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SLEEP DISORDERS (P GEHRMAN, SECTION EDITOR)

Cannabis, Cannabinoids, and Sleep: a Review of the Literature

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Abstract
Purpose of Review The current review aims to summarize the state of research on cannabis and sleep up to 2014 and to review in detail the literature on cannabis and specific sleep disorders from 2014 to the time of publication.
Recent Findings Preliminary research into cannabis and insomnia suggests that cannabidiol (CBD) may have therapeutic potential for the treatment of insomnia. Delta-9 tetrahydrocannabinol (THC) may decrease sleep latency but could impair sleep quality long-term. Novel studies investigating cannabinoids and obstructive sleep apnea suggest that synthetic cannabinoids such as nabilone and dronabinol may have short-term benefit for sleep apnea due to their modulatory effects on serotonin-mediated apneas. CBD may hold promise for REM sleep behavior disorder and excessive daytime sleepiness, while nabilone may reduce nightmares associated with PTSD and may improve sleep among patients with chronic pain.
Summary Research on cannabis and sleep is in its infancy and has yielded mixed results. Additional controlled and longitudinal research is critical to advance our understanding of research and clinical implications.

Keywords Cannabis · Cannabinoids · Sleep · Insomnia · Sleep apnea

This article is part of the Topical Collection on *Sleep Disorders*

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Introduction

Rates of cannabis use within the USA continue to increase, with 8.3% of the US population reporting cannabis use within the past month [1]. Cannabis use has been associated with the development of cannabis use disorders, particularly among "at-risk" populations. In contrast, there has also been evidence to suggest that cannabis may have therapeutic potential. Indeed, as of January 1, 2017, 26 states and the District of Columbia have legalized cannabis for medical purposes, while 7 states and the District of Columbia have legalized the recreational use of cannabis. Understanding the research on both sides of this coin is important for clinical, research, and policy purposes.

The current paper seeks to provide a state-of-the-science review of the research on cannabis and sleep, a condition for which individuals often report using cannabis [2]. Previous review papers have provided an overview of the research on cannabis and sleep up through 2014. Therefore, within this review, we will provide a summary of the hallmark work in this area through 2014 along with an update of new research from 2014 to the end of 2016. First, we will provide a primer on cannabis and cannabinoids and how they relate to sleep. We will then provide an overview of research on both sides of this topic, namely, the risk and potential benefits of cannabis on sleep and the impact of poor sleep on cannabis use. Finally, we will provide an overview of the research on cannabis and specific sleep disorders. We will conclude with an integrative summary and call for future directions.

Introduction to Cannabinoids

The cannabis flower is comprised of over 100 different cannabinoids, the active compounds found within the cannabis plant. Cannabinoids work on the endocannabinoid system

(ECS) which consists of a series of neuromodulatory lipids and receptors located throughout the brain and central and peripheral nervous system, which accept endogenous cannabinoids (anandamide, 2-arachidonoylglycerol) and phytocannabinoids (plant-based). The CB1 and CB2 receptors are two main receptors within the ECS [3]. The two most well-researched phytocannabinoids are delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the primary psychoactive component of cannabis which is responsible for the "high" associated with cannabis use. THC acts on CB1 receptors and yields a biphasic effect such that the impact of THC varies between low and high doses. CBD is a non-intoxicating constituent of cannabis which acts on CB2 receptors. CBD has been shown to counter the effects of THC and has received a lot of attention for its potential therapeutic effects [4].

Based on the potential therapeutic impact, cannabis-based medicine extracts have been developed. These extracts are synthetic THC (dronabinol, nabilone), CBD (Charlotte's web), and nabiximols (1:1 CBD/THC, Sativex) which are delivered orally. The development of synthetic extracts has allowed for investigation of the effects of specific cannabinoids.

