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Review

REVIEW

Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials

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Abstract

Study Objectives: We conducted a systematic review to explore the effectiveness of medical cannabis for impaired sleep.

Methods: We searched MEDLINE, EMBASE, CENTRAL, and PsychINFO to January 2021 for randomized trials of medical cannabis or cannabinoids for impaired sleep vs. any non-cannabis control. When possible, we pooled effect estimates for all patient-important sleep-related outcomes and used the GRADE approach to appraise the certainty of evidence.

Results: Thirty-nine trials (5100 patients) were eligible for review, of which 38 evaluated oral cannabinoids and 1 administered inhaled cannabis. The median follow-up was 35 days, and most trials (33 of 39) enrolled patients living with chronic cancer or noncancer chronic pain. Among patients with chronic pain, moderate certainty evidence found that medical cannabis probably results in a small improvement in sleep quality versus placebo (modeled risk difference [RD] for achieving the minimally important difference [MID], 8% [95% CI, 3 to 12]). Moderate to high certainty evidence shows that medical cannabis vs. placebo results in a small improvement in sleep disturbance for chronic non-cancer pain (modeled RD for achieving the MID, 19% [95% CI, 11 to 28]) and a very small improvement in sleep disturbance for chronic cancer pain (weighted mean difference of –0.19 cm [95%CI, –0.36 to –0.03 cm]; interaction $p = .03$). Moderate to high certainty evidence shows medical cannabis, versus placebo, results in a substantial increase in the risk of dizziness (RD 29% [95%CI, 16 to 50], for trials with ≥3 months follow-up), and a small increase in the risk of somnolence, dry mouth, fatigue, and nausea (RDs ranged from 6% to 10%).

Conclusion: Medical cannabis and cannabinoids may improve impaired sleep among people living with chronic pain, but the magnitude of benefit is likely small.

Statement of Significance

Our review identified 39 trials that reported the effects of medical cannabis or cannabinoids on sleep, most of which enrolled people living with chronic pain. Compared to placebo, medical cannabis provided an improvement in sleep quality and sleep disturbance for a minority of patients. Specifically, 1 of every 13 patients treated with cannabis reported improved sleep quality. For sleep disturbance, effects were different based on the type of pain. One in 5 patients with chronic noncancer pain reported reduced sleep disturbance, but the effects were smaller for chronic cancer pain. Medical cannabis is also associated with a modest risk of dizziness (1 in 3 patients effected), and a smaller risk of other temporary side effects such as fatigue and nausea.

Key words: medical cannabis; cannabinoid; sleep; randomized controlled trial; systematic review

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Introduction

The prevalence of sleep disorders in the general population is approximately 20% [1], and cannabis is increasingly promoted as a management strategy to improve sleep [2]. A US survey of 1000 adults attending a cannabis dispensary found that 74% reported using cannabis to improve sleep and 84% of this population reduced or discontinued their sleep medication [3]. An international survey completed by 953 participants from 31 countries indicated that sleep disorders were among the top five conditions for which they used medical cannabis [4].

There are two systematic reviews that have assessed the effect of cannabinoids on sleep [5, 6]; however, neither conducted meta-analyses to pool effect estimates nor evaluated the overall certainty of evidence [5, 6], and the literature search of one review was outdated [5]. We conducted a systematic review of the effect of medical cannabis and cannabinoids on impaired sleep that addressed these limitations.

Materials and Methods

We registered our review on PROSPERO (CRD42018103266) and followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [7].

Data sources and searches

We searched MEDLINE, EMBASE, CENTRAL, and PsychINFO from inception to January 19, 2021, using search strategies designed by an academic librarian (Appendix A). We reviewed reference lists of relevant systematic reviews and all included studies to identify additional eligible trials.

Eligibility criteria

We included randomized controlled trials (RCTs), in any language, evaluating the effect of medical cannabis or cannabinoids on sleep. Trials were eligible if they: 1) enrolled patients aged 18 or older with impaired sleep; 2) randomized them to any form of medical cannabis or cannabinoid vs. a noncannabis control, and 3) collected outcome data ≥14 days after treatment. We excluded open-label trials, trials that enrolled individuals using cannabis for recreational purposes, and studies exploring treatment for cannabis use disorder or cannabis withdrawal.

Study selection and data extraction

Paired reviewers screened titles and abstracts of identified citations and reviewed full texts of all potentially eligible studies, independently and in duplicate. The same pair of reviewers extracted data, independently and in duplicate, including patient characteristics, intervention details, effects on sleep quality, sleep disturbance, other sleep-related outcomes, and all adverse events reported by ≥5 trials.

Risk of bias assessment

Two reviewers assessed risk of bias among eligible trials, independently and in duplicate, using a modified Cochrane risk of bias instrument [8, 9].

Data analysis

We used the adjusted kappa (κ) statistic to assess the interrater agreement for inclusion of trials at the full-text screening stage. Our included studies used various instruments to measure sleep quality and sleep disturbance, with the most reported measure being the 10 cm visual analog scale (VAS). To facilitate statistical pooling in natural units, we converted other measures of sleep quality or sleep disturbance to a 10 cm VAS, as long as they had ≥4 categories of response options, according to the method of Thorlund et al [10]. We re-scaled measures, when necessary, to ensure that higher scores indicated worse sleep quality or sleep disturbance. When possible, we pooled effects across trials using random-effects models and the DerSimonian-Laird method.

