Sleep Medicine Reviews 18 (2014) 477–487

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The effects of cannabinoid administration on sleep: a systematic review of human studies

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ARTICLE INFO

Article history:
Received 2 December 2013
Received in revised form
27 February 2014
Accepted 27 February 2014
Available online 7 March 2014

Keywords:
Cannabis
Marijuana
Sleep
Insomnia

SUMMARY

This paper reviews the literature regarding the effects of cannabinoid administration on sleep in humans. A literature search using a set of cannabinoid and sleep-related terms was conducted across eight electronic databases. Human studies that involved the administration of cannabinoids and at least one quantitative sleep-related measure were included. Review papers, opinion pieces, letters or editorials, case studies (final $N < 7$), published abstracts, posters, and non-English papers were excluded. Thirty-nine publications were included in the review. Findings were mixed and showed various effects of cannabinoid administration on several aspects of sleep. Methodological issues in the majority of studies to date, however, preclude any definitive conclusion.

Introduction

Cannabis is the most frequently used illicit drug around the globe and is estimated to be used by approximately 4.5% of the world's population – a prevalence which is currently increasing [1]. Cannabis use is especially prevalent among younger age groups compared to older age groups who may instead begin to embrace new roles and responsibilities [2]. This pattern of use is especially concerning as it is well established that early onset to cannabis use and frequent use are significant predictors of a range of health problems including mental health concerns [3] and reduced educational outcomes [4], as well as respiratory complaints [5] and cannabis use disorder [6]. In contrast, through the isolation of the two main active components of cannabis – the 'cannabinoids' tetrahydrocannabidiol (THC) and cannabidiol (CBD) among at least 60 others [7] – cannabis-based medicines (CBM) have been developed which have been used to treat a range of health problems, most notably those involving pain and muscle spasm [8].

As with any psychoactive substance there are many different motivations to use cannabis, however; it is typically used for enjoyment or fun and for promoting social cohesion [9]. A less well understood motive is use to assist with sleep problems. This motive is not uncommon and has been reported by one quarter of a large sample of cannabis using high school graduates [9]. Indeed, intoxication from cannabis use is most commonly described to involve a feeling of relaxation [10]. Interestingly, there have been few studies specifically focussed on the relationship between cannabis use and sleep. This may be surprising given the health importance of sleep. That is, insomnia, the most common sleep disorder [11], is a known risk factor for multiple impairments across quality of life domains (most notably depression and anxiety) [12], which ultimately leads to an increase in the utilisation of health care resources amongst sufferers [13].

Early investigations of cannabis use and sleep gained momentum in the 1970s. Many of these studies used objective measures (polysomnograph technology) to investigate sleep and have been reviewed by Schierenbeck and colleagues [14]. These authors noted that a reduction to rapid eye movement (REM) sleep and REM density was the most consistent finding, however; their interpretation of findings was not considered reliable due to the small sample sizes of the studies reviewed. More recent understanding has come from medicinal cannabis use trials which include a secondary measure of sleep as a gauge of positive treatment outcomes (with a primary measure relating specifically to the illness under study). A subsection of these trials involving clinical studies of Sativex (a THC and CBD based oral spray) have recently been reviewed by Russo and colleagues [15]. These authors concluded that the use of Sativex for the treatment of spasticity and

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http://dx.doi.org/10.1016/j.smrv.2014.02.005
1087-0792/

Abbreviations

AIDS	acquired immunodeficiency syndrome
ALS	amyotrophic lateral sclerosis
CBD	cannabidiol
CBM	cannabis-based medicine
EEG	electroencephalogram
HIV	human immunodeficiency virus
MS	multiple sclerosis
NREM	non-rapid eye movement
PTSD	post-traumatic stress disorder
REM	rapid eye movement
S1–S4	stage one to stage four sleep
SWS	slow wave sleep
THC	delta-9-tetrahydrocannabinol

pain was likely to improve subjective sleep parameters but was unlikely to result in a significant change in sleep architecture.

Unfortunately, the current understanding of the effects of cannabis use on sleep is clouded by mixed findings between studies that typically lack statistical control for confounding factors. Notably, medicinal cannabis use has recently been described to alleviate sleep problems by medicinal users [16–18], while cannabis use is a reported risk factor for sleep problems in the community [19–22]. Moreover, sleeping problems are among the most commonly experienced withdrawal symptoms when abstaining from cannabis use [23,24]. Despite this, research designed to develop a better understanding of the effects of cannabis use on sleep in humans is rarely conducted.

Recognising the effects of cannabis use on sleep is important for both the cannabis user and for health providers tasked with assisting behavioural change. If demonstrated to be harmful, this knowledge may act as a motivational tool for those deciding whether or not to use cannabis. In addition, such evidence may assist clinicians to reduce the risk of relapse to cannabis use among their clients by assessing and addressing sleep problems as necessary. In order to clarify the effects of cannabis on sleep, we conducted a systematic review of all papers which included human participants and an assessment of sleep following the administration of a measured cannabis dose. Unlike previous reviews, we include: 1) studies that used either objective or subjective measures of sleep; 2) studies that involved the administration of any cannabinoid or CBM; and 3) an assessment of the risk of bias present in each study. As participants in those trials of CBM suffered from illnesses that likely impact on their sleep, the associated articles are presented separately to isolate possible attribution bias.