The Impact of Cannabis on Sleep

Research on the impact of cannabis on sleep started in the 1970s and included a number of studies examining polysomnography (PSG)-based sleep. This resulted in mixed findings with some work showing a decrease in sleep onset latency [5] and wake after sleep onset [6], while other work did not replicate these findings [7], but instead observed an increase in slow wave sleep [7, 8] and a decrease in REM [6, 7, 9]. Additional work from this era also suggested that cannabis may have a short-term benefit on sleep, particularly in reducing sleep onset latency [10]; however, chronic use of cannabis could be associated with habituation to the sleep inducing and slow wave sleep-enhancing properties [8, 11–13]. This initial work suggested that long-term use could have a negative impact on sleep in two primary ways. First, individuals may find themselves in a vicious cycle of using cannabis to manage sleep, habituating to the effects, and using more cannabis in order to obtain the desired impact, resulting in problematic patterns of use. Second, sleep disturbances are the hallmark of cannabis withdrawal and may serve to maintain use and predict relapse.

Sleep and Cannabis Relapse A breadth of evidence has converged to demonstrate that poor sleep is a critical risk factor for predicting cannabis cessation success [14–16]. Poor sleep quality prior to a quit attempt has been shown to increase the risk of early lapse/relapse to cannabis [16] and be associated with less of a reduction in cannabis use frequency among cannabis-dependent veterans [15]. Post-quit sleep has also been shown to impact quit success and rates of lapse/relapse to use [14, 17–19]. For example, Budney and colleagues [14] demonstrated that 65% of cannabis users reported poor sleep as the primary reason for lapse/relapse to cannabis during a prior quit attempt.

Cannabis Withdrawal and Sleep Nonclinical and clinical research has now characterized the profile of cannabis withdrawal, with sleep disturbances and vivid dreams representing hallmark cannabis withdrawal symptoms [20]. Indeed disturbed sleep can last up to 45 days post-cessation making this the longest lasting withdrawal symptom [20]. Disturbed sleep is commonly reported with 67–73% of adults and 33–43% of adolescents reporting disturbed sleep during a quit attempt [14, 21, 22]. This work has combined to suggest that sleep disturbance is one of the most severe cannabis withdrawal symptoms [23]. While a majority of this work was initially based on self-reported sleep questionnaires, more recent work has demonstrated objective changes in sleep during cannabis withdrawal. In a cross-sectional study using PSG, Bolla and colleagues [24] demonstrated that abrupt cannabis cessation among heavy users was associated with a decrease in total sleep time, sleep efficiency, and %REM. In addition, increases in wake after sleep onset, sleep onset latency, and periodic limb movements were observed. Vandrey and colleagues [19] examined PSG-measured sleep in a sample of heavy cannabis users who completed a within-subject crossover study which alternated between periods of cannabis use and an abstinence phase supplemented by administration of either a placebo or zolpidem. Results demonstrated that abrupt cessation was associated with an increase in sleep onset latency and %REM, while a decline in sleep efficiency was observed. Administration of zolpidem attenuated the effects such that there was no difference in PSG sleep between the zolpidem and cannabis use phases. In addition, zolpidem reversed the abstinence-induced changes in stage 2 sleep and REM. Taken together, self-reported sleep and objective indices of poor sleep have been consistently demonstrated during cannabis withdrawal.

The Role of the Endocannabinoid System on the Circadian Sleep–Wake Cycle

The role of sleep in cannabis use and withdrawal is not surprising as recent work has demonstrated that the ECS is involved in the regulation of the circadian sleep–wake cycle [25], including the maintenance and promotion of sleep [26]. Specifically, it has been hypothesized that the ECS serves as the link between circadian regulation systems (i.e., superchiasmatic nucleus) and the behavioral and physiological processes that are affected, including sleep [26].

The role of the ECS on circadian rhythms has been further supported by work demonstrating that a lack of normal sleep

causes dysregulation within the ECS [26], while elevation in the ECS at the receptor level is involved in the homeostatic recovery of sleep after non-normal sleep [26]. Based on this backdrop, the ECS is a critical system involved in the regulation of the circadian rhythm sleep–wake cycle, highlighting the importance of examining the impact of cannabinoids on sleep.

Effects of Cannabinoids on the Sleep–Wake Cycle

The mid-2000s has seen resurgence in research focused on cannabis and sleep. In comparison to the work done in the 1970s, the majority of this work has focused on self-reported sleep and has also started to investigate the potential therapeutic impact of cannabinoids for sleep. This resurgence in research is likely due to an increased sophistication and understanding of cannabis and the constituent components. Indeed, recent research has demonstrated that the type of cannabinoids (THC, CBD), ratio of cannabinoids, dosage, timing of administration, and route of administration all play a critical role in outcomes.

