14, 21 and 28) • Clinical Global Impression scales (assessed at baseline and compared at days 7, 14, 21 and 28)

Hardy 2020 *(Continued)*

	• Combined physical and emotional (pain, tiredness, nausea, shortness of breath, drowsy, appetite, anxiety, depression, well-being) at each time point. Each symptom will be rated from 0 to 10 on the ESAS. Scores will be collected at each time point (assessed at days 7, 14, 21 and 28) • DASS-21 score assessing combines depression, anxiety and stress (assessed at baseline and compared at days 7, 14, 21 and 28) • OME. Conversion of various opioids to an equianalgesic dose of oral morphine (mg/24 hour). 24-hr opioid consumption will be measured as OMEs by review of medical records. Opioid conversion example: oxycodone multiplication factor 1.5; fentanyl multiplication factor of 0.3 (mean used at baseline and days 7, 14, 21 and day 28) • Patient determined effective dose of the 1:1 THC/CBD formulation (defined as the dose that achieves symptom relief with acceptable adverse effects by day 14) • Quality of Life using questionnaire EORTC QLQ-C15 PAL (assessed at baseline and compared at days 7, 14 and 28)
Starting date	9 September 2019
Contact information	**Name:** Ms Georgie Cupples **Address:** Clinical Trial Coordinator Palliative and Supportive Care Mater Misericordiae Ltd Raymond Terrace South Brisbane, Qld 4101 Australia **Telephone:** +61 7 3163 6057 **Email:** Georgie.Cupples@mater.org.au
Notes	**Funding:** National Health and Medical Research Council (NHMRC)/Medical Research Future Fund (MRFF) and Mater Misericordiae Ltd

NCT04042545

Study name	Safety and efficacy of inhaled cannabis for the uncontrolled pain relief in patients with advanced cancer (PLENITUDE)
Methods	Phase 2 Allocation: randomised Primary purpose: treatment Blinding: participant, care provider, investigator, outcomes assessor Assignment: parallel
Participants	78 participants with uncontrolled cancer pain relief
Interventions	1 cannabis dosing capsule inhaled 3 times a day with a vaporiser device vs 1 placebo dosing capsule inhaled 3 times a day with a vaporiser device
Outcomes	**Primary outcome** • Uncontrolled cancer pain measured using a patient self-administered questionnaire (change from baseline in the EORTC-QLQ-C15-PAL pain multi-item scale score at week 4). EORTC-QLQ-C15-PAL items rated on a scale of 1 (not at all) to 4 (very much). High scores on a symptom scale correlate to increased symptom burden **Secondary outcome** • Overall health-related quality of life of participants with uncontrolled symptoms related to advanced cancer measured using the self-rating EORTC-QLQ-C15-PAL (change from baseline to week

NCT04042545 *(Continued)*	4). EORTC-QLQ-C15-PAL single-item scale is rated from 1 (very poor) to 7(excellent). High scores on a functional scale correspond to better functioning • Physical, emotional and total symptom distress measured using self-administered ESAS-r-CS (change from baseline to weeks 1 and 4): 11 core symptoms: pain, tiredness, nausea, depression, anxious, drowsiness, appetite, feeling of well-being, shortness of breath, constipation and trouble sleeping. 11-point scale ranging from 0 (no symptom) to 10 (worst possible). • Palliative Performance Scale version 2 scored by a healthcare professional for measuring functional status in people at end of life (change from baseline to weeks 1 and 4). Scores each dimension from 100% to 0% (death), with 10% denoting the lowest level of functioning. • Satisfaction of family caregivers of people with advanced cancer measured using a caregiver-administered questionnaire (change from baseline to weeks 1 and 4). Scale range is a left to right on a 7-item scale for caregiver. Each item is scored from 5 (much more satisfied now) to 1 (much less satisfied now). • Distress of people with advanced cancer measured using a patient-administered questionnaire (change from baseline to week 4). Distress thermometer adopted as a screening measure to identify and address psychological distress in people with cancer. Results support a cut-off score of 3 on the distress thermometer to indicate people with clinically elevated levels of distress
Starting date	30 July 2020
Contact information	Contact: Suzanne Sisley, MD Scottsdale Research Institute Address: Cave Creek, Arizona, 85331, USA
Notes	Sponsors and collaborators: Tetra Bio-Pharma

BPI: Brief Pain Inventory; CBD: cannabidiol; CR: controlled release; CTCAE: Common Terminology Criteria for Adverse Events; delta 9-THC: delta 9-tetrahydrocannabinol; DASS-21: 21-item Depression, Anxiety and Stress Scale; EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires – Cancer; EORTC QLQ PAL-Q30/EORTC-QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Palliative; ESAS TSDS: Edmonton Symptom Assessment System Total Symptom Distress Score; ESAS-r-CS: Revised Edmonton Symptom Assessment System – Core Symptoms; NPRS: Numeric Pain Rating Scale; NRS: Numeric Rating Scale; OME: oral morphine equivalent; UKU: Udvalg for Kliniske Undersøgelser.

DATA AND ANALYSES

Comparison 1. Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Patient Global Impression of Change (PGIC) of much improved or very much improved	3	996	Risk Difference (IV, Random, 95% CI)	0.06 [0.01, 0.12]
1.1.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	94	Risk Difference (IV, Random, 95% CI)	0.11 [-0.12, 0.34]
1.1.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	3	805	Risk Difference (IV, Random, 95% CI)	0.06 [0.00, 0.12]
1.1.3 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	97	Risk Difference (IV, Random, 95% CI)	0.02 [-0.20, 0.24]