Method

Literature search

English language studies on human participants were located through online search of eight electronic databases (Embase, CINAHL, Cochrane Library/EBM Reviews, Medline, and PsycINFO for published studies and Project Cork, DRUG, and PsycEXTRA for grey literature). The search strategy included the keywords "cannabinoid/s, or, tetrahydrocannabinol, or THC, or cannabis/marijuana" and "sleep, or sleep onset, or sleep apnea, or sleep treatment, or sleep wake cycle, or sleep deprivation, or rapid eye movement (REM) sleep, or non-rapid eye movement (NREM) sleep, or sleep disorder, or insomnia". In addition we attempted to contact primary investigators who had conducted studies including measures of both cannabis and sleep but did not describe the two in the results of their manuscript. Review papers, posters, qualitative articles, opinion pieces, letters or editorials, case reports (final $N < 7$), and published abstracts were excluded. For purposes of this review, only those papers involving the administration of cannabinoids or CBM were included while papers describing the prevalence of sleep problems among cannabis users or those on associations between use and sleep (41 studies), and papers describing cannabis withdrawal (44 studies) were excluded. This review included all papers current to the end of 2012 and did not exclude studies on the basis of methodological flaws.

Initial searching resulted in 2215 manuscripts being identified, which were independently reviewed by two research staff (PG and LA) in order to remove duplicates and articles meeting exclusion criteria. A consensus was reached and a total of 730 duplicates and 1446 articles meeting exclusion criteria were removed, leaving 39 relevant articles. These articles were either: 1) studies involving the administration of cannabis to recreational cannabis users or cannabis naïve individuals which included a measure of its effect on sleep (11 articles), or 2) clinical trials involving medicinal cannabis use for a health condition which included a measure of its effect on sleep (28 articles).

Article quality

In order to assess the risk of bias in each article, a custom assessment of article quality and risk of bias was purpose built following suggestions from the Cochrane Collaboration's Risk of Bias Assessment Tool [25], the Effective Practice and Organisation of Care Review Group Data Collection Checklist [26] and the assessments of risk of bias by Viswanathan and colleagues [27]. A ratio (reported as a percentage) was calculated to represent which of 38 different factors that the article had adequately addressed compared to the number left unaddressed. As such, a score of 100% was awarded when the article addressed all appropriate risks of bias adequately, while 50% was awarded when the article addressed an equal number of risks of bias compared to those left unaddressed.

Results

Non-medicinal cannabis use and sleep

A total of 11 studies investigated the impact of recreational cannabis use on sleep with a collective sample size of 203 participants (see Table 1). The overall quality of these studies was poor (range: 17–84%, average: 42.6%), meaning that a substantial risk of bias was introduced across the literature. This risk was most commonly due to a lack of control for confounding factors such as pre-existing sleep problems or participant gender and age. This is significant as the prevalence of insomnia increases with age and is greater among females [11]. Further, it is noteworthy that no study was conducted outside of the US and Canada. Moreover, meaningful comparisons between studies were limited as the employed measure of sleep and the cannabis dose and dosing duration all varied substantially. A total of six studies employed objective measures of sleep [electroencephalogram (EEG)] [28–33], although only one of these studies was conducted within the past decade [31]. These studies are summarised separately from the remaining studies which employed subjective measures of sleep.

There was little consistency in the results of the six studies with objective sleep measures. That is, slow wave sleep was described to increase in one study [28] (although this decreased by the eighth day of withdrawal), three studies reported a decrease [31–33], and one study showed no change [30]. REM sleep was reported to

Table 1
Articles relating to the effects of cannabis administration on sleep among non-medicinal cannabis users.