The Role of THC on the Sleep–Wake Cycle Preclinical research has suggested that circadian rhythms are less pronounced (assessed by body temperature over 2 weeks) during THC administration [27]. In addition, within the context of early clinical research, chronic administration of THC has been shown to result in the development of tolerance to sleep effects [26]. Further work among adults (n = 8) has demonstrated that 15 mg of THC did not have an impact on nocturnal sleep and resulted in increased sleepiness and delayed sleep onset the following day as well as changes in mood and memory difficulty [28].

The Role of CBD on the Sleep–Wake Cycle Administration of CBD has been shown to have differential effects on sleep based on dose. Indeed, low-dose CBD has a stimulating effect, while high-dose CBD has a sedating effect. In a study among individuals with insomnia, results suggested that administration of 160 mg/day of CBD increased total sleep time and decreased the frequency of arousals during the night [29], while low-dose CBD has been associated with increased wakefulness [28, 30].

Summary

Taken together, research suggests that short-term use of cannabis may have a therapeutic impact on sleep, specifically related to sleep onset latency and slow wave sleep. However, long-term chronic use is associated with habituation to the sleep-enhancing benefits and is associated with increased risk for cannabis dependence. Sleep disruption (self-reported and objective) is a primary withdrawal symptom from cannabis and may play a role in cannabis lapse/relapse during cessation attempts. While this work has been focused on the cannabis flower, recent work has suggested that specific cannabinoids (THC and CBD) have a differential impact on sleep. This is further influenced by the dosage, ratio of cannabinoids, timing of administration, and route of administration. Initial work examining specific cannabinoids suggests a potential therapeutic effect of high-dose CBD and low-dose THC for sleep. What follows is an overview of the impact of cannabis, and specific cannabinoids, on a number of sleep disorders for which this research has been examined (see Table 1 for an overview of studies).

Cannabinoids and Specific Sleep Disorders

Insomnia/Sleep Quality

Insomnia is defined as dissatisfaction with sleep quantity or quality associated with difficulty falling asleep, difficulty maintaining sleep throughout the night, and/or waking up early in the morning with an inability to return to sleep that causes significant distress or impairment in functioning [52]. General prevalence rates of insomnia have increased in recent years from 17.5% in 2002 to 19.2% of the adult US population, representing 46.2 million [53•].

Recent work in animal models has focused on the effect of CBD on sleep quality and the sleep–wake cycle [32, 33]. Chagas and colleagues found an increase in total percentage of sleep in rats after administration of mid-range and high-dose CBD injections as compared to placebo. The effects on REM varied by dosage such that high-dose CBD increased REM sleep latency on the day of administration and mid-range dose CBD decreased REM sleep latency the day after administration [33]. Meanwhile, Hsiao and colleagues found that CBD blocked anxiety-induced REM sleep suppression but had no effect on NREM sleep [32]. This work is further supported by a recent case report in which administration of CBD oil reduced insomnia symptoms and PTSD-related sleep disturbances [54•]. Together, these findings suggest that CBD may impact sleep quality through its anxiolytic effects.

However, recent work measuring sleep in young adults has suggested that CBD may decrease stage 3 sleep, when used in combination with THC [28]. On the other hand, THC and synthetic THC preparations have been associated with decreased sleep latency [28, 55]. However, in Gorelick and colleagues synthetic THC administration study, overall amount of nighttime sleep decreased over time suggesting a potential effect of tolerance [55].

Recent studies on whole plant cannabis and sleep quality are similarly conflicting. Studies of medicinal cannabis users have found that individuals commonly report using cannabis for insomnia [31, 35•]. Among medical cannabis users,

