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SYSTEMATIC REVIEW

Cannabinoids in the Treatment of Insomnia Disorder: A Systematic Review and Meta-Analysis

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Abstract

Background Insomnia is associated with significant comorbidity, disability and impact on quality of life and, despite advances in pharmacotherapy and psychotherapy, remains a significant burden to society. Cannabinoids are gaining acceptance for use as medicines in the treatment of insomnia disorder.

Objective We conducted a systematic review and meta-analysis to evaluate the efficacy of cannabinoids in the treatment of insomnia disorder.

Methods We performed a systematic review of the PubMed, Cochrane Library, MEDLINE, and Cumulative Index to Nursing and Allied Health Literature Complete databases from inception to 5 December 2019, and again prior to data abstraction, for studies of cannabis-based products for the treatment of insomnia disorder in adults. Inclusion criteria were (1) clinical studies, (2) participants aged ≥ 18 years, (3) insomnia disorder either formally diagnosed against contemporaneous diagnostic criteria or quantified with validated instruments and (4) compared cannabis-based products with the standard of care, placebo or a sedative. No language restrictions were imposed. Non-primary research, animal studies and studies of cannabis-induced insomnia were excluded. Risk of bias was assessed using the RoB 2 tool for randomised controlled trials (RCTs) and Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool for non-randomized trials. Heterogeneity was assessed with the I^2 statistic.

Results A total of five studies (two RCTs and three non-randomised studies) with 219 study participants were included, of which three could be combined. The three non-randomised studies contributed data on the Pittsburgh Sleep Quality Index Questionnaire score, showing a favourable effect of cannabinoids at ≤ 4 weeks of follow-up (mean difference − 1.89 [95% confidence interval {CI} − 2.68 to − 1.10]; $n = 176$) and at 8 weeks of follow-up (mean difference − 2.41 [95% CI − 3.36 to − 1.46]; $n = 166$). One double-blind crossover RCT ($n = 32$) reported that, compared with amitriptyline, nabilone—a synthetic analogue to tetrahydrocannabinol (THC)—improved Insomnia Severity Index scores after 2 weeks of treatment (adjusted difference − 3.25 [95% CI − 5.26 to − 1.24]) and resulted in a more restful sleep as a sub-measure of the Leeds Sleep Evaluation Questionnaire (LSEQ) (difference 0.48 [95% CI 0.01–0.95]) but with no effect on overall sleep quality as measured by the LSEQ. In a single ascending-dose RCT ($n = 9$), THC reduced sleep-onset latency compared with placebo at 10 mg, 20 mg and 30 mg doses (mean difference − 43.00 min [95% CI − 82.76 to − 3.24], − 62.00 [95% CI − 103.60 to − 20.40] and − 54.00 [95% CI − 103.93 to − 4.07], respectively). All the included studies were assessed as poor quality, mainly due to small sample sizes, short treatment periods, uncertain clinical significance and high risk of bias.

Conclusions Few studies have examined the efficacy of cannabinoids in the treatment of insomnia disorder. Despite some possible signals for efficacy, the heterogeneity of participants, interventions, efficacy outcomes and results, and the high risk of bias across included trials, do not reliably inform evidence-based practice. This review highlights shortcomings in the existing literature, including lack of diagnostic clarity, poorly defined participant groups, non-standardised interventions and studies of inappropriate design, duration and power to detect clinically meaningful outcomes. Further research in the form of high-quality RCTs are required before drawing any conclusions about the efficacy of cannabinoids in the treatment of insomnia disorder.

Trial Registration PROSPERO registration number, CRD42020161043.

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Key Points

This systematic review and meta-analysis evaluated the efficacy of cannabinoids in the treatment of insomnia disorder.

Few studies have examined the efficacy of cannabinoids in the treatment of insomnia disorder.

From the literature available, despite some possible signals for efficacy, evidence for the use of cannabinoids in insomnia disorder is insufficient to reliably inform practice in a clinically meaningful way.

1 Background

Insomnia disorder is defined by both the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) [1] and the *International Classification of Sleep Disorders—Third Edition* (ICSD-3) [2]. Both classification systems describe a shared symptom profile, including difficulties with sleep initiation or maintenance despite adequate opportunity and circumstances to sleep, daytime consequences or functional impairments, and a duration criterion of 3 months, along with a frequency criterion of at least three times per week [3].

1.1 The Problem of Insomnia

Insomnia disorder is a significant problem in society. Between one-third and one-half of the adult population report symptoms of insomnia with a point prevalence of a formal diagnosis of insomnia disorder between 6 and 15% [4, 5]. In the primary care setting, up to 69% of patients complain of at least occasional insomnia symptoms [6]. The DSM-5 removed the distinction between primary and secondary insomnia found in previous editions to reflect the increasing understanding of the bidirectional relationship between insomnia and coexisting medical and psychiatric disorders [7]. Insomnia is a predictor for suicide and for developing mental health problems such as anxiety, depression, bipolar disorder and substance abuse [4, 5] and is a risk factor for cardiovascular disease, hypertension, type 2 diabetes mellitus, asthma and gastroesophageal disease [5]. It is also associated with significant disability and reduced quality of life on almost all aspects of the 36-item Short Form Health Survey of the Medical Outcomes Study [8] and—in the workplace—has been associated with absenteeism, decreased concentration, difficulty performing duties and work-related accidents [9]. In 2007, the financial burden of insomnia disorder was estimated to be over $US5000 per person annually for each individual with this condition [10], and data obtained in 1994 indicated a conservative estimate of $US92–107.5 billion annually to the American public in total [11]. These consequences of lack of sleep suggest individual, public health and economic imperatives to examine treatment modalities for this complex biopsychosocial disorder.

