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Cannabis and Cannabinoids for the Treatment of People with Chronic Non-Cancer Pain Conditions: A Systematic Review and Meta-Analysis of Controlled and Observational Studies

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Abstract

This review examines evidence cannabinoids in chronic non-cancer pain (CNCP), and addresses gaps in the literature by: considering differences in outcomes based on cannabinoid type and specific CNCP condition; including all study designs; and following IMMPACT guidelines. MEDLINE, Embase, PsycINFO, CENTRAL and clinicaltrials.gov were searched in July 2017. Analyses were conducted using Revman 5.3 and Stata 15.0. A total of 91 publications containing 104 studies were eligible (n = 9958 participants), including 47 RCTs and 57 observational studies. Forty-eight studies examined neuropathic pain, seven studies examined fibromyalgia, one rheumatoid arthritis, and 48 other CNCP (13 MS-related pain, 6 visceral pain, and 29 samples with mixed or undefined CNCP). Across RCTs, PERs for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo), significant effect for cannabinoids, number needed to treat to benefit (NNTB): 24 (95%CI 15-61); for 50% reduction in pain, PERs were 18.2% vs. 14.4%; no significant difference. Pooled change in pain intensity (standardised mean difference: -0.14, 95%CI -0.20, -0.08) was equivalent to 3mm on a 100mm visual analogue scale greater than placebo. In RCTs, PERs for all-cause AEs were 81.2% vs. 66.2%; number needed to treat to harm (NNTH): 6 (95%CI 5-8). There were no significant impacts upon physical or emotional functioning, and low-quality evidence of improved sleep and patient global impression of change. Evidence for effectiveness of cannabinoids in CNCP is limited. Effects suggest NNTB are high, and NNTH low, with limited impact on other domains. It appears unlikely that cannabinoids are highly effective medicines for CNCP.

Keywords: Cannabis, chronic non-cancer pain, neuropathy, systematic review, meta-analysis, number needed to treat

Introduction

There has been increasing attention to the use of cannabis and cannabinoids in the treatment of chronic non-cancer pain (CNCP). Changes in legislation and use globally mean that it is likely that there will be an increase in the coming years in availability and use of cannabis and cannabinoid products for CNCP. In the United States, these products are most commonly cited for use in CNCP [29]. CNCP conditions are prevalent, and rank among the most significant causes of disability globally [14].

Recent reviews of cannabis and cannabinoids for medicinal purposes have increased our knowledge in the understanding of their effectiveness on pain [30; 50; 51], though they are limited in the case of CNCP management and conclusions have been conflicting, with some reviews reporting moderate to large effects [29; 51], while others have reported minimal [35] or no benefit [3]. Existing reviews have been limited in their searching for CNCP studies (e.g. with a focus on specific types of cannabinoids [2], or study designs [35]) and no single review has considered: all types of evidence; different CNCP conditions individually; potential differential effects of different cannabinoids; and the safety of cannabis for CNCP patients. Each of these limitations reduces our understanding of the evidence for the use of cannabinoids for CNCP.

CNCP conditions are varied, and many people with CNCP live with complex physical and mental health comorbidities [4; 40]. Pain is considered by leading clinicians and researchers to be only one of a range of core outcomes that must be considered evaluating interventions for CNCP [48]. The current review addresses the limitations of previous reviews and is the first to examine the evidence for the effectiveness of cannabinoids for CNCP for all study designs, all CNCP types, all types of cannabis and cannabinoids, and using the outcomes specified in the Initiative on Methods, Measurement, and Pain Assessment in

Clinical Trials (IMMPACT) [48].

Methods

Search strategy and study eligibility

To ensure full coverage of the literature, we conducted a multi-phase search, comprising an initial review of reviews for cannabis and cannabinoids to treat CNCP, followed by four condition-specific systematic reviews.

A systematic review of reviews in October 2016 in the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Database of Systematic Reviews to identify all reviews (and empirical studies contained within) that evaluated the evidence base for the administration of cannabis and cannabinoids to treat CNCP (PROSPERO registration CRD42016049475).

This search was supplemented by four systematic searches of empirical studies in July 2017 in the electronic databases MEDLINE, Embase, PsycINFO, the Cochrane Database of Systematic Reviews and clinicaltrials.gov to identify any trial that evaluated cannabis or cannabinoids in treating the specific pain conditions: neuropathic pain (PROSPERO registration: CRD42017065248), fibromyalgia (PROSPERO registration: CRD42017067057), arthritis (PROSPERO registration: CRD42017067059) and other or mixed groups of CNCP (Supplementary Material, page 6). Date of publication was restricted to between 1980 and July 2017. No restrictions were placed on language or publication type. Medline search strategies are shown in **Appendix A** of the supplementary appendix (available online at http://links.lww.com/PAIN/A592). Corresponding subject headings were used in each database where specialised thesauri existed.