Authors, reference number	Quality rating (%)	Country of origin	Cannabis type administered	Cannabis dose and duration	Comparisons made (effectiveness of blinding)	Sleep measure	Experimental/statistical controls	Participant details[a] (total *N*)	Outcome
Babor et al. 1976 [34]	42.4	US	2% THC in a 1g joint	21 d with monitored access; typical use was 2.6 (0.9) joints/d, peaking at 5.7 (1.7) joints/d (heavy users)	Comparisons were made between participants and alcohol-only drinkers, and between light and heavy cannabis users (unclear blinding)	Hourly observations of time asleep as part of a Behaviour Inventory	Education, IQ, SES	100% male, all recent cannabis users ($n = 38$ [14 were heavy users + matched sample of alcohol-only $n = 11$])	Time asleep ⇧ compared to alcohol-only. On the day after consumption, time asleep ⇧ for heavy users compared to moderate users
Barratt et al. 1974 [28]	16.7	US	0.2 mg/kg of THC in each joint	10 d with 2 joints provided per day	Compared with drug naïve group (unclear blinding)	EEG measures	None shown	100% male, aged 21–26 y, ($n = 12$ [8 participants were administered cannabis])	Body movement ⇩ initially, then by day eight ⇧; S2 by day 10 ⇧; and SWS ⇧ initially then ⇩ by day eight; No effect on S1, REM or time asleep
Chait 1990 [36]	48.6	US	2.1% THC in a 1g joint	Four puffs of the joint twice per night for two nights	Comparisons made to placebo (unclear blinding)	Leeds sleep evaluation questionnaire	Substance use, psychiatric and physical health	75% male, aged 21 (18–26) y, all current cannabis users ($n = 12$)	Sleep latency ⇩; No effect on sleep quality, 'morningness' and awakenings
Chait & Perry 1994 [35]	54.1	US	3.6% THC in a 1g joint	Four puffs of the joint twice per night for two nights (repeated with and without 40 min of access to alcohol)	Compared with placebo, and alcohol + cannabis use (unclear blinding)	Leeds sleep evaluation questionnaire	Substance use, psychiatric and physical health	71.4% male, aged 24.5 (21–34) y, all current cannabis and alcohol users ($n = 18$)	Sleep latency ⇩, sleep quality ⇧ compared to placebo and alcohol + cannabis; no effect on 'morningness' and# of awakenings
Chait & Zacny 1992 [37]	30.6	US	Access to 10–15 mg of 2.3–3.6% THC in a joint or oral dose of 2.5–10 mg THC	Six to seven puffs on a joint or two capsules on two nights	Comparisons made to placebo (unclear blinding)	Leeds sleep evaluation questionnaire	None	73% male, aged 22 (18–31) y, recent cannabis users ($n = 33$ [10 received joints, 11 tablets and 12 neither])	No effect on sleep latency, quality, 'morningness' or awakenings
Cousens & DiMascio 1973 [38]	38.9	US	Oral dose of 10, 20 and 30 mg THC	Single dose of each over three experiment nights	Compared to placebo, (Double-blind)	Quarter-hourly visual observation of all sleep activity	Substance use, anxiety, psychosis	100% male, aged 21–40 y, all drug naïve, mild insomniacs ($n = 9$)	Sleep latency ⇩. No effect on night time awakenings and time awake
Hosko MJ et al. 1973 [29]	44.8	US	Oral dose of 200 mg/kg then 300 mg/kg THC	Both doses were administered over two experiment nights (four nights total) with each followed by five nights of placebo	Compared to placebo (Double-blind)	EEG measures	Substance use	100% male, aged 24–28 y, 71% were recent cannabis users ($n = 7$)	28.6% had SWS ⇧; 57.1% had an initial REM ⇧ then ⇩ (on high dose only and on orientation night – reported as no net drug effect). Time asleep, S1 and S2 time were similar
Karacan et al. 1976 [30]	52.8	Canada	Use as usual	Participants' usual use was an average of 9.2 joints per day; experimental period was for eight nights	Compared to drug naïve (unclear blinding)	EEG measures	Other substance use, daytime napping	50% were recent cannabis users, 50% were "matched controls", otherwise unclear ($n = 64$)	Sleep latency to S1, and REM time ⇧; time asleep, # of awakenings, and time in S1–S4 were similar

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Table 1 (*continued*)

Authors, reference number	Quality rating (%)	Country of origin	Cannabis type administered	Cannabis dose and duration	Comparisons made (effectiveness of blinding)	Sleep measure	Experimental/statistical controls	Participant details[a] (total *N*)	Outcome
Nicholson et al. 2004 [31]	84.4	UK	Four-way crossover trial with 15 mg THC, 5 mg THC with 5 mg CBD, 15 mg THC with 15 mg CBD oral spray, and placebo	Single dose across three experimental nights with fourth night on placebo	Compared to placebo (unclear blinding)	EEG measures	Substance use, family history of schizophrenia, personal history of psychiatric problems	50% male, aged 25.3 y on average, all recent cannabis users ($n = 8$)	S3 ⇩ on 5 mg and 15 mg THC/CBD, time awake ⇧ on 15 mg THC, sleep latency ⇩ and next day sleepiness ⇧ on 15 mg THC and 15 mg THC/CBD. No effect on time asleep, time in S1–S4, number of awakenings, and sleep efficiency
Pranikoff et al. 1973 [32]	32.4	US	Unclear dose, reported as use until "reaching a subjective high"	Two nights (data recorded on second night only), unclear quantity	Compared to drug naïve (no blinding)	EEG measures	Personality profile	100% male, aged 20–25 y, 50% recent cannabis smokers, 50% drug naive ($n = 20$)	S4 time ⇩; S2 ⇧. No effect on time asleep, S1, S3 and REM time, number of awakenings, sleep latency and sleep efficiency
Tassinari et al. 1999 [33]	22.9	Unclear	0.7–1.4 mg/kg of THC as oral dose	Single dose following one to two nights with no drug administration	Comparison made between the first one or two control nights and subsequent cannabis administration (unclear blinding)	EEG measures	Substance use	Aged 21–25 y, "drug naive university students" ($n = 9$)	S2 ⇧, SWS and REM ⇩. "Abnormal movements" ceased after cannabis use

CBD = cannabidiol, EEG = electroencephalogram, IQ = intelligence quotient, REM = rapid eye movement sleep, S1 = stage one sleep, S2 = stage two sleep, S1–S4 = stages one to four sleep time, SES = socio-economic status, SWS = slow wave sleep, THC = delta-9-tetrahydrocannabinol.

[a] For each article the participants' gender breakdown, age in y (expressed as the mean [standard deviation] when given), history of cannabis use, ethnicity, and other relevant demographic variables are provided subject to the detail published in the associated article.

increase in one study [30], decrease in a second study [33], while four studies showed no effect [28,29,31,32]. Stage two sleep was reported to increase in two studies [28,33], while four studies showed no effect [29–32]. Sleep latency was reported to increase in one study [30], decrease on a high THC dose in a second study [31], while two studies showed no effect [28,32] and two studies did not measure sleep latency [29,33]. A single study reported cessation of body movement during sleep following a single dose [33], while an another study showed an initial decrease throughout the first week of dosing followed by an increase in the number of movements [28], while four studies did not report on body movements [29–32]. In contrast, cannabis was not reported to significantly impact on overall sleep time or time spent in stage one sleep.

