Cannabinoid co-administration may enable reduced opioid doses for analgesia. This updated systematic review on the opioid-sparing effects of cannabinoids considered preclinical and clinical studies where the outcome was analgesia or opioid dose requirements. We searched Scopus, Cochrane Central Registry of Controlled Trials, Medline, and Embase (2016 onwards). Ninety-two studies met the search criteria including 15 ongoing trials. Meta-analysis of seven preclinical studies found the median effective dose (ED50) of morphine administered with delta-9-tetrahydrocannabinol was 3.5 times lower (95% CI 2.04, 6.03) than the ED50 of morphine alone. Six preclinical studies found no evidence of increased opioid abuse liability with cannabinoid administration. Of five healthy-volunteer experimental pain studies, two found increased pain, two found decreased pain and one found reduced pain bothersomeness with cannabinoid administration; three demonstrated that cannabinoid co-administration may increase opioid abuse liability. Three randomized controlled trials (RCTs) found no evidence of opioid-sparing effects of cannabinoids in acute pain. Meta-analysis of four RCTs in patients with cancer pain found no effect of cannabinoid administration on opioid dose (mean difference −3.8 mg, 95% CI −10.97, 3.37) or percentage change in pain scores (mean difference 1.84, 95% CI 1.03, 1.24); five studies found more adverse events with cannabinoids compared with placebo (risk ratio 1.13, 95% CI 1.01, 1.24). Of five controlled chronic non-cancer pain trials; one low-quality study with no control arm, and one single-dose study reported reduced pain scores with cannabinoids. Three RCTs found no treatment effect of dronabinol. Meta-analyses of observational studies found 39% reported opioid cessation (95% CI 0.15, 0.64, I² 95.5%, eight studies), and 85% reported reduction (95% CI 0.64, 0.99, I² 92.8%, seven studies). In summary, preclinical and observational studies demonstrate the potential opioid-sparing effects of cannabinoids in the context of analgesia, in contrast to higher-quality RCTs that did not provide evidence of opioid-sparing effects.

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INTRODUCTION

Opioids are widely prescribed for chronic pain, but due to concerns related to harms, recommendations have been made to reduce reliance on higher doses [1]. One strategy to reduce opioid dose requirements has been through use of opioid-sparing medicines. Opioid-sparing medicines can (1) delay or prevent the initiation of treatment with opioid analgesics (2) decrease the duration of opioid treatment (3) reduce the total dosages of opioid used or (4) reduce opioid-related adverse outcomes, without causing an unacceptable increase in pain [2].

There is substantial interest in the opioid-sparing potential of cannabinoids in the context of pain management. Preclinical data have consistently demonstrated opioid-sparing effects [3]. Interest from policy makers has been further driven by ecological and epidemiological research [4]; however, highly publicized findings have recently been questioned [5]. The overlapping neuroanatomical distribution of opioid and cannabinoid receptors in the central and peripheral nervous system in areas involved with anti-nociception support potential opioid-sparing effects. Opioids and cannabinoids have comparable

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neurobiological properties with significant degree of functional interaction [6]. Opioid and cannabinoid receptors are G₁₂₀-protein-coupled receptors with similar intracellular signaling mechanisms, including: inhibition of the adenylate cyclase activity, reduced activity of voltage-dependent calcium channels, activation of inwardly-rectifying potassium channels, and stimulation of the MAP kinase cascade. Cannabinoid type-1 (CB1) and mu receptors can interact directly as functional heterodimers when co-expressed in the same neuron [7] and cannabinoid administration may stimulate the synthesis and release of endogenous opioid peptides centrally and peripherally [8]. Each of these properties would predict a synergistic interaction between opioids and cannabinoids, yet further complexity is afforded by the pharmacological profile of the drug. For example, in the case of protein agonists the level of activation of cannabinoid receptors (both constitutive and stimulated) impacts upon the observed pharmacological effect [9, 10], whilst partial agonists such as the endocannabinoid anandamide could act as an antagonist in the presence of a more efficacious agonist [11].

Our previous systematic review and meta-analysis found robust preclinical evidence supporting the opioid-sparing potential of delta-9-tetrahydrocannabinol (THC), but limited clinical research testing the opioid-sparing effects of cannabinoids [3]. With the proliferation of research in the past five years, this review aims to provide an updated synthesis of preclinical and clinical studies on the opioid-sparing effects of cannabinoids.

MATERIALS AND METHODS

Search
We conducted an updated systematic literature search in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12]. The initial searches conducted on October 29, 2015, had no date limits and the findings have been reported earlier, along with the methods (in lieu of a published/registered protocol) [3]. The updated searches were conducted on December 20, 2020 via Scopus, Cochrane Central Registry of Controlled Trials, Medline, and Embase databases and results were combined with the earlier search. A combination of search terms relating to opioids (e.g., analgesics, opioid*, opiate), cannabinoids (e.g., cannabis, sativex, nabiximol, cannabidiol, tetrahydrocannabinol) and outcomes of interest (e.g., pain, opioid sparing, opioid dose, antinociceptive) were used, consistent with the initial search (Appendix 1). Additional targeted searches of reference lists from identified studies and review articles were conducted to find additional studies not identified by the main searches.

Study eligibility
Eligible studies included: (i) human or animal studies; (ii) for human studies, controlled clinical and preclinical studies where cannabinoids were administered within a medical or clinical therapeutic framework and the study outlined details of cannabinoid administration; (iii) documented concurrent administration of opioids and cannabinoids; (iv) an outcome of either pain/analgesia (including acute, chronic, cancer and non-cancer and experimental pain studies) or opioid requirements/opioid-sparing. Studies were excluded based on the following criteria: (i) wrong intervention (e.g., cannabinoid use not defined, no cannabinoid administered, non-concurrent opioid and cannabinoid use, non-therapeutic opioid use); (ii) wrong study design (e.g., case reports, epidemiological studies, reviews, letters without empirical data, commentary or news article); (iii) no outcome measure of interest (i.e., pain/analgesia or opioid dose); (iv) full text unavailable; (v) duplicate manuscript; (vi) abstract where full paper published; (vii) unable to confirm eligibility details, or access required data from authors (Appendix 2).

Titles and abstracts, and full texts were screened independently by two authors (SN, LMP, JM, BM, GC, MG, LP and K-EK) using Covidence software [13]. Where inconsistencies were identified, the authors were able to reach consensus on each occasion.

Data extraction and outcomes
The same data extraction forms used in the initial review were used. All data were extracted by one of the authors (SN, LMP and BW, BM) and checked by a second author (SN, LP, BM, JM, MG or K-EK). These same authors reviewed and resolved any inconsistencies. For abstracts without a full text, and missing data, attempts were made to contact authors for additional information.

Outcome measures
For preclinical studies, the primary outcome was the dose of opioid required to give an equivalent antinociceptive effect in the presence and absence of cannabinoids.

Analysis

Preclinical studies. Data were extracted and, where studies that were sufficiently similar in design and outcome measures, meta-analysis was undertaken. For the residual studies, a narrative review was conducted. To prepare the data for the meta-analysis, the ED₅₀ and either confidence limits or standard error were extracted from the relevant literature. ED₅₀ is calculated on the log₁₀ scale. Therefore, to meet the assumption of normality, the log₁₀ ED₅₀ must be used in the meta-analysis. The log₁₀ of the confidence limits must also be determined to calculate the standard deviation (SD) of the log₁₀ ED₅₀:

\[ SD \left( \log_{10} ED_{50} \right) = \log_{10} UL - \log_{10} ED_{50} / 1.96 \]

where UL is the upper confidence limit.

When only standard error was reported, the confidence limits were calculated using the method of Litchfield and Wilcoxon [14] and the above procedure was repeated to calculate the standard deviation. This method also allowed for the inclusion of studies that did not report exact sample sizes for all treatment groups, as sample size was not required for the calculation of standard deviation.

For data for the meta-analysis were analyzed using Review Manager 5.4 (Cochrane Collaboration, Oxford, UK). When calculating the continuous outcome of an equally effective opioid dose (e.g., the log₁₀ED₅₀ for morphine when administered alone versus when administered with a cannabinoid), the inverse variance statistical method and random effects model were used to compensate for study heterogeneity.

No statistical difference was found in outcomes between the studies that used different rodent species or nociceptive assays. Therefore, the mean difference of log₁₀ED₅₀ and the corresponding 95% confidence intervals were calculated. Due to the nature of log calculations, the mean difference—when back-transformed to the original units—represents the response ratio. For easier interpretation, we present the reciprocal of the response rate.

