Systematic Review

# Analgesic Effect of Cannabinoids for Fibromyalgia: A Systematic Review and Meta-Analysis

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**Background:** Fibromyalgia is a kind of complex chronic pain syndrome that exerts a profound impact on patients' lives. Current pharmacological treatments for fibromyalgia often yield suboptimal results. Cannabinoids have emerged as a potential therapeutic alternative to these treatments.

**Objectives:** Our study aimed to assess the analgesic efficacy of cannabinoids in treating fibromyalgia.

**Study Design:** A systematic review and meta-analysis.

**Methods:** We conducted a comprehensive literature search using PubMed (MEDLINE), EMBASE, ISI Web of Knowledge, Cochrane Library, and Clinicaltrials.gov to analyze randomized controlled trials and observational studies that investigated the analgesic efficacy of cannabinoids in individuals diagnosed with fibromyalgia. The primary outcome was the effect of cannabinoids on pain intensity, quantified by the standardized mean difference (SMD) in pain levels before and after the treatment. We registered our review protocol in PROSPERO (CRD42024495525). The quality of the evidence was evaluated using the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) method.

**Results:** Twelve clinical studies, consisting of 2 randomized controlled trials and 10 observational studies, (14 comparisons, 1,248 patients) were selected. Cannabinoids reduced pain intensity with statistical significance (SMD = –1.41, 95% CI = –1.98 to –0.84, $P < 0.001$), which was associated with a low GRADE rating. Both short-term (< 3 months, SMD = –1.37, 95% CI = –2.32 to –0.43, $P = 0.004$) and longer-term (≥ 3 months, SMD = –1.43, 95% CI = –2.22 to –0.65, $P < 0.001$) follow-ups showed statistically significant pain score reduction. Patients also experienced statistically significant improvements in sleep quality, anxiety, depression and quality of life ($P$-values < 0.05). Common adverse effects included dizziness, dry mouth, and drowsiness, while serious adverse effects were rare.

**Limitations:** Our analyses revealed that the results demonstrated considerable heterogeneity, which was attributed to variations in study designs, interventions, and outcome measurements across the included studies. These factors could potentially influence the validity of the findings. Thus, the results should be interpreted with these variations in mind.

**Conclusion:** Cannabinoids may provide analgesic benefits for patients with fibromyalgia. Cannabinoid use was also associated with improvements in sleep, anxiety, depression and quality of life. However, the findings should be interpreted with caution due to the quality of the evidence, heterogeneity, and small amount of available data from randomized controlled trials.

**Key words:** Fibromyalgia, chronic non-cancer pain, cannabinoids, pain management, systematic review, meta-analysis

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Fibromyalgia is a multifaceted chronic pain disorder impacting approximately 0.2% to 6.6% of people worldwide, marked by pervasive musculoskeletal pain, fatigue, disrupted sleep, cognitive difficulties, and various somatic symptoms (1-3). The condition has a negative impact on patients' physical well-being, social functioning, mental health, and quality of life (4), in addition to posing a significant economic burden (5). Nonpharmacological therapies such as patient education, exercise, tai chi, cognitive behavioral therapy, and meditation are useful for treating fibromyalgia (6). Nevertheless, pharmacological treatment is a core component of the multidisciplinary management of the disorder. The U.S. Food and Drug Administration (FDA) has approved pregabalin, milnacipran, and duloxetine for the treatment of fibromyalgia (7). Other medications commonly used to treat fibromyalgia include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and tramadol, but their overall efficacy appears to be limited (6,8-10). Despite recommendations against the use of opioids because of their limited long-term efficacy and problems with tolerance, physical dependence, and opioid misuse/abuse, they remain commonly prescribed in clinical practice for chronic non-cancer pain and fibromyalgia (11,12). Alternative pharmacological treatment options are needed.

Cannabinoids have been increasingly studied for treating chronic non-cancer pain, including fibromyalgia (12). The most important active components in cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD) (13). Clinical evidence has shown that treatment with cannabinoids is associated with a small reduction in chronic non-cancer pain, as well as improvements in sleep and physical functioning (12,14). However, the literature on the efficacy of cannabinoids for treating fibromyalgia is inconclusive (15). Although clinical studies have shown benefits for patients with fibromyalgia in the forms of pain intensity reduction, sleep improvement, and alleviation of anxiety and depressive symptoms, high-quality evidence is lacking (15-20). Because the evidence for the analgesic efficacy of cannabinoids has been unclear, guidelines recommend that physicians offer them only on a trial basis for fibromyalgia refractory to standard treatments (21-23). Previous systematic reviews on this topic did not include quantitative analysis. A deeper evaluation of the currently available evidence is important to determine the efficacy and adverse-effect profile of cannabinoids for fibromyalgia.

This systematic review and meta-analysis was conducted to synthesize the current evidence and assess the analgesic efficacy of cannabinoids for the treatment of fibromyalgia. The primary objective was to evaluate the efficacy of cannabinoids on pain intensity. Additionally, we aimed to evaluate the efficacy of cannabinoids on secondary outcomes, including sleep quality, psychiatric status, quality of life, and adverse-effect profiles. The study was intended to provide valuable information n the use of cannabinoids in fibromyalgia management, potentially guiding clinicians in making informed decisions to enhance patient outcomes and quality of life.

## Methods

The protocol of this systematic review and meta-analysis was registered in PROSPERO (CRD42024495525), adhering to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (24). Any post hoc modifications to the protocol are detailed in Suppl. File S1.

### Search Strategy and Data Sources

The literature search included randomized controlled trials and observational studies that evaluated the analgesic efficacy of cannabinoids for fibromyalgia. The inclusion of both types of studies in systematic reviews has been considered appropriate (25) and employed in previous pain research (26). Original articles were identified using title/abstract keywords or Medical Subject Headings (MeSH) from each database's inception until September 2024. The databases that were searched included PubMed (MEDLINE), the Institute for Scientific Information Web of Science, EMBASE, the Cochrane Library, and Clinicaltrials.gov. Two investigators (PML and CHS) performed the literature search independently. Any disagreements regarding the study selection were resolved through the discussion (PML, FW, and CHS). The title or abstract had to contain the following key words: "cannabinoids" or "cannabis," "fibromyalgia," and either "randomized controlled trial" or "observational study." The detailed study selection process and the extensive search strategy are depicted in Suppl. File S2.

### Selection Criteria of Studies

Two investigators (PML and CHS) independently reviewed all included articles according to their titles, abstracts, and full texts. Any disagreements were resolved through discussions (PML, FW, and CHS). The

study population consisted of adults with chronic widespread pain of unknown origin who either (1) met the American College of Rheumatology (ACR) 1990 or 2010 criteria, or (2) were clinically diagnosed with fibromyalgia by a physician (27,28). To be included in the study, at least one intervention group had to receive cannabinoids or derivatives containing delta-9-tetrahydrocannabinol and/or cannabidiol. Both published and unpublished studies were reviewed for eligibility. Randomized controlled trials and observational studies were included. Nonoriginal articles, health-economic analyses, and preclinical studies were excluded. Studies that recruited pediatric patients or did not report pain intensity as an outcome were also excluded, as were studies with follow-up periods of less than 2 weeks. Comprehensive details regarding the inclusion and exclusion criteria can be found in the Suppl. File S3.