The most recent study was conducted in 2004 and was of the highest quality (84.4%) [31]. This study recruited four male and four female occasional cannabis users into a double-blind, placebo-controlled, crossover trial. Each participant received a single dose (administered using oral sprays one week apart) of 15 mg THC extract, 5 mg THC with 5 mg CBD extracts, 15 mg THC with 15 mg CBD extracts and placebo at 22:00 h, 30 min before 'lights out'. Other substance use (including caffeine) was kept to a minimum, although two participants were regular tobacco smokers. This study not only objectively investigated sleep using EEG immediately following drug administration, but also included a subjective measure of morning after sleepiness. The study found that the effects of 15 mg THC without the concomitant administration of CBD produced no statistically significant effects on sleep compared to placebo with the exception that morning after sleepiness increased significantly. In contrast, time spent in stage 3 sleep decreased, and duration of wakefulness increased significantly compared to the placebo for the 15 mg THC + CBD dose only (not the 5 mg dose). No significant morning after effect was observed for the 5 mg THC + CBD dose, however; the 15 mg THC + CBD dose was associated with significantly increased sleepiness. The authors summarised that "THC would appear to be a sedative compound, whereas CBD would appear to have some alerting properties" ([31] p310). In addition to the very small sample size (and resulting lack of statistical power) there were two main limitations to this study that should be considered. First, although the authors described the study to be double-blind, the fidelity of blinding methods were not confirmed in the study results. Second, the experimental procedures used allowed for the objective measurement of sleep on one night following administration of a single dose of cannabis and thus excluded investigation of longer term use.

A total of five studies [34–38] employed subjective measures of sleep, most commonly the Pittsburgh sleep quality index [39]. Across these studies, the most consistently reported impact of administering cannabis on sleep was a decrease to sleep latency (decreased in three studies [35,36,38], no effect shown in one study [37], and not measured in one study [34]). In contrast, no study reported a significant effect on number of night time sleep awakenings (investigated in four studies [35–38]) or daytime behaviour upon waking (investigated in three studies [35–37]) and there were mixed results regarding overall sleep time (in one study heavy cannabis users slept longer than moderate users on days following consumption and all cannabis users slept longer than alcohol-only users [34], however; no effect was reported in a second study [38]) and measures of sleep quality or satisfaction (increased in one study [35], while two studies did not find an effect [36,37] and two studies did not include this measure [34,38]).

A total of three studies included varying cannabis doses [34,37,38]. The majority of these studies reported no effect of dose (using subjective measures). That is, higher doses improved sleep in one study [34], while two studies showed no effect of dose [37,38].

Table 2
Articles relating to the effects of cannabis-based medicine administration on sleep.

Authors, reference number	Quality rating (%)	Country of origin	Dose/Duration	Comparisons made (effectiveness of blinding)	Sleep measure	Controls	Participant details[a] (Baseline/Final *N*)	Outcome
Nabilone								
Beaulieu et al 2006 [44]	61.1	Canada	Four doses of either 1 mg ($n = 11$) or 2 mg ($n = 9$) nabilone capsules on one experimental day	Compared with active drug (ketoprofen; $n = 11$) and placebo ($n = 10$) (unconfirmed double blind)	Numerical rating on quality of sleep	Unclear	20% male, typically aged over 44 y, all suffering pain ($n = 41/41$)	No significant difference on sleep quality across groups
Bestard et al. 2010 [46]	35.1	Canada	Flexible daily dose of self-administered nabilone capsules (1−3 mg) administered over six months	Comparison with active drug (gabapentin) and no-treatment control (no blinding)	Medical Outcomes Study sleep scale (reported as index score only) and Brief Pain Inventory (sleep interference item)	Age, gender, pain ratings	40.4% male, typically aged over 60 y, all suffering pain ($n = 249/180$)	Sleep problems and pain related sleep interference ⇩ at six months compared to no-treatment control. No significant difference between active treatments
Frank et al. 2008 [48]	48.6	UK	Escalating dose from 0.25 to 2 mg of nabilone over six weeks and 240 mg dihydrocodeine over six weeks (with a two week 'washout')	Compared with active drug -dihydrocodeine (unconfirmed double blind)	Number of hours slept and "details of sleep disruptions" kept in diary	Age, gender, pain ratings, substance abuse	52.1% male, all suffering pain ($n = 96/64$)	Results were reported in a table as "sleep" and no drug effects were found (dose effect was unclear)
Fraser 2009 [66]	20.0	US	Graduating doses of nabilone (0.5−6.0 mg) taken one hour before bed over an unclear period described to end upon "satisfactory results"	Compared with baseline data (no blinding)	Likert scale on "nightmare intensity" and hours of sleep	None described	43% male, aged 44 (9) y, all suffering PTSD ($n = 47/47$)	Results did not report on hours of sleep, 72% experienced cessation or lessening of nightmares (dose effect was unclear)
Toth et al. 2012 [51]	59.5	Canada	Flexible daily dose of 1 −4 mg nabilone (daily dose was 2.9 [1.1] mg on average) over five weeks or placebo	Compared to placebo (unclear blinding)	Medical Outcomes Study sleep scale	Age, substance use, physical health	45% male, aged 62.2 (9.3) y, 94% Caucasian, all suffering pain ($n = 26/25$)	Sleep index score showed improved sleep over placebo at weeks two, four and five (dose effect was unclear)
Ware MA et al. 2010 [67]	56.8	Canada	One capsule of nabilone (0.5 mg−1 mg) taken daily over two weeks and a 10 −20 mg capsule of amitriptyline taken daily over two weeks (with a two week washout period)	Compared to active drug (amitriptyline), (Double blind)	Insomnia severity index, Leeds sleep evaluation questionnaire	Substance use, psychiatric disorder, pain and seizure ratings	81.3% male, aged 49.5 (11.2) y, all suffering Fibromyalgia ($n = 32/29$)	Insomnia severity ⇩; difficulty in awakening from sleep ⇩, sleep restfulness ⇧. No effect on sleep latency, and number of awakenings (dose effect was unclear)
Dronabinol								
Bedi et al. 2010 [64]	58.3	US	Graduating dose of dronabinol capsules (increasing from 20 mg to 40 mg) taken four times daily over 16 d and 16 d on placebo	Comparisons between placebo and between active drugs (unsuccessful blinding)	Objective Nightcap sleep monitor and unclear numerical rating scales	Age, weight, mood, substance use, stable medical condition	100% male, aged 36.6 (1.3) y, all suffering HIV ($n = 14/12$; seven with sleep data)	Sleep efficiency ⇧ on days 1 −8 only due to ⇧ in time in S1−S4 and ⇩time awake. Sleep satisfaction, "slept well" and "awoken on less days" all ⇧ on days 1−8 only (dose effect was unclear).
Haney M et al. 2007 [65]	69.4	US	Daily dose of THC (2% and 3.9%), taken four times daily over four days and then daily dose of dronabinol (5 mg or 10 mg) taken four times daily over four days,	Comparisons between placebo and between active drugs (unsuccessful blinding)	St. Mary's Hospital sleep questionnaire (one item) and objective Nightcap sleep monitor	Substance use, psychiatric and physical health	90% male, aged 40.1 (1.9) y, 10% Caucasian, all suffering HIV ($n = 10/10$; seven with sleep data)	No effect on objective sleep time. Subjective ratings on sleep time, satisfaction and "slept well" were ⇧ on 3.9% THC only (comparing overall average ratings)