1.2 Current Treatments for Insomnia

Psychotherapy and pharmacotherapy for insomnia disorder both target improved sleep quality and/or quantity, with the desired outcome being improved daytime function. Cognitive behavioural therapy for insomnia (CBT-I), combining educational, behavioural and cognitive approaches, is widely used and considered first line [4, 5, 12–14]. However, pharmacotherapy may be required if CBT-I is ineffective or unavailable [13]. Benzodiazepines and benzodiazepine receptor agonists, previously the mainstay of pharmacotherapy for insomnia disorder [15], are of limited use because of their adverse effects, which include over-sedation, psychomotor impairment, dependence and abuse [4, 5]. For newer agents, such as histamine-1 receptor antagonists, melatonin receptor agonists and orexin receptor antagonists [5], scientific proof of long-term efficacy remains elusive [15]. Although short-term sleep disturbance can be adequately managed, longer-term insomnia disorder remains a major problem.

1.3 The Endocannabinoid System, Exogenous Cannabinoids and Sleep Architecture

The endocannabinoid system (ECS) is expressed in the human central and peripheral nervous system and comprises endocannabinoids (endogenous lipid-based retrograde neurotransmitters), cannabinoid (CB) receptors and CB receptor proteins (see Table 1 for definitions of the terms used in this article). The endocannabinoid *N*-arachidonoylethanolamide (anandamide) exhibits a circadian rhythm in healthy humans that can be disrupted in sleep dysregulation [16]. The exogenous CB tetrahydrocannabinol (THC), found in the *Cannabis sativa* plant, acts as an agonist with high affinity to CB receptors abundant in the brain [17, 18]. Activation of the CB_{-1} receptor induces sleep, an effect that can be reversed with CB_{-1} receptor antagonists [19, 20]. The role of the exogenous CB cannabidiol (CBD) in the ECS is uncertain. Animal studies suggest that CBD may act as an antagonist at CB_{-1} [21], raising the possibility of CBD reducing the sedative effects of THC. The specific action of other exogenous CBs such as terpenes, with or without THC and CBD, on the ECS is uncertain and a developing area of research [22].

Sleep is commonly divided into two main stages, rapid-eye movement (REM) and non-REM or slow-wave sleep [20]. REM sleep is characterised by reduced amplitude and faster frequency cortical electroencephalogram (EEG) and is associated with learning and memory consolidation [23]. Slow-wave sleep is characterised by high voltage and slower frequency EEG activity and is thought to be important in sleep cognition, including declarative memory consolidation and physiological functions such as energy restoration, hormonal regulation, immunity and cleaning of metabolites [24]. Endocannabinoids promote both REM and non-REM sleep [25]. In polysomnography studies, low-dose THC causes mild sedation, decreases sleep-onset latency and REM sleep and increases total sleep time and slow-wave sleep [26]. In high doses, THC still decreases REM sleep but decreases slow-wave sleep time and increases sleep-onset latency [26]. Chronic THC use is associated with long-term suppression of slow-wave sleep and tolerance to the effects on sleep-onset latency and REM [26]. While no evidence exists of an effect of CBD on sleep architecture in healthy volunteers [27], CBD may have a biphasic sedative effect [28], with alerting properties at low doses [29] and sedating properties at higher doses [30, 31].

Regardless of recent pre-clinical and clinical science, cannabis has a long history of use recreationally, medicinally and culturally, with reports dating back over 5000 years [32]. Its acceptance within modern western society is evolving as legislating bodies have moved towards increasing legal access for recreational and medicinal purposes [32]. Insomnia is increasingly accepted as a reason for the therapeutic use of cannabis. In a survey of users of cannabis for therapeutic purposes in Canada, 85% of respondents reported using cannabis for their 'sleep' [33].

The potential utility of cannabinoids for insomnia has been described in the medical literature. In 2019, Kuhathasan et al. [34] published a critical review of clinical trials on the use of cannabinoids for sleep, suggesting that THC and THC derivatives, alone or in combination with CBD, may improve self-reported sleep quality and sleep disturbances and decrease sleep-onset latency. However, Kuhathasan et al. [34] did not assess the evidence for the use of cannabinoids in the treatment of formally diagnosed insomnia, either according to a formal classification system (such as the ICSD-3 [2] or the DSM-5 [35]) or using a validated instrument (e.g. the Pittsburgh Sleep Quality Index [PSQI] [36]). Nor did they systematically review the literature. Similarly, Babson et al. [37] critically assessed the literature but not in a systematic way. This approach suffers from a risk of bias in the overall findings, which is important with an intervention such as cannabis with multiple social, legal and other biological actions. Therefore, the aim of this review was to assess the efficacy of cannabis-based products in treating formally diagnosed insomnia using validated instruments to measure outcomes.