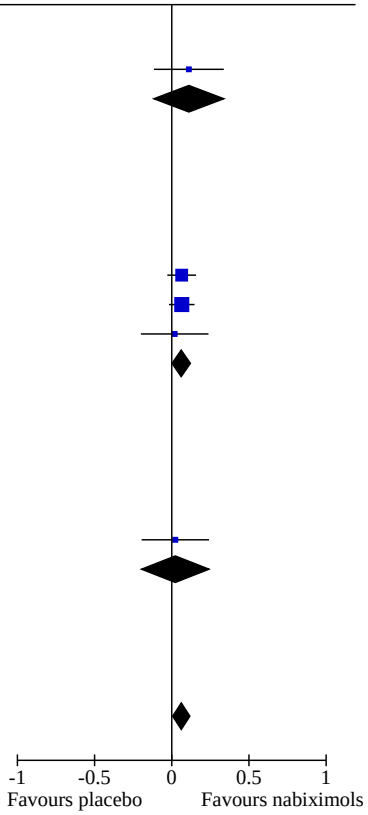
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Withdrawal due to adverse events	4	1332	Risk Difference (IV, Random, 95% CI)	0.04 [0.00, 0.08]
1.2.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	-0.05 [-0.21, 0.11]
1.2.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	1002	Risk Difference (IV, Random, 95% CI)	0.05 [-0.00, 0.09]
1.2.3 THC 6–10 sprays (THC 16.2–27 mg)	1	88	Risk Difference (IV, Random, 95% CI)	0.05 [-0.07, 0.18]
1.2.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	0.08 [-0.09, 0.25]
1.3 Pain relief ≥ 30%	4	1332	Risk Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]
1.3.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.19, 0.16]
1.3.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	1003	Risk Difference (IV, Random, 95% CI)	0.03 [-0.04, 0.09]
1.3.3 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Risk Difference (IV, Random, 95% CI)	0.00 [-0.18, 0.18]
1.3.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.20, 0.16]
1.4 Pain relief ≥ 50%	4	1333	Risk Difference (IV, Random, 95% CI)	0.01 [-0.02, 0.05]
1.4.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	0.13 [-0.01, 0.28]
1.4.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/ CBD 15–25 mg)	4	1004	Risk Difference (IV, Random, 95% CI)	0.01 [-0.03, 0.05]
1.4.3 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
1.4.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	0.01 [-0.13, 0.15]
1.5 Mean pain intensity	4	1315	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.40, 0.02]
1.5.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Mean Difference (IV, Random, 95% CI)	-0.80 [-1.57, -0.03]
1.5.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	993	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.42, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.3 THC 6–10 sprays (THC 16.2–27 mg)	1	80	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.84, 0.44]
1.5.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.85, 0.65]
1.6 Sleep problems	4	1314	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.19, 0.06]
1.6.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	120	Std. Mean Difference (IV, Random, 95% CI)	-0.33 [-0.74, 0.08]
1.6.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	993	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.23, 0.12]
1.6.3 THC 6–10 sprays (THC 16.2–27 mg)	1	82	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.47, 0.44]
1.6.4 THC/CBD 11–16 sprays (THC/CBD 29.7–43.2 mg/CBD 27.5–40 mg)	1	119	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.37, 0.46]
1.7 Daily maintenance opioid dosage	3	970	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.10, 0.27]
1.7.1 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	3	883	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.14, 0.19]
1.7.2 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.05, 0.85]
1.8 Daily breakthrough opioid dosage	3	957	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.23, 0.07]
1.8.1 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	3	877	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.25, 0.01]
1.8.2 THC 6–10 sprays (THC 16.2–27 mg)	1	80	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.21, 0.71]
1.9 All central nervous system adverse events	4	1331	Risk Difference (IV, Random, 95% CI)	0.11 [0.05, 0.17]
1.9.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	0.07 [-0.10, 0.25]
1.9.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	1002	Risk Difference (IV, Random, 95% CI)	0.10 [0.03, 0.17]
1.9.3 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Risk Difference (IV, Random, 95% CI)	0.12 [-0.07, 0.31]
1.9.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	0.24 [0.06, 0.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 All psychiatric adverse events	4	1330	Risk Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.04]
1.10.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.15]
1.10.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	1001	Risk Difference (IV, Random, 95% CI)	0.01 [-0.01, 0.03]
1.10.3 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Risk Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.09]
1.10.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	0.18 [0.04, 0.32]
1.11 Any serious adverse event	4	1330	Risk Difference (IV, Random, 95% CI)	0.02 [-0.03, 0.07]
1.11.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)	1	122	Risk Difference (IV, Random, 95% CI)	0.13 [-0.06, 0.31]
1.11.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)	4	1001	Risk Difference (IV, Random, 95% CI)	-0.01 [-0.06, 0.04]
1.11.3 THC 6–10 sprays (THC 16.2–27 mg)	1	87	Risk Difference (IV, Random, 95% CI)	0.12 [-0.03, 0.27]
1.11.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)	1	120	Risk Difference (IV, Random, 95% CI)	0.04 [-0.14, 0.23]

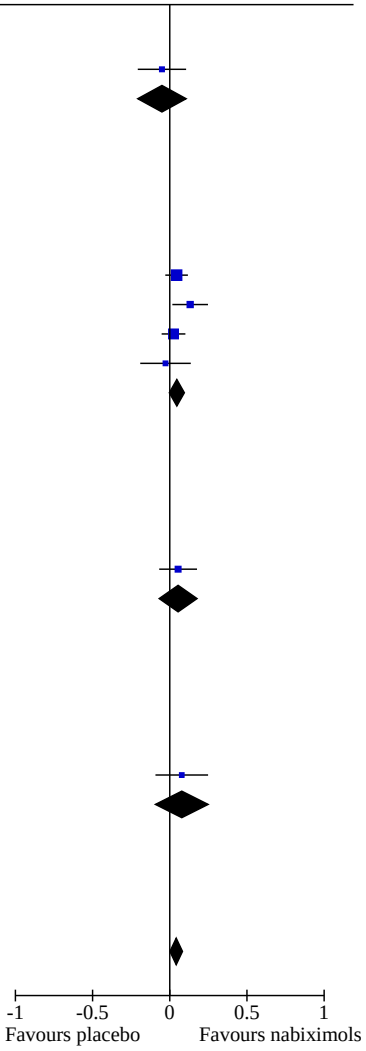
Analysis 1.1. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 1: Patient Global Impression of Change (PGIC) of much improved or very much improved

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.1.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	34	70	9	24	6.0%	0.11 [-0.12 , 0.34]
Subtotal (95% CI)		**70**		**24**	**6.0%**	**0.11 [-0.12 , 0.34]**
Total events:	34		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.1.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	55	175	46	184	35.8%	0.06 [-0.03 , 0.16]
Lichtman 2018	39	172	29	179	45.3%	0.06 [-0.02 , 0.15]
Portenoy 2012	25	71	8	24	6.5%	0.02 [-0.20 , 0.24]
Subtotal (95% CI)		**418**		**387**	**87.5%**	**0.06 [0.00 , 0.12]**
Total events:	119		83			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 2 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.1.3 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	26	73	8	24	6.5%	0.02 [-0.20 , 0.24]
Subtotal (95% CI)		**73**		**24**	**6.5%**	**0.02 [-0.20 , 0.24]**
Total events:	26		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**561**		**435**	**100.0%**	**0.06 [0.01 , 0.12]**
Total events:	179		100			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 4 (P = 0.98); $I^2 = 0\%$						
Test for overall effect: Z = 2.17 (P = 0.03)						
Test for subgroup differences: $Chi^2 = 0.30$, df = 2 (P = 0.86), $I^2 = 0\%$						



