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CLINICAL REVIEW

# Cannabinoid therapies in the management of sleep disorders: A systematic review of preclinical and clinical studies

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SUMMARY

Cannabinoids, including the two main phytocannabinoids $\Delta^9$-tetrahydrocannabinol (THC) and cannabidiol (CBD), are being increasingly utilised as pharmacological interventions for sleep disorders. THC and CBD are known to interact with the endocannabinoid and other neurochemical systems to influence anxiety, mood, autonomic function, and circadian sleep/wake cycle. However, their therapeutic efficacy and safety as treatments for sleep disorders are unclear. The current systematic review assessed the available evidence base using PubMed, Scopus, Web of Science, Embase, CINAHL and PsycInfo databases. A total of 14 preclinical studies and 12 clinical studies met inclusion criteria. Results indicated that there is insufficient evidence to support routine clinical use of cannabinoid therapies for the treatment of any sleep disorder given the lack of published research and the moderate-to-high risk of bias identified within the majority of preclinical and clinical studies completed to-date. Promising preliminary evidence provides the rationale for future randomised controlled trials of cannabinoid therapies in individuals with sleep apnea, insomnia, post-traumatic stress disorder-related nightmares, restless legs syndrome, rapid eye movement sleep behaviour disorder, and narcolepsy. There is a clear need for further investigations on the safety and efficacy of cannabinoid therapies for treating sleep disorders using larger, rigorously controlled, longer-term trials.



## Introduction

Sleep is a vital physiological process that plays an important role in restorative functions that are essential for normal daytime function [1]. Optimal sleep health involves multiple factors, including adequate duration, timing, efficiency, and a sense of having restorative sleep that leaves the individual feeling alert and functional throughout the day [2]. Inadequate sleep is reported in approximately 30–35% of the general population [3], which may be partly due to lifestyle choices, employment, or other demands, and partly attributable to untreated sleep disorders [4]. Sleep disorders such as insomnia and obstructive sleep apnea (OSA) are associated with an increased risk of depression [5,6], cardiovascular disease [7,8], and dementia [9,10]. The direct and indirect financial costs of sleep disorders, such as those attributable to health care, lost productivity and road traffic accidents, are substantial. Annual costs arising from chronic insomnia disorder are estimated at approximately $30 - $107 billion in the USA [11]; indicating a strong need for clinical intervention.

*Abbreviations:* AHI, apnea hypopnea index; CBD, cannabidiol; $CB_1$, cannabinoid receptor 1; $CB_2$, cannabinoid receptor 2; EEG, electroencephalography; OSA, obstructive sleep apnea; PSG, polysomnography; PTSD, post-traumatic stress disorder; RCT, randomised controlled trial; REM, rapid eye movement; RBD, rapid eye movement sleep behaviour disorder; RLS, restless legs syndrome; THC, $\Delta^9$-tetrahydrocannabinol.

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*Cannabis sativa* has been used for its pain-relieving and soporific effects since ancient times [12]. Sleep disorders are one of the most common reasons individuals report using cannabis for medicinal purposes, alongside chronic pain and anxiety [13–15]. The growing legal availability of medicinal cannabis around the world is prompting an upswing of research into the effects of cannabinoids such as $\Delta^9$-tetrahydrocannabinol (THC) and cannabidiol (CBD) as novel treatments for a variety of sleep disorders [16]. Both THC and CBD interact with the endogenous cannabinoid (endocannabinoid) system, a complex and ubiquitous neuromodulatory network that includes cannabinoid 1 ($CB_1$) and 2 ($CB_2$) receptors, the endogenous ligands for these receptors such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for the biosynthesis and inactivation of these ligands [17]. Our understanding of the pharmacological influence of the endocannabinoid system on the circadian sleep–wake cycle is gradually evolving [18]. Clinical and preclinical studies describe a circadian rhythm in circulating endocannabinoid concentrations [19–21], with plasma 2-AG levels increasing from mid-sleep to early afternoon in humans; an effect amplified by sleep restriction [22]. Pharmacological inhibition of monoacylglycerol lipase (MAGL), the rate-limiting enzyme responsible for the degradation of 2-AG, leads to elevated brain 2-AG concentrations and wake-promoting effects in rats, including reductions in both NREM and REM sleep [23].

In contrast to 2-AG, AEA is associated with sleep-promoting effects: increasing endogenous AEA, via pharmacological inhibition of the degradative enzyme fatty acid amide hydrolase (FAAH), normalised deficits in stage N3 (or "slow wave") sleep in cannabis-dependent males undergoing cannabis withdrawal [24]. Preclinical data similarly show that AEA promotes slow wave sleep, possibly via increases in extracellular adenosine concentrations [25–27]. In preclinical models, the sleep-promoting effects of AEA are blocked by co-administration of the $CB_1$ inverse-agonist, rimonabant, indicating a $CB_1$-specific mechanism of action for AEA on sleep [28]. In human clinical trials, insomnia and other sleep disorders were common with rimonabant treatment and occurred more frequently than placebo [29–32]. Like AEA, THC is a partial agonist at the $CB_1$ receptor, and, thus, may exert sleep promoting effects via this direct pharmacological action [33]. CBD, on the other hand, has a weak binding affinity for the $CB_1$ receptor and instead, acts predominantly as a negative allosteric modulator at $CB_1$ (i.e., it can reduce the potency and/or efficacy of other ligands such as THC but does not activate the receptor itself) [34]. CBD has also shown to increase AEA concentrations via FAAH inhibition [35] and also via action on fatty acid-binding proteins (FABPs) [36], which provides an alternative pharmacological mechanism by which CBD may promote sleep. Overall, this highlights a complex modulatory role for the endocannabinoid system, and potential mechanisms for THC and CBD, in regulating the sleep–wake cycle.

A recent authoritative review concluded that there was moderate evidence that exogenously administered cannabinoids (primarily nabiximols, a buccal spray containing equal parts of THC and CBD) were effective for improving short-term sleep outcomes in individuals with sleep disturbance secondary to pain conditions such as multiple sclerosis and fibromyalgia [37]. However, it remains unclear whether this is due to an improvement in sleep *per se* or an improvement in the associated underlying condition (i.e., pain). Despite increased use of medicinal cannabis to treat insomnia and other sleep disorders, the evidence supporting therapeutic utility of cannabinoid therapies in sleep disorders is unclear. This systematic review presents a synthesis and evaluation of the preclinical and clinical evidence for cannabinoid therapies for the treatment of defined sleep disorders. To extend prior reviews on this topic [38–40] using a more specific focus, both preclinical and clinical studies that involved: (a) patients with a sleep disorder (or a preclinical model of a sleep disorder); and (b) the administration of any cannabinoid in an attempt to treat or manage an underlying sleep disorder were considered in this review. The aim was to synthesise the extant research on cannabinoids as therapeutics for sleep in a manner that informs policy, research priorities, and clinical decision-making.

## Methods

### *Search strategy and data sources*

Relevant preclinical and clinical studies were identified by searching the electronic databases PubMed, Embase, PsycINFO, Scopus, Web of Science, and CINAHL from inception until the 26th June 2019 using the following Boolean expression: (*cannabis* OR *cannabinoid* OR *marijuana* OR *tetrahydrocannabinol* OR *THC* OR *cannabidiol* OR *CBD* OR *nabilone* OR *sativex* OR *nabiximols* OR *dronabinol* OR *marinol* OR *namisol*) AND (*sleep* OR *sleep disorder* OR *sleep apnea* OR *insomnia* OR *narcolepsy* OR *idiopathic hypersomnolence* OR *excessive daytime sleepiness* OR *REM sleep behaviour disorder* OR *restless legs syndrome* OR *parasomnias* OR *night terrors* OR *circadian rhythm sleep disorder* OR *shift work sleep disorder* OR *sleep phase syndrome* OR *bruxism*). The search was restricted to English-language articles only, and terms were adapted as needed to meet the specific requirements of each database. The primary literature search was undertaken by one reviewer (AS) who imported the articles into reference management software (EndNote, Clarivate Analytics, PA, USA) where duplicates were removed. Two independent reviewers (AS, DM) then systematically screened each article against the eligibility criteria, first by title and abstract, and subsequently, by full text, to identify relevant studies. Disagreements were resolved by consensus through discussion with a third independent reviewer (CMH). The search was updated in November 2019 to capture any recent publications. One reviewer (AS) also searched the reference lists of all included studies and prior major reviews for missing publications and several major clinical trial registries (ClinicalTrials.gov, The Australian New Zealand Clinical Trials Registry, and The European Union Clinical Trials Register) for ongoing or unpublished investigations. This systematic literature review was conducted in accordance with the Preferred Reported Items for Systematic Reviews and Meta-analyses (PRISMA) statement [41].

Studies were evaluated against the following inclusion criteria:

1. Presented original data (i.e., not a review).
2. Conference abstracts were excluded if data had been published in an article that was already included in the review.
3. Population: sleep disorder or self-reported symptoms of a sleep disorder.
4. Intervention: involved administration of cannabis, a cannabinoid or a modulator of the $CB_1$ and/or $CB_2$ receptors (e.g., $CB_1$ receptor inverse agonist such as rimonabant) at any dose, via any route of administration, in an attempt to treat or manage the underlying sleep disorder in a controlled setting.
5. Primary outcome assessed changes in sleep-related clinical outcomes via any method.
6. Research did not involve participants with a sleep disorder secondary to a primary condition (e.g., insomnia secondary to chronic pain or cannabis withdrawal syndrome) *except* if the primary outcome was measuring a sleep-related outcome OR the sleep disorder was secondary to a psychiatric condition (e.g., anxiety or post-traumatic stress disorder).
7. Research did not involve participants who were subjected to an experimental condition that modelled a sleep disorder (e.g.,

simulated night shift work or sleep deprivation in healthy volunteers).
8. Research could be either observational or interventional.

For preclinical studies, criterion (3) was adapted to include preclinical models of sleep disorders (e.g., serotonin-induced reflex apnea to model OSA in humans), but excluded models in which sleep behaviour was manipulated (e.g., REM sleep deprivation) to induce a phenotype other than a sleep disorder (e.g., aggressiveness [42]). The study characteristics, methods, and measurement of any and all sleep-related outcomes of the included studies were extracted in duplicate (AS, MJB) into a template spreadsheet.

*Risk of bias*

The SYRCLE tool was used to assess risk of bias in preclinical studies [43]. It comprised 10 domains covering six types of biases: sequence generation, baseline characteristics, allocation concealment, random housing, researcher blinding, random outcome assessment, outcome assessor blinding, incomplete outcome data, selective outcome reporting, and "other sources of bias". Data on the timing and/or phases of the light/dark cycle were also extracted as an additional indicator of study quality. All clinical studies were assessed for risk of bias using the revised Cochrane Risk of Bias tool (RoB 2.0) [44]. The RoB 2.0 comprises five domains, including the randomisation process, deviation from intended interventions, missing data, measurement of the outcome, selective outcome reporting, and "other sources of bias". Two independent assessors performed the risk of bias assessments for preclinical (AS and MB) and clinical (AS and NSM) studies, with any disagreement resolved by consensus.