We reported pooled effect estimates of continuous outcomes as both the weighted mean difference and, when possible, the modeled risk difference (RD) of achieving the minimally important difference (MID) to optimize interpretability [11, 12]. The MID is the smallest amount of improvement that patients recognize as important [13] and is approximately 1 cm for the 10 cm VAS for sleep quality and sleep disturbance [14]. We reported the pooled effects on binary outcomes as relative risks and RDs. For all meta-analyses, we used change scores from baseline to the end of follow-up to account for interpatient variability. If change scores were not reported, we calculated them using the baseline and end-of-study scores and the associated standard deviation (SD) using a correlation coefficient derived from the largest trial at the lowest risk of bias that reported a change score.

When treatment effects were reported simply as nonsignificant without accompanying data, we contacted study authors to request these data. If unsuccessful, we addressed the risk of overestimating the magnitude of effect by imputing a weighted mean difference (WMD) of 0 or a relative risk (RR) of 1 for missing effect estimates. We derived the associated variance for missing non-significant results with the hot-deck approach [15]. When individual studies did not provide data that allowed for their inclusion in meta-analysis, we explored the consistency of their findings with pooled effects. Stata statistical software version 15.1 (StataCorp) was used for all analyses, and comparisons were 2-tailed using a $p \leq .05$ threshold for statistical significance.

Subgroup analysis, meta-regression, and sensitivity analysis

We used Cochran's chi-squared test and the I-square statistic to examine statistical heterogeneity of pooled treatment effects [16]. We tested the following a priori subgroup hypotheses that larger treatment effects for beneficial outcomes were associated with: (1) shorter vs. longer length of follow-up; (2) noncancer vs. cancer-related chronic pain; (3) high tetrahydrocannabinol (THC) vs. THC and cannabidiol (CBD) vs. high CBD products; and (4) high vs. low risk of bias on a component-by-component basis. We made the same assumptions for harm outcomes, except we anticipated greater harms with longer vs. shorter follow-up. We conducted subgroup analyses only if there were two or more studies in each subgroup. We assessed the credibility of subgroup effects using ICEMAN criteria [17]. We performed meta-regression for length of follow-up, duration of treatment, and loss to follow-up.

We also conducted post hoc sensitivity analyses to assess the robustness of our results by excluding studies in which the WMD for non-significant effects was imputed.

Assessing certainty of evidence

We used the GRADE approach to summarize the certainty of evidence for all outcomes [18], and followed GRADE guidance for communicating our findings [19]. We assessed for small-study effects when there were at least 10 studies available for meta-analysis by visual assessment of asymmetry of funnel plots for each outcome, and Egger's test [20] for continuous outcomes, and Harbord's test [21] for binary outcomes. If no credible subgroup effect was found for risk of bias components, then we pooled all trials and did not rate down for risk of bias. If a credible subgroup effect was found, then we only reported the pooled estimate of effect among trials at low risk of bias. If a subgroup effect for risk of bias could not be explored for a given outcome, due to <2 trials per group, we rated down for risk of bias if the relative contribution of trials at high risk of bias to the pooled effect estimate was >20%.

We considered pooled effects for continuous outcomes imprecise if the associated 95% CI included ½ the MID, which equates to approximately a 10% RD, and binary outcomes if