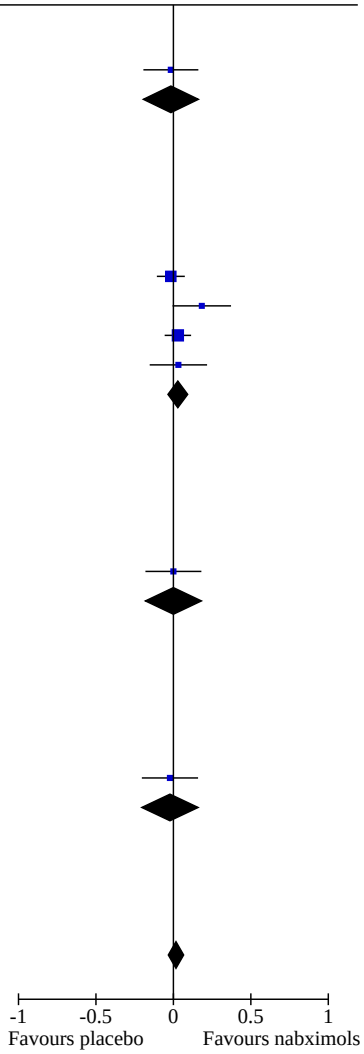
Analysis 1.2. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 2: Withdrawal due to adverse events

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.2.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	13	91	6	31	6.7%	-0.05 [-0.21 , 0.11]
Subtotal (95% CI)		**91**		**31**	**6.7%**	**-0.05 [-0.21 , 0.11]**
Total events:	13		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.2.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	38	200	29	199	30.6%	0.04 [-0.03 , 0.12]
Johnson 2010	10	60	1	29	12.3%	0.13 [0.02 , 0.25]
Lichtman 2018	40	199	35	198	27.7%	0.02 [-0.05 , 0.10]
Portenoy 2012	15	87	6	30	6.1%	-0.03 [-0.19 , 0.14]
Subtotal (95% CI)		**546**		**456**	**76.7%**	**0.05 [-0.00 , 0.09]**
Total events:	103		71			
Heterogeneity: Tau² = 0.00; Chi² = 3.23, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 1.84 (P = 0.07)						
1.2.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	7	58	2	30	10.9%	0.05 [-0.07 , 0.18]
Subtotal (95% CI)		**58**		**30**	**10.9%**	**0.05 [-0.07 , 0.18]**
Total events:	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.2.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	25	90	6	30	5.6%	0.08 [-0.09 , 0.25]
Subtotal (95% CI)		**90**		**30**	**5.6%**	**0.08 [-0.09 , 0.25]**
Total events:	25		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						
Total (95% CI)		**785**		**547**	**100.0%**	**0.04 [0.00 , 0.08]**
Total events:	148		85			
Heterogeneity: Tau² = 0.00; Chi² = 4.80, df = 6 (P = 0.57); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 1.58, df = 3 (P = 0.66), I² = 0%						



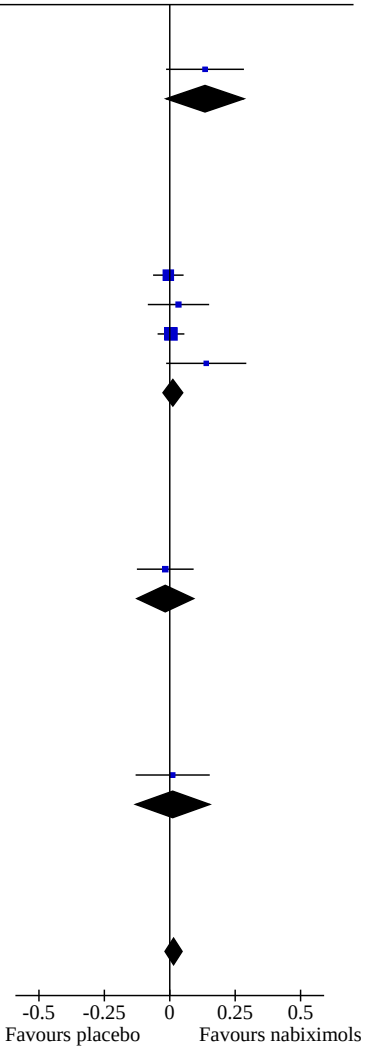
Analysis 1.3. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 3: Pain relief ≥ 30%

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.3.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	22	91	8	31	7.7%	-0.02 [-0.19 , 0.16]
Subtotal (95% CI)		**91**		**31**	**7.7%**	**-0.02 [-0.19 , 0.16]**
Total events:	22		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
1.3.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	59	200	62	199	30.0%	-0.02 [-0.11 , 0.07]
Johnson 2010	23	60	6	30	6.8%	0.18 [-0.01 , 0.37]
Lichtman 2018	53	199	47	198	33.5%	0.03 [-0.06 , 0.11]
Portenoy 2012	26	87	8	30	7.1%	0.03 [-0.15 , 0.22]
Subtotal (95% CI)		**546**		**457**	**77.4%**	**0.03 [-0.04 , 0.09]**
Total events:	161		123			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.53$, df = 3 (P = 0.32); $I^2 = 15\%$						
Test for overall effect: Z = 0.88 (P = 0.38)						
1.3.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	12	58	6	29	7.5%	0.00 [-0.18 , 0.18]
Subtotal (95% CI)		**58**		**29**	**7.5%**	**0.00 [-0.18 , 0.18]**
Total events:	12		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.3.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	22	90	8	30	7.4%	-0.02 [-0.20 , 0.16]
Subtotal (95% CI)		**90**		**30**	**7.4%**	**-0.02 [-0.20 , 0.16]**
Total events:	22		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**785**		**547**	**100.0%**	**0.02 [-0.03 , 0.07]**
Total events:	217		145			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.97$, df = 6 (P = 0.68); $I^2 = 0\%$						
Test for overall effect: Z = 0.66 (P = 0.51)						
Test for subgroup differences: $Chi^2 = 0.47$, df = 3 (P = 0.92), $I^2 = 0\%$						



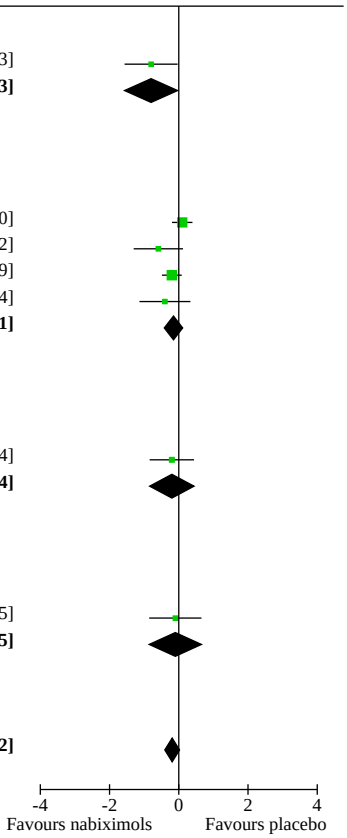
Analysis 1.4. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 4: Pain relief ≥ 50%