## Results

*Characteristics of the included studies*

The primary search identified 4342 records from 6 databases: PubMed (743), Embase (1137), PsycINFO (420), Scopus (826), Web of Science (958), CINAHL (258) (see Fig. 1). After removing duplicates, there were 1689 records for title and abstract screening. Following this, the full-texts of 16 preclinical studies and 20 clinical studies were checked for eligibility with a further 10 excluded (three preclinical and seven clinical studies - see Fig. 1 for reasons). The study characteristics and outcomes for each of the 14 preclinical studies (11 full-text articles and three abstracts) and the 12 clinical studies (10 full-text articles, one abstract, and one Letter to the Editor) are summarised in Tables 1 and 2, respectively. All clinical studies involved oral cannabinoid administration aside from one case study reporting on five individuals with severe restless legs syndrome (RLS) who smoked illicit cannabis to manage symptoms [45] – an exception for inclusion in the current review due to the specific focus of the research on a sleep disorder.

Nine preclinical studies (all conducted by the same research group) investigated the therapeutic effects of dronabinol (synthetic THC), AM251 and SR141716A ($CB_1$ receptor antagonists), AM630 ($CB_2$ receptor antagonist), chromenopyrazole 13a ($CB_1$ receptor agonist), and HU-308 ($CB_2$ receptor agonist) in a variety of animal models of OSA: four studies using acute serotonin (5-HT)-induced reflex apnea (intravenous administration of 5-HT can reduce upper airway muscle tone and increase apnea susceptibility in anesthetized rats) [46–49], four studies using adult rats as natural models of central sleep apnea [50–53], and one study using mechanical airway obstruction [54]. All nine studies used male rats. Two clinical trials used dronabinol in patients with OSA: a 3-wk open-label trial [55] and a 6-wk randomised controlled trial (RCT) [56]. Two ongoing pre-registered clinical trials in patients with OSA were also identified, with the first an open-label trial assessing the effects of 10 mg dronabinol and palmitoylethanolamide [57], and the second, an RCT investigating the effects of 10 mg THC with 200 mg of a proprietary mineral supplement [58] (see Table S1).

Four preclinical studies investigated the effects of cannabinoid treatment including CBD, oleamide, and AM251 and SR141716A in different animal models of disordered sleep, mainly stress-induced. Two studies utilised maternal separation [59,60]. One study used the 'flowerpot technique' to induce REM sleep deprivation; this method involves housing the rat on a small platform where a loss of muscle tone (e.g., during REM sleep) causes it to fall into water [61]. One study used a model of persistent stress in which the animals were repeatedly exposed to anxiety-provoking tests such as the open-field test (50 min) and a subsequent elevated plus-maze test (10 min) over four consecutive days [62]. All of these studies used male rats. No RCTs administered cannabinoids to participants with clinician-diagnosed insomnia. Six studies were identified in which cannabinoids were administered to participants with self-reported insomnia or sleep difficulties. Of those, three studies evaluated CBD formulations [63–65], two evaluated nabilone, a synthetic analogue of THC [66,67], and one evaluated a 95% pure THC product in dehydrated alcohol [68]. Four ongoing pre-registered clinical trials in chronic insomnia disorder were identified: three studies are using different ratios of THC and CBD [69–71] with one study also co-administering cannabinol (CBN) alongside THC and CBD [71], and one study administering 200 mg CBD/night [72] (see Table S1). One preclinical study administered CBD to examine effects on excessive sleepiness in an animal model of narcolepsy using hypocretin-deficient rats [73]. No clinical studies of cannabinoid treatment in patients with narcolepsy or excessive daytime sleepiness were identified. Two studies were identified assessing the effects of nabilone in males with PTSD-related nightmares [74,75]. One case series reported on the effects of CBD as an adjunct to standard treatment in four participants with REM sleep behaviour disorder (RBD) and Parkinson's disease [76]. Another case series reported on six patients with severe RLS who self-medicated with cannabis of varying composition to manage RLS symptoms [45].

*Risk of bias in individual studies*

The results of the risk of bias assessment for preclinical and clinical studies are reported in Tables 3 and 4, respectively. All preclinical studies, except two, exhibited high risk of bias in at least four of the domains. Ten out of 13 preclinical studies adequately reported their outcomes in an unbiased manner. No study reported using techniques of random housing, sequence generation, allocation concealment, or blinded caregivers/investigators. The timing of drug administration during the light/dark phase was only reported in three (23%) studies.

No clinical study was deemed to have an overall low risk of bias, with three studies identified as having 'some concerns' and all others a high risk of bias. The most frequent problems were bias arising from the randomisation process and selection of the reported results. Of the eight prospective studies conducted after 2005 (when trial pre-registration was mandated [77]), only three studies were pre-registered. A decision around the interpretability of the available evidence was made by categorising preclinical and clinical studies by the research question and rating them based on their quality (as per the relevant risk of bias assessment) (see Table 5).

## Discussion

This review identified 12 clinical studies examining the therapeutic effects of cannabinoid therapies across a range of sleep

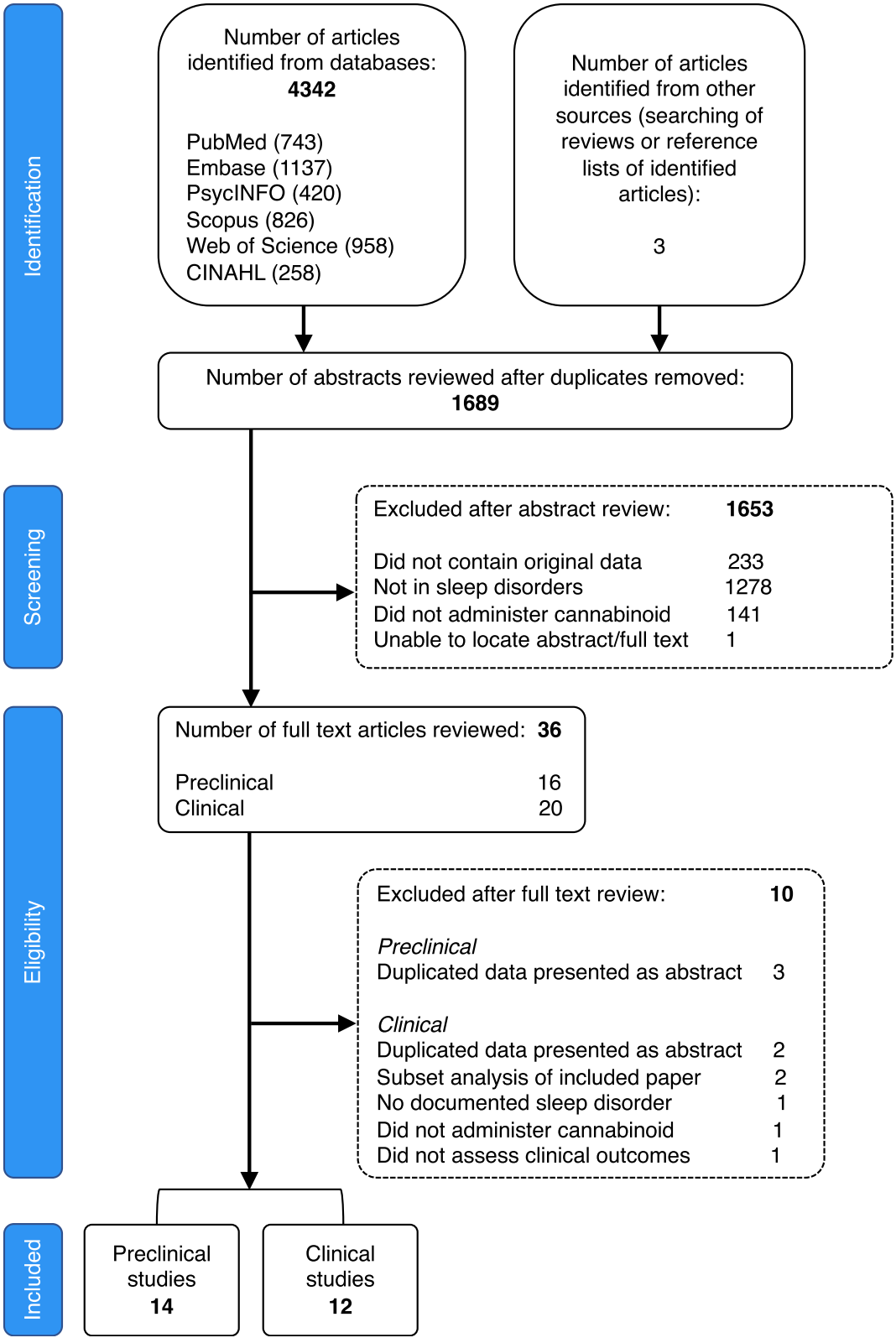


**Fig. 1.** PRISMA diagram illustrating the procedure used for identifying the eligibility of studies for review inclusion.

**Table 1**
Preclinical studies investigating the effects of cannabinoids or compounds that target the endocannabinoid system in models of sleep disorders.

| Authors, year [reference number] | Country of origin | Animal species ($n$) | Animal model | Intervention | Measure(s) | Results |
|---|---|---|---|---|---|---|
| *Models of obstructive sleep apnea* | | | | | | |
| Calik & Carley 2019 [53] | USA | Sprague Dawley rats ($n = 12$; all M) | Natural model of central sleep apnea | Each rat received each of the eight IP injections exactly one time in random order:<br><br>I: Vehicle alone (25% DMSO; one mL)<br>II: Dronabinol alone (10 mg/kg)<br>III: AM251 alone (5 mg/kg)<br>IV: AM630 alone (5 mg/kg)<br>V: (III) + (IV)<br>VI: (II) + (III)<br>VII: (II) + (IV)<br>VIII: (II) + (V) | PSG (EEG and EMG) | No significant change in sleep apnea or sleep efficiency with dronabinol (dissolved in 25% DMSO) when compared to vehicle. |
| Calik & Carley 2017 [50] | USA | Sprague Dawley rats ($n = 22$; all M) | Natural model of central sleep apnea | Each rat received each of the eight IP injections exactly one time in random order:<br><br>I: Vehicle alone (DMSO; one mL)<br>II: Dronabinol alone (10.0 mg/kg)<br>III: AM251 alone (5 mg/kg)<br>IV: AM630 alone (5 mg/kg)<br>V: (III) + (IV)<br>VI: (II) + (III)<br>VII: (II) + (IV)<br>VIII: (II) + (V) | PSG (EEG and EMG) | Compared to vehicle, dronabinol:<br>↓ apnea events ($p < 0.01$)<br>↓ post-sigh apneas ($p < 0.01$)<br>↓ sleep efficiency ($p < 0.05$)<br>↓ REM sleep ($p = 0.02$) with no changes in REM bouts or REM bout duration<br>Pre-treatment with $CB_1$, but not $CB_2$, receptor antagonists blocked apnea suppression by dronabinol. |
| Calik & Carley 2016 [47] | USA | Sprague Dawley rats ($n = 30$; all M) | Acute 5-HT-induced reflex apneas | Rats (n = 6/group) were administered the following treatments via ICV injection:<br><br>I-IV: Dronabinol (100, 10, 1, or 0.1$\mu$g/3$\mu$L DMSO<br>V: Vehicle (3$\mu$LDMSO) | EMGgg and respiratory responses | No significant change in apnea durations, average breath duration, or tonic/phasic EMGgg with dronabinol (all doses) when compared to vehicle. |
| *Carley & Topchiy 2015 [54] | USA | Sprague Dawley rats ($n = 6$; all M) | Brief airway occlusions | Rats were injected with 1 mg/100 $\mu$L dronabinol directly into nodose ganglia | EMGgg and respiratory responses | Compared to baseline, dronabinol:<br>↑ phasic EMGgg ($p = 0.04$) |
| *Topchiy et al., 2015 [52] | USA | Sprague Dawley rats ($n$ = not specified; gender not specified) | Natural model of central sleep apnea | Each rat received each of the seven IP injections exactly one time in random order: | EEG, nuchal EMG and respiratory responses | Compared to vehicle, chromenopyrazole 13a: ↓ apneas ($p < 0.05$) at both |