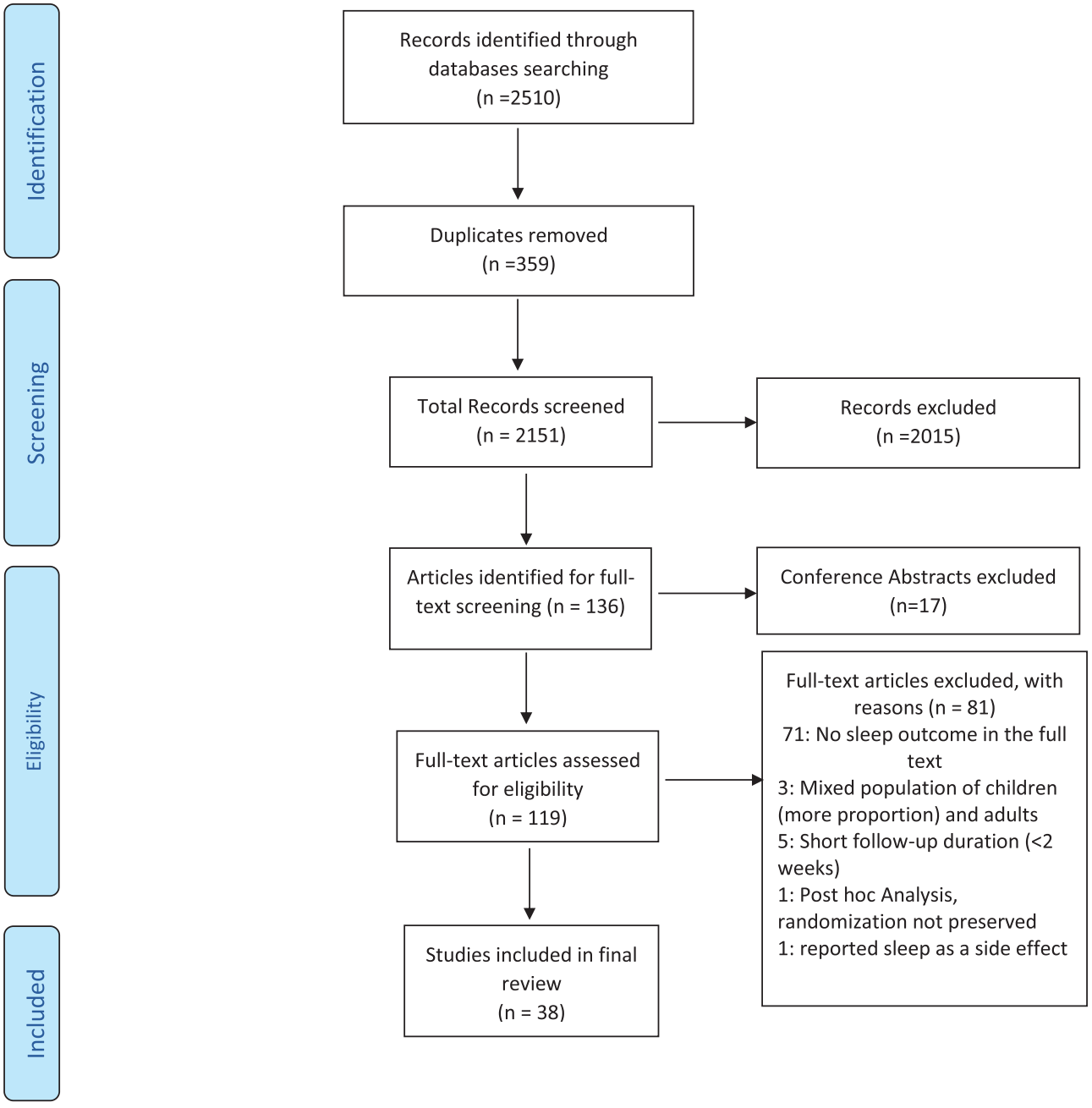

Figure 1. Study flow diagram.

Table 1. GRADE evidence profile of medical cannabis and cannabinoids vs placebo predominantly for patients with chronic pain included in randomized clinical trials*

Outcome	No. of patients (trials)	Follow-up range in weeks	Risk of bias [a]	Inconsistency [b]	Indirectness [c]
Sleep quality (VAS: 0 to 10 cm)	2052 (16 RCTs)	2–14	Not serious [e]	Not seriousI-squared = 57.9%	Not serious
Sleep disturbance (non-cancer patients) (VAS: 0 to 10 cm)	906(11 RCTs)	2–12	Not serious [e]	Not seriousI-squared = 71.4%	Not serious
Sleep disturbance (cancer patients) (VAS: 0 to 10 cm)	1249 (5 RCTs)	5–8	Serious [g]	Not seriousI-squared = 0%	Not serious
Nausea(RCTs ≥3 months follow-up)	1163 (4 RCTs)	12–14	Not serious [e]	Not seriousI-squared = 0%	Not serious
Nausea (RCTs <3 months follow-up)	2380 (18 RCTs)	2–8	Not serious [e]	Not seriousI-squared = 0%	Not serious
Dizziness (RCTs ≥3 months follow-up)	1824(5 RCTs)	13–16	Not serious [e]	Not seriousI-squared = 59.7%	Not serious
Dizziness (RCTs < 3 months follow-up)	2481(19 RCTs)	2–4	Not serious [e]	Not seriousI-squared = 0%	Not serious
Diarrhea	1777 (12 RCTs)	2–14	Not serious [e]	Not seriousI-squared = 0%	Not serious
Disturbance in attention	1086 (7 RCTs)	2–14	Serious [h]	Not seriousI-squared = 0%	Not serious
Vomiting	1538 (9 RCTs)	2–14	Not serious [e]	Not seriousI-squared = 0%	Not serious

*22 studies of medical cannabis for chronic non-cancer pain, 7 for chronic cancer pain, one for multiple sclerosis and one for Parkinson's disease.
[a]We used a modified Cochrane risk of bias instrument for assessing risk of bias.
[b]An I^2 value between 75% and 100% may demonstrate considerable heterogeneity.
[c]We considered the evidence indirect if, among contributing trials, the intervention, patients, or outcomes were different from our review question.
[d]We assessed symmetry of the funnel plot and used Egger's test to assess publication bias when there were at least 10 studies available.
[e]We did not rate down for risk of bias as subgroup analysis showed no significant difference in low vs. high risk of bias on a component-by-component basis, or the relative contribution of trials at high risk of bias to pooled estimate was < 15% (Supplementary Table S7 in Appendix D).
[f]The 95%CI includes ½ the MID
[g]Four out of five studies (Fallon et al.[39]; Portenoy et al.[45]; Turcott et al.[47]; Lichtman et al.[53]) had a high loss to follow up (26%, 27%, 36% and 27%, respectively), the result of meta-regression for loss to follow-up was significant ($p < .001$) and the relative contribution of trials at high risk of bias to pooled estimate was greater than 20%.
[h]One study (Serpell[24]) reported high loss to follow-up (30%) and the relative contribution of this trial to pooled estimate was 23%.
[i]Confidence intervals include benefit and harm.

the associated 95%CI included both benefit and harm. We also rated down significant effects for imprecision if they were informed by <300 patients for continuous outcomes or <300 events for binary outcomes [22]. We did not rate down the same effect estimate twice for both inconsistency and imprecision.