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.4.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	24	91	4	31	4.8%	0.13 [-0.01 , 0.28]
Subtotal (95% CI)		**91**		**31**	**4.8%**	**0.13 [-0.01 , 0.28]**
Total events:	24		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.78 (P = 0.08)						
1.4.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/ CBD 15–25 mg)						
Fallon 2017a	19	200	20	199	30.2%	-0.01 [-0.06 , 0.05]
Johnson 2010	6	60	2	30	7.7%	0.03 [-0.08 , 0.15]
Lichtman 2018	15	199	14	198	38.7%	0.00 [-0.05 , 0.06]
Portenoy 2012	24	88	4	30	4.5%	0.14 [-0.01 , 0.29]
Subtotal (95% CI)		**547**		**457**	**81.0%**	**0.01 [-0.03 , 0.05]**
Total events:	64		40			
Heterogeneity: Tau² = 0.00; Chi² = 3.21, df = 3 (P = 0.36); I² = 6%						
Test for overall effect: Z = 0.61 (P = 0.54)						
1.4.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	3	58	2	29	8.9%	-0.02 [-0.13 , 0.09]
Subtotal (95% CI)		**58**		**29**	**8.9%**	**-0.02 [-0.13 , 0.09]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.4.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	13	90	4	30	5.3%	0.01 [-0.13 , 0.15]
Subtotal (95% CI)		**90**		**30**	**5.3%**	**0.01 [-0.13 , 0.15]**
Total events:	13		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Total (95% CI)		**786**		**547**	**100.0%**	**0.01 [-0.02 , 0.05]**
Total events:	104		50			
Heterogeneity: Tau² = 0.00; Chi² = 6.09, df = 6 (P = 0.41); I² = 1%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Chi² = 2.86, df = 3 (P = 0.41), I² = 0%						



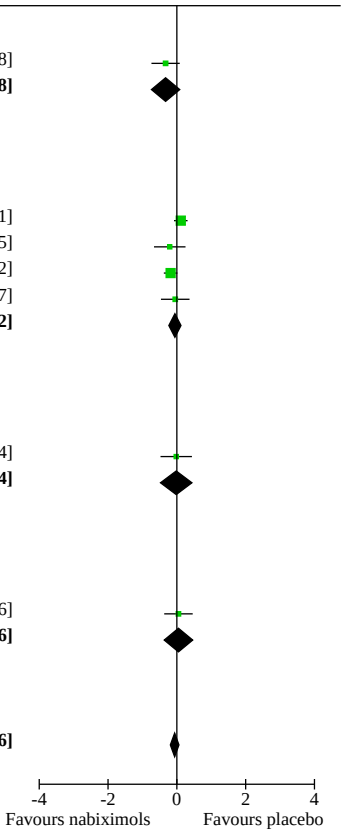
Analysis 1.5. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 5: Mean pain intensity

Study or Subgroup	Nabiximols Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)								
Portenoy 2012	-1.6	2.1	91	-0.8	1.8	31	7.0%	-0.80 [-1.57 , -0.03]
Subtotal (95% CI)			**91**			**31**	**7.0%**	**-0.80 [-1.57 , -0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.05 (P = 0.04)								
1.5.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)								
Fallon 2017a	-0.9	1.5	198	-1	1.5	199	29.9%	0.10 [-0.20 , 0.40]
Johnson 2010	-1.32	1.64	53	-0.73	1.51	28	7.9%	-0.59 [-1.30 , 0.12]
Lichtman 2018	-0.8	1.4	199	-0.6	1.5	198	31.0%	-0.20 [-0.49 , 0.09]
Portenoy 2012	-1.2	1.7	88	-0.8	1.8	30	7.5%	-0.40 [-1.14 , 0.34]
Subtotal (95% CI)			**538**			**455**	**76.3%**	**-0.15 [-0.42 , 0.11]**
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 4.66$, df = 3 (P = 0.20); $I^2 = 36\%$								
Test for overall effect: Z = 1.13 (P = 0.26)								
1.5.3 THC 6–10 sprays (THC 16.2–27 mg)								
Johnson 2010	-0.93	1.15	52	-0.73	1.51	28	9.5%	-0.20 [-0.84 , 0.44]
Subtotal (95% CI)			**52**			**28**	**9.5%**	**-0.20 [-0.84 , 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.5.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)								
Portenoy 2012	-0.9	1.9	90	-0.8	1.8	30	7.2%	-0.10 [-0.85 , 0.65]
Subtotal (95% CI)			**90**			**30**	**7.2%**	**-0.10 [-0.85 , 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.79)								
Total (95% CI)			**771**			**544**	**100.0%**	**-0.19 [-0.40 , 0.02]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.58$, df = 6 (P = 0.27); $I^2 = 21\%$								
Test for overall effect: Z = 1.76 (P = 0.08)								
Test for subgroup differences: $Chi^2 = 2.54$, df = 3 (P = 0.47), $I^2 = 0\%$								



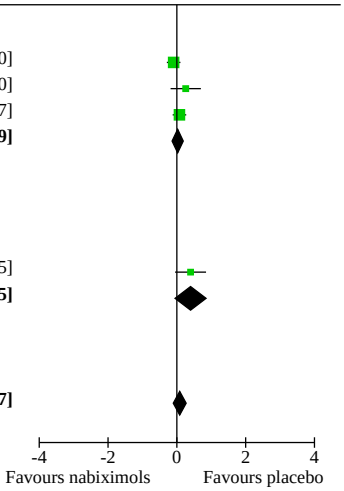
Analysis 1.6. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 6: Sleep problems

Study or Subgroup	Nabiximols Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.6.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)								
Portenoy 2012	-1.5	2.1	89	-0.8	2.2	31	8.6%	-0.33 [-0.74 , 0.08]
Subtotal (95% CI)			**89**			**31**	**8.6%**	**-0.33 [-0.74 , 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.56 (P = 0.12)								
1.6.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)								
Fallon 2017a	-0.9	1.8	198	-1.1	1.7	199	30.3%	0.11 [-0.08 , 0.31]
Johnson 2010	-0.59	1.88	54	-0.21	1.72	28	7.0%	-0.21 [-0.66 , 0.25]
Lichtman 2018	-0.8	1.7	199	-0.5	1.6	198	30.2%	-0.18 [-0.38 , 0.02]
Portenoy 2012	-0.9	2.1	87	-0.8	2.2	30	8.4%	-0.05 [-0.46 , 0.37]
Subtotal (95% CI)			**538**			**455**	**75.9%**	**-0.06 [-0.23 , 0.12]**
Heterogeneity: Tau² = 0.01; Chi² = 4.82, df = 3 (P = 0.19); I² = 38%								
Test for overall effect: Z = 0.63 (P = 0.53)								
1.6.3 THC 6–10 sprays (THC 16.2–27 mg)								
Johnson 2010	-0.25	2.33	54	-0.21	1.72	28	7.0%	-0.02 [-0.47 , 0.44]
Subtotal (95% CI)			**54**			**28**	**7.0%**	**-0.02 [-0.47 , 0.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.94)								
1.6.4 THC/CBD 11–16 sprays (THC/CBD 29.7–43.2 mg/CBD 27.5–40 mg)								
Portenoy 2012	-0.7	2.1	89	-0.8	2.2	30	8.5%	0.05 [-0.37 , 0.46]
Subtotal (95% CI)			**89**			**30**	**8.5%**	**0.05 [-0.37 , 0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.82)								
Total (95% CI)			**770**			**544**	**100.0%**	**-0.06 [-0.19 , 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 6.76, df = 6 (P = 0.34); I² = 11%								
Test for overall effect: Z = 1.01 (P = 0.31)								
Test for subgroup differences: Chi² = 1.88, df = 3 (P = 0.60), I² = 0%								