(*continued on next page*)

**Table 1** (*continued*)

| Authors, year [reference number] | Country of origin | Animal species (*n*) | Animal model | Intervention | Measure(s) | Results |
|---|---|---|---|---|---|---|
| | | | | I: Vehicle alone (undefined)<br>II-IV: Chromenopyrazole 13a (0.1, 1 and 10 mg/kg)<br>V-VII: HU-308 (0.1, one or 10 mg/kg) | | doses<br>HU-308 did not significantly change in apnea index at any dose. |
| Calik & Carley 2014 [46] | USA | Sprague Dawley rats ($n = 36$; all M) | Acute 5-HT-induced reflex apneas | Rats (n = 6/group) received the following pre-treatments via IP injection:<br><br>I-II: AM251 (0.5 or 5 mg/kg)<br>III-IV: AM630 (0.5 or 5 mg/kg)<br>V: AM251 + AM630 (5 mg/kg each)<br>VI: Vehicle (15% DMSO)<br>Dronabinol (100$\mu$g/5 $\mu$L sesame oil) was injected into nodose ganglia to all groups directly followed by 5-HT infusion. | EMGgg and respiratory responses | Compared to baseline, dronabinol:<br>↓ apneas ($p = 0.03$)<br>↑ phasic and tonic EMGgg ($p < 0.05$)<br>Both AM251 and AM630 pre-treatment reversed dronabinol's reduction in reflex apneas. |
| Calik et al., 2014 [48] | USA | Sprague Dawley rats ($n = 24$; all M) | Acute 5-HT-induced reflex apneas | Rats (n = 6/group) received the following treatment via direct injection into the nodose ganglia:<br><br>I: Dronabinol (100$\mu$g/5$\mu$L sesame oil)<br>II: Dronabinol (10$\mu$g/5 $\mu$L sesame oil)<br>III: Vehicle (5 $\mu$L sesame oil)<br>IV: Sham group (no treatment) | EMGgg and respiratory responses | Compared to baseline, dronabinol:<br>↓ 5-HT-induced apnea (n.s.)<br>↓ apnea duration at both doses ($p < 0.05$)<br>↑ phasic EMGgg ($p < 0.01$)<br>No effect of dronabinol on tonic EMGgg. |
| *Topchiy et al., 2012 [49] | USA | Sprague Dawley rats ($n = 6$; all M) | Brief airway occlusion and acute 5-HT-induced reflex apneas | Dronabinol (dose not specified) injected directly into nodose ganglia | EMGgg and respiratory responses | Compared to baseline, dronabinol:<br>• Reduced 5-HT-induced apneas ($p = 0.04$)<br>• Did not reverse the effects of airway occlusion on EMGgg and EMGgg pre-activation time) (n.s.) |
| Carley et al., 2002 [51] | USA | Sprague Dawley rats ($n = 11$; all M) | Natural model of central sleep apnea | Each rat received each of the 12 IP injections exactly one time in random order:<br><br>I-III) Vehicle (saline, DMSO, or peanut oil)<br>IV-VI) THC alone (0.1, 1.0, or 10 mg/kg)<br>VII-IX: OLE alone (0.1, 1.0, or 10 mg/kg)<br>X: 5-HT alone (0.79 mg/kg)<br>XI: THC (0.1 mg/kg) → 5- | PSG (EEG and EMG) | Compared to vehicle, Δ9THC:<br>↓ frequency of apneas during NREM ($p = 0.03$ for 1.0 and 10 mg/kg)<br>↓ frequency of apneas during REM ($p = 0.03$ for 10 mg/kg only)<br>Compared to |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | HT (0.79 mg/kg)<br>XII: THC (0.1 mg/kg)→OLE (0.1 mg/kg)→5-HT (0.79 mg/kg) | | vehicle, oleamide: ↓ frequency of apneas during NREM ($p < 0.05$ all doses) |
| *Models of disordered sleep* | | | | | | |
| Perez-Morales et al., 2014 [59] | Mexico | Wistar rats ($n = 24$; all M) | Maternal separation | Two groups of rats (MS or no-MS, n = 6/group) received the following treatments via ICV injection into lateral hypothalamus:<br><br>I: Vehicle (100% DMSO)<br>II: AM251 (0.01 $\mu$g)<br>III: 2-AG (0.01 $\mu$g)<br>IV: (II) + (III) | Implanted EEG/EMG | 2-AG restored sleep (i.e., ↓wakefulness and ↑NREM and REM) in MS rats ($p < 0.05$). AM251 blocked these effects ($p = 0.001$). |
| Prieto et al., 2012 [60] | Mexico | Wistar rats ($n = 40$; all M) | Maternal separation | Rats (n = 10/group) received the following treatments via IP injection:<br><br>I: OLE (1 mg/kg)<br>II: AM251 (1.6 mg/kg)<br>III: (I) + (II)<br>IV: Vehicle (30% DMSO) | Implanted EEG/EMG | Compared to vehicle, OLE normalised sleep (i.e., ↓wakefulness and ↑NREM and REM) in MS rats ($p < 0.05$). |
| Hsiao et al., 2012 [62] | Taiwan | Wistar rats ($n = 28$; all M) | Repeated combination tests (50 min of open field test and 10 min of EPM for four consecutive days) | Rats (n = 7/group) were subjected to either RCT or SD before receiving microinjections into the CeA with the following treatments:<br><br>I: RCT + Vehicle (2% DMSO)<br>II: RCT + CBD (0.5$\mu$g/1 $\mu$l)<br>III: RCT + CBD (1$\mu$g/1 $\mu$l)<br>IV: SD + Vehicle (2% DMSO) | Implanted EEG | Compared to vehicle, high dose CBD (1$\mu$g) blocked anxiety-induced REM sleep suppression during hours 4–10 of the light period ($p < 0.05$). |
| Navarro et al., 2003 [61] | Mexico | Wistar rats ($n = 24$; all M) | REM sleep deprivation using the 'flowerpot technique' | Rats (n = 6/group) were subjected to SD or no-SD before receiving the following ICV injections:<br><br>I: SD + Vehicle (saline, 5$\mu$L)<br>II: SD + SR141716A (3$\mu$g)<br>III: No-SD + ICV saline (5 $\mu$L)<br>IV: No-SD + SR141716A (3$\mu$g) | Implanted EEG/EMG | Compared to vehicle, $CB_1$ receptor antagonism partially prevented stress-induced REM sleep rebound ($p < 0.05$). |
| *Model of narcolepsy* | | | | | | |
| Murillo-Rodriguez et al., 2019 [73] | Mexico | Wistar rats (n = 15, all M) | HCRT2/SAP-lesioned rats | Rats (n = 5/group) received the following treatments via IP injection:<br><br>I: Control + Vehicle<br>II: HCRT2/SAP + Vehicle<br>III: HCRT2/SAP + CBD (5 mg/kg) | Implanted EEG | Compared to vehicle, CBD ↓excessive somnolence in hypocretin-deficient rats over a 5-h period only ($p < 0.05$). |

2-AG = 2-Arachidonoylglycerol; 5-HT = serotonin; $CB_1$ = cannabinoid receptor 1; $CB_2$ = cannabinoid receptor 2; CBD = cannabidiol; CeA = central nucleus of amygdala; DMSO = dimethyl sulfoxide; EEG = electroencephalography; EMG = electromyography; EMGgg = genioglossus electromyography; EPM = elevated plus maze; HCRT2/SAP = hypocretin-2-saporin; ICV = intracerebroventricular; IP = intraperitoneal; M = male; MS = maternal separation; n.s. = not significant; OF = open field; OLE = oleamide; PSG = polysomnography; RCT = repeated combination tests (to provoke anxiety); REM = rapid eye movement; THC = tetrahydrocannabinol; SD = sleep deprivation; *Conference abstract.

*For ease of reference*: AM251 = $CB_1$ receptor antagonist; AM630 = $CB_2$ receptor antagonist; Chromenopyrazole 13a = $CB_1$ receptor agonist; HU-308 = $CB_2$ receptor agonist; SR141716A = $CB_1$ receptor antagonist.

