


Cannabinoids for adult cancer-related pain: systematic review and meta-analysis

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ABSTRACT

Objectives There is increased interest in cannabinoids for cancer pain management and legislative changes are in progress in many countries. This study aims to determine the beneficial and adverse effects of cannabis/cannabinoids compared with placebo/other active agents for the treatment of cancer-related pain in adults.

Methods Systematic review and meta-analysis to identify randomised controlled trials of cannabinoids compared with placebo/other active agents for the treatment of cancer-related pain in adults to determine the effect on pain intensity (primary outcome) and adverse effects, including dropouts. Searches included Embase, MEDLINE, PsycINFO, Web of Science, ClinicalTrials.gov, Cochrane and grey literature. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed.

Results We identified 2805 unique records, of which six randomised controlled trials were included in this systematic review (n=1460 participants). Five studies were included in the meta-analysis (1442 participants). All had a low risk of bias. There was no difference between cannabinoids and placebo for the difference in the change in average Numeric Rating Scale pain scores (mean difference –0.21 (–0.48 to 0.07, p=0.14)); this remained when only phase III studies were meta-analysed: mean difference –0.02 (–0.21 to 0.16, p=0.80). Cannabinoids had a higher risk of adverse events when compared with placebo, especially somnolence (OR 2.69 (1.54 to 4.71), p<0.001) and dizziness (OR 1.58 (0.99 to 2.51), p=0.05). No treatment-related deaths were reported. Dropouts and mortality rates were high.

Conclusions Studies with a low risk of bias showed that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain.

Trial registration number CRD42018107662.

INTRODUCTION

Cancer-related pain is common, occurring in up to 60% of patients undergoing anti-cancer therapy and 90% of those with advanced disease.¹ There is an increased recent interest in cannabinoids (including cannabis) for pain management along with more permissive legislative changes in many countries.^{2 3} The medicinal use of cannabis is already legal in 40 countries and 29 US states.⁴ The WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents suggest that data analysis is needed on cannabinoids for cancer pain.⁵

Patients with cancer use cannabinoids. An anonymous survey (2040 out of 3138 surveys (65%) were returned) in Canada showed that 356 (18%) patients reported cannabis use within the preceding 6 months. Of these, 80% acquired cannabis through friends and 46% of patients used it for cancer-related pain.⁶ In another anonymous survey of adult patients with cancer in a cancer centre in a US state with legalised cannabis, random urine testing of sampled participants was used.⁷ The response rate was 34% (926/2737); of these, 21% had used cannabis in the last month, most frequently for pain.⁷

A systematic review was performed to identify all randomised controlled trials (RCTs) of cannabinoids compared with placebo or other active agents for the treatment of cancer-related pain in adults. A meta-analysis was performed to determine cannabinoid effectiveness and adverse effects, including dropouts. A recent systematic review and meta-analysis that assessed the efficacy, tolerability and safety of medical cannabis and cannabis-based medicines for cancer pain reported very low quality evidence for a non-significant 50% reduction in

pain ($p=0.82$).⁸ This work supplements the systematic review by Häuser *et al.*⁸ The current systematic review has a broader search strategy, and authors were contacted to provide additional findings and information on study design. The primary outcome in this systematic review was the absolute change in mean pain intensity, which is a more sensitive outcome than a dichotomous outcome, for example, proportion of participants who report a pain relief of 50% or greater from baseline to end of study.^{9 10} The aim was to determine the beneficial and adverse effects of cannabinoids compared with placebo or other active agents for the treatment of cancer-related pain in adults from RCTs.

METHODS

This systematic review was prepared according to the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) statement¹¹ and was conducted/reported following an a priori protocol according to the PRISMA guidelines.¹²

The review protocol was registered on PROSPERO (<http://www.crd.york.ac.uk/PROSPERO>) before the searches were performed.¹³

Search strategy

Electronic searches

Strategies were devised to be inclusive of all potentially relevant studies using both Medical Subject Heading (MeSH) terms and text word searches to increase the search sensitivity. Terms for “cannabis/cannabinoids”, “cancer/neoplasms” and “pain” were combined to identify relevant studies. The search terms for cannabinoids included individual drug names and generic terms “cannabinoids” and “cannabis”. The cancer search included the MeSH term “exp neoplasms/” and text word searches for synonyms for cancer. The “pain” search included terms and synonyms for pain. The Embase search strategy is included as an online supplementary file. Search strategies from all other databases are available on request from the authors.

In August 2018, the following electronic databases were searched: Embase (Ovid); Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; PsycINFO (Ovid); Conference Proceedings Citation Index–Science (Web Of Science; Thomson Reuters, New York City, NY); ClinicalTrials.gov (US NIH); ISRCTN registry (BMC); Cochrane Database of Systematic Reviews (Wiley); Cochrane Central Register of Controlled Trials (Wiley); Database of Abstracts of Reviews of Effect (Wiley). All searches were repeated on 1 August 2019 to ensure that there were no further publications since the original searches.

Searches were also conducted for grey literature using the following online databases: the Bielefeld Academic Search Engine (BASE) (<https://www.base-search.net/>), OpenGrey (<http://www.opengrey.eu/>) and Mednar (<https://mednar.com/>).