Results

Among 2510 citations identified, 136 articles were reviewed in full text and 38 publications reporting 39 RCTs [23–60] with 5100 enrolled patients met eligibility criteria. (Figure 1). Agreement between reviewers regarding eligibility of full-text articles was substantial ($\kappa = 0.78$).

Study characteristics

The median of the average age of participants enrolled among included trials was 53 years (interquartile range, 48–58 years) and 53% (2726 of 5100) of patients were female. Twenty-five trials enrolled patients with chronic noncancer pain, 8 with chronic cancer-related pain, 2 with Parkinson's disease, and single trials enrolled patients with PTSD, sleep apnea, anorexia nervosa, and multiple sclerosis. Only one trial administered inhaled cannabis [33]; the remaining 38 trials administered oral formulations of cannabinoids (i.e., drops, capsules, sprays). The median follow-up duration was 35 days (IQR, 28–56 days). Most trials, 29 (74%) were fully or partially funded by industry (Supplementary Table S1 in Appendix D).

Risk of bias

The proportion of trials at low risk of bias for each domain was as follows: adequately generated randomization sequence (82%); adequately concealed allocation (92%); blinded patients (100%); blinded caregivers (100%); blinded data collectors (100%); blinded outcome assessors (97%); and low (≤20%) missing outcome data (67%) (Supplementary Table S2 in Appendix D).

Outcomes for Medical Cannabis vs. Placebo

Sleep quality

Moderate certainty evidence from 16 RCTs (2,052 patients) [24–27, 31–33, 37, 40, 43, 44, 49, 55, 57, 58, 60] suggests that, compared to placebo, medical cannabis and cannabinoids result in a small increase in the proportion of patients experiencing an improvement in sleep quality at or above the MID (modeled risk RD 8% mean difference [95% CI, 3 to 12]; based on a WMD of -0.43 cm on a 10cm VAS [95% CI -0.18 to -0.67]; Table 1, Figure 2).

Imprecision	Publication bias [d]	Risk difference for achieving the MID (95% CI)	WMD-RR (95% CI)	Quality of evidence
Serious [f]	Undetected (p = .22)	8% (3 to 12)	MD 0.43 lower (0.18 lower to 0.67 lower)	Moderate
Not serious	Undetected (p = .94)	19% (11 to 28)	MD 0.99 lower (0.57 lower to 1.41 lower)	High
Not serious	Uncertain: only five trials	No baseline data available	MD 0.19 lower (0.03 lower to 0.36 lower)	Moderate
Not serious	Uncertain: only four trials	10% (5 to 17)	RR 2.64 higher(1.83 higher to 3.80 higher)	High
Not serious	Undetected (p = .28)	3% (1 to 6)	RR 1.49 higher(1.11 higher to 1.98 higher)	High
Not serious	Uncertain: only five trials	29% (16 to 50)	RR 4.28 higher(2.76 higher to 6.65 higher)	High
Not serious	Undetected (p = .72)	8% (4 to 12)	RR 2.03 higher(1.60 higher to 2.58 higher)	High
Not serious	Undetected (p = .06)	2% (0 to 5)	RR 1.74 higher(1.07 higher to 2.82 higher)	High
Not serious	Uncertain: only seven trials	2% (0 to 7)	RR 4.7 higher(1.77 higher to 12.5 higher)	Moderate
Serious [i]	Uncertain: only nine trials	2% (0 to 6)	RR 1.56 higher (0.97 lower to 2.49 higher)	Moderate

Consistent with these results, four studies [35, 36, 54, 56] that did not report data suitable for pooling all found medical cannabis significantly improved sleep quality, compared with placebo (Supplementary Table S3 in Appendix D).

Sleep disturbance

Use of cannabinoids showed a small increase in the proportion of patients reporting improved sleep disturbance compared to placebo (modeled RD for achieving the MID 13% [95% CI 7 to 20]); however, we found a significant subgroup effect for chronic noncancer vs. cancer pain (test of interaction p = .001; Figure 3). We also found a subgroup effect based on loss to follow-up; however, this was of only low credibility (Supplementary Table S5a in Appendix D) and was almost completely confounded with study population in that trials of chronic cancer pain patients also reported the highest proportion of missing data.

High certainty evidence (Table 1) from 11 RCTs [23, 27, 28, 30, 38, 40, 41, 48, 50, 51, 59] of people living with chronic noncancer pain (n = 906) showed that, compared to placebo, cannabinoids increased the proportion reporting reduced sleep disturbance (modeled RD for achieving the MID 19% [95%CI 11 to 28]; based on a WMD of -0.99 cm on a 10cm VAS [95%CI –0.57 to –1.41]. Moderate certainty evidence from 5 RCTs [39, 45, 47, 53] of people living with chronic cancer pain (n = 1249) found medical cannabis results in a very small improvement in sleep disturbance, versus placebo (WMD –0.19 cm on a 10cm VAS [95%CI –0.03 to –0.36]; Table 1).

