Cannabinoids for cancer-related pain in adults: systematic review and meta-analysis.

Dr Elaine G Boland[a], Professor Michael I Bennett[b] , Dr Victoria Allgar[c] Dr Jason W Boland[d*]

[a]*Hull University Teaching Hospitals NHS Trust, Cottingham, HU16 5JQ*

[b]*Academic Unit of Palliative Care, University of Leeds, LS2 9LJ, UK*

[c]*Hull York Medical School, University of York, York, YO10 5DD, UK*

[d]*Hull York Medical School, University of Hull, Hull, HU6 7RX, UK*

*Corresponding author: Dr Jason Boland, Senior Clinical Lecturer and Honorary Consultant in Palliative Medicine.

Address: *Hull York Medical School, University of Hull, Hull, HU6 7RX, UK*.

Tel: +44 1482 463482; fax: +44 1482 464705.

E-mail address: Jason.Boland@hyms.ac.uk

Abstract

Objectives

There is increased interest in cannabinoids for cancer pain management and legislative changes are in progress in many countries. Aim: to determine the beneficial and adverse effects of cannabis/cannabinoids compared to 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 to 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 (PRISMA) guidelines were followed. It was registered on PROSPERO (CRD42018107662).

Results

We identified 2805 unique records, of which 6 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, 0.07, p=0.14)); this remained when only Phase 3 studies were meta-analysed: mean difference -0.02 (-0.21, 0.16, p=0.80). Cannabinoids had a higher risk of adverse events when compared to placebo, especially somnolence (OR=2.69, (1.54, 4.71), p<0.001) and dizziness (OR=1.58, (0.99, 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.

Keywords: cannabis, cannabinoids, neoplasia, cancer pain, systematic review

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 World Health Organization 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 cancer patients 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 to 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 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 Hauser 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 e.g. 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 to 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) statement [11] and was conducted/reported following an *a priori* protocol according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]
The review protocol was registered on PROSPERO (http://www.crd.york.ac.uk/PROSPERO) before the searches were performed (registration no. CRD42018107662).[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 a 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); and Database of Abstracts of Reviews of Effect (Wiley). All searches were repeated on the 1st August 2019 to ensure 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/).

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 to 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 sub-group, 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.

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 (RCTs)	Cohort studies, prospective and retrospective observational studies, case studies and database analysis

Two authors (E.G.B. and J.W.B.) independently reviewed all titles and abstracts (in duplicate) to assess 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. E.G.B. and J.W.B. 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 (M.I.B.). 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 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Figure 1).[12]

Data extraction

Two authors (E.G.B. and J.W.B.) 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 (M.I.B.). 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 Numerical 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 (E.G.B. and J.W.B.) using the Cochrane Collaboration risk of bias tool for RCTs which graded the risk of bias as high, low or unclear in 6 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 (M.I.B.). 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 randomization baseline to the end of treatment in average pain NRS score was calculated and 95% confidence interval was calculated for each study. Data on the numbers of patients experiencing adverse events for each group, the odds ratio (OR) and 95% confidence interval (CI) were calculated for each study AE. The mean difference or OR's 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 the Cochran's Q test. The 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 (i) magnitude and direction of effects and (ii) strength

of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2). A funnel plot was used to test for publication bias.

Results

We identified 2805 unique records of which 6 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), 5 studies were included in a meta-analysis (representing a total of 1442 participants) and 6 studies were included in a narrative analysis (representing a total of 1460 participants).

Study characteristics

From the 6 included RCTs (two were reported in a single publication), one was a small cross-over pilot randomized study, two were phase 2 studies and three were phase 3 studies (Table 2). From the two early randomized double-blind phase 2 studies in patients with advanced cancer and pain unrelieved by opioids,[16, 17] one reported that cannabinoids had analgesic effects,[16] the primary outcome of the other was negative.[17] Subsequent to these studies, three phase 3 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: percent change in the average pain NRS score),[19] reported a positive effect of nabiximols compared to placebo on their primary endpoints. These studies had a low risk of bias.