## Data Extraction

Two investigators, working independently (PML and CHS), extracted data from the selected studies, covering such aspects as publication year, fibromyalgia diagnostic criteria, type of intervention, administration route, follow-up period, sample size, and study results. Any disagreements were resolved through discussions (PML, FW, and CHS). For articles with 2 or more study arms, only the data from the relevant arms were included. In cases with multiple follow-ups, the outcome from the longest one was recorded. The outcomes from the longest follow-up within 3 months were also extracted to evaluate the efficacy and safety of treatments. Rating scales with a numerical correspondence were considered eligible outcome measures. The numbers of adverse effects reported in the included studies were also extracted. The Numeric Rating Scale (NRS), Brief Pain Inventory (BPI), visual analog scale (VAS), Fibromyalgia Assessment Status (FAS), Fibromyalgia Impact Questionnaire (FIQ), Revised Fibromyalgia Impact Questionnaire (FIQR), and other questionnaires were considered suitable for evaluating pain intensity. Eligible assessment tools for assessing sleep quality included the Single-Item Sleep Quality Scale (SQS), FAS, FIQR, and other questionnaires. The Generalized Anxiety Disorder 7-item scale (GAD-7), Zung Self-Rating Anxiety Scale, Hospital Anxiety and Depression Scale (HADS), FIQ, FIQR, and other questionnaires were considered suitable for testing anxiety. The Zung Self-Rating Depression Scale, HADS, FIQ, FIQR, and other questionnaires were considered suitable for assessing depression. The total scores from the FIQ, the FIQR, and other questionnaires were considered acceptable for assessing patients' health-related quality of life.

## Assessment of Risk of Bias

Nonrandomized trials were evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool (29). The assessed bias domains consist of baseline confounding, patient selection, classification of intervention, protocol deviation, missing data, measurement and selective reporting (29). For randomized controlled studies, Version 2 of the Cochrane risk of bias tool (RoB2) was used (30). The assessed bias domains consist of sequence generation, blinding of patients, allocation concealment, blinding of outcome assessment, selective reporting, attrition, and other potential biases (30).

## Assessment of the Quality of the Evidence

The quality of evidence for the outcome in each meta-analysis was assessed through the Grade of Recommendations Assessment, Development, and Evaluation (GRADE) method (31). The evaluation considered 5 primary domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of the evidence was grouped into 4 categories: high, moderate, low, or very low. Any identified limitations within these domains led to a downgrading of the evidence level in accordance with the established guidelines (Suppl. File S4).

## Outcome Measurement

The primary outcome was pain intensity before and after cannabinoid treatment. Secondary outcomes encompassed various factors such as sleep quality, anxiety, depression, quality of life, and adverse effects. Given the diverse range of scales used to measure pain intensity and other secondary outcomes, we assessed the effect size with the standardized mean difference (SMD) for different pain scales and secondary metrics. The study's classification for clinical effect size with SMD was based on Cohen's: SMD < 0.2 (as negligible), SMD < 0.5 (as small), SMD < 0.8 (as moderate), and SMD > 0.8 (as large) (32). An SMD of 0.2 or more was considered minimally clinically significant. The random effects (RE) model using DerSimonian and Laird was chosen to estimate the SMD. Hedges's g was applied to adjust SMD for small sample sizes (33-35).

$$J = \frac{3}{4(n_1 + n_2) - 9}$$

To assess the stability of the meta-analysis findings, a leave-one-out (LOO) sensitivity analysis was performed. This process involved systematically omitting each study one at a time from the data set and then recalculating the combined effect size and the corresponding 95% confidence interval (CI) for each iteration. This process helps to identify whether the removal of any individual study substantially impacts the overall results. By identifying studies that might disproportionately influence the results, this approach ensures the stability and reliability of the conclusions.

To estimate the frequency of adverse effects across different populations and settings, prevalence rates were utilized. Heterogeneity among studies was assessed using Q and $I^2$ statistics. A meta-regression analysis was conducted to explore the association between covariates and effect sizes. To assess publication bias, Funnel plots and Egger's regression test were utilized (36,37). The Duval-Tweedie trim-and-fill approach was employed to account for potentially missing effect sizes resulting from unpublished studies (38). All statistical analyses were performed with Comprehensive Meta-Analysis V4, with statistical significance determined by a 2-sided *P*-value of less than 0.05.

## Results

### Eligible Studies

A comprehensive search yielded 253 studies from database searching, with one additional study found through citation searching (Fig. 1). After removing duplicates, 191 studies remained and were screened based on their titles and abstracts. This initial screening led to 26 studies being selected for an in-depth eligibility review through full-text examination. Of these, 14 studies were excluded for the following reasons: not being randomized controlled trials (RCTs) or observational studies (n = 9), lack of reported pain scores (n = 2), follow-up duration of less than 2 weeks (n = 1), and not being in English (n = 2). Consequently, 12 studies satisfied the inclusion criteria and were subsequently included in the systematic review and meta-analysis (Suppl. File S5) (39-50).

### Study Characteristics and Risk of Bias

Two randomized control trials and 10 observational studies were included for evaluation. Eight studies used the employed ACR criteria for diagnosing fibromyalgia, and 4 studies included patients who had received clinical diagnoses of fibromyalgia by a physician. The analysis encompassed a total of 1,248 patients. The studies had an average duration of 6 months. Six clinical studies investigated the analgesic effects of THC-dominant products, one study investigated the analgesic effects of CBD-dominant products, and the remaining studies did not specify the particular type of cannabinoid. Detailed characteristics of these studies can be found in Table 1. Among the included studies, one was evaluated as having a low risk of bias, another one had an unclear risk of bias, and the remaining ten had a moderate risk of bias (Suppl. File S6 and S7).

### Meta-Analysis for Analgesic Effects of Cannabinoids

The meta-analysis consisted of 12 studies (14 comparisons). There was a large, statistically significant decrease in pain intensity after the patients were treated with cannabinoids (SMD = -1.41, 95% CI = -1.98 to -0.84, $P < 0.001$) (Fig. 2A). The pooled analysis result had a low GRADE rating (Table 2) and significant heterogeneity (Q = 439, $I^2$ = 97%, $P < 0.001$). The LOO sensitivity analysis revealed that the estimates of the overall effect size were consistent regardless of which individual study was excluded. The recalculated effect sizes varied between -1.24 and -1.54, with 95% confidence intervals consistently excluding zero. Those findings indicated that excluding any individual study did not significantly impact the overall outcomes (Fig. 2B).

### Sub-Group Meta-Analysis for Analgesic Efficacy

A meta-regression analysis was performed to compare the effectiveness of pain relief between studies with follow-up durations of under 3 months and those with follow-up periods of 3 months or more. The analysis revealed no statistically significant difference between the 2 groups of studies ($P > 0.05$). For studies with follow-ups shorter than 3 months, patients treated with cannabinoids experienced a large and statistically significant decrease in pain intensity (SMD = -1.37, 95% CI = -2.32 to -0.43, $P = 0.004$) (Fig. 2C). This finding had a low GRADE rating (Table 2) and significant heterogeneity (Q = 77, $I^2$ = 95%, $P < 0.001$). In studies with follow-up periods of at least 3 months, cannabinoids also resulted in a large, statistically significant decrease in pain intensity (SMD = -1.43, 95% CI = -2.22 to –0.65, $P < 0.001$) (Fig. 2D). This outcome was associated with a moderate GRADE rating (Table 2) and significant heterogeneity (Q = 280, $I^2$ = 97%, $P < 0.001$).