Table 1 Recent studies on cannabis and sleep

Study (primary author, year)	Sample	Cannabinoid or cannabis-based medicine	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
				Insomnia				
Nicholson, 2004 [28]	Healthy young adults age (21–34) *N* = 8	THC CBD	Placebo	15 mg THC 10 mg THC/CBD 1:1 30 mg THC/CBD 1:1	Oral 10:00 PM	Stanford Sleepiness Scale; Sam-Perelli fatigue rating	EEG EOG EMG Sleep Latency Test	No effect of 15 mg THC on nocturnal sleep but increased sleepiness and decreased sleep latency the following morning Combination low and high doses resulted in decreased stage 3 sleep Combination high dose increase wakefulness
Tringale, 2011 [31]	Medical cannabis users *N* = 147	Cannabis (flower)	No cannabis use; no sleep problems	Varied	Varied	Sleep Latency	None	Decreased sleep latency in both groups after cannabis use
Hsiao, 2012 [32]	Male Wistar rats *N* = 28	CBD	Placebo	0.5 μg, 1.0 μg	CeA injection 20 min prior to light onset	None	EEG EMG	CBD blocked anxiety-induced REM sleep suppression but had no effect on NREM sleep
Chagas, 2013 [33]	Male Wistar rats *N* = 28	CBD	Placebo	2.5 mg/kg 10 mg/kg 40 mg/kg	Intraperitoneal injection 7:00 AM–8:00 AM	None	ECoG EMG	Increase in total percentage of sleep in 10 and 40 mg/kg conditions Increase in REM sleep latency in light period on day of administration (40 mg/kg) Decrease REM sleep latency day after administration (10 mg/kg)
Gorelick, 2013 [34]	Daily cannabis users *N* = 13	Marinol	None	20 mg single dose; 40-120 mg daily	Around-the-clock oral admin	MEQ; St. Mary's Hospital Sleep	None	Higher synthetic THC concentrations in the evening were associated with decreased sleep latency Overall amount of nighttime sleep decreased during study
Study (primary author, year)	Sample	Cannabinoid	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
Belendiuk, 2015 [35•]	Medical cannabis users *N* = 163	Cannabis (flower)	None	Varied	Varied	PSQI	None	Participants reported using cannabis for insomnia (*N* = 81) and nightmares (*N* = 14)

Table 1 (continued)

Study (primary author, year)	Sample	Cannabinoid or cannabis-based medicine	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
								Those using for nightmares preferred sativa strains Individuals with insomnia and greater sleep latency reported using higher CBD concentrations Sleep medication use was associated with use of lower THC concentration
Ogeil, 2015 [36•]	Alcohol and/or cannabis users *N* = 248	Cannabis (flower)	None	Varied	Varied	PSQI	None	Poor sleep quality was associated with problematic alcohol and cannabis use Women had poorer sleep outcomes than men
Shannon, 2016 [37]	Female with PTSD, age 10	CBD	Patient before CBD	25 mg capsule 3 mg spray	Oral administration 6:00 PM capsule and 2–4× spray at varied times	Sleep Disturbance Scale for children	None	CBD oil reduced insomnia and sleep disturbances in the patient
				Obstructive sleep apnea (OSA)				
Carley, 2002 [38]	Male Sprague-Dawley rats *N* = 11	THC Oleamide	Crossover design	THC = 0.1, 1.0, or 10 mg/kg Oleamide = 0.1, 1.0, 10 mg/kg Seratonin = 0.79 m-g/kg Combination = 0.1 mg/kg THC = 0.79 mg/kg serotonin or 0.1 mg/kg oleamide	12 intraperitoneal injections 15 min prior to PSG			Reduction in apnea index among THC and oleamide conditions
Jumpertz, 2010 [39]	Patients with sleep apnea	OEA AEA 2-AG	Healthy control	N/A	N/A	None	Oronasal airflow; Respiratory distress index	Three times higher concentrations of OEA in sleep apnea group suggesting a role of endocannabinoids in regulating wakefulness associated with respiratory distress
Study (primary author, year)	Sample	Cannabinoid	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
Prasad, 2013 [40]	Adults with sleep apnea *N* = 17	Dronabinol	None	2.5 mg titrated to 10 mg	Oral administration 30 min prior to bed	None	EEG EOG EMG ECG	Reduction in apnea–hypopnea index from baseline to night 21

Table 1 (continued)