**Table 2**
Clinical studies investigating the effect of cannabinoid therapies in the treatment of sleep disorders.

| Authors, year [reference number] | Country of origin | Overall risk rating | Study design | Participant details (*n*, gender, mean ± SD age) | Treatment period | Intervention, dose, and timing | Primary outcome (measure) | Primary outcome result | Adverse events |
|---|---|---|---|---|---|---|---|---|---|
| *Obstructive sleep apnea* | | | | | | | | | |
| Carley et al., 2018 [56] | USA | *Some concerns* | DB, PC<br>Parallel | $n = 73$ (52 M)<br>I: 52.7 ± 7.7 y II: 54.7 ± seven y<br>C: 58.8 ± 6.1 y | 6 weeks | Dronabinol (oral capsules)<br>I: 2.5 mg/day<br>II: 10 mg/day<br>C: Placebo capsule<br>Self-administered 1 h before bedtime | Change in AHI relative to placebo at W6 | Baseline AHI:<br>I: 28.2 ± 12.5<br>II: 26.0 ± 11.9<br>C: 23.9 ± 9.6<br>Compared to placebo, change in AHI at 6 weeks:<br>*Note:* Adjusted values in brackets<br>I: ↓ 2 (6.6 ± 5.9*)<br>II: ↓ 4 (8.5 ± 5.2**)<br>C: ↑ 8.5 (4.1 ± 5.5)<br>Unadjusted values extrapolated from Tabl 2 in Carley et al. (2018) | • AE rate: 96.3%<br>• Common: sleepiness/drowsiness (63%), headache (48%), nausea/vomiting (33%)<br>• Two SAEs (one related to dronabinol treatment − diarrhea and vomiting requiring hospitalisation)<br>• Four withdrew due to treatment-related AEs |
| Prasad et al., 2013 [55] | USA | *High risk* | UB, open-label<br>Comparison to baseline | $n = 17$ (6 M)<br>I: 51.6 ± 7.9 y | 3 weeks | Dronabinol (oral capsules)<br>I: 10 mg/day<br>Self-administered 0.5 h before bedtime | Change in AHI relative to baseline at W3 | Baseline AHI:<br>48.4 ± 17.6<br>I: ↓ 14.1 ± 17.5** | • AE rate: 75%<br>• Common: somnolence (50%)<br>• No SAEs<br>• Two withdrew due to treatment-related AEs |
| *Insomnia/individuals with sleep difficulties* | | | | | | | | | |
| Shannon et al., 2019 [64] | USA | *High risk* | UB, medical chart review<br>Comparison to baseline | $n = 25$ (9 M)<br>I: 36.5 y | 3 months | CBD (oral capsules)<br>I: 25 mg/day<br>*Note*: Some patients received 50 or 75 mg/day<br>Self-administered "after dinner" | PSQI | ↓ PSQI<br>Baseline: 13.08 ± 3.03<br>3-months: 9.33 ± 4.63 | • AE rate: not stated<br>• Common: fatigue (n = 2), mild sedation (n = 3), abnormal behaviour (n = 1), and dry eyes (n = 1) |
| Shannon et al., 2016 [65] | USA | *High risk* | UB, open-label<br>Comparison to baseline | *n = 1* (1 F)<br>10 y<br>*PTSD-related insomnia disorder and anxiety* | 5 months (ongoing) | CBD (25 mg capsule)/night and CBD (12 mg sublingual spray)/day<br>Self-administered CBD capsule "before bed" and CBD sublingual spray "during the day" | Sleep Disturbance Scale for Children | ↓ 21 points relative to baseline | None observed |
| #Zalai et al., 2015 [67] | Canada | *High risk* | DB, PC<br>Crossover | $n = 11$ (age not specified)<br>*Insomnia disorder and chronic pain* | 2 × 4 weeks | Nabilone (oral capsules)<br>I: Dose unspecified<br>C: Placebo<br>Timing of drug administration not reported | Sleep parameters (PSG, MWT, MSLT at baseline, W4, and W8) | Sleep efficiency:<br>↑ +3.8% (n.s.)<br>Total sleep time:<br>↑ +3.8% (n.s.)<br>Arousal index:<br>↓ −24.3% (n.s.)<br>Sleep onset latency:<br>↑+31.8 min ($p < 0.05$) | Not reported |
| Ware et al., 2010 [66] | Canada | *Some concerns* | DB, AC<br>Crossover | $n = 32$ (5 M)<br>49.5 ± 11.2 y<br>*Insomnia disorder and fibromyalgia* | 2 × 2 weeks separated by 2-week WO | Nabilone (oral capsules)<br>I: 0.5−1 mg/day<br>II: 10 mg amitriptyline<br>Dose-escalation to 1 mg nabilone or 20 mg amitriptyline for W2<br>Self-administered "before bed" | PSQI & ISI | Compared to amitriptyline:<br>PSQI ↓ 3.25 points (n.s.)<br>ISI ↓ −3.25 adjusted difference (CI, −5.26 to − 1.24) (n.s.) | • 91 AEs possibly or probably related to nabilone<br>• Common: dizziness, nausea, and dry mouth<br>• No SAEs |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Carlini et al., 1981 [63] | Brazil | *Some concerns* | DB, PC<br>Crossover | $n = 15$<br>*Age/gender not specified*<br>*Relatives of research staff with subjective complaints of sleep difficulties* | Single dose | CBD (oral capsules)<br>I: 40 mg CBD<br>II: 80 mg CBD<br>III: 160 mg CBD<br>CI: Placebo<br>CII: 5 mg Nitrazepam<br>Self-administered 0.5 h before bedtime | Non-validated 10-point sleep questionnaire | All CBD doses ↓ remembering dreams*<br>160 mg CBD ↑duration of sleep* | AE rate not specified<br>Four participants reported experiencing somnolence |
| Cousens et al., 1973 [68] | USA | *High risk* | DB, PC<br>Crossover | $n = 9$ (9 M)<br>21–40 y | Single dose | 95% THC (oral liquid)<br>I: 10 mg THC<br>II: 20 mg THC<br>III: 30 mg THC<br>C: Placebo<br>Administered 1.5 h before the "average sleep time of the group" | Sleep latency ("experienced sleep observer-rater") | I: ↓137 min*<br>II: ↓118 min**<br>III: ↓126 min*<br>C: 180 min | Pre-sleep AEs: perceptual/cognitive distortions, loss of control and judgement, dry mouth<br>Post-sleep AEs: dizziness/grogginess, dry mouth, funny taste in mouth. |
| *REM sleep behaviour disorder* | | | | | | | | | |
| Chagas et al., 2014 [76] | Brazil | *High risk* | Case series, UB<br>Comparison to baseline | $n = 4$ (4 M)<br>63.5 ± 5.3 y<br>*RBD and Parkinson's disease* | 6 weeks | CBD (oral capsules)<br>Three patients received 75 mg/day while one received 300 mg/day<br>Self-administered "at night under supervision of relatives/caretakers" | Frequency of RBD events (patient & carer self-report) | "Prompt, substantial and persistent reduction in RBD events after 6 weeks" | None observed |
| *Restless legs syndrome* | | | | | | | | | |
| ˆMegelin & Ghorayeb 2017 [45] | France | *High risk* | Case series, UB<br>Comparison to baseline | $n = 6$ (2 M)<br>43.2 ± 11.3 y | Self-reported acute use | Smoked cannabis ($n = 5$)<br>Sublingual CBD ($n = 1$)<br>Not reported | Frequency of RLS symptoms (patient self-report) | "All patients reported spontaneous relief of RLS symptoms" | Not reported |
| *PTSD-related nightmares* | | | | | | | | | |
| Jetly et al., 2015 [75] | Canada | *Some concerns* | DB, PC,<br>Crossover | $n = 10$ (10 M)<br>43.6 ± 8.2 y | 2 × 7 weeks separated by 2-week WO | Nabilone (oral capsules)<br>I: 0.5 mg/day up to 3 mg<br>C: Placebo<br>Self-administered 1 h before bedtime | Change in nightmare frequency (CAPS Recurring and Distressing Dream score) | CAPS Frequency:<br>I: −1.9 ± 1.3*<br>C: −0.4 ± 1.4<br>CAPS Intensity:<br>I: −1.7 ± 1.3 (n.s.)<br>C: −0.6 ± 1.1 | AE rate:<br>I: 50%<br>C: 60%<br>Common: dry mouth and headache |
| Fraser 2009 [74] | Canada | *High risk* | UB, open-label<br>Comparison to baseline | $n = 47$ (20 M)<br>44 ± 9 y | 4–12 months | Nabilone (oral capsules)<br>I: 0.5 mg/day up to 6 mg<br>Self-administered 1 h before bedtime | Subjective self-report of nightmare frequency | "Total cessation of nightmares," n = 28, 60%<br>"Satisfactory reduction", n = 6, 12%) | AE rate: 28% (all 28% withdrew)<br>Common: light-headedness, memory impairment, dizziness, and headache |

AC = active control; AE = adverse events; AHI = apnea hypoxia index; C = control; CAPS = clinician-administered post-traumatic stress scale; CBD = cannabidiol; CI = confidence interval; DB = double-blind; I = intervention; ISI=Insomnia Severity Index; M = males; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; OSA = obstructive sleep apnea; PC = placebo-controlled; PTSD = post-traumatic stress disorder; PSG = polysomnography; PSQI=Pittsburgh Sleep Quality Index; RBD = rapid eye movement sleep behaviour disorder; REM = rapid eye movement; RLS = restless legs syndrome; SAE = serious adverse events; THC = tetrahydrocannabinol; UB = unblinded; W = week; WO = wash-out; #Conference abstract; ˆLetter to the Editor *p < 0.05 relative to placebo **p < 0.01 relative to placebo.

**Table 3**
Risk of bias of individual preclinical studies using the SYRCLE risk of bias tool.

| | Selection bias | | | Performance bias | | Detection bias | | Attrition bias | Reporting bias | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| **Authors, year [reference number]** | ***Sequence generation*** | ***Baseline characteristics*** | ***Allocation concealment*** | ***Random housing*** | ***Investigator blinding*** | ***Random outcome assessment*** | ***Blinded outcome assessment*** | ***Incomplete outcome data*** | ***Selective outcome reporting*** | ***Other risk of bias*** |
| *Models of obstructive sleep apnea* | | | | | | | | | | |
| Calik & Carley (2019) [53] | High risk | Unclear | High risk | High risk | High risk | Low risk | Low risk | Low risk | Low risk | High risk |
| Calik & Carley (2017) [50] | Unclear | Low risk | High risk | High risk | High risk | Low risk | Low risk | Unclear | High risk | Unclear |
| Calik & Carley (2016) [47] | High risk | High risk | High risk | High risk | High risk | High risk | High risk | Unclear | Low risk | Unclear |
| *Carley & Topchiy (2015) [54] | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low risk | Unclear |
| *Topchiy et al., (2015) [52] | Unclear | Unclear | Unclear | Unclear | Unclear | Low risk | Unclear | Unclear | Low risk | Low risk |
| Calik et al., (2014) [48] | High risk | High risk | High risk | High risk | High risk | High risk | High risk | Unclear | Low risk | Unclear |
| Calik & Carley (2014) [46] | High risk | Low risk | High risk | High risk | High risk | High risk | High risk | Unclear | Low risk | Unclear |
| *Topchiy et al., (2012) [49] | High risk | Unclear | High risk | Unclear | High risk | Unclear | High risk | Low risk | Low risk | Unclear |
| Carley et al., (2002) [51] | Unclear | High risk | High risk | High risk | High risk | High risk | High risk | Unclear | Low risk | High risk |
| *Models of sleep disturbances* | | | | | | | | | | |
| Pérez-Morales et al., (2014) [59] | High risk | Low risk | High risk | High risk | High risk | High risk | High risk | Low risk | Low risk | Low risk |
| Hsias et al., (2012) [62] | High risk | High risk | High risk | High risk | High risk | High risk | High risk | Low risk | Low risk | Low risk |
| Prieto et al., (2012) [60] | High risk | Low risk | High risk | High risk | High risk | High risk | High risk | Unclear | Low risk | Unclear |
| Navarro et al., (2003) [61] | High risk | High risk | High risk | Unclear | High risk | High risk | High risk | Unclear | High risk | High risk |
| *Models of narcolepsy* | | | | | | | | | | |
| Murillo-Rodríguez et al., 2019 [73] | High risk | High risk | High risk | High risk | High risk | High risk | Low risk | Low risk | Unclear | Low risk |