Table 1 Eligibility criteria for inclusion of studies

PICOS factors	Inclusion criteria	Exclusion criteria
Population	Patients with any type of cancer, including haematological and solid tumours	Patients undergoing surgery, cannabis taken recreationally and cannabis in addiction, animal studies
Intervention	Multiple doses of cannabinoids via any route, for pain cancer-related management (studies where only the minority of the exposed group received cannabis and cannabinoids were excluded)	Single-dose studies
Comparison/control	Any type of comparator, including placebo	No comparator/control group
Outcome	Pain as the primary outcome	Pain not the primary outcome
Study design	Randomised controlled trials	Cohort studies, prospective and retrospective observational studies, case studies and database analysis

Manual searches

In addition to the electronic search, reference lists from reviews on cannabis/cannabinoids to treat cancer pain were manually searched as were identified publications. Experts in the field were consulted to ensure that no articles were missed. Unpublished studies were also included in the search. When only a conference abstract was available and the full study was unpublished, authors were contacted to try to ascertain further information. No language date or publication type restrictions were applied to the search.

Inclusion, exclusion and selection criteria

Studies were included if they were RCTs which assessed the effect of cannabinoids (THC:CBD, THC extract, nabiximols, Sativex, medical cannabis) compared with placebo or other active agents for the treatment of cancer-related pain in adults, with pain as the primary outcome (table 1).

Cochrane protocols determining studies for inclusion were followed, only including studies where the whole patient population had cancer pain. If this was not the case but results were presented separately for the cancer pain subgroup, the study and extracted data for the target subgroup were included.

Studies were excluded if they did not meet the eligibility criteria (table 1). Studies conducted in patients undergoing surgery, healthy volunteers or animals were excluded from this systematic review as these groups have different cannabinoid usage (duration, administration schedule) compared with patients on cannabinoids for cancer pain. Studies other than RCTs potentially have too much bias to be included. Studies not having pain as the primary outcome were not included as they would not be designed or powered to determine the effect of cannabinoids on pain.

Two authors (EGB and JWB) independently reviewed all titles and abstracts (in duplicate) to assess

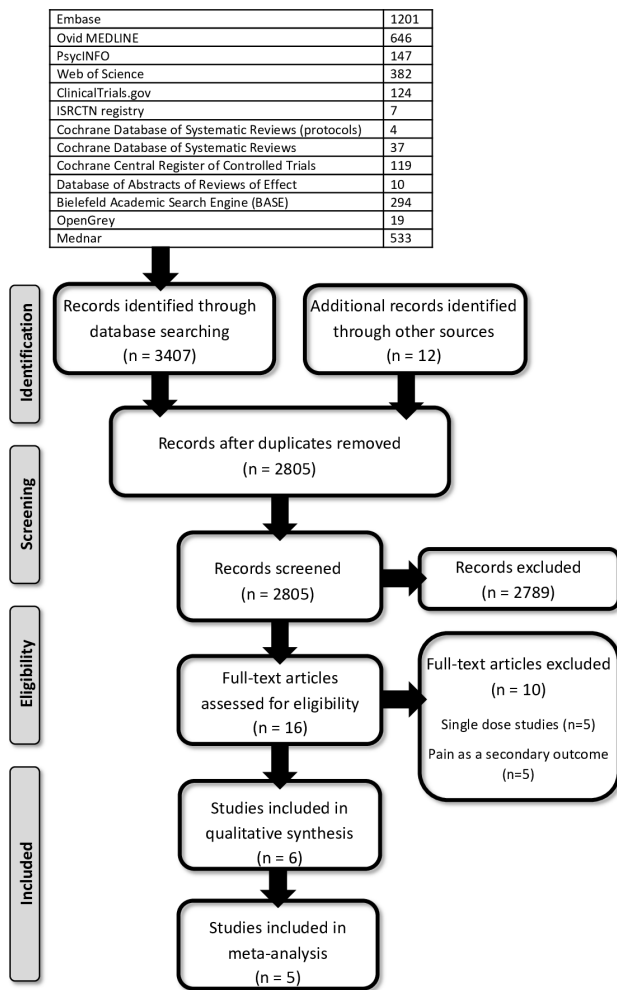


Figure 1 PRISMA flow diagram.

their relevance for inclusion. Full-text papers were retrieved for those fulfilling the criteria and also for those publications for which the ability to assess their eligibility could not be assessed on the basis of the titles and abstracts alone. EGB and JWB then independently assessed the full texts of all potentially relevant studies.

Disagreement at all stages was resolved by consensus and with recourse to a third review author (MIB). If a study was rejected at the full-text stage, a reason was given. The results of these searches and selections are shown in the PRISMA flow diagram (figure 1).¹²

Data extraction

Two authors (EGB and JWB) independently extracted data from each included paper regarding study aims/objectives, design, patient population, intervention (cannabinoid used and dose), comparator, clinical outcome measures (eg, pain) and results (association between cannabinoid use and pain and reported adverse events). Disagreement was resolved by consensus and with recourse to a third review author (MIB). When data were not reported in full, authors were contacted for additional information.

Outcomes

The primary outcome of interest was absolute mean change from baseline to the end of treatment in average pain on a Numeric Rating Scale (NRS). Secondary outcomes were adverse effects and study dropouts.