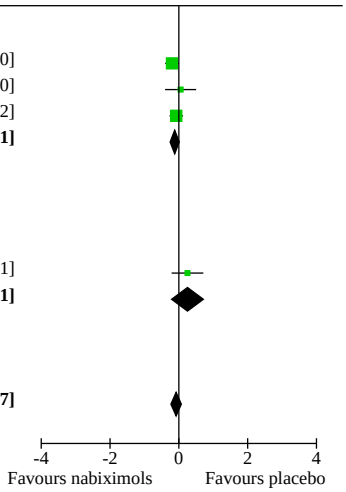
Analysis 1.7. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 7: Daily maintenance opioid dosage

Study or Subgroup	Nabiximols Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.7.1 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)								
Fallon 2017a	-1.5	38.2	197	1.9	34.3	199	36.3%	-0.09 [-0.29 , 0.10]
Johnson 2010	-3.5	108.44	60	-41.4	201.27	30	13.9%	0.26 [-0.18 , 0.70]
Lichtman 2018	0.2	20.9	199	-1.3	18.7	198	36.3%	0.08 [-0.12 , 0.27]
Subtotal (95% CI)			**456**			**427**	**86.5%**	**0.02 [-0.14 , 0.19]**
Heterogeneity: Tau² = 0.01; Chi² = 2.70, df = 2 (P = 0.26); I² = 26%								
Test for overall effect: Z = 0.29 (P = 0.77)								
1.7.2 THC 6–10 sprays (THC 16.2–27 mg)								
Johnson 2010	26.9	152	58	-41.4	201.27	29	13.5%	0.40 [-0.05 , 0.85]
Subtotal (95% CI)			**58**			**29**	**13.5%**	**0.40 [-0.05 , 0.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.74 (P = 0.08)								
Total (95% CI)			**514**			**456**	**100.0%**	**0.08 [-0.10 , 0.27]**
Heterogeneity: Tau² = 0.01; Chi² = 5.26, df = 3 (P = 0.15); I² = 43%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Test for subgroup differences: Chi² = 2.36, df = 1 (P = 0.12), I² = 57.6%								



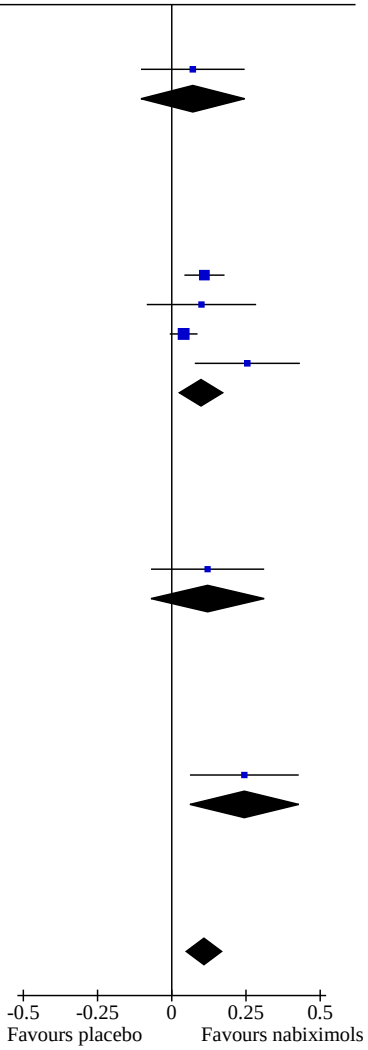
Analysis 1.8. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 8: Daily breakthrough opioid dosage

Study or Subgroup	Nabiximols Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.8.1 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)								
Fallon 2017a	-4.4	27.7	198	0.5	20.5	199	39.9%	-0.20 [-0.40 , -0.00]
Johnson 2010	0.72	0.82	54	0.68	0.66	29	10.3%	0.05 [-0.40 , 0.50]
Lichtman 2018	0.1	22.2	199	1.8	23.6	198	40.0%	-0.07 [-0.27 , 0.12]
Subtotal (95% CI)			**451**			**426**	**90.1%**	**-0.12 [-0.25 , 0.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.41, df = 2 (P = 0.49); I² = 0%								
Test for overall effect: Z = 1.78 (P = 0.08)								
1.8.2 THC 6–10 sprays (THC 16.2–27 mg)								
Johnson 2010	0.88	0.85	52	0.68	0.66	28	9.9%	0.25 [-0.21 , 0.71]
Subtotal (95% CI)			**52**			**28**	**9.9%**	**0.25 [-0.21 , 0.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
Total (95% CI)			**503**			**454**	**100.0%**	**-0.08 [-0.23 , 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 3.71, df = 3 (P = 0.29); I² = 19%								
Test for overall effect: Z = 1.03 (P = 0.30)								
Test for subgroup differences: Chi² = 2.30, df = 1 (P = 0.13), I² = 56.6%								



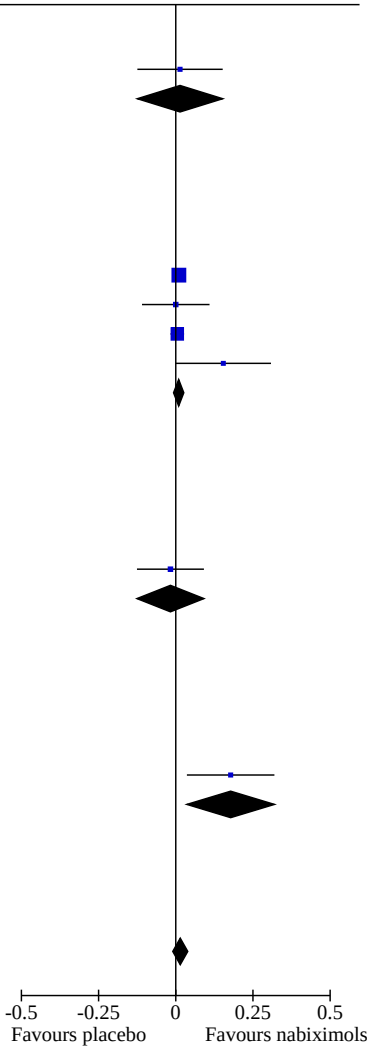
Analysis 1.9. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 9: All central nervous system adverse events