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Table 2 (*continued*)

Authors, reference number	Quality rating (%)	Country of origin	Dose/Duration	Comparisons made (effectiveness of blinding)	Sleep measure	Controls	Participant details[a] (Baseline/Final *N*)	Outcome
			and four days placebo between doses					
Narang et al. 2008 [40]	53.3	US	One to three oral tablet doses per day of dronabinol on a graduating dose plan (5–60 mg over four weeks) following pilot testing of single dose of placebo, 10 mg and 20 mg	Compared with pre-dose baseline (study blinding failed for over half of participants)	Medical Outcomes Study sleep scale and Brief Pain Inventory (sleep interference item)	Gender, cannabis use, medications, substance abuse, psychiatric disorder	47.7% male, aged 43.5 (11.8) y, 96.7% Caucasian, all suffering pain ($n = 30/24$)	Sleep disturbance, and problems ⇩, sleep adequacy ⇧; pain interference in sleep ⇩ (dose effect was unclear)
Weber et al. 2010 [61]	46.9	Switzerland	Two daily doses of dronabinol (5 mg) for two weeks with two week run in and two week washout or placebo	Compared to placebo (unconfirmed blinding)	Sleep disorder questionnaire (seven items)	Substance abuse, psychiatric disorder	74% male, aged 57 (12) y, all suffering ALS ($n = 25/22$)	No effect on "insomnia" symptoms (dose effect was unclear)
Sativex								
Berman et al. 2004 [45]	45.9	UK	Three, 13 d periods of sativex, THC and placebo doses (graduating doses of up to 48 doses per day of 27 mg/ml THC + 25 mg/ml CBD or 27 mg/ml THC only; the average daily dose was 21.6 mg THC and 20 mg CBD per day)	Compared with placebo (unconfirmed double blind)	Numerical rating on sleep quality and number of sleep disruptions for last seven days of treatment	History of mental health concerns, substance abuse	95.8% male, aged 39 y on average, all suffering pain ($n = 48/45$)	Sleep disturbance and quality ⇧ (dose effect was unclear)
Blake et al. 2006 [47]	56.8	UK	An average of 5.4 (0.8) daily doses of sativex (2.7 mg THC and 2.5 mg CBD) over two weeks	Comparison with placebo group ($n = 27$) (double blind)	Numerical rating on quality of sleep	Age, gender, substance abuse, height, weight, previous cannabis use	21% male, aged 62.8 (9.8) y, all suffering pain ($n = 58/54$)	Sleep quality ⇧ (dose effect was unclear)
Brady et al. 2004 [58]	36.1	UK	Graduating dose of sativex oral sprays (each 2.5 mg/ 2.5 mg THC/CBD with a daily mean of 33.7 mg) over a mean of eleven weeks then THC oral spray (2.5 mg with a daily mean of 31.2 mg) over a mean of 10 weeks	Compared to baseline (no blinding)	Unclear numerical rating scale	Substance use	19%, aged a mean of 48 y, all suffering MS ($n = 21$ [9 with sleep data]/15)	"Trouble sleeping" ⇩for the THC dose at weeks 15 and 16 only (dose effect was unclear)
Collin et al. 2010 [52]	56.7	Multi-national	Mean of 8.5 oral spray doses of sativex (each 2.7 mg/2.5 mg THC/CBD) daily for 14 weeks or placebo	Compared to placebo (unconfirmed blinding)	Numerical rating on sleep quality	MS severity ratings, psychiatric disorder, age, gender	39% male, aged 47.5 (9.6) y, all suffering MS ($n = 337/305$)	Sleep quality was not affected overall but improved for 61% of those who reported >30% improvement in spasticity (dose effect was unclear)
Johnson et al. 2010 [63]	69.4	UK	Graduating daily dose of sativex (each dose was 2.7 mg THC, 2.5 mg CBD; average of 8.8 doses) over two weeks, or graduating daily dose THC (each dose was 2.7 mg; average of 8.3 doses) over two weeks, or placebo	Comparisons between placebo and active drugs (double blind)	Unclear numerical rating on sleep quality and quality of life questionnaire (one item on "insomnia")	Age, gender, type of cancer, substance use	54% male, aged 60.2 (12.3) y, 98% Caucasian, all suffering cancer ($n = 177/144$)	No effect on sleep quality and "insomnia" severity