Our sensitivity analysis excluding two studies [23, 41] for which the WMDs for non-significant effects were imputed, found no important difference in results (Supplementary Figure S2 in Appendix B).

One placebo-controlled study that did not contribute to our pooled analyses showed consistent results. Low certainty evidence from this study suggests that palmitoylethanolamide may reduce sleep disturbance among patients with chronic pain due to carpal tunnel syndrome (42 patients) [56] (Supplementary Table S3 in Appendix D).

Other Sleep-Related Outcomes

Low certainty evidence from one trial (73 patients) suggests that nabilone, versus placebo, may reduce the frequency and intensity of nightmares among PTSD patients (mean change in the clinician-administered PTSD scale [CAPS], –3.6 ± 2.4 vs. –1.0 ± 2.1), but may provide no benefit for total sleep time or numbers of awakenings each night [23].

Very low certainty evidence from one trial (56 patients) suggests that nabilone, compared to placebo, may not improve

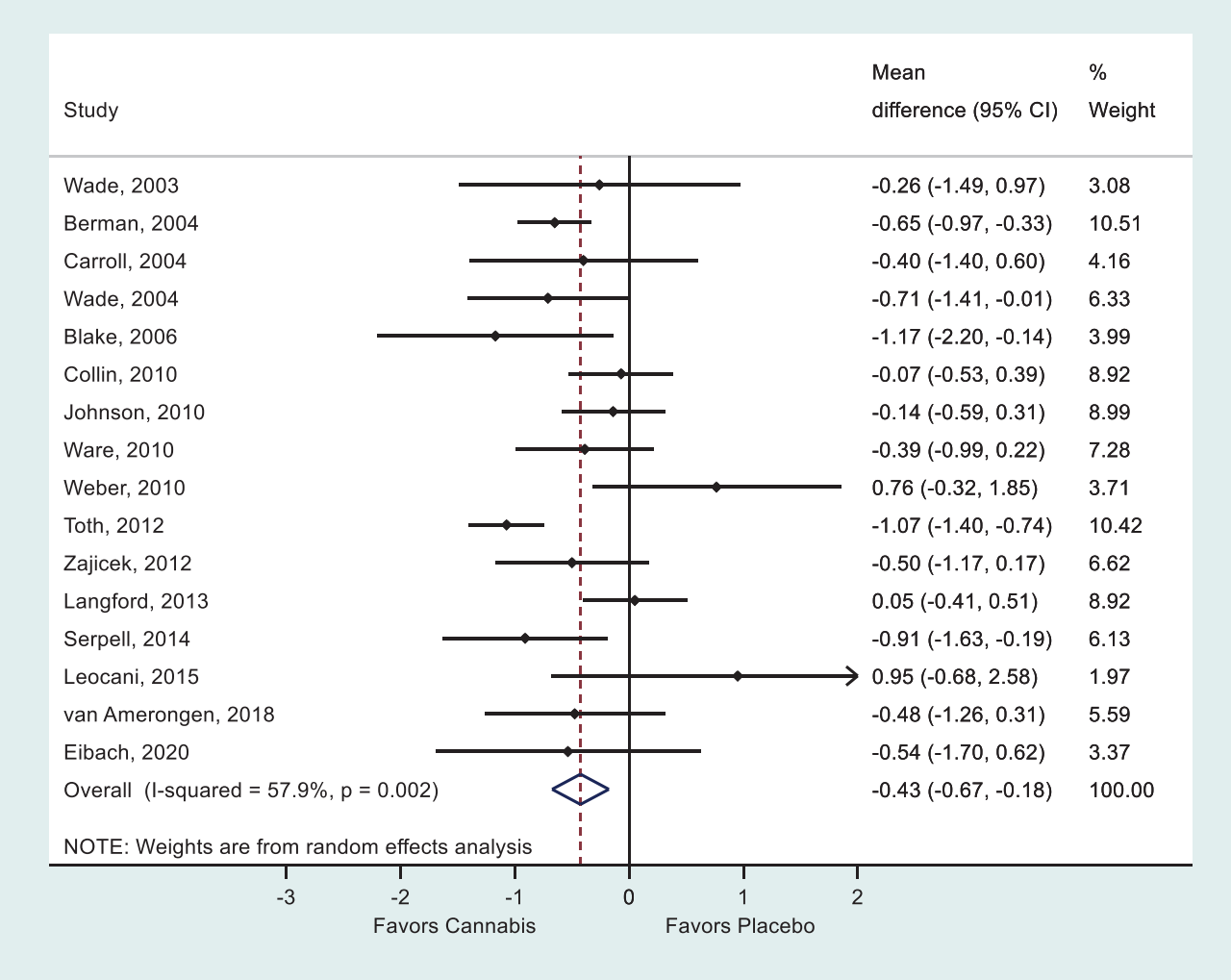

Figure 2. Sleep quality on a 10-cm visual analog scale among people living with, predominantly, chronic pain who received medical cannabis vs placebo.

sleep among patients undergoing radiotherapy for head and neck carcinomas [42].