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.9.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	27	91	7	31	9.0%	0.07 [-0.10 , 0.25]
Subtotal (95% CI)		**91**		**31**	**9.0%**	**0.07 [-0.10 , 0.25]**
Total events:	27		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.43)						
1.9.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	39	199	17	198	26.1%	0.11 [0.04 , 0.18]
Johnson 2010	18	60	6	30	8.3%	0.10 [-0.08 , 0.28]
Lichtman 2018	16	199	8	198	31.6%	0.04 [-0.01 , 0.09]
Portenoy 2012	40	88	6	30	8.8%	0.25 [0.08 , 0.43]
Subtotal (95% CI)		**546**		**456**	**74.8%**	**0.10 [0.03 , 0.17]**
Total events:	113		37			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 7.20$, df = 3 (P = 0.07); $I^2 = 58\%$						
Test for overall effect: Z = 2.64 (P = 0.008)						
1.9.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	19	58	6	29	7.8%	0.12 [-0.07 , 0.31]
Subtotal (95% CI)		**58**		**29**	**7.8%**	**0.12 [-0.07 , 0.31]**
Total events:	19		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.24 (P = 0.21)						
1.9.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	43	90	7	30	8.3%	0.24 [0.06 , 0.43]
Subtotal (95% CI)		**90**		**30**	**8.3%**	**0.24 [0.06 , 0.43]**
Total events:	43		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.62 (P = 0.009)						
Total (95% CI)		**785**		**546**	**100.0%**	**0.11 [0.05 , 0.17]**
Total events:	202		57			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 10.65$, df = 6 (P = 0.10); $I^2 = 44\%$						
Test for overall effect: Z = 3.56 (P = 0.0004)						
Test for subgroup differences: $Chi^2 = 2.36$, df = 3 (P = 0.50), $I^2 = 0\%$						



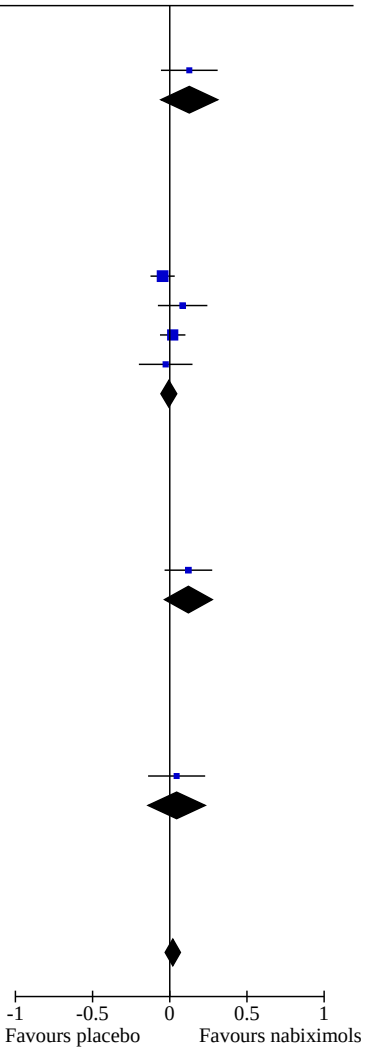
Analysis 1.10. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 10: All psychiatric adverse events

Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.10.1 THC/CBD 1–4 sprays (THC/CBD 2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	13	91	4	31	2.9%	0.01 [-0.12 , 0.15]
Subtotal (95% CI)		**91**		**31**	**2.9%**	**0.01 [-0.12 , 0.15]**
Total events:	13		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
1.10.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	2	199	0	198	44.3%	0.01 [-0.01 , 0.03]
Johnson 2010	4	60	2	30	4.5%	0.00 [-0.11 , 0.11]
Lichtman 2018	3	199	2	198	38.6%	0.00 [-0.02 , 0.03]
Portenoy 2012	25	87	4	30	2.4%	0.15 [-0.00 , 0.31]
Subtotal (95% CI)		**545**		**456**	**89.7%**	**0.01 [-0.01 , 0.03]**
Total events:	34		8			
Heterogeneity: Tau² = 0.00; Chi² = 3.56, df = 3 (P = 0.31); I² = 16%						
Test for overall effect: Z = 1.12 (P = 0.26)						
1.10.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	3	58	2	29	4.6%	-0.02 [-0.13 , 0.09]
Subtotal (95% CI)		**58**		**29**	**4.6%**	**-0.02 [-0.13 , 0.09]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
1.10.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	25	90	3	30	2.8%	0.18 [0.04 , 0.32]
Subtotal (95% CI)		**90**		**30**	**2.8%**	**0.18 [0.04 , 0.32]**
Total events:	25		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.46 (P = 0.01)						
Total (95% CI)		**784**		**546**	**100.0%**	**0.01 [-0.01 , 0.04]**
Total events:	75		17			
Heterogeneity: Tau² = 0.00; Chi² = 9.20, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 5.62, df = 3 (P = 0.13), I² = 46.6%						



Analysis 1.11. Comparison 1: Nabiximols (tetrahydrocannabinol (THC) and cannabidiol (CBD)) versus placebo for individuals with opioid-refractory cancer pain, Outcome 11: Any serious adverse event