The small cross-over pilot randomized study (n=18) assessed nabiximols vs placebo for use for treatment of chemotherapy-induced neuropathic pain and reported no statistically significant difference between nabiximols and placebo on the numeric rating scale for pain intensity: mean pretreatment score=6.75; and at the end of 4 weeks, nabiximols group score=6.00 whilst placebo group score=6.38.[20] However, further analysis in 5 patients who responded to treatment showed an average decrease of 2.6 on an 11-point numeric rating scale 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 eg 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 3 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 (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 (Supplementary Figure 1) showed that distribution was roughly symmetrical, indicating that publication bias was not likely to be present.

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 2018	To assess adjunctive nabiximols (Sativex), in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.	Phase 3, double-blind, randomized placebo-controlled trial 2-week titration period followed by 3 weeks treatment period	Patients with advanced cancer Average cancer-related pain Numerical Rating Scale (NRS) scores >4 and ≤8 despite optimized opioid therapy (morphine equivalents dose/day ≥90mg) 114 centres	Nabiximols oral mucosal spray (n =199) started as 1 spray/day, titrated by one additional spray/day (maximum daily dosage of 10 sprays)	Placebo (n= 198)	Median percent 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%) nabiximols patients and 35 (17.7%) placebo patients	Low in all domains
Fallon 2017 Study-1	To assess the analgesic efficacy of adjunctive Sativex in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.	Phase 3, double-blind, randomized, placebo-controlled trial 2-week titration period followed by 3 week treatment period	Advanced cancer and average pain numerical rating scale (NRS) scores ≥ 4 and ≤ 8 at baseline, despite optimized opioid therapy. (morphine equivalents dose/day ≥90mg) 101 centres	Sativex (n=200) Started as 1 spray/day, titrated by one additional spray/day (maximum daily dosage of 10 sprays)	Placebo (n= 199)	Percent improvement in average daily pain NRS scores from baseline, Sativex 7.2% vs placebo 9.5% (median difference 1.84%, 95%CI -6.19%, 1.50%; P=0.274)	Estimated treatment effect: for average pain NRS score 0.12, 95% CI -0.18, 0.42 (P=0.434), for worse pain NRS score 0.11, 95% CI -0.21, 0.44 (P=0.496) Estimated treatment effect: for daily maintenance opioid dose -3.63, 95% CI -10.80, 3.55 (P=0.321), for daily	38 (19%) in nabiximols group vs 29 (14.6%) placebo group	Low in all domains

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
							breakthrough opioid dose -4.17, 95%CI -8.76, 0.42 (P=0.075), for daily total opioid dose -9.35, 95%CI -18.81, 0.12 (P=0.053)		
Fallon 2017 Study-2	To assess the analgesic efficacy of adjunctive Sativex in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy.	phase 3, double-blind, randomized, placebo-controlled trial, enrichment enrolment with randomized withdrawal design 2-week titration period followed by 5-week treatment period	Advanced cancer and average pain numerical rating scale (NRS) scores ≥ 4 and ≤ 8 at baseline, despite optimized opioid therapy. (morphine equivalents dose/day ≥90mg) 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 randomized 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 whilst the analogous values in the placebo group were 3.1 and 3.6 respectively. The estimated treatment effect -0.02, 95% CI -0.42, 0.38 P=0.917) 78/ 406) failure to demonstrate a 15% improvement in average pain NRS score during titration	Estimated treatment effect: for percent improvement in average pain NRS score -1.23, 95% CI -9.05, 6.59 (P=0.757), for worse pain NRS score -0.32, 95% CI -0.73, 0.09 (P=0.124) Estimated treatment effect: for daily maintenance opioid dose -8.93, 95% CI -19.69, 1.84 (P=0.104), for daily breakthrough opioid dose 1.81, 95%CI -10.34, 13.96 (P=0.769), for daily total opioid dose -7.11, 95%CI -23.92, 9.69 (P=0.405)	71 (17.5%) in the titration period nabiximols vs placebo: 21 (20.4%) vs 13 (12.6%) in the 5-week double-blind treatment period	Low in all domains

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 2014	To investigate nabiximols in the treatment of chemotherapy-induced neuropathic pain	Double-blind randomized, placebo-controlled crossover 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 2012	To evaluate the efficacy and safety of nabixomols in 3 dose ranges in patients with cancer pain not controlled with opioids	Randomized, double-blind, placebo-controlled, graded-dose study. 5- to 14-day baseline period, a 5-week titration	Patients with advanced cancer and opioid-refractory pain average pain - NRS scores ≥ 4 and ≤ 8 at baseline	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	Total nabiximols 53 (19.8%) 13 (14.3%) nabiximols at a low dose 15 (17.2%) nabiximols	Low in all domains