Individual studies that were identified (N= 107) in the systematic review of reviews of cannabinoids for the treatment of pain were screened for eligibility in full by two independent reviewers. For reviews of empirical studies for neuropathic pain, fibromyalgia, arthritis, and CNCP, two reviewers independently examined titles and abstracts using the web-based systematic review program Covidence [49]. All articles identified as potentially relevant (including review articles) were obtained in full and screened by two independent reviewers. Study screening was conducted in duplicate by two independent reviewers (any of GC, ES, MW, DZ, SN and RR). Inter-rater disagreement was resolved via consultation with an independent third reviewer (any of LD, GC, ES, MW, DZ and RR).

Types of pain conditions

We included studies that examined impacts of cannabis and cannabinoids on any CNCP condition. We followed Cochrane protocols determining studies for inclusion and extracting data; at least 80% of the patient population was required to be experiencing one of the included pain conditions (neuropathic pain, CNCP, arthritis or fibromyalgia). If less than 80% of the sample had one of the target pain conditions but results were presented separately for the sub-sample experiencing one of these pain conditions, we included the study and extracted data for the target subgroup. Studies were required to examine cannabis and cannabinoids as a primary or secondary indication for pain, and to measure at least one of our three primary pain outcomes: pain intensity, 30% or 50% reduction in pain.

Types of interventions

We considered studies examining: tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol + cannabidiol; plant-based cannabis (e.g. cannabis sativa); and other cannabinoids e.g. tetrahydrocannabinolic acid (thca), cannabidiolic acid, cannabidivarin, and the synthetic delta-9-tetrahydrocannabinol formulations nabilone and dronabinol.

Types of studies

We included randomised controlled trials (RCTs), non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies, analytical cross-sectional studies, observational studies, self-report, and N-of-1 studies. For studies with a comparison group, we considered any type of comparator, including placebo, waitlist controls and other interventions.

Outcomes

Guided by the IMMPACT core outcome domains for clinical trials in CNCP [48], we grouped the outcomes of interest into six categories: pain intensity, physical functioning, emotional functioning, global impression of change, adverse events and withdrawals. We assessed the clinical significance of the changes by extracting data for a 30% reduction in pain (a 'moderate' effect) and a 50% reduction in pain (a 'substantial' effect) [11].

Assessment of risk of study bias

We used the Cochrane Collaboration risk of bias tool for RCTs [19]. RCTs were judged to have an overall 'low risk' of bias if they had 6-8 risk domains rated as having a low risk of bias, 'unclear risk' if 4 or more domains were judged as being unclear, and 'high risk' if 3 or more domains were judged as being high risk. We additionally examined risk of bias due to sample size, where studies comprising at least 100 participants per treatment arm were classified as 'low risk', studies comprising 30-100 per arm were classified as 'unclear risk' and studies comprising <30 participants per arm were classified as 'high risk'. Observational studies or case study reports were evaluated using an adapted version of the Cochrane Collaboration risk of bias in non-randomised studies of interventions (ROBINS-I) assessment tool [44]. Overall risk of bias was determined by the most serious risk of bias allocated to that study across the tool.

Grading of evidence

As the review included RCTs and observational trials we used an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool to grade the overall study methodology [36]. RCTs began with a high rating that was downgraded if important limitations were identified in the study methodology. Observational trials began with a low rating and were upgraded if important strengths were identified. We additionally conducted a GRADE assessment using GRADEPro (https://gradepro.org/) for each reported pooled estimate that evaluated the risk of bias, inconsistency, indirectness, imprecision and publication bias (via visual inspection of funnel plots).

Data extraction

We extracted details on the participants, interventions, comparisons, outcomes and study design (PICOS) of each study, including: sample N, age, gender, medical and pain condition/s, length and type of treatment (including route of administration, place in therapeutic hierarchy, dose, and co-interventions), comparator type, study country, year and design. Outcomes were extracted following IMMPACT recommendations. When data were not reported in full, we contacted authors for additional information. When studies reported multiple measures of a single domain (e.g. pain intensity), we applied a hierarchy of evidence. Where authors reported multiple analyses (e.g. intention to treat [ITT], available case or per protocol), we extracted the more conservative with a preference for ITT analyses. We reported adverse events according to high-level Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/) categories and report the 18 most common single adverse events.

Data extraction, risk of bias, and GRADE assessments were conducted in duplicate by two independent reviewers (any of GC, ES, MW, DZ, SN and RR). Inter-rater disagreement was resolved via consultation with an independent third reviewer (any of LD, GC, ES, MW, DZ and RR).