Clinical studies. The outcomes of interest in clinical studies were: (1) reduction in total opioid doses, (2) reductions in pain through the addition of a cannabinoid, (3) adverse events, and (4) evidence of abuse liability. A broad range of study designs were considered. Where studies used sufficiently similar methods and outcome measures, meta-analyses were conducted.

Clinical trials. Meta-analysis for clinical trials was conducted with Revman 5.4, where medians and interquartile ranges were required to be converted into means and standard deviations to allow inclusion in meta-analyses, we used methods established by Luo et al. [15] and Wan et al. [16].

Observational studies
For observational studies, meta-analyses on proportions reporting changes in opioid dose outcomes were conducted using a random effect model in Stata (metaprop, code available on request). A pooled prevalence was calculated with 95% confidence intervals for each of the identified outcomes that were comparable; (i) reduced opioid use, (ii) ceased opioid use. For remaining outcomes, a narrative synthesis was conducted. Clinical studies were scored for quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [17]. Quality ratings were not applied to preclinical studies. As all meta-analyses had less than ten studies funnel plots were not used to assess bias [18].

RESULTS
Ninety eligible publications representing data from 92 studies were identified; 29 in the initial searches and 63 in the updated
searches. Forty preclinical (21 since 2016) and 37 clinical studies (controlled trials n = 20 [12 since 2016] and observational n = 17 [13 since 2016]) were identified for inclusion (see Appendix 3). Fifteen registered clinical trials, where data were not yet available were also identified.

**Summary of preclinical studies**

Forty preclinical studies were identified in which the analgesic effect of opioid and cannabinoid co-administration was examined [19–58]. Sixteen of these studies examined delta-9-THC, while smaller numbers of studies examined 20 other cannabinoids, including agonists mixed CB1/CB2 agonists (CP55,940, WIN55,212-2, HU-210), CB1 agonists (ACEA, ACPA), CB2 agonists (beta-caryophyllene, JWH-015, JWH-133, LY2828360), antagonists/ inverse agonists at the CB1 (AM-251) and CB2 receptor (JTE-907) and other cannabinoids (AM1241, cannabiol, cannabidiol [CBD], CP 56,667, delta-8-THC, 11-hydroxy-delta-9-THC, dextronantradol, levonantradol and GP1a) (Table 1 and Appendix 4). Opioids examined included morphine, codeine, and other agonists at the mu, delta or kappa opioid receptor including buprenorphine, etorphine, fentanyl, heroin, oxycodone, hydromorphone, methadone, LAAM, meperidine, pentazocine, spiradoline, tramadol, and SNC80. Most studies used rodents; however, three used rhesus monkeys and one used guinea pigs. The most common antinociceptive assays were of thermal nociception although assays of mechanical and chemical nociception were also utilized.

Evidence of opioid-sparing effects or synergism were found for all mixed CB1/CB2 agonists (CP55,940, delta-9-THC, HU-210, WIN55,212-2). Morphee-induced analgesia increased with the CB1 selective agonist ACEA, though the effect was additive as opposed to synergistic [40]. In contrast, the CB1 selective agonist ACPA, and DAMGO (selective mu agonist) appeared to act antagonistically when administered together in a model of mechanical hyperalgesia [41]. The CB1 antagonist/inverse agonist AM-251 reduced the analgesic effect of morphine [40]. Conflicting outcomes were seen for CB2 selective agonists (some evidence of opioid-sparing effects for GP1a, JWH-015, LY2828360, but not for beta-caryophyllene or JWH-133). JTE-907 (a CB2 antagonist) and cannabinoids with more complex pharmacology (CBD and beta-caryophyllene or JWH-133). JTE-907 (a CB2 antagonist) and opioids examined included morphine, codeine, and other agonists at the mu, delta or kappa opioid receptor including buprenorphine, etorphine, fentanyl, heroin, oxycodone, hydromorphone, methadone, LAAM, meperidine, pentazocine, spiradoline, tramadol, and SNC80. Most studies used rodents; however, three used rhesus monkeys and one used guinea pigs. The most common antinociceptive assays were of thermal nociception although assays of mechanical and chemical nociception were also utilized.

**Measures of abuse liability.** Six studies reported on measures of abuse liability including intracranial self-stimulation (ICSS) [38], conditioned place preference [43, 44], oxycodone self-administration [50], and drug discrimination [32, 33]. None provided evidence that cannabinoids increased abuse liability. CP55,940 had no effect on ICSS with morphine or tramadol [38], JWH105 when co-administered with morphine reduced conditioned place preference, and LY2828360 when administered with morphine blocked condition place preference [43, 44]. THC reduced oxycodone self-administration [50], and attenuated the discriminative stimulus effect of morphine and heroin in nondependent monkeys, but not in dependent monkeys [33]. CP55,940 and WIN55,212 reduced the discriminative stimulus effect of morphine and decreased heroin self-administration, both effects were reversed by the CB1 receptor inverse agonist rimonabant [32].

**Meta-analysis of preclinical studies.** Seven studies used sufficiently similar approaches to enable a meta-analysis [19–24, 47] (Fig. 1). All studies included in the meta-analysis used rodents and reported comparable antinociceptive doses of morphine alone and morphine co-administered with delta-9-THC.

**Results from clinical studies**

Thirty-five eligible publications representing 37 clinical studies with 5180 participants provided data relevant to the research question (Table 2).

**Clinical trials—experimental pain.** Five laboratory-based studies in healthy volunteers (n = 82) examined pain responses with co-administered opioids and cannabinoids using double-blind within-patient study designs (Table 2a). Four studies examined oral dronabinol (2.5–20 mg) [59–62] and one examined smoked cannabis [63]. Inconsistent outcomes were observed; two studies found evidence of increased pain, two found some measures of decreased pain, and one study found effects of cannabinoids on pain “unpleasantness” but not pain ratings. One study found low dose dronabinol (2.5 mg) decreased the analgesic effects of oxycodone as measured with a pressure algometer with no effect of 5 or 10 mg dronabinol on analgesic outcomes [61]. Another study noted potentially hyperalgesic effects of cannabinoids [59]. This was in contrast to the analgesic effect observed on pain threshold and tolerance with a cold pressor test when smoked cannabis was administered with 5 mg oxycodone compared oxycodone or cannabis alone, although effects were not found on measure of outcomes of pain intensity or bothersomeness [63]. Dunn et al. [62] demonstrated analgesic effects from dronabinol 2.5 mg when co-administered with hydromorphone on thermal pain measures, but not with higher doses of dronabinol, or on other measures of pain. Roberts et al. [60] found that the co-administration of dronabinol and morphine resulted in reduced pain “unpleasantness” compared to either drug alone. Three experimental studies included measures of abuse liability, and found that smoked cannabis and dronabinol may increase the abuse liability ratings of oxycodone and hydromorphone using measures such as ratings of feeling high and drug liking [61–63].

**Clinical trials—acute pain.** Three double-blind randomized controlled trials (n = 545) examined the opioid-sparing effects of CBD in acute pain [64–66]. Nabilone and dronabinol were examined in acute post-operative pain and CBD in acute low back pain (<30 days duration). No benefit on opioid dose requirements or analgesic outcomes was identified (Table 2b).