Study (primary author, year)	Sample	Cannabinoid or cannabis-based medicine	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
							Oronasal airflow; pulse oximetry; body position	
Calik, 2014 [41•]	Male Sprague-Dawley rats *N* = 24	Dronabinol	Vehicle control	100 μg/5 μl 10 μg/5 μl	Injection in nodose ganglia	None	EMGgg Piezoelectric strain gauge	Reduction in apneas and hypopneas in dronabinol condition
Farabi, 2014 [42•]	Adults with sleep apnea *N* = 17	Dronabinol	None	2.5 mg titrated to 10 mg	Oral administration 30 min prior to bed	None	EEG	Shift in EEG power toward delta and theta frequencies and strengthening of ultradian rhythms associated with increasing doses of dronabinol
Calik, 2014 [43•]	Male Sprague-Dawley rats *N* = 36	Dronabinol	Vehicle control	100 μg/5 μl	Injection in nodose ganglia	None	EMGgg Piezoelectric strain gauge	Reduction in reflex apneas in the dronabinol condition
Calik, 2016 [44•]	Male Sprague-Dawley rats *N* = 30	Dronabinol	Vehicle control	100 μg/3 μl 10 μg/3 μl 1 μg/3 μl 0.1 μg/3 μl	Injection in right lateral ventricle	None	EMGgg Piezoelectric strain gauge	No Reduction in peripherally induced reflex apneas in the dronabinol condition
				REM sleep behavior disorder (RBD)				
Chagas, 2014 [45•]	Patients with RBD *N* = 4	CBD	None	75 mg/day 300 mg/day	Oral	None	PSG	Reduction in REM sleep behavior disorder symptoms after CBD treatment
Study (primary author, year)	Sample	Cannabinoid	Control group	Dose(s)	Route/Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
				Nightmares				
Fraser, 2009 [46]	Patients with treatment-resistant PTSD *N* = 47	Nabilone	None	0.5 mg titrated up to a max of 4 mg daily	Oral administration 1 h prior to bed	Nightmare presence and intensity; hours of sleep	None	Reduction in nightmares after nabilone
Cameron, 2014 [47•]	Adult male inmates with serious mental illness *N* = 104	Nabilone	None	Mean initial dose 1.4 mg/day titrated to 4 mg/day	Oral	Sleep hours per night and nightmares per week	None	Reduction in nightmares and increase in hours of sleep per night after nabilone
Roitman, 2014 [48•]	Outpatients with PTSD *N* = 10	THC	None	2.5 mg 2×/day titrated to 5 mg 2×/day	Oral administration 1 h after waking up and 2 h prior to bed	PSQI NFQ NES	None	Reduction in nightmares and improvement in sleep quality after THC
Jetly, 2015 [49•]	Male military personnel with PTSD *N* = 10	Nabilone	Placebo	0.5 mg titrated to 3 mg	Oral administration 1 h prior to bed	CAPS sleep items; PTSD dream rating scale; sleep diary	None	Reduction in nightmares in the nabilone condition
				Sleep in pain conditions				
Ware, 2010 [50]	Fibromyalgia patients with insomnia *N* = 29	Nabilone	Amitriptyline	0.5 mg 1 mg	Oral	ISI Leeds Sleep Evaluation	None	Greater improvement in sleep quality in the nabilone condition

Table 1 (continued)

Study (primary author, year)	Sample	Cannabinoid or cannabis-based medicine	Control group	Dose(s)	Route/timing of administration	Sleep measure (self-report)	Sleep measure (PSG)	Results
Study (primary author, year)	Sample	Cannabinoid	Control group	Dose(s)	Route/timing of administration	Sleep Measure (Self-report)	Sleep measure (PSG)	Results
				Excessive daytime sleepiness (EDS)				
Nicholson, 2004 [28]	Healthy young adults age (21–34) *N* = 8	THC CBD	Placebo	15 mg THC 10 mg THC/CBD 1:1 30 mg THC/CBD 1:1	Oral 10:00 PM	Stanford Sleepiness Scale Sam-Perelli fatigue rating	EEG EOG EMG Sleep latency	15 mg THC increased sleepiness and decreased sleep latency the following morning Combination high-dose increase wakefulness
Dzodzomenyo, 2015 [51•]	Pediatric patients *N* = 383	THC	Negative THC screen	Varied	Varied	None	Multiple Sleep Latency Test	Patients who screened positive for THC evidenced significantly more excessive daytime sleepiness symptoms and were more likely to meet criteria for narcolepsy