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
		and treatment period, and a post-study visit after 2 weeks. The maximum duration was 9 weeks	84 centres (360 randomised, 263 completed)				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, -0.22; P = 0.006) and for medium-dose was -1.1 points (95% CI: -0.89, 0.18; P = 0.19) groups compared to placebo. No significant difference between groups in the use of regular opioids, or number of opioid used for breakthrough pain. Using the opioid composite score more patients in the nabiximol groups had a better responder profile compared to those in the placebo group (54% vs 43%, OR =1.54, 95% CI: 0.95, 2.5; P=0.077).	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 to placebo	

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 2010	Efficacy of THC:CBD and THC vs placebo, in relieving pain in patients with advanced cancer with pain uncontrolled by opioids	Double-Blind, Randomized, 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 two-week study (2-day baseline and 2-week treatment). Patients were randomized 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, 6.5; P=0.006). THC group responders was similar to placebo (12 [23%] vs. 12 [21%]). Number of days of use of breakthrough medication used was similar amongst all groups (p=0.70). There was a reduction observed in the mean number of daily doses of all breakthrough medication (THC:CBD -0.19; THC -0.14, Placebo -0.15) but the difference in change from baseline	THC:CBD 10 (16.7%), THC extract 7 (12%), placebo 3 (5%)	Low in all domains

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
							between treatment groups was not significantly different.		

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, Johnson et al,[16] Fallon et al,[18] Lichtman et al [19] and a secondary outcome in Portenoy et al.[17] Lynch et al measured change in the numeric rating scale 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, 0.07, p=0.14). Including only Phase 3 studies in the meta-analysis, there was no benefit from cannabinoid use: mean difference -0.02 (-0.21, 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 was 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 to placebo. Fallon et al, Lichtman et al and Portenoy et al reported only the adverse events in ≥5% of patients.[17, 18, 19] In Johnson et al, it is only those reported in 3 or more patients.[16] Lynch et al reported more adverse events compared to 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.

Table 3: Treatment-emergent adverse events (TEAE)

	Total	Dizziness	Nausea/ Vomiting	Somnolence /Fatigue
Lichtman 2018 *	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 2017 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 2017 Study-2 single-blind enrichment phase *	128 (31.7%)	Dizziness 21 (5.2%)	Nausea 21 (5.2%)	somnolence 42 (10.4%)
Fallon 2017 Study-2 double-blind RCT *	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 2014	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 2012	Number of TEAE Nabiximols at a low dose 270, medium dose 311, high dose 334, all 915, placebo 215. Serious TEAE: low dose Nabiximols 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 2010 ***	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)

The meta-analysis shows a higher odds of somnolence (OR=2.69, (1.54, 4.71), p<0.001) and dizziness (OR=1.58, (0.99, 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, 2.05), p=0.08) and vomiting in the cannabinoid group (OR=1.34, (0.85, 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, 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.

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 to placebo. This work complements and builds on the systematic review by Hauser 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 2 studies and three phase 3 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, were on regular opioids, randomized 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-v-tetrahydrocannabinol (THC) or nitrogen-containing benzopyran derivative, modification of delta-1-trans-tetrahydrocannabinol (NIB).[21, 22, 24] The 5th 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 different in efficacy compared to codeine.[21, 22, 24] The 5th 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, diarrhoea.[25] A systematic review evaluating the adverse effects of medical cannabinoids reported patients using medical cannabinoids had 1.86 higher risk of non-serious adverse effects compared to controls whilst 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 adverse events compared to 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 to 30% or 50% decrease in pain.

Despite the detailed search strategy, it is possible that not all relevant studies were included. There were inconsistences 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 3 studies show benefit of cannabinoids. One of the phase 2 studies showed benefit in their primary outcome,[16] 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.

Contributors

EGB, MIB and JWB, contributed to study design. EGB and JWB performed the searches contributed to data collection and data analysis. JWB and EGB drafted the article. VA undertook the statistical analysis. MIB contributed to writing of the article. All authors were responsible for approval of the final report.

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Conflict of interest

All authors declare that there are no conflicts of interest.