A subgroup meta-analysis was conducted to

evaluate the analgesic effects of THC-dominant products. Its results showed a large, statistically significant effect-size decrease in pain intensity (SMD = -1.27, 95% CI = -2.13 to -0.41, $P$ = 0.004) (Fig. 2E). The finding had a moderate GRADE rating (Table 2) and significant heterogeneity (Q = 67, $I^2$ = 93%, $P$ < 0.001). Only the clinical trial by Yassin et al evaluated CBD-dominant products. Their study found that patients' pain scores decreased from 8.1 to 3.3 after 6 months of intervention. A statistically significant decrease in pain intensity was observed (50).

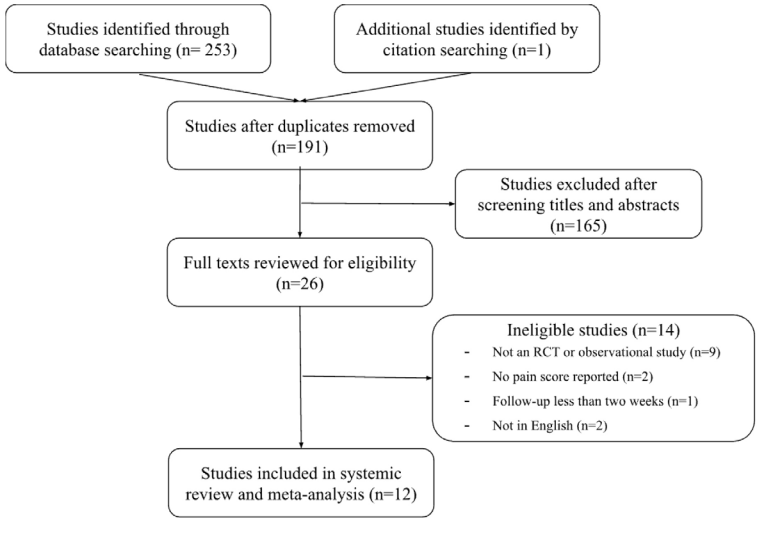


Fig. 1. *Flow diagram illustrating the selection process of research studies following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.*

We also conducted a subgroup meta-analysis to evaluate the analgesic effects of oral and sublingual THC-dominant products. The subgroup meta-analysis of oral cannabinoid products showed a statistically significant and large decrease in pain intensity (SMD = -1.48, 95% CI = -2.32 to -0.64, $P$ = 0.001) (Fig. 2F). That finding received a moderate GRADE rating (Table 2) and exhibited significant heterogeneity (Q = 19, $I^2$ = 84%, $P$ < 0.001). For sublingual cannabinoid products, there was no statistically significant difference between the groups (SMD = -0.86, 95% CI = -2.44 to 0.72, $P$ > 0.05) (Fig. 2G). This result was associated with a low GRADE rating (Table 2) and significant heterogeneity (Q = 8.6, $I^2$ = 88%, $P$ = 0.003).

## Meta-Analysis for Secondary Outcomes

Meta-analyses were performed to evaluate secondary outcomes across several measures, including sleep quality (5 comparisons), anxiety (8 comparisons), depression (5 comparisons), and quality of life (5 comparisons). In sleep quality, patients treated with cannabinoids showed a moderate, statistically significant improvement (SMD = -0.78, 95% CI = -1.09 to -0.47, $P$ < 0.001) (Fig. 3A). That result had a moderate level of GRADE rating (Table 2) and significant heterogeneity (Q = 25, $I^2$ = 84%, $P$ < 0.001). In anxiety, cannabinoids had a statistically significant but small improvement (SMD = -0.42, 95% CI = -0.62 to -0.22, $P$ < 0.001) (Fig. 3B). That finding had a moderate GRADE rating (Table 2) and significant heterogeneity (Q = 19, $I^2$ = 64%, $P$ = 0.007). Patients treated with cannabinoids had large, statistically significant improvements in depression scores (SMD = -0.81, 95% CI = -1.45 to -0.17, $P$ = 0.013) (Fig. 3C). That outcome was rated as moderate on the GRADE (Table 2) and had significant heterogeneity (Q = 38, $I^2$ = 89%, $P$ < 0.001). There was also a statistically significant difference in the quality of life (SMD = -0.85, 95% CI = -1.49 to -0.21, $P$ = 0.01) (Fig. 3D), a finding rated as moderate on the GRADE (Table 2), with significant heterogeneity (Q = 12, $I^2$ = 75%, $P$ = 0.007).

## Adverse Effects

The prevalence of various adverse effects among patients using cannabinoids was evaluated when sufficient studies were available (Supplemental File S8). The most frequently reported side effects included dizziness (18.2%), dry mouth (17.9%), and sleepiness (16.6%). However, no serious adverse effects were reported.

## Comparison of Cannabinoids and Placebos in Randomized Controlled Trials

Given the small number of randomized controlled trials that compared cannabinoids to a placebo, a qualitative assessment of the results was necessary. The 2 RCTs included in this analysis evaluated the effectiveness of cannabinoids in managing pain and enhancing quality of life (39,46). Both studies found that cannabinoids outperformed placebos significantly, leading to greater pain reduction and

Table 1. *Characteristics of the included studies.*

| Author (Year) | Diagnostic Criteria | Agent | Type of Therapy | Design | Duration (Months) | Patients | Study Outcomes | Risk of Bias |
|---|---|---|---|---|---|---|---|---|
| Schley et al (2006) (45) | ACR 1990 | Delta-9-THC | THC-dominant | Prospective observational study | 3 | 4 | Pain score (VAS), electrically induced flare responses, quality of life, psychometric variables, adverse effects | Moderate* |
| Skrabek et al (2008) (46) | ACR 1990 | Nabilone | THC-dominant | Parallel RCT | one | 20 | Pain score (VAS), number of tender points, the average tender point pain threshold, quality of life, adverse effects | Some concern# |
| Weber et al (2009) (49) | ACR 1990 | Delta-9-THC | THC-dominant | Prospective observational study | 3 | 32 | Pain score (VRS and NRS), psychometric assessment, concomitant analgesic consumption, adverse effects | Moderate* |
| Habib et al (2018) (42) | ACR 2010 | Medical cannabis (not specified) | Others | Retrospective observational study | 2 | 26 | Quality of life, concomitant analgesic consumption, adverse effects | Moderate* |
| Sagy et al (2019) (44) | ACR 2010 | Medical cannabis (THC-dominant or CBD- dominant) | Others | Retrospective observational study | 6 | 367 | Treatment response, pain intensity (NRS), quality of life, perception of the general effect of cannabis, concomitant analgesic consumption, adverse effects | Moderate* |
| Yassin et al (2019) (50) | Clinical diagnosis | 1:4 THC-to-CBD medical cannabis therapy | CBD-dominant | Prospective cross-over observational study | 6 | 31 | Pain score (VAS), functional limitation due to spine disorder, patients' global impression of change, concomitant analgesic consumption | Moderate* |
| Chaves et al (2020) (39) | ACR 2010 | Cannabis oil (THC-dominant) | THC-dominant | Parallel RCT | 2 | 8 | Quality of life, adverse effects | Low# |
| Giorgi et al (2020) (41) | ACR 2010 | Bedrocan/Bediol | THC-dominant | Prospective observational study | 6 | 66 | Measurements of widespread pain, fatigue, sleep disturbances, mood, overall well-being, and the components of health status, adverse effects | Moderate* |
| Mazza et al (2021) (43) | ACR 2010 | FM2/Bediol/FM1/ Bedrocan/Pedanios | Others | Retrospective observational study | 12 | 35 | Pain score (NRS), disability, mood disorders, and severity of FMS, adverse effects | Moderate* |
| Sotoodeh et al (2023) (47) | Clinical diagnosis | Medical cannabis (THC-dominant or CBD-dominant or THC+CBD-balanced) | Others | Prospective observational study | 12 | 323 | Pain intensity (BPI), pain-related sleep problems, adverse effects | Moderate* |
| Wang et al (2023) (48) | Clinical diagnosis | Medical cannabis (not specified) | Others | Retrospective observational study | 12 | 306 | Pain score (VAS), fibromyalgia symptom severity, sleep quality, patients' global impression of change, anxiety, quality of life, concomitant analgesic consumption, adverse effects | Moderate* |
| Giardina et al (2024) (40) | Clinical diagnosis | Bedrocan | THC-dominant | Prospective observational study | 6 | 30 | Pain score (NRS), psychosocial conditions | Moderate* |