**Clinical trials—cancer pain.** Seven controlled trials (1795 participants) investigated the opioid-sparing effect of cannabinoids in patients with different forms of cancer pain. One small, non-randomized study found a non-significant effect of cannabis on pain control [67], and a second pilot found no effect of medical cannabis on pain, but an increase in opioid dose in a group that received delayed cannabis [68] (Table 2c). The remaining studies were all larger single or double-blind randomized trials. Five randomized controlled trials (reported in four publications) examined THC and nabilimols compared to placebo in patients with cancer pain who were taking opioids [69–72]. Two studies found improved analgesia with nabilimols compared to the placebo. Johnson et al. [69] found no effect of nabilimols on breakthrough opioid dose requirements. Portenoy et al. [70] conducted a dose-ranging study, and a significant analgesic effect was only found in the lowest dose group, with poorer tolerability observed for higher doses. The remaining three studies found no

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**S. Nielsen et al.**

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**Meta-analysis identified an opioid-sparing effect with morphine and delta-9-THC co-administration with one study [47] added to the previous meta-analysis, Z = 4.46, p < 0.001 (mean difference in log_{10}ED_{50} = -0.54 [-0.78, -0.31]). As there was significant heterogeneity in the data (I^2 = 99%), a random effects model was used. When back-transformed to the original units, the response ratio was 3.5 (95% CI 2.04, 6.03) indicating that the median effective dose (ED_{50}) of morphine was 3.5 times lower when administered with delta-9-THC compared to when administered alone.
Table 1. Summary of opioid-sparing outcomes in preclinical studies by cannabinoid type.

| Cannabinoid type | Potential synergism/opioid-sparing effects | Opioid-sparing effect not clearly observed$^a$ or tested |
|------------------|------------------------------------------|-------------------------------------------------------|
| **Mixed CB1/CB2 agonists** |                                           |                                                       |
| CP55,940 (mixed CB1/CB2 agonist) | Evidence of opioid-sparing effect: Alsalem et al. 2019 (morphine “potential synergy” mechanical nociception) Maguire and France 2018 (morphine, thermal nociception); Maguire 2013 (Rhesus monkey, morphine, thermal nociception) | Evidence of synergy/opioid-sparing not found: Alsalem et al. 2019 (tramadol, mechanical nociception) Welch 1992 (morphine, thermal nociception); Maguire and France 2016 (spiradoline, thermal nociception) Maguire and France 2018 (etorphine, thermal nociception); Minervini 2017 (spiradoline, thermal nociception) |
| Delta-9-THC (partial agonist CB1/CB2) | Evidence of opioid-sparing effect: Cox 2007 (morphine, mechanical nociception) Cichewicz 2005 (guinea pigs, fentanyl and buprenorphine, mechanical nociception) Maguire and France 2018 (morphine, thermal nociception) Nguyen 2019 (oxycodeone “possibly synergistic, thermal nociception) Nilges 2020 (Rhesus monkeys, heroin, thermal nociception)) Cichewicz 1999 (range of opioid agonists, thermal nociception) Cichewicz 2003 (morphine and codeine, thermal nociception) Li 2008 (Rhesus monkey, morphine, thermal nociception)) Pugh 1996 (morphine, thermal nociception) Smith 1998 (morphine, thermal nociception) Smith 2007(morphine, thermal nociception) Welch 1992(morphine, thermal nociception) Williams 2006 (codeine and morphine, thermal nociception) Williams 2008 (morphine, thermal nociception) | Evidence of synergy/opioid-sparing not found: Maguire and France 2018 (etorphine, thermal nociception) Opioid-sparing/synergism not directly tested: Wakley 2011—synergism not tested, (mechanical nociception) Reche 1996—only one dose of morphine examined (thermal nociception) |
| HU-210 (mixed CB1/CB2 agonist) | Evidence of potential opioid-sparing effect: Sierra 2019 (SNC80 [delta opioid agonist] mechanical nociception with neuropathic pain model) | Evidence of synergy/opioid-sparing not found: Alsalem et al. 2020 morphine and tramadol, mechanical nociception) Wilson 2008 (morphine, thermal nociception) |
| WIN55,212–2 (mixed CB1/CB2 agonist) | Evidence of opioid-sparing effect: Alsalem et al. 2020 (tramadol mechanical nociception); Chen et al. 2019 (morphine, thermal nociception and formalin) Yesilurt 2003 (morphine, thermal nociception) | Evidence of synergy/opioid-sparing not found: Alsalem et al. 2020 (not morphine, mechanical nociception) |
| **CB1 selective agonist** |                                           |                                                       |
| ACEA | Evidence of synergy/opioid-sparing not found: Altun 2015 (morphine, thermal nociception) |                                                       |
| ACPA | Evidence of synergy/opioid-sparing not found: Auh et al. 2016 (DAMGO, mechanical nociception) |                                                       |
| **CB1 antagonist/inverse agonist** |                                           |                                                       |
| AM-251 (also has agonist activity at GPR55) | Evidence of synergy/opioid-sparing not found: Altun 2015 (morphine, thermal nociception) |                                                       |
| **CB2 selective agonist** |                                           |                                                       |
| JWH-015 | Evidence of opioid-sparing effect: Grenald et al. 2017 (morphine, mechanical and thermal nociception, formalin pain assay) | Evidence of synergy/opioid-sparing not found: |

$^a$ indicates evidence of potential opioid-sparing effect, but not clearly observed or tested.
benefit of adding cannabinoids on their primary outcome of analgesia. Although Lichtman et al. [72] did not find a significant effect of cannabinoids on pain in an intention to treat analysis, the per-protocol analysis did find a significant effect (Table 2c). Four of seven studies required maintenance opioid doses to be kept stable [70–72]; five studies measured breakthrough opioid doses requirements as an outcome with no evidence of a difference found [69–72]. No cancer pain studies included measures of abuse liability.

Meta-analyses were possible on the outcomes of change in mean total oral morphine equivalent daily dose (OMEDD) from baseline (n = 4 studies), percent change in pain score from baseline (n = 4 studies) and adverse events (n = 5 studies). Meta-analysis of four studies (n = 1119 participants) found no effect of
Table 2. Clinical studies.