Rog et al. 2005 [54]	44.4	UK	Flexible oral spray dose of sativex (up to 48 doses daily, each 2.7 mg/2.5 mg THC/CBD) for five weeks or placebo	Compared to placebo (unconfirmed blinding)	Numerical rating on "pain related sleep disturbance"	MS severity ratings, medications, age, gender	21.2% male, aged 49.2 (8.3) y, all suffering MS ($n = 66/64$)	Pain related sleep disturbance ⇩ (dose effect was unclear)
Novotna et al. 2011 [53]	70	Multi-national	Mean of 8.3 oral spray doses of sativex (each 2.7 mg/2.5 mg THC/CBD) for 16 wk or placebo	Compared to placebo (unconfirmed blinding)	Numerical rating on "sleep quality"	Substance abuse, MS severity ratings, medications, psychiatric disorder, age, gender, BMI	39% male, aged 48.6 (9.3) y, 100% Caucasian, all suffering MS ($n = 241/224$)	Sleep quality ⇧ (dose effect was unclear)
Nurmikko et al. 2007 [42]	48.6	Multi-national	An average of 10.9 (6.8) doses of sativex oral spray per day (each dose was 2.7 mg THC 2.5 mg CBD) over five weeks	Compared with placebo (no blinding)	Numerical rating on 'sleep disturbance'	Pain medication, physical and mental health	40.8% male, aged 53.4 y, 97% Caucasian, all suffering pain ($n = 163/103$)	Sleep disturbance ⇩ during weeks two to five, no effect at week one or at four-week post-treatment follow-up (dose effect was unclear)
Portenoy et al. 2012 [41]	54.1	Multi-national	Two-16 oral spray doses per day of sativex on a graduating dose plan (5.4 −43.2 mg THC and 5 −40 mg CDB over nine weeks)	Compared with placebo (unconfirmed double blind)	Numerical rating on sleep disruption	Gender, ethnicity, cannabis use, medications, physical health	51.7% male, aged 58.0 (12.2) y, 77.2% Caucasian, all suffering pain ($n = 360/263$)	Sleep disruption ⇩ on low dose only (one to four doses per day)
Vaney et al. 2004 [55]	54.1	Germany	Graduating dose of oral spray sativex up to 12 doses (each 2.5 mg/0.9 mg THC/CBD) over four weeks or placebo	Compared to placebo (unconfirmed blinding)	Diary recordings on "falling asleep fast" and "waking up again"	Age, gender, substance use, MS severity ratings	49.1% male, aged 54.9 (10.0) y, all suffering MS ($n = 57/37$)	No effect on indicators of sleep latency or sleep quality were found
Wade et al. 2004 [56]	40.5	UK	Graduating dose of oral spray sativex up to 48 doses daily − typically 15 doses (each 2.7 mg/2.5 mg THC/CBD) for six weeks	Compared to placebo (unconfirmed blinding)	Visual analogue scale on sleep quality, time asleep, and "feeling upon waking"	Age, gender, substance abuse, MS severity ratings	38.1% male, typically aged over 50 y, all suffering MS ($n = 160/154$)	Quality of sleep ⇧; No effect on time asleep and 'feeling upon wakening' (dose effect was unclear)
Other cannabis-based medicines								
Gross et al. 1983 [62]	52.8	US	Graduating doses of THC capsules increasing from 2.5 mg to 10 mg, three times per day over four weeks then graduating dose of diazepam (3−15 mg three times daily) over four weeks	Compared to diazepam (unconfirmed blinding)	Hopkins symptom checklist-90 (one unclear item on sleep disturbance)	Age, substance use, weight, significant health concerns	0% male, aged 23.6 (1.8) y, 100% Caucasian, all suffering primary anorexia nervosa ($n = 11/8$)	Sleep disturbance ⇧ on THC compared to Diazepam (dose effect was unclear)
Haroutiunian et al. 2008 [49]	17.2	Israel	Oral dose of THC (5 mg) two to three times daily for the period of the participant's "ongoing analgesic drug regimen"	Unclear impact rating only (no blinding)	Numerical rating on "sleeping better"	None	53.8% male, aged 46 (17) y, all suffering pain ($n = 13/13$)	Impact of THC on 'sleeping better' was rated as an average of 3.1 out of 10
Notcutt et al. 2004 [50]	45.2	UK	Oral spray dose of THC and CBD alone, or THC combined with CBD (all 2.5 mg), and placebo − all taken two to eight times daily in a randomised order for two weeks (12 experimental weeks total)	Compared to placebo (unconfirmed double blind)	Number of hours slept and percentage of nights with "good quality sleep"	Mental health, pain ratings, previous cannabis use	29% male, aged 45.5 y on average, all suffering pain ($n = 34/31$)	Percentage of "good" nights favoured THC with CBD (55.4%), over THC (42.9%), CBD (36.9%), and placebo (17%). No effect on time asleep (dose effect was unclear)