Data analysis

We extracted data from all reported time points in each trial. Our primary analysis included data from the primary endpoint (or longest follow-up) in each trial. If multiple assessments were made on participants on the same day, we analysed the data taken from the longest follow-up.

Data were analysed separately for RCTs and observational study designs. All analyses were conducted using Review Manager (RevMan) version 5.3 [46] and Stata 15.0 [43]. Continuous outcomes were pooled using fixed-effects generic inverse variance meta-analysis and expressed as standardised mean differences (SMDs) with 95% confidence intervals (CIs). To aid clinical interpretation of the continuous outcome of change in pain intensity, we additionally re-expressed the SMD for overall change in pain intensity as a mean difference on a 100mm visual analogue scale (VAS) by multiplying the pooled SMD by a typical baseline among-person standard deviation on a 100mm VAS, obtained from the included studies [19; 21]. Dichotomous outcomes were summarised as odds ratios (ORs) using the Mantel-Haenszel fixed effect model [9]. For observational studies, we pooled event rates using the Stata **metaprop** command [32]. Heterogeneity was assessed using the I^2 statistic, and described as low (≤25%), moderate (>25% and ≤50%) or high (≥75%) [18]. Where data permitted, we assessed publication bias in the pooled estimates using the Stata15.0 **metabias** command to detect small study effects [16]. If the test of small study effects was significant, we used the Stata15.0 metatrim command to conduct Duval and Tweedie's non-

parametric trim and fill procedure and provide an adjusted treatment effect [10]. We conducted sensitivity analyses using the inverse variance random effects model where I^2 values exceeded 50%. For the primary pain intensity outcomes (30% reduction in pain, 50% reduction in pain and change in pain intensity) we conducted subgroup analyses to assess for differences in RCT pooled estimates based on overall study risk of bias (low, unclear or high), study risk of bias due to sample size (low [100+ participants per treatment arm], unclear [30-100 per arm], high [<30 per arm]), intervention length (one-day studies, very short term [<4 weeks], short term [4-12 weeks], intermediate term [13-26 weeks] or long term [>26 weeks]), and imputation method (none/ITT, completer-only, or last observation carried forward [LOCF]). We followed Cochrane Collaboration methods to overcome unit-of-analysis errors for multi-arm studies [18]. Where raw data were not reported, we used the Generic Inverse Variance fixed effect model to pool effect estimates and their standard errors [18].

For dichotomous outcomes with at least a moderate GRADE rating, we calculated numbers needed to treat to benefit (NNTB) and numbers needed to treat to harm (NNTH) and their 95% CIs. We used pooled estimates of relative effect measures (ORs) to take into account the event rate in control groups [6]. NNTB was calculated for the outcomes 30% reduction in pain, 50% reduction in pain, and change in patient global impression of change. NNTH was calculated for all-cause adverse events and study withdrawals due to adverse events. **Panel G1 in Appendix G** summarises the core statistics and metrics used in this paper (available online at http://links.lww.com/PAIN/A592).

Results

The combined searches resulted in 2525 results. In total, 91 publications were eligible and included in the review, which reported on 104 distinct studies (**Figure 1, Figure B1 Appendix B**). **Tables 1** (RCTs) and **B1** in **Appendix B** (observational studies) contain the list of included studies. The search additionally identified 17 ongoing studies for which results are yet to be reported (Appendix **Table B2**). Excluded studies are listed in Appendix **Table B3** (appendices available online at http://links.lww.com/PAIN/A592).

Figure 1 about here

Study characteristics

Characteristics of included studies, including sample characteristics, pain classification, cannabinoid classification, treatment length, dose, study outcomes, risk of bias rating and imputation method are provided in **Table 1** (RCTs) and Appendix **Table B1** (observational studies, available online at http://links.lww.com/PAIN/A592). The 104 studies comprised 47 RCTs (24 parallel RCTs, 23 cross-over RCTs), and 57 observational studies, comprising a total of 9958 participants (n= 4271 RCTs; 5687 observational studies). We contacted nine authors for additional information; six responded and two provided data which were used in analyses. Most studies were conducted in Western Europe (n=47) or the United States (n=34, see **Table 2**).

Where possible, we have examined CNCP categories separately. Overall, we found 48 studies of neuropathic pain (of which 16 were MS-related and 32 were non-MS-related), seven studies for fibromyalgia, one for arthritis (specifically rheumatoid arthritis), and 48 studies for other = CNCP (of which 13 were MS-related pain, 6 were visceral pain, and 29 were studies of samples with mixed or undefined non-MS-related CNCP, and, **Table 3**).