THC delta-9 tetrahydrocannabinol, *CBD* cannabidiol, *EEG* electroencephalography, *EOG* electrooculography, *EMG* electromyography, *CeA* central nucleus of the amygdala, *REM* rapid eye movement sleep, *NREM* non-rapid eye movement sleep, *ECoG* electrocorticography, *EMGgg* genioglossus electromyogram, *MEQ* Morning-Eveningness Questionnaire, *PSQI* Pittsburgh Sleep Quality Index, *OEA* oleoylethanolamide, *AEA* anandamide, *2-AG* 2-arachidonoylglycerol, *RBD* REM behavior disorder, *PTSD* posttraumatic stress disorder, *NFQ* Nightmare Frequency Questionnaire-Revised, *NES* nightmare effects survey, *CAPS* Clinical Administered PTSD Scale, *ISI* Insomnia Severity Index

individuals with insomnia and greater sleep latency reported using cannabis with higher CBD concentrations. Additionally, in this sample, sleep medication use was associated with use of lower THC concentrations [35•]. Tringale and colleagues found that medicinal cannabis users, both with and without reported sleep problems, experienced decreased sleep latency after cannabis use [31]. However, in a recent study of self-identified alcohol and/or cannabis users, cannabis use was associated with poor sleep quality [36•]. Taken together, these mixed findings suggest that cannabinoid concentration, dose, and route of administration may have differential effects on sleep quality and insomnia symptoms.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is the most prevalent form of sleep-disordered breathing in the USA affecting 9% of American adults [56]. Standard treatment for OSA is a mechanical device that keeps the airway clear for unlabored breathing called a continuous positive airway pressure (CPAP) machine. While CPAP machines are an effective treatment for OSA, many patients are noncompliant due to the discomfort associated with treatment [57•]. A number of animal and human studies have been conducted to examine cannabinoids as potential therapeutic alternatives for treating OSA.

This program of research was initiated in animal models. In an initial study, Carley and colleagues [38] sought to determine the role of endogenous and exogenous cannabinoids in modulating respiration during sleep among Sprague-Dawley rats. Results showed that both the endocannabinoid oleamide and the exogenous cannabinoid THC reduced apneic events, providing initial evidence to suggest that the cannabinoid system may function to suppress the serotonin-mediated symptoms of OSA. Indeed, serotonin has been shown to have a tonic (excitatory) effect on the upper airway motoneurons which serve to maintain upper airway patency and reduce apnea [58]. Years later, Calik and colleagues [41•] investigated the efficacy of injections of dronabinol (synthetic THC) into the nodose ganglion in reducing serotonin-induced apneas among Sprague-Dawley rats. The authors found that dronabinol reduced serotonin-induced apneas and modulated upper airway muscles responsible for regulating breathing during sleep, providing preliminary data for the use of dronabinol in treating adults with OSA. A follow-up study was then conducted to investigate the mechanism of action of dronabinol in preventing induced reflex apneas among adult male Sprague-Dawley rats [43•]. The authors pretreated the rats with AM251 and AM630 and CB_1 and CB_2 receptor antagonists, respectively, to determine whether this prevented the efficacy of injecting dronabinol into the nodose ganglia to reduce apneas. Results suggested that dronabinol's effects in suppressing apneas are facilitated by its action at both CB_1 and CB_2 receptors. Finally, in the most recent work, Calik and colleagues [44•] investigated the effect of intracerebroventricular injections of dronabinol in suppressing apneas among Sprague-Dawley rats. The authors found no significant reductions in apneas among the rats treated with intracerebroventricular injections of dronabinol, which suggests that the efficacy of dronabinol in suppressing apneas is facilitated by peripheral rather than central nervous system activity.