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ISRCTN registry	7
Cochrane Database of Systematic Reviews (protocols)	4
Cochrane Database of Systematic Reviews	37
Cochrane Central Register of Controlled Trials	119
Database of Abstracts of Reviews of Effect	10
Bielefeld Academic Search Engine (BASE)	294
OpenGrey	19
Mednar	533

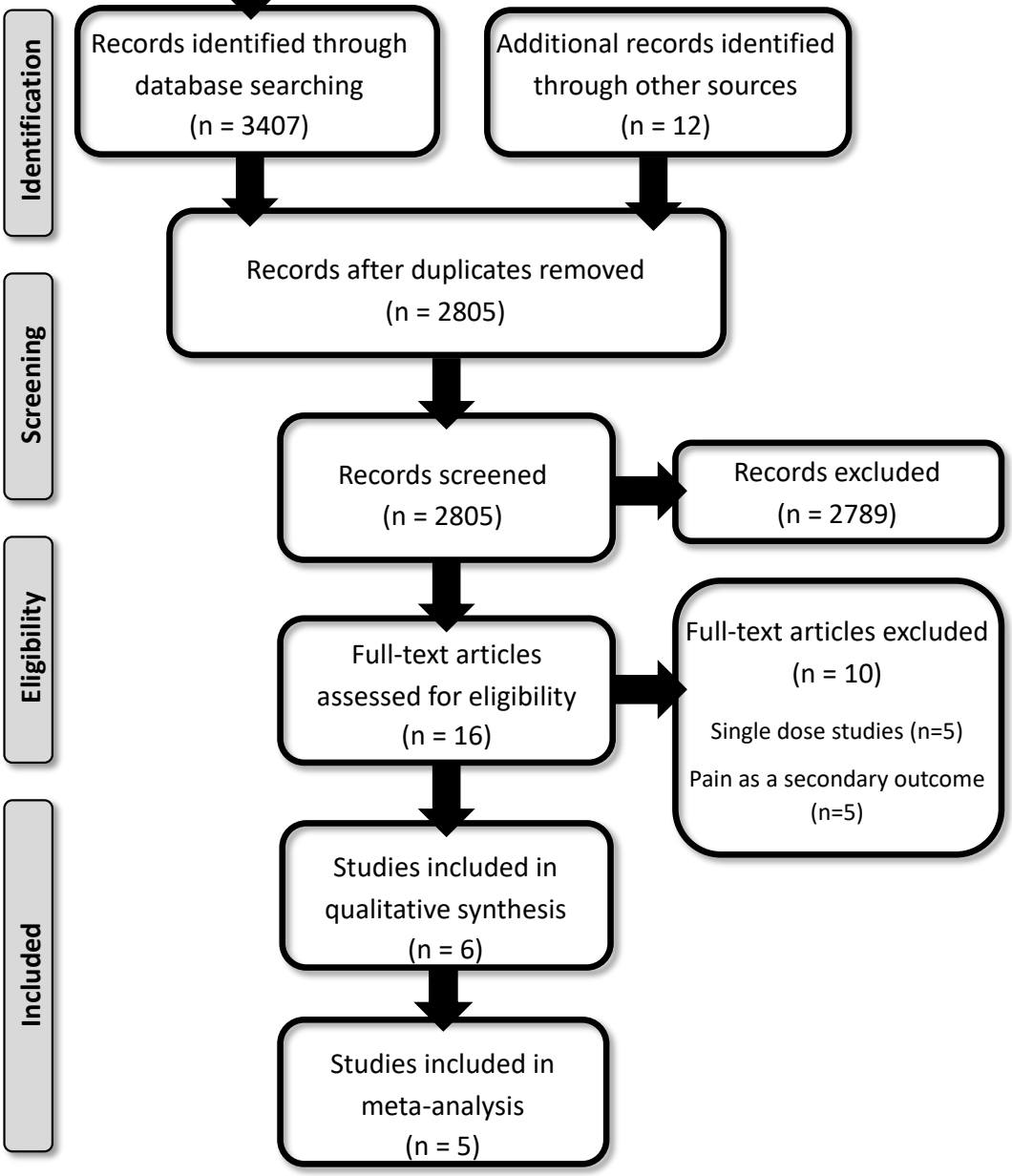