Quality assessment of data

Assessment of risk of study bias was independently assessed by two authors (EGB and JWB) using the Cochrane Collaboration risk of bias tool for RCTs which graded the risk of bias as high, low or unclear in six domains (Selection bias: random sequence generation and allocation concealment; Performance bias: blinding of participant and personnel; Detection bias: blinding of outcome assessment; Attrition bias: incomplete outcome data; Reporting bias: selective reporting).¹⁴ Disagreement at all stages was resolved by consensus and with recourse to a third review author (MIB). When this information was not available in the publication, authors were contacted.

Data analysis

For the meta-analysis, the difference in the mean change from the randomisation baseline to the end of treatment in average pain NRS score was calculated and 95% CI was calculated for each study. Data on the numbers of patients experiencing adverse events for each group, the OR and 95% CI were calculated for each study adverse event. The mean difference or ORs were pooled using a fixed-effect model or random-effects model (the Mantel-Haenszel method) and the corresponding 95% CIs were calculated.

Where the analysis indicated significant heterogeneity, a random-effects model was chosen, otherwise a fixed-effects model was applied. Statistical heterogeneity was assessed using Cochran's Q test. Cochran's Q tests the presence versus the absence of heterogeneity and the p value is stated. The I^2 index describes the percentage of variation across studies that is due to heterogeneity rather than chance. Interpretation is as follows: low, moderate and high to I^2 values of 25%, 50% and 75%, respectively.¹⁵ The importance of the observed value of I^2 depends on (1) magnitude and direction of effects and (2) strength of evidence for heterogeneity (eg, p value from the χ^2 test or a CI for I^2). A funnel plot was used to test for publication bias.

RESULTS

We identified 2805 unique records of which six RCTs were included in this systematic review. Due to the heterogeneous nature of some of these studies (in study design, duration/dose of cannabinoid administered, timing of outcome measurement), five studies were included in a meta-analysis (representing a total of 1442 participants) and six studies were included

Table 2 Data extraction

Study (author/year)	Research question/aim	Study design	Patient population/setting	Intervention	Comparator	Primary outcome	Secondary outcome(s)	Withdrawal from study due to adverse events	Risk of bias
Lichtman <i>et al</i> 2018 ⁹	To assess adjunctive nabiximols (Sativex) in patients with advanced cancer with chronic pain unalleviated by optimised opioid therapy	Phase III, double-blind, randomised placebo-controlled trial 2-week titration period followed by 3-week treatment period	Patients with advanced cancer Average cancer-related pain Numeric Rating Scale (NRS) scores >4 and ≤8 despite optimised opioid therapy (morphine equivalents dose/day ≥90 mg) 114 centres	Nabiximols oral mucosal spray (n=199) started as one spray/day, titrated by one additional spray/day (maximum daily dosage of 10 sprays)	Placebo (n=198)	Median per cent improvements in average pain NRS score from baseline to end of treatment in the nabiximols and placebo groups were 10.7% vs 4.5% (p=0.0854)—ITT population	Mean change from baseline to end of treatment: average pain NRS score, worse pain NRS score Estimated treatment difference for daily maintenance opioid dose 1.46 (p=0.6410), daily breakthrough opioid dose -1.84 (p=0.4217) and daily total opioid dose -0.34 (p=0.9328)	40 (20.1%) in nabiximols patients and 35 (17.7%) in placebo patients	Low in all domains
Fallon <i>et al</i> 2017 ¹⁸ Study 1	To assess the analgesic efficacy of adjunctive Sativex in patients with advanced cancer with chronic pain unalleviated by optimised opioid therapy	Phase III, double-blind, randomised, placebo-controlled trial 2-week titration period followed by 3-week treatment period	Advanced cancer and average pain NRS scores ≥4 and ≤8 at baseline, despite optimised opioid therapy (morphine equivalents dose/day ≤90 mg) 101 centres	Sativex (n=200) Started as one spray/day, titrated by one additional spray/day (maximum daily dosage of 10 sprays)	Placebo (n=199)	Per cent improvement in average daily pain NRS scores from baseline, Sativex 7.2% vs placebo 9.5% (median difference 1.84%, 95% CI -6.19% to 1.50%; p=0.274)	Estimated treatment effect: for average pain NRS score 0.12, 95% CI -0.18 to 0.42 (p=0.434), for worse pain NRS score 0.11, 95% CI -0.21 to 0.44 (p=0.496) Estimated treatment effect: for daily maintenance opioid dose -3.63, 95% CI -10.80 to 3.55 (p=0.321), for daily breakthrough opioid dose -4.17, 95% CI -8.76 to 0.42 (p=0.075), for daily total opioid dose -9.35, 95% CI -18.81 to 0.12 (p=0.053)	38 (19%) in nabiximols group vs 29 (14.6%) in placebo group	Low in all domains
Fallon <i>et al</i> 2017 ¹⁸ Study 2	To assess the analgesic efficacy of adjunctive Sativex in patients with advanced cancer with chronic pain unalleviated by optimised opioid therapy	Phase III, double-blind, randomised, placebo-controlled trial, enrichment enrolment with randomised withdrawal design 2-week titration period followed by 5-week treatment period	Advanced cancer and average pain NRS scores ≥4 and ≤8 at baseline, despite optimised opioid therapy (morphine equivalents dose/day ≥90 mg) 65 centres	All patients (n=406) titration of Sativex for 10 days, followed by 4 days of Sativex at the titrated dose. Patients with a ≥15% improvement from baseline in pain score were randomised 1:1 to Sativex (n=103) or placebo (n=103)	Placebo (n=103)	During the treatment period, Sativex group mean change in average daily pain NRS scores increased from 3.2 to 3.7 while the analogous values in the placebo group were 3.1 and 3.6, respectively. The estimated treatment effect -0.02, 95% CI -0.42 to 0.38 (p=0.917) 78/406 failure to demonstrate a 15% improvement in average pain NRS score during titration	Estimated treatment effect: for per cent improvement in average pain NRS score -1.23, 95% CI -6.05 to 6.59 (p=0.757), for worse pain NRS score -0.32, 95% CI -0.73 to 0.09 (p=0.124) Estimated treatment effect: for daily maintenance opioid dose -8.93, 95% CI -19.69 to 1.84 (p=0.104), for daily breakthrough opioid dose 1.81, 95% CI -10.34 to 13.96 (p=0.769), for daily total opioid dose -7.11, 95% CI -23.92 to 9.69 (p=0.405)	71 (17.5%) in the titration period vs placebo: 21 (20.4%) vs 13 (12.6%) in the 5-week double-blind treatment period	Low in all domains