This basic research has now been extended into work among humans with OSA. In a preliminary study, Jumpertz and colleagues [39] studied the function of endocannabinoids including oleoylethanolamide (OEA), anandamide (AEA), and 2-arachidonyl-glycerol (2-AG) in patients with OSA compared to healthy controls. The authors found higher concentrations of OEA but not AEA or 2-AG among patients with OSA, which were associated with difficulty breathing. This finding suggests that endocannabinoids, specifically OEA, may function to protect the brain from the symptoms of sleep apnea. Additional research was then conducted to examine the impact of dronabinol among humans with OSA. Here, Prasad and colleagues [40] investigated the safety, tolerability, and efficacy of dronabinol in decreasing the severity of OSA symptoms among adults. The authors found that dronabinol was safe, well tolerated, and demonstrated efficacy in reducing apneas among adults with OSA in doses ranging from 2.5 to 10 mg daily. In a separate study, Farabi and colleagues [42•] examined the effects of dronabinol on objective measures of the sleep process in adults with OSA. The authors found that dronabinol was associated with a change in delta and theta frequencies and an increase in ultradian rhythms, which was correlated with improvement in apneas and a decrease in sleepiness.

Overall, initial research conducted in animal models and preliminary work in humans suggests that synthetic forms of THC may have a therapeutic potential in the treatment of sleep apnea in the short term. Long-term follow-up studies and controlled trials are needed.

REM Behavior Disorder

REM sleep behavior disorder (RBD) is a parasomnia in which individuals lose muscle rigidity during REM sleep accompanying nightmares and may act out behaviors linked with dreams [59]. Research on the impact of cannabinoids on RBD is relatively limited. However, to date, one study has examined this relation. Specifically, Chagas and colleagues [45•] investigated the efficacy of CBD, the non-intoxicating constituent of cannabis, in reducing symptoms of RBD among four adults with Parkinson's disease. The authors found that CBD suppressed behaviors associated with RBD and was tolerated well by all patients. However, controlled research among larger samples, as well as long-term prospective

studies, has not been conducted, limiting the conclusions that can be drawn.

Nightmares

Nightmares associated with posttraumatic stress disorder (PTSD) are often a residual symptom that remains difficult to treat despite improvements in other domains [60]. Prasozin, an alpha-adrenergic blocker, is the only current pharmacological treatment for PTSD-related nightmares [61]. However, military veterans are increasingly using cannabinoids to treat symptoms of PTSD including nightmares [62•]. This has sparked some initial research to examine the impact of cannabinoids on nightmares. Here, Fraser [46] reported on a study examining the effect of nabilone, a synthetic form of THC, in managing nightmares linked with PTSD. The authors found that treatment with nabilone produced a reduction in nightmare presence and intensity and increased participants' hours of sleep per night. Additional research conducted with a short-term follow-up has suggested that nabilone has been well-tolerated and reduced nightmares in military service members [49•] and male prison inmates [47•]. Finally, an open-label pilot study investigating the use of THC in the treatment of PTSD, found that THC led to an improvement in sleep quality and a reduction in the frequency of nightmares. However, mild adverse effects were reported among some patients such as dry mouth, headache, and dizziness [48•]. Additional, controlled trials among larger, more diverse samples with the inclusion of long-term follow-up are needed.

Sleep in Pain Conditions

Chronic pain is a substantial public health issue, which affects about 20% of adults and is expected to increase as advancements in medical science allow people to live longer [63•]. Chronic pain impacts individuals' ability to get restful sleep. Recent work has started to examine the potential role of cannabinoids in addressing sleep disturbances in the context of chronic pain [63•]. The majority of this work has examined the impact of Sativex, a 1:1 THC/CBD cannabis-based medicine extract, on sleep in chronic pain. A review of clinical trials demonstrated self-reported improvement in sleep quality among chronic pain patients treated with Sativex [64]. However, other studies have suggested that 1:1 THC/CBD preparations do not increase sleep duration despite producing subjective improvements in sleep quality [65•]. Nabilone, a synthetic THC, has also been examined within this context. Specifically, Ware and colleagues [50] conducted a study investigating the effectiveness of nabilone, compared with amitriptyline, in improving sleep among patients with fibromyalgia. The authors found that patients in both conditions evidenced improvements in sleep; however, treatment with nabilone was associated with greater improvements in sleep compared to amitriptyline.

Daytime Sleepiness

Excessive daytime sleepiness (EDS) is a common symptom characterized by the urge to fall asleep during the light hours of the day with a number of causes including certain medications, various medical conditions, psychiatric conditions, and sleep disorders such as narcolepsy and OSA. The negative consequences of EDS which include behavioral, attention, memory, and immune impairment can have a significant impact on quality of life [66•].