| Study reference | Study design  | Population | Observation period | Opioid used | Cannabinoid Used | Comparator | Effect of cannabinoid on opioid dose | Outcome on analgesia observed | GRADE rating and other notes |
|-----------------|---------------|------------|--------------------|-------------|-----------------|------------|-------------------------------------|------------------------------|-------------------------------|
| Babaloni 2019   | Within-subject crossover, randomized, double-blind placebo-controlled design. Analgesia was assessed with cold pressor, pressure algometer, hot thermode, cold hyperalgesia | Healthy volunteers (n=10), aged 18-50 years, without acute or chronic pain conditions and no recent opioid or cannabinoid use. Six females, mean age of 26.3 years | Nine outpatient experimental sessions (8.5 mg) with a minimum of 48h separating each session; dronabinol administered 1h before oxycodone, pain measures up to 6h after dronabinol administration | Oxycodone 0, 5, 10 mg (oral) | Dronabinol 0, 2.5, 5 mg (oral) | Placebo dronabinol capsules and placebo oxycodone tablets | Cold pressor test: 2.5mg dronabinol + 5mg oxycodone decreased tolerance (17.9 ± 2.4; 5.8 points) compared with the 5 mg oxycodone dose alone (34.3 ± 17.7) | Pressure algometer: Dronabinol + 2.5mg dose decreased the analgesic effects of 10 mg oxycodone (no effect from 5 mg dronabinol). No effect on other pain measures (pressure algometer, cold pressor test and hot thermode). | GRADE rating ‘moderate’, placebo-controlled blinded study, indirect evidence as use of experimental pain. Dronabinol increased abuse liability ratings of oxycodone |
| Cooper 2018     | Within-subject randomized, placebo-controlled, double-blind study. Analgesia was assessed with cold pressor test | Healthy volunteers (n = 21, 21-45 years, with who current cannabis use. Six (33%) female, mean age 29.9 years | 6 outpatient experimental sessions. Placebo or oxycodone was administered 45min before cannabis. Observations for 5h after cannabis administration; repeated pain assessments until 3h, 72h washout between sessions | Oxycodone 0, 2.5 or 50 mg (oral) | Cannabis cigarettes (0.0 or 5.6% THC content); Participants smoked 70% of an 800mg cannabis cigarette (CBD content not stated) | Placebo cannabis capsules (30% THC); Placebo oxycodone capsules | Cannabis and low dose of oxycodone (2.5mg) did not elicit analgesia on their own; when administered together, pain (with cold pressor test) was significantly reduced, pointing to the opioid-sparing effects | Cannabis and 2.5mg and 5mg oxycodone increased pain threshold on cold pressor test compared to the cannabis alone (p<0.05). Mean reductions from pain (McGill Pain Questionnaire) Placebo 2.2 ± 0.5; THC alone 1.5 ± 0.5; 2.5 mg OXY 2.0 ± 0.5; 2.5 mg THC – OXY 0.7 ± 0.6; 5 mg OXY 1.7 ± 0.4; 5 mg OXY – THC 1.2 ± 0.4. Pain Intensity and bothersomeness Scales did not differ between cannabis, oxycodone, the combination or placebo | GRADE rating ‘moderate’, placebo-controlled blinded study, indirect evidence as use of experimental pain. Smoked cannabis increased subjective abuse liability measures for oxycodone |
| Dunn 2021       | Double-blind, within-subject randomized, placebo-controlled, human laboratory study using quantitative sensory testing measures of acute thermal, pressure pain; thermal, punctate probe temporal summation; cold pressor; conditioned pain modulation and chronic pain (capsaicin 10% topical cream with thermal rekindling) | Healthy adults (n = 29) with no history of drug use disorders, 52% females, mean age 30.4 years | Five outpatient laboratory sessions (min. 7 days apart). Sessions lasted 8h. Study drugs co-administered, with hourly pain assessments for 4h | Hydromorphone 4 mg (oral) | Dronabinol 2.5, 5.0, 10 mg (oral) | Placebo hydromorphone (no placebo dronabinol condition) | Opioid dose held constant across all sessions | Limited evidence of dronabinol enhancement of hydromorphone on pain measured. Dronabinol 2.5mg had a significant effect of thermal threshold and tolerance. Most pain measures did not show a significant difference between dronabinol + hydromorphone and hydromorphone alone. No dose effect with dronabinol | GRADE rating ‘moderate’, indirect evidence as use of experimental pain. Higher doses of dronabinol 3 mg and 10 mg also showed greater evidence of potential for abuse and adverse effects |
| Neef 2003       | Experimental naive volunteers (n = 12), 6 female, mean age 25 years | Healthy cannabis naive volunteers (n = 12); median age 25 years | Four study sessions with at least seven days washout between sessions. Study medications co-administered, with pain measurements hourly for up to 6h | Morphine 30 mg (oral) | Dronabinol 20 mg (oral) | Matched placebo capsule compared with THC, alone, morphine alone or THC-morphine combination | No significant analgesic effect of dronabinol or morphine-dronabinol combination on heat pressure and cold tests. Additive effect of morphine on transcutaneous electrical stimulation test | Potentiation of analgesia not observed in this experimental pain study. Potential hyperalgesic effect of cannabinoids noted which may reduce analgesic effects of morphine | GRADE rating ‘moderate’, indirect evidence as use of experimental pain |
| Roberts 2006    | Experimental thermal pain. Double-blind, four treatment with within-subject design | Healthy volunteers (n = 13) with no recent opioid or cannabinoid use. Six females aged 18-49 years | Four lab sessions; Dronabinol administered, 90 min later morphine administered; thermal pain measured 15 min after morphine administration | Morphine 0.02 mg/kg intravenous (1.4 mg dose for 70 kg adult) (i.e., sub-analgesic) | Dronabinol 5 mg (oral) | Placebo dronabinol capsule and placebo morphine injection (normal saline) | Not applicable (opioid dose held constant) | Combination of dronabinol and morphine did not have effect on pain intensity. The combination was reported to have a synergistic effect on affective response to pain (unpleasantness) compared with either drug alone (p = 0.012) | GRADE rating ‘moderate’, placebo-controlled blinded study, indirect evidence as use of experimental pain. Noted difficulties with extrapolation to clinical practice |
| Bebee 2021      | Randomized, double-blind, placebo-controlled clinical trial (ACTRN12618000487213) | Adults with acute (<30 days duration) non-traumatic lower back pain (n=100). Median age 47 years, 44% female | 48 h Oxycodone (5 mg every 6h, with additional rescue dosing as required) | CBD 400mg (oral) | Color matched placebo prepared (medium chain triglyceride oil) | 31/50 patients in the CBD group and 27/50 in the placebo group required oxycodone. Total oxycodone dose in the CBD group was 230mg compared with 215mg in the placebo group | Mean pain scores at 2h were similar for the CBD (6.2 points; 95% CI, 5.5–6.9 points) and placebo groups (5.8 points; 95% CI, 5.1–6.6 points; absolute difference, 0.3 points; 95% CI, –1.3–6.0 points) | GRADE rating ‘high’ |
Table 2. continued