(*continued on next page*)

Table 2 (*continued*)

Authors, reference number	Quality rating (%)	Country of origin	Dose/Duration	Comparisons made (effectiveness of blinding)	Sleep measure	Controls	Participant details[a] (Baseline/Final *N*)	Outcome
Ware et al. 2010 [43]	48.6	Canada	Smoked 0%, 2.5%, 6% and 9.4% THC joints three times daily, over four, two week periods	Compared with placebo (double blind)	Leeds sleep evaluation questionnaire	Cannabis use, history of mental health, substance abuse	47.8% male, aged 45.4 (12.3) y, all suffering pain (n = 23/21)	Getting to sleep was faster and sleep felt more restful on high dose (9.4%) THC joints only; No effect on number of night time awakenings and sleep quality
Zajicek et al. 2003 [59]	45.9 (Trail A)	UK	Either Marinol or Cannador capsules were administered (each 2.5 mg/1.25 mg THC/CBD) at an average of six to eight daily doses daily (maximum dose of 25 mg THC daily) over 14 wk or placebo	Comparisons between placebo and active drugs (50% and 77% of placebo and treatment groups reported group allocation correctly)	Unclear numerical ratings scale on sleep quality and percentage of participants showing "improvement"	Age, gender, spasticity medication, MS severity ratings, BMI and mental health	34% male, typically aged over 50 y, all suffering MS (n = 657/630)	Sleep quality ⇧ for both treatments and sleep 'improved' for significantly more participants on both treatments over placebo (50% improved on Cannador, 47% on THC and 36% on placebo) (dose effect was unclear)
Zajicek et al. 2005 [60]	21.1 (Trail B)	UK	Following the initial 'Trial A' (above), participants were offered to extend treatment with 52 wk of home dosing of either Marinol, Cannador, or placebo with a maximum daily dose of 25 mg THC	Comparisons between placebo and active drugs (unconfirmed blinding)	Percentage of participants showing "improvement" to sleep	Unclear (those who continued were described to be similar to those who discontinued from Trial A)	Details of those who continued from Trial A were not provided (n = 383/355)	Sleep 'improved' for significantly more participants on both treatments over placebo (38% improved on Cannador, 34% on THC and 26% on placebo) (dose effect was unclear)
Zajicek et al. 2012 [57]	43.2	UK	Graduating dose of THC/CBD capsules (0.8–1.8 mg CBD and 2.5 mg THC), increasing from one to ten doses, taken daily over 12 wk or placebo	Compared to placebo (unconfirmed blinding)	Unclear numerical ratings scale	Age, gender, ethnicity	36.8% male, typically aged over 50 y, 99% Caucasian, all suffering MS (n = 279/224)	Sleep disturbance ⇩ at four, eight, and 12 wk (dose effect was unclear)

ALS = amyotrophic lateral sclerosis, BMI = body mass index, CBD = cannabidiol, MS = multiple sclerosis, PTSD = post-traumatic stress disorder, S1–S4 = stages one to four sleep time, THC = delta-9-tetrahydrocannabinol.

[a] For each article the participants' gender breakdown, age in years (expressed as the mean [standard deviation] when given), history of cannabis use, ethnicity, and other relevant demographic variables are provided subject to the detail published in the associated article.

Medicinal cannabis use and sleep (28 studies; combined 'N' = 3658)

A total of 28 medicinal cannabis use studies included a measure of sleep as a treatment outcome for various illnesses with a collective sample size of 3658 participants (see Table 2 for an overview). Ailments under investigation included pain (12 studies [40–51]), multiple sclerosis (nine studies [52–60]), and other conditions such as anorexia, cancer, and immune deficiency (seven studies [61–67]). The studies were of synthetic analogues of THC including marinol or dronabinol and nabilone (14 studies [40,43,44,46,48,49,51,57,61,62,64–67]); synthetic analogues of CBD (Cannador; Institute for Clinical Research, IKF, Berlin, Germany) (four studies [50,57,59,60]); or cannabis extracts with a similar ratio of THC to CBD; referred to as nabiximols (Sativex; GW Pharma Ltd., Wiltshire, UK) (14 studies [41,42,45,47,50,52–56,58–60,63]). The THC analogue capsules have shown promise for the treatment of cancer-related nausea and vomiting, and for anorexia associated with weight loss in patients with acquired immune deficiency syndrome [8]. In turn, the CBD analogue capsules have shown anxiolytic and antipsychotic like actions [7]. Finally, the nabiximols oromucosal spray has shown particular promise for treating peripheral neuropathic, cancer and spasticity related pain [15].

The quality of these CBM trials with measures of sleep was poor. Scores ranged from 17% to 69%, with an average score of 48.6%. Across studies, the low quality scores were commonly a result of non-validated measures of sleep (typically simple numerical ratings) and a lack of confirmation that participants were adequately blinded to the dose of cannabis used (particularly among nabilone and dronabinol trials while blinding adequacy is more likely in sativex/nabiximol trials [68]).