*Conference abstracts are difficult to assess for risk of bias due to restricted word limits. For more information on each SYRCLE risk of bias domain, see: https://doi.org/10.1186/1471-2288-14-43

**Table 4**
Risk of bias of individual clinical studies using revised Cochrane Risk of Bias (RoB 2.0) tool.

| **Authors, year [reference number]** | **Randomisation process** | **Deviations from intended intervention** | **Missing data** | **Measurement of outcomes** | **Selection of the reported results** | **Overall risk of bias** |
|---|---|---|---|---|---|---|
| *Obstructive sleep apnea* | | | | | | |
| Carley et al., (2018) [56] | Some concerns | Low risk | Low risk | Low risk | Low risk | **Some concerns** |
| Prasad et al., (2013) [55] | High risk | Some concerns | Low risk | Low risk | Some concerns | **High risk** |
| *Insomnia or sleep disturbances* | | | | | | |
| Shannon et al., (2019) [64] | High risk | High risk | High risk | High risk | Some concerns | **High risk** |
| Shannon et al., (2016) [65] | High risk | High risk | Low risk | High risk | Some concerns | **High risk** |
| *Zalai et al., (2015) [67] | Some concerns | High risk | High risk | Some concerns | Some concerns | **High risk** |
| Ware et al., (2010) [67] | Low risk | Low risk | Low risk | Low risk | Some concerns | **Some concerns** |
| Carlini et al., (1981) [63] | Some concerns | Low risk | Low risk | Low risk | Some concerns | **Some concerns** |
| Cousens et al., (1973) [68] | Some concerns | Low risk | Low risk | High risk | Some concerns | **High risk** |
| *PTSD-related nightmares* | | | | | | |
| Jetly et al., (2015) [75] | Some concerns | Low risk | Low risk | Low risk | Some concerns | **Some concerns** |
| Fraser (2009) [74] | High risk | High risk | High risk | High risk | High risk | **High risk** |
| *REM sleep behaviour disorder* | | | | | | |
| Chagas et al., (2014) [76] | Some concerns | Low risk | Low risk | High risk | Some concerns | **High risk** |
| *Restless legs syndrome* | | | | | | |
| Megelin et al., (2017) [45] | High risk | High risk | High risk | High risk | High risk | **High risk** |

*Conference abstracts are difficult to assess for risk of bias due to restricted word limits.

disorders and 14 preclinical studies involving animal models of these disorders. The majority of these studies carried a substantial risk of bias such that the conclusions from this review are only tentative. The discussion will focus on synthesis of the existing data for each research question.

*Do cannabinoids improve sleep-related breathing outcomes in obstructive sleep apnea?*

The current evidence for the use of THC (dronabinol) in individuals with OSA is weak, but the potential therapeutic benefits

**Table 5**
Synthesis of the available preclinical and clinical studies based on their interpretability (availability and quality), categorised by the research question.

| Research question | Preclinical studies | Clinical studies | Evidence for Use |
|---|---|---|---|
| Do cannabinoids improve… | | | |
| 1. Sleep-related breathing outcomes in obstructive sleep apnea? | Interpretable | Interpretable | Weak |
| 2. Sleep-related outcomes in insomnia disorder? | Interpretable | Interpretable | None |
| 3. Sleep-related outcomes in PTSD-related nightmares? | – | Interpretable | Weak |
| 4. Sleep-related outcomes in REM sleep behaviour disorder? | – | Not interpretable | None |
| 5. Sleep-related movement outcomes in restless legs syndrome? | – | Not interpretable | None |
| 6. Sleep/wake-related outcomes in narcolepsy? | Interpretable | – | None |

Dash (–) signifies no studies identified; 'Interpretable' signifies studies were identified and deemed to have a low-moderate risk of bias; 'Not interpretable' signifies studies were identified but deemed to have a high risk of bias. REM = rapid eye movement; PTSD = post-traumatic stress disorder.

warrant further investigation. All but two preclinical studies [47,53] found that THC reduced apneic events in rats when administered intraperitoneally but not when administered via intracerebroventricular injection [47]. This finding, and the results of other studies, suggest that the effects of THC on reflex apnea may be peripherally mediated via suppression of vagal nerve activity by the endocannabinoid system. Specifically, one study showed that THC inhibition of reflex apnea could be reversed with administration of $CB_1$ and $CB_2$ receptor antagonists [46]. Another study indicated that THC may dampen afferent vagal feedback to the medulla via actions on the nodose ganglia, a component of the vagus nerve that expresses excitatory serotonin type 3 ($5\text{-}HT_3$) and inhibitory $CB_1$ receptors [47]. This is a plausible mechanism through which THC could stabilise respiratory patterns and increase activation of upper airway dilating muscles during sleep in a manner largely independent of cannabinoid receptors located in the central nervous system [78].

Two clinical studies of oral dronabinol as a potential treatment for OSA showed reductions in the apnea-hypopnea index (AHI) after treatment. In their initial open-label, pre-post, proof of concept trial in individuals with moderate to severe OSA ($n = 15$), Prasad et al. (2013) reported a significant 14.1 ± 17.5-point reduction in AHI relative to baseline (AHI = 48.4 ± 17.6) after three weeks of dronabinol treatment [55]. The subsequent 6-wk RCT by Carley et al. (2018) in individuals with moderate to severe ($n = 73$) also identified a positive effect [55]. However, findings from this trial should be interpreted with caution as the statistically significant reduction in the adjusted AHI of 12.9 ± 4.3-points with 10 mg/d dronabinol treatment was at least partly attributable to a potentially clinically meaningful baseline imbalance in AHI (placebo = 23.9 ± 9.6 vs. 10 mg/d dronabinol = 26.2 ± 11.9) and a significant 8.5-point increase in AHI in the placebo-treated group after six weeks. Baseline AHI was statistically controlled for in the analyses along with age, race, and ethnicity as additional covariates. After adjustment, the increase in AHI from baseline in the placebo group was smaller (−4.1 ± 5.5-points) and not statistically significant. This resulted in a 12.9-point difference relative to placebo for the 10 mg/d dronabinol-treated group. The authors hypothesised the worsening AHI in the placebo group may have been due to the participant's discontinuation of other interventions (e.g., continuous positive airway pressure (CPAP)) one month prior to the trial, although, this was not objectively confirmed. Neither dose of dronabinol showed a statistically significant reduction in AHI relative to baseline. Furthermore, of the 39 participants who received dronabinol treatment, only six (15.4%) met the trial's responder criteria (i.e., AHI≤15 and AHI reduction of 50% or more from baseline). Treatment-related adverse events occurred in 75% and 96% of participants receiving 10 mg/d in the Prasad et al. (2013) and Carley et al. (2018) trial, respectively. The most common adverse event in the Carley et al. (2018) trial was drowsiness (63% vs. 0% in placebo group) followed by headache (48% vs. 15% in placebo group) and nausea/vomiting (33% vs. 4% in placebo group) [79]. Four participants withdrew due to treatment-related adverse events (dizziness and vision changes; vertigo; ECG arrhythmias; headache, dizziness, and vomiting). One serious adverse event related to dronabinol treatment was reported (diarrhea and vomiting requiring hospitalisation).

It is worthwhile noting that a 2018 position statement from the *American Academic of Sleep Medicine* warned clinicians against prescribing dronabinol as a treatment for OSA and argued that OSA should not be a certifiable health condition for medical cannabis programs due to unknown short- and long-term side effects of dronabinol in patients with OSA [80]. Additional research in this area is recommended, especially studies that evaluate clinical response in specific OSA phenotypes [81]. Thus, despite a positive signal, dronabinol is not currently recommended for the treatment of OSA. Well-designed randomised controlled short-term trials as well as longer-term studies are needed to further determine the efficacy and safety of dronabinol in individuals with OSA. Indeed, one pre-registered Phase IIa placebo-controlled clinical trial will test the effects of 10 mg THC with a 200 mg proprietary mineral supplement over a 6-week period [58], while a second open-label Phase IIa clinical trial will assess the effects of an oral formulation containing 10 mg dronabinol in combination with 800 mg palmitoylethanolamide (PEA), an endogenous fatty acid amide, in 30 patients with OSA over a 4-wk period [57] (see Table S1). The primary outcome for both trials is AHI index post-treatment as compared to baseline using overnight polysomnography. The Phase IIa trial of dronabinol in combination with PEA recently announced top line findings for 10 patients in a press release [82]. No serious adverse events were reported, with one patient withdrawing due to treatment-related dizziness. Of the remaining nine participants, just over half showed a significant reduction in average AHI from 24.2 ± 5.0 at baseline to 11.2 ± 6.8 at four weeks. The press release cited the "encouraging tendency of the results" as the main reason for early study recruitment closure.

### *Do cannabinoids treatment improve sleep-related outcomes in insomnia disorder?*

There were no published RCTs investigating the effects of cannabinoid therapies in patients with clinician-diagnosed insomnia, limiting any conclusions regarding their utility for insomnia disorder. THC displays minimal toxicity and lethality [83], inferring a safety advantage over hypnotic medications. However, abrupt discontinuation of daily, or near daily cannabis use may lead to abstinence-induced insomnia [84] and sleep difficulty is a commonly reported symptom of cannabis withdrawal among frequent cannabis users (e.g., at least 25 days/mo) [85]. Poor sleep quality has also been shown to be a risk factor for lapse following a cannabis quit attempt in cannabis dependent users [86]. Laboratory studies have shown that cannabis abstinence-induced sleep

disturbance is pharmacologically specific to THC exposure, as it can be reversed with administration of dronabinol or by a return to cannabis use [87,88]. It is important to note that this research has mainly focused on heavy recreational (non-medicinal) use of cannabis. Although not covered in the present review, there is moderate evidence for the use of Sativex, an oromucosal spray delivering equal parts THC and CBD, in improving short-term sleep outcomes in individuals with sleep disturbances secondary to a pain condition [89], however, no studies have assessed its effects in individuals with a primary sleep disorder.

In an animal model of sleep disturbances induced by repeated exposure to anxiety-provoking environments, CBD microinjected into the central nucleus of the amygdala reversed stress-induced REM suppression, with little effect on NREM sleep [62]. This suggests improvements in sleep via an anxiolytic mechanism not yet fully understood, but which may involve serotonin 1A (5-$HT_{1A}$) receptor activation [90] and/or enhancement of AEA signalling by inhibition of FAAH and FABPs [91]. Other preclinical evidence suggests that CB1 receptor activation via endocannabinoids, oleamide and 2-AG, normalised maternal separation-associated sleep disturbances such as increased wakefulness and decreased NREM and REM sleep duration [59,60]. Other preclinical evidence suggests endocannabinoids may also play a role in modulating REM sleep generation following sleep deprivation in rats [61]. This is in line with previous work suggesting that endocannabinoid signalling is necessary to promote sleep stability [18].