| Study reference     | Study design                                                                 | Population                        | Observation period | Opioid used                          | Cannabinoid Used | Comparator                  | Effect of cannabinoid on opioid dose | Outcome on analgesia observed | GRADE evidence rating and other notes |
|---------------------|-------------------------------------------------------------------------------|-----------------------------------|--------------------|--------------------------------------|------------------|----------------------------|--------------------------------------|----------------------------------|----------------------------------|
| Levin 2017          | Single-center randomized double-blind controlled trial (NCT02115529)           | Patients scheduled for elective surgery under general anesthesia who had a preoperative risk of post-operative nausea or vomiting (n = 340), Mean age 69 years, 100% female | 30 min or until discharge from post-anesthesia care unit | Specific opioid not reported, converted into OMEDD | Nabilone 0.5 mg (oral) | Matched placebo capsule | Morphine equivalents (mg) given in operating room: Nabilone 21.3 (SD 15.2) vs placebo 20.0 (SD 13.4), p = 0.40; Morphine equivalents (mg) post-surgery: Nabilone 5.8 (SD 2.9) vs placebo 5.4 (SD 6.9), p = 0.62 | No differences in pain score (out of a possible 10) between groups; Maximum pain score (at rest) Nabilone 3.17 (SD 3.13) vs placebo 3.66 (SD 3.25), p = 0.43 | Maximum pain score (with movement) Nabilone 3.34 (SD 3.30) vs placebo 4.0 (SD 3.33), p = 0.92 |
| Seeling 2006        | Randomized double-blind controlled trial (two groups)                         | Prostate cancer patients <70 years, (all male) undergoing surgery (n = 105) in 3 groups in 2 centers | From the day prior to surgery to 2 days post-operation | Placebo oral mucosal spray | No effect of nabiximols on total OMEDD = 9.95, 95% CI: 18.81-6.012 (p = 0.053); maintenance OMEDD = 3.63, 95% CI: −10.80, 3.55 (p = 0.321); breakthrough OMEDD = −4.17, 95% CI: −8.76, 0.42 (p = 0.073) (note patients instructed to continue pain medication) | No differences in median percent improvement from baseline average pain NRS score: nabiximols 7.2% vs placebo 9.5% (median difference: −1.84; confidence interval: −6.19%, 1.50%; p = 0.374) Median treatment effect 0.02; 95% CI: −0.42, 0.38, p = 0.917 | NATO rating "high" |
| Fallon 2017a        | Study 1: multisite (patients at 101 centers in 12 different countries) randomized, double-blind, placebo-controlled trial (NCT01361607) | Adults (n = 399) with advanced incurable cancer, unselected by an optimized opioid therapy, Mean age 61.5 years, 49% female | 49 days (2 weeks after medication ceased) | Placebo oral mucosal spray | No effect of nabiximols on total OMEDD = 7.1, 95% CI: 13.9, 9.7 (p = 0.405); maintenance OMEDD = 8.9, 95% CI: 9.2, 6.7 (p = 0.104); breakthrough OMEDD = 1.8, 95% CI: 10.3, 14.0 (p = 0.769) (note patients instructed to continue pain medication) | Mean average pain scores increased from 3.2 to 3.7 in the nabiximols group and 3.1 to 3.6 in the placebo group, i.e., a worsening of equal severity in both the nabiximols and placebo groups (estimated treatment effect −0.02; 95% CI: −0.42, 0.38, p = 0.917) | NATO rating "high" |
| Fallon 2017b        | Study 2: 2-part enriched enrollment with randomized withdrawal design ("responders" randomized, Single-blind titration for 10 days followed by double-blind randomization to Sativex or placebo (NCT01424566) | Adults (n = 406) randomized with advanced incurable cancer, unselected by an optimized opioid therapy, Mean age 61.5 years, 43% female | 49 days (2 weeks after medication ceased) | Placebo oral mucosal spray | No effect of nabiximols on total OMEDD = 7.1, 95% CI: 13.9, 9.7 (p = 0.405); maintenance OMEDD = 8.9, 95% CI: 9.2, 6.7 (p = 0.104); breakthrough OMEDD = 1.8, 95% CI: 10.3, 14.0 (p = 0.769) (note patients instructed to continue pain medication) | Mean average pain scores increased from 3.2 to 3.7 in the nabiximols group and 3.1 to 3.6 in the placebo group, i.e., a worsening of equal severity in both the nabiximols and placebo groups (estimated treatment effect −0.02; 95% CI: −0.42, 0.38, p = 0.917) | NATO rating "moderate" |
| Johnson 2010        | Multicenter, randomized, double-blind, placebo-controlled parallel-group trial (NCT00674609) | Adults with cancer and refractory opioid dosing (n = 327), with inadequate analgesia measured using the Brief Pain Inventory, Mean age 60 years, 56% female | 2 weeks | Placebo oral mucosal spray (Baseline OMEDD for placebo group 120 mg) | Patients allowed to use breakthrough medication as needed, no change in median amount of breakthrough opioid medication in any group. Mean change in opioid dose from baseline Placebo −41.4 (SD 201.27), THC 36.8 (SD 152.00), THC:CBD = 3.5 (SD 108.44); Median changes in all groups 0 mg Change in pain score (out of 10) in favor of THC:CBD compared with placebo (−1.37; p = 0.014); THC:CBD compared with THC alone (−1.36; p = 0.009); THC:CBD compared with THC alone (−1.36; p = 0.009); THC:CBD compared with THC alone (−1.36; p = 0.009) | Change in pain score (out of 10) in favor of THC:CBD compared with placebo (−1.37; p = 0.014); THC:CBD compared with THC alone (−1.36; p = 0.009); THC:CBD compared with THC alone (−1.36; p = 0.009) | NATO rating "high" |
| Lichtman 2018        | Randomized, multisite double-blind, placebo-controlled study (12 countries) (NCT01262651) | Adults (n = 397) with advanced cancer-related chronic pain not controlled by optimal opioid therapy, Mean age 60 years, 46% female | 50 days if not entering extension study | Placebo oral mucosal spray | Nabilones did not impact maintenance OMEDD (Estimated treatment difference [ETD] 1.46, 95% CI: −4.67, 7.60; p = 0.64); breakthrough OMEDD (THC = 1.84, 95% CI: −6.33, 2.66; p = 0.40) or total OMEDD (ETD = −0.34, 95% CI: −8.26, 7.62; p = 0.93). Protocol stated that medications including opioids, should have been continued at stable doses if possible | Average pain score from baseline to end of treatment (primary endpoint) no significant 10.7% median improvement with nabiximols compared to placebos (p = 0.08); Nabiximols did not improve average pain NRS (p = 0.25) or worst pain NRS score (p = 0.68). Prospective per-protocol analysis favored nabiximols over placebo (p = 0.04) | NATO rating "moderate", unclear blinding and randomization. Nabiximol was also associated with greater improvements than placebo in scores on the Subject Global Impression of Change, Patient Global Impact of Change, and Patient Satisfaction Questionnaire |
| Lissoni 2014         | Two groups (not randomized) | Adults (n = 26) with untreatable cancer, median dose of THC was given as Melatonin 20–100 mg | Not stated | Placebo oral mucosal spray | S1/2 (42%) achieved control of pain without pain medication | The number that achieved pain control | NATO rating "low", no-randomization |
| Study reference          | Study design                                                                 | Population                                                                 | Observation period | Opioid used                                                                                                                                                                                                 | Cannabinoid Used                                                                 | Comparator                                                                 | Effect of cannabinoid on opioid dose                                                                 | Outcome on analgesia observed                                                                 | GRADE evidence rating and other notes                                                                 |
|-------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| S. Nielsen et al. 2022  | Pilot randomized controlled trial comparing early cannabis use to delayed start cannabis (DC) | Adults (n = 30) with stage IV cancer requiring opioids. Patients in the EC group were similar to DC group with respect to mean age (57 SD = 9 years vs 55 (SD = 13) years) and percentage female (47% vs 53%), respectively | 3 months           | Opioid type not specified. OMEED measured using daily diary                                                                                                                                               missed daily intake was permitted during the washout period. | Maintenance dose of 30–40 mg of THC and 30–40 mg of CBD per day, titrating up over 2–4 weeks | Early versus late start cannabis                                                                                                       | EC group had stable opioid use; 3/9 in EC group and 4/9 in DC group increased OMEED by ≥20%. Three patients in the EC group increased their daily OMEED by 20% | GRADE rating: “low” small sample with high attrition. Also examined dosing patterns: THC per patient each month was nearly twice that of CBD (average 343 mg THC vs 166 mg CBD) |
| Abrams 2020             | Randomized double-blind, crossover design (NCT01771731)                        | Adults with sickle cell disease with chronic pain (n = 23), 21 of whom were taking opioids. Mean age, 37.6 years; 50% female | 5 patient days with 30-day washout followed by another 5 patient days | Hydromorphone, oxycodone, hydrocodone, morphine, fentanyl, methadone, and oxymorphone                                                                                                                     | VapORIZED cannabis dose of 0.9 g of 4.4% THC and 4.9% CBD which were vaporized and inhaled 3 times per day | VapORIZED placebo cannabis                                                                                                          | The mean (SD) difference in log OMEED dose between the cannabis and placebo periods in this study was not significant (2.05 (0.21) vs 2.09 (0.22), p = 0.20) | Pain score: reduction from 34.8 (95% CI: 29.4, 40.1) on baseline to 24.1 (95% CI: 18.8, 29.4) on day 5 with morphine and from 43.8 (95% CI: 38.6, 49.1) on baseline to 33.6 (95% CI: 28.5, 38.6) on day 5 with oxycodone. Significant reduction overall | GRADE rating: “low”, No control arm, placebo effects cannot be excluded. No pharmacokinetic interaction observed. Cannabis inhalation produced a subjective “high”. |
| De Vries 2016            | Randomized, single-dose, double-blind, placebo-controlled, two-way crossover study (NCT01918369) | Adults aged 18 and above with chronic abdominal pain from chronic pancreatitis (n = 24, 12 of whom were taking opioids). Mean age of sample 52 years, 9 of 24 patients were female | 6h                 | Pethidine: tramadol and codeine (patients’ usual medicinal)                                                                                                                                       | Dronabinol 8 mg                                                                 | Diazepam 10 mg                                                                                     | The pharmacokinetic parameters of THC were similar between opioid and non-opioid users. Opioid dose requirements were not an outcome of the single-dose study | Primary analysis showed no treatment effect of THC. When only patients on opioids were considered, the mean VAS pain score at 2h was similar for patients in THC arm (2.917, SD 2.205) and the placebo (active plus placebo) arm (2.53, SD 1.702) | GRADE rating: “low”, Small sample size and unclear blinding procedures and crossover design |
| De Vries 2017            | Randomized, single-dose, double-blind, placebo-controlled, two-way crossover study (NCT01562483 and NCT01511511) | Two clinical trials where the samples were combined: (1) Adults with painful chronic pancreatitis (CP) (n = 23) and (2) adults with chronic postsurgical abdominal pain (PPAP), n = 27, mean age 52.9 years, 50% female | 61 days            | Codeine, tramadol, oxycodone, fentanyl and morphine (patients’ usual medicines)                                                                                                                        | Dronabinol tablet increased to 8 mg three times a day over 10 days, with the option to reduce to 5 mg three times a day, if tolerated. Those not tolerating 5 mg three times a day were withdrawn | Matched dronabinol placebo tablet                                                                                                   | Not reported: Patients were asked to continue taking their medications (including analgesics) according to prescription | Primary analysis (all patients) VAS scores did not differ between THC and placebo. For patients on opioids, THC (29.4, SD 2.10) compared with placebo (20.5, SD 2.65). For patients on non-opioids, THC (31.7, SD 3.27) compared with placebo (21.5, SD 3.46). | GRADE rating: “moderate”, Small sample size and high attrition in the active arm for the CP group. Additional data provided by authors |
| Nasang 2008              | Phase 1 randomized, single-dose, double-blind, OMEED mean 60.0 mg (SD: 32.2), Dronabinol 10 and 20 mg | Adults taking opioids for chronic pain (n = 21)                                                                 | 10 days            | Codeine, tramadol, oxycodone, fentanyl and morphine (patients’ usual medicines)                                                                                                                        | Dronabinol tablet increased to 8 mg three times a day over 10 days, with the option to reduce to 5 mg three times a day, if tolerated. Those not tolerating 5 mg three times a day were withdrawn | Matched dronabinol placebo tablet                                                                                                   | Not reported: Patients were asked to continue taking their medications (including analgesics) according to prescription | Primary analysis (all patients) VAS scores did not differ between THC and placebo. For patients on opioids, THC (29.4, SD 2.10) compared with placebo (20.5, SD 2.65). For patients on non-opioids, THC (31.7, SD 3.27) compared with placebo (21.5, SD 3.46). | GRADE rating: “moderate”, Small sample size and high attrition in the active arm for the CP group. Additional data provided by authors |