Characteristics of participants

Detailed characteristics of participants in the studies are provided in **Table 1** (RCTs) and Appendix **Table B1** (observational studies). Details of ongoing studies with no data available at time of current review are detailed in Appendix **Table B2**. Details of studies excluded at the full text review stage are presented in Appendix **Table B3** (available online at http://links.lww.com/PAIN/A592). The number of participants ranged from 1 to 649, with a median of 42 (mean 136.8). All studies were conducted in adult samples, except for two case series of two adolescents (aged 14 and 15) [38] and an open label trial in young girls with adverse drug effects following vaccination [34]. Where reported, mean age of adult participants ranged from 28 [25] to 67 [5] years (median 49.2, mean 50.5), and percentage of males ranged from 0-100% (median 46.7%; mean 45.1%). Mean baseline pain intensity scores were 59.6 (SD = 14.6; range: 30.1 to 87.5) on a 100mm VAS, suggesting patients had moderate to severe pain intensity at study intake [17].

Pain was the primary indication in 76 studies and a secondary indication in 28 studies. Of the 104 included studies, four [7; 37; 39; 45] (n = 47 participants) examined cannabinoids as a first-line therapy, and 87 examined cannabinoids as a second-line therapy in addition to existing medication regimens. In 13 studies, the place of cannabinoids in the therapeutic hierarchy was not reported or unclear. The most common other adjunct medications were opioids, NSAIDS and anti-spasticity medications. In nearly all RCT studies, patients were required to be on a stable dose of current medication before commencement of the trial.

The most commonly studied cannabinoid was nabiximols, followed by cannabis sativa. See **Table B4** for more information on the cannabinoids used in the included trials, including route of administration, duration and dose.

Risk of bias ratings

Most parallel and cross-over RCTs were rated as unclear risk of bias across all domains because information was not fully reported or could not be obtained from the authors (see **Appendix C** for ratings of risk of bias, available online at http://links.lww.com/PAIN/A592). Several were rated as at high risk of bias because of selective reporting or other biases, such as omission of data and confidence intervals, changes in selection of the primary endpoint or a failure to take account of within-subjects effects in cross-over studies (see **Appendix C Figures C1, C2**, available online at http://links.lww.com/PAIN/A592). Observational studies were judged to be at serious or critical risk of bias for key domains because of confounding, intervention measurement, high dropout, and selection of the reported result (see **Figure C3**).

Outcomes

Tables D1 and **D2** in **Appendix D** (available online at http://links.lww.com/PAIN/A592) describe IMMPACT outcomes collected in RCTs and observational studies respectively. The most commonly studied outcomes were pain intensity (n=100), adverse events (n=81) and withdrawals (n=71). Fewer studies reported on physical functioning (n=52), emotional functioning (n = 43), and patient's global impression of change (n = 24). Only two studies in which pain was the primary indication reported on all six outcomes [23; 47].

Pain

30% reduction in pain

RCT evidence

Of the 47 included RCTs, 13 assessed 30% reduction in pain (See **Table D1** in Appendix D; available online at http://links.lww.com/PAIN/A592), of which 8 RCTs (based on 9 data points) reported sufficient data and were used in the meta-analysis. Across all cannabinoids

and CNCP conditions, cannabinoids were more likely than placebo to produce a 30% reduction in pain ([1; 20; 22; 23; 31; 41; 42; 52], n = 1734, OR 1.46, 95%CI 1.16-1.84, see **Table 4** and **Table E1** and **Figure E1** in **Appendix E**; available online at http://links.lww.com/PAIN/A592). A summary of key outcomes, including NNTB is shown in Table 6. No evidence of small study effects was detected (p = 0.08). We found significant effects for plant-based cannabis, THC:CBD extract and ajulemic acid but these were each based on a single study and our GRADE ratings for these estimates was moderate to very low. Among the specific pain conditions, we found effects for neuropathic pain, and MS-related CNCP (see **Table 4 and Figure E1**). Of the remaining 5 studies that assessed 30% reduction in pain but for which data were not reported or obtained from study authors, three reported a significant positive effect and two reported no benefit. When examined by overall study risk of bias rating and risk of bias due to sample size, the effect estimate remained significant for studies classified as having low risk and for studies with more than 100 participants per treatment arm, but was not significant for studies at unclear risk of bias, or for studies with less than 100 participants per arm, with notably larger but non-significant effects for the smallest studies (<30 participants per arm; see Figures E1.1 and E1.1a),. No significant differences in effect sizes were identified between studies with interventions of very short term (<4 weeks), short-term (4-12 weeks) and intermediate term (13-26 weeks, see Figure E1.2). All studies assessed outcomes using ITT analyses without imputation.