ACR: American College of Rheumatology; THC: tetrahydrocannabinol; CBD: cannabidiol; VAS: visual analog scale; VRS: Verbal Rating Scale; NRS: numerical rating scale; BPI: Brief Pain Inventory.

*: evaluated with Risk Of Bias In Non-randomized Studies of Interventions tool (ROBINS-I)

#: evaluated with revised Cochrane risk-of-bias tool (RoB2)

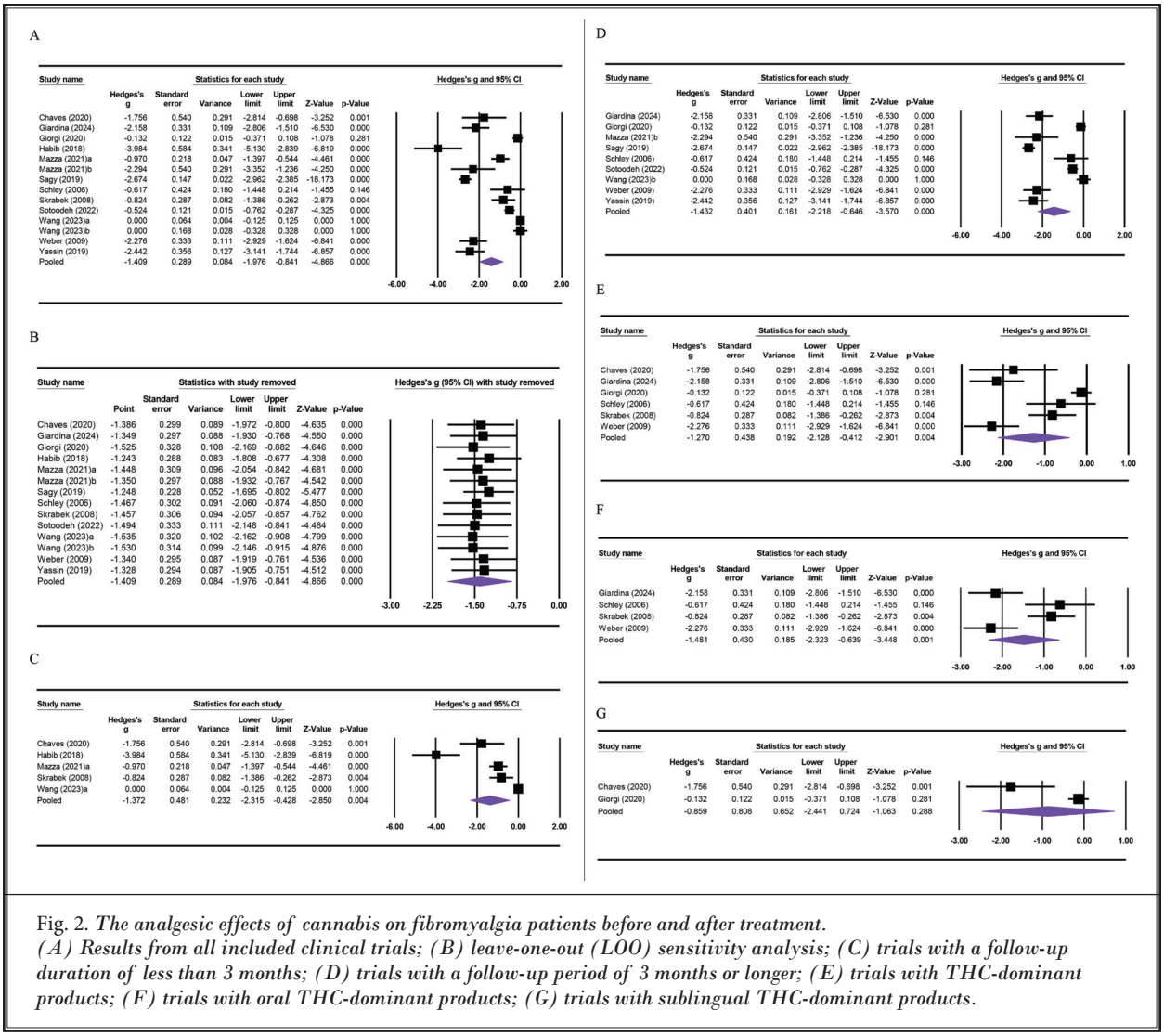


Fig. 2. *The analgesic effects of cannabis on fibromyalgia patients before and after treatment. (A) Results from all included clinical trials; (B) leave-one-out (LOO) sensitivity analysis; (C) trials with a follow-up duration of less than 3 months; (D) trials with a follow-up period of 3 months or longer; (E) trials with THC-dominant products; (F) trials with oral THC-dominant products; (G) trials with sublingual THC-dominant products.*

improved quality of life, with statistically significant *P*-values (< 0.05).

### Evaluation of Publication Bias

The Egger's regression test showed a *P*-value of 0.014, suggesting possible publication bias. For our meta-analysis, we initially used a random effects model to calculate the pooled effect size of the studies. The point estimate of the SMD was -1.41 with a 95% CI of -1.98 to -0.84. That finding suggested a significant overall effect in the negative direction, indicating a substantial impact of the intervention. After we applied the trim-and-fill method, the imputed point estimate was -0.26 with a 95% CI of -0.88 to 0.35. This adjusted estimate included the null value within its confidence interval, suggesting that the initial significant effect might have been overestimated due to the publication bias. The funnel plot with imputed studies is depicted in Fig. 4.