**Table 2.** continued
Table 2. continued

| Study reference | Study design | Population | Observation period | Opioid used | Cannabinoid used | Comparator | Effect of cannabinoid on opioid dose | Outcome on analgesia observed | GRADE evidence rating and other notes |
|-----------------|--------------|------------|--------------------|-------------|-----------------|------------|-------------------------------------|--------------------------------|-----------------------------------|
| Placebo-controlled, crossover trial. Primary outcome measure Total Pain Relief score (Phase 2 extension study in Table 2b) (NCT00153192) | 4 (n = 30). Pain diagnosis: non-malignant (N = 7), nociceptive (N = 7), mixed neuropathic and nociceptive (N = 11), and unclassified (N = 5). Mean age 43.5 years, 53% female | 12 months following treatment initiation | Not specified, median of weak (n = 118) and strong (n = 56) opioids at baseline | range 7.5–228 | Randomized and placebo-controlled, double-blind, parallel-group design | 42% reduction (27 mg MOEDD (95% CI: 9.89, 15.65) reduction (p < 0.001). Opioid cessation at 12-month follow-up: 24% using weak and 20% using strong opioids. | Total pain relief: 31.1 in placebo: 39.7 with dronabinol 10 mg and dronabinol 20 mg. | No significant difference in analgesia (OMEDD or total OMG dose/status of stay). Significantly lower than total OME consumption during stay: Dronabinol group (252.5 mg ± 131.5 mg) vs control group (313.3 mg ± 185.4 mg). | GRADE rating “low” Evidence of effectiveness. No control group. |
| Aviram 2020 Prospective observational cohort study | Adults with any form of cancer-related pain (n = 29) | Not specified, calculated at OMEDD | 10 mg capsules of 1:1 THC and CBD taken orally every 8–12 h. | 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidiol (CBD), 0.9 mg cannabidiolic acid (CBD), 0.8 mg cannabinol (CBC), and >1% botanical terpene blend | OMEDD not captured. Fifty of the 94 (53.2%) participants using the CBD hemp extract were able to reduce opioid medications at week 8. Of the fifty who reduced, two ceased completely | Baseline pain (PEG) scale at (6.4 ± 0.4) to 5.31 (the 12% reduction in pain, considered clinically significant). | Not reported by opioid status | GRADE rating “low” observational data. |
| Bellinier 2018 Observational pre-post study | Adults (n = 113) with moderate-severe chronic pain for at least 3 years and stable opioids for at least 1 year (mean = 113.7 years, 68% female) | Not stated, requirement to be taking at least 50 mg OMEDD for 12 months prior to enrollment | 15.7 mg CBD, 0.5 mg THC, 0.3 mg cannabidiol (CBD), 0.9 mg cannabidiolic acid (CBD), 0.8 mg cannabinol (CBC), and >1% botanical terpene blend | 4 and 8 weeks | OMEDD not captured. Fifty of the 94 (53.2%) participants using the CBD hemp extract were able to reduce opioid medications at week 8. Of the fifty who reduced, two ceased completely | Pain outcomes not available for the subsample on opioids | Not reported by opioid status | GRADE rating “low” observational data with no control. |
| Habib 2018 Retrospective cohort study | Adults aged 18 and above with fibromyalgia (n = 26), female patients (73%), mean 37.8 ± 7.6 years | Median cannabis duration 3 months | Codeine, tramadol, oxycodone, fentanyl or buprenorphine. | NA | NA | NA | Not reported by opioid status | GRADE rating “very low”, small, retrospective cohort with no control group, short follow-up. |
| Hamonotsson 2016 Prospective, observational cohort study | Adults (n = 73/274) 18 years + above 18 with chronic pain, 73% prescribed opioids. Mean age 51.2 years, 62% female | 6 months | Morphine, oxycodone fentanyl, hydromorphone, buprenorphine, methadone and tramadol. | Smoked (THC 6–14%, CBD 0.2–3%) and oral (THC 11–19%, CBD 0.5–5%). The mean (SD) monthly prescribed amount of morphine was 432 (179.9) mg (79 formulations) | NA | 32/73 (44%) ceased opioids. (p < 0.001). Median OMEDD among participants receiving opioids at follow-up (n = 41) decreased from 60 mg (95% CI: 45–90 to 45 mg (95% CI: 30–90, p = 0.19, Mann-Whitney) | Pain outcomes not available for the subsample on opioids. | Not reported by opioid status | GRADE rating “low”, non-randomized single-arm open-label study. |
| Hickernell 2018 Retrospective cohort study | Adults (n = 243) who had total knee or hip arthroplasty. Mean age 62.3 years, 64% female | Mean length of stay 2–3 days | Oral oxycodone 10 mg up to three doses mg plus immediate release oxycodone 5–10 mg mg as required | Dronabinol 5 mg twice a day during hospital stay (n = 81) | Patients who did not receive dronabinol (n = 162) over the same time period | No significant difference in OMEDD or total OME dose/status of stay. Significantly lower than total OME consumption during stay: Dronabinol group (252.5 mg ± 131.5 mg) vs control group (313.3 mg ± 185.4 mg). | No significant difference in pain scores between the groups on any day post-surgery | GRADE rating “low” non-randomized retrospective study. Mean length of stay lower for the dronabinol group compared with control (2.3 ± 0.9 vs 3.0 ± 1.2 days, p = 0.02) | |
| Hoggart 2015 Open-label extension study from 2 clinical trials | Adults (n = 380) with peripheral neuropathic pain | 38 weeks | Strong and weak opioids | THC/CBD oral mucosal spray G7 | NA | NA | No change in the proportion of the whole | Not reported by opioid status | GRADE rating “moderate”, non-randomized extension trial. |
| Study reference | Study design | Population | Observation period | Opioid used | Cannabinoid Used | Comparator | Effect of cannabinoid on opioid dose | Outcome on analgesia observed | GRADE evidence rating and other notes |
|----------------|--------------|------------|--------------------|-------------|------------------|------------|--------------------------------------|-----------------------------|----------------------------------|
| across 66 study sites (38 centers in six countries) | neuropathic pain, mean age 57.8 years, 47% female | | | mg of THC and 2.5 mg of CBD per spray | | | sample taking strong opioids (56380 at baseline and 57380 at follow-up) or other opioids (1126380 at baseline to 123380 at follow-up) following cannabinoid use | Data on other outcomes not provided by opioid use status | randomized sample. Rigorous data collection |
| Lynch 2002 | Observational case series | Adults with pain codes (n = 3) (peripheral neuropathy, multiple sclerosis, lower back pain), Aged 35–47 years, 33% female | 1–9 month observation period | Morphine (varied doses) | Smoked cannabis plant, unknown content | NA | Mean baseline morphine dose 195 mg (SD 147 mg) compared with mean 33 mg (SD 31 mg) after commencing smoked cannabis. Opioid dose reduction or cessation in each case | Improved pain control described with patients either reducing or ceasing morphine dose | GRADE rating “very low”, unblinded observational study |
| Maida 2008 | Prospective observational study | Adults with advanced cancer (n = 112), 47 of whom were treated with nabilone (mean age 67 years, 38% female) | 30 days | Nabilone group baseline OMEDD 603 mg (SD 646); comparison group OMEDDD 67.5 mg (SD 101.0) | Nabilone, mean of 1.79 mg/daily | People with advanced cancer who were not treated with nabilone | Log OMEDD in nabilone group 3.8 mg compared with 4.3 mg in the untreated group (p = 0.016), remained significant after adjusting for baseline symptom level and propensity score | Pain score in nabilone group 3.7 compared with 5.0 in the untreated group (p = 0.003), remained significant after adjusting for baseline symptom level and propensity score with pain score of 3.0 in the nabilone group and 5.5 in the comparison group (p < 0.001) | GRADE rating “low”. Nabilone prescribing based on symptom-related distress on the initial consultation, leading to selection bias, but managed with propensity scoring |
| Maida 2017 | Observational case series | Adults with pyoderma gangrenosum (n = 2) on opioids. Female (50 years) and male (76 years) | 6–25 days | Opioid analgesic type not specified | Topical cannabinoid of THC/CBD 3.6 mg/mL or THC/CBD 7.9 mg/mL | NA | Mean Baseline OMEDD 26.7 mg (SD 9.9). Mean follow-up 6.4 mg (SD 8.7) | Mean pain at baseline 67.6 mg (SD 64.6); pain was 60.3 mg (SD 64.6) after initiating topical cannabinoid (i.e., clinically meaningful reduction) | GRADE rating “very low”, very small case series |
| Maida 2020 | Observational case series | Two adults (aged 86 and 69, both female), with painful and non-healing leg ulcers, of greater than 6 months duration | 57–68 days | Case 1: Codeine (with acetaminophen), Case 2: 188 mg oral morphine equivalents (opioid type not stated) | Topical cannabinoid product THC < 1 mg/mL; CBD 3.75 mg/mL | NA | Both patients ceased opioids | Not reported, opioid requirements used as proxy for pain | GRADE rating “very low”, very small case series |
| Nasang 2008 | Open-label extension following randomized, single-dose, double-blind, crossover trial (Table 2d) | Patients on opioids for chronic pain (98%); 4 (n = 28). (see Table 2d for participant characteristics) | Four weeks | OMEDD mean 68 mg (SD 57.2, range 7.5–228) (ml of oxycodone, morphine, methadone, hydrocodone, hydromorphone) | Flexible dose schedule of dronabinol 5 mg daily – 20 mg three times a day | NA | Opioid dose not reported compared with mean NRS of 6.9 for chronic pain (98%) on opioids of 90–240 mg (age and gender not reported) | Mean baseline NRS of 6.9 reduced by 5.2 after 4 weeks of dronabinol (24% reduction in pain). Statistically significant reduction, but does not meet the 30% reduction in pain to be clinically significant | GRADE rating “low”, improvements (p < 0.005) in sleep, energy, pain relief, and social functioning. Lack of placebo control means effects may be non-specific/ placebo |
| Rod 2019 | Open-label prospective opioid taper study | Patients with chronic pain (n = 600), on opioid doses of 90–240 mg (age and gender not reported) | Six months | Mean OMEDD 120 mg (Range 90–240 mg) | CBD and THC (4–6%). Doses related directly to the opioid taper: 0.5 g/day for each 10% reduction in opioid dose, as needed by sputumical, oral or inhalation by vaporization | NA | 156 patients (29% of patients) decreased their opioid (n = 39) patients (18%) taking more than 60 mg oral morphine equivalents per day; a further 329 patients (55%) reduced opioid use by an average of 30%. Cannabis use among these patients ranged from 1–3 mg/day | Pain not quantified. One patient increased opioid intake; all other patients expressed satisfaction with their pain control, sleep and quality of life | GRADE rating “low”, evidence-based online psychological support provided (e.g., cognitive behavioral therapy and mindfulness) |
| Safakish 2020 | Prospective observational cohort study | 82/751 chronic pain patients, who were using opioids. Mean age of 45.6 years, 57% female | 12 months | Mixed opioids, oral conversion morphine equivalent doses | 7% to 29% THC and/or CBD. | NA | Baseline (n = 82) OMEDD 26.2 (SD 48.1), month 3 (n = 26) 3.3 (SD 8.6), month 6 (n = 9) 3.0 (SD 6.3) month 12 (n = 4) 1.4 (SD 0.1), p < 0.001 | Not reported by opioid status | GRADE rating “very low”, open-label single-arm study with high attrition |
| Schneider-Smith 2020 | Retrospective matched cohort study | Adults with traumatic injury: 33 cases (mean age 39.9 years, 76% male) and 33 matched controls (mean age 30.0 years, 50% female) | 48–96h after admission | Not stated, opioid use reported in OMEDD | Dronabinol (usually 5–10 mg twice a day) | NA | OMEDD reduction in group dronabinol, (59 mg (SD20), p < 0.001), OMEED for controls unchanged from baseline (1.8 (mg), p = 0.63) | Adjunctive dronabinol reduce pain scores. Average change in pain scores (NRS) were similar between cases and controls (–0.6 vs. 0.6, p = 0.78) | GRADE rating “low”, non-randomized retrospective study |
| Takakuwa 2020 | Retrospective cohort study | Adults with low back pain (n = 61) who Data extracted from 1997–2019 from a | | Variable products reported in grams | NA | 31/61 ceased, 9 reduced and 1 increased their | Not reported | GRADE rating “very low”, small |
### Table 2. continued