Low certainty evidence from one trial (73 patients) suggests dronabinol, versus placebo, may reduce sleepiness among patients with moderate to severe obstructive sleep apnea at a dose of 10 mg/day (mean change in the Epworth Sleepiness Scale, 2.3 ±1.2, p = .05), but not at a lower dose of 2.5 mg/day [46].

Low certainty evidence from one trial (42 patients) suggests ultra-micronized palmitoylethanolamide, versus usual care, may increase continuous sleep time among patients with chronic carpal tunnel syndrome [56].

Adverse Events

Nausea

Medical cannabis or cannabinoids increased the risk of nausea (RD 5% [95% CI, 3 to 8]), and longer use was associated with greater risk (test of interaction p = .03, Supplementary. Figures S3 & S3.1 in Appendix C). High certainty evidence from 4 RCTs [24–26, 28] (1163 patients) that followed patients for ≥3 months shows that medical cannabis and cannabinoids, versus placebo, results in a larger increase in the risk of nausea (RD 10% [95% CI, 5 to 17]) compared to trials that followed patients for <3 months (RD 3% [95% CI, 1 to 6]; 18 RCTs [2380 patients]) [27, 30, 32, 33, 35, 37–41, 43, 45, 49, 51, 53, 55, 57, 60] (Table 1).

Dizziness

Use of medical cannabis or cannabinoids increased the risk of dizziness (RD 13% [95% CI, 9 to 20]); however, the risk was greater with longer use (test of interaction p = .007; Supplementary Figures S4 & S4.1 in Appendix C). High certainty evidence from 5 RCTs (1824 patients) [25, 26, 28, 36, 44] that followed patients for ≥3 months shows that medical cannabis or cannabinoids, versus placebo, results in a large increase in risk of dizziness (RD 29% [95%CI, 16 to 50]), compared to trials with <3 months follow-up (RD 8% [95% CI, 4 to 12]; 19 RCTs [2481 patients]) [27, 30–33, 37–41, 43, 45, 49, 51, 53, 55, 57, 58, 60] (Table 1).

Diarrhea

High certainty evidence from 12 RCTs (1777 patients) [24, 26, 28, 30, 35, 37, 38, 45, 50, 55, 57, 60] shows that cannabinoids probably slightly increase the risk of diarrhea, compared with placebo