Continued

Table 2 Continued

Study (author/year)	Research question/aim	Study design	Patient population/setting	Intervention	Comparator	Primary outcome	Secondary outcome(s)	Withdrawal from study due to adverse events	Risk of bias
Lynch <i>et al</i> 2014 ²⁰	To investigate nabiximols in the treatment of chemotherapy-induced neuropathic pain	Double-blind randomised, placebo-controlled cross-over pilot study Had an extension phase where 10 participants were given nabiximols to use up to 6 months Titration phase followed by 4-week treatment period and a 2-week washout period	Patients with established chemotherapy-induced neuropathic pain average 7-day intensity pain of NRS ≥ 4	Nabiximols (n=9) (oral mucosal cannabis-based spray)	Placebo (n=9)	A 0–10 point numeric rating scale for pain intensity (NRS-Pi) No statistically significant difference between the treatment and the placebo groups	Quantitative sensory testing (dynamic tactile allodynia and pinprick hyperalgesia) No statistically significant effect as compared with a placebo	No withdrawals due to adverse effects	Low in all domains
Portenoy <i>et al</i> 2012 ¹⁷	To evaluate the efficacy and safety of nabiximols in three dose ranges in patients with cancer pain not controlled with opioids	Randomised, double-blind, placebo-controlled, graded-dose study. 5-day to 14-day baseline period, a 5-week titration and treatment period, and a post-study visit after 2 weeks. The maximum duration was 9 weeks	Patients with advanced cancer and opioid-refractory pain average pain—NRS scores ≥ 4 and ≤ 8 at baseline 84 centres (360 randomised, 263 completed)	Nabiximols at a low dose (n=71) (1–4 sprays/day), medium dose (n=67) (6–10 sprays/day) or high dose (n=59) (11–16 sprays/day)	Placebo (n=66)	30% reduction in baseline pain in the mean 11-point NRS not statistically different between active drug and placebo (p=0.59)	Continuous responder analysis of average daily pain from baseline to end of study demonstrated that the proportion of patients reporting analgesic benefit was greater for nabiximols than placebo (p=0.035) In the low-dose group, the adjusted mean change in pain score was -1.5 points on the 11-point NRS (95% CI -1.28 to 0.22; p=0.006) and for medium dose was -1.1 points (95% CI -0.89 to 0.18; p=0.19) No significant difference between groups in the use of regular opioids, or number of opioids used for breakthrough pain Using the opioid composite score, more patients in the nabiximols groups had a better responder profile compared with those in the placebo group (54% vs 43%, OR 1.54, 95% CI 0.65 to 2.5; p=0.077)	Total nabiximols 53 (19.8%) 13 (14.3%) Nabiximols at a low dose 15 (17.2%) Nabiximols at a medium dose 25 (27.8%) Nabiximols at a high dose 16 (17.6%) placebo Adverse events were dose related; only the high-dose group had more adverse events compared with placebo	Low in all domains