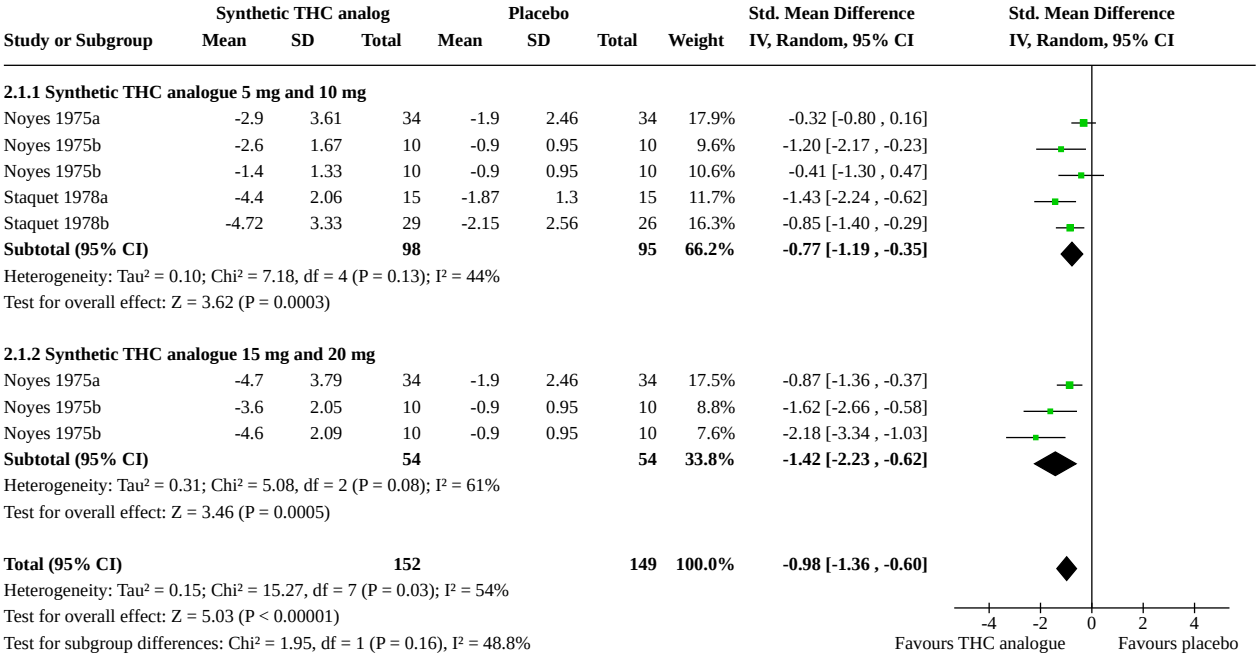
Study or Subgroup	Nabiximols Events	Nabiximols Total	Placebo Events	Placebo Total	Weight	Risk Difference IV, Random, 95% CI
1.11.1 THC/CBD 1–4 sprays (2.7 mg/2.5 mg to 10.8 mg/10 mg)						
Portenoy 2012	35	91	8	31	6.9%	0.13 [-0.06 , 0.31]
Subtotal (95% CI)		**91**		**31**	**6.9%**	**0.13 [-0.06 , 0.31]**
Total events:	35		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
1.11.2 THC/CBD 6–10 sprays (THC 16.2–27 mg/CBD 15–25 mg)						
Fallon 2017a	35	199	44	198	31.3%	-0.05 [-0.12 , 0.03]
Johnson 2010	13	60	4	30	8.9%	0.08 [-0.08 , 0.24]
Lichtman 2018	47	199	43	198	29.0%	0.02 [-0.06 , 0.10]
Portenoy 2012	18	87	7	30	7.6%	-0.03 [-0.20 , 0.15]
Subtotal (95% CI)		**545**		**456**	**76.8%**	**-0.01 [-0.06 , 0.04]**
Total events:	113		98			
Heterogeneity: Tau² = 0.00; Chi² = 2.62, df = 3 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.11.3 THC 6–10 sprays (THC 16.2–27 mg)						
Johnson 2010	13	58	3	29	9.6%	0.12 [-0.03 , 0.27]
Subtotal (95% CI)		**58**		**29**	**9.6%**	**0.12 [-0.03 , 0.27]**
Total events:	13		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.11.4 THC/CBD 11–16 sprays (THC 29.7–43.2 mg/CBD 27.5–40 mg)						
Portenoy 2012	28	90	8	30	6.8%	0.04 [-0.14 , 0.23]
Subtotal (95% CI)		**90**		**30**	**6.8%**	**0.04 [-0.14 , 0.23]**
Total events:	28		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**784**		**546**	**100.0%**	**0.02 [-0.03 , 0.07]**
Total events:	189		117			
Heterogeneity: Tau² = 0.00; Chi² = 6.59, df = 6 (P = 0.36); I² = 9%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Chi² = 3.97, df = 3 (P = 0.26), I² = 24.5%						



Comparison 2. Experimental studies with synthetic tetrahydrocannabinol (THC) analogue versus placebo for individuals with cancer pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Mean pain intensity	4	301	Std. Mean Difference (IV, Random, 95% CI)	-0.98 [-1.36, -0.60]
2.1.1 Synthetic THC analogue 5 mg and 10 mg	4	193	Std. Mean Difference (IV, Random, 95% CI)	-0.77 [-1.19, -0.35]
2.1.2 Synthetic THC analogue 15 mg and 20 mg	2	108	Std. Mean Difference (IV, Random, 95% CI)	-1.42 [-2.23, -0.62]

Analysis 2.1. Comparison 2: Experimental studies with synthetic tetrahydrocannabinol (THC) analogue versus placebo for individuals with cancer pain, Outcome 1: Mean pain intensity

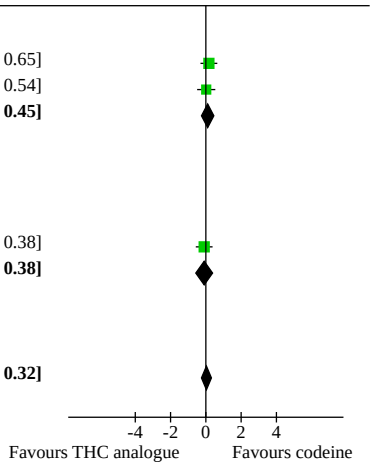


Comparison 3. Experimental studies with synthetic tetrahydrocannabinol (THC) analogue versus codeine for individuals with cancer pain

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean pain intensity	2	194	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.25, 0.32]
3.1.1 Synthetic THC analogue 4 mg or 10 mg versus codeine 50 mg or 60 mg	2	126	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.25, 0.45]
3.1.2 Synthetic THC analogue 20 mg versus codeine 120 mg	1	68	Std. Mean Difference (IV, Random, 95% CI)	-0.09 [-0.57, 0.38]

Analysis 3.1. Comparison 3: Experimental studies with synthetic tetrahydrocannabinol (THC) analogue versus codeine for individuals with cancer pain, Outcome 1: Mean pain intensity

Study or Subgroup	Synthetic THC analog Mean	SD	Total	Codeine Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
3.1.1 Synthetic THC analogue 4 mg or 10 mg versus codeine 50 mg or 60 mg								
Noyes 1975a	-2.9	3.61	34	-3.6	4.37	34	35.0%	0.17 [-0.30 , 0.65]
Staquet 1978a	-4.72	3.33	29	-4.79	3.19	29	29.9%	0.02 [-0.49 , 0.54]
Subtotal (95% CI)			**63**			**63**	**64.9%**	**0.10 [-0.25 , 0.45]**
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%								
Test for overall effect: Z = 0.58 (P = 0.56)								
3.1.2 Synthetic THC analogue 20 mg versus codeine 120 mg								
Noyes 1975a	-4.7	3.79	34	-4.3	4.55	34	35.1%	-0.09 [-0.57 , 0.38]
Subtotal (95% CI)			**34**			**34**	**35.1%**	**-0.09 [-0.57 , 0.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.70)								
Total (95% CI)			**97**			**97**	**100.0%**	**0.03 [-0.25 , 0.32]**
Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%								
Test for overall effect: Z = 0.23 (P = 0.82)								
Test for subgroup differences: Chi² = 0.43, df = 1 (P = 0.51), I² = 0%								