Figure 1: PRISMA flow diagram

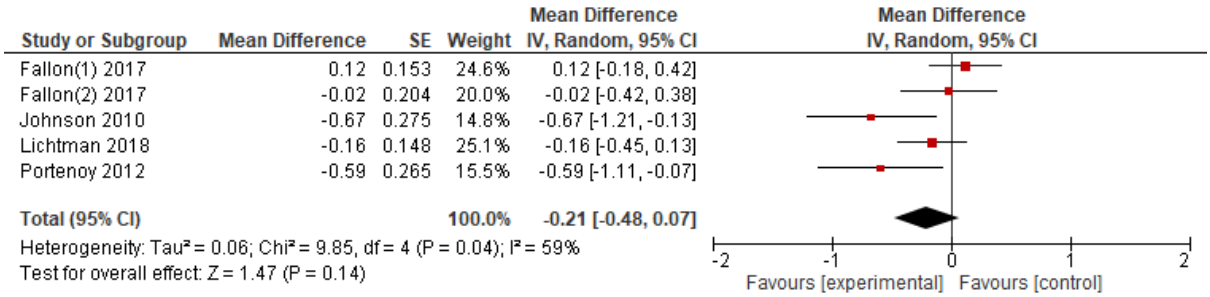


Figure 2: Forest plot for change in pain intensity for the phase 2 and 3 studies.

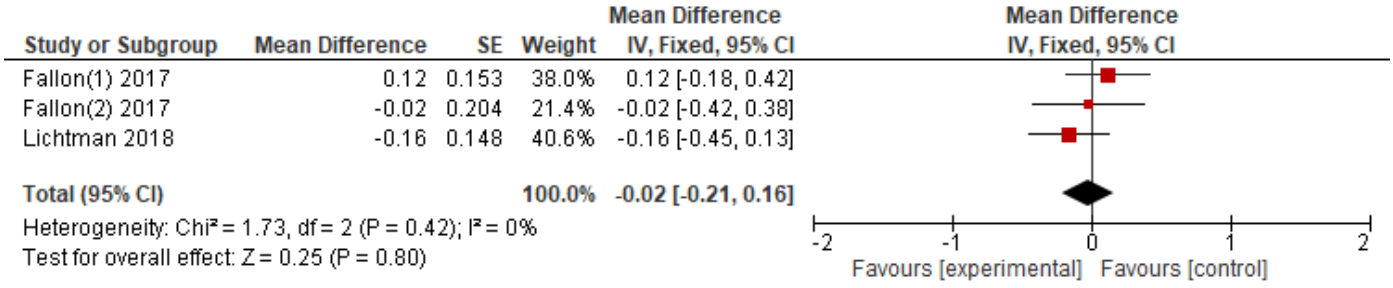
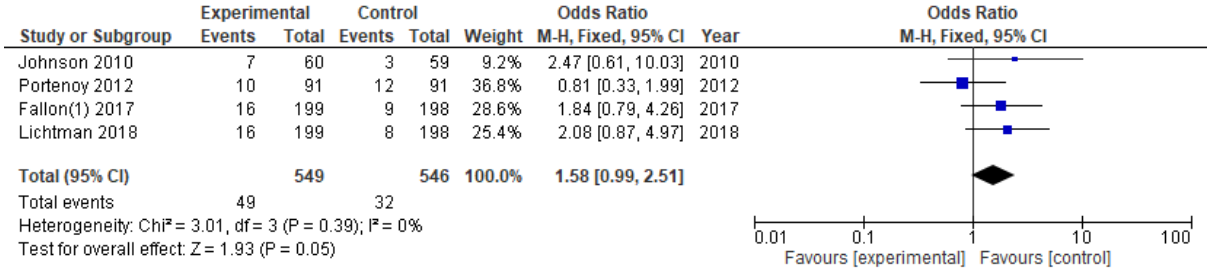
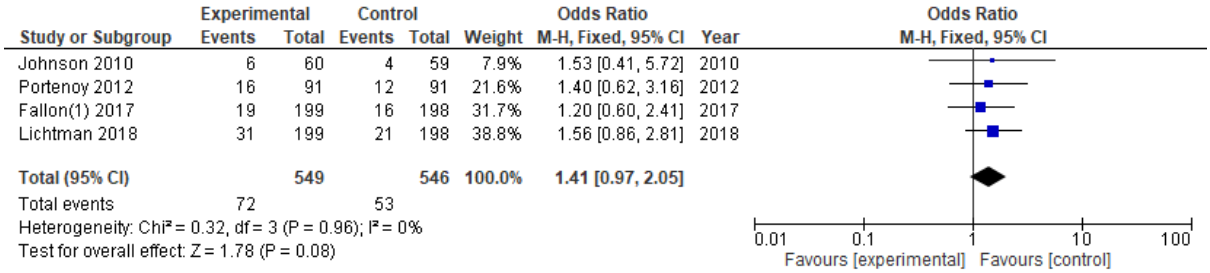


Figure 3: Forest plot for change in pain intensity for the phase 3 studies.