## Discussion

This study demonstrated that cannabinoids may reduce pain levels in fibromyalgia patients. Reductions in pain intensity were observed with both short-term (less than 3 months) and longer-term treatments (3 months or more) treatments. In addition to pain relief, cannabinoids were associated with better sleep quality, enhanced overall quality of life, and reductions in anxiety and depression. No serious adverse effects were reported. The most commonly reported nonserious adverse effects included dizziness, dry mouth, and sleepi-

Table 2. *Evaluation of quality of evidence using Grade of Recommendations Assessment, Development, and Evaluation (GRADE) approach.*

| Meta-Analysis | Number of Comparisons | Treatment SMD (95% CI) | GRADE Level of Evidence |
|---|---|---|---|
| Pain score in all clinical studies | 14 | -1.42 (-2.01 to -0.83) | ⊕⊕○○ |
| Pain score (< 3 months) | 5 | -1.37 (-2.32 to -0.43) | ⊕⊕○○ |
| Pain score (≥ 3 months) | 9 | -1.44 (-2.24 to -0.65) | ⊕⊕⊕○ |
| Pain score (THC-dominant therapy) | 6 | -1.27 (-2.13 to -0.41) | ⊕⊕⊕○ |
| Pain score (oral THC-dominant therapy) | 4 | -1.48 (-2.32 to -0.64) | ⊕⊕⊕○ |
| Pain score (sublingual THC-dominant therapy) | 2 | -0.86 (-2.44 to 0.72) | ⊕⊕○○ |
| Sleep quality | 5 | -0.78 (-1.09 to -0.47) | ⊕⊕⊕○ |
| Anxiety | 8 | -0.42 (-0.62 to -0.22) | ⊕⊕⊕○ |
| Depression | 5 | -0.81 (-1.45 to -0.17) | ⊕⊕⊕○ |
| Quality of life | 4 | -0.85 (-1.49 to -0.21) | ⊕⊕⊕○ |

SMD: standardised mean difference; CI: confidence interval; THC: tetrahydrocannabinol; CBD: cannabidiol; ⊕⊕⊕⊕: High—the true effect is close to the estimated one; ⊕⊕⊕○: Moderate—the true effect is likely to be close to the estimated one but may be substantially different; ⊕⊕○○: Low—the true effect may be substantially different from the estimated one; ⊕○○○: very low—the true effect will likely be substantially different from the estimated one.

ness. When compared to placebos in 2 randomized controlled trials, cannabinoids were found to enhance pain relief and improve quality of life. However, the quality of evidence involving the analgesic effect was low.

Numerous systematic reviews have been performed to study the efficacy of cannabinoids as a treatment for fibromyalgia (15,17-20). Findings from these reviews have suggested that cannabinoids may result in improved pain intensity, sleep, quality of life, and anxiety/mental health scores (15,17-20). A 2016 Cochrane review that included 2 RCTs found low-quality evidence that THC could relieve pain and improve sleep quality but did not find benefits on patients' mood or quality of life (20). Systematic reviews by Strand et al and Kurlyandchik et al, which included both RCTs and observational studies, suggested that cannabinoids could benefit patients with fibromyalgia by relieving pain, improving sleep, and potentially enhancing quality of life and mood (15,18). Another systematic review, which included reviews, RCTs, and observational studies, suggested that medical cannabis was an effective and safe alternative for treating fibromyalgia (17). However, quantitative analyses were not performed in those previous systematic reviews (15,17-20). Earlier meta-analyses that investigated the effectiveness of cannabinoids for alleviating chronic non-cancer pain but did not focus specifically on fibromyalgia indicated only a modest decrease in pain intensity when compared to placebo controls (12,51). By contrast, our meta-analysis revealed a substantial decrease in pain scores among fibromyalgia patients treated with cannabinoids. It is important to highlight that our meta-analysis findings were based on pre- and post-treatment comparisons with cannabinoids. Differences in effect size with such comparisons may be larger than those observed in between-group comparisons (e.g., cannabinoids versus control group) due to factors such as the placebo effect, spontaneous resolution of symptoms, and regression to the mean (52). During the follow-ups to both short-term (less than 3 months) and longer-term (3 months or more) treatments, cannabinoids were associated with reduced pain. This finding is particularly important because fibromyalgia is a kind of chronic pain condition that typically requires sustained, ongoing treatment. Moreover, the 2 RCTs included in our review reported that the cannabinoid group experienced statistically significant reductions in pain scores when compared to the placebo group, supporting the findings of our meta-analysis (39,46).

There was moderate-level evidence showing that THC-dominant products reduced pain in patients with fibromyalgia. THC is known to exert its analgesic effect by binding to CB1 and CB2 receptors (17,18). Only one of the studies in our review evaluated the effect of CBD-dominant products (50). That study also demonstrated that CBD-dominant products (CBD to THC ratio of 4:1) resulted in statistically significant reduction in pain amongst patients with fibromyalgia. CBD may achieve pain reduction via its anti-inflammatory effects and synergistic interaction with THC (17,18,41). The limited number of studies investigating CBD-dominant cannabinoid products and balanced THC:CBD products precluded subgroup analyses to compare the effects of different THC:CBD ratios.

Van de Donk et al conducted an RCT that investigated the analgesic effects of THC-dominant, CBD-