The acute and chronic effects of CBD on sleep are poorly understood currently, and there is a lack of empirical data in which CBD has been evaluated among individuals with disordered sleep. In clinical trials involving 25/mg/kg CBD (Epidiolex) in children with severe epilepsies, increased somnolence and sedation was observed. However, in these studies, CBD was found to be a potent metabolic inhibitor of concurrently-administered anticonvulsant medications, which may have driven the sedating effects reported in these trials [92,93]. Drowsiness was reported as the fourth most common side effect in an ascending dose Phase 1 trial of CBD in healthy volunteers, but the incidence did not differ from placebo and the greatest frequency of somnolence observed was with an acute dose of 6000 mg, which far exceeds the typical dose found in retail CBD products (for example, the unit dose of CBD in Epidiolex is 100 mg) [94]. In another laboratory study of healthy adults, 100 mg CBD administered orally and via vaporization did not impact subjective ratings of alertness and sleepiness [95]. Because CBD can act as a negative allosteric modulator of the $CB_1$ receptor [34], it is feasible that CBD could exhibit stimulating properties at certain doses, however, this has not been clearly demonstrated in controlled studies.

In summary, there is no published evidence to-date assessing the effects of cannabinoid therapies in individuals with clinician-diagnosed insomnia disorder. Future studies should use validated objective measures to assess the therapeutic impact of pharmaceutical-grade cannabinoid therapies in individuals with clinician-diagnosed insomnia in both the short- and long-term. Four pre-registered randomised placebo-controlled trials (ranging from one night to 9-wk treatment periods) are currently underway administering either CBD alone [72] or proprietary combinations of CBD, THC and CBN [69–71] in individuals with chronic insomnia (see Table S1). Two studies will use objective primary outcome measures (overnight polysomnography to assess various sleep metrics such as total sleep time and wake after sleep onset) [69,70]. The other two studies will use the Insomnia Severity Index (ISI) [71,72] with one study also co-administering an additional standardised self-report questionnaire [72]. One of these studies, a 2-wk Phase Ib/IIa RCT of a proprietary combination of THC, CBD, and CBN ('ZLT-101') [71], recently announced top line findings in a press release, recruiting 23 of its intended 30 participant target [96]. ISI scores significantly decreased from 18.0 ± 3.7 at baseline to 12.9 ± 5.3 at two weeks post-treatment. Dry mouth, dizziness, and headache were the most common adverse events, with no serious adverse events reported. These new clinical trials represent a useful step in advancing our understanding of the potential therapeutic effects of cannabinoids in insomnia disorder.

### *Do cannabinoids improve sleep-related outcomes in PTSD-related nightmares?*

There is accumulating evidence that the synthetic THC analogue nabilone may be effective in the management of nightmares among individuals with PTSD. In both an RCT and an open label study, nabilone (0.5 mg/d up to a maximum of 3 mg/d) significantly reduced the frequency of nightmares. Mild adverse effects were reported among 50% of patients, the most common being dry mouth, headache and dizziness. The small sample size in the RCT and open-label design of the study by Fraser et al. [74] are notable limitations and further well-designed trials with larger, more diverse clinical populations (i.e., inclusion of females and individuals with non-trauma-related nightmare disorders), along with longer-term follow-up, are needed to consolidate these findings. While the limited available evidence indicates that nabilone reduces PTSD-related nightmares, the long-term safety of $CB_1$ receptor agonists in this population is unclear, particularly given their complex comorbidities and increased risk of substance abuse.

### *Do cannabinoids improve sleep-related outcomes in REM sleep behaviour disorder?*

No RCTs assessing the effects of cannabinoid therapies in REM sleep behaviour disorder (RBD) in Parkinson's disease were identified. In a subset of patients with Parkinson's disease and RBD, a low-to-moderate dose of CBD resulted in a rapid and substantial reduction in the frequency of RBD-related events with nil adverse events reported [76]. This clearly requires further placebo-controlled investigation to identify potentially more effective and safer therapies for patients with this neurodegenerative disease.

### *Do cannabinoids improve sleep-related movement outcomes in restless legs syndrome?*

The case series of patients with treatment-resistant RLS involved spontaneous self-report to their clinical team of an instant and complete reduction in RLS symptoms with illicit cannabis products (including one patient using sublingual CBD). These observations are promising and warrant further investigation using a RCT design. This is particularly important given that standard treatment with dopaminergic agents is often associated with severe side effects such as augmentation, a worsening of RLS symptoms after starting dopaminergic medication [97] or dopamine agonist-related impulse control [98], limiting their long-term usefulness. Despite the promising patient self-reports, there is no available evidence from studies using prospective study design that would warrant clinical use of cannabinoids for RLS at present.

*Do cannabinoids improve sleep/wake-related outcomes in narcolepsy?*

A similarly difficult-to-treat disorder is narcolepsy, with the characteristic symptom of excessive daytime somnolence. While no clinical studies administering cannabinoid therapies were identified, a recent preclinical study showed that peripheral injection of CBD partially blocked excessive sleepiness in hypocretin-deficient rats, an animal model of narcolepsy [73]. This adds to a larger body of existing preclinical work from this group describing the potential wakefulness-promoting properties of CBD [99–101]. Indeed, a recent study indicated that CBD (i.e., 30 mg/kg *i.p.*) enhances alertness, and decreases slow wave sleep and REM sleep during the 'lights-on' period in rats [102]. These effects were associated with increases in neuronal activation of lateral hypothalamus and dorsal raphe nuclei (areas implicated in alertness control) and elevated extracellular dopamine concentrations [99,100], consistent with the well-documented role for dopamine in mediating wakefulness and arousal [103]. Given the favourable safety profile of CBD in humans, this initial evidence provides impetus to translate the findings into a properly designed RCT of CBD as an adjunctive treatment in individuals with excessive daytime sleepiness such as in patients with narcolepsy, OSA, and idiopathic hypersomnolence.

*Safety considerations*

The short- and long-term safety risks of cannabinoid therapies for individuals with sleep disorders are still being determined. Although THC displays minimal toxicity and lethality [83], moderate doses of THC (>10 mg) in naïve or occasional cannabis users can produce significant intoxication and/or impair cognitive performance (e.g., reaction time tasks) [68,104]. THC can also impair driving performance [105,106]. While the majority of clinical studies identified in the current review administered the cannabinoid treatment prior to bedtime (acute impairment was less of a concern), residual next-day effects of cannabinoid treatment on cognition, alertness, and driving performance should also be explored for safety. For instance, somnolence was the most common side-effect of dronabinol in the OSA trials. However, Carley et al. (2018) reported that participants receiving 10 mg/d dronabinol showed significantly decreased self-reported daytime sleepiness relative to baseline as measured on the Epworth Sleepiness Scale at 6-weeks [56]. Nonetheless, in places where cannabis products are legally accessible, use of THC-containing products for sleep disorders and the potential adverse events (e.g., daytime sleepiness) must be carefully considered and managed, particularly when unregulated products are being accessed.

CBD is non-intoxicating and has shown to be safe and well-tolerated in humans [107] – even at very high doses (e.g., 1500 mg twice daily for six days or as an acute dose of 6000 mg) [94]. No evidence of a withdrawal syndrome was evident following abrupt cessation of 4-wk treatment with 750 mg CBD twice daily in healthy volunteers [108]. THC and CBD are potent substrates and inhibitors of the cytochrome P450 enzymatic pathways which is involved in the biotransformation of many commonly prescribed medications [109]. Potential drug–drug interactions with cannabinoids are theoretically possible, as now shown between CBD and the anticonvulsant drug, clobazam, in children with severe epilepsy [92]. Few specific directives can be made at this stage due to the limited data on drug–drug interactions with CBD and THC, therefore, healthcare professionals should familiarise themselves with potential drug–drug interactions relevant to the patient's medication history and hepatic function [109,110]. Finally, the comparative safety and efficacy of cannabinoid medications relative to conventional treatment approaches is also a worthy area of investigation.

*Strengths and limitations*

This is the first systematic review focused specifically on cannabinoid therapies for sleep disorders that covers both the preclinical and clinical literature. This systematic review has several limitations. Firstly, only English-language articles were included. Second, despite our systematic approach, we cannot be completely certain that all relevant articles were retrieved via our literature search. Finally, most of the included clinical studies had small sample sizes and poor methodological quality including most studies with a high-risk of bias, limiting the strength of the conclusions that can be drawn from this review.

## Conclusion

At present, there is limited evidence to support the clinical use of cannabinoid therapies for the treatment of any sleep disorder given the dearth of published research and the moderate-to-high risk of bias identified within the majority of clinical and preclinical studies completed to-date. Nonetheless, there are promising signs in a number of therapeutic applications that warrant additional study and there is a clear need for intensification of high-quality research into the safety and efficacy of cannabinoid therapies for treating sleep disorders. Research should utilize well-defined cannabinoid products, validated assessments, and include measures of next-day function (i.e., cognition and driving performance). Additional scientific endeavour is required to define the mechanisms through which the endocannabinoid system affects sleep and sleep-related physiology and the pharmacological actions of various cannabinoid agents in relation to sleep. Currently ongoing clinical trials of cannabinoids in obstructive sleep apnea and insomnia are a positive step to a better understanding of the role of cannabinoid therapies in the treatment of sleep disorders.

**Practice points**

1) Individuals who use medicinal cannabis often do so to treat or manage sleep disorders such as insomnia, with many self-reporting that is highly effective in managing their symptoms.
2) Our systematic review deemed the available clinical and preclinical evidence to have a moderate-to-high risk of bias precluding any definitive conclusions regarding their therapeutic efficacy of cannabinoids in sleep disorders.
3) Promising preliminary evidence from preclinical and clinical studies provide the rationale for future randomised, controlled trials of cannabinoid therapies in individuals with sleep apnea, insomnia, post-traumatic stress disorder-related nightmares, REM sleep behaviour disorder, restless legs syndrome, and narcolepsy.
4) The safety profile of acute and chronic treatment with cannabinoids in sleep disorders is not yet well understood.
5) In places where cannabis products are legally accessible, use of THC-containing products for sleep disorders and the potential adverse effects on next-day function such as driving must be carefully considered and managed, particularly when unregulated products are being used.

**Research agenda**

To further examine the therapeutic utility of cannabinoid therapies on sleep disorders, future research should:

1) utilise validated objective and subjective measures of sleep-related outcomes to assess therapeutic efficacy of cannabinoids;
2) utilise robustly designed randomised, controlled trial designs, employing properly powered sample sizes with an adequate comparator (placebo and active treatment, where available);
3) consider the ecological validity of administering cannabinoids as an adjunctive treatment as opposed to a stand-alone treatment given the potential implications of drug−drug interactions on safety;
4) explore dose-dependent effects of THC in order to identify the optimal dose that confers clinical efficacy without causing next-day impairment such as drowsiness;
5) further explore the opposing effects of CBD on the sleep/wake cycle and to prioritise research on CBD given its non-intoxicating properties and nil potential for abuse or dependence.