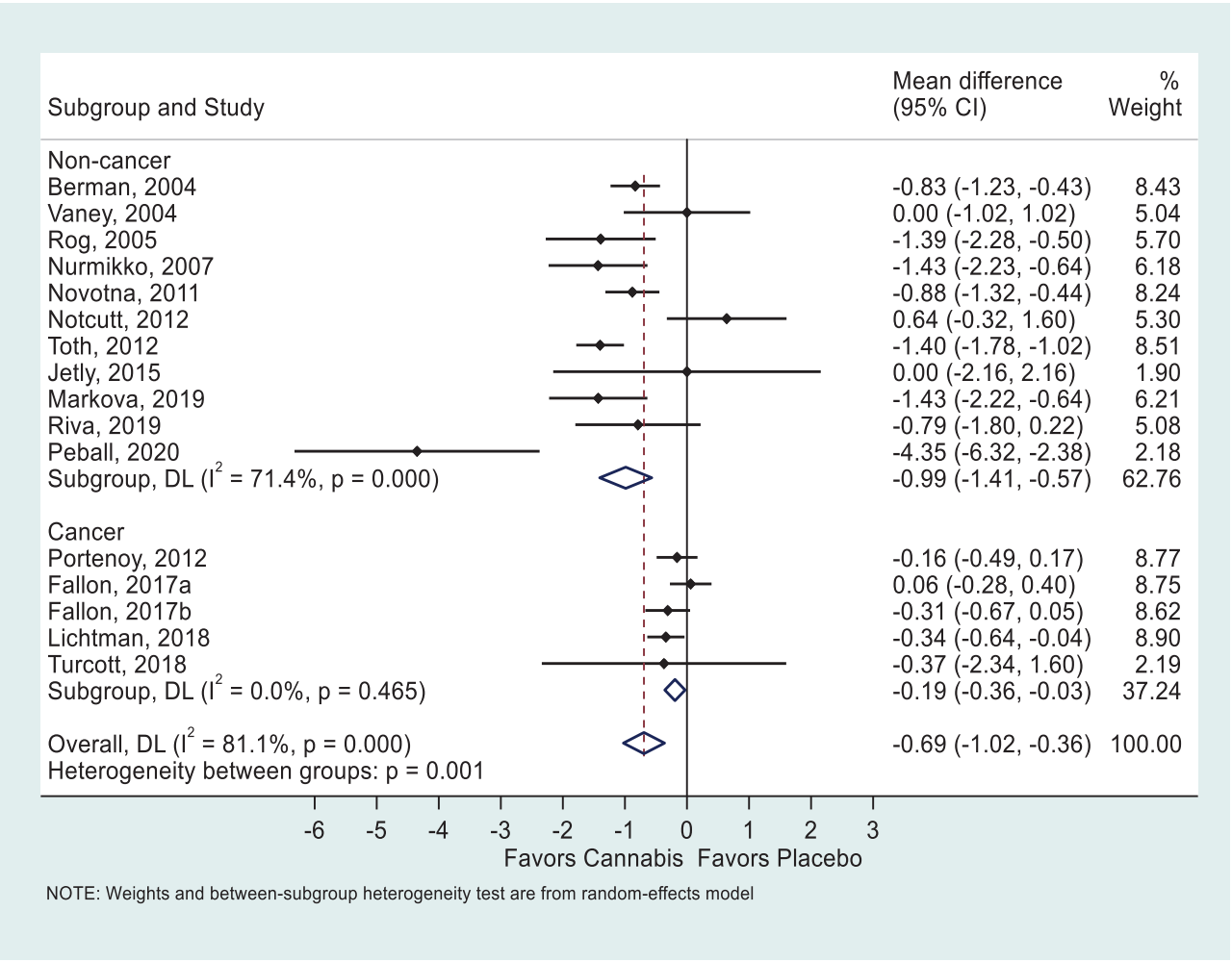

Figure 3. Subgroup analysis of sleep disturbance for cancer vs non-cancer pain (interaction p = .001).

(RD, 2% [95% CI, 0% to 5%]; Table 1, Supplementary Figure S5 in Appendix C).

Disturbance in attention

Moderate certainty evidence from 7 RCTs (1086 patients) [24, 26, 30, 37, 38, 55, 60] indicates that cannabinoids, compared to placebo, probably slightly increases the risk of disturbance in attention (RD, 2% [95% CI, 0% to 7%]) (Table 1, Supplementary Figure S6 in Appendix C).

Vomiting

Moderate certainty evidence from 9 RCTs (1538 patients) [24, 26, 30, 32, 33, 38, 43, 45, 55] showed that medical cannabis or cannabinoids may slightly increase the risk of vomiting (RD, 2% [95% CI, 0% to 6%]) (Table 1, SupplementaryFigure S7 in Appendix C).

Headache

Moderate certainty evidence from 14 RCTs (1819 patients) [24, 26–28, 30, 32, 33, 35, 37, 38, 44, 49, 55, 60] showed medical cannabis or cannabinoids vs. placebo may make little to no difference in the risk of headache (RD, –1% [95% CI, –3% to 2%]) (Supplementary Table S6 in Appendix D, SupplementaryFigure S8 in Appendix C).

Fatigue

High certainty evidence from 13 RCTs (2087 patients) [24–26, 28–30, 37, 38, 44, 49, 50, 55, 60] found that cannabinoids increases the incidence of fatigue compared to placebo (RD, 6% [95% CI, 3% to 11%]) (Supplementary Table S6 in Appendix D, Supplementary Figure S9 in Appendix C).

Dry mouth

Our results showed that medical cannabis and cannabinoids increase the risk of dry mouth compared with placebo (RD 7% [95% CI, 3 to 12]), (Supplementary Figure S10 in Appendix C); however, studies with longer follow-up showed greater risk. High certainty evidence (Supplementary Table S6 in Appendix D) from 5 RCTs [24–26, 36, 44] (1,829 patients) that followed patients for ≥3 months showed that medical cannabis or cannabinoids,

versus placebo, results in a larger increase in the risk of dry mouth (RD 10% [95% CI, 5 to 17]) than trials that followed patients for <3 months (RD 4% [95% CI, 0 to 10]; 10 RCTs [905 patients]) [27, 30, 32, 33, 38, 45, 49, 51, 57, 60] (test of interaction $p = .040$ (Supplementary Figure S10.3 in Appendix C).

Somnolence

High certainty evidence from 14 RCTs (2753 patients) [24–26, 28, 30, 37–40, 43, 45, 49, 51, 55] shows that cannabinoids, versus placebo, increases the risk of somnolence (RD 6% [95% CI, 3% to 9%]) (Supplementary Table S6 in Appendix D; Supplementary Figure S11 in Appendix C).

Constipation

Low certainty evidence from 8 RCTs (1659 patients) [24, 32, 39, 41, 45, 53, 57, 60] suggested no significant association between cannabinoid use and the risk of constipation (RD –1% [95% CI, –2 to 2]) (Supplementary Table S6 in Appendix D and Supplementary Figure S12 in Appendix C).

Outcomes for Medical Cannabis vs Active Comparators

Medical cannabis vs. amitriptyline

Low certainty evidence from one trial (32 fibromyalgia patients) suggests that nabilone, compared to amitriptyline, may provide greater improvement in symptoms of insomnia (mean difference on the insomnia severity index 3.25 [95%CI, 5.26 to 1.24]) and a slightly more restful sleep (mean difference on the Leeds Sleep Evaluation Questionnaire [LSEQ] 0.48; 95%CI 0.01 to 0.95) [29].

Medical cannabis vs. opioids

Low-quality evidence from one trial (96 patients with chronic neuropathic pain) suggests that nabilone may make little to no difference in sleep interruptions compared to dihydrocodeine (mean difference on a 0–10cm VAS, 0.2 [95%CI, –0.1 to 0.5]; $p = .20$) [34].