APPENDICES

Appendix 1. Terminology

Term	Definition	Examples/typical products
(Herbal) Cannabis, marijuana	The whole plant or parts or material from the plant (e.g. flowers, buds, resin, leaves).	*Cannabis sativa*, hashish
Medical or medicinal cannabis	The terms 'medical/medicinal cannabis' (or 'medical/medicinal marijuana') is used for cannabis plants, plant material or full plant extracts used for medical purposes.	Bedrocan, Bedrobinol, Tilray 10THC/10CBD
Cannabinoids	Cannabinoids are biologically active constituents of cannabis, or synthetic compounds, usually having affinity for, and activity at, cannabinoid receptors.	THC, CBD, CP55, 940, WIN55, 212-2, HU210
Phytocannabinoid	A cannabinoid found in the cannabis plant or purified/extracted from plant material.	THC, CBD
Endocannabinoid	An endogenous ligand found in the body of humans and other animals and which has affinity for, and activity at, cannabinoid receptors.	Anandamide, 2-AG
Endocannabinoid system modulators	In addition to individual phytocannabinoids, cannabis-derived or cannabis-based medicines, and cannabis extracts, other pharmacological approaches under development for manipulation of the endocannabinoid system include selective synthetic cannabinoid receptor agonists or antagonists, and inhibitors of the catabolism (e.g. fatty acid amide hydrolase (FAAH) inhibitors) or reuptake of endocannabinoids.	PF-04457845, URB597, Rimonabant

(Continued)

Cannabis-based (or cannabis-derived) medicines	Registered, regulatory body approved medicinal cannabis extracts with defined and standardized phytocannabinoid content, particularly THC and THC/CBD.	Nabiximols (Sativex), Dronabinol, Marinol, Epidiolex

Soliman 2019, adapted from Häuser 2018.

CBD: cannabidiol; THC: tetrahydrocannabinol.

Appendix 2. Search strategies

CENTRAL

#1 MeSH descriptor: [Cannabis] this term only

#2 ((cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannabinoid*)):ti,ab,kw (Word variations have been searched)

#3 MeSH descriptor: [Cannabinoids] explode all trees

#4 ((dronabinol or marinol or nabilone or cesamet or "HU 211" or dexanabinol or nabiximols or sativex or dronabinol or tetrahydrocannabinol)):ti,ab,kw (Word variations have been searched)

#5 (CANNABIDIOL):ti,ab,kw (Word variations have been searched)

#6 (cannabinol):ti,ab,kw (Word variations have been searched)

#7 #1 or #2 or #3 or #4 or #5 or #6

#8 MeSH descriptor: [Neoplasms] explode all trees

#9 ((cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*)):ti,ab,kw (Word variations have been searched)

#10 #8 or #9

#11 MeSH descriptor: [Pain] explode all trees

#12 (pain):ti,ab,kw (Word variations have been searched)

#13 #11 or #12

#14 #7 and #10 and #13

MEDLINE (Ovid)

1 Cannabis/

2 (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannabinoid*).tw.

3 exp Cannabinoids/

4 (dronabinol or marinol or nabilone or cesamet or "HU 211" or dexanabinol or nabiximols or sativex or dronabinol or tetrahydrocannabinol).tw.

5 CANNABIDIOL.tw.

6 cannabinol.tw.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp Neoplasms/

9 (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw.

10 8 or 9

11 exp Pain/

12 pain.tw.

13 11 or 12

14 7 and 10 and 13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 or/15-21

23 exp animals/ not humans.sh.

24 22 not 23

25 14 and 24

Embase (Ovid)

1 Cannabis/

2 (cannabis or hemp or marijuana or ganja or hashish or marihuana or bhang or cannabinoid*).tw.

3 exp Cannabinoid/

4 (dronabinol or marinol or nabilone or cesamet or "HU 211" or dexanabinol or nabiximols or sativex or dronabinol or tetrahydrocannabinol).tw.

5 CANNABIDIOL.tw.

6 cannabinol.tw.

7 1 or 2 or 3 or 4 or 5 or 6

8 exp Neoplasm/

9 (cancer* or neoplas* or tumo* or carcinoma* or hodgkin* or nonhodgkin* or adenocarcinoma* or leuk?emia* or metasta* or malignan* or lymphoma* or sarcoma* or melanoma* or myeloma* or oncolog*).tw.

10 8 or 9

11 exp Pain/

12 pain.tw.

13 11 or 12

14 7 and 10 and 13

15 random$.tw.

16 factorial$.tw.

17 crossover$.tw.

18 cross over$.tw.

19 cross-over$.tw.

20 placebo$.tw.

21 (doubl$ adj blind$).tw.

22 (singl$ adj blind$).tw.

23 assign$.tw.

24 allocat$.tw.

25 volunteer$.tw.

26 Crossover Procedure/

27 double-blind procedure.tw.

28 Randomized Controlled Trial/

29 Single Blind Procedure/

30 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31 (animal/ or nonhuman/) not human/

32 30 not 31

33 14 and 32

HISTORY

Protocol first published: Issue 2, 2022

CONTRIBUTIONS OF AUTHORS

All authors participated in writing the protocol.

WH developed the search strategy together with Joanne Abbott (PaPaS Information Specialist).

EF, LR, RFB, PW and WH selected studies for inclusion and extracted data from the studies.

RFB and WH assessed risk of bias.

PW and WH entered data into Review Manager 5 and carried out the analyses.

EF, RAM and WH rated the certainty of the body of evidence.

All review authors interpreted the analysis.

WH drafted the final review.

All authors commented on the draft.

DECLARATIONS OF INTEREST

WH was a member of the PaPaS Editorial Board and had no input into the editorial decisions or processes for this review. WH is treating people with cannabis-based medicines.

PW is treating people with cannabis-based medicines.

EF was a member of the PaPaS Editorial Board and had no input into the editorial decisions or processes for this review.

LR is treating people with cannabis-based medicines.

RFB: none.

RAM was a member of the PaPaS Editorial Board and had no input into the editorial decisions or processes for this review.

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- None, Other

External sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes from our protocol (Häuser 2022).

- We changed the order of the secondary outcomes with outcomes of efficacy first and outcomes of tolerability and safety second.
- The protocol required a minimum of 20 participants per arm because of growing evidence of bias in small studies (Dechartres 2014; Moore 1998). We amended this into 10 participants per treatment arm in order to review all available information and maximise results.
- The outcome "proportion of participants reporting a pain relief of 30% or greater and overall opioid use reduced or stable compared to baseline" could not be included in the summary of findings table because no study analysed this outcome. Instead, we included the outcome "mean pain intensity" in the summary of findings table.
- A search in the IACM databank was not possible because it was no longer accessible.