## Conflicts of interest

RRG and NSM have received discounted investigational products for an unrelated clinical trial from Neurim Pharmaceuticals Inc. RRG and NSM have also received investigational product and matched placebo from Teva Pharmaceutical in unrelated clinical trials. ISM is a consultant for Kinoxis Therapeutics, and is an inventor on several patents relating to novel cannabinoid therapeutics. RV has received income as a consultant or advisory board member from Zynerba Pharmaceuticals, Canopy Health Innovations Inc., and FSD Pharma. The other authors have no conflicts of interest to disclose.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2020.101339.

## References

[1] Buxton OM, Broussard JL, Zahl AK, Hall M. Effects of sleep deficiency on hormones, cytokines, and metabolism. Impact of sleep and sleep disturbances on obesity and cancer. Springer; 2014. p. 25−50.
[2] Murawski B, Wade L, Plotnikoff RC, Lubans DR, Duncan MJ. A systematic review and meta-analysis of cognitive and behavioral interventions to improve sleep health in adults without sleep disorders. Sleep Med Rev 2018;40:160−9.
[3] Liu Y. Prevalence of healthy sleep duration among adults—United States, 2014, vol. 65. Morbidity and Mortality Weekly Report; 2016.
[4] Hillman D, Mitchell S, Streatfeild J, Burns C, Bruck D, Pezzullo L. The economic cost of inadequate sleep. Sleep 2018;41(8):zsy083.
[5] Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. J Affect Disord 2011;135(1−3):10−9.
[6] Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. Sleep Med Rev 2009;13(6):437−44.
[7] Bertisch SM, Pollock BD, Mittleman MA, Buysse DJ, Bazzano LA, Gottlieb DJ, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: sleep Heart Health Study. Sleep 2018;41(6):zsy047.
[8] Golbin JM, Somers VK, Caples SM. Obstructive sleep apnea, cardiovascular disease, and pulmonary hypertension. Proc Am Thorac Soc 2008;5(2):200−6.
[9] Buratti L, Luzzi S, Petrelli C, Baldinelli S, Viticchi G, Provinciali L, et al. Obstructive sleep apnea syndrome: an emerging risk factor for dementia. CNS Neurol Disord - Drug Targets 2016;15(6):678−82.
[10] Hung C-M, Li Y-C, Chen H-J, Lu K, Liang C-L, Liliang P-C, et al. Risk of dementia in patients with primary insomnia: a nationwide population-based case-control study. BMC Psychiatr 2018;18(1):38.
[11] Kraus SS, Rabin LA. Sleep America: managing the crisis of adult chronic insomnia and associated conditions. J Affect Disord 2012;138(3):192−212.
[12] Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M, et al. Cannabis sativa: a comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol 2018;227:300−15.
[13] Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. J Psychoact Drugs 2013;45(3):199−210.
[14] Lintzeris N, Driels J, Elias N, Arnold JC, McGregor IS, Allsop DJ. Medicinal cannabis in Australia, 2016: the cannabis as medicine survey (CAMS-16). Med J Aust 2018;209(5):211−6.
[15] Pledger MJ, Martin G, Cumming J. New Zealand Health Survey 2012/13: characteristics of medicinal cannabis users. N Z Med J 2016;129(1433):29.
[16] Choi S, Huang BC, Gamaldo CE. Therapeutic uses of cannabis on sleep disorders and related conditions. J Clin Neurophysiol 2020;37(1):39−49.
[17] Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov 2004;3(9):771.
[18] Pava MJ, Makriyannis A, Lovinger DM. Endocannabinoid signaling regulates sleep stability. PloS One 2016;11(3):e0152473.
[19] Hanlon EC, Tasali E, Leproult R, Stuhr KL, Doncheck E, De Wit H, et al. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. Sleep 2016;39(3):653−64.
[20] Vaughn LK, Denning G, Stuhr KL, De Wit H, Hill MN, Hillard CJ. Endocannabinoid signalling: has it got rhythm? Br J Pharmacol 2010;160(3):530−43.
[21] Hanlon EC. Impact of circadian rhythmicity and sleep restriction on circulating endocannabinoid (eCB) N-arachidonoylethanolamine (anandamide). Psychoneuroendocrinology 2020;111:104471.
[22] Hanlon EC, Tasali E, Leproult R, Stuhr K, Doncheck E, De Wit H, et al. Circadian rhythm of circulating levels of the endocannabinoid 2-arachidonoylglycerol. J Clin Endocrinol Metabol 2015;100(1):220−6.
[23] Wyatt RM, Fraser I, Welty N, Lord B, Wennerholm M, Sutton S, et al. Pharmacologic characterization of JNJ-42226314, [1-(4-Fluorophenyl)indol-5-yl]-[3-[4-(thiazole-2-carbonyl)piperazin-1-yl]azetidin -1-yl]methanone, a reversible, selective, and potent monoacylglycerol lipase inhibitor. J Pharmacol Exp Therapeut 2020;372(3):339−53.
[24] D'Souza DC, Cortes-Briones J, Creatura G, Bluez G, Thurnauer H, Deaso E, et al. Efficacy and safety of a fatty acid amide hydrolase inhibitor (PF-04457845) in the treatment of cannabis withdrawal and dependence in men: a double-blind, placebo-controlled, parallel group, phase 2a single-site randomised controlled trial. The Lancet Psychiatry 2019;6(1):35−45.
[25] Murillo-Rodriguez E, Blanco-Centurion C, Sanchez C, Daniele P, Shiromani PJ. Anandamide enhances extracellular levels of adenosine and induces sleep: an in vivo microdialysis study. Sleep 2003;26(8):943−7.
[26] Mechoulam R, Fride E, Hanu L, Sheskin T, Bisogno T, Di Marzo V, et al. Anandamide may mediate sleep induction. Nature 1997;389(6646):25−6.
[27] Murillo-Rodrıguez E, Sanchez-Alavez M, Navarro L, Martınez-Gonzalez D, Drucker-Colın R, Prospero-Garcıa O. Anandamide modulates sleep and memory in rats. Brain Res 1998;812(1−2):270−4.
[28] Murillo-Rodríguez E, Cabeza R, Méndez-Díaz M, Navarro L, Prospéro-García O. Anandamide-induced sleep is blocked by SR141716A, a CB1 receptor antagonist and by U73122, a phospholipase C inhibitor. Neuroreport 2001;12(10):2131−6.
[29] Després J-P, Golay A, Sjöström L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005;353(20):2121−34.
[30] Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, Group R-NAS. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North