| Study reference | Study design | Population | Observation period | Outcome on analgesia | Comparator | Cannabis used | Opioid used | Study design | Opioid and cannabinoid used | Opoid dose | GRADE evidence rating |
|-----------------|--------------|------------|--------------------|----------------------|------------|-------------|------------|--------------|----------------------------|------------|------------------------|
| Nielsen et al. 2019 | Prospective observational multi-centre cohort study | Adults (n=58) with acute pain, mostly pain from fibromyalgia already on standard medical cannabinoids | 6 months | Reduction in OME | Nabilone group [89]; Comparison with patients that had not received it, using propensity scoring to adjust for the greater severity of the nabilone prescribed | Nabilone | Oxycodone 5 mg | Prosp.observational multi-centre cohort study | Opioid and cannabinoid use | Opioid and cannabinoid use | None | Not reported |

Clinical trials—chronic non-cancer pain. Five clinical trials (139 participants, Table 2d) examined the effects of dronabinol [73–75] and smoked cannabis [76, 77] in patients with chronic non-cancer pain. Most studies had short observation periods (5 h to 5 days) [74–77], and used crossover designs [73–76]. Opioid dose was an outcome in one study, with no difference between smoked cannabis and placebo [76]. All five studies reported on analgesic outcomes with conflicting findings. A single-arm open-label study (with no comparison group) recruited people with mixed types of chronic non-cancer pain (n = 24) who were prescribed opioids, and found significant overall reductions from baseline pain ratings following co-administration of cannabinoids [77]. In contrast, a double-blind crossover study in sickle cell patients found no significant differences analgesia effects between placebo and vaporized cannabis [76]. Two studies recruited patients with chronic pancreatitis and found no effect of dronabinol on pain measures compared with placebo [73, 74]. A sub-analysis in patients with chronic postsurgical abdominal pain found lower pain among those who received dronabinol compared with placebo [73]. A single-dose study in patients with mixed-chronic pain conditions, found dronabinol 10 and 20 mg was associated increased analgesia compared with placebo [75]. These studies did not include measures of abuse liability.

Clinical studies—observational. Seventeen observational studies (n = 2674) examined the opioid-sparing effects of cannabinoids; three small retrospective case series of two to three patients each [78–80], two retrospective cohort studies [81, 82], two retrospective matched cohort studies [83, 84], and ten prospective observational cohort studies [85–93], including two open-label extension studies [75, 93] (see Table 2e). Two retrospective matched cohort studies examined acute analgesia with traumatic injury [83] and joint arthroplasty [84]. Both found no difference in pain scores, but reduced opioid consumption on at least one measure. For pain management following joint arthroplasty, there was no change in daily opioid dose with dronabinol administration, but a reduced total opioid consumption due to significantly shorter hospital stays in the dronabinol group [84]. One study compared those prescribed nabilone with those that had not received it, using propensity scoring to adjust for the greater severity of the nabilone prescribed group [89]. The remaining observational studies did not have control conditions and examined opioid use in patients with a range of different types of chronic non-cancer pain. Seven studies reported on the outcome of OME after commencing medical cannabinoids, with reductions from 9 to 140 mg OME reported (Table 2b). Four studies quantified the reduction in pain scores, which ranged from 12% to 70%, with two studies exceeding the minimum threshold of a 30% reduction in pain to be clinically meaningful. Meta-analysis was possible for studies that reported the proportion of patients who reported opioid reduction or cessation; eight studies reported the proportion of patients who ceased opioids (range 2–100%), with a pooled prevalence of 0.39 (95% CI 0.15, 0.64, I² = 95.47%) (Appendix 5a). Seven studies reported on the proportion of patients reducing opioid use (range 44–100%) with a pooled prevalence of 0.85 (95% CI 0.64, 0.99, I² = 92.82%) (Appendix 5b). Statistically significant heterogeneity was identified in both meta-analyses.
Fig. 1 Forrest plot for meta-analysis examining the opioid-sparing effect of delta-9-THC when co-administered with morphine. Note mean difference and standard deviation values are of log_{10}ED_{50}.