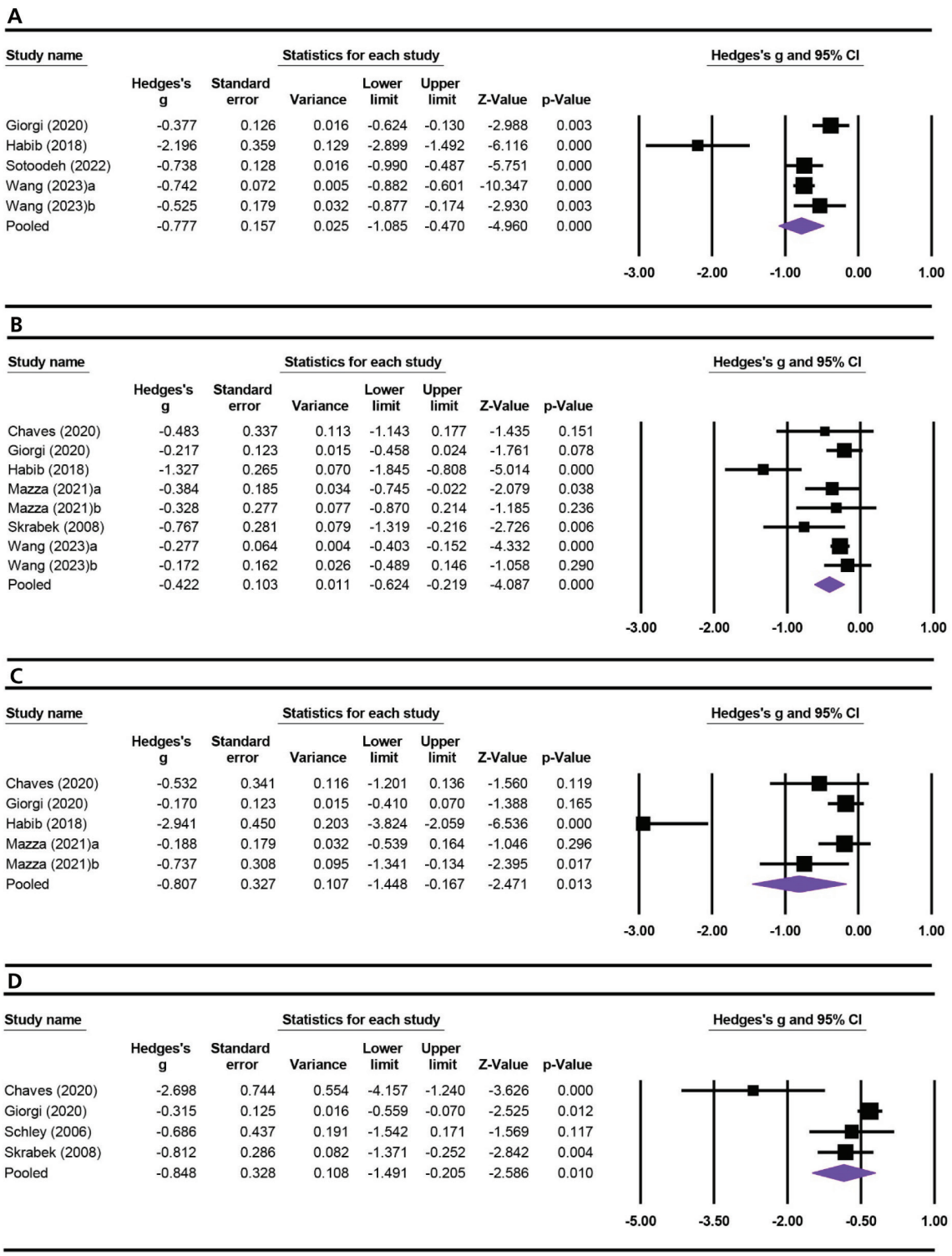


Fig. 3. *Secondary outcomes. (A) Effect on sleep quality; (B) impact on anxiety intensity; (C) impact on depression levels; (D) effect on quality of life.*

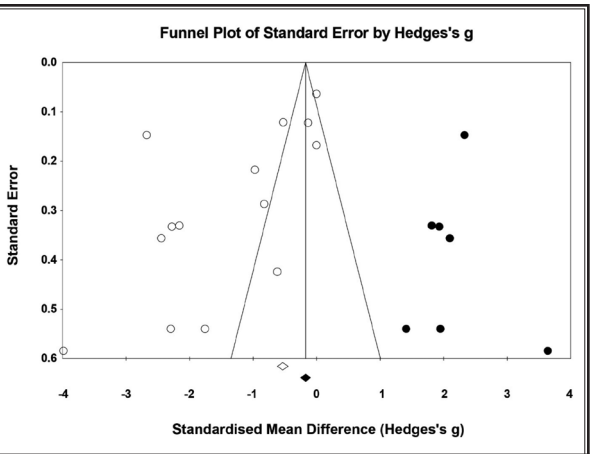


Fig. 4. *Funnel plot with imputed studies. The white circles indicate the original studies, while the solid circles refer to the imputed studies.*

dominant, and balanced THC:CBD products over a 3-hour duration (53). During this short period, the researchers showed that more patients with fibromyalgia responded to balanced THC:CBD products than to the other 2 types of cannabinoid products (53). Additional studies are needed to further evaluate the relative analgesic effects of different THC:CBD ratios.

The route of administration may also influence the efficacy of cannabinoids. Our meta-analysis evaluated the analgesic effects of oral and sublingual THC-dominant products and demonstrated a statistically significant reduction in pain scores when administration was oral but not when administration was sublingual. Previous studies have suggested that oral THC exerts its effects primarily through central or systemic mechanisms, resulting in significant pain reduction in patients with fibromyalgia (45). Furthermore, oral administration allows for precise, incremental titration, which may help minimize adverse effects (18).

Treating fibromyalgia is regarded as challenging. An important barrier to effective management is that patients often also experience psychiatric conditions (e.g., depression and anxiety), fatigue, loss of physical functioning, and sleep disturbances (1). Depression and anxiety often occur together with fibromyalgia as comorbid conditions (54). There may be a bidirectional relationship in which pain from fibromyalgia aggravates anxiety and depression, which in turn further worsens pain and quality of life (55). Therefore, the management of psychiatric conditions such as depression and anxiety is essential in the multidisciplinary treatment of fibromyalgia. Medication that can reduce pain intensity as well as anxiety and depression would potentially be highly beneficial. In this study, moderate-level evidence showed that cannabinoids were associated with reductions in fibromyalgia patients' anxiety and depression scores. This is a promising result that suggests that cannabinoids may have multimodal clinical benefits for treating fibromyalgia.

Pain intensity has been shown to be correlated with poor quality of sleep in fibromyalgia patients (56). Our meta-analysis also showed that in addition to reducing pain intensity, the use of cannabinoids was associated with improved sleep quality. These outcomes are consistent with a randomized controlled trial that indicated that cannabinoids enhanced sleep quality with an effectiveness comparable to amitriptyline (57). A review of cannabinoids for sleep disorders suggested that the products might help regulate the sleep circadian rhythm by boosting endogenous CB1R signalling (58). This possibility is particularly relevant because poor sleep quality is a prevalent and serious issue that profoundly affects mental health, daily functioning, and quality of life for fibromyalgia patients (1,59). Additionally, it is important to note that sleep quality can also have a significant impact on anxiety and depression levels (60,61). Therefore, the positive effect of cannabinoids on sleep quality may also contribute to the reduction of depression and anxiety. Improvements in sleep quality, along with the alleviation of depression and anxiety, can ultimately enhance patients' overall quality of life.

The findings of our study suggest that cannabinoids may be a safe alternative for managing fibromyalgia. The adverse effects reported, including dizziness, dry mouth, sleepiness, and drowsiness, were similar to those observed in patients with other chronic non-cancer pain conditions (12,62). These adverse effects are also commonly associated with conventional medications used in the treatment of fibromyalgia, such as amitriptyline, duloxetine, and gabapentinoids (10,63,64). Moreover, these side effects may diminish with long-term use. Among the included studies, only the one by Mazza et al reported adverse effects both before and after 3 months. That study reported 49 episodes of adverse effects (n = 35) at one month, while only 2 episodes of adverse effects (n = 18) were noted at both 3 and 12 months (43). Reduction in the incidence of adverse effects over time may be due to tolerance, although that possibility was not directly reported in the included studies. However, the decrease in the incidence of adverse effects may also be attributed to

patient dropout. Previous studies have suggested that mental confusion, dry mouth, and eye redness are usually transient and occur mainly during the initial weeks of treatment (42-44,65,66). Furthermore, no serious adverse effects were reported in association cannabinoids. Since there are no cannabinoid receptors within important areas of the brain stem, such as the respiratory center, the chances of serious adverse effects occurring may be less (67). There were no reports of cannabis use disorder, tolerance, withdrawal or psychiatric/psychotic disorders. The absence of such reports is an essential issue, since these potential adverse effects are the main reason for legal restrictions (68,69). Three of the clinical studies included had a follow-up of a maximum of 12 months. Therefore, the risk that these adverse effects will occur in the first 12 months is probably low. Nevertheless, a larger sample size than available from the current study (614 patients followed up to 12 months) is needed to evaluate the risk for uncommon adverse effects more precisely.

### Limitations

There were some limitations in this study. Firstly, the analyses revealed considerable heterogeneity, which could be attributed to variations in study designs, interventions, and outcome measurements across the included studies. Some of them did not document the types, dosages, and administration methods of the cannabinoid treatment. The lack of specification may impact the validity of evidence, since these factors determine the treatment's efficacy and potential adverse effects (19). Therefore, the results should be interpreted with these limitations in mind.

Secondly, the inclusion of observational studies may introduce potential bias due to unidentified confounders (70). The absence of a control group in these studies also limits the ability to draw causal inferences.