Observational evidence

In observational studies with a comparison group, one small open-label study with a randomised-withdrawal phase (n = 26[47])and found that nabilone was significantly more likely to produce a 30% reduction in pain relative to placebo (See **Table 4**). In observational

studies with no comparison group, the pooled prevalence of receiving cannabinoids reported achieving a 30% reduction in pain was 72% (95%CI 66-78%) (see **Figure E5 and Appendix F** available online at http://links.lww.com/PAIN/A592)**.**

50% reduction in pain

RCT evidence

Five of the 47 included RCTs assessed 50% reduction in pain, all of which provided sufficient data for meta-analysis. We found no significant evidence that cannabinoids reduced pain by 50% compared to placebo (OR 1.43, 95% CI 0.97-2.11, see **Table 4** and **Table E1** and **Figure E2** in **Appendix E** available online at http://links.lww.com/PAIN/A592). We found no effect for any of the specific cannabinoids, however among pain conditions, a significant effect was found for non-MS-related neuropathic pain (see **Table 4**). No evidence of small study effects was detected (p = 0.12). No subgroup analysis was able to be conducted for overall study risk of bias as all studies were classified as low risk. When examined by risk of bias due to sample size, effects were larger and had substantial uncertainty for studies of <100 participants per treatment arm compared to studies with 100+ participants, but all estimates fell within overlapping bounds of uncertainty and were non-significant (see **Figure E2.1.a**). No differences were detected between studies with interventions of very short term (<4 weeks), short-term (4-12 weeks) and intermediate term (13-26 weeks, see Figures E2.1 and E2.2). All studies assessed outcomes using ITT analyses without imputation.

Observational evidence

Two observational studies with a comparison group found evidence of a significant effect for 50% reduction in pain, however the GRADE rating for this outcome was very low(see **Table 4** and **Table E1** in **Appendix E** available online at http://links.lww.com/PAIN/A592).

Outcomes for observational studies with no comparison group were equivocal and are summarised narratively in **Appendix F.**

Change in pain intensity

RCT evidence

Of the 47 RCTs included in the review, 45 reported data on pain intensity of which 30 (comprising 34 data points) reported sufficient data and were used in the meta-analysis for change in pain intensity. We found that cannabinoids overall produced a larger reduction in pain intensity than placebo (SMD -0.14, 95%CI -0.20 to -0.08, see **Table 4** and **Table E1** and **Figure E3** in **Appendix E** available online at http://links.lww.com/PAIN/A592). We calculated this to be roughly equivalent to a reduction of 2.9mm on a 100mm VAS (95%CI: -4.61 to -1.46) greater than placebo groups. Among the cannabinoids, there were significant effects for nabiximols and THC extract, both with a moderate GRADE rating (Table E1). We found an effect for neuropathic pain (MS and non-MS-related), and rheumatoid arthritis, but the latter was based on one small study and had a very low grade rating (see **Table 4**). No evidence of small study effects was detected (p = 0.49). Of the remaining 15 studies that assessed pain intensity but for which data were not reported or obtained from study authors, 12 reported a significant positive effect and three reported no benefit. When examined by overall risk of bias rating, the effect estimate remained significant for studies classified as low risk but was not significant for studies at unclear or high risk of bias (**Figure E3.1**), and effect sizes were larger for studies with smaller sample sizes (Figure E3.1a) . When examined by study intervention length effects appeared to dissipate with increasing study length: one-day and very short term (< 4 weeks) studies remained significant, however studies conducted in the short (4-12 weeks), intermediate (13-26 weeks) or long-term (>26 weeks) did not, with decreasing effect sizes as study length increased (see **Figure**

E3.2). The effect remained significant for studies using ITT analyses, however was smaller and not significant for studies using LOCF imputation methods, or where the handling of missing data was not reported (**Figure E3.3**).

Observational evidence

In the observational studies with a comparison group, we found no significant evidence of effect for cannabinoids in reducing pain intensity (see Table 4). A significant reduction in pain intensity was identified in within-person pre-post assessments of pain in observational studies with no comparison group (see **Appendix F** available online at http://links.lww.com/PAIN/A592)**.** Five RCTs examined reductions in analgesic use. People taking nabiximols had a greater reduction in the frequency and quantity of use of rescue analgesics compared to placebo (SMD -0.13, 95% CI -0.26 to -0.01, I^2 =48%); this had a moderate GRADE rating.