Continued

Table 2 Continued

Study (author/year)	Research question/aim	Study design	Patient population/setting	Intervention	Comparator	Primary outcome	Secondary outcome(s)	Withdrawal from study due to adverse events	Risk of bias
Johnson <i>et al</i> 2010 ¹⁶	Efficacy of THC:CBD and THC vs placebo, in relieving pain in patients with advanced cancer with pain uncontrolled by opioids	Double-blind, randomised, placebo-controlled, parallel-group study 2-day baseline followed by 2-week treatment period	177 patients with cancer pain (NRS scores ≥ 4), who experienced inadequate analgesia despite chronic opioid dosing, entered a 2-week study (2-day baseline and 2-week treatment). Patients were randomised to THC:CBD extract (n=60), THC extract (n=58) or placebo (n=59) 28 centres	THC:CBD extract (n=60) THC extract (n=58)	Placebo (n=59)	Change from baseline in mean pain NRS score was statistically significant for THC:CBD compared with placebo (improvement of -1.37 vs -0.69). THC extract was a significant change (-1.01 vs -0.69). No significant difference between groups on the no of days breakthrough medication was used	Twice as many patients taking THC:CBD showed a reduction of more than 30% from baseline pain NRS score when compared with placebo (23 (43%) vs 12 (21%)). The OR of responders between THC:CBD and placebo was 2.81 (95% CI 1.22 to 6.5; $p=0.006$). THC group responders were similar to placebo (12 (23%) vs 12 (21%)). No of days of use of breakthrough medication was similar among all groups ($p=0.70$). There was a reduction observed in the mean no of daily doses of all breakthrough medications (THC:CBD -0.19 ; THC -0.14 ; placebo -0.15), but the difference in change from baseline between treatment groups was not significantly different	THC:CBD 10 (16.7%), THC extract 7 (12%), placebo 3 (5%)	Low in all domains

ITT, intention to treat.

in a narrative analysis (representing a total of 1460 participants).

Study characteristics

From the six included RCTs (two were reported in a single publication), one was a small cross-over pilot randomised study, two were phase II studies and three were phase III studies (table 2). From the two early randomised double-blind phase II studies in patients with advanced cancer and pain unrelieved by opioids,^{16 17} one reported that cannabinoids had analgesic effects,¹⁶ and the primary outcome of the other was negative.¹⁷ Subsequent to these studies, three phase III placebo RCTs with a similar methodology have been reported. Data from two RCTs were reported in a single publication, with the primary efficacy endpoints (percent improvement (study 1) and mean change (study 2) in average daily pain NRS scores).¹⁸ Neither these nor the third RCT (primary endpoint: per cent change in the average pain NRS score)¹⁹ reported a positive effect of nabiximols compared with placebo on their primary endpoints. These studies had a low risk of bias.

The small cross-over pilot randomised study (n=18) assessed nabiximols versus placebo for use for treatment of chemotherapy-induced neuropathic pain and reported no statistically significant difference between nabiximols and placebo on the NRS for pain intensity: mean pretreatment score=6.75; and at the end of 4 weeks, nabiximols group score=6.00 while placebo group score=6.380.²⁰ However, further analysis in five patients who responded to treatment showed an average decrease of 2.6 on an 11-point NRS for pain intensity.²⁰

Studies used a pump-action oromucosal spray for medication delivery which used 1:1 THC:CBD extract versus placebo. Some studies had additional arms, for example, THC extract.¹⁶ Dose titration differed between studies. Patients self-titrated to the optimal dose^{16 20} or were randomly assigned to different doses.¹⁷ In the phase III studies, patients titrated medication according to a pre-specified dose escalation protocol until they achieved pain relief, developed adverse events or reached the maximum dose of 10 sprays/day.^{18 19}

Study quality

Quality assessment of included studies was performed using the Cochrane Risk of Bias Tool (online supplementary table 1). The studies included were at low risk of bias. Although the studies were funded (or had medication supplied) by industry, and publication bias is more common when most of the published studies are funded by industry, taken in the context of the results, these are overall negative studies making publication bias less likely. The funnel plot (online supplementary figure 1) showed that distribution was

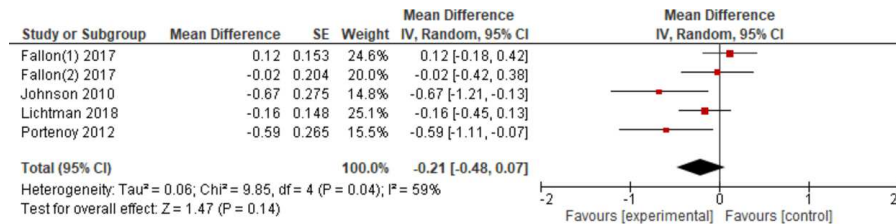


Figure 2 Forest plot for change in pain intensity for the phase II and III studies.

roughly symmetrical, indicating that publication bias was not likely to be present.

Pain

Change in pain intensity was the primary outcome of interest in this systematic review. Change in pain intensity was the primary outcome in the studies of Johnson *et al*,¹⁶ Fallon *et al*¹⁸ and Lichtman *et al*,¹⁹ and a secondary outcome in Portenoy *et al*.¹⁷ Lynch *et al* measured change in the NRS for pain intensity and reported that there was no statistically significant difference between the treatment and the placebo groups, but as this study only included people with chronic neuropathic pain and was a small exploratory study, it was not included in the meta-analysis.²⁰

The meta-analysis is shown in figure 2. There was no difference between cannabinoids and placebo for the difference in the change in average NRS pain scores: mean difference -0.21 (-0.48 to 0.07 , $p=0.14$). Including only phase III studies in the meta-analysis, there was no benefit from cannabinoid use: mean difference -0.02 (-0.21 to 0.16 , $p=0.80$) (figure 3).^{18 19} The change in pain intensity was a secondary outcome in Portenoy *et al*; their primary outcome (30% reduction in baseline pain) was not statistically different between cannabinoids and placebo ($p=0.59$).¹⁷ In Portenoy *et al*, data were not available for the mean pain difference of all three doses combined,¹⁷ so only the low dose (1–4 sprays) was used in the meta-analysis as this was the most effective dose.