Table 1 Terms and definitions

Term	Definition
Cannabis	Shortened form of *Cannabis sativa* L., which encompasses all varieties of the cannabis plant. Dependent on plant variety, it may be used in the production of fibre and textiles or used for its drug effect
Cannabinoids	Chemical molecules of similar structures that are thought to interact with cannabinoid receptors Phyto-cannabinoids (plants based) primarily have a C_{21} terphenolic skeleton. More than 100 have been identified. The amount and variation of phyto-cannabinoids in a plant determine the phenotype and subsequent drug effects Endocannabinoids (produced in the endogenous endocannabinoid system) are lipid based and are physiological ligands for the cannabinoid receptors
Endocannabinoids	Chemical molecules produced within the endogenous (e.g. human body) cannabinoid system that act as neurotransmitters. Examples of human endocannabinoids are anandamide (AEA), 2-arachidonyl glycerol (2-AG), virodhamine, palmitoylethanolamide, oleoylethanolamide (OEA) and noladin ether
Tetrahydrocannabinol	Shortened form of delta-9-tetrahydrocannabinol (Δ9-THC or THC). Phyto-cannabinoid, described as 'psycho-active' and responsible for euphoric or 'high' effect associated with cannabis use
Cannabidiol	Also known as CBD. Phyto-cannabinoid, does not induce euphoric effect. Potential therapeutic actions include anti-inflammatory, anti-anxiety and anti-seizure effects. Molecular target still undefined, poor affinity with cannabinoid receptors. May downregulate the effect of THC when taken in combination
Cannabidivarin	Also known as CBD-V. Phyto-cannabinoid, homolog of CBD, some evidence of anti-epileptic effects
Cannabidiolic acid	Also known as CBDA. Phyto-cannabinoid precursor to CBD. Prominent in raw cannabis material. Converts to CBD with heat and processing
Cannabichrome	Shortened form of cannabichromene (CBC). Phyto-cannabinoid; does not induce euphoric effects. Animal studies demonstrate antimicrobial, anti-inflammatory, analgesic and anti-depressant-like activity

2 Methods

The review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [38]. The protocol was determined before the review was conducted and is registered in Prospero (CRD42020161043). The protocol was designed to be broad to ensure all studies examining the impact of cannabinoids on insomnia were captured. No amendments were made to the protocol and no protocol violations made. Notably, papers were screened in a fashion appropriate to their date of publication (e.g. how insomnia is diagnosed has changed over time).

2.1 Search Strategy

An information technologist assisted in the development of the search strategy. Four databases (PubMed, the Cochrane Library, MEDLINE, and Cumulative Index of Nursing and Allied Health Literature Complete) were searched on 5 December 2019 from their inception and again prior to data extraction to detect any newly published studies. Search strings were designed to find the literature associated with sleep, cannabinoids and outcome and combined with the Boolean classifier AND. The full search strings are provided in appendix one in the Electronic Supplementary Material. The grey literature was not considered relevant, and peer review was considered essential to ensure the quality of the included studies.

2.2 Inclusion and Exclusion Criteria

Eligible papers included randomised and non-randomised studies that administered any form of cannabis-based products for the treatment of insomnia disorder in adults aged ≥ 18 years. This could include a natural cannabis product, a synthetically derived cannabinoid or a pharmaceutically available product of any dose or formulation. The comparisons of interest were between a cannabis-based product and the standard of care appropriate to insomnia (treatment as usual), placebo or a comparator sedative. The studies did not need to be blinded. In accordance with the modern DSM-5, insomnia disorder could be either primary (the primary complaint) or secondary (deemed 'caused by' another condition) and could either be formally diagnosed according to guidelines contemporaneous with the trial (e.g. DSM, ICSD, or *International Classification of Diseases*) or—in studies where sleep was evaluated as a secondary outcome—quantified with validated instruments (i.e. PSQI score > 5 [36] or Insomnia Severity Index [ISI] score > 15 [39]). Changes in sleep quality and/or quantity needed to be assessed objectively or using validated tools (e.g. PSQI [36], ISI [39, 40], Leeds Sleep Evaluation Questionnaire [LSEQ] [41]) (Box 1). No time limit to the intervention was specified, and no language restrictions were applied to the search. Papers were excluded if they were non-primary research or animal studies or if insomnia resulted from prior cannabis use (e.g. cannabis use disorder, cannabis withdrawal).

Box 1 PICO

Patient population	Adults aged ≥18 years with insomnia disorder
Intervention	A cannabis-based product. This could be a natural cannabis product, a synthetically derived cannabinoid or a pharmaceutically available product of any dose or formulation
Comparison	Standard care appropriate to insomnia (treatment as usual), placebo or a comparator sedative
Outcome	Changes in sleep quality and/or quantity assessed objectively or using validated tools

2.3 Study Selection/Screening

Studies were selected by at least two authors who independently screened titles and abstracts using the Covidence systematic review software (Veritas Health Innovation) to manage the data. Full texts were obtained for the relevant titles, which were then screened for eligibility by at least two authors (of CB, MD, SK). Any conflicts that arose at each stage of screening were resolved during further discussion with a third independent reviewer (GNH).

2.4 Data Extraction

A data extraction sheet was developed in Microsoft Excel and tested to ensure conformity of data extracted by all reviewers. Data were extracted independently in duplicate by two authors, and authors discussed the results to resolve differences where results were disparate. Characteristics of each study were extracted, including demographic data, cannabis and comparator product and outcome measurements. Methods for the diagnosis of insomnia at baseline were noted, taking standard practice at publication date into consideration for each study. Subjective outcomes extracted for sleep included PSQI total score, ISI total score and LSEQ total score. The objective outcome extracted included the post-treatment time to sleep, in minutes. Data relating to adverse events were collected. Where standard deviation (SD) values were unavailable, they were calculated from available data (p values, t values, confidence intervals [CIs] or standard errors).