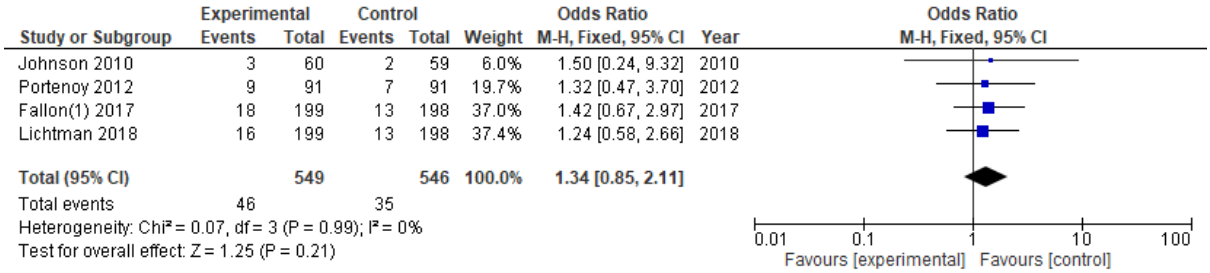
Dizziness



Nausea



Vomiting



Somnolence

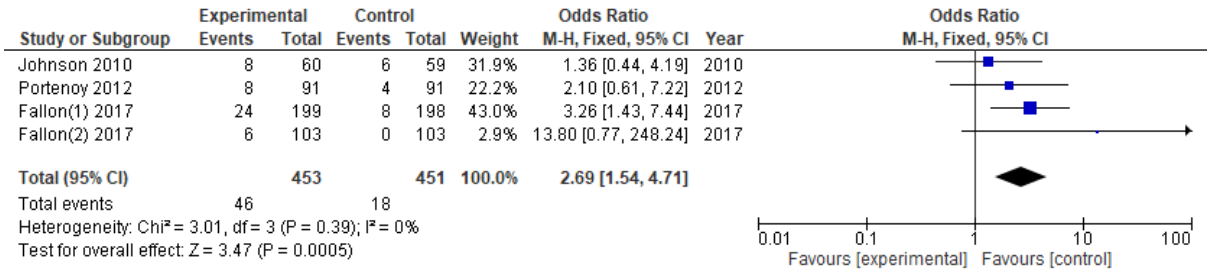


Figure 4: Forest plots for the main adverse effects for the phase 2 and 3 studies. (Fallon study 2 not included for adverse effects where <5% had adverse effect).

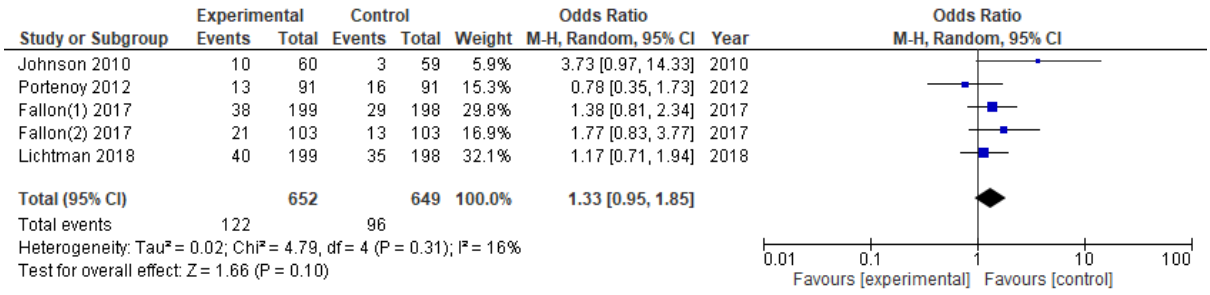


Figure 5: Dropouts due to adverse events