Adverse events

All studies reported on adverse events (table 3). Dizziness, nausea, vomiting, somnolence and fatigue were the main reported adverse events. In general, cannabinoids were reported to have a higher risk of adverse events compared with placebo. Fallon *et al*, Lichtman *et al* and Portenoy *et al* reported only the adverse events in $\geq 5\%$ of patients.^{17–19} In Johnson *et al*, it is only those reported in three or more patients.¹⁶

Lynch *et al* reported more adverse events compared with placebo, but as this study only included people with chronic neuropathic pain and was a small pilot study, it was not included in the meta-analysis.²⁰ In the meta-analysis, only the low dose (1–4 sprays) was used from Portenoy *et al* for consistency with the pain score meta-analysis.

The meta-analysis shows a higher odds of somnolence (OR 2.69 (1.54 to 4.71), $p<0.001$) and dizziness (OR 1.58 (0.99 to 2.51), $p=0.05$) in the cannabinoid group (figure 4).^{16–19} There was also a higher odds of nausea (OR 1.41 (0.97 to 2.05), $p=0.08$) and vomiting in the cannabinoid group (OR 1.34 (0.85 to 2.11, $p=0.21$)), but these were not statistically significant (figure 4).^{16–19}

Dropouts due to adverse events

In Johnson *et al*, dropouts due to adverse events were 16.7% in the THC:CBD group and 5% in the placebo group.¹⁶ In Portenoy *et al*, adverse event discontinuations were dose related: 19.8% in all patients on nabiximols and 17.6% in the placebo group.¹⁷ In study 1 by Fallon *et al*, 19% Sativex patients and 14.6% placebo patients discontinued due to adverse events.¹⁸ In study 2 by Fallon *et al*, during the 2-week single-blind Sativex titration period, 17.5% patients discontinued Sativex due to adverse events.¹⁸ In the treatment period, 20.4% withdrew from the Sativex group and 12.6% withdrew from the placebo group.¹⁸ In Lichtman *et al*, discontinuation due to adverse events was 20.1% in the Sativex group and 17.7% in the placebo group.¹⁹ No treatment-related deaths were reported in any study. Figure 5 shows the dropouts due to adverse events which shows a higher odds of dropouts due to adverse events in the cannabinoid group (OR 1.33 (0.95 to 1.85, $p=0.10$)), but not statistically significant. In the meta-analysis, only the low dose (1–4 sprays) was used from Portenoy *et al* for consistency with the pain score meta-analysis.

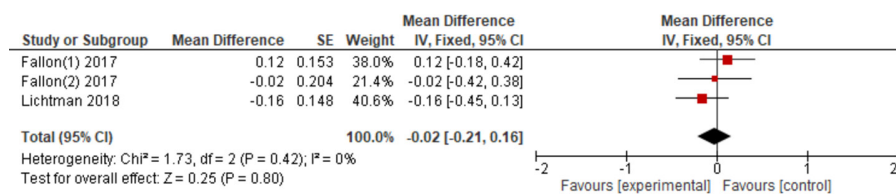


Figure 3 Forest plot for change in pain intensity for the phase III studies.

Table 3 Treatment-emergent adverse events (TEAEs)

	Total	Dizziness	Nausea/ Vomiting	Somnolence /Fatigue
Lichtman <i>et al</i> 2018 ^{19*}	Nabiximols vs placebo: 70 (35.2%) vs 41 (20.7%)	Nabiximols vs placebo: 15 (7.5%) vs 5 (2.5%)	Nabiximols vs placebo: nausea 17 (8.5%) vs 10 (5.1%)	Occurred at an incidence of <5% within each treatment group
Fallon <i>et al</i> 2017 ¹⁸ Study 1*	Nabiximols vs placebo: 64 (32.2%) vs 41 (20.7%)	Nabiximols vs placebo: 15 (7.5%) vs 6 (3.0%)	Nabiximols vs placebo: nausea 10 (5.0%) vs 8 (4.0%)	Nabiximols vs placebo: somnolence 18 (9.0%) vs 6 (3.0%)
Fallon <i>et al</i> 2017 ¹⁸ Study 2 single-blind enrichment phase*	128 (31.7%)	Dizziness 21 (5.2%)	Nausea 21 (5.2%)	Somnolence 42 (10.4%)
Fallon <i>et al</i> 2017 ¹⁸ Study 2 double-blind randomised controlled trial*	Nabiximols vs placebo: 16 (15.5%) 12 (11.7%)	Occurred at an incidence of <5% within either treatment group	Occurred at an incidence of <5% within either treatment group	Nabiximols vs placebo: somnolence 6 (5.8%) vs 0 (0.0%)
Lynch <i>et al</i> 2014 ²⁰	Not reported	Nabiximols vs placebo: 6 (66.7%) vs 0	Nabiximols vs placebo: Nausea 6 (66.7%) vs 1 (11.1%)	Nabiximols vs placebo: Fatigue 7 (77.8%) vs 0
Portenoy <i>et al</i> 2012 ¹⁷	No of TEAEs Nabiximols at a low dose 270, medium dose 311, high dose 334, all 915, placebo 215. Serious TEAE: nabiximols low dose 34 (37.4%), medium dose 18 (20.7%), high dose 27 (30%), all 79 (29.5%); placebo 22 (24.2%)	Nabiximols low dose 10 (11%), medium dose 21 (24.1%), high dose 20 (22.2%) vs placebo 12 (13.2%)†	Nabiximols for nausea low dose 16 (17.6%), medium dose 18 (20.7%), high dose 25 (27.8%) vs placebo 12 (13.2%)† Nabiximols for vomiting low dose 9 (9.9%), medium dose 14 (16.1%), high dose 19 (21.1%) vs placebo 7 (7.7%)†	Nabiximols for somnolence low dose 8 (8.8%), medium dose 16 (18.4%), high dose 15 (16.7%) vs placebo 4 (4.4%)† Nabiximols for fatigue low dose 4 (4.4%), medium dose 4 (4.6%), high dose 5 (5.6%) vs placebo 4 (4.4%)†
Johnson <i>et al</i> 2010 ^{16‡}	From all patients: 106 (60%)	THC:CBD 7 (12%), THC extract 7 (12%) vs placebo 3 (5%)	Nausea: THC:CBD 6 (10%), THC extract 4 (7%) vs placebo 4 (7%) Vomiting: THC:CBD 3 (5%), THC extract 4 (7%) vs placebo 2 (3%)	Somnolence: THC:CBD 8 (13%), THC extract 8 (14%) vs placebo 6 (10%)