2.5 Assessment of Paper Quality and Risk of Publication Bias

Bias was independently assessed by two authors using the risk of bias (RoB) 2 tool for randomised controlled trials (RCTs) [42] and the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) for non-randomized controlled trials [43]. Any disagreement was resolved by discussion among the authors.

Heterogeneity was assessed with the I^2 statistic, with increasing I^2 indicating greater heterogeneity. It was expected that publication bias would be assessed using the trim and fill method [44] if five or more papers existed for a single outcome.

2.6 Meta-analysis

RevMan 5.3 was used to analyse the data using a random-effects model. Meta-analysis was performed for two or more studies with a similar design and outcome measure as per the a priori protocol. Continuous data were reported using means, SDs and sample sizes. Forest plots were developed to graphically display the results of meta-analysis.

3 Results

3.1 Included Studies

Figure 1 shows the flow of identified and excluded studies. The searches identified 2637 articles; after duplicates were removed, the titles and abstracts of 1755 publications were screened. Of 213 full-text articles reviewed for suitability, 208 records were excluded and the full text of one study was unavailable, leaving five studies for data analysis (Fig. 1, Table 2), of which three could be combined. None of the non-English studies identified during abstract screening met the inclusion criteria for this review.

Details of the included trials are outlined in Table 2. Of the five included trials, two examined patients with the primary complaint of insomnia [45, 46] and three examined patients for whom insomnia was not the primary complaint [47–49]. All fulfilled an insomnia disorder diagnosis. Sleep measures were the primary outcome in three trials [45–47] and secondary outcomes in the remaining two [48, 49]. We identified two RCTs: one double-blind, placebo-controlled trial of single ascending doses of THC in patients diagnosed with mild insomnia, with 'time to sleep' as the primary outcome ($n = 9$) [45], and one double-blind crossover trial of nabilone 0.5–1.0 mg, a synthetic analogue to THC, versus amitriptyline 10–20 mg, a comparator sedative, in patients with fibromyalgia with chronic insomnia, and mean ± SD ISI baseline scores of 18.3 ± 5.2 ($n = 32$) [47]. Three non-randomised studies were included in the analysis: one experimental pilot study of THC 2.5–5 mg in patients with post-traumatic stress disorder and mean ± SD PSQI baseline scores of 17.20 ± 2.65 ($n = 10$) [49]; one retrospective case series of patients with sleep ($n = 25$) and anxiety ($n = 47$) disorders with baseline PSQI scores of 10.98 ± 3.43 and 13.08 ± 3.03, respectively, who self-titrated a CBD extract [46]; and one single-arm cohort study of a hemp extract in patients with chronic pain ($n = 97$) and PSQI scores of 10.3 ± 4.3 at baseline [48]. Three studies were completed in the USA [45, 46, 48], one in Canada [47] and one in Israel [49].

3.2 Study Participants

Across all five studies, 219 study participants were included at baseline (89 males, 130 females). Four studies reported an average age (47.7 years; range 18–72; $n = 210$). In all, 34 patients had a primary diagnosis of a sleeping disorder [45, 46] and 185 patients had other primary health conditions in which sleep was analysed as a secondary outcome using validated instruments that indicated patients had insomnia disorder at baseline [46–49].

3.3 Cannabis-Based Products: Treatment Regimen

All included studies used different orally administered cannabis-based products, either with [46–49] or without [45] concomitant medication. In one RCT, patients received a single dose of THC 10 mg, 20 mg or 30 mg or placebo each week in a randomised order, and the results over a single night were observed [45]. The other RCT included 32 patients who completed a 2-week intervention of either nabilone (synthetic Δ^9-THC) 0.5 mg daily or amitriptyline 10 mg daily, with the opportunity to double this dose after 7 days for the remaining 7 days to achieve a greater beneficial effect [47]. The patients then underwent a 2-week washout period and were administered the other intervention for 2 weeks. In the open-label pilot study, patients were administered an add-on treatment of THC 2.5 mg in olive oil twice daily, increased to 5 mg twice daily if well-tolerated, for a period of 3 weeks [49]. In the case series of patients receiving CBD as an adjunctive therapy, most patients were administered CBD 25 mg daily, whereas some were given 50 mg daily and one participant received 175 mg daily over a 3-month period [46]. The cohort study patients were prescribed hemp-derived CBD-rich soft gels containing CBD 15.7 mg, THC 0.5 mg, cannabidivarin 0.3 mg, cannabidiolic acid 0.9 mg, cannabichrome 0.8 mg and > 1% botanical terpene blend, with a recommended dose of two gel capsules per day for 8 weeks [48] (Table 1). None of the studies examined the role of terpenes within cannabis.

3.4 Outcome Measures

The outcome measures in each study are listed in Table 2. Three studies included the PSQI, as either a co-primary outcome variable [46] or a secondary outcome variable [48, 49]. One study assessed the ISI and the LSEQ as primary outcome variables [47] and one study measured sleep-onset latency [45]. Four studies reported side effects and/or adverse effects [45–47, 49].