Thirdly, fibromyalgia was not diagnosed using the full ACR criteria in 4 of the 12 studies. In 2 studies, the diagnosis of fibromyalgia was supported by the Widespread Pain Index and Symptom Severity Scale (the core components of the ACR 2010 criteria) (40,48). In another 2 studies, the use of the ACR criteria was not mentioned in the manuscript (47,50). The inclusion of these studies may increase the risk of bias. However, our decision to include them may also enhance the clinical relevance and applicability of the findings to real-world practice, since the routine use of ACR criteria may be difficult due to the time required to complete the assessment (47).

Fourthly, subgroup analyses to compare the effects of different THC:CBD ratios were not possible due to the limited number of studies on both CBD-dominant and balanced THC:CBD products. Inconsistent reporting of dosage parameters (e.g., initial, maximum, and post-intervention doses) also precluded subgroup analyses based on dosage.

Another limitation was that the included studies did not specifically address important issues such as cannabis use disorder, tolerance, withdrawal, or the development of psychiatric or psychotic symptoms. Although these adverse effects are often associated with recreational use of cannabis, they were not the focus of the studies analyzed (69,71).

Moreover, we included only studies in English.

Finally, the potential for publication bias necessitates cautious interpretation of the meta-analysis results.

## Conclusions

In conclusion, cannabinoids were associated with a decrease in fibromyalgia patients' pain levels. This phenomenon was present with treatments of both short-term (less than 3 months) and longer-term (at least 3 months) duration. Additionally, the use of cannabinoids was associated with improved sleep quality, enhanced quality of life, and a reduction in depression and anxiety. These findings suggests that cannabinoids may provide multiple benefits for fibromyalgia patients. The use of cannabinoids increased the risk of nonserious adverse effects, but the absence of serious adverse effects suggests that cannabinoids may be a safe treatment option when prescribed by physicians.

### Acknowledgments

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### Author Contributions

Pui Ming Lam: study concept, study design, screening of papers, data extraction, data interpretation, drafting of manuscript, and final review; Fengfeng Wang: study concept, study design, data extraction, data analysis, data interpretation, drafting of manuscript, and final review; Chung Hin Shing: screening of papers, data extraction, and final review; Hung Chak Ho: data interpretation and final review; Marc Russo: data interpretation and final review; Stanley Sau Ching Wong: study concept, study design, data interpretation, and final review.

**Supplemental material is available at www.painphysicianjournal.com**

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Suppl. File S1. *Post hoc changes to protocol*.

The protocol of this systemic review and meta-analysis was registered in PROSPERO (CRD42024495525). Several post hoc changes were made to improve the analysis. These changes were as follows:

1. The search date was extended to September 2024 to include more studies.
2. To enhance the assessment of the risk of bias, the original Cochrane risk of bias tool (RoB), which the protocol stated would be used in the review, was replaced with Version 2 of the Cochrane risk of bias tool (RoB2), the latest iteration thereof (1).
3. Initially, we planned to use the mean difference of the scores from the rating scales as the effect measure. However, due to the heterogeneity of those scales, we instead used the standardized mean difference (SMD) to measure the outcomes.
4. No analysis of cannabinoids' effect on the "global impression of change" was conducted. This change occurred because only 2 studies reported results for this outcome and the rating scales used were not comparable. Wang et al (2023) used a scale ranging from 1 (no change or worse) to 7 (a great deal better), while Yassin et al (2019) employed a different 7-point scale that ranged from 1 (very much worse) to 7 (very much improved), with 4 indicating no change (2,3).
5. The analysis of cannabinoids' effect on fatigue was not conducted, since only 2 studies reported results for this outcome.
6. We originally selected the Fibromyalgia Impact Questionnaire (FIQ) and the Revised Fibromyalgia Impact Questionnaire (FIQR) as the outcome measures for functional outcomes. However, because those 2 questionnaires included domains of overall impact and symptoms, we utilized the reported results to conduct an analysis of patients' "quality of life" instead.

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Suppl. File S2. *Complete search strategy on different search platforms*.

**PubMed**

1. Cannabinoids [MeSH Terms] OR Cannabis [MeSH Terms] OR Medical Marijuana [MeSH Terms] OR Cannabinoid Receptor Modulators [MeSH Terms] OR Cannabinoid Receptor Agonists [MeSH Terms] OR Cannabidiol [MeSH Terms] OR Cannabinol [MeSH Terms] OR Dronabinol [MeSH Terms] OR Endocannabinoids [MeSH Terms]
2. Nabilone [Supplementary Concept] OR HU 211 [Supplementary Concept] OR nabiximols [Supplementary Concept] OR hempseed oil [Supplementary Concept] OR Hashish oil [Supplementary Concept]
3. Cannabinoids [Text Word] OR Cannabis [Text Word] OR Medical Marijuana [Text Word] OR Cannabinoid Receptor Modulators [Text Word] OR Cannabinoid Receptor Agonists [Text Word] OR Cannabidiol [Text Word] OR Cannabinol [Text Word] OR Dronabinol [Text Word] OR Endocannabinoids [Text Word] OR nabilone [Text Word] OR HU 211 [Text Word] OR nabiximols [Text Word] OR hempseed oil [Text Word] OR Hashish oil [Text Word] OR Hemp [Text Word] OR Marijuana [Text Word] OR Ganja [Text Word] OR Hashish [Text Word] OR Marihuana [Text Word] OR Bhang [Text Word] OR Hemp Plant [Text Word] OR Cannabis indica [Text Word] OR Cannabis sativa [Text Word] OR Marinol [Text Word] OR Cesamet [Text Word] OR Dexanabinol [Text Word] OR tetrahydrocannabinol-cannabidiol combination [Text Word] OR Sativex [Text Word] OR Tetrahydrocannabinol [Text Word] OR Delta-9-Tetrahydrocannabinol [Text Word]
4. 1 OR 2 OR 3
5. Fibromyalgia [MeSH Terms] OR Fibromyalgia [Text Word] OR fibrositis [Text Word]
6. Randomized Controlled Trial [Publication Type] OR Controlled Clinical Trial [Publication Type] OR Observational Study [Publication Type] OR Cross-Over Studies [MeSH Terms] OR Prospective Studies [MeSH Terms] OR Retrospective Studies [MeSH Terms] OR Pilot Projects [MeSH Terms]
7. 4 AND 5 AND 6

**EMBase**

1. (Cannabinoids or Cannabis or Medical Marijuana or Cannabinoid Receptor Modulators or Cannabinoid Receptor Agonists or Cannabidiol or Cannabinol or Dronabinol or Endocannabinoids or nabilone or HU 211 or nabiximols or hempseed oil or Hashish oil or Hemp or Marijuana or Ganja or Hashish or Marihuana or Bhang or Hemp Plant or Cannabis indica or Cannabis sativa or Marinol or Cesamet or Dexanabinol or tetrahydrocannabinol cannabidiol combination or Sativex or Tetrahydrocannabinol or Delta 9 Tetrahydrocannabinol).kw,tw.
2. (Fibromyalgia or fibrositis).kw,tw.
3. (Randomized or Controlled or Trial or Observational or Cross-Over or Prospective or Retrospective or Pilot). kw,tw.
4. 1 AND 2 AND 3