*Treatment-emergent adverse events in ≤5% of patients.

†Treatment-emergent adverse events reported by ≥5% of patients.

‡Treatment-related adverse events (reported by ≥3 patients).

DISCUSSION

Studies with a low risk of bias showed that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain compared with placebo. This work complements and builds on the systematic review by Häuser *et al.*⁸ Although the same overall conclusions were attained, this systematic review and meta-analysis is based on additional methodological information and thus supported by higher-quality evidence (as included studies were deemed to have lower risk of bias). Furthermore, the primary outcome in this systematic review is a more sensitive outcome to detect minimal changes in pain.⁹ This systematic review provides good evidence that cannabinoids do not have a role in cancer-related pain.

In all the included RCTs, pain was the primary reason for administering cannabinoids and change in pain score or pain intensity was the primary outcome. Five RCTs were included in the meta-analysis (n=1442) where cannabinoids were given as an adjuvant treatment in addition to their existing stable dose of opioids. In the meta-analysis, the two phase II studies and three phase III studies included patients with chronic cancer pain (average pain duration of all studies of 1.2–2.0

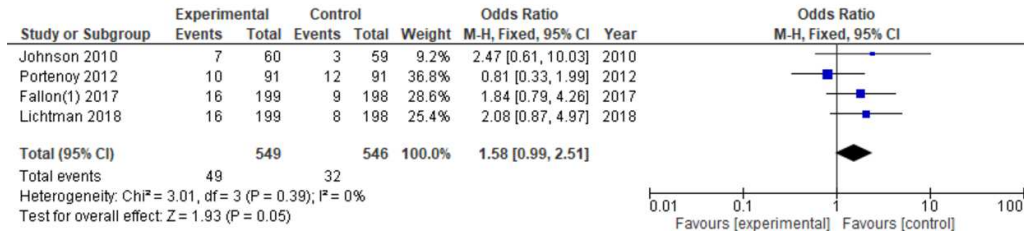
years), with an average pain ≥4 and ≤8 on 0–10 NRS pain score, who were on regular opioids, randomised to the same THC:CBD medication and had a placebo comparator.

Five trials from four publications in the 1970s (including a total of 128 participants) were excluded as these were single-dose studies, assessing short-term effects of cannabinoids at 6–7 hours.^{21–24} Four of these studies evaluated delta-9-tetrahydrocannabinol (THC) or nitrogen-containing benzopyran derivative, modification of delta-1-*trans*-tetrahydrocannabinol (NIB).^{21 22 24} The fifth study used the cannabinoid benzopyranoperidine.²³ Of these five single-dose studies assessing efficacy at 6–7 hours, three used THC or NIB and reported no difference in efficacy compared with codeine.^{21 22 24} The fifth study used the cannabinoid benzopyranoperidine and reported that about 30% of patients had increased pain intensity with this drug.²³

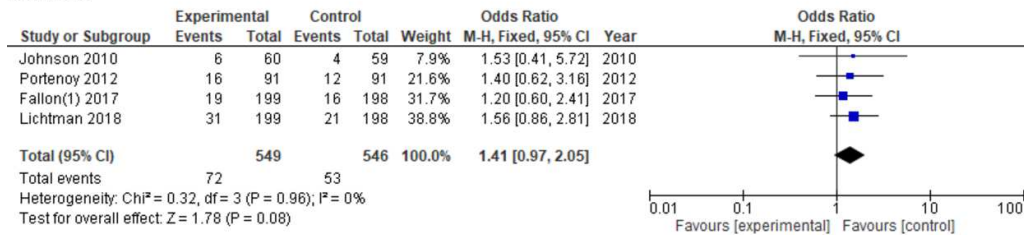
Side effects

Cannabinoids are associated with short-term adverse effects including drowsiness, dizziness, confusion, hallucinations, euphoria, nausea and vomiting, and