Research on cannabinoids and EDS is limited. However, a couple of notable studies have emerged in the past few years. Dzodzomenyo and colleagues' retrospective study of drug screens found that patients who screened positive for THC, indicating recent cannabis use, presented with more EDS and were more likely to meet criteria for narcolepsy [51•]. Conversely, experimental evidence indicates the potential role of CBD in managing somnolence [67•]. In fact, recent work on sleep and early morning behavior demonstrates CBD's impact on wakefulness. In this study, CBD administered in a 1:1 ratio counteracted the sedative effect of THC [28].

Conclusions

The purpose of this paper was to provide a state of the science review of the basic and human research on the associations between cannabis and cannabinoids and sleep, including specific sleep disorders. Overall, a breadth of work has demonstrated that sleep problems increase risk for lapse/relapse to cannabis [15, 16], and disturbed sleep is a hallmark withdrawal symptom that can last months after a cessation attempt [20]. Research examining the impact of whole plant cannabis on sleep has yielded mixed findings, with some work showing that cannabis use is associated with a decrease in sleep onset latency [5] and wake after sleep onset [6], while other work has not yielded these effects but instead noted an increase in slow wave sleep [7, 8] and a decrease in REM [6, 7, 9]. These mixed results are likely due to the heterogeneous nature of whole plant cannabis.

Research in recent years has been marked by sophistication in understanding the component constituents of cannabis and how these cannabinoids may have a differential impact on sleep and sleep disorders. Here, research has combined to suggest that THC may have a short-term sleep benefit; however, chronic administration of THC is associated with habituation to the sleep-enhancing qualities [26, 55]. In addition, THC has been associated with a less pronounced circadian rhythm [27] and has been associated with daytime sleepiness, delayed sleep onset latency (particularly at high doses and

over time), and negative mood and memory alterations [28, 51•]. However, preliminary research has suggested a potential therapeutic effect of dronabinol and nabilone (THC based medicine extracts) on OSA [38–40, 41•, 42•, 43•, 44•] and nightmares [46, 47•, 48•, 49•], respectively.

Work examining CBD, a non-intoxicating cannabinoid with a low addiction profile, has demonstrated differential effects based on dose. Specifically, low doses of CBD have been shown to be stimulating [28, 30] and has been investigated within the context of EDS [67•]. In comparison, medium- and high-dose CBD is sedating [28, 30] and has been examined in the context of a number of sleep disorders including insomnia. Here, initial basic research has suggested that medium-/high-dose CBD is associated with an increase in the percentage of total sleep [32, 33]. This is supported by a pilot study in humans showing that high-dose CBD was associated with improved sleep [28]; however, when combined with THC may result in a decrease in slow wave sleep [28]. A preliminary study has also suggested that CBD may suppress REM behavior disorder in individuals with Parkinson's disease [45•].

The majority of the studies that have examined the impact of cannabinoids on sleep have actually been done within the context of chronic pain conditions. A review of phase I and II clinical trials has suggested that a 1:1 THC/CBD ratio (Sativex) has been associated with sleep improvements among patients with chronic pain conditions [64]. Outside of this area of research, the work examining cannabinoids' association with sleep has been relatively limited which makes drawing conclusions difficult at this early stage of research.

Taken together, the research on cannabinoids and sleep is in its infancy and studies are limited by small sample sizes, short-term follow-up, and a lack of controls [c.f. 60]. However, the role of the endocannabinoid system on the circadian regulation system demonstrates the theoretical connection between cannabinoids and sleep. This highlights the critical need for continued research in this area to examine these questions in large samples, with adequate controls and long-term follow-up assessments in order to understand the long-term effects, a major question which still remains. Future research is needed to continue to examine the impact of specific cannabinoids on sleep, including objective measures of sleep. Within these studies, it is critical to examine the impact of cannabinoid ratios, dose, the timing of the dose, and route of administration as the current work combines to indicate these factors result in differential outcomes.

Compliance with Ethical Standards

Conflict of Interest James Sottile and Danielle Morabito declare that they have no conflict of interest.

Kimberly A. Babson has received personal fees from Insys Therapeutics.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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