(a) Nabilomix vs Placebo

| Study or Subgroup  | Nabilmix Mean | Placebo Mean | Mean Difference IV, Random, 95% CI |
|--------------------|---------------|--------------|-----------------------------------|
| Fallon 2017a       | 12.46         | 21.96        | -2.48 [-7.19, 2.23]               |
| Fallon 2017b       | 34.5          | 25.26        | -9.74 [-7.53, 6.05]               |
| Johnson 2010       | 12.7          | 22.4         | 5.36 [0.50, 10.22]                |
| Lichtman 2018      | 13.7          | 22.4         | 4.36 [0.05, 8.67]                 |
| Total (95% CI)     | 553           | 556          | 1.84 [-2.05, 5.72]                |
| Heterogeneity: Tau^2 = 8.96; Chi^2 = 7.10, df = 3 (P = 0.07); I^2 = 58% |
| Test for overall effect: Z = 0.93 (P = 0.35) |

(b) Nabilomix vs Placebo

| Study or Subgroup  | Nabilmix Mean | Placebo Mean | Mean Difference IV, Random, 95% CI |
|--------------------|---------------|--------------|-----------------------------------|
| Fallon 2017a       | -6.5          | 53.9         | -8.80 [-18.35, 0.75]              |
| Fallon 2017b       | 9             | 46.6         | -50 [-23.60, 10.60]               |
| Johnson 2010       | -3.5          | 108.44       | 37.90 (20.33, 96.13)              |
| Lichtman 2018      | 0.3           | 34.7         | -0.30 [-8.10, 7.50]               |
| Total (95% CI)     | 560           | 559          | -3.86 [-10.97, 3.37]              |
| Heterogeneity: Tau^2 = 12.58; Chi^2 = 3.87, df = 3 (P = 0.28); I^2 = 23% |
| Test for overall effect: Z = 1.04 (P = 0.30) |

(c) Cannabinoids vs Placebo

| Study or Subgroup  | Cannabinoids Events | Placebo Events | Risk Ratio M-H, Random, 95% CI |
|--------------------|---------------------|---------------|-------------------------------|
| Fallon 2017a       | 59                  | 199           | 7.6% (0.53, 1.18)             |
| Fallon 2017b       | 33                  | 103           | 2.06 (1.21, 3.51)             |
| Johnson 2010       | 26                 | 118           | 1.86 (0.86, 4.03)             |
| Lichtman 2018      | 47                 | 199           | 1.09 (0.76, 1.56)             |
| Portenoy 2012      | 201                | 28           | 1.20 (0.80, 1.78)             |
| Total (95% CI)     | 887                | 649           | 1.23 (0.89, 1.70)             |
| Total events       | 222                | 133           |                               |
| Heterogeneity: Tau^2 = 0.08; Chi^2 = 9.63, df = 4 (P = 0.05); I^2 = 58% |
| Test for overall effect: Z = 1.20 (P = 0.20) |

(d) Cannabinoids vs Placebo

| Study or Subgroup  | Cannabinoids Events | Placebo Events | Risk Ratio M-H, Random, 95% CI |
|--------------------|---------------------|---------------|-------------------------------|
| Fallon 2017a       | 59                  | 199           | 7.6% (0.93, 1.82)             |
| Fallon 2017b       | 21                  | 103           | 2.24 (0.69, 2.20)             |
| Coyle 2010         | -3.5                | 108.44        | 1.09 (0.92, 1.30)             |
| Lichtman 2018      | 69                 | 199           | 1.30 (0.96, 1.75)             |
| Portenoy 2012      | 223                | 28            | 1.10 (0.97, 1.25)             |
| Total (95% CI)     | 887                | 649           | 1.13 (1.03, 1.24)             |
| Total events       | 468                | 228           |                               |
| Heterogeneity: Tau^2 = 0.09; Chi^2 = 7.10, df = 3 (P = 0.005); I^2 = 12% |
| Test for overall effect: Z = 1.0 (P = 0.3) |

Footnotes
1. Cannabinoid groups combined in Johnson 2010
2. Combined the three cannabinoid conditions for Portenoy 2012

Fig. 2 Opioid-sparing outcomes from clinical trials in people with cancer pain. Meta-analysis comparing cannabinoids with placebo on outcomes of a percent improvement in pain score, b change in mean total Oral Morphine Equivalent Daily Dose (OMEDD), c serious adverse events from baseline, and d adverse events excluding serious adverse events, in clinical trials of people with cancer pain.
Quality ratings of clinical studies

The clinical studies were rated using the GRADE criteria. Of the clinical trials, five laboratory studies provided moderate evidence, three clinical trials in acute pain provided high quality evidence, six clinical studies provided low-high quality evidence in cancer pain, and five studies in chronic non-cancer pain were assessed as low-moderate quality. The seventeen observational studies were assessed to be low to very-low-quality evidence (Table 2).

Ongoing clinical trials. We identified 15 registered clinical trials which, based on published protocols and clinical trial registry entries, may provide important data for future updated reviews (Appendix 6).

DISCUSSION

The current update represents the largest synthesis of studies examining the opioid-sparing effects of cannabinoids, with double the number of preclinical studies, four times as many clinical studies and more than six times the number of participants (>5000) compared to our earlier review [3], reflecting the rapid growth of clinical research in this area.

Most preclinical studies found synergistic effects with opioids and cannabinoids co-administration, predominantly with mixed CB1/CB2 agonists such as delta-9-THC, though effects varied with different cannabinoids, opioids and pain assays. Meta-analyses (with one addition preclinical study since 2015) demonstrated that morphine dose required to produce an equivalent analgesic effect was 3.5 times lower when co-administered with delta-9-THC, consistent with the previous review [3]. This effect would be clinically meaningful if replicated in well-controlled clinical studies. However, preclinical studies often have larger effect sizes, attributed to the reduced heterogeneity compared to clinical populations [94]. This body of preclinical research may help to identify specific cannabinoids and mechanisms that underlie an opioid-sparing effect, with the most consistent effects observed with mixed CB1/CB2 agonists, and evidence of potential antagonistic effects between CB1 agonist and mu receptor agonists in models of mechanical hyperalgesia.

A rapidly growing number of clinical studies have measured opioid-sparing endpoints, though findings were inconsistent. The highest quality studies were conducted in patients with cancer pain, where meta-analysis of four studies did not find significant effects on opioid dose or analgesia. Conflicting findings were found in studies of experimental pain, and in patients with chronic non-cancer pain. Further studies are needed to clarify the results found here given the small number of studies.

A limited number of controlled studies demonstrated benefits of combining cannabinoids with opioids for analgesia. Experimental pain studies found cannabinoids improved [62, 63] and worsened [61] analgesia. These effects were not dose dependent, with significant effects seen with lower but not higher doses of delta-9-THC. Opioid-sparing effects were not seen in well-conducted RCTs with acute pain, or in meta-analyses of RCTs in cancer pain, and studies that did find positive effects have important limitations such as no control group [77], small sample sizes [67, 75], and the mixed quality of the study design. Furthermore, some RCTs instructed patients to continue their pain medication in the same doses, which may preclude identifying a change in opioid dose [70–73, 77], although changes in breakthrough opioid requirements were a secondary outcome in six studies [69–72, 75]. Some clinical studies demonstrated beneficial effects of opioid and cannabinoid co-administration on other outcomes such as sleep, and functioning in chronic pain patients [75, 77]. Conflicting results were found between preclinical studies and clinical trials on measure of abuse liability. Evidence of reduced abuse liability was found in some animal models, which contrasted directly with evidence of increased drug liking and subjective effects in human studies.

Finally, observational studies had methodological concerns including small sample sizes (several observational studies included in meta-analysis had two to three patients), no control groups or blinding, selection bias, and were likely to have been impacted by expectancy effects.

Although our review is much broader, we have drawn similar conclusions to earlier reviews. For example, a review of cross-sectional surveys and cohort studies, representing lower quality evidence, found large reductions in opioid doses, though study designs prevented the drawing of causal conclusions [95]. A later review with five randomized trials with patients with chronic pain and 12 observational studies further concluded that there was uncertainty in the evidence [96], although this review considered a substantially smaller number of clinical trials than we consider. Future studies may benefit from focusing on populations with higher opioid tolerance, or higher motivation to reduce opioid doses, where clinical benefits may be greatest [97]. Standardization of outcomes for opioid-sparing research may assist with harmonization of outcome measures and support meta-analysis with future clinical trials [2].

Despite the inclusion of a larger number of studies, and the increased size and quality of clinical trials in recent years, our conclusions have not changed substantially from our earlier review. Nevertheless, we did identify 15 registered clinical trials indicating that this continues to be an active area of research in which the science is likely to continue to evolve.

In conclusion, preclinical studies support the opioid-sparing effect of delta-9-THC and other mixed CB1/CB2 agonists. Observational studies support the opioid-sparing potential of cannabinoids. However, findings from clinical trials provide conflicting results that may highlight important areas for future research. These include identifying optimal doses and populations who may experience benefits with cannabinoids. With numerous clinical trials currently underway, we will update our review, as higher-quality data may enable stronger conclusions to be made.

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