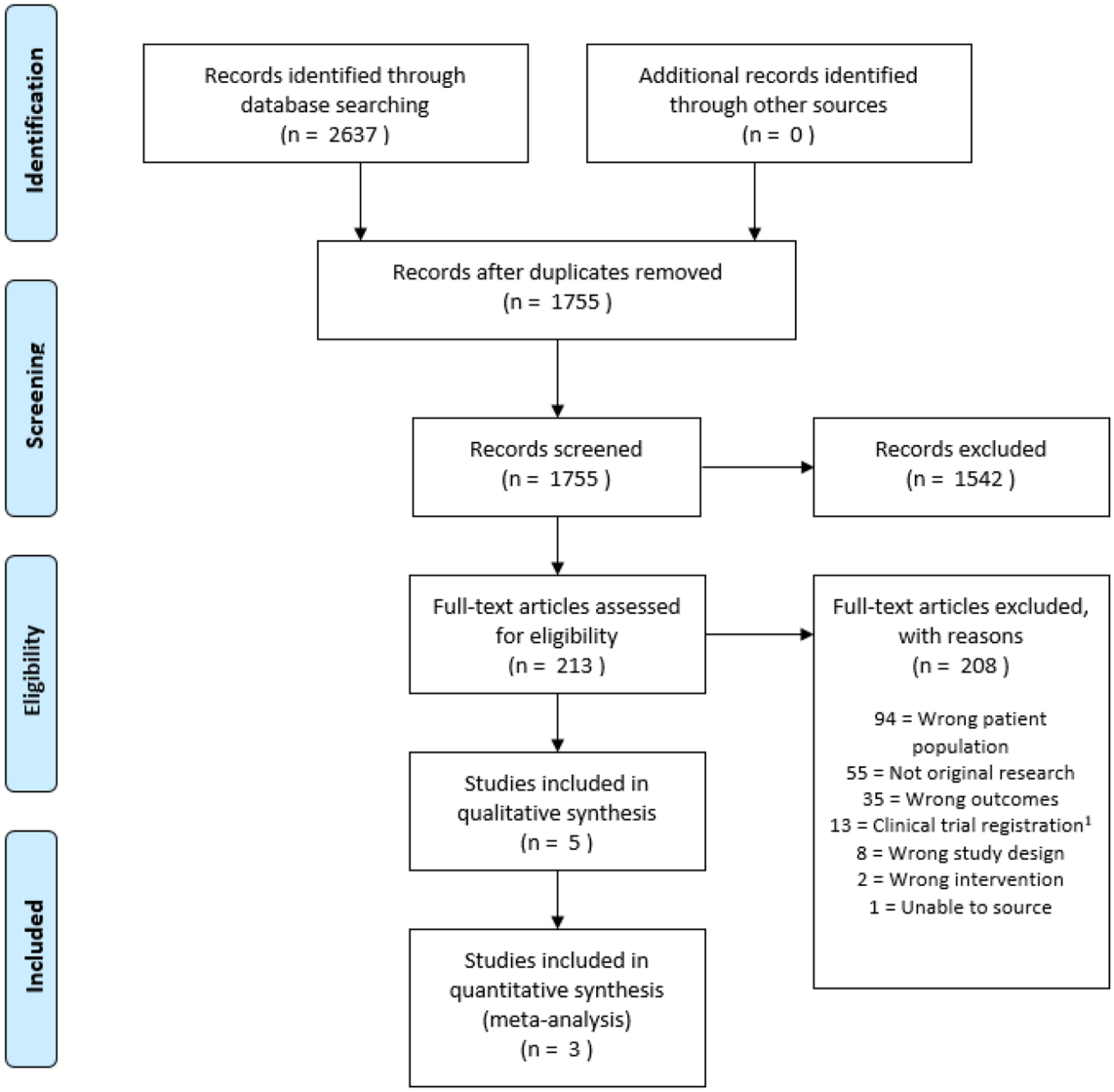

Fig. 1 Flow of studies through systematic review. [1]Clinical trial registration indicates a record of a clinical trial without results, registered on https://clinicaltrials.gov/ identified through the current database search

3.5 Efficacy Endpoints

3.5.1 Pittsburgh Sleep Quality Questionnaire

All three non-RCT studies contributed data to the effects of cannabinoids on PSQI score at ≤ 4 weeks follow-up, with a favourable effect of cannabinoids compared with baseline (mean difference − 1.89 [95% CI − 2.68 to − 1.10]; $n = 176$) (Fig. 2). Two non-RCTs contributed data at 8 weeks follow-up, with a favourable effect of cannabinoids (mean difference − 2.41 [95% CI − 3.36 to − 1.46]; $n = 166$) (Fig. 3).

3.5.2 Insomnia Severity Index

The double-blind crossover trial reported that nabilone improved the ISI score more than did amitriptyline after 2 weeks of treatment (adjusted difference − 3.25 [95% CI − 5.26 to − 1.24]; $n = 32$) [47]. No additional data were presented to allow further analysis.