Physical functioning

No significant effect of cannabinoids on overall physical functioning in 18 RCTs, see **Table E2** and **Figure E6**) or quality of life (n=11 RCTs) compared with placebo (see **Table E2** and **Figure E8)**. There was a significant effect of cannabinoids in reducing sleep problems when compared to placebo (SMD -0.29, 95%CI -0.40 to -0.19), but the GRADE assessment for this was low (see **Table E2** and **Figure E7**). We found a reduction in sleep problems when compared to placebo for nabiximols with a moderate GRADE rating (SMD -0.32, 95%CI -0.44 to -0.20, see **Table E3** in Appendix E available online at http://links.lww.com/PAIN/A592). No small study effects were detected for any of these outcomes (p's range from 0.14 to 0.84).

Emotional functioning

Patients receiving any cannabinoids did not report any difference compared to comparator groups in overall emotional functioning, or in depressive or anxiety symptoms specifically (see **Table E2** and **Figures E9-E11**). No evidence of small study effects was identified for overall emotional functioning (p = 0.10_ or anxiety symptoms (p = 0.06), however a significant effect was detected for depression (p = 0.01). The trim and fill procedure to account for small study effects revealed that the adjusted estimate did not differ significantly from the original estimate (SMD 0.04, 95%CI -0.14 to 0.22, see **Table E2**). A significant improvement in emotional functioning was identified for dronabinol compared to placebo based on a single study; we had low confidence in this effect (see **Table E3** in Appendix E available online at http://links.lww.com/PAIN/A592).

Patient global impression of change

In the four RCTs which reported patient global impression of change as a continuous outcome on the seven-item PGIC scale, there were significant increases among patients receiving any cannabinoid compared to placebo (see **Table E2** and **Figure E12**), with no evidence of small study effects (p = 0.28). Nine RCTs reported PGIC scores as a dichotomous outcome (much or very much improved vs slightly improved, no change or worse), with significant improvement among patients receiving any cannabinoid compared to placebo (see Table 4 and Figure E13), and no evidence of small study effects (p = 0.3). Confidence in these outcomes was low to very low. Most of the evidence was for nabiximols, with some evidence for nabilone, cannabis sativa and THC extract.

Study withdrawals

CNCP patients who received a cannabinoid had two times the odds of withdrawing from a trial for any reason than patients who received placebo (see **Table E4** in Appendix E available online at http://links.lww.com/PAIN/A592). They had 3.47 times the odds of withdrawing because of adverse events (see **Table 5**), no evidence of small study effects (p = 0.44). CNCP patients who received placebo were slightly more likely to withdraw from trials because of a lack of efficacy than those receiving cannabinoids. There was some variation between cannabinoids in reasons for withdrawal (see **Table E4** in **Appendix E** available online at http://links.lww.com/PAIN/A592).

Adverse events

CNCP patients receiving cannabinoids had 2.33 times the odds of experiencing an adverse event compared to placebo. (see **Table 5 and Table E4 in Appendix E** available online at http://links.lww.com/PAIN/A592). Significant evidence of small study effects was detected (p = 0.01), however the adjusted estimate did not differ significantly from the original (OR = 2.22, 95%CI 1.60 to 3.01). Serious adverse events were reported in a smaller number of studies (see **Table 5**), and patients receiving cannabinoids had higher rates of serious adverse events, but this did not reach statistical significance. No small study effects were detected (p = 0.52). Compared with placebo, patients receiving cannabinoids were more likely to report individual adverse events such as: dizziness (OR 5.52, 95%CI 4.47 to 6.83), cognitive attention or disturbance (OR 5.67, 95%CI 2.72 to 11.79) and confusion and disorientation (OR 5.35, 95%CI 2.31 to 12.39, **Table 5**).

Summary statistics

Table 6 summarises the pooled ORs, pooled event rates for cannabinoids vs. placebo groups, and NNTB or NNTH for dichotomous outcomes with a moderate or higher GRADE rating in RCTs. Note since we only had continuous measures of sleep outcomes, cannabinoids' impacts on improving sleep cannot be included in these summary statistics.

For cannabinoids' impact on pain outcomes, pooled event rates for 30% reduction in pain intensity were 29.0% vs 25.9%, respectively. The NNTB was 24 (95%CI 15 to 61, see **Table 6**).

For a 50% reduction in pain, the pooled event rate for cannabinoids was 18.2%, compared with 14.4% for placebo (see **Table 6**).The NNTB for 50% reduction in pain was unable to be calculated as the estimate crossed the line of no effect.

For studies where outcomes were presented dichotomously, participants receiving cannabinoids had slightly increased odds of reporting global improvements (PGIC) than patients who received placebo (see **Table 6**). In participants receiving cannabinoids, the pooled percentage reporting "much" or "very much" global improvement was 18.9% compared to 11.8%; the NNT was 38 (95%CI 27 to 62).