Although the majority of studies did not include a validated measure of sleep, most studies reported a significant and positive impact on sleep in the clinical trial. That is, 20 studies showed an improvement to sleep [40–43,45–47,50,51,53,54,56–60,62,64–67], although this improvement was no longer significant at the end of the experiment in two studies [58,64] while one study did not report on sleep per se but showed a lessening of bad dreams [66]. Research regarding whether cannabis-based medicines are more beneficial to sleep than alternative experimental drugs was mixed. Two studies supported the sleep enhancing effects of CBM over diazepam (when treating primary anorexia nervosa) [62] and amitriptyline (treating insomnia among patients with fibromyalgia) [67], however; three studies did not support CBM over ketoprofen (when treating pain and nausea) [44], gabapentin [46] or dihydrocodeine (both treating neuropathic pain) [48]. Finally, six studies did not find a significant association between medicinal cannabis use and sleep [44,48,52,55,61,63] and one article (quality rating of 17.2%) referred only to the impact of THC on sleep and this was rated as 3.1 out of 10 (anchor-point descriptions were not provided) [49].

A total of seven studies included a validated subjective measure of sleep [40,43,46,51,61,65,67] – most commonly the Medical Outcomes Study sleep scale [69] or the Leeds sleep evaluation questionnaire [70]. The results from these seven studies were varied. In summary, four studies reported on sleep disturbance/problems: each showed a reduction [40,46,65,67] although this reduction was no greater than reductions associated with an alternative active drug [46] and one study showed a reduction only on high dose [65]. Three studies reported on sleep quality: two showed an increase [40,65] while one reported no effect [43]. Two studies reported on sleep latency: one study reported an improvement although on high cannabis dose only [43], while the other showed no effect [67]. Two studies reported on sleep restfulness: both showed a positive effect [43,67]. Two studies reported on an overall index score: one study showed significant improvement [51] and the other no effect [61]. In contrast, two studies reported on night time awakenings and neither showed an effect [43,67].

In addition, two notable studies included an objective measure of sleep [64,65]. The first included controls for substance use and health problems and reported only on total sleep time [65]. This study showed no effect by objective measure, however; a significant effect was seen by subjective measure on high dose (10 mg THC, four times daily for four days) [65]. The second study included similar controls but utilised a greater dose of THC (increasing dose of 20–40 mg administered four times daily for 16 d) [64]. In this study, a significantly greater period of NREM sleep was reported across the first eight days only, along with fewer night time awakenings, and a higher quality sleep compared to baseline.

Finally, three studies included an analysis on the effect of dose [41,43,65], two of which included validated measures of sleep [43,65]. These two studies each reported that the high dose of cannabis (3.9% and 9.4% THC) outperformed the low dose (2% and 2.5–6% THC, respectively). The third study (without a validated measure of sleep) reported that the low dose (1–4 doses of 5.4 mg/5 mg THC/CBD) outperformed the high dose (5–16 doses) [41].

Conclusions

We have reviewed 39 manuscripts that involved the administration of cannabis and included a quantitative measure of sleep. Overwhelmingly these articles described studies that carried a substantial risk of bias, typically by failing to control for other substance use, using measures without psychometric validation and, in the case of many clinical trials, failing to blind participants. As such, conclusions from this review are tentative due to existing studies suffering a number of methodological issues and findings being largely mixed. That said, the evidence indicates that following cannabis use there may be a decrease in slow wave sleep (SWS) times and a corresponding increase in time spent in stage 2 sleep. There does not appear to be a consistent effect on total sleep time. Among those with a medical condition that impacts upon sleep, reductions in sleep disturbance (not necessarily causing early awakening) appear to improve quality of sleep without impacting on total sleep time. Although there appears to be a small dose effect, without further study the impact of varying doses of cannabis is less clear.

These results are consistent with one interpretation that cannabis is typically not beneficial to sleep except among medicinal cannabis users who are identified by the presence of pre-existing sleep interrupting symptoms such as pain. As such, cannabis may be thought to improve sleep via the mediating improvement of these confounding symptoms. In particular, this interpretation of results is supported by the two studies that included a measure of pain-related sleep problems [43,46] and an additional study which showed that only those participants reporting a reduction in spasticity showed improved sleep [52]. In addition, CBM and natural cannabis are categorically different beyond the fact that medicinal cannabis is typically taken orally. That is, each consists of varying levels of cannabinoids, particularly the ratio of THC to CBD, which may contribute to differences in sleep-related outcomes [31]. Indeed, nabiximols contain a roughly equal THC:CBD ratio, while natural cannabis is very low in CBD [71], limiting the generalisation between the two.

The results of the reviewed studies, although mixed, indicate that cannabis may have an effect on various aspects of sleep, including sleep architecture and subjective sleep quality. Given the risk of bias associated with the reviewed studies, there is a clear need for a large scale, longitudinal and well controlled study on the

specific effects of cannabinoids on sleep. The health impact of these effects is also unclear and is a necessary topic for future research among samples of cannabis users.

Practice points

Cannabinoid use among recreational users:

1) may interrupt the normal cycles of sleep – particularly SWS sleep; and
2) does not appear to consistently cause any significant change to the time spent asleep or the number of night time awakenings, but may leave an impression of non-restful sleep.

Cannabinoid use among users with a medical condition known to disturb sleep:

1) shows some consistency across studies of improved sleep via reduced night time disturbances, although the majority of these studies do not include psychometrically validated measures; and
2) shows relatively inconsistent effects on sleep among studies with objective measures.

Research agenda

To better clarify the impact of cannabinoid use on sleep further study is required that:

1) is longitudinal to assess the impact of tolerance;
2) includes both an objective and validated subjective measure of sleep and sleep-related health outcomes to assess any changes to sleep and how these changes are experienced;
3) includes varying doses of cannabinoids to assess the impact of frequency and intensity of use; and
4) includes controls for confounding variables such as age, gender and substance use history.

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