3.5.3 Leeds Sleep Evaluation Questionnaire

The double-blind crossover trial reported no difference between nabilone and amitriptyline in overall sleep quality as measured by the LSEQ but that nabilone resulted in

Table 2 Summaries of the included studies

Study	Study design	Sample/patients	Intervention	Comparator	Duration	Primary outcomes and results	Secondary outcomes	Risk of bias
Cousens et al. [45]	Randomised, DB, PC, CO trial	9 male adults (aged 21–40 years) with mild insomnia (i.e. 60-to 90-min sleep latency)	Single dose THC 10 mg, 20 mg or 30 mg	Placebo	6 weeks. Each condition completed 1 week apart after 2 weeks' familiarization sleeping at the hospital	Time to sleep. Number of awakenings. Duration of awakenings. THC significantly decreased sleep latency ($p < 0.05$); no effect on frequency or duration of awakenings ($p > 0.05$)	Within an hour of awakening: 33-item questionnaire about how they felt just before going to sleep the previous night, how they felt in the morning. Side effects	Some concerns (RoB 2)
Ware et al. [47]	Randomised, DB, CO trial	32 adults (mean age 49.5 years; range 26–76; 16% male) with fibromyalgia and self-reported insomnia (i.e. disturbed sleep either every night or every other night for the past 6 months)	Nabilone 0.5 mg, optional increase to 1.0 mg after 7 days upon review	Amitriptyline 10 mg, optional increase to 20 mg after 7 days upon review	10 weeks: 2 weeks each of initial washout period ($n = 32$), first study drug ($n = 29$), washout period ($n = 29$), second study drug ($n = 29$), final washout period ($n = 29$)	ISI, LSEQ. Nabilone had a greater effect than amitriptyline on ISI (adjusted difference − 3.25; 95% CI − 5.26 to − 1.24)	McGill Pain Questionnaire. Profile of Mood States. Fibromyalgia Impact Questionnaire. Treatment preference (if applicable). Vital signs. Adverse effects	High risk (RoB 2)
Roitman et al. [49]	Non-randomised experimental pilot study	10 adults (mean age 52.3 ± 8.3 years; 70% male) with PTSD	THC in olive oil, 2.5 mg BID, increased to 5 mg BID if well tolerated	Not applicable	3 weeks. Tested at: baseline and 3 weeks	CGI, PSQI with PTSD addendum, NFQ, NES. Significant effect of THC on PSQI; improved sleep ($p < 0.05$)	Blood pressure. Heart rate. Weight. BMI. Side effects	Serious risk (ROBINS-I)
Shannon et al. [46]	Case series	72 patients: 47 with anxiety disorder (mean age 34 years; range 18–70; 59.6% males); 25 with sleep disorder (mean age 36.5 years; range 18–72; 36% males)	CBD (mostly 25 mg/day; some were given 50 mg/day or 75 mg/day; one patient received 175 mg/day)	Not applicable	3 months. Tested at baseline ($n = 72$), 1 month ($n = 72$), 2 months ($n = 41$), 3 months ($n = 27$)	PSQI, HAM-A. No statistical analysis completed	Side effects and tolerability of CBD	Critical risk (ROBINS-I)

Table 2 (continued)

Study	Study design	Sample/patients	Intervention	Comparator	Duration	Primary outcomes and results	Secondary outcomes	Risk of bias
Capano et al. [48]	Single-arm cohort study	97 adults (mean age 56.1 years; range 39–70; 32% male) with moderate-to-severe chronic pain for at least 3 years and stable opioid use for at least 1 year 94/97 participants used the CBD soft gels	Hemp-derived CBD-rich soft gels (CBD 15.7 mg, THC 0.5 mg, CBDV 0.3 mg, CBDA 0.9 mg, CBC 0.8 mg, > 1% botanical terpene blend)	Not applicable	8 weeks. Tested at baseline, 4 weeks, 8 weeks	Effectiveness of CBD-rich extract to reduce opioid dependence	PDI, PHQ-4, PEG, PSQI. Significant effect of CBD on PSQI; improved sleep ($p = 0.03$)	Serious risk (ROBINS-I)

BID twice daily, *BMI* body mass index, *CBC* cannabichrome, *CBD* cannabidiol, *CBDA* cannabidiolic acid, *CBDV* cannabidivarin, *CGI* Clinical Global Impression Scale, *CI* confidence interval, *CO* crossover, *DB* double blind, *HAM-A* Hamilton Anxiety Rating Scale, *ISI* Insomnia Severity Index, *LSEQ* Leeds Sleep Evaluation Questionnaire, *NES* Nightmare Effects Survey, *NFQ* Nightmare Frequency Questionnaire, *PC* placebo controlled, *PDI* Pain Disability Index, *PEG* Pain Enjoyment of Life and General Activity Scale, *PHQ-4* 4-item Patient Health Questionnaire, *PSQI* Pittsburgh Sleep Quality Index, *PTSD* post-traumatic stress disorder, *RoB 2* risk of bias 2 tool, *ROBINS-I* Risk Of Bias In Non-randomized Studies—of Interventions, *THC* tetrahydrocannabinol

a more restful sleep as a sub-measure of LSEQ compared with amitriptyline (difference 0.48 [95% CI 0.01–0.95], $n = 32$) [47]. No additional data were presented to allow further analysis.

3.5.4 Sleep Latency

In a single ascending-dose trial ($n = 9$), compared with placebo, a single dose of THC reduced sleep latency at the 10 mg dose (mean difference − 43.00 [95% CI − 82.76 to − 3.24]), 20 mg dose (mean difference − 62.00 [95% CI − 103.60 to − 20.40]) and 30 mg dose (mean difference − 54.00 [95% CI − 103.93 to − 4.07]) [45].

3.6 Adverse Effects

All five studies reported adverse effects from the collective group of patients reviewed. Commonly reported side effects included dry mouth (26 reports) [45, 47–49], nausea/vomiting (16 reports) [45, 47], insomnia/disturbed sleep (15 reports) [45, 47, 48], fatigue/drowsiness (13 reports) [45, 46], dizziness (12 reports) [47, 48], headache/migraine (seven reports) [47, 49] and constipation (four reports) [47]. Cognitive impairment (135 reports) [45, 47] was also commonly reported, particularly in the study by Cousens et al. [45], which reported various types of cognitive impairment rather than the number of patients who experienced some form of cognitive impairment as a result of cannabinoid administration. Two participants were reported to discontinue treatment due to fatigue [46]. After taking THC the night before, participants also reported dizziness/grogginess (14 reports, from nine patients after three doses of THC) and cognitive impairment the morning after, especially after the 20 mg (nine reports) and 30 mg (20 reports) doses [45].

3.7 Study Quality

All the included studies were of poor quality, mainly due to small sample sizes, short treatment periods, uncertain clinical significance and high risk of bias (Table 2). One RCT was considered at high risk of bias because of reporting bias and unclear attrition bias [47], and one had some concerns due to unclear detection bias [45]. The pilot and cohort studies [48, 49] were assessed as being at serious risk because of concerns about potential confounding factors, participant selection and study design, and the case series [46] was at critical risk of bias because of potential confounding factors and lack of blinding of participants and assessors.

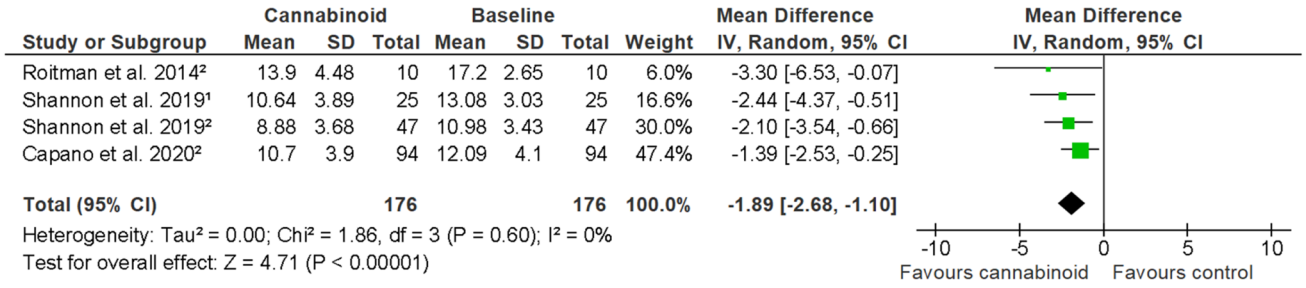

Fig. 2 Effect of cannabinoids on Pittsburgh Sleep Quality Index scores at ≤4 weeks. Roitman et al. [49] assessed effects of Δ9-tetrahydrocannabinol on PSQI at 3-weeks [25], while Shannon et al. [46] and Capano et al. [48] assessed the effects of cannabidiol and a mixture of cannabinoids, respectively, on PSQI at a 4-week follow-up [26, 27]. [1]Participants presenting with a sole, or primary diagnosis of a sleep disorder [46]. [2]Participants presenting with a secondary diagnosis of insomnia (i.e. primary diagnosis of anxiety disorder [46], chronic pain [48], and post-traumatic stress disorder [49]). *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

4 Discussion

This review is, to our knowledge, the first systematic review of the literature to examine the impact of cannabinoids on insomnia disorder. Patients included both those with primary and those with secondary insomnia, so long as contemporaneous diagnostic criteria or cut-off criteria diagnostic of insomnia using validated instruments were met. A range of instruments were used to assess sleep, and a variety of cannabis-based products and dosages were assessed, rendering meta-analysis impossible, with the exception of one common outcome measure across three studies. Despite some possible signals for efficacy of cannabis-based products in insomnia, the heterogeneity of participants, efficacy outcomes and results and the high risk of bias across included trials do not reliably inform evidence-based practice at this time.

In three studies, PSQI score improved following the administration of cannabinoids [46, 48, 49], with the effect of cannabinoids on PSQI maintained at 8 weeks [46, 48] and 12 weeks [46]. The forest plots indicated that the different types of cannabinoids had similar efficacy, but the minimal clinically important difference (MCID) in the PSQI is 3 [36, 50], a threshold exceeded only by THC [49]. However, it should be noted that a dropout rate of 63% at 3 months limited the findings of the CBD study [46]. The studies that reported outcome measures other than PSQI cited positive results but were limited by small sample sizes and a high degree of bias as assessed by the RoB 2 and ROBINS-I tools, and the results were of uncertain clinical significance because of changes in sleep measures rarely exceeding MCID values [45, 47]. Overall, these results highlight the scarcity of the data available as opposed to providing clear clinical direction in insomnia disorder.

This review has highlighted many shortcomings in the existing literature, including the scarcity of studies, lack of diagnostic clarity when measuring insomnia disorder, poorly defined patient groups, non-standardised treatments administered, confounding variables and studies of inappropriate design, duration and power to detect meaningful outcomes. The diagnostic difficulty is perhaps not surprising. Three of the included studies did not specifically diagnose insomnia disorder. Instead, this was interpreted by way of the data available, validated instruments used and correlation with diagnostic criteria for insomnia disorder at the time of the study's publication. Insomnia disorder is predominantly a

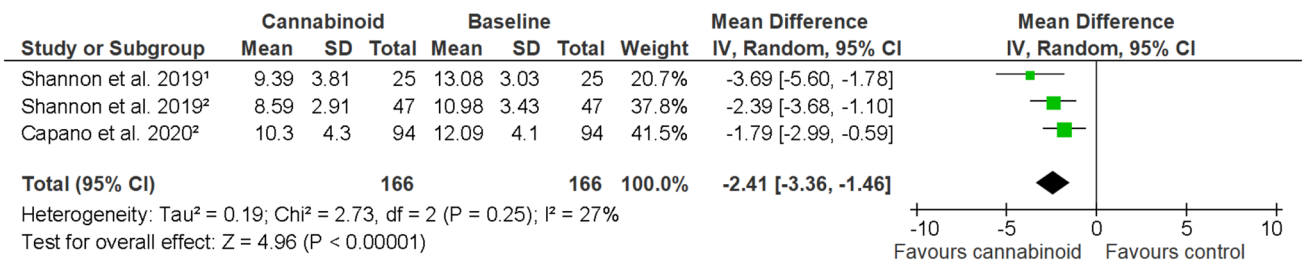

Fig. 3 Effect of cannabinoids on Pittsburgh Sleep Quality Index scores at 8 weeks. [1]Participants presenting with a sole, or primary diagnosis of a sleep disorder [46]. [2]Participants presenting with a secondary diagnosis of insomnia (i.e. primary diagnosis of anxiety disorder [46], chronic pain [48]). *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

clinically diagnosed condition that has changed over time [2, 8, 51], with current guidelines (DSM-5, ICSD-3) shifting away from differentiating between a 'primary' condition (solely insomnia) and a 'secondary' condition in light of increasing recognition of the bidirectional nature between insomnia disorder and other conditions. However, this leaves patients who meet the criteria of insomnia secondary to another clinical condition in a grey area. Indeed, many of the included studies examined insomnia disorder as a secondary metric, which rendered them vulnerable to confounding variables such as heterogeneity of participants and efficacy outcomes potentially being the result of improvement in symptoms related to the primary metric. A true test of efficacy for cannabinoids in insomnia lies in appropriately designed RCTs, only two of which we could include in this review, although none were of sufficient timeframe to be certain of long-term effects. The absence of randomisation to a placebo or other appropriate comparators in the three non-RCTs rendered these studies vulnerable to the bias of the placebo effect. There was no commonality of cannabis-based products or doses between the included trials, and the duration of the trials ranged from a single-dose study to 12 weeks of treatment, which would be considered relatively short treatment periods given the diagnostic duration criterion of 3 months for insomnia disorder itself.

There are reportedly high rates of cannabis use for ameliorating sleep difficulties [33, 52, 53], a practice that appears to be supported in some way in the medical literature as evidenced by our initial search yielding in excess of 1700 results. However, as we have established in this systematic review, this practice is not supported by high-quality evidence. Given the potential harms from cannabis, as indicated by the adverse effects described in the studies, prescription of cannabis-based products for insomnia should be in the context of an experimental and cautious addition to a pre-existing treatment regimen for patients with a stubborn condition that has so far proven resistant to established therapies and behavioural change. Patients should be appropriately advised of the lack of an appropriate evidence base for its use; the lack of evidence relating to the appropriate formulation, dose frequency and treatment duration; the experimental nature of the treatment; and possible harms of cannabis-based products and should provide their consent for a trial of the product accordingly.

In the interim, appropriately designed and adequately powered RCTs are urgently needed to examine the safety and efficacy of cannabis-based medicines in appropriately defined and selected patient groups using validated outcome measures with meaningful MCIDs. Specific exploration of cannabinoids is needed both separately and in varying combinations and ratios to generate a greater understanding of the biological mechanisms of cannabinoids in sleep, their effects on sleep architecture and clinical sleep patterns, their individual safety profiles and interactions with other medications and their efficacy in the treatment of insomnia. If efficacy is demonstrated, then further studies will be required to elucidate not only effectiveness but also the optimal formulations and dosing regimens and medium- to long-term safety outcomes. This information is required to ensure cannabis-based products can be effectively and safely prescribed to patients diagnosed with insomnia disorder.

5 Conclusion

This review highlights the potential promise of cannabis-based products in the treatment of insomnia disorder. However, the evidence remains in its infancy. The available studies generally cannot be appropriately translated in a clinically meaningful way. Further research in the form of high-quality RCTs is required before drawing any firm conclusions about the efficacy of cannabinoids in the treatment of insomnia disorder. Prescriptions for cannabis-based products should be approached cautiously at this time, and patients should be appropriately informed of the currently experimental nature of these treatments.

Declarations

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Conflict of interest Dr. Irene Braithwaite and Dr. Karen Oldfield have undertaken unrelated consultant work for RuaBio, ZHM, Whakaora Pharma and Helius Therapeutics. Dr. Irene Braithwaite, Dr. Karen Oldfield and Dr. Giles Newtown-Howes are members of the Medical Cannabis Research Collaborative. Dr. Giles Newton-Howes sits on the New Zealand Pharmacology and Therapeutics Advisory Committee and the international advisory board for The Australian Centre for Cannabinoid Clinical and Research Excellence. Chiranth Bhagavan, Stacey Kung, Marjan Doppen, Mary John and Iva Vakalalabure have no conflicts of interest that are directly relevant to the content of this article.

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