Medical cannabis vs. diazepam

Low-quality evidence from one trial (11 female patients) suggests that THC may improve sleep disturbance versus diazepam for anorexia nervosa (–2.09 vs. –1.91 [$p = .004$] on the Hopkins Symptom Checklist) [52].

Four studies eligible for our review did not report data suitable for pooling. Three reported responder analyses instead of the mean change on continuous outcome measures [35, 36, 54], and one reported results on a 3 category scale [56]. We describe their findings in Supplementary Table S3, Appendix D. No additional subgroup analysis or meta-regression were credible apart from those reported above (Supplementary Tables S4 & S5 in Appendix D and Appendices B & C).

Discussion

Moderate to high certainty evidence shows that, compared to placebo, medical cannabis or cannabinoids result in small improvements in sleep quality among patients living with chronic cancer or noncancer pain, small improvements in sleep disturbance among patients living with chronic noncancer pain, and very small improvements in sleep disturbance among chronic cancer pain patients. Compared to placebo, use of medical cannabis or cannabinoids shows small increases in the risk of dizziness (and large increases in risk with more prolonged use), somnolence, dry mouth, fatigue, and nausea, but not vomiting, constipation, or headache.

Nabilone might be more effective for symptoms of insomnia than amitriptyline, and equivalent to dihydrocodeine for reducing sleep interruptions; however, these findings were supported by only low certainty evidence. Our results were restricted to 2 to 16 weeks of treatment and, almost exclusively, to non-inhaled cannabinoids.

The most recent systematic review of cannabinoids for the management sleep disorders only included 3 [23, 29, 46] of the 39 RCTs that we identified [6]. In part, this was due to their eligibility criteria, which excluded sleep disorders secondary to a primary condition unless the trial used a sleep-related outcome as their primary outcome measure. An earlier systematic review of cannabinoids for sleep identified 19 of 39 trials in our review [5]. Neither review conducted meta-analyses nor assessed the overall certainty of evidence. Both concluded that further research was needed to establish the role of cannabinoids in sleep disorders. Our review extends these findings by substantially increasing the evidence considered by prior reviews, quantifying treatment effects, and assessing the certainty of evidence on an outcome-by-outcome basis.

Strengths and limitations

This systematic review is the first to statistically pool treatment effects of medical cannabis and cannabinoids on impaired sleep. When possible, we converted all significant pooled mean effects to RDs to facilitate interpretation and used the GRADE approach to appraise the certainty of evidence on an outcome-by-outcome basis. We explored causes of heterogeneity among pooled effects and assessed the credibility of all subgroup effects.

Our review has several limitations including: 1) most evidence we found was for non-inhaled cannabinoids provided to people living with chronic pain, and our findings may not be generalizable to smoked or vaporized forms of cannabis or to patients without chronic pain; 2) the evidence for cannabis or cannabinoids vs. active comparators was only low to very low certainty; 3) although the 10cm VAS was the most frequent measure used among trials eligible for our review, there are better validated measures of impaired sleep (e.g. insomnia severity index [ISI]) [61]; 4) we could not explore the association between dose and effect estimates as most trials (28 of 39; 72%) allowed for post-randomization titration by patients; 5)we calculated change scores, when not reported, using a correlation coefficient from the largest trial at lowest risk of bias. An alternate approach would be to use a correlation coefficient of 0.5 and then conduct a sensitivity analysis using extreme ranges (0.1 and 0.9); however, we believe that our approach, which uses data from studies eligible for our review, is likely to generate plausible correlation coefficients; 6) eligible trials did not report on concurrent use of other medications that may interact with medical cannabis; and 7) trials in our review followed patients for relatively brief periods of time (median of 35 days), which

precludes confident inferences about long-term use of medical cannabis on sleep. One recent observational study has found use of medical cannabis may improve sleep in the short-term, but that long-term use is associated with problems initiating and maintaining sleep [62].

Conclusions

We found moderate to high certainty evidence that, when compared to placebo, use of medical cannabis or cannabinoids results in small improvements in sleep quality among patients living with chronic pain; small improvements in sleep disturbance among patients living with chronic noncancer pain, very small improvement in sleep disturbance among chronic cancer pain patients, and small increases in several adverse side effects (with a large increase in dizziness with longer treatment). The effects of medical cannabis and cannabinoids on impaired sleep, compared to active treatment, is uncertain as the evidence is only low to very low certainty.

Supplementary material

Supplementary material is available at *SLEEP* online

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Author Contributions

Mahmood AminiLari, Jason Busse and Li Wang had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Jason Busse, Mahmood AminiLari, and Li Wang. Literature search: Rachel Couban and Mahmood AminiLari. Acquisition, analysis, or interpretation of data: Mahmood AminiLari, Jason Busse, Li Wang, Samuel Neumark, Candidate; Taranah Adli and Aidan Giangregorio. Clustering outcome measures: Colleen E. Carney, Jason Busse and Mahmood AminiLari. Statistical analysis: Li Wang. Drafting of the manuscript and critical revision of the manuscript for important intellectual content: Mahmood AminiLari, Jason Busse, Li Wang, and Colleen Carney. Supervision: Jason Busse.

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