Pooled statistics for AEs and study withdrawals are also presented in **Table 6**. The estimated pooled rate of all-cause AEs was 81.2% among people receiving cannabinoids, compared with 66.2% of those receiving placebo; the NNTH was 6 (95%CI 5 to 8). The pooled event rate for study withdrawals due to AEs was 15.8% in those receiving cannabinoids compared to 4.6% of those receiving placebo, and the NNTH was 40 (35 to 49).

Discussion

To our knowledge, this is the first systematic review of the evidence for the effectiveness and safety of cannabinoids for CNCP that included all cannabinoids, all study designs, and considered all outcomes recommended by the IMMPACT group. We also assessed the clinical relevance of these findings using event rates, NNTB and NNTH.

We found moderate evidence for a reduction in pain for cannabinoids when compared to placebo. Pooled analyses suggested that 30% reduction in pain was reported by 29.0% in cannabinoids, compared with 25.9% in placebo groups. A 50% reduction in pain was reported by 18.2% in cannabinoid groups and 14.4% in placebo groups, however this did not reach statistical significance. The NNTB to achieve a 30% reduction in pain for one person using cannabis or cannabinoids (compared to placebo) was estimated at 24 (95% CI 15 to 61), and the NNTH for one person to experience any adverse event was 6 (95% CI 5 to 8). Although caution needs to be used in comparing NNTs across studies involving different groups and timeframes [26], these NNTB are much higher than those for other analgesics: previous studies in neuropathic pain suggested NNTs for strong opioids of 4.3 (95%CI 3.4–5.8), pregabalin (7.7, 95%CI 6.5–9.4) and tricyclic antidepressants (3.6, 95% 3.0–4.4) [13]. The NNTH in our review was similar to that for opioids for CNCP, with a recent Cochrane review indicating that the NNTH for one person using opioids to experience any adverse event (compared to placebo) was 5 (95% CI 4 to 9) [12]. When re-expressed as a mean change on the commonly used 100mm VAS, the pooled SMD for the continuous outcome of change in pain intensity was equivalent to a 3mm greater reduction on this scale compared to placebo, which is well below the 30mm reduction regarded to represent a clinically important difference in pain intensity [24; 33]. In contrast to more optimistic conclusions from earlier reviews (e.g. [2; 29]), our findings are largely consistent with a recent Cochrane

review examining cannabinoids for neuropathic pain, indicating that these medicines are unlikely to be effective in the treatment of pain [28]. In their review, Mücke and colleagues [28] report an NNTB of 20 for 50% or greater reduction in pain, and NNTHs of 3 and 6 for adverse events relating to nervous system and psychiatric disorders respectively, suggesting a similar efficacy and safety profile of cannabinoids for pain as reported in our review.

The evidence on the effectiveness of cannabinoids for CNCP is limited for several reasons. First, sample size is an issue, with only 21 of the 104 included studies having at least 100 participants per treatment arm. While we made multiple attempts to minimise risk of bias in the effect estimates due to small sample sizes, this risk cannot be fully mitigated. For some estimates, effect sizes were notably larger in studies with <30 participants per treatment arm compared to studies of 100+ per arm, however these estimates fell within overlapping bounds of uncertainty. There is a growing body of evidence indicating that effect estimates tend to be larger in studies with small sample sizes [8], and as such, caution should be taken when interpreting outcomes based on studies with small sample sizes in this review. Well conducted, large RCTs comprising at least 100 participants per treatment arm should be considered a priority in this spaceSecond, most studies were of limited duration (median of eight weeks): given that CNCP is a chronic condition, this sheds little light on the appropriateness of long-term use of cannabinoids in CNCP, in terms of both treatment efficacy and safety. Of the little evidence available, we found that reductions in pain intensity were largest for one- day studies, and smaller and non-significant in studies of 13 weeks duration or longer, providing some initial suggestion that the effectiveness of cannabinoids for CNCP may diminish over time. Third, the issues of cannabinoid tolerance, risks of iatrogenic dependence, and of withdrawal symptoms if long-term cannabinoids are ceased, remain poorly understood. Short term clinical trials such as those included in this