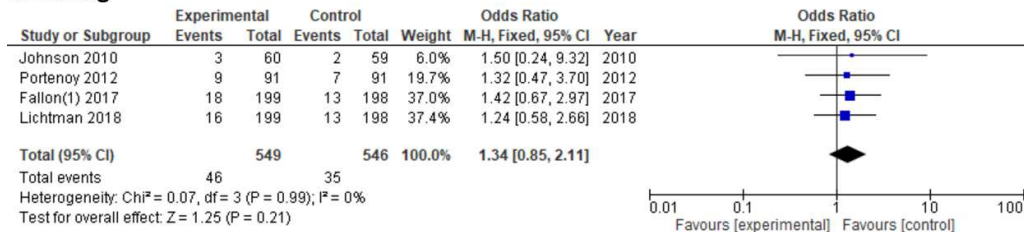
Dizziness



Nausea



Vomiting



Somnolence

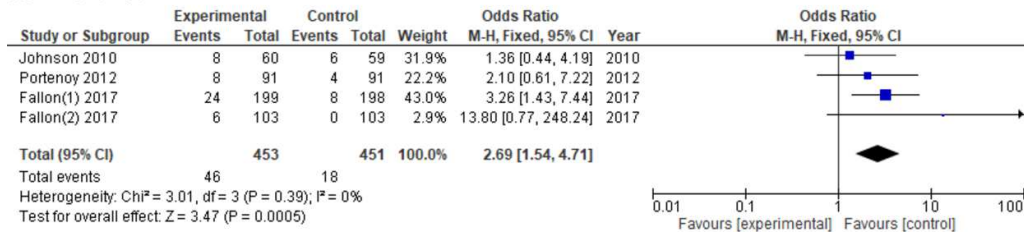


Figure 4 Forest plots for the main adverse effects for the phase II and III studies (Fallon study 2 not included for adverse effects where <5% had adverse effect).

diarrhoea.²⁵ A systematic review evaluating the adverse effects of medical cannabinoids reported patients using medical cannabinoids had 1.86 times higher risk of non-serious adverse effects compared with controls

while there was no significant difference between serious adverse effects.²⁶

Our analysis echoed this, showing that in general cannabinoids were reported to have a higher risk of

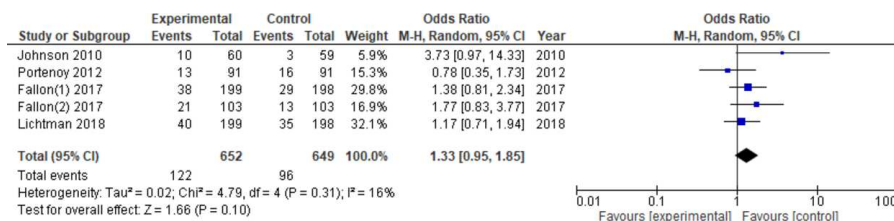


Figure 5 Dropouts due to adverse events.

adverse events compared with placebo with somnolence and dizziness reaching statistical significance.

Strengths and limitations

This is a rigorously conducted systematic review that included 'grey' literature and authors were contacted when data and methodological information was not included in the publication. This enabled the included studies to be considered at low risk of bias. The studies included were RCTs that assessed clinically relevant cannabinoids as an adjuvant to opioid medications in patients with advanced cancer that had mixed aetiologies of pain due to their cancer. Change in pain score was used as the primary outcome to assess if cannabinoids had an effect on pain as this is more sensitive to changes compared with 30% or 50% decrease in pain.

Despite the detailed search strategy, it is possible that not all relevant studies were included. There were inconsistencies between studies in the patients included, the interventions, comparators and outcomes. In the meta-analysis, a secondary outcome was used for Portenoy *et al* (as this was the primary outcome for this systematic review).^{16 17}

The included studies had several potential limitations. Self-reported NRS pain score might not be the best measure for such trials, as this simple instrument does not capture the complexity of pain especially when it has been long-standing problem. The fidelity of the use of the oromucosal spray, which affects absorption and pharmacokinetic factors, was not assessed and this might also affect the effectiveness of the medication used and the outcome measured. Some of the included studies had kept the maintenance doses of opioid and other medications the same throughout the trial; ways to decrease doses when appropriate should be considered as this might also have an impact on adverse effects. The negative results from some of the RCTs could be due to a relatively high number of patient withdrawals and high mortality rate.^{16–19} Publication bias is more common when most of the published studies are funded by industry. However, the primary outcome for most of these studies was negative, making publication bias less likely for these studies. Aside from lack of therapeutic efficacy, the negative results from some of the RCTs could also be due to a relatively high number of patient withdrawals from studies, and also high mortality rate and increased number of lost patients.^{16–19}

CONCLUSION

For a medication to be useful, there needs to be a net overall benefit, with the positive effects (analgesia) outweighing adverse effects. None of the included phase III studies show benefit of cannabinoids. One of the phase II studies showed benefit in their primary outcome¹⁶; the other was negative in its primary outcome, although a secondary outcome was positive.¹⁷ When statistically pooled, there was no decrease

in pain score from cannabinoids. There are, however, significant adverse effects and dropouts reported from cannabinoids. Based on evidence with a low risk of bias, cannabinoids cannot be recommended for the treatment of cancer-related pain.

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