**Web of Science**

1. TS = Cannabinoids or Cannabis or Medical Marijuana or Cannabinoid Receptor Modulators or Cannabinoid Receptor Agonists or Cannabidiol or Cannabinol or Dronabinol or Endocannabinoids or nabilone or HU 211 or nabiximols or hempseed oil or Hashish oil or Hemp or Marijuana or Ganja or Hashish or Marihuana or Bhang or Hemp Plant or Cannabis indica or Cannabis sativa or Marinol or Cesamet or Dexanabinol or tetrahydrocannabinol cannabidiol combination or Sativex or Tetrahydrocannabinol or Delta 9 Tetrahydrocannabinol
2. TS = Fibromyalgia or fibrositis
3. ALL = Randomized or Controlled or Trial or Observational or Cross-Over or Prospective or Retrospective or Pilot
4. 1 AND 2 AND 3

**Clinicaltrials.gov**

- Condition: Fibromyalgia
- Intervention: Cannabinoids OR Cannabis OR Medical Marijuana OR Cannabinoid Receptor Modulators OR Cannabinoid Receptor Agonists OR Cannabidiol OR Cannabinol OR Dronabinol OR Endocannabinoids OR nabilone OR HU 211 OR nabiximols OR hempseed oil OR Hashish oil OR Hemp OR Marijuana OR Ganja OR Hashish OR Marihuana OR Bhang OR Hemp Plant OR Cannabis indica OR Cannabis sativa OR Marinol OR Cesamet OR Dexanabinol OR tetrahydrocannabinol cannabidiol combination OR Sativex OR Tetrahydrocannabinol OR Delta 9 Tetrahydrocannabinol

**Cochrane Central**

1. Cannabinoids or Cannabis or Medical Marijuana or Cannabinoid Receptor Modulators or Cannabinoid Receptor Agonists or Cannabidiol or Cannabinol or Dronabinol or Endocannabinoids or nabilone or HU 211 or nabiximols or hempseed oil or Hashish oil or Hemp or Marijuana or Ganja or Hashish or Marihuana or Bhang or Hemp Plant or Cannabis indica or Cannabis sativa or Marinol or Cesamet or Dexanabinol or tetrahydrocannabinol cannabidiol combination or Sativex or Tetrahydrocannabinol or Delta 9 Tetrahydrocannabinol: ti,ab,kw
2. Fibromyalgia or fibrositis: ti,ab,kw
3. Randomized or Controlled or Trial or Observational or Cross-Over or Prospective or Retrospective or Pilot: all text
4. 1 AND 2 AND 3

Suppl. File S3. *Criteria for study selection*.

## Inclusion Criteria

1. Patients were diagnosed with fibromyalgia.
2. At least one interventional group received medical cannabis or derivatives containing delta-9-tetrahydrocannabinol and/or cannabidiol.
3. Pain was one of the study outcomes.

## Exclusion Criteria

1. Study population:
   (a) Had well-defined causes of chronic pain unrelated to fibromyalgia.
   (b) Did not report their pain scores.
   (c) Had a follow-up of less than 2 weeks.
   (d) Were pediatric patients.

2. Publication type:
   (a) Guidelines, perspectives, correspondence, abstracts, posters, letters, editorials
   (b) Narrative reviews, systematic reviews, and/or meta-analyses

3. Study type:
   (a) Cost-effectiveness analysis
   (b) Mortality or survival analyses; diagnostic assay or test performance studies.
   (c) Cross-sectional studies
   (d) Incomplete studies or studies with unavailable results
   (e) Articles not published in English

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Suppl. File S4. *Grade of Recommendations Assessment, Development, and Evaluation (GRADE) framework for level-of-evidence assessment.*
*Based on the GRADE guidelines, the quality of evidence was initially graded as "high" and then downgraded to "moderate," "low," or "very low" according to the criteria of 5 domains below (4).*

| **Risk of bias** | **This domain is not considered, since none of the included studies has a high risk of bias.** |
|---|---|
| Inconsistency | Downgrade by one level if significant heterogeneity is identified (I2 >50%). |
| Indirectness | This domain is not considered, since the relevance of included studies is ensured by the inclusion criteria. |
| Imprecision | Downgrade by one level if the confidence interval crosses the null. |
| Publication bias | Downgrade by one level if publication bias is strongly detected by the funnel plot. |

Suppl. File S5. *Studies included in this review.*

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- Sagy I, Schleider LBV, Abu-Shakra M, Novack V. Safety and efficacy of medical cannabis in fibromyalgia. *J Clin Med* 2019; 8:807.
- Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. *Curr Med Res Opin* 2006; 22:1269-1276.
- Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone or the treatment of pain in fibromyalgia. *J Pain* 2008; 9:164-173.
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- Wang C, Erridge S, Hovley C, et al. Assessment of clinical outcomes in patients with fibromyalgia: Analysis from the UK Medical Cannabis Registry. *Brain Behav* 2023; 13:e3072.
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- Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: An observational cross-over single centre study. *Clin Exp Rheumatol* 2019; 37: S13-S20.

Suppl. File S6. *Quality assessment of nonrandomized interventional studies using ROBINS-I (5).*

| Outcome: Pain | Baseline Confounding | Patient Selection | Classification of Intervention | Protocol Derivation | Missing Data | Outcome Measures | Selective Reporting | Overall |
|---|---|---|---|---|---|---|---|---|
| Giardina et al, 2024 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Giorgi et al, 2020 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Habib et al, 2018 | Low | Low | Moderate | Low | Low | Moderate | Low | Moderate |
| Mazza et al, 2021 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Sagy et al, 2019 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Schley et al, 2006 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Sotoodeh et al, 2022 | Low | Low | Moderate | Low | Low | Moderate | Low | Moderate |
| Wang et al, 2023 | Low | Low | Moderate | Low | Low | Moderate | Low | Moderate |
| Weber et al, 2009 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |
| Yassin et al, 2019 | Low | Low | Low | Low | Low | Moderate | Low | Moderate |

Supplemental File S7. *Quality assessment of randomized controlled trials using revised Cochrane RoB2 (1).*

| Outcome: Pain | Randomization Process | Deviations from the Intended Interventions | Missing Outcome Data | Measurement of the Outcome | Selection of the Reported Result | Overall |
|---|---|---|---|---|---|---|
| Chaves et al, 2020 | Low | Low | Low | Low | Low | Low |
| Skrabek et al, 2008 | Low | Low | Low | Low | Some concerns | Some concerns |

Suppl. File S8. *Prevalence of adverse events experienced by patients using cannabis*.

| Types | Prevalence | 95% CI |
|---|---|---|
| Confusion | 6.5% | [0.013, 0.268] |
| Dizziness | 18.2% | [0.095, 0.321] |
| Drug high | 3.4% | [0.004, 0.226] |
| Dry mouth | 17.9% | [0.118, 0.263] |
| Headache | 5.9% | [0.017, 0.189] |
| Hunger feeling | 7.6% | [0.040, 0.141] |
| Memory impairment | 4.7% | [0.022, 0.097] |
| Nausea/vomiting | 10.7% | [0.065, 0.171] |
| Sleepy | 16.6% | [0.076, 0.323] |

## Suppl. References


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2. Wang C, Erridge S, Holvey C, et al. Assessment of clinical outcomes in patients with fibromyalgia: Analysis from the UK Medical Cannabis Registry. *Brain Behav* 2023 13:e3072.
3. Yassin M, Oron A, Robinson D. Effect of adding medical cannabis to analgesic treatment in patients with low back pain related to fibromyalgia: An observational cross-over single centre study. *Clin Exp Rheumatol* 2019; 37 Suppl 11:13-20.
4. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64:401-406.
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