review are often of insufficient power and duration to detect potential harms and adverse events associated with long-term cannabis use, such as elevated risk of psychosis and substance dependence [15; 27]. It is crucial that these long-term outcomes identified in the epidemiological literature are considered alongside evidence of efficacy from clinical trials when determining overall suitability of cannabinoids as medicines for CNCP. Fourth, cannabinoid dose was often poorly recorded. Often only a maximum recommended dose was reported and data on participants' actual cannabinoid consumption were seldom recorded, so it is difficult to make strong recommendations on doses that are maximally effective and safe. Fourth, by far the greatest amount of high quality evidence was for nabiximols, resulting in small numbers of studies (and in some cases, single studies) in some analyses for other types and formulations of cannabinoids (e.g. ajulemic acid), meaning we are be less confident about their efficacy. Fifth, although almost all studies reported data on change in pain intensity, very few reported outcomes for 30% and 50% reduction in pain. Given that pain was a secondary outcome in many studies, it is possible that authors did not report these outcomes as they are drawn from the pain-specific IMMPACT guidelines, however, there is also the possibility that study authors chose not to report outcomes for 30% and 50% reduction in pain when the continuous pain intensity outcome indicated no benefit. While we have made multiple attempts to account for publication bias throughout this review, there remains the possibility that the studies for which 30% and 50% reduction in pain were not reported did not find evidence of effect. If this is the case, NNTBs for these outcomes may be higher than reported here, however our overall conclusion that cannabinoids are unlikely to be effective medicines for CNCP will remain unchanged. Finally, to ensure all the available evidence of cannabinoids as a treatment for CNCP was considered in this review, we included evidence from RCTs and less rigorous observational study

designs. This approach allows researchers, clinicians and policy makers to map current research activity and to identify knowledge gaps. While observational studies provide some insight into the efficacy of cannabinoids for CNCP, ultimately only data from high quality RCTs will be used to inform national treatment guidelines. We noted that most of the higher quality, RCT evidence was for neuropathic pain and MS-related pain. There is scant, low quality evidence on cannabinoids used for fibromyalgia or visceral pain, and very few studies of cannabinoids' use in the most common and burdensome CNCP conditions, namely back/neck problems, migraines and arthritides. Thus, the conclusions of this review primarily relate to neuropathic or MS-related pain. Several ongoing studies targeting these more common CNCP conditions were identified and will be analysed when results become available.

Most studies used a placebo comparator and added cannabinoids to stable doses of analgesics, NSAIDS and anti-spasticity drugs, so the evidence for cannabinoid use in CNCP is largely around cannabinoids as adjuvant medicines. Often multiple analgesics were used, which varied between groups, and the ways they were used was not consistently reported. Most studies held doses of other analgesic medications constant, though some studies documented changes in breakthrough medication or adjunctive analgesia.

Limitations of this review

The findings of this review need to be considered in light of several potential limitations. Some of these limitations have already been noted and include the high risk of bias in many studies because of small N, and missing information on study design and rigour of controls; most studies also evaluated cannabinoids as adjunct to other analgesic medications. We attempted to assertively minimise these limitations. Many documents were reviewed by a

small research team, which might have led to errors in assessing eligible studies. However, internal checks were conducted by members within this team and a process of double and triple checking existed; we also checked all identified reviews to ensure that no studies had been missed that had been reported in any other reviews of evidence. Third, errors may have been made in data interpretation. To reduce such errors, all sources and data extracted were double-checked by at least two reviewers and conflicts were resolved by third reviewer when necessary.

Conclusions

It appears unlikely that cannabinoids are highly effective medicines for CNCP. There is moderate to high grade evidence supporting use of nabiximols to achieve modest reductions in pain as adjunctive therapy in MS-related pain. However, NNTB were high and NNTH low, with high rates of dropout for adverse events, and long-term efficacy and safety is unknown. We also found minimal evidence that cannabinoids are effective in improving other important domains in people with CNCP such as emotional and physical functioning. Cannabinoids are unlikely to be a monotherapy for CNCP. People living with CNCP often have complex comorbidities [4; 40], and multidisciplinary treatment that includes physical and psychological therapy rather than reliance on medicines alone is likely to be most effective.

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Non-author contributions

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Author contributions

LD and MF conceived the Review. ES, GC, SN, DZ, RR, and MW did the systematic search, selected papers, and extracted data. ES conducted statistical analyses. GC, LD and WH drafted the manuscript with critical revisions from all authors. BM provided clinical important intellectual content. All authors reviewed the paper before submission.

Conflicts of interest

GC, SN, MF and LD have all been investigators on untied investigator-driven educational grants funded by Reckitt Benckiser. MF and LD have received an untied educational grant from Mundipharma for post-marketing surveillance studies of a potentially tamper-resistant formulation of controlled-released oxycodone. SN, MF and LD have been investigators on untied investigator-driven educational grants funded by Indivior. MF and LD have been investigators on an untied investigator-driven educational grant funded by Seqirus.

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Supplemental video content

Video content associated with this article can be found at http://links.lww.com/PAIN/A593.

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Figure legends

Figure 1. PRISMA flowchart showing the process of selection of studies into the review. See Figure B1 in Supplementary Appendix B for the PRISMA flowchart of the systematic review of reviews.