America: a randomized controlled trial. J Am Med Assoc 2006;295(7):761–75.
[31] Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, Group R-DS. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006;368(9548):1660–72.
[32] Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S, Group R-ES. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005;365(9468):1389–97.
[33] Murillo-Rodríguez E. The role of the CB1 receptor in the regulation of sleep. Prog Neuro Psychopharmacol Biol Psychiatr 2008;32(6):1420–7.
[34] Tham M, Yilmaz O, Alaverdashvili M, Kelly ME, Denovan-Wright EM, Laprairie RB. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. Br J Pharmacol 2019;176(10):1455–69.
[35] McPartland JM, Duncan M, Di Marzo V, Pertwee RG. Are cannabidiol and Δ9-tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol 2015;172(3):737–53.
[36] Elmes MW, Kaczocha M, Berger WT, Leung K, Ralph BP, Wang L, et al. Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). J Biol Chem. 2015;290(14):8711–21.
[37] Abrams DI. The therapeutic effects of cannabis and cannabinoids: an update from the national academies of sciences, engineering and medicine report. Eur J Intern Med 2018;48:7–11.
[38] Babson KA, Sottile J, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. Curr Psychiatr Rep 2017;19(4):23.
[39] Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. Sleep Med Rev 2014;18(6):477–87.
[40] Kuhathasan N, Dufort A, MacKillop J, Gottschalk R, Minuzzi L, Frey BN. The use of cannabinoids for sleep: a critical review on clinical trials. Exp Clin Psychopharmacol 2019;27(4):383–401.
[41] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2010;151(4):264–9.
[42] Hicks RA, Moore JD, Hayes C, Phillips N, Hawkins J. REM sleep deprivation increases aggressiveness in male rats. Physiol Behav 1979;22(6):1097–100.
[43] Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14(1):43.
[44] Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[45] Megelin T, Ghorayeb I. Cannabis for restless legs syndrome: a report of six patients. Sleep Med 2017;36:182.
[46] Calik MW, Carley DW. Cannabinoid type 1 and type 2 receptor antagonists prevent attenuation of serotonin-induced reflex apneas by dronabinol in Sprague-Dawley rats. PloS One 2014;9(10):e111412.
[47] Calik MW, Carley DW. Intracerebroventricular injections of dronabinol, a cannabinoid receptor agonist, does not attenuate serotonin-induced apnea in Sprague-Dawley rats. J Negat Results Biomed 2016;15(1):8.
[48] Calik MW, Radulovacki M, Carley DW. Intranodose ganglion injections of dronabinol attenuate serotonin-induced apnea in Sprague-Dawley rat. Respir Physiol Neurobiol 2014;190:20–4.
[49] Topchiy I, Waxman J, Radulovacki M, Carley D, editors. Effects of dronabinol on vagally mediated respiratory reflexes and upper airway motor output. Sleep; 2012 (Vol. 35, pp. A55-A55). One Westbrook Corporate Ctr, Ste 920, Westchester, IL 60154 USA: Amer Acad Sleep Medicine.
[50] Calik MW, Carley DW. Effects of cannabinoid agonists and antagonists on sleep and breathing in Sprague-Dawley rats. Sleep 2017;40(9).
[51] Carley DW, Pavlovic S, Janelidze M, Radulovacki M. Functional role for cannabinoids in respiratory stability during sleep. Sleep 2002;25(4):388–95.
[52] Topchiy I, Petukhov P, Petukhova V, Hickok J, Thatcher G, Carley DW. Peripheral cannabinoid receptor agonists chromenopyrazole 13a and HU-308 attenuate sleep apneas in rats. Sleep 2015;38.
[53] Calik MW, Carley DW. DMSO potentiates the suppressive effect of dronabinol, a cannabinoid, on sleep apnea and REM sleep. bioRxiv 2019:769463.
[54] Carley DW, Topchiy I. Activation of nodose ganglion cannabinoid receptors potentiates upper airway muscle activation. Barcelona: 3rd Sleep and Breathing Conference; 2015.
[55] Prasad B, Radulovacki MG, Carley DW. Proof of concept trial of dronabinol in obstructive sleep apnea. Front Psychiatr 2013;4:1.
[56] Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, Abbott SM, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: effects of dronabinol in obstructive sleep apnea. Sleep 2018;41(1).
[57] ClinicalTrialsgov. A study to examine the efficacy of a therapeutic THX-110 for obstructive sleep apnea. 2018 [updated 22 Nov 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03646552.
[58] ANZCTR. The effects of novel medicinal cannabis formulation IHL-42X on apnoea hypopnea index in adults with suspected or diagnosed mild to moderate obstructive sleep apnoea [updated 22 Nov 2019. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=378058&isReview=true; 2019.
[59] Pérez-Morales M, Fajardo-Valdez A, Méndez-Díaz M, Ruiz-Contreras AE, Prospéro-García O. 2-Arachidonoylglycerol into the lateral hypothalamus improves reduced sleep in adult rats subjected to maternal separation. Neuroreport 2014;25(18):1437–41.
[60] Prieto NMR, López AR, Morales MP, Pech O, Méndez-Díaz M, Contreras AER, et al. Oleamide restores sleep in adult rats that were subjected to maternal separation. Pharmacol Biochem Behav 2012;103(2):308–12.
[61] Navarro L, Martínez-Vargas M, Murillo-Rodríguez E, Landa A, Méndez-Díaz M, Prospéro-García O. Potential role of the cannabinoid receptor CB1 in rapid eye movement sleep rebound. Neuroscience 2003;120(3):855–9.
[62] Hsiao Y-T, Yi P-L, Li C-L, Chang F-C. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology 2012;62(1):373–84.
[63] Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. J Clin Pharmacol 1981;21(S1). 417S-27S.
[64] Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in anxiety and sleep: a large case series. Perm J 2019;23.
[65] Shannon S, Opila-Lehman J. Effectiveness of cannabidiol oil for pediatric anxiety and insomnia as part of posttraumatic stress disorder: a case report. Perm J 2016;20(4):108.
[66] Ware MA, Fitzcharles M-A, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg 2010;110(2):604–10.
[67] Zalai D, Chung S, Hussain N, Shapiro C. Does cannabinoid really improve sleep? Testing the sleep effects of nabilone in chronic pain patients: a placebo-controlled, randomized, pilot study. Psychother Psychosom 2015;84.
[68] Cousens K, DiMascio A. (−) δ 9 THC as an hypnotic. Psychopharmacologia 1973;33(4):355–64.
[69] ANZCTR. A single-dose, double-blind, placebo-controlled, randomised, crossover study of an oral cannabis-based medicine (ETC120) on sleep, cognition, and next-day function in adults with chronic insomnia disorder Australian New Zealand Clinical Trials Registry. Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=377330; 2019.
[70] ClinicalTrialsgov. Investigation of the efficacy and safety of CHI-921 in insomnia. 2019. Available from: https://clinicaltrials.gov/ct2/show/NCT03984604.
[71] ANZCTR. A trial to evaluate an oral medicinal cannabis extract compared with placebo for the treatment of insomnia Australian New Zealand Clinical Trials Registry. 2019. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373959.
[72] ANZCTR. Cannabidiol (CBD) treatment for insomnia: a three-week randomised controlled pilot trial with a placebo run-in period (CBD-INS) Australian New Zealand Clinical Trials Registry. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379003&isReview=true; 2020.
[73] Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Morales-Lara D, Mechoulam R, Drucker-Colín R. Cannabidiol partially blocks the sleepiness in hypocretin-deficient rats. Preliminary data. CNS & Neurological Disorders Drug Targets 2019;18(9):705–12.
[74] Fraser GA. The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). CNS Neurosci Ther 2009;15(1):84–8.
[75] Jetly R, Heber A, Fraser G, Boisvert D. The efficacy of nabilone, a synthetic cannabinoid, in the treatment of PTSD-associated nightmares: a preliminary randomized, double-blind, placebo-controlled cross-over design study. Psychoneuroendocrinology 2015;51:585–8.
[76] Chagas MH, Eckeli A, Zuardi AW, Pena-Pereira MA, Sobreira-Neto MA, Sobreira E, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. J Clin Pharm Therapeut 2014;39(5):564–6.
[77] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the international committee of medical journal. Circulation 2005;111(10):1337–8.
[78] Carley DW, Radulovacki M. Pharmacology of vagal afferent influences on disordered breathing during sleep. Respir Physiol Neurobiol 2008;164(1–2):197–203.
[79] ClinicalTrialsgov. Safety and efficacy study of dronabinol to treat obstructive sleep apnea (PACE). Available from: https://clinicaltrials.gov/ct2/show/results/NCT01755091?term=PACE; 2017.
[80] Ramar K, Rosen IM, Kirsch DB, Chervin RD, Carden KA, Aurora RN, et al. Medical cannabis and the treatment of obstructive sleep apnea: an American Academy of Sleep Medicine position statement. J Clin Sleep Med 2018;14(4):679–81.
[81] Zinchuk AV, Gentry MJ, Concato J, Yaggi HK. Phenotypes in obstructive sleep apnea: a definition, examples and evolution of approaches. Sleep Med Rev 2017;35:113–23.
[82] Therapix biosciences announces positive topline results from phase IIa clinical trial of THX-110 for obstructive sleep apnea program therapix biosciences. Available from: http://therapix.investorroom.com/2019-11-13-Therapix-Biosciences-Announces-Positive-Topline-Results-From-Phase-IIa-Clinical-Trial-of-THX-110-for-Obstructive-Sleep-Apnea-Program; 2019.

[83] Organisation Wh. WHO expert committee on drug dependence: critical review - delta-9-tetrahydrocannabinol 2018. Available from: https://www.who.int/medicines/access/controlled-substances/THCv1.pdf?ua=1; 25 Nov 2019.
[84] Gates P, Albertella L, Copeland J. Cannabis withdrawal and sleep: a systematic review of human studies. Subst Abuse 2016;37(1):255–69.
[85] Vandrey R, Smith MT, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. Drug Alcohol Depend 2011;117(1):38–44.
[86] Babson KA, Boden MT, Harris AH, Stickle TR, Bonn-Miller MO. Poor sleep quality as a risk factor for lapse following a cannabis quit attempt. J Subst Abuse Treat 2013;44(4):438–43.
[87] Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. Drug Alcohol Depend 2007;86(1):22–9.
[88] Vandrey R, Stitzer ML, Mintzer MZ, Huestis MA, Murray JA, Lee D. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. Drug Alcohol Depend 2013;128(1–2):64–70.
[89] Russo EB, Guy GW, Robson PJ. Cannabis, pain, and sleep: lessons from therapeutic clinical trials of Sativex®, a cannabis-based medicine. Chem Biodivers 2007;4(8):1729–43.
[90] Fogaça MV, Reis F, Campos A, Guimarães FS. Effects of intra-prelimbic prefrontal cortex injection of cannabidiol on anxiety-like behavior: involvement of 5HT1A receptors and previous stressful experience. Eur Neuropsychopharmacol 2014;24(3):410–9.
[91] Lutz B, Marsicano G, Maldonado R, Hillard CJ. The endocannabinoid system in guarding against fear, anxiety and stress. Nat Rev Neurosci 2015;16(12):705.
[92] Geffrey AL, Pollack SF, Bruno PL, Thiele EA. Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy. Epilepsia 2015;56(8):1246–51.
[93] Gaston TE, Bebin EM, Cutter GR, Liu Y, Szaflarski JP, Program UC. Interactions between cannabidiol and commonly used antiepileptic drugs. Epilepsia 2017;58(9):1586–92.
[94] Taylor L, Gidal B, Blakey G, Tayo B, Morrison G. A phase I, randomized, double-blind, placebo-controlled, single ascending dose, multiple dose, and food effect trial of the safety, tolerability and pharmacokinetics of highly purified cannabidiol in healthy subjects. CNS Drugs 2018;32(11):1053–67.
[95] Spindle TR, Cone EJ, Goffi E, Weerts EM, Mitchell JM, Winecker RE, et al. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug and Alcohol Dependence 2020;211:107937.
[96] ProactiveInvestors. Zelira Therapeutics achieves primary endpoints of medicinal cannabis trial for insomnia. 2020. Available from: https://www.proactiveinvestors.com.au/companies/news/913189/zelira-therapeutics-achieves-primary-endpoints-of-medicinal-cannabis-trial-for-insomnia-913189.html.
[97] Comella CL. Restless legs syndrome: treatment with dopaminergic agents. Neurology 2002;58(suppl 1):S87–92.
[98] Cornelius JR, Tippmann-Peikert M, Slocumb NL, Frerichs CF, Silber MH. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep 2010;33(1):81–7.
[99] Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. FEBS (Fed Eur Biochem Soc) Lett 2006;580(18):4337–45.
[100] Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R. The nonpsychoactive Cannabis constituent cannabidiol is a wake-inducing agent. Behav Neurosci 2008;122(6):1378.
[101] Murillo-Rodríguez E, Sarro-Ramírez A, Sánchez D, Mijangos-Moreno S, Tejeda-Padrón A, Poot-Aké A, et al. Potential effects of cannabidiol as a wake-promoting agent. Curr Neuropharmacol 2014;12(3):269–72.
[102] Murillo-Rodríguez E, Di Marzo V, Machado S, Rocha NB, Veras AB, Neto GA, et al. Role of N-Arachidonoyl-Serotonin (AA-5-HT) in sleep-wake cycle architecture, sleep homeostasis, and neurotransmitters regulation. Front Mol Neurosci 2017;10:152.
[103] Wisor JP. Dopamine and wakefulness: pharmacology, genetics, and circuitry. In: Handbook of experimental pharmacology. Springer International Publishing; 2018 [Internet].
[104] Vandrey R, Herrmann ES, Mitchell JM, Bigelow GE, Flegel R, LoDico C, et al. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. J Anal Toxicol 2017;41(2):83–99.
[105] Rogeberg O, Elvik R. The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction 2016;111(8):1348–59.
[106] Arkell TR, Lintzeris N, Kevin RC, Ramaekers JG, Vandrey R, Irwin C, et al. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. Psychopharmacology 2019;236(9):2713–24.
[107] Machado Bergamaschi M, Helena Costa Queiroz R, Waldo Zuardi A, Crippa AS. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf 2011;6(4):237–49.
[108] Taylor L, Crockett J, Tayo B, Checketts D, Sommerville K. Abrupt withdrawal of cannabidiol (CBD): a randomized trial. Epilepsy Behav 2020;104:106938.
[109] Rong C, Carmona NE, Lee YL, Ragguett R-M, Pan Z, Rosenblat JD, et al. Drug-drug interactions as a result of co-administering Δ9-THC and CBD with other psychotropic agents. Expet Opin Drug Saf 2018;17(1):51–4.
[110] Taylor L, Crockett J, Tayo B, Morrison G. A phase 1, open-label, parallel-group, single-dose trial of the pharmacokinetics and safety of cannabidiol (CBD) in subjects with mild to severe hepatic impairment. J Clin Pharmacol 2019